RETINAL CHARACTERISTICS OF MYOPIC EYES IN A SEMI-RURAL UK POPULATION

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Doctor of Optometry

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Thesis Summary

All levels of myopia are associated with an increased risk of ocular diseases such as glaucoma, and retinal detachment. The prevalence of myopia is increasing at an alarming rate across the globe so an increase in ocular morbidity would be expected unless action is taken.

The studies in this thesis were carried out to investigate how the retina, and optic nerve head change in appearance at different levels of myopia. Identification of signs indicating future progression would allow targeting of interventions to minimise the ultimate degree of myopia.

This thesis describes four community-based studies investigating retinal appearance in myopic eyes. A mixture of retrospective cross-sectional and longitudinal assessments using previously obtained digital fundus images are presented, along with a prospective cross-sectional study of the peripheral retina. The participants had myopia ≤-0.50 D and were mainly of white European ethnicity.

Crescent width was found to increase with both age and level of myopia. Those with inferior-temporally located crescents had the highest levels of myopia. Tilted discs were associated with higher levels of myopia and smaller optic discs. Upon longitudinal assessment of disc measures, the optic cup measures, and crescent width were found to increase. Peripheral retinal lesions were observed in 27 % of eyes. Pigmentary degeneration was the most frequently observed and was associated with increasing age and the widest crescents. White without pressure was found in 5.8 % of eyes and was associated with a higher magnitude of myopia. Static retinal vessel analysis showed no significant relationships between retinal vessel calibre summary measures and myopia, age, or optic nerve head measures.

The position of the myopic crescent is a possible predictor of future myopic progression. Further longitudinal study is needed to investigate this. The vertical disc diameter remained constant justifying the use of the quotient of the maximum crescent width to vertical disc diameter to determine crescent width change without the need for magnification correction.

Keywords: Myopia, optic disc, retina, crescent, periphery

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AL	Axial length
AMD	Age-related macular degeneration
ARIC	Atherosclerosis Risk in Communities' Study
ATOM	Atropine for Treatment of Myopia Study
AVR	Artery to vein ratio
BMES	Blue Mountains Eye Study
CD	Cup to disc ratio
COMET	Correction of Myopia Evaluation Trial
CRA	Central retinal artery
CRAE	Central retinal artery equivalent
CRVE	Central retinal vein equivalent
CSLO	Confocal scanning laser ophthalmoscope
CNV	Choroidal Neovascularization
CW	Crescent width
D	Dioptres
DC	Dioptres cylinder
DS	Dioptres sphere
ECM	Extracellular matrix
ERG	Electroretinography
F	Female
GEM	Genes in myopia study
GWA	Genome-wide association
HRT	Heidelberg Retinal Tomograph
IOP	Intra-ocular pressure
HCDR	Horizontal cup to disc ratio
HCD	Horizontal cup diameter
HDD	Horizontal disc diameter
JPEG	Joint Photographic Experts Group
LAT	Lattice degeneration
LED	Light emitting diode
Log MAR	The logarithm of the minimum angle of resolution
M	Male

META-PM	Meta-analyses of pathologic myopia
mm	Millimetres
mmHg	Millimetres of mercury
MMP	Matrix metalloproteinase
MRI	Magnetic resonance imaging
MWU	Mann Whitney U test
NICER	Northern Ireland Childhood Errors of Refraction Study
NRR	Neural retinal rim
OCT	Optical coherence tomography
ONH	Optic nerve head
OR	Odds ratio
p	Probability
PD	Pigmentary degeneration
POAG	Primary open angle glaucoma
PPA	Peri-papillary atrophy
PPP	Preferred practice pattern
PSD	Paving stone degeneration
PVD	Posterior vitreous detachment
QOL	Quality of life
RRD	Rhegmatogenous retinal detachment
RH	Retinal hole
RPE	Retinal pigment epithelium
RVC	Retinal vessel calibre
SER	Spherical equivalent refraction
SD	Standard deviation
SMS	Sydney myopia study
STD	Snail track degeneration
STAMP	Study of Theories about Myopia Progression
TGF-β	Transforming growth factor beta
USA	United States of America
UK	United Kingdom
VA	Visual acuity
VDD	Vertical disc diameter
VCD	Vertical cup diameter

VCDR	Vertical cup to disc ratio
WESDR	Wisconsin Epidemiological Study of Diabetic retinopathy
WHO	World Health Organisation
WWOP	White without pressure
µm	micrometre
X^2	Chi-square
µ	Mean
°	Degrees
%	Percentage
>	Greater than
<	Less than
≥	Greater than or equal to
≤	Less than or equal to
±	Plus, or minus

Chapter 1 Introduction

1.0 Background

Myopia is far from just an inconvenience due to its association with conditions leading to visual morbidities such as glaucoma, maculopathy and retinal detachment. With the increasing prevalence of myopia, the impact of its consequences is set to rise significantly (1). The increased size of the myopic eye leads to changes in several structures, including the retina and optic nerve head (2). Both structures are routinely examined in every eye examination. Detection of sub-clinical changes could facilitate the targeting of strategies to inhibit myopic progression and reduce the risk of visual loss.

1.1 Research aim and objectives

The purpose of this study is to determine the retinal characteristics of myopic eyes in a semi-rural UK population, using equipment available in a high street optometry practice. This is to be achieved via the following objectives:

1. Present relevant background information to highlight the significance of the study.
2. Identify the prevalence of retinal changes in a white European population of myopic eyes.
3. Determine the level of myopia at which retinal changes can be observed in this population.
4. Investigate how age affects the structures at different levels of myopia.
5. Explore possible relationships between peripheral and central retinal changes in myopic eyes.
6 Compare longitudinal retinal vessel measurements in progressing and stable myopes.

1.2 Myopia

Myopia, commonly known as short-sightedness, is a condition of the eye where the incident light focuses in front of, rather than on the retina; resulting in the image that is seen when looking at a distant object to be out of focus, but in focus when looking at a close object without the need for accommodation. Myopia occurs when the eye is too long, known as axial myopia, or when its optics are too powerful, referred to as refractive or index myopia (Figure 1.1A).

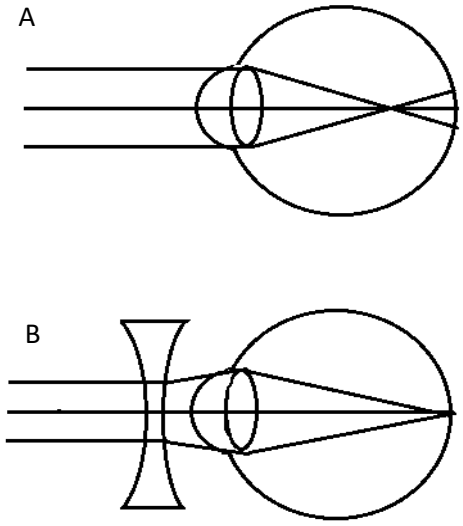


Figure 1.1. (A) shows the focus falling in front of the retina and (B) shows a diverging lens placed before the eye to focus the light on the retina.

The refractive state of the eye is predominately determined by the corneal power, lens power, anterior chamber depth, and length of the vitreous chamber. The first three components follow a normal distribution, while vitreous chamber depth does not unless those with myopia in excess of 6.00 D are excluded (3). The vitreous chamber depth is considered the principle structural correlate of myopia (4). Figure 1.2 shows the main refracting elements with average values based on those reported by Sorsby (5).

Myopia results when the corneal and lens powers can no longer compensate for the increased axial length (5). The myopic eye is long mainly from an enlarged vitreous chamber, with a 1 mm increase approximating to a 2.5 dioptre increase in myopia (6).

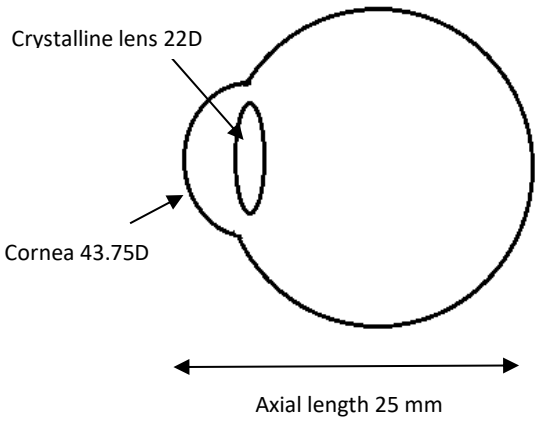


Figure 1.2. Schematic diagram of the eye showing main refracting elements and the average parameters from the survey by Sorsby et al. (5).

Myopia is most frequently corrected using spectacles or contact lenses, but also through the use of refractive surgery. The corrective lenses have a negative optical power (Figure 1.1B).

1.2.1 Prevalence of myopia

Myopia is one of the most common ocular conditions affecting 1.5 billion people worldwide (7) and around a third of the United Kingdom's adult population (8). Recent reports demonstrate myopia prevalence has increased across the world over the last few decades albeit not uniformly (9–11). Myopia is considered an epidemic in some parts of East and Southeast Asia, with surveys suggesting 70-80 % of children graduate from high school as myopes (9,12). The prevalence in mainland Europe and the United Kingdom is significantly lower than that reported in the Far East at 20-25 % (13). However, it is still increasing in the younger generations (13). In the United States, the prevalence has increased from 25 % to 41 % since the 1970s (10). The Aston Eye Study showed almost 30 % of 12-13-year-old children to be myopic in the cosmopolitan city of Birmingham; when ethnicity was considered 18.6 % of white European children were found to be myopic compared to 36.8 % of those of South Asian ethnicity (14). The Northern Ireland Childhood Errors of Refraction (NICER) study group, with an exclusively white European group, recently reported the proportion of children aged between 10 and 16 years with myopia had

more than doubled over the last 50 years by comparing their data to that of Sorsby (15). The effect of sex on the prevalence of myopia is not apparent; some studies report a higher prevalence in females, while others report no difference (11,16,17). The disagreement between studies may be in part due to the age of subjects. From the age of nine females are seen to have a higher prevalence until the end of the growth period (16). This may be to differences in the pattern of progression and inherent structural differences between male and female eyes (18) or due to the greater emphasis on education and near related activities in girls (19). Another factor suggested by Rudnicka et al. is insufficient statistical power to detect differences (19).

Along with the increased prevalence, onset is occurring at a younger age (15,20) resulting in higher magnitudes of myopia (7), presumably from more years of progression (21). The prevalence of high myopia, usually defined as myopia over 6.00 D, is reported to be 9-21 % in the Far East (9) but closer to 2 % in white European populations (10). A survey published in 2012 reported 20 % of graduates in South Korea reached myopia greater than 6.00 dioptres by age 19 (22). Six dioptres is the level which is traditionally associated with increased risk of ocular morbidity (23).

Comparison of prevalence studies is hampered by several factors including inconsistent definitions of myopia, differing methodologies, age groups, and environments. Despite these complicating factors, a clear temporal shift of increased myopia prevalence is occurring (8,24,25).

The question of the “epidemic” has been addressed in a recent paper by Morgan and colleagues (26). They reviewed the prevalence of myopia across many countries in East and Southeast Asia, concluding culture, rather than ethnicity to be the significant factor explaining the differing prevalence in different countries. The divergence in prevalence pattern across some parts of the world is of great interest, and many of the proposed factors influencing this will be outlined in subsequent sections.

1.2.2 Classification of myopia

Classification of a condition such as myopia is useful when studying associations and interrelationships. Many contributors to the field of myopia have introduced schemes to classify myopia. In addition to the terms axial and refractive myopia mentioned earlier, other classification schemes include classification by the degree of myopia, associated pathology, the rate of progression, and age of onset (Table 1.1).

Table 1.1. Showing some of the classifications used to categorise myopia.

Type	Categories	Features
Age of onset (27)	Congenital	-Present at birth
	Early onset	-Onset between age 5 and early teens
	Early adult onset	-Onset in late teen years to early twenties
	Late adult onset	-Onset after age 40
Clinical entity (28)	Simple myopia	-Normal VA
	Pseudomyopia	-Over accommodation
	Pathologic myopia	-Related to ocular disease
	Induced myopia	-e.g. drug-induced
	Night myopia	-Empty field over focus
Physiological		-Usually, low magnitude and each component follows a normal distribution
Intermediate		-Higher myopia but no pathological signs other than optic disc crescent
Pathological (2)		-Typically, higher levels of myopia and more likely to be associated with morbidity. May also be labelled degenerative
Rate of progression (29)	Stationary	-Stationary in adulthood
	Temporarily progressive	-Progresses into the twenties
	Permanently progressive	-Rapidly advances in early adulthood
Anatomical features (29)	Axial	-Increased anterior chamber depth /vitreous chamber
	Refractive	-Steep corneal curvature, index,

Myopia is often described based on the age of onset. Grosvenor describes myopia present at birth as congenital, and when onset occurs between age six and early teen years as early-onset. Myopia arising in the early twenties as early-adult onset, and adult-late adult onset when myopia develops after the age of 40 (27).

The term physiological myopia has been used when each of the optical components (corneal curvature, lens power and axial length) lies within the normal distribution of the population (2). Physiological myopia is also considered as myopia that is not classed as pathological myopia. Pathological myopia occurs when normal growth fails to stop (30), and may also be termed degenerative myopia which carries the highest risk of ocular morbidity (31). Myopia greater than 6.00 D has traditionally been considered the cut-off between physiological and pathological myopia (23), although this has been challenged due to the number of common diseases such as glaucoma, cataract, and retinal detachment associated with lower levels of myopia (32). The term "intermediate myopia" was proposed some time ago for eyes with increased axial length, but not displaying the classic degenerative fundus changes, other than an optic disc crescent, used to define pathological myopia (2). Most classifications share the common problem of ambiguity in cut-off values. Further issues arise from inaccuracy when the subject is asked to recall information such as time of onset which may not coincide with the first correction (33). The method of refraction may lead to misclassification; for example, myopia may be overestimated when auto-refraction is used without cycloplegia.

In the research setting, myopia is most commonly defined by magnitude in terms of the spherical equivalent refraction (SER) or axial length. SER is calculated by adding half the cylinder power to the spherical component and is expressed in dioptres (D). A value of ≤ -0.50 D is often taken to be myopic (14,15), but not by all workers, with some using an SER ≤ -0.75 D, or ≤ -1.00 D as the cut-off point (10). Moderate myopia is frequently defined as SER of at least -3.00 D, while high myopia is denoted as an SER of at least -6.00 D, and ≤-10.00 D as very high myopia (34). The American Academy suggests a definition for high myopia using axial length ≥ 26.5 mm (16). Comparison of studies is further complicated by some studies reporting spherical refraction instead of SER, and by use of stratification rather than a continuous scale of refraction level.

1.2.3 Impact of myopia

Myopia is often regarded as an inconvenience rather than a disease, especially at lower levels, by both those having myopia, parents, and many eye care providers (35–37). Wolffsohn et al. (38) through the use of an online survey found practitioners in Asia were significantly more concerned than those in the UK, 90 % compared to 58 %. This could be expected due to the increasing prevalence of myopia in Asia over recent decades. The public health campaigns that run in Singapore and Hong Kong demonstrate how seriously myopia is taken in these countries (Figure 1.3).

Figure 1.3. A selection of public health posters from the Singapore public health campaign. www.nas.gov.sg/archivesonline/posters/record-details/32b52437-115c-11e3-83d5-0050568939ad

Kemplin et al. (39) suggested in 2004 that as many as 2.5 billion people would be myopic by 2020, and recently Holden et al. (7) predict that this will increase to 5 billion by 2050. The need to unlock the mechanisms underlying myopia development is more significant than ever. Morgan (40) describes some diseases being effectively treated without a full understanding of the disease mechanism. However, for myopia, he infers this is not possible. As without a clear understanding of the treatment, it may induce the conditions to increase myopia, that it was postulated to reduce. Over the last quarter of a century, there has been a flurry of work (36) aiming to determine the mechanisms of myopia onset and progression, along with possible management options which will be summarised in subsequent sections.

1.2.4 Morbidity due to myopia

For those with low myopia, vision is generally normal when spectacles are worn, whereas with higher levels of myopia spectacle correction induced image minification may be detrimental to visual acuity and asthenopia may result from changes to accommodation (2). From a more sinister perspective, it is well documented that myopia is associated with many ocular abnormalities that lead to ocular morbidity (23).

The World Health Organisation (WHO) classes pathological, and uncorrected myopia as significant causes of visual loss (41), with the treatment of myopia being a WHO priority as part of the drive to eliminate avoidable blindness. Recent reports list myopic maculopathy as the most common cause of visual loss in Japan (42), the second in China (43), and in the top five in many developed countries including the United Kingdom (44). With the higher prevalence of high myopia in younger cohorts, especially in the urban hotspots of East Asia, the occurrence of visual morbidity is an increasing public health concern in these populations (25).

Several large-scale epidemiological studies have shown an association between myopia and common conditions such as cataract, glaucoma, and retinal detachment, at lower degrees of myopia (45–48). The far higher prevalence of low and moderate levels of myopia makes it likely the incidence of the conditions above will rise significantly. The association between lower levels of myopia and ocular pathology have led to the question “Is there a safe level of myopia where it is only an inconvenience?” Flitcroft in a recent review argues the term “physiological myopia” should be rejected in light of these findings (32).

1.2.5 Quality of life and myopia

Quality of life (QOL) ratings reflect the positives and negatives of life and how they affect an individual's well-being. QOL has been assessed in relation to both physiological and higher levels of myopia. Various methods are used to determine a measure of QOL which makes comparison of studies difficult. Instruments used by some are generic, these provide a general sense of well-being but at the expense of sensitivity. Commonly used measures are the utility score, a value of 1.0 is perfect health, and a score of 0.0 is death. Time trade-off years reports the number of years willing to be sacrificed not to have the condition, and the standard gamble technique assesses the risks the person is willing to accept with the treatment. Vision-specific instruments such as the national eye institute visual functioning questionnaire can be more sensitive (49).

A study of myopic adolescents in Singapore rated physical and psychosocial scores at a level similar to those without myopia using the PedsQL 4.0 Generic Core Scales (50). Lim and co-workers (51) assessed utility values finding no relationship to the level of myopia in a group of medical students in Singapore. Quality of life and function have been assessed more often in adults. A survey in Japan (instrument not specified by authors) that included responses from 200 highly myopic adults revealed a lower quality of life score than those with low myopia. The questions assessing psychological status over the last month were not significantly different between the high and low myopes (52). A review by Lamoureux and Wong (53) concluded that high myopes suffer from a negative effect on quality of life from a cosmetic, functional, psychological, financial, and general health aspect, whereas those with lower amounts of myopia suffered little if any reduction in quality of life. The effects were found to vary with age and geographical location. A point of interest comes from the WHO target to reduce uncorrected refractive error. Several of the studies reviewed by Lamoureux (53) show uncorrected myopes to report visual functioning problems affecting the quality of life whereas corrected myopes without co-pathology rated to a similar level to those without myopia (54).

1.2.6 Financial impact of myopia

From an economic view, in addition to the cost of correcting the refractive errors through spectacles, contact lenses and refractive surgery, there are the costs of managing associated disease and continuing care for those unfortunate to lose their sight. Quality of life reduction and limitations of occupation and recreational activities also add to the social burden and cost. Various estimates of the cost of myopia are found in the literature, although different social and health care systems, along with multiple confounding factors, reduce the usefulness of the figures. However, the high headline figures may give credence to the drive for investment in myopia control research. Lim and Frick (55) attempt to determine what would be saved if myopia could be cured by providing an economic evaluation for the 900 million myopes who pay for eye care worldwide. They suggested $45 billion excluding costs to governments and health insurance for dealing with the associated diseases.

1.3 Aetiology of myopia

Despite the many hypotheses, the exact mechanism for the development of myopia is not clear. However, it is known to involve a wide range of mechanisms affecting the retina, choroid, sclera, and central nervous system (32). The complex combination of optics, the shape of the posterior segment and biochemical mechanisms, determine how the eye grows (32). An understanding of the process of myopia development and progression may hold the key to developing effective treatments such as pharmacological agents, multifocal contact lenses, and spectacles (56). Work in this field covers many disciplines involving work on humans and animals along with investigations of genetics. Firstly, it is important to consider normal refractive development.

1.3.1 Normal refractive development

From birth to puberty the eye undergoes significant growth to produce a leptokurtic distribution of refractive error strongly favouring emmetropia (57). The average newborn is hyperopic, having a mean refraction of +2.00 dioptres with a normal distribution. Myopia being present in approximately a quarter (28) of this age group. Hypermetropia increases from birth reaching its peak at around six months followed by a gradual reduction towards the adult distribution centred around emmetropia (Figure 1.4).

Emmetropisation is the term used to describe the shift from the newly born state of ametropia towards emmetropia in early life. The most rapid period of change occurs between 6 months and two years with Ingram et al. (58) suggesting that the process is complete in 80 % of children by one year of age. Following the initial rapid period of change, emmetropisation continues at a slower rate until around the age of 6 years (59).

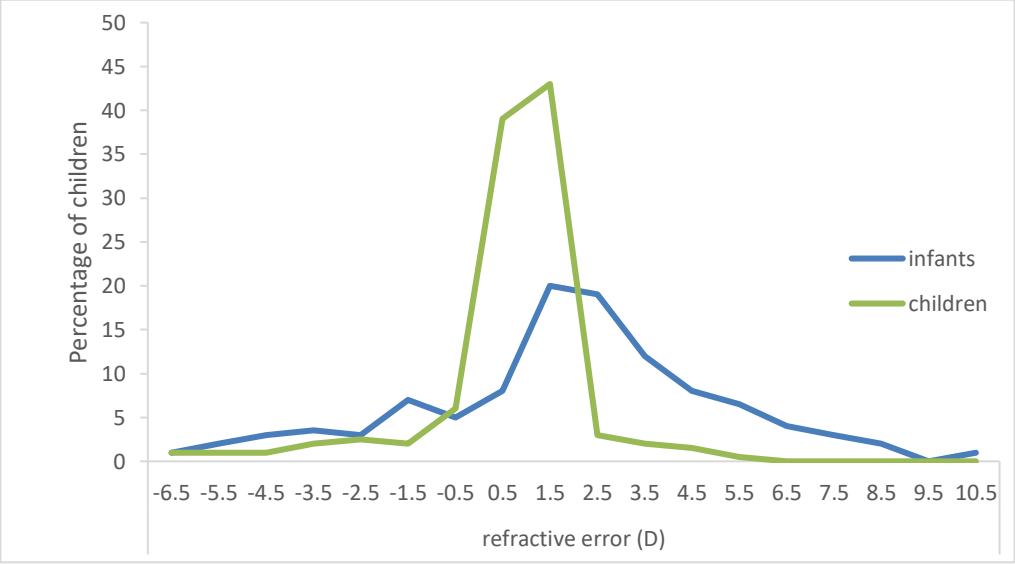


Figure 1.4. Comparison of the distribution of refractive error between newborns (0-3 months) and children (age 6), re-drawn using data from that presented by Zadnik (33), demonstrating the shift in mean refraction towards myopia.

The higher than expected amount of emmetropia led to the suggestion of two processes of emmetropisation: an active, and a passive process. The passive process is postulated to be genetically driven with the increased axial length being compensated for by a reduction in the

optical power of the eye through changes in the cornea and crystalline lens (60). The passive phase accounts for the rapid changes seen in the first year or so of life. The active process involves visual feedback to modulate eye growth (60). Evidence from studies involving young humans and animals demonstrate that visual experience has an important role in refractive development (60–62). Animal studies are discussed in more detail in section 1.3.4.

Myopia prevalence decreases at age 2 to around 2-3 % before rising again to 6 % at age 6 (63). This is also the age that in some ethnic groups myopia increases more rapidly than in white European groups (11). Beyond the age of six years, the prevalence of myopia is seen to increase as the lens loses its ability to compensate for the increased axial length. The cornea is thought to reach adult levels by around the age of 4 years leaving the crystalline lens to compensate for further axial length increases (64). After age twelve increases in axial length translates to increased myopia (65). Typically, early onset myopia, often referred to as Juvenile onset myopia, levels off in the mid-teen years as general growth slows. Sorsby et al. (3) showed that by age 13-14 years the average values of the refractive components were similar to those of young adults concluding that eyes do not grow appreciably after this age. Many myopes still progress, or even have an onset beyond this age (29). Sorsby's figures are averages hence why changes beyond age 14 were not significant, compounded by the lower prevalence of adult-onset myopia in the 1960s.

Against-the-rule astigmatism is common in the newborn, it usually reduces by age 3.5 years and shifts towards with-the-rule in adulthood (66). The persistence of against-the-rule astigmatism has been associated with juvenile onset myopia and progression (67).

With the majority of myopia developing after the period of normal emmetropisation it has been suggested myopia is a result of a failure of mechanisms to maintain emmetropia, whereas hypermetropia is considered a failure of emmetropisation (68).

1.3.2 Genetic influence on myopia development

Over the years the weight given to the importance of genetics in myopia development has shifted. Curtin in his 1985 book states *"it's difficult to chide the scientist who scoffs at the theories that proposed environmental causes of myopia"* (2). The reverse is argued by Morgan and Rose who consider myopia as being due to environmental factors, stating *"the rapid increase in prevalence seen over recent decades as not fitting with evolutionary change"* (69).

In the investigation of genetic influences on myopia development, the challenge is to determine how much myopia present in families is due to genetic factors, and how much is a result of shared environmental exposures. The genetic basis for myopia is supported by evidence from family (70,71) and twin studies (34,72). Many workers have shown that having two myopic parents poses a greater risk than just having one (12,15,71). The NICER study of 12 to 13-year-old children reported odds ratios of 2.91 and 7.79 for one and two myopic parents (15). In a group of Singaporean school children, parental myopia was also shown to be a risk factor for greater progression (73). The Framingham Offspring Eye Study presented odds ratios of between 2.50 and 5.13 (dependent on age) for myopic siblings (74). A moderate correlation ($r = 0.37$) was shown for sibling refraction in the Beaver Dam Survey (75). Klein investigated a broader family association, showing a stronger correlation for refractive error between sibling and cousin than parent and child (76). This may be explained by changes in environmental influences over time.

Heritability studies aim to quantify the extent to which genetic and environmental factors contribute to myopia. Heritability is scored on a range of 1.0, if entirely genetic, to 0 when due to exclusively environmental factors. Twin studies provide a unique opportunity to investigate the relationship between environment and genetics, providing useful insight, although limited by certain assumptions; such as twins experiencing the same environmental factors often resulting in an overestimation of genetic contribution. In twin studies, comparisons of the presence of a condition in identical (monozygotic) and non-identical (dizygotic) twins provide a measure of heritability. For myopia, this has been reported to be between 0.77 and 0.91 in white

European populations (72,77). Twin studies show a high heritability of the underlying structural changes such as increased axial length and corneal curvature (77,78).

Several of the large twin registries have been used to search for genes associated with myopia. The Genes in Myopia Study (GEM) used the Australian registry of 31,000 twins, identifying several possible genetic loci linked to the more common school onset myopia (78). The first genetic association identified for myopia was chromosome Xq28i in 1990 (79). Genes have now been identified for syndromes such as Sticklers and Marfan syndromes, both associated with high myopia, and for high myopia not associated with a syndrome. These high myopias are of low prevalence and the genes identified do not appear to be involved in the more common moderate myopia (80).

The use of genome-wide association studies (GWA) appears to be the most powerful method for identifying genetic loci in common but complex conditions such as myopia (81). The cost of these studies, which include tens of thousands of participants, has been a barrier. However, large shared databases along with enhanced software are making this method more practical. GWA studies use hundreds of thousands of markers across the genome to evaluate associations between phenotypes in different conditions. Nakanishi (82) was the first to report an association with high myopia on chromosome 11q24.1 using GWA. Subsequently, several other loci associated with low and high myopia have been identified from the large CREAM (83) and 23 and ME (84) studies. These two studies had different methodology but with very similar outcomes and 20 loci in common. Many of the loci identified are generally of small effect but may interact (8).

The current consensus appears to be the acceptance of some genetic forms of myopia; usually with high myopia and often part of a syndrome (34). However, most myopia occurs through environmental factors that may be influenced by many genes of small effect (34).

1.3.3 Non-genetic factors in myopia development

Many factors have been associated with an increased risk of myopia onset and progression. Near work, often in the form of educational attainment (22), or occupation (85) has featured as a risk for myopia development for many years and there is valid evidence for this (26). Goldschmidt et al. reported myopia to be ten times more common in university students compared to unskilled workers (86). Occupations involving close work, such as microscopy, have been associated with myopia development and progression (85). Increased risk has been reported regarding books read per week (87), a reading distance of less than 30 cm (88), and reading continuously for more than 30 minutes (88). The increased use of handheld visual display units, along with the culture of intensive education from a young age in some East and South-east Asian countries has been suggested as an explanation for the spiralling prevalence in such regions (11).

Many workers have investigated the relationship between myopia and accommodation with inconsistent findings (89,90). The retinal-defocus theory, suggests an inaccurate accommodative response produces hyperopic defocus driving increased eye growth (56). Some reports show greater accommodative lag in myopic eyes (89,91), while some have not (92). Gwiazda et al. (89) demonstrated increased lag before myopia onset whereas Mutti et al. (93) only found increased lag after the onset of myopia. If the less accurate accommodation occurs after the onset the defocus theory appears less viable (56). The Correction of Myopia Evaluation Trial (COMET) study (94) found a more significant reduction in myopia progression when progressive power lenses were worn in those with near esophoria and high accommodative lag adding support to this theory. Although, the Studies of Theories about Myopia Progression (STAMP) study found no greater effect in those with inaccurate accommodation (95). Initially, the success of atropine in reducing myopia progression added further support to the involvement of accommodation. Although, evidence now suggests the mechanism by which atropine has its effect may be non-accommodative and local to the retina (96). Further doubt about the role of inaccurate accommodation comes from animal studies. Multiple short periods of clear vision in animal

models are protective against the development of lens-induced myopia (97). If this applies to children, they would need to be engaged continuously in near activities (26), this is unlikely due to the surrounding area being focused on the peripheral retina (98). Winawer and Wallman suggest the frequency and duration, of glances away from the close work may be a factor following work investigating varying intervals of no lens wear in chicks (98).

Many studies considering near work have several potential sources of error, such as the reliance on the parental recording of time at the near task, and other confounding factors such as age, ethnicity, and parental myopia clouding associations (88,99). These factors have led to a shift in interest, with time spent outdoors now considered a more significant environmental factor. Work from teams in several locations has shown that children who spend more time outdoors are less likely to become myopic (69,100,101). The exact mechanisms are not clear. However, the light-induced release of dopamine appears a plausible biological pathway (26,71).

Other areas of extensive investigation in the pre-myopic eye have included: binocular status (102), the accuracy of accommodation (93), the form of the peripheral optics of the eye (section 1.3.7), and the level of refraction at specific age points. Recently published work (70) found refraction at age 8 to be a strong predictor of myopia risk.

1.3.4 Animal work and myopia

Despite clear differences in the structure and development of human and animal eyes, it is widely agreed that the use of animal models has enhanced the understanding of myopia development in humans. Several species have been shown to be suitable models including marmosets, monkey, chick, mouse, and tree shrew (103,104).

Initial use of animal models considered form deprivation, this was followed by lens induced defocus, and more recently circadian rhythms. Work by Wiesel et al. (105) in the 1970s accidentally discovered that suturing the lids of a monkey led to myopia development through an increase in axial length. This finding has been replicated in other species using translucent occluders (103).

The next significant discovery was compensatory eye growth to both positive and negative lenses in several species (104,106). The use of negative lenses in young animals to alter feedback led to an increase in axial length, whereas positive lenses led to a reduction in axial length (62). The ability to compensate precisely in both directions led to the conclusion that the mechanism for emmetropisation is an active feedback process (107). The search for the signal that detects the sign of defocus guiding the eye to emmetropia has included the blur hypothesis, the potential of several monochromatic and chromatic aberrations, although no one mechanism seems likely (103). Whatever the mechanism of feedback it has classically been believed to be via the central nervous system. This has been questioned due to the finding that lens compensation still occurs in chicks when the optic nerve is cut (61), or blocked with a neurotoxin in tree shrew models (108). Although compensation still occurs, the accuracy has been shown to be reduced, suggesting central nervous input is necessary for fine-tuning (109).

A favoured theory explaining myopia development and progression has been retinal defocus resulting from inaccurate accommodation (56). Support for this includes the results of studies using bifocal lenses and work with atropine eye drops. Animal models have cast doubt on the role of accommodation in myopia development. Schaeffel et al. (110) found chicks still

compensated to minus lenses when accommodation was rendered ineffective. Further evidence against accommodation is the observation that atropine reduces myopia progression in animals with striated ciliary body muscle, which is not affected by atropine due to absence of muscarinic receptors (111), suggesting the effect may be retinal, not accommodative (96).

Evidence from animal models has supported the role of the peripheral retina in controlling eye growth. In monkey models, Smith et al. (112) found that peripheral occlusion resulted in axial elongation. This was also the case when hyperopic defocus was induced just in the periphery (113). Further evidence of the role of the peripheral retina in eye growth comes from a study that demonstrated lens compensation following laser ablation of the fovea (114). These findings were not observed in chick models (115) suggesting inherent differences between species.

Interfering with circadian rhythms by altering the light-dark cycles has been shown to influence post-natal growth (116). Myopia induced by deprivation has been shown to reduce dopamine levels (117) in chicks, and the systemic administration of melatonin which modulates dopamine release led to axial elongation in normal chick eyes (118). Melatonin is involved in seasonal timing and as well as ocular rhythms and may explain why myopia progresses more during the winter (119). Although the majority of work has involved chick eyes, diurnal rhythms have been demonstrated in choroidal thickness and axial length in mammals and humans (120). Recent work has suggested that changes in the phase of circadian rhythms may explain why outdoor time has more effect on some eyes more than others (121).

The choroid has been found to show changes in its thickness in response to defocus in several animals models, and humans (62). In the chick eye, a transient thickening of the choroid is seen in the early stage of recovery from lens-induced myopia before thinning as the axial length reduces. The effect observed in humans and other primates are less than the chick eye; however, rapid changes occur in choroidal thickness after 60 minutes of lens wear (122).

Work investigating the biological link between the retina, choroid, and sclera has led to the identification of several potential messengers. Glucagon, retinoic acid, transforming growth factor-beta (TGF-β) and dopamine have been shown to increase or decrease depending on whether myopic, or hypermetropic defocus is induced (123). In myopia, the TGF-β levels are reduced very soon after myopia development. TGF-β has been implicated in the differentiation of scleral fibroblasts to myofibroblasts in response to stress, possibly further contributing to the progression of myopia (124). Retinoic acid has been proposed as a signalling molecule between the retina and sclera (125). The levels of retinal, retinoic acid synthesis were shown to decrease as myopia was induced and increase during recovery in chick, marmoset and guinea pig eyes (125). Wallman concludes that none of these molecules is a solitary key messenger (103).

There are limitations to using animal models. Studies have tended to use high amounts of defocus, and the developmental age is often different from the time humans usually develop myopia. Despite these limitations, findings are generally considered applicable to humans once the observations have been confirmed in monkey models (104).

1.3.5 The sclera and myopia

The sclera is the tough fibrous connective tissue that forms the outer coat of the eye and is commonly referred to as the "white of the eye". The many functions of the sclera include: defining the shape of the eye, being a strong framework for the retina, withstanding the force generated by intraocular pressure and eye movements, providing a pathway for aqueous outflow, protecting the contents of the eye from external trauma and providing attachment for the extraocular muscles (126,127).

The strongest structural correlate of myopia is increased axial length, or more specifically elongation of the vitreous chamber (2). The dynamic nature of the sclera is regulated by both environmental and genetic factors (127). Remodelling of the sclera, which occurs throughout life, has been studied extensively over the last century. Work on postmortem human sclera has

been supplemented, with enormous benefit to understanding by work on animals-mostly tree shrew and marmoset, as despite size and functional differences, they provide reliable models (128). The mammalian sclera consists of up to 90 % collagen by dry weight; collagen type 1 dominates but others including types 3 and 5 are also found (129). Histologically, the sclera is divided into three layers: the episclera, the stroma which constitutes most of the thickness, and the innermost lamina fusca. The stroma is primarily made up of collagen fibres arranged in a fan-like pattern posteriorly, while anteriorly they follow a more equatorial course to enhance the hold of the extraocular muscles (130). Compared to the cornea, the scleral fibrils are more varied in size and orientation. The size of the scleral collagen fibrils in adults varies between 25-250 nm with the average being 94-102 nm (128). The thickness of the normal sclera ranges from 0.3 mm where the rectus muscles attach to the globe, to 1 mm posteriorly (126).

Between the lamellae of fibril bundles lies the extracellular matrix (ECM). Evidence, in vivo and in vitro, implies the ECM is involved in scleral reshaping through the continuous synthesis and degradation of the ECM components. The ECM is key to the maintenance of rigidity, strength, and elasticity (128). Proteoglycans form a significant part of the ECM despite only comprising 0.7-0.9 % of the total dry weight of the sclera (128). Their role involves modulation of collagen fibril arrangement and probably scleral hydration due to the negative charge they carry (131). Synthesis of proteoglycans continues into the fourth decade; an abnormality of this synthesis may affect the biomechanical features of the sclera and thus the scleral shell size (127,128). Mice studies by Austin et al. (132) support this hypothesis; young mice made deficient in proteoglycans, exhibited changes in fibril diameter and organisation with scleral thinning and increases in axial length. Troilo and colleagues reported a negative correlation between axial elongation and proteoglycan synthesis in marmosets, suggesting ECM to be a significant factor in scleral remodelling (123).

Matrix metalloproteinases (MMP's) are the most studied of the protease enzymes present in the sclera. MMP's have been found to initiate degradation of collagen and other ECM components

(133). The levels of MMP increased in the sclera of mammals as myopia is induced and then decrease during recovery (134). The primary cells of the sclera are the ECM secreting fibroblasts; these are found throughout the sclera between the lamellae of fibril bundles (126). Fibroblasts are linked to the biomechanical properties of the sclera by the myofibroplastic properties that many fibroblasts display. The myofibroplastic feature allows the sclera to respond to stress, protecting the surrounding tissues. Poukens et al. showed these cells with elastic properties to be more prevalent in the sclera of older individuals after the usual period of myopia development (135). From a clinical perspective Marfan's syndrome, a condition showing mutations in the fibrillin gene features abnormal scleral rigidity resulting in high myopia (136). The thinner sclera of the myopic eye shows greater extensibility, referred to in the literature as “scleral creep”, than controls in human and tree shrew samples (137). Reduced thickness, rather than changes in the properties of the tissue, seems responsible, although Phillips and McBrien suggest no more than 20 % of the increase in eye size could be accounted for by a simple stretch (137). This finding suggests that other factors, such as biochemical changes, are likely to be more significant as the eye elongates with myopic progression (129). Scleral creep in tree shrews occurs in both posterior and equatorial regions within a few days of myopia development and is strongly correlated to the amount of myopia (138). In vivo studies, in which the intraocular pressure is increased in mammalian eyes show initial creep followed by a subsequent shortening of the eye (138).

The sclera of highly myopic eyes is characterised by thinning of the collagen fibre bundles and a reduction in the size of the individual fibrils, along with shape changes in some fibrils (2). Electron microscopy shows the reduced fibril diameter especially at the posterior pole, this along with alterations to the ECM result in a loss of dry weight (127), rather than a simple stretch of tissue to cover the larger area suggesting a biological factor. When the sclera of high myopes is compared with age-matched emmetropes, the myopic posterior sclera can be half the thickness, even without posterior staphyloma (137). Caution needs to be exercised as this information

obtained post-mortem does not allow causation to be inferred along with possible tissue changes during preparation. Work using animal models deals with some of the issues. Kang et al. (139) demonstrated the fibril size, and spacing remained normal for the first few weeks after myopia had been induced in tree shrew models, and McBrien (129) also noted that fibril size reduction was only observed when the animals remained myopic for several months. Scleral thinning in response to induced myopia occurs rapidly in young tree shrews followed by a slower thinning over the following months, even though the myopia is still progressing (127).

There is a growing body of evidence suggesting growth signals generated in the retina lead to changes in the scleral ECM (127,128). The basis for this comes from animal work showing that myopia can still be induced and recover in eyes where the optic nerve is cut or blocked (61) as discussed in section 1.3.4. Growth factors such as TGF-β can increase proteoglycan synthesis. TGF-β is also important in the regulation of extracellular matrix turnover and control of collagen production via fibroblasts (124). Hung (140) suggested a theory he termed the "incremental retinal-defocus theory". This theory suggests that an increase in the retinal defocus area, leads to an increase in proteoglycan synthesis through neuro-modulator release in the retina.

The position of the retina is generally controlled by the location of the scleral shell with some additional adjustment made by the thickness of the choroid (141). The highly vascular choroid has been shown to synthesise growth factors and MMP's which are also present and active in scleral tissue. Marzani et al. (142) demonstrated that the choroidal molecules could inhibit scleral proteoglycan synthesis in the sclera of chicks. Recovery from induced myopia in the chick begins with choroidal thickening before scleral changes occur (62). The chick sclera varies from mammalian sclera in that it has an inner cartilaginous layer. Rada postulates that in recovery the choroid thickens, the rate of vitreous chamber elongation slows, followed by the extra fluid in the choroid inhibiting scleral proteoglycan synthesis to slow elongation of the eye (128).

1.3.6 Eye shape

Wallman and Winawer (143) suggested the much greater area and neural input of the peripheral retina, may play a part in the defocus signal influencing the process of emmetropisation and development of myopia. Many investigations of the eye and retinal shape have ensued. However, the role of the peripheral retina in the development of myopia remains uncertain (144).

The determination of eye shape has evolved from post-mortem examination and X-ray imaging, to increasingly sophisticated in vivo methods such as high-resolution magnetic resolution imaging (MRI) with 3D reconstruction. Assumptions of eye shape are also made from the assessment of peripheral refractive error (145). Eye shape has been assessed in all types of refractive error but most frequently in myopic eyes, especially of the higher degrees, and most often in cross-sectional investigations. Verkicharla and colleagues (145) make it clear in their review that retinal and eye shape are not the same although they are related.

The shape of the central retina is often described using ellipsoids (146). Eyes with hyperopia and emmetropia are usually oblate in shape, flatter at the posterior pole (Figure 1.5a), while myopic eyes are usually less oblate and maybe prolate, more curved at the posterior pole (Figure 1.5b).

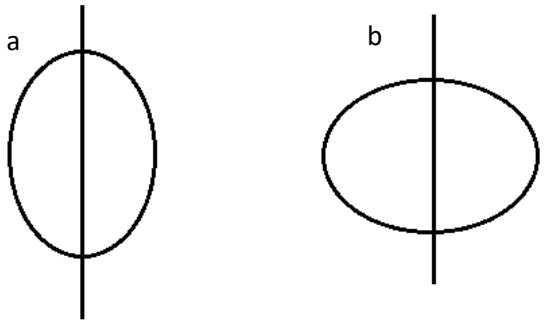


Figure 1.5. Showing ellipsoids used to describe the retinal shape. The left image shows an oblate ellipse and the right picture a prolate ellipse.

Strang et al. (147) in a paper considering factors limiting visual resolution in myopia, suggested three patterns of stretch in myopic eyes. Equatorial stretching (peripheral) in which the area of change is parallel to the visual axis, central where the elongation occurs at the posterior pole,

and global expansion when elongation occurs in both the peripheral and central areas (Figure 1.6). Verkicharla et al. (145) added a fourth, the axial expansion model, which is a combination of equatorial and posterior pole expansion. Considering eyes based on these shapes and the ellipsoids, which imply symmetry, is deemed to be an oversimplification, as eyes are generally not rotationally symmetrical due to the insertion of the optic nerve (145). Atchison et al. (146) investigated the symmetry of eye growth in adult eyes using MRI. Myopic eyes were found to have greater axial growth than emmetropic eyes. However, less difference in the height, and even less in width was observed. They went on to suggest the reason for the differential growth was most likely a result of orbital constraint rather than local variations in scleral flexibility, although, the earlier work of Chau (148) suggested orbital size was not related to eye size.

Figure 1.6. Models of retinal stretching in myopia: a) global, b) equatorial, c) posterior polar, and d) axial expansion. The solid lines represent the emmetropic eye and the dashed lines the myopic retina. Reproduced with permission (145).

The use of 3D MRI allows high-resolution imaging of general and localised eye stretch but is limited by cost and availability (145). Moriyama et al. (149) classified 44 highly myopic eyes (≤-8.00 D) into four distinct shapes, nasally distorted, temporally distorted, cylindrical, and barrel type, using 3D MRI. When they investigated eye shape in relation to the presence of myopic maculopathy no association with any of the forms was observed. Guo et al. (150) identified six eye shapes (Figure 1.7) in a group of 95 high myopes (≤-6.00 D) using 3D MRI. The most irregular eye shapes were in those with higher levels of myopia (SER), and greater axial length as expected, but also in the older age group. 50 % of the eyes were still of a regular spheroid shape. In contrast to Moriyama, Guo observed several associations; barrel, and temporally distorted eyes

showed greater maculopathy, while nasally and temporally distorted eyes had poorer visual acuity.

Figure 1.7. Fundus image and 3D MRI images reproduced with permission from Guo et al. (150) 95 eyes. The numbers between the images indicate the number in the group.

1.3.7 Peripheral refraction

After many years, the interest in peripheral refraction and its relationship to myopia development and progression has been re-ignited. This has been driven by strong evidence from animal model's indicating a role for the peripheral retina as discussed in section 1.3.4 (112,113), and the re-assessment of two papers reporting the peripheral refraction of Dutch pilots in training from 1971 (151,152).

The relationship between peripheral refraction and the development and progression of myopia has been the subject of many studies (113,153,154). It is generally understood that hyperopes and emmetropes usually have a relatively myopic peripheral refraction, while myopes have a relatively hyperopic peripheral refraction, at least in the horizontal field (6,145) (Figure 1.8).

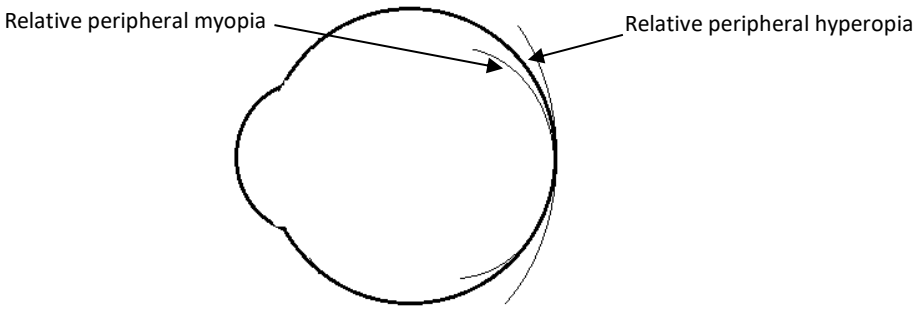


Figure 1.8. Showing peripheral focus shells for relative peripheral myopia and hyperopia.

The second theory explored as part of the STAMP study, "the mechanical tension theory", postulates that ciliary-choroidal tension in the anterior portion of the globe reaches a critical point when the proportional growth of the globe is no longer possible. This results in elongation of the eyeball and increased myopia as the crystalline lens can no longer flatten and decrease power to compensate (56). As a result of the axial growth, the posterior eye becomes more prolate in shape which is associated with greater relative peripheral hyperopia (144).

Peripheral refraction is most commonly measured using an open field auto-refractor, with the patient changing fixation. Other methods include retinoscopy or aberrometers, but as none are designed for the purpose, the measurement is prone to errors (144). Most workers have measured the refraction along the horizontal meridian at varying eccentricities out to 30° (56,155). Vertical measurements are less often reported, and when they are most eyes show a relative myopic defocus in the vertical meridian (154).

In 1971 Rempt and colleagues (151) reported the results of peripheral retinoscopy along the horizontal axis at an eccentricity of 60˚ in a group of 442 Dutch trainee pilots. They described five patterns of peripheral refraction. It was the associated study of Hoogerheide et al. (152) that has been interpreted to indicate relative peripheral hyperopia may be an indicator of future myopia. This study followed 214 of the trainee pilots from the previous study finding those with peripheral hyperopic refractive errors were more likely to have developed myopia. The main point of contention in the interpretation is the uncertainty whether the peripheral refraction was

measured before or after the development of myopia, and over what length of time the group were followed (156). These points led Rosen et al. (156) to conclude that a relative peripheral hyperopic refraction is a consequence rather than a cause of myopia development and progression. This was also the conclusion in a review presented by Charman and Radhadkrishnan (144).

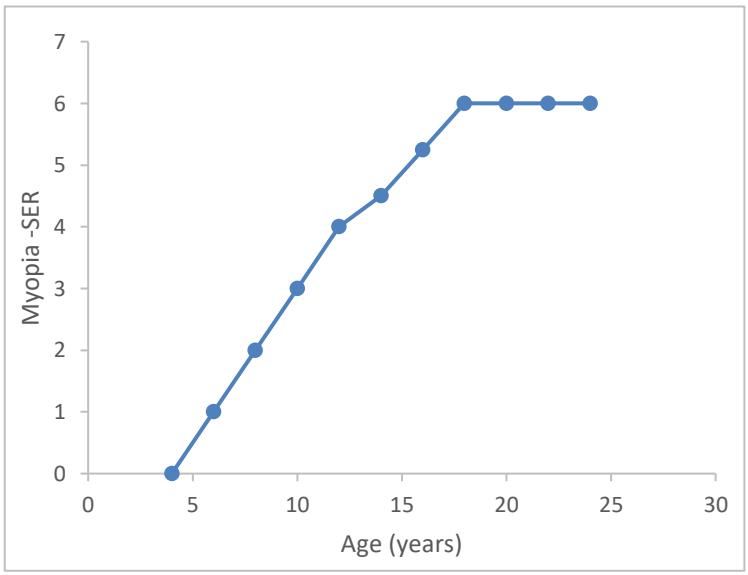
In 2007 Mutti et al. (6) reported the results of a longitudinal study including 979 children aged 6-14 years; 605 of the children became myopic during the research and amongst other measures showed a relative hyperopic peripheral refraction up to two years before the onset of myopia. A later study by the same group in a similar cohort of multi-ethnicity children contradicted the earlier study finding no predictive value in pre-myopia peripheral refraction (155). The same conclusion has been drawn by several other studies (153,157–159).

Despite the evidence suggesting peripheral refraction is a consequence of myopia, many clinical trials of interventions that introduce more positive power in the periphery have shown significant reductions in myopia measured in terms of both axial length and SER (160). These include specialised spectacle lenses and various designs of contact lens (section 1.4.2).

Flitcroft (32) considers the impact of the dioptric values of the visual environment which links accommodation and peripheral focus. He suggests the varying demands of accommodation in the enclosed indoor environment and its effect on peripheral focus to be a factor in progression compared to the relative flatness of the outdoor scene in accommodation terms (32).

1.3.8 Myopia progression

Despite significant variation, generally, once myopia occurs in a child, it will progress in most cases (161). Knowledge of typical patterns of progression is essential in determining the optimum period in which intervention is most beneficial (36). Often progression is rapid upon onset, before slowing with the different types of myopia having varying endpoints (29). Typical patterns of progression for the various types of myopia onset have been presented with early-onset myopia having an almost abrupt onset and then showing a linear increase until levelling off in the mid-teen years (Figure 1.9) (161). Goss (28) describes Hirsch's report which states that following onset myopia tends to increase by 0.50 D a year until the mid-teen years when it stabilises, he also observed the progression of adult-onset myopia to be significantly slower. Goss himself demonstrated a similar amount of annual progression through analysis of the records of 299 patients from his American optometric practice. All patients had at least four visits with refractions between the ages of 6 and 24 years. A mean annual progression of 0.42 D for males and 0.48 D for females was observed (161).



Gompertz function

$R = R_e + R_c\,(0.07295)^{a(x-t_o)}$

Figure 1.9. The left figure shows the typical pattern of Early Onset Myopia progression. Data replotted from Goss (29). Right shows the Gompertz double exponential growth function where the spherical equivalent refractive error at a given age R equals the initial refractive error (Re) plus the overall refractive change (Rc) times a double exponential function with the base (0.07295) representing the proportion of Rc that occurs when maximum acceleration is reached, a is a curvature coefficient, t_o is the age of onset and x is age.

Various mathematical methods have been used to describe the pattern of myopia progression. Thorn et al. (162) using a modified growth function, referred to as a Gompertz function (Figure 1.9), demonstrated a good fit for longitudinal data of 72 eyes from white children. The double exponential growth function was used to describe the progression from emmetropia, through the progressive stage of myopia to stability. For the individual eyes, they were able to calculate that myopia stabilises in 90 % of cases by age 15. It also highlighted that progression slows on average 4.5 years before stabilisation is reached (162). Goss and Winkler quote the age of cessation to be 15 and 16 years of age for females and males respectively but also noted considerable variation (161). Hardy et al. (94) longitudinally assessed the time of stabilisation in an ethnically diverse group of 426 children. The progression pattern was found to fit the Gompertz function in 91 % of cases. The age of cessation was close to previous studies, at 16.3 years for females and 16.4 years for males. Ethnic differences in time of stabilisation were observed, with African Americans stabilising earlier with lower levels of myopia, while Asian children were older before stabilisation with higher levels of myopia.

Myopia developing during early adulthood tends to progress more slowly. Goss et al. (28) described three patterns seen in adulthood: most commonly they found myopia to stabilise after progressing during adolescence, a second group would continue with a slower progression into adulthood, and the third group progression increased after adolescence. Ellingsen and colleagues (163) reviewed the records of 432 patients in a clinic setting over a ten-year period finding myopic shifts continued into the seventh decade. The amount of annual progression was seen to reduce in each decade from 0.60 D in the third decade to 0.30 D in the fifth decade.

Myopic shifts in the older generations are often due to media changes rather than increased axial length (85). Grosvenor and Skeates considered changes in refraction during the period of presbyopia onset and development in hyperopes, emmetropes, and myopes (164). They reviewed the records of 300 individuals straddling the time of presbyopia onset. The hyperopes

and emmetropes were found to shift towards increased hyperopia, whereas the myopes were split-66 % remained stable, and 15 % showed an increase in myopia, while the remainder moved towards hyperopia.

Much like the aetiology of myopia, the study of myopia progression has seen many hypotheses over the years such as associations with close work (12), higher intra-ocular pressure in myopes leading to increased size of vitreous chamber (165,166), the presence of optic disc crescents (167), the stresses applied directly to the sclera by the extraocular muscles during convergence (168), and variations in accommodation (89). With it seeming likely that inaccurate accommodation is a result, rather than a cause of myopia, it has been suggested inaccurate accommodation may be implicated in myopia progression (90,93). Berntsen tested this theory in two studies finding no association between lag of accommodation and myopia progression in children (95,169).

In summary, there appear to be several mechanisms with many factors, both environmental and genetic, that influence progression. Knowledge of the pattern of progression is important as studies of interventions indicate the treatments are most effective in slowing the increase during the periods of rapid myopia progression (56).

1.4 Possible treatments for myopia

Identifying effective methods to control myopia progression, or prevent its onset, are important for far more than the lifestyle benefits and the feel-good factor of a lower prescription. Brennan (170) calculates that a 33 % reduction in progression would result in a 73 % reduction in the frequency of myopia over 5 dioptres, moving a large number of myopes into the lower risk categories. The increasing prevalence of myopia worldwide cannot be ignored with eyecare practitioners being encouraged to take action rather than waiting years for definitive evidence (171,172). However, in a recent worldwide survey, most practitioners still reported correcting myopia with single vision lenses (38). The reasons for this may be the uncertainty about when to intervene, how long treatment needs to be continued, lack of clarity about mechanisms and availability. The methods reported to control myopia can be classified into three categories: pharmacological, environmental, and optical.

1.4.1 Pharmacological

Various concentrations of the nonselective anti-muscarinic atropine sulphate have been investigated. The randomised Atropine for Treatment of Myopia Study (ATOM) used 1 % atropine in one eye of 400 children. During the two-year trial, a significant reduction in progression was observed. However, a significant rebound occurred upon cessation (173). Atropine 1 % used in both eyes would adversely affect the ability to read, and comfort outdoors, which led the ATOM 2 study to use three lower concentrations of atropine (0.01 %, 0.1 %, and 0.5 %) in both eyes. The higher concentrations showed the greatest treatment effect at one year, but after a year of no treatment, those having the lowest dose demonstrated the least progression (174). An extension to the study reintroduced the lower concentration to those that had progressed by ≥ 0.50 D during the year washout period (175). The eyes that began the trial on the lower dose showed the least progression over the total five years of the study. The authors concluded that low dose atropine should be the first line of treatment in children aged

6 to 12 years with > 0.50 D myopic progression in the preceding year (175). Other studies have also shown slowing of progression regarding SER and axial length using atropine 1 % (176). The mechanism of atropine's effect is not fully understood but is believed to be local to the retina and probably not related to accommodation (96).

Topical pirenzepine is a selective anti-muscarinic; it has been shown to reduce progression by up to 50 %, without the disadvantages of atropine (177). However, it is not commercially available, and the initial studies have not been followed up. Trier et al. (178) reported some success with oral 7-methylxanthine, a metabolite of caffeine, finding up to a 66 % reduction in progression in Danish children. The authors recommended continued use up to the age of 20.

Despite the use of drugs in otherwise healthy eyes being a contentious issue, atropine is now used in several countries (179) with multi-centre trials planned to begin in the UK shortly.

1.4.2 Optical

Several studies have investigated the use of multifocal spectacle lenses, with and without prisms, to control myopia (171). The hypothesis being that by eliminating defocus from inaccurate accommodation, axial elongation would cease (89). The participants of studies were often selected as having near esophoria or high lags of accommodation. Statistically, but not always clinically significant reductions in progression have been reported (94,180). A general trend of a clear treatment effect in year one, followed by lower effects in subsequent years is often reported (181). Bifocals or progressive power lenses are reported to offer an average reduction in progression of 30 % usually over the first year (171). Most studies have used the same near addition for the whole group rather than the tailored treatment that can be given in clinical practice; Aller (171) suggests this uniformity is a likely reason for the variability in treatment effect. Despite studies spanning 20 years showing statistically significant results the use of multifocal spectacles has not become standard practice possibly due to the effect not being clinically significant.

The interest in peripheral refraction has led to the suggestion the effect observed with multifocal lenses is due to the myopic blur they impose on the superior retina (160) rather than related to accommodation. The hypothesis that peripheral hyperopia drives eye growth has driven the development of spectacle and contact lenses that aim to reduce relative peripheral hyperopia (7). Sankaridurg et al. (182) used three spectacle lenses designed to minimize peripheral hyperopic defocus. A reduction in progression was found relative to single vision lenses albeit not reaching statistical significance in the whole group. Recently Lam et al. (183) described a lens with multiple peripheral bubbles of around +3.00 D to create myopic defocus. Over the two years observed to date, a significant reduction in progression compared to controls (AL 60%, SER 59%, $p<0.001$) was reported.

The use of contact lenses to reduce relative peripheral hyperopia has shown promising results. Contact lens treatments have the advantage over spectacle lens options in that they move with the eye maintaining the position of the treatment zone. Contact lens treatments can be in the form of orthokeratology, soft multifocal lenses, and custom designed soft lenses. Walline et al. (184) reported a 51 % reduction in progression using the commercially available Proclear® multifocal lens (CooperVision USA) compared to controls wearing single focus distance contact lenses. Children between age eight and eleven years old wore a distance centre lens with a +2.00 add over a two-year period. The treatment effect was maintained in the second year of the study with the most significant effect occurring in low myopes, suggesting the need to start treatment when the child is young. Some practitioners may feel the risks of contact lens wear in children outweigh the benefits. Johnson (172) addresses this by pointing out that a myopic eye is 32 times more likely to suffer from glaucoma than microbial keratitis linked to contact lens wear.

Anstice and Phillips (185) used a custom-made lens with a central distance portion surrounded by concentric zones to create a relative myopic defocus of 2.00 D on the peripheral retina. The custom-made lens was worn in one eye, and a standard single-focus in the other before a

crossover after ten months. Progression was reduced in the eye wearing the custom-made lens by more than 30 % in 7 out of 10 eyes over a 12-month period. Sankaridurg et al. (186) using a similar lens reported a 34% reduction in SER progression compared to a single vision wearing control group after 12 months. A daily disposable myopia control lens (Mi Sight-CooperVision) is commercially available in several countries. The Mi Sight lens has a central distance area surrounded by concentric treatment zones that create peripheral defocus. Three-year data from a randomised double-masked trial involving 144 children from various ethnicities showed a 59 % reduction in myopia progression with the lens being worn for ten hours six days a week (187).

Orthokeratology has been found to reduce progression in several studies (188,189). Orthokeratology involves the overnight wear of reverse geometry rigid gas permeable lenses, and despite the perceived more complicated fitting, it does have the advantage that all treatment is done at home. A recent meta-analysis (188) looked at seven studies showing a combined reduction in progression of 45 %. In a recent survey of practitioner's attitudes toward myopia control, orthokeratology was graded as the most effective method. However, due to the extra equipment and the perceived risks of corneal damage, soft lens options were more likely to be selected (38).

1.4.3 Lifestyle

As stated earlier, many studies have shown that children who spend more time outdoors are less likely to become myopic (69,71,190). Jones et al. (71) followed 514 children from age 8 to 13 years. By age 13, those who performed less outdoor activity where more likely to have become myopic. After initial reports suggested active outdoor pursuits were the critical factor the cross-sectional Sydney Myopia Study demonstrated that just being outside seemed to be the most significant aspect; even children who undertook high amounts of close work but spent time outdoors were protected (190). Two interventional studies have shown that forcing children

outside during the school day reduces the incidence of new myopes (100,191). Wu et al. (100) found that 80 minutes of outdoor time each day decreased incidence by 50 % compared to a control school; while He et al. (191) with 40 minutes of outdoor time each school day showed incidence to reduce by 23 % over three years. In a recent review, Morgan and his colleagues recommend 2 hours a day of outdoor time to minimise the risk of myopia development (26). The effect of time spent outdoors and myopia progression is less clear (69).

The mechanism by which outdoor time reduces myopia onset is not fully understood but is likely to be linked to the significantly higher light levels outdoors (69). Other possible hypotheses include: greater viewing distances requiring less adjustment of accommodation (32), being outdoors may reduce the amount of time engaged in close work (71), and the smaller pupil may increase the depth of focus reducing retinal defocus (69). The favoured explanation is the light stimulation of dopamine release (26,69). Dopamine production is stimulated by light and has been shown to be involved in eye growth (192). Animal studies have shown eye growth to be slowed by the use of dopamine agonists (193).

1.5 Visual function of the myopic eye

1.5.1 Visual acuity in myopia

It has long been appreciated that visual acuity is often reduced in highly myopic eyes, with the reduction being more evident with increasing age (2). Visual acuity in myopic eyes can be reduced by visible pathological changes such as chorioretinal atrophy, posterior staphyloma, and macular lesions. However, other factors both optical, such as aberrations, and retinal in respect to photoreceptor spacing may affect the resolving power of the eye (194).

The negative-powered spectacle lenses used to correct myopia minify the image. For a refractive myope, this will reduce the size of the image compared to an emmetropic eye. However, this should not be the case for an axial myope (147). When contact lenses are used to correct axial myopia, the image should be larger than it would be in an emmetropic eye hence better visual acuity could be anticipated. Strang et al. (147) compared the impact of spectacle lens and contact lens corrections in a group of 34 visually normal young axial myopes. With increasing myopia, the visual acuity reduced with both forms of correction and the superior visual acuity expected with contact lens correction was not observed. Reasons for this deviation from the finding predicted by paraxial optics may include insensitivity of the Bailey-Lovie chart, residual astigmatism, and aberrations (147). Eyes with higher levels of myopia have been shown to suffer from increased monochromatic aberrations (195).

The second non-visible factor influencing visual acuity is the separation of the photoreceptors. The closer together the receptors the smaller the minimum resolvable angle (194). For two points of an image to be seen as separate two receptors need to be stimulated, separated by one unstimulated receptor. It is postulated that as the eye elongates and the retina stretches, the separation of the photoreceptors increases thus reducing the resolving power of the eye (194). Strang et al. (147) discuss how the pattern of eye growth might affect the resolving power. If the growth is at the posterior pole, the receptors will become wider apart reducing visual acuity; whereas growth limited to the equatorial regions would not affect visual acuity. Visual acuity

may also be reduced in the axially elongated eye from a reduction in the Stiles-Crawford effect (196).

1.5.2 Effect of myopia on the visual field

Several features of the myopic eye are associated with visual field defects. Tilting of the optic disc is frequently observed in myopic eyes (197), with field loss reported in 19 % of cases (198). The visual field defect found in association with disc tilt is typically arcuate and bitemporal (199). Differentiation from post-chiasmal lesions is possible as the defect tends not to respect the vertical midline, and from glaucoma as the horizontal midline is breached. It has been reported that the defects associated with tilted discs can diminish when the refractive correction is matched to the retinal location (200). Interestingly, the visual field defect associated with disc tilt was rare in young myopes but appeared to develop later (201). Tilting of the optic disc is discussed in detail in chapter 3.

One of the earliest and classic features of a myopic eye is the development of a peripapillary crescent (2). As myopia progresses, the area of peripapillary atrophy may increase and lead to enlargement of the blind spot (202). Peripapillary atrophy (Figure 1.10) has also been linked to some forms of glaucoma (203). The two main types of peripapillary atrophy, beta and alpha show absolute and relative field loss respectively (202).

In eyes with high myopia, the overall sensitivity of the retina can reduce as the separation of the photoreceptors increases as a result of tissue stretch (204). For the clinician, one of the significant challenges is differentiating the normal from the glaucomatous eye (205). The similarity in the pattern of visual field loss in eyes with tilted discs and peripapillary atrophy to those with glaucoma add to this challenge. With glaucoma being a progressive condition, multiple examinations are required to confirm the diagnosis by showing progression which can be further hampered by the adverse effects of high-powered spectacle lenses.

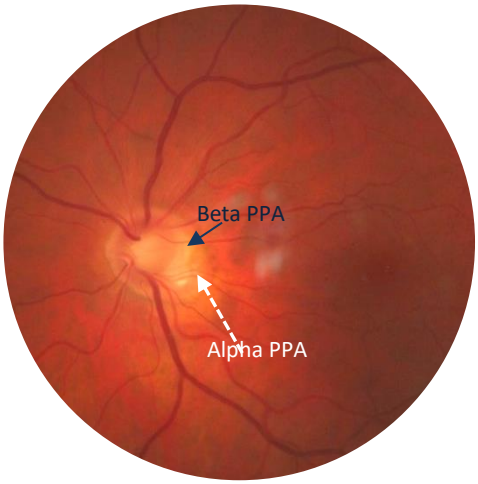


Figure 1.10. Image of a myopic disc showing lack of clarity of disc margins and alpha and beta PPA. The dashed white arrow indicates alpha peripapillary atrophy and the blue arrow beta peripapillary atrophy.

1.5.3 Retinal function in myopia

Electrophysiology tests, such as electroretinography (ERG) measure the electrical responses of various types of cells in the retina, usually via electrodes placed on the cornea or the skin close to the eye. ERG is used to detect and monitor several retinal disorders. Some time ago Perlman (206) showed the ERG a-wave to be reduced in the myopic eye. Westall et al. (207) confirmed this and demonstrated the reduction to be positively correlated with the level of myopia and inversely correlated to axial length, suggesting abnormal photoreceptor function. The b-wave of the ERG has also been found to be reduced in myopia, although due to the effect of the a-wave magnitude on the b-wave, it is not clear if myopia reduces the b-wave or it is reduced as the a-wave is reduced (206).

The inner retina function is assessed by considering oscillatory potentials and retinal adaptation. Chen et al. (208) demonstrated that retinal adaptation varied with the level of myopia and suggested that this finding may be associated with the hypothesis that dopamine is linked to myopia development. Dopamine is an important chemical messenger for retinal cells including amacrine and ganglion cells. Oscillatory potentials reflect amacrine cell function, which has led to the suggestion that changes in dopamine levels in the retina are associated with myopia (192). Luu (209) warns that caution needs to be taken with these findings as outer retina changes also

affect the oscillatory potentials. Multifocal ERG has been used to assess macular function in myopic eyes, with a pattern of reducing amplitude with increasing myopia (209).

Despite the clear reduction in the ERG response in adult myopic eyes, the mechanism is not certain. Suggested mechanisms include, decreased retinal illumination (210) and increased axial length, making the distance from the recording electrode and electrical source greater, in addition to the reduced photoreceptor density, and other possible retinal changes in longstanding myopia (209).

1.6 Pathology associated with myopia

Numerous eye diseases are associated with myopia. Myopia is causative of some pathology whereas for other diseases the relationship is not as clear. Many pathologies become more prevalent and severe, with not only increasing myopia but also with advancing age (36). As the axial length increases, so does the volume of the eye; this along with the earlier and more marked vitreous degeneration in myopic eyes leads to changes in both the central and peripheral retina. Structural changes to the optic nerve head may predispose the eye to optic neuropathies such as glaucoma (211), and changes at the posterior pole to myopic macular degeneration (212), while areas of reduced retinal thickness increase the likelihood of retinal detachment (213). Changes to these three areas will be outlined in the following section, along with evidence for the association of myopia with some forms of cataract. The retinal vasculature is also considered due to its close relationship to the aetiology of many ocular pathologies.

1.7 The normal optic nerve head

The ONH marks the point of exit from the eye for the retinal nerve fibres. It is visible during ophthalmoscopy, usually appearing paler than the surrounding retina. It is located approximately 4 mm nasally and 1 mm above the fovea and is devoid of photoreceptors resulting in a small physiological scotoma (126). The ONH is bordered by the scleral ring of Elschnig.

Elschnig's ring is a fibrous tissue that arises from the anterior scleral edge to fuse with Bruch's membrane as depicted in figures 1.11 and 1.12. When the layers of the retina and underlying structures prematurely terminate a crescent is formed (214). Within the scleral ring, the nerve bundles leave the eye supported by the lamina cribrosa. The nerve tissues are observed as the neuro-retinal rim (NRR). The central area without axons is referred to as the optic cup through which the central retinal vessels pass (Figure 3.1).

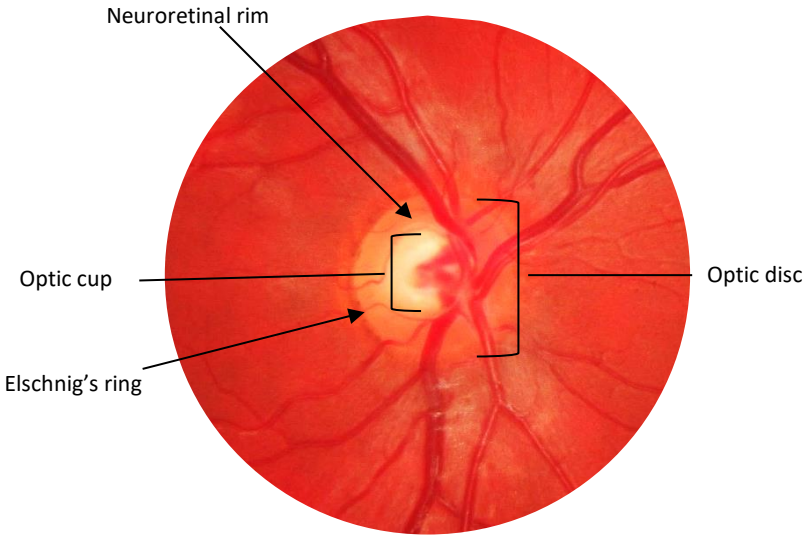


Figure 1.11. Fundus photograph of optic nerve head and adjacent tissues showing cup, neuroretinal rim, scleral (Elschnig's) ring and central retinal vessels.

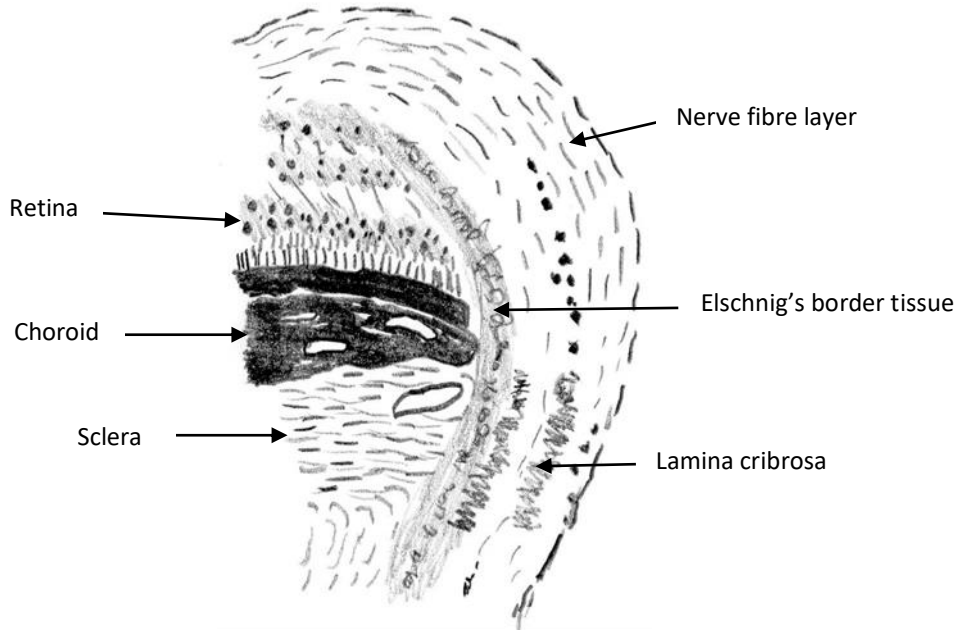


Figure 1.12. Schematic diagram showing the tissue of Elschnig and position of other related structures. Redrawn from Pipe and Rapley (126).

The lamina cribrosa is a supporting network that extends across the scleral canal. The central retinal vessels and nerve fibres pass through the lamina cribrosa. The lamina cribrosa consists of a meshwork of collagen fibres with numerous pores that can often be seen ophthalmoscopically as grey spots (126). Histological investigations of the lamina cribrosa show thinning and shape change in advanced glaucomatous optic neuropathy (215). In high myopia, thinning and elongation of the pores has been described; a change which has been postulated to increase susceptibility to glaucoma development (216). The relationship between the cornea and lamina cribrosa has also been investigated, with the hypothesis that the two structures may share mechanical properties due to their associations with glaucoma. This relationship has been studied histologically (217) and more recently using OCT (218). Neither study showed any relationship in the thickness of the two structures suggesting the increased risk of glaucoma with a thinner cornea is not related to corresponding changes in the ONH (217).

In normal eyes, the ONH is usually vertically oval with a horizontally oval cup (219). However, there is great variation in the appearance of the normal ONH. The ONH is on average 1.7 mm in height and 1.5 mm horizontally (126,220). Differences occur inter, and intra race (219); those with ancestors originating closer to the equator tend to have larger optic discs (221). ONH size seems not to be associated with sex, age, or body stature (222). The optic nerve head changes in size markedly in the first years of life and then appears relatively stable during adulthood (220). The retinal cell count reduces with age at a rate of 0.3 % per year of life (223). White Europeans have been reported to lose approximately 5000 axons a year from a population of around 1.4 million (220). It remains unclear how this loss presents clinically, although it has been suggested it is the height of the neuro-retinal rim that reduces rather than the width (220).

Examination of the fundus and assessment of the ONH qualitatively and quantitatively is a mandatory part of an eye examination. In community practice, the use of a slit lamp with a condensing lens is the most commonly used method of assessing the ONH. This permits the

measurement of certain disc parameters by using the slit height and a magnification correction factor for the condensing lens (224). The use of stereo photographs is considered the gold standard in ONH assessment (220); although there are challenges in determining the true size of features due to ocular and camera magnification and the assumptions made in the correction calculations (Section 2.2) (225,226). Modern imaging modalities that provide quantitative information such as confocal scanning laser ophthalmoscopy (CSLO), and optical coherence tomography (OCT) are becoming more widely used. These instruments often struggle to identify the ONH margins correctly, which can be indistinct in myopic eyes, reducing the accuracy of the measurement (220,227). Secondly, the cup is measured at a predetermined depth from the retinal surface which may lead to discrepancies in myopic eyes with shallow cups (228).

Changes in the optic disc margin anatomy can be age (229), myopia (221,230), or disease-related such as in glaucoma (231). Different mechanisms are likely to underlie the various causes (232).

1.7.1 The ONH in the myopic eye

The classic myopic ONH may be tilted, have an elongated vertically ovoid shape, shallow cupping, and low contrast between the neuro-retinal rim and cup; although the most frequently observed feature is a myopic crescent (2,231).

The size of the ONH in myopic eyes has been studied extensively. The classic understanding that myopia is associated with a large ONH (2) is not a consistent finding in the literature. Leung assessed 133 healthy myopic eyes, using OCT and confocal laser scanning ophthalmoscopy, finding a general increase in disc size with increased axial length and myopia (233). The Rotterdam study using a stereoscopic fundus camera found a 1.6 % increase in disc size for each dioptre of myopia (234). However, several studies have shown disc size to be independent of refractive error within the range +4.00 D to -8.00 D (233,235,236).

Curtin reports the description of optic disc crescents in myopic eyes dating back to the late 19th century by the classic workers Donders, and Heine (2). The crescent seen adjacent to the optic

nerve head has been described using several terms including peri or parapapillary atrophy, myopic crescent, temporal crescent, sickle or conus myopicus (237). Optic nerve crescents have been studied by many workers most notably in recent times by Jonas (211,220,238,239). He describes the typical crescent associated with axial myopia as being white and sharply demarcated. Curtin states that eyes with physiological myopia should not have a crescent unless congenital, which is usually located inferiorly, is non-progressive, and is no greater than 10 % of the disc diameter (2). Congenital crescents are described as being a result of local developmental changes and are usually stationary, whereas eyes with intermediate myopia (<-6.00 with no visible retinal changes) typically have a crescent which may increase in size as myopia progresses (2). However, crescents are observed in eyes with significantly lower amounts of myopia than Curtin reports (231,240). As the crescent size increases, the sharply demarcated borders become less distinct, which may increase the size of the blind spot (202). The myopic crescent seen at the non-pathologic levels of myopia are typically temporal but can occur in several positions as depicted in figure 1.13.

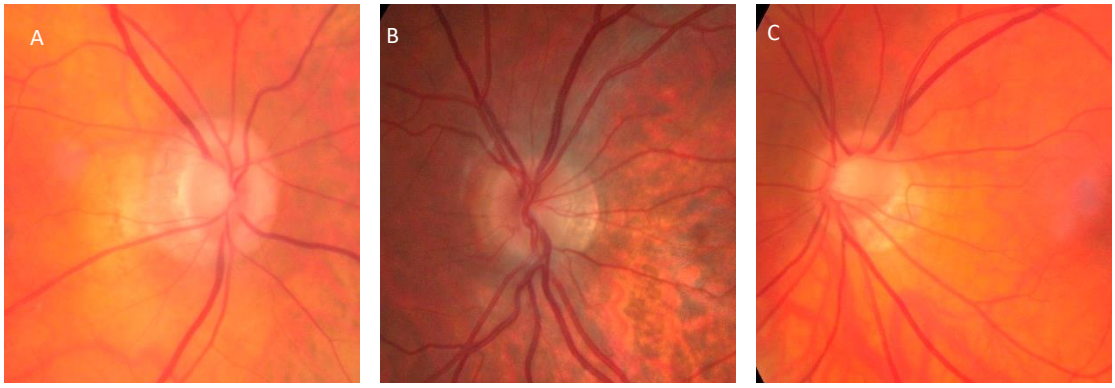


Figure 1.13. Fundus photographs showing different positions of optic nerve crescents. A-halo type crescent, B-temporal, and C-inferior temporal crescent.

The colouration of the crescent is influenced by the patient's pigmentation and the structures that are misaligned at the disc margin. Grosvenor describes several types of crescent dependent on the tissues remaining (28). He describes a scleral crescent as a pale-yellow colour where the retina and choroid have pulled away from the disc margin. A choroidal crescent occurs when the

outer layers of the choroid remain, often being a result of a congenital misalignment of the choroid and RPE (28).

Peripapillary atrophy and its association with levels of myopia <-6.00 D is widely documented (232,237,241,242). Numerous studies have considered the formation and structure of the crescent tissue in eyes with higher degrees of myopia, in vivo, and histologically (214,237,243,244). This has resulted in the postulation of several mechanisms, such as mechanical stretching, slippage of tissues and primary changes in the RPE, choriocapillaris and Bruch's membrane (245). Mechanical stretching leading to atrophy of retinal layers and the underlying sclera is the favoured explanation (2,246), a theory initially proposed by Vogt in 1924, described by Curtin (2). Jonas et al. (237) compared the peripapillary region in highly myopic and non-myopic enucleated eyes showing a gap greater than 0.5 mm between the start of Bruch's membrane and the edge of the optic nerve in the eyes with high myopia. Histological examination of the peripapillary region in the highly myopic eyes showed the sclera to be thinned; Bruch's membrane, the choroid, retinal pigment epithelium and photoreceptors were absent, with only the nerve fibre layer remaining (237). Some caution needs to be exercised with histological investigations due to possible tissue shrinkage and that the eyes are often enucleated due to ocular pathology. However, these issues may be negated with in-vivo investigations using OCT technology (244).

The peripapillary atrophy has traditionally been described as two areas (202); an alpha zone which is furthest from the disc margin and shows as areas of hyper-, and hypo-pigmentation (Figure 3.4B). The alpha zone is more prevalent and has been shown to give rise to a relative scotoma (202). The beta zone is always closer to the disc and has a characteristic white appearance due to the loss of RPE and choriocapillaris, leaving just the sclera and some choroidal vessels. The beta zone gives rise to an area of absolute scotoma (202). The significance of beta PPA and its association with glaucoma comes from it being a possible indicator of glaucoma

onset, and progression (203,211,244). Recent histological findings suggest that the parapapillary area should also be described with two additional categories, delta, and gamma PPA (239). Gamma PPA is defined as an area without Bruch's membrane and is associated with axial myopia but not glaucoma (239). Gamma PPA was previously described as a beta zone variant by Hayashi using OCT examination (247). Delta PPA has only been observed histologically, and in eyes with high myopia as an area with an absence of small blood vessels and a thinned scleral flange. Delta PPA is believed not to be associated with glaucoma but may increase susceptibility to glaucoma development (216), possibly due to reduced nutrient supply to the nerve fibres from decreased perfusion (237).

PPA is often observed in non-myopic eyes; being associated with increasing age and glaucoma. From digital photographs, it is not possible to differentiate myopic from age-related atrophic PPA, although OCT examination does allow a more detailed assessment of the remaining tissues to enable some differentiation in vivo. It has been suggested non-mechanical factors are more likely in non-myopic cases (233). Postmortem histological examinations provide evidence suggesting age-related changes result from tissue atrophy (229), which has been confirmed using OCT (232). Hwang (232) compared the temporal optic disc margin anatomy in 3 groups: a non-myopic and young control, young myopes with PPA, and aged non-myopic subjects with PPA. In the aged non-myopic group, only the photoreceptors were affected whereas in the myopic group most of the retinal layers were involved. Curcio (229) suggests that age-related PPA is linked to RPE and Bruch's membrane degeneration leading to photoreceptor loss. Histology studies (229,243) show Bruch's membrane to thicken with age which may lead to impaired blood supply to the RPE and photoreceptors. The OCT images from Hwang's work show Elschnig's border tissue to be more obliquely orientated in the myopic eyes but not in the aged group or control, again indicating a mechanical mechanism in myopic PPA. Curtin (2) makes the point that tissue atrophy as the underlying mechanism of myopic crescent development conflicts with the clinical picture of crescents observed in young eyes that are otherwise healthy. Jonas investigated the

difference between myopic and glaucoma-related PPA finding that in highly myopic PPA remnants of the nerve fibre layer and the inner limiting membrane covered the sclera while in the glaucomatous eyes Bruch's membrane was seen between the remnants of retina and sclera (203).

Nasal super traction also referred to as situs inversus, is another feature seen in conjunction with myopic crescents. In super traction, it appears as if the retinal and choroidal tissues have been dragged temporally (Figure 1.14A.) with the temporal vessels appearing to make an acute angle as they leave the optic disc.

Super-traction is most likely to be observed in the higher levels of myopia and may give the appearance that the nerve is tilted (2). Vongphanit et al. (198) found nasal super traction to occur in 70 % of eyes with tilted discs.

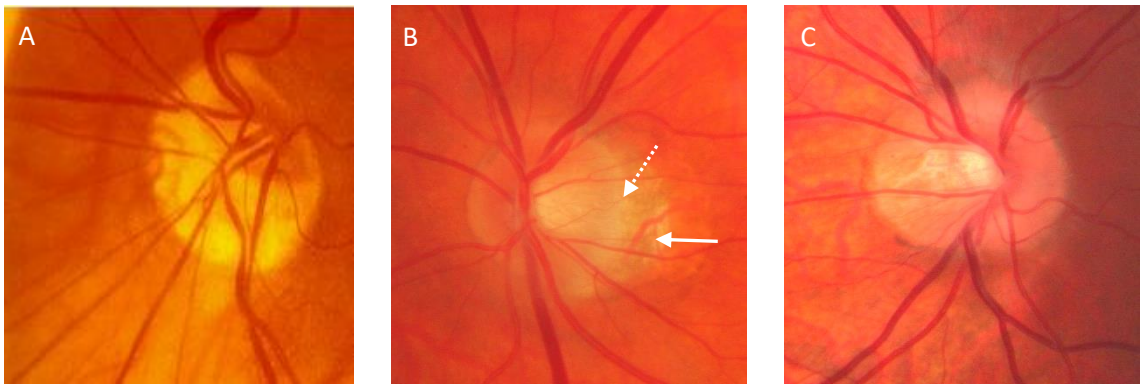


Figure 1.14. Fundus photographs showing: A-nasal super-traction, B- alpha (solid arrow) and beta (dashed arrow) zones of peripapillary atrophy, and C-tilted disc with blurring of the nasal margin.

The optic disc can be tilted in different planes. A true tilt has been described to be around the vertical axis (221); usually with the nasal margin being more anterior (248). Tilt is also commonly superior-nasal, with an inferior temporally located crescent (214,249). Tilted discs are generally considered to be a congenital finding due to the abnormal closure of the embryonic optic fissure (214), although this is not certain as several workers have shown longitudinal changes in disc tilt with increasing axial length (240,246).

Tilted discs are reported to occur in 0.36 to 3.5 % (197) of the general population. However, much higher prevalences are observed in myopic populations (221,230). Samarawickrama (221) in a group of 1227 Singaporean adolescents with myopia greater than 0.50 D, reported a prevalence of 37 % while Chang et al. (230) reported a prevalence of 57 % in a group of 359 adults of a similar ethnic mix with high myopia (≤-6.00 D). As well as tilted discs being more commonly seen in myopic eyes, there is a strong association with astigmatism (221,250). Ethnicity also seems to have influence, tilted discs being more prevalent in Asian than white European or African populations (221). In addition to the factors mentioned a further explanation for the significant range of prevalence might stem from the lack of a clear definition of a tilted disc (197). For example, You et al. (250) defined a tilted disc as a small optic disc, oblique insertion of the optic nerve, and no other abnormality; whereas, Samarawickrama (221) defined tilt as one margin raised in comparison to the opposite margin. Witmer et al. (197) suggest that some studies consider tilt and disc torsion as one. They differentiate the two in their review. Firstly, tilt being the angle the optic nerve enters the eye, which is assessed by looking at the disparity between the highest and lowest height of the optic nerve head as shown in figure 1.15. This is not directly measurable with most studies relying on expert observation of stereo fundus images (221,248,250), which poses challenges in correctly identifying those with small amounts of disc tilting. However, high repeatability has been reported (221).

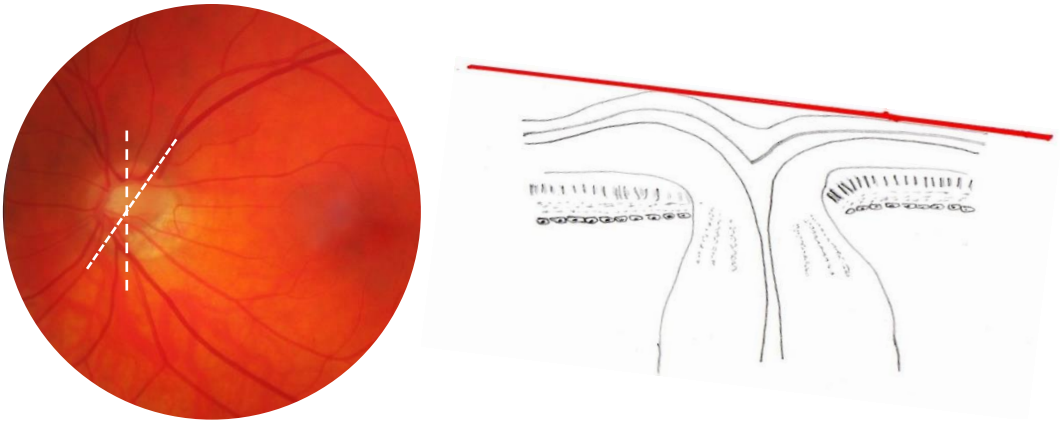


Figure 1.15. A-fundus photograph showing disc torsion (superior). B-schematic diagram showing raised nasal disc margin in a tilted disc.

Ophthalmoscopically the tilted disc appears as if the optic nerve has entered the eye obliquely with tilting around the vertical axis appearing to increase the oval-ness. Tay (251) suggests the "index of tilt" to describe the ovality by taking the ratio of the minimum disc width to the maximum. Although used by several workers, there seems to be conflict on setting a threshold for significance (197). Ohno-Matsui (252) pointed out that misclassification may occur when the nerve is wide but tilted which would lead to a lower index of tilt compared to a non-tilted narrow disc. The Tanjong Pager study defined tilt as an index of tilt less than 0.75 showing a sensitivity of 56.7 % and specificity of 94 % compared to the gold standard of stereoscopic assessment (253).

Secondly, the disc may also be rotated about the sagittal axis; often referred to as disc torsion. Disc torsion, rotation, or twist is present if the longest diameter is beyond 15 degrees from the vertical meridian (Figure 1.15A). Although, some studies classify any degree of deviation from the vertical as torsion inflating the prevalence's reported (254). Disc torsion has been the interest of recent work suggesting that inferior rotation, which is anti-clockwise for the right eye, to be more common in glaucoma regarding associations with higher intraocular pressure and prediction of visual field defect location (254). Sung (254) assessed disc torsion in healthy myopic eyes finding 57 % to be superiorly rotated (clockwise for the right eye) by more than 15°. In those that had an inferior twist, the SER and IOP were both higher ($p = 0.043$, $p<0.001$). It is hypothesised that the rotation of the disc causes mechanical stress on the inferior nerve fibres (255).

The term *"tilted disc syndrome"* is often used to describe a tilted disc associated with other features such as; a crescent, inferonasal rotation of the disc, changes in the retinal vessel pattern, and a visual field defect classically affecting the superior temporal quadrant (197,199,214). The visual field defect rarely respects the vertical midline facilitating differentiation from post-chiasmal lesions (252), although it may mimic some forms of glaucomatous field loss (198). The stationary nature of the visual field loss is used to differentiate from other causes, although the

non-progressive (214) course of disc tilt is questionable. Kim (246) describes a progressive tilting with increasing myopia through examination of fundus images. Hence it would not be unreasonable to expect a change in the visual field. The evidence suggesting tilt is non-progressive is mainly from cross-sectional studies showing no increase in prevalence or severity with age (197). This conflicts with the two studies from Singapore mentioned above where the prevalence was 20 % greater in the study with older participants.

In addition to the challenge of diagnosing glaucoma when the disc is tilted, it has been proposed that a tilted disc may be more susceptible to glaucoma (228). Suggested mechanisms include changes in the lamina cribrosa with the resultant diminished support of the nerve fibres as they pass into the optic nerve through a more acute angle (45,221), and also altered permeability of the lamina cribrosa (215). However, How et al. (253) showed no higher prevalence of glaucoma in those with tilted discs.

1.72 Optic nerve head pathology

Glaucoma is the term used to describe a wide variety of conditions that result in the loss of retinal ganglion cells and subsequent visual field loss. The most common type is primary open angle glaucoma (POAG) which may be associated with raised intraocular pressure. POAG is a leading cause of irreversible visual impairment globally, responsible for over 12 % of blindness (256). The worldwide prevalence of POAG in the general population was recently reported to be 2.2 % (19). However, in a large cross-sectional study the prevalence was 4.5 % in moderate and high myopes but only 1.5 % in emmetropes (45).

Several large epidemiological studies covering a range of populations have shown an association between myopia and POAG (45,242,257) (Table 1.2). The BMES (45), Barbados Eye Study (258) and the Singapore Malay Eye Study (230) all showed a dose-related response. Not all studies show such a clear association; in the Beijing Eye Study only those with myopia <-6.00 dioptres

were associated with a higher risk of glaucoma (216), while the Beaver Dam Eye Study found no increase of POAG prevalence with higher levels of myopia (259). Marcus et al. (257) conducted a meta-analysis of 11 cross-sectional population-based studies. They concluded that having a myopic refraction roughly doubled the risk of developing POAG (OR 1.92 CI 1.54-2.38). High myopes defined as myopia <-3 dioptres had a greater odds ratio (2.46 CI 1.93-3.15) than low myopia (1.77 CI 1.41-2.33). Due to the considerable variation between studies, they also presented data with studies at the extremes removed. The resulting pooled odds ratio was 1.88 for any myopia.

Large epidemiological studies reduce some of the bias that occurs with clinic-based surveys, although comparisons are complicated due to variations in the way both myopia and glaucoma are defined. Some studies rely on the optic disc appearance which is complicated by the classic features of the myopic disc such as tilt, shallower cups, and the presence of peripapillary atrophy (205). Others use a combination of disc appearance and visual field loss. Although more robust than disc appearance alone, the myopic optic disc is associated with several types of visual field defect as described earlier in section 1.5.2.

Table 1.2. Summary of large-scale cross-sectional studies showing the risk of POAG at various levels of myopia (SER)

Study	Population	Sample size	Level of myopia	Odds ratio
Barbados (258)	Afro-Caribbean	4709	<-0.50	1.48 (1.12-1.95)
BMES (45)	Australian in urban setting	3654	-1.00 to -3.00	2.3 (1.2-3.8)
			<-3.00	3.3 (1.7-6.4)
Beaver Dam (259)	USA mixed ethnicity	4670	≤-1.00	1.6 (1.10-2.40)
			<-3.00	1.50 (0.80-2.60
Beijing (216)	Chinese	4439	-3.00 to -6.00	0.61 (0.25-1.48)
			<-6.00	4.67 (1.75-12.46)

Two theories explaining the ganglion cell loss in POAG are commonly described (260). The mechanical theory suggests direct damage to the nerve fibres from the intraocular pressure. In contrast, the vascular theory proposes reduced perfusion of the fine vessels supplying the nerve fibres leading to ganglion cell loss (261). It is generally accepted that one of the two, or a combination of the hypotheses may be responsible. The exact mechanism for the increased risk in the myopic eye is not fully understood, but several of the structural changes to the optic nerve head and the surrounding area have been implicated.

The lamina cribrosa is a support mechanism for the neurones exiting the eye (126). Increasing axial length, and the associated change in eye shape is thought to lead to deformation of the lamina cribrosa, leaving the nerve fibres more susceptible to damage (95). The larger optic disc, more often seen in higher myopia, may be at an increased risk of glaucoma development due to the poorer support of nerve fibres by the stretched lamina cribrosa (262,263). The deformation of the lamina cribrosa appears to make the optic nerve of the myopic eye more prone to damage at lower levels of IOP (254). Further structural change is observed in the peri-papillary region as the tissues of the choroid and retina are pulled away from the edge of the optic nerve head. The choroidal vessels are believed to be an important supply of nutrition to the lamina cribrosa (126). As the choroid and circle of Haller-Zinn move away from the optic nerve head, vascular support may be compromised increasing susceptibility to glaucomatous optic neuropathy (237). Studies considering retinal blood vessel calibre have further supported the vascular theory. Several studies show straightening and narrowing of retinal vessels (264–266) in eyes with glaucoma and myopia, which may affect blood circulation and optic nerve function (264). However, it is not certain whether these changes are the cause or result of ganglion cell loss (264).

1.8 Peripheral fundus changes

The peripheral retina is defined as the area outside the vascular arcades, extending to the ora serrata anteriorly (267). The ora serrata lies around 8 mm from the limbus and 21 mm from the ONH (126). The peripheral retina is differentiated from the posterior pole by changes in structure; cone density reduces, and rods become prominent gradually becoming shorter closer to the ora serrata (126). Ganglion cell density also decreases in the periphery as receptive field size increases (268). The peripheral retina can be described in terms of the near, middle, far, and extreme periphery as depicted in figure 1.16. The vortex veins provide a landmark as they lie just posterior to the equator (Figure 1.16).

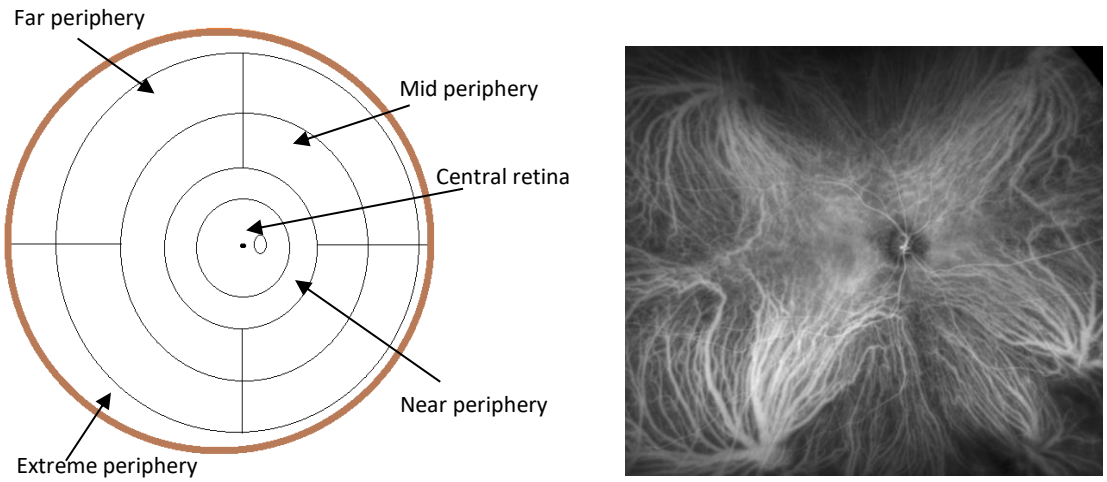


Figure 1.16. The left figure shows a schematic representation showing the zonal classification of the peripheral retina. The right image highlights the vortex ampulla in an indocyanine green image. Reproduced with permission from Optos plc.

Many physiological variations in the peripheral anatomy can be seen during ophthalmoscopic examination, with several being more prevalent in myopic eyes (2). Some of these features are benign, while others increase the risk of morbidity, most often from the association with retinal detachment. The retinal vasculature is also known to differ in the periphery, especially in eyes with higher levels of myopia. Myopes appear to have lower blood flow rates in the peripheral retina (269), which may be the result of reduced metabolic demand from the thinner tissues

(270). These variations lead to different pathological responses, for example, myopic eyes seem to have some protection from diabetic retinopathy (270).

The peripheral features most often seen in myopic eyes will be outlined in the following sections along with a summary of rhegmatogenous retinal detachment. The vitreous humour will be described due to its intimate relationship with the retina. The interaction between the retina and vitreous is responsible for the increased risk of retinal damage in myopic eyes (271).

1.81 Vitreous humour and posterior vitreous detachment

The vitreous is a transparent gel-like substance that fills the posterior chamber of the eye. It has a volume of around 4 ml and consists of 98 % water and 2 % protein, mainly in the form of type 2 collagen (126). It does not have a homogenous structure with variances of refractive index across the posterior chamber (126). The normal vitreous is firmly attached anteriorly at the vitreous base - the junction of the pars plana of the ciliary body and peripheral retina. The outer boundary of the vitreous referred to as the vitreous cortex has a higher density of collagen compared to the central more gel-like substance. The vitreous cortex is in contact with the inner limiting membrane of the retina; posteriorly the vitreous is attached to the margins of the ONH and at the centre of the fovea (272). The presence of other areas of attachment between the retina and vitreous can increase the risk of rhegmatogenous retinal detachment (RRD), these can be visible, for example in the case of lattice degeneration (described in section 4.3), or invisible until damage occurs (273).

The vitreous changes with advancing age, the gel structure liquifies and becomes more mobile with resultant forces leading to the vitreous cortex pulling away from the retina, termed posterior vitreous detachment (PVD). The traction the detaching vitreous exerts on the retina at the various sites of normal and abnormal attachment may lead to retinal damage. Typically, detachment of the vitreous occurs between the age of 50 and 70 but has been shown to occur earlier in myopic eyes (274,275). Several factors have been suggested for this including the

myopic vitreous containing more liquid (276), elongation of the eye and increased stress generated from the myopic retina (271). PVD may be asymptomatic but when present symptoms can include arc-like flashing lights usually in the temporal field, and floaters which are often described as cobwebs or flies. Posterior vitreous detachment has traditionally been considered a rapid process. However, investigation with new imaging technologies suggests a slower course of several months in some eyes (267).

1.8.2 Lattice Degeneration (LAT)

Lattice degeneration is the peripheral lesion that carries the greatest risk of rhegmatogenous retinal detachment (275,277). Gonin is accredited as being the first to describe lattice degeneration histologically as an area of retinal thinning back in 1904 (2). Ophthalmoscopically, lattice degeneration shows as discrete spindle-shaped areas of retinal thinning, often having several holes within the lesion, and an overlying area of abnormal vitreous. It takes its name from the thin white sclerotic vessels crossing it; however, this feature is only seen in approximately 9 % of lattice lesions (277). Pigmentation is sometimes found within the lesion; this is believed to be a result of RPE hyperplasia (277) (Figure 1.17).

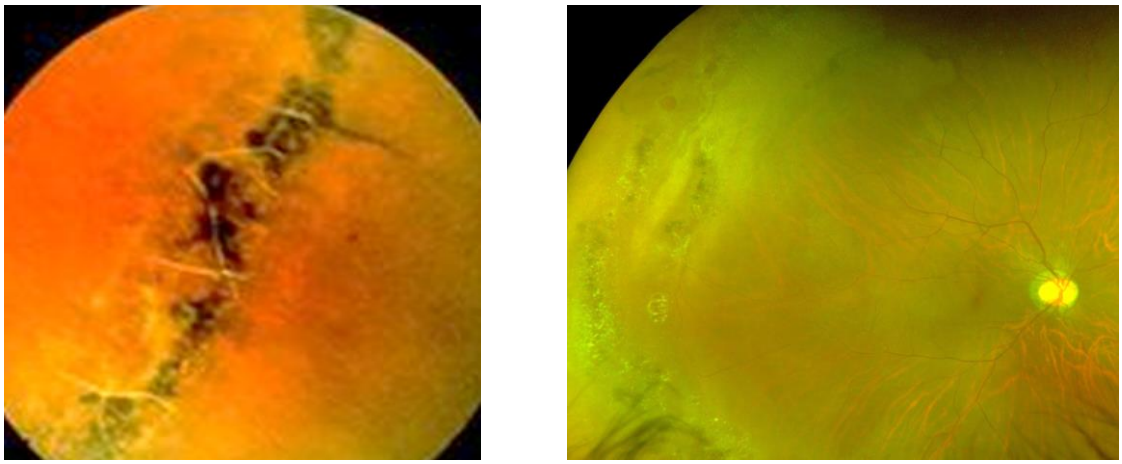


Figure 1.17. The left image shows the classic pattern of Lattice degeneration; the right image shows lattice with retinal holes. Image courtesy of Optos plc.

The reported prevalence of lattice degeneration is between 6-10 % (278) in the general population and approximately double that amongst myopes (2,279). Karlin (280) showed the frequency to significantly increase in longer eyes, with a more significant effect in younger eyes, which was also the observation of Pierro et al. (281). Lattice is bilateral in around 50 % of cases and is usually present by the age of 20 (2). Interestingly, Curtin reports high bilateral involvement in unilateral myopes suggesting there may be some genetic aspect to lattice development (2). Lattice is most commonly found in the superior retina running parallel to the ora serrata between the equator and ora serrata (268). It has been suggested the risk of retinal detachment is greater with lattice that is located more posteriorly (268).

The aetiology of lattice degeneration is unclear (277). Vitreous liquefaction is seen overlying the lattice with strong vitreoretinal attachments along the edges of the lesion (282). Mrejen and Engelbert (273) describe several unproven theories including; loss of perfusion from the choroid to the outer layers of the retina, and lattice being primarily a vitreous disease with secondary retinal degeneration.

Lattice degeneration is present in 18 to 40 % of eyes with retinal detachment (267,278). The retinal detachment related to lattice can result from round or atrophic holes within the area of lattice, or horseshoe-shaped tears which are typically located at the posterior border of the lesion (Figure 1.17). Hole related detachments are usually seen in younger myopes (283), are not related to vitreous traction, and progress slowly. In contrast, horseshoe-shaped breaks are more often observed in older myopes associated with vitreous traction and are more likely to progress to a significant area of retinal detachment (267).

1.8.3 White-without-pressure (WWOP)

WWOP is generally considered a benign lesion although it must be differentiated from retinal detachment (2). It is found just anterior to the equator and consists of areas of sensory retinal disorganisation possibly caused by vitreoretinal traction (284). WWOP appears in a variety of ways with a grey-white appearance, that may be flat or elevated (Figure 1.18) and is most often seen in the inferior temporal quadrant (280). It is often found in isolation but can occur with lattice especially in younger adults where the lattice is usually located at the posterior border of the WWOP (273). Although considered benign, retinal breaks occasionally develop along the posterior edge of the lesion and may progress to retinal detachment, albeit slowly (280). Prophylactic treatment is only appropriate if a spontaneous giant retinal tear is detected in the other eye (267). White with pressure is only seen with scleral indentation and is often associated with areas of lattice and retinal holes (2).

Nagpal et al. (284) found all patients with WWOP had undergone posterior vitreous detachment. Although the vitreous was not detached around the WWOP; which suggests WWOP would only be seen in the fifth decade and beyond which conflicts with Karlin's report (280). He reported WWOP to be more common in younger and longer eyes with the prevalence reducing in those over 40 years of age. WWOP is also reported to be more common in blacks (2) although this may be as it is easier to visualise in eyes with more pigmentation. Pierro et al. (281) found WWOP to be present in 23 % of 513 myopic eyes in a group with a mean age of 48 years which is similar to that reported by Lai (285) in a slightly younger population of myopes. Whereas Karlin (280) found WWOP to be present in 36 % of those under 20 years, and 9.5 % of those over 40 years of age. It has been suggested that the lower prevalence in the older group is due to WWOP being a phase in the development of other retinal changes (280,284).

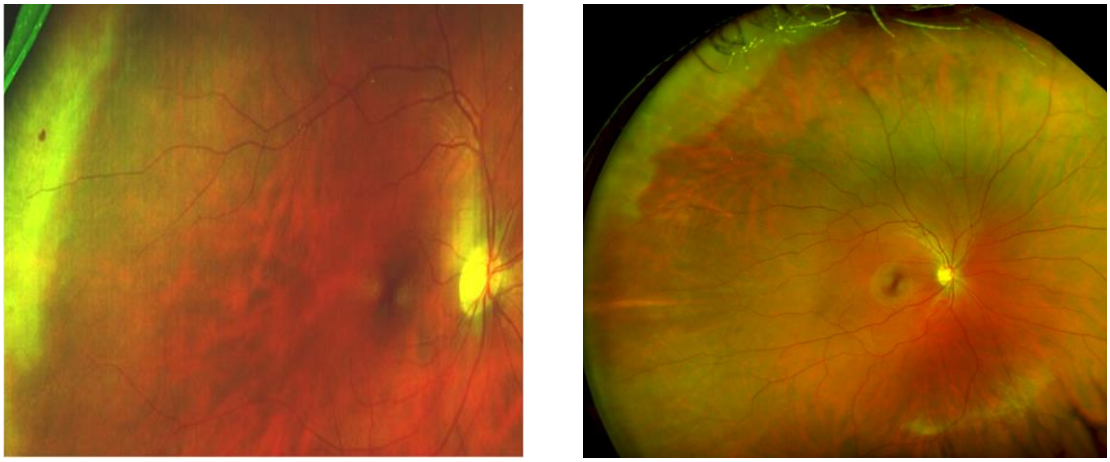


Figure 1.18. Fundus images of WWOP. The left image shows a small haemorrhage within the lesion. Images used with permission from Optos plc.

1.8.4 Snail-track degeneration (STD)

Snail-track degeneration is a vitreoretinal degeneration like lattice degeneration. It appears as an oblong shape with a shiny whitish-yellowish frost-like appearance (Figure 1.19). Snail-track is usually found running parallel to the ora serrata and may have holes within it. Some (267,286) suggest snail-track degeneration is a precursor to lattice degeneration because of the shared location and tendency towards vitreoretinal adhesions, leading some clinics to classify snail track and lattice degenerations as one entity (2). This may explain why some studies of peripheral changes do not mention snail track. The risk of retinal detachment is low as vitreoretinal traction is seldom present (267).

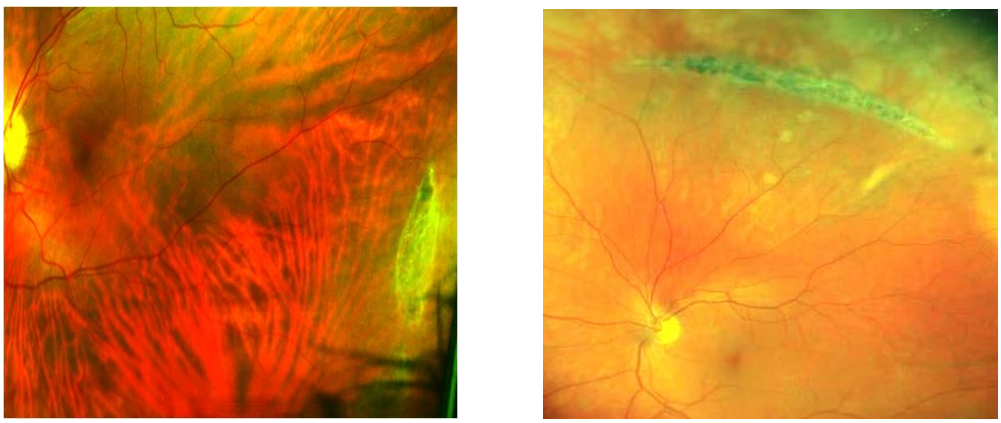


Figure 1.19 Fundus images showing snail track degeneration. Images courtesy of Optos plc.

1.8.5 Atrophic retinal holes (RH)

Retinal holes are not uncommon, and only rarely progress to retinal detachment (2). They are usually found between the equator and the vitreous base and may be associated with areas of lattice degeneration. In an autopsy study, 75 % of all round holes were found within areas of lattice (287). The position of holes in the general population tends to be inferior although superiorly located holes are reported more frequently in myopic eyes (273). Atrophic retinal holes are often found in younger eyes than other types of retinal break and are believed to be the result of retinal thinning rather than vitreoretinal traction (283). Investigations using fluorescein angiography show areas of non-perfusion of the retina and choroid surrounding the holes supporting a vascular aetiology (288). A full thickness hole may allow the liquefied vitreous to pass through the break to the potential space underneath the sensory retina leading to retinal detachment. If a halo of oedema is present, it indicates an increased risk of retinal detachment (289). Byer calculates the likelihood of RRD in eyes with atrophic holes to be 0.274 %, the risk being greater in young high myopes (289).

Operculated retinal holes are like atrophic retinal holes in position, size, colour, and position but are caused by vitreoretinal traction pulling a plug out of the retina, which is then seen floating over the hole (Figure 1.20). When the operculum is seen the traction on the retina has been released.

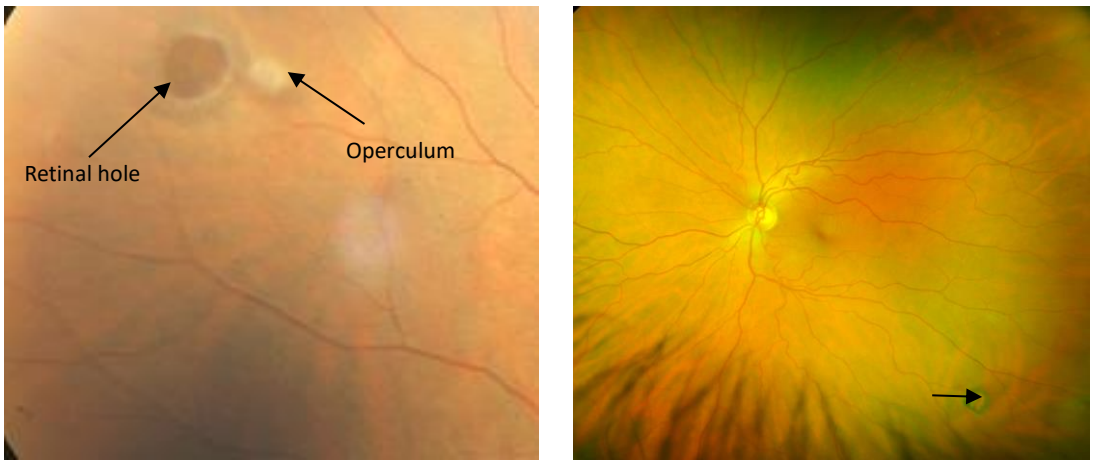


Figure 1.20. Left shows a superiorly located retinal hole with overlying operculum, the right image shows an inferiorly located retinal hole (images courtesy of Optos plc).

1.8.6 Pigmentary Degeneration (PD)

Pigmentary degeneration is most often observed in the far periphery as fine to large pigment clumps (280) (Figure 1.21a). This lesion is most commonly seen in the superior temporal quadrant, is frequently bilateral, and increases with age (2). Pigmentary degeneration is closely associated with axial length and is rarely seen in eyes with axial lengths below 21 mm (2). Reported prevalence levels range from 6 % (280) to 51 % (290), with the lower levels in children and the higher levels in the axially elongated eyes of adults. The pigment has been attributed to migration of RPE cells possibly from interaction with the vitreous leading to vascular or biochemical changes (280). Some have suggested pigmentary degeneration is a later stage of lattice degeneration (2) as the two lesions are often observed in the same eye. Two recent studies (285,290) report pigmentary degeneration as the most prevalent lesion observed in the periphery although they provide no new hypotheses about its aetiology. With the increased use of OCT further explanation of this lesion would be expected. Pigmentary degeneration is generally benign but can be associated with lattice, retinal holes, and tears (280).

1.8.7 Paving stone Degeneration (PSD)

Paving stone degeneration is not considered as a risk for retinal detachment. It presents as round yellow to white patches of chorioretinal atrophy varying in size between 0.5 and 1.5 mm. The edges may be pigmented due to clumping of the RPE; choroidal vessels are frequently visible within the lesions (Figure 1.21b). Over time multiple discrete lesions may become confluent to form scallop-edged areas (267). The lesion is observed in around 25% of the population (267), although higher prevalence levels have been reported in longer eyes and with increasing age (280). Between 38-57 % of cases have bilateral lesions (280,291). Paving stone degeneration is usually located between the equator and ora serrata and is more commonly seen in the inferior temporal quadrant.

It is believed paving stone degeneration stems from alterations to choroidal circulation (292). Histological investigations have shown an absence or attenuation of the photoreceptors, choriocapillaris, and RPE, along with adhesions between the surrounding sensory retina and underlying structures which limits detachment (273).

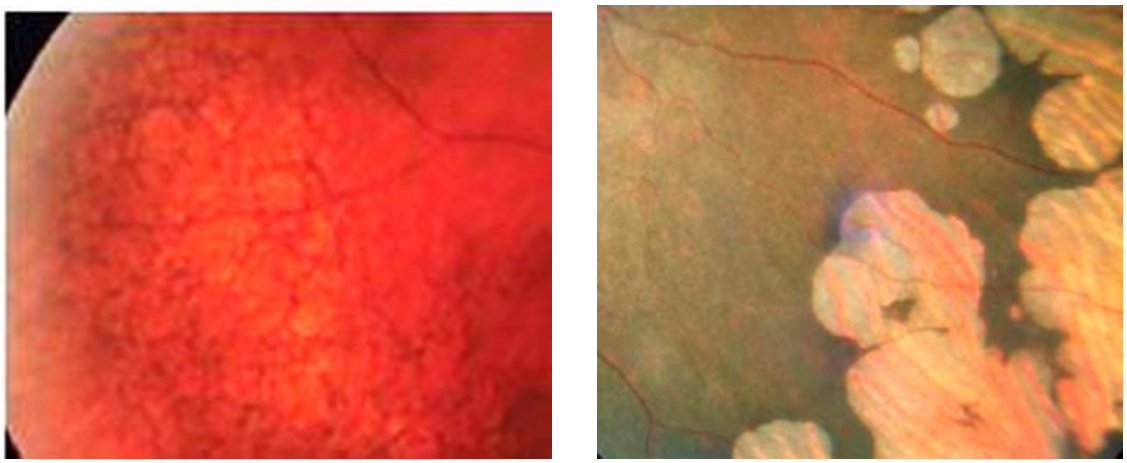


Figure 1.21. Fundus image showing pigment degeneration. Right image depicts confluent paving stone degeneration.

1.8.8 Retinal Detachment

Retinal changes more prevalent in myopic eyes, such as lattice degeneration and white without pressure, are seen more often in eyes with tears and holes than in the general population (274).

Retinal detachment occurs when the neurosensory retina separates from the RPE (Figure 1.22). Generally, the detachment associated with myopia involves either a tear or break and is referred to as a rhegmatogenous retinal detachment. Tears can vary in size from giant tears which are often associated with trauma, to tears less than a quarter of a disc diameter, which is reported to be the case in three-quarters of tears (289). Not all tears progress to a detachment. The two main factors predisposing the myopic eye to retinal detachment are vitreoretinal adhesions and vitreous gel changes (271). An intact vitreous stops many tears from progressing to a detachment (271). As mentioned earlier vitreous changes occur at a younger age in myopic eyes (274,275) which may explain why myopes tend to progress to RRD more often. During PVD, the vitreous initially comes away from the retinal surface and optic nerve head before separating from its anterior base close to the ora serrata, a frequent location of retinal breaks (275). When

the vitreous has not fully separated at sites of abnormal attachments the continued traction can lead to a retinal tear, this then allows the passage of fluid into the subretinal space detaching the retina. Vitreoretinal attachments can be visible such as lattice, or invisible, and only become apparent when a tear occurs; this type of attachment is reported to be common in myopia (271). In the absence of symptoms, most tears or holes do not progress to a retinal detachment. Whether these lesions should be treated prophylactically has been the subject of a Cochrane review which concluded the evidence to treat was insufficient (278). When symptoms are present they include, new floaters, flashes of light-typically in the temporal field, and visual loss as the fluid passes through the hole or break detaching the retina. Breaks are more common in the superior temporal quadrant and most commonly result from horseshoe tears or the result of advancing operculated holes (293).

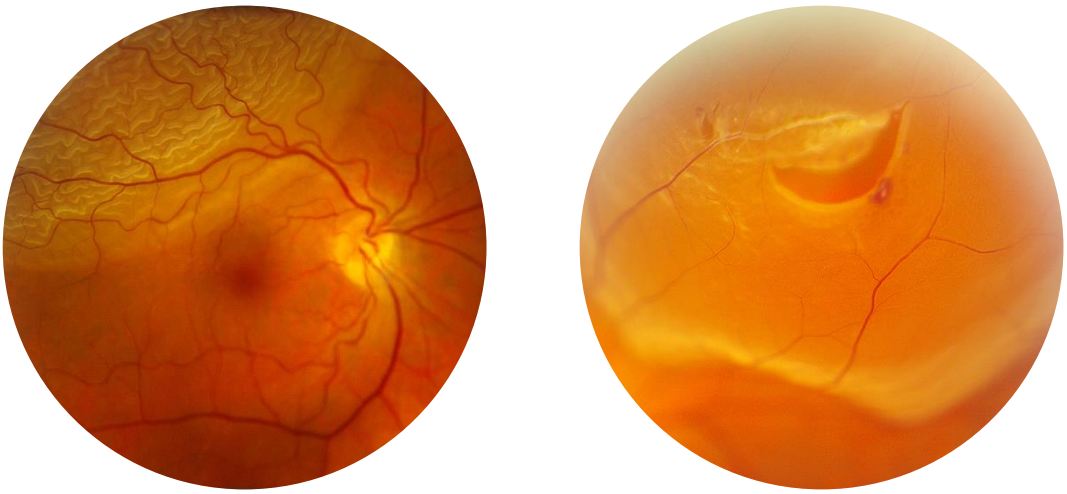


Figure 1.22. Fundus images showing superior retinal detachment and horseshoe tear and associated retinal detachment. By permission from Eye rounds.org.

Non-traumatic retinal detachment has an incidence of 1/10000 person/year (293) with over 40% of detachments occurring in myopic eyes (267). The risk of retinal detachment has been shown to increase with the degree of myopia (294). Myopia is the dominant risk factor for RRD (32). Ogawa showed the odds ratio for detachment in eyes with myopia below three dioptres to be 3.14 but increasing to 80 for myopia over 15 dioptres (295). Half of all retinal detachments occur in those with low myopia (≥-4.00 D) as the lower levels are more prevalent (32). Curtin quotes

work by Bohringer who estimated the lifetime risk of retinal detachment in a person with myopia <-5.00 dioptres to be 2.4 %, compared to emmetropia at 0.06 % (2).

Two peaks in the incidence of non-traumatic RRD have been reported. Firstly in young myopes, often from atrophic holes, followed by a second peak around the time of PVD occurrence (283,296). In the large Scottish retinal detachment study (297) 8 % of fellow eyes were found to have a full-thickness detachment, but figures of up to 30 % have been reported elsewhere (298) indicating the need for careful examination of both eyes. Cataract surgery in high myopia is associated with retinal detachment in 1.69 % of cases rising to 4.6 % in those with prior repair of retinal breaks or detachment (299).

1.9 Retinal blood vessel assessment

Changes in the architecture of the retinal vasculature have been studied extensively in relation to many systemic and ocular conditions (300–303). It is well documented that changes in the retinal vessels reflect changes in the microvascular systems elsewhere in the body (300,304,305). The microvascular structure of the retina is like many other tissues throughout the body but has the distinct advantage of being observable in vivo and non-invasively with the minimum of discomfort to the patient. Traditionally, a subjective assessment of the retinal vasculature forms part of a standard eye examination. The increased availability and use of digital fundus imaging, has led to the development of computer software to facilitate a more objective and useful assessment of the retinal vasculature (306), albeit primarily in the research setting.

Most of the blood supply to the retina is via the central retinal artery (CRA) which branches from the ophthalmic artery. The CRA enters the optic nerve approximately 10 mm behind the eye, where it passes to the optic disc (126). At the optic disc, it divides to form superior and inferior branches before further division to create nasal and temporal branches; these vessels, which lie in the retinal nerve fibre layer each supply the respective quadrant. Further division creates the

arterioles and capillary beds which nourish the middle layers of the retina. Drainage is primarily to the central retinal vein (CRV), which closely follows the route of the CRA, but leaves the optic nerve slightly further back. The arterioles and venules, with widths between 100 and 300 μm, form the retinal microvasculature (126). The arterioles are typically narrower than the equivalent venules and have a brighter appearance due to the oxygenated blood they carry. Figure 1.23 shows the branching of the CRA and CRV and highlights the difference in appearance between the vessel types.

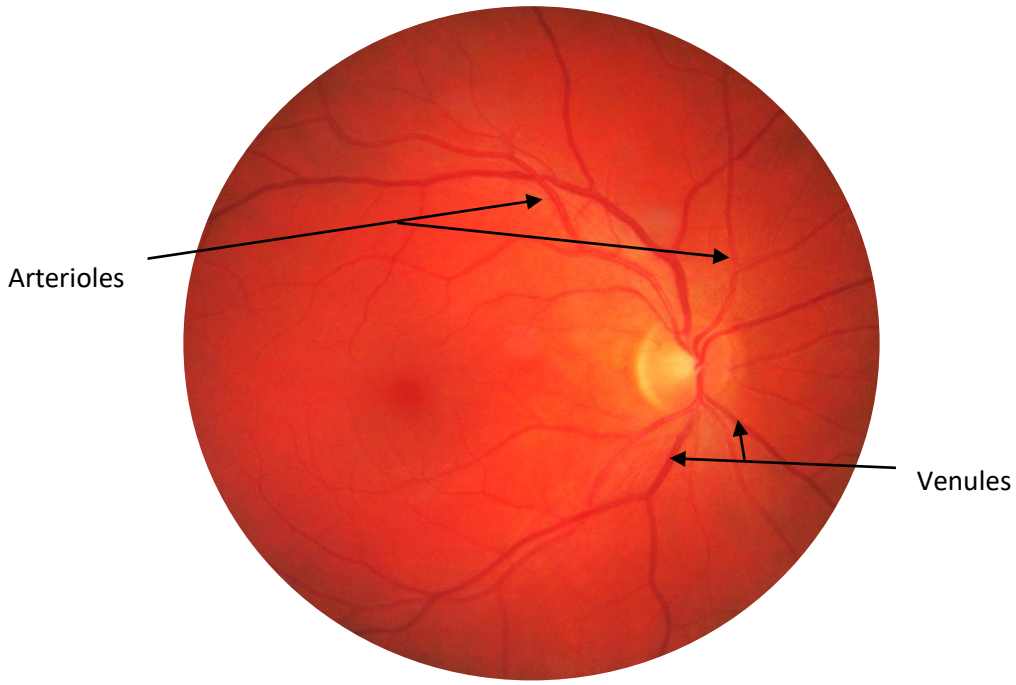


Figure 1.23. Fundus image highlighting the difference in appearance between the arterioles and venules and the typical branching pattern of the vessels.

The outer layers of the retina receive nourishment and remove waste via the vessels of the choroid. Vessels of the circle of Haller-Zinn formed from the short posterior ciliary arteries supply the portion of the optic nerve as it reaches the globe. These vessels may extend onto to the retina, usually supplying the area between the optic disc and macula (126).

1.9.1 Retinal vascular parameters

Both dynamic and static descriptors of the retinal vasculature have been reported (307,308). With advances in imaging such as the Doppler OCT and Dynamic Vessel Analyser, retinal blood flow has been studied in relation to several conditions such as diabetic retinopathy (305) and pathological myopia (308).

Traditionally, static assessment has involved manually viewing the fundus with an ophthalmoscope and estimating the ratio of the artery to vein width (AVR), usually at the first bifurcation of the vessels. AVR determined in this way has been shown to be inaccurate and strongly biased to place of education (306). Over recent years semi-automated methods of assessing several aspects of retinal vessel appearance have been developed adding the significant advantage of quantification. Static descriptors of retinal vessels include fractal analysis, tortuosity, bifurcation angle, and vessel calibre (Table 1.3).

Table 1.3. Description and limitations of techniques used in static vessel quantification.

	Description	Comments
Fractal analysis	Quantifies the branching pattern of the vascular tree. Reported as the fractal dimension (Fd)	Ability to predict clinical outcomes is unclear. The vascular bed is not adequately described (307)
Tortuosity	Actual path length of vessel segment divided by the length of a straight line	No agreed standard of measurement location or calculation method (309)
Branching angle	The first angle subtended between 2 daughter vessels at each bifurcation.	In disease, the angle is wider leading to slower blood flow (310)
Vessel calibre	Summary measures CRAE and CRVE calculated from 6 largest arterioles and venules	Physiological variations may confound findings (304)
Arteriovenous ratio	Traditionally taken as the ratio of the vein to artery width or calculated from CRAE/CRVE	Vessels can change independently so change may be masked (311)

Retinal vessel calibre (RVC) is the cross-sectional width of the vessel and is the most frequently reported method of describing the retinal microvasculature via ancillary software. These often

semi-automated methods measure the blood column which approximates to the internal lumen width (305,312). The calibre of retinal vessels is typically expressed as a summary measure which describes the average retinal vessel calibres of the eye, referred to as the central retinal artery equivalent (CRAE), and central retinal vein equivalent (CRVE). Determination of these measures involves identifying vessel pairs within a defined area known as zone B. Zone B is the width of half a disc diameter and located one and a half and two-disc diameters from the centre of the optic disc as shown in figure 1.24. The area of measurement across the various methods is chosen for several reasons. Firstly consistency, secondly, larger vessels facilitate the differentiation of arterioles and venules (313), and thirdly, as smaller arterioles are more vulnerable to hypertension so could distort measurements.

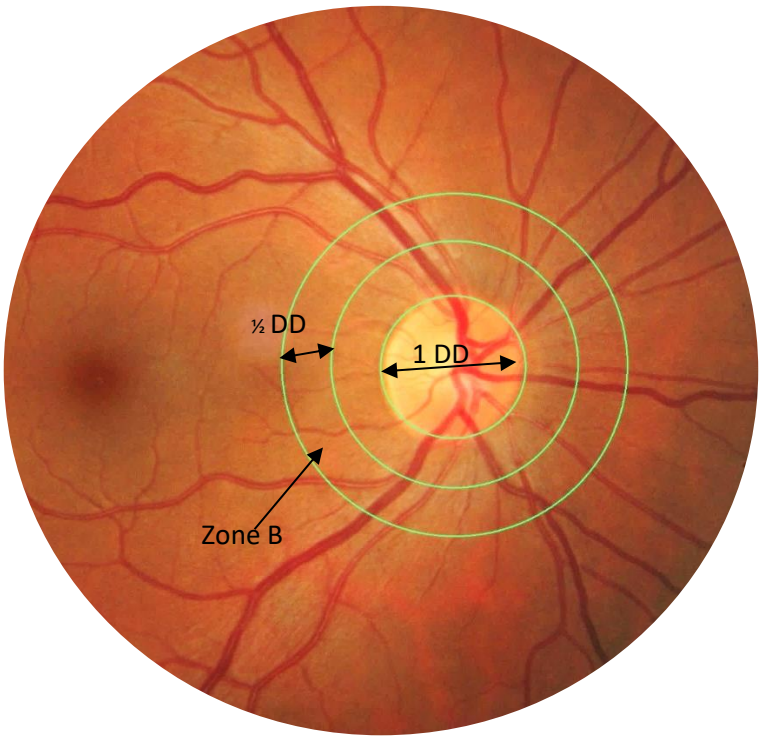


Figure 1.24. Fundus image showing the position of the measurement zone. (zone B).

The AVR is then calculated from the CRAE and CRVE. The AVR computed this way has been shown to be higher than manual estimations (306). Using the AVR has the advantage of negating the magnification issues associated with absolute measures but has its limitations. Both the

CRAE and CRVE can each independently decrease or increase in response to various factors, physiological and pathological. Hence an increase in one, or a decrease in the other can change the AVR in the same direction. The use of CRAE and CRVE individually has been suggested as a more appropriate clinical measure and as a biomarker for future disease (307,314).

1.9.2 Retinal vessel calibre and systemic disease

Alterations in the retinal vessels occur in response to both physiological and pathological factors (304,315). Age, ethnicity, and lifestyle factors such as smoking have been shown to affect retinal vascular calibre, along with a probable genetic influence (304). Many disease outcomes have been associated with retinal vessel calibre. The Atherosclerosis Risk in Communities study (ARIC) (300) was the first to present an association between elevated blood pressure and narrower arteries using semi-automated measurements; this has been confirmed in many subsequent studies across different ethnic groups (316–318). A smaller AVR was related to coronary heart disease in the ARIC study, with a stronger association being seen in females. This was also the finding in a meta-analysis of six studies (319) with over twenty thousand participants. Both clinical and sub-clinical stroke have been shown in prospective studies to be associated with wider venules (320,321).

Diabetes Mellitus can lead to microvasculature disease across many regions of the body. The two main aspects described in the literature are the association of vessel calibre to incident diabetes, and secondly, the relationship between retinal vessels to incidence, and progression of retinopathy. Both cross-sectional and longitudinal study designs have been utilised to investigate these relationships with some conflicting results, especially concerning arteriolar changes. Jeganathan (322) and Nguyen (323) using cross-sectional designs reported venular and arteriolar widening to be associated with the presence of diabetes. The longitudinal ARIC (300), and Beaver Dam Eye Study (324) found smaller AVR to be related to incident type 1 and type 2 diabetes respectively, whereas the Rotterdam study (325), also longitudinal in design, showed

an association with venular widening and decreased AVR. Smaller AVR was also related to incident diabetes in a meta-analysis presented by Muris et al., with no relationship being observed for arteriolar or venular calibre alone (326). A recent meta-analysis of 5 population-based longitudinal studies concluded venular widening alone to be associated with incident diabetes (327). The study included 18,771 participants with a follow up of 10 years (median), 2581 cases with incident diabetes (327). Other frequent complications of diabetes that have been linked to retinal vessel calibre changes include diabetic nephropathy (328), neuropathy (307,329) and stroke (307,330,331).

Several studies have investigated relationships between retinal vessel calibre and diabetic retinopathy (311,329,332). The longitudinal Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR) showed larger retinal vessels to be associated with four-year progression of retinopathy in type 1 diabetics (333), but no significant relationships were reported with type 2 diabetes (329). This agreed with the observations of Rogers et al. (334) who followed 906 Australian diabetics for five years, those with type 1 showed an association with wider arterioles and incident retinopathy that was not observed in type 2 diabetics. Ikram suggests this difference is due to the older age of type 2 diabetics in this cohort along with the higher prevalence of hypertension which is associated with arteriolar narrowing (307). In contrast, a recent study, including 878 type 2 diabetics, found significantly wider CRAE and CRVE in eyes with diabetic retinopathy that was not observed in those without retinopathy (332).

Retinal vascular changes have been investigated in relation to Alzheimer's disease and other forms of dementia. In 2014 Cheung et al. (301) presented results showing a smaller venule calibre to be associated with Alzheimer's disease. However, not all studies agree (335). Despite variations, a large meta-analysis including ten studies supports Cheung et al. findings (315). The authors suggest several reasons for the differences. The age group of those with dementia are likely to have cardiovascular confounders, and secondly, different stages or types of dementia

may result in differing responses in the retinal vasculature (315). These issues make the prediction that optometrists would be detecting Alzheimer's before symptom onset through assessment of RVC a more distant concept.

1.9.3 Retinal vessel calibre and ocular conditions

Retinal vessel calibre has been investigated in relation to many ocular diseases. Glaucoma (265), age-related macular degeneration (336), central retinal vein occlusion (337), birdshot chorioretinopathy (338), myopic retinopathy (339), non-arteritic ischaemic optic neuropathy (340), and diabetic retinopathy as discussed in section 5.4, have been studied.

Interest in the association between glaucoma and retinal vessel calibre stems from the likely vascular element to its aetiology (341). Narrower arterioles have been shown to be associated with thinning of the retinal nerve fibre layer (342). Mitchell et al. (265) found that eyes with POAG were 2.7 times more likely to demonstrate arteriolar narrowing. The Singapore Malay Eye Study (264) showed associations for both arteriole and venular thinning with the presence of glaucoma. Kawasaki (266) and his team retrospectively assessed changes in CRAE and CRVE over a 10-year period in 104 eyes and reported an increased risk (OR 1.77) for POAG in those who had a smaller CRAE at baseline. A similar but shorter study failed to observe any association (302). Recently, a hospital-based study in South Korea found narrowing of retinal vessels to be most significant in those with normal tension glaucoma (343).

Li et al. used data from the BMES (339) to compare the CRAE and CRVE in eyes with myopic retinopathy, defined as general chorioretinal atrophy, posterior staphyloma, lacquer cracks or Fuchs' spot to a group of myopes without retinopathy, and a group of emmetropes. Correction for camera magnification was applied using Bengtsson's formula (344). Both CRAE and CRVE were smaller in those with myopic retinopathy independent of the level of myopia. However, only the association with arteriolar calibre remained once adjustment for arteriolar calibre was

considered in relation to CRVE (339). Liew et al. (345) suggest controlling for the fellow vessel to reduce the confounding from associations with the fellow vessel. It is postulated that attenuation of the retinal blood vessels may be part of the degenerative changes that occur in myopia rather than related to the level of refraction (339). Myopes seem to have some protection from diabetic retinopathy which may be due to a lower blood flow rate (269). It has also been suggested this protection may occur because of decreased retinal function, and hence lower oxygen demand (270). This is supported by the finding of areas of non-perfusion in the highly myopic peripheral retina (346).

Age-related macular degeneration (AMD) is intimately related to the retinal vasculature. Jeganathan et al. (336) found wider venules to be associated with early age-related macular degeneration after adjustment for confounders, but no association was observed in eyes with late AMD. They postulate a mechanism of underlying microvascular inflammatory changes resulting from oxidative stress. Other studies have failed to show any relationship (347). The variations between studies may be related to poor design, especially small sample sizes or due to the many confounding factors with advancing age. The macula area is readily investigated using OCT, and these observations in relation to RVC assessment may give useful information in the future.

1.9.4 Retinal vessel calibre, myopia, and retinal structures

Retinal vessel calibre has been studied in relation to overall eye size and key features of the eye, such as optic disc size, corneal curvature, and retinal nerve fibre layer thickness. It is believed that understanding these relationships may aid understanding of the pathophysiology of myopia (342). The associations with the level of myopia have been considered in both terms of axial length and SER, in various ethnic and age groups. Not all studies correct for ocular magnification which has led to conflicting findings (Table 1.4).

Table 1.4. Summary of cross-sectional population-based studies considering myopia and RVC.

Study/year	Year	Participants	Magnification	Findings
Cheung (348)	2007	Singaporean 7-9-year olds	Bengtsson	No association once mag corrected
La Spina (308)	2015	White European adults	Not corrected	↓RVC with ↑AL
Lim (349)	2011	Singaporean adults	Bengtsson	↓RVC with ↑AL and myopic refraction
Gopinath (303)	2013	Australian infants and teenagers	Not corrected	↓RVC with ↑AL
Tai (350)	2017	Malay girls 6-12 years	Bengtsson	↓CRAE with ↑AL
Wong (318)	2004	American adults	Not corrected	↓RVC with ↑myopia
Li (339)	2011	White 49-97 high myopia	Bengtsson	No association
Li (351)	2011	Singaporean infants	Bengtsson	↓RVC with ↑AL

Several reports show increasing myopia to be associated with narrower retinal vessels (303,308,317). Li et al. (351) examined 469 pre-school children aged between 48-72 months; those with greater axial length were found to have narrower calibres of both the arterioles and venules after correction for ocular magnification. A recent report by Tai et al. found a 4.25 µm reduction in CRAE for each mm increase in axial length, but no relationship was observed between axial length and CRVE in a group of Malay school girls (350). An inverse association with axial length has also been shown to be present in adult populations (318,349), although not consistently when ocular magnification has been taken into account (352). The Beaver Dam eye study (318) found that a more myopic refraction was also significantly associated with small retinal vessels which corresponds with the findings of Lim et al. (349). Lim et al. also considered other vessel descriptors, finding less tortuosity with increasing myopic refraction supporting the hypothesis of vessel stretching with eye elongation.

The relationship between corneal curvature and retinal vessel calibre is of interest due to the hypothesis of corneal properties mirroring those of the lamina cribrosa as discussed in section 1.7.1. Reports are inconsistent; some show both arteriole and venules being larger with flatter

corneae (303), others (351), show association only with venular calibre, while some studies report no association (350).

Understanding the association between retinal structures and retinal vessel calibre may help in the understanding of various eye diseases (342). Of particular interest is the likely vascular aetiology of glaucoma (261), and the finding that non-arteritic ischaemic neuropathy is more common in eyes with small optic discs (353). Lee et al. (340) using data from the Beaver Dam cohort of mainly white adults found narrower arterioles and venules in those with the smallest discs, although the relationship tailed off in the groups with larger discs. A similar finding was reported in a school-based study of Singaporean 7-9-year-olds (348) and also in a racially mixed group of adolescents (354). Lim et al. looked at several aspects of the optic disc using OCT, and fundus photographs to determine retinal vessel calibres, in school-aged Chinese children. Associations between thinner optic disc rims with narrower arterioles and venules and larger cup to disc ratio with narrower venules were reported (342). Despite these associations, each group outline the issues of measurement accuracy along with the many confounding factors which may account for the lack of further studies being reported over recent years.

1.10 Cataract and myopia

An association between myopia and cataract has been reported in several large community-based studies (46,47,355). Oxidative stress is considered a significant factor in cataract development and has been found to occur earlier in myopic eyes (356). Nuclear sclerosis cataract has shown the most consistent association with myopia. Although, causality cannot be confirmed due to the associated index myopia with this type of cataract, as demonstrated by Wong et al. (357). They found myopia to increase without any increase in axial length in a survey of Chinese aged between 40 to 80-years old. The Australian Blue Mountains Eye Study (BMES) of adults aged 49 years and older, reported odds ratios for nuclear sclerosis cataract in high myopia <-3.50 D of 3.4 and 2.1 for myopia >-3.50 D (47).

Posterior sub-capsular cataract also shows an association with myopia, especially when the myopia onset was before age 20 (355). Odds ratios of 2.1, 3.1 and 5.5, for low, moderate, and high myopia were reported in the BMES (355). The Tanjong Pagar (357) study showed a statistically significant association between myopia and posterior subcapsular cataract. However, this was not the case in the Beaver Dam Eye Study (358) which only showed an association between nuclear sclerosis cataract and myopia (OR 1.74). The third common type of cataract, cortical, shows more inconsistency in the relationship to myopia (23).

1.11 Posterior pole changes

Changes at the posterior pole are typically only observed at higher levels of myopia and usually show a clear progression (31). Degeneration of the chorioretinal tissues, believed to result from mechanical stretching, is initially seen as localised thinning resulting in increased tessellation before coalescing to form larger areas of choroidal atrophy (212). Loss of choroidal circulation within the areas of atrophy increases the risk for choroidal neovascular (CNV) membranes (359). The collective term used is myopic maculopathy.

1.11.1 Grading and classification of posterior pole changes

Accurate recording of clinical signs is essential and has been facilitated in recent times with objective imaging. However, grading classifications allow quantification of level changes by grouping signs. Grading systems are used in many aspects of ophthalmology and optometry. Possibly the best-known being for diabetic eye disease. Some systems use images, and others use descriptors to categorise the stage of the disease. The effectivity of grading systems is often reduced by flaws in design, leading to different interpretations, and disagreements between authorities in the field. Several grading systems have been used in the area of myopic maculopathy. Tokoro (360) suggested four categories of myopic maculopathy: tessellated fundus, diffuse chorioretinal atrophy, patchy chorioretinal atrophy, and macular haemorrhage. A more detailed classification was presented by Avila (361) (Table 1.5), although this classification has been criticised for not reflecting the typical pattern of progression (212). Another flaw in the Avila classification is highlighted with new imaging technologies, which show lacquer cracks can occur earlier than this system suggests (31). Other schemes have been used for individual studies such as the BMES; this study defined myopic retinopathy as staphyloma, lacquer cracks, Fuchs' spot, chorioretinal thinning or chorioretinal atrophy (362).

Table 1.5. Summary of classification of myopic maculopathy by Avila et al. (361).

Grade	Features
M0	normal appearing posterior pole
M1	choroidal pallor and tessellation
M2	M1 + posterior staphyloma
M3	M2 + lacquer cracks
M4	M3 + focal areas of deep choroidal atrophy
M5	M4 + large areas of geographic chorioretinal atrophy and bare sclera

The META-PM classification was derived by a group of myopia specialists in 2015 with the aim of reflecting the natural progression of myopic maculopathy (31). The lesions are classified into one of 5 groups along with three plus signs that may be associated with any of the five groups (Table 1.6). Category 2 and greater, or the presence of a plus sign, or staphyloma, is classified as myopic maculopathy in this scheme. One limitation of the classification is that tessellation is found in eyes with low levels of myopia and even hypermetropia in some fairer white Europeans.

Table 1.6. META-PM classification for myopic maculopathy (31).

Category	Feature	Plus, signs
0	No myopic retinal lesions	1 Lacquer cracks
1	Tessellated fundus only	2 Myopic CNV
2	Diffuse chorioretinal atrophy	3 Fuch's spot
3	Patchy chorioretinal atrophy	
4	Macular atrophy	

Figure 1.25. Showing myopic maculopathy META-PM study classification using colour photographs. (a)-tessellated fundus, (b) diffuse chorioretinal atrophy, (c) atrophy and a well-defined round atrophic lesion, (d)-advanced patchy atrophy, (e)-lacquer crack (white arrow), (f)-Fuchs spot (black arrow). Re-produced with permission (31).

1.11.2 Myopic Maculopathy

Myopic maculopathy is usually a complication of high myopia and is associated with loss of central vision. The prevalence increases with age (212), however, it is occasionally found in teenage children with high myopia (212,221). The BMES showed 25.5 % of eyes with myopia greater than 5.00 D had some signs of myopic maculopathy which increased to over 50 % for myopia over 9.00 D (362). Myopic maculopathy is typically slowly progressive, with the visual loss resulting from atrophy of the retinal pigment epithelium or subretinal neovascularization (212).

Category one in the META-PM classification is increased tessellation. The term tessellated or tigroid fundus is used to describe hypoplasia of the RPE giving the fundus a paler appearance (Figure 1.26). Tessellation tends to begin around the optic disc, predominantly on the temporal side and often extending to the fovea (2). It is frequently observed in younger eyes with higher levels of myopia; Tokoro (360) reported it to be present in 90 % of eyes with an axial length

greater than 26 mm. The pigmentation of the eye influences the appearance, with its development being more readily observed in pigmented eyes. The use of this lesion as an indicator of change is less reliable in blonde individuals as the fundus is naturally pale. Animal models have suggested tessellation is a result of mechanical stretching (363). It can also be observed in the ageing eye possibly as a result of attenuation of the choroidal vasculature (364). In Asian populations, eyes with tessellated fundi have been shown to be stable, with any progression to other lesions associated with increased risk of visual loss being slow (31).

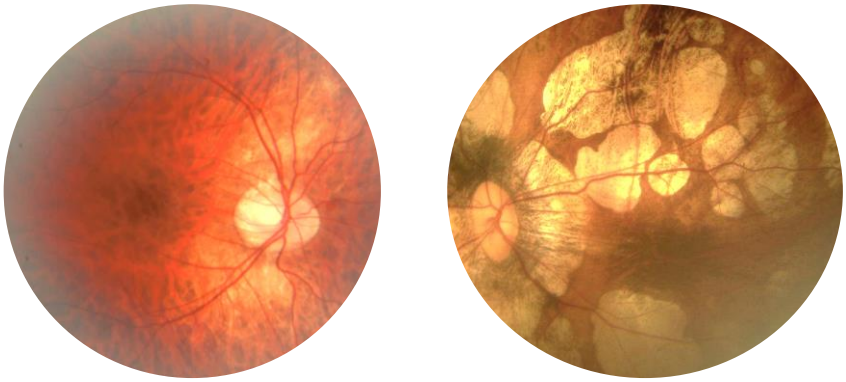


Figure 1.26. Left fundus photograph is showing tessellation and right patchy chorioretinal atrophy.

Both increasing age and axial length have been shown to be risk factors for progression to diffuse and patchy chorioretinal atrophy (212). Patchy chorioretinal atrophy increases the risk of choroidal neovascularization (CNV) which usually signifies the start of visual loss (212). This level of choroidal changes is most often observed in the fifth decade, even though the significant progression of myopia may have ceased many years before (359). Several longitudinal studies, both clinic and population-based, have shown the progression of myopic maculopathy. Hayashi et al. (212), with a mean 12.7-year follow-up, found 40 % of eyes showed significant progression. Whereas the population-based BMES, with a shorter follow-up (5 years), demonstrated less progression (17.4 % of eyes) indicating time is a factor. Other elements such as a clinic or population setting, and severity at baseline, may have contributed to some of the differences reported (362).

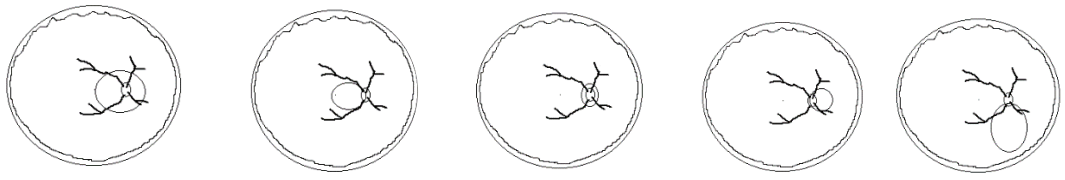
Myopic CNV is often bilateral and frequently affects those under 60 years of age. In a survey of 1227 myopic adolescents only one case of macular changes was identified (221), which agrees with the findings of Cheng et al. in a similar population (365). Hayashi et al. found the younger adults with high myopia who were unfortunate to develop myopic CNV, suffered a more rapid visual loss associated with choroidal neovascularization, rather than the progressive atrophic changes seen in the older high myopes (212). Prevalence of myopic CNV has been reported to be between 5 and 11 % in those with high myopia (2,212). Most cases of myopic CNV occur following the development of lacquer cracks (212,366). Lacquer cracks are breaks in Bruch's' membrane that are believed to occur due to continued thinning from mechanical stretching of the choroid and RPE (367). The breaks are typically accompanied by a retinal haemorrhage and indicate a poor prognosis due to the association with choroidal neovascularization (361). Lacquer cracks show as yellow lines, usually running horizontally across the macula. Persistent meta-morphopsia occurs when the lesions affect the fovea. Lacquer cracks can be seen at a relatively young age although the frequency increases with advancing age (367). The course of myopic CNV is often limited, unlike age-related macular degeneration, although vision usually deteriorates due to increasing chorioretinal atrophy and the development of Fuchs' spot (31). Fuchs' spot is a pigmented lesion that is typically elevated and usually located in the macula. It forms due to the proliferation of the RPE following CNV membrane-associated haemorrhage. It is reported to occur across a wide range (3.2-20 %) of patients with myopic CNV (368).

Optical coherence tomography facilitates the observation of myopic macular holes and foveoschisis. Foveoschisis, also referred to as myopic traction maculopathy and macular retinoschisis is a splitting of the foveal layers and may be part of the same vitreomacular pathology as macular hole formation (369). Macular hole formation is more frequently seen in myopic eyes especially following trauma (267).

1.11.3 Posterior staphyloma

Thinning of the sclera may lead to localised outpouching of the posterior sclera referred to as posterior staphyloma. It is typically associated with higher levels of myopia, however, has been observed in eyes with axial lengths of 25.1 mm (370). Posterior staphyloma is more frequently seen in older myopes. Curtain reports 13.2 % of young high myopes (3-19 years old) and 53.3 % of older high myopes (60-86 years old) have a discernible outpouching (370). These figures are from 40 years ago and are likely to be an underestimation due to the difficulty in diagnosing early staphylomas at that time. Despite advances in imaging, the best method of detecting these outpouchings is still not clear (371). The earliest sign of staphyloma development is an optic nerve crescent followed by pallor changes at the posterior pole. As the staphyloma develops, the blood vessels are seen to straighten, and vision gradually reduces if the macula is involved due to the stretching of the choroid and RPE (2).

Curtin described five primary types of staphyloma by the area of the eye affected using ophthalmoscopy and fundus drawings (2), along with several other forms which are generally combinations of the five primary types. Type 1-which surrounds the optic nerve and extends to the macula was the most frequent variation; this with type 3, the least common variant-which encircles the optic nerve without extending to the macula, are most likely to lead to significant degrees of ectasia (2). Recently Ohno-Matsui (371) used a combination of 3D MRI and wide field fundus imaging to propose a scheme where the staphyloma are named according to location and extent (Figure 1.27).



Type 1	Type 2	Type 3	Type 4	Type 5
wide macular	narrow macular	peripapillary	nasal	inferior

Figure 1.27. Showing the position of Curtin's (370) classification (top line). The lower line shows the renaming proposed by Ohno-Matsui et al. (371).

This scleral thinning and outpouching can lead to several changes under the umbrella term myopic maculopathy (discussed in section 1.6.6). The presence of posterior staphyloma increases the risk of maculopathy progression (371). Eyes with staphyloma have been shown to have reduced visual acuity (372). Interestingly eyes with shallower outpouchings had poorer visual acuity; the authors suggest in the case of a shallower staphyloma the choriocapillaris is preserved which is a prerequisite for CNV (371). Treatment of staphyloma has been attempted by reinforcing the sclera since the early 1970s with mixed results and still no clear consensus on the benefit compared to risk (31).

1.12 Summary

The increasing burden of myopia worldwide, along with an anecdotal observation of a low level of awareness concerning morbidity associated with myopia, led the author to this topic. The low awareness, and possibly concern, appears both amongst the myopic population, and even more alarming amongst fellow optometrists (38). Since the inception of this study, the subject of myopia control has had more coverage in the general optical press as well as being on the programme at many continuing education events.

As discussed, the number of diseases (45,235) associated with myopia in combination with the increasing prevalence (26) observed over recent decades is a good reason for concern. Both the response of the World Health Organisation (WHO) (41) and the UK's commitment to the worldwide 20:20 vision to reduce preventable blindness by 2020 (257) indicates the issue is now being taken seriously.

The number of high myopes in the United Kingdom is low compared to some parts of the world. However, the number of moderate myopes, combined with the fact people are living longer, mean myopia related eye disease is likely to cause a significant burden in the future. Investigation of this group is appropriate, as for glaucoma there are clear and generally effective treatments.

A significant amount of effort is being applied in the field of myopia prevention and retardation of progression. Strategies such as outdoor time (69), multifocal contact lenses (184), and the use of non-selective muscarinic antagonists (373) have shown potential. Identifying pre-clinical changes may facilitate the targeting of treatment strategies, improving the overall risk and benefit ratio. The second element is to increase awareness of retinal changes that are observable at lower degrees of myopia and how they may relate to common eye disease, with the goal of earlier diagnosis of conditions such as primary open-angle glaucoma.

This study aimed to determine how the level of myopia (SER) relates to clinical and structural changes using equipment found in a high street optometry practice. Previous studies have investigated retinal changes across various age groups, often in highly myopic eyes, in South and South-east Asian populations (158,221,250,254). This study was carried out on a UK population predominately of white European ethnicity.

Chapter two describes the instrumentation used, along with an outline of the magnification issues of this type of work.

Chapter three investigates the optic nerve head and the surrounding tissues. Firstly, through a retrospective cross-sectional review of fundus images. Secondly, by analysing a second set of images from subsequent examinations to give a longitudinal insight in those with stable and increasing myopia (SER). The associations of optic nerve head metrics, peripapillary changes, and disc tilt were considered.

The vast peripheral area of the retina is investigated prospectively in chapter four. The prevalence of peripheral fundus features and their associations to the level of myopia, age and optic nerve head features was assessed.

Chapter five considers retinal vessel calibre in a small set of myopic eyes. Summary measures for the arteriolar and venular calibre are assessed, regarding the level of myopia and optic nerve head size. Secondly, changes in vessel calibre between examinations in those with no change in myopia (SER) and a group with an increase in myopia were investigated. Conclusions for the whole study are drawn in Chapter six along with suggestions for further research.

Chapter 2 Methods

2.0 Introduction

This chapter describes the instruments and methods used in the studies described in this thesis. One of the main principles of the project is the use of equipment to the standard, and specification, found in a typical high street optometry practice. Hence no adaptations were made to the equipment used.

2.1 Fundus photography

The adoption of fundus cameras in primary care has embedded visual records into the care of patients, facilitating the identification, monitoring, and recording of subtle retinal features. A digital fundus camera is a specialised low power microscope based on the reflex-free indirect ophthalmoscope with a high-resolution digital single-lens reflex (SLR) camera attached (224). Digital cameras have several advantages over the earlier film-based cameras, in terms of reduced consumable costs and the ability to see the image almost instantaneously. The current study utilises the Nidek AFC-210 camera (Nidek Co Ltd, Tokyo, Japan) which is widely used in optometric practice due to its ease of use. The camera has a resolution of 12.8 megapixels with a 45-degree field in the standard operation. The Nidek AFC 210 is a non-mydriatic camera with auto tracking and focus which facilitates repeatability of patient positioning. An infrared split bright target is used for focusing. The light source for observation is a halogen 12V 50W bulb, and for the flash, a xenon flash lamp is used. The image is displayed on a 5.7-inch thin film transistor liquid crystal display (TFT LCD) monitor attached to the instrument (Figure 2.1). The patient fixates a green light emitting diode (LED) target in the camera which can be moved by the operator.

A fundus camera can have a telecentric system, which produces an image at infinity, and has the benefit of providing a constant correction factor for magnification over the normal range of refractions; or as in this case, non-telecentric. In a non-telecentric system, the correction factor must be modified for each level of ametropia (226).

Figure 2.1. The Nidek AFC 210 fundus camera in use.

Once the image has been acquired Navis-Lite® (Nidek Co Ltd, Japan) image filing software is used to transfer the data by networking to the viewing stations in the consulting room. Navis-Lite runs on a windows platform (Microsoft, Redmond, United States). The software also provides tools through its image wizard utility for measuring various aspects of the images, in addition to drawing and image processing properties. Images can be exported as jpeg and bitmap files for use in other software programs. The image wizard software, via callipers, allows measurement of image features displaying the output in mm and pixels (Figure 2.2). Nidek have been approached for more information on the correction factors used to calculate the image size but were unable to supply any useful information other than the system is non-telecentric.

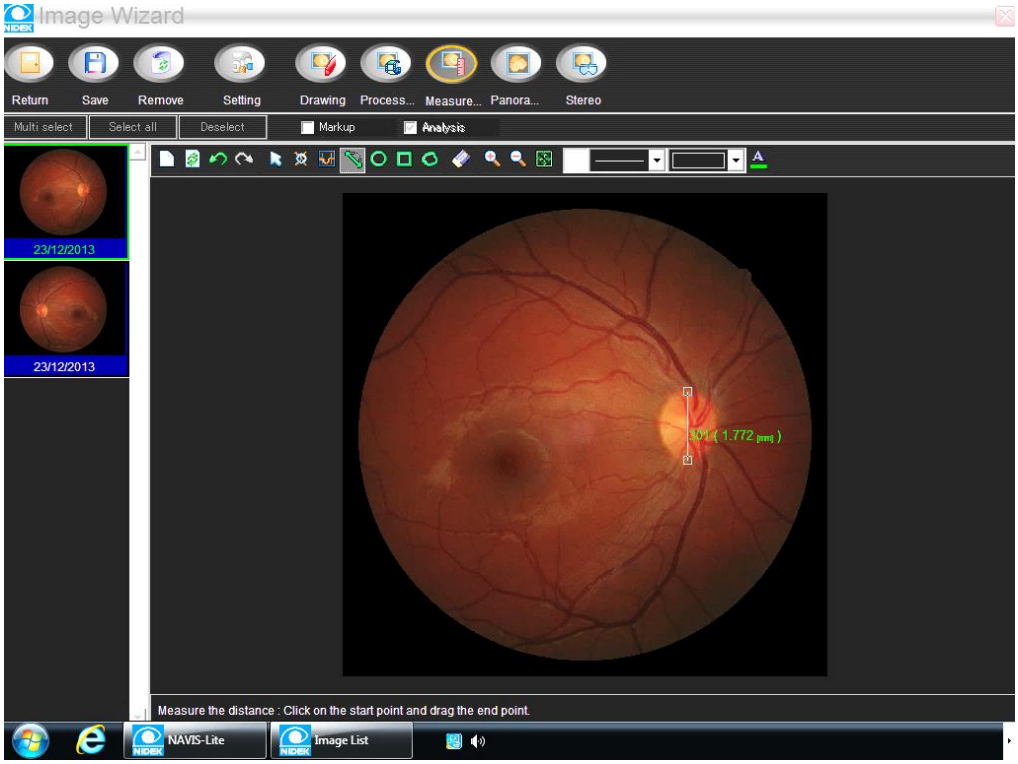


Figure 2.2. Screenshot of Navis-Lite image capture and image analysis page with callipers set to measure the vertical disc height.

2.2 Magnification correction

When examining the fundus, the size of features, such as the optic disc, is important in determining the relevance of certain findings. For example, a large cup in a large disc is not unusual, but a large cup in a small disc is suspicious (219). In longitudinal studies, the participants can serve as their own control when the equipment and positioning are kept constant (374). However, when the optic nerve head parameters are to be compared between participants an absolute measurement is desirable (374).

The actual size of a fundus feature is not easily measured so instead the image of the feature is measured. The issue of magnification and determination of true retinal image size is a challenge that has been addressed by several workers, most notably Littmann (225), Bengtsson (344), and Bennett (375), but not to an entirely satisfactory end.

The measured retinal image size denoted as ***s,*** is influenced by both the camera optics, and the magnitude of ametropia. Two correction factors, one for the camera optics, referred to as ***p***, and

secondly, for the ametropia of the eye, ***q***, are needed to determine the true retinal image size (226,376) (Figure 2.3). The fundus camera is based on the optics of an in-direct ophthalmoscope hence the greater the level of myopia the smaller the measured image is compared to the actual size.

$$t = p \times q \times s$$

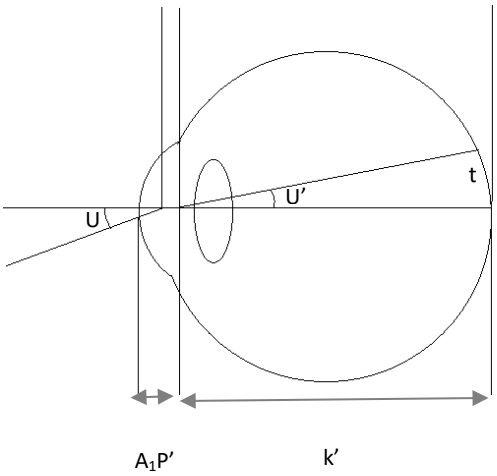


Figure 2.3. Littmann's equation for determining true image size. ***t***- True image size, ***p*** - camera correction factor, ***q***- correction for ametropia, ***s***- measured size.

Several of the quantities used in Littmann's equation cannot be easily measured. The starting point for most of the methods are the classic model eyes of Gullstrand, Emsley, and Bennett (377). The use of these eyes involves the acceptance of approximations for a number of the quantities.

The correction factor for the camera (*p*) would ideally be obtained from the camera manufacturer. However, not all manufacturers will discuss technical details as was the case when Nidek were approached. Given these difficulties, Rudnicka et al. (226) determined the correction factors for several fundus cameras, both telecentric and non-telecentric, using a model eye and ray tracing. As mentioned in section 2.1, in a telecentric system the anterior focal point of the camera coincides with the first principle point of the eye meaning the correction factor is applicable for a wide range of ametropia. For the non-telecentric systems, Rudnicka et al. produced an equation from the linear relationship observed between ***p*** and ametropia to

compensate for the variation with the level of ametropia. It was found that *p* could vary by up to 10 % in the refractive range of plano to ± 10 D and even greater for high ametropia hence significant errors can be induced (226). In their paper, they list the correction factors for 11 commonly used fundus cameras. Some workers have used an average value for the vertical disc diameter as an internal reference to determine camera magnification (332). This method would seem flawed due to the well-documented variations in disc size with level of ametropia and ethnicity (220).

The magnification relating to the eye has received significant attention (225,344,375). Factor ***q*** is dependent on the vergence of the internal axis of the eye (k' in figure 2.3) and can be calculated from a knowledge of the axial length, ocular refraction, or corneal and lens powers (378). Littmann (225,379) developed a correction for the Zeiss telecentric fundus camera he designed. In this method, ***q*** is determined from a set of curves on the principle that equal angular diameters correspond to equal differences on film. The first method he described required knowledge of the ametropia and keratometry readings (Figure 2.4). Later he produced curves that provided a more accurate determination of ***q*** when the axial length was known. In his second method, the axial length and ametropia were used to determine a theoretical value for corneal curvature. This was used with the ametropia to determine ***q*** from the original curves. Quigley (380) suggested that Littmann's formulae result in an underestimation of disc size which becomes more evident in longer eyes, whereas Coleman et al. found Littmann's formulae to agree with their findings. Coleman et al. (374) inserted tacks of known size into the eyes of monkeys close to the optic nerve head and then photographed them using a Zeiss camera, although the shorter length of the primate eye may be a source of error.

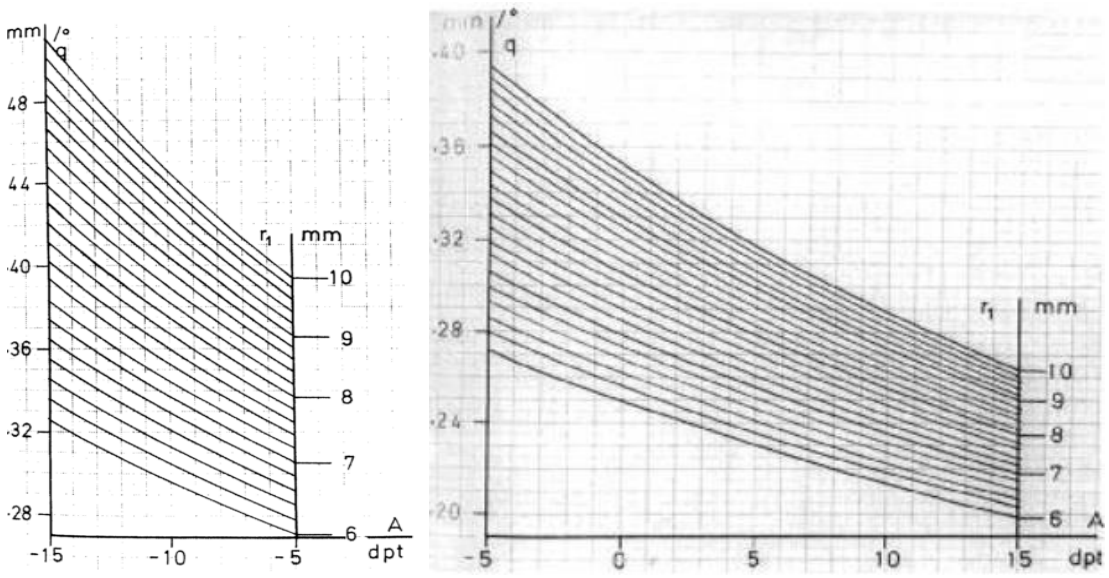


Figure 2.4. Littmann's curves for calculating q from the corneal radius and ametropia. The factor q is read off the left-hand vertical axis. Reproduced with permission from Williams T. Determination of the True Size of an Object on the Fundus of the Living Eye (translation) (225).

Bennett et al. (375) investigated methods to improve Littmann's formula concluding that the simplest way is to reduce the axial length by a constant of 1.82 mm, suggesting the use of a modified formula to reflect this (q = AL-1.82*1.37). In an assessment of eleven methods of ocular magnification correction, Bennett's method was considered the most accurate (378). Knaapi et al. (376) conducted a study to validate Bennett's formula. They used a custom designed octopus perimeter program to plot the blind spot to allow calculation of the angle between the fovea and disc. This was compared to the measurements obtained from a Zeiss telecentric camera using Bennett's correction; good agreement was demonstrated with the conclusion it is appropriate to use Bennetts formula (376). In addition to the Zeiss camera, a non-telecentric Topcon (TRC-50DX) (Topcon, Itabashi, Japan) camera was assessed and found to function close to the telecentric Zeiss camera.

More advanced imaging technologies such as the Heidelberg retina tomograph (HRT) (Heidelberg Engineering, Dossenheim, Germany) determine the power of the eye from the divergence of the laser beam (378). The HRT also allows keratometry readings and refraction to be entered to for automatic correction of the image sizes. The Stratus OCT (Carl Zeiss Meditec, Dublin, CA) also

allows the refractive information to be entered however does not use it to correct for ocular magnification (228). The agreement between the different imaging modalities is weak (381). This could be due to differences in magnification correction, and possibly more related to slightly different structures being measured. This is often the case with systems that automatically determine the optic disc margins (233) (381).

Alternative approaches to determining image magnification include using the freely available image analysis package image J (nih.gov/ij/download); with calibration via an image of known size (228,382). Bartling et al. (383) suggested determining the true size by measuring the fovea to disc distance which they suggested to be constant in normal eyes with ametropia between -9.00 to +4.00 dioptres, at 4.73mm SD±0.29 mm. A significant number of myopic eyes have extensive changes temporal to the disc and may stray from this assumption. Rudnicka et al. (226) advise comparing the image from a camera with a known correction factor to the camera that the correction factor is unknown.

When manufacturers are forthcoming with information on the camera correction factor, the details and assumptions made are often not available, inhibiting analysis of probable errors. Other sources of possible error include the position of the camera, unclear images, and the location of the feature in the camera field (378). The point of interest should be within 20 degrees of the optical axis hence in foveal centred images the optic disc may be close to this limit (226,384). Most of the corrections were derived when 35mm film was widely used. Ewen et al. (385) compared the images of 62 patients taken with a 35 mm film camera and a digital camera. Mean values for disc and cup measures were slightly smaller on film than digital format.

The number of assumptions and sources of small measurement errors can be many, and at best the magnification correction is an approximation. Most workers correct ocular magnification despite the limitations. It is not always clear from the reports how the magnification was addressed if at all. When a correction is used, the majority use Littmann's or Bengtsson's

formulae. Both Littmann and Bennett make it clear that the method chosen needs to be practical (375,379). In this study, only refraction data were available for all participants, so the formula derived by Bengtsson and Krakau (344) was chosen to correct for ocular magnification. In the formula (1–0.017 G) G is the spectacle refraction. Measurement error for factor G should be small as it was obtained as part of a subjective refraction in a mainly adult group. The SER was used instead of the ocular refraction, due to the vertex distance not being available for all cases, as others have done (348,386). It is not clear which should be used in the papers from Bengtsson (344,387). The participant's in this study generally had low and moderate levels of myopia making effectivity differences low. Garway-Heath et al. (378) in their analysis of the methods of determining q found Bengtsson's method to underestimate q in long eyes.

2.2 Keeler Binocular Indirect Head Mounted Ophthalmoscope

The Keeler vantage indirect ophthalmoscope (Keeler Ltd, Windsor, UK) has been developed from that designed by Charles Schepens and presented in 1946 (388). The head-mounted ophthalmoscope is widely used in practice and hospital settings (224). The instrument has several advantages over other methods of fundus examination including a large field of view, which allows appreciation of the landscape, facilitating the detection of subtle colouration differences. The intense light offers a significant resolution of detail, and the binocular viewing provides a stereoscopic view. An LED light source produces a clear, cooler image than its predecessors.

The headset is used in combination with a handheld condensing lens held at arm's length from the examiner, and at the focal length of the lens from the subjects' eye (Figure 2.5). The most commonly used lens was selected; this has a power of 20 dioptres (Volk Optical Inc, Mentor, OH, US) and is held at 5 cm from the subject's eye to maximise the field of view. The 20-dioptre condensing lens provides approximately 3x magnification and a 40° field of view (224). A dilated

pupil is necessary to obtain the full benefit of the instrument. The procedure for use will be described in chapter 4.

Figure 2.5. Binocular indirect Ophthalmoscope and position of the condensing lens.

Ideally, the subject is supine to facilitate a full 360° examination of the fundus. In the high-street practice setting, this is less likely to be possible due to architectural constraints, as was the case in this study. The examination was performed with the patient seated upright. The optics (Figure 2.6) produce an aerial image that is inverted and laterally reversed.

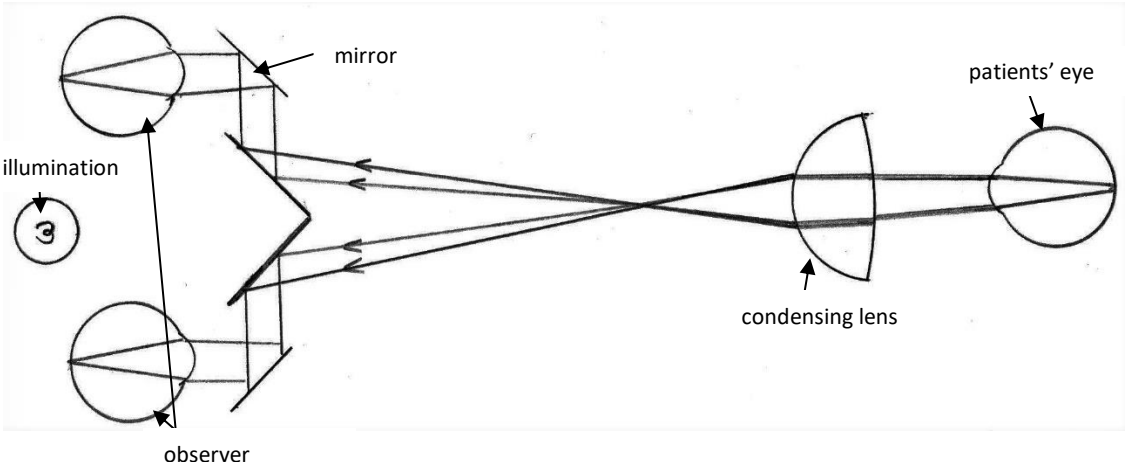


Figure 2.6. Figure showing the layout of the binocular headband indirect ophthalmoscope. (re-drawn from Bennett and Rabbetts) (194).

2.3 Mydriasis

Mydriasis is required for a thorough examination of the fundus. This is especially the case when looking for peripheral features or disease (224). Two groups of topically applied drugs are typically used to achieve pupil dilation. Firstly, those that mimic the sympathetic innervation, such as phenylephrine. Phenylephrine has its effect on the iris dilator muscle. Secondly, are those having an anti-muscarinic action, for example, tropicamide. Tropicamide blocks the acetylcholine muscarinic receptors of the sphincter pupillae resulting in pupil dilation, and also those of the ciliary muscle impairing the ability to accommodate (224). Using a combination of the two types of drug is reported to give maximal dilation (389). In optometric practice, tropicamide alone is the most commonly applied method of obtaining mydriasis, due to the short duration and lesser cycloplegic effect than other anti-muscarinic drugs. Single-use minim eye drops (Bausch and Lomb Ltd, Kingston-Upon-Thames, UK) are commonly used in UK practice to eliminate the need for preservatives and minimise cross-infection. Tropicamide in this form is available in concentrations of 0.5 % and 1 %. The desired mydriatic effect with tropicamide is achieved by 20-30 minutes in most cases. The duration of action is typically 4 to 8 hours depending on the level of pigmentation, and age (224). The 1 % concentration of tropicamide was used in this study although Siderov et al. (390) recommend the use of 0.5 % reporting no clinical benefit with the higher concentration.

The use of a topical anaesthetic before the use of tropicamide to aid comfort, and reduce drug wash out by reducing reflex lacrimation, is advocated by some (391). In addition to increased contact time, it has been suggested that the anaesthetic has its effect by altering the corneal integrity leading to greater permeability (392). Enhanced mydriasis regarding speed (392) and duration of effect (393) have been reported. Siderov only observed an enhanced effect in lighter coloured eyes (394).

Pupil dilation forms part of the routine optometric examination in several countries and is widely used in diabetic screening programmes across the UK. The two main reasons for not using a mydriatic routinely are the effect on vision and the risk of inducing acute angle closure. The visual side effects of tropicamide include those due to the pupil size, and secondly from the cycloplegic action, which mainly affects those with latent hyperopia (395). The dilated pupil results in increased spherical aberration, glare, photophobia, and reduced depth of focus. In disease-free eyes, Chew et al. (396) found reductions in both visual acuity and contrast sensitivity following dilation. A greater reduction was noted when glare was added. Post dilation visual acuity dropped below 6/12 in 13 % of the eyes. With the addition of glare, 20 % fell below 6/12. Goel et al. (391) also reported a statistically significant reduction in visual acuity. When the participants were asked about driving, 14 % indicated they would not feel comfortable or safe driving, although they still met the 6/12 threshold. Potamitis et al. (397) using a driving simulator found none of the measures of simulator performance to show significant differences pre-and post-dilation despite visual acuity being poorer post dilation. The impact on near vision was assessed by Montgomery et al. (395). In the older participants, already wearing reading spectacles, visual acuity was unaffected, and for the younger participants the cycloplegic effect had worn off an hour after instillation. Systemic side effects are rare with tropicamide (224). The use of tropicamide may lead to an increase in intraocular pressure in eyes with narrow angles and possibly lead to acute angle closure. Liew et al. (398) conclude the chance of inducing angle closure is very small even in eyes with narrow angles, they suggest dilate and advise about symptoms of angle closure. Guidance issued by the College of Optometrists recommends assessment of the anterior chamber angle along with pre- and post-dilation measurement of intraocular pressure, as well as giving verbal and written advice about driving and operating machinery (399).

2.4 Intraocular pressure

Tonometry, the measurement of intraocular pressure (IOP), is used mainly in the screening, diagnosis, and review of glaucoma. In this study, it was used to detect post-dilation increases in IOP. Goldmann applanation tonometry is considered the gold-standard method to measure IOP (400). Non-contact tonometry has traditionally been considered to be less accurate. Hubanova et al. showed this only to be the case with the Pulsair when the IOP is 40 mmHg or greater (401).

A Keeler Pulsair Intellipuff tonometer (Keeler Ltd, Windsor, UK) was used to measure the IOP in mmHg, before instillation of the dilating drops, and following completion of the examination in study three. The Pulsair is a portable handheld instrument with an air generator. It is usually connected to mains electricity. The instrument measures over a wide range of IOP (5-50 mmHg) and is used at a working distance of 20 mm (Figure 2.7). The Pulsair Intellipuff tonometer is a non-contact tonometer that generates a puff of air to flatten the cornea. The point of applanation is determined by a system of emitting and receiving diodes. A transducer is used to measure the actual air pressure at the point of applanation. An infrared alignment system is employed; when correctly aligned the puff of air is automatically discharged. No topical anaesthesia is required, reducing the risk of corneal damage and ocular infection. If consistent readings are achieved only two readings in each eye are needed (402).

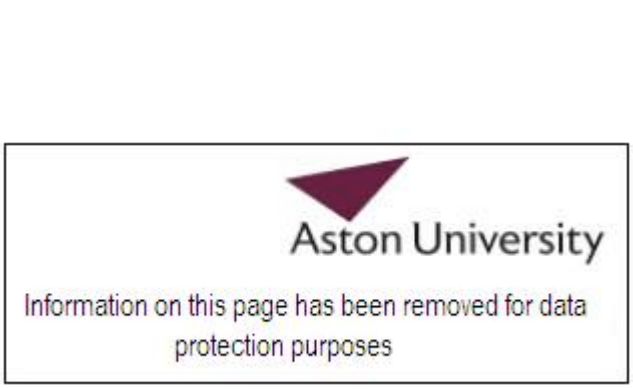


Figure 2.7. Pulsair Intellipuff in use (a) and the head of the instrument showing the controls (b).

2.5 Auto-Keratometer

Traditionally, corneal curvature has been measured using a manual keratometer. Automatic instruments, with multiple functions such as auto-refraction and auto-keratometry, have become widely used, and have been shown to agree with manual keratometry (403,404). Auto-keratometers determine the corneal curvature by analysis of a ring of infrared light reflected off the cornea. The Huvitz 3300 closed field auto-refractor/keratometer (Huvitz, Gyeonggi-do, Korea) was used to measure corneal curvature in this study. This instrument has a measurement range between 5-10 mm, in 0.01 steps, and axis determination in 1° steps. Calibration is checked via a model eye with a radius of 7.8 mm. The patient is positioned on a chin rest as shown in figure 2.8 and fixates a target of a distant house; the operator aligns the instrument using a joystick before the reading is taken automatically. Three readings are taken, and the instrument calculates the average in dioptres and mm.

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Figure 2.8. Huvitiz 3300 auto-refractor/keratometer operators view and in use.

2.6 Slit lamp biomicroscopy

Slit lamp biomicroscopes are used in many parts of the eye examination. With the use of supplementary lenses, the retina can be viewed stereoscopically. A slit lamp consists of an illumination and a viewing system which a have a common point of focus unless de-coupled. The instrument is movable laterally and vertically via joystick control. Several filters and apertures along with slit width and height controls facilitate examination of various structures. A CSO SL 990 (Firenze, Italy) Zeiss style slit lamp was used. This instrument provides a range of magnification (6-40x) and employs a LED illumination source which is controlled via a rheostat.

Figure 2.9. Slit lamp in use with an ancillary lens being used to examine the fundus.

2.7 Indirect ancillary lenses

The Volk Super Field NC non-contact condensing lens (Volk Optical Inc, Mentor, OH, US) is used in conjunction with a slit lamp biomicroscope (Figure 2.9). This widely used general purpose lens is double aspheric and provides a wide field of view (95°) and a magnification of 0.76. The Volk 66D which provides greater magnification was used to examine lesions in more detail. The magnification of the slit lamp lenses is multiplied by the slit lamp magnification which was set at ten times and increased to 16X if required. The third ancillary lens used was a Volk 20D BIO lens,

this was used with the headband ophthalmoscope described in section 2.2. These lenses have aspheric surfaces designed to minimise field curvature, astigmatism, and coma. Table 2.2 summarises the lens statistics.

Table 2.2. Showing the variables for the three Volk lenses used. The FOV (field of view), the second number indicates FOV with lens tilted. (information supplied by Keeler Windsor UK)

	Magnification	FOV	Working distance
Super field	0.76X	96/116	7mm
Super 66	1.0X	80/96	11mm
20D	3.13X	46/60	50mm

2.8 Anterior chamber angle assessment

The current gold standard method for anterior chamber assessment is gonioscopy. In community practice, the anterior chamber angle is usually estimated using the method suggested by van Herrick. This method involves no contact with the eye and has been shown to have good intraobserver repeatability and agreement with gonioscopy (405). The van Herrick method consists of the use of a slit lamp with the magnification set at 10x and the slit width at approximately 1mm wide. The illumination is separated by an angle of 60˚ from the observation system to maintain consistency between measures. A corneal section is formed as close as possible to the limbus. The estimation is made by comparing the width of the corneal section and that of the dark gap behind. The grading system is shown in table 2.3. It is usual to assess the angle temporally, although it has been suggested the nasal angle may be preferable despite being more challenging to measure in some patients (405).

Table 2.3. van Herrick grading criteria

Cornea: Gap	Grade	Angle
1: 1	4	open
1 : ½-1	3	open
1: ¼-1/2	2	possible closure
1: <1/4	1	possible closure
closed	0	closed

2.9 Definitions and classification of myopia:

Spherical equivalent refraction (SER) of -0.50 D or larger was recorded as myopic. The result of the subjective refraction was converted into SER (sphere power in dioptres + ½ cylinder power in dioptres). Individuals with astigmatism greater than 2 dioptres were excluded as it could lead to increased variance in the parameters obtained because full field focus cannot be achieved any longer. All subjects were stratified into levels of myopia as detailed in table 2.4 and age in table 2.5 for use in analysis requiring categorical groupings. The categories of myopia were chosen to represent low, moderate, moderate to high, high and very high. Age categories were selected as school years, college, early adult working years, adult years, pre-presbyopic, presbyopia and retirement years.

Table 2.4. Stratification of levels of myopia

1	2	3	4	5
-0.50 to -2.49 SE	-2.50 to -3.99 SE	-4.00 to -5.99 SE	-6.00 to -7.99 SE	≤ -8.00 SE

Table 2.5. Stratification of age for analysis

1	2	3	4	5	6	7
< 15yrs	16-20	21-25	26-35	36-50	51-65	≥ 66years

2.10 Data analysis and statistics

The data were entered into a Microsoft Excel spreadsheet (Microsoft, Washington, US). The statistical analyses were completed using SPSS version 23 (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp). The normality of data was assessed, and the appropriate parametric or non-parametric tests were selected. The tests used will be described in each experimental chapter.

2.11 Sample size determination

Sample size calculations were completed using G*Power 3 software (Dusseldorf University, Germany). The outputs for each study are given in the relevant chapter.

Chapter 3 Retrospective analysis of central fundus images

3.0 Aims

- To collect a cross-sectional sample of patients of different ages and levels of myopia (SER) to provide data on the frequency of myopia related ONH features.
- To assess associations between level of myopia and ONH features.
- To assess whether a change in the features can be detected between two points in time (varying periods of time).
- To determine if changes in ONH parameters occur with myopia (SER) progression and if they are also evident in those with stable myopia.
- To assess the position of the crescent in relation to the level of myopia.

3.1 Introduction

This study investigates the features of the optic nerve head (ONH), and adjacent area, to determine if, and how, they relate to the magnitude of myopia (SER) and age. The second part of this chapter, through retrospective longitudinal review, considers change over time area in a subset of the participants.

The ONH, also referred to as the optic disc, is arguably the key fundus feature to be observed in every eye examination. There is significant information to be gained by examining the ONH and adjacent area, with changes in the morphology being key in the diagnosis of many conditions.

The normal optic nerve head is described in section 1.7 along with an in-depth discussion of the changes observed in the myopic eye. Several changes to the optic nerve head and adjacent tissues are seen in myopic eyes. These changes include tilting of the OHN, vertically elongated discs, shallow cupping and the formation of a myopic crescent (Figure 3.1).

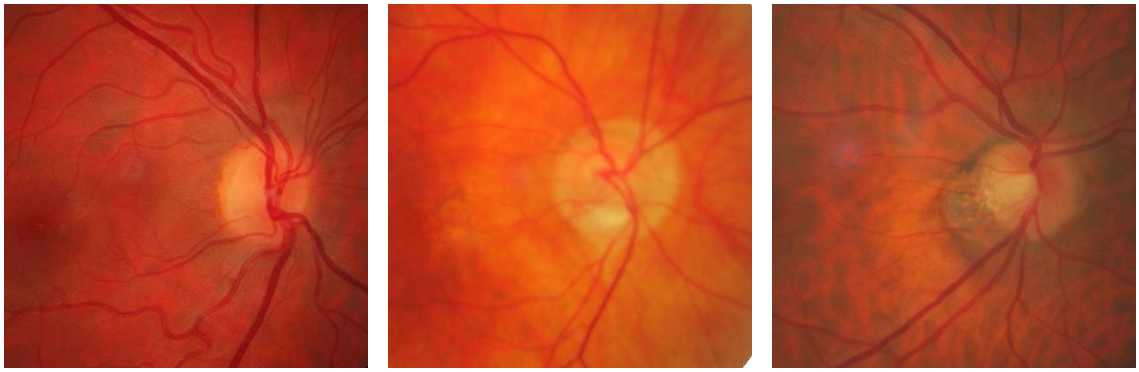


Figure 3.1. Classic features seen in a myopic eye. A-shallow cupping and nasal supratraction. B-Halo of PPA and tesselation of the adjacent area. C-large inferior temporally located crescent.

Most work, although not exclusively, has involved higher levels of myopia often in hospital settings. Cross-sectional studies predominate with only a handful of longitudinal studies. This study aims to determine the prevalence of ONH features and to investigate if, and how, a change in the features manifest between eye examinations in a community setting of mainly white Europeans.

3.2 Methods and materials

3.3 Participants: Study 1

For this study, patient records of those with previously obtained clear digital fundus images were examined. Myopic patients of all ages were identified from the database of a high-street optometry practice (Specsavers Opticians Newmarket, Suffolk, UK). The search criteria were all eye examinations after March 2009 (the time the practice obtained a digital fundus camera) where the refraction (prescribed) was at least a sphere of -0.50 dioptres with no more than 2.00 dioptres of (minus cylinder) astigmatism as others have done (248,262). Refraction was subjective as part of a full eye examination to General Ophthalmic Services or Opticians Act Regulations (406). The oldest image was used to maximise the time interval for study 2. As well as the refractive inclusion criteria those with a history of ocular surgery, or other pathology that may affect the ONH were excluded. The data, for both eyes, extracted from the patient's records were as follows:

- Retinal images obtained using a non-mydriatic fundus camera (Nidek AFC-210, Nidek Co Ltd, Japan). The 45-degree images were centred on the fovea.
- Demographic and refractive data: age, sex, ethnicity, refractive status (obtained from subjective refraction).
- Distance visual acuity (Snellen) converted to Log MAR using Log MAR=Log(n/n).

3.4 Ethics

The study abided by the tenets of the declaration of Helsinki. Ethical approval was granted by Aston University Life and Health Sciences, Ethics Committee (project number 642). The research ethics application form has been included in Appendix B. Consent was not sought due to the retrospective nature of the study.

3.5 Retinal Image Analysis

The 45° fundus images were viewed on a desktop computer and several metrics, (Table 3.1), were measured using Navis-Lite image Wizard software (Nidek Co Ltd, Japan) by one investigator (DH). The software described in section 2.1 provides measurement outputs in mm and pixels. The investigator was masked to the level of refractive error at the time of grading. A subset of 25 images was measured twice to assess intra-observer variability, and ten randomly chosen images were measured ten times to allow calculation of the coefficient of variation.

Table 3.1. List of optic nerve head metrics and observations.

Vertical disc height VDD (1)
Horizontal disc width HDD (2)
Vertical cup height VCD (3)
Horizontal cup width HCD (4)
Crescent width CW (5)
Crescent position (6)
Optic disc tilt (7)
Optic disc area (8)
Optic cup area (9)

Before the image analysis, all images were assessed regarding suitability and image quality based on the overall focus and visibility of disc margins. The number of non-gradable images was recorded. The measurements, along with demographics and refractive information, were entered into an Excel (Microsoft, Redmond, Washington, US) spreadsheet.

3.6 Rationale for selection of data taken from the fundus images

The measurements taken from the images are shown in figure 3.2. Quotients for the cup to disc, maximum crescent width to vertical disc height, and horizontal disc to vertical disc width were calculated from the measurements (Table 3.2). The absolute measures were corrected for ocular magnification using the method proposed by Bengtsson (344). The formula (1–0.017 G), where G is the spectacle refraction, was used.

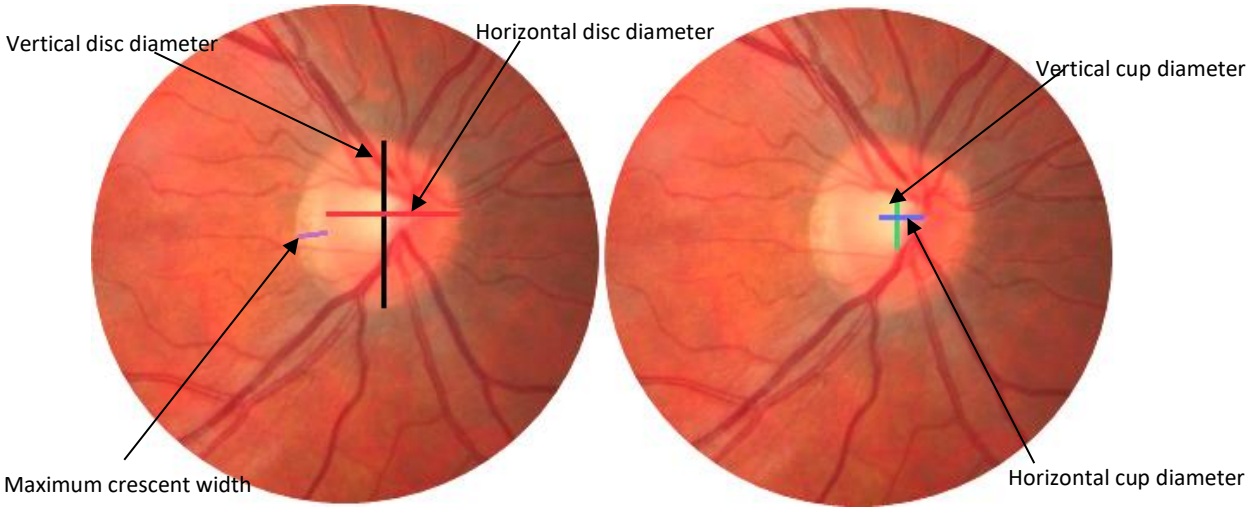


Figure 3.2. Fundus photograph showing the metrics taken from the images using Navis Lite software.

The area within the scleral ring of Elschnig was considered as the optic disc, and the optic cup was assessed in relation to disc contour rather than pallor changes as recommended by Jonas (219). ONH and cup area are the most reported measurements in both studies using disc photographs and more advanced imaging techniques such as OCT and HRT (232,233,248,407). Jonas (222) reports the use of a formula for a modified ellipse (area = π/4 x horizontal disc diameter x vertical disc diameter) to describe the area of the disc, or modified to calculate cup area allowing determination of NRR area. The advent of newer technologies such as OCT with greater computing power can more accurately determine the area of irregular shapes by pixel counting (408,409).

The vertical and horizontal dimensions of the ONH and cup are commonly assessed in studies using planimetry which allows determination of the cup to disc ratio. The use of quotients to describe the ONH negates the need to deal with magnification. In addition to the vertical and horizontal cup to disc ratios, the ratio of the horizontal to vertical disc diameter has been used to describe the ovality of the disc as a surrogate measure of disc tilt (251,254). Some workers describe ovality by taking the quotient of the vertical to horizontal disc (248,254). We determined tilt by visual assessment of the images. A disc was classed as tilted when one side of the disc appeared raised in relation to its opposite side. The gold standard for research remains expert observation of stereo-photographs (197).

The quotient of the maximum crescent width to the vertical disc height was calculated as used by others as a description of crescent size (246,248). This descriptor is useful in determining changes in the crescent width as the vertical disc height has been shown not to change significantly (234).

Table 3.2. Quotients calculated and reasoning for inclusion.

Quotient	Reasoning
Vertical cup to vertical disc (VCDR)	College of Optometrists guidance suggests its use as a minimum in practice (399)
Horizontal cup to horizontal disc (HCDR)	Useful in determining glaucomatous NNR loss when taken as a ratio to VCDR (219)
horizontal disc to vertical disc (HDD/VDD)	Provides an objective index of tilt (251) (limited to tilt around the vertical axis)
maximum crescent width to vertical disc (CW/VDD)	Can detect an increase in crescent width as vertical disc constant (248)

The location of the crescent may indicate differential weaknesses or attachments of the tissues to the ONH margins. The presence, position, and maximum width of any crescent were recorded. The width was recorded in millimetres. The crescent was taken from Elschnig's border tissue to the edge of the pigmentary change. Figure 3.3 shows the recording card for crescent position modified from Curtin (2).

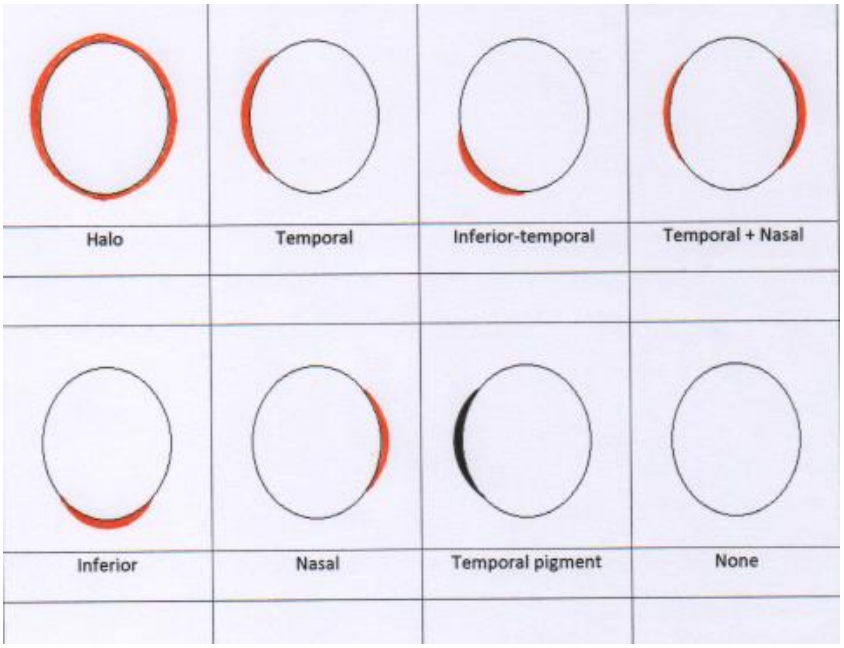


Figure 3.3. Diagram showing the classification of the crescent type for the right eye.

Other measures used by previous workers include the fovea to temporal disc margin and fovea to the temporal edge of the crescent (240,245). The images were generally obtained without mydriasis resulting in the foveal reflex being difficult to identify in many cases hence this method was not suitable for use in this study.

3.7 Participants: Study 2

Out of the 400 participants from study one, 267 were identified as having returned to the practice for subsequent eye examinations and still met the inclusion criteria regarding the level of SER, had not undergone refractive or cataract surgery, and had further gradable images. The minimum time interval between images was seven months.

3.8 Image analysis

The most recent image was analysed to determine the metrics using the same process as described in study 1. The second set of images were measured by the same examiner (DH) but at a different time and without access to the first measurements. The metrics (Table 3.1), were entered into a spreadsheet along with the refractive details of the visit. Using the calculation tools of Excel 2016 (Microsoft, Redmond, US) the differences in time between visits and change in SER were calculated. The time between visits was calculated in months, and the change in SER, dioptres. The quotients for the vertical cup-to-disc, horizontal cup-to-disc, and maximum crescent width to vertical disc height were calculated from the absolute measures.

3.9 Statistical Analyses

All data were analysed using SPSS version 23 (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp). Before any statistical test to compare groups, the data was assessed for distribution normality using the Shapiro Wilks test and comparison of the mean and median to select the most appropriate statistical test. Regression analysis was used to evaluate the relationships between the variables and t-tests to compare groups. The presence or absence of features linked with myopia progression, such as crescent presence and crescent size were explored using frequency analysis. Repeatability of disc measurements was assessed by using

Bland-Altman plots. Ten randomly selected images were independently measured ten times to allow calculation of the mean coefficient of variation.

In all cases, the selected participants met the inclusion criteria in both eyes. The correlation between the right and left eyes for SER was 0.917 $p<0.01$ and for vertical disc height 0.814 $p<0.01$. An independent samples t-test was carried out for SER, VDD and CW. All three measures showed no differences ($p = 0.727$, $p = 0.912$ and $p = 0.621$). The right eye was used unless specified. When appropriate both eyes were considered in relation to some of the analysis of disc tilt.

3.10 Sample size calculation

The sample size was calculated using G*power software (University of Dusseldorf, Germany). For a power of 95% and alpha value as 0.05, a sample size of 138 would be required. Retrospective record reviews range significantly in the number of cases reviewed. To allow a meaningful analysis of sub-groups a sample size of 400 participants was chosen.

Participant numbers of study 2 were 267. Sample size calculations show that this sample will provide 95% power.

3.11 Results

3.12 Demographic information

The 400 participants in study one consisted of 290 females (73 %) and 110 males (27 %) (Figure 3.4), with an age range of 7 to 81 years at the time of the first visit. The mean age was 41 years SD ±16.24. Figure 3.5 shows the age distribution of participants at the time of the first visit with a peak in the fourth and fifth decades.

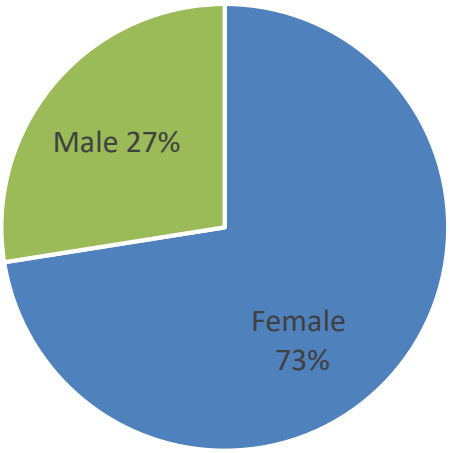


Figure 3.4. Showing the sex split of the participants n = 400.

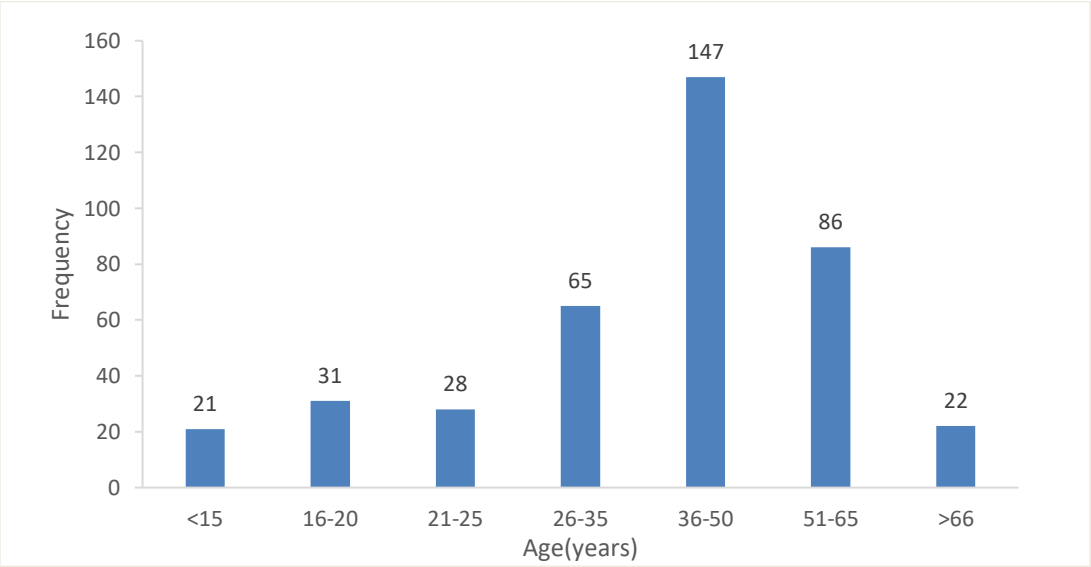


Figure 3.5. The age of subjects when the first image was captured n = 400. The numbers above the columns indicate the number of subjects within the category.

The ethnicity of the participants mirrored the demographics of Suffolk (410) with 96 % being white European (Figure 3.6). The average level of myopia (SER) was -3.74 D SD ±2.32 with a range of -0.50 to -14.00 in the right eye, and -3.72 D SD ±2.33 with a range of -0.50 to -13.50 in the left eye. The distribution of SER was skewed towards lower levels as shown in figure 3.7.

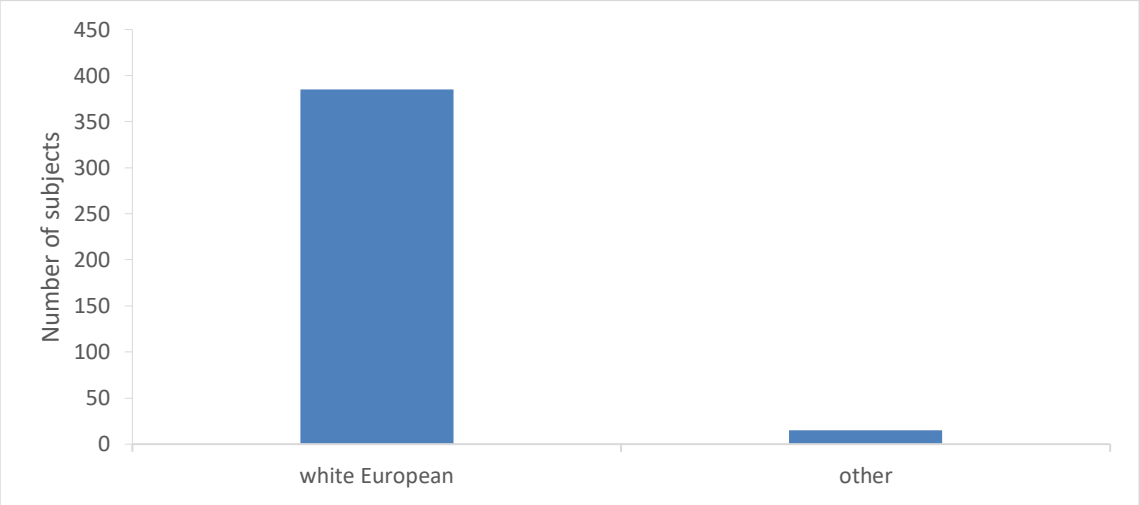


Figure 3.6. Showing the ethnicity of participants n=400.

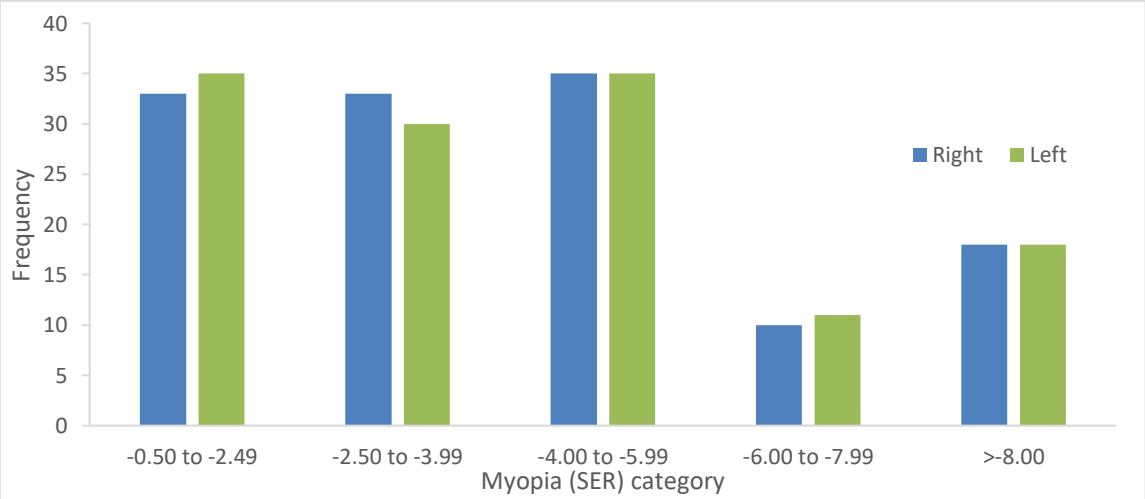


Figure 3.7. Distribution of spherical equivalent refraction for both right (blue columns) and left eye (green columns).

Visual acuity was converted from Snellen notation to Log MAR. The mean visual acuity was Log MAR 0.00 SD ±0.07 (range -0.08 to 0.40) in the right eye, and -0.01 SD ±0.07 (range -0.08 to 0.30) in the left. In study one, 535 pairs of images were reviewed. 135 pairs were rejected due to the poor quality of one or both images, resulting in 400 suitable image pairs for data analysis.

Reasons for rejecting images were poorly taken images and a group with cataract reducing the clarity of the disc features. Nuclear sclerosis cataract is associated with an index related myopic shift (411). However, rejections were primarily on the grounds of poor image quality. All results are for the right eye unless stated. Both eyes were assessed when the bilateral nature of the lesion was of interest.

3.13 Optic Disc parameters

The height and width of the disc and cup were measured in millimetres (mm). A summary is shown in table 3.3 along with the quotients for the vertical and horizontal cup to disc ratios. More than a twofold difference was seen in disc height and width. 83 % of discs had a crescent, and 18 % of eyes did not display any cupping. The Shapiro-Wilk test showed that only the horizontal disc width followed a normal distribution, the remaining parameters did not. The median was close to the mean for most parameters, and the size of the group allows for the use of parametric tests.

Table 3.3. Disc metrics, corrected for ocular magnification, and quotients for vertical and horizontal meridians (n400). The final column shows the Shapiro Wilk test for normality.

Parameter n=400	Mean	Median	Standard Deviation ±	Range	Shapiro-Wilk test p
VDD (mm)	1.75	1.76	0.21	0.90-2.96	0.01
HDD (mm)	1.51	1.52	0.21	0.88-2.20	0.27
VCD (mm)	0.42	0.44	0.28	0-1.45	P<0.01
HCD (mm)	0.40	0.42	0.27	0-1.26	P<0.01
Disc area (mm^2)	2.11	2.10	0.51	0.92-4.09	P<0.01
Cup area (mm^2)	0.19	0.14	0.20	0-1.43	P<0.01
CW (mm)	0.24	0.19	0.24	0-1.85	P<0.01
VCDR	0.23	0.25	0.15	0-0.65	P<0.01
HCDR	0.26	0.28	0.16	0-0.72	P<0.01
Max CW/VD	0.14	0.11	0.15	0-1.21	P<0.01

3.14 Relationship between disc metrics and refractive error

Univariate analysis for the ONH quotients and SER showed the ratio of the crescent width to vertical disc height to be significantly correlated with SER for all eyes and when those without a crescent were excluded (r=-0.43 p <0.0.1, r=-0.44 p<0.01). No significant correlations for the vertical and horizontal cup to disc ratios were observed (r =-0.065 p = 0.196 and r =-0.067 p = 0.184). Figures 3.8-3.10.

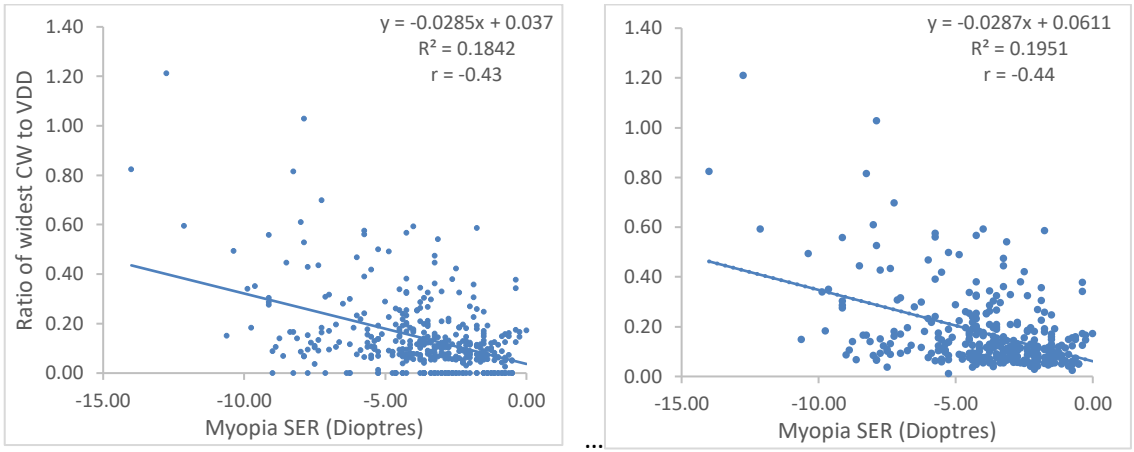


Figure 3.8. Scatterplot showing ratio of widest crescent width to vertical disc diameter plotted against myopia (SER) for the right eye. The left plot includes all cases (n=400), and the right has those without a crescent removed (n=334).

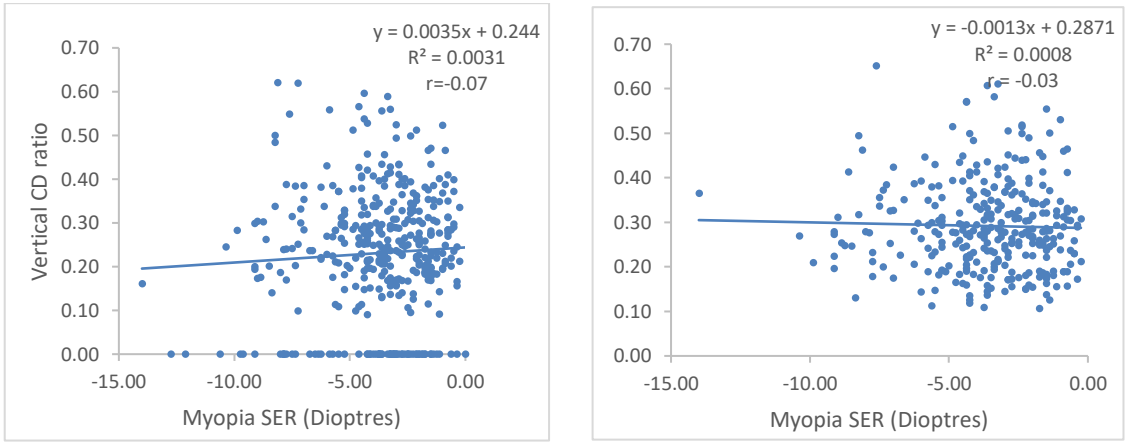


Figure 3.9. Scatterplot showing vertical cup to disc ratio plotted against SER for the right eye. The left plot shows all cases (n=400), in the left plot, those without a vertical cup to disc ratio have been removed (n=320).

A two-way between groups analysis of variance exploring the impact of age and level of myopia on the vertical cup to disc ratio showed no interaction effect (p = 0.89) and the main effects were not significant (age p = 0.09, myopia p = 0.11).

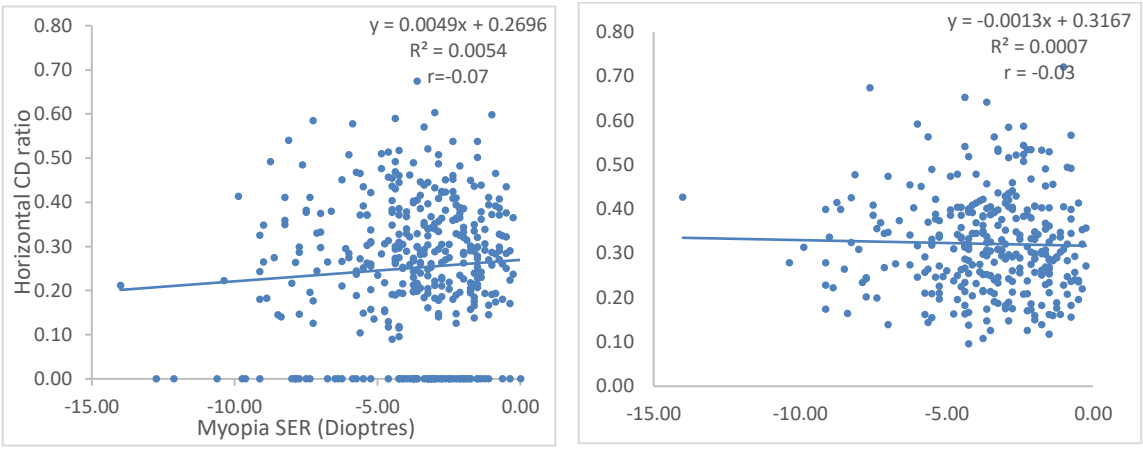


Figure 3.10. Scatterplot showing the horizontal cup to disc ratio plotted against SER for the right eye. The left plot shows all cases (n=400), and in the right plot, those without a horizontal cup to disc ratio have been removed (n=320).

Multivariate modelling controlling for age at the time of image capture, sex, and SER explained 24.4 % of the variance for the quotient of crescent width to vertical disc height. Of the three variables SER (β -0.426, p<0.01) and age (β 0.245, p<0.01) were significant predictors while sex was not (β -0.037, p=0.401). Sex was found to be a significant predictor for both the horizontal and vertical cup to disc ratios, but this may be biased by the sample being 73 % female.

Table 3.4. Summary of multiple regression analysis for the three quotients controlling for age, SER, and sex.

	CW: VDD		VCDR		HCDR	
	R^2 0.244	**P<0.001**	R^2 0.027	**P=0.012**	R^2 0.024	P=**0.021**
	β	p	β	p	β	p
SER	-0.426	**<0.001**	0.061	0.197	0.063	0.206
Age	0.245	**<0.001**	-0.064	0.220	-0.072	0.147
Sex	-0.037	0.401	0.143	**0.004**	0.128	**0.011**

Simple linear regression analysis was also performed for the absolute ONH measures (Figures 3.11 to 3.14). The uncorrected crescent width was seen to increase as the level of myopia (SER) increased (r= -0.40, p<0.01); correction for ocular magnification resulted in a stronger relationship (r = -0.44, p<0.01). When those without a crescent were excluded (Figure 3.11), no difference in the correlation was observed (p = 0.61). (paired t-test)

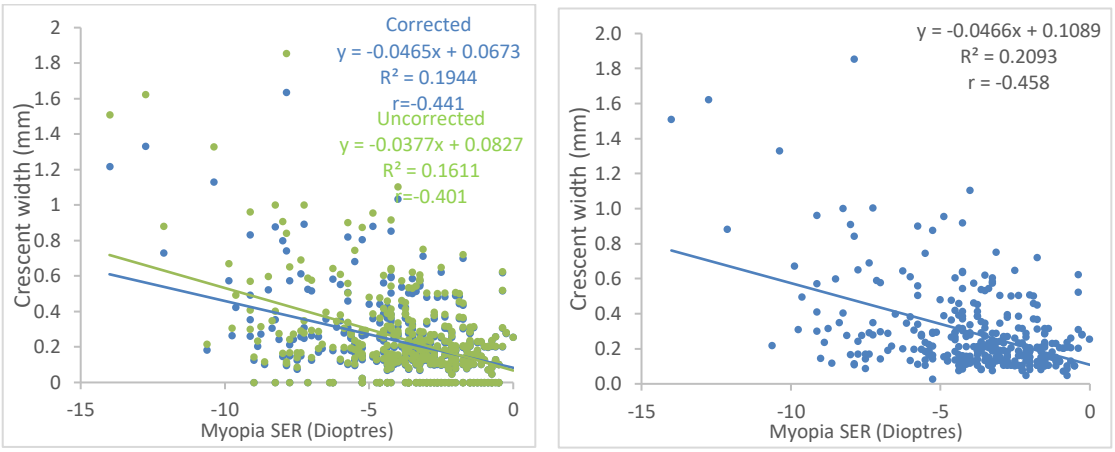


Figure 3.11. Left scatterplot showing crescent width (mm) plotted against SER (n=400). Blue points and line uncorrected and green corrected for ocular magnification. Right shows those with no crescent removed (corrected for ocular magnification) n=334.

Partial correlation analysis was used to explore the relationship between crescent width and myopia (SER) while controlling for age. There was a strong negative partial correlation between crescent width and myopia (SER), controlling for age ($r = -0.453$, $p<0.01$). Greater myopia was associated with a wider crescent.

Neither the corrected vertical disc height or horizontal disc width showed any correlation to the level of SER ($p = 0.78$ and 0.768).

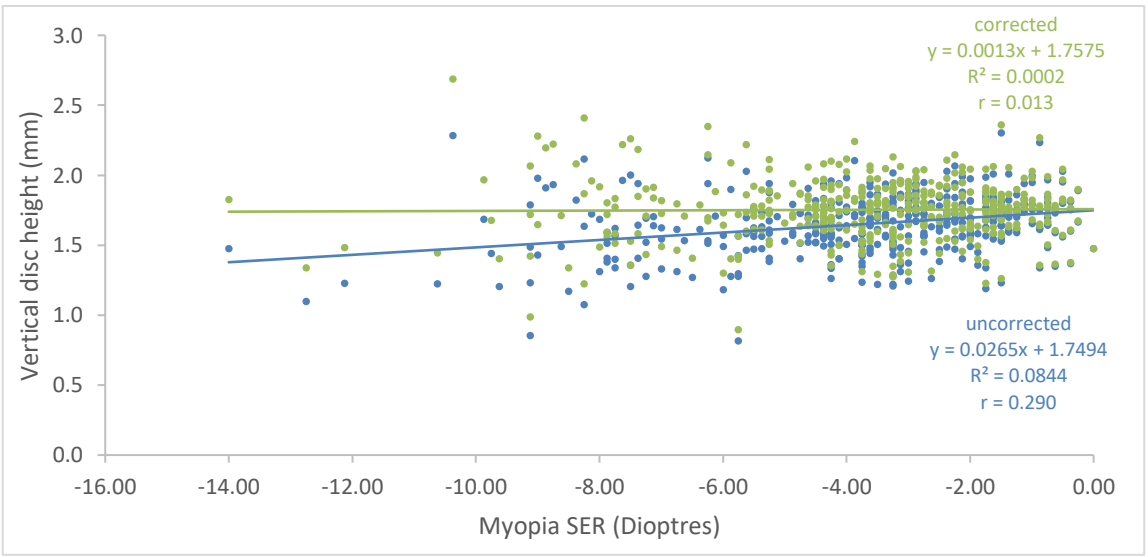


Figure 3.12. Scatterplot showing vertical disc height and its relationship to SER. Blue points and line uncorrected and green corrected for ocular magnification.

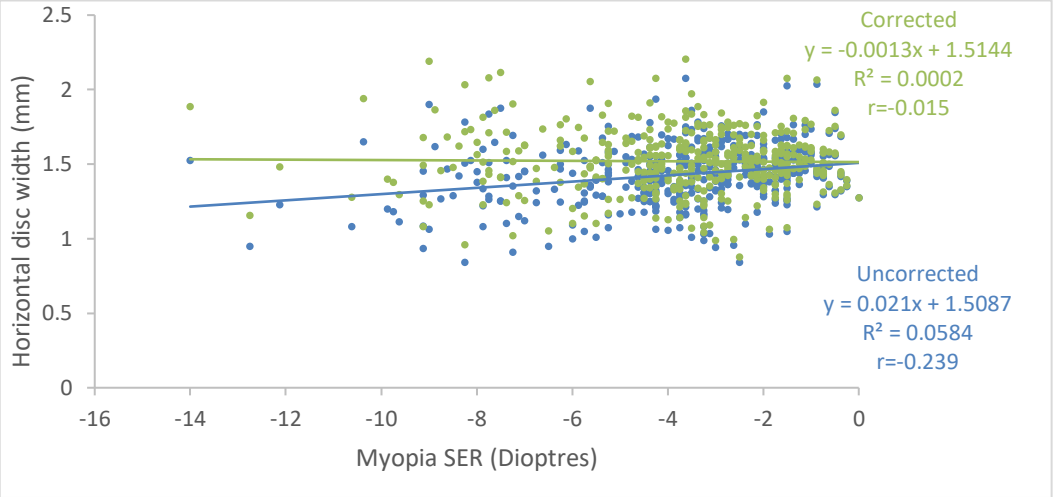


Figure 3.13. Scatterplot showing horizontal disc width and its relationship to SER. Blue points and line uncorrected and green corrected for ocular magnification.

The area of the disc was calculated as described in section 3.4. The relationship between area and SER was moderate (r = 0.274 p <0.01) before correction for ocular magnification but reduced to r = 0.02, p = 0.792 with correction. (Figure 3.14).

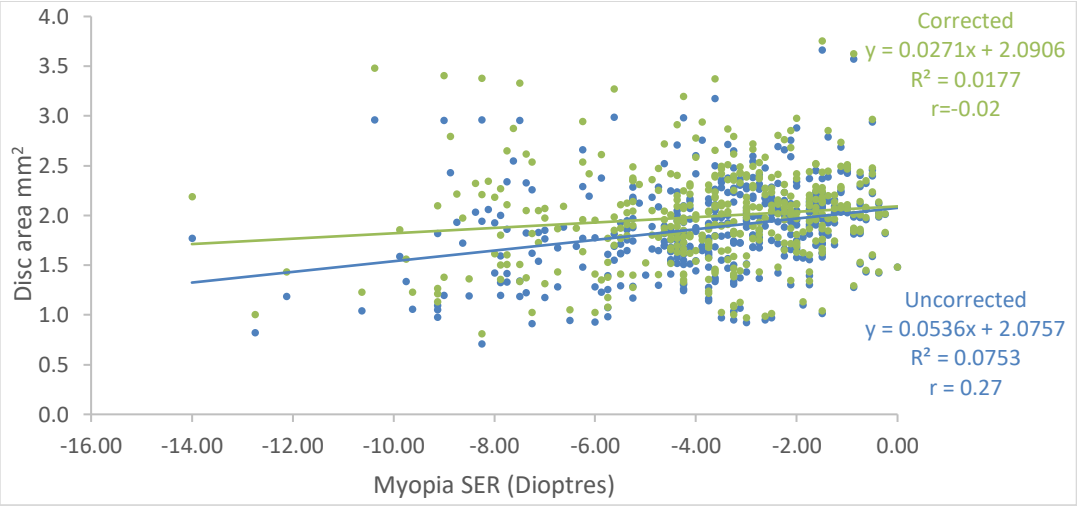


Figure 3.14. The relationship between disc area and myopia (SER). Blue points and line uncorrected and green corrected for ocular magnification.

To test the hypothesis that eyes with the highest level of myopia had the smallest discs the differences across the categories of SER was assessed (Table 3.5) using an independent samples Kruskal-Wallis test. The analysis showed no significant difference across the groups (p = 0.946) with the magnification corrected VDD. When the difference was tested prior to magnification correction a significant difference was observed (p<0.01).

Table 3.5. Myopia by category with the vertical disc (mm) uncorrected and corrected for ocular magnification.

Myopia category (D)	VDD(SD)	Corrected VDD (SD)
-0.50 to -2.49	1.71 ±0.2	1.76 ±0.2
-2.50 to -3.99	1.65 ±0.2	1.74 ±0.2
-4.00 to -5.99	1.62 ±0.2	1.75 ±0.2
-6.00 to -7.99	1.58 ±0.2	1.74 ±0.3
<-8.00	1.53 ±0.4	1.78 ±0.4
	p <0.01*	p = 0.946*

Kruskal-Wallis test*VDD-vertical disc diameter

3.15 Relationship of age and disc metrics

The relationship between age and SER (Figure 3.15) showed no correlation (r=0.014). The two measures of crescent size (maximum crescent width and the ratio of the maximum crescent to vertical disc) did increase with advancing age (r = 0.259 p<0.01 and r = 0.247 p<0.01) (Figure 3.16). Whereas, all other disc metrics did not show any correlations. Table 3.6 shows the results for the all the disc features and age. A partial correlation analysis between age and crescent width showed a slightly stronger correlation (r=0.282 p<0.01) when controlling for myopia (SER).

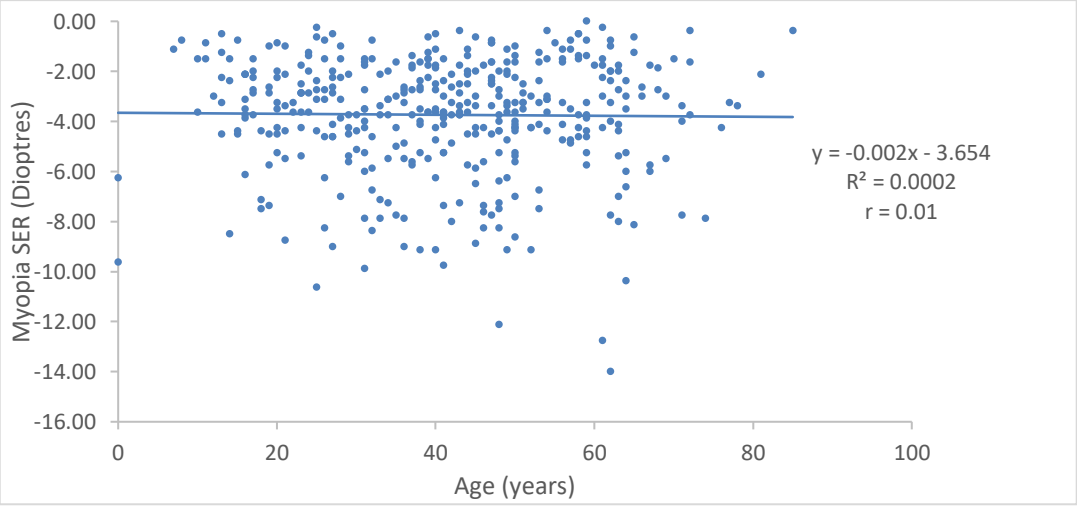


Figure 3.15. SER showing no relationship to age (r=0.014) n400.

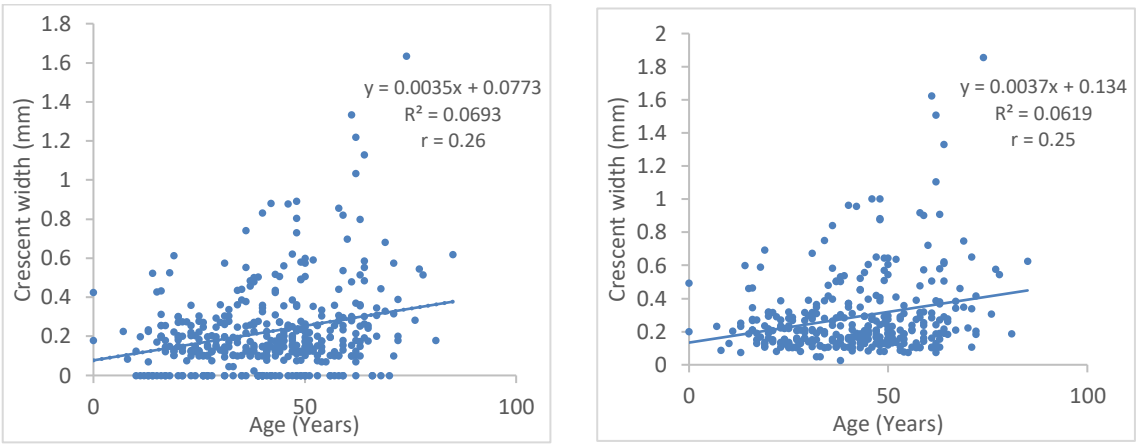


Figure 3.16. Age plotted against the corrected crescent width for the right eye. The left plot shows all cases (n=400) and the right with those without a crescent removed (n=334).

Table 3.6. Pearson's correlations for disc features (magnification corrected) and age for all eyes and repeated with those cases with a CDR of zero and no crescent removed.

	All eyes		Zero removed	
Feature	r	p	r	p
VCDR	-0.05	0.23	-0.02	0.67
HCDR	-0.06	0.22	-0.03	0.58
CW: VDD	0.25	**<0.01**	**0.24**	**<0.01**
VDD	-0.08	0.13		
HDD	-0.06	0.22		
VCD	-0.07	0.17	-0.05	0.33
HCD	-0.07	0.15	-0.07	0.22
Disc area	-0.07	0.17		
CW	0.26	**<0.01**	**0.25**	**<0.01**

Two-way analyses of variation were also conducted to assess the impact of age and level of myopia on VDD, HDD, VCD and HCD. No interaction or main effects were found for any of the ONH measures.

3.16 Sex and ONH features

No significant difference (p = 0.66) was observed in the level of myopia (SER) between the sexes. The vertical, and horizontal cup size were significantly larger in the male group, as were the cup to disc ratios (Table 3.7). No difference was observed in the overall disc size or maximum crescent width.

Table 3.7. Sex differences in the ONH parameters (mean and SD).

	Female n290	Male n110	p
Myopia (Dioptres)	-3.77 ±0.14	-3.66 ±0.20	0.66
VDD (mm)	1.75 ±0.21	1.76 ±0.42	0.73
HDD (mm)	1.51 ±0.21	1.54 ±0.22	0.19
HCD (mm)	0.38 ±0.26	0.46 ±0.29	**0.01**
VCD (mm)	0.40 ±0.26	0.48 ±0.31	**<0.01**
VCDR	0.22 ±0.01	0.27 ±0.01	**0.01**
HCDR	0.24 ±0.01	0.29 ±0.01	**0.01**
CW: VDD	0.15 ±0.10	0.14 ±0.13	0.49
CW (mm)	0.24 ±0.25	0.24 ±0.23	0.78

Independent samples t-test

3.17 Position of optic nerve crescent

No crescent was observed in 16.75 % (67) of eyes. The position of the peripapillary was most frequently temporal (69 %) (Table 3.8) followed by inferior temporal (17 %). The eyes with no crescent had a mean SER of -3.03 D, those with an inferior temporal crescent -5.01 D, and in eyes with a temporally located crescent -3.50 D. A one-way between groups analysis of variance was conducted to explore the relationship between myopia (SER) and position of the crescent. A statistically significant difference across the groups was found, $F = 5.2$ $p < 0.01$. Post-hoc comparisons using the Tukey HSD test indicated that the level of SER was significantly different between those with no crescent and an inferior-temporally located crescent and between temporal and inferior-temporal crescents. The other comparisons did not differ significantly.

Table 3.8. Frequency distribution for the crescent position (n400) with percentages (n334) for those with a crescent only. The mean SER for each position of the crescent is shown.

Crescent position	n	%	Mean SER
None	67	--	-3.03
Halo	18	5.4	-4.64
Temporal	230	69	-3.50
Inferior temporal	56	16.8	-5.01
Nasal and Temporal	2	0.6	-4.50
Inferior	5	1.5	-5.32
Nasal	3	0.9	-6.20
Pigmented temporal	19	5.7	-3.58

The size of the crescent in relation to the position is shown in figure 3.17. The largest crescents were those located on the temporal-nasal region (mean 0.485 mm) which is position four in figure 3.3. The smallest crescents were observed on the temporal aspect of the ONH.

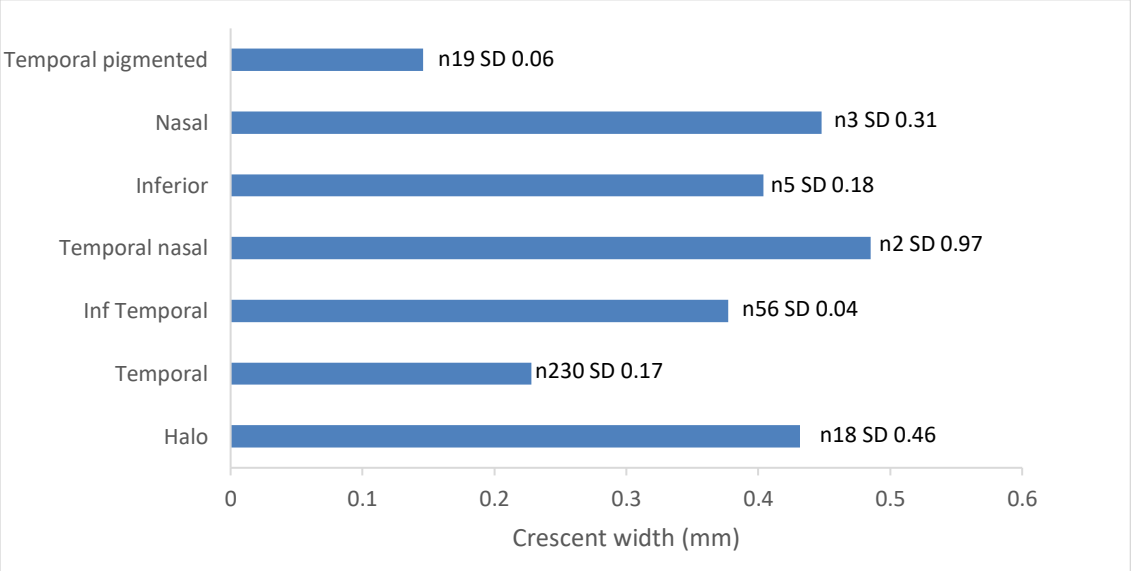


Figure 3.17. Crescent size by location (mean). The number in each position and the standard deviation of the mean crescent size are marked on the chart.

The presence of a peripapillary crescent was assessed in relation to the level of myopia (Figure 3.18). 92 % of eyes had a crescent in the highest category of myopia (<-8.00D) compared to 79% in the group with the lowest level of myopia. When those with a crescent less than 10 % of the disc diameter were excluded 88 % in the highest category were still recorded as having a crescent but only 45 % in the lowest category. When age was assessed in the same manner, the

relationship was not linear although the younger eyes had fewer crescents than those in the older groups (Figure 3.19). A two-way analysis of variance exploring the impact of myopia and age on crescent size showed no interaction effect. The main effects did not reach statistical significance for either age or myopia.

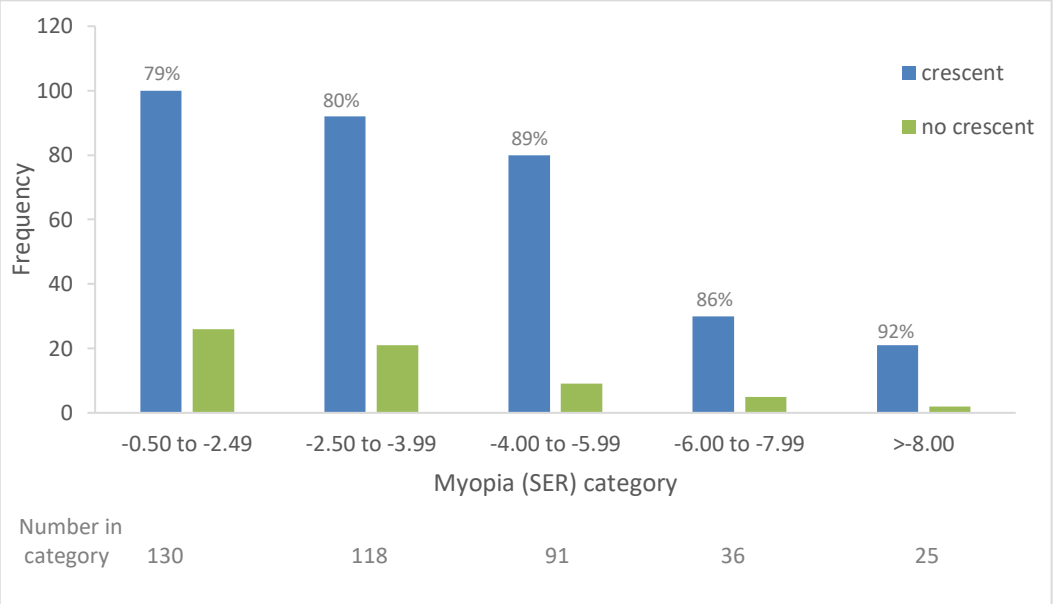


Figure 3.18. The frequency of presence/absence of ONH crescent split by category of myopia (SER). Figures above the columns show percentage in the category having a crescent and the numbers at the bottom of the chart the numbers in each category.

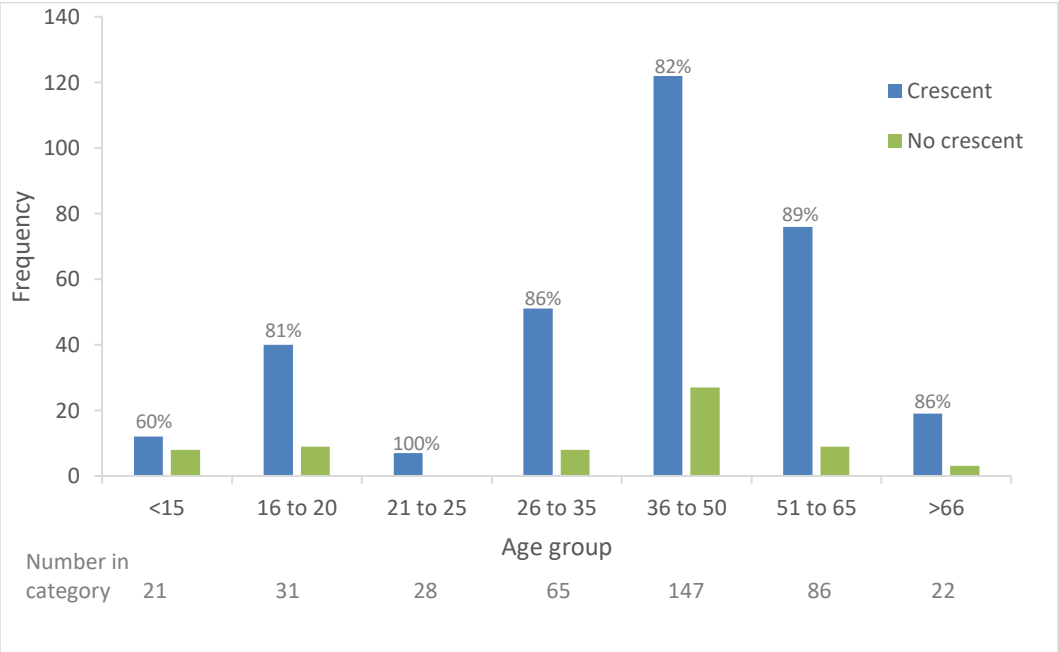


Figure 3.19. Bar chart showing the frequency of presence/absence of ONH crescent across age groupings. Figures above the columns show the percentage in each group having a crescent and the numbers at the bottom of the chart the numbers in each category.

3.18 Optic disc tilt

Tilting of the disc was considered in both eyes to assess the bilateral nature of the feature. Tilting of the disc was observed in 37 (9.25 %) of the right eyes and 33 (8.25 %) of the left eyes. The mean SER of those with a tilted disc was -5.22 D SD ±2.3 (R-5.30 D SD ±2.5, L-5.11 D SD ±2.2) while in those not having a tilted disc the mean SER was -3.59 D SD ±2.3. The tilt was unilateral in 24 participants and bilateral in 23. In those with unilateral tilted discs there was no significant difference (paired t-test, p = 0.833) in SER between the eye with tilt (-4.83 D SD ±2.1), and the eye without (-4.69 D SD ±2.1). Those with astigmatism > 2.00 dioptres were excluded from this study. No difference in the level of astigmatism was observed between those with a tilted disc and those without (independent samples t-test p = 0.11).

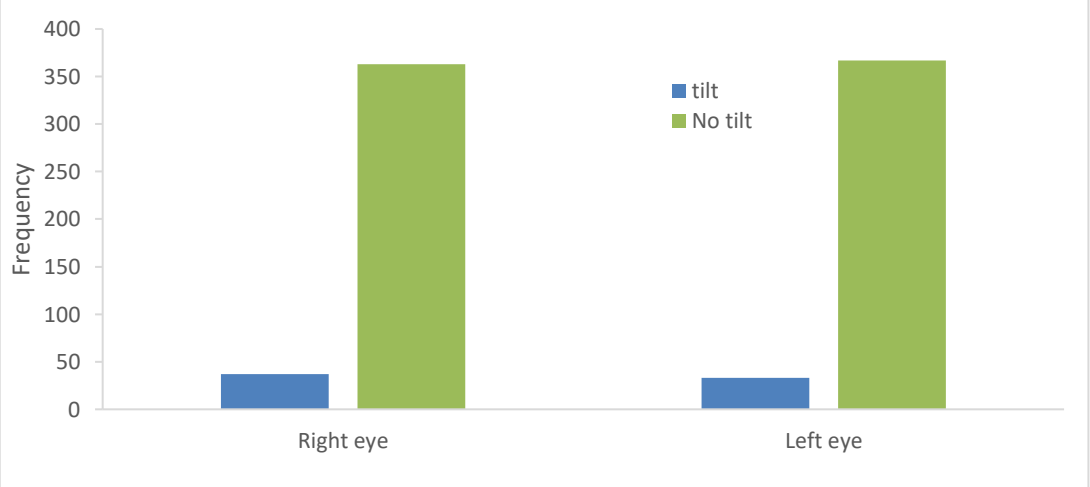


Figure 3.20. The frequency of tilted discs in the right and left eyes respectively.

A wider crescent was observed in eyes with tilted discs. The mean crescent width (right eye) for those with a tilt was 0.42 mm SD ± 0.25 compared to 0.22 mm SD ± 0.2 in those with no tilt ($p<0.01$). In the eyes with tilted discs, the crescent was most frequently observed in the inferotemporal position (54.3 %), followed by temporal crescents. 10 % of the eyes with tilted discs had no crescent.

The index of tilt was calculated by taking the ratio of the horizontal and vertical disc diameters. The ratio was no different between the groups (p = 0.703) (Figure 3.21).

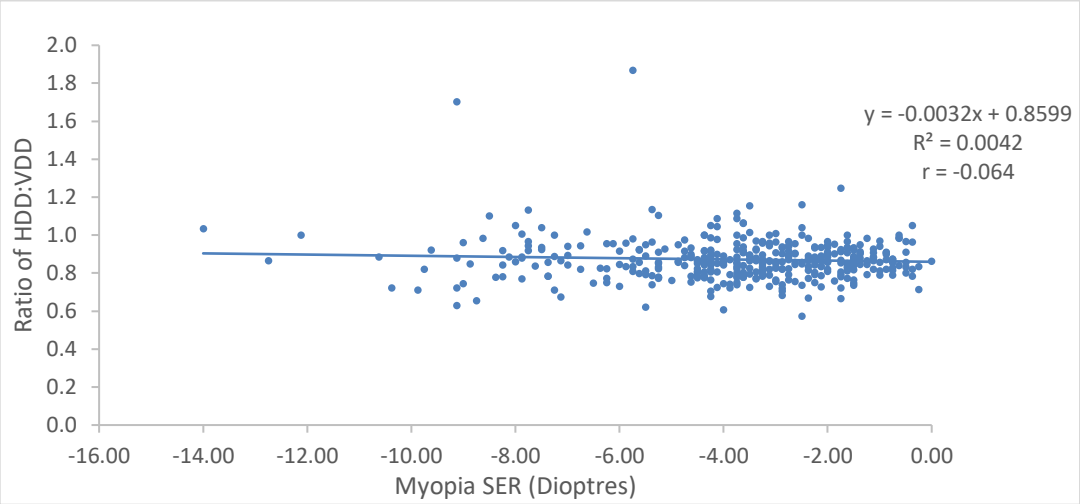


Figure 3.21. Scatterplot showing no relationship between the quotient of the horizontal disc diameter to vertical disc diameter (also referred to as the index of tilt) with myopia (SER).

Both the mean vertical ($p<0.01$) and horizontal ($p<0.01$) disc dimensions were found to be smaller in the tilted disc group as summarised in table 3.9. The prevalence of disc tilt was similar between the sexes (Female 9.4%, Male 9.6%).

Table 3.9. Differences between corrected ONH metrics in discs classified as tilted n37, and those without disc tilt n363. (right eye)

	Tilted Disc SD	Not tilted SD	*p*
SER (D)	-5.01 ±2.5	-3.58 ±2.3	**<0.01**
CW (mm)	0.42 ±0.29	0.22 ±0.23	**<0.01**
VDD (mm)	1.54 ±0.28	1.77 ±0.20	**<0.01**
HDD (mm)	1.37 ±0.24	1.53 ±0.42	**<0.01**
HCD (mm)	0.21 ±0.22	0.42 ±0.27	**<0.01**
VCD (mm)	0.22 ±0.25	0.44 ±0.28	**<0.01**
VCDR	0.13 ±0.14	0.24 ±0.14	**<0.01**
HCDR	0.14 ±0.15	0.26 ±0.16	**<0.01**
HDD/VDD	0.92 ±0.25	0.87 ±0.09	0.703

Independent samples t-test

The percentage of tilted discs in each category of age and SER was calculated and are shown graphically in figures 3.22 and 3.23.

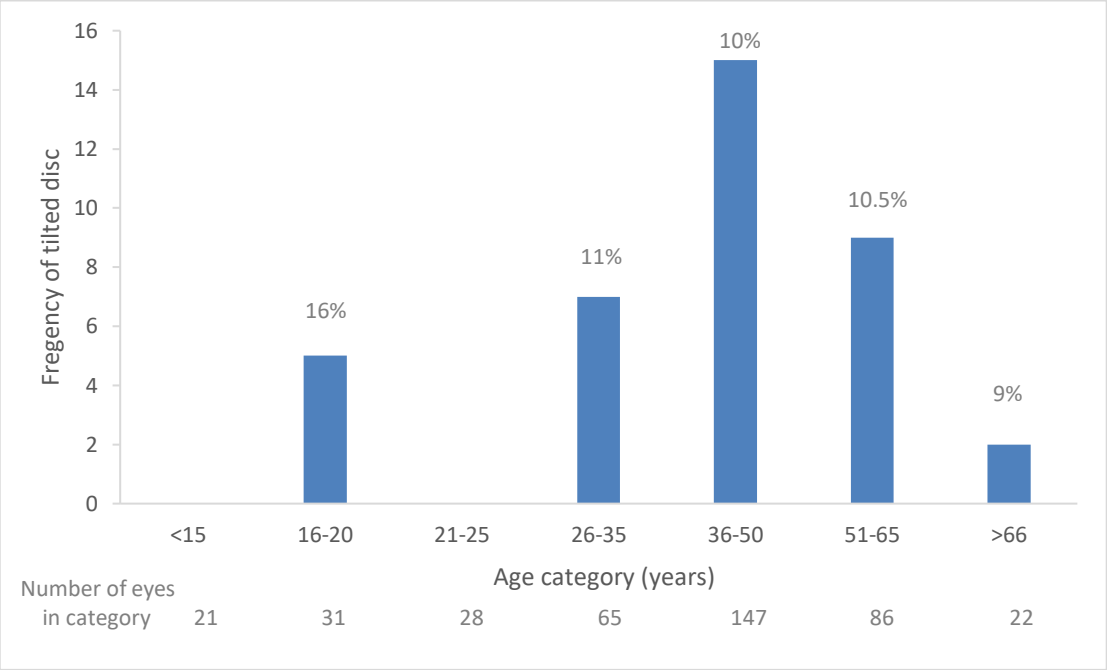


Figure 3.22. Chart showing frequency of eyes with tilted discs across age categories. Numbers above the columns show the percentage of eyes within the age category having a tilted disc and numbers at the bottom of the chart show the number of eyes within each age category. (right eye)

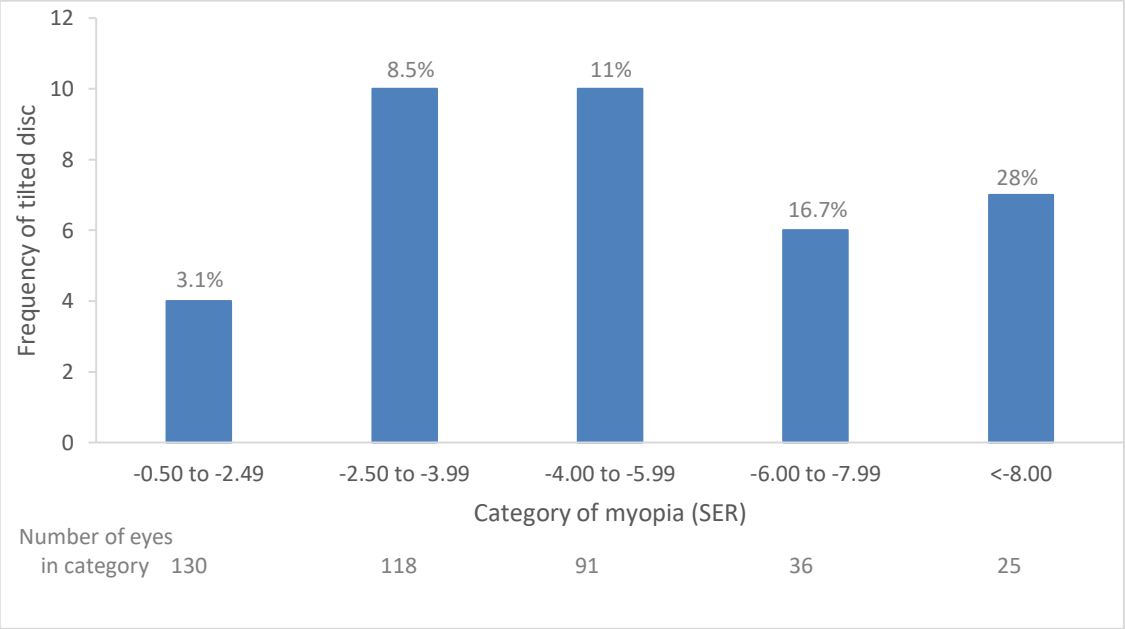


Figure 3.23. Chart showing the frequency of tilted discs by category of myopia. Numbers above the columns show the percentage of eyes within the category having a tilted disc and numbers at the bottom of the chart show the number of eyes within the category of myopia. (right eye)

3.19 Study 2 results

3.20 Demographic information

Study two investigated how time and change in refraction are related to disc features in myopic eyes. A range of refractive change was observed during the time between the images.

267 (66.8 %) of the 400 participants from study 1 had a second gradable image and were included in study 2. The mean age at the time of the second image was 46 years SD ±13 (range 8 to 79 years). 97.8 % of the group were of white European ethnicity, with the majority being female (196) and 71 males. The average interval between image 1 and 2 was 43 months SD ±20 (range of 7-82 months). The mean level of refractive change between the images was -0.32 D SD ±0.64 (range +1.13 to -3.00). Sixty-five (24 %) of the participants showed no change in the magnitude of myopia (SER). Those in which myopia had increased were younger (37 years compared to 44 years p = 0.03 (Independent samples t-test). The mean visual acuity remained the same between the two sets of images at Log MAR 0.01. Table 3.10 summarises the participant characteristics with figures 3.24-25 showing the refractive change and image intervals graphically.

Table 3.10. Study two participant characteristics (right eye).

	Visit 1	Visit 2
Age (years)	42 SD±15	46 SD±13
Level of myopia (Dioptres)	-3.88 SD±2.2	-4.18 SD±2.4
Visual acuity Log MAR	0.01 SD± 0.1	0.01 SD± 0.1
Change in refraction (SER)	-0.32D SD±0.64 (range +1.13 to -3.00)	
Time interval between images (months)	43 SD±20 (range 7-82)	
Sex	Male 71 (26.6%)	Female 196 (73.4%)
Ethnicity	White 261	97.8%
	Black 1	0.4%
	Asian (not Chinese) 4	1.5%
	Chinese 1	0.4%

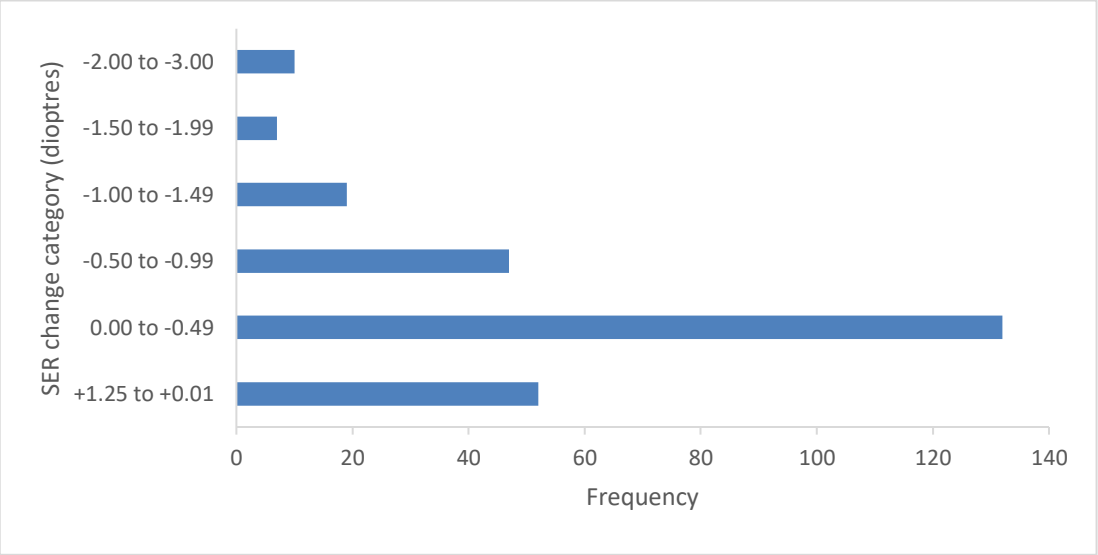


Figure 3.24. Categorised refractive (SER) change between the two images.

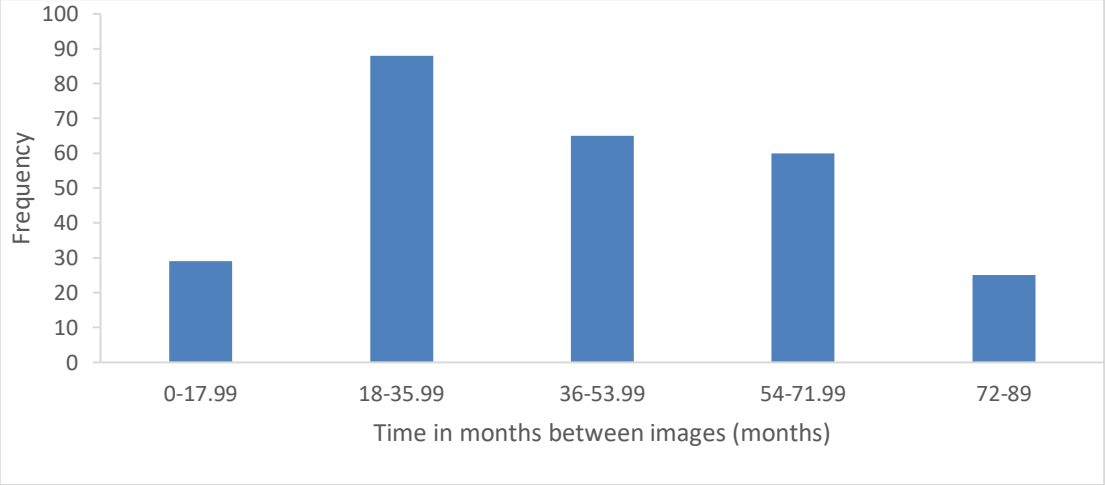


Figure 3.25. The frequency of categorised time intervals between the two images.

The mean disc parameters for the two images (right eye) are summarised in table 3.11. Normality of the data was assessed using the Shapiro-Wilk test which showed the differences were not normally distributed, but due to the median and mean being similar and the size of the cohort the paired samples t-test was used to test for statistical significance in the difference between the two sets of measurements.

Statistically significant differences were obtained for vertical cup height ($p<0.01$) and horizontal cup width ($p<0.01$). Neither the mean disc height, or width changed significantly ($p = 0.982$, $p = 0.208$). The mean crescent width increased by a statistically significant amount between the two visits (0.025 mm, $p = 0.01$).

Table 3.11. ONH parameters (mean), difference between visits and p-value for paired sample t-test.

n=267	Visit 1 (mm)	Visit 2 (mm)	Diff (mm)	t (df)	p
VDD	1.643	1.644	0.001	-0.022 (266)	0.982
HDD	1.419	1.429	0.002	-1.263 (266)	0.208
VCD	0.396	0.420	0.024	-5.336 (266)	**<0.01**
HCD	0.381	0.410	0.031	-5.907 (266)	**<0.01**
CW	0.231	0.256	0.025	-7.475 (266)	**<0.01**

The differences between the quotients for the vertical and horizontal cup-to-disc and maximum crescent width to vertical disc height were also analysed using the paired samples t-test. All three quotients were found to have significant differences, the vertical CD ratio ($p<0.01$) and crescent width to vertical disc ($p<0.01$) increased while the horizontal CD ratio decreased ($p = 0.013$) (Tables 3.11 &3.12).

Table 3.12. Mean changes in the cup to disc ratio, and crescent width to vertical disc diameter, between the visits.

n=267	Visit 1	Visit 2	t (df)	p
VCDR	0.23	0.26	-8.779 (266)	**<0.01**
HCDR	0.26	0.25	2.506 (266)	**0.013**
CW: VDD	0.15	0.17	-6.329 (266)	**<0.01**

Paired samples t-test

The Kruskal-Wallis test was used to assess differences in disc parameters across the categories of refractive change (Figure 3.26) and categories of initial level of myopia (Figure 3.27). No significant difference was observed between the crescent width, vertical and horizontal disc size, vertical cup, or the ratios across the categories of refractive change (Table 3.13). However, the horizontal cup diameter was found to differ. The Mann-Whitney U test was used as a post-hoc test to compare pairs of categories; the results are shown in table 3.14 with a Bonferroni adjustment. A significant difference for horizontal cup diameter was observed between the two lowest categories of myopia increase.

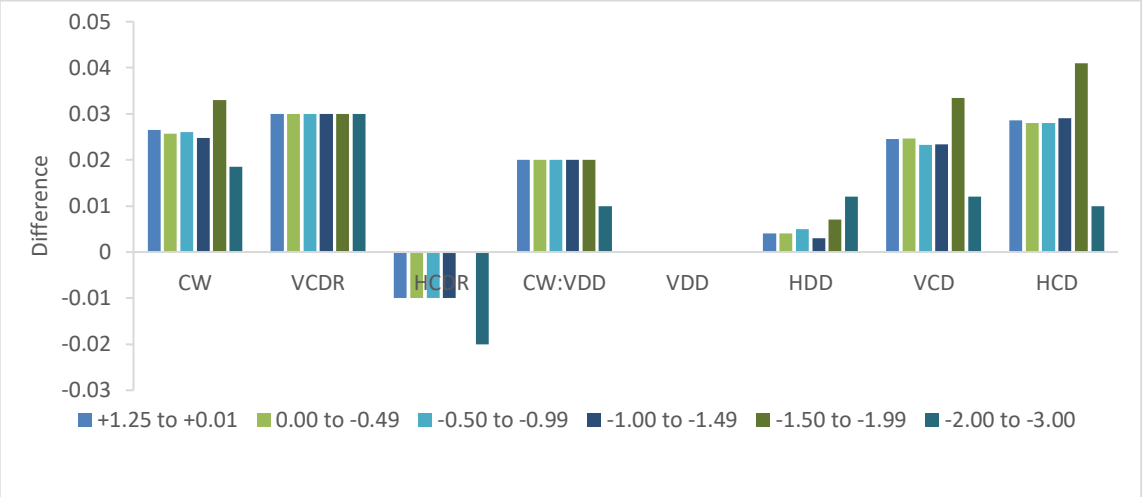


Figure 3.26. Changes between images for ONH parameters split by category of refractive change. The difference is in mm for the absolute measures.

Table 3.13. Results of the Kruskal-Wallis test for categories (Figure 3.26) of refractive change and disc measures.

Feature	p
CW	0.364
VCDR	0.705
HCDR	0.064
CW to VDD	0.325
VDD	0.744
HDD	0.916
VCD	0.513
HCD	**0.013**

Table 3.14. Mann Whitney U test comparisons of SER change categories for the difference in horizontal cup diameter between image 1 and 2.

SER category	p
0.00 to -0.49 & <-2.00	0.060
0.00 to -0.49 & -1.50 to -1.99	0.328
0.00 to -0.49 & -1.00 to -1.49	0.299
0.00 to -0.49 & -0.50 to -0.99	**0.001**

Bonferroni adjusted alpha value 0.0125.

The initial level of myopia had no influence on the change in disc parameters measured on the second visit.

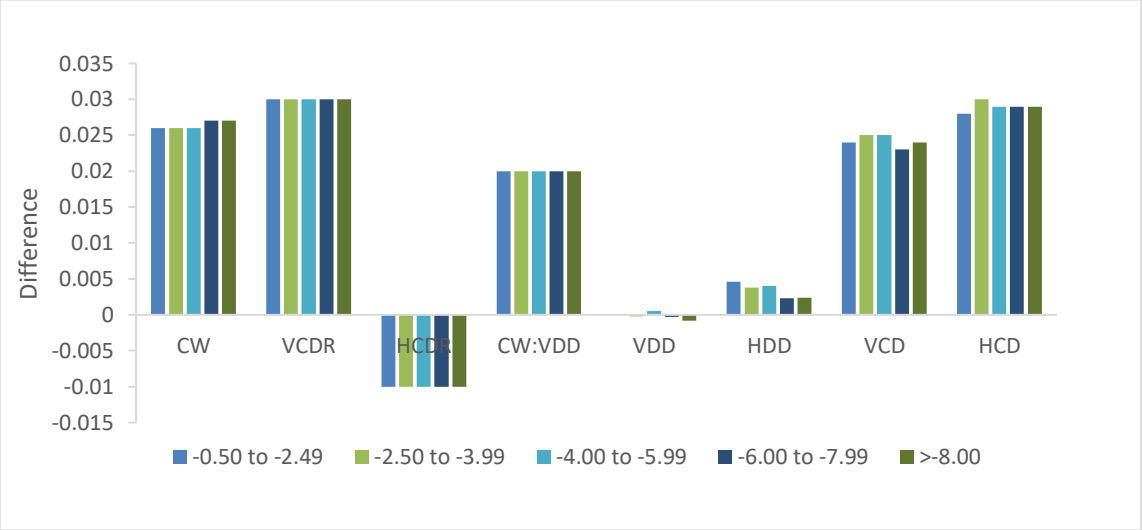


Figure 3.27. Mean difference in disc parameters (mm) between the images plotted against the initial level of myopia at first image — categories listed at the bottom of the chart.

The difference in the optic disc parameters in relation to categorised time between images was also assessed using the Kruskal-Wallis test. None of the disc parameters showed any difference across the image interval categories (Table 3.15).

Table 3.15. Results of the Kruskal-Wallis test assessing change in disc measures across time interval between images.

Feature	p
CW	0.446
VCDR	0.235
HCDR	0.504
CW to VDD	0.318
VDD	0.275
HDD	0.769
VCD	0.347
HCD	0.846

3.21 Reliability of measures

The variability for the five optic disc metrics was plotted in the form of Bland-Altman plots (Figures 3.28 a-e). Each measure generally shows good agreement.

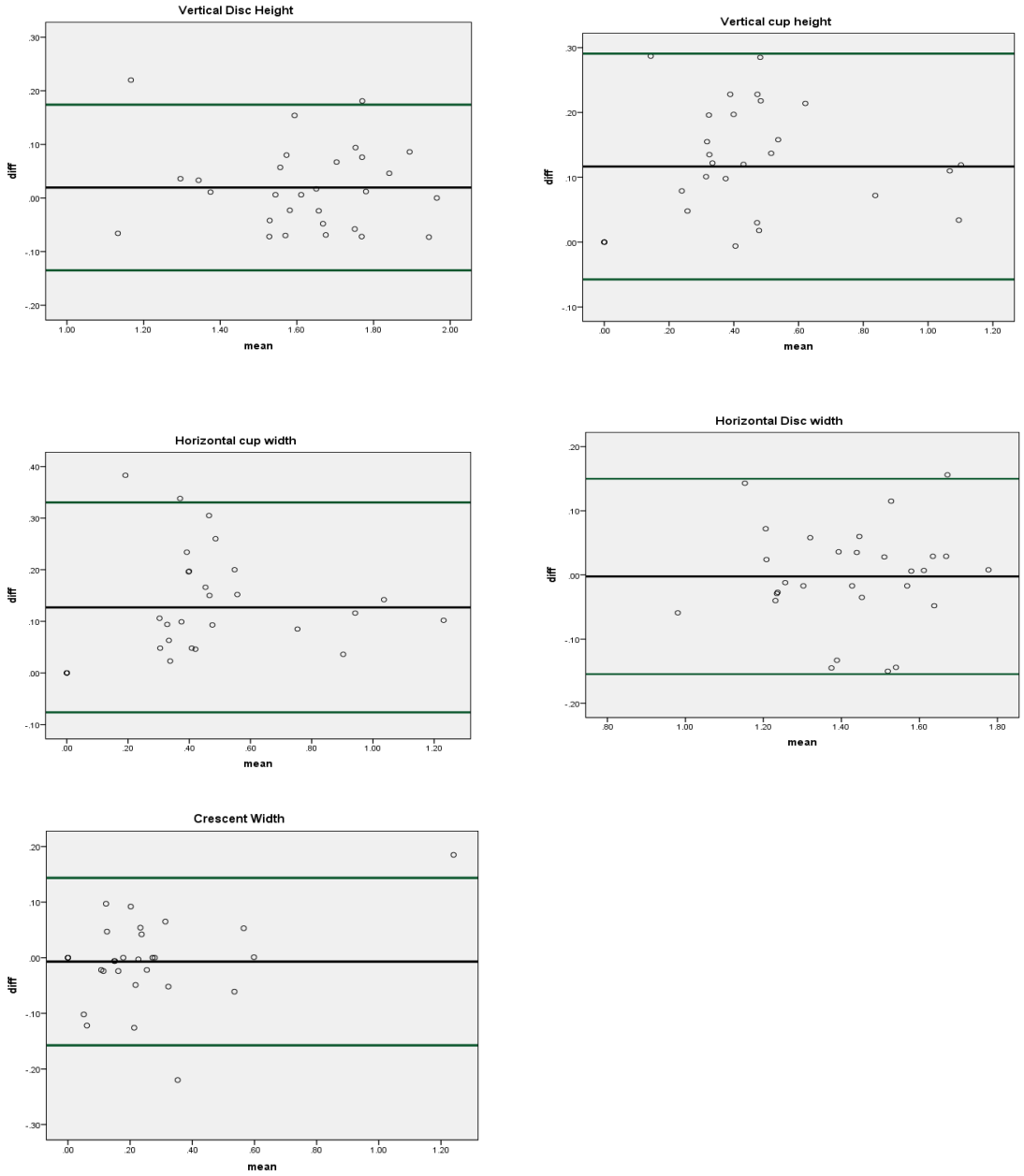
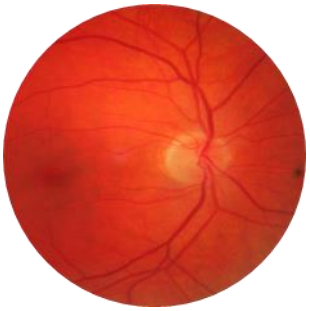
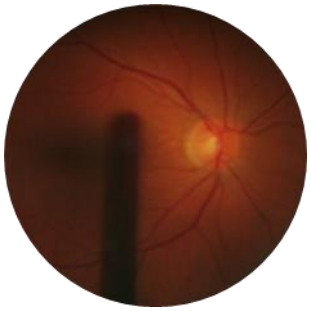
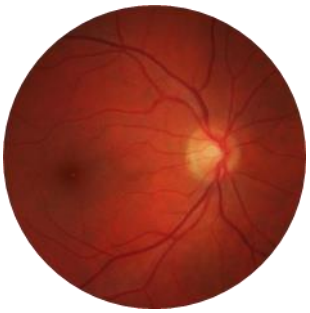
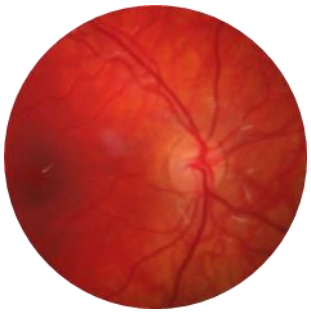
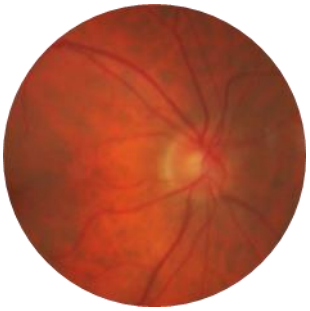
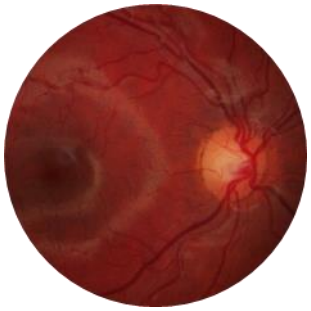
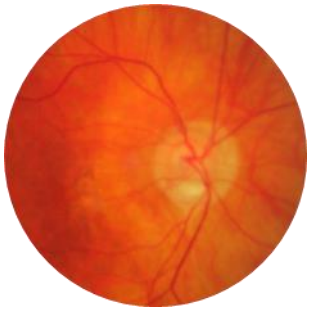


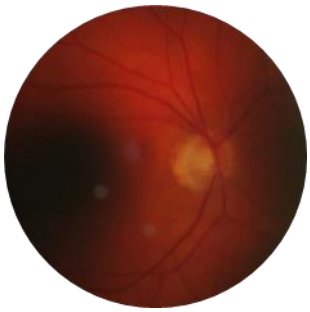
Figure 3.28. Bland-Altman plots- (a) vertical disc height, (b) vertical cup height, (c) horizontal cup width, (d) horizontal disc width, (e) crescent width.

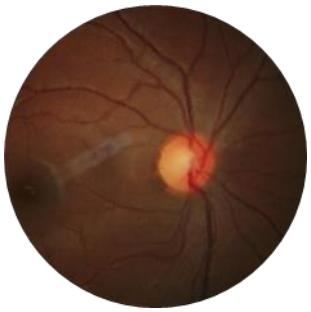
The coefficient of variation was calculated by measuring the optic disc features ten times on ten randomly selected images (Figure 3.29). The results show good repeatability, with the cup height and width being the most variable of the metrics (Table 3.16).

		
1.54 ±0.03 (1.51-1.58)	**VDD**	1.63 ±0.04 (1.54-1.66)
1.42 ±0.03 (1.40-1.46)	**HDD**	1.36 ± 0.03 (1.31-1.40)
0.37 ±0.03 (0.32-0.42)	**VCD**	0.60 ±0.03 (0.56-0.67)
0.36 ±0.05 (0.30-0.42)	**HCD**	0.49 ±0.03 (0.43-0.54)
0.19 ±0.02 (0.15-0.20)	**CW**	0.18 ±0.18 (0.16-0.19)
		
1.64 ±0.04 (1.59-1.69)	**VDD**	1.44 ±0.03 (1.41-1.51)
1.27 ±0.04 (1.21-1.33)	**HDD**	1.35 ±0.03 (1.30-1.38)
0.61 ±0.20 (0.58-0.63)	**VCD**	0.35 ±0.04 (0.28-0.44)
0.59 ±0.03 (0.55-0.63)	**HCD**	0.27 ±0.03 (0.23-0.36)
0.26 ±0.03 (0.24-0.30)	**CW**	0.14 ±0.01 (0.13-0.16)
		
1.63 ±0.05 (1.53-1.69)	**VDD**	1.72 ±0.02 (1.70-1.75)
1.39 ±0.03 (1.35-1.45)	**HDD**	1.44 ±0.02 (1.41-1.46)
0.58 ±0.03 (0.54-0.65)	**VCD**	0.89 ±0.02 (0.87-0.93)
0.53 ±0.04 (0.47-0.60)	**HCD**	0.74 ±0.02 (0.70-0.78)
0.22 ±0.03 (0.18-0.26)	**CW**	0.12 ±0.01 (0.12-0.14)



1.31 ±0.03 (1.25-1.35)	**VDD**	1.74 ±0.03 (1.69-1.80)
1.63 ±0.03 (1.53-1.69)	**HDD**	1.46 ±0.02 (1.43-1.48)
0.48 ±0.05 (0.39-0.54)	**VCD**	0.50 ±0.03 (0.49-0.57)
0.58 ±0.04 (0.52-0.65)	**HCD**	0.53 ±0.03 (0.49-0.57)
0.41 ±0.04 (0.36-0.49)	**CW**	0.17 ±0.02 (0.13-0.20)





1.71 ±0.02 (1.70-1.74)	**VDD**	1.59 ±0.02 (1.55-1.62)
1.36 ±0.04 (1.33-1.43)	**HDD**	1.51 ±0.02 (1.49-1.53)
0.66 ±0.04 (0.60-0.65)	**VCD**	0.60 ±0.02 (0.58-0.60)
0.60 ±0.04 (0.54-0.65)	**HCD**	0.57 ±0.05 (0.53-0.63)
0.45 ±0.03 (0.40-0.49)	**CW**	0.25 ±0.02 (0.23-0.27)

Figure 3.29. The repeatability of measures was assessed with ten images being measured ten times. The measures (mean) are in mm with SD ± and (range).

Table 3.16. Mean and SD for the coefficient of variation calculated from the 10 randomly selected images shown in figure 3.29.

	Mean coefficient of variation (%) SD	The range of COV over the 10 images
VDD	1.95 ±0.57	1.33-2.84
HDD	2.24 ±0.70	1.22-3.47
VCD	6.34 ±3.29	2.61-12.64
HCD	7.32 ± 3.17	3.20-13.27
CW	10 ±2.80	6.01-14.29

3.22 Discussion

Study one has documented features of the ONH and adjacent region from digital photographs in a predominately white European population. Associations between feature presence and size were investigated in relation to the level of myopia and age.

Absolute measures along with quotients for the cup to disc ratios were assessed. Quotients have been used by several workers (180,234,248) with the primary purpose of negating the need to deal with magnification factors relating to the eye and camera (discussed in section 2.2); although absolute measures are desirable for several reasons. The VCDR is correlated with disc size in non-glaucomatous eyes (219) meaning the clinical usefulness of the CD ratio is diminished without knowledge of the absolute measure of vertical disc size. Also, the size of the optic disc can predispose the eye to pathologies; glaucoma may be associated with larger discs (412), whereas non-arteritic anterior ischaemic optic neuropathy has been linked to small optic discs (353).

In common with most biological structures the size of the ONH shows considerable variability (220), as was the case in this study. The largest VDD was 200 % larger than the smallest. The mean VDD was 1.75 mm SD±0.2, range 0.9-2.7, and the HDD 1.51 mm SD±0.2, range 0.9 to 2.2, which agrees with that reported by Ewen et al. (385) in a North American population, and Mataki et al. (413) in a Japanese non-highly myopic group. Larger vertical disc diameters have been reported (221,414). Ethnicity may account for some of the differences, although Jonas et al. (415) reported a mean VDD of 1.92 mm in a white European population, albeit with myopia greater than 8.00 D. A further variation is likely to result from the method of magnification correction (262,378).

The mean VDD was 12.5 % greater than the HDD in this group which is above the range of 7-10% reported as normal by Jonas et al. (222). Some of this variation may result from disc tilting

around the vertical axis leading to a smaller measured horizontal width from two-dimensional non-stereoscopic images.

Changes in vertical cup size are key in detecting glaucomatous optic neuropathy (412). Mean vertical cup values between 0.75-1.53 mm have been reported (220) which is noticeably greater than the 0.42 mm SD±0.26 found in this study. Reasons for this difference may include the current studies exclusion of those with glaucoma, or under observation as a glaucoma suspect, which meant some with larger physiological cups were excluded. The depth and margins of the cup also affect the assessment of the cup. When the cup is deep and punched out, the determination of the cup borders is easier than when the cup is shallow with sloping margins, as frequently seen in myopic eyes (2) (Figure 3.30). The reliability testing found both the vertical and horizontal cups to show the highest measurement variability (6.34 %, 7.32 %). Further to this, we did not have stereo images which may have resulted in a systematic underestimation of cup size.

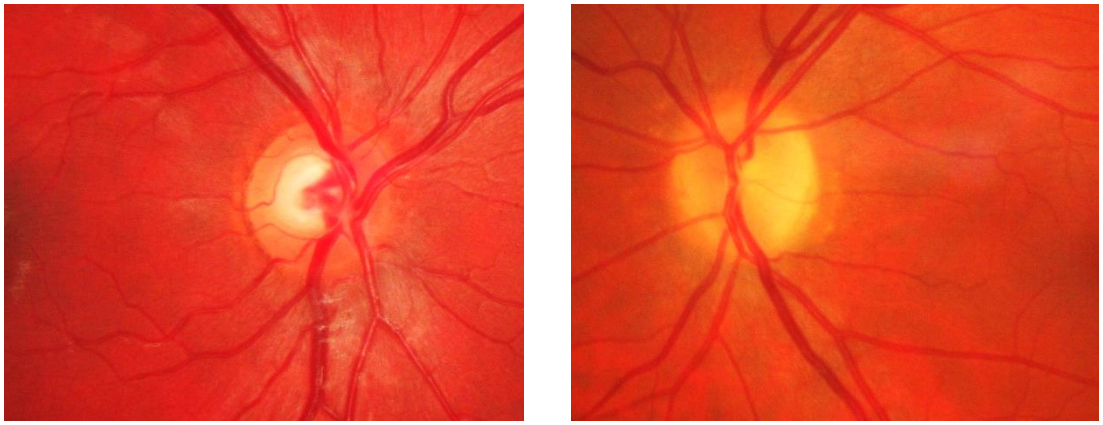


Figure 3.30. Fundus photographs showing the difference between a deep punched out cup (left) and shallow cupping.

The mean area of the ONH and cup were 2.12 mm^2 and 0.19 mm^2, which is similar to that reported for white Europeans (234) but less than for Indians (414), Japanese (413) and Chinese (233). In this study, the formula for a modified ellipse was used to calculate disc area, as others have done (219,220). However, because this method involves assumptions around the disc

shape being uniform, which is probably not the case in higher levels of myopia or disc tilt, this method inadequately describes the ONH. Newer technologies improve the quality of area measurements through pixel counting within a defined area; however, information on ONH shape is lost (409).

Conflict exists as to the influence of the refractive error on disc size. Univariate analysis showed the measures of the ONH (VDD, HDD, VCD, HCD and disc area) to decrease as myopia increased. When correction for ocular magnification was applied, the relationships became neutral. This highlights the importance of adjusting for magnification when using absolute measures. The majority of studies which exclude high myopia (defined as <-6.00 D) agree with this study's findings (233,235,414), while the Rotterdam study found disc size to increase as myopia increased (234). No change in disc area was observed as myopia increased which is in conflict with the findings of Rudnicka et al. (262) who observed a significant increase in disc size as myopia increased. The smaller area found in the current study may be due to the irregular disc shape, more often seen with higher levels of myopia, which may decrease the accuracy of using the modified ellipse formula.

It appeared that disc size was only larger in moderate myopia, with the higher levels of myopia having smaller discs, often without physiological cupping. These observations have been noted previously (262,416). It was hypothesised, against the findings of Jonas et al. (415), that the smallest discs are more common in the higher myopes in this study group. Carpel suggests this observation can be explained by forces leading to posterior staphyloma formation rather than changes to the optic canal diameter (416). To test this hypothesis, the differences in disc size across the categories of myopia was assessed using the Kruskal-Wallis test. No significant differences ($p = 0.946$) were found. The observations in the formation of this hypothesis may be partially explained by the minification when viewing images before magnification correction was

applied, or the occasional disc with hypoplasia that stands out. Optic disc hypoplasia is a frequent finding in unilateral high myopia (417).

The mean VCDR and HCDR in this study were 0.23 (range 0-0.62) and 0.26 (range 0-0.67). Most studies have found the mean VCDR to be larger than the current study (180,227,234,415). As discussed above the cup measures were smaller which reflects in the small cup to disc ratios. The finding that the HCDR was greater than the VCDR agrees with the pattern seen in non-glaucomatous eyes (415). Both the VCDR and HCDR showed a weak negative and insignificant relationship to SER (r=-0.065 p=0.196, r=-0.067 p=0.184). Bae et al. (227) found the mean VCDR to be 0.50 ±0.14 in young Korean men, and like this study, no significant correlation with SER (p=0.138) was observed. Table 3.17 summarises several studies determining disc feature metrics.

Table 3.17. Summary of studies reporting cup to disc ratio along with vertical disc height when reported.

Study	VCDR	HCDR	VDD/area	Population	Method
Present study	0.23	0.26	1.75 mm 2.12 mm^2	White European	Digital planimetry
Jonas (415)	0.34	0.39	1.92 mm	White European	Fundus camera
Rotterdam eye study (234)	0.49 ±0.14	0.40 ±0.14	2.42 mm^2	White European	Image analyser
Bae et al. (227)	0.50 ±0.14			Korean males	OCT
Vellore eye study (414)	0.56	0.66	2.58 mm^2	Indian	Fundus camera
Kuang et al. (180)	0.44 ±0.17		1.77 mm	Chinese aged 72+	Slit lamp 78D lens
Singapore Malay eye study (418)	0.40 ±0.15			Malay aged 40-80	Slit lamp 78D
Ewen et al. (385)	0.39		1.73 mm	North American	Digital planimetry
BMES (419)	0.43		1.5 mm	Australian aged 49+	Fundus camera

VCDR-vertical cup to disc ratio, HCDR-horizontal cup to disc ratio, VDD-vertical disc diameter

Univariate analysis showed neither the VCDR or HCDR to be correlated with age. This finding has been reported by others when glaucomatous eyes were excluded (234,418); while some have noted increases in the VCDR in older eyes (419,420). It is known that the nerve fibre count

reduces with age (223,421). Hence it would sound sensible that the CD ratio would increase with age. It has been proposed a reduction in the height of the papilla may occur and explain the possible maintenance of the CD ratio (220). McClelland et al. postulate changes in VCDR they observed in children of different age groups may be due to nerve fibre re-arrangement (422). Most of the studies on healthy eyes are cross-sectional limiting the full understanding of how the nerve density loss manifests. However, Moya et al. (423) retrospectively assessed a group with no glaucoma over a 13 year period finding no change in rim area over the period.

Like age, the relationship between sex and disc features is unclear. Females accounted for 73% of the participants in this study which may have biased the analysis. Myopia has been reported to be slightly more prevalent in females (42). However, the reason for the greater number of females is likely to be the finding that females are more likely to attend routine health appointments more regularly (424). In this study larger VCDR and HCDR's were observed in the male group ($p=0.01$) as was the case in the Tanjong Pagar Study (425), and the Singapore Malay Eye Study (418). However, not all studies have found sex differences in ONH size measures (180,234). From the absolute measures, only VCD and HCD were significantly larger in the male group ($p=0.017$). Multivariate modelling controlling for sex, age and SER explained only 2.7 % and 2.4 % in the variance for the horizontal and vertical cup to disc ratios.

Despite the benefits of calculating cup to disc ratios, it has been argued that errors are likely from the difficulties in identifying the cup borders from fundus photographs (232,426). In myopic eyes, the cup is typically shallow making the cup contour challenging to judge. This assessment can be exacerbated by increasing age and pathology (252). The variability was assessed for all parameters using Bland Altman plots finding good agreement, (Table 3.19) and agreeing with levels of repeatability reported by Garway-Heath et al. (378).

Several studies have used OCT and CLSO to obtain disc measures; these instruments measure the cup at a set depth which is another potential source of variance between instruments (231).

Leung et al. (233) compared the measurement obtained with OCT and CLSO finding a significant difference in the vertical and horizontal CD ratios between the two methods; they suggested the most likely reason for this is that different structures are being measured. From a clinical perspective, a false positive referral may result when different methods of measuring the VDD are used. Secondly, if no adjustment is made for magnification, the VDD would be smaller in a myopic eye, giving more significance to a larger VCDR. Given the increased use of technology in shared care schemes, consistency becomes more important.

The presence, location, and size of optic nerve crescents, along with relationships to the level of myopia and age were documented. 83.5% of eyes had a discernible crescent which is similar to the classic study of Jonas (211) but greater than the 59 % reported in the Rotterdam study (234). These studies measured the crescent area, whereas the current study, and others (246), measured maximum crescent width due to this measurement being more practical. However, the mean refraction was less myopic than in the current study. In eyes with crescents, six positions of the crescent were observed. Temporally located crescents were the most frequently occurring (69 %), followed by inferior-temporal (16.8 %). Curtin (2) described 12 types of crescent by location also finding temporally located crescents to be the most frequent (62 %), with inferior-temporal crescents occurring in 2.3 % of cases. In this study, eyes with higher levels of myopia were more likely to have an inferior-temporal crescent, and those without a crescent had the lowest levels of myopia. The eyes with no crescent had a mean SER of -3.03 D compared to -5.01 D in those with an inferior temporal crescent ($p<0.01$).

Perkins (427) found that eyes with more than four dioptres of myopia usually had a crescent, and Grosvenor (28) reported that children with myopia of -3.00 dioptres invariably had a crescent, whereas those with 1.50 D of myopia or less tended not to. In this study, only 8 % of eyes in the highest category of myopia (<-8.00 D) did not have a crescent, although in the lower categories of myopia crescents were still present in 79 % of eyes. This high prevalence in those with low

myopia (>-2.50) may be due to the inclusion of congenital crescents and the significant number of older participants in our group; age has also been associated with peripapillary changes (232). When those with a crescent less than 10 % of the disc width, the size Curtin classes as congenital, were excluded the overall prevalence dropped to 58.5 % with only 45 % in the lowest category having a crescent compared to 88 % of those within the highest category of myopia (<-8.00 D). An equally pronounced effect was seen when the smaller crescents were excluded and the prevalence of crescents in the age categories re-calculated. The prevalence of crescent increased by 100 % between the youngest and oldest category. Some of this variance may be explained if those in the lower categories of myopia were still progressing, especially if they were younger. However, the level of myopia showed no relationship to age in this study ($r=0.01$, $p= 0.78$).

Crescent size showed a strong correlation to the level of myopia ($r=-0.44$, $p<0.01$). A partial correlation analysis controlling for age resulted in a slight increase in the correlation between crescent width and myopia ($r=-0.45$, $p<0.01$). Fulk (167) investigated the influence of increased axial length on crescent incidence finding myopic eyes were more likely to have a crescent than eyes that remained emmetropic despite an increased axial length, concluding the level of myopia (SER) was a better predictor of crescent size than axial length. In his summary, he also suggested the presence of a crescent in a younger person may predict a more rapid progression of myopia although presented little evidence for this suggestion.

The size of the crescent varied according to its location. The widest crescents were halo, temporal-nasal, and nasal. However, the number of eyes with these positions of crescent was small (13, 3, and 3 respectively) and may be considered as abnormal variations. A more useful finding being temporal crescents were the smallest, and were associated with lower SER, allowing the inference of more regular eye shape. In contrast to this study, Jonas reported nasal crescents to be the least frequent and also the smallest (211). The second measure of peripapillary crescent used was the ratio of the crescent width to the vertical disc diameter. This

ratio was found to be significantly correlated to SER (r=-0.43, p<0.01), which agrees with Hyung's (248) findings in a slightly younger Korean group (r=-0.53, p<0.01), and Kim et al. in children (246).

Many of the retinal changes seen in the myopic eye appear to develop once the progression of myopia has ceased (23). Our finding that larger crescents were observed in older myopes (r=0.263, p<0.01) supports this. Partial correlation controlling for SER showed an increased correlation between crescent width and age (r=0.282, p<0.01). Age was also significantly correlated with CW/VDD albeit less strongly (r=0.247, p<0.01). Multivariate modelling controlling for SER, age, and sex explained 24.4 % of the variance in the CW/VDD, with SER and age being significant predictors. It has been demonstrated that increases in both the alpha and beta zones occur with age (232,238). Longitudinal review (246) has shown the progression of childhood myopia, regarding both SER and axial elongation, to result in enlargement of the crescent over a relatively short follow up of 38 months. Nakazawa (240) presented serial disc images of 10 Japanese low and moderate young adult myopes showing crescent formation as myopia progressed. Healey et al. (428) investigated the inheritance of peripapillary changes in 506 pairs of adult twins. The prevalence of peripapillary changes was similar between the monozygotic and dizygotic twins indicating little or no genetic association although the heritability was high (75%).

If the size of the optic disc is greater with higher levels of myopia, and the crescent is wider in higher levels of myopia, then the crescent should be wider in eyes with larger discs. This is the conclusion Jonas (219) suggests, which partially conflicts with the current study's observations. It is agreed that higher myopia is associated with greater PPA. However, some cases with high myopia and, or tilted discs had smaller discs but larger areas of PPA. Crescent width was found to decrease as the vertical disc size increased (r=-0.243, p<0.01) further supporting this observation. Even in the higher levels of myopia, a crescent was often absent. Due to axial length

measures not being available, it is not possible to say whether the myopia was due to refractive factors rather than axial length increase. Strang et al. (147) described three models of eye stretching, global expansion, posterior pole, and equatorial stretching. When equatorial stretching alone occurs the posterior pole would be unaltered, and it is plausible any crescent would not increase in size. Chapter four considers relationships between peripheral and central retinal changes to investigate this further. It has been hypothesized that the absence of a crescent may be the result of a more elastic Bruch's membrane (2), or increased scleral canal diameter (252), allowing eye expansion without tissues pulling away from the optic disc margin.

Determining the pathological associations to the crescent position, and how this relates to differing levels of scleral resistance and patterns of eye growth could facilitate the targeting of treatment to prevent visual loss. The structural changes in the parapapillary region, mainly of highly myopic eyes, have been investigated histologically (239,243), and in vivo using OCT, fluorescein and indocyanine green angiography (429). Angiography differentiates the zones of peripapillary change with beta zone showing no choroidal filling whereas the alpha zone displays decreased filling suggesting a vascular element in the development of PPA (429). Histological and clinical findings indicate tissue stretching is involved in myopic PPA, while non-mechanical factors in age-related PPA are supported by the finding of thickening of the RPE-Bruch's complex, which is postulated to lead to photoreceptor degeneration (229).

Within the literature the terminology describing changes in the peripapillary area is confusing. The term *"crescent"* is used by Curtin (2) to describe all change in the peripapillary area. Others use the term myopic crescent to mean a sharply demarcated area adjacent to the disc that may be congenital. As discussed, the myopic crescent can increase with elongation of the eye and become less distinct as the tissues stretch at different rates. Chui et al. (245) use the term *"peripapillary crescent"* as do others (229,240,428). Jonas, almost exclusively, uses the term parapapillary atrophy to describe changes outside the ONH. He differentiates the areas into

alpha, beta, gamma, or delta (discussed earlier) but not by aetiology (239). The additional terms scleral and choroidal are also used to describe congenital misalignments depending on the eyes pigmentation (28). The extensive use of the term atrophy, initially championed by Donders, is arguably incorrect. Some age-related crescents and those associated with glaucoma may be atrophic in nature whereas other crescents are the result of a congenital misalignment of tissues or stretching with eye growth. As mentioned previously, newer technologies like OCT facilitate in-vivo differentiation of PPA aetiology although more work is needed to determine reliable markers (245,430). A clearer categorisation may be useful, especially if the presence, size, or location of peripapillary changes are identified as predictors of myopic progression or future ocular morbidity.

Tilted discs were observed in 9 % of participants in this study which is higher than the range (0.36-3.5 %) reported for the general population in a review by Witmer et al. (197). Higher prevalence has been reported in some myopic cohorts, with the exception of the Beijing eye study (250), which limited the level of myopia to -8.00 dioptres, reporting a prevalence of 0.4 %. Two studies involving Singaporean children and adults with higher levels of myopia reported tilted disc prevalences of 37 % and 57 % with significant associations to the level of myopia (SER) and axial length (221,241). The wide range of prevalence is likely to be a result of varying definitions of tilt and methods of grading (197). Examination of stereo-photographs is currently considered the gold standard for identifying a tilted disc (197,409). In this study, the tilt was determined from observation of digital images, although the images were not stereoscopic hence some misclassification in the borderline cases may have occurred. The index of tilt, calculated from the ratio of the horizontal to vertical disc diameters, has been suggested to allow an objective description of disc shape. This method has drawbacks; wider tilted discs would have a lower index than narrower discs with less tilt (252) and also when the tilt is in a plane other than around the vertical axis. In our group, those judged to have a tilted disc through observation of the images had a mean index of tilt of 0.92 which is higher than the generally accepted value

for classification as tilted (197). No difference in tilt ratio between those judged to be tilted and not tilted by observation was found ($p = 0.703$). Some of the disagreement between the index of tilt and observation in the current study may be due to some torted discs being classified as tilted and tilt in planes other than around the vertical axis.

The studies of Samarawickrama et al. and Chang et al. were in Asian populations in which higher prevalence's of tilted discs are reported (221), while our population was predominately white European. Those with astigmatism greater than two dioptres were excluded from the current study. Astigmatism has been reported to have a strong association with disc tilt (221,250). No difference in the prevalence of disc tilt was observed between the sexes which agrees with previous studies (198,221). The frequency of bilateral tilt is reported to be 37-80 % (197). Tilt was bilateral in 50 % of cases in this study and was usually asymmetrical.

The participants with a tilted disc were found to be more myopic (-5.00 D to -3.60 D $p<0.01$) which agrees with the findings of the Beijing eye study (250) and Tanjong Pagar study (253). In those participants with unilateral tilt, there was not a significant difference in SER between the eye with or without the tilted disc ($p = 0.833$). Both the horizontal and vertical size of the OHN were significantly smaller ($p<0.01$) in the presence of tilt. This agrees with the findings of Tong et al. (431) who compared disc parameters in a large group with 174 having tilted discs. Samarawickrama et al. (221) also reported all optic nerve parameters to be significantly smaller, except vertical disc height, in those with tilted discs. A wider crescent was found in those with tilted discs (0.38 v 0.207 mm $p<0.01$). The position of maximum crescent width was examined in the eyes with a tilted disc. The most frequent location was in the inferior temporal region (54.3 %) which agrees with the Beijing eye study (250). Classically, the crescent is considered to be acquired and the tilted disc congenital and therefore stationary (214). The retrospective nature of this work is unable to suggest this is untrue. Longitudinal studies to follow those with tilt over a long-time frame even when myopia progression has ceased would help elicit the

answer as to whether disc tilt is progressive, and how initial disc morphology may be linked to subsequent changes. Kim et al. (246) demonstrated increased tilt as myopia progressed in a group of children through examination of serial photographs albeit over a fairly short time span (mean 38 months). Hwang et al. (232) suggest acquired tilt occurs due to the optic nerve being pulled in a temporal direction as the axial length and myopia increases. If the nerve is pulled temporally during axial elongation, a raised temporal margin would appear more plausible which is the opposite to that usually observed. Jonas (219) suggests that increased axial length leads to the ONH moving more to the nasal wall resulting in a change in the plane of the fundus viewed ophthalmoscopically which would give an impression of a narrower horizontal disc and possible underestimation of disc size.

A retrospective longitudinal case study was used in study two to determine if a change in the intrapapillary and peripapillary area could be detected between examinations. Longitudinal studies of non-glaucomatous ONH features are limited in number, with relationships to ageing being determined via inferences from cross-sectional surveys.

267 right eye images were analysed from the 267 participants having a second suitable image. As the aim was to consider change rather than the absolute measures no correction for ocular magnification was undertaken. It has been suggested that correction is not needed for this type of observation as small changes in refraction would make negligible differences (374). The mean interval between images was 43 months. Of the ONH measures only the VCD ($p<0.01$), and HCD ($p<0.01$) showed significant increases. Change in the rim area is of interest in the detection and monitoring of glaucoma. It is unclear how ageing affects the NRR, some reports showing an increase in cup size in normal eyes (420) and others showing no change (262). Healey et al. reported an increase in cup diameter of 0.01 mm per decade with more significant axon loss after the age of 60 (421). The VCDR was found to increase, in terms of both statistical, and clinical significance. However, the HCDR decreased by a statistically but not clinically significant amount.

In glaucomatous optic neuropathy, the ratio of the VCDR to HCDR increases from less than 1 in a healthy nerve to greater or nearer to 1 in a nerve with loss of vertical cup tissue. As the eyes were not classed as glaucoma suspects following a full ocular examination, a more likely explanation for this finding is the temporal disc margin being the hardest to determine, which may have been more the case in the second image. If the ONH was hard to assess in study one, it was rejected. In contrast to our findings, Moya (423) reported no significant difference in rim area in normal eyes with 13 years of follow-up.

Longitudinal studies of the peripapillary area are more numerous, usually as part of glaucoma studies that have included a normal control group. The absolute measure of crescent width increased significantly between the images ($p = 0.01$) as did the quotient of the crescent width to vertical disc height ($p<0.01$). The vertical disc diameter remained constant which justifies the use of the quotient of the crescent width to vertical disc height as a measure of crescent change. The size of the crescent was investigated as part of the Ocular Hypertension Treatment Study (432) with a median follow up of 13 years. The area of the PPA beta zone was found to increase by 10 % in the normal eyes with no greater increase in those who converted to glaucoma. They concluded that the longitudinal measurement of PPA is no benefit in diagnosing conversion to glaucoma. In addition to the associations with glaucoma, optic nerve crescents have been described as being predictive for future myopic progression in terms of higher SER (167), and development of myopic maculopathy (433). Recently Yokoi et al. (433) retrospectively reviewed the images of 29 Asian children collected over a 20 year period. 83 % of the eyes that developed pathological myopia were seen to show atrophic changes in the peripapillary area as children. The authors suggest this could be useful as a biomarker for advanced chorioretinal atrophy. The study was clinic-based, and the children had high myopia from a young age and may not be representative of the broader population.

The initial level of myopia was not related to change in any of the measures between the images. This conflicts with our expectations and the findings reported in a longitudinal study by Kim et al. (246). It was expected those with higher levels of myopia, which may have stabilised, to show degenerative changes in the parapapillary region between the images based on previous reports (2,31). Kim et al. (246) assessed the images of a group of low but progressing adolescent myopes with a mean interval between images of 38 months, which was less than the mean in the current study (43 months SD±20). Their methods involved identification of eyes that had a change in the appearance of the ONH between the images rather than a change in SER. Several variables were assessed in the two groups. The CW/VDD was found to be larger in the change in crescent group ($p<0.01$), with a moderate level of correlation ($r=0.408$, $p<0.01$) between myopic progression and the ratio. This study was clinic-based, and the children were under review due to having suspicious discs unlike the current study from a predominately normal population. Nakazawa et al. (240) also retrospectively reviewed the images of a small group of Japanese eyes ranging in age from 5 to 55 years with low to moderate levels of myopia at baseline. Video files were used to demonstrate a change in the ONH and peripapillary area. The ONH was seen to move nasally supporting the hypothesis of Jonas (219). Most of Nakazawa's group had significant progression of their myopia between the images possibly resulting in a magnified effect. The time between images in the current study ranged from 7 to 82 months with no correlation to the level of change in any of the time categories. This may be due to the short time course between some of the images.

3. 23 Limitations of the study

There are several limitations to note mainly due to this being a practice-based study. SER was used as a measure of myopia and in the magnification calculations as axial length measurements were not available. SER has been shown to be correlated to axial length (27) and using SER is more accessible for the research findings to be applied in clinical practice. Although fundus image planimetry is reported to be the gold standard, its subjective nature leads to the disadvantage of inter and intra observation variability; only one observer was used in our study. The assessment of repeatability was generally high. As most images were obtained through undilated pupils, this may have led to some images being more difficult to measure. The camera is classed as non-mydriatic hence the lack of pupil dilation is believed to be minimal. Visual determination of disc tilt from non-stereoscopic images may have led to some misclassification. The bias towards females may have affected the power some analyses, and in hindsight, it may have been better to have had more equal sex groups.

This study has shown that absolute measures need adjusting for ocular magnification to avoid erroneous associations. Despite the adjustment, any study seeking absolute measures needs to be aware there are still several assumptions and other related measurement factors, that make all measures at best an approximation. As the size of the measures agree with previous studies, and that several quotients were used negating the need for magnification correction, confidence can be had that any errors would be small.

To minimise selection bias, the participants were selected based on refraction and quality of images, in customer number order from a list generated by Specsavers IT department. Older participants may have been underrepresented due to smaller pupils affecting image quality, and children, as it is not our usual practice to take fundus images in those under 16 years of age. The studies were retrospective, and as such, there was no control over image capture. However, the fundus camera has auto alignment, so positioning errors and their impact on image magnification should be minimal.

In summary, features of the ONH and adjacent area were investigated providing reference data for a semi-rural white European population. It was shown via two measures, that crescent width is related to the level of myopia, and measurable change can be identified between visits. The crescent position was found to be related to the level of myopia and disc tilt. The importance of magnification correction and the possible consequences of not correcting were highlighted. Given this, manufacturers should be encouraged to allow entry of refractive parameters and calculation tools to allow a more useful assessment of disc size.

3.24 Summary

- 400 pairs of images had disc metrics taken.
- 267 had a second set of gradable images with a mean interval of 43 months and an increase in SER of -0.32 D.
- Crescent width was correlated with SER.
- The peripapillary crescent position was related to the level of myopia (SER).
- Eyes with tilted discs had smaller disc size and greater myopia (SER).
- Statistically significant changes in the vertical and horizontal cup to disc ratios were observed between visits.
- Many of the measures reduce the description of shape to a single number which can be argued to be inappropriate given the variety of shape.
- Future work should consider disc shape change longitudinally to investigate how it relates to myopia progression.
- Ocular magnification should be considered to avoid erroneous associations.
- Visible stretch observed adjacent to the disc could be used to highlight the risks of myopia, with the aim of boosting compliance with myopia treatment, or attendance for routine checks to consider glaucoma for example.

4.0 Chapter 4 Peripheral fundus features in myopic eyes

4.1 Aims

- Document the prevalence of peripheral retinal features in myopic eyes.
- Determine peripheral fundus features in relation to SER, sex, and age.
- Investigate possible relationships between peripheral and central fundus features.
- Consider the clinical guidelines relating to peripheral fundus changes in optometric practice.

4.2 Introduction

Several of the lesions observed in the vast area of the peripheral retina are more commonly seen in the myopic eye (2). The periphery can be a challenge to examine. However, it is important key signs are detected due to the risk of rhegmatogenous retinal detachment (RRD) and possible associated total loss of vision. This consequence often affects those of working age leading to significant socio-economic impact. The thinner retina associated with axial myopia and presence of abnormal vitreous attachments increases the risk of retinal detachment when myopic eyes experience trauma or posterior vitreous detachment (PVD). PVD has been shown to occur at a younger age in myopic eyes (272). The most significant lesions increasing the risk of retinal detachments are lattice degeneration, snail-track degeneration, white-without-pressure, atrophic holes and operculated holes (2). These were discussed in detail in section 1.8 along with rhegmatogenous retinal detachment and changes in the vitreous. This chapter prospectively considers peripheral retinal features in eyes with a range of myopia (SER). Associations between the presence of lesions to the level of myopia and age will be assessed. The coexistence of changes involving the peripheral retina and the region of the optic nerve head will also be investigated.

Due to the risk of complete visual loss from a retinal detachment, there is great value to be obtained from identifying those at risk. The increasing prevalence of myopia, high myopia, and the ageing population all add to the growing urgency to determine mechanisms and effective intervention to slow myopia progression. The bimodal peak of retinal detachment shown in the populations with high prevalence's of myopia indicates that different processes are likely to be involved.

Studies of eye shape in high myopia show some eye shapes are more likely to manifest certain features of myopic maculopathy (150). Vitreous changes are implicated in peripheral degenerations however it is unclear how eye shape, and its change, with increasing myopia, relate to peripheral degenerations. It is possible that some eyes are more at risk from changes at one part of the retina than at other locations.

4.3 Methods and materials

Study 3

4.4 Participants

Participants were recruited for this prospective cross-sectional study from patients attending a community optometry practice (Specsavers Opticians, Newmarket, Suffolk) for routine eye examinations or contact lens aftercare appointments between March 2015 and July 2017. Recruitment occurred via two methods: patients attending the practice were asked about participating, or they inquired in response to a poster displayed in the store waiting area (Appendix A).

The inclusion criteria were clear ocular media, and a myopic refraction of at least -0.50 D with astigmatism no greater than -2.00 DC to maintain full field focus for the central retinal imaging and this is the general rule in myopia studies (248,262). Exclusions were: those who had a history of refractive or cataract surgery, other known eye disease, and those with narrow anterior chamber angles.

The participants were provided with verbal and written explanations covering the procedure and the precautions associated with the use of dilating drops (Appendix B-C). After providing time for questions written informed consent was obtained from the participant.

The study abided by the tenets of the declaration of Helsinki. Ethical approval was granted by Aston University Life and Health Sciences, Ethics Committee (project number 642). The research ethics application forms are attached (Appendix E).

4.5 Procedure

Before dilation, a history was taken from the participant to identify reasons for not proceeding, such as previous adverse reactions to mydriatics, before the anterior segment was examined using a slit lamp biomicroscope. The anterior chamber angle was graded using the Van Herrick

method (Section 2.8). If the angle was graded less than grade 2, the subject was not dilated or included in the study unless there were other clinical reasons to dilate such as posterior vitreous detachment symptoms, or reduction in best corrected visual acuity for example. Intraocular pressure was measured by non-contact tonometry using a Pulsair Intellipuff® (Keeler Ltd, UK) which is described in section 2.4. Dilation was achieved using eye drops: Tropicamide 1 % (single use preservative free eye drops from Bausch and Lomb Ltd, Kingston-Upon-Thames, UK). One drop was instilled in each eye. The pupils were left to dilate for at least 30 minutes. Following pupil dilation, two different methods were used to inspect the peripheral retina.

(1) Binocular indirect ophthalmoscopy (slit lamp and Volk superfield, Volk Optical Inc., Mentor, OH) using a slit lamp set on X10 magnification. The retina was assessed in the primary position and eight peripheral positions of gaze (up, up and left, left, down and left, down, down and right, right, up and right).

(2) Headband binocular indirect ophthalmoscope (Keeler Vantage Plus Keeler Ltd, UK) with a Volk 20 dioptre condensing lens to allow a wider area of the fundus to be viewed. The lens was held at 5 cm from the cornea, and the area around the eye was viewed for a few seconds to aid adaptation for the patient. The patients' gaze was then directed upwards to the extreme, to the left, inferiorly and then to the right, before the posterior pole was viewed.

The presence and position of lesions were recorded on a paper chart, before being entered into an Excel spreadsheet (Microsoft, Washington, United States) (Table 4.1, Figure 4.1).

Table 4.1. Features recorded during the examination of the peripheral fundus.

	Feature
1.	Lattice degeneration (LAT)
2.	White without pressure (WWOP)
3.	Pigmentary degeneration (PD)
4.	Paving stone degeneration (PSD)
5.	Retinal hole (RH)
6.	Snail track degeneration (STD)

The appearance of the central fundus was recorded using a digital fundus camera (Nidek AFC-210 Nidek, Japan) with a 45° field centred on the macula. The vertical disc height and maximum crescent width were measured using the inbuilt analysis software (Navis -Lite Nidek Japan) as described in section 2.1. The position of the maximum crescent was also noted from the images. Corneal curvature was measured using a Huvitz auto-keratometer (Huvitz, Gyeonggi-do, Korea) for each participant. Demographic, refractive data and visual acuity were taken from the patient records. The optic nerve head measurements were corrected for ocular magnification using refraction in the formula described by Bengtsson (344).

Upon completion of the assessment, the intraocular pressure was re-assessed. In those where the pressure increased it was re-measured every 15 minutes until it reduced. There were no cases where the pressure increased significantly. Any significant increase would have been managed according to the College of Optometrists Guidelines (399). The advice was reiterated regarding the use of tinted spectacles or a peaked hat to enhance short-term comfort.

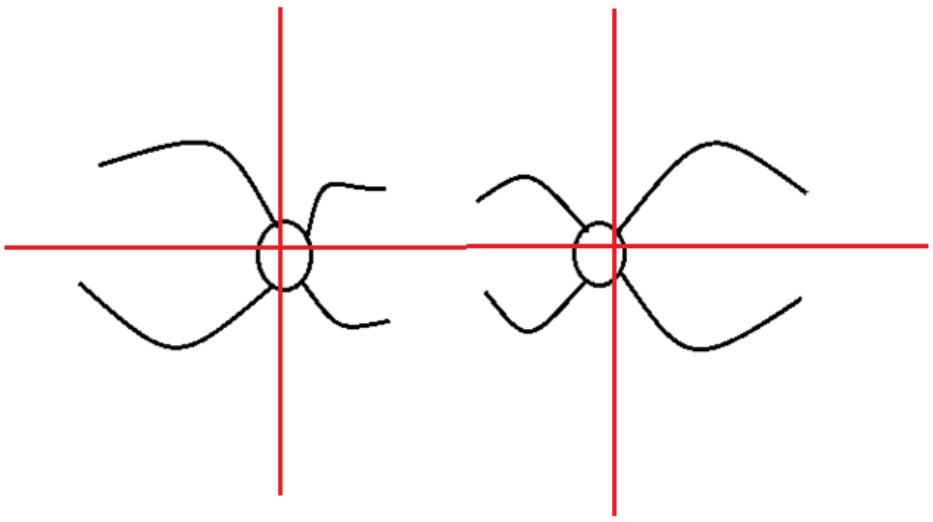


Figure 4.1. Showing the chart used to record features of the fundus observed in the dilated subjects.

4.6 Sample size calculation

A priori power analysis was performed using G*Power 3 (Dusseldorf University Germany). A sample size of 111 was needed for a t-test with a power of 95% and a medium effect size.

The previous main studies considering peripheral lesions in myopic eyes included 213 eyes in the Lam et al. (290) study, 337 eyes in Lai's study (285), while Pierro included 513 eyes (281).

4.7 Analysis

Both eyes were used in the initial analysis to allow investigation of the number of bilateral lesions. Due to the high correlation in myopia (SER) between the right and left eyes (r = 0.94) groups were compared using the right eye alone. Lam (290) and Chang (230) who looked at highly myopic eyes used the most myopic eye while others chose the right eye only (365).

All data were analysed using SPSS version 23.0 (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp). Descriptive statistics, t-tests or MWU tests and linear regression analysis were used to assess relationships between the lesions, level of myopia (SER), age and central fundus changes. The Kruskal-Wallis test was used to test for difference between categories. Data are presented as a mean and standard deviation.

4.8 Results

4.9 Demographic Information

A total of 258 eyes (129 participants) with myopia ≤-0.50 D were examined. The mean age was 47 years SD±17 (range 12 to 84 years). Eighty-seven (64.4 %) of the participants were female, with 117 (91 %) being of white European ethnicity. The mean level of myopia (SER) was -4.35 D SD±2.6 (range of -0.50 D to -13.00 D) (R -4.37 D SD±2.66 range -0.50 D to -13.00D, and L -4.33 D SD±2.62 range -0.62 D to -12.50 D). The distribution of myopia (SER) by category is shown in figure 4.2. All participants had a corrected visual acuity of 0.20 Log MAR or better. There was no correlation between age and level of myopia (SER) (Figure 4.3). The mean corneal curvature was 7.76 mm SD±0.26 (range 7.06 to 8.41 mm). Corneal curvature (right eye) showed a weak correlation to myopia (r = 0.278, p=0.01) (Figure 4.4). Due to the strong correlation between the two eyes (r = 0.94, p<0.01) only the right was included in analyses where this association breached the assumptions of standard statistical testing.

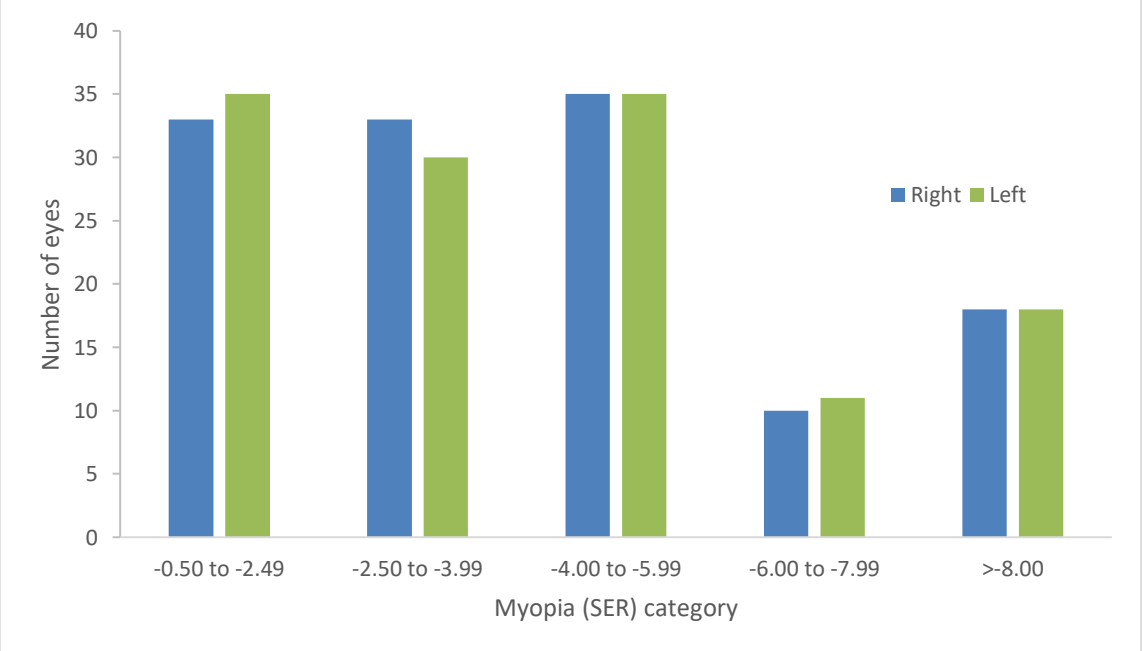


Figure 4.2. Frequency distribution of myopia (SER) by category for both eyes n 258.

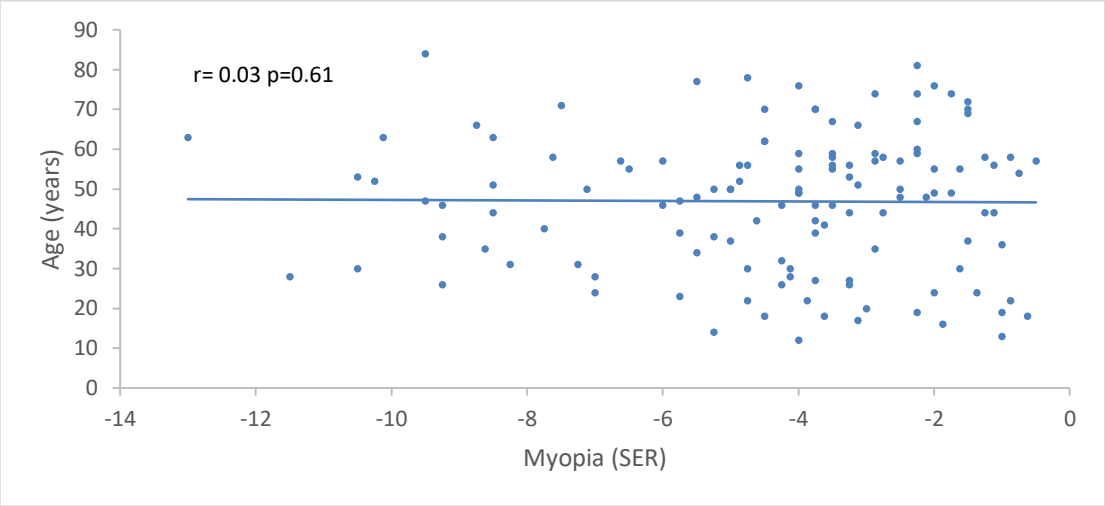


Figure 4.3. Scatterplot showing no correlation (Pearson's correlation) between age and level of myopia for the right eye (n129).

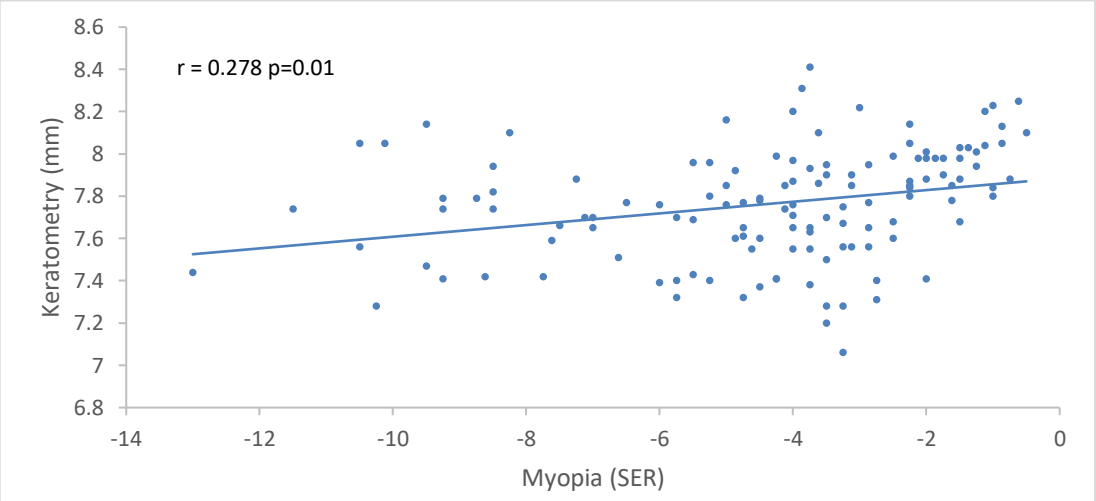


Figure 4.4. Scatterplot showing a weak correlation (Pearson's correlation) between corneal curvature and myopia (n129).

4.10 Presence of peripheral lesion

The frequency of the peripheral lesions is shown in tables 4.2 and 4.3 for the right eye, and both eyes respectively. Sixty-nine (27 %) eyes from 42 participants were found to have at least one peripheral lesion, and 189 eyes had no lesions. The most frequent lesion was pigmentary degeneration (7.8 %) followed by lattice (5.8 %) and white without pressure (5.8 %). Retinal holes were observed in 10 eyes (3.9%).

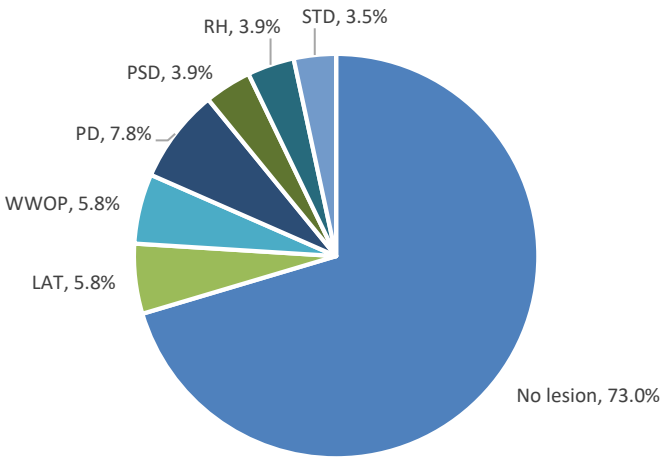


Figure 4.5. Pie chart showing the distribution of peripheral lesions (both eyes) n 258.

Lesions were present in 27.9 % of right eyes and 25.6 % of left eyes. The mean SER in right eyes with and without a lesion was -5.18 D SD±3.2 and -4.08 D SD±2.4 (p = 0.07). There was no difference in age between those with and without lesions (p = 0.982).

Table 4.2. The frequency of myopia-related peripheral lesions, mean SER, and mean age for those with no lesion and each type of lesion for the right eye only (n=129).

	Number of eyes	Percentage of eyes	Mean SER SD	p	Mean Age (years) SD	p
No lesion	95	73.6%	-4.08 D ±2.4		46.87 ±18.4	
Any lesion	34	26.4%	-5.18 D ±3.2	0.072	46.94 ±13.6	0.982
LAT	8	6.2%	-4.95 D ±2.8	0.525	44.4 ±9.1	0.471
WWOP	8	6.2%	-5.78 D ±3.6	0.122	39.1 ±13.8	0.190
PD	12	9.3%	-5.58 D ±4.1	0.292	54.8 ±14.8	0.098
PSD	5	3.9%	-5.52 D ±2.7	0.324	60.8 ±10.4	0.066
RH	5	3.9%	-2.70 D ±1.6	0.153	44.6 ±6.6	0.500
STD	5	3.9%	-4.00 D ±3.1	0.752	37.6 ±12.9	0.221

Independent samples t-test is comparing lesion type to eyes with no peripheral lesions for SER and age. LAT-lattice degeneration, WWOP-white without pressure, PD-pigment degeneration, PSD-paving stone degeneration, RH-retinal hole, STD-snail track degeneration

Eyes with a retinal hole had the lowest level of myopia (-2.70 D SD±1.6), and eyes with WWOP the highest (-5.78 D SD±3.6). Neither were different from the no lesion group (p = 0.153 and p = 0.122). The mean age was lowest in those with snail track degeneration (37.6 SD±12.9 years) while eyes with pigmentary or paving stone degeneration had the highest mean age (Table 4.2).

The mean and SD of the level of myopia and age for each lesion are shown in figures 4.6 and 4.7.

None of the lesion groups was significantly different in age to the group with no lesions.

Table 4.3. The frequency of myopia-related peripheral lesions, mean SER, and mean age considering both eyes (n=258).

	Number of eyes	Percentage of eyes	Mean SER SD	Mean Age (years) SD
No lesion	189	73%	-4.18 D ±2.5	46.6 ±18
Any lesion	69	27%	-4.84 D ±2.9	47.6 ±14
LAT	15	5.8%	-4.94 D ±2.7	44.5 ±9
WWOP	15	5.8%	-5.91 D ±3.0	41.7 ±12
PD	20	7.8%	-5.52 D ±3.8	53.5 ±13
PSD	10	3.9%	-4.31 D ±2.4	52.6 ±17
RH	10	3.9%	-2.50 D ±1.2	49.5 ±13
STD	9	3.5%	-4.07 D ±2.9	36 ±12

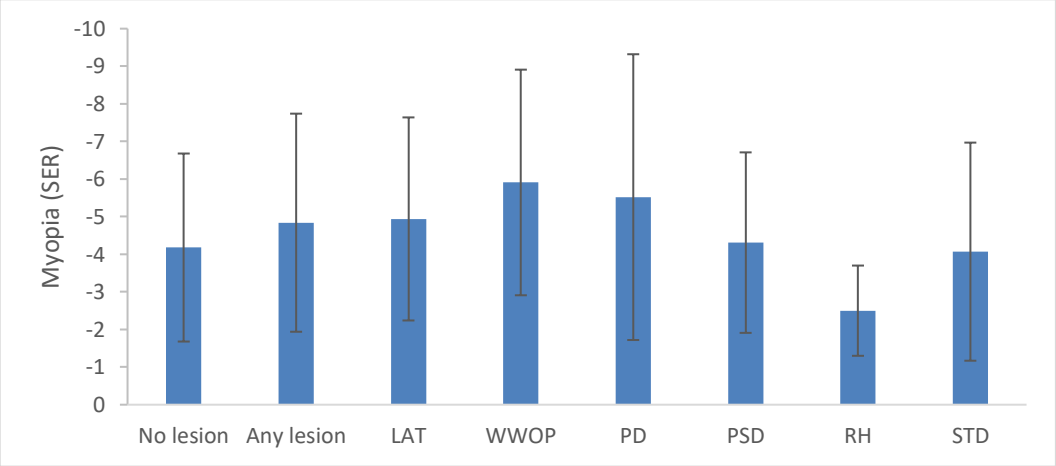


Figure 4.6. Figure showing the mean level of myopia (SER) for each lesion. Error bars indicate the standard deviation. (both eyes)

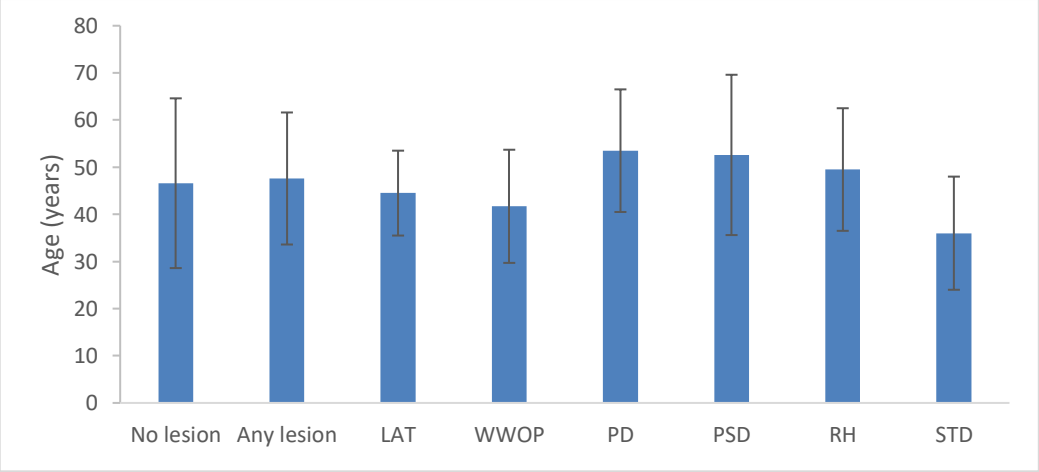


Figure 4.7. Figure shows mean age and standard deviation for each lesion type. (both eyes)

Multiple lesions were observed in 10 of the 258 eyes (3.8 %), with one eye having more than two lesions (Table 4.4). In twenty-three participants (17.8 %) the same lesion was observed in both eyes. This included six participants with pigmentary degeneration, five with lattice, and five with white without pressure (Table 4.5).

Table 4.4. The number of peripheral lesions in a single eye (both eyes).

Number of features	Number of eyes	Percentage
0	189	73 %
1	59	23 %
2	9	3.5 %
>2	1	0.4 %

Table 4.5. The number of participants with the same lesion in both eyes.

	Number of participants with the same lesion in both eyes
Any lesion	23
LAT	5
WWOP	5
PD	6
PSD	1
RH	2
STD	4

4.11 Presence of peripheral lesions and sex group

The percentage of eyes with lesions was similar between the male and female groups. Peripheral lesions were observed in 29.3 % of female eyes and 33.3 % of male eyes. The level of myopia was similar between the sexes (M -4.33 D, F -4.39 D, p=0.90), the males were older (M 51 years, F 44.9 years) but not significantly (p=0.06). None of the individual lesions was biased toward a sex group. Table 4.6 shows data for the right eye and 4.7 the frequency data for both eyes.

Table 4.6. Number, and percentage of eyes with each lesion split by sex for the right eye.

	Male (42 eyes)		Female (87 eyes)		p
	n	%	n	%	
LAT	2	4.8	6	6.9	0.935
WWOP	2	4.8	6	6.9	0.935
PD	5	11.9	7	8	0.487
PSD	3	7	2	2.3	0.329*
RH	1	2.4	4	4.6	1.000*
STD	2	4.8	3	3.4	0.600*
Total lesions	15	35.7	28	32	0.808

Chi ^{2} test for independence or Fishers exact test*

Table 4.7. Number, and percentage of eyes with each lesion split by sex (both eyes).

	Male (84 eyes)		Female (174 eyes)	
	n	%	n	%
LAT	4	4.8	11	6.3
WWOP	6	7.1	9	5.2
PD	7	8.3	13	7.5
PSD	4	4.8	6	3.4
RH	3	3.6	7	4.0
STD	3	3.6	6	3.4
Total lesions	27	32.1	52	29.9

4.12 Right eye lesions and relationship to myopia and age

Myopia (SER) was divided into five categories (Table 4.8), and age into seven categories (Table 4.9), to investigate the frequencies in relation to age and level of myopia (SER) for each lesion type. At an alpha value of 0.05, none of the differences across groups for the level of myopia was statistically significant. When age was assessed, a statistically significant difference across the categories was observed in those with paving stone degeneration (p = 0.046).

Table 4.8. The frequency of right eye lesion according to the category of myopia. Column two shows the number of eyes studied within the SER category. Total number of eyes 129.

SER	Number of eyes	LAT n (%)	WWOP n (%)	PD n (%)	PSD n (%)	RH n (%)	STD n (%)
-0.50 to -2.49	34	0 (0)	2 (5.9)	3 (8.8)	0 (0)	3 (8.8)	2 (5.9)
-2.50 to -3.99	33	5 (15)	1 (3)	1 (3)	1 (3)	1 (3)	1 (3)
-4.00 to -5.99	35	1 (2.9)	1 (2.9)	3 (8.6)	3 (8.6)	1 (2.9)	1 (2.9)
-6.00 to -7.99	11	0 (0)	2 (18)	0 (0)	0 (0)	0 (0)	2 (18)
<-8.00	16	4 (25)	5 (31)	6 (37)	1 (6.3)	0 (0)	1 (6.25)
		p = 0.344	p = 0.261	p = 0.378	p =0.340	p = 0.084	p = 0.560

Kruskal-Wallis test

Table 4.9. The frequency of right eye lesion according to the age category. Column two shows the number of participants within the age category.

Age	Number of participants	LAT n (%)	WWOP n (%)	PD n (%)	PSD n (%)	RH n (%)	STD n (%)
<15	3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0(0)
16-20	8	0 (0)	1 (12.5)	0 (0)	0 (0)	0 (0)	1 (12.5)
21-25	7	0 (0)	1 (14)	0 (0)	0 (0)	0 (0)	0 (0)
26-35	18	1 (5.5)	1 (5.5)	1 (5.5)	0 (0)	0 (0)	0 (0)
36-50	36	5 (13.8)	3 (8.3)	2 (5.5)	1 (2.8)	5 (13.8)	1 (2.8)
51-65	37	2 (5.4)	2 (5.4)	6 (16.2)	3 (8.1)	0 (0)	1 (2.7)
>66	20	0 (0)	0 (0)	1 (5)	1 (5)	0 (0)	0 (0)
		p = 0.358	p = 0.665	p = 0.053	**p = 0.046**	p = 0.828	p = 0.679

Kruskal-Wallis test

4.13 Location of lesion

Lesions observed to span across quadrants were recorded as positive in more than one quadrant. Figure 4.8 and Table 4.10 summarise the feature positions. Lesions were more frequently observed in the superior and inferior temporal quadrants. Pigmentary degeneration was found more diffusely throughout the peripheral retina, and snail track degeneration was observed to span across quadrants more than any other lesion.

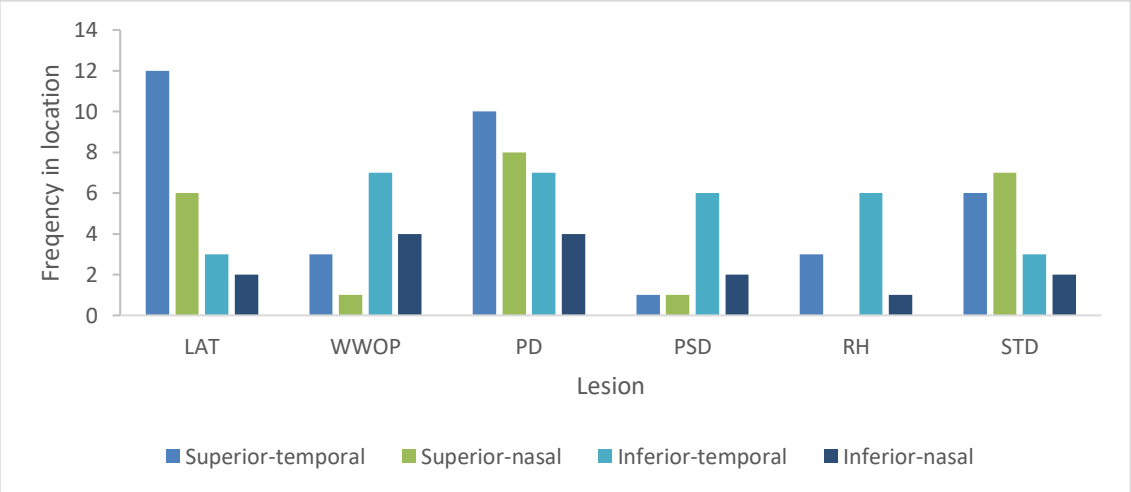


Figure 4.8. Chart showing the frequency of peripheral lesion location by quadrant. (Both eyes)

Table 4.10. The frequency of lesions in each quadrant of the retina. Both eyes.

	Superior temporal	Superior nasal	Inferior temporal	Inferior nasal
LAT	12	6	3	2
WWOP	3	1	7	4
PD	10	8	7	4
PSD	1	1	6	2
RH	3	0	6	1
STD	6	7	3	2

LAT-lattice degeneration, WWOP-white without pressure, PD-pigment degeneration, PSD-paving stone degeneration, RH-retinal hole, STD-snail track degeneration

4.14 Optic disc parameters and peripheral lesions

The mean vertical optic disc diameter in eyes with no peripheral lesion was 1.76 mm SD±0.23. Eyes with white without pressure had the largest optic discs (1.96 mm SD±0.35). The smallest disc height was observed in the eyes with pigmentary degeneration. Vertical disc diameter (VDD) and SER showed no relationship (r = -0.06, p = 0.519) hence the difference in VDD between each lesion was compared to the group with no peripheral lesion using an independent samples t-test. No differences were found between the VDD in any of the lesion groups compared to the no lesion group (Table 4.11).

Table 4.11. Magnification corrected disc metrics (mean, SD, and range) for each lesion type. p is comparing eyes without the lesion to eyes with each type of lesion. n129 (right eye)

	VDD (mm)	SD range	P
No lesion	1.76	±0.23 (1.19-2.44)	
Any lesion	1.80	±0.21 (1.46-2.06)	0.270
LAT	1.87	±0.16 (1.61-2.14)	0.243
WWOP	1.96	±0.35 (1.61-2.44)	0.167
PD	1.74	±0.17 (1.43-1.99)	0.732
PSD	1.75	±0.18 (1.53-1.94)	0.761
RH	1.75	±0.16 (1.59-1.98)	0.758
STD	1.77	±0.23 (1.46-1.98)	0.962

(Independent samples t-test)

Peripapillary crescents were present in 181 eyes (70 %) and 90 right eyes (70 %). The widest crescents were observed in eyes with paving stone degeneration (0.49 mm ±0.34) and the smallest in eyes with lattice degeneration (0.19 mm ±0.14). When comparing the crescent width between each lesion type, and the group without a peripheral lesion no differences were observed. Table 4.12 shows the crescent size in eyes without a peripheral lesion compared to each lesion type, and the position of the crescent for each lesion type (right eyes only).

The position of the crescent was predominantly temporal (67 eyes) (Figure 4.9 and 4.10). In eyes, with snail track degeneration a significant number of eyes had an inferior temporally located crescent (40 %) when the right eye was considered alone.

The maximum crescent width was moderately correlated to SER (r = -0.38, p<0.01). A one-way between groups analysis of covariance was conducted to compare the optic disc crescent width of the lesion group to the group with no peripheral lesion. After adjusting for SER no difference between the groups was observed, F (1,129) = 0.64, p = 0.425, r^2 = 0.005).

Table 4.12. Maximum crescent width (CW) (mean, SD, and range) and position of the crescent for each lesion type.(right eye only)

	CW (mm)	p	Crescent position (%)			
			None	T	IT	Other
No lesion	0.26 ±0.24 (0-1.32)		32.6	50.5	14.7	3.2
Any lesion	0.29 ±0.32 (0-1.10)	0.364	26.5	73.5	14.7	11.8
LAT	0.186 ±0.14 (0-0.34)	0.530	25	75	0	0
WWOP	0.21 ±0.17 (0-0.47)	0.733	25	62.5	12.5	0
PD	0.43 ±0.45 (0-1.40)	0.293	25	50	8.3	16.7
PSD	0.49 ±0.34 (0.163-0.89)	0.085	0	80	0	40
RH	0.20 ±0.21 (0-0.44)	0.692	40	40	20	0
STD	0.22 ±0.24 (0-0.49)	0.824	20	40	40	0

p is comparing CW in eyes with no lesions to those with each lesion. (Mann-Whitney U test) T-temporal, IT-inferior-temporal,

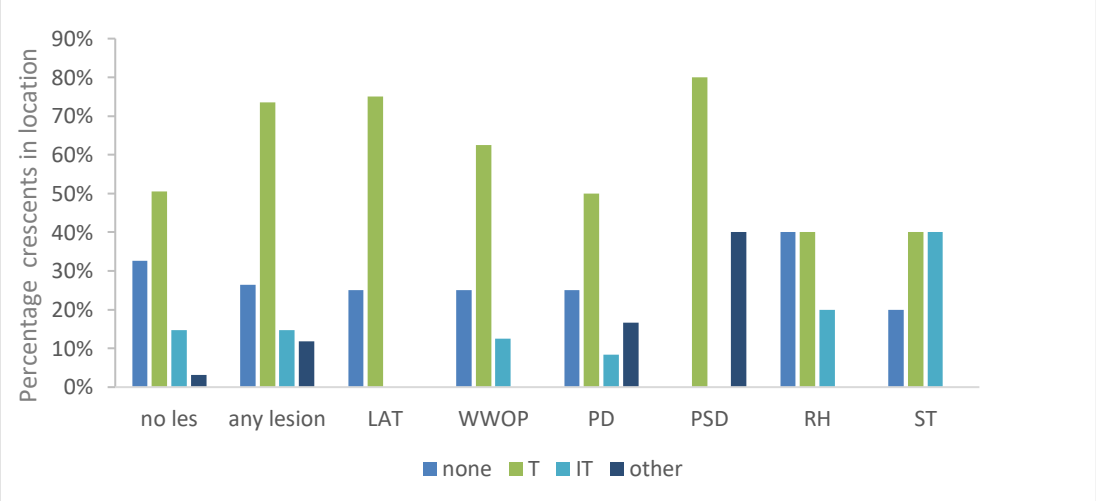


Figure 4.9. Peripapillary crescent position frequency for eyes with each lesion (percentage), eyes with any lesion, and eyes with no lesion. T-temporal, IT-inferior-temporal (right eye).

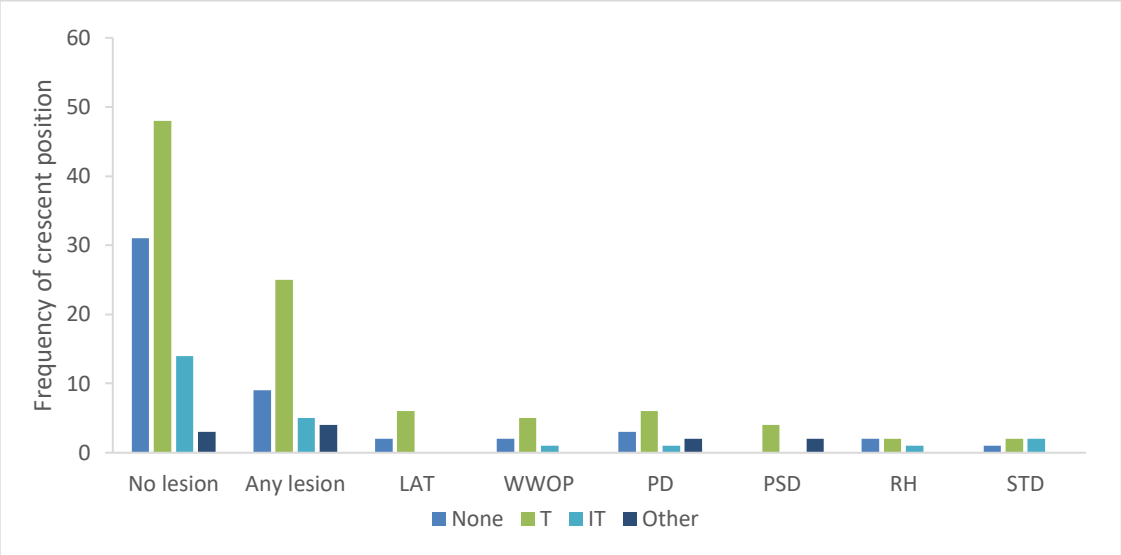


Figure 4.10. Peripapillary crescent position frequency for eyes with each lesion, eyes with any lesion, and eyes with no lesion. T-temporal, IT-inferior-temporal (right eye).

4.15 Discussion

Myopia has become more prevalent over recent generations and is a trend that looks set to continue. If myopia is causative of ocular pathology, an increase in disease would be expected to follow making the importance of determining early clinical signs indicative of future morbidity greater than ever. Ageing is seen as a major factor in myopia related pathology (31,434). However, retinal detachment is often observed at a younger age (2). In this study, indirect ophthalmoscopy was performed through dilated pupils in participants attending for routine eye examinations, to determine the prevalence of peripheral fundus lesions, and their associations to the level of myopia (SER) and age.

Sixty-nine (27 %) of the 258 eyes examined (42 (32.5%) of participants) had one or more peripheral lesion, with ten eyes having more than one lesion type. Lam et al. (290) reported 71 % of a group Chinese adults with myopia <-6.00 and mean age of 33 years, to have at least one peripheral lesion, while Lai et al. (285) in a similar population found a peripheral lesion in 56 % of eyes. Like other studies, the level of myopia (SER) and age were compared between those with and without peripheral lesions finding no difference (SER $p = 0.188$ and age $p = 0.597$). In contrast, the study by Lai et al. (285) found greater myopia and younger age to be associated with the presence of any peripheral lesion ($p<0.01$ and $p = 0.05$).

Lai and Lam, like this study, reported pigmentary degeneration to be the most frequent peripheral change. However, in these two studies, the prevalence of pigmentary degeneration was over 35 % compared to 7.8 % in the current study. This may be due to the level of myopia being greater in these two studies, those with PD in this study had the second highest level of myopia. Karlin (280) found PD to become increasingly prevalent with increasing axial length and age in a white European group, suggesting prolonged myopic stress on the retina as a possible mechanism (280). In this study, the mean age of those with pigmentary degeneration was older than those without (52.6 to 46.6 years, $p = 0.063$). The two Chinese studies of adults had mean ages of 33 and 36 years. A further study of Chinese adolescents, again including only myopes <-

6.00 D, reported pigment degeneration in 4.2 % of eyes (365) suggesting ethnicity may not be a significant factor but age maybe. Like previous studies (280) PD was found to be located primarily in the superior temporal quadrant. This shared location with lattice forms the basis of the link between the two lesions (2). A possible explanation for the variances reported in prevalence may be due to differing classifications of PD, and its position in the far periphery means it may be missed without scleral indentation.

Lattice degeneration is associated with retinal detachment (280,289,294). In a study of myopic Taiwanese subjects attending a clinic for retinal tears, 21 % were associated with lattice, and 18% had lattice in the fellow eye (283). In this study, lattice was observed in 5.8 % of eyes which is less than half the prevalence reported by others (281,290), but greater than the prevalence reported in Cheng's study of myopic adolescents (365). The association between lattice and the level of myopia is not clear with conflicting reports. Some have found lattice to increase with increasing axial length (281), while others report associations with low and mid-levels of myopia that tails off at higher levels (365). Lattice was observed in a wide range of myopia (-2.00 D to -9.50 D) with the greatest frequency occurring in the <-8.00 D category, and in eyes in the fourth and fifth decades. This is in conflict with previous reports which suggest lattice prevalence peaks in the second decade (277). Both eyes were affected in 5 participants (50 %). Byer reports bilateral lesions in 42 % with a striking symmetry in location between the eyes (277). In the 15 eyes with lattice, the lesion was predominantly found in the superior temporal quadrant as reported by others (287), although Lam et al. found the inferior temporal quadrant to be the most affected quadrant (290). The superior temporal area is considered the danger area for retina tears and subsequent RRD (278). Lattice co-existed with another lesion (WWOP, PD, RH) in six eyes.

Snail track degeneration is considered by some to be a variant of lattice (2,277). In this study, it was recorded as a separate feature as others have done (365) as I found the appearance to be

distinctively different. STD was observed in 3.5 % of eyes and was bilateral in 3 cases. Cheng et al. (365) found STD in 2.5 % of a group of highly myopic adolescent eyes. The theory of snail track being a precursor of lattice is supported by this study's finding that those with this lesion were the youngest with a mean age of 36 years. However, the location was mainly inferior compared to the superior retina for lattice.

WWOP is considered by some to be a transient condition that may be a precursor to some other degeneration due to it being found more frequently in younger eyes (281), which was the case in this study. WWOP was observed in 5.8 % of eyes with a mean age of 42 years. The prevalence was lower than previous reports in younger eyes (Table 4.13). In a group of adolescents, Cheng et al. found 52 % of eyes to show WWOP whereas studies involving older participants have shown lower prevalence's (281,285,290). The lower prevalence in this study may be due to the predominance of white Europeans making detection more difficult, and the older age of the participants. Greater pigmentation may provide more contrast between the WWOP and the background facilitating its detection (267). Those with WWOP had the highest level of myopia compared to the eyes with other lesions. WWOP was bilateral in 5 cases, with a preference for the inferior temporal quadrant.

Retinal holes are also considered a risk for retinal detachment. Ten eyes (3.9 %) were found to have retinal holes in this study. The hole was predominately located in the inferior temporal quadrant which agrees with Byers' summary (277), whereas others report retinal holes in myopic eyes to be more often seen superiorly (273). Lai et al. (285) found retinal holes to be present in 6.2 % of eyes, and Lam et al. (290) in 7.5 %, in groups with high myopia defined as ≤-6.00 D. Interestingly in this study those with retinal holes had the lowest levels of myopia (-2.50 D SD±1.2). Myopia may still have been progressing in this group, although given the mean age this is less likely. All the retinal holes in this study were asymptomatic.

Paving stone degeneration was observed in 3.9 % of eyes which agrees with levels reported by others (290). PSD was most often located inferiorly with a mean age of 53 years. Pierro et al. (281) found a higher prevalence of PSD (27 %) with a significant relationship to increasing age.

Table 4.13. Summary of studies describing the frequency of peripheral retina changes in myopic eyes. The second row indicates the studies inclusion criteria for the level of myopia.

	Present study	Lai (285)	Lam (290)	Pierro (281)	Cheng (365)
SER	<-0.50	<-6.00	<-6.00	AL>24 mm	<-6.00
Mean age	47	36	33	53	12-18
LAT	5.8%	14%	12.2%	13.2%	3.3%
WWOP	5.8%	21%	31%	5%	51.7%
PD	7.8%	37.7%	51.2%	14%	4.2%
PSD	3.9%		5.2%	27%	0
RH	3.9%	6.2%	7.5%	12%	
STD	3.5%				2.5%

LAT-lattice degeneration, WWOP-white without pressure, PD-pigment degeneration, PSD-paving stone degeneration, RH-retinal hole, STD-snail track degeneration

The sex groupings were similar regarding age and level of myopia, with no difference in lesion prevalence between the males and females, as was the case in previous studies (281,285,365). Interestingly, the proportion of males agreeing to participate was slightly greater than the number of males in the retrospective studies included in this thesis. Despite women being disproportionally represented they appeared to decline involvement when pupil dilation was discussed. Possible reasons for this could be men being more relaxed about dilation and less time-pressured when in the consulting room, or that a male asked them to participate.

Several factors may explain some of the variances in peripheral lesion prevalence between studies. The inclusion criteria for SER may affect the recorded prevalence. Age is pertinent as some conditions are more prevalent in younger eyes whereas others, such as pigmentary and paving stone degeneration, are more often observed in older eyes (281). As mentioned previously it has been suggested that some lesions may be transitory, which could not be assessed in this cross-sectional investigation. Choice of examination technique may account for differences; some workers use several methods while others just one. In this study, a slit lamp

biomicroscope with a condensing lens, and binocular indirect ophthalmoscopy were used. Others have used a Goldmann 3 -mirror lens, indirect binocular ophthalmoscopy with scleral indentation (290), and some use widefield imaging as a screening tool before indirect ophthalmoscopy (285).

Many of the retinal changes observed in myopic eyes develop, and progress, after myopia, has stabilised (2). However, this appears not to be the case with most peripheral retinal lesions, with the possible exceptions of pigmentary and paving stone degenerations (281). Alterations to the sclera, choroid, and retina occur in myopia from mechanical stretching resulting in thinning of the tissues (281). The peripheral RPE cells become flattened, and alteration to the choroidal vessels may result in chronic ischaemia of peripheral retina (270). The lower number of nerve fibres and lack of large vessels in the periphery may increase the susceptibility of the peripheral retina to damage (23). The normal equatorial post-natal growth pattern described by Curtin may make this area more susceptible to retinal degenerations (2). As described earlier, four simplified models of myopic eye stretch have been described (Figure 4.11) (145,147). To investigate, if certain eyes were more susceptible to retinal changes in specific regions the presence of peripheral lesions in relation to vertical disc height and maximum crescent width were assessed. Both measurements were corrected for ocular magnification using the method proposed by Bengtsson et al. (344). Section 2.2 discusses the magnification factors in detail.

Figure 4.11. Models of retinal stretching in myopia: a) global, b) equatorial, c) posterior polar, and d) axial expansion. The solid lines represent the emmetropic eye and the dashed lines the myopic retina. Reproduced with permission (Verkicharla et al. 2012) (145).

From Strang's descriptions of eye stretch, it would sound plausible that eyes with posterior polar stretch would be more likely to display a peripapillary crescent (147), while peripheral retinal changes would be expected in eyes with equatorial stretch . From this, it could be expected any crescent would be smaller, and the vertical disc height to be average despite the higher myopia due to less stretching of the scleral canal with equatorial stretch. The lack of information about eye shape hindered the testing of this hypothesis satisfactorily. The vertical disc height was found to be greatest in eyes with lattice, and smallest in eyes with pigmentary degeneration, although none of the lesion groups were statistically different from the no lesion group (Table 4.8).

Optic nerve crescents are reported to be the earliest manifestation of myopic related structural changes in the eye (2). This is disputable if lattice, WWOP and snail track degeneration are considered as myopia related. Lattice has been reported to have a peak prevalence in the second decade (277), and WWOP and snail track are generally seen in younger eyes (273). The presence of peripapillary crescents has been reported in studies also considering peripheral changes (285,365) but not in relation to specific peripheral lesions. This would appear to be a weakness as not all lesions are related to the implications of myopic related tissue stretch. The small number of eyes in some lesion groups may be a reason that relationships to specific lesions were not considered or reported. In this study, crescents were found to be present in 70 % of eyes with peripheral lesions. The widest crescents were observed in the group with pigmentary degeneration and the smallest in those with retinal holes. Those with pigmentary degeneration had significantly higher levels of myopia and were older than those with retinal holes which correspond with the findings in study one. In study one it was shown that crescent width increased with increasing myopia ($r = -0.44$, $p<0.01$), and age ($r = 0.26$, $p<0.01$). Cheng et al. (365) investigated several potential risk factors for both peripapillary crescent and any peripheral retina change. They found the axial length to be a more powerful predictor of crescent width than refraction or age. The position of the majority of peripapillary crescents was temporal in all

lesion types. Interestingly 33 % of eyes with PSD had the crescent in the other category. In study one this category consisted of eyes with higher levels of myopia. PSD is arguably the least associated with myopia. Another point of interest was the difference between eyes with lattice and STD. All the crescents in eyes with lattice were temporal to the disc while 40 % of eyes with STD showed maximum crescent width in the inferior temporal region, a finding strongly associated to higher myopia in study one. The mean level of myopia in the STD group was lower than eyes with lattice. The finding that those with STD were younger, and associated with inferior temporally located crescents may have potential as a predictor for progression of SER.

In addition to changes in the retina, choroid and sclera, alterations to the vitreous and its interface with the retinal surface have been linked to several peripheral lesions (277,280). The high frequency of PVD in eyes with lattice and WWOP indicates the vitreous is important in the development of some peripheral retinal lesions. The presence of PVD was not recorded in the current study as it is not always easy to determine the stage of vitreous detachment using slit lamp examination. Pierro and colleagues (281) found 48 % of the eyes in their group of adult myopes had undergone PVD. They suggested lattice and WWOP result from interaction with the vitreous while pigmentary and paving stone degeneration are atrophic in nature.

4.16 Clinical recommendations

Although the central retinal changes associated with higher levels of myopia are more often discussed regarding visual loss, peripheral changes can have a much more profound effect on the person's life as total visual loss may occur. Treatment of retinal detachment has developed enormously over the last few decades but still involves substantial worry for the patient, and often comes with other complications. It is common to need cataract surgery within a short time after vitrectomy, which brings the risk of further detachment (294). Anisometropia, diplopia from muscle damage, and central metamorphopsia if the macula is involved all add to morbidity.

Patient education on danger symptoms may facilitate early appreciation of problems before any tear has led to a detachment, which may result in a less invasive intervention.

It was observed that without dilation many lesions would have been missed. Some recommend that all high myopes have periodic dilated fundus examinations (365), while others advise annual review with pupil dilation for those with peripheral lesions such as lattice and WWOP (267,282) (Table 4.14). It is essential to examine both eyes due to the bilateral nature of some lesions (297). Wide-field imaging and its ability to document the periphery without dilation is a welcome addition in monitoring and detecting lesions, although clinical examination is still considered the gold standard (435). The practitioner should be aware of the bimodal pattern of RRD and be vigilant when examining young myopes, as well as those likely to be undergoing PVD. Those with pre-identified retinal lesions should be educated to seek assessment if new PVD symptoms occur (275,282,290).

Table 4.14 Recommended follow-up for peripheral lesions in optometric practice (213,267,275,436).

	Suggested follow-up	Risk
LAT	Dilated exam every 1-2years	Moderate
WWOP	Dilated exam every 1-2 years	Low
PD	Routine exam every 2 years	Low
PSD	Routine exam every 2 years	Low
RH	Possibly refer	Moderate
STD	Dilated exam every 1-2 years	Low-Moderate
High myopia	Dilated annual exam	Moderate

LAT-lattice degeneration, WWOP-white without pressure, PD-pigment degeneration, PSD-paving stone degeneration, RH-retinal hole, STD-snail track degeneration

Due to the potential morbidity that retinal detachment can lead to there has been much debate on whether prophylactic treatment of lattice and asymptomatic holes would be appropriate. Byer (289) followed a group with lattice over an average period of 11 years reporting less than 1 % incidence of retinal detachment over the period. He advised not to treat prophylactically unless the fellow eye had suffered a detachment; a conclusion also drawn from a Cochrane review (278) with a summary suggesting the evidence is not robust enough to support

intervention although, as advised already, enhanced vigilance is warranted. Only horseshoe tears show strong evidence for intervention (213).

Education of the optometric workforce must occur before the patient can be counselled appropriately. Detailed guidance on examination protocols and intervals would appear apt given the likely increased incidence with the increasing prevalence of myopia. The College of Optometrist's guidance (399) has a section covering examination of those presenting with flashes and floaters however it fails to provide guidance on how those with peripheral lesions associated with increased risk of RRD should be monitored. The Royal College of Ophthalmologists has guidance on the management of acute retinal detachment while the American Academy of Ophthalmology in the form of preferred practice pattern guidance (PPP) provides more detailed advice on those with PVD, symptomatic and asymptomatic holes, as well as lattice degeneration (436). Regarding lattice degeneration the PPP states, "myopic patients with lattice degeneration and round holes need careful follow-up and must clearly understand the symptoms of progression".

4.17 Strengths and limitations of the study

This prospective cross-sectional study has several strengths including being community-based, with participants of mixed age, having a range of myopia and one examiner.

Limitations related to the cross-sectional design that could be addressed with a longitudinal design include; the determination of whether some lesions are transient or the precursor to others. The age of onset which cannot be ascertained from the current study type. The axial length of the eye is correlated with pathological changes (23). Axial length measurements were not available hence the surrogate measure of SER, which has been shown by many workers to have a strong correlation to axial length, was used (27). Scleral indentation was not utilised, this may have led to some lesions in the far periphery being missed. Scleral indentation is associated

with some discomfort and was not appropriate in the setting of this study. In hindsight, the presence of PVD would have been noted, and the opportunity used to delve deeper into associated symptoms and other possible associations such as the age of myopia onset. The number of participants was close to that estimated using the Gpower3 software. However, some categories had small numbers of participants which is likely to have limited our power to detect statistically significant associations. Using both eyes allowed the assessment of the bilateral nature of lesions but may have confounded some findings due to eyes showing some correlation. This was minimised by using only the right eye when using both would have violated the general assumptions of the standard statistical tests.

Self-selection bias was minimised by asking all myopes if they would take part and having various methods of recruitment. Those with symptoms of posterior vitreous detachment may have been more likely to have agreed to volunteer. Further bias may have resulted from the exclusion of participants with current or previous eye disease.

4.18 Conclusions

This study considered peripheral retinal changes in a group of predominantly white Europeans. This study is unique, in that the more common lower levels of myopia were considered. The prevalences of six peripheral lesions are presented for this population. The locations of lesions were found to match those of previous studies. The study has gone further than previous work in describing not only the presence of optic nerve crescent but also the position which deserves longitudinal study to assess potential as a predictor of myopic progression. The significance of each lesion is highlighted. Pupil dilation is recommended to facilitate the detection of peripheral lesions followed by observation and education of the patient.

4.19 Summary

- 1 in 4 eyes had at least one peripheral lesion.
- Lesions were bilateral in 67 % of cases.
- Pigmentary degeneration was the most prevalent lesion.
- WWOP was associated with the highest level of myopia (SER).
- PD and PSD were most often observed in older eyes.
- Vertical disc height was not associated with peripheral lesions.
- Snail track degeneration was associated with inferior temporal crescent position. This may be a marker for myopic progression.
- Dilated fundus examination facilitates peripheral lesion detection.
- The focus should be on education of practitioners and patients with lesions predisposing to RRD.

Chapter 5 Assessment of retinal vessel calibre

5.1 Chapter Aims

- Measure retinal vessel calibre (RVC) on a group of myopic eyes using semi-automated software.
- Investigate relationships between vessel calibre and level of myopia (SER).
- To ascertain if changes in the central retinal artery equivalent (CRAE), central retinal vein equivalent (CRVE), and the ratio of the artery to vein (AVR) can be detected between routine eye examination intervals.
- To determine if changes in RVC can be measured in eyes with increasing myopia.
- Assess if vessel measures are related to optic nerve head metrics.
- Discuss the use and practicality of RVC measurement in community practice.

5.2 Introduction

The retinal vasculature is easily visualised and as such provides a unique means of determining information about the microvasculature of the body. Both ocular and systemic conditions have been shown to be associated with retinal vessel features (304). A closer inspection of the retinal vessels has the potential to identify signs of disease earlier, as well as increasing the understanding of the pathophysiology of such diseases. Glaucoma, as discussed in section 1.7.2 is more prevalent in myopic eyes and is believed to have a vascular element to its aetiology, justifying the exploration of this aspect of the ocular anatomy.

This study retrospectively investigates associations between retinal vessel calibre to the level of myopia (SER), age, and optic nerve head metrics in a white European population. Secondly, through retrospective longitudinal review, retinal vessel calibre is assessed between routine eye examination intervals. The potential value of retinal vessel calibre as a biomarker is significant when the long pre-clinical phase of many common diseases, during which interventions could be

applied, is considered (307). For this use, a potential biomarker needs to be: reliable, reproducible, easy to use, and cost-efficient (338). Data from several longitudinal studies have indicated that smaller arteriolar width is a predictor of future systemic hypertension in both adults and children (232,244). Venule changes have been linked to future cerebral microvascular disease (301), vascular dementia, stroke and coronary heart disease (304,331). As discussed previously retinal vessel calibre may be a useful biomarker of retinopathy progression in Type 1 diabetes and also for incident diabetes (333). Despite the promising results presented the many factors; methodological, physiological, genetic, pathological, and interactions between them make the confounding factors many and may explain some of the variations in reports.

5.3 Methods and materials

5.4 Participants

This practice-based cross-sectional study included 115 participants selected from study one. Inclusion criteria were two sets of suitable digital retinal images with a refractive criterion of myopia ≤-0.50 D, with no more than -2.00 Dioptres of astigmatism to maintain full field focus for the central retinal imaging and this is the general rule in myopia studies (248, 262). Those with known ocular disease were excluded. The subjects were also selected to fit one of two categories: either no change in SER between the baseline and second visit or myopia that had progressed by ≥ 0.75 D between visits. Age was defined as age at baseline in years. The refraction (SER) by subjective refraction and visual acuity were taken from the participant's records.

5.5 Image analysis

The fundus images were obtained using a Nidek fundus camera (AFC-210, Nidek Co Ltd, Japan), which is described in detail in section 2.1. Due to the study design being retrospective, the images were macula centred, non-stereoscopic, and predominately obtained without mydriasis. The images were exported in JPEG (joint photographic experts' group) format, having been labelled to identify the eye, participant code, and visit number. A new software package from Vito Health Technology was used to measure the retinal vessel width in this study. The package, named IFLEXIS (Vito Health Technology, Mol, Belgium) allows semi-automated quantification of several static blood vessel features including, vessel calibre, fractal dimension, and branching pattern.

The IFLEXIS software was loaded onto a desktop computer to facilitate viewing of the image detail. The colour images were transferred into one folder. The image is converted to red free by deselecting one colour channel to create a binary image. The software locates the optic nerve using a pre-determined circular template that is calculated from the camera settings, the

resolution and image angle which were 12.8 million pixels and 45°. The user can manually adjust the alignment using a mouse. Potential disc locations are defined as the darkest oval area. Failure of the software to correctly locate the optic disc was predominantly due to the presence of peripapillary atrophy, or image artefacts. Confirmation and adjustment of the disc location was carried out for all images before the analysis began. Once the analyse command is given, three further concentric circles are marked on the image to define the area of measurement, termed zone B (300) (Figure 5.1).

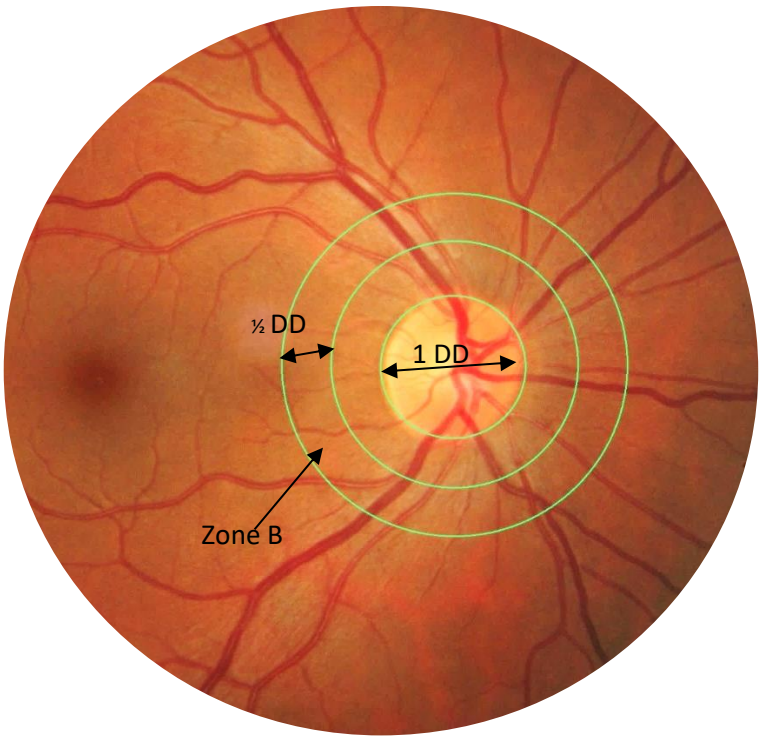


Figure 5.1. Fundus image showing the position of the measurement zone. (zone B).

The software identifies all the arterioles and venules within the measurement zone (Figure 5.2) by creating a binary image to detect the vessel borders. All arterioles and venules with a diameter wider than 40 µm are identified. The output of this process shows the arterioles marked in red, and the venules in blue (Figure 5.3). The operator then checks to ensure the vessel type has been correctly identified. Correction of misclassifications is completed by using the mouse to click the vessel; this highlights the misclassified vessel. A drop-down menu allows selection of the "change vessel type" option. The need to correct the vessel type only occurred

in the darker images, and in those cases, it was always arterioles that had been marked as venules. Once this check is completed, the summary measures are calculated using the modified Knudtson-Parr-Hubbard formula (313) (described in section 5.5). The arterio-venous ratio (AVR) was calculated from the CRAE and CRVE with an AVR of 1 indicating the arterioles and venules had the same diameter.

The optic disc metrics for the vertical disc height, horizontal disc width, vertical and horizontal cup to disc ratios, and crescent width were taken from data collected as part of study 1. The retinal vessel measurements along with disc metrics were corrected for ocular magnification using the method proposed by Bengtsson (344), (1-0.017G) where G was taken as the SER.

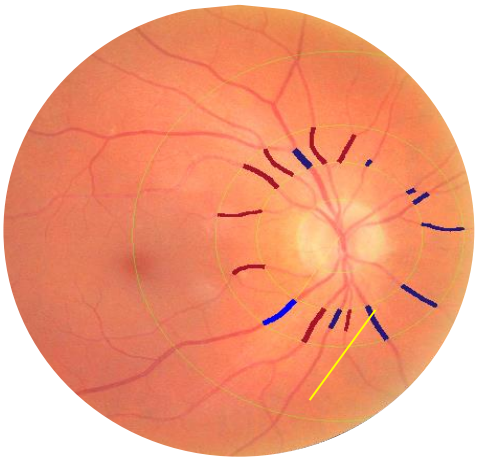


Figure 5.2. Screenshot of the IFLEXIS vessel classification screen. The yellow line from the centre of the disc shows the selected vessel.

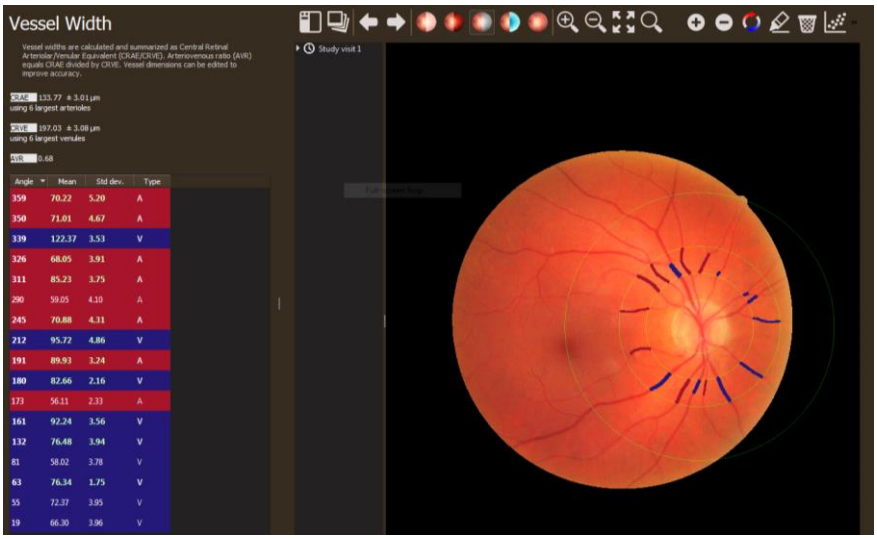


Figure 5.3. Screenshot of the IFLEXIS with individual vessel measurement and summary measures of CRAE, CRVE and AVR.

5.5 Determination of CRAE and CRVE

The introduction of automated and semi-automated methods to assess the diameters of the retinal vessels has seen the formulae for quantification evolve. Parr (438) in 1974 introduced a formula for calculation of the central retinal artery equivalent which considers all arteriolar trunk vessels. Hubbard (300) later added a similar formula for CRVE to allow calculation of the AVR. The formulae compare pairs of narrower and wider vessel diameters from within zone B converting them into estimates of their larger trunk diameters. Pairs of trunk diameters are summarised into the single summary figure of CRAE or CRVE. To deal with the issues of the varying number of vessels in zone B, and the use of constants in the previous formulae that were unit dependent, a modified formula was presented by Knudtson et al. (313). The revised formula (Figure 5.4) aimed to increase the power to detect associations. The issues were addressed firstly by using the six biggest arterioles and venules in zone B, and secondly taking into consideration branch measurements if the trunk width is ≥ 85µm (439). An example of a calculation is shown in table 5.1. Knudtson et al. (313) also showed the number of vessels did not affect the summary measures.

$$W = 0.88 * (w_1^2 + w_2^2)^{\frac{1}{2}}$$

$$W = 0.95 * (w_1^2 + w_2^2)^{\frac{1}{2}}$$

Figure 5.4. Modified equations for calculating CRAE (equation 1) and CRVE (equation 2) (313). *W* is the parent trunk, w_1 and w_2 are the smaller and larger branch diameters.

Table 5.1. Example of calculation for CRAE using measures from the image in figure 5.3. The largest and smallest vessels are entered into equation 1, this is then repeated with the results until there are only two left which then are used to calculate the final summary measure of CRAE. In this case, 133.77µm as shown in figure 5.3 using the software

6 largest arterioles

70.22	$W=0.88\ (89.93^2+68.05^2)^{1/2}$ = 99.24
71.01	$W=0.88\ (85.23^2+70.22^2)^{1/2}$ = 97.18
85.23	$W=0.88\ (71.01^2+70.88^2)^{1/2}$ = 88.29
89.93	$W=0.88\ (99.24^2+88.29^2)^{1/2}$ = 116.89
70.88	$W=0.88\ (116.89^2+97.18^2)^{1/2}$= **133.77 = CRAE**
68.05	

5.6 Ethics

The study abided by the tenets of the declaration of Helsinki. Ethical approval was granted by Aston University Life and Health Sciences, Ethics Committee (project number 642). The research ethics application form has been included in Appendix B. Consent was not sought with this being a retrospective study.

5.7 Sample size calculation

GPower3 was used to calculate sample size for Pearson's correlation coefficient. For a power of 80 %, medium effect size of 0.30, and an alpha value of 0.05 a sample of 84 is required.

5.8 Statistical analysis

The right eye was used in the analysis due to previous reports showing a strong correlation between eyes (312,318). Wong et al. assessed the correlations between right and left eyes concluding that using the mean of both eyes may increase the power to detect differences, but one eye should be sufficient (318). Using an average of both eyes would not be appropriate in this study design. Intra and inter grader correlation coefficients have been shown to be good for several different types of semi-automated software (318,440).

All data were entered into an Excel spreadsheet (Excel 2016 Microsoft, Washington), before analysis using SPSS 23 (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp). Myopia and age were treated as continuous variables due to the small sample size. The data for CRAE and CRVE where shown to be normally distributed using the Shapiro Wilk test. Paired sample t-tests were used to compare differences between the pairs of measures and independent sample t-tests were used to compare the differences between the two categories. Simple linear regression analysis was conducted to identify possible relationships between the vessel measurements, myopia, and age. Partial correlations and multivariate analyses were used to identify significant predictors and change per unit increase in ONH parameters.

5.9 Results

From a total of 230 images (115 participants), 216 images from 108 participants were suitable for analysis. The images rejected at this stage were due to insufficient vessel pairs within the measurement zone.

The mean age at first image capture was 42.4 years SD±15.1 (range 13-74 years) with a mean SER of -3.82 D SD±2.2 (range -0.50 to -9.63 D) and logMAR visual acuity of 0.0 or better. Eighty females (74.1 %) and 28 males (25.9 %) were included. The ethnicity of the group was white European. The participants were divided into two groups; those with no change in SER, and those in which the myopia (SER) had increased by at least 0.75 D (change group). The mean interval between images was 44.5 SD±20 months (range 11-83 months). At the time of the first image there was no difference in mean SER between the change and no change groups (p=0.132), however, at the time of the second image, the difference in mean SER was statistically significant (p<0.01). There was a statistically significant difference in the mean age of the two groups (p=0.02), the no change group being older. Table 5.2 summarises the characteristics of the groups.

Table 5.2. Participant characteristics of the change and no change groups.

	No change n61		Change n47		
	Mean	SD ±	Mean	SD ±	p
Age (years)	46.6	11.8	37	17.2	**0.02**
SER (baseline)	-3.55 D	2.2	-4.19 D	2.2	0.132
SER (after image 2)	-3.55 D	2.2	-5.57 D	2.4	**<0.01**
Change in SER (D)	0.00		-1.39	0.65	**<0.01**
Time between images (months)	38.4	19	52.4	16.7	**<0.01**
M/F	13 48		15 32		X^2*0.305

p-value calculated from independent samples t-test or *chi-square

The mean CRAE for the first image was 150.2 µm SD±27, CRVE 233.2 µm SD±31.5 and AVR 0.65 SD±0.1. At the time of the second image, the mean CRAE was 145.3 µm SD ±24, CRVE 231.7 µm SD ±38.6, and AVR 0.63 SD±0.1. The differences in RVC measures between the two visits are shown in table 5.3. All three measures were lower at the time of the second image, but only the

CRAE showed a significant difference (p<0.01). The difference in CRAE and CRVE before and after correction for ocular magnification was assessed using a paired t-test. The difference was significant (t = -17.208, df 107, p < 0.01 and t = -17.926, df 107, p < 0.01).

Table 5.3. Summary of mean vessel calibre for the two images corrected for ocular magnification (groups combined).

Variable	Visit 1	SD	Visit 2	SD	Difference	p
CRAE (µm)	**150.2**	27	**145.3**	24	-4.9	**0.024**
CRVE (µm)	**233.2**	31.5	**231.7**	38.6	-1.5	0.651
AVR	**0.65**	0.1	**0.63**	0.1	-0.2	0.256

paired t-test

Table 5.4 shows the visits split by the "change" and "no change" groups. None of the RVC measures in the change group showed significant changes between the visits. In the group showing no change in SER, the CRAE and AVR both had changed significantly (p<0.01 and p = 0.019).

Table 5.4. Summary of vessel measures between the no change and change in SER.

NC n61	Visit 1	SD	Visit 2	SD	p
CRAE (µm)	**152.6**	21.9	**145.6**	20.7	**<0.01**
CRVE (µm)	**235.4**	29.8	**235.3**	34.8	0.983
AVR	**0.65**	0.1	**0.62**	0.1	**0.019**

C n47	Visit 1	SD	Visit 2	SD	p
CRAE (µm)	**147.1**	32.5	**144.9**	27.4	0.570
CRVE (µm)	**230.4**	33.9	**227.1**	42.9	0.554
AVR	**0.64**	0.1	**0.65**	0.1	0.761

NC-no change in SER, C-change in SER, p-value calculated from paired t-test

The level of myopia and age were not significantly different between the sexes. Table 5.5 shows the relationship between sex and RVC. When the participants were separated by sex, the CRAE was larger in the females, while the CRVE was larger in the males. However, only the AVR was found to be significantly different (p = 0.04), being greater in the females (0.66 SD±0.1 and 0.62 SD±0.1).

Table 5.5. Showing differences between sexes, mean and SD. Independent samples t-test.

	Female (n=80)	Male (n=28)	p
SER (D)	-3.90 ±2.3	-3.62 ±1.8	0.529
CRAE (µm)	152.75 ±26.8	143.1 ±27	0.103
CRVE (µm)	232 ±30.6	234 ±34.6	0.892
AVR	0.66 ±0.1	0.62 ±0.1	**0.04**
AGE (years)	42.7 ±15.2	41.5 ±15	0.703

5.10 Retinal vessel calibre, myopia, and age

Linear regression analysis was used to assess relationships between vessel measures, level of myopia, and age (Figures 5.5-5.10). The absolute measures of CRAE and CRVE are plotted both before and after correction for ocular magnification. No significant associations were observed although the trend after adjustment for magnification was wider RVC as the level of myopia (SER) increased. As reported elsewhere (386) the AVR did not change after magnification correction.

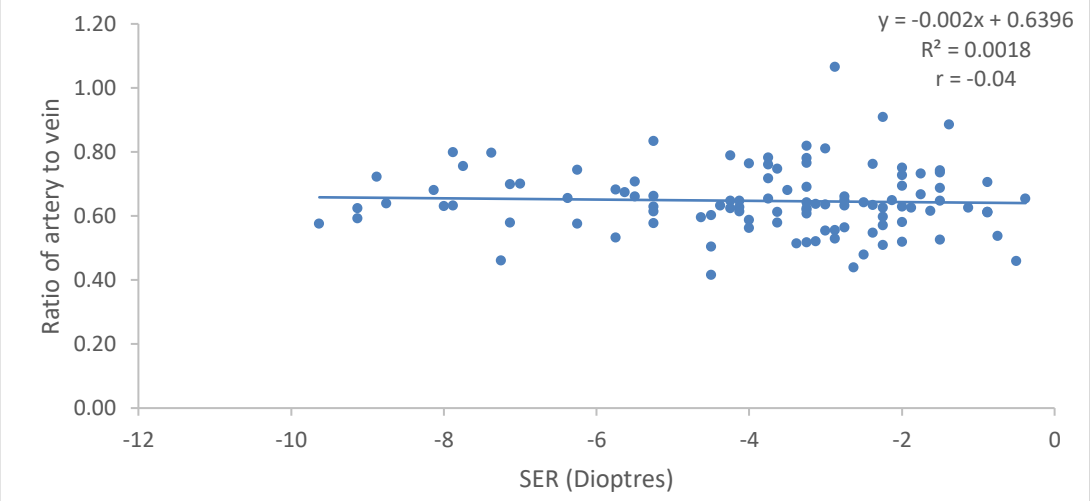


Figure 5.5. Scatterplot showing level of myopia (SER) at first image and the ratio of the artery to vein.

Partial correlation analysis was used to explore the relationship between myopia (SER) and the three vessel measures while controlling for age. Controlling for age did not affect any of the relationships. When the associations between age and CRAE, CRVE and AVR, controlling for myopia, were assessed all three showed a slightly weaker correlation (r= -0.06, -0.145 and 0.003 respectively).

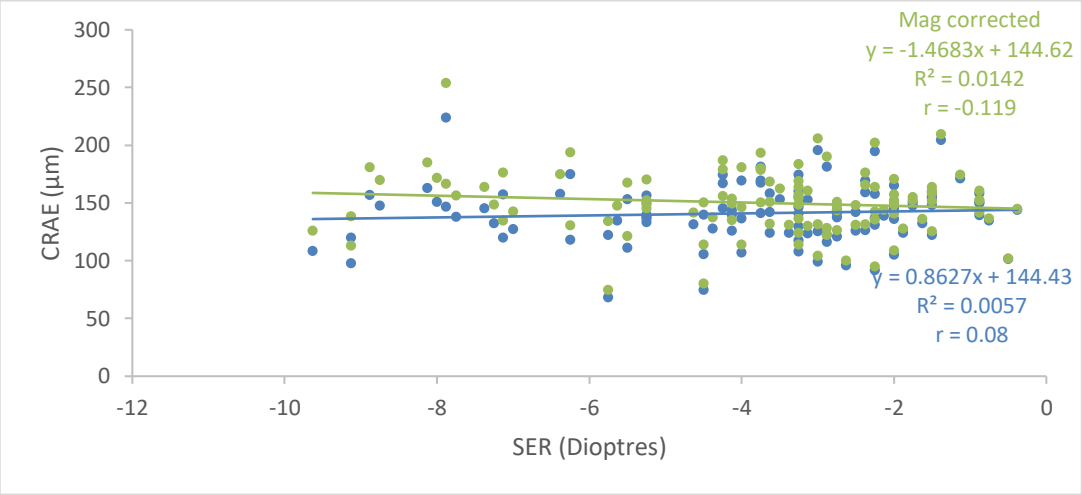


Figure 5.6. Scatterplot showing level of myopia (SER) at first image and CRAE. Grey line/dots corrected for ocular magnification and black line/dots uncorrected.

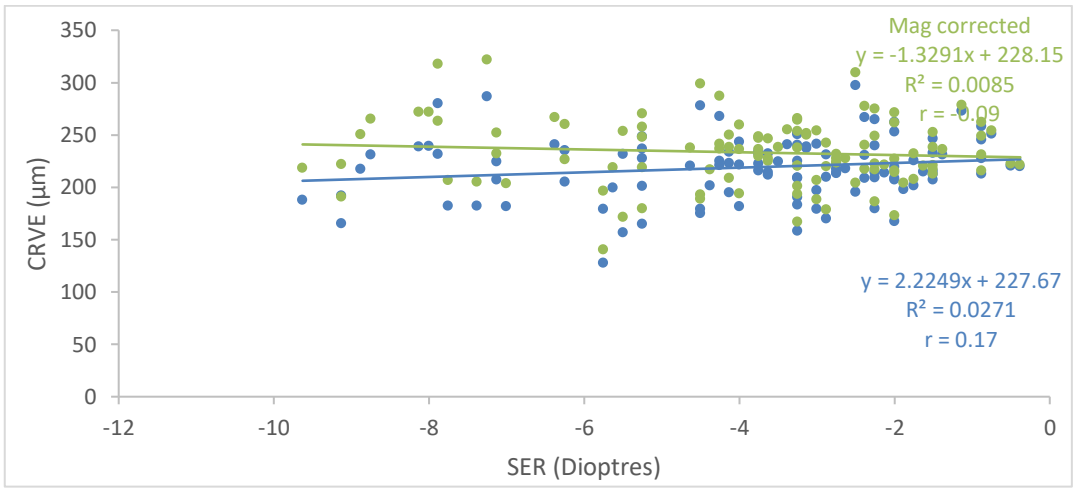


Figure 5.7. Scatterplot showing the level of myopia at first image and CRVE. Grey line/dots corrected for ocular magnification and black line/dots uncorrected.

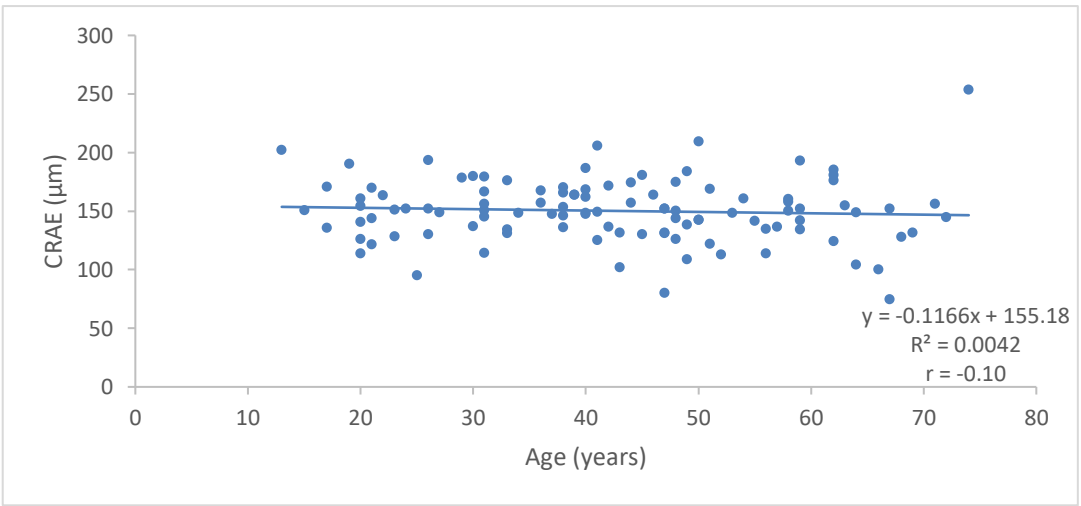


Figure 5.8. Scatterplot showing age at first image plotted against CRAE.

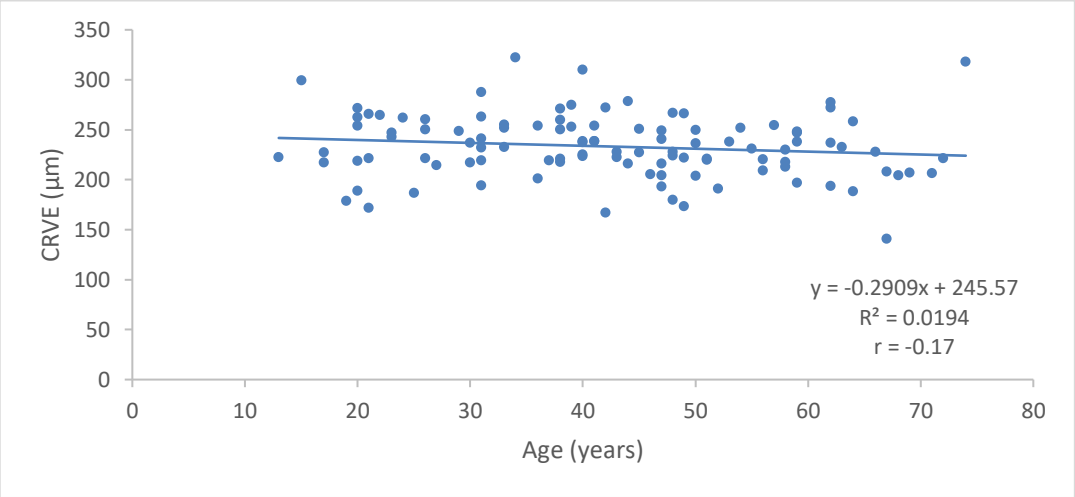


Figure 5.9. Scatterplot showing age at first image plotted against CRVE.

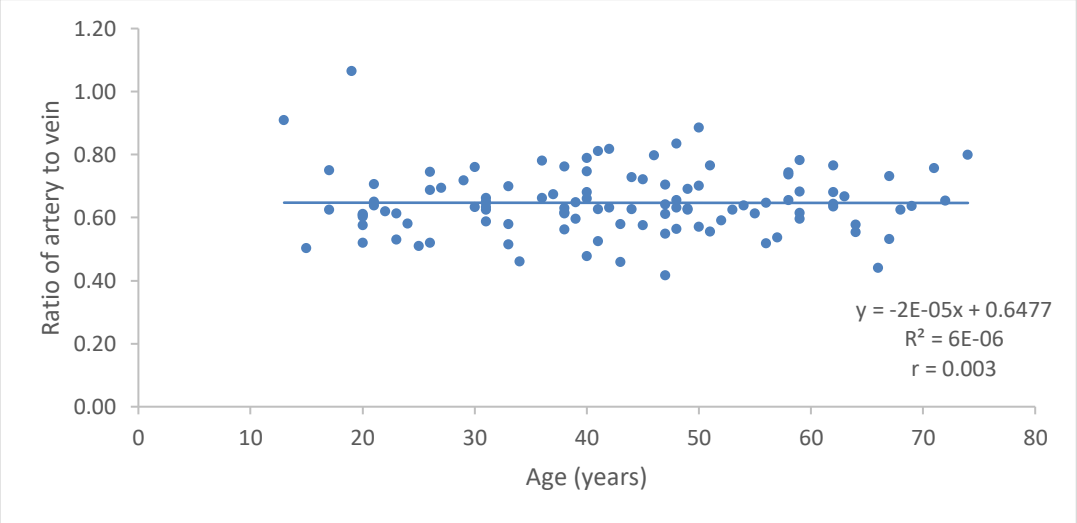


Figure 5.10. Scatterplot showing age at first image plotted against the ratio of the artery to vein.

Multivariate modelling controlling for SER, age, sex, and the vessel partner accounted for 33.4 % and 32.4 % of the variability for CRAE and CRVE. (Table 5.6). With CRAE as the dependent variable, sex ($p = 0.047$) and fellow vessel type ($p<0.01$) were significant predictors. In the model with CRVE as the dependent variable, the fellow vessel partner was the only significant predictor ($p <0.01$).

In the second model without the fellow vessel type the power of the model to predict the RVC reduced, and the models for all three vessel measures became non-significant ($F=1.5$ $p=0.213$ $R^2=0.04$, $F=1.0$ $p=0.396$ $R^2=0.03$, $F=1.3$ $p=0.286$ $R^20.04$); the multiple regression was not pursued. A strong correlation between the CRAE and CRVE existed ($r=0.56$, $p<0.01$).

Table 5.6. Multiple regression summaries for retinal calibre measures controlling for SER, age, sex, and fellow vessel.

	CRAE		CRVE	
	R^2 0.334		R^2 0.324	
	β	p	β	p
SER	-0.059	0.464	-0.031	0.702
Age	0.005	0.948	-0.099	0.225
Sex	-0.162	0.047	0.099	0.230
CRAE			0.556	**<0.01**
CRVE	0.548	**<0.01**		

5.11 Disc metrics and retinal vessel measures

Linear regression analysis was performed to explore the relationships between vessel calibres and optic nerve head metrics obtained from study one (Table 5.7, 5.8). Before any parameters were corrected for ocular magnification vertical disc diameter showed borderline associations with CRAE and AVR (r = -0.19, p = 0.06 and r = -0.17, p = 0.09). When all parameters had been corrected for ocular magnification the same two borderline relationships were still the only relationships approaching statistical significance (r = -0.17, p = 0.08 and r = -0.17, p = 0.08). The relationship between RVC and vertical disc diameter are shown in figures 5.11-13. Pearson's correlation was not significant agreeing with inspection of the scatterplots. Horizontal disc diameter, vertical and horizontal cup to disc ratios, crescent width, or disc area all showed no correlation to RVC measures. CRVE generally showed the weakest relationships with the vessel measures.

Table 5.7. Results of bivariate Pearson's' correlations with no parameters corrected for ocular magnification.

	VDD	HDD	VCDR	HCDR	CW	D area
CRAE	-0.185	-0.07	-0.021	-0.057	0.16	-0.144
	p 0.06	*p 0.463*	*p 0.826*	*p 0.555*	*p 0.10*	*p 0.138*
CRVE	-0.05	-0.12	-0.048	-0.061	0.104	-0.09
	p 0.61	*p 0.219*	*p 0.625*	*p 0.964*	*p 0.284*	*p 0.377*
AVR	-0.166	0.046	0.056	0.02	0.098	-0.073
	p 0.09	*p 0.635*	*p 0.567*	*p 0.841*	*p 0.315*	*p 0.451*

VDD-vertical disc diameter, HDD-horizontal disc diameter, VCDR-vertical cup to disc ratio, HCDR-horizontal cup to disc ratio, CW-crescent width, D area-disc area.

Table 5.8. Results of bivariate Pearson's correlations with both vessel and disc metrics corrected for ocular magnification.

	VDD	HDD	VCDR	HCDR	CW	D area
CRAE	-0.17	-0.06	-0.07	-0.10	0.132	-0.136
	p 0.08	*p 0.554*	*p 0.496*	*p 0.31*	*p 0.17*	*p 0.160*
CRVE	-0.032	-0.10	-0.11	-0.11	0.07	-0.07
	p 0.744	*p 0.286*	*p 0.257*	*p 0.253*	*p 0.472*	*p 0.463*
AVR	-0.17	0.05	0.056	0.02	0.09	-0.08
	p 0.08	*p 0.630*	*p 0.567*	*p 0.841*	*p 0.334*	*p 0.42*

VDD-vertical disc diameter, HDD-horizontal disc diameter, VCDR-vertical cup to disc ratio, HCDR-horizontal cup to disc ratio, CW-crescent width, D area-disc area.

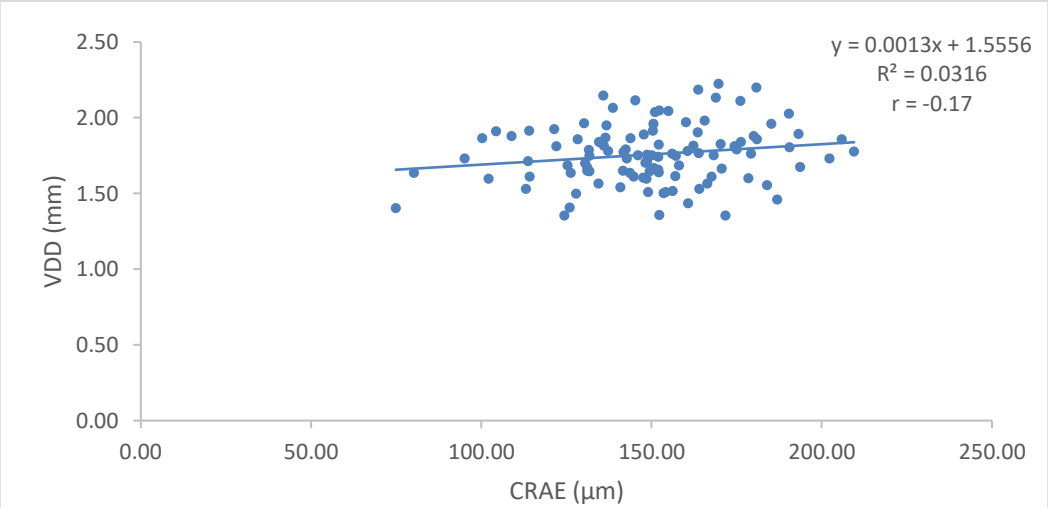


Figure 5.11. Scatterplot showing the relationship between CRAE and vertical disc diameter.

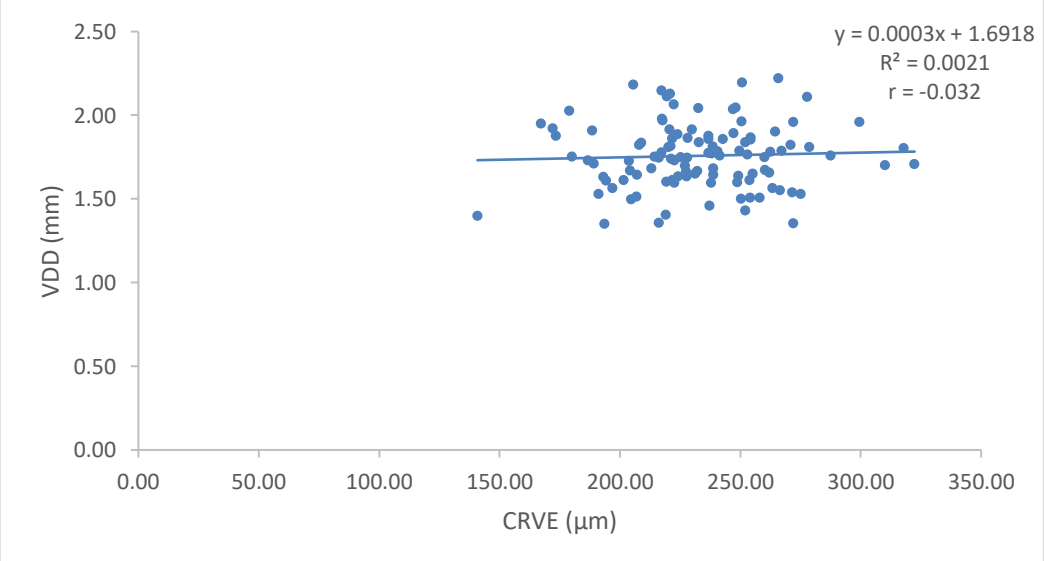


Figure 5.12. Scatterplot showing the relationship between CRVE and VDD.

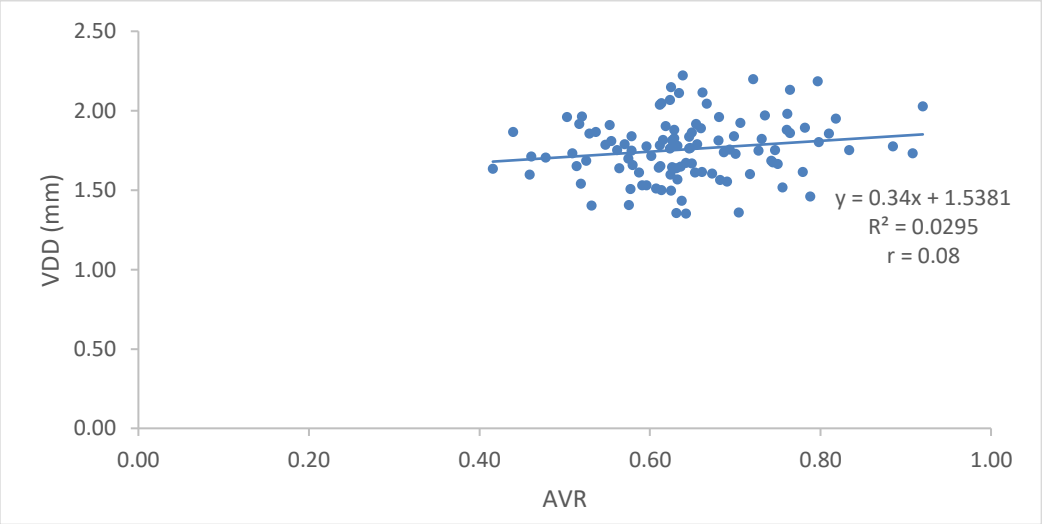


Figure 5.13. Scatterplot showing the relationship of crescent width and AVR.

Multiple regression models were used to assess possible predictors for RVC. Variables used in the model were SER, age, sex, and each optic nerve head measure in turn. None of the models were significant with a summary of the results shown in table 5.9.

Table 5.9. Summary of models to assess potential predictors of RVC. All control for SER, age, sex, and each optic nerve head measure in turn as the independent variable.

	Adjusted CRAE			Adjusted CRVE		
	F	p	R^2	F	p	R^2
VDD	1.935	0.110	0.070	0.749	0.561	0.028
HDD	1.170	0.329	0.043	0.972	0.427	0.036
VCD	1.259	0.293	0.035	0.926	0.431	0.026
HCD	1.232	0.302	0.034	0.906	0.464	0.034
HCDR	1.219	0.307	0.045	0.862	0.490	0.032
VCDR	1.143	0.341	0.043	0.878	0.444	0.035
CW	1.693	0.157	0.062	0.939	0.444	0.035
Disc area	1.555	0.192	0.057	0.825	0.512	0.031

CRAE and CRVE as dependent variables.

5.12 Discussion

The ease with which the retinal vasculature can be viewed, measured, and monitored non-invasively is unique. In this study, the widely used measures of AVR, CRAE, and CRVE were used to quantify the retinal vasculature in a group of white Europeans of mixed age across a range of myopia (SER).

The mean CRAE (150.2 µm) sits within the ranges of CRAE (133.6 to 169.8 µm) reported to be normal in a review by Iwase et al. (382), as did the mean CRVE (233.2 µm), suggested range (202 to 242.6 µm) and AVR (0.65) calculated from the CRAE and CRVE.

The study participants were ethnically homogeneous with white Europeans only and biased towards females. The demographics of Suffolk are 96 % white European (410). Females have been shown to attend for routine health examinations more frequently (424). RVC has been investigated in relation to sex, and ethnicity by several workers. Cheung (352) found no sex difference in the vessel calibres of children. Other studies have shown females to have larger vessel calibre over a range of age groups (316,330,332). In this study, the CRAE and AVR were greater in females, but only AVR was significantly so. The imbalance of the sex groups in the current study may have reduced the power to detect differences. The age and level of myopia were similar between sex groups. It has been suggested biological sex differences are responsible for differential vessel responses to pathologies (319). Wellman et al. (441) postulated female hormone changes to be implicated which fits with the average age of female in this study.

Wong et al. (318) showed myopic refraction to be associated with smaller vessel diameters, the arterioles and venules reducing by 2.5 µm and 3.3 µm for each dioptre increase in myopia (SER) after correcting for ocular magnification, and controlling for age and sex. Cheung et al. (352) reported no association with refraction after adjustment for magnification. Gopinath (303) showed axial length to be related to vessel calibre even when the eye was emmetropic which

suggests knowledge of the SER may not be relevant when calculating the effect of magnification. The results of this study conflict with previously reported work in that the magnification corrected measurements for CRAE and CRVE were seen to increase with increasing myopia ($r = -0.12$, $p= 0.220$ and $r = -0.09$, $p = 0.342$). Possible explanations for this unexpected trend include the possibility that more of the participants in the current study were refractive myopes, rather than axial myopes. This is supported by the finding that eyes with greater corneal curvature are associated with wider retinal vessels (303). As in previous studies considering RVC (342,386), ocular magnification was corrected using Bengtsson's formula. Lim et al. (349) using Bengtsson's correction on measurements obtained with OCT retained a statistically significant inverse relationship for both axial length and SER after correction for ocular magnification. A possible explanation for the narrowing of both arteriole and venule in myopic eyes is mechanical stretching as the axial length increases (23,281). In addition to mechanical factors, biological influences have been implicated based on observations of decreased retinal pulse and blood flow in myopes (269).

Due to the many confounding factors, both intrinsic and extrinsic, the participants of this study were selected to have had more than one visit to determine if changes in RVC could be detected over the usual period between eye examinations. It was hypothesised that the group whose myopia (SER) had increased would show a greater change (decrease) in vessel calibre than the group whose myopia had remained stable. It has been shown that with increasing myopia the vessel complexity reduces presumably as the vessels straighten as a result of stretching (310). The arteriolar and venular calibre were constant in the change group whereas statistically significant changes were found in the no change group with a decrease in CRAE, and an increase in AVR. Possible reasons for these findings may be the small sample size along with the lack of information on possible systemic confounders, measurement errors and the older age of the no-change group. The measure of minimum detectable change has been discussed (382) with 4 µm being quoted for CRAE and CRVE which is similar to the significant difference in mean CRAE

between the two sets of images. Repeatability is important in both research and clinical practice. Several workers have assessed the repeatability of retinal vessel measurements (Table 5.10) showing strong agreement both intra and inter-examiner (300,442).

Table 5.10. Showing the measures of agreement in terms of the intra-class correlation coefficient (ICC).

Study	CRAE	CRVE	Software	Number of images assessed
Li et al.(351)	0.95	0.96	IVAN	50
Heitmar et al.(306)	0.97	0.98	Vessel map	2
Drobnjak et al.(332)	0.8	0.9	IVAN	Not stated
Hubbard et al. (300)	0.69	0.89	manual	140

Studies of vessel calibre can be complicated, especially in older populations, even without known pathology, where age-related physiological changes may confound findings (305). This has made collecting normative results, which are essential for clinical use, difficult. Several workers (303,351,352) have used infant participants free of age-related vessel changes. It could be argued infant's eyes are different from adult eyes as they are still developing. Samarawickrama et al. (354) address this by using an adolescent cohort arguing eye growth is almost complete at this age, and they are less likely to have the vascular diseases of adults. Accuracy is also affected by optical issues. Some workers address ocular magnification, while camera magnification is often not discussed. The most common method reported is using the formula derived by Bengtsson (344), M = (1-0.017G), where G is the spectacle power. This method has been shown to be less accurate, especially with greater axial length, than methods using more ocular parameters (378). A recent report by Iwase et al. (382) suggests the need for individualised correction for the camera and ocular magnification using a model eye based on Gullstrand's data with paraxial ray tracing. This study found a significant difference after magnification correction but feel the suggestion by Iwase to have too many limitations for clinical practice. Firstly, it requires a telecentric camera, secondly a camera manufacturer willing to share the correction factors. The adjustment is only applicable if the prescription is within the range -13 to +12 D and not appropriate for those with intra-ocular lenses. The eye must be correctly positioned, and

the focus must be the same across the field with images centred on the optic disc (439). Due to the retrospective nature of this study, the images were centred on the macula. It has been argued that correction for magnification is not necessary for epidemiologic purposes (386), but for individual risk assessment, absolute measures would be ideal. A further source of measurement error is the need for the vessels to be measured at a constant distance from a reference point. Some vessel measurement systems base the calibration for measurement on disc size, often taken as 1.8 mm; the average taken from population-based studies (443). It was shown in study one that disc size varies significantly (0.9 to 2.2 mm). If the disc is not 1.8 mm in size the measurement zone distance from the centre of the disc is constant. However, the distance from the edge of the disc is not, which has the potential to affect the vessel size measured.

A myopic eye is often described as elongated and stretched (2). This led to the investigation of how features of the optic disc relate to retinal blood vessel calibre. Several optic disc parameters were investigated in relation to RVC. It was hypothesised that narrower vessels would be associated with signs of eye growth such as crescent formation based on the observations in study one. Larger discs have been linked to higher myopia in some studies (219,234), so on these grounds, an association would sound plausible although in conflict with others that describe smaller optic discs being associated with smaller RVC (340,354). Despite the current study not finding the expected relationship between narrower vessels and myopia, the relationship between vertical disc height and CRAE showed borderline significance ($r = -0.17$, $p = 0.08$) although visual inspection of the scatterplots failed to show any association. No correlation was observed for CRVE ($r = -0.032$, $p = 0.74$). Several workers have assessed vertical disc size in relation to RVC. Lee et al. (340) found narrower vessels to be associated with the smallest optic discs in an older population which corresponds with the findings of Cheung et al. (348) in healthy children. In contrast, Neubauer (426) and Lim (342) reported no significant association between vertical disc size and retinal vessel calibre. Differences may be due to sample size variance as the

actual differences are often minimal and arguably not clinically significant. Inherent ethnic differences in the vascular structure should also be considered. Different image capture methods are used for optic nerve head metrics across studies with OCT measurements often being smaller than planimetry of digital images (349).

Horizontal disc and parapapillary parameters are of interest due to the area of eye stretch typically being temporal to the optic disc along the horizontal meridian (2). In study one a moderate correlation between the level of myopia (SER) and crescent width ($r=-0.406$ $p<0.01$) was observed. Nakazawa et al. (240) showed measurable growth in the crescent area through analysis of serial photographs in those with progressing myopia. Thinner optic disc rims have been shown to be associated with narrower arterioles and venules (342). In this study, no associations between crescent width or horizontal disc width and RVC were observed.

Lim (342) considering disc relationships to vessel calibre in Asian children found larger vertical CD ratio to be associated with smaller venules but not arterioles. Cheung (352) in a similar population found no relationship between RVC and VCDR. Given the primary motivation for investigating such relationships, Amerasinghe et al. (264) found a larger vertical cup to disc ratio to be associated with narrower vessels in adults with glaucoma. This supports the vascular mechanism in the aetiology of glaucomatous optic neuropathy. The use of OCT allows the thickness of the macula and nerve fibre layer to be determined, both a thicker macula and nerve fibre layer have been shown to be associated with wider vessels which has been postulated to be due to the greater metabolic demand leading to wider vessels (354).

The ratio of the artery to vein is mainly independent of refraction and is a useful summary measure when magnification corrections cannot be applied (300,317,318). The results of this study confirmed that AVR was not affected by ocular magnification correction. Several high-quality studies have reported AVR in relation to prediction of hypertension, stroke, and coronary heart disease (300,317). AVR was assessed against, SER, age, and disc parameters. No significant

associations with SER and age were observed. Vertical disc height showed the strongest relationship to AVR ($r = -0.17$, $p = 0.08$) whereas all other optic nerve measures showed no associations. No other studies report disc parameters in relation to AVR using planimetry of digital images.

As mentioned previously, the use of AVR has the significant disadvantage of being affected by changes in both arterioles and venules in response to different physiological and pathological factors. A venular calibre increase or decrease in arteriolar calibre would change the AVR in the same direction hence the suggestion of CRAE and CRVE being more appropriate measures (314). Like knowledge of the vertical disc height increases the clinical usefulness of the cup to disc ratio, knowing the arteriole and venule size would make the AVR more relevant in comparing change over time.

This study used a new vessel measurement package (IFLEXIS, Mol, Belgium). IFLEXIS software has not been reported in any published studies to the best of our knowledge. The software was used due to the ease of use, its compatibility with different cameras, the ability to load the images in various file formats, and the availability of the program. The difference between the findings of this study to those reported previously may be partially due to the software, although as mentioned earlier it is reassuring the RVC measures were in the range similar to previous studies (382). Validation of the software and comparison with other more widely used packages is needed. Yip et al. (444) compared three frequently used vessel measurement systems: Singapore 1 Vessel assessment (National University of Singapore), Integrative Vessel Analysis (University of Wisconsin, Madison) and Retinal analysis (University of Wisconsin, Madison) finding poor agreement in absolute measures. Despite finding a poor agreement the associations with systemic conditions, such as total cholesterol, and mean arteriole blood pressure, remained. To facilitate useful comparisons between the systems an algorithm was developed with which the difference in results between the systems was no longer significant. Axial length appears to

be a significant factor in agreement of measures using algorithms, with more error occurring in longer eyes (444). Hence knowledge of axial length would be beneficial.

The IFLEXIS software failed to identify the optic disc location correctly in 60 % of cases which corresponds to that reported by Iwase et al. (382) using similar software. The reason for this failure in the current study was mainly due to the participant details being marked on the top of the image which confused the software. A manual correction was necessary in these cases. Misidentification of vessel type occurred in only 6 % of cases, Iwase et al. (382) found 20 % were misclassified in Asian eyes. The images in the current study, mainly obtained through non-dilated pupils, were often darker making it harder for determination of arterioles due to the lower contrast with the background. This has been suggested as a source of error in ethnicities with greater pigmentation. Such challenges, along with the need to obtain accurate measures in sub-optimal quality images has driven the development of more sophisticated vessel detection strategies (312). Choosing the right eye helped maximise image brightness as the right eye image is generally captured first. Post flash miosis often affected the quality of the left eye image. Variations due to heartbeat have been reported to be up to 15 % (445) and ideally requires photography to be synchronised to the cardiac cycle (300). With this study being retrospective and practice-based this control was not possible.

Due to the challenge of establishing population norms individual changes over time may be a more sensitive indicator of developing clinical disease, especially when used as part of a risk assessment system. In contrast, Schuster et al. (317) suggest a snapshot may have clinical applicability in their report. They looked at the relationship of commonly used cardiovascular risk assessments; the PROCAM score, and SCORE index which give an index of cardiovascular mortality, finding an inverse association with AVR and CRAE (317). Bhuiyan et al. (442) conclude that using RVC measures along with consideration of age, sex, smoking history, diabetic status, and blood pressure can increase the ability to detect CVD at an earlier stage. It has been

suggested for this purpose magnification correction would not be necessary (318). Drobnjak in a recent study predicts vessel assessment will become part of routine practice in respect of determining those who will develop diabetic retinopathy (332).

A primary aim of this practice-based study was to determine if retinal vessel assessment could add value to community practice. The three key questions are: is the available evidence strong enough, are the techniques sensitive enough to detect clinically significant changes and is it practical to implement vessel measurement into routine practice. For retinal vessel calibre measurement to fit into community practice, there needs to be a paradigm shift. Hubbard (300) in the seminal 1999 paper on methods for measuring vessels states as a limitation, *"measurement of AVR using a computerised image processor is practical in a research setting, but currently could not be done in a clinical setting"*. This is no longer the case with only a few issues remaining such as variation between methods regarding calibration and clarifying the position of the measurement zone. The next step would be the education of the optometric community. Currently, qualitative vessel assessment is the norm and factors such as nipping and changes in vessel reflex are the most commonly considered aspects along with the subjective determination of AVR (224). The author has anecdotally found many optometrists are unaware of the terms CRAE and CRVE, and often the only known condition affecting the retinal vasculature is hypertension. The third step to creating value is the need for integrated working with other health professionals through clearly defined referral pathways to facilitate the use of pre-clinical signs to reduce both ocular and systemic morbidity. In summary, barriers remain, and, in my opinion, the greatest need is for clear evidence of association and identification of the key confounders to control driven by cross speciality research groups.

5.13 Strengths and limitations of the study

Strengths of this study include having a community-based population, a semi-automated computer-assisted method of measurement with a single grader. There are several limitations and shortfalls of this study that should be mentioned. Firstly, magnification correction using axial length, and having a camera manufacturer who would provide correction factors would allow greater confidence in the use of absolute measures. Secondly, the study size is small which is likely to affect the statistical power of the observations. The design, being retrospective and cross-sectional has its disadvantages such as limited control of all possible confounders and inability to infer causality. Exclusion of those with a history of cardiovascular disease recorded was a possibility, but others may have had yet to be diagnosed. Smoking status is not usually recorded unless age-related macular degeneration is a concern. A prospective design would have allowed these factors to have been considered along with current blood pressure status.

5.14 Conclusions

In conclusion, this study has documented the relationships of age, level of myopia (SER) and optic disc parameters to retinal vessel measures in a healthy white European group of mixed age. Despite some limitations in design, the study shows the potential of using vessel analysis software as part of community eye care. The model of optometric practice is generally recall driven facilitating longitudinal assessment of CRAE and CRVE using semi-automated computer software. Quantitative vessel measures could be combined with other examinations to increase the power to detect subtle changes before more obvious signs manifest, once the disease process is more established.

5.15 Summary

- Myopia (SER) and age were not related to RVC.
- No sex difference was observed between CRAE and CRVE.
- Fellow vessel type was the strongest predictor of RVC.
- Optic nerve head parameters were not significantly associated with RVC.
- Vessel quantification is a practical assessment to use in community optometric practice.
- More work is needed to identify key confounders and set protocols for clinical use.

Chapter 6 Conclusions and future work

6.1 Conclusions

Myopia is one of the most common ocular conditions (7) and is recognised as a major cause of visual impairment worldwide (23). It is not only those with high myopia that are at risk of visual loss. The more frequently occurring lower levels of myopia are associated with increased risk of visual impairment from common conditions such as glaucoma and retinal detachment. This has led to the suggestion there is no safe level of myopia (32). The prevalence of myopia is increasing worldwide with it being labelled an epidemic in some regions (26). With this increasing prevalence, related pathology would also be expected to become more prevalent.

The common goal is to identify those eyes in which myopia will progress so that timely interventions can be implemented to minimise the ultimate level of myopia. Many studies have looked at different aspects of myopia development in search of the key factors in relation to lifestyle, environment, genetics, anatomical, and biochemical pathways. In most cases as myopia increases the eye stretches. When a threshold is reached, signs of this stretch may be seen in the fundus. These signs include crescent development, super traction, and generalised fundus tessellation. Some of the structural changes seen ophthalmoscopically occur once the progression in terms of SER has ceased; however, this is not always the case. Strang et al. (147) proposed three patterns of eye stretch associated with increasing myopia: global expansion, posterior pole, and equatorial stretching. It is agreed this model is an oversimplification. However, it demonstrates that some areas may respond differently to the stress of increasing myopia.

This thesis describes four studies which aimed to investigate the impact of myopia and age on different regions of the retina. Myopic changes to the optic nerve head may increase susceptibility to ocular disease and complicate the assessment, which may result in the delayed detection of glaucoma. Peripheral lesions may increase the risk of retinal detachment.

Chapter three, the first experimental chapter, focused on the optic nerve head and adjacent peripapillary area. The optic nerve head is the key feature examined during an eye examination, providing a wealth of information. The myopic optic nerve shows several characteristic features and is also associated with an increased risk of glaucoma (263). Several disc metrics from the 400 participants were assessed in relation to the level of myopia (SER), age and sex. A 200 % variation in vertical disc diameter was observed, which agrees with previous reports (415). After correction for ocular magnification, this study failed to find a relationship between vertical and horizontal disc diameters with myopia or age. Several ONH metrics were larger in the males. However, only the vertical and horizontal cups and both cup to disc ratios were significantly larger. Crescent formation may indicate a regional weakness in the tissues of the eye. A discernible crescent was observed in 83 % of eyes; most were located on the temporal margin of the disc. Those with inferior-temporally located crescents had significantly higher levels of myopia (SER) than eyes without crescents, and eyes with temporal crescents. This may indicate that the position of crescent could be useful as a predictor of future myopia progression. 92 % of eyes in the highest category of myopia (<-8.00 D) had a crescent compared to 79 % in the lowest category. After exclusion of crescents less than 10 % of disc width, the size Curtin classes as congenital, 45 % in the lowest category of myopia and 88 % in the highest category still had a crescent. The crescent size was found to reduce with increasing disc size. Increasing age was associated with wider crescents, a relationship that remained after controlling for myopia.

Tilted discs judged subjectively from the two-dimensional digital images were present in 9 % of eyes. The level of myopia was found to be significantly greater in those with tilted discs. This study confirmed the findings of Tong et al. (431) in which both vertical and horizontal disc size was smaller in eyes with tilted discs. Neither sex or age was related to the presence of tilt. The crescent in eyes with tilted discs was primarily observed in the inferior-temporal aspect and was significantly larger than eyes without tilted discs.

The second study of chapter 3 assessed ONH features through retrospective longitudinal review. This subgroup of 267 participants from study 1 included both those whose myopia had remained stable and those who had progressed. The mean interval between visits was 43 months. Only the vertical and horizontal cup diameters and crescent width increased significantly between the images. The second measure of crescent width, selected to negate magnification issues, was the quotient of the maximum crescent width to vertical disc diameter. The finding of no significant change in VDD between images validates this as an accurate measure of crescent change when magnification correction is not possible. The short time interval between some images and measurement errors resulting from less clear second images may have reduced the effects observed. Small differences in the crescent width were found in both eyes with an increase in myopia, and eyes with no increase. This may be due to atrophic as well as myopic stretch mechanisms. It is not possible to differentiate between age and myopia related peripapillary changes from fundus images. However, newer forms of OCT allow investigation of the microstructure and possible differentiation of myopic stretch and age-related atrophy (232).

Study three attempted to understand the relationship between central and peripheral retinal changes in myopic eyes in a prospective study of the peripheral retina. The peripheral retina is a vast area compared to the ONH and posterior pole. Retinal detachment is a serious cause for concern due to the risk of total blindness. Several of the lesions investigated in the study are associated with an increased risk of retinal detachment; most notably lattice degeneration. This study involved assessment of the fundus through dilated pupils. Twenty-seven per cent of eyes had at least one peripheral lesion. The level of myopia and age were not significantly different between those with any lesion and no lesion. Pigmentary degeneration was the most frequently observed lesion (7.8 %), followed by lattice degeneration (5.8 %), and WWOP (5.8%). Retinal holes were found in 10 eyes (3.9 %). WWOP was associated with the highest level of myopia. Interestingly, the eyes with a retinal hole had the lowest level of myopia. The retina-vitreous interaction may be causative for some lesions such as lattice, WWOP, and snail-track

degeneration (271). Whereas, the lesions associated with older age, pigmentary degeneration and paving stone degeneration, are considered to have an age-related atrophic aetiology (281). Multiple lesions were observed in 10 eyes, and 23 participants had the same lesion in both eyes. The locations of the six lesions were investigated. The majority were found to occupy the superior temporal quadrant in concordance with previous work (287,365). This is significant as retinal tears in this region are more likely to progress to a rhegmatogenous retinal detachment (278). To test the hypothesis of equatorial growth affecting the periphery, but not the central retina crescent size and position were assessed in relation to the presence of a peripheral lesion. The widest mean crescent was observed in eyes with pigmentary degeneration; this lesion was also associated with greater age. In all other peripheral lesion groups, the crescent was no wider than the eyes without a peripheral lesion. The crescent was predominantly temporal to the disc in all lesion types other than snail track degeneration where inferior temporally located crescents were observed in 40 % of cases. Further investigation into the potential of STD as a predictor of myopic progression is justified, as study one found inferior temporal crescents to be associated with higher levels of myopia. The vertical disc size was no different in any of the lesion categories compared to those without a peripheral lesion. The findings of the current study do not fit with the differential stretch models suggested by Strang et al. (147), although insufficient information on eye shape was available to investigate this fully.

The final study considered static blood vessel analysis in 115 participants from study one. The determination of pre-clinical biomarkers of future disease is important to prevent morbidity, by ideally avoiding the event, or by determining the need for intervention at an earlier time point. This study aimed to determine the summary measures of the retinal vasculature and compare with the level of myopia, age, and optic nerve head metrics using a new semi-automatic vessel measurement program (Iflexis, Mol, Belgium). No relationship between the summary measures, CRAE and CRVE, were observed with myopia, age, or any of the disc metrics. Others have

reported associations, although there is a significant inconsistency between studies, possibly due to the many confounding factors affecting retinal vessel calibre.

The final part of this study retrospectively investigated the change in RVC between two images. The participants were selected to be in one of two groups. Group one, had no change in myopia (SER) between images, and the second having an increase of at least 0.75 D. In keeping with previous studies; we expected that those with increasing myopia would show a decrease in RVC. However, a greater reduction was seen in the no increase in myopia group. The lack of effect observed compared to other studies may be the result of the short time interval and not controlling for systemic confounders.

The Iflexis semi-automated vessel measurement software was easy to use and would fit into community practice. However, the many confounding factors, especially with increasing age, and the challenges of collecting relevant normative data make its appeal less. Possibly the best use is part of an integrated care pathway, being used with other predictors to determine the risk of disease, to allow appropriate targeting of strategies to reduce morbidity, whether it be ocular or systemic.

In summary, this thesis has examined the prevalence of retinal features in myopic eyes and the relationships to the level of myopia and age. This study differs from others as the more common low and moderate levels of myopia are considered. The findings of OHN size confirm the results of previous work that the presence of some features is related to the level of myopia. Furthermore, this thesis shows that the size of the crescent is linked to the degree of myopia. The present study also found inferior-temporally located crescents were associated with higher myopia (SER), snail track degeneration, smaller discs, and tilted discs. Further longitudinal investigation would allow temporal change to be assessed and possible mechanisms to be determined. The visible stretch, readily seen on digital fundus images, could be used to boost compliance with myopia control treatments and attendance for eye examinations. From the

observations in study three, it is recommended those with moderate and high myopia have periodic dilated fundus examinations and are counselled to respond appropriately should danger symptoms occur.

6.1 Future work

To assess the predictive values of ONH parameters for myopia development, it is essential to determine whether change occurs concurrently with the progression, or whether there are markers before myopia development. This would involve the recruitment of children with low levels of hyperopia to be followed for a significant number of years. Some of these children will develop myopia which will progress, and it would be with this cohort we could better elucidate the relationship.

In study one, myopia (SER) was shown to be related to the crescent position. The crescent size was seen to increase between images in study two. To understand how the crescent position changes over time, and to test its potential as a marker of myopic progression, or as a possible indicator of risk for glaucoma, further longitudinal study would be needed. A prospective study would allow additional measures such as axial length along with other variables such as keratometry to maximise accuracy in the adjustment for magnification. Using imaging technology that can track the retinal location accurately to ensure consistency in positioning between images would be beneficial in detecting small changes. Several OCT instruments have this facility, and rather than being used alone due to issues in identifying the disc margins accurately in eyes with PPA, it may be used in addition to digital photography which is still considered the gold standard. Ideally, the time interval would be extended with several images rather than just a baseline and final. This would allow a more in-depth investigation of the temporal changes. Having a group of progressing myopes, typically through the teenage years, and an older group after the time myopia has usually stabilised would allow an investigation as

to the pathophysiology of crescent formation during progression when mechanical stretch would by the expected mechanism, compared to atrophic change in those where the myopia has stabilised. OCT could be used to image this area to assess if the structural change is different between the groups.

Study three highlighted that an inferior-temporally located crescent was associated with the presence of snail track degeneration. Those with STD were also the youngest. Recruitment was a challenge as the explanation about the effects of dilation deterred many potential participants from taking part. This is a challenge in community practice compared to a clinic-based study where patients are dilated as standard. A longitudinal study would allow assessment of STD as a biomarker of a higher endpoint of myopia.

The IFLEXIS vessel measurement software was quick and easy to use, and as mentioned previously would fit into community practice. Before it could be used it would need to be compared to other systems and algorithms developed to facilitate useful comparisons. Further investigation of vessel parameters over a more extended period using a prospective design to include more co-variables and identification of confounders such as blood pressure and medications may strengthen the case for retinal vessel calibre to be adopted into community optometry practice. The recall driven optometry system would lend itself to this kind of study.

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Appendices

Appendix A Poster displayed in practice waiting area

VOLUNTEERS NEEDED

Myopia, commonly known as short-sightedness, is the most common ocular disorder worldwide. The number of people affected has increased significantly over the last two decades. The myopic eye is too long-the length of the eye increasing as myopia progresses.

Being myopic is often just thought of as an inconvenience but it is far from that. Even low levels of myopia increase the risk of several common eye diseases including glaucoma, retinal detachment, and cataract.

We are conducting a study looking at changes that occur in the eye to investigate how the changes relate to the level of myopia and age.

We are looking for volunteers who as part of their usual eye examination will consent to the instillation of a dilating eye drop to enable a full examination of the retina.

If you are interested in helping, please ask the store team for more information.

Appendix B Participant information sheet

Participant Information Sheet and Consent Form

Research Workers, School and subject area responsible

Mr David Hill, Dr Nicola Logan and Dr Rebekka Heitmar

Ophthalmic Research Group, Life and Health Sciences, Aston University, Birmingham, UK

Project Title

Retinal characteristics of myopic eyes in a UK population

Invitation

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and ask any questions you may have before deciding to participate.

What is the purpose of the study?

Myopia, commonly known as short-sight or near sighted is becoming increasingly more common with an earlier age of onset worldwide. Several common eye diseases are associated with myopia and are likely to become more common with increasing myopia and the ageing population. The purpose of this study of myopic eyes is to describe the retinal changes associated with different magnitudes of myopia, and to determine the prevalence of retinal changes at different levels of myopia, and how age influences this.

Why have you been chosen?

You have been chosen as you fit the inclusion criteria of being myopic and have also had photographs taken of the back of your eye previously at Specsavers Opticians, Newmarket.

What will happen to me if I take part?

By volunteering to participate extra photographs will be taken of the retina (back of the eye) in additional to the central retinal photograph taken as part of your standard eye examination. This involves you looking up, down, right and left in addition to the usual straight ahead. In order to obtain good photographs, eye drops (Tropicamide 1%) will be instilled to enlarge your pupils. Dilating drops are widely used in routine Optometric practice, and more information is given below. Your participation will not require additional visits and your time in the practice will be similar to that for your previous eye examination visits. All examinations take place at Specsavers Opticians in Newmarket.

Are there any potential risks in taking part in the study?

There is a risk of breaching confidentiality in relation to your clinical records. This risk will be minimised by keeping your data anonymous at all times. As an employee of Specsavers Newmarket, David Hill has access to your clinical records. He will be responsible for putting your results onto a database and maintaining your privacy and confidentiality. Other members of the research team will only be given access to the database after your identity has been removed.

The dilation drops used in this study are Tropicamide 1.0%
The eye drops used in the study are used to make the pupils larger than normal allowing the investigator to photograph the back of the eye more easily. When applied to the eye, they may sting for a few moments. The drops take about 15 to 30 minutes to work and around 6 hours to wear off, off (in some cases up to 24 hours.) The resultant large pupils will make you more sensitive to light, whilst distant and near objects may appear slightly blurred. Consequently, you shouldn't perform any activities such as driving and/ or cycling for at least 12 hours after the drops have been instilled. On a bright day, sunglasses may be advisable. It is very unlikely, but should you experience any unusual symptoms such as severe pain and/ or bloodshot around the eye and cloudy vision during this period please contact Specsavers Newmarket [redacted] or go to A&E (local A & E departments are located at Addenbrookes Hospital, Cambridge and West Suffolk Hospital, Bury St Edmunds) as you may be experiencing an adverse reaction to the drops.

Do I have to take part?

No, you do not have to participate if you do not wish to do so. You are free to withdraw at any time from the project. No sanctions will be taken against any patient that wishes to withdraw from the project.

Expenses and payments

There are no expenses or payments for participation in this project.

Will taking part in this study be kept confidential?

Yes, your participation in the study will be confidential. There will be no way to link any research data to any individual participant.

What will happen to the results of the research study?

Our aim is to publish the findings in an academic journal. However, there will be no reference to any individuals identifying details.

Who is funding the research?

There is no funding for this research project.

Who has reviewed the study?

The research has been reviewed by and given a favourable opinion by Aston University's LHS Ethics Committee.

Who do I contact if something goes wrong or I need further information?

Please feel free to contact Dr Nicola Logan at Aston University (n.s.logan@aston.ac.uk, [redacted]) or Mr David Hill at Specsavers, Newmarket (d.j.hill@aston.ac.uk, [redacted])

Who do I contact if I wish to make a complaint about the way in which the research is conducted?

If you have any concerns about the way in which the study has been conducted, then you should contact the Secretary of the University Research Ethics Committee Mr J Walter (j.g.walter@aston.ac.uk or telephone [redacted]

Aston University
Birmingham

Volunteer Consent Form

Title of Project: Retinal characteristics of myopic eyes in a UK population

Name of Researchers: Mr David Hill, Dr Nicola Logan and Dr Rebekka Heitmar

		Initial box
1	**I confirm that I have read and understand the information sheet for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.**	
2	**I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.**	
3	**I agree to take part in the above study.**	

_____ _____ _____

Name of volunteer Date Signature

_____ _____ _____

Investigator taking consent Date Signature

2 copies: 1 for participant

1 for investigator

Appendix C College of Optometrists tropicamide information leaflet

Appendix D Peripheral fundus examination record

Peripheral fundus examination record

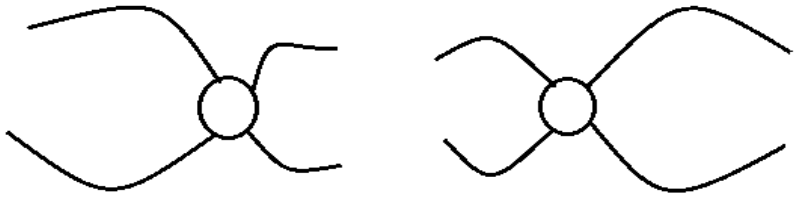
ID: _____ DOB:_____ Rx R_____ Date:_____

Rx L_____

Drug information

Pre drop IOP: R mmHg L mmHg @ Post IOP: R mmHg L mmHg

VH: grade



Peripheral codes

1. Lattice degeneration
2. White without pressure
3. Pigmentary degeneration
4. Paving stone degeneration
5. Retinal hole
6. Snail track degeneration

Other notes:

Appendix E Ethics application

Purpose

The purpose of this retrospective cross-sectional study is to determine the retinal characteristics of myopic eyes in a UK population using equipment found in a high street Optometry practice. This is to be achieved via the following objectives:

1. Identify the prevalence of retinal changes in a UK population of myopic eyes
2. Determine the level of myopia at which retinal changes can be observed in this population
3. Investigate how age affects the changes at different levels of myopia
4. Explore how the findings can be used to increase the UK's focus on myopia control as a means to reduce sight loss and associated costs
5. Formulate evidence-based recommendations highlighting the importance of the Optometrist's role in delivering advice to patients in order to minimise the progression of myopia in order to reduce associated disease risk.

Methods

David Hill will identify myopic patients from the database of a high street Optometry practice. Previously obtained retinal images will be assessed and optic disc metrics obtained using Nidek image wizard software. The research will focus on the area of retina captured by a standard fundus camera (45 degrees) with the image centred on the fovea. The subjects will be divided into level of myopia and age in the primary analyses. A secondary arm involves recording in more detail peripheral retinal features of myopic eyes beyond the field obtained with a standard fundus photograph. This will involve recording more details during scheduled eye examinations over the first two years of the study in patients seen by David Hill at Specsavers Newmarket. No extra examinations will be carried out to those expected in a normal eye examination. This data will be analysed by David Hill. The findings form part of David Hill's Ophthalmic Doctorate course.

Justification

Myopia is known to be associated with many ocular abnormalities that lead to ocular morbidity and cost to society. The World Health Organisation (WHO) classes uncorrected myopia and pathological myopia as major causes of visual loss. High myopia carries a high risk of retinal

degeneration and is the second most common reason for visual loss in China (43) and is in the top five in many western countries . More relevant for the proposed study is that several epidemiological studies have shown a relationship between myopia and common conditions such as cataract, glaucoma and retinal detachment at lower degrees of myopia(45,235). These findings have led to the question "is there a safe level of myopia where it is only an inconvenience?" Flitcroft in a recent review argues the term "physiological myopia" should be rejected (32) in light of these findings.

The prevalence of myopia is growing worldwide especially in the Far East with surveys suggesting 80% of children are graduating from high school as myopes(9). Earlier onset is leading to greater magnitudes of myopia with 20% of graduates in Jung's survey reaching myopia greater than -6.00 dioptres at age 19(22); the level which has traditionally been associated with increased risk of ocular morbidity(23). In the UK, the prevalence of myopia is lower but still increasing. The Aston Eye Study showed almost 30% of teenagers to be myopic in a cosmopolitan British city (14).

Previous studies have investigated retinal changes across various age groups in East Asian populations. The proposed study will be carried out on a UK population and aims to show how retinal changes are associated with the degree of myopia and how these may differ with age.

How our study meets current needs

With the increasing prevalence and magnitude of myopia, there is a need to identify the level of myopia that retinal changes occur. Evidence of changes at lower magnitudes will increase the focus and funding to identify effective interventions to slow/prevent myopic progression/development to general public health and economic benefit.

Current debates on the approach

The relationship between high myopia and pathology is well known while the risk at lower levels of myopia needs to be considered. The UK's response, to the worldwide vision 20:20 commitment, to reduce preventable blindness by 2020 specifically mentions glaucoma. Several well-designed studies have shown low and moderate levels of myopia to be a risk factor for POAG.

Why is our approach appropriate and what is already generally accepted practice?

There is currently a significant amount of effort being applied in the field of myopia prevention and retardation with some strategies such as outdoor activity (69), multifocal contact lenses(184) and the use of non-selective muscarinic antagonists (373)showing potential. In the UK pathological complications of myopia are not given significant thought, by the sufferer or average practitioner, unless the myopia is high. Identifying the level of myopia that structural changes start to occur will give the practitioner further information to facilitate decision making and start to focus the health policy decision-makers on the benefits of investing in preventing or controlling myopia.

Research participants

Which research participants will be involved and what will be done

Myopic patients with clear fundus images will be identified from the database at Specsavers Newmarket. The main part of the research will involve reviewing records and previously obtained digital fundus images from David Hill's practice in Newmarket. A secondary arm involves recording in more detail peripheral retinal features of myopic eyes beyond the standard fundus photograph field. This is to be achieved by examining and recording features of the peripheral retina in patients attending for scheduled eye examinations over the first two years of the study by David Hill at Specsavers Newmarket. No extra examinations will be carried

Appendix F Case reports

From the 129 patients examined, three were referred to secondary care. A summary of the three cases and the outcomes are presented below.

Case report 1

AP a 56-year-old white male, presented for his bi-annual eye examination in response to a recall letter. He complained of long-term floaters in his right eye; he had noticed flashes in his temporal field over the last six weeks. There was no history of trauma. His visual acuity with his correction of -3.25-0.50x160 was 6/6 in the right eye and -3.00 DS 6/6 in the left; his visual fields by supra-threshold testing were normal. The intraocular pressure was 16mmHg in each eye. As the symptoms had been present for several weeks, there was no great concern. AP had seen the poster for the study in the waiting area and enquired about taking part. Consent was obtained, and both eyes were dilated using tropicamide 1 %. Neither eye showed the presence of Schaeffer's sign. During the 8-point examination of the peripheral retina using a Volk super-field and slit lamp, a small horseshoe tear was discovered located in the upper superior temporal quadrant right at the edge of the view. Confirmation was facilitated by increasing the illumination. His appointment was at 6.45 pm, the next morning the local eye clinic was called, an appointment was arranged for 3 pm. At the eye clinic, the tear was confirmed and sealed with laser retinopexy. AP returned home and was reviewed two weeks later when he was discharged.

Case report 2

PH a 23-year trainee equine vet presented as a new patient to the practice for her routine check. She had no symptoms. Her refraction of R-8.50 DS and L-7.75 DS carries an increased risk of retinal problems. Having discussed the study with PH she agreed to participate, and consent was obtained. Upon dilated examination lattice degeneration was observed in the superior temporal

segment of both eyes. In the left eye, two small holes were also present within the lesion. She had no symptoms, but due to her level of myopia and young age, she was referred routinely to the local eye clinic. When the Ophthalmologist assessed her, she was referred to the local specialist centre where prophylactic laser was performed on the lesion.

Case report 3

SC a 36-year-old lady presented with no symptoms, and as a long-term patient of the practice agreed to be dilated. SC is a low, adult onset, myope (R-1.25-0.50x170 L-1.00 DS). Dilated examination showed lattice degeneration superiorly in both eyes and a round hole. She was referred to the local eye clinic, but in this case, no treatment was given. Although no treatment was given this case shows that without dilation many lesions are missed. SC had been to the practice many times with no mention of lattice in the records.