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THE MORPHOLOGY OF THE OPTIC NERVE HEAD IN TWO REPRESENTATIVE SOUTH-EAST ASIAN POPULATIONS



by

Rupert Richard Alexander Bourne

A thesis submitted to the University of London
for the degree of
DOCTOR OF MEDICINE

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Abstract

Purpose:

1. To evaluate techniques of optic disc analysis in two population-based glaucoma surveys in South-East Asia.
2. To use these techniques to assess the normal distribution of optic disc characteristics in a Chinese and Thai population (currently unknown), and to compare with other ethnic groups.

Methods: Optic disc data was obtained from 470 subjects aged ≥ 50 years from the Rom Klao glaucoma survey of Thailand, and 929 subjects aged ≥ 40 years from the Tanjong Pagar glaucoma survey of Singapore, using clinical biomicroscopy and a novel planimetric method involving stereo-photographs. Exclusion of subjects with an abnormal visual field test &/or an occludable angle &/or intraocular pressure (IOP) > 97.5 th percentile in either eye, resulted in 'normal' datasets of 292 Thai and 622 Singapore subjects. A sub-study using the Heidelberg Retina Tomograph-II (HRT) was conducted with 143 Thai subjects.

Results: Systematic differences in disc parameter measures were found between biomicroscopy, planimetry and HRT. Mean planimetric disc area (DA) and neuroretinal rim area (RA) were similar in the two studies. No gender differences in DA and RA were found after multiple variable analysis. RA was unrelated to age in both studies. DA was positively correlated with AL, height and corneal thickness. RA was significantly lower in those with a history of migraine. The 'normal' biomicroscopic cup/disc ratio (CDR) distribution was similar between the two studies (median, 0.4; 97.5th percentile=0.7), with CDR increasing with increasing disc size.

Conclusions: The inter-correlation of disc parameters and the relationships between parameters and biometric variables were similar to those reported in Caucasians. The distribution of CDR was very similar to that found in several ethnic groups. Other parameters, such as neuroretinal rim configuration, were different. This research should assist clinicians, epidemiologists and diagnostic instruments in the judgment of normality of a given optic disc in these populations.

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Chapter 1. Introduction

1.1 Overview

Glaucoma is now recognized as the leading cause of irreversible blindness worldwide. Reports using different models and evidence bases have estimated between 5.2 million (Thylefors B 1994) and 6.7 million blind (Quigley 1996) due to glaucoma globally.

Current opinion regards glaucoma as being a form of optic neuropathy that is characterized by structural changes that can be detected at the optic nerve head occurring in association with functional changes such as visual field loss. The importance of detection of these optic nerve changes is further emphasised by evidence that suggests that they may occur before changes can be measured reproducibly by psychophysical means (Airaksinen, Tuulonen et al. 1992) (Sommer, Miller et al. 1977) (Quigley, Katz et al. 1992) (Pederson and Anderson 1980) (Sommer, Pollack et al. 1979) (Sommer, Katz et al. 1991) (Quigley, Addicks et al. 1982).

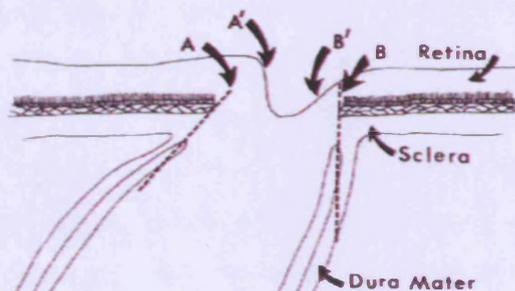
The optic nerve is formed of approximately one million axons arising from retinal ganglion cells. Visual field defects may arise from localized insults to the retinal nerve fibre layer or in the optic nerve head. Axons converging toward the optic disc enter the optic nerve via an opening in the outer retina, the choroid and sclera. The size of this opening may exceed the volume occupied by the axons, blood vessels and supporting glial tissue, resulting in a physiological excavation (Bengtsson 1976). The chorioscleral canal is usually vertically oval and in addition more nerve fibres enter the superior and inferior poles of the disc than in the temporal or nasal sectors. This arrangement results in a more or less circular optic cup (Kirsch and Anderson 1973) (Figure 1.1).

Figure 1.1 Normal optic nerve configuration. The height of the disc is greater than the width. The width of the neuroretinal tissue is also greater in the vertical meridian than in the nasal and temporal meridians resulting in a round physiologic cup.



The obliquity of the wall of the canal through the choroid and sclera affects the shape of the physiologic cup. The wall of the cup is steep where the wall of the canal is angled outward. Where the canal has a wall perpendicular to the ocular coats, the cup has a sloping wall (Figure 1.2). The slope of the cup may vary from one sector to another, and there is considerable individual variation in the size and shape of the choriocleral canal and therefore of the optic cup.

Figure 1.2. Influence of the tilt of the scleral canal on the slope of the canal. An outward slope of the choriocleral canal (A) corresponds to a steep wall of the cup (A'). A perpendicular wall of choriocleral canal (B) corresponds to a sloping wall of the cup (B'). *Illustration courtesy of Duane's Ophthalmology (2000 Lippincott Williams & Wilkins).*



The mechanism by which optic neuropathy occurs in glaucoma is unknown. There appear to be intraocular pressure-dependent and pressure-independent factors, such as optic nerve blood flow (Anderson and Quigley 1992). In typical cases of chronic glaucoma, the damage occurs over a prolonged period of time. After the most susceptible axons are already damaged, it may be speculated that damage to other, previously unaffected axons may occur as a result of factors such as age, structural weakening of the disc due to partial cupping, or progressive rise or fluctuations in the intraocular pressure (Hernandez 2000).

When axonal loss occurs more predominantly in certain bundles, cupping characteristically extends toward the disc rim in the sector that has lost neural tissue. If the preferential loss is in the most typical location (in the polar sectors), the cup expands vertically (Kirsch and Anderson 1973) and may form a notch at the disc rim (Figure 1.3), most often at the poles of the optic disc. In contrast, when axon loss is evenly diffuse, the cup expands concentrically (Figure 1.4) (Pederson and Anderson 1980). In the middle of the spectrum, where the majority of cases lie, there may be widespread loss of axons that is more severe near the pole of the disc. Thus, as the cup extends and deepens vertically, there is also temporal and nasal unfolding of the cup. Four characteristic patterns of glaucomatous optic nerve appearance have been described (Nicollela MT 1996) (focal ischaemic discs, myopic glaucomatous discs, senile sclerotic discs, and disc with generalized enlargement of the optic cup) which appear to have distinctly different effects on the visual field (Geijssen and Greve 1987). The risk factors that affect glaucoma may also determine the appearance of the damaged glaucomatous optic nerve head (Broadway, Nicollela et al. 1999).

Figure 1.3 A glaucomatous optic disc with inferior notch.

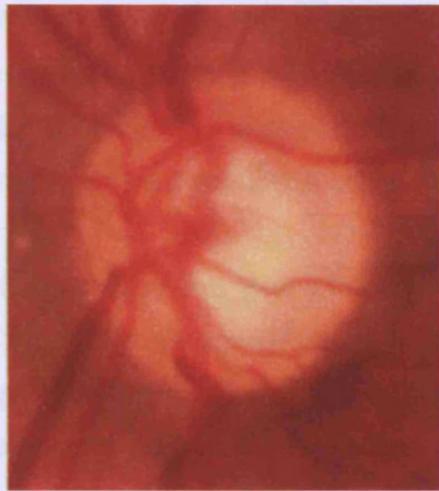
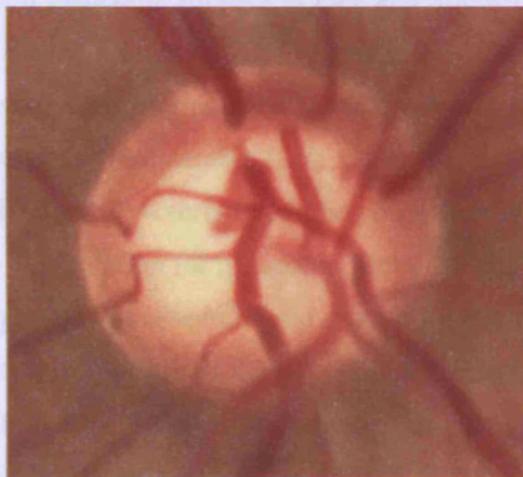


Figure 1.4. A glaucomatous optic disc with concentric cupping.



Several different techniques are available for optic disc assessment in either clinic-based or population-based settings. The examination methodology of population-based glaucoma surveys varies greatly and it is therefore difficult to generalize about which techniques of optic disc assessment are more widely used. One can derive a range of complexity: direct ophthalmoscopy with an undilated pupil, direct ophthalmoscopy through a dilated pupil, a stereoscopic image using a slitlamp with an indirect lens with or without mydriasis, using a contact lens with or without a measuring graticule, to stereophotography, which may employ a range of different analysis techniques which vary in reproducibility and accuracy. As a general rule, as the level of sophistication increases, the reproducibility and accuracy of the

measurements also improve. In recent years, confocal scanning laser ophthalmoscopy (Iester, Broadway et al. 1997; Bathija, Zangwill et al. 1998; Bartz-Schmidt, Thumann et al. 1999) and scanning laser polarimetry (Tjon-Fo-Sang, van Strik et al. 1997; Greaney, Hoffman et al. 2002; Medeiros, Zangwill et al. 2003), have emerged as instruments that can be used to obtain extremely accurate measurements of the optic disc.

Population-based surveys are useful as they give a truer reflection of the pattern of disease in the population than clinic or hospital-based studies where the subjects are, by definition, a selected group and therefore information gathered from these subjects is subject to bias. Information derived from a sample representative of the population, can be used for reference in a clinic-based setting to compare the findings in an individual to those of the 'normal' population, thereby allowing a measure of the risk of abnormality of a given individual or eye.

Recent population-based glaucoma surveys in East and South-East Asia (Foster, Baasanhu et al. 1996; Foster, Oen et al. 2000) (Bourne RR 2003) have shed light on the prevalence and mechanisms of glaucoma in these population groups. Previously only hospital-based studies were available (Loh 1968).

Knowledge of the optic disc characteristics of the population is of relevance when attempting to 'screen' a population for glaucoma. Both the Thai and Singapore surveys conducted as part of this research used criteria for detection of the disease by sampling a representative proportion of the population. Screening is a public health intervention intended to reduce the population burden of a condition or its consequences, and strictly can only be applied when subjecting an entire population at risk to a specific test or enquiry (Wilson, Jungner, 1968). However, a screening test may be used in a survey situation, as it may in other clinical situations which do not meet the more rigorous criteria of a screening program. A screening test should be simple, safe, precise and validated, and the distribution of test values in the target population should be known and a suitable cut-off level defined and agreed. In addition, the test should be acceptable to the population, and there should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals. Other criteria relate to the condition, the treatment and the screening programme itself.

One of the principle problems with screening for glaucoma is the lack of a clear understanding of the natural history of the disease. The three tests necessary for the

diagnosis of glaucoma, namely an intraocular pressure measurement, an optic disc examination and a visual field assessment, all perform badly as single tests, with both low sensitivity and positive predictive value. The combination of intraocular pressure and disc assessment alone only marginally improves the validity (Tielsch, Katz et al. 1991).

No information exists regarding the optic disc characteristics of these South-East Asian populations, which may differ from that of Caucasians. Knowledge of the normal structure of the optic disc and the associations with demographic variables, biometric and systemic disease in these populations would provide an important reference and may assist in the understanding of how these discs respond to a disease such as glaucoma.

1.2 Characteristics of the optic disc

1.2.1 Disc parameters

Historically, cup/disc ratio (CDR) has been the principle measure of the optic nerve head, with a large CDR indicating that the disc is more likely to be abnormal. CDR is only an indirect measure of the amount of neural tissue, since an increasing diameter of the nerve head may be associated with decreasing neural rim width and increasing cup size, despite a stable area of neural tissue (Bengtsson 1980; Balazsi, Drance et al. 1984). Loss of neuroretinal rim tissue has a greater effect on CDR when the CDR is small (Garway-Heath, Ruben et al. 1998) (Montgomery 1993).

The distribution of CDR in the general population has been reported in several studies, but the results differ according to the examination technique used. Using direct ophthalmoscopy, Armaly (Armaly 1967) reported a non-Gaussian distribution of CDR, where most eyes have a CDR of between 0 to 0.3 and only 1-2% have a CDR of 0.7 or more. Other studies have reported CDR values of 0.65 or more, occurring in 2.2% to 4% of discs (Snydacker 1964; Sommer, Pollack et al. 1979; Carpel and Engstrom 1981). With a stereoscopic view, Schwartz (Schwartz, Reuling et al. 1975) reported a Gaussian distribution with a mean CDR of 0.4 and approximately 5% with a CDR of 0.7 or more. Stereoviewing of the disc (with a Hruby lens) has been shown by one study to give larger values (mean CDR, 0.38) for CDR than with direct ophthalmoscopy (mean CDR, 0.25) (Carpel and Engstrom 1981).

It is recognized that optic disc size is subject to large interindividual variation (Nicolela MT 1996), up to a six-fold variation in disc area as reported by some studies (Jonas, Gusek et al. 1988; Jonas, Gusek et al. 1988). This clinical observation has been confirmed histopathologically (Kronfeld 1976; Quigley, Brown et al. 1990).

The cup/disc ratio is also subject to considerable inter-individual variation, much of which is due to variation in disc diameter (Quigley, Brown et al. 1990).

In addition to studies that have looked at the total areas of disc, cup and rim, some studies have divided the disc head into sectors and reported on sectoral areas. Jonas (Jonas, Fernandez et al. 1993) reported that neuroretinal rim area changes in size according to the disc sector. He observed that the rim was largest in the inferotemporal sector, followed by the superotemporal sector, nasal, with the temporal

sector the smallest. This regional distribution of rim area is correlated with visibility of retinal nerve fibre layer bundles (usually better detected in the inferotemporal region than the superotemporal), diameter of the retinal vessels (larger in the inferotemporal arcade than superotemporal) and the location of the fovea which is situated approximately 0.5mm inferior to the midpoint of the optic disc (Airaksinen, Drance et al. 1985; Weber, Dannheim et al. 1990; Bowd, Weinreb et al. 2000). There is also correlation with the morphology of the inner surface of the lamina cribrosa which has the largest pores and highest summed pore area in the superior and inferior regions, and least in the nasal and temporal regions (Quigley, Addicks et al. 1981; Ogden, Duggan et al. 1988).

1.2.2 Intra-eye and inter-eye correlation of disc parameters

It is known from studies of disc photographs (Bengtsson 1976) and image analysis (Garway-Heath, Ruben et al. 1998) (Healey PR 1997) that CDR increases with an increase in size of the disc. Several studies, using image analysis, have demonstrated a linear relationship between cup size and disc size (Bengtsson 1980; Britton, Drance et al. 1987; Caprioli and Miller 1987; Garway-Heath, Ruben et al. 1998). Neuroretinal rim area also increases with increasing optic disc size (despite an increase in cup/ratio) (Britton, Drance et al. 1987; Caprioli and Miller 1987; Kee, Koo et al. 1997; Garway-Heath, Ruben et al. 1998) (Jonas, Gusek et al. 1988). However, the contour of the cup may influence this correlation. For example, cups with flat temporal slopes will have a greater increase in rim area for a given increase in disc area than those discs with steep circular cups.

Inter-eye correlation of disc parameters has also been reported. Cup size has been shown to have a high degree of symmetry (Armaly 1967; Fishman 1970; Schwartz, Reuling et al. 1975) (Holm OC 1972). There is also high inter-ocular symmetry for CDR, Armaly (Armaly 1967) reporting asymmetry of more than 0.2 occurring in only 1% of the normal population.

Knowledge of the patient's disc area is of relevant when screening for primary open-angle glaucoma, as the vertical cup/disc ratio depends on the disc area (Jonas, Gusek et al. 1988). In addition, if one uses the same planimetric method to determine the disc

area and rim area, linear regression can be used to determine how deviant the rim area and vertical cup/disc ratio are in comparison with a general population.

1.2.3 Effect of age, gender and race

1.2.3.1 Age

The effect of age on optic disc characteristics is controversial and is more unclear due to the fact that different studies have used different subject groups, age groups and measurement techniques to arrive at their conclusions. In the following summary of current research in this area, the majority of the studies quoted are those that have reached their conclusions using data from 'normal' subjects, rather than those with glaucoma.

Bengtsson (Bengtsson 1980) reported a slight increase in disc size with age, but this may have been artefactual (Balazsi, Drance et al. 1984) relating to the method used to correct for ocular magnification (Bengtsson B 1977), with magnification of the disc image resulting from increased refractive power of lens in older age (Garway-Heath and Hitchings 1998). Other studies have found the disc size to remain constant with age (Jonas, Gusek et al. 1988; Quigley, Brown et al. 1990; Tsai, Ritch et al. 1992; Garway-Heath and Hitchings 1998).

The size of the cup has been reported to increase with age by several studies (Pickard 1948; Bengtsson 1980) (Schwartz, Reuling et al. 1975) (Schwartz 1980; Carpel and Engstrom 1981), whereas several more found no change with age (Snydacker 1964; Hollows and McGuinness 1966; Armaly 1967; Armaly and Sayegh 1969; Jonas, Gusek et al. 1988; Varma, Tielsch et al. 1994; Garway-Heath, Ruben et al. 1998).

Neuroretinal rim area has variously been described as reducing with age (Schwartz, Reuling et al. 1975; Bengtsson 1976; Carpel and Engstrom 1981; Balazsi, Rootman et al. 1984; Tsai, Ritch et al. 1992; Garway-Heath, Wollstein et al. 1997) or remaining stable with age (Jonas, Gusek et al. 1988; Funk, Dieringer et al. 1989; Airaksinen, Tuulonen et al. 1992; Kee, Koo et al. 1997). It has been suggested (Kee, Koo et al. 1997) that some studies that have investigated rim area and age in isolation, have failed to take into account the optic disc size, which, if larger in an older age group, may give the false impression that rim area was unchanged with age, whereas in reality it had decreased.

Using the Heidelberg Retina Tomograph, Garway-Heath et al (Garway-Heath, Wollstein et al. 1997) reported that the mean CDR increased by about 0.1 between the ages of 30 and 70 years. Another study reported no change in CDR with age (Tsai, Ritch et al. 1992).

1.2.3.2 Gender

Several studies have investigated gender differences in optic nerve head characteristics, almost exclusively among Caucasian subjects. Cup/disc ratio has been reported by some authors to be unrelated to gender (Britton, Drance et al. 1987) while others have found women to have smaller CDR's than men (Leibowitz, Krueger et al. 1980) and smaller cup and rim volumes (Tsai 1995) and 2-3% smaller disc sizes (Varma, Tielsch et al. 1994). Several studies (Armaly 1967; Garway-Heath, Ruben et al. 1998) (Hollows and McGuinness 1966; Schwartz, Reuling et al. 1975; Bengtsson 1980) have found no gender difference in cup size. Garway-Heath et al (Garway-Heath, Ruben et al. 1998) reported that neuroretinal rim area was unrelated to gender. Quigley (Quigley Arch Ophthalmol 1990; 108 51-7) reported narrower discs in women, despite no differences in vertical disc diameter. Other biometric variables such as axial length and keratometry may influence the magnification characteristics of imaging systems used to measure the disc. Women have been reported to have significantly larger keratometry values than men (Tsai 1995) and shorter axial lengths (Britton, Drance et al. 1987; Tsai, Ritch et al. 1992). From a histological standpoint, Jonas reported no gender difference in optic nerve fibre count (Jonas, Schmidt et al. 1992).

1.2.3.3 Race

Racial differences exist in the prevalence of glaucoma (Quigley 1996). Ethnic differences in glaucoma prevalence may be related to differences in intraocular pressure (Coulehan JL 1980), and may (Chi, Ritch et al. 1989) (Burk, Rohrschneider et al. 1992) or may not (Gusek GC 1988; Varma, Tielsch et al. 1994) be related to optic disc anatomy and histology.

The data from most previous studies of optic disc parameters, has been taken from participants selected from those presenting to clinics or hospitals (Pickard 1948) (Snydacker 1964) (Armaly and Sayegh 1969) (Schwartz, Reuling et al. 1975) (Bengtsson 1976) (Carpel and Engstrom 1981) (Beck, Messner et al. 1985) (Britton,

Drance et al. 1987) (Jonas, Gusek et al. 1988) (Caprioli and Miller 1988) (Chi, Ritch et al. 1989). The data from these studies are thus subject to selection bias and may not be representative of the general population. Several of these clinic-based studies have attempted to investigate for racial differences (Chi, Ritch et al. 1989) (Beck, Messner et al. 1985; Tsai 1995).

The relatively few population-based glaucoma studies that have assessed the optic disc (Mitchell, Smith et al. 1996) (Dielemans, Vingerling et al. 1994) (Hollows and Graham 1966) (Foster, Baasanhu et al. 1996) have generally involved racially homogeneous populations, the majority Caucasian. However, a study by Varma et al (Varma, Tielsch et al. 1994) involved two races (Caucasian and African-American) within the same study by nature of the population examined (East Baltimore, U.S.A), allowing comparisons to be made between races with regard to optic disc characteristics.

Several of the major studies are illustrated in Table 1.1. A wide range of techniques of optic disc image-acquisition and analysis have been used in the various studies. This causes difficulty when attempting to compare between the population-based studies on differing racial groups. This is certainly the case when considering accurate planimetric measurements which rely heavily on the magnification properties of the image acquisition device. When comparing ratios (eg. cup-disc ratio) this may be less of a concern.

The clinic-based studies recruited smaller numbers of participants, yet have the advantage of comparing different races under similar conditions and with the same instrument. Techniques such as scanning laser ophthalmoscopy (Tsai 1995) which may be more difficult to use in a population-based setting from a practicable standpoint, may allow precise comparisons to be made between races by virtue of the high reproducibility and accuracy of such instruments.

Varma et al ((Varma, Tielsch et al. 1994)), using stereophotography, found the mean optic disc area of American blacks to be 12% larger than whites, but the mean neural rim area was very similar in the two racial groups. The cup area and CDR were larger and the neural rim-to-disc area ratio was smaller in blacks compared to whites. Beck et al (Beck, Messner et al. 1985) evaluated stereoscopic photographs from 100 black and 100 white volunteers and estimated horizontal, vertical, and average CDR's. They

found that blacks had greater CDR than whites. Chi et al (Chi, Ritch et al. 1989) found that blacks had larger disc areas, larger CDR's, and similar neural rim areas. Quigley et al (Quigley, Brown et al. 1990) made histological measurements of the optic disc in normal eye bank eyes from 24 blacks and 36 whites and found that blacks had greater vertical optic disc diameters than whites but similar horizontal diameters.

Varma showed that the neural rim area is linearly related to disc area in blacks. This finding had also been demonstrated in whites (Britton, Drance et al. 1987; Caprioli and Miller 1987; Jonas, Gusek et al. 1988). However, at each disc size, blacks had a lower neural rim area than whites, and this disparity widened with increasing disc size. From histological studies, Quigley et al and Jonas et al (Quigley, Coleman et al. 1991; Jonas, Schmidt et al. 1992) reported that larger optic discs had greater numbers of nerve fibres. Accepting this histological evidence, Varma concluded that neural rim area was proportional to nerve fibre number. Therefore, they reasoned that although blacks appear to have on average, a larger scleral canal opening at the optic disc, they have fewer nerve fibres than whites for any given optic disc size.

Varma found no age-related or refractive error-related differences in any of the topographic optic disc measurements, but they did find that males had statistically significantly larger (about 2 to 3% larger) discs than female subjects. However, this was the only one of the disc measures to show a gender-difference.

Tsai et al (Tsai 1995), in a cross sectional university-based study, compared optic disc characteristics of African-American, Asian, Hispanic and white subjects, using the Heidelberg Retina Tomograph scanning laser ophthalmoscope. Their paper does not specify a more accurate region of origin of the Asian students. They had several exclusion criteria (Table 1.1) which included tilted and asymmetric discs. They found that the mean optic disc area, cup area, cup-disc area ratio, cup volume below the surface, and cup volume below the reference in Asians and Hispanics occupied an intermediate position between those of African-Americans (the largest) and whites (the smallest).

Table 1.1 Population-based and clinic-based studies that have either attempted to define optic disc characteristics in a population or have investigated differences between ethnic groups

POPULATION-BASED	Name or location of study/ author	No. Subjects (who had discs examined)	Racial Origin	Age range of subjects	One/ both eyes	Image Acquisition	Image Processing	Image Analysis	Parameter Type	Parameters
	Rotterdam (Dielemans, Vingerling et al. 1994) (Wolfs, Ramrattan et al. 1999)	5143	Caucasian	≥ 55 yrs	At least one eye	Direct & indirect ophthalmoscopy Colour transparencies	Transparencies digitised	Topcon ImageNet	Ratios	Vertical CDR
	Blue Mountains, Australia (Mitchell, Smith et al. 1996) (Healey and Mitchell 1999)	3654	Caucasian	≥ 49 yrs	Both	Sequential stereo colour transparencies	Donaldson stereoviewer (Klein, Magli et al. 1985)	Plastic template (Pickett circles)	Absolute measures and Ratios	Vertical disc diameter Vertical CDR
	Kongwa, Tanzania (Buhmann, Qigley et al. 2000)	3247	Black African	>40 yrs	Both	Indirect ophthalmoscopy + graticule (3247 eyes) & Glaucoma-Scope† (497 eyes)	Glaucoma-Scope images recorded on video film	Not specified	Ratios	CDR
	Zulus (Rotchford AP 2002)	1005	Black African	>40 yrs	Both	Binocular indirect ophthalmoscopy Sequential Stereo Disc photography	Stereoviewer	Not specified	Ratios	VCDR
	Tanjong Pagar, Singapore (Foster, Oen et al. 2000)	1232	Singapore Chinese	> 40 yrs	Both	Fundus contact lens x40 and eyepiece graticule & colour transparencies	Transparencies digitised	Planimetric ‡	Stereometric measures & ratios	VCDR & Disc, rim and cup areas in 10 degree sectors

POPULATION-BASED (continued)	Name or location of study/ author	No. Subjects (who had discs examined)	Racial Origin	Age range of subjects	One/ both eyes	Image Acquisition	Image Processing	Image Analysis	Parameter Type	Parameters
	Rom Klao, Thailand (Bourne RR 2003)	701	Thai	≥50 yrs	Both	Fundus contact lens x16 and eyepiece graticule & colour transparencies	Transparencies digitised	Planimetric ‡	Stereometric measures & ratios	VCDR & Disc, rim and cup areas in 10 degree sectors
	Baltimore (Varma, Tielsch et al. 1994)	1534 1853	Black Am White Am	≥ 40 yrs	Both	Simultaneous Stereo colour transparencies	Transparencies digitised	Topcon ImageNet* Modified Littman corr factor**	Stereometric measures & ratios	Disc area, NRR area, Neural rim area-disc area ratio, VCDR & HCDR, cup area
	Vellore Eye Study (Jonas, Thomas et al. 2003)	70	Indian	Mean 47.5 yrs	One	Sequential stereophotos Zeiss fundus camera	Projection on a scale of 1-15	Manual measurement	Stereometric measures & ratios	Disc area, NRR area, Neural rim area-disc area ratio, VCDR & HCDR, cup area
CLINIC- OR HOSPITAL-BASED										
	Chi (Chi, Ritch et al. 1989)	30 31	Black American White American	18-35 yrs	Both	Video-ophthalmography RODA		RODA + stereophotos to define disc edges		CDR, disc area, cup vol, disc rim area
	Beck (Beck, Messner et al. 1985)	100 100	Black American White American	Mean 39 yrs Mean 37 yrs	Both	Simultaneous Stereo transparencies Zeiss camera	Film only	Stereoviewer Observer estimated CDR	Ratios	CDR
	Tsai (Tsai 1995)	43 45 48 44	African-American Asian Hispanic White	Mean 28 yrs	One	HRT	HRT	HRT	Stereometric measures & ratios	Disc, cup, rim areas. CDR, rim vol, cup depth

CLINIC- OR HOSPITAL-BASED (continued)	Name or location of study/ author	No. Subjects (who had discs examined)	Racial Origin	Age range of subjects	One/ both eyes	Image Acquisition	Image Processing	Image Analysis	Parameter Type	Parameters
	Kee (Kee, Koo et al. 1997)	104	Korean	40-68 yrs	Both	Topcon SS ^a	Topcon SS	Topcon SS	Stereometric measures & ratios	Disc, cup, rim areas. CDR, vol, cup depth
	(Rudnicka AR 2001)	121	Not specified	16-35 yrs	One	Carl Zeiss Jen Retinophot fundus camera §	Digitised	Image J software †	Monoscopic planimetry	Disc, cup, rim areas

Exclusion criteria used in the preparation of distributions of optic disc characteristics for each study population:

Rotterdam (Dielemans, Vingerling et al. 1994) (Wolfs, Ramrattan et al. 1999), Blue Mountains (Australia (Mitchell, Smith et al. 1996)), Kongwa, Tanzania (Buhrmann, Quigley et al. 2000): no exclusions

Tanjong Pagar, Singapore (Foster, Oen et al. 2000): subjects with abnormal visual fields

Tsai (Tsai 1995): IOP \geq 19mmHg, VA $<$ 20/25, hyperopia $>$ 3.0D, myopia $>$ -6D, angle \leq grade 1, assymetrical CDR $>$ 0.1, or evidence of intraoc pathology, history of ocular or systemic pathology.

Chi (Chi, Ritch et al. 1989): IOP $>$ 21mmHg, VA \leq 20/20, ocular or systemic disorders known to affect optic nerve

Beck (Beck, Messner et al. 1985): history of glaucoma or optic nerve disease, blood relative already in the study.

Baltimore (Varma, Tielsch et al. 1994): patients with glaucoma and those with other optic neuropathies as defined in main glaucoma study ((Tielsch, Sommer et al. 1990))

* Topcon Imagenet, Topcon Instrument Corp of America

**Axial length not used in correction factor as not taken in Baltimore Eye Survey

† The 'Glaucoma-Scope' (Ophthalmic Imaging Systems, Sacramento, CA, USA) (Dan JA 1996)

‡ the analysis of these colour transparencies constitutes part of this MD thesis

^a Topcon SS, Laser Diagnostic Technologies Inc

§ Carl Zeiss Jena, Jena, E. Germany

† ImageJ 1.16, NIMH, Bethesda, MD.

RODA: Rodenstock Optic Disc Analyser

1.3 Techniques available for assessment of the optic disc and agreement in measurement

One can derive a range of complexity in the techniques available for assessment and measurement of the optic disc: direct ophthalmoscopy with an undilated pupil, direct ophthalmoscopy through a dilated pupil, a stereoscopic image using a slitlamp with an indirect lens with or without mydriasis, using a contact lens with or without a measuring graticule, to stereophotography, which may employ a range of different analysis techniques which vary in reproducibility and accuracy. As a general rule, as the level of sophistication increases, the reproducibility and accuracy of the measurements also improve. In recent years, confocal scanning laser ophthalmoscopy (eg. The Heidelberg Retina Tomograph, Appendix II) and scanning laser polarimetry, have emerged as instruments that can be used to obtain extremely accurate measurements of the optic disc. Qualitative clinical examination of the optic nerve head may be performed using direct or indirect ophthalmoscopy. Direct ophthalmoscopy with a hand-held ophthalmoscope affords a magnified view of the disc with the disadvantage that this is monocular and has a relatively limited field of view. A magnified stereoscopic view can be obtained using slit-lamp biomicroscopy. The disc may be viewed using a +78 D or +90 D hand-held lens or with a fundoscopic contact lens, which although requiring a coupling medium, allows the observer to stabilize the eye. The observer can record his findings by carefully drawing the optic disc (Pickard 1948).

Quantitative clinical measurements can also be made of the optic disc. The observer can estimate the CDR by comparing his/her observations with a set of standard photographs of a range of CDR, or comparison with diagrammatic charts (Snydacker 1964; Hollows and McGuinness 1966) (Hitchings RA 1983). The direct ophthalmoscope has a graticule incorporated in the instrument, allowing an estimate of cup parameters such as CDR and disc size to be made (Romano. 1983) or the smallest round white light spot of the Welch Allyn direct ophthalmoscope, which projects a 1.5mm diameter spot on the retina in most eyes, can be used as a measure. In the case of slit-lamp biomicroscopy, measurements of the disc can be made by overlaying the slit-lamp beam over the disc feature to be measured and reading off the height of the beam. Magnification correction factors (Ruben 1994) (Spencer AF 1994) (Jonas and Papastathopoulos 1995) can then be

used to convert the beam height measurements into actual measures. In addition, a measuring eyepiece graticule (Haag-Streit, Bern, Switzerland) can be used in conjunction with either of these lenses to take measurements of the disc, thereby affording greater accuracy. The use of an eyepiece graticule and a modified 60 dioptre lens was shown to yield very good interobserver agreement by Haslett et al (Haslett RS 1997). However, due to unequal lateral and axial magnifications, a certain amount of image distortion occurs, with the result that the Goldmann and 90-dioptre lens give a decrease in apparent depth and the Hruby lens give a slight increase (Repka MX 1986). Binocular viewing of the disc has been noted by several reports to result in a CDR estimation that is larger than that under monocular conditions (Lichter 1976) (Carpel and Engstrom 1981) (Varma, Steinmann et al. 1992) (Montgomery 1991). Dilation of the pupil increases inter-observer agreement when performing slit-lamp biomicroscopy with an indirect lens. A study by Kirwan et al (Kirwan, Gouws et al. 2000) reported mean 95% limits of agreement values for all CDR values of 0.27 for examination without mydriasis and 0.13 for examination with mydriasis.

Photographic techniques, in black-and-white or colour, allow relative dimensions of the pallor and cup to be measured directly on the photograph (Gloster J 1974; Hitchings RA 1983), but this technique is limited by the absence of stereo-cues that assist in the delineation of the cup margin, although one study found that monocular and stereoscopic photographs gave similar levels of accuracy (Sharma NK 1983). To improve recognition of the cup contours, fine parallel lines can be projected on to the disc in either two-dimensional or stereoscopic photographs (Cohan 1978; Kennedy SJ 1983).

Stereoscopic photographs can be produced either sequentially or simultaneously. In the sequential approach, the observer either manually repositions the camera or uses a sliding carriage adaptor (Allen separator) (Allen 1964). To achieve simultaneous photographs, one can either use two cameras that utilize the indirect ophthalmoscopic principle (Donaldson stereoscopic fundus camera (Donaldson 1965)) or a twin-prism separator (Saheb NE 1972). More modern simultaneous stereo-imaging systems provide the stereo pair on two halves of the same frame (eg. Nidek 3Dx), offering significantly better stereoscopic quality (Greenfield DS 1993). These photographs can be analysed manually or with the aid of computing software. Manual photogrammetry used a stereoplotter

operated by a skilled technician who made depth measurements from simultaneous stereophotographs of known stereoscopic separation. Portney (Portney 1975; Portney 1976) and Schwartz (Schwartz 1976; Schwartz 1986) were among the first to apply this technique to the optic nerve in glaucoma approximately twenty years ago. Computer software, such as DISC DATA, Thot Informatique (Pr Bechetoille, Angers, France) program (Garway-Heath and Hitchings 1998) has also been developed to measure digitised stereo-photographs. The accuracy of these imaging systems is dependent on the accuracy of the biometric variables that are entered for a given subject to correct for ocular (Littmann 1982) (Garway-Heath, Rudnicka et al. 1998) and camera magnification (Rudnicka, Burk et al. 1998). Interobserver agreement is better with stereoscopic rather than monoscopic photographs, Varma (Varma, Steinmann et al. 1992) reporting median weighted kappas of 0.57 (monoscopic) and 0.67 (stereoscopic). Tielsch et al (Tielsch, Katz et al. 1988) reported a mean kappa of 0.74 for vertical CDR from stereophotographs, although the criteria for weighting was different.

Digitized simultaneous stereoscopic videographic images have been used to measure structural characteristics of the optic nerve head and peripapillary retina. Initial studies evaluated the reproducibility and reliability of the Rodenstock Analyzer (Mikelberg, Douglas et al. 1984) (Heijl A 1989) (Caprioli, Klingbeil et al. 1986; Shields, Martone et al. 1987) (Bishop, Werner et al. 1988)). A similar device developed by Topcon Instruments (Imagenet) has the added advantage of taking video input both from patients and from photographs (Varma, Steinmann et al. 1988) (Varma, Douglas et al. 1989). In recent years, confocal laser scanning has recently been applied to the optic nerve and retina. A series of scans are made at sequential tissue depths, allowing a three-dimensional structure to be reconstructed. The reproducibility of the technique is better (Cioffi, Robin et al. 1993) than that of conventional imaging. High levels of reliability have been reported using the Heidelberg Retinal Tomograph (Rohrschneider, Burk et al. 1994). However, there may be difficulties encountered with small pupils, Tomita (Tomita, Honbe et al. 1994) reporting a significant increase in the coefficient of variation of volume and depth measurements after miosis with pilocarpine compared with the untreated same eye. The mean standard deviation equivalents of test-retest variability in the glaucoma patients and controls were reported by Chauhan et al (Chauhan, LeBlanc et

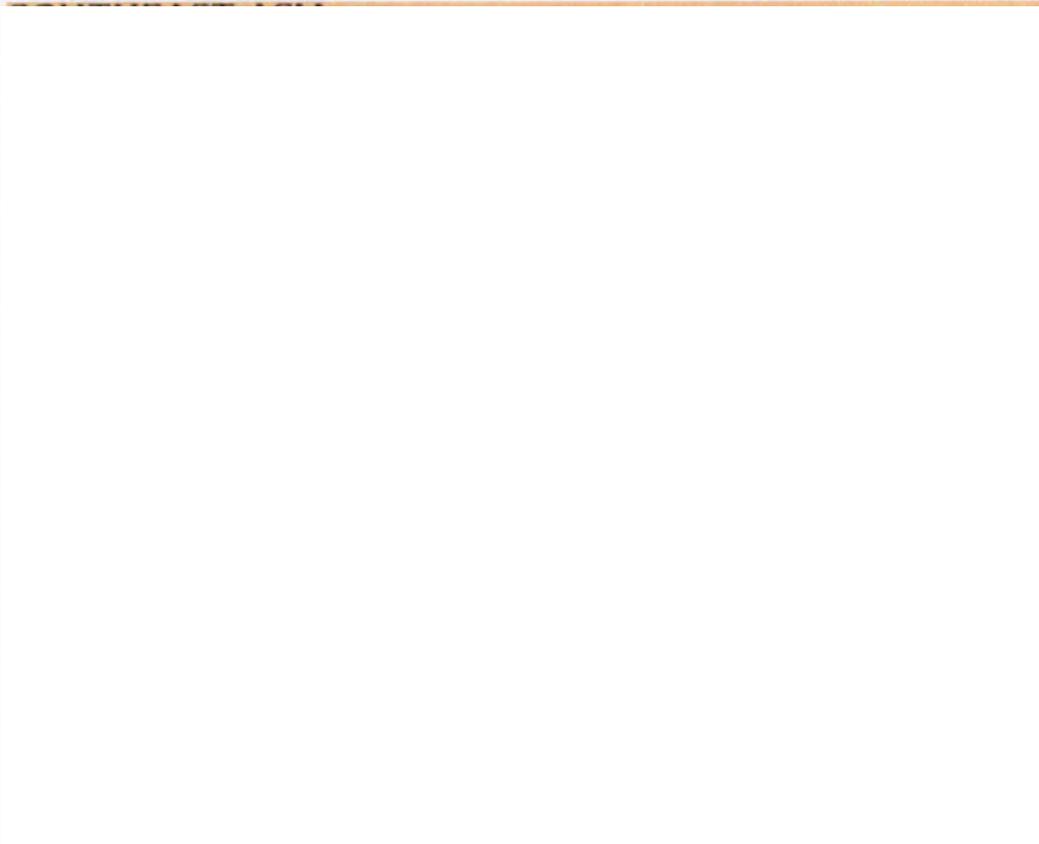
al. 1994) as 31.20 and 25.94 microns, respectively. These differences were statistically significant and variability also increased significantly with patient age. High levels of agreement between CDR measurements made by glaucoma experts using stereophotographs, and the CDR measurements made with a confocal scanning laser ophthalmoscope have been reported (Zangwill, Shakiba et al. 1995). Interestingly, differences were smaller between clinician estimates and instrument measurements of horizontal and vertical CDR of patients with glaucoma than normal subjects.

1.4 Glaucoma & optic disc morphology in East and South-East Asia

1.4.1 Glaucoma

A map of South-East Asia is presented in Figure 1.5.

Figure 1.5 A map of South-East Asia



The prevalence and characteristics of glaucoma in the people of Southeast Asia have until recently not been well documented. A recent population-based study of Singapore Chinese (Foster, Oen et al. 2000) showed primary open-angle glaucoma (POAG) to be the predominant form (49%) in this population, with primary angle-closure glaucoma (PACG) accounting for 31% and secondary glaucoma 16%, of all glaucoma. A prospective, island-wide incidence study (Seah, Foster et al. 1997) confirmed the supposition that Chinese ethnicity carried a significantly higher risk of symptomatic primary angle-closure (PAC) compared with non-Chinese Singaporeans (relative risk: 2.8). There were insufficient numbers to calculate incidence figures for Malay and

Indian people in Singapore. Hospital discharge data have helped determine the magnitude of PACG morbidity in the two smaller ethnic groups of Singapore; the discharge rate (per 100,000 per year) for PACG among Malay people was 6.0, and 6.3 for Indians. The rate among Chinese was 12.2 (Wong, Foster et al. 2000). These figures probably represent the rate of symptomatic disease, as most non-acute care is provided on an out-patient basis. The rate of symptomatic PAC among Thai people was reported to be 7.0/100,000/year (Fujita K 1996). The concordance between these figures for Thai and Malay people is striking.

The lack of information regarding the prevalence of glaucoma in South-East Asia was the basis for a population-based glaucoma survey in urban Thailand (Bourne R 2003), conducted by the author and a Thai research fellow, Paradon Sukudom. The analysis of the survey provided data on the prevalence and mechanisms of glaucoma, an overview of which will be given here.

In the Thai survey, glaucoma was the second most common cause of unilateral (12%) and bilateral (11%) blindness after cataract. This result is similar to that of a survey of hospital records in Thailand in 1973 (Limpaphayom and Wangspa 1973) where glaucoma was found to account for 11.2% of 18,170 cases of blindness. The prevalence of glaucoma increased with age in both sexes. In the 50 to 59 year age group, the prevalence of glaucoma in males was 2.6%, and 1.2% in females. These proportions were increased in those aged 70 years or more, to 6.8% and 10.1% respectively. In 1996, Quigley (Quigley 1996) published a statistical model of glaucoma prevalence world wide derived from available published data. These data suggested a linear relationship between open-angle glaucoma and age in Asians. Both the Thai study and a recent study of Chinese Singaporeans (Foster, Oen et al. 2000) suggest a non-linear increase in POAG with age (Figure 1.6). The pooled data model of POAG prevalence overestimates the rate in those under the age of 70 and underestimates in those over this age.

The relative proportions of glaucoma attributable to POAG, PACG and secondary glaucoma found in this Thai study is presented in Figure 1.7 alongside data obtained from other studies (some requiring more detailed data from personal communication with Dandona L, (MD MPH), and Foster PJ (FRCSEd)) (Foster, Oen et al. 2000) (Foster, Baasanhu et al. 1996) (Dandona, Dandona et al. 2000) (Coffey, Reidy et al. 1993). These

studies have used similar diagnostic criteria and were compared by direct standardization to the population of Thailand (U.S. Bureau Census 2000) . The populations of Singapore and Thailand, are intermediate between the extremes of Mongolia (Foster, Baasanhu et al. 1996), where there is relatively more PACG, and Ireland (Coffey, Reidy et al. 1993), where there is relatively more POAG. Dandona et al (Dandona, Dandona et al. 2000) classified ocular hypertensives with occludable angles as cases of PACG. This would have increased the number of PACG cases, when comparing with the other studies illustrated. The ratio of POAG: PACG in Singapore Chinese (1.6:1) compared to that of Thais (3.2:1) and Indians (2.4:1), reflects the findings of a glaucoma incidence study in Singapore (Seah, Foster et al. 1997) where Malays and Indians were found to be at lower risk of symptomatic PAC in comparison to the Chinese population. It also reflects the findings of a study in Thailand (Fujita K 1996) where the incidence of PACG was much lower than in Singaporean Chinese.

With the population expansion of those aged 50 or more that is expected in Thailand in coming years, one can project that the prevalence of glaucoma will also substantially increase. Applying the findings of this survey to such a population projection (U.S. 2000) (Figure 1.8), the number of males affected by glaucoma is expected to rise three-fold, and for females four-fold, over the next fifty years. The findings of this survey and these future projections emphasise the importance of glaucoma as a cause of visual impairment in Thailand and throughout South-East Asia.

Figure 1.6 The prevalence of open-angle glaucoma with age in Thailand (diamonds) and Singapore (Foster, Oen et al. 2000) (squares), presented with the assumed prevalence made by Quigley in 1996 (Quigley 1996) (crosses).

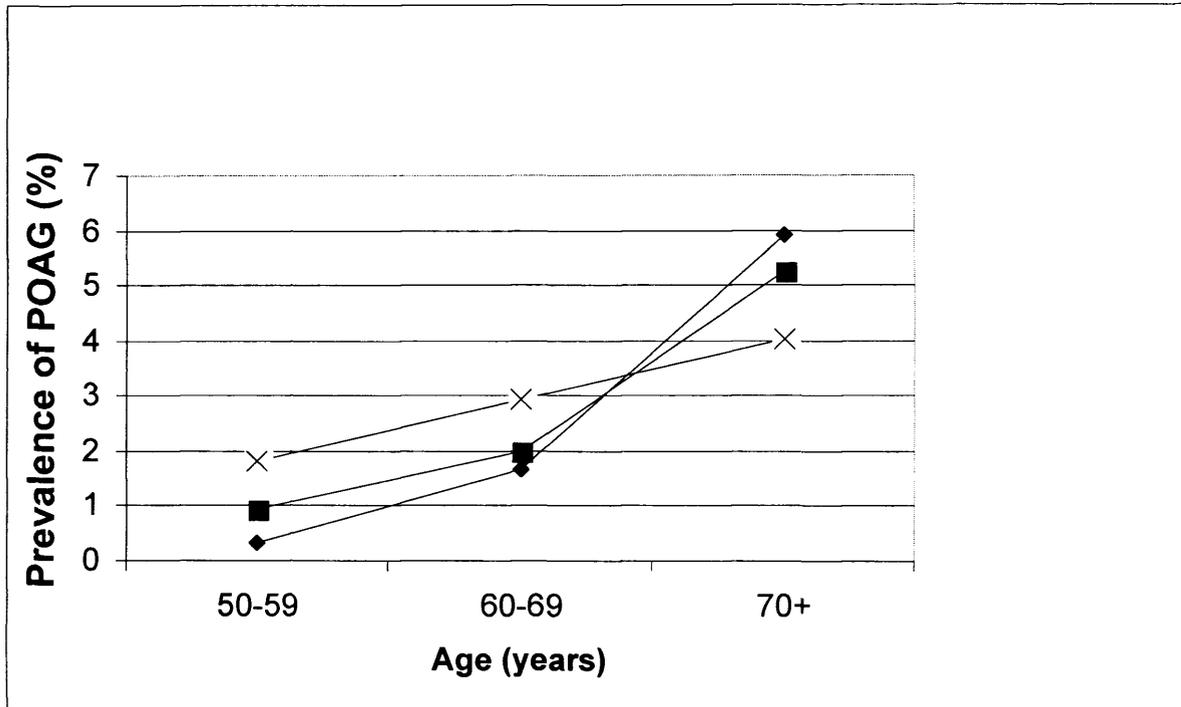
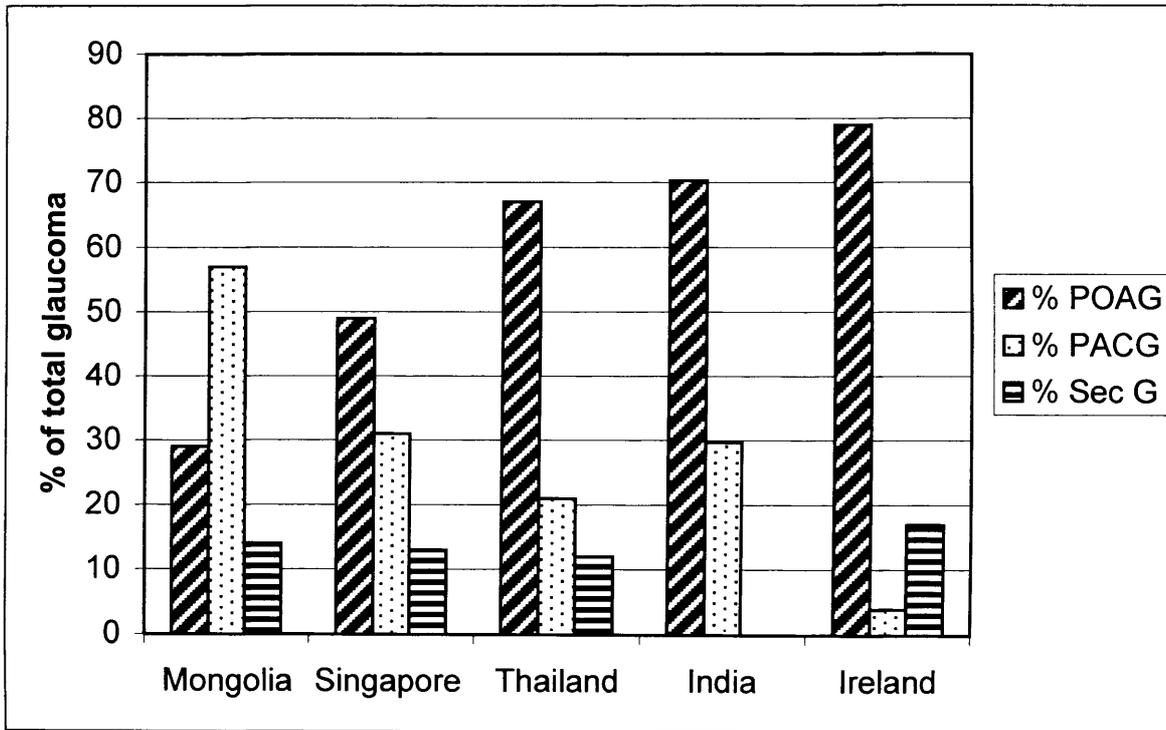


Figure 1.7 The relative proportion of primary glaucoma attributable to POAG, PACG and SecG found in Mongolia and Singapore (unpublished data from Foster PJ, FRCSEd, 2000), Thailand (current study), Andhra Pradesh in India (unpublished data from Dandona L, MD MPH, 2000) and Ireland (Coffey, Reidy et al. 1993). All data is directly standardized to the urban population of Thailand.

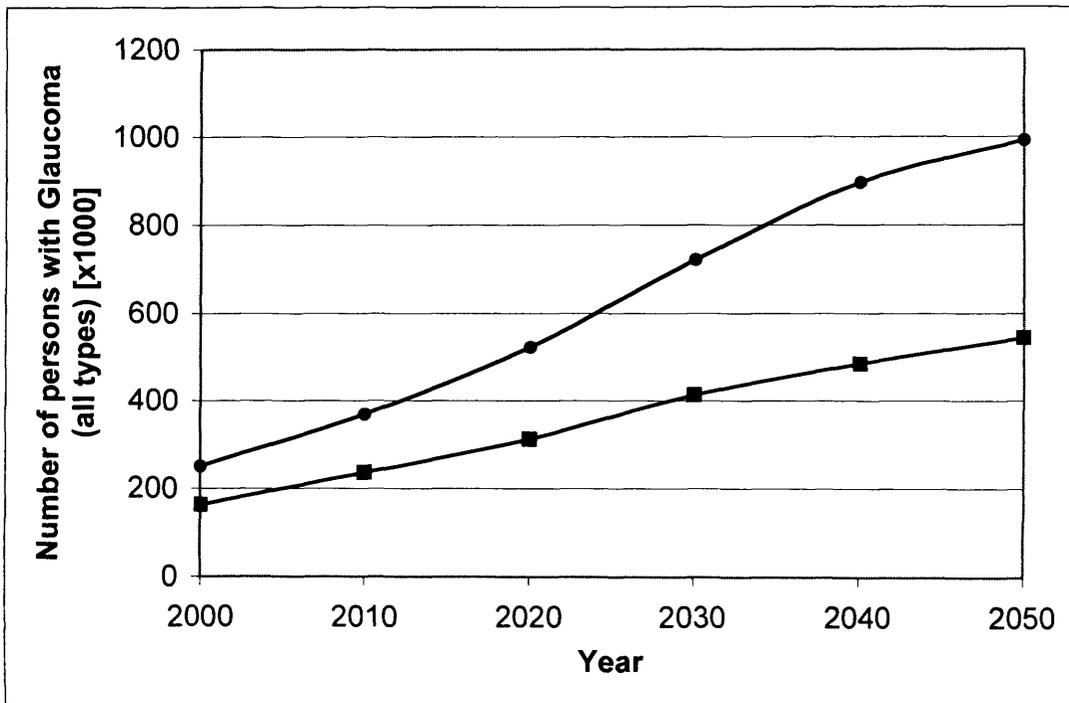


POAG= Primary Open Angle Glaucoma

PACG= Primary Angle-closure Glaucoma

Sec G= Secondary Glaucoma

Figure 1.8 The projected number of people in Thailand affected by glaucoma from Year 2000 until Year 2050 (demographic data obtained from age and sex specific country population data (U.S. Bureau Census 2000)). Figures given were calculated using age and sex-specific glaucoma prevalence figures for all glaucomas (squares, men; circles, women).



1.4.2 Optic Disc Morphology

Limited data exists on the morphology of the optic disc in East Asian and South-East Asian populations. The principle reason for this is that only two population-based glaucoma surveys (Foster, Oen et al. 2000; Bourne RR 2003) have been performed in this region with the intention to characterise the optic disc as part of the glaucoma examination. The Tanjong Pagar survey of Singapore measured the optic disc of 1090 subjects aged 50 years or older, through a dilated pupil at the slitlamp. The optic disc was examined through a fundus contact lens at x40 magnification. The vertical dimensions of the disc and cup were measured using an eyepiece graticule etched in 0.1mm units (Measuring Eyepiece; Haag-Streit, Bern). The authors defined the margins of the cup as the point of inflexion of contour, and measured the cup diameter as the vertical distance between the points of maximum centrifugal extension of the cup between the 11- to 1-o'clock and the 5- to 7-o'clock positions. The cup-disc ratio measurements of subjects with normal visual fields are given in Table 1.2.

Table 1.2 Cup-Disc Ratio in Singapore Chinese subjects (Foster, Oen et al. 2000) with normal visual fields

	CDR			Left to Right Asymmetry
	Right	Left	Right & Left	
CDR measurements, No.	840	843	1683	762*
Satisfactory field test completed, No.	834	835	1669	755
Percentiles				
0.5 th	0.01	0.11	0.08	-0.29
2.5 th	0.19	0.23	0.21	-0.16
Median	0.46	0.48	0.47	0.01
97.5 th	0.69	0.71	0.71	0.21
99.5 th	0.80	0.83	0.81	0.32

* this figure represents the number of individuals for whom CDR measurements were available for both eyes

In addition to the clinical biomicroscopy described in their report (Foster, Oen et al. 2000), the authors also photographed the optic discs of each subject with sequential stereophotography. The analysis of these photographs using a novel planimetric method is one of the subjects of this thesis.

Racial differences in optic nerve head morphology have been described above, while those that have involved Asian subjects are described here. Tsai (Tsai 1995) performed a cross sectional university-based study, using the scanning laser ophthalmoscope (HRT) to compare Asian optic discs with those of African-American, Hispanic and white subjects. Their paper does not specify a more accurate region of origin of the Asian students. They found that the mean optic disc area, cup area, cup-disc area ratio, cup volume below the surface, and cup volume below the reference in Asians and Hispanics occupied an intermediate position between those of African-Americans (the largest) and whites (the smallest). Vertical CDR (but not horizontal CDR) were largest in African-Americans. A study of Koreans (Kee, Koo et al. 1997) used scanning laser ophthalmoscopy (TopSS, Laser Diagnostic Technologies Inc) to measure optic discs of 104 Koreans aged 40 to 68 years, who had no history of ocular disease. The study correlated various optic nerve head parameters, and reported that there were significant correlations between disc size and other disc variables, yet age did not have any significant influence on optic disc variables. They did not compare their findings with those of other racial groups.

1.5 Aims and objectives

The characterization of the optic discs of a specific ethnic group in population-based studies is important to develop normative databases that can be used in both population and clinic-based settings. In the light of this background, the overall aim of this study was to establish a range of normal values for the parameters of the optic disc in representative East Asian populations, which are currently unknown.

The thesis set out to achieve the following objectives:

1. To evaluate various techniques of optic disc analysis in two population-based glaucoma surveys in South-East Asia. These techniques include two modern methods (stereoscopic planimetry using new computer software and confocal scanning laser ophthalmoscopy with the Heidelberg Retina Tomograph-II) that have not been previously used or validated.
2. To use these techniques to assess the normal distribution of optic disc characteristics in a Chinese and Thai population, and the findings between these two populations.
3. To compare the optic disc findings within these East Asian populations to those of other ethnic groups.

Chapter 2. Materials and Methods

2.1 Comparison of methods used to measure the optic disc

Several different techniques were used to evaluate the optic discs of the subjects of the two population-based glaucoma surveys (Rom Klao, Thailand and Tanjong Pagar, Singapore). These techniques are compared in the following report. The specific details of the two surveys and a more detailed description of some of these examination techniques follows this section. A detailed description of the Heidelberg Retina Tomograph (HRT II) can be found in Appendix II.

2.1.1 A comparison of cup/disc ratio measurements using direct ophthalmoscopy with and without mydriasis, and indirect ophthalmoscopy with mydriasis

This study was undertaken during the population-based glaucoma survey in Rom Klao, Thailand. The objectives of this substudy were as follows:

1. To compare the CDR values of each subject obtained from each of three methods, by investigating for systematic bias and level of agreement between methods.
2. To examine whether agreement varied according to the value of CDR, with each method and whether there were significant differences between the examination methods in this respect.
3. To assess the effect of mydriasis on direct ophthalmoscopy of the optic disc in the population-based setting.

Ninety-five consecutive subjects arriving at the survey station for the systematic examination for glaucoma were recruited for the study. Three methods of assessing the cup/disc ratio were used:

Method A: direct ophthalmoscopy (undilated pupil)

Method B: direct ophthalmoscopy (dilated pupil)

Method C: indirect ophthalmoscopy (dilated pupil) with a fundus contact lens at the slit-lamp, using an eyepiece graticule (Haag-Streit, Bern). The graticule was used to measure the vertical disc diameter and the vertical cup diameter. The cup/disc ratio was computed later.

In the assessment of each optic disc, the examiner chose the point of maximum inflection of the neuroretinal rim vessels as the indicator of the edge between rim and cup. A standardized chart of optic disc photographs ranged from CDR of 0.1 to 1.0 was used in Methods A and B for comparative measurement. Method C was considered as the 'gold standard' method of measurement. Measurements using these three methods were attempted by Dr Rupert Bourne (RB) with all subjects. Due to the nature of the lengthy examination process involving many individuals, sometimes with examinations spread over a two-day period, R.B was unaware of the result obtained using one method when subsequently repeating the measurement later using another technique. The inter-method agreement was analysed.

2.1.2 Interobserver and Intraobserver agreement in the measurement of optic discs using planimetric and HRT-II techniques

a. Planimetry. Intraobserver agreement was measured for Rupert Bourne on 33 right eyes which were analysed planimetrically on two occasions one month apart. The observer was masked to the result of the first analysis when performing the analysis for the second time. Interobserver agreement was assessed by comparing measurements made by 3 individual observers on 15 optic discs. Observer 1 was an ophthalmologist experienced in the use of planimetric software and also experienced in the measurement of optic discs. Observer 2 was a non-ophthalmologist who had been trained in the use of this specific software, and who later performed traced the margins of the optic disc and cup of the Thai study. Observer 3, Rupert Bourne, had considerable experience in using the software, having been involved in its design, and subsequently traced the margins of the optic disc and cup of the subjects from the Singapore study.

b.HRT-II. Intraobserver agreement was measured by the analysis of twenty consecutive optic discs by Rupert Bourne (R.B.) on two occasions three months apart. On the second occasion ('retest'), R.B. was masked to the results of the first analysis ('test'). In order to assess inter-observer agreement twenty consecutive optic discs imaged by the HRT-II instrument during the Thai survey, were analysed by Rupert Bourne (R.B.), using fundus photographs as a guide to the disc rim. Subsequently Mr Ted Garway-Heath (G.H.), a

glaucoma consultant with a specialist interest in optic disc morphology, analyzed the same images, while being masked to the results by RB.

2.1.3 Comparison of cup/disc ratio measurement between clinical biomicroscopy with graticule, planimetry using photographs and confocal laser scanning tomography

Measurements of cup/disc ratio of optic discs of fifty right eyes from the Thai study were compared using the following techniques:

- a. Biomicroscopy using a graticule (dilated pupil)
- b. Planimetric analysis using digitised sequential stereophotographs (taken through a dilated pupil)
- c. Heidelberg Retina Tomograph-II

These eyes all had good quality HRT-II images, with a mean standard deviation of less than 40 and were 'normal' eyes (see the Thai HRT study subsection for details).

Agreement in terms of cup/disc ratio was investigated. Rupert Bourne performed all these measurements.

2.1.4 Comparison of measurements of optic disc parameters between confocal laser scanning tomography and planimetry of photographs

Fifty right eyes from the Thai study were imaged with the HRT-II and also analysed planimetrically using sequential stereophotographs. These eyes all had good quality HRT-II images, with a mean standard deviation of less than 40 and were 'normal' eyes (see the Thai HRT study subsection for details). Agreement in terms of disc and rim area was investigated. Rupert Bourne performed all these measurements. When performing the measurement using one of the techniques, he was masked to the results obtained from both of the other techniques.

2.2 The Rom Klao Glaucoma Survey, Thailand and substudies

2.2.1 Sampling strategy

Rom Klao is a suburban area of Lat Krabang district situated about 35 kilometres southeast of the central business district of Bangkok (Figure 2.1).

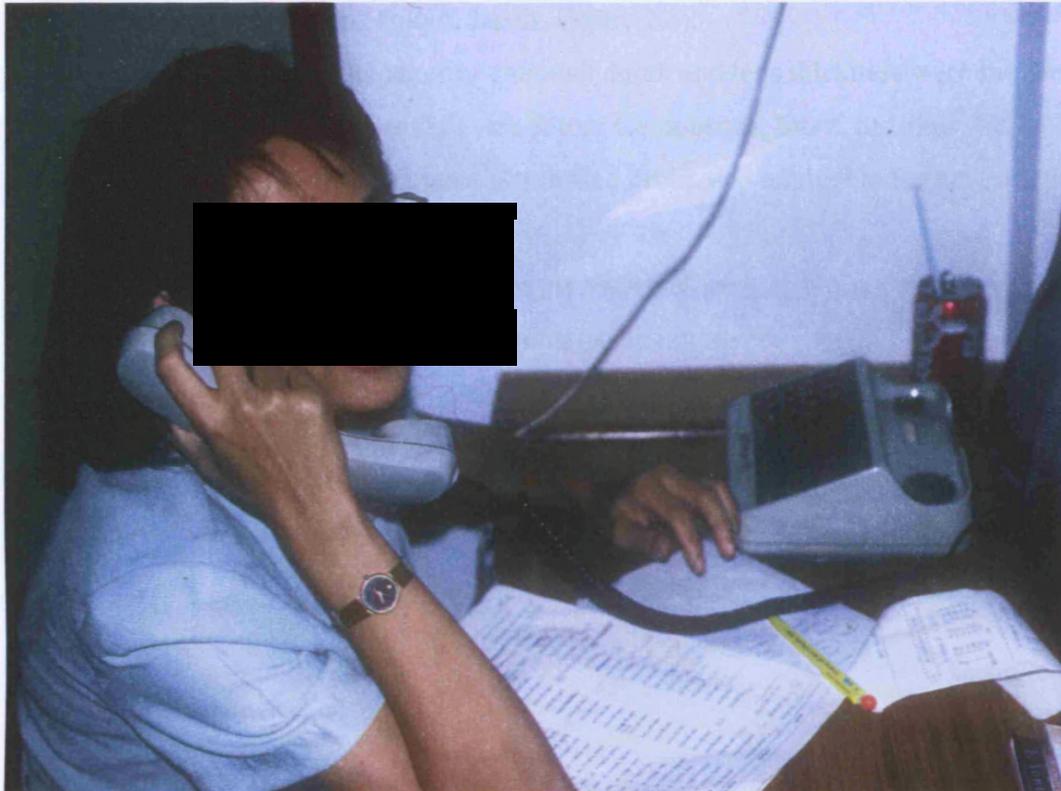
Figure 2.1 A typical scene in Rom Klao- a suburban district of Bangkok.



In 1997, the Department of Geriatric Medicine, Chulalongkorn University Hospital, Bangkok conducted a census of all households in Rom Klao in order to select a cohort of subjects aged 50 years or older for a study of medical problems, their risk factors and determinants of health among this age group. This suburban area was judged to be demographically and socioeconomically representative of suburban Thailand. In order to qualify for selection, one or more of the individuals in a household had to own the home and individuals selected had to have no intention to move from the area within 3 years, to allow further longitudinal studies to take place. 941 persons were identified from a total population of 15,003. During the two years that elapsed before the glaucoma survey, 68 subjects emigrated, 64 subjects died, and a further 8 subjects refused to continue to

participate. 57 of these 140 subjects were men and 83 women (mean age 66.8 +/-10.5 (standard deviation)). The remaining cohort of 801 people were contacted in late 1999 (Figure 2.2) in order to conduct the glaucoma survey.

Figure 2.2 An interviewer inviting and collecting demographic information from a subject by telephone.



2.2.2 Ophthalmic Examination

Approval for the study was obtained from the Institutional Review Board at Chulalongkorn University Hospital, Bangkok. Informed consent was obtained from each subject. This study was carried out in accordance with the World Medical Association's Declaration of Helsinki.

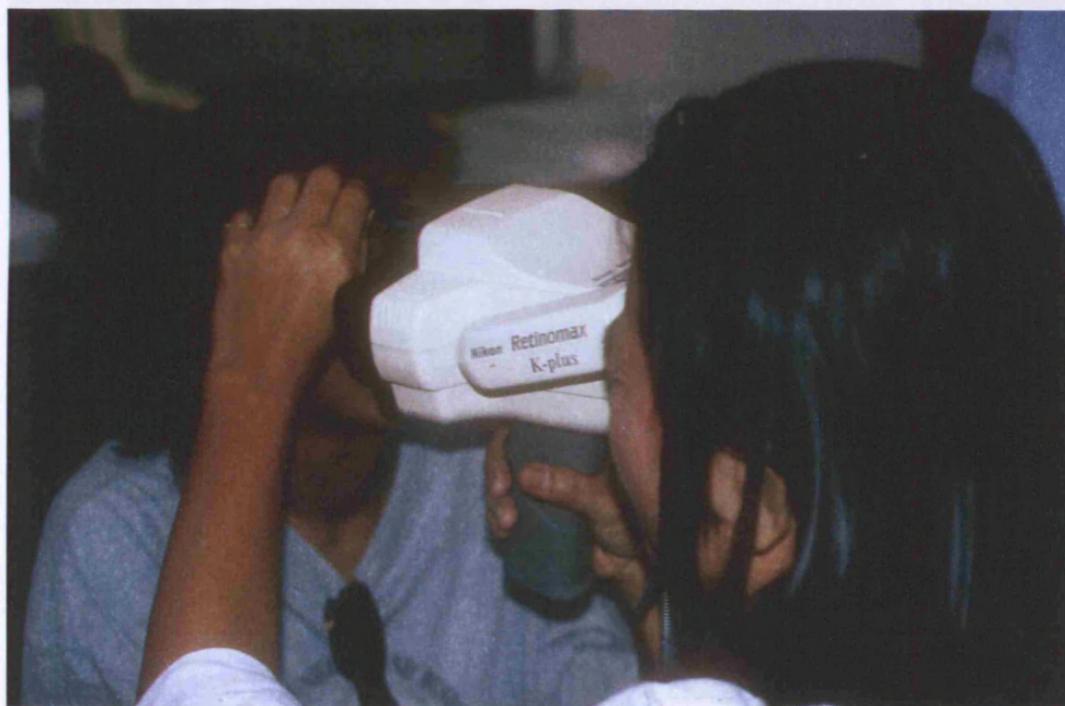
The staff consisted of two interviewers and enumerators, two nurses, and two ophthalmologists (Paradon Sukudom, a Thai research fellow, and Rupert Bourne).

Presenting visual acuity (with spectacles if worn) was measured in each eye separately at 4 metres using the Reduced LogMAR tumbling E chart (Rosser, Laidlaw et al. 2001) which was initially validated against an ETDRS chart (Lighthouse) (Bourne RRA 2003). If the subject was unable to correctly identify the orientation of one or more of the E's on the top line, they were moved to 1m, and the acuity tested again. The refractive error and corneal curvature radius of both eyes of each subject was measured with an automated refractor (Retinomax, Nikon, Tokyo, Japan; Figure 2.3).

Measurements of axial length, anterior chamber depth and lens thickness were measured using a 10Mhz A-mode ultrasound device (Storz Compuscan, Storz, St Louis, MO, USA). The hard tipped corneal contact ultrasound probe was applied to the anaesthetized corneal surface manually.

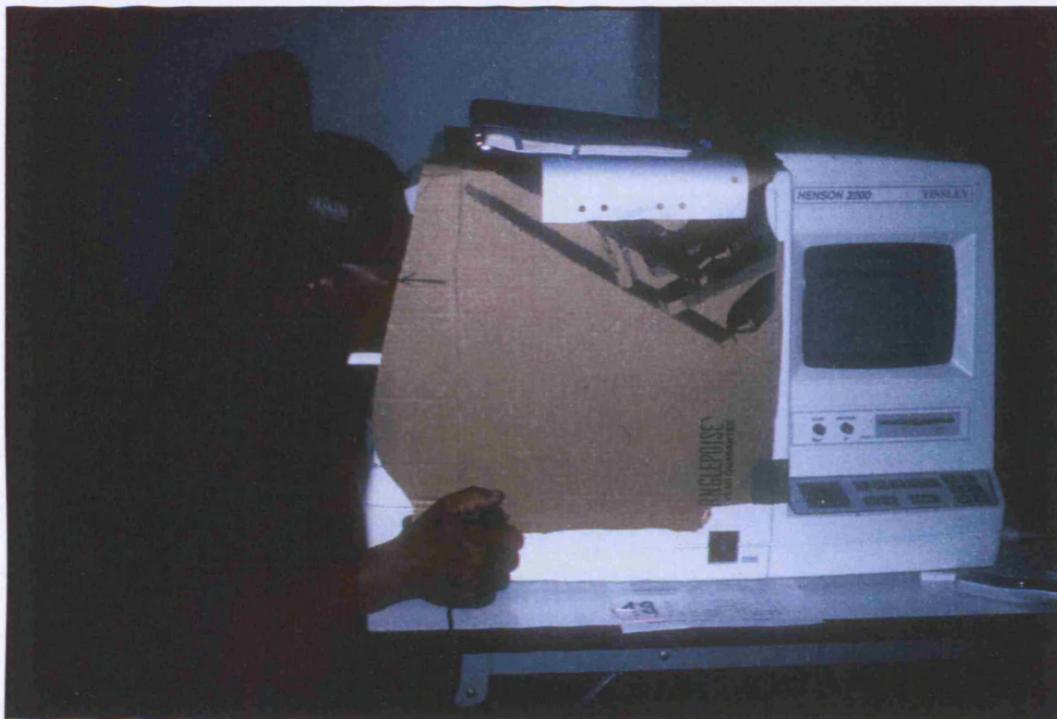
Height and weight were recorded but systemic variables such as blood pressure or past medical history (other than past ocular history) were not noted.

Figure 2.3 Nikon Retinomax autorefractor.



A 26-point static, threshold-related suprathreshold visual field screening test was carried out with near-refractive correction (Henson CFA 3200; Tinsley Medical, Newbury Berks, England; Figure 2.4). If one or more points were missed, the test was automatically extended to 66 points. If the machine registered a “suspect” or “definite” defect, the subject repeated the suprathreshold test after resting for at least 30 minutes.

Figure 2.4 A monk performing visual fields with the Henson Visual Field Analyser.

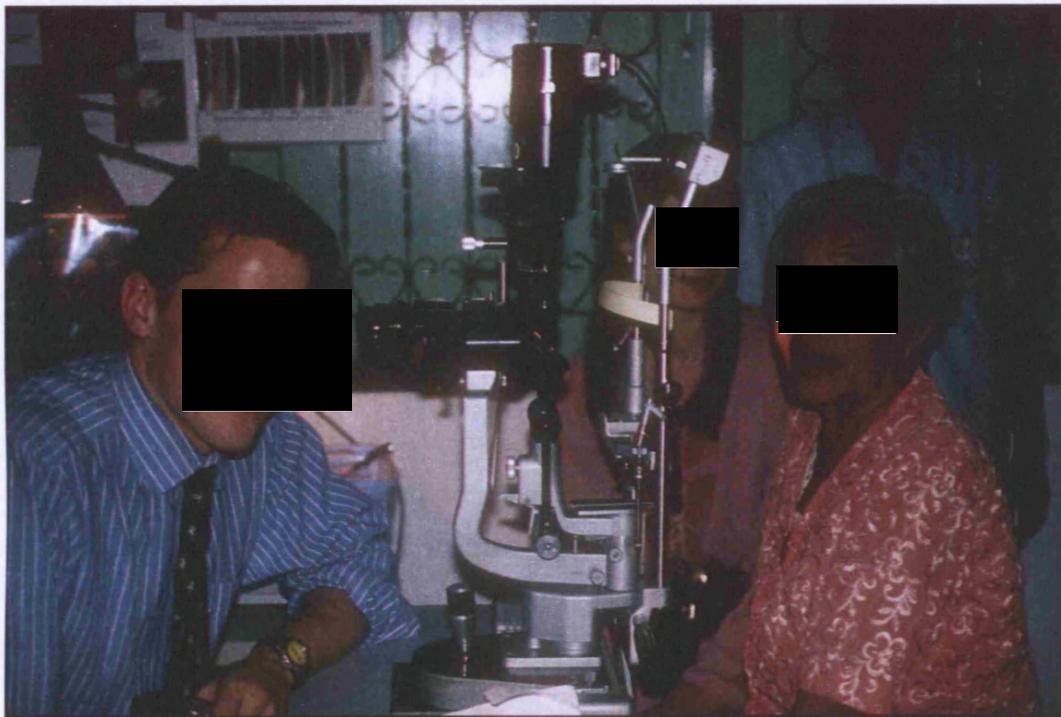


If, after repeated suprathreshold visual field testing, a reproducible (see “diagnostic definitions”) visual field defect was identified for which no cause could be found on ocular examination, a threshold visual field test was performed. Similarly, if any of the following optic disc features were identified, regardless of the suprathreshold field test result: cup/disc ratio (CDR) of 0.70 or more; focal notching of the neuroretinal rim (rim width reduced to 0.1 CDR or less (between 11 to 1 o’clock or 5 to 7 o’clock)); CDR asymmetry of 0.20 or more; disc margin haemorrhage, a threshold visual field test was performed. Threshold visual tests were performed the following day. These values for

CDR and asymmetry of CDR were chosen with reference to normative data on Singaporean Chinese people (Foster, Oen et al. 2000).

Anterior chamber examination with the slit-lamp (BM model, Haag-Streit, Bern, Switzerland; Figure 2.5) was specifically directed at detection of signs of angle-closure, pigment dispersion syndrome, pseudoexfoliation, and other secondary causes of glaucoma. Signs of previous surgery were also noted.

Figure 2.5. Slit-lamp examination.



Intraocular pressure (IOP) was measured by Goldmann applanation tonometry (calibrated daily) (Haag Streit, Bern, Switzerland), with the median of three consecutive readings taken as the IOP for each eye. The measurements were taken by one ophthalmologist (RB) following a small validation study with a colleague (PS; 36 subjects) which showed no significant difference in measurements between observers, ($P>0.2$).

Gonioscopy was carried out on all subjects using a Goldmann-type 1-mirror lens (model 902; Haag Streit) at x16 magnification with low-ambient illumination. The angle was

described as 'occludable' if less than 90° of the posterior (usually pigmented) trabecular meshwork could be seen without manipulation or indentation with the eye in the primary position. In cases where the ciliary body band could not be seen, dynamic, 4 mirror gonioscopy was performed (Carl Zeiss, Oberkochen, Germany), to establish whether peripheral anterior synechiae were present. Pupils were pharmacologically dilated using tropicamide (1%; Alcon-Couvreur SA, Puurs, Belgium) and phenylephrine (2.5%; Moorfields Eye Hospital, London, UK) in all subjects. Subjects were warned of the symptoms of angle-closure and asked to return should these be experienced. Each was given a tablet of acetazolamide (250mg; Wyeth Laboratories, Maidenhead, UK) after dilation and a further tablet to be taken several hours later. No subjects experienced an acute episode of angle closure following dilation.

Lens opacity was graded according to the LOCS III grading system (Chylack, Wolfe et al. 1993). Grading was performed by comparing the appearance on the slit-lamp with six slit-lamp images of nuclear colour and of nuclear opalescence, five retroillumination images for grading cortical cataract, and five retroillumination images for grading posterior subcapsular cataract. Cataract severity was graded on a decimal scale, with the standards spaced at regular intervals.

The optic disc was examined using a contact lens at x16 magnification. A measuring eyepiece graticule (Haag-Streit, Bern, Switzerland) was used to measure the vertical optic disc diameter and vertical cup diameter. An initial validation study of 36 eyes involving the examining ophthalmologist (RB) and a colleague (PS) showed close agreement using this method. The posterior pole was examined for pathology. Sequential stereophotographs of the optic disc were taken with a Kowa FX 500C fundus camera.

2.2.3 Diagnostic Definitions

2.2.3.1 Visual fields

If two suprathreshold fields were performed on an eye, a defect was judged reproducible if 50% or more of the points missed on the first test were each subsequently missed on the second.

Threshold visual fields were judged acceptable for analysis if there were 50% or fewer false positives (false negatives and fixation losses were ignored). After excluding the superior four points and the four points immediately adjacent to the blind spot, a defect was considered present if it was $18^{\circ} \times 12^{\circ}$ or larger in size and 10 dB or more below the age-specific threshold normal in either or both superior and inferior hemifields. Edge points were also counted except the superior four as described.

2.2.3.2 Optic disc parameters

The distribution of vertical cup/disc ratio (VCDR) of the normal non-glaucomatous population was calculated from data from subjects with a “normal” result on suprathreshold field screening in both eyes.

2.2.3.3 Definition of glaucoma

Cases of glaucoma were defined using the International Society of Geographical and Epidemiological Ophthalmology (ISGEO) scheme (Foster PJ 2001). The scheme classifies cases of glaucoma according to three levels of evidence or ‘categories’ (Table 2.1) and is intended for use in prevalence surveys.

Glaucoma suspects were divided into five groups:

- i. Disc suspects- those who met Category 1 disc criteria , but were not proven to have definite field defects.
- ii. Field suspects- those with definite field defects, but not meeting Category 1 disc criteria
- iii. Those with optic disc margin haemorrhages
- iv. Those with an IOP \geq 97.5th percentile of the normal population with open angles but with normal visual fields and optic discs.
- v. Those with an occludable drainage angle but normal optic discs, visual fields and an IOP $<$ 97.5thile.

Cases of primary angle closure (PAC) were defined by the presence in either eye of an occludable angle with an IOP equal to or greater than the 97.5th percentile and/or peripheral anterior synechiae.

Table 2.1 Classification of Glaucoma (Foster PJ 2001).

Category	CDR	CDR asymmetry	Visual Field	Visual Acuity	Other
1 [†]	≥ 97.5 th percentile; NRR width ≤ 0.1 CDR*	≥ 97.5 th percentile	≥ 18° x 12° & ≥ 10 dB below age-specific normal. ≤ 50% FP	-	-
2 [†]	≥ 99.5 th percentile	≥ 99.5 th percentile	Cannot complete satisfactorily	-	-
3	i	Disc not seen	Impossible	<3/60	IOP > 99.5 th percentile
	ii	Disc not seen	Impossible	<3/60	Evidence of glaucoma filtering surgery

Percentiles refer to those of the normal population, i.e. those subjects with normal visual fields in both eyes

*between 11 to 1 o'clock or 5 to 7 o'clock

†no alternative explanation for CDR findings (dysplastic disc or marked anisometropia) or the visual field defect (retinal vascular disease, macular degeneration or cerebrovascular disease)

(FP= False Positives; CDR=cup/disc ratio; NRR=neuroretinal rim)

2.2.3.4 Definition of blindness

An eye was considered blind if the visual acuity (using available refractive correction) was worse than logMAR 1.3 (< 3/60 Snellen).

2.2.4 Follow-up care of established glaucoma cases

Subjects in whom ocular pathology was detected were referred to either the local district hospital or to Chulalongkorn University Hospital, for further management. The ophthalmologists involved in the study were unaware of the results of subsequent validation of ocular pathology which may have occurred at the hospital.

2.2.5 Establishing population-based normative data of optic nerve head structure with the Heidelberg Retinal Tomograph II: feasibility and results.

The Heidelberg Retinal Tomograph II (HRT-II) is a confocal scanning laser ophthalmoscope which has been designed for the routine clinical assessment of the optic nerve head (Appendix II). Its main application is for glaucoma assessment and follow-up. The original HRT has generally served as a research tool and has been extensively evaluated for reproducibility (Chauhan, LeBlanc et al. 1994; Azuara-Blanco, Harris et al. 1998; Hatch, Flanagan et al. 1999) and inter-observer variation (Garway-Heath, Poinosawmy et al. 1999). The main advantage of the HRT-II over the original system, from a clinical standpoint, is that this system has greater automation and requires less input from the examiner. However, the ease of use in clinical settings has not yet been reported.

To date, no population-based glaucoma study has used the HRT-II to generate population-based normative data, or assessed the feasibility of its use in this context.

The study described set out to fulfil the following objectives:

1. To investigate the practical aspects of operating the HRT-II in a population-based setting.
2. To investigate the effect of lens opacity on image quality.
3. To characterise the optic disc morphology of a sample of Thai adults (≥ 50 years of age).

The subjects for this study were drawn from the 701 subjects who were examined during the population-based Rom Klao glaucoma survey in Thailand. The subjects were examined first as part of the main survey and then invited to return for examination with the HRT-II alone (Figure 2.6).

Figure 2.6 The Heidelberg Retina Tomograph – II



The HRT-II was installed in the survey station towards the end of the glaucoma survey period. A half-day was spent training the operator, an ophthalmologist (Dr Paradon Sukudom) in the use of this instrument. The system occupied the same amount of space as a slit-lamp.

No mydriasis was required. The imaging procedure was explained to the subject by the operator, and the patient details entered into the software. The keratometry readings and refractive error had previously been recorded during the main survey (Nikon Retinomax, Nikon, Japan). The refractive error was used to set the HRT-II focus settings and the HRT-II position adjusted so that the laser entered the pupil, while the patient fixated an internal fixation light. In some cases, where a patient was unable to appreciate the internal fixation device, the operator pointed to a target drawn on the wall behind the operator which served as an external fixation device. The operator activated the acquisition process once the optic disc was clearly seen on the display. The system then automatically acquired three series of confocal images, and computed the mean topography image.

Analysis involved the ophthalmologist (Rupert Bourne) drawing around the optic disk edge. Stereoscopic optic disk photographs, taken previously in the main glaucoma survey, were used to assist with the task of delineating this contour. The drawing of the disc edge contour was validated first with a glaucoma specialist (Mr D Garway-Heath). Once this manual process was complete, the system computed the stereometric parameters of each optic disc.

2.3 The Tanjong Pagar Glaucoma Survey, Singapore

The Tanjong Pagar Glaucoma Survey was performed in advance of this thesis by Foster et al. (Foster, Oen et al. 2000). The methods are briefly described as follows.

2.3.1 Study population and recruitment

This study was carried out in accordance with the World Medical Association's Declaration of Helsinki. Singapore has a population of 3.2 million, 78% of whom are ethnic Chinese, with ancestry in the provinces of Fujian and Guandong. The 2000 subjects aged 40 to 79 years residing in the Tanjong Pagar district were selected from the electoral register (13% of 15,082), using a disproportionate, stratified, clustered, random-sampling procedure. As electoral registration is a legal requirement in Singapore, the register provides a complete record of all citizens aged 21 years and older. The demographic and socioeconomic characteristics of Tanjong Pagar are similar to those of Singapore as a whole. Five hundred people were drawn from each of 4 age strata: 40 to 49, 50 to 59, 60 to 69, and 70 to 79 years. The percentage of men and women were determined by the sex ratio of that age group in the district. A small number of subjects reached an age greater than 79 years between selection of the sample and examination. These people, aged 80 and 81 years, were included in a separate age category, although of a small number. All subjects were offered an examination in a research clinic setting. If they did not accept this offer, an attempt was made to assess them in their homes.

2.3.2 Ophthalmic examination

Examinations were carried out in a research clinic or at the subject's home between October 10, 1997, and August 14, 1998. The following examination was performed on subjects seen at the research clinic. A logMAR chart (The Lighthouse, Long Island, NY) was used to measure best-corrected visual acuity using a subjectively refined refractive correction. A 26-point static, threshold-related suprathreshold visual field screening test was carried out with near-refractive correction (Henson CFA 3200; Tinsley Medical, Newbury Berks, England). This was extended to a 66-point test, if the initial test was graded "suspect" or "defect" by the instrument's classification algorithm. A screening-mode frequency doubling technology test (model 710, software version 1.2; Welch Allyn,

Skaneateles Falls, NY) was performed with the subject's own available distance refractive correction if worn, and without correction if glasses were not worn.

A slitlamp (model BQ 900; Haag-Streit, Bern, Switzerland) was used to examine the anterior segment for evidence of secondary glaucoma and to detect the ischemic sequelae of primary angle-closure. Intraocular pressure was estimated using an applanation tonometer (Goldmann model; Haag-Streit). The cornea was anesthetized using 0.5% amethocaine hydrochloride mixed with 1 drop of 2% sodium fluorescein (both Minims; Chauvin Pharmaceuticals, Romford, England). Three readings were made, and the median taken as the pressure for that eye. Gonioscopy was carried out using a Goldmann-type 1-mirror lens (model 902; Haag Streit) at x25 magnification with low-ambient illumination. Angles were graded occludable or not occludable (see "Diagnostic Definitions" section).

The pupils of all subjects were dilated with 1% tropicamide (Alcon-Couvruer, Puurs, Belgium) and 2.5% phenylephrine hydrochloride (Alcon Laboratories, Fort Worth, Tex) drops. The optic disc was examined at the slitlamp through a fundus contact lens at x40 magnification. The vertical dimensions of the disc and cup were measured using an eyepiece graticule etched in 0.1-mm units (Measuring Eyepiece; Haag-Streit, Bern). Measurements of vertical disc diameter excluded areas of peripapillary atrophy and Elschnig ring. The margins of the cup were defined by stereoscopic examination as the point of maximum inflexion of contour. The height of the cup was measured as the vertical distance between the points of maximal centrifugal extension of the cup between the 11- to 1-o'clock and the 5- to 7-o'clock positions. The narrowest portion of the neuroretinal rim was measured. The intraocular pressure (IOP) of all subjects was remeasured using a Tonopen (Mentor, Norwell, Mass) before they left the clinic. Subjects judged to have an occludable drainage angle were routinely given acetazolamide (500 mg by mouth) (Apotex, Toronto, Ontario) 2 hours after leaving and again at bedtime. All these subjects were instructed to return the following day or contact the emergency ophthalmic service if they suffered adverse symptoms.

Measurements of axial length, anterior chamber depth and lens thickness were measured using a 10Mhz A-mode ultrasound device (Storz Compuscan, Storz, St Louis, MO, USA). The hard tipped corneal contact ultrasound probe was mounted on a tonometer set

to the individual's intraocular pressure. The mean of 16 separate measurements was recorded, together with standard deviation of each parameter. Refractive error and corneal curvature radius was measured using a hand held autorefractor/ keratometer (Retinomax, Nikon, Tokyo, Japan). A single optometrist performed a subjective refinement of the refraction using a phoropter, based on the results of the objective refraction.

Five tests were used to determine provisional glaucoma suspect status of an eye. These were visual field screening (Henson CFA 3200 field screener; Tinsley Medical, Newbury Berks, England) (suspect or defect category); frequency doubling technology test (3 locations showing mild relative loss or worse); applanation tonometry (IOP >19 mm Hg); gonioscopy (occludable angle); and examination of the optic disc (cup-disc ratio [CDR], 0.71; CDR asymmetry, 0.21; or narrowest neuroretinal rim, <0.1 of CDR). If either eye of a subject met any of these criteria, or the subject was unable to satisfactorily complete 1 of the tests, he or she was asked to return for a threshold visual field test (30-2 program) (instrument model 750; Humphrey Instruments, San Leandro, California, USA), unless another explanation for test failure was identified. Of the normal subjects, 10% were also invited for testing. Any tests on the Humphrey machine graded unreliable or compatible with glaucoma were repeated.

Home examination was offered to subjects who did not attend for a clinic examination. Visual acuity in each eye was measured using a 3-m Snellen chart, with distance spectacles if worn. If the visual acuity was less than 6/12, it was remeasured using a pinhole. The anterior segment was examined using a portable slitlamp (model 904; Clement Clarke, Harlow, England). The depth of the anterior chamber at the temporal limbus was estimated, and if less than 25% of corneal thickness was present, gonioscopy was performed. Intraocular pressure was measured in each eye using a Tonopen. Optic discs were examined through dilated pupils using the slitlamp and a +78 diopter lens (Volk, Mentor, Ohio) to grade the CDR (with reference to standard photographs) and narrowest width of the neuroretinal rim. Sequential stereophotographs were taken of each optic disc of all subjects using a Nikon NF-505 camera (Nikon, Tokyo, Japan). All subjects were offered a follow-up examination in the research clinic. If subjects were

classified as glaucoma suspects (on the same basis as clinic subjects) they were offered follow-up investigation and treatment.

2.3.3 Diagnostic definitions

A threshold examination of the central 30° of visual field (30-2 program) showing a glaucoma hemifield test (GHT) outside normal limits and a cluster of 4 contiguous points on the pattern-deviation plot ($P < 0.5\%$ of occurrence in age-matched normal subjects) not crossing the horizontal meridian were considered compatible with glaucoma. Test reliability was determined by the instrument's algorithm (fixation losses, $< 20\%$; false positives, $< 33\%$; and false negatives, $< 33\%$). Test results compatible with glaucoma were repeated and considered definite if the GHT and the identical 4 points on the pattern-deviation plot were reproduced in reliable tests.

The distribution of CDR in the nonglaucomatous population was calculated using people who passed both the conventional field screening and the frequency doubling technology tests, or those who did not pass either test, but then completed a reliable 30-2 threshold field examination with a GHT within normal limits. This therefore represents a "hypernormal" population. Glaucoma was diagnosed using the same diagnostic criteria as for the Rom Klao Thailand survey (Foster PJ 2001).

For the preparation of this thesis, a planimetric analysis of the optic disc photographs taken by this study was undertaken. This was the first time that these images had been analysed.

2.4 Planimetric Analysis

2.4.1 Development

As stated in the introduction, image analysis presents a more sophisticated technique than clinical examination for the analysis of the optic disc. In 1997, Mr Garway-Heath (now Consultant Ophthalmologist at Moorfields Eye Hospital, London) collaborated with a computer company that specialised in medical applications of imaging (Virtual Presence, London). This resulted in the development of software that presented digitised stereo-pairs optic discs on a computer screen, which can be visualised in stereo by an observer wearing shutter glasses (Nuvision Technologies, Inc. Oregon, USA). This collaboration yielded a prototype program, which was further tested and refined by Rupert Bourne and Mr Garway-Heath, until it was judged of suitable quality for the purposes of this thesis.

2.4.2 Operation of planimetric hardware and software

The planimetric programme was installed in a computer with memory capable of storing large numbers of image files at the Reading Centre of Moorfields Eye Hospital. 35mm slide photographs taken with a Kowa FX500C (Thai survey) and the Nikon NF-505 cameras (Singapore survey) were scanned (Nikon Coolpix), resulting in two libraries, each comprising of pairs of digitised optic disc images (each image occupied approximately 3.5Mb). A model eye was photographed with each camera in order to calculate the magnification characteristics of each camera system (Appendix I), and to establish whether each camera was telecentric (Rudnicka, Burk et al. 1998) (no significant relationship between camera magnification and refractive error). This magnification constant was entered into the planimetric programme software, in addition to biometric parameters (keratometry, anterior chamber depth, refractive error, axial length, lens thickness) relating to each subject. The latter were used to compute a constant for ocular magnification, based on a modification of the Littman algorithm (Littmann 1982), reported by Garway-Heath et al (Garway-Heath, Rudnicka et al. 1998). The stereo-pairs of digitised images were visualized with shutter-glasses. The display provides parallax information to the eyes, by alternating rapidly the left and right images of the optic disc on the monitor screen. When the viewer looks at the screen through shuttering eyewear, each shutter is synchronised to occlude the unwanted image

and transmit the wanted image. Thus each eye sees only its appropriate perspective view. The left eye sees only the left view and the right eye only the right view. With the images refreshed (changed or written) fast enough (at 60Hz), the result is a flickerless stereoscopic image.

The observer moved a cursor across the monitor screen to draw around the edges of the disc and the cup. The software computed the areas (by counting pixels and then converting into units of mm^2) of each 10 degree sector of the disc, rim and cup. The software also presented the areas of each disc segment (superotemporal, inferotemporal, nasal and temporal). These sectors are illustrated in Figure 2.7. The process of drawing around the optic disc using shutter glasses is shown in Figure 2.8.

Figure 2.7 The 30-degree sectors of the right optic disc measured by the planimetric software. The temporal sector occupies the area between 150 and 210 degrees, the superotemporal sector, 60 to 150 degrees, the inferotemporal sector, 210 to 300 degrees, and the nasal sector, 60 to 300 degrees.

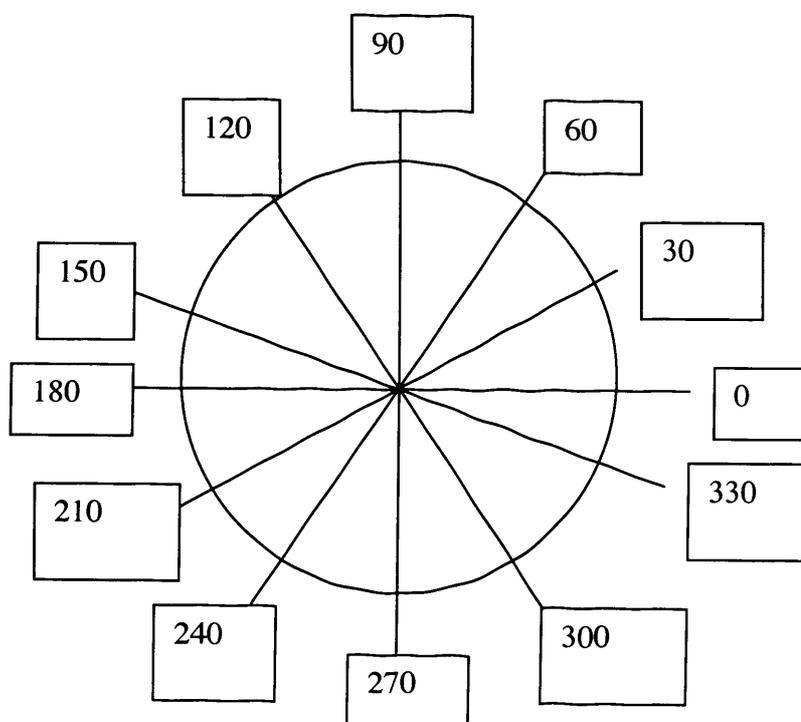


Figure 2.8 The process of image analysis using the planimetric software. Two digitised sequential stereoimages of the optic disc are viewed with shutter glasses. Contours are drawn around the disc and cup edges by the operator using a hand-held 'mouse'. The software then computes the disc, cup and rim area for each ten-degree sector.



Optic disc features were demarcated using established criteria. The optic disc area was defined as the area within the inner aspect of the scleral ring of Elschnig (Jonas, Gusek et al. 1988) (Britton, Drance et al. 1987). The cup margin was defined by a change in slope along the inner edge of the neuroretinal rim and not by a change in pallor. The neuroretinal rim area was outlined by the margins of the optic disc and optic cup. Blood vessels were included in the neuroretinal rim area if they were clearly embedded in neural tissue (Airaksinen, Drance et al. 1985). If a vessel was isolated in the cup and not in attached to neural tissue, it was considered as cup rather than rim (Britton, Drance et al. 1987). Changes of direction of vessels in the optic disc were also used as a guide to the position of the neuroretinal rim edge. These definitions of topographical anatomy of the optic disc have been widely used and are generally accepted.

In situations where no physiological cupping existed, neuroretinal rim area was determined as the disc area minus the area occupied by the passage of blood vessels through the centre of the optic disc (Rudnicka AR 2001).

2.5 Statistical Methods

Measures of agreement between methods of optic disc analysis and between observers were performed using the Bland-Altman method (Bland and Altman 1986). The criteria used to select subjects for the planimetric and HRT-II datasets for analysis are described in detail in the 'Results' section.

Right eyes were analysed in the planimetric analysis of both Thai and Singapore studies. Planimetric analysis revealed the distributions of disc area and neuroretinal rim area to be right-skewed in both the Thailand and Singapore studies. For this reason, the median was given in addition to the mean as a measure of central tendency, a non-parametric test was used to describe correlation (Spearman's rho), and the logarithm of disc area and neuroretinal rim area was used for subsequent univariate and multiple variable regression analyses. In order to investigate the association between optic disc parameters and biometric and systemic variables, univariate regression analysis was used. Subsequently multiple variable linear regression was used.

Chapter 3. Results

3.1 Comparison of techniques of optic disc assessment

3.1.1 A comparison of cup/disc ratio measurements using direct ophthalmoscopy with and without mydriasis, and indirect ophthalmoscopy with mydriasis

190 eyes of 95 subjects were examined using Methods A (direct ophthalmoscopy through an undilated pupil), B (direct ophthalmoscopy through a dilated pupil) and C (indirect ophthalmoscopy through a dilated pupil with a fundus contact lens at the slit-lamp, using an eyepiece graticule).

The optic disc was not visible by direct ophthalmoscopy through an undilated pupil in 50 eyes (26 %), due to media opacity (principally cataract). With dilation, only 13 optic discs were not visible (7 %), and using indirect ophthalmoscopy and graticule, this proportion was further reduced to 6 eyes (3 %).

Agreement between Methods A and B was constant whilst that between B and C and between A and C depended on the size of the disc being measured (Figures 3.1 and 3.2). Stratified tertiles were constructed to estimate bias (Table 3.1).

Figure 3.1 The difference plotted against the mean (Bland and Altman 1986) for Methods B and Method C.

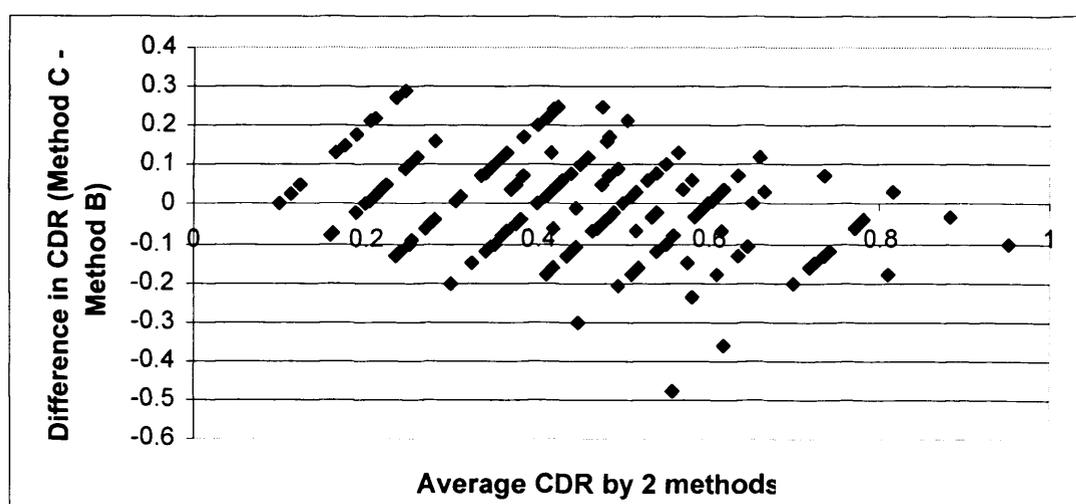


Figure 3.2 The difference plotted against the mean (Bland and Altman 1986) for Method A and Method C.

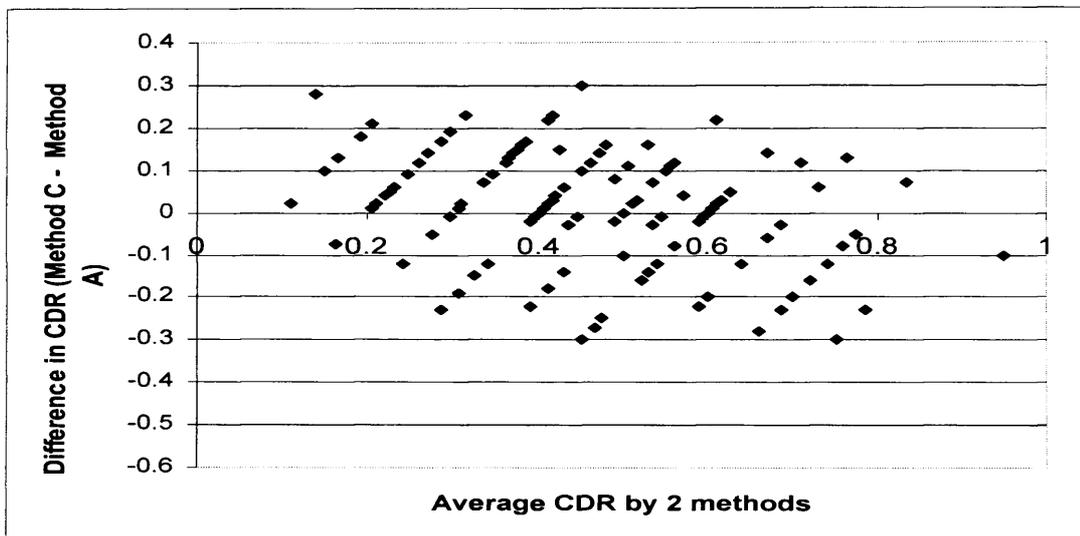


Table 3.1. Estimates of bias.

	A-B	cdr ≤ 0.4		cdr > 0.4 & cdr ≤ 0.55		cdr > 0.55	
		A - C	B - C	A - C	B - C	A - C	B - C
n	70	25	31	24	34	22	23
Mean of differences	0.011	0.008	0.012	-0.021	-0.043	-0.006	-0.03
SE (mean differences)	0.013	0.029	0.024	0.025	0.019	0.031	0.022
P-value	0.43	0.78	0.64	0.40	0.03	0.84	0.16

Table 3.1 indicates that there was some evidence of bias between B and C at higher CDR measures - albeit not clinically. No evidence of bias between methods A and B and between methods A and C was found (Figures 3.1 and 3.2). Right and left eyes were analysed separately and showed consistent findings.

To compare the degree of agreement between direct ophthalmoscopy with and without mydriasis, the 95% limits of agreement for A versus C and B versus C were calculated for cases where the examination had been performed with all three techniques (n=73; Table 3.2). The 95% limits of agreement for A versus C were slightly wider than those for B versus C (F-Test, P = 0.06).

Table 3.2 95% limits of agreement between methods.

	A minus B	A minus C	B minus C
n	73	73	73
Mean (difference)	0.008	-0.006	-0.013
SD (differences)	0.112	0.136	0.109
95 % limits of agreement	(-0.212, 0.228)	(-0.273, 0.261)	(-0.227, 0.201)

3.1.2 Inter- and intra-observer agreement for Planimetric and HRT-II analysis

3.1.2.1 Planimetry

Intraobserver agreement and inter-observer agreement was measured using the 'Eye_2' planimetric software.

Intraobserver agreement

This was measured for Rupert Bourne on 33 right eyes which were analysed planimetrically on two occasions one month apart. The observer was masked to the result of the first analysis when performing the analysis for the second time.

The results for optic disc area and optic cup area are presented in Figures 3.3 and 3.4 in the form of a Bland-Altman plot (Bland and Altman 1986).

Figure 3.3 Intraobserver agreement for total disc area for the Eye_2 planimetric software using 33 right eyes.

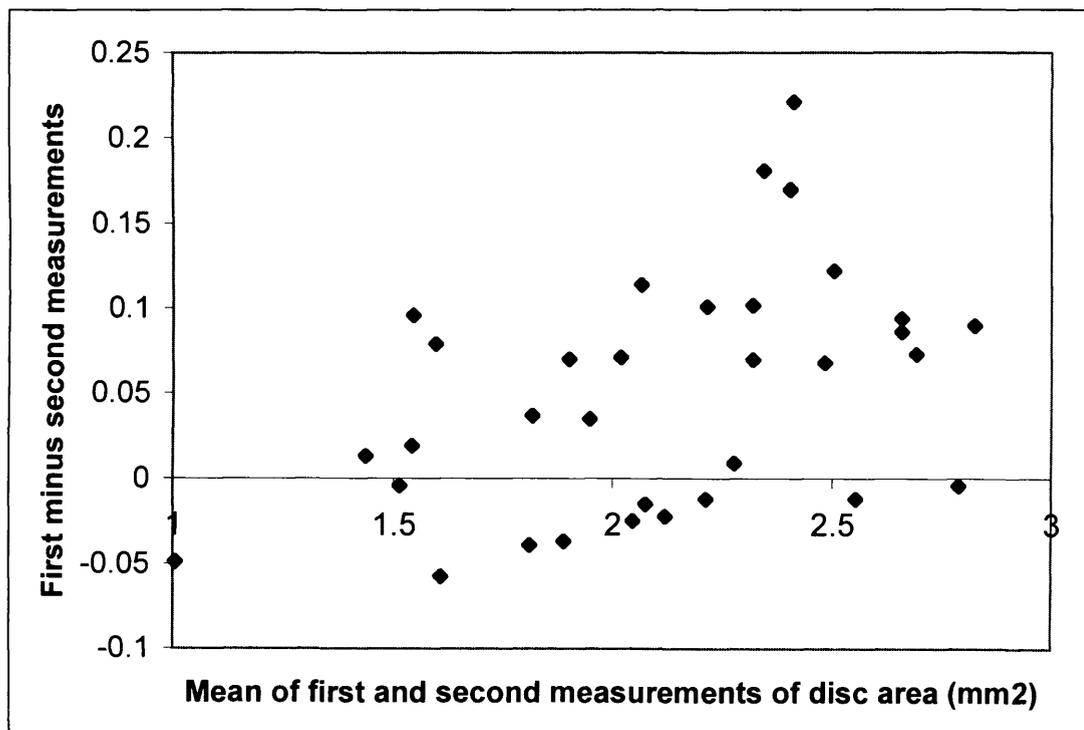


Figure 3.4 Intraobserver agreement for total cup area for the Eye_2 planimetric software using 33 right eyes.

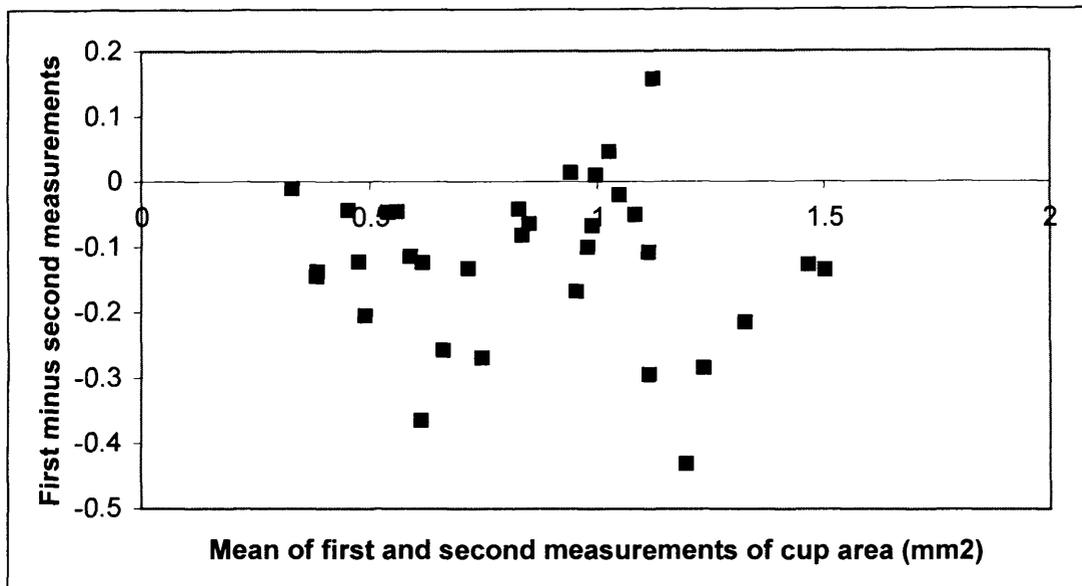


Figure 3.3 shows that in terms of disc area, there was a tendency for the first measurement to be higher than the second. The difference increased with increasing disc area. The mean difference between first and second measures of disc area was 0.05mm^2 , the first measurement (mean, 2.13mm^2) being significantly greater than the second (mean, 2.08mm^2 ; $p < 0.001$). This difference constitutes a systematic bias. The upper and lower 95% limits of agreement were -0.086mm^2 to 0.186mm^2 , respectively.

In the case of cup area (Figure 3.4), the mean difference was 0.12mm^2 , the first measurement (mean, 0.79mm^2) being significantly less than the second (mean, 0.91mm^2 ; $p < 0.001$). This also demonstrates systematic bias, with upper and lower 95% limits of agreement were -0.358mm^2 to 0.117mm^2 , respectively.

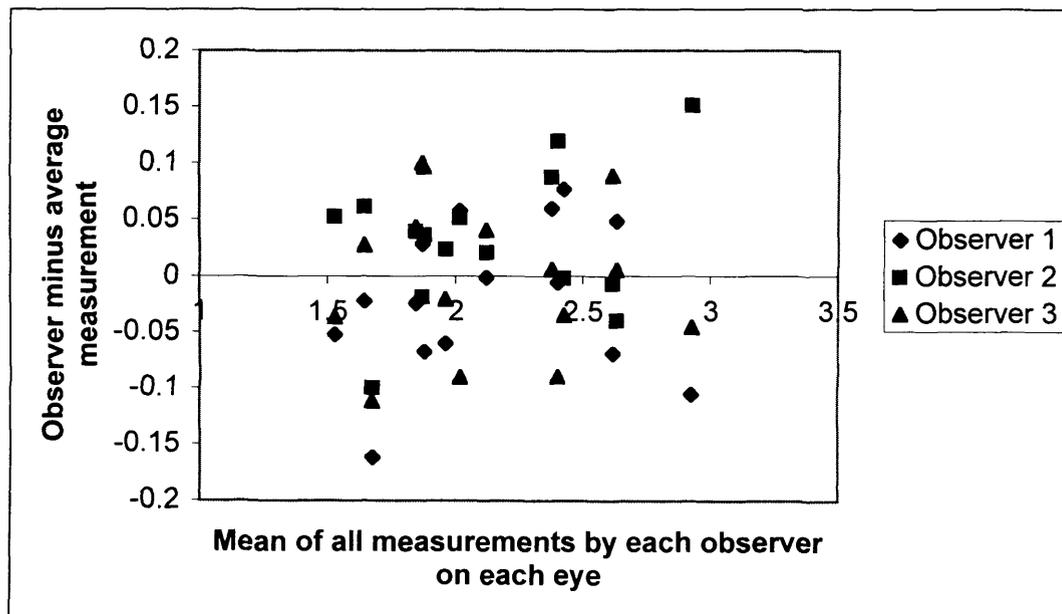
Inter-observer agreement

Planimetric measurements were compared between 3 individual observers on 15 optic discs. Observer 1 was an ophthalmologist experienced in the use of planimetric software and also experienced in the measurement of optic discs. Observer 2 was a non-

ophthalmologist who had been trained in the use of this specific software, and who later traced the margins of the optic disc and cup of the Thai study. Observer 3, Rupert Bourne, had considerable experience in using the software, having been involved in its design, and subsequently traced the margins of the optic disc and cup of the subjects from the Singapore study. The inter-observer agreement for disc area and cup area is illustrated in Figure 3.5. Mean difference between pairs of observers and the 95% limits of agreement are given in Table 3.3.

Figure 3.5 Interobserver agreement for the Eye_2 planimetric software using 15 right eyes:

i. Disc area



ii. Cup Area

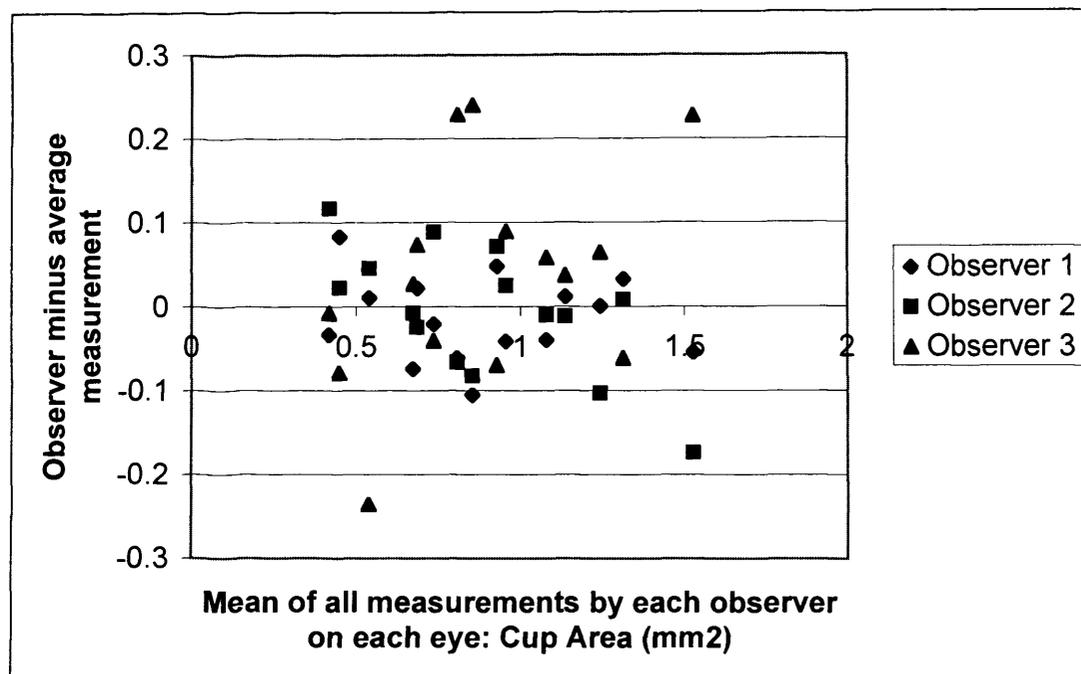


Table 3.3 Planimetric measurements of optic disc and cup area compared between 3 individual observers on 15 optic discs. Mean differences between observers and 95% limits of agreement are given.

Pairing of Observers	Mean difference in Disc Area, mm ² (p value*)	Mean difference in Cup Area, mm ² (p value*)	Cup Area 95% limits of agreement (mm ²)	Disc Area 95% limits of agreement (mm ²)
1 & 2	0.052 (0.037)	0.008 (0.678)	-0.153 to 0.137	-0.223 to 0.119
1 & 3	0.018 (0.439)	0.052 (0.255)	-0.381 to 0.278	-0.196 to 0.159
2 & 3	0.033 (0.212)	0.043 (0.396)	-0.420 to 0.333	-0.159 to 0.225

* paired t test

3.1.2.2 HRT-II

Intraobserver agreement and inter-observer agreement was measured using the HRT-II software.

Intraobserver agreement

Twenty consecutive optic discs were analysed by Rupert Bourne (R.B.) on two occasions three months apart. On the second occasion ('retest'), R.B. was masked to the results of the first analysis ('test'). There was no significant difference (paired t test, $P=0.528$) between mean disc area measured at the second analysis (mean, 2.04 mm^2) and that measured initially (mean, 2.01 mm^2). This was also the case for mean cup area ($P=0.342$) and mean rim area ($P=0.120$). Figures 3.6 and 3.7 present this data in the form of Bland-Altman charts (Bland and Altman 1986). The 95% limits of agreement for disc area, cup area and rim area, were -0.332 to 0.384 mm^2 , -0.503 to 0.402 mm^2 , and -0.336 to 0.489 mm^2 , respectively.

Figure 3.6 A Bland-Altman (Bland and Altman 1986) plot that illustrates agreement between measurements of disc area (mm^2) made by the HRT-II on 2 occasions three months apart by Rupert Bourne.

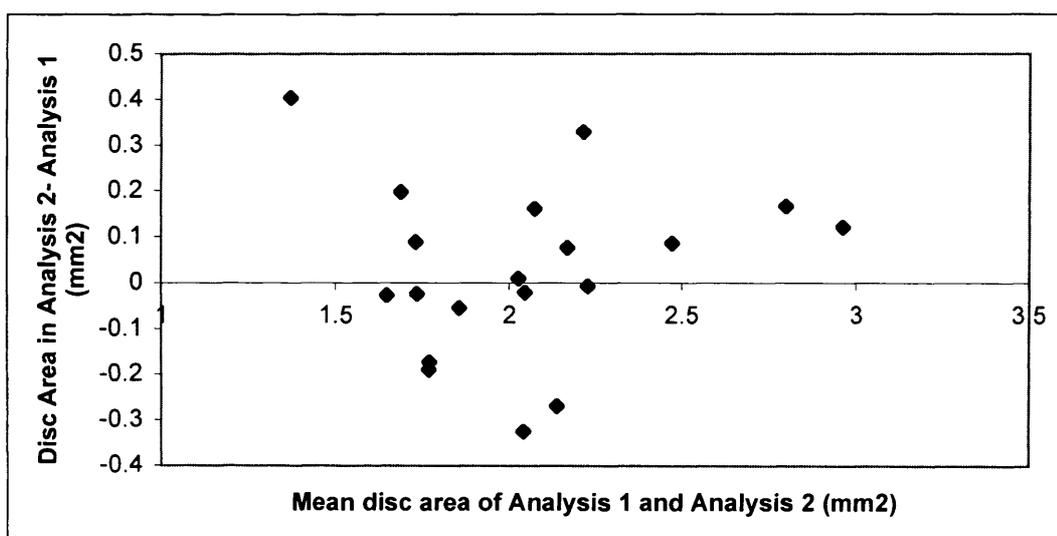
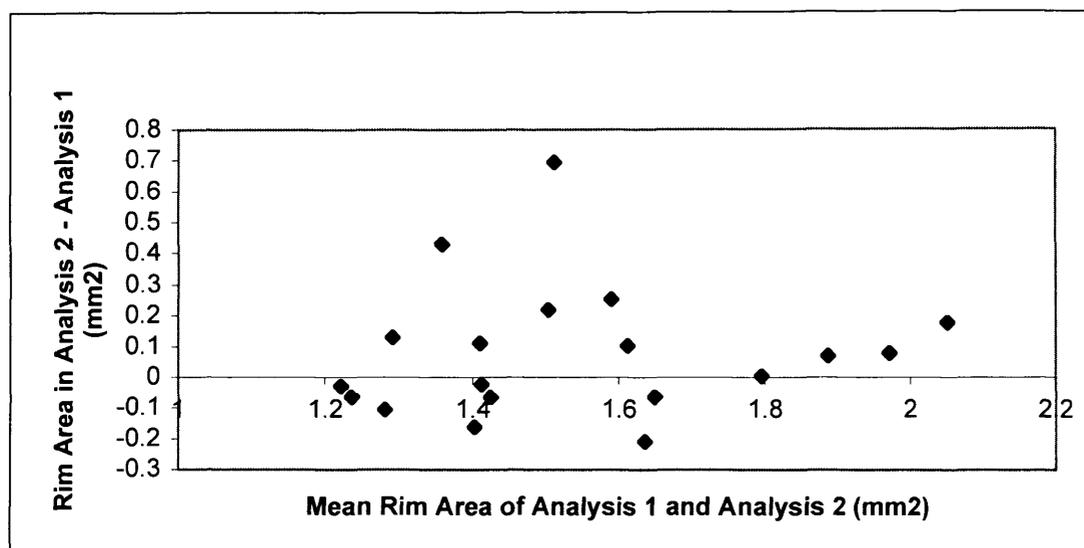


Figure 3.7 A Bland-Altman (Bland and Altman 1986) plot that illustrates agreement between measurements of neuroretinal rim area (mm^2) made by the HRT-II on 2 occasions three months apart by Rupert Bourne.



Interobserver agreement

Twenty consecutive optic discs imaged by the HRT-II instrument during the Thai survey, were analysed by Rupert Bourne (R.B; Observer 1), using fundus photographs as a guide to the disc rim. Subsequently Mr Ted Garway-Heath (G.H.; Observer 2), a glaucoma consultant with a specialist interest in optic disc morphology, analyzed the same images, while being masked to the results by RB.

Figures 3.8 and 3.9 illustrate the interobserver agreement for total disc area and total cup area, respectively. The total disc area as measured by G.H. (mean, 2.18mm^2) was significantly (paired t test, $p=0.002$) larger than that measured by R.B. (mean, 2.04mm^2). There was no significant difference (paired t test, $P=0.23$) between total cup area as measured by G.H. (mean, 0.45mm^2) and that measured by R.B. (mean, 0.46mm^2). The differences were not normally distributed, therefore the 95% limits of agreement were not calculated.

Figure 3.8 Interobserver agreement for total disc area (mm^2) for the HRT-II software using 20 right eyes.

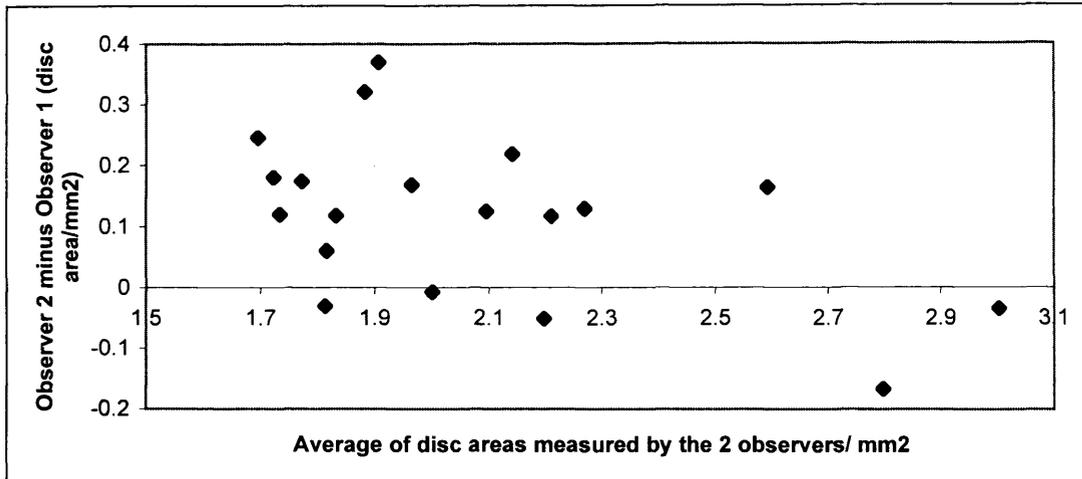
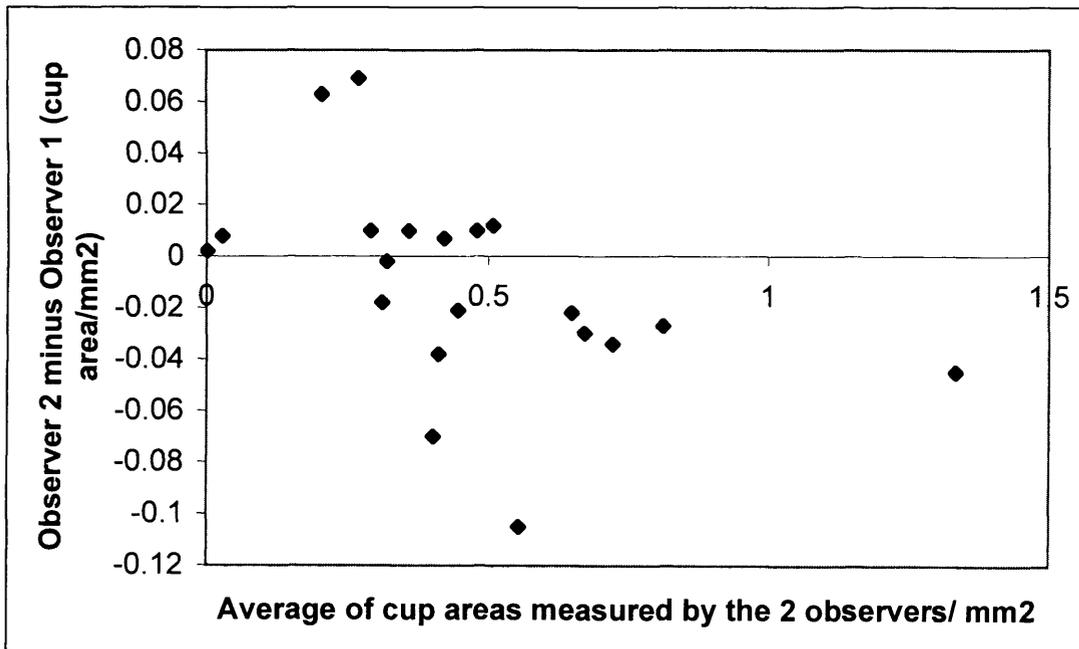


Figure 3.9 Interobserver agreement for total cup area (mm^2) for the HRT-II software using 20 right eyes.



3.1.3 Comparison of cup/disc ratio measurement between clinical biomicroscopy with graticule, planimetry using photographs and confocal laser scanning tomography (HRT-II)

The optic discs of fifty right eyes from the Thai study were first examined with biomicroscopy using a graticule and then imaged with the HRT-II and also analysed planimetrically using sequential stereophotographs. These eyes all had good quality HRT-II images, with a mean standard deviation of less than 40 and were 'normal' eyes (see the Thai HRT study subsection for details). Agreement in terms of cup/disc ratio was investigated. Rupert Bourne performed all these measurements. The differences between measurements of vertical cup/disc ratio by the three techniques are illustrated in Figure 3.10. The mean differences in vertical cup/disc ratio measurement between techniques and the 95% limits of agreement for each of the different pairings of techniques are given in Table 3.4.

Figure 3.10 Bland-Altman plot (Bland and Altman 1986) showing the difference between measurements of vertical cup/disc ratio by the HRT-II, the planimetric technique and clinical stereo-biomicroscopy with graticule (50 normal eyes).

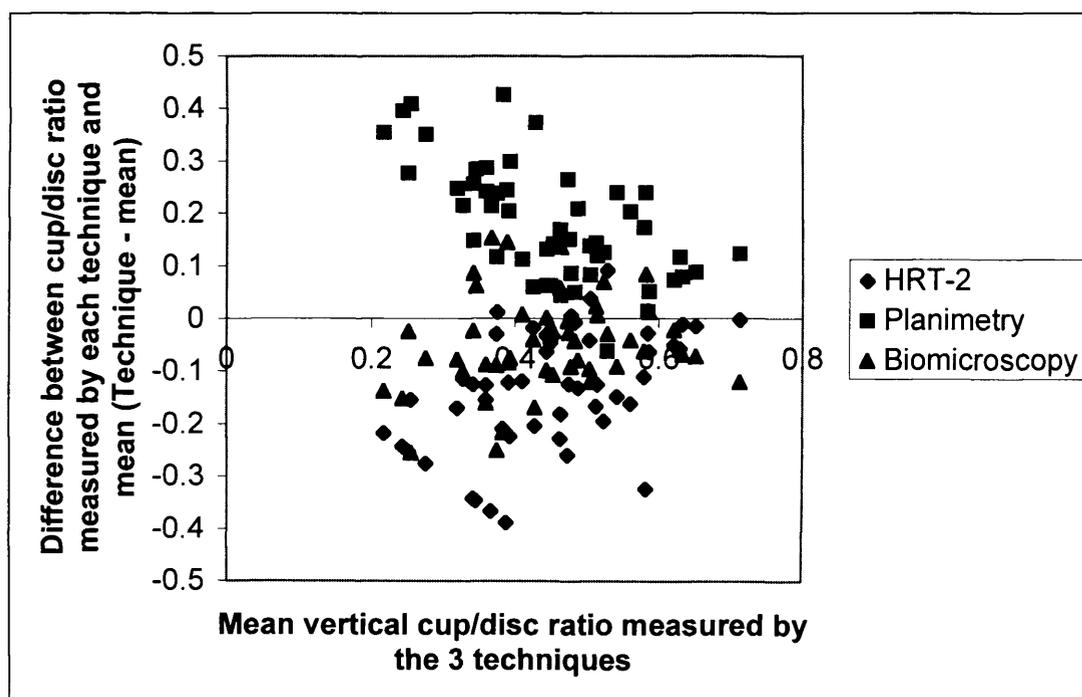


Table 3.4 The mean differences in vertical cup/disc ratio measurement between techniques and the 95% limits of agreement for each of the different pairings of techniques.

Pairing of Techniques	Mean difference in Vertical Cup/Disc Ratio, (p value*)	Vertical Cup/Disc Ratio 95% limits of agreement (mm ²)
HRT & Planimetry	-0.314 (<0.001)	-0.715 to 0.088
HRT & Biomicroscopy	-0.085 (0.001)	-0.423 to 0.253
Planimetry & Biomicroscopy	0.229 (<0.001)	-0.100 to 0.558

* paired t test

3.1.4 Comparison of measurements of optic disc parameters between HRT-II and planimetry of photographs

Fifty right eyes from the Thai study were imaged with the HRT-II and also analysed planimetrically using sequential stereophotographs. The total rim area as measured by the HRT-II (mean, 1.57mm²) was significantly (p<0.001) larger than that measured by planimetry using photographs (mean, 1.30mm²). The rim area/disc area ratio measured by the HRT-II (mean, 0.77) was also significantly (p<0.001) larger than that measured by planimetrically using photographs (mean, 0.59). The HRT-II measured disc area larger than with the planimetric method (HRT II: mean, 2.06mm²; Planimetry: mean, 2.25 mm²; P<0.001).

Bland-Altman (Bland and Altman 1986) plots were used to compare measurements for disc area (Figure 3.11) and for rim area (Figure 3.12) using the two techniques.

These graphs show that for disc area, the agreement between the two techniques strengthens as the optic disc area increases. Systematic bias is less evident for neuroretinal rim area. The 95% limits of agreement for disc area and neuroretinal rim area were -0.813 to 0.367 mm^2 , and -0.303 to 1.011 mm^2 , respectively.

Figure 3.11. Bland-Altman plot(Bland and Altman 1986) showing the difference between measurements of total optic disc area by the HRT-II and disc area determination by planimetry of optic disc photographs plotted against the average measurement for each eye using the two techniques (50 normal eyes).

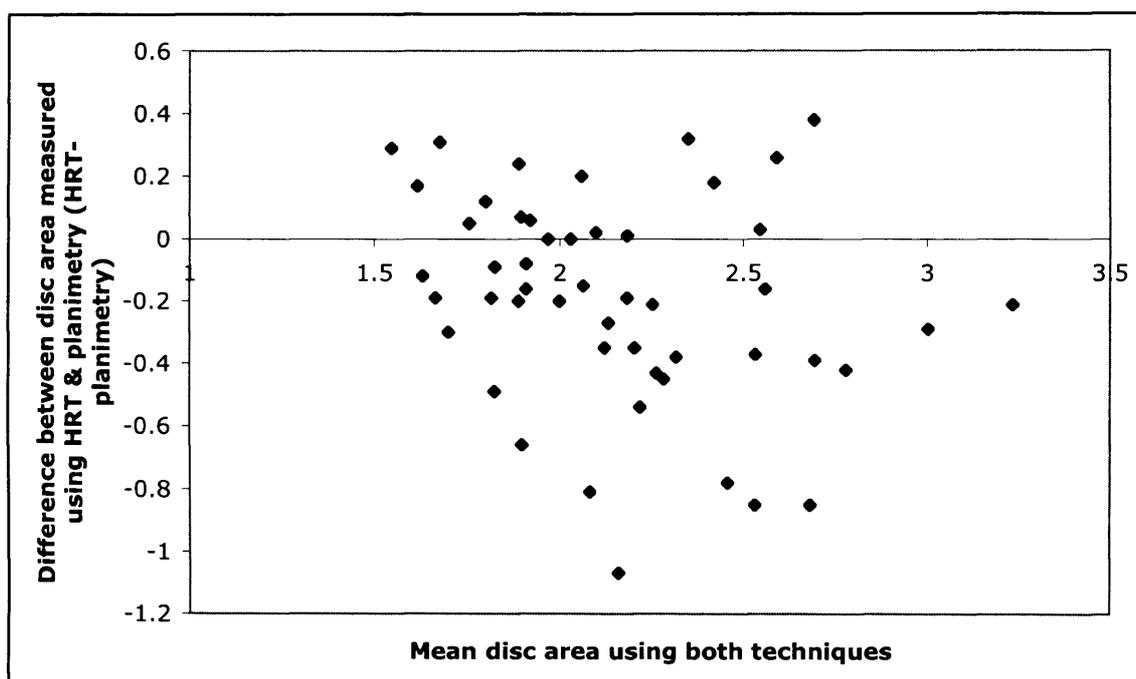
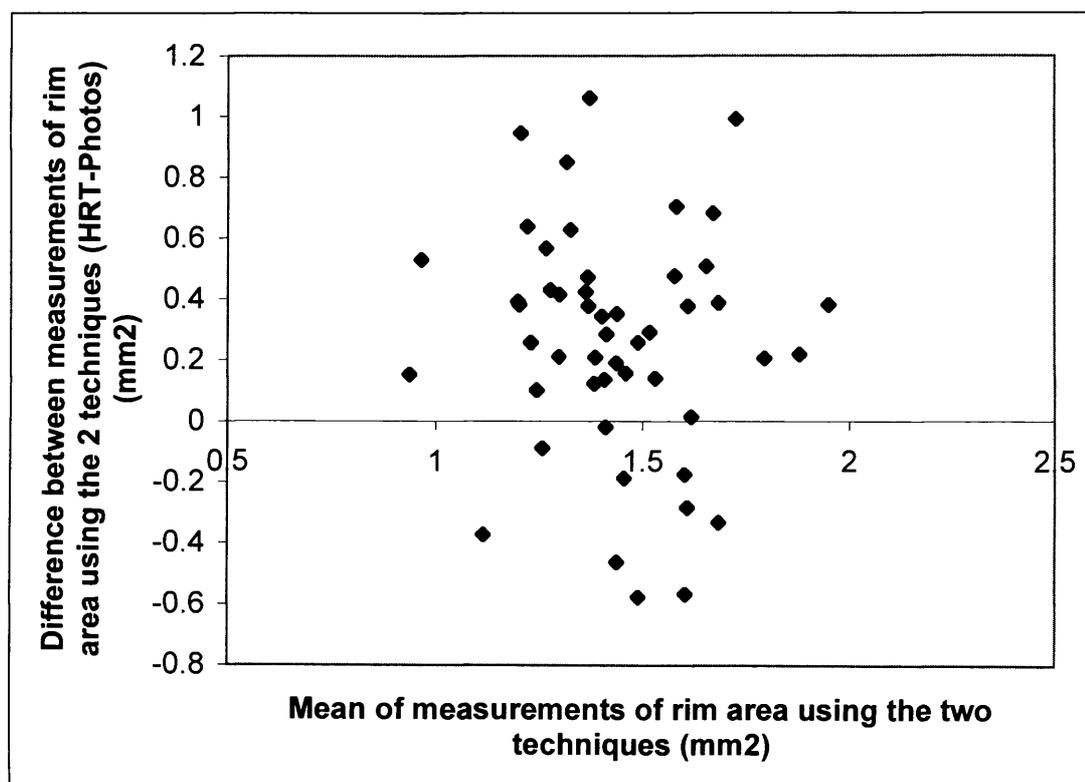


Figure 3.12 Bland-Altman plot (Bland and Altman 1986) showing the difference between measurements of total neuroretinal rim area by the HRT-II and rim area determination by planimetry of optic disc photographs plotted against the average measurement for each eye using the two techniques (50 normal eyes).



3.2 The Rom Klao Glaucoma Survey, Thailand and substudies.

3.2.1 Demographics of subjects in the main survey

Among the 801 subjects identified, 5 had died, 5 had moved away from the district and 1 was hospitalised. Therefore 790 were considered eligible for the study. 701 subjects were examined in the clinic. Of the 89 persons not seen in the clinic, 27 (30.3%) were immobile due to ill health, and 62 refused offers of examination. The response rate was therefore 88.7% (701/ 790). Table 3.5 summarises the demographics of the 790 subjects who were considered eligible for the study. The 140 subjects (mean age, 66.8 years +/- 10.47) who were lost from the cohort between 1997 and 1999 were older than the 701 subjects (mean age, 63.3 +/- 7.4 (SD) years) examined, but there was no significant difference in gender between the two groups. Among the non-responders at the time of the survey, there were more men than women. However, among those examined, there were more women than men. This difference in gender between those examined and the non-responders was significant (Pearson's Chi square $p < 0.001$).

Table 3.5 Demographics of the Rom Klao (Thailand) study sample.

Age	50-59		60-69		70-79		80+		Total
	M	F	M	F	M	F	M	F	
Subtotal for Sex	101	163	125	229	57	75	13	27	790
Refused/ Immobile	25	4	11	15	8	11	3	12	89
Examined at clinic (% eligible subjects examined)	76 (75.2)	159 (97.5)	114 (91.2)	214 (93.4)	49 (85.9)	64 (85.3)	10 (76.9)	15 (55.5)	701 (88.7)

(M: male; F: female)

3.2.2 Clinical Biomicroscopy: Optic Disc Parameters

Ophthalmoscopy (with a contact lens at x16 magnification with measuring eyepiece graticule) of subjects with normal suprathreshold visual fields (right and left eyes), resulted in a median VCDR of 0.45 with 97.5th and 99.5th percentiles of 0.72 and 0.86 respectively. The mean CDR asymmetry (left minus right VCDR) was 0.002 ($P>0.5$), with 97.5th and 99.5th percentiles of 0.21 and 0.29 respectively. These results are presented in Table 3.6.

Table 3.6 The distribution of cup/disc ratio (CDR) in those subjects with normal suprathreshold visual fields in both eyes.

	R CDR	L CDR	CDR ALL	CDR ASSYMETRY
N	498	498	996	498
Mean	.43	.43	.43	.002
Median	.46	.45	.45	.000
Standard dev.	.17	.16	.17	.10
Percentiles 97.5	.74	.72	.72	.21
Percentiles 99.5	.88	.84	.86	.29

3.2.3 Planimetric analysis

3.2.3.1 Demographics of subjects in the planimetric analysis subgroup

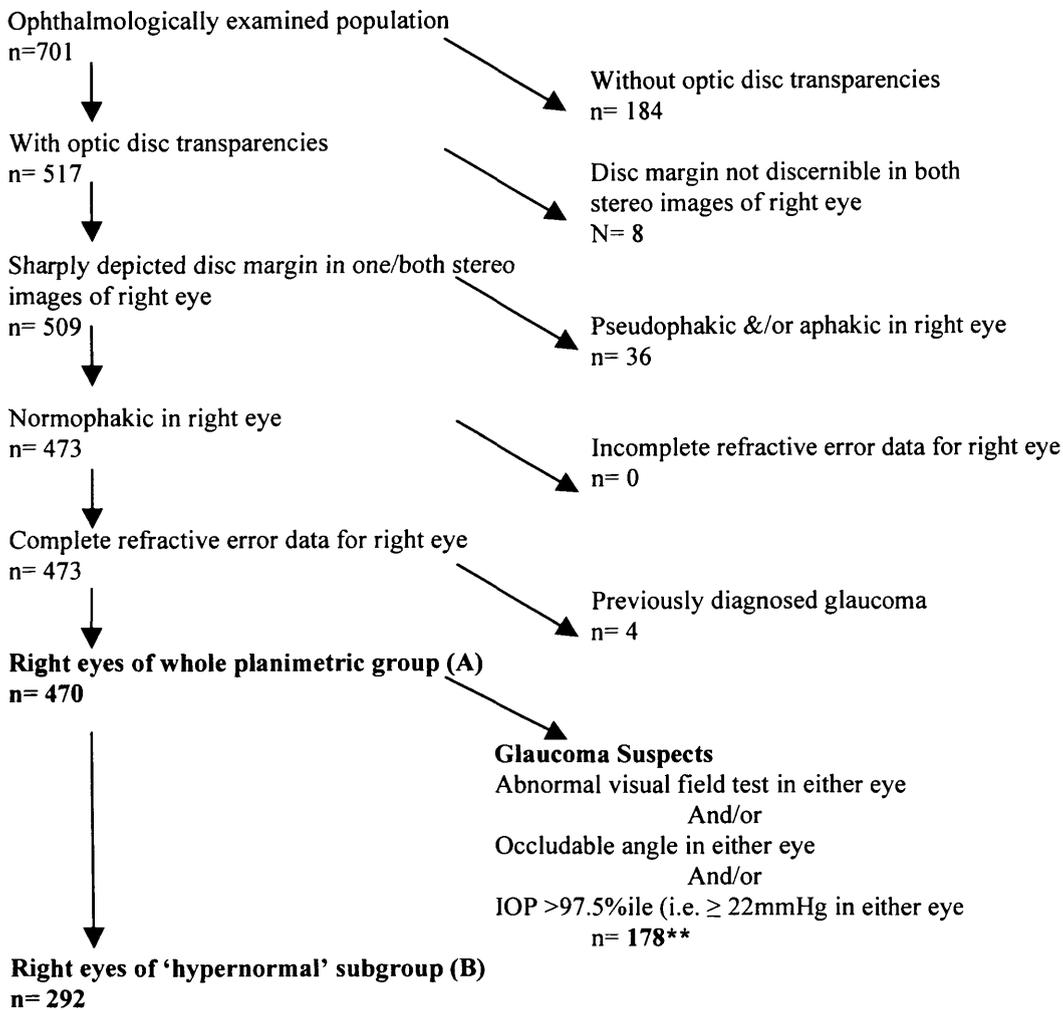
The flowchart below (Figure 3.13) details the subject selection for planimetric analysis. The flowchart ends with the selection of two groups of subjects for analysis. The first is a group (Subgroup A) which includes all subjects for whom planimetric measurements were obtained, but excludes those with poor quality images, those who had been previously diagnosed with glaucoma and those who had had cataract surgery, and those for whom no refractive error data was available. The second group (subgroup B) is a 'hypernormal' group in which those with abnormal visual fields, occludable angles or an abnormally high intraocular pressure are additionally excluded.

Table 3.7 summarises the demographics of all subjects examined and the group on whom planimetry measures were performed. The mean age of subjects was significantly higher in the total examined group (mean, 63.3 (SD, 7.4)) than in the planimetry group (mean, 62.3; SD, 7.0; $P=0.016$). In terms of gender, men were significantly older than women in both the overall survey (mean age of men, 63.9 years (SD, 7.43); women, 63.0 years (SD 7.8); $P=0.013$) and the planimetry sub-group (mean age of men, 63.2 years (SD, 7.3); women, 61.8 years (SD 6.8); $P=0.034$). Comparing between the groups, men were significantly older in the overall survey than men in the planimetry group, and this was also the case with women.

The mean IOP in the overall examined group was 13.4mmHg (SD, 3.9) and 13.2mmHg (SD, 3.2) in the planimetry group. This was not a significant difference ($P=0.34$). In addition there was no significant gender difference in mean IOP within or between groups.

Axial length did not differ significantly between the two groups (mean, 23.1mm in both groups), yet there were significant gender differences within each group. Men had longer axial lengths than women in the overall examined group (men: mean, 23.46mm (SD, 0.88); women: mean, 22.96 (SD, 0.93); $P<0.001$) and in the planimetry group (men: mean, 23.40mm (SD, 0.77); women: mean, 22.90 (SD, 0.87); $P<0.001$). There was no significant difference in axial length between men in either group or women in either group.

Figure 3.13 Flowchart detailing the selection of subjects for planimetric optic disc analysis (Thailand).



**The numbers of subjects that met each/combinations of the exclusion criteria:

Exclusion criterion	Number of subjects
Abnormal visual field only (a)	94
Occludable angle only (b)	58
IOP >95%ile only (c)	1
(a) and (b)	21
(a) and (c)	2
(b) and (c)	1
(a) and (b) and (c)	1

Note: No subject had ametropia in the right eye of >15 D, nor an anatomical disc aberration in the right eye

There was no significant difference in height between the two groups, but within each group men were taller than women (overall group: mean height of men, 1.62m (SD, 0.06), of women, 1.52m (SD, 0.06), $P<0.001$; planimetry group: mean height of men, 1.63m (SD, 0.06), of women, 1.53m (SD, 0.06), $P<0.001$). Between groups, there was no significant difference in height for men, or for women.

Table 3.7 Characteristics of study participants and those whose optic discs were analysed planimetrically (Rom Klao, Thailand).

Characteristic	Participants with ophthalmic examination (n=701) (a)		Participants included in statistical analyses of Optic Disc Data Group A. (n=470) (b)	
	Men (C)	Women (D)	Men (E)	Women (F)
Age Yrs)				
Mean (SD)	63.9 (7.43)	63.0 (7.38)	63.2 (7.3)	61.8 (6.8)
Range	52, 85	50, 91	52, 85	50, 85
50-59	76	159	58	125
60-69	114	214	80	138
70-79	49	64	25	31
80+	10	15	7	6
Mean IOP, mmHg (SD)†	13.1 (4.26)	13.5 (3.83)	13.1 (3.35)	13.3 (3.05)
Mean Axial Length, mm‡	23.46 (0.88)	22.96 (0.93)	23.40 (0.77)	22.90 (0.87)
Mean height, m (SD)**	1.62 (0.06)	1.52 (0.06)	1.63 (0.06)	1.53 (0.06)

† Intraocular pressure (IOP) data was missing for 6 right eyes in group a and 1 right eye of group b.

‡ Axial length data was missing for 12 right eyes in group a and 2 right eyes of group b.

**Height data was missing for 1 person in group a and 1 person of group b.

Independent samples t tests were used to test for significant differences in the means of the following groups:

Mean age: a vs b, $P=0.016$; C vs E, $P=0.361$, D vs F, $P=0.018$; C vs D, $P=0.13$; E vs F, $P=0.034$

Mean IOP: a vs b, $P=0.338$; C vs E, $P=0.892$, D vs F, $P=0.264$; C vs D, $P=0.189$; E vs F, $P=0.53$

Mean axial length: a vs b, $P=0.562$; C vs E, $P=0.698$, D vs F, $P=0.580$; C vs D, $P<0.01$; E vs F, $P<0.01$

Mean height: a vs b, $P=0.144$; C vs E, $P=0.480$, D vs F, $P=0.113$; C vs D, $P<0.01$; E vs F, $P<0.01$

Figure 3.13 illustrated how the planimetric group (Group A) was divided into two subgroups, the glaucoma suspects and 'hypernormals' (subgroup B). These latter two groups were also compared demographically. Glaucoma suspects were significantly ($P < 0.001$) older (mean age, 64.4 years) than the 'hypernormal' subjects (mean age, 61.0 years). In addition, univariate analysis showed glaucoma suspects to be shorter in terms of height (mean, 1.55m) and axial length (mean, 22.9mm) than 'hypernormal' subjects (mean height, 1.57m [$p < 0.001$]); mean axial length, 23.2mm [$p < 0.001$]). There was no significant difference between these groups in terms of intraocular pressure.

3.2.3.2 Optic Disc Parameters

3.2.3.2.1 Subgroup comparisons

Tables 3.8 and 3.9 summarise the planimetric data for 292 right eyes in Subgroup B (the 'hypernormal group') and 470 right eyes in Group A (all good quality planimetric images).

Table 3.8 Optic disc measurements of 292 right eyes from the Rom Klao survey, Thailand. Dataset for Subgroup B ('hypernormal' subjects).

Disc Parameter*	Mean (SD)	SE	Median	Range	Comparison with Group A
Optic Disc					P, indep t test
Area (mm ²)	2.29 (0.46)	0.027	2.26	1.40, 3.80	0.73
Area in men* (n=118)	2.40 (0.48)	0.044	2.36	1.53, 3.80	0.99
Area in women* (n=174)	2.23 (0.43)	0.033	2.17	1.40, 3.79	0.86
Disc Diameter (mm)					
Horizontal	1.59 (0.17)	0.010	1.58	1.17, 2.07	0.49
Vertical	1.78 (0.19)	0.011	1.78	1.32, 2.34	0.91
Horizontal/vertical	0.89 (0.07)	0.004	0.89	0.69, 1.13	0.43
Neuroretinal rim					
Area (mm ²), total	1.36 (0.35)	0.021	1.36	0.47, 2.28	0.49
Superotemporal	0.35 (0.10)	0.006	0.35	0.07, 0.73	0.58
Temporal	0.19 (0.07)	0.004	0.19	0.00, 0.35	0.77
Inferotemporal	0.35 (0.16)	0.009	0.35	0.00, 0.71	0.53
Nasal	0.45 (0.16)	0.009	0.44	0.00, 0.88	0.45
Optic Cup					
Area (mm ²), total	0.93 (0.36)	0.021	0.89	0.22, 2.45	0.26
Diameter (mm)					
Horizontal	1.00 (0.22)	0.013	0.99	0.44, 1.70	0.19
Vertical	1.11 (0.22)	0.013	1.09	0.57, 1.83	0.31
Cup/Disc area ratio	0.40 (0.12)	0.007	0.39	0.14, 0.73	0.20
Cup/Disc vertical diameter ratio	0.62 (0.09)	0.006	0.63	0.37, 0.85	0.21

SD= standard deviation; SE= standard error; * Disc area of men was significantly greater than women, P=0.002)

Planimetric data of the 'glaucoma suspects' (those excluded from Group A to form Subgroup B) were compared with the hypernormal group. There was no significant difference between these groups in terms of disc area, disc diameter, total or sectoral neuroretinal rim area. Glaucoma suspects had significantly smaller cup areas (mean cup area, 0.85mm²) than the hypernormal group (mean, 0.93mm²; P=0.02). Glaucoma suspects also had significantly smaller cup area/disc area ratios (mean, 0.37) than hypernormals (mean, 0.40; P=0.008).

Table 3.9 Optic disc measurements of 470 right eyes from the Rom Klao survey, Thailand. Dataset for Group A (all subjects with good quality images for planimetry).

Disc Parameter*	Mean (SD)	SE	Median	Range
Optic Disc				
Area (mm ²)	2.29 (0.47)	0.022	2.24	1.10, 3.87
Area in men	2.40 (0.47)	0.036	2.35	1.47, 3.87
Area in women	2.22 (0.46)	0.026	2.17	1.10, 3.79
Disc Diameter (mm)				
Horizontal	1.58 (0.18)	0.008	1.57	1.02, 2.07
Vertical	1.78 (0.19)	0.009	1.78	1.27, 2.37
Horizontal/vertical	0.89 (0.07)	0.003	0.89	0.69, 1.18
Neuroretinal rim				
Area (mm ²), total	1.38 (0.36)	0.017	1.36	0.47, 3.19
Superotemporal	0.36 (0.11)	0.005	0.35	0.07, 0.98
Temporal	0.19 (0.07)	0.003	0.19	0.00, 0.43
Inferotemporal	0.36 (0.14)	0.007	0.36	0.00, 0.82
Nasal	0.45 (0.16)	0.007	0.45	0.00, 1.34
Optic Cup				
Area (mm ²), total	0.90 (0.36)	0.017	0.85	0.11, 2.45
Diameter (mm)				
Horizontal	0.98 (0.22)	0.010	0.98	0.30, 1.70
Vertical	1.09 (0.33)	0.011	1.08	0.39, 1.83
Cup/Disc area ratio	0.39 (0.12)	0.006	0.39	0.08, 0.74
Cup/Disc vertical diameter ratio	0.61 (0.10)	0.005	0.62	0.26, 0.85

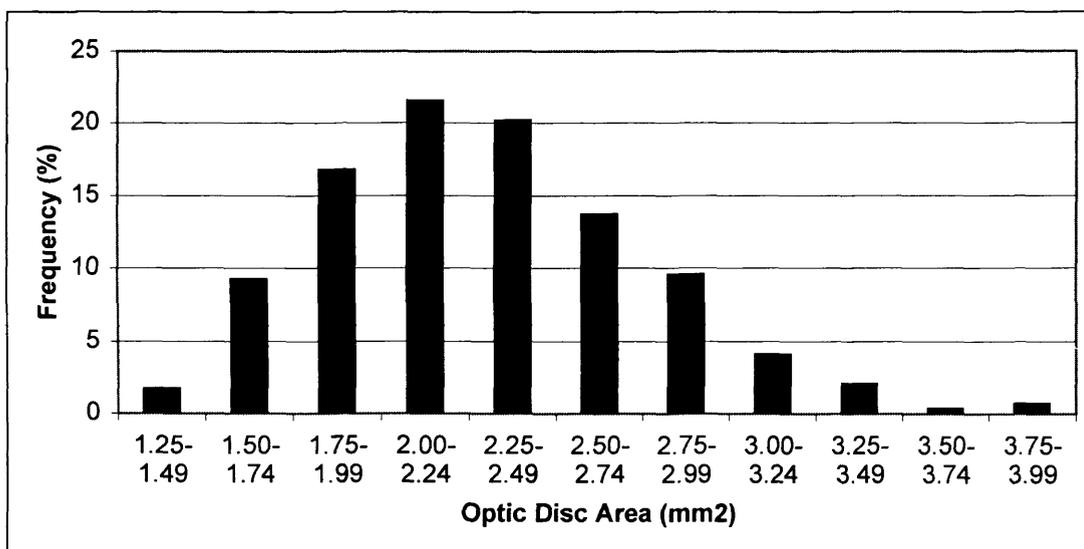
SD= standard deviation; SE= standard error

Selected optic disc parameters using data from Subgroup B ('hypernormal' subjects) are presented in more detail in the subsections below.

3.2.3.2.2 Optic disc area

The area of the optic disc with a mean of 2.29 mm² showed an interindividual variability of 1: 2.7 (Table 3.8). The distribution of disc area was right-skewed (Figure 3.14). Men had a significantly larger ($p=0.002$) disc than women (Table 3.8). The optic disc area was positively correlated with cup area (Spearman's rho, 0.604; $P<0.001$).

Figure 3.14 Distribution of optic disc area of 292 right eyes from the 'hypernormal' subgroup of the Rom Klao Thailand survey.



The shape of the optic disc was generally vertically oval with the vertical disc diameter being approximately 11% greater than the horizontal diameter (Table 3.8). In 268 (91.8%) eyes, the vertical disc diameter was longer than the horizontal diameter, and in 20 (6.8%) eyes, the horizontal disc diameter was longer than the vertical diameter. In 4 eyes, the horizontal and vertical diameters were equal.

Figure 3.15 presents the relationship of disc area to selected variables. Due to the right-skewed distribution of disc area, it was logarithmically transformed.

Figure 3.15 The relationship of disc area on a **log scale** with selected variables (i. Age; ii. Height; iii. Axial length; iv. Anterior chamber depth; v. Refractive error; vi. Keratometry; vii. Lens thickness; viii. Corneal thickness). Thailand study 'hypernormal' dataset (n=292). Regression lines have been added with the regression equation presented.

Figure 3.15i. The relationship of log disc area with age.

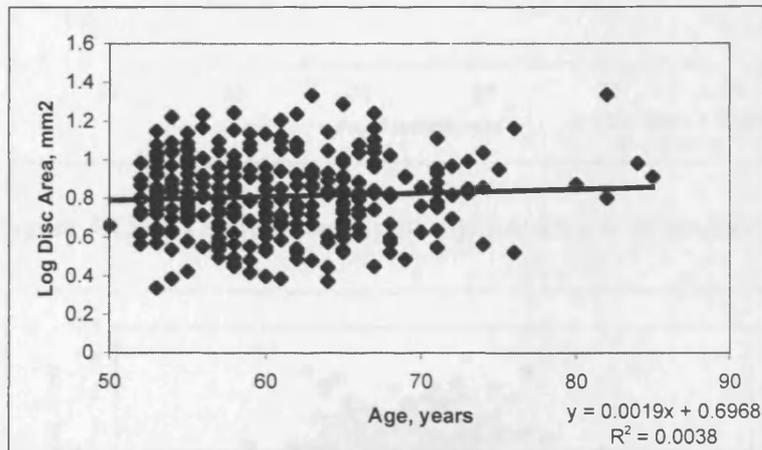


Figure 3.15ii. The relationship of log disc area with height.

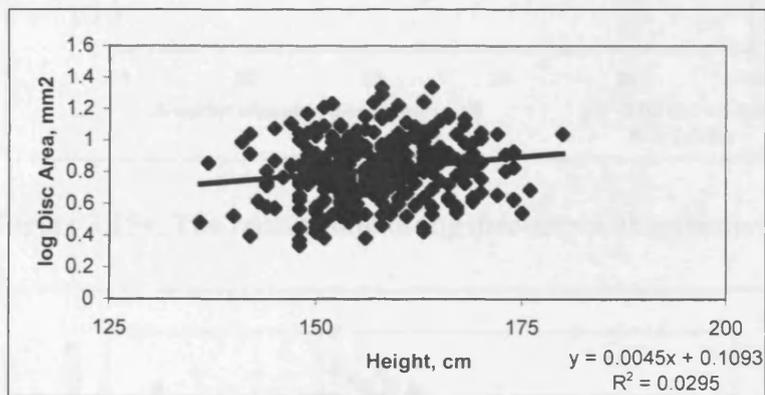


Figure 3.15iii The relationship of log disc area with axial length.

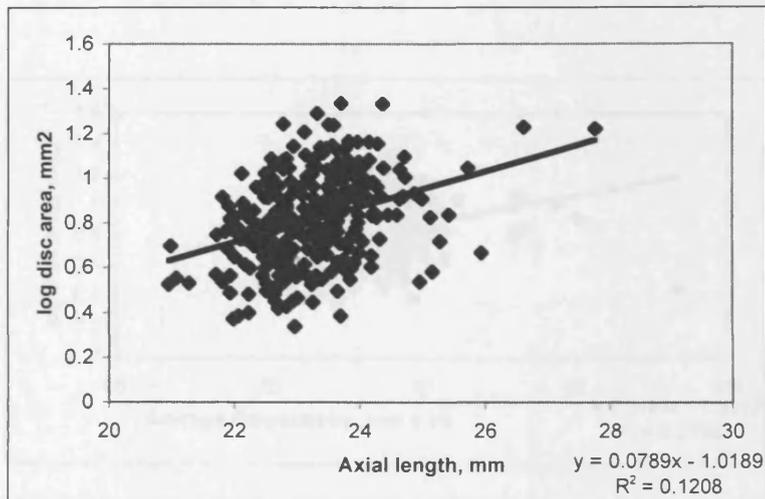


Figure 3.15iv. The relationship of log disc area with anterior chamber depth.

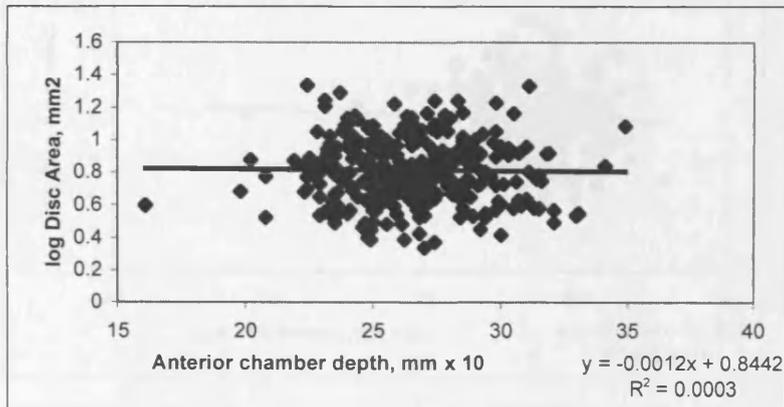


Figure 3.15v. The relationship of log disc area with refractive error.

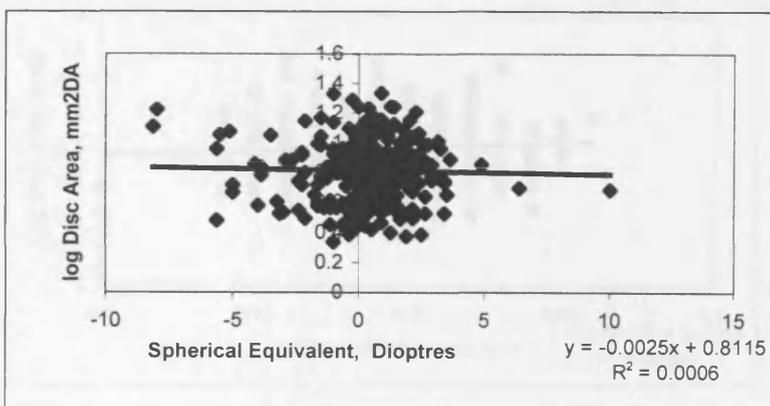


Figure 3.15vi. The relationship of log disc area with keratometry.

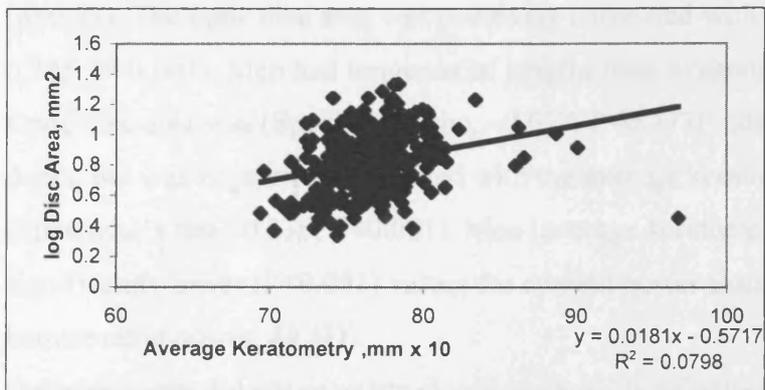


Figure 3.15vii. The relationship of log disc area with lens thickness.

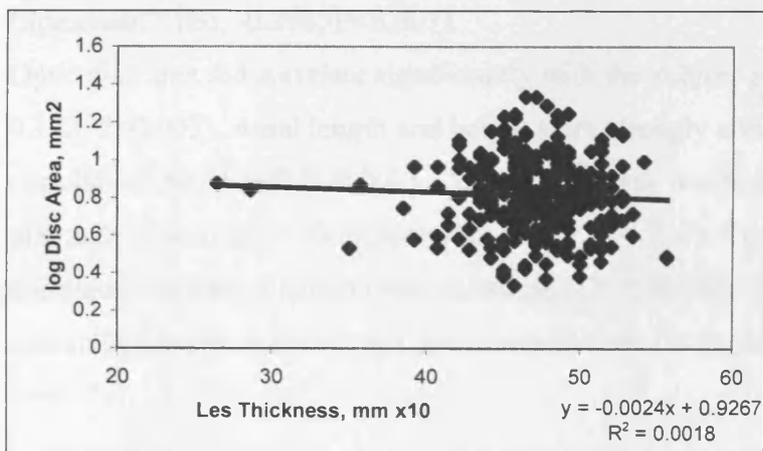
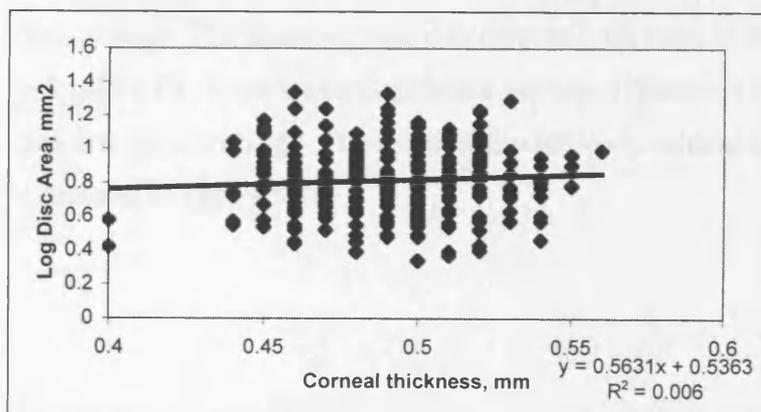


Figure 3.15viii. The relationship of log disc area with corneal thickness.



Disc area was unrelated to age ($p=0.27$; this was also the case for Group A ($p=0.52$)). In addition, there was no relationship of disc area with age with men ($p=0.62$) or women ($p=0.73$). The optic disc area was positively correlated with axial length (Spearman's rho, 0.345; $P<0.001$). Men had longer axial lengths than women (Table 3.7).

Optic disc area was (Spearman's rho, -0.017 ; $P=0.777$) independent of anterior chamber depth, but was negatively correlated with the average keratometric power in dioptres (Spearman's rho, -0.336 ; $P<0.001$). Men (average keratometric power, 43.6D had significantly lower ($P<0.001$) values for corneal power than women (average keratometric power, 44.5D).

Optic disc area did not correlate significantly with refractive error (Spearman's rho, 0.046; $P=0.433$), although axial length correlated positively with refractive error (Spearman's rho, -0.298 ; $P<0.001$).

Optic disc area did correlate significantly with the subject's height (Spearman's rho, 0.172; $P=0.003$). Axial length and height were strongly correlated ((Spearman's correlation rho, 0.345; $P<0.001$). Corneal thickness was not significantly associated with disc area (Spearman's correlation rho, 0.074; $P=0.210$). Corneal thickness was positively correlated with axial length (Pearson's r , 0.142; $P=0.016$). There was no significant association between intraocular pressure and optic disc area (Spearman's rho, -0.064 ; $P=0.279$).

3.2.3.2.3 Cup/disc ratio

Vertical cup/disc ratio was measured planimetrically from the geometric centre of the disc contour. The mean vertical cup/disc ratio for each of the ten-year age groups is given in Table 3.10. There was a significant increase (Pearson's $r = 0.206$; $P<0.001$) in vertical cup-disc ratio with age. The relationship between vertical cup-disc ratio and disc area is illustrated in Figure 3.16.

Figure 3.16 Relationship between vertical cup/disc ratio and disc area (292 right eyes from the 'hypernormal' subgroup of the Rom Klao Thailand survey). The 50th and 95th percentiles are given for the regression line.

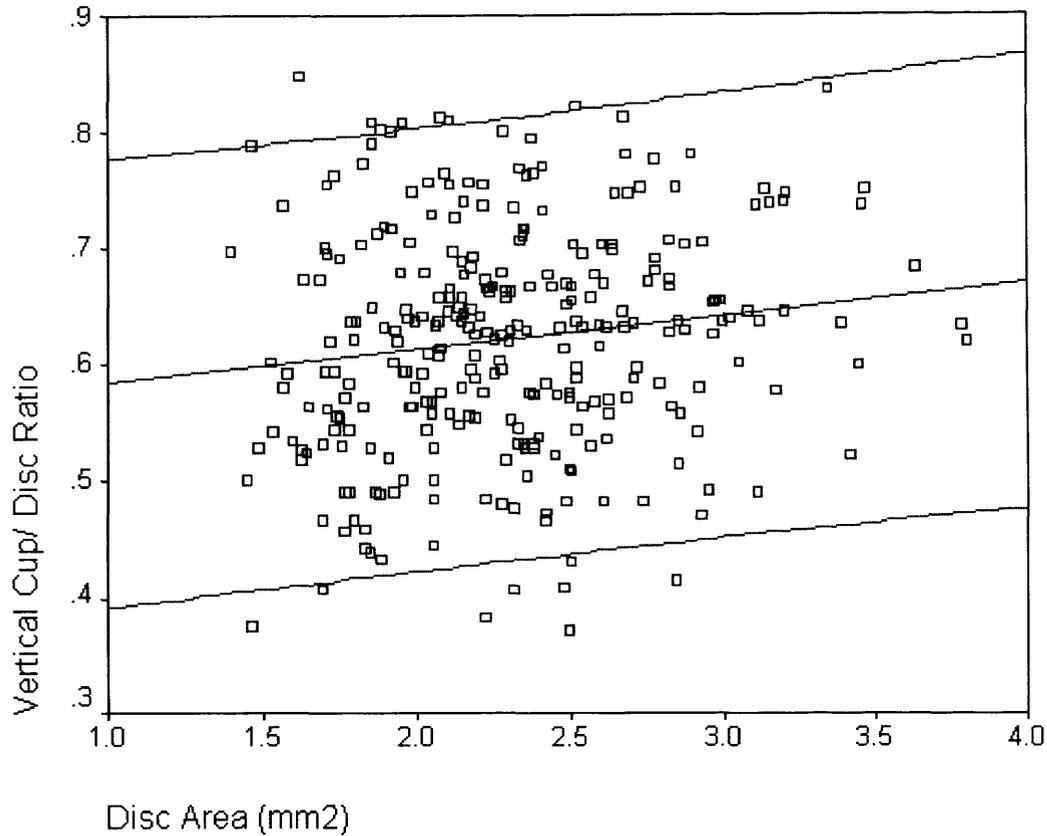


Table 3.10 Vertical cup/disc ratio for optic discs of the right eye in each of the ten-year age groups in the Thai study (Subgroup A dataset).

Age (years)	Number of eyes	Mean Vertical cup/disc ratio
50-59	183	0.61
60-69	218	0.61
70+	69	0.62

Vertical cup-disc ratio was not significantly correlated with intraocular pressure (Subgroup A: Spearman's correlation rho, 0.058; P=0.211; Subgroup B: Spearman's

correlation rho, 0.013; $P=0.819$), nor with neural rim area-disc ratio (Subgroup A: Spearman's correlation rho, -0.061 ; $P=0.190$; Subgroup B: Spearman's correlation rho, -0.009 ; $P=0.876$) for either dataset. Cup diameter was not significantly correlated with intraocular pressure (Subgroup A: Spearman's correlation rho, 0.029; $P=0.533$; Subgroup B: Spearman's correlation rho, 0.000; $P=0.996$).

3.2.3.2.4 Neuroretinal Rim Area

The mean area of the neuroretinal rim was 1.36 mm^2 (SD, 0.35). The frequency distribution was right-skewed (Figure 3.17). Rim area was significantly and positively correlated with the size of the optic disc (Spearman's rho 0.623; $P<0.001$; equation of regression line: neuroretinal rim area (mm^2) = $0.48 \times$ (optic disc area (mm^2)) + 0.26; Figure 3.18) and negatively correlated with the area of the optic cup (Spearman's rho, -0.182 ; $P=0.002$).

Figure 3.17 Distribution of neuroretinal rim area of 292 right eyes from the 'hypernormal' subgroup of the Rom Klao Thailand survey.

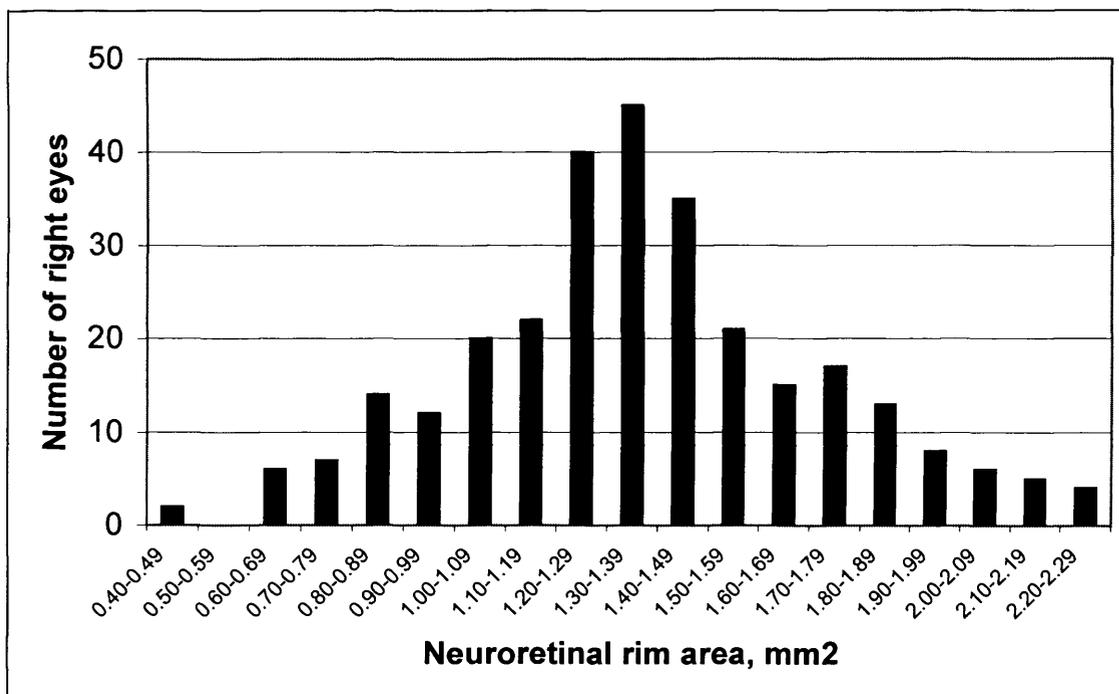


Figure 3.18 Graph of the correlation between neuroretinal rim area and disc area in Thais ('hypernormal' subjects).

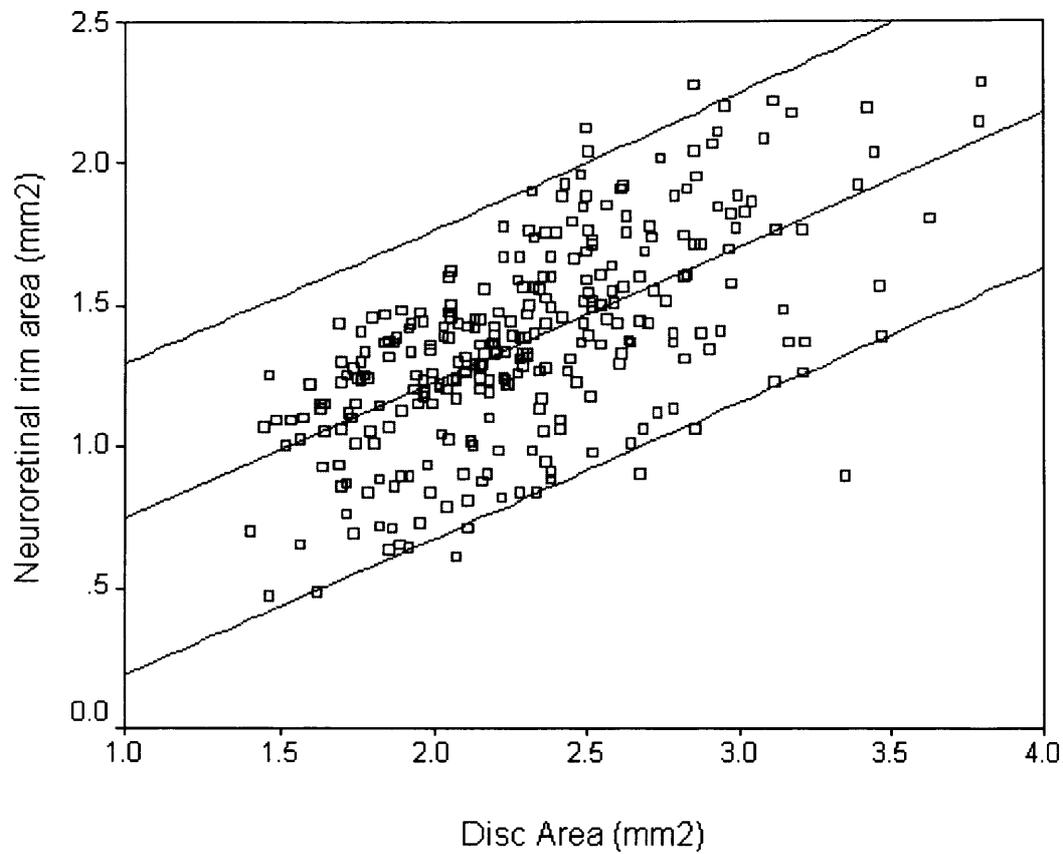


Figure 3.19 presents the relationship of neuroretinal rim area with selected variables. Due to the right-skewed distribution of neuroretinal rim area, it was logarithmically transformed.

Figure 3.19 The relationship of neuroretinal rim area on a **log scale** with selected variables (i. Age; ii. Height; iii. Axial length; iv. Anterior chamber depth; v. Refractive error; vi. Keratometry; vii. Lens thickness; viii. Corneal thickness; ix. Intraocular pressure). Thailand study 'hypernormal' dataset (n=292). Regression lines have been added with the regression equation presented.

Figure 3.19i. The relationship of log neuroretinal rim area with age.

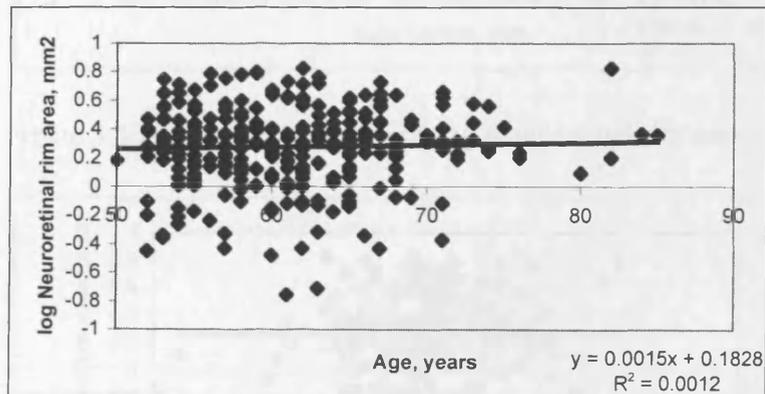


Figure 3.19ii The relationship of log neuroretinal rim area with height.

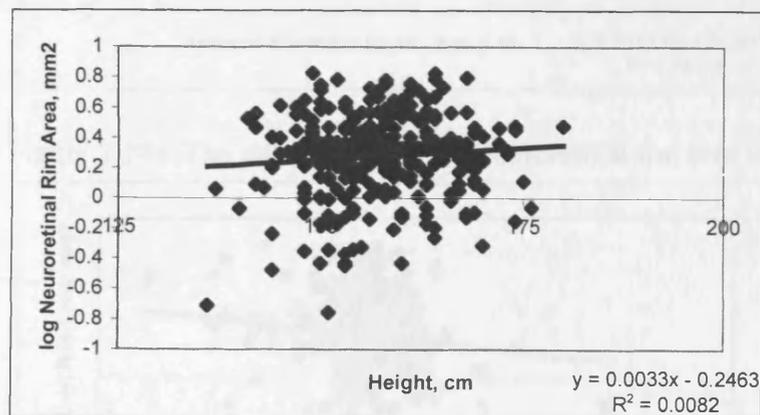


Figure 3.19iii. The relationship of log neuroretinal rim area with axial length.

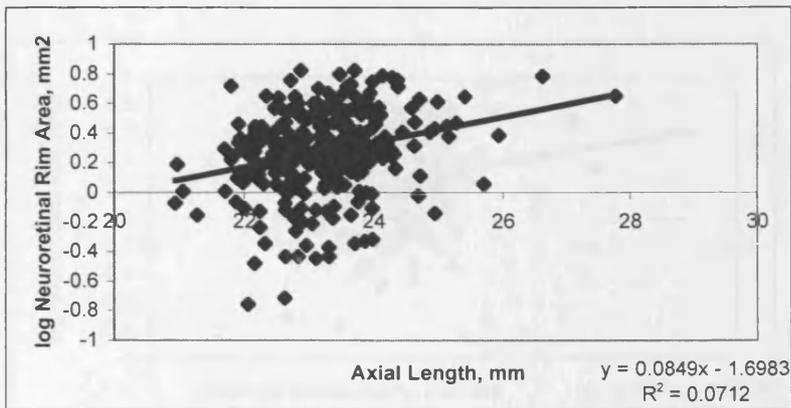


Figure 3.19iv. The relationship of log neuroretinal rim area with anterior chamber depth.

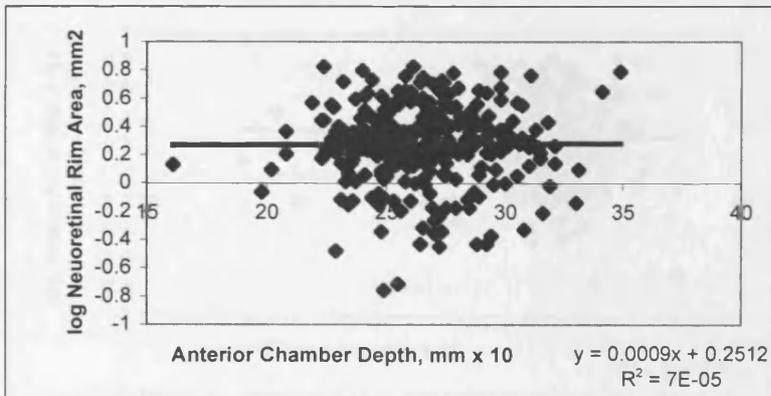


Figure 3.19v. The relationship of log neuroretinal rim area with refractive error.

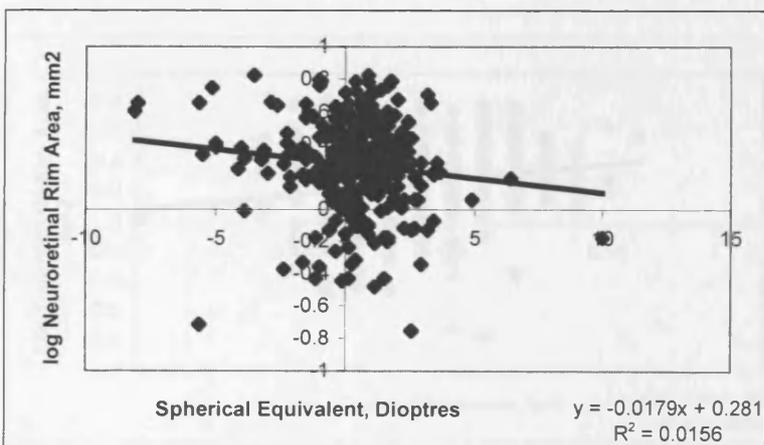


Figure 3.19vi. The relationship of log neuroretinal rim area with keratometry.

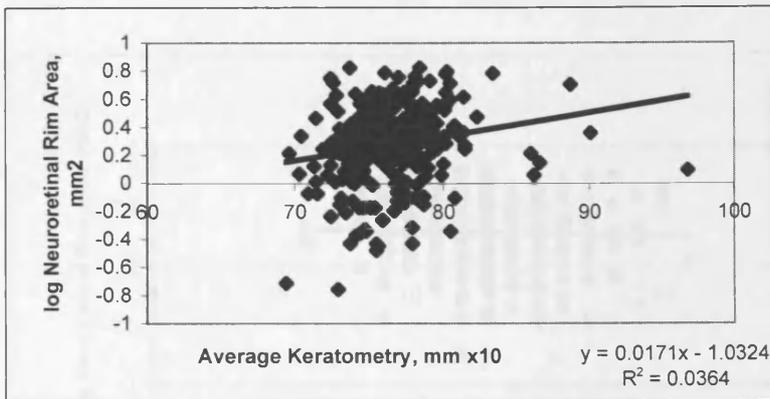


Figure 3.19vii. The relationship of log neuroretinal rim area with lens thickness.

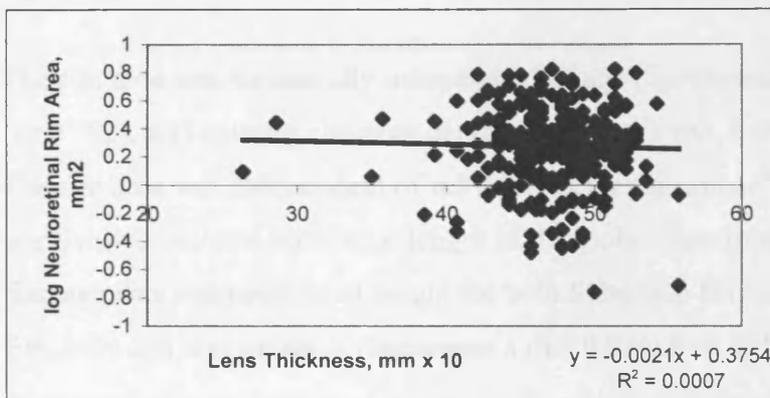


Figure 3.19viii. The relationship of log neuroretinal rim area with corneal thickness.

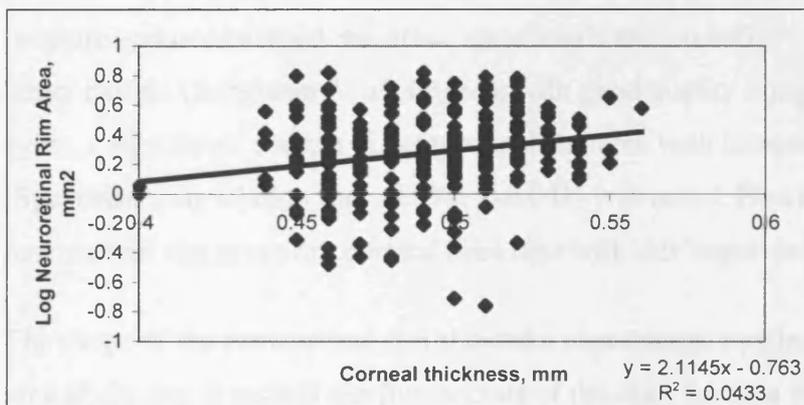
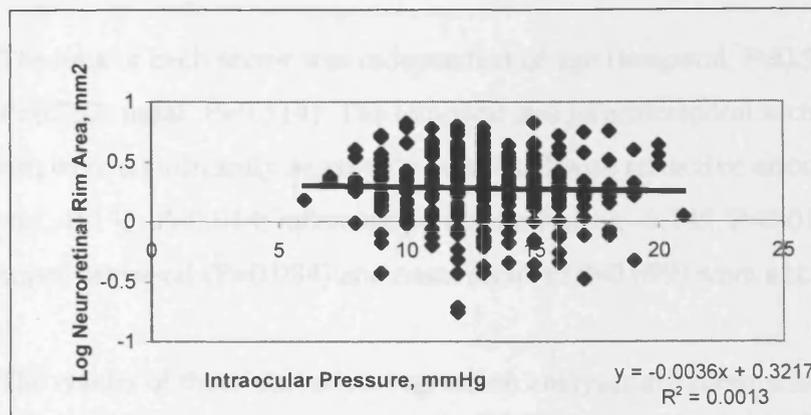


Figure 3.19ix. The relationship of log neuroretinal rim area with intraocular pressure.



The rim area was statistically independent of age (Spearman's rho, 0.015; $P=0.798$), sex ($P=0.192$), and anterior chamber depth (Spearman's rho, 0.003; $P=0.966$).

The rim area was independent of refractive error (Spearman's rho, -0.101; $P=0.087$), but positively correlated with axial length of the globe (Spearman's rho 0.258; $P<0.001$). The rim area was independent of height for both Subgroup B (Spearman's rho, 0.056; $P=0.340$) and also group A (Spearman's rho, 0.035; $P=0.451$).

Corneal thickness was significantly associated with neuroretinal rim area (Spearman's correlation rho, 0.21; $P<0.001$). No significant association existed between intraocular pressure and neuroretinal rim area (Spearman's rho, -0.040; $P=0.494$). However, with the larger dataset (Subgroup A: all subjects with good quality images for planimetry, 470 eyes), a significant decline in neuroretinal rim area with increasing intraocular pressure (Spearman's correlation rho, -0.094; $P=0.041$) was noted. However, the relationship of neuroretinal rim area with corneal thickness with this larger dataset remained unchanged.

The shape of the neuroretinal rim showed a characteristic pattern. Considering the mean area of the rim in each of the four sectors of the disc, the area was smallest in the temporal horizontal sector. The rim area was significantly less (paired t test; $P<0.001$) in the temporal horizontal disc sector than in any of the other three disc sectors. The mean

inferotemporal neuroretinal rim area was larger (0.36mm^2) than the superotemporal sector (0.35mm^2) but this was not a significant difference (paired t test, $P=0.275$).

The area of each sector was independent of age (temporal, $P=0.591$; inferotemporal, $P=0.792$; nasal, $P=0.514$). The temporal and inferotemporal sectors of the neuroretinal rim were significantly negatively correlated with refractive error (temporal: Spearman's rho, -0.145 , $P=0.014$; inferotemporal: coefficient, -0.145 , $P=0.014$), while superotemporal ($P=0.084$) and nasal sectors ($P=0.099$) were not.

The results of these univariate regression analyses are summarised in Table 3.11, where predicted percentage change in optic disc and neuroretinal rim area are given for unit increases in the associated variables (these regression analyses are unadjusted for the effect of the other explanatory variables). Due to the right-skewed distributions of disc area and neuroretinal rim area, these values were obtained from logarithmic transformation of these areas.

Table 3.11 Summary of Univariate Log Linear Regression Analysis (Rom Klao, Thailand; 'hypernormal' group). Predicted Percentage change in Optic Disc Area and Neuroretinal rim area is per unit increase in selected explanatory variables.

Explanatory Variable	Predicted Change in Optic Disc Parameter for stated increase of explanatory variable			
	Optic Disc Area, n=292*		Neuroretinal Rim Area, n=292*	
	% (95% CI's)	Adjusted R ²	%	AdjustedR ²
1-mm increase in axial length	8.21 (5.54,10.85)	0.118	8.86 (5.02, 12.74)	0.068
1-D increase in ocular refraction	-0.25 (-1.41,0.90)	-0.003	-1.81 (-0.356, -0.100)	0.012
0.1mm increase in ACD	-0.12 (-1.00, 0.70)	-0.003	0.09 (-1.11, 1.31)	-0.003
0.1mm increase in LT	-0.24 (-0.90,0.40)	-0.002	-0.21 (-1.11, 0.70)	-0.003
0.1mm increase in keratometry	1.82 (1.11,2.53)	0.077	1.72 (0.70, 2.74)	0.033
1-year increase in age	0.19 (-0.20, 0.50)	0.000	0.15 (-0.30, 0.60)	-0.002
1-cm increase in height	0.45 (0.20,0.70)	0.026	0.33 (-0.10, 0.80)	0.005
1-mmHg increase in intraocular pressure	-0.23 (-1.11, 0.60)	-0.002	-0.36 (-1.51, 0.80)	-0.002
0.1mm increase in corneal thickness	5.79 (-2.74, 15.03)	0.003	23.5 (10.19, 38.54)	0.040

* Values for axial length were missing for 1 subject, lens thickness in 1 subject, and height in 1 subject.

3.2.3.2.4 Multiple Variable Analysis

The relationship between disc area and axial length was tested while adjusting for the effect of height using multiple variable regression analysis. The relationship between disc area and height was also tested while adjusting for the effect of axial length. This was also performed for neuroretinal rim area. The results are summarized in Table 3.12. In the case of disc area the positive association between disc area and axial length remains significant when the association with height is taken into account, while height is no longer significantly associated with disc area when adjustment is made for axial length. Similar findings were observed for neuroretinal rim area.

Table 3.12 Multiple variable regression analysis of log disc area, log neuroretinal rim area, axial length and height (Thai subjects, Subgroup B).

	Beta coefficient	Significance (P value)
Log Disc Area		
Axial Length	0.074	<0.001
Height*	0.170	0.266
Log Neuroretinal Rim Area		
Axial Length	0.084	<0.001
Height [†]	0.023	0.918

* this relationship remains non-significant (P=0.818) when data from Group A is analysed.

[†] this relationship remains non-significant (P=0.982) when data from Group A is analysed.

The relationships of optic disc area and neuroretinal rim area with several more variables are given in Tables 3.13 and 3.14, respectively, following a multiple variable regression analysis. The results are presented using the two datasets (Groups A and subgroup B).

Table 3.13 Multiple variable regression analysis of the logarithm of optic disc area with selected biometric and demographic variables. Thai subjects.

	Subgroup	Beta coefficient	Standard Error	Standardized coefficient	t	Significance (P)
Axial Length (mm)	A	0.078	0.011	0.328	7.17	<0.001
	B	0.073	0.013	0.322	5.49	<0.001
Intraocular Pressure (mmHg)	A	-0.002	.003	-0.03	-0.70	0.484
	B	-0.003	.004	-0.046	-0.821	0.412
Height (cm)	A	-0.290	0.152	-0.11	-1.91	0.057
	B	-0.053	0.204	-0.020	-0.258	0.796
Age (years)	A	0.0005	0.001	0.016	0.357	0.721
	B	0.0016	0.002	0.053	0.917	0.360
Sex	A	-0.072	0.025	-0.17	-2.93	0.004
	B	-0.028	0.032	-0.069	-0.887	0.376

Table 3.14 Multiple variable regression analysis of the logarithm of neuroretinal rim area with selected biometric and demographic variables. Thai subjects.

	Subgroup	Beta coefficient	Standard Error	Standardized coefficient	t	Significance (P)
Axial Length (mm)	A	0.066	0.015	0.208	4.33	0.028
	B	0.085	0.019	0.266	4.39	<0.001
Intraocular Pressure (mmHg)	A	-0.006	0.004	-0.068	-1.50	0.134
	B	-0.005	0.006	-0.05	-0.868	0.386
Height (cm)	A	-0.048	0.214	-0.014	-0.227	0.821
	B	0.0009	0.296	0.000	0.003	0.998
Age (years)	A	0.0013	0.002	0.035	0.739	0.460
	B	0.0014	0.003	0.033	0.561	0.575
Sex	A	-0.015	0.034	-0.027	-0.449	0.654
	B	-0.005	0.046	-0.009	-0.107	0.915

Following adjustment using the variables axial length, intraocular pressure, height, age and sex, disc area was significantly and positively associated with axial length in both subgroups, and sex in Group A only. Neuroretinal rim area was also significantly and positively associated with axial length. There were no other significant associations found using these variables.

3.2.4 HRT-II analysis

3.2.4.1 Demographics of subjects

Although the intention was to collect HRT-II images on all subjects attending for examination, due to a technical failure, only 143 subjects could be recruited for this substudy using the HRT-II. Of these 58 were men and 85 women, with a mean age of 60.5 years (range: 52 to 76 years; Table 3.15).

There was a significant difference (Pearson's Chi squared test, 0.254) in gender structure between subjects in the main survey (men: women; 1:1.81) and HRT-II substudy (1:1.47). There was no significant difference in age structure between the two studies.

Table 3.15 Demographics of the study sample: Age distribution.

	Parent survey	HRT-II study	Total
50-59	235	66	301
60-69	328	62	390
70+	138	15	153
Total	701	143	844

3.2.4.2 Practical aspects of operating the HRT-II

Total time for image acquisition per patient was approximately 7 minutes. Two minutes were spent explaining the test to the subject, the majority spent in explaining the internal fixation device. The time taken by the observer to adjust the position of the subject and acquire the images of each disc was approximately 2.5 minutes per eye.

3.2.4.3 Image quality

Images of only one eye were obtained in 5 subjects; the reasons are given in Table 3.16. Each mean topography image is compiled from three single topographies. The mean standard deviation is the average standard deviation of the height measures for equivalent pixels in the three single topographies, and is an indirect measure of the quality of the image. A linear relationship between nuclear opacity and the mean standard deviation was found (Figure 3.20 and 3.21: $R^2 = 0.116$).

Table 3.16 Reasons for absent HRT-II images.

Sex	Age (years)	Refractive error	Reason for no image*
Male	72	Unable to record	Cataract (NO 5, P 5)
Male	54	Unable to record	Cataract (NO 6, P 6)
Female	61	1.5 / -1.00 x 100	Cataract (NO 3)
Female	64	Unable to record	Cataract (NO 4, P 5)
Male	70	Unable to record	Phthisical eye

Lens Opacity Grading System III (Chylack, Wolfe et al. 1993) (NO= Nuclear Opalescence; P= Posterior Subcapsular opacity)

Figure 3.20 The relationship between Mean Deviation of the topography image and lens opacity (nuclear opacity (Chylack, Wolfe et al. 1993); right eyes only). $R^2 = 0.116$.

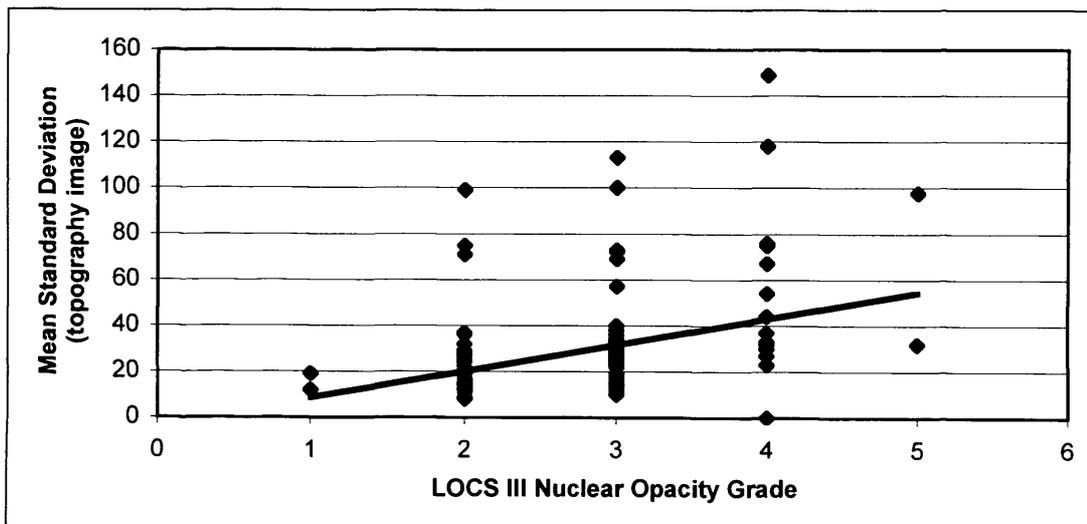
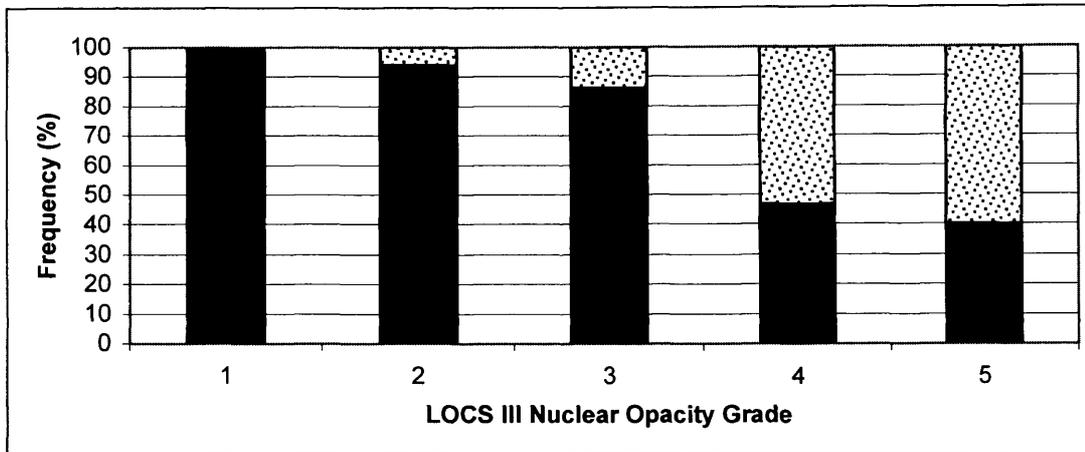


Figure 3.21 The frequency (%) of images with Mean Standard Deviation of less than 40 (solid bars) and 40 or more (dotted bars) in relation to lens opacity (nuclear opacity (Chylack, Wolfe et al. 1993); right eyes only).



3.2.4.4 The 'normal' sample

To describe the normal range of optic disc measurements, 82 right eyes and 79 left eyes were selected. The frequency of criteria for excluding eyes is given in Table 3.17 (79 subjects were excluded).

Table 3.17 Exclusion criteria used in the formation of a 'normal' sample

Exclusion Criterion	Number	
Abnormal STVF†	32 subjects	
IOP > 97.5 th ile (20mmHg) In either eye	4 subjects	
No images for subject	5 subjects	
Defective images	5 subjects	
> 40 MSD*	Right Eyes	22
	Left Eyes	18

*MSD= Mean Standard Deviation. Some were excluded on the basis of more than one criterion.

†STVF= Suprathreshold Visual Field test.

3.2.4.5 Optic disc parameters and associated variables

The HRT-II presents optic disc parameter values for the entire disc (global), and for six sectors (temporal, temporal/superior, temporal/inferior, nasal, nasal/superior and nasal/inferior). Table 3.18 summarizes the mean global parameter values for right and left eyes separately, for all eyes combined, and an analysis of symmetry between right and left eyes. Cup area, vertical and horizontal CDR, neural rim/ disc area ratio, cup volume and retinal nerve fibre layer thickness and cross-sectional area demonstrated a significant inter-eye difference.

Differences in optic disc parameters between those images of ≤ 40 MSD and those of > 40 MSD were investigated. Retinal nerve fibre layer thickness and cross-sectional area were significantly greater in the group of better image quality. Vertical cup/ disc ratio was significantly larger in the group of poorer image quality.

Table 3.18 Optic disc parameters for the 'normal' sample.

Disc measure	All Eyes (95% C.I)	Right Eyes (95% C.I)	Left Eyes (95% C.I)	Asymmetry# (p value)
n	161	82	79	71
DA, mm ²	2.07 (2.01, 2.13)	2.09 (2.01, 2.17)	2.05 (1.96, 2.13)	0.389
CA, mm ²	.471 (0.421, 0.521)	0.49 (0.41, 0.56)	0.455 (0.38, 0.52)	.069
VCDR	.29 (0.25, 0.32)	0.30 (0.25, 0.35)	0.27 (0.22, 0.32)	.043*
HCDR	0.45 (0.42, 0.48)	0.46(0.42, 0.51)	0.44 (0.39, 0.49)	.019*
RA, mm ²	1.59 (1.55, 1.64)	1.60 (1.55, 1.66)	1.59 (1.53, 1.66)	.503
RA/DA	0.78 (0.76, 0.80)	0.778 (0.750, 0.806)	0.788 (0.759, 0.816)	.09
CV (mm ³)	.098 (0.08, 0.11)	0.102 (0.08, 0.12)	0.093 (0.07, 0.11)	.109
RV (mm ³)	0.44 (0.42, 0.46)	0.43 (0.39, 0.46)	0.45 (0.41, 0.48)	0.008*
CSM	-.183 (-0.192, -0.173)	-0.186 (0.201, - 0.171)	-.179(-0.193, - 0.166)	.508
RNFLT (mm)	0.261 (0.250, 0.272)	0.254 (0.241, 0.267)	0.269 (0.251, 0.286)	0.005*
RNFLCSA	1.32 (1.27, 1.38)	1.29 (1.23, 1.36)	1.35 (1.267, 1.441)	0.009*

*significant difference (paired t test) at 95% level

both eyes of 71 subjects were analysed, using a paired t test to assess for asymmetry.

DA: disc area; CA: cup area; VCDR: vertical cup/disc ratio; HCDR: horizontal cup/disc ratio; RA: Neural Rim Area; RA/DA:

Neural rim area-to-disc area ratio; CV: Cup Volume; RV: Rim Volume; CSM: Cup Shape Measure; RNFLT: Retinal nerve fibre layer thickness; RNFLCSA: Retinal nerve fibre layer cross-sectional area.

3.2.4.5.1 Correlation between ophthalmic and optic nerve head parameters

No significant correlation was observed between axial length, refraction or intraocular pressure and the selected optic disc parameters. Disc area increased with increasing maximum cup depth (Pearson's correlation, 0.326, $p = 0.003$). Cup volume increased with increasing disc area and increasing maximal cup depth (0.56 and 0.75, respectively, $p < 0.01$ for both). Rim area increased with increasing disc area (0.482, $p < 0.01$) and decreased with increasing maximum cup depth (-0.364, $p = 0.001$). Rim volume was independent of disc area (0.035, $p = 0.756$), but reduced with increasing maximum cup depth (-0.41, $p = 0.01$). Cup area positively correlated with disc area (Pearson's correlation, 0.70, $p < 0.01$). Vertical CDR increased significantly with increasing disc area (Pearson's correlation, 0.39, $p < 0.01$). When disc size increased from 1 to 2 mm², the CDR also increased from 0.04 to 0.28mm².

3.2.4.5.2 Age-related differences in optic disc measurements

An increase in vertical cup/disc ratio with age approached significance (Pearson's coefficient: 0.202, $P=0.07$). There was no significant correlation between other disc parameters and age of the subject.

3.2.4.5.3 Refractive error-related differences in disc measurements

The average mean spherical equivalent for all subjects was 0.73 D (range -4.37 to +2.93). Only 3 eyes had a spherical equivalent of $> \pm 3$ D. Cup area increased significantly with increasing (more positive) refractive error (Pearson's coefficient: 0.242 ($p=0.028$) whereas rim volume decreased (Pearson's coefficient: 0.297, $p=0.007$). No significant association was found between refractive error and disc area, rim area, or cup volume.

3.2.4.5.4 Gender-related differences in disc measurements

The biometric variables of keratometry and axial length were both significantly larger in men than in women, even when controlling for age. No significant gender differences were found for the optic disc parameters.

3.2.4.5.5 Comparison of the Thai optic disc parameters with the HRT-II database of normal Caucasian eyes

The HRT-II incorporates a database of Caucasian normals (Wollstein, Garway-Heath et al. 1998). The 112 individuals used in this database were volunteers for a hospital-based study with similar strict visual field and intraocular pressure criteria to those used in this study. The data from the present study are compared with this Caucasian database in Table 3.19.

Table 3.19 Comparison of disc parameters between Thai optic discs (current study) and those of normal Caucasians(Wollstein, Garway-Heath et al. 1998):

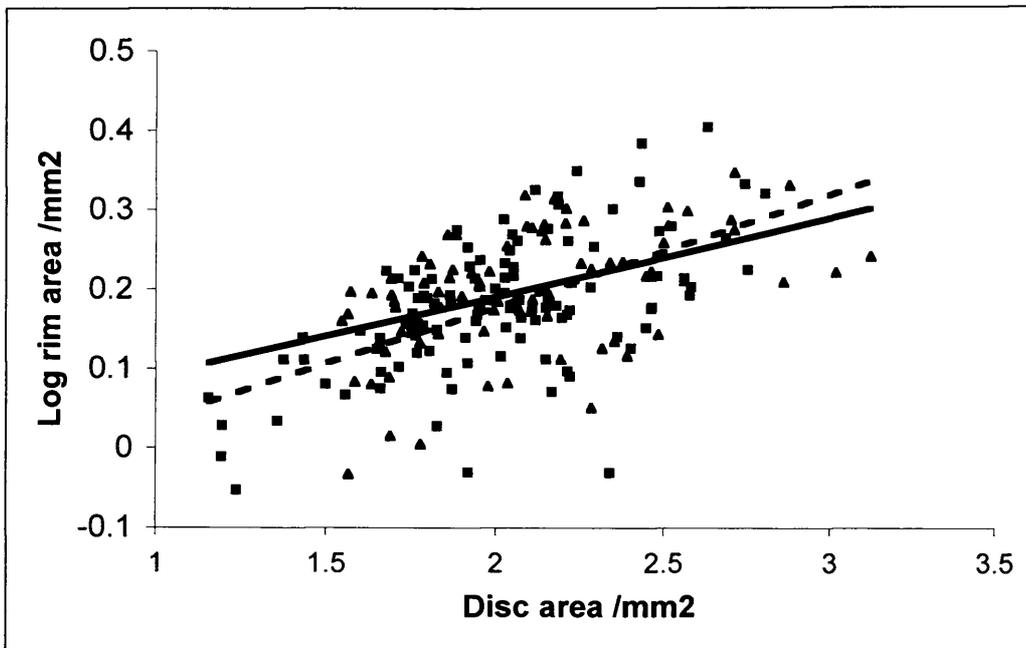
	Thais (current study)* +/- SD	Caucasians (Wollstein, Garway- Heath et al. 1998)# +/- SD
Age of subjects (years)	60.5 +/- 5.9	57.5 +/- 12.4
Disc area /mm ²	2.09 +/- 0.36	2.00 +/- 0.35
Rim area /mm ²	1.59 +/- 0.27	1.53 +/- 0.3
Cup area /mm ²	0.47 +/- 0.33	0.47 +/- 0.3
Cup volume /mm ²	0.09 +/- 0.10	0.10 +/- 0.1
Number of eyes	82	112

* only right eyes

one eye selected randomly per subject

The HRT-II software compares the stereometric parameters of a given image against the normative database. A linear regression analysis was used to indicate how closely the neuroretinal rim area matches the prediction intervals of the linear regression between optic disc area and logarithm of rim area. Figure 3.22 compares the relationship of the logarithm of rim area and disc area between the two subject groups. The difference between the slopes of the two regression lines was not significant.

Figure 3.22 The relationship between logarithm of neuroretinal rim area and disc area for Thai adults (current study: triangles, regression line: solid) and Caucasians (squares, regression line dashed) (Wollstein, Garway-Heath et al. 1998)

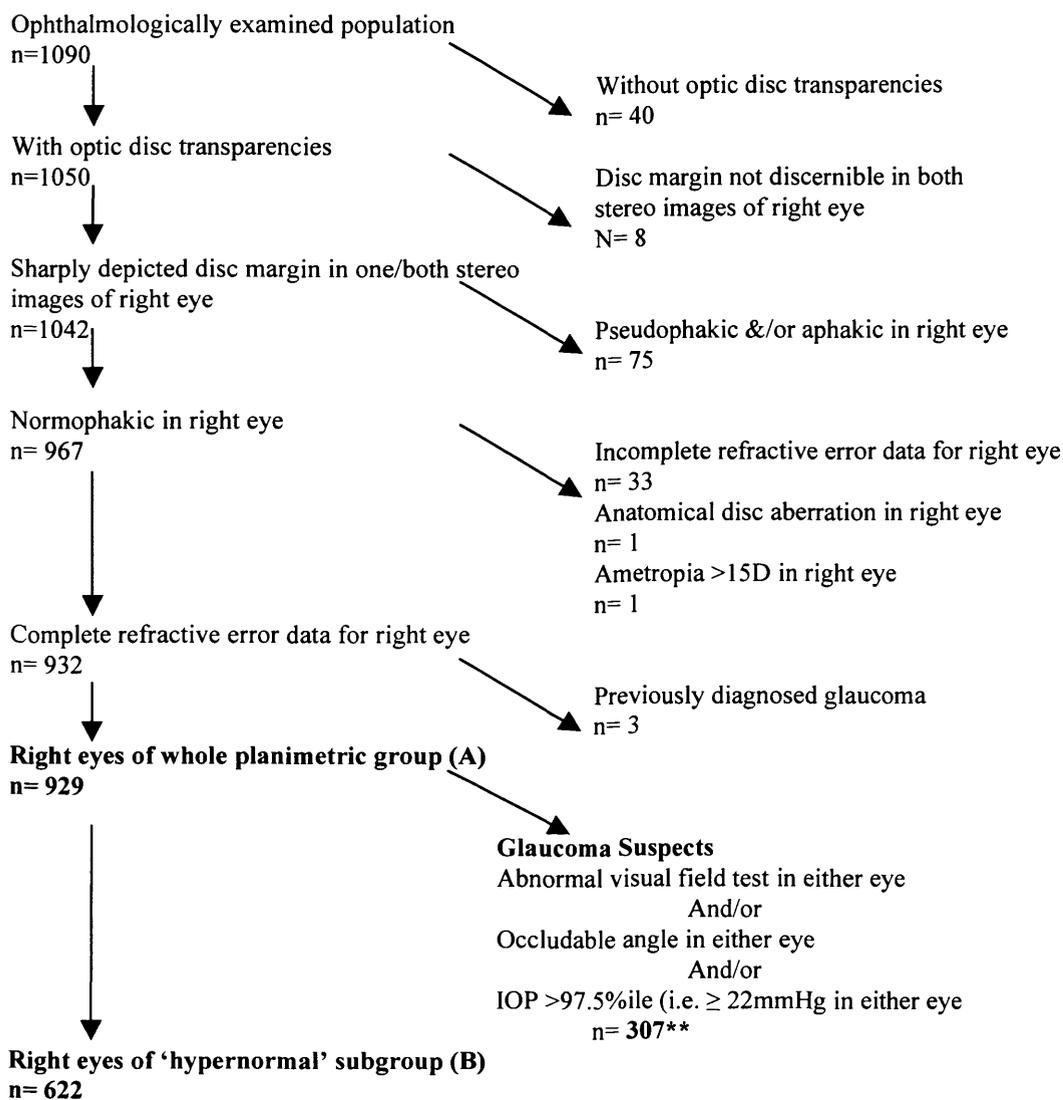


3.3 The Tanjong Pagar Glaucoma Survey, Singapore.

3.3.1 Demographics of subjects in main survey and planimetric analysis subgroup

1090 subjects were examined, comprising 497 (45.6%) men and 593 (54.4%) women. The flowchart below (Figure 3.23) details the subject selection for planimetric analysis.

Figure 3.23 Flowchart detailing the selection of subjects for planimetric optic disc analysis.



* Morning Glory Syndrome

**The following table presents the numbers of subjects that met each/combinations of the exclusion criteria:

Exclusion criterion	Number of subjects
Abnormal visual field only (a)	201
Occludable angle only (b)	53
IOP >95%ile only (c)	20
(a) and (b)	17
(a) and (c)	10
(b) and (c)	4
(a) and (b) and (c)	2

*** Subjects with an abnormal suprathreshold visual field using either the Henson or the Welch Allyn instruments, were excluded. As explained above, some subjects underwent a threshold visual field test (30-2 program) (instrument model 750; Humphrey Instruments, San Leandro, Calif) in addition. If the result of this test was normal, the subject (or eye) was not excluded.

Table 3.20 summarises the demographics of all subjects examined and the group on whom planimetry measures were performed. The mean age of subjects was significantly higher in the total examined group (mean, 59.3 (SD, 11.1)) than in the planimetry group (mean, 57.7; SD, 10.7; $P=0.001$). There were no significant gender differences within each group. Comparing between the groups, men were significantly older in the overall survey than men in the planimetry group, and this was also the case with women.

The mean IOP in the overall examined group was 14.7mmHg (SD, 3.7) and 14.6mmHg (SD, 3.4) in the planimetry group. This was not a significant difference ($P=0.68$). In addition there was no significant ($P>0.05$) gender difference in mean IOP within or between groups.

Axial length did not differ significantly between the two groups (overall examined group: mean= 23.2mm (SD, 1.2); planimetry group: mean= 23.3 (SD, 1.8; $P=0.204$) yet there were significant gender differences within each group. Men had longer axial lengths than women in the overall examined group (men: mean, 23.5mm (SD, 1.2); women: mean, 22.9 (SD, 1.3); $P<0.001$) and in the planimetry group (men: mean, 23.5mm (SD, 1.1); women: mean, 22.9 (SD, 1.1); $P<0.001$). There was no significant difference in axial length between men or women in the two groups.

There was no significant difference in height between the two groups, but within each group men were taller than women (overall group: mean height of men, 1.65m (SD, 0.06), of women, 1.53m (SD, 0.06), $P<0.001$; planimetry group: mean height of men, 1.65m (SD, 0.06), of women, 1.53m (SD, 0.06), $P<0.001$). Between groups, there was no significant difference in height for men, or for women.

Table 3.20 Characteristics of study participants and those and those whose optic discs were analysed planimetrically: Tanjong Pagar, Singapore survey.

Characteristic	Participants with ophthalmic examination (n=1090) (A)		Participants included in statistical analyses of Optic Disc Data Group A. (n=929) (B)	
	Men (C)	Women (D)	Men (E)	Women (F)
Age Yrs)				
Mean (SD)	59.6 (11.1)	59.0 (11.1)	57.9 (10.8)	57.5 (10.6)
Range	40, 81	40, 81	40, 81	40, 81
40-49	121	140	117	136
50-59	108	176	98	170
60-69	153	143	129	121
70-79	107	126	66	83
80+	8	8	5	5
Mean IOP, mmHg (SD)†	14.6 (4.1)	14.8 (3.3)	14.4 (3.6)	14.8 (3.2)
Mean Axial Length, mm‡	23.5 (1.2)	22.9 (1.3)	23.5 (1.1)	22.9 (1.1)
Mean height, cm (SD)**	164.6 (6.3)	153.0 (5.9)	164.8 (6.3)	153.2 (5.7)

† Intraocular pressure (IOP) data was missing for 7 right eyes in group A.

‡ Axial length data was missing for 113 right eyes in group A and 55 right eyes of group B.

**Height data was missing for 25 subjects in group A and 10 subjects of group B.

Independent samples t tests were used to test for significant differences in the means of the following groups:

Mean age: a vs b, P=0.001; C vs E, P=0.023, D vs F, P=0.021; C vs D, P=0.349; E vs F, P=0.490

Mean IOP: a vs b, P=0.678; C vs E, P=0.517, D vs F, P=0.974; C vs D, P=0.216; E vs F, P=0.052

Mean axial length: a vs b, P=0.204; C vs E, P=0.722, D vs F, P=0.433; C vs D, P<0.01; E vs F, P<0.01

Mean height: a vs b, P=0.716; C vs E, P=0.609, D vs F, P=0.310; C vs D, P<0.01; E vs F, P<0.01

Figure 3.23 (above) shows how the planimetric group (Group A) is divided into two subgroups, the glaucoma suspects and 'hypernormals' (subgroup B). These latter two groups were also compared demographically. Glaucoma suspects were significantly

($P < 0.001$) older and had higher ($P < 0.001$) intraocular pressures (mean age, 63.9 years; mean IOP, 15.7 mmHg) than the 'hypernormal' subjects (mean age, 54.7 years; mean IOP, 14.1 mmHg). In addition, univariate analysis showed glaucoma suspects to be shorter in terms of height (mean, 1.56 m) and axial length (mean, 23.1 mm) than the 'hypernormal' subjects (mean height, 1.59 m [$p < 0.001$]; mean axial length, 23.3 mm [$p = 0.025$]).

3.3.2 Planimetric Analysis: Optic disc parameters

3.3.2.1 Subgroup comparisons

Tables 3.21 and 3.22 summarise the planimetric data for 622 right eyes in Subgroup B (the 'hypernormal group' and 929 right eyes in Group A (all good quality planimetric images)).

The area of the optic disc, neuroretinal rim (total and for each of the four segments) and cup did not differ significantly (independent samples, t test) between the datasets A and B. This was also the case for vertical and horizontal disc and cup diameters, and ratios of cup/disc area and cup/disc vertical diameter. There was no gender difference in disc area between the two groups.

Planimetric data of the 'glaucoma suspects' (those excluded from Group A to form Subgroup B) were compared with the hypernormal group. There was no significant difference between these groups in terms of disc area, disc diameter, total neuroretinal rim area, cup area or cup area/disc area ratio. Glaucoma suspects had significantly smaller neuroretinal rim area in the nasal sector (mean area, 0.48mm^2) than the hypernormal group (mean, 0.51mm^2 ; $P=0.006$), while there were no significant differences between groups with respect to the other rim sectors.

Selected optic disc parameters using data from Subgroup B ('hypernormal' subjects) are presented in more detail in the subsections below.

Table 3.21 Optic disc measurements of 622 right eyes from the Tanjong Pagar survey, Singapore. Dataset for Subgroup B ('hypernormal' subjects).

Disc Parameter*	Mean (SD)	SE	Median	Range	Comparison with Group A
Optic Disc					P, indep t test
Area (mm ²)	2.17 (0.46)	0.018	2.09	1.10, 4.01	0.909
Area in men* (n=290)	2.26 (0.46)	0.027	2.20	1.30, 3.56	0.884
Area in women* (n=332)	2.09 (0.45)	0.025	2.00	1.10, 4.01	0.918
Disc Diameter (mm)					
Vertical	1.73 (0.19)	0.008	1.71	0.79, 2.43	0.880
Horizontal	1.58 (0.18)	0.007	1.56	1.02, 2.19	0.905
Horizontal/vertical	0.91 (0.09)	0.003	0.91	0.59, 1.77	0.980
Neuroretinal rim					
Area (mm ²), total	1.43 (0.29)	0.011	1.39	0.62, 2.49	0.476
Superotemporal	0.37 (0.08)	0.003	0.36	0.09, 0.77	0.646
Temporal	0.19 (0.05)	0.002	0.18	0.04, 0.54	0.571
Inferotemporal	0.36 (0.09)	0.004	0.36	0.12, 0.77	0.786
Nasal	0.51 (0.15)	0.006	0.48	0.24, 1.04	0.235
Optic Cup					
Area (mm ²), total	0.74 (0.35)	0.014	0.69	0.01, 1.90	0.667
Diameter (mm)					
Vertical	0.97 (0.24)	0.009	0.97	0.10, 1.62	0.644
Horizontal	0.92 (0.24)	0.009	0.92	0.12, 1.65	0.705
Cup/Disc area ratio	0.33 (0.11)	0.004	0.34	0.01, 0.62	0.699
Cup/Disc vertical diameter ratio	0.55 (0.10)	0.004	0.57	0.06, 0.77	0.433

SD= standard deviation; SE= standard error; * Disc area of men was significantly greater than women, P<0.001)

Table 3.22 Optic disc measurements of 929 right eyes from the Tanjong Pagar survey, Singapore. Dataset for Group A (all subjects with good quality images for planimetry).

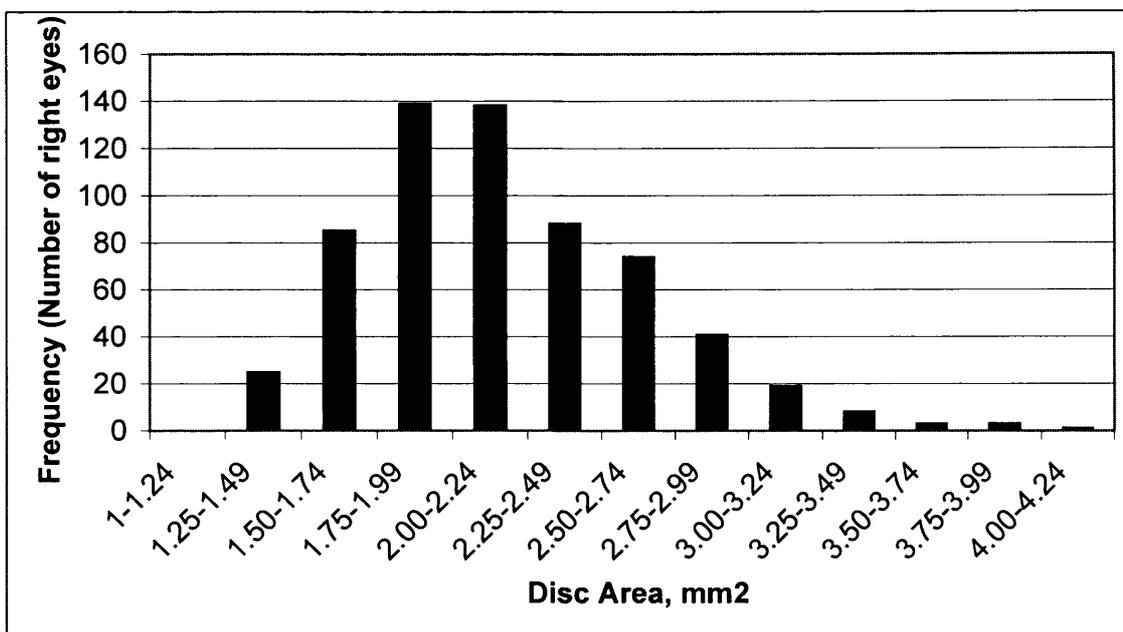
Disc Parameter	Mean (SD)	SE	Median	Range
Optic Disc				
Area (mm ²)	2.17 (0.47)	0.015	2.10	1.10, 4.81
Area in men* (n=415)	2.26 (0.46)	0.023	2.20	1.25, 3.79
Area in women* (n=514)	2.09 (0.46)	0.020	2.01	1.10, 4.81
Disc Diameter (mm)				
Vertical	1.73 (0.19)	0.006	1.71	0.79, 2.53
Horizontal	1.57 (0.19)	0.006	1.56	0.96, 2.41
Horizontal/vertical	0.91 (0.08)	0.003	0.91	0.55, 1.77
Neuroretinal rim				
Area (mm ²), total	1.42 (0.29)	0.010	1.38	0.48, 2.67
Superotemporal	0.37 (0.08)	0.003	0.36	0.09, 0.77
Temporal	0.19 (0.06)	0.002	0.19	0.04, 0.54
Inferotemporal	0.36 (0.09)	0.003	0.36	0.10, 0.77
Nasal	0.49 (0.15)	0.005	0.47	0.12, 1.39
Optic Cup				
Area (mm ²), total	0.75 (0.35)	0.012	0.69	0.01, 2.80
Diameter (mm)				
Vertical	0.97 (0.24)	0.008	0.97	0.10, 1.90
Horizontal	0.93 (0.23)	0.008	0.92	0.12, 1.90
Cup/Disc area ratio	0.33 (0.11)	0.004	0.34	0.01, 0.64
Cup/Disc vertical diameter ratio	0.56 (0.10)	0.003	0.57	0.06, 0.80

SD= standard deviation; SE= standard error; * Disc area of men was significantly greater than women, P<0.001)

3.3.2.2 Optic Disc Area

The area of the optic disc with a mean of 2.17mm^2 , showed an interindividual variability of 1:3.6 (Table 3.22 above). The distribution of disc area was right-skewed (Figure 3.24). Male subjects had a significantly larger ($p < 0.001$) disc than female subjects (Table 3.22). The optic disc area was positively correlated with cup area (Spearman's rho, 0.766; $P < 0.001$).

Figure 3.24 Distribution of optic disc area of 622 right eyes from the 'hypernormal' subgroup of the Tanjong Pagar Singapore survey.



The shape of the optic disc was generally vertically oval with the vertical disc diameter being approximately 9% greater than the horizontal diameter (Table 3.22). In 538 (86.4%) eyes, the vertical disc diameter was longer than the horizontal diameter, and in 70 (11.2%) eyes, the horizontal disc diameter was longer than the vertical diameter. In 14 eyes, the horizontal and vertical diameters were equal.

Figure 3.25 presents the relationship of disc area to selected variables. Due to the right-skewed distribution of disc area, it was logarithmically transformed.

Figure 3.25 The relationship of disc area on a **log scale** with selected variables (i. Age; ii. Height; iii. Axial length; iv. Anterior chamber depth; v. Refractive error; vi. Keratometry; vii. Lens thickness; viii. Corneal thickness). Singapore study 'hypernormal' dataset (n=622). Regression lines have been added with the regression equation presented.

Figure 3.25i The relationship of log disc area with age.

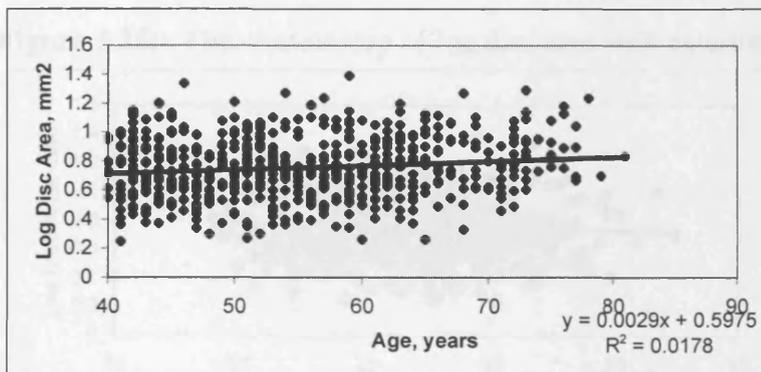


Figure 3.25ii The relationship of log disc area with height.

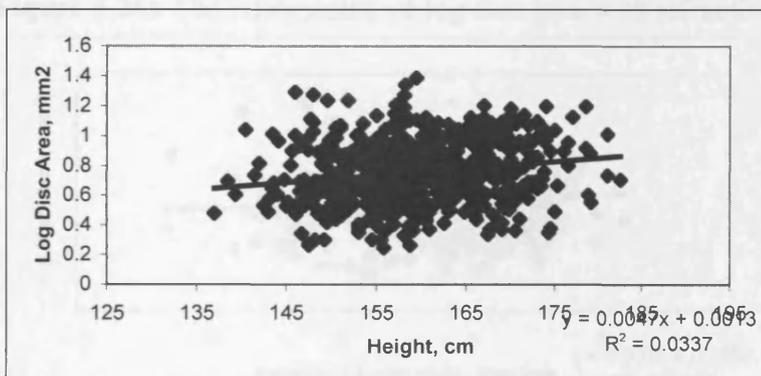


Figure 3.25iii The relationship of log disc area with axial length.

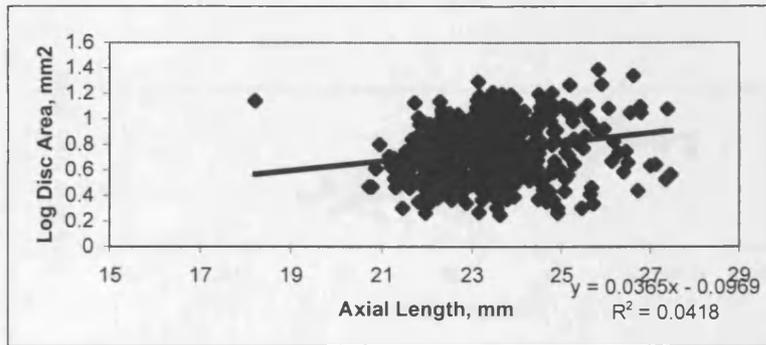


Figure 3.25iv The relationship of log disc area with anterior chamber depth.

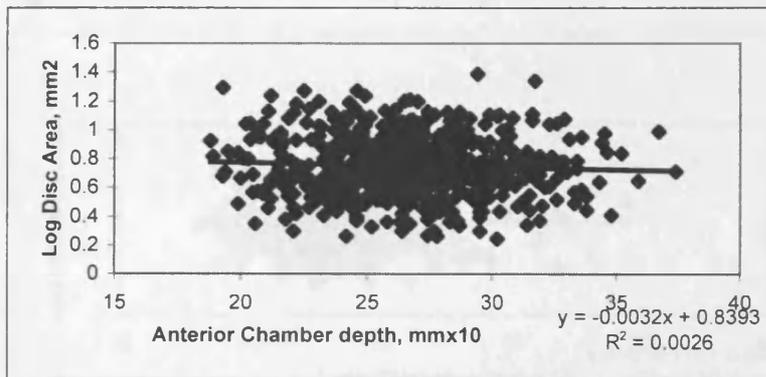


Figure 3.25v The relationship of log disc area with refractive error.

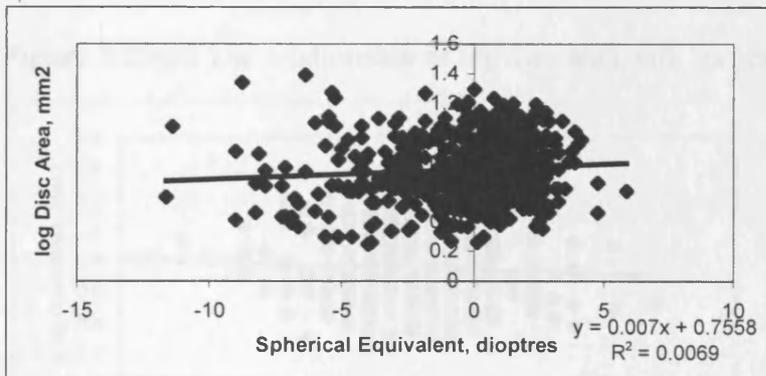


Figure 3.25vi The relationship of log disc area with keratometry.

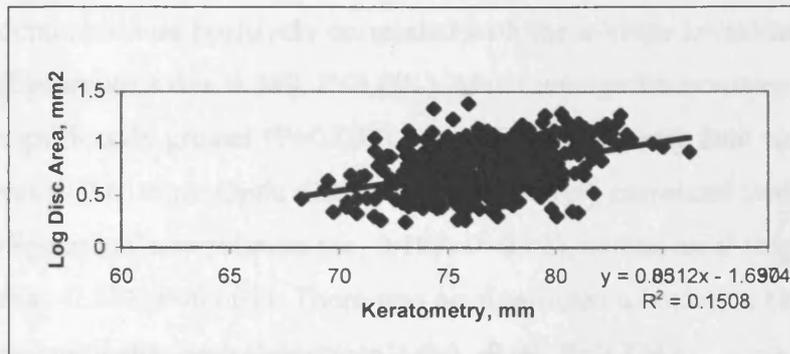


Figure 3.25vii The relationship of log disc area with lens thickness.

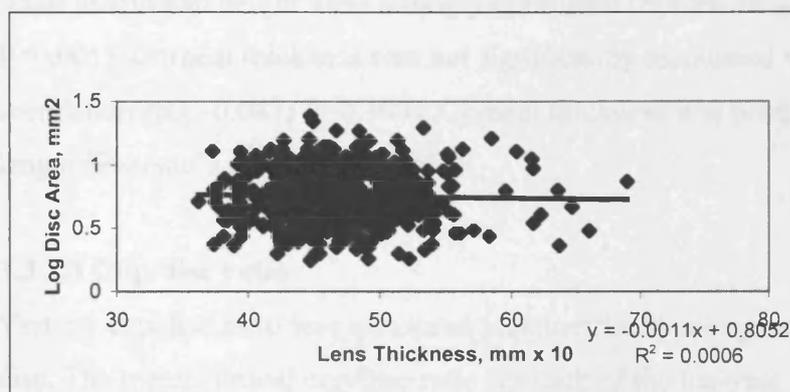
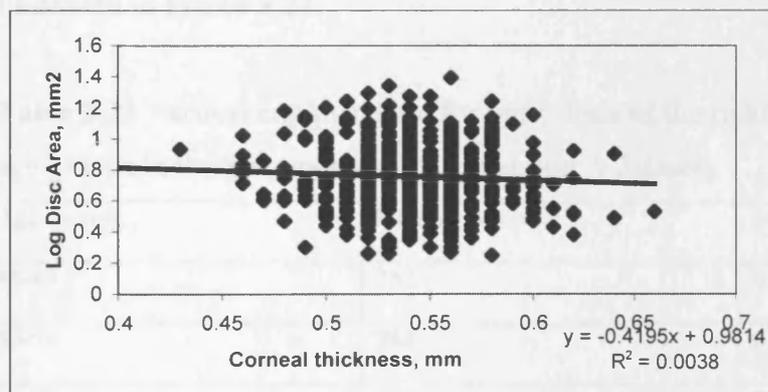


Figure 3.25viii The relationship of log disc area with corneal thickness.



Disc area was positively correlated with age (Spearman's rho, 0.115; $p=0.004$). This was also statistically significant for men (Spearman's rho, 0.125; $p=0.033$) but not for women (Spearman's rho, 0.087; $p=0.115$). The optic disc area was positively correlated with axial length (Spearman's rho, 0.236; $P<0.001$).

Optic disc area was (Spearman's rho, -0.044 ; $P=0.275$) independent of anterior chamber depth, but was positively correlated with the average keratometric power in millimetres (Spearman's rho, 0.349 ; $P<0.001$). Men (average keratometry value, 7.83mm) had significantly greater ($P=0.037$) values for keratometry than women (average keratometry value, 7.61mm). Optic disc area was positively correlated with refractive error, (Spearman's correlation rho, 0.107 ; $P=0.01$), as was axial length (Spearman's correlation rho, -0.571 ; $P<0.001$). There was no significant association between intraocular pressure and optic disc area (Spearman's rho, -0.04 ; $P=0.324$).

Disc area was positively correlated with height (Spearman's rho, 0.197 ; $P<0.001$).

Axial length and height were strongly correlated (Spearman's correlation rho, 0.311 ; $P<0.001$). Corneal thickness was not significantly associated with disc area (Spearman's correlation rho, -0.041 ; $P=0.309$). Corneal thickness was positively correlated with axial length (Pearson's r , 0.120 ; $P=0.003$).

3.3.2.3 Cup/disc ratio

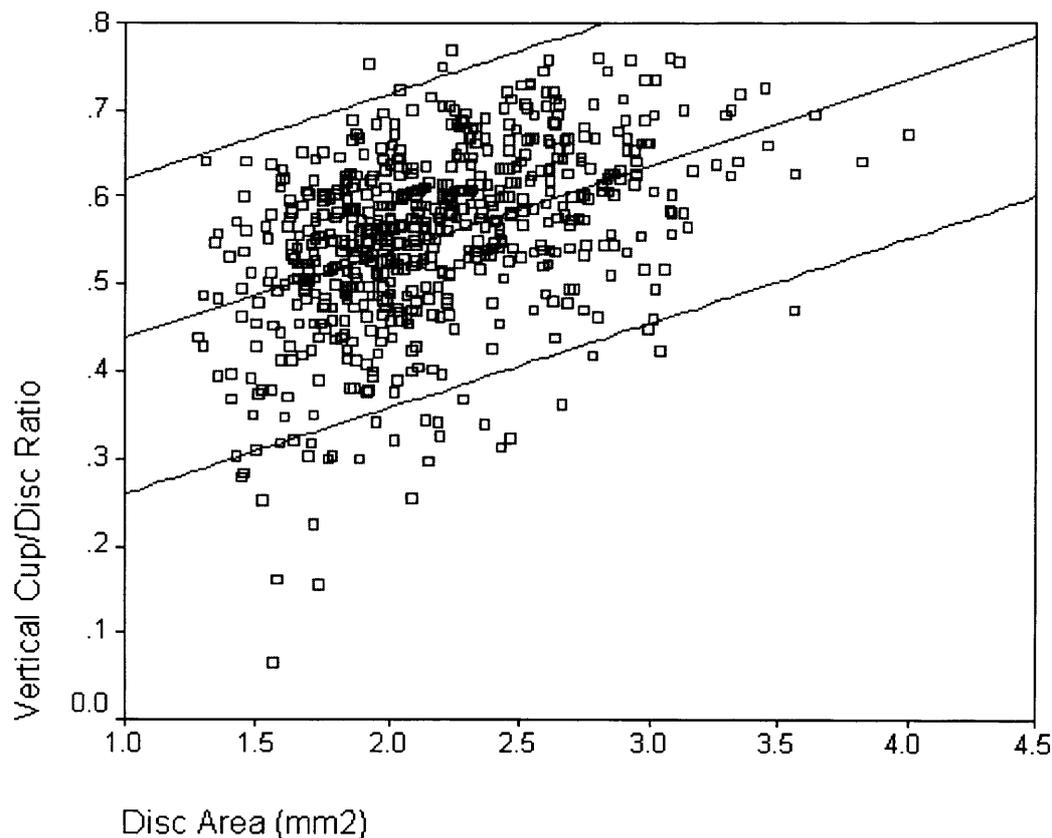
Vertical cup/disc ratio was measured planimetrically along the longest axis of the optic disc. The mean vertical cup/disc ratio for each of the ten-year age groups is given in Table 3.23. There was a significant increase (Pearson's $r = 0.154$; $P<0.001$) in vertical cup-disc ratio with age. The relationship between vertical cup-disc ratio and disc area is illustrated in Figure 3.27.

Table 3.23 Vertical cup/disc ratio for optic discs of the right eye in each of the ten-year age groups in the Singapore study (Subgroup A dataset).

Age (years)	Number of eyes	Mean Vertical cup/disc ratio
40-49	253	0.53
50-59	268	0.56
60-69	249	0.57
70+	159	0.57

Vertical cup-disc ratio was not significantly correlated with intraocular pressure (Group A: Spearman's correlation rho, 0.053; P=0.107; Subgroup B: Spearman's correlation rho, 0.065; P=0.107), nor with neural rim area-disc ratio (Group A: Spearman's correlation rho, -0.056; P=0.086; Subgroup B: Spearman's correlation rho, -0.077; P=0.055) for either dataset. Cup diameter was not significantly correlated with intraocular pressure (Group A: Spearman's correlation rho, 0.003; P=0.925; Subgroup B: Spearman's correlation rho, 0.022; P=0.585).

Figure 3.26. Relationship between vertical cup/disc ratio and disc area (622 right eyes from the 'hypernormal' subgroup of the Tanjong Pagar Singapore survey). The 5th, 50th and 95th percentiles are given for the regression line.



3.3.2.4 Neuroretinal Rim Area

The mean area of the neuroretinal rim was 1.43 mm^2 (SD, 0.29). It showed an interindividual variability of 1:4.0. Rather than observing a normal distribution, the distribution of total neuroretinal rim area was right-skewed (Figure 3.27). It was significantly and positively correlated with the size of the optic disc (Figure 3.28; Spearman's rho, 0.624; $P < 0.001$; equation of regression line: Rim area = $0.4083 [\text{Disc area}] + 0.5456$) but not significantly correlated with cup area (Spearman's rho, 0.036; $P = 0.367$).

Figure 3.27 Distribution of neuroretinal rim area of 622 right eyes from the 'hypernormal' subgroup of the Tanjong Pagar Singapore survey.

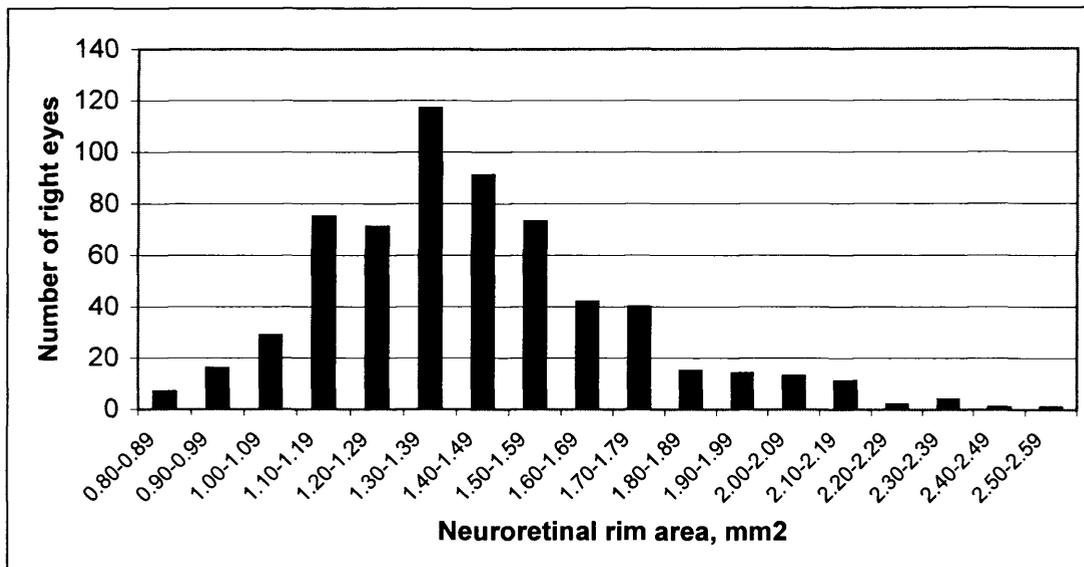


Figure 3.28 Graph showing the correlation between neuroretinal rim area and disc area in Singaporeans ('hypernormal' subjects). The 5th, 50th and 95th percentiles of the regression line are given (the equation for the regression line: $y=0.4083x + 0.5456$; $R^2=0.4311$).

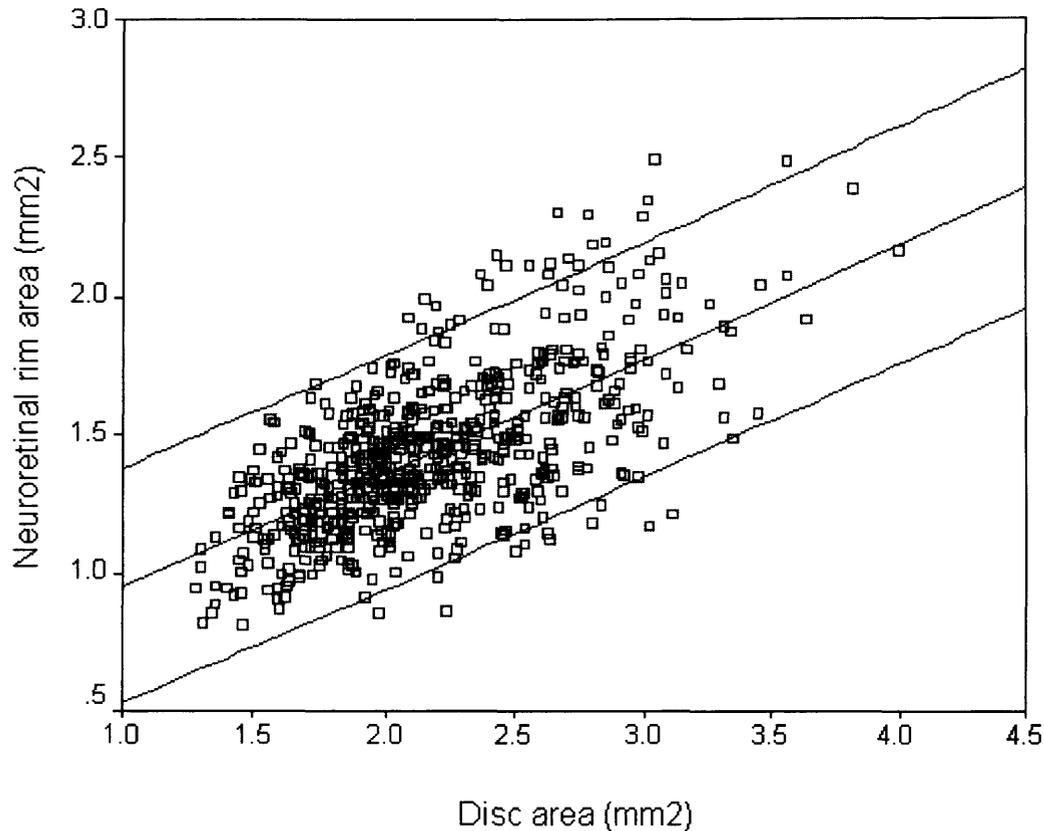


Figure 3.29 presents the relationship of neuroretinal rim area with selected variables. Due to the right-skewed distribution of neuroretinal rim area, it was logarithmically transformed. The rim size was statistically independent of age (Spearman's rho, -0.041; $P=0.308$), sex ($P=0.192$), and anterior chamber depth (Spearman's rho, 0.047; $P=0.239$). Men had significantly ($P<0.001$) larger neuroretinal rim areas (mean, 1.48 (SD:0.28)) than women (mean, 1.39 (SD:0.28)). Neuroretinal rim area was positively correlated with height (Spearman's rho, 0.217; $P<0.001$).

Figure 3.29 The relationship of neuroretinal rim area on a **log scale** with selected variables (i. Age; ii. Height; iii. Axial length; iv. Anterior chamber depth; v. Refractive error; vi. Keratometry; vii. Lens thickness; viii. Corneal thickness; ix. Intraocular pressure). Singapore study 'hypernormal' dataset (n=622). Regression lines have been added with the regression equation presented.

Figure 3.29i The relationship of log neuroretinal rim area with age.

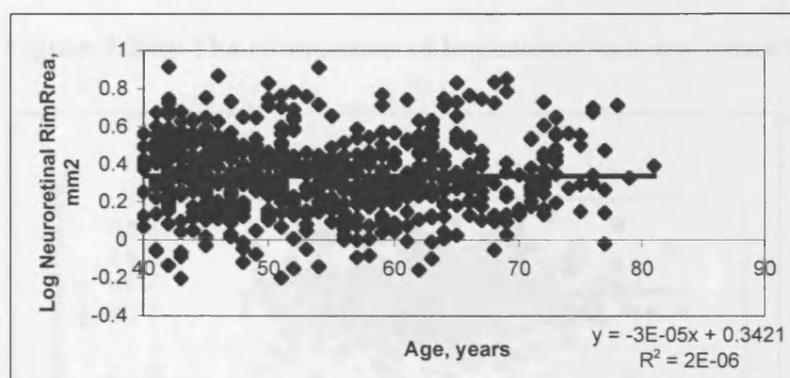


Figure 3.29ii The relationship of log neuroretinal rim area with height.

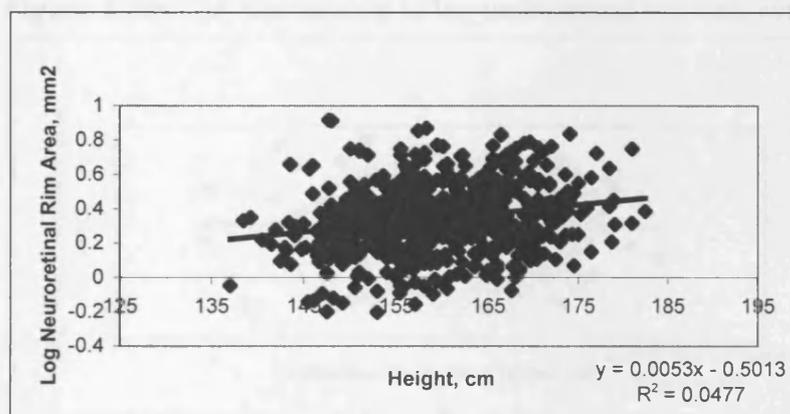


Figure 3.29iii The relationship of log neuroretinal rim area with axial length.

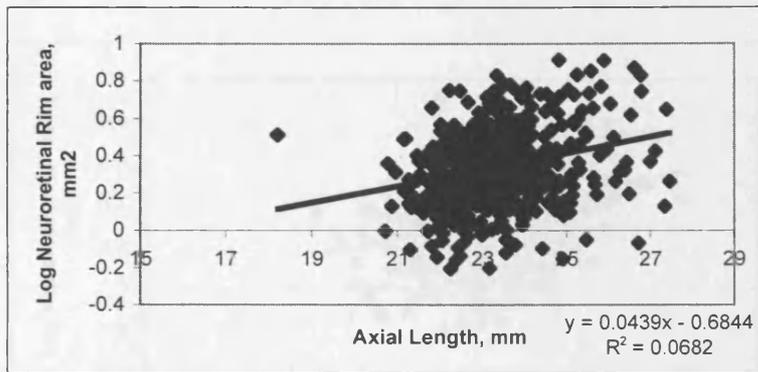


Figure 3.29iv The relationship of log neuroretinal rim area with anterior chamber depth.

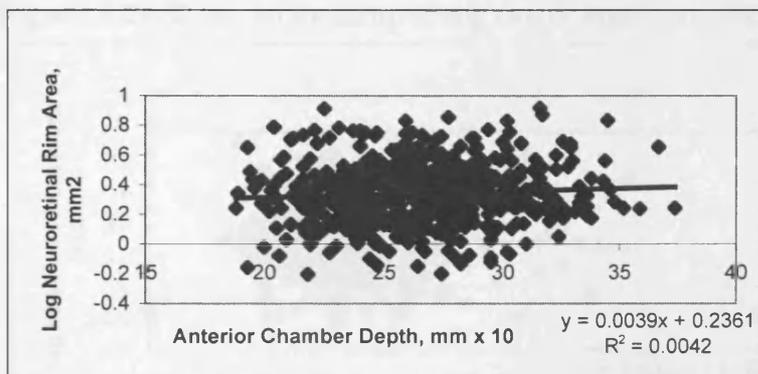


Figure 3.29v The relationship of log neuroretinal rim area with refractive error.

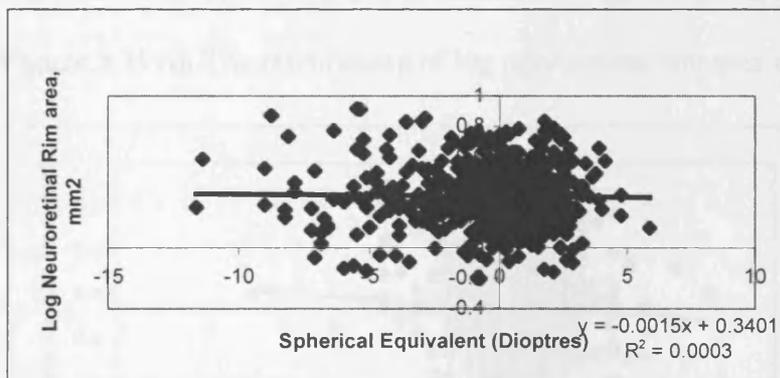


Figure 3.29vi The relationship of log neuroretinal rim area with keratometry.

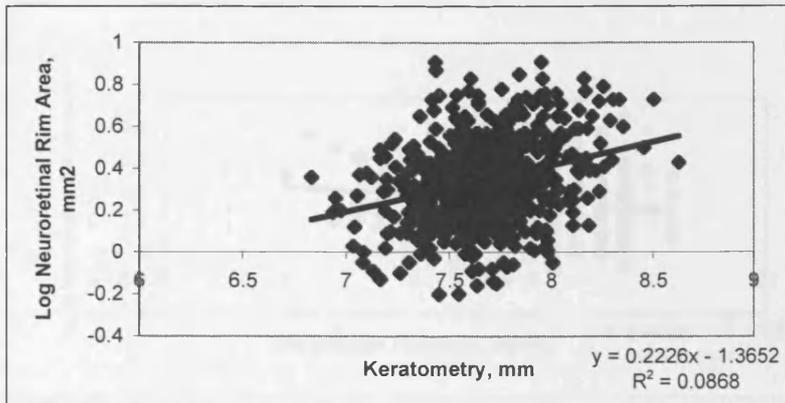


Figure 3.29vii The relationship of log neuroretinal rim area with lens thickness.

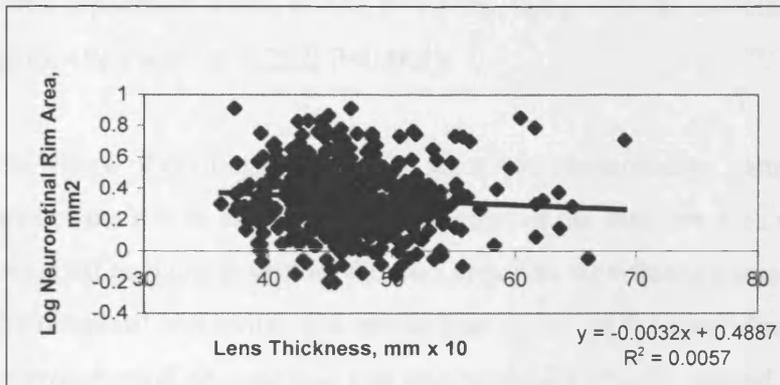


Figure 3.29viii The relationship of log neuroretinal rim area with corneal thickness.

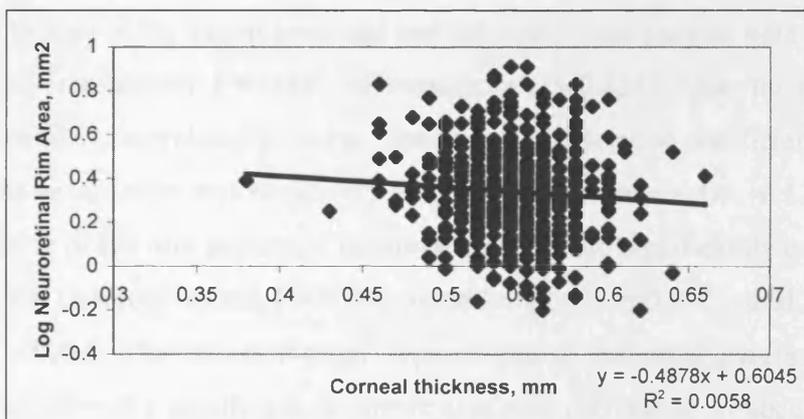
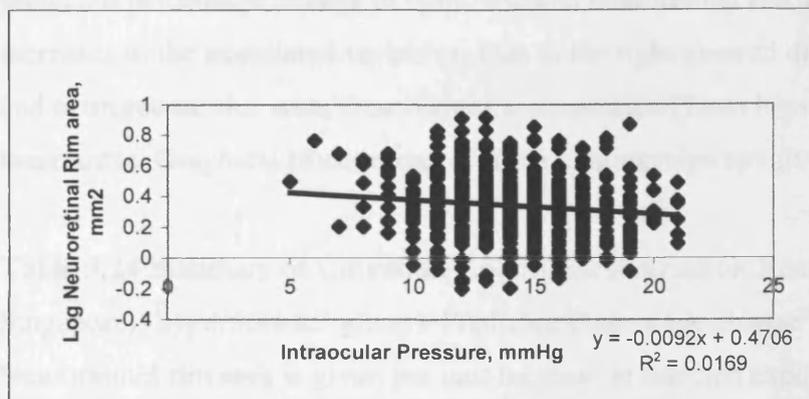


Figure 3.29ix The relationship of log neuroretinal rim area with intraocular pressure.



Neuroretinal rim area was not significantly correlated with spherical equivalent refractive error (Spearman's rho, 0.002; $P=0.965$), but positively correlated with axial length of the globe (Pearson's r , 0.252; $P<0.001$).

The shape of the neuroretinal rim showed a characteristic pattern. Considering the mean area of the rim in each of the four sectors of the disc, the area was smallest in the temporal horizontal sector. The rim area was significantly less (paired t test; $P<0.001$) in the temporal horizontal disc sector than in any of the other three disc sectors. The mean inferotemporal neuroretinal rim area was significantly (paired t test, $P=0.031$) smaller (0.36mm^2) than the superotemporal rim area (0.37mm^2).

The area of the superotemporal and inferotemporal sectors were independent of age (superotemporal, $P=0.466$; inferotemporal, $P=0.435$), while the temporal sector area was positively correlated with age (Spearman's correlation coefficient, 0.135; $P=0.001$), while the nasal sector was negatively correlated (Spearman's rho, -0.123; $P=0.002$).

None of the four sectors of neuroretinal rim were significantly correlated with refractive error (inferotemporal, $P=0.054$; superotemporal, $P=0.690$; nasal, $P=0.073$; temporal, $P=0.054$). The inferotemporal, superotemporal and nasal quadrants of the neuroretinal rim showed a significant decline in area with increasing intraocular pressure (regression coefficients for each quadrant: inferotemporal, -3.59×10^{-3} , $P=0.006$; superotemporal, -2.36×10^{-3} , $P=0.046$; nasal, -6.39×10^{-3} , $P=0.003$; temporal, -1.41×10^{-3} , $P=0.081$).

The results of these univariate regression analyses are summarised in Table 3.24, where predicted percentage change in optic disc and neuroretinal rim area are given for unit increases in the associated variables. Due to the right-skewed distributions of disc area and neuroretinal rim area, these values were obtained from logarithmic transformation of these areas. Graphical illustrations of these relationships are given in Figure 3.29.

Table 3.24 Summary of Univariate Log Linear Regression Analysis (Tanjong Pagar, Singapore; ‘hypernormal’ group). Predicted Percentage change in Optic Disc Area and Neuroretinal rim area is given per unit increase in selected explanatory variables.

Explanatory Variable	Predicted Change in Optic Disc Parameter for stated increase			
	Optic Disc Area, n=622*		Neuroretinal Rim Area, n=622*	
	% (95% CI's)	Adjusted R ²	%	AdjustedR ²
1-mm increase in axial length	3.72 (2.22, 5.23)	0.04	4.49 (3.15, 5.86)	0.067
1-D increase in ocular refraction	0.00 (0.00, 1.41)	0.005	-0.15 (- 0.80, 0.50)	-0.001
0.1mm increase in ACD	0.32 (- 0.80, 0.20)	0.001	0.39 (- 0.10, 0.90)	0.003
0.1mm increase in LT	-0.11 (- 0.50, 0.30)	-0.001	-0.32 (- 0.70, 0.00)	0.004
0.1mm increase in keratometry	3.15 (2.53, 3.77)	0.149	2.22 (1.71, 2.84)	0.085
1-year increase in age	0.29 (0.10, 0.50)	0.016	0.00 (- 0.20, 0.20)	-0.002
1-cm increase in height	0.47 (0.30, 0.70)	0.032	0.53 (0.30, 0.70)	0.046
1-mm increase in intraocular pressure	0.37 (- 1.00, 0.20)	0.001	-0.92 (- 1.51, - 0.40)	0.015
0.1mm increase in corneal thickness	-4.27 (- 10.07, 1.21)	0.002	-5.00 (- 10.41, 0.20)	0.004

* Values for axial length were missing for 21 subjects, anterior chamber depth in 2 subjects, lens thickness in 22 subjects.

3.3.2.4 Associations of optic disc parameters and systemic disease

Associations between neuroretinal rim area and various systemic diseases were investigated among the dataset for Group A (all with planimetric data) and Subgroup B ('hypernormal' dataset). Total disc area was unrelated to diabetes (Group A: Spearman's rho, -0.017, $P=0.608$; Subgroup B: Spearman's rho, 0.040; $P=0.321$), myocardial infarction (Group A: Spearman's rho, 0.062, $P=0.059$; Subgroup B: Spearman's rho, 0.009; $P=0.824$), or stroke (Group A: Spearman's rho, 0.039, $P=0.237$; Subgroup B: Spearman's rho, -0.016; $P=0.693$). However, disc area was inversely associated with a history of migraine in Group A (Spearman's rho, -0.075, $P=0.022$) but not in Subgroup B (Spearman's rho, -0.034; $P=0.391$).

Total disc area was positively correlated with systolic blood pressure (Group A: Spearman's rho, 0.080, $P=0.015$; Subgroup B: Spearman's rho, 0.087; $P=0.030$) but unrelated to diastolic blood pressure (Group A: Spearman's rho, 0.034, $P=0.296$; Subgroup B: Spearman's rho, 0.030; $P=0.454$).

Neuroretinal rim area was not significantly associated with systolic (Group A: Spearman's rho, 0.016, $P=0.617$; Subgroup B: Spearman's rho, 0.016, $P=0.617$) nor diastolic blood pressure (Group A: Spearman's rho, -0.011, $P=0.744$; Subgroup B: Spearman's rho, -0.011, $P=0.714$). In addition there was no significant relationship with diabetes mellitus (Group A: Spearman's rho, -0.025, $P=0.443$; Subgroup B: Spearman's rho, 0.066; $P=0.102$), a history of myocardial infarction (Group A: Spearman's rho, 0.043, $P=0.189$; Subgroup B: Spearman's rho, 0.019; $P=0.635$) or stroke (Group A: Spearman's rho, 0.006, $P=0.850$; Subgroup B: Spearman's rho, 0.015; $P=0.707$). A significant and negative correlation between neuroretinal rim area and a history of migraine was found in Group A (Spearman's rho, -0.076, $P=0.020$).

The mean neuroretinal rim area among the 17 subjects in Group A who gave a history of migraine (mean: 1.26mm^2 , SD: 0.22mm^2) was significantly ($P=0.007$) lower than in that among the 911 subjects with no history of migraine (mean: 1.42mm^2 , SD: 0.29mm^2). The difference was not significant at the 95% level for Subgroup B ($P=0.077$).

To test the relationship between neuroretinal rim area and history of migraine, an adjustment was made for the effect of disc area (which had been found to be negatively correlated with a history of migraine). Adjustment for disc area resulted in a lack of

association between history of migraine and neuroretinal rim area (Group A: Beta coefficient, 0.409, P=0.193).

3.3.2.5 Multiple variable analysis

The relationship between disc area and axial length was tested while adjusting for the effect of height using multiple variable regression analysis. The relationship between disc area and height was also tested while adjusting for the effect of axial length. This was also performed for neuroretinal rim area. The results are summarized in Table 3.25. In the case of disc area the positive association between disc area and axial length remains significant when the association with height is taken into account and vice versa. Similar findings were observed for neuroretinal rim area.

Table 3.25 Multiple variable regression analysis of log disc area, log neuroretinal rim area, axial length and height (Singapore subjects, Subgroup B).

	Beta coefficient	Significance (P)
Log Disc Area		
Axial Length	0.0292	<0.001
Height	0.0038	<0.001
Log Neuroretinal Rim Area		
Axial Length	0.0364	<0.001
Height	0.0039	<0.001

The relationships of optic disc area and neuroretinal rim area with several more variables are given in Tables 3.26 and 3.27, respectively, following a multiple variable regression analysis. The results are presented using the two datasets (Group A and subgroup B).

Table 3.26 Multiple variable regression analysis of the logarithm of optic disc area with selected biometric and demographic variables. Singapore subjects.

	Subgroup	Beta coefficient	Standard Error	Standardized coefficient	t	Significance (P)
Axial Length (mm)	A	0.0345	0.006	0.192	5.67	<0.001
	B	0.0319	0.007	0.179	4.35	<0.001
Intraocular Pressure (mmHg)	A	-0.0053	0.002	-0.087	-2.66	0.008
	B	-0.0033	0.003	-0.045	-1.13	0.259
Height (cm)	A	0.0021	0.001	0.084	1.77	0.076
	B	0.0027	0.001	0.105	1.88	0.061
Age (years)	A	0.0036	0.001	0.184	5.36	<0.001
	B	0.0035	0.001	0.161	3.96	<0.001
History of Migraine	A	-0.0653	0.050	-0.042	-1.290	0.196
	B	-0.0045	0.063	-0.003	-0.072	0.943
Sex	A	-0.0344	0.019	-0.082	-1.771	0.077
	B	-0.0301	0.023	-0.073	-1.32	0.187

Table 3.27 Multiple variable regression analysis of the logarithm of neuroretinal area with selected biometric and demographic variables. Singapore subjects.

	Subgroup	Beta coefficient	Standard Error	Standardized coefficient	t	Significance (P)
Axial Length (mm)	A	0.0337	0.006	0.197	5.788	<0.001
	B	0.0362	0.007	0.215	5.28	<0.001
Intraocular Pressure (mmHg)	A	-0.0084	0.002	-0.144	-4.41	<0.001
	B	-0.0078	0.003	-0.111	-2.84	0.005
Height (cm)	A	0.003	0.001	0.125	2.641	0.008
	B	0.0034	0.001	0.141	2.541	0.011
Age (years)	A	0.0018	0.001	0.098	2.832	0.005
	B	0.0011	0.001	0.054	1.341	0.180
History of Migraine	A	-0.0649	0.048	-0.044	-1.346	0.179
	B	-0.040	0.059	-0.026	-0.679	0.497
Sex	A	-0.0085	0.019	-0.021	-0.458	0.647
	B	-0.0077	0.021	-0.020	-0.361	0.718

Following adjustment using the variables axial length, intraocular pressure, height, age, history of migraine and sex, disc area was significantly and positively associated with axial length and age. There was also a negative association with intraocular pressure found in Subgroup A, which was not significant when the 'hypernormal' Subgroup B was analysed. Neuroretinal rim area was also significantly and positively associated with axial length and also with height. In addition, there was a significant negative association of neuroretinal rim area with intraocular pressure. An association with age was found in Subgroup A, which was not significant when the 'hypernormal' Subgroup B was analysed. The observation in Subgroup A of a positive association of rim area with age was most probably due to the effect of disc area with age in this study. The inclusion of disc area in the multiple variable analysis, was found to render the observed change in neuroretinal rim area with age insignificant (Beta coefficient, -0.0002, P-0.728).

3.4 Rom Klao and Tanjong Pagar surveys: optic disc parameter results adjusted for an alternative magnification correction factor

One of the objectives of this research was to compare the absolute values of optic disc parameters of the Thai and Singapore datasets with two other population-based planimetric studies, the Rotterdam Study (Ramrattan, Wolfs et al. 1999) and the Vellore Eye Study (Jonas, Thomas et al. 2003). These two other studies corrected disc measurements for magnification by the eye and camera system using Littmann's correction factor calculated from spherical refractive equivalents and keratometry data (Littmann 1988). The collection of additional biometric data, in particular axial length, lends more accuracy to the absolute values obtained from the Thai and Singapore studies (Garway-Heath, Rudnicka et al. 1998), hence the use of the axial length method of Bennett (Bennett, Rudnicka et al. 1994) with these datasets. In order to compare absolute values of optic disc parameters between these studies, the values obtained from the Thai and Singapore subjects were recalculated using the Littmann correction factor calculated from spherical refractive equivalents and keratometry data alone. The results of this recalculation are given in Table 3.28 for Subgroup B of the Thai and Singapore datasets.

Table 3.28 Optic disc measurements (mean, median, 97.5th percentiles and ranges) for Subgroup B of the Thai and Singapore datasets following recalculation using the Littmann magnification correction factor calculated from spherical refractive equivalents and keratometry data alone.

Optic Disc Parameter	Thailand [n=292] [mean; median +/- SEM (97.5 th ; range)]	Singapore [n=622] [mean; median +/- SEM (97.5 th ; range)]
Disc Area (mm ²)	2.53; 2.47 +/- 0.0338 (3.86; 1.40-4.69)	2.53; 2.47 +/- 0.0253 (3.66; 1.25-4.61)
Neuroretinal Rim Area (mm ²)	1.51; 1.49 +/- 0.0254 (2.43; 0.12-2.99)	1.67; 1.64 +/- 0.0131 (2.45; 0.75-3.23)
Cup Area (mm ²)	1.03; 0.97 +/- 0.0241 (2.01; 0.08-2.68)	0.86; 0.82 +/- 0.0159 (1.74; 0.01-2.43)

97.5th= the value of the 97.5th percentile; SEM= standard error of the mean

Chapter 4. Discussion

4.1 Study design and subject demographics

Both the Rom Klao survey in Thailand and the Tanjong Pagar survey of Singapore were based in the population rather than in a hospital or clinic scenario. This gives a truer reflection of the distribution of normality and pattern of disease in the population than in clinic or hospital-based studies where the subjects are a selected group and therefore data from such studies is subject to bias.

The sampling strategy for the Thai survey was purposive, involving review of all eligible individuals within an urban settlement, who had been previously enumerated for a medical study prior to the glaucoma survey. The lower age limit was therefore set as 50 years of age, as this was the lower age limit chosen by the medical study previously. The strategy for the Singapore survey involved a disproportionate, stratified, clustered, random-sampling procedure that selected 2000 subjects aged 40 to 79 years from the electoral register of Tanjong Pagar district. Both Rom Klao and Tanjong Pagar were considered representative of urban Thailand and Singapore, respectively with respect to demographic and socioeconomic characteristics. The number of subjects examined by the Singapore survey (1090 subjects) was considerably larger than that of the Thai survey (701 subjects), and this was reflected in the numbers of subjects within the datasets prepared for planimetric analysis (Subgroup A: Singapore, 929 right eyes; Thailand, 470 subjects).

Selection of datasets for planimetric analysis was performed in the same manner for both the Thai and Singapore studies. For each study, two planimetric datasets were prepared. The first was a group (Group A) that included all subjects for whom planimetric measurements were obtained, but excluded those with poor quality images, those who had been previously diagnosed with glaucoma and those who had had cataract surgery, and those for whom no refractive error data was available. The second group (subgroup B) was a 'hypernormal' group in which those with abnormal visual fields, occludable angles or an abnormally high intraocular pressure were additionally excluded. Importantly, optic disc characteristics were not used in the definition of a 'hypernormal'

group, as this would likely have introduced bias. The subject selection for planimetric analysis was based on that used in the Rotterdam Study (Ramrattan, Wolfs et al. 1999). However, the Rotterdam Study excluded subjects who were found by the study to have open-angle glaucoma in at least one eye, while the Thai and Singapore planimetry selection process excluded those with a previous diagnosis of glaucoma only. As the definition of glaucoma used in the Rotterdam glaucoma survey is actually based on optic disc characteristics, the approach used for the Thai and Singapore studies is less likely to introduce bias than the Rotterdam Study (Ramrattan, Wolfs et al. 1999). Other studies have attempted to describe optic disc morphology in the 'normal' population (Jonas, Thomas et al. 2003) (Varma, Tielsch et al. 1994) (Rudnicka AR 2001) (Kashiwagi K 2000) by including those who had been previously diagnosed as normal on the basis of visual field and optic disc characteristics, thereby potentially introducing bias. The numbers of subjects in the 'hypernormal' datasets (Subgroup B: Thailand, 292 subjects; Singapore, 622 subjects), were considerably smaller than the datasets that included all those with planimetry (Group A: Thailand, 470 subjects; Singapore, 929 subjects), therefore both subgroups were analysed. It is possible that in the formation of the 'normal' subsets for the Thai and Singapore studies, some subjects with early glaucoma may have been included, due to pre-perimetric disease or due to false negative results from the visual field testing.

The average age of those subjects selected for planimetric analysis (Group A) was younger than in the overall surveys both for the Thai and Singapore studies. This is probably due to increased media opacity in older age groups (resulting in a poor quality optic disc image), and the tendency for those with previously diagnosed glaucoma or with operated cataract to be older. However, mean intraocular pressure, axial length, height were no different between the groups in either study.

In both studies, the planimetric group (Group A) was divided into two subgroups, the glaucoma suspects and 'hypernormals' (subgroup B). Both the Thai and Singapore studies found the glaucoma suspects to be older than the 'hypernormal' subjects. This is unsurprising in that older subjects are more likely to have visual field defects either due

to glaucoma or other ocular pathology. In addition, occludable angles are more common in older age groups due to the shallowing of the anterior chamber with increasing age (Arkell, Lightman et al. 1987) (Bourne, Sorensen et al. 2001). The final exclusion criterion of 'ocular hypertension' is also more common with increased age (Jonasson, Damji et al. 2003) (Bourne 2003). Indeed, IOP was higher among the glaucoma suspects in the Singapore study, but the Thai study reported no statistical difference. Both studies also found that glaucoma suspects had shorter axial lengths and shorter height than the hypernormal group. This can be partly explained by the fact that older subjects were shorter. Occludable angles are also more common in people of shorter stature, who will also have smaller anterior segments (Wong, Foster et al. 2001).

The 'glaucoma suspects' were also compared with the 'hypernormals' in terms of optic disc parameters, for both studies. Neither study found a difference between these groups in terms of mean disc area, disc diameter, or total rim area. The Thai study found smaller cup areas and cup/disc area ratios in the glaucoma suspects which was unexpected, while the Singapore study did not find such a difference. The Singapore study also found a smaller nasal rim area in the glaucoma suspects unlike the Thai study which found no sectoral rim differences.

Unfortunately, due to a technical difficulty, the number of subjects who had HRT-II images was limited to 143 subjects. Eighty-two right eyes were subsequently selected as a 'normal' subgroup. Although the number of eyes is considerably smaller than the number of eyes in the 'hypernormal' datasets used for planimetry, the number is comparable to numbers used in other studies of optic disc morphology using confocal laser scanning tomography (Vellore Eye Study (Jonas, Thomas et al. 2003), 70 subjects; Japan (Kashiwagi K 2000), 92 eyes).

4.2 Statistical analysis

Right eyes were analysed in the planimetric analysis of both Thai and Singapore studies. Other studies have also used right eyes only (Kashiwagi K 2000). An alternative approach would have been to use data from both right and left eyes and then to subsequently correct for correlation between the eyes (Varma, Tielsch et al. 1994) (Ramrattan, Wolfs et al. 1999). The latter approach has been described as more efficient, some claiming that it offers greater precision (Glynn and Rosner 1992). The approach to this is controversial, and indeed some studies do not give details on how an eye was chosen for analysis (Jonas, Thomas et al. 2003) (Rudnicka AR 2001). Inter-eye correlation was calculated in the HRT-II Thai analysis (71 pairs of eyes) and this showed no significant inter-eye differences in terms of disc, cup or rim area (interocular differences were found for retinal nerve fibre layer thickness and rim volume measurements with the HRT-II).

Planimetric analysis revealed the distributions of disc area and neuroretinal rim area to be right-skewed in both the Thailand and Singapore studies. For this reason, the median was given in addition to the mean as a measure of central tendency, a non-parametric test was used to describe correlation (Spearman's rho), and the logarithm of disc area and neuroretinal rim area was used for subsequent univariate and multiple variable regression analyses. Other studies (Rudnicka AR 2001) have used log transformation of the optic disc parameters to stabilize the variance before performing any linear regression, while others who have noted a right-skewed distribution of disc area (Ramrattan, Wolfs et al. 1999) and neuroretinal rim area (Jonas, Thomas et al. 2003), have not. These latter studies have also used parametric tests despite reporting that the optic disc parameters were not normally distributed. A small study of 57 subjects involving the HRT by Kergoat (Kergoat H 2001) reported that the optic nerve head parameters were normally distributed.

4.3 Techniques used for optic disc assessment

The use of several different techniques of optic disc assessment in the Thailand study permitted comparison of the optic disc measurements recorded by these techniques. The software used for planimetric analysis had not been used before, and therefore inter- and intraobserver studies were performed to evaluate this technique. This was also the first occasion in which the HRT-II had been used in a population-based study, hence there was considerable interest in its practical use. The findings of each of these substudies are summarised below with reference to the ophthalmic literature.

4.3.1 A comparison of cup/disc ratio measurements using direct ophthalmoscopy with and without mydriasis, and indirect ophthalmoscopy with mydriasis

This study suggested that pupillary mydriasis significantly improves the examination of the optic disc in the setting of a field survey. In this cohort of older people with a relatively high prevalence of media opacity, only 74% were considered able to be accurately examined by direct ophthalmoscopy without a dilated pupil examination. Following mydriasis, 94% could be examined in this way. Agreement between direct ophthalmoscopy and stereo biomicroscopy was significantly improved by performing the examination through a dilated pupil. There was no overall evidence of systematic measurement bias in this study, but cup/disc ratio value measurements using stereo biomicroscopy were larger than for direct ophthalmoscopy (with and without mydriasis) for small cup/disc ratio values and the converse was true for large cup/disc ratio values. For a field survey, an important consideration is the sensitivity of an examination to detect suspicious cases, which could then be further investigated. One could use the 97.5th percentile of the normal distribution as a 'cut-off' between a 'normal' and 'abnormal' cup/disc ratio (Foster PJ 2001). The choice of where to place this 'cut-off' is arbitrary and partially flawed by the fact that there is overlap between the range of CDR in those with and without glaucomatous visual field loss. The use of the 97.5th percentile also avoids making the assumption that CDR is normally distributed. In this setting, the sensitivity of the non-mydriatic examination to detect a given 97.5th percentile cup/disc ratio value (0.745 in this population) was 75% and that of the mydriatic examination 100%.

Corresponding specificities were 94% and 96%. However, for a more stringent degree of cupping this difference in sensitivities may well be considerably less.

Possible bias was minimised as the examiner was not aware of the previous findings when performing each examination. As large numbers of subjects were examined over a relatively short period of time, the chance of the examiner remembering individual findings was likely to be small.

A previous, clinic-based study (Kirwan, Gouws et al. 2000) reported that mydriasis markedly improved inter-observer agreement using stereo biomicroscopy. In that study, the 95% limits of agreement were reduced by half with mydriasis. In the Thai study, stereo biomicroscopy with mydriasis was used as a 'gold standard' and agreement between tests, but by the same examiner, was studied. Because the Thai study involved one examiner rather than multiple examiners (as in the study by Kirwan et al), the difference in the 95% limits of agreement with non-mydriatic and mydriatic direct ophthalmoscopy was likely to be less striking and indeed this was the case.

A mydriatic examination may have significant implications for population-based glaucoma studies as subjects have to remain at the survey site for a second examination and the sequence and timing of the examination process needs to be carefully organised. In populations with a high prevalence of occludable angles, the rare (Patel, Javitt et al. 1995) possibility of iatrogenic angle closure also needs to be considered. These data should be useful for those planning surveys when choosing the most appropriate option.

4.3.2 Inter& intraobserver studies with the Planimetry and the HRT II

4.3.2.1 Planimetry.

Intraobserver agreement for measurements of disc and cup area using planimetry showed some systematic bias, yet the differences between test and retest measurements were so small as to be clinically irrelevant.

There was relatively close agreement between observers who differed in their experience with this planimetric system. There was also no apparent systematic bias in agreement across the range of disc areas nor cup areas. The 95% limits of agreement for disc area were relatively close and were similar for each pairing of observers. However, the 95% limits of agreement for cup area were wider than measurements of optic disc area, which

is unsurprising in that it is widely accepted that drawing around the optic cup edge is subject to more variability than the disc edge. The expertise of the observers is obviously an important consideration when assessing agreement of measures and studies that compare the findings of inexperienced observers with experts such as ophthalmologists with a speciality interest in glaucoma. Such inter-observer studies provide useful data, particularly if one is planning to use a technique in a population-based setting, where it may not be feasible to obtain a disc measurement from a glaucoma expert.

4.3.2.2 Heidelberg Retina Tomograph -II.

The manual tracing of a contour line along the disc margin introduces a potential source of variability that may negatively affect the result of the examination. In addition, several observers may be involved in the process of image acquisition and processing which introduces another source of error. The agreement studies performed here were related to the drawing of the contour line rather than the image acquisition process. In terms of intraobserver agreement, there was little evidence of any association between agreement and size of the measure, for disc area, cup area or rim area. The 95% ranges of agreement were broadly similar although widest for cup area, then rim area and narrowest for disc area.

No systematic bias was seen in the inter-observer agreement study using the HRT-II. Because the differences between disc areas and cup areas measured by the two observers were not normally distributed, it was not possible to summarise with 95% levels of agreement. Generally there was good agreement between observers, but there were several outliers, which may have been a result of the small numbers of subjects involved in this agreement study.

There have been several studies published on the subject of reproducibility of measures with the HRT. Most of these have addressed intraobserver interimage reproducibility (Kruse, Burk et al. 1989) (Rohrschneider, Burk et al. 1993) (Janknecht and Funk 1994) (Azura-Blanco, Harris et al. 1998). Intraobserver intraimage and interimage reproducibility was evaluated by Orgul et al (Orgul, Croffi et al. 1997), who reported a wide range of values for the coefficient of variation of the repeated measures. Hatch et al (Hatch, Flanagan et al. 1999), reporting on interobserver reproducibility using the

intraimage assessment of a single original topography image, found a substantial to almost perfect agreement in the evaluation of intraclass correlation coefficient. Miglior et al (Miglior S 2002) confirmed the findings of several of these studies and emphasised that the greatest source of variability in the HRT examination was the image acquisition process.

Garway-Heath et al (Garway-Heath, Poinoosawmy et al. 1999) compared intra-observer variability between a planimetric technique with similar characteristics (software: DISC-DATA, Thot Informatique) to that used in the Thai and Singapore studies and the HRT. Using planimetry, they reported that interobserver agreement was dependent on observer experience, while for the HRT it was independent. They reported inter-observer agreement for optic disc area (standard deviation of differences as a percentage of the median) as 4.0% to 7.2% for planimetry and 3.3% to 6.0% for the HRT, while for the neuroretinal rim area it was 10.8% to 21.0% (planimetry) and 5.2% to 9.6% (HRT). The combined effects of optic disc edge and cup edge estimates involved in planimetric analysis (Tielsch, Katz et al. 1988) causes much greater variability in the measurement of neuroretinal rim area, compared with the HRT. However, even with the improved agreement found with the HRT, the variation in disc margin definition, together with the subsequent variation in reference height and cup definition, leads to a variation in rim area estimation which may be clinically significant in cross sectional (diagnostic) studies (Garway-Heath, Poinoosawmy et al. 1999).

4.3.3 Comparison of cup/disc ratio measurement between clinical biomicroscopy with graticule, planimetry using photographs and confocal laser scanning tomography (HRT II)

Measurements of vertical cup/disc ratio were compared between clinical biomicroscopy with graticule, planimetry using photographs and the HRT-II. Each of these techniques measure vertical cup/disc ratio differently. The clinical biomicroscopy involved measurement of the vertical disc diameter and the vertical cup diameter along the vertical axis centred on the centre of the optic disc. The HRT chooses the geometric centre of the optic disc, as defined by the contour line marked by the observer performing the analysis. The planimetric measurement measured the cup/disc ratio along the longest axis of the

optic disc (personal communication, Garway-Heath). The Bland-Altman plot revealed systematic bias in the measurements with closer agreement between each of the techniques and the mean with increasing vertical cup/disc ratios. This may reflect the greater clarity of the cup edge when the cup edge of discs with larger cup/disc ratios are delineated. Measurements of vertical cup/disc ratio made by HRT-II were less than by planimetry or biomicroscopy, while planimetric measurements were significantly greater than those measured by biomicroscopy. The latter finding was also reinforced by the findings of the main study groups (Mean vertical cup/disc ratio: Singapore, 0.46 (biomicroscopy) and 0.55 (planimetry: Group A); Thailand, 0.43 (biomicroscopy) and 0.62 (planimetry: Group A)).

There was a suggestion of closer agreement of vertical cup/disc ratio between the HRT-II and biomicroscopy. This is most probably due to the fact that the axis on which the cup/disc ratio is measured is vertical, rather than using the long axis of the disc, in the case of the planimetric technique. Hrynychak et al (Hrynychak, Hutchings et al. 2003) compared cup/disc ratio evaluation using stereobiomicroscopy and digital imaging and reported that the percentage of cup/disc ratios that differed by ≥ 0.2 were between 5 and 25% of evaluations. These findings in addition to the findings from the Thai and Singapore studies, lead one to recommend caution when using clinical biomicroscopic, planimetric or HRT-II evaluations of cup/disc ratio interchangeably.

4.3.4 Comparison of measurements of optic disc parameters between confocal laser scanning tomography (HRT II) and planimetry of photographs

These graphs show that for disc area, the agreement between the two techniques appeared to weaken as the optic disc area increased. Systematic bias was less evident for neuroretinal rim area. The 95% limits of agreement for disc area and neuroretinal rim area were -0.813 to 0.367 mm^2 , and -0.303 to 1.011 mm^2 , respectively.

Comparing measurements made by the HRT-II with planimetric measurements using optic disc photographs revealed that the HRT-II measurements of total rim area and neural rim/disc area ratio were significantly larger than the planimetric measurements, while measurements of disc area were smaller with the HRT-II. This finding agrees with

a study by Jonas et al (Jonas, Mardin et al. 1998) involving 139 normal subjects. Their planimetric technique involved the Littmann correction for magnification. As explained above ('Results' section) this approach tended to yield larger measurements of disc and rim area than the planimetric approach used in the Thai and Singapore studies. Another study involving a smaller cohort of subjects also reported a similar relationship (Dichtl, Jonas et al. 1996).

Planimetric studies have demonstrated interocular differences in cup and disc diameter (Bengtsson 1980) and rim area (Jonas, Gusek et al. 1988). Performing HRT on 80 normal subjects over 50 years of age, Ghergel (Gherghel, Orgul et al. 2000) reported significant interocular differences of nerve fibre layer thickness and cross sectional area, with lower values in right eyes. A similar relationship was observed in our study. However, we found a significant interocular difference in rim volume unlike Ghergel. This may be a true interocular difference or alternatively may be a result of differences in reference plane determination.

The findings of this comparison between HRT-II and planimetry leads one to recommend that measures of disc area or rim area from each of these techniques should not be used interchangeably. Studies that report comparisons between these techniques should be interpreted with caution.

4.3.5 Practical aspects of using the HRT-II or photography and planimetry in a population-based setting

The Thailand study provided the first opportunity to use the HRT-II in a population-based glaucoma survey. From a practical point of view, the HRT-II has a number of advantages over other methods of optic disc assessment, such as photography or clinical biomicroscopy, when considering its use in a population-based situation. The machine is lightweight and portable, involves minimal training, is almost fully automated, and does not require the use of mydriatics to obtain good quality images.

In this study only 5 (1.74%) of 246 eyes could not be imaged, principally due to cataract. Most population-based glaucoma surveys have a minimum age in the region of 40 to 60 years of age. In these older age groups the prevalence of media opacity is greater than in

younger ages (Zangwill, Berry et al. 1999). Other studies have investigated the effect of image quality and cataract (Zangwill L 1997) (Janknecht P 1995). In this study, a reduction in image quality with increasing nuclear lens opacity was demonstrated. A mean standard deviation cut-off of 40 was used, above which images were judged insufficient quality for accurate parameter measurements. This is an arbitrary value, judged by the manufacturers to include images of 'acceptable' quality (personal communication; Gerhard Zinser, Heidelberg Engineering, Heidelberg, Germany). The percentage of eyes with mean standard deviation of 40 or more in the HRT-II survey was 0%, 6%, 14%, 53% and 60% for LOCS grades of nuclear opacity of 1, 2, 3, 4 and 5, respectively. If one extrapolates this to the parent glaucoma survey, of 1188 eyes where a LOCS grade of 1 to 5 was recorded, 259 eyes (22%) would be expected to have an MSD of 40 or more. Total time for image acquisition per patient was approximately 7 minutes. The acquisition of images can be carried out in the 'field' setting as in the Thai survey, with subsequent analysis carried out at a later date in a different location. The time taken for subsequent analysis of each disc, by drawing around the optic disc, should also be considered. During the Thai survey, approximately two minutes were required to access the image from archives and draw a contour line, using a photograph of the optic disc as a guide. The use of a photograph as a guide for the contour line adds to the accuracy of the drawing, yet requires a photograph to have been taken at the time of the original survey. Although the HRT-II instrument is designed to be almost completely automated, it does require considerable expertise when archiving the images afterwards. A lack of technical knowledge in this regard contributed to the smaller than expected number of subjects available for analysis during the Thai HRT-II study.

This study has demonstrated that the HRT-II can be used in a population-based setting. The characterization of the optic discs of a specific ethnic group in population-based studies is important to develop normative databases that can be used in both population and clinic-based settings.

The planimetric method involved taking photographs of the optic disc through a dilated pupil. Considerably more training is required for fundus photography than operation of the HRT-II. Dilation of the pupils of the subject for fundus photographs is also expensive in terms of time, although a non-mydratic camera could be used. Subsequent scanning of

the photographs and then drawing around the optic disc and the optic cup required trained individuals and took approximately 7 minutes per optic disc. In order to obtain accurate planimetric measurements, biometric variables such as anterior chamber depth, axial length and keratometry and refractive error also required measurement which placed both a time and financial burden on the survey.

The above observations need to be taken into account when considering which technique to use in the assessment of the optic disc in a population-based glaucoma survey. An important consideration is the question of which of the two methods may better reflect the degree of glaucomatous damage. Jonas et al (Jonas, Mardin et al. 1998) correlated rim measurements of both instruments (planimetry using a different technique and the original HRT instrument) with the mean visual field defect and with the visibility of the retinal nerve fibre layer. He reported significantly higher correlation coefficients for the planimetric rim determinations than for the measurements by the HRT. However, I would concur with the authors' note that 'one should not forget the many clinical and practical advantages offered by the HRT, such as the three dimensional assessment of the optic cup, the determination of the contour of the retinal nerve fibre layer in the parapapillary region, the high reproducibility, its probable superiority in follow up examinations, the fast availability of the results, and the fact that the HRT does not require full pupillary dilatation and that the HRT examination as a semiautomatic technique can partially be delegated to technicians'.

4.4 Characteristics of the optic disc in the two South-East Asian populations

4.4.1 Introduction

This chapter summarises the main findings of the two studies with respect to the relationship of the optic disc to demographic, biometric and systemic variables. Comparison is also made between the findings of these studies and the published literature on the subject. In comparing the results of the South-East Asian studies with others, caution must be exercised due to a number of factors that may differ between studies, such as study design, subject characteristics, optic disc measurement technique. Where possible, these differences are highlighted. Additional information relating to the design of the referenced studies may be found in Table 1.1 of the Introduction.

4.4.2 Age and optic disc parameters

Interestingly the Thai and Singapore studies found different results in terms of the relationship of age with disc area. The Thai study found no relationship for either sex using both planimetry and the HRT-II, while in the Singapore study, disc area was found to significantly increase with age but only in men. Multiple variable analysis (adjustment for the effects of sex, intraocular pressure, height and axial length) showed the disc area to increase significantly with age for both Singapore datasets (Group A and subgroup B). A recent study of normal elderly Canadian subjects (Kergoat H 2001) compared disc size in 27 elderly subjects (aged between 75 and 88 years) and a group of younger subjects (aged between 20 and 32 years). This cross-sectional comparison using the HRT found a 12% increase in disc area with senescence. Bengtsson (Bengtsson 1980) also reported an increase in disc area with age, but this may have been artefactual (Balazsi, Drance et al. 1984) relating to the method used to correct for ocular magnification (Bengtsson B 1977), with magnification of the disc image resulting from increased refractive power of lens in older age (Garway-Heath and Hitchings 1998). Rudnicka (Rudnicka AR 2001) reported a positive univariate association between disc area with age but also raised the important issue of confounding by axial length. In an exponential model of disc area the effect associated with age was greatly reduced and non-significant. The longer axial lengths of

men than women may partly explain the positive association between age and disc area in the Singapore study.

Several other studies have failed to disclose a relationship of disc size with age (Jonas, Gusek et al. 1988; Quigley, Brown et al. 1990; Tsai, Ritch et al. 1992; Garway-Heath and Hitchings 1998) (Gundersen, Heijl et al. 1998) (Britton, Drance et al. 1987) (Varma, Tielsch et al. 1994) (Ramrattan, Wolfs et al. 1999) (Jonas, Thomas et al. 2003).

The age-related enlargement of disc size in the study by Kergoat et al (Kergoat H 2001) was explained by a reduction of retina nerve fibre layer thickness, which was believed to move the outer border location radially outwards on both the inner and outer edges, thereby causing an increase in cup and disc area without a change in rim area with age.

Neither the Singapore nor the Thai studies found a significant relationship between neuroretinal rim area and age with their respective 'hypernormal' datasets (Subgroup B). The HRT-II Thai analysis also found no significant association. There was no significant relationship after adjustment was made for other selected variables (multiple variable analysis) in the Thai study (Group A and subgroup B) and Subgroup B of the Singapore study, while in the Singaporean Subgroup A, the neuroretinal rim area increased with age. This observation is most probably due to the effect of disc area with age in this study, as the addition of disc area in the multiple variable analysis, rendered the observed change in neuroretinal rim area with age insignificant.

The relationship of neuroretinal rim area with age is controversial. Neuroretinal rim area has variously been described as reducing with age (Schwartz, Reuling et al. 1975; Bengtsson 1976; Carpel and Engstrom 1981; Balazsi, Rootman et al. 1984; Tsai, Ritch et al. 1992; Garway-Heath, Wollstein et al. 1997) or remaining stable with age (Jonas, Gusek et al. 1988; Funk, Dieringer et al. 1989; Airaksinen, Tuulonen et al. 1992; Kee, Koo et al. 1997) (Ramrattan, Wolfs et al. 1999) (Jonas, Thomas et al. 2003) (Rudnicka AR 2001) (Kashiwagi K 2000) (Kergoat H 2001) (Varma, Tielsch et al. 1994). In terms of absolute numbers of nerve fibres rather than neuroretinal rim area, Jonas (Jonas, Muller-Bergh et al. 1990) estimated that 5426 optic nerve fibres are lost per year with advancing age (in a group of subjects aged 20 to 75 years), corresponding to approximately a 26% loss of retinal ganglion cell axons in a lifetime. Mikelberg (Mikelberg, Drance et al. 1989) estimated a decrease of 4000 to 12000 fibres per year.

Other studies have reported an age-related decline in retinal nerve fibre layer thickness (Kergoat H 2001) yet with no change in rim area with age.

In both the Thai and Singapore studies, it was possible to investigate the relationship of rim area with age for each of the four quadrants. While in the Thai study there remained no significant age-related change in rim area, in the Singapore study, the temporal sector area increased significantly with age while the nasal sector decreased. Few studies report age-related changes of different sectors of the neuroretinal rim. A study using confocal laser topography in normal Japanese subjects (Kashiwagi K 2000) found no change in rim area for each of the sectors nor the global area. Despite a review of the literature, no planimetric or histomorphometric explanation could be found to explain this difference between nasal and temporal rim area variation with age.

In terms of vertical cup/disc ratio the Thai and Singapore studies showed an increase in vertical cup/disc ratio with age. Other studies but of Caucasians have also reported a increase in vertical cup/disc ratio with age, Garway- Heath et al (Garway-Heath, Wollstein et al. 1997) reporting an increase of 0.1 between the ages of 30 and 70 years. The Thai and Singapore studies described herein have the advantage over other cross-sectional studies in that they were population-based, whereas the majority of the studies described above were clinic or hospital-based. An important consideration raised by Garway-Heath et al (Garway-Heath, Wollstein et al. 1997) when reporting a decline in neuroretinal rim area with age is the distinction between a loss of neuroretinal tissue with age or that subjects born more recently are born with more neuroretinal tissue (a cohort effect). To make this distinction, longitudinal studies are needed, but these studies require a very long time period between examinations to detect change. Garway-Heath et al (Garway-Heath, Wollstein et al. 1997) predicted that 18 years would be needed between examinations to detect a 5% change). Two longitudinal studies reported on this issue. Airaksinen et al (Airaksinen, Tuulonen et al. 1992) followed five normal subjects over a mean of 10 years. None showed a statistically significant decrease in neuroretinal rim area. Caprioli (Caprioli 1994) used a population-based study to compare photographs of 100 normal subjects taken 9-16 (mean 13) years apart. He reported mean change as 1.2%, which was less than the 1.8% mean change found in a control group of photograph pairs taken on the same day.

4.4.3 Correlation between disc parameters and biometric variables

Both the Thai and Singapore studies found a positive correlation between optic disc area and axial length. For a 1-mm increase in axial length, the Thai study found an 8.21% increase in optic disc area, and the Singapore study, an increase of 3.7%.

As would be expected from the relationship between disc area and neuroretinal rim area, neuroretinal rim area also increased with increasing axial length. Axial length and subject height were strongly correlated in both studies. Multiple variable analysis in both studies was used to test the positive association between disc area (and neuroretinal rim area) and axial length after adjustment for height. Despite this adjustment, the association between disc area (and neuroretinal rim area) and axial length remained significant.

The relationship between axial length and optic disc area is of importance when calculating ocular magnification. Both the Thai and Singapore studies had the advantage over some other population-based planimetric studies (Varma, Tielsch et al. 1994; Ramrattan, Wolfs et al. 1999) in that axial length and other biometric parameters such as anterior chamber depth were measured. A variety of formulae are available for calculation of ocular magnification. Formulae such as Littmann's 'keratometry and ametropia' method (Littmann 1982) that do not use axial length will underestimate ocular magnification in long eyes and overestimate ocular magnification in short eyes (Garway-Heath 2000). For this reason, studies that report relationships between height, gender and refractive error and optic disc size without accounting for axial length (eg. The Rotterdam Study (Ramrattan, Wolfs et al. 1999)) need to be interpreted with caution.

The Thai study found no significant association between optic disc area and spherical equivalent refraction, while the Singapore study actually showed a positive correlation when using a non-parametric test of correlation (but non-significant if Pearson's correlation was used).

A clinic-based study of normal subjects by (Rudnicka AR 2001) showed a statistically significant positive relationship between axial length and all optic disc parameters, and in all cases axial length was the strongest predictor compared with other factors. However, this study did not use axial length in the calculation of ocular magnification. Other studies have found no correlation between disc area and axial length or between disc area and spherical equivalent refraction (Jonas, Gusek et al. 1988) (Britton, Drance et al.

1987) (Mansour 1991) (Heijl A 1993) (Varma, Tielsch et al. 1994). However, these studies included subjects with relatively low degrees of ametropia and certainly a narrower range of axial lengths than the study by Rudnicka et al (Rudnicka AR 2001). Two studies by Jonas illustrate how the relationship may be affected by the degree of ametropia. In a group of myopes of more than -8 D, he reported a correlation between disc area and axial length (Jonas, Gusek et al. 1988), yet this was not present in a group of subjects with less than 8D of myopia (Jonas, Gusek et al. 1988). Other studies have shown a weak relationship between disc area and axial length (Bottoni 1989). The Rotterdam Study (Ramrattan, Wolfs et al. 1999) and the study by Rudnicka et al (Rudnicka 2001) have shown an increase in disc area with increasing myopia, unlike the findings of the Thai and Singapore studies. The differences in results may be explained by the exclusion of axial length from the ocular magnification formula by the former studies and probably more importantly, the different ranges of ametropia between studies. Both axial and non-axial factors contribute to the spherical equivalent of a given eye. Presumably non-axial factors such as lens refractive index are responsible for the lack of association between spherical equivalent and disc area in the Thai and Singapore studies, as axial length and keratometric power were found to be both positively associated with the area of the optic disc.

Histomorphometric studies (Jonas, Gusek et al. 1988) have shown that the size of the optic disc is governed by the size of the scleral canal. It is very likely that the size of the scleral canal increases as the globe extends in myopia. The neuroretinal rim area also increases, corresponding with the increase in disc area.

The Rotterdam Study (Ramrattan, Wolfs et al. 1999) reported a weak association between body height and disc area. The authors explained that this association was weaker than would be expected when considering the closer correlation between body height, axial globe length and disc area in childhood, which had been noted by another cross-sectional study (Rimmer S 1993). They further concluded that the weaker association observed in adulthood was due to the variability in subsequent increases in height during adolescence.

Neither the Singapore nor the Thai studies showed a significant association between corneal thickness and optic disc area. While there was also no association with neuroretinal rim area in the Singapore study, the Thai study showed a significant and positive correlation between corneal thickness and neuroretinal rim area. Both studies revealed a positive correlation between axial length and corneal thickness, yet the significant association observed in the Thai study remained significant after adjusting for the effect of axial length. Ehlers (Ehlers M 1976) found no association between corneal thickness and refraction, concluding that the former was a 'relatively independent biometric parameter'. The Thai study found no significant association (Pearson's r , -0.073; $P=0.217$) between corneal thickness and spherical equivalent, yet in Singapore there was a significant negative correlation (Pearson's r , -0.213; $P<0.001$).

Using the 'hypernormal' datasets, the Singapore and Thai studies gave conflicting results when examining for an association between intraocular pressure and neuroretinal rim area, the Singapore study finding a negative association while no association was found in the Thai study. However, when a larger dataset (Subgroup A: all subjects with good quality images for planimetry, 470 eyes) was used for the Thai study, a significant decline in neuroretinal rim area with increasing intraocular pressure was noted, in agreement with the results from Singapore using both the Singapore datasets. There was no association between disc area and intraocular pressure in either study. Clinical studies of chronic open angle glaucoma have reported significant increases in neuroretinal rim area associated with prolonged IOP reduction (Shin, Bielik et al. 1989). After adjusting for age and disc area in the Baltimore Eye Study (Varma, Hilton et al. 1995), white Americans had a 6% decrease in neural rim area for every 10-mm Hg increase in IOP ($P = .0001$). In black Americans, there was a quadratic relationship between neural rim area and IOP, with little decline with IOP up to approximately 17 mm Hg, after which neural rim area declined significantly with higher IOP ($P = .001$). Similarly, the neural rim area-to-disc area ratio decreased and the vertical cup-to-disc ratio increased with increasing IOP in both black and white Americans. The Thai and Singapore studies showed no significant relationship between vertical cup/disc ratio and intraocular pressure for both datasets. Neither was there a significant relationship between neural rim area-to-disc area ratio with intraocular pressure, nor between cup diameter and intraocular pressure. A

planimetric clinic-based study of Caucasians ('normal subjects' with normal visual fields and an IOP of less than 21mmHg) reported no significant association between cup diameter, neuroretinal rim area and intraocular pressure (Garway-Heath, Wollstein et al. 1997).

4.4.4 Sex and optic disc parameters

Optic disc area and neuroretinal rim area were significantly greater in men than in women for both the Thai and Singapore studies. The Singapore analysis showed that axial length, height and average keratometric power were significantly positively correlated with disc area. The Thai study found similar relationships except height which was unrelated. Both studies also found men to be significantly taller, to have significantly longer axial lengths and lower keratometric power (longer radius of curvature) than women. These findings would account for the detected gender difference in disc and neuroretinal rim area.

Multiple variable analysis for both studies showed that the gender difference observed in univariate analyses failed to exist when variables such as axial length, keratometry and height were taken into account. The exception to this was in Group A of the Thai study where a gender difference in disc area persisted after adjustment for multiple variables. Similar gender differences of keratometry and axial length have been reported by other studies (Tsai 1995) (Britton, Drance et al. 1987; Tsai, Ritch et al. 1992).

Planimetric studies of Caucasians by Garway-Heath (Garway-Heath, Ruben et al. 1998) and by Rudnicka (Rudnicka AR 2001) have reported that neuroretinal rim area and disc area were unrelated to gender. A study by Varma et al (Varma, Tielsch et al. 1994) reported significantly larger disc areas in men than in women for both black and white Americans from the Baltimore Eye Survey. However, this study that analysed digitized simultaneous stereoscopic optic disc photographs using the Topcon Imagenet system (Topcon Imagenet, Topcon Instrument Corp of America), did not take into account the axial length of subjects (this was not measured in the Baltimore Eye Survey). The Rotterdam Study (Ramrattan, Wolfs et al. 1999) reported the disc area to be 3.2% and neuroretinal rim area as 4.3% smaller in women than men (a significant difference, $P < 0.01$), which was unchanged in significance after adjusting for refractive error. Axial length was not measured in the Rotterdam study and no adjustment was therefore made

for this in the ocular magnification algorithm, nor in subsequent multivariate analyses. Allowance for axial length differences in both the Baltimore and Rotterdam studies may have affected the gender difference in this study, in a similar way to that encountered in the Thai and Singapore analyses. The Vellore Eye Study (Jonas, Thomas et al. 2003), which did not incorporate axial length in the calculation of ocular magnification, reported no significant gender difference in disc area, while also reporting that there was no statistically significant gender difference in axial length.

The Thai sub-study using HRT-II found no gender differences in optic disc parameters. This agrees with another study, conducted in Japanese eyes with confocal laser topography (Kashiwagi 2000) which reported no significant gender difference in disc or neuroretinal rim areas.

One of the few studies to compare genders in terms of optic nerve fibre counts reported no gender difference (Jonas, Schmidt et al. 1992).

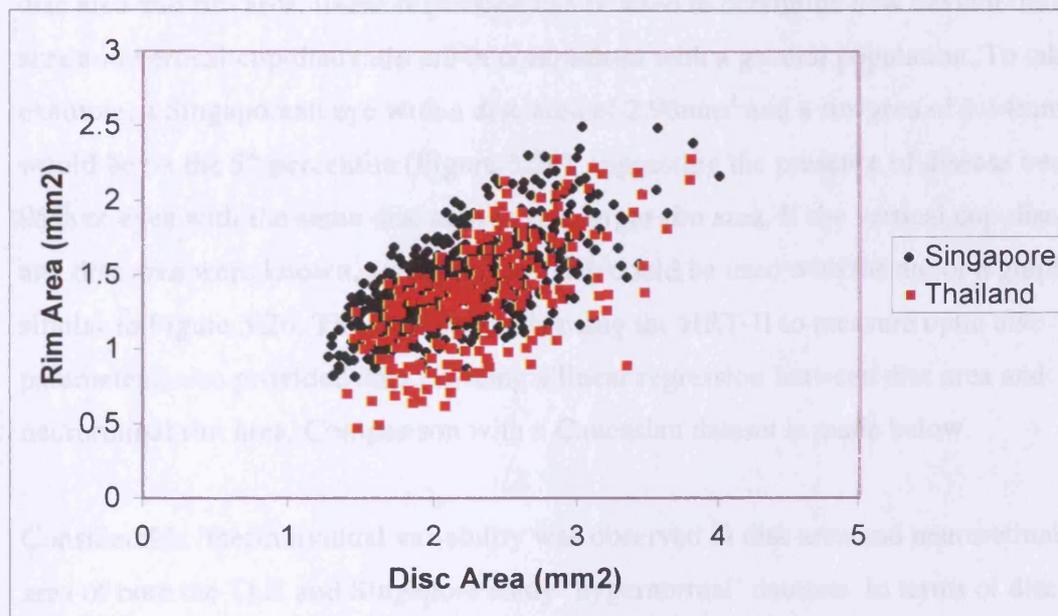
4.4.5 Inter-correlation of disc parameters

Both the Singapore and Thai studies found a significant and positive association between neuroretinal rim area and optic disc area. In addition, the HRT-II sub-study in Thais confirmed this. Cup area and disc area were also positively correlated in these studies. Several other studies have also reported that neuroretinal rim area increases with increasing optic disc size (Britton, Drance et al. 1987; Caprioli and Miller 1987; Kee, Koo et al. 1997; Garway-Heath, Ruben et al. 1998) [Jonas JB, 1988 #507] (Jonas, Gusek et al. 1988) (Wollstein, Garway-Heath et al. 1998) (Montgomery 1993).

The use of linear regression between disc area and neuroretinal rim area to define the normal range has been advocated previously (Britton, Drance et al. 1987) (Caprioli and Miller 1987) (Montgomery 1991) using a clinical method (Montgomery 1991), computer-assisted planimetry (Garway-Heath and Hitchings 1998) and more recently, using the HRT (Wollstein, Garway-Heath et al. 1998). The relationship of optic disc area and neuroretinal rim area has been used as strong predictor of glaucomatous loss (Wollstein, Garway-Heath et al. 1998). The linear regression results from the Singapore and Thailand studies (both using Subgroup B datasets) are given individually in Figures 3.18 and 3.28, and combined in Figure 4.1. The variability in neuroretinal rim area

increased in both studies as the rim area itself increased. This observation is in agreement with other studies (Britton, Drance et al. 1987; Wollstein, Garway-Heath et al. 1998) (Jonas, Gusek et al. 1988).

Figure 4.1 The combined linear regression results comparing rim area and disc area from the Singapore and Thailand studies (both using Subgroup B ‘hypernormal’ datasets)



The slopes of the regression lines in the Singapore and Thai studies are 0.41 and 0.48, respectively. This slope represents the increase of the rim area with the increase in disc area and is similar to the results of clinic-based studies of normal Caucasian subjects which report the slope to be within the range 0.30 to 0.58 (Wollstein, Garway-Heath et al. 1998) (Britton, Drance et al. 1987) (Jonas, Gusek et al. 1988) (Montgomery 1993). Wollstein et al (Wollstein, Garway-Heath et al. 1998) reported that using the linear regression between the optic disc area and the log of the neuroretinal rim area has the highest specificity (96.3%) and sensitivity (84.3%) values to separate between normal subjects and patients with early glaucoma. Attempting to use the same approach for the Thai and Singapore studies, would be problematic due to the small numbers of subjects found to have glaucoma in these prevalence studies.

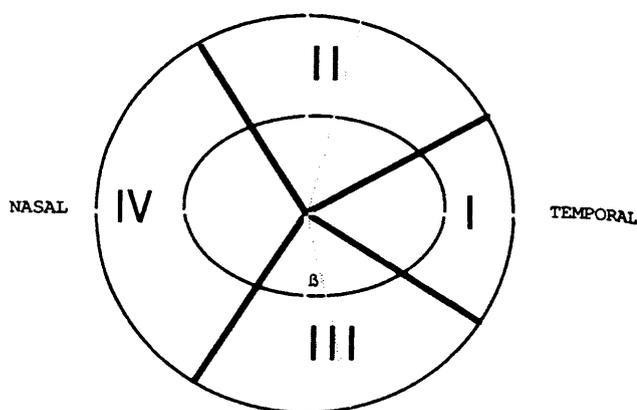
The Thai and Singapore studies provide data for statistically abnormally sized optic discs in these non-Caucasian populations. A slit-lamp and gonioscope can be used to measure the optic disc diameter (Spencer AF 1994), and hence it can be determined clinically whether a patient has a statistically abnormal disc area using the data provided by these studies. Knowledge of the patient's disc area is of relevance when screening for primary open-angle glaucoma, as the vertical cup/disc ratio depends on the disc area (Jonas, Gusek et al. 1988). In addition, if one uses the same planimetric method to determine the disc area and rim area, linear regression can be used to determine how deviant the rim area and vertical cup/disc ratio are in comparison with a general population. To take as an example, a Singaporean eye with a disc area of 2.98mm^2 and a rim area of 1.34mm^2 would be on the 5th percentile (Figure 3.28), suggesting the presence of disease because 95% of eyes with the same disc area have a larger rim area. If the vertical cup-disc ratio and disc area were known, a similar approach could be used with the aid of a graph similar to Figure 3.26. The Thai substudy using the HRT-II to measure optic disc parameters, also provided data enabling a linear regression between disc area and neuroretinal rim area. Comparison with a Caucasian dataset is made below.

Considerable interindividual variability was observed in disc area and neuroretinal rim area of both the Thai and Singapore study 'hypernormal' datasets. In terms of disc area, the interindividual variability was 1:2.7 in the Thai study and 1:3.6 in the Singapore study. This compares with 1:6.9 in a Caucasian study of 457 optic nerve heads using a planimetric method (Jonas, Gusek et al. 1988), and 1:3.6 in a population-based study of Indians using the HRT (Jonas, Thomas et al. 2003). When considering interindividual variability of neuroretinal rim area, this was 1:4.8 in the Thai study and 1:4.0 in the Singapore study. This compares with 1:5.8 in the Caucasian study (Jonas, Gusek et al. 1988), and 1:2.6 in the population-based Indian study (Jonas, Thomas et al. 2003). Interindividual variability described by different studies is strongly reliant on the demographics of the sample involved, hence caution should be exercised when making comparisons. For example, Jonas et al (Jonas, Gusek et al. 1988) reported up to a 10-fold variation in disc area, with a high mean value for disc area of 6.87mm^2 , but their sample contained a larger proportion of subjects with higher degrees of myopia.

There was remarkable concordance in the distribution of vertical cup/disc ratio measured using the clinical biomicroscopy with an eyepiece graticule in Thailand and in the Singapore studies. Values for median, 97.5th and 99.5th percentiles of vertical cup/disc ratio were 0.47, 0.71 and 0.81 in Singapore and 0.45, 0.72 and 0.86 in Thailand.

Jonas et al (Jonas, Gusek et al. 1988) reported the planimetric results of a study of 457 unselected normal optic nerve heads from a clinic-based study of Caucasians. The authors divided the optic disc into four sectors which are similar (Figure 4.2) in degrees of circumference to the method used in the Thai and Singapore studies (Figure 2.7).

Figure 4.2 The optic disc divided into four sectors. Sectors II and III are right-angled, and their middle axes (double dotted lines) are tilted 13° (angle beta) temporal to the vertical optic disc axis. Sectors I (temporal side, 64°) and IV (nasal side, 116°) cover the remaining areas. Reproduced from Jonas et al. (Jonas, Gusek et al. 1988)



This report by Jonas et al described what was later coined the '*ISNT* rule', defined with the neural rim being usually broadest in the *Inferior* disc region, followed by the *Superior* disc region, the *Nasal* disc area, and finally the *Temporal* disc region. In addition to neuroretinal rim width, the neuroretinal rim area was also significantly larger in the inferotemporal region than superotemporally. In only 17% of optic discs was the rim area

smaller in the inferotemporal sector than in the superotemporal sector. The authors (Jonas, Gusek et al. 1988) suggested that their finding of a larger inferotemporal than superotemporal rim area was due to the macula's location inferior to the optic disc's centre (Hogan, Alvarado et al. 1971). The rim area was also smallest in the temporal horizontal sector in both the Singapore and Thai studies, and also in the recent Vellore Eye Study (Jonas, Thomas et al. 2003). However, the Thai study found no significant difference in area between the inferotemporal and superotemporal sectors, while the Singapore study actually showed the reverse, with significantly larger superotemporal areas than inferotemporal areas. Interestingly, the Vellore Eye Study, which was conducted by Jonas et al using the same planimetric method as his original study on Caucasian subjects, found that the rim was not significantly broader in the inferior temporal disc sector than in the superior temporal disc sector or the nasal disc region. Jonas noted that these features of the neuroretinal rim configuration in Caucasian eyes are of utmost importance in the diagnosis of early glaucomatous optic nerve damage in ocular hypertensive eyes before the development of visual field defects in white on white perimetry (Jonas, Budde et al. 1999).

There may be several reasons why these studies have reported differences in 'normal' neuroretinal rim configuration, such as the exclusion of high myopes in some studies, the examination techniques, examined populations and the type of study. However, as Jonas et al (Jonas, Thomas et al. 2003) noted in the Vellore Eye Study, the most important part of the ISNT rule, that the smallest rim part is located in the temporal horizontal sector, was confirmed for the Singaporean and Thai studies, the Indian study, and Caucasians examined in previous studies (Jonas, Budde et al. 1998).

4.4.6 Correlation between disc parameters and systemic variables

The Singapore glaucoma survey recorded information regarding systemic disease, specifically diabetes, hypertension and history of migraine or myocardial infarction. The Thai survey did not collect this information, therefore the correlation between disc parameters and systemic variables is reported for the Singapore study only.

Other than for systolic blood pressure, disc area was unrelated to the other variables of systemic disease in the Subgroup B dataset, but in Group A migraine was associated with smaller disc area.

The finding of an association between migraine and neuroretinal rim area was very interesting, considering the small numbers of subjects who reported a history of migraine. Subjects with migraine had a significantly lower rim area than those without a history. The study has also shown that disc area is positively correlated with neuroretinal rim area. When adjustment was made for the effect of disc area, the association between migraine and neuroretinal rim disappeared. This suggests that smaller disc areas are associated with migraine, and as a consequence, the neuroretinal rim area will also be smaller in these individuals. An extensive literature search failed to disclose any reports of an association between rim area and migraine in the normal population, yet there are studies that have implicated migraine as risk factor in glaucomatous optic neuropathy (Drance 1975; Nicolela MT 1996) (Flammer 1992) (Wang, Mitchell et al. 1997). In a very large study of 1,711 subjects with glaucoma or under review as glaucoma suspects, Nicolela (Nicolela MT 1996) reported that migraine was 2.5 times more frequent in subjects with focal ischaemic changes to the optic disc than in those with other characteristic glaucomatous optic disc appearances (myopic glaucomatous discs, senile sclerotic discs, and generalized enlargement of the optic cup discs). They postulated that vasospasm or the basis for migraine could possibly be an important factor in the pathogenesis of the glaucomatous loss in this group. The Blue Mountains study in Australia, a population-based study, also reported increased odds for open angle glaucoma (OAG) among people giving a history of typical migraine headache and aged 70-79 years (OR, 2.5; 95% CI 1.2-5.2), after adjusting for variables found associated with glaucoma (Wang, Mitchell et al. 1997). This association was marginally stronger for high-pressure OAG cases (OR, 2.7; 95% CI, 1.1-5.6). These data suggested the possibility of an association between history of typical migraine headache and OAG, which could be modified by age. The data from Singapore may also indicate that migraine may have a deleterious effect on the neuroretinal rim which may be a contributory factor in the pathogenesis of glaucomatous optic neuropathy.

4.5 Comparison of disc morphology between the two South-East Asian populations and with other population-based surveys

A remarkable concordance was noted in the distribution of vertical cup/disc ratio measured using clinical biomicroscopy in the Thai and in the Singapore studies. The 97.5th percentile of this distribution was 0.7 for both studies. This is identical to the value of 0.7 reported by the Rotterdam Study (Wolfs, Borger et al. 2000). The 97.5th percentile for cup/disc ratio asymmetry was reported as 0.2 in the Thai and also the Singapore studies. The Baltimore Eye Survey (Varma, Tielsch et al. 1994) reported the 95th percentile as 0.2 in American whites. Median and 99.5th percentiles of vertical cup/disc ratio were also very similar in the Thai and Singapore studies (0.47 and 0.81 in Singapore and 0.45 and 0.86 in Thailand, respectively). The Blue Mountains glaucoma survey of Australia (Mitchell, Smith et al. 1996) reported the prevalence of a vertical cup/disc ratio (measured from stereo optic disc photographs with a Donaldson stereoviewer with a plastic Pickett circles template) in excess of 0.7 or a cup/disc ratio difference of ≥ 0.3 to be 5.6% in a population-based sample of Australians aged 49 years and older. The mean, median, 97.5th and 99th percentiles for the 'normal population' were reported as 0.42, 0.43, 0.68 and 0.73, respectively. In a clinic-based survey of American whites, Schwartz et al (Schwartz, Reuling et al. 1975) measured horizontal cup/disc ratio (using stereo biomicroscopy) among a sample of 160 normal twin subjects and reported a mean cup/disc ratio of 0.4 & approximately 5% with a cup/disc ratio of 0.7 or more. Using an image analyser, Varma et al (Varma, Tielsch et al. 1994) reported larger cup/disc ratios in the American black population than the American white population (mean cup/disc ratio: blacks, 0.56; whites, 0.49). Buhrmann et al (Buhrmann, Quigley et al. 2000) examined (stereo biomicroscopy) 3268 East Africans aged over 40 years in a population-based survey, and reported a mean cup/disc ratio of 0.41 (SD, +/- 0.16). They also reported that 5.6% of left eyes and 4.2% of right eyes equalled or exceeded a cup/disc ratio of 0.7. Asymmetry between fellow eyes of higher than 0.2 occurred in fewer than 2.5% of persons. A population-based study of glaucoma in Zulus (Rotchford AP 2002) reported a mean vertical cup/disc ratio (stereo-ophthalmoscopy) of 0.34 (standard deviation, 0.19) for both right and left discs, with a 97.5th percentile of 0.7, with or without inclusion of subjects with glaucoma. The Barbados Eye Study (Leske, Connell et al. 1994) reported a

mean vertical cup/disc ratio of 0.3 (SD, +/- 0.2) in normal subjects aged 40 years and older (optic discs photographs were graded). The Proyecto VER (Quigley, West et al. 2001), a population-based study of Hispanic adults (aged 40 years and older) found a mean vertical cup/disc ratio of 0.35 (SD, 0.14) using a combination of biomicroscopy and analysis of stereophotographs. Another study involving Hispanic subjects, the Los Angeles Latino Eye Study (Varma, Ying-Lai et al. 2004) reported a 97.5th percentile of cup/disc ratio in subjects aged 40 years and older as 0.7 using a combination of stereophotograph grading and biomicroscopy (the mean and standard deviation were not published). These values are very similar to the distribution reported from Thailand and Singapore and the Caucasian studies mentioned above, showing remarkable consistency in cup/disc ratios between different ethnic groups. Unfortunately no specific optic disc information is currently available from population-based studies of glaucoma in other East Asian populations (Iwase A., Suzuki Y., et al. 2004) (Shiose Y., Kitazawa Y., et al. 1991).

The concordance of cup/disc ratio measurements between these population-based studies noted above, would suggest that a value of 0.7 would be a reasonable value to choose to represent the 97.5th percentile of cup/disc ratio, when planning a study that involved case detection of glaucoma. The 97.5th percentile for vertical cup/disc ratio has been recommended as a statistical cut-off for abnormality by Foster et al (Foster PJ, Buhrmann R., et al. 2001) in their scheme designed to identify glaucoma cases in population-based prevalence surveys, and was indeed the glaucoma classification system used for both the Thai and Singapore surveys described herein. However, two issues warrant discussion in this regard. Firstly, the use of a single measure for the 97.5th percentile does not take into account the variation of cup/disc ratio with disc size. The Thai and Singapore studies both showed an increase of vertical cup/disc ratio with increasing disc area. This issue was well described in the Blue Mountains Eye Study (Crowston, J., Hopley, C.R., et al. 2004) where the overall (size-independent) 97.5th percentile was 0.7. However, the size-adjusted 97.5th percentile cut-off in their study increased from 0.6 for 1.2mm optic discs to 0.75 for 1.9mm optic discs. Using 0.7 as a cut-off could potentially lead to high numbers of false negatives in eyes with small optic discs and high numbers of false

positives in larger optic discs. These findings highlight the need for routine evaluation of vertical disc diameter in clinical practice.

Secondly, the measurement technique used to determine cup/disc ratio is undoubtedly of importance when comparing studies. The substudy (discussed in Section 4.3.3) that compared cup/disc ratio measurement between biomicroscopy, planimetry and confocal laser scanning tomography showed that each of these methods gave significantly different results, in particular planimetric analysis resulted in higher values of cup/disc ratio than biomicroscopy. This was further shown by the results of the main studies. For this reason, the 97.5th percentile of the cup/disc ratio for the population would be expected to be considerably higher if a planimetric method were to be used for case detection.

Finally, the composition of the sample used to calculate a cup/disc ratio cut-off for case detection needs to be considered carefully. In the Thai and Singapore studies, the planimetrically derived mean cup/disc ratio did not differ significantly between Group A (all phakic subjects with good quality images for planimetric analysis excluding cases of known glaucoma) and Subgroup B, a 'hypernormal' group with glaucoma suspects excluded. This issue was highlighted in the Blue Mountains Eye Study (Crowston, J., Hopley, C.R., et al. 2004), where inclusion of glaucomatous eyes in the data analysis had a minimal effect on the median values of any optic disc diameter but resulted in a modest increase in the 95th (range 0 to 0.05) and 97.5th percentiles (range 0 to 0.08) and a larger increase in the 99th percentiles (range 0.04 to 0.17). Their study also noted that inclusion of glaucomatous optic discs in the analysis had more effect on the percentile values for smaller than for larger optic discs.

Comparison of absolute values for optic disc parameters was made between the Thai and Singapore 'hypernormal' datasets. The mean disc area and rim area of the Thai subjects were 2.29mm² (standard deviation, 0.46mm²) and 1.36mm² (standard deviation, 0.35mm²), while in Singapore these values were 2.17mm² (standard deviation, 0.46 mm²) and 1.43mm² (standard deviation, 0.29mm²), respectively. These values of central tendency appear very similar between these two populations. Multiple variable regression analysis (using the logarithm of disc area and rim area) was used to adjust for the factors

that the studies had revealed as potential confounders, namely age, sex, and axial length. Adjustment for these factors showed that these population-derived datasets were significantly ($P=0.01$) different in terms of disc area and rim area.

As explained in the last section of the 'Results' section, an objective of this research was to compare the absolute values of optic disc parameters of the Thai and Singapore datasets with other population-based planimetric studies. Comparison of absolute values (rather than ratios eg. cup/disc ratio) of optic disc parameters between studies can be problematic. Differences between studies may be partly attributed to magnification methods used to convert image size measurements into absolute units and the demographics of the sample. Population-based studies that have attempted to describe planimetric measurements in the 'normal' population are scarce, but two studies, the Rotterdam Study (Ramrattan, Wolfs et al. 1999) and the Vellore Eye Study (Jonas, Thomas et al. 2003) used a planimetric method which used Littmann's correction factor calculated from spherical refractive equivalents and keratometry data. Despite the fact that the correction factor used to obtain parameters for the Thai and Singapore studies is more accurate (Garway-Heath, Rudnicka et al. 1998), in order to compare absolute optic disc parameter values between these four studies, a similar correction factor was used for the Thai and Singapore data. Optic disc parameters from these four studies are compared in Table 4.1.

Table 4.1 Optic disc parameters of ‘normal’* subjects reported from four population-based studies. For comparative purposes, Littmann’s correction factor (calculated from spherical refractive equivalents and keratometry data), has been used to calculate disc parameters.

Study	Number of subjects (men, women)	Age of subjects	Disc Area		Rim Area		Cup Area	
			[mean +/- SEM (97.5 th ; range)]		[mean +/- SEM (97.5 th ; range)]		[mean +/- SEM (97.5 th ; range)]	
Rom Klao Survey, Thailand	292 (118, 174)	≥ 50 years	2.53 +/- 0.0338 (3.86; 1.40-4.69)		1.51 +/- 0.0254 (2.43; 0.12-2.99)		1.03 +/- 0.0241 (2.01; 0.08-2.68)	
Tanjong Pagar Survey, Singapore	622 (290, 332)	≥ 40 years	2.53 +/- 0.0253 (3.66; 1.25-4.61)		1.67 +/- 0.0131 (2.45; 0.75-3.23)		0.86 +/- 0.0159 (1.74; 0.01-2.43)	
The Rotterdam Study	5114 (2134, 2980)	≥ 55 years	Men	Women	Men	Women	Men	Women
			2.47 +/- 0.0083 (3.54;0.81-5.44)	2.38 +/- 0.0083 (3.42;0.50-4.94)	1.87 +/- 0.0079 (1.25;0.77-4.64)	1.79 +/- 0.0069 (1.18;0.34-3.97)	0.60 +/- 0.0072 (1.39;0.0082-2.47)	0.59 +/- 0.006 (1.34;0.009-2.06)
Vellore Eye Study	70†	Unpublished	Men 2.68 +/-0.15 (range: 1.44-5.15)	Women 2.51 +/-0.08 (range: 1.43-3.60)	1.60 +/- 0.37‡ (1.08-2.85)		0.98 +/- 0.40‡ (0.22-2.30)	

* The Rotterdam Study. Subjects with open angle glaucoma were excluded.

The Vellore Eye Study. ‘Normal’ subjects were those without an occludable anterior chamber angle upon gonioscopy.

The definitions of this ‘hypernormal’ group can be found in the ‘Methods’ section above.

† The number of men and women was not published.

‡ Standard Error. The 97.5th percentile was not published.

An ideal comparison between these four studies would involve the complete datasets with adjustments made for age, sex, and axial length, as was performed when comparing the Thai and Singapore studies. However, despite the fact that the planimetric method used for the Vellore and Rotterdam studies was different to that used in the Thai and Singapore studies, there is remarkable similarity between the studies for mean disc area, rim area and cup area. The Baltimore Eye Survey (Varma, Tielsch et al. 1994) measured the optic discs of 3475 eyes of white American subjects and reported a mean disc area of 2.63mm^2 (95% confidence interval, 2.61-2.65), a mean rim area of 1.92mm^2 (95% confidence interval, 1.90-1.94), and a mean cup area of 0.71mm^2 (95% confidence interval, 0.69-0.73). Despite the use of a different image analyser system (Topcon Imagenet, Topcon Instrument Corp of America) in the Baltimore Eye Survey, these values are remarkably similar to the four other studies presented in Table 4.1. Curiously, planimetric measurements from another study in south India, the Andhra Pradesh Eye Disease Study (Sekhar, Prasad et al. 2001) reported a mean disc area of 3.37mm^2 (standard deviation, 0.68mm^2 ; range $1.95\text{-}6.82\text{mm}^2$) and mean rim area of 1.60mm^2 (standard deviation, 0.37mm^2). This study used a similar planimetric method to the Rotterdam and Vellore studies. It is questionable whether the optic disc parameters in this population, which, like Vellore, is also in south India, are truly different, or whether the technique used in correcting the magnification of the fundus images may be responsible for the discrepancy between these Indian studies. The observation that the mean rim area was quite similar between the studies but not the mean disc area, may be explained by a methodological difference in the plotting of the border between the optic cup and rim between the two studies. Several studies have reported larger disc areas in blacks than in whites (Varma, Tielsch et al. 1994) (Chi, Ritch et al. 1989) (Tsai 1995). In the Baltimore Eye Study, Varma et al reported significantly larger disc areas in blacks (mean disc area of 2.94mm^2 (95% confidence interval, 2.91-2.97)) than whites (mean disc area of 2.63mm^2 (95% confidence interval, 2.61-2.65)), yet the rim areas (mean rim area of 1.90mm^2 (95% confidence interval, 1.88-1.92) were not significantly different. The disc area of American blacks reported by that study (Varma, Tielsch et al. 1994) is considerably greater than the Thai, Singapore and Vellore studies, but the rim areas are

4.6 Conclusions and recommendations

The research conducted in the Thai and Singapore studies provides the first planimetric data on 'normal' optic discs to be obtained from population-based glaucoma studies. The wealth of data collected in these surveys enabled relationships between optic disc parameters and demographic variables such as age and gender to be explored, in addition to associations with biometric variables, such as axial length. Differences were demonstrated between the Thai and Singapore studies in terms of optic disc parameters, and also when compared with data from studies involving Caucasians. However, the distribution of some parameters such as vertical cup/disc ratio showed remarkable similarities between these studies. The collection of systemic data from the Singapore data enabled an interesting analysis of the association of systemic disease such as migraine with disc parameters. In addition to this, a spectrum of different techniques of optic disc analysis were compared, ranging from clinical biomicroscopy, to confocal laser scanning tomography using the Heidelberg Retinal Tomograph-II, the first time that the latter has been used in a population-based glaucoma survey. A novel planimetric technique was used and compared with other techniques. Several agreement studies have examined the differences between these techniques and between observers.

The collection of data on optic disc morphology was only a part of the Rom Klao Glaucoma Survey (Bourne RR 2003) which has established the prevalence and mechanisms of glaucoma in this region of South-East Asia. The survey found that glaucoma was the second most common cause of blindness after cataract, and projected a two to three-fold increase in the prevalence of glaucoma over the next fifty years (in those aged 50 years or more). The survey also reported that only 26% of glaucoma cases had been previously diagnosed. This finding emphasises the importance of improving detection of glaucoma in this population. Sixty-nine percent of the primary open-angle cases detected had an intraocular pressure lower than the 97.5th percentile (21mmHg) of the population, which demonstrates that substantial numbers of cases would be missed if one were to test intraocular pressure alone. This thesis makes a contribution to the effort of characterizing the optic disc in these populations so that clinicians can make an informed population-specific judgement in deciding whether the parameters of a given optic disc are normal or abnormal.

Chapter 5. Future Work

Further age- and sex-specific data involving non-Caucasian racial groups, preferably derived from population-based studies, are needed to test whether the currently available analytical programs are appropriate to detect glaucomatous damage to the optic disc in all racial groups. Future work by the candidate in this field involves a large planimetric and HRT-II analysis of the optic discs of 23,000 adults in the Pakistan National Eye Survey and a comparative analysis of different racial groups using the HRT. The work with the planimetric technique used for the Thai and Singapore surveys has resulted in the formation of an 'optic disc' reading centre which is part of a newly-established Reading Centre at Moorfields Eye Hospital, London. It is hoped that this new dimension to the Reading Centre will result in more research into this field.

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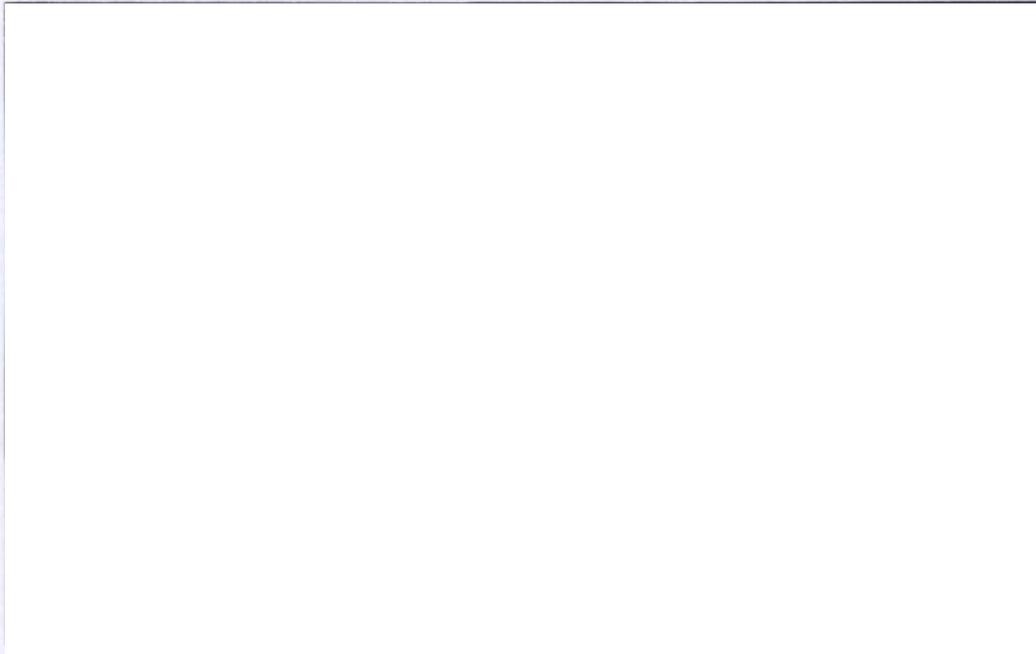
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Appendix I Magnification of the camera camera used in this research study

In longitudinal studies, individuals typically wear their low vision aids, which may have lead to magnification compared to baseline values. Therefore, an analysis such as those described in

Photograph of the staff at Rom Klao.



$$M = 1.37 \times s$$

M relates to the true size t of a radial feature to the measured size s of its image on the input camera film. The coefficient 1.37 is a constant specific to the Zeiss Ikon camera instrument used by Littmann. A different camera camera may have a different coefficient, referred to as the camera magnification factor. The factor is a variable dependent on the optical characteristics of the given eye. The formula used by Littmann depends on a refractive camera system, in which the magnification factor is constant over a range of optical refractive. However, in a nonrefractive system, the value of M varies with the patient's ocular refraction.

Appendix I Magnification of the fundus cameras used in this research study

In longitudinal studies, individuals can serve as their own controls, with optic nerve head dimensions compared to baseline values. However, in studies such as those described in this thesis, which compare optic nerve heads among individuals, absolute levels of measurement are important.

Each of the imaging systems used in the studies described has differing magnification properties. To allow comparison of topography results obtained with different imaging systems, knowledge of these magnification properties is particularly relevant.

Approximations of the real dimensions of optic nerve heads have been attempted by histopathological correlations and with theoretical estimates using curves developed by Littmann (Littmann 1988). Histopathological comparisons are affected by tissue shrinkage, and the location chosen for the disc's edge may be different for those in clinical observation (Quigley, Brown et al. 1990). Littmann devised a technique for determining the true size of a given fundus feature for the Zeiss Oberkochen telecentric fundus camera. Littmann's formula is:

$$t = 1.37 qs$$

This relates to the true size t of a retinal feature to the measured size s of its image on the fundus camera film. The coefficient 1.37 is a constant specific to the Zeiss Oberkochen instrument used by Littmann. A different fundus camera may have a different coefficient, referred to as p , or the camera correction factor. The factor q is a variable dependent on the optical dimensions of the given eye. The rationale used by Littmann depends on a telecentric camera system, in which the correction factor p remains constant over a range of ocular refraction. However, in a nontelecentric system, the value of p varies with the patient's ocular refraction.

The value of q was determined for an eccentricity of 15 degrees, which is the approximate eccentricity of the optic disc.

Appendix I. Table 1. Values for q according to refractive error set by the model eye.

Refractive Error	q
11	0.247
10	0.251
8	0.258
6	0.266
5	0.27
4	0.274
3	0.279
2	0.283
1	0.288
0	0.293
-1	0.298
-2	0.303
-3	0.308
-4	0.314
-5	0.319
-6	0.325
-8	0.338
-10	0.352
-12	0.366

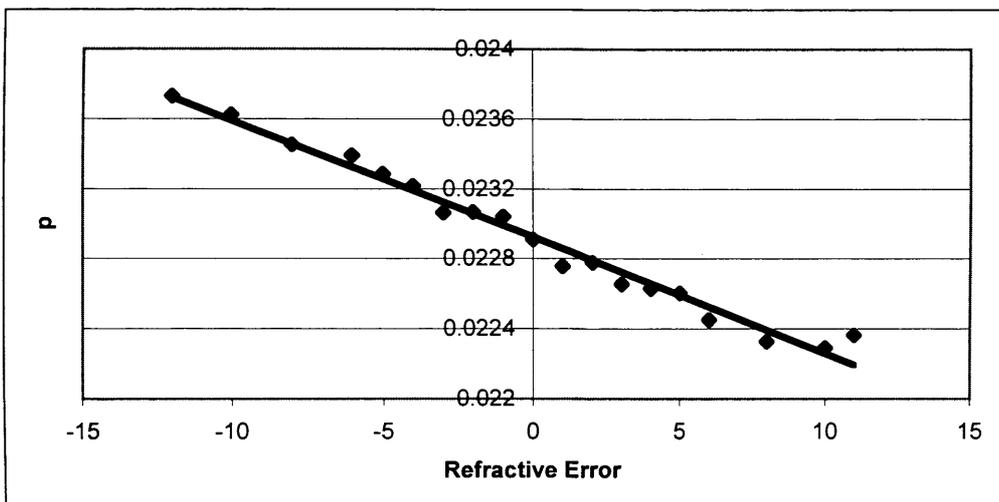
Kodachrome 35mm photographic slides were taken using the Nikon NF-505 (Nikon Corporation, Nikon Instech. Co.,Ltd, Kanagawa, Japan) camera (Singapore study) and the Kowa FX500-C (Kowa Optimed Inc., Torrance, California, USA) The film was developed and each transparency digitised (Nikon Coolscan, Nikon Corporation, Nikon Instech. Co.,Ltd, Kanagawa, Japan) to a 1280 x 960 pixel (resolution 1 pixel/inch) bit tagged image format. Images were imported into Paint Shop Pro version 7.0 (Jasc

Software, Inc., Eden Prairie, MN) Shareware where the median of two vertical diameters and two horizontal disc diameters of the model eye disc was measured in pixels.

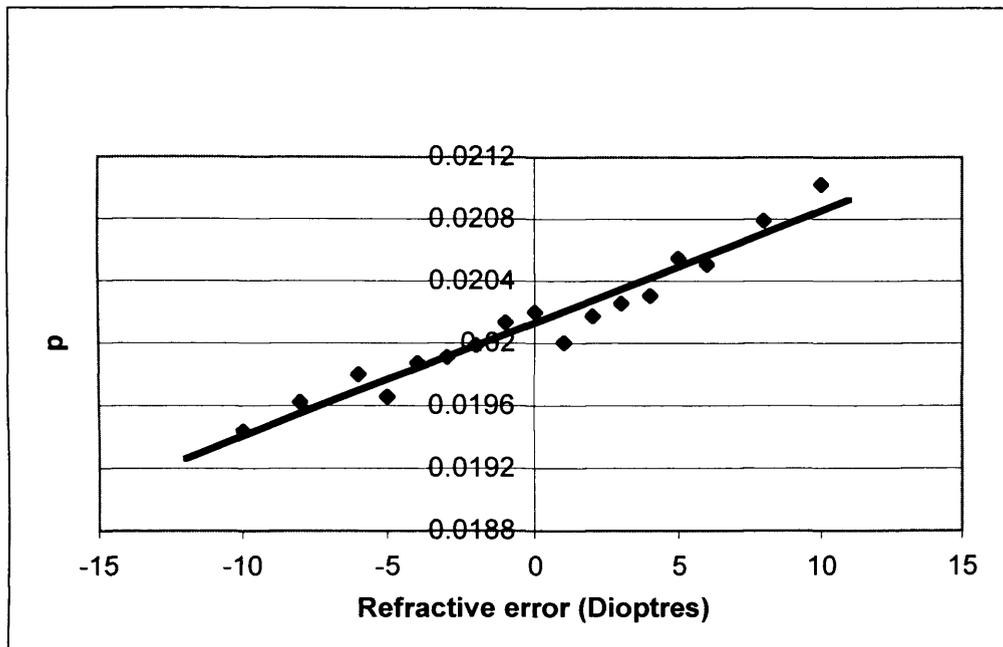
Using the formula, $p = t / q.s$, the values for p were calculated over a range of ocular refraction, for each of the two fundus cameras (Figures 1i and 1ii).

These values for p were then inserted into the Eye_2 software (Virtual Presence, London, UK) thereby allowing the correct magnification factor to be applied to each measurement over a range of subject's ocular refraction.

Appendix I. Figure 1i Kowa FX500-C (25 degree field): Graph of p (camera magnification) against refractive error of model eye (Equation of regression line: $y = -7E-05x + 0.0229$)



Appendix I. Figure 1ii Nikon NF505: Graph of p (camera magnification) against refractive error of model eye (Equation of regression line: $y = 7E-05x + 0.0201$)



Values of p varied with refractive error of the model eye, therefore neither camera is telecentric. To verify that these values for p were correct, the images of the model eye were analysed using the Eye_2 (Virtual Presence, London, UK) software. Summary values for disc area are given in Tables 1i and 1ii, for each of the cameras. The optic disc area of the model eye is known (diameter=1.95mm; area= 2.984mm²). These tables show that the Kowa camera is 99.7% (2.977/2.984x100) accurate when the refractive error is set at 0 dioptries, ranging from 99.9% at -10 dioptries to 98.9% at +10 dioptries. For the Nikon camera, these values are 99.1% (0 dioptries), 98.8% (-10 dioptries), and 97.6% (+10 dioptries), respectively.

Appendix I. Table 2i. Kowa FX500-C (25 degree field). The model eye disc area is given for differing values of refractive error. All other constants were the same.

Model eye Refractive Error (dioptries)	Average Keratometry (mm)	Ocular Magnification*	Model Eye Disc Area
0	7.9	0.292	2.977
+10	7.9	0.250	2.954
-10	7.9	0.351	2.986

*Calculated by Eye_2 software.

Appendix I. Table 2ii. Nikon NF505. The model eye disc area is given for differing values of refractive error. All other constants were the same.

Model eye Refractive Error (dioptries)	Average Keratometry (mm)	Ocular Magnification*	Model Eye Disc Area
0	7.9	0.292	2.958
+10	7.9	0.250	2.912
-10	7.9	0.351	3.019

*Calculated by Eye_2 software.

Appendix II

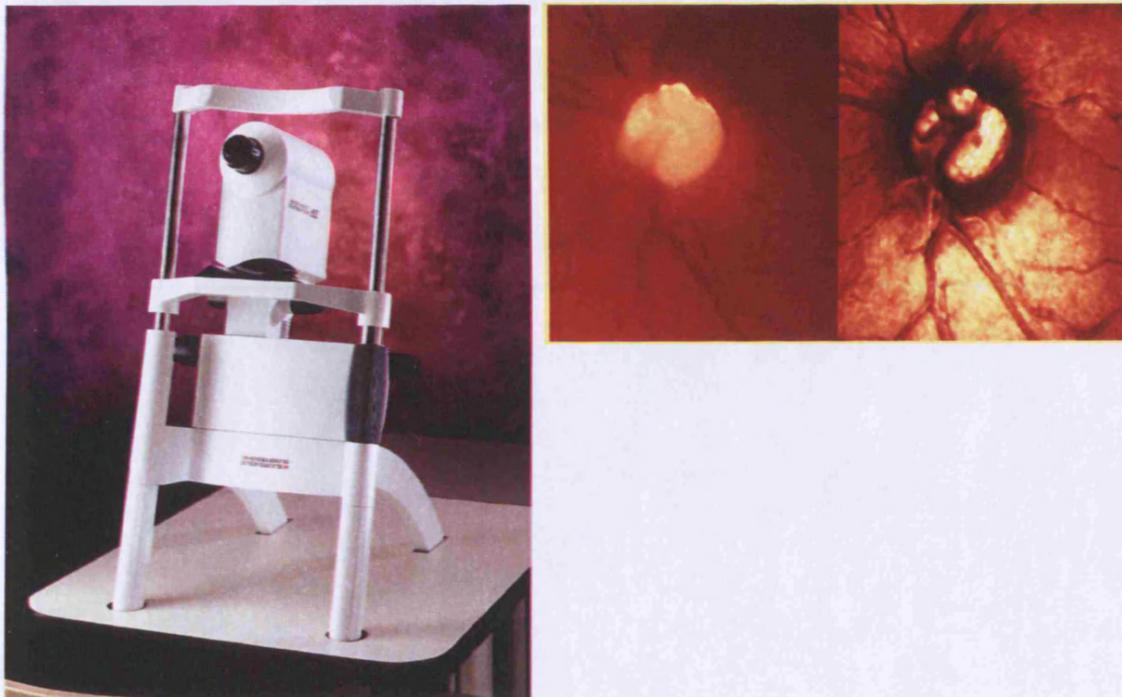
The Heidelberg Retina Tomograph

The Heidelberg Retina Tomograph (see photograph below) is a confocal laser scanning system for acquisition and analysis of three-dimensional images of the posterior segment of the eye. Data collected by this instrument can be used to quantitatively describe the retinal topography and the follow-up topographic changes. The three-dimensional image acquired by the HRT is a series of optical section images at different locations of the focal plane. From this layered three-dimensional image, a topography image is computed that consists of more than 65,000 local measurements of the retinal surface height. The topography image is colour coded, with dark colours representing elevated structures and light colours representing depressed structures. The operator draws around the optic disc margin, and the HRT software then computes a set of stereometric parameters that quantitatively describe the shape of the optic nerve head. The results of the topographic description are then used to classify an optic nerve head as being normal or outside normal limits using 'normal' data that is stored in the software database. These parameters can also be used to describe glaucomatous progression.

The HRT-II has been designed as a clinical routine instrument specifically for optic nerve head analysis, following the use of the HRT which has been developed mainly as a research tool for the last ten years. This research has shown that the variability of the topographic measurements is small enough to make these measurements clinically useful. The reproducibility of local height measures at each of the 65,000 locations of a topography image is between 10 and 20 microns (Bathija, Zangwill et al. 1998). The coefficients of variation of the stereometric parameters are about 5% (Rohrschneider, Burk et al. 1994). Methods have been developed to separate glaucomatous eyes from normal eyes and to detect very early glaucomatous changes to the optic nerve head. The most important methods are multivariate discriminant analysis procedures (Iester, Mikelberg et al. 1997) and the regression analysis of the rim area to disc area that showed very high sensitivity and specificity to detect early glaucoma (Wollstein, Garway-Heath et al. 1998), and which can detect pre-perimetric glaucoma (Kamal, Viswanathan et al. 1999).

The restriction of the HRT-II to topographic optic nerve head analysis allows an almost completely automatic system. Technical specifications are given in the table below. An internal fixation target centres the optic nerve head in the image. The total examination time is only a few minutes and the system is light, small and portable, and can be operated with a notebook computer.

Appendix II. Figure 1. Photograph of the HRT-II instrument and a topographic image of the optic nerve head generated by the instrument.



Appendix II. Table. A summary of the technical data of the Heidelberg Retina Tomograph-II.

Field of view (transverse)	15- x 15-
Scan depth	1.0 to 4.0 mm (automatic)
Focus range	-12 to +12 dioptres (automatic)
Digitized image size	2D images: 384x384 pixels 3D images: 384x384x16 to 384x384x64 voxels
Optical resolution (limited by the eye)	Transverse 10 microns Longitudinal 300 microns
Digital resolution	Transverse 10 microns/pixel Longitudinal 62 microns/pixel
Scan time per image	2D images: 0.024 seconds 3D images: 0.4 to 1.5 seconds