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Quality-of-life and clinical outcomes in age-related macular degeneration.

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2017

Doctor of Philosophy

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Acknowledgements

Firstly, I would like to thank my supervisors, Dr Jennifer Acton, Prof Tom Margrain and Prof John Wild. I am so grateful for your continuous support, encouragement and guidance throughout my PhD. I have enjoyed our meetings and the academic discussions that went along with them.

A special thanks goes to the participants who took part in my research, this thesis would not have been possible without them. I am also grateful to those at UHW who helped with recruitment, and specifically to Mr Chris Blyth and Prof Marcela Votruba for their assistance. I also want to thank Fight for Sight for their funding.

With respect to the data collection and analysis. Alex Nagle, without you the normative database would not have been possible so thank you so much. Helen Court, thank you for the training in Rasch analysis. I would like to thank the Statistics clinic at Cardiff University and Mark Kelson for the statistics advice I received. A special thanks goes to Tony Redmond, not only as my advisor, but also as my R guru.

A huge thank you must go to everyone who has presided in 2.10 at some point during my time here, you have made this experience special for me. Tamsin, Shindy, Flors, Aysha, Lindsay and Louise thank you for the coffees, catch ups and cocktails. A big thank you to Stacy for being a constant support and a reliable drinking partner. An extra special thank you also goes to Grant, we started this thing together and we've finished it together, this experience would have been much less fun without you.

I would not be the person I am today without the unconditional love and support from my family. Mum and Dad thank you for supporting me in everything I choose to do, and for teaching me that the sky is the limit. Suziee your constant support means the world to me, thanks for always being a cheerful voice at the end of the phone.

Last, but by no means least, thank you to Will. The reasons to thank you are endless, but most importantly thank you for ensuring that I kept smiling and sane throughout.

Abstract

Age-related macular degeneration (AMD) is of increasing concern given the ageing population, and the associated economic and social burdens. Vision-related quality-of-life (QoL) is arguably one of the most important factors in the management of those with AMD. Consequently, there is a clear need for an understanding of the clinical outcomes that influence vision-related QoL in order to inform management strategies. The principle aim of the studies described herein was to determine the factors that predict vision-related QoL in those with AMD, over 1 year.

Experimental procedures were undertaken at baseline (n=52 individuals with AMD) and repeated after 1 year (n=32 individuals with AMD). These included: visual acuity, contrast sensitivity, reading speed, microperimetry, optical coherence tomography and fundus photography. A questionnaire interview included assessment of vision-related QoL (Impact of Visual Impairment questionnaire), health status (EQ-5D), level of depressive symptoms (PHQ-9) and well-being (Warwick-Edinburgh Well-Being Scale).

At baseline, the optimum multiple regression model accounted for 41% of the variance in vision-related QoL and included Mean Total Deviation or Mean Sensitivity with level of depressive symptoms. After 1 year, the optimum model to predict change in vision-related QoL accounted for 43% of the variance and included baseline contrast sensitivity and change in health status and reading speed.

The most clinically useful measures of visual function, in identifying those with a reduced QoL or those at risk of a reduced QoL were contrast sensitivity, microperimetry, and reading speed. These outcomes may allow a better understanding of vision-related QoL if they were adopted in a clinical setting. In conclusion, the studies provide sufficient evidence to encourage a review of the clinical outcome measures most relevant to vision-related QoL.

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Abbreviations

ANOVA	Analysis of Variance
AMD	Age-related macular degeneration
Anti-VEGF	Anti-vascular endothelial growth factor
AO	Adaptive optics
AREDS	Age-related Eye Disease Study
BCEA	Bivariate contour ellipse area
BCVA	Best corrected VA
CFP	Colour fundus photography
CNV	Choroidal neovascularisation
CS	Contrast sensitivity
dB	Decibels
DLS	Differential light sensitivity
ELM	External limiting membrane
ETDRS	Early Treatment Diabetic Study
EZ	Ellipsoid zone
FAF	Fundus autofluorescence
FFA	Fundus fluorescein angiography
GA	Geographic atrophy
GCL	Ganglion cell layer
HFA	Humphrey Field Analyzer
ICGA	Indocyanine green angiography
INL	Inner nuclear layer
IOP	Intra ocular pressure
IPL	Inner plexiform layer

IR	Infrared
IRest	International Reading Speed Texts
IRF	Intraretinal fluid
IS	Inner segment
IVI	Impact of Vision Impairment scale
LLD	Low luminance deficit
LLVA	Low luminance VA
LOCS	Lens Opacity Classification System
MAIA	Macular Integrity Assessment
MD	Mean Deviation
MTD	Mean Total Deviation
mfERG	Multifocal electroretingram
MMSE	Mini-mental state examination
MPD	Mean Pattern Deviation
MRSS	Median retinal sensitivity score
MS	Mean Sensitivity
MVF	Macular visual field
nAMD	Neovascular AMD
NEI VFQ	National Eye Institute's Visual functioning questionnaire
NICE	National Institute for Health and Care Excellence
OPL	Outer plexiform layer
ORTs	Outer retinal tubulations
OS	Outer segment
PD	Pattern Deviation
PDT	Photodynamic therapy

PED	Pigment epithelial detachment
PHQ-9	Patient Health Questionnaire-9
QoL	Quality-of-life
RCT	randomised control trial
RNFL	Retinal nerve fibre layer
RPD	Reticular pseudodrusen
RPE	Retinal pigment epithelium
SAP	Standard automated perimetry
SD-OCT	Spectral domain optical coherence tomography
SLO	Scanning laser ophthalmoscope
SRF	Subretinal fluid
SW A-F	Short wavelength auto-fluorescence
TD	Total Deviation
TTO	Time-trade off
VA	Visual acuity
VF-14	Visual Function Index
WEMWBS	Warwick-Edinburgh Mental Well-being scale

Chapter 1: Introduction

1.1 Summary

An overview of age-related macular degeneration (AMD) including classification methods, pathogenesis and clinical presentation is presented in this chapter. Clinical measures are reviewed including functional measures and imaging techniques relevant to AMD. Quality-of-life (QoL) is also addressed and discussed in the context of AMD.

1.2 Age-related macular degeneration

Age-related macular degeneration is the leading cause of visual impairment in the developed world and is the primary cause of registered sight impairment in the UK (Evans, Fletcher and Wormald 2004; Bunce, Xing and Wormald 2010; Klein et al. 2013). It is a degenerative disease, which causes a varied reduction in central visual function leading to severe deficits in late stage disease.

Early AMD involves gradual, moderate reductions in visual function. Late stage AMD can be divided into two types; geographic atrophy (GA) or neovascular AMD (nAMD). GA and nAMD have similar prevalence of 6.7% and 6.3% respectively, in those over 80 years old in the UK population (Owen et al. 2012). However, GA accounts for a larger amount of registered sight impairment (42%) in the UK compared to nAMD (29.7%) (Rees et al. 2014). Despite this, the sudden vision loss associated with nAMD has more profound initial effects than the gradual progression of GA.

1.2.1 Clinical presentations

1.2.1.1 Stages of AMD

Early to intermediate stages of AMD are characterised by the presence of differing sizes of drusen, with or without the addition of hyper- or hypopigmentary abnormalities (Ferris et al. 2013).

1.2.1.2 Drusen

Drusen are the first sign of AMD that can be recognised clinically. They are extracellular deposits that accumulate between the retinal pigment epithelium (RPE) and inner collagenous zone of Bruch's membrane (Abdelsalam, Del Priore and Zarbin 1999). They are composed of undigested metabolic debris and lipofuscin, which would normally be removed in younger eyes, but in ageing eyes, in which transport between RPE and Bruch's membrane is dysfunctional, the debris accumulates (Moore, Hussain and Marshall 1995).

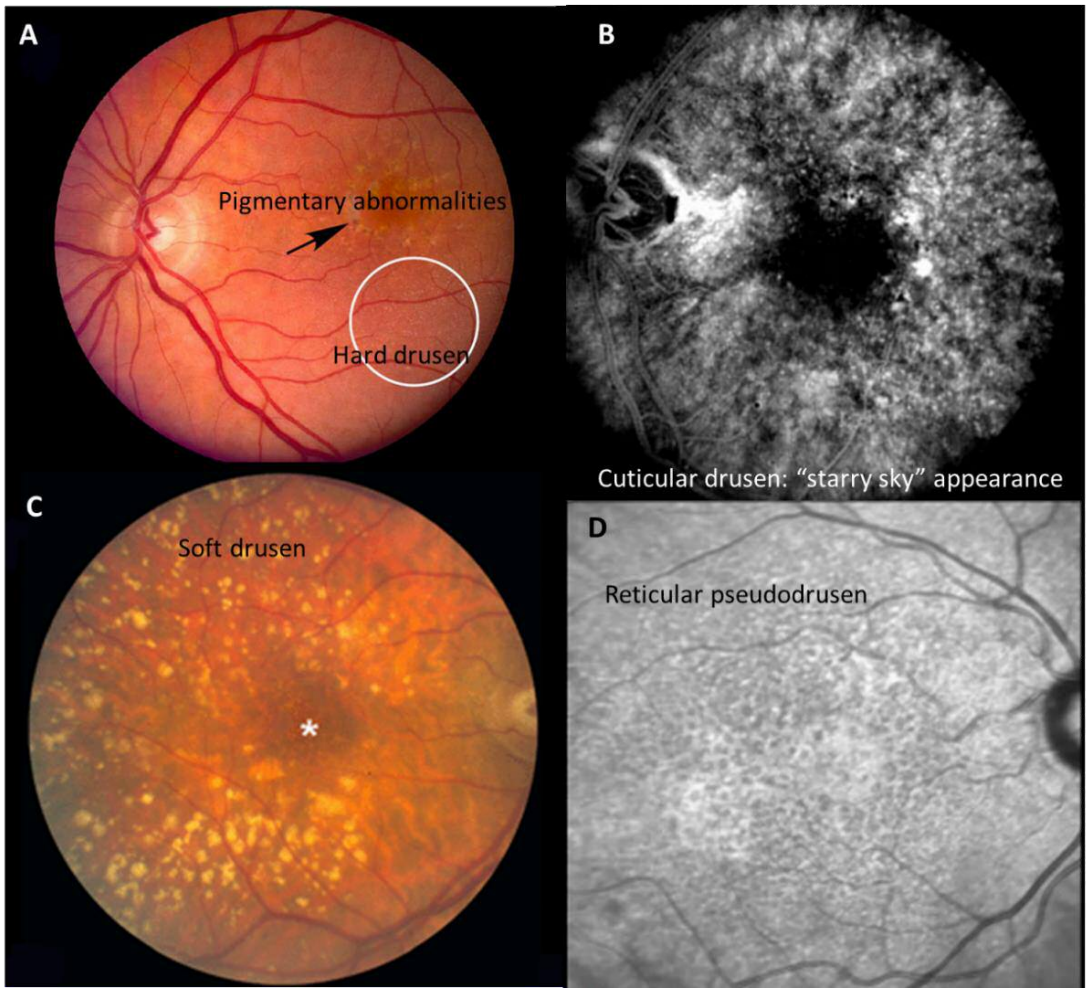


Figure 1.1. Clinical presentation of the different types of drusen. A: Colour fundus photography (CFP) of pigmentary abnormalities and hard drusen, B: Fundus fluorescein angiography of cuticular drusen presenting as a "starry sky" appearance, C: CFP with soft drusen and some calcified drusen present, D: Infra-red image showing reticular pseudodrusen. Adapted from: (Kolb et al. 2011; Sivaprasad et al. 2016) © from Elsevier.

Drusen can be defined clinically by size and area, and into several types; hard drusen, soft drusen, cuticular drusen and reticular pseudodrusen (RPD)(Figure 1.1) (Sarks, Sarks and Killingsworth 1994; Smith et al. 2009; Khan et al. 2016). A clinical

description of the different types of drusen can be found in Table 1.1. Calcified drusen are not a specific type of drusen, all drusen are calcified to some extent and it is suggested that the level of calcification is associated with age of druse (Khan et al. 2016). A small number of hard drusen, also referred to as drupelets (<63μm), at the macula are suggested to be a normal ageing change of the retina (Sarks et al. 1999). However, when they increase in number and become confluent they become a risk factor for the development of AMD (Ferris et al. 2013). This risk factor is well established and has led to confluent drusen at the macula being classified as early stage AMD (Abdelsalam, Del Priore and Zarbin 1999; Midena et al. 1997; Ferris et al. 2013). The presence and severity of drusen is also a risk factor for the progression to advanced AMD (Chew et al. 2014; Klein et al. 1997), as is the presence of RPD (Klein et al. 2008; Zhou et al. 2016).

1.2.1.3 Pigmentary abnormalities

Pigmentary abnormalities are characterised as areas of increased (hyperpigmentation) or decreased pigment (hypopigmentation) due to RPE dysfunction (Bhutto and Lutty 2012). The presence of pigmentary abnormalities leads to the classification of intermediate AMD with the well-established AREDS (AREDS 2001) and Beckman classification systems (Ferris et al. 2013), as these changes with the additional presence of drusen are predictive of AMD progression (Chiu et al. 2014; Finger et al. 2016). Hyperpigmentation is suggested to precede nAMD, whereas hypopigmentation is proposed to be predict the development of GA (Bhutto and Lutty 2012).

Type of druse	Clinical description
Hard	CFP: Located in central and peripheral retina. Small (<63μm) defined yellow-white punctate deposits. Associated with normal ageing as well as AMD. SD-OCT: small hyperreflective sub-RPE deposits FFA and ICGA: hyperfluorescent SW A-F: areas of reduced AF
Cuticular	CFP: Located in central and peripheral retina (more numerous in the periphery). Multiple (>50) small (25-75μm) dot like deposits. SD-OCT: triangular (”saw-tooth”) hyperreflective sub-RPE deposits FFA: Numerous hyperfluorescent dots (“starry sky” appearance) ICGA: early hyperfluorescent SW A-F: areas of reduced AF
Soft	CFP: Located at the posterior pole, most frequently in the central macula and in the superior and temporal quadrants. Large (≥125μm) less well defined mound-like elevations. Non uniform Yellow appearance. SD-OCT: Large sub-RPE hyperreflective deposits. FFA: Some late hyperfluorescence ICGA: Hyperfluorescent SW A-F: Moderate hyperAF
Reticular pseudodrusen	CFP: Located in perifoveal area (more predominant superiorly). Ranging from 100 to 250μm in size. Yellow-white ill-defined interlacing pattern (whiter than other drusen). Enhanced visibility under red-free light but best images on infrared reflectance (IR) imaging SD-OCT: Deposits between RPE and inner segment ellipsoid lines later breaking though the ellipsoid line and subsequently fading. FFA: Hypofluorescence or no change ICGA: Hypofluorescence in late stage SW A-F: Reticular pattern, hypoAF

Table 1.1 Clinical description of drusen type, assessed by colour fundus photography (CFP), spectral domain optical coherence tomography (SD-OCT), fundus fluorescein angiography (FFA), indocyanine green angiography (ICGA) and short wavelength auto-fluorescence (SW A-F). Adapted from: (Abdelsalam, Del Priore and Zarbin 1999; Saade and Smith 2014; Smith et al. 2009; Khan et al. 2016; Sivaprasad et al. 2016).

1.2.1.4 Geographic atrophy

Geographic atrophy is characterised by a sharply defined area of RPE atrophy, in which choroidal vessels are visible (Figure 1.2) (Chaikitmongkol, Tadarati and Bressler 2016). GA occurs due to RPE loss and photoreceptor thinning at the macula. It initially affects the parafovea, gradually increasing in size and sparing the fovea until later stages (Brader et al. 2013; Chaikitmongkol, Tadarati and Bressler 2016).

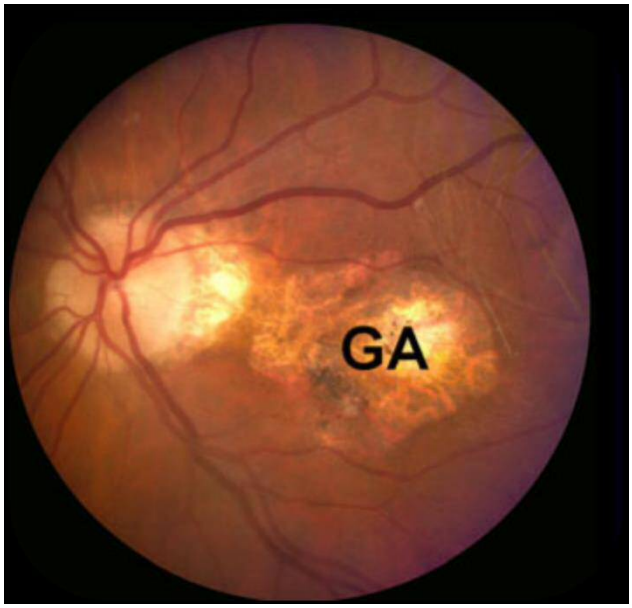


Figure 1.2 Colour fundus photograph of an eye with late stage AMD, with a central area GA involving the fovea. Image from: (Kolb et al. 2011)

1.2.1.5 Neovascular AMD

Neovascular AMD refers to the presence of choroidal neovascularisation (CNV), either between the RPE and Bruch's membrane (sub-RPE) or between the neural retina and RPE (subretinal) (Ambati et al. 2003). nAMD can be characterised by any of the following features; RPE detachments, subretinal or sub-RPE neovascular membranes, haemorrhages, hard exudates within the macular area, or glial tissue or fibrin deposits (Bird et al. 1995). The new abnormal blood vessels leak blood into the retina (sub-RPE, subretinal, intraretinal or pre-retinal); subretinal or sub-RPE haemorrhages are generally the first clinical sign of nAMD (Bhutto and Lutty 2012). These haemorrhages can cause distortion and reduced vision, and if left untreated lead to disciform scarring (Figure 1.3) (Ambati et al. 2003). Additionally, the presence

of nAMD in one eye significantly increases the risk of progression to nAMD in the second eye (Mitchell et al. 2002; Wang et al. 2007).

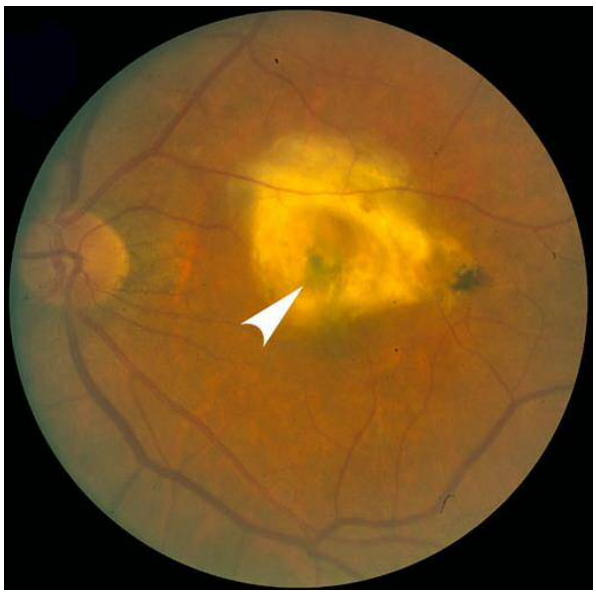


Figure 1.3 Colour fundus photograph colour of an eye with late stage AMD with a disciform scar at the macula due to CNV. Image from (Kolb et al. 2011).

1.2.1.6 Retinal Pigment Epithelial Detachment

Retinal pigment epithelial detachment (PED) is the detachment of the inner layers of Bruch's membrane away from the RPE (Schmidt-Erfurth et al. 2017). AMD associated PEDs can be defined as serous, drusenoid, or fibrovascular (haemorrhagic). Serous PEDs appear as a smooth well-defined dome-shaped RPE elevation on spectral domain optical coherence tomography (SD-OCT) and are commonly associated with nAMD (Schmidt-Erfurth et al. 2017). Drusenoid PEDs are formed by the coalescence of soft drusen and exhibit uneven RPE elevation with irregular borders when visualised with SD-OCT (Ambati et al. 2003; Zayit-Soudry, Moroz and Loewenstein 2007). Fibrovascular PEDs are caused by new vessel growth through Bruch's membrane resulting in an elevation of the RPE. On SD-OCT this appears as well defined areas of uneven RPE elevation with additional back scattering due to fibrous proliferation and often with adjacent areas of sub retinal fluid (Zayit-Soudry, Moroz and Loewenstein 2007) (Figure 1.4). PEDs can resolve to normal or can result in GA, nAMD, or retinal tears, leading to functional loss in individuals with AMD (Ambati et al. 2003; Ogino et al. 2014).

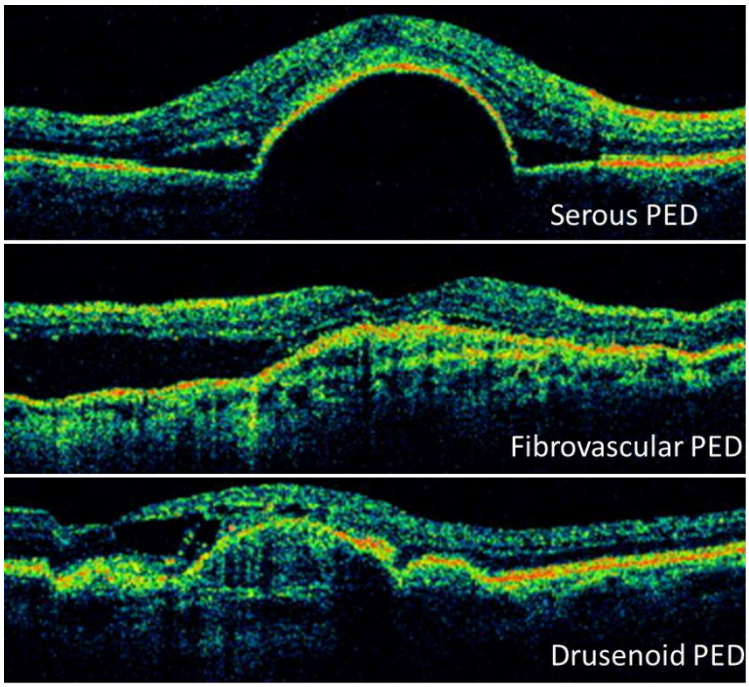


Figure 1.4 SD-OCT images of serous pigment epithelial detachment (PED) (top), fibrovascular PED (middle) and drusenoid PED (bottom). Images from: (Zayit-Soudry, Moroz and Loewenstein 2007) © from Elsevier.

1.2.2 Treatment

Currently nAMD is the only form of AMD that can be treated in clinical practice. Supplementation (Gorusupudi, Nelson and Bernstein 2017), alterations in diet (Carneiro and Andrade 2017) and lifestyle recommendations (Sin, Liu and Lam 2013) are currently suggested to reduce progression in early or intermediate AMD. However, recent technological developments provide an optimistic prospect for future treatments such as prosthetic retinal implants (Riazi-Esfahani et al. 2014; Mills, Jalil and Stanga 2017) and stem cell research (Kuriyan et al. 2017).

Anti-vascular endothelial growth factor (anti-VEGF) agents block the growth of abnormal vessels and are a proven method of nAMD treatment, preventing vision loss and even improving vision in some cases (Avery et al. 2006; Jiang, Park and Barner 2014). Bevacizumab (Avastin, Genentech), Ranibizumab (Lucentis, Genentech), Pegaptanib sodium (Macuggen, Pfizer Inc) and Aflibercept (Eyelea, Bayer Pharma) have all been demonstrated as effective when used to treat nAMD (Costagliola et al. 2009; Avery et al. 2006; Studnička et al. 2013; Schmidt-Erfurth et al. 2014). However,

currently only Ranibizumab and Aflibercept are National Institute for Health and Care Excellence (NICE) approved to treat nAMD (NICE 2014). Prior to the NICE recommendation of anti-VEGF treatments, photodynamic therapy (PDT) was used to treat subfoveal nAMD. The method involves an intravenous injection of verteporfin that accumulates in abnormal vessels, and when subjected to a low-energy laser leads to thrombosis and subsequent occlusion of these vessels (Cruess et al. 2009). Although less frequently used PDT is currently indicated when subfoveal nAMD is unresponsive to anti-VEGF treatment (Amoaku et al. 2015).

Before the development of anti-VEGF agents, the treatment of nAMD required surgical intervention, such as submacular surgery, which initially gave poor results. Subsequent surgical intervention for both nAMD and GA included macular translocation (van Romunde et al. 2015), and RPE and choroid transplants (Alexander et al. 2015; van Zeeburg et al. 2012). However, the introduction of anti-VEGF treatments revolutionised the treatment of nAMD and led to infrequent use of these surgical interventions.

1.2.3 Grading

There are a number of classification systems used to define the clinical signs of AMD. The most widely used and well established methods are the Wisconsin Age-related Maculopathy Grading system (Klein et al. 1991), the International Classification and Grading system (Bird et al. 1995) and the Age-related Eye Disease Study (AREDS) grading system (AREDS 2001). The most recently developed grading method is the Beckman grading scale (Ferris et al. 2013).

The original grading scale was the Wisconsin Age-related Maculopathy Grading system and this was used for several large scale AMD studies including the Blue mountains and Beaver dam studies (Mitchell et al. 1995; Klein, Klein and Linton 1992). It has also been utilised in the development of other grading scales. The International Classification and Grading system has similar principles to the Wisconsin Age-related Maculopathy Grading System, using a standard grid to define lesions, and was used in the large scale Rotterdam study (Klaver et al. 2001). The AREDS grading system was also developed based upon the Wisconsin Age-related Maculopathy Grading System, again using a standardised grid to grade stereoscopic colour fundus photographs (CFPs) (AREDS 2001). The AREDS classification uses a standard Early Treatment Diabetic Study (ETDRS) grid and standardised circles to grade AMD related features on CFPs (Figure 1.5).

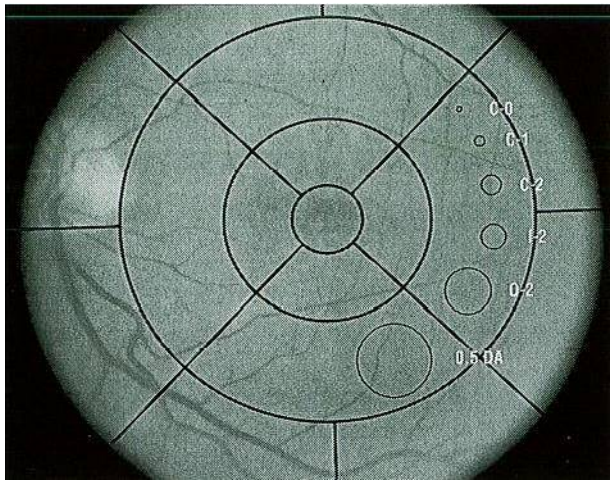


Figure 1.5. Grid and standard circles used to grade AMD with the AREDS system. C=central, I = inner and O = outer subfields. Diameter of circles: C-0=0.042 disk diameter (DD), C-1 = 0.084 DD, C-2=0.167 DD, I-1 = 0.120 DD, I-2 = 0.241 DD,)-1 = 0.219 and O-2 = 0.439 DD. (Davis et al. 2005; AREDS 2001) © from Elsevier.

Size and presence of pigment abnormalities, GA and drusen are all graded by comparison with the standardised circles and the overall grades are based upon the size and presence of different features (Table 1.2).

AREDS classification	Criteria
1	Drusen maximum size <C-0 (63μm diameter) and total area <C-1 (125μm diameter)
2	Presence of one or more of the following: •Drusen max size ≥C-0 but <C-1 •Drusen total area ≥C-1 •Pigment abnormalities consistent with AMD, defined as one or more of the following in the central or inner subfields: a) Depigmentation b) Increased pigment >C-1 c) Increased pigment present and depigmentation at least questionable
3	Presence of one or more of the following: •Drusen maximum size ≥C-1 •Drusen maximum size ≥C-0 and total area >I-2 and type is soft indistinct •Drusen maximum size >C-0 and total area >O-2 and type is soft distinct •GA within grid but none in centre of macula
4 (Late)	Presence of one or more of the following: •GA in central subfield with at least questionable involvement of centre of macula •Evidence of nAMD: a) Fibrovascular/serous PED b) Serous (or haemorrhagic) sensory retinal detachment c) Subretinal pigment epithelial haemorrhage d) Subretinal fibrous tissue e) Photocoagulation for AMD

Table 1.2 AREDS classification system

The Beckman classification was developed to include the main clinical phenotypes of AMD, whilst limiting the grading to only direct or indirect ophthalmoscopy. The proposed classification includes 5 stages: 'no apparent ageing changes', 'normal ageing changes', 'early AMD', 'intermediate AMD' and 'late AMD' (Table 1.3) (Ferris et al. 2013).

Classification	Definition
No apparent ageing changes	No drusen and no pigmentary abnormalities
Normal ageing changes	Only druplets (small drusen ≤63μm) and no pigmentary abnormalities
Early AMD	Medium drusen (> 63μm and ≤125μm) and no pigmentary abnormalities
Intermediate AMD	Large drusen (>125μm) and/or any pigmentary abnormalities
Late AMD	Neovascular AMD and/or any geographic atrophy

Table 1.3 Beckman AMD classification.

A disadvantage to all the current grading scales is the lack of SD-OCT images in the grading process. This is a limitation as SD-OCT can identify AMD lesions that may not be visible by CFPs or clinical examination alone, for example PEDs and subretinal fluid (Mokwa et al. 2013). Subsequently, a combination of SD-OCT in addition to one of the existing grading methods would be a preferential method to grade AMD severity.

1.2.4 Pathogenesis

The pathogenesis of AMD is a multifactorial process that is still not fully understood. A number of processes have been suggested to contribute including oxidative stress, choroidal vascular changes, Bruch's membrane changes, metabolic insufficiency and inflammatory processes (Zarbin 2004; Ambati et al. 2003; Ambati and Fowler 2012; Gelfand and Ambati 2016; Tan, Bowes Rickman and Katsanis 2016). These processes are not mutually exclusive and a flow diagram to visualise the multidimensionality is presented in Figure 1.6.

To explore the pathogenesis of AMD normal ageing should firstly be addressed. AMD is proposed to be an extreme version of the normal retinal ageing process. Normal ageing occurs due to the production of damaging toxins (such as reactive oxygen intermediates, ROI's) from metabolic interactions between biological chemicals. Accumulation of these damaging toxins over time lead to age-related diseases (Ardeljan and Chan 2013). The normal ageing process of the retina involves Bruch's membrane thickening, drusen formation, lipofuscin accumulation leading to RPE degeneration, oxidative stress, increased mitochondrial damage and macrophage imbalance. Normal ageing also involves a decreased choroidal blood flow due to a reduction in density and diameter of choriocapillaris (Ardeljan and Chan 2013). It is apparent that there is overlap between the mechanisms of AMD pathogenesis and normal ageing processes. These mechanisms will be examined in more detail.

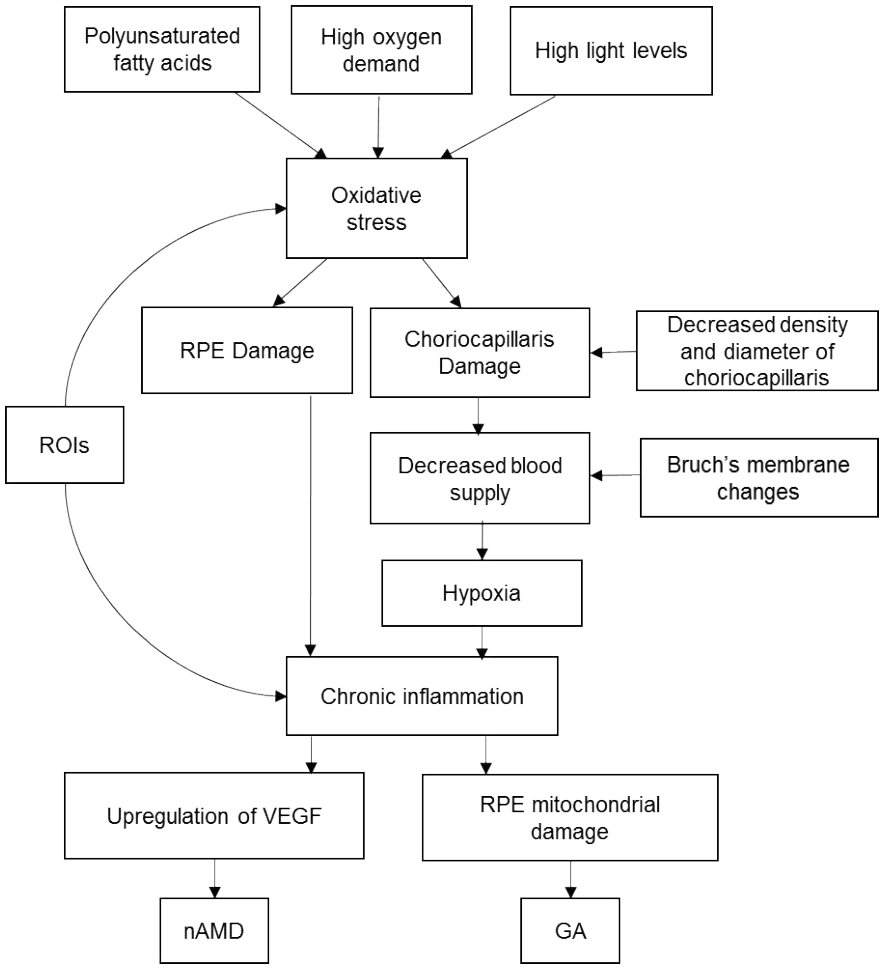


Figure 1.6 Flow diagram depicting the multifactorial processes of the pathogenesis of age-related macular degeneration (AMD) including both neovascular AMD (nAMD) and geographic atrophy (GA). ROIs: reactive oxygen intermediates.

1.2.4.1 Bruch's membrane

Bruch's membrane functions as a physical and biochemical barrier between the RPE and choriocapillaris. The thickening of Bruch's membrane with age, ultimately impedes photoreceptor function and, consequently, the metabolic exchange between the choroid and retina (Ambati et al. 2003). The diffusion capabilities of Bruch's membrane are inhibited by an increase in lipids, increased membrane thickness and an accumulation of abnormal deposits in Bruch's membrane, which result from the incomplete phagocytosis of the photoreceptor outer segments by the RPE (Booij et al. 2010).

1.2.4.2 Oxidative stress

Oxidative stress occurs due to the production of ROIs at enzyme active sites after oxidation. ROIs remove electrons from other molecules to achieve a stable state, resulting in those molecules becoming unstable (cytotoxic chain reaction). An accumulation of the unstable molecules results in oxidative stress (Beatty et al. 2000). The retina is vulnerable to oxidative stress, firstly, due to having the highest oxygen demand of any tissue in the body (Vanderkooi, Erecińska and Silver 1991). Secondly, the high light exposure that the retina receives produces ROIs (Beatty et al. 2000) as does phagocytosis of photoreceptor outer segments, but to a lesser extent (Ambati et al. 2003). Finally polyunsaturated fatty acids, which are found in photoreceptor outer segment membranes, are readily oxidised and, therefore, can initiate a cytotoxic chain reaction (Beatty et al. 2000). ROIs increase the production of VEGF and decrease pigment epithelial derived factor (PEDF), promoting vessel growth and resulting in nAMD (Ambati et al. 2003; Ambati and Fowler 2012).

1.2.4.3 Metabolic insufficiency

The macula is the most metabolically active area of the retina. Yet, the supply of oxygen is limited as it is solely supplied by the choriocapillaris, which is not autoregulated, resulting in an increased risk of ischaemia when oxygen demand is greatest. It has been suggested that AMD is linked to reduced choroidal blood flow caused by decreased density and diameter of the choriocapillaris (Grunwald et al. 1998). This abnormal choroidal flow and perfusion leads to ischaemia and hypoxia, which contribute to the activation of VEGF and the subsequent growth of new abnormal vessels in nAMD (Boltz et al. 2010). In individuals with GA, a 50% reduction in the choriocapillaris area was found in regions with RPE atrophy, and the remaining choriocapillaris was significantly constricted (McLeod et al. 2009). Additionally, choriocapillaris atrophy extends further than RPE atrophy in GA, suggesting that choriocapillaris atrophy precedes GA (Biesemeier et al. 2014).

1.2.4.4 Chronic inflammation

It has also been proposed that chronic inflammation is associated with the pathogenesis of AMD (Donoso et al. 2006; Kauppinen et al. 2016). The complement cascade is the primary immune mechanism to foreign microorganisms, it regulates the immune responses of removal of foreign particles and the recruitment of inflammatory cells (Anderson et al. 2002; Anderson et al. 2010). In AMD, the complement system lacks the correct regulation required to avoid damage to healthy ocular tissue. It is suggested that a combination of oxidative stress, abnormal deposits and oxidised proteins lead to a prolonged dysregulated inflammation, which result in changes within the choroid and breakdown of the blood retinal barrier (Bhutto and Lutty 2012; Chen and Xu 2015).

1.2.4.5 Risk factors

Having described the pathogenic processes, some risk factors for AMD will be briefly summarised. There are many suggested risk factors for AMD including genetic risk factors, environmental risk factors such as sunlight, obesity, smoking and socioeconomic status, and additional factors including age, gender and race for a comprehensive review see Lambert et al. (2016).

There have been numerous studies investigating AMD associated genes. There is a strong familial link, which accounts for up to 71% of those with AMD, with the age-related maculopathy susceptibility protein 2 (ARMS2) gene being significantly associated with an increased risk of AMD (Priya, Chew and Swaroop 2012; Seddon 2005; Sobrin and Seddon 2014). The individual differences in AMD severity and progression is also proposed to be 50% due to genetic factors (Mousavi and Armstrong 2013). Mutations in complement factor H, complement factor B, complement factor C3 and serpin peptidase are genetically linked with AMD, but are also associated with the immune response mechanism, in particular the complement pathway (Grassmann, Fauser and Weber 2015; Kauppinen et al. 2016).

The largest controllable environmental risk factor for AMD is smoking, where smokers are 2-3 times more likely to develop AMD than non-smokers (Ambati and Fowler 2012; Chakravarthy et al. 2010). Diet and obesity have also been associated with an increased risk of AMD (Zhang et al. 2016), leading to recommendations of a healthy diet and regular exercise in those with AMD or a family history of AMD (Sobrin and Seddon 2014; Lambert et al. 2016). Other environmental risk factors include exposure to sunlight, and wearing UV protective glasses is recommended due to the protective effect (Schick et al. 2016).

Additional to these environmental factors, other factors that increase the susceptibility for AMD include age, gender and race. Whereby, AMD risk increases with age; females are more susceptible to AMD than males; and those of Caucasian decent are significantly more likely to develop more severe AMD (AREDS 2000; Lambert et al. 2016).

1.2.4.6 Summary

In summary, the pathogenesis of AMD is complex, but it is believed to be closely related to the normal ageing process. Whilst the reason that AMD develops in some individuals and not in others is equivocal, it is suggested that several aspects, including genetic and environmental factors, may be involved. Bruch's membrane changes occur at an early stage and lead to metabolic insufficiency and hypoxia. Several other processes cause inflammation, oxidative stress, lipofuscin deposition and reduced choroidal blood flow. These processes ultimately lead to GA and/or nAMD.

1.3 Imaging

Imaging techniques enable visualisation of the retina, such that AMD associated retinal features may be viewed. These include CFP, fluorescein angiography (FA),

optical coherence tomography (OCT), fundus autofluorescence (FAF) and infrared (IR) imaging.

1.3.1 Colour fundus photography

Colour fundus photography is the traditional method for grading AMD (Section 1.2.3). It allows en-face visualisation of drusen and pigmentary changes that are associated with early AMD, and can be used to monitor other morphological changes indicative of development of late stage disease (Klein et al. 2007; Ferris et al. 2013; AREDS 2001). However, fundus photography cannot identify certain pathological changes associated with AMD, and is unable to localise these to a specific retinal layer (Kanagasingam et al. 2014). CFP and OCT provide complimentary information and both have a role in the detection and monitoring of AMD (Gregori et al. 2011; Holz et al. 2017).

1.3.2 Optical coherence tomography

Optical Coherence Tomography is a non-invasive imaging technique that enables a cross-sectional view of the retinal structures. It was first reported in 1991 and has since become a well-established commercial technique (Huang et al. 1991; Fujimoto and Swanson 2016). Early studies established OCT as a useful measure in macular disease detection, allowing identification of sub- and intra-retinal fluid, which enabled detection and monitoring of nAMD and the assessment of treatment efficacy (Hee et al. 1996). Subsequently, OCT is the recommended technique in the management of nAMD (Amoaku et al. 2015).

Comparable to B-scan ultrasonography, OCT uses optical reflections (rather than sound) from biological structures to provide spatial information, providing a reflectivity profile of the tissue being investigated (Huang et al. 1991). OCT utilises the principle of low-coherence light interferometry measuring reflectivity at certain depths in the tissue at regular intervals and increasing depth (Fujimoto and Swanson 2016). An axial A-scan is a reflectivity depth profile at one specific point in the measured structure. Lateral movement of the scanning system produces a series of adjacent A-scans to form a two-dimensional B-scan, and moving the system in two directions forms a three-dimensional C-scan (Figure 1.7) (Van Velthoven et al. 2007).

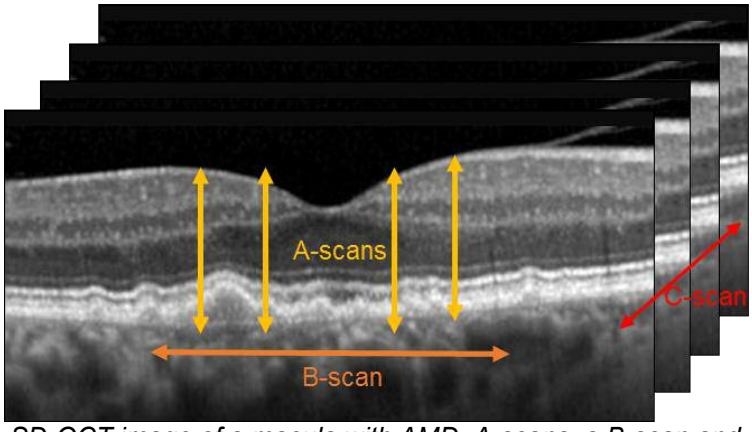


Figure 1.7 Cirrus SD-OCT image of a macula with AMD, A-scans, a B-scan and a C-scan are illustrated. Modified from (Regatieri, Branchini and Duker 2011).

1.3.2.1 Instrumentation

Currently, SD-OCT is the standard commercially available instrument, with imaging speeds ranging from 25,000 to 80,000 A scans per second (Van Velthoven et al. 2007; Cense et al. 2004; Fujimoto and Swanson 2016). The fast acquisition time reduces the effect of degrading artefacts such as eye movements, and decreases exposure of the eye (Yun et al. 2003; Wojtkowski et al. 2004). The capability of SD-OCT to amass large three dimensional datasets in a short acquisition time enables high quality data to be collected, in individuals with and without AMD (Menke, Dabov and Sturm 2008). However, SD-OCT is constrained by a fixed 800nm wavelength, which limits the visualisation of structures more posterior to the RPE, such as the choroid. It is also unable to image blood flow within the retinal capillaries.

The development of enhanced depth imaging OCT, swept-source OCT and of instruments with imaging performed at longer wavelengths has enabled visualisation of the choroid (Povazay et al. 2009b; Povazay et al. 2009a; Mrejen and Spaide 2013). Functional OCT techniques such as doppler OCT or OCT angiography, allow measurement of blood flow velocity and visualisation of the retinal vasculature (Drexler and Fujimoto 2008; Gao et al. 2016). This technique facilitates detailed imaging and quantification of the area of vasculature and of the blood flow, and has a potential utility in nAMD (Jia et al. 2014; Al-Sheikh et al. 2017). Additionally, reductions in blood flow which are associated with regions of atrophy can be used to identify GA (Choi et al. 2015; Schmidt-Erfurth et al. 2017).

Whilst techniques such as long wavelength OCT are advantageous, SD-OCT is a ubiquitous clinical instrument and is a recommended technique in the management of nAMD (Mowatt et al. 2014; Amoaku et al. 2015; Fujimoto and Swanson 2016). The selection of a specific SD-OCT device for research purposes should consider the performance of different devices. The Spectralis HRA-OCT (Heidelberg Engineering, Heidelberg, Germany) and Cirrus HD-OCT (Carl Zeiss Meditec, Inc.) demonstrated high repeatability and reproducibility when examining nerve fibre thickness (Pierro et al. 2012; Bentaleb-Machkour et al. 2012; Tan et al. 2012). The Spectralis HRA-OCT is a widely used SD-OCT, enhanced by the addition of a confocal scanning laser ophthalmoscope (SLO) to monitor eye movement. It has an acquisition speed of 40,000 per second with an axial resolution of 3.9μm (Sayegh et al. 2011). A variable number of B-scans are collated to produce a mean image of high resolution that is corrected for artefacts (Schütze et al. 2011). The Cirrus HD-OCT is a well-established SD-OCT. It has an axial resolution of 5μm, a scan speed of 27,000 a-scans per second, a scanning depth of 2mm and scans an area 6 x 6 mm at the macula (Brautaset et al. 2014). The Cirrus is reported to have good test-retest repeatability when used to measure retinal thickness in individuals with AMD. However, increased

severity of AMD is likely to have an effect on the variability due to factors such as poor fixation (Keane et al. 2009; Parravano et al. 2010a). Three-dimensional OCT (Topcon 3-D OCT-1000) combines CFP and SD-OCT. It has acquisition speed of 18,000 per second with an axial resolution of 6μm. One study comparing these three devices in GA reported that the Spectralis and Cirrus instruments acquire the highest quality images (Schütze et al. 2011). However, the Spectralis device gave significantly more segmentation errors than the Topcon and Cirrus devices (Schütze et al. 2011). Furthermore, the Cirrus device acquires a greater number of volume scans and also has a higher resolution under a similar acquisition speed than the Spectralis.

1.3.2.2 OCT quantification

Originally, hand segmentation of OCT scans allowed for quantification of retinal thicknesses. However, this was not clinically viable, due to the time consuming nature of marking the intra-retinal layer boundaries manually. Subsequently, automated segmentation methods were developed (Garvin et al. 2009). For example, OCT Explorer is part of the Iowa Reference Algorithm (Retinal Image Analysis Lab, Iowa Institute for Biomedical Imaging, Iowa City, IA), and the automated segmentation module is called OCTSeg (Abràmoff, Garvin and Sonka 2010; Quellec et al. 2010; Antony et al. 2011; Xinjian Chen et al. 2012). Version 3.6 of the automated segmentation software segments 11 retinal boundaries or 10 retinal layers (Figure 1.8). Using graph theory optimisation, it was initially designed for use with time domain OCT, and further developed for use with SD-OCT (Garvin et al. 2009; Kang et al. 2006).

Many of the commercially available SD-OCTs also have on-board segmentation software, however many of these only segment two boundaries to give total retinal thickness. A number of recent instruments such as the Topcon DRI OCT-1 Atlantis (Topcon Corp, Tokyo, Japan) and the Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany; software version 6.0) have the capability to segment intra-

retinal layers. However, the Iowa Reference Algorithm can segment images acquired from several different devices, and was found to be more repeatable than the 3D-OCT 1000 (Topcon Corp, Tokyo, Japan) and Cirrus HD-OCT on-board software (Carl Zeiss Meditec, Inc., Dublin, CA) (Terry et al. 2016). Furthermore, it has been validated in diabetic oedema (Sohn et al. 2013) and nAMD (Xinjian Chen et al. 2012; Quellec et al. 2010).

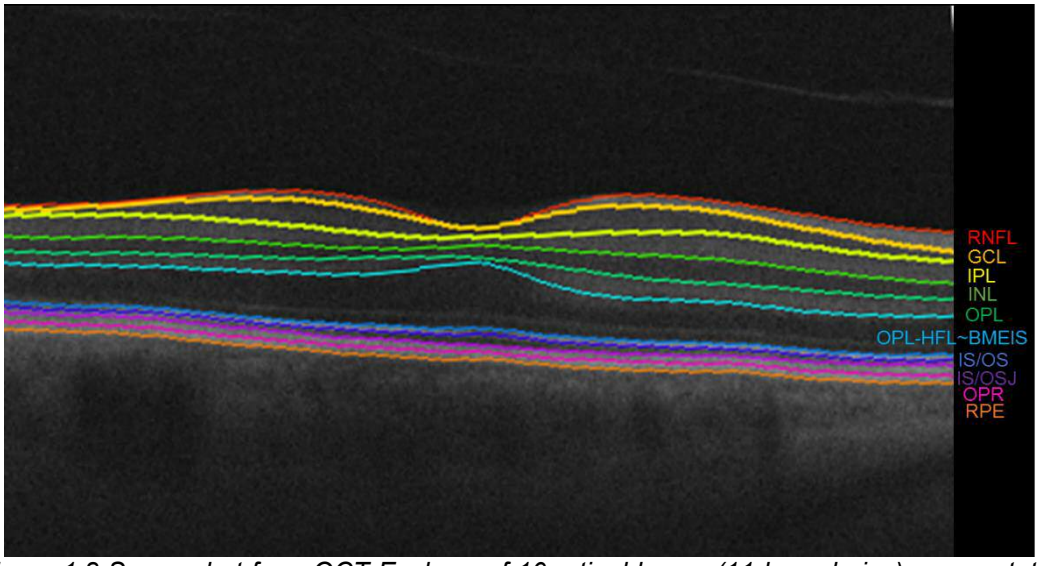


Figure 1.8 Screenshot from OCT Explorer of 10 retinal layers (11 boundaries) segmentation of a Cirrus HD-OCT image. Layers 1-10 as defined by the software: retinal nerve fibre layer (RNFL); ganglion cell layer (GCL); inner plexiform layer (IPL); inner nuclear layer (INL); outer plexiform layer (OPL); outer plexiform-Henle fibre layer to boundary of myoid and ellipsoid of inner segments (OPL-HFL~BMEIS); photoreceptor inner/outer segment layer (IS/OS); inner and outer segment junction to inner boundary of photoreceptor outer segment and retinal pigment epithelium complex (OPR); and retinal pigment epithelium (RPE).

Quantification of SD-OCT imaging in AMD also includes the measurements of drusen area and volume. The presence of drusen is associated with disease progression in AMD (Yehoshua et al. 2011), and therefore, the quantification of drusen is a useful biomarker. The level of precision in quantifying drusen size, area and volume from SD-OCT images is superior to the measures that may be obtained from fundus photography (Jain et al. 2010). The Cirrus HD-OCT has the capability to measure drusen volume (Gregori et al. 2011). Drusen volume measurement calculates the difference between the RPE segmentation and the virtual 'normal' RPE, which gives a measure of abnormality and describes drusen area and volume (Gregori et al. 2011). The segmentation software is reported as a reliable assessment of drusen

development over time and has been proposed as a useful strategy to monitor disease progression (Yehoshua et al. 2011).

1.3.3 Other imaging modalities

Fundus fluorescein angiography is utilised to identify and diagnose CNV; it is an invasive technique that involves intravenous injection of a fluorescent dye. This technique allows for identification of new vessels associated with CNV, which are not always visible on fundus photography (Nivison-Smith et al. 2014; Chalam and Sambhav 2016).

Fundus autofluorescence enables non-invasive visualisation of retinal fluorophores accumulating in the RPE (Wu et al. 2015d; Delori et al. 1995). Hyper or hypo autofluorescence are associated with lipofuscin levels in the RPE and can be indicative of drusen, GA and CNV (Rossberger et al. 2013; Holz et al. 2007; Peng, Dong and Zhao 2013; Paavo et al. 2017).

Infra-red imaging is a useful imaging modality in monitoring drusen and in the identification of RPD (Acton et al. 2011; Elsner et al. 1996; Hogg 2014). IR light is absorbed less by the RPE compared to visible light and therefore improves visualisation of subretinal structures (Acton et al. 2011; Elsner et al. 1996; Hogg 2014). Furthermore, it is advantageous in elderly individuals with media opacities, whereby IR light is absorbed less by the lens opacities compared to visible light used by other imaging techniques (Acton et al. 2011; Hartnett and Elsner 1996; Nivison-Smith et al. 2014).

Adaptive optics (AO) was designed to compensate for ocular aberrations that cause degradation of images. AO has been implemented in fundus photography, SLO and OCT devices, yet mainly within the research environment rather than commercial settings (Pircher and Zawadzki 2017). AO-OCT acquires high resolution images of the retinal layers allowing for visualisation of cone photoreceptors (Zayit-Soudry et al.

2013), retinal nerve fibre bundles (Kocaoglu et al. 2011) and retinal blood vessels (Zawadzki et al. 2005). However it has disadvantages, especially in those with AMD, as it is affected by motion artefacts which are high in those with poor fixation due to macular disease (Pircher and Zawadzki 2017).

A novel retinal imaging technique is multispectral imaging, which can provide information about molecules, structures and cells within the retina due to the different reflectance properties they exhibit. One recent study measured retinal oxygen saturation and haemoglobin level in normal individuals, in those with systemic hypoxia and in individuals with glaucoma (Desjardins et al. 2016). A second study investigated oxygen saturation and macular pigment density in a healthy population (Kaluzny et al. 2017).

To conclude, a combination of CFPs and SD-OCT imaging will provide extensive visualisation of the structural changes associated with AMD. Standardised classification methods of CFPs will enable AMD severity to be defined, whilst quantification of retinal thickness and drusen will allow more in depth analysis of AMD-associated retinal changes.

1.4 Functional measures

Functional measures are vital for the early detection and monitoring of AMD. These measures provide a better understanding of an individual's everyday visual experiences and how these may affect their daily functioning. There are a range of measures typically used to assess visual function in AMD. These include visual acuity (VA), contrast sensitivity (CS), reading speed and microperimetry, and will be discussed in detail. Additional measures relevant to AMD will be summarised. Further information can be found in a comprehensive review by Neelam et al. (2009).

1.4.1 Visual acuity

Visual acuity measures the spatial resolving power of the visual system at high contrast. It is the most commonly used clinical test of visual function. The ETDRS logMAR chart is an accurate and repeatable measure of VA and has subsequently become the gold standard for measuring VA in clinical trials (Kaiser 2009; Falkenstein et al. 2008). VA is the recommended functional method to judge treatment response in nAMD (Huang et al. 2015; Guymer et al. 2013; Amoaku et al. 2015) and is often the only visual function outcome in clinical trials in AMD (Ying et al. 2013; Waldstein et al. 2016).

Visual acuity has some limitations. Firstly, it measures the visual function at high contrast and, therefore, does not assess the sensitivity of the entire visual system. Secondly, VA only examines foveal function and cannot provide localised information about visual function across the macula. Additionally, the fovea has a high proportion of cones, which perform best under photopic conditions and, consequently, under mesopic conditions VA will be reduced.

The implications of these limitations include, firstly, a lack of sensitivity in the detection of early functional deficits in AMD. In early AMD, CS is significantly reduced, however due to VA measurement being performed at high contrast, this impairment in CS would not be detected (Midena et al. 1997). Secondly, AMD-related morphology is not solely located at the fovea. Some individuals with AMD maintain good VA, despite the presence of retinal lesions and functional deficits that are located outside of the foveal area. Finally, given that early AMD primarily affects the rod photoreceptors, the reduced functional ability under low light levels (Curcio, Medeiros and Millican 1996), may not be identified by VA. Alternative functional measures, such as microperimetry, CS and dark adaptation, are more sensitive to changes in early AMD, and more useful when monitoring longitudinal change or efficacy of treatment (Midena et al. 2004; Parravano et al. 2010a; Owsley et al. 2001; Midena et al. 1997).

Low luminance VA (LLVA) is a modified measure of VA, which addresses one of the limitations of VA with respect to contrast. It involves the measurement of VA with the ordinarily lit ETDRS letter chart, and a 2.0 log unit neutral density lens in place (reduces luminance by 100 times) (Wu et al. 2014b; Sunness et al. 2008). The difference between the LLVA and best corrected VA (BCVA) gives the low luminance deficit (LLD), which has been found to be associated with night vision symptoms in intermediate AMD (Wu, Guymer and Finger 2016), and vision loss in GA (Sunness et al. 2008).

The ETDRS logMAR chart is the most appropriate measure of threshold acuity in vision research (Johnston 1991). Comprehensive assessment of visual functioning requires a combination of VA and additional measures of visual function.

1.4.2 Contrast sensitivity

Contrast refers to the difference in luminance between a target and the background (Pelli and Bex 2013). CS measures the ability of the visual system to distinguish a target from the background at different contrasts, and is expressed in log units. CS is a more realistic measure of the visual system and of the 'real world' visual functioning than VA (Monés and Rubin 2005). CS detects reduced visual function even in individuals with no significant drop in VA (Kleiner et al. 1988). In AMD, CS has a high test-retest variability; to a greater extent in early than in late stage disease (Patel et al. 2009).

Letter CS charts are now the most ubiquitous method to measure CS in a clinical environment. Since 1988, the Pelli-Robson (PR) chart has been one of the most common CS charts. It is a letter optotype chart consisting of Sloan letters arranged into 16 groups of triplets of the same contrast (Pelli, Robson and Wilkins 1988). It has good reliability and repeatability in an extensive range of patients (Bühren et al. 2006; Richman, Spaeth and Wirostko 2013; Mäntyjärvi and Laitinen 2001). The Mars Letter Contrast Sensitivity test is a more recent design, which also uses Sloan letters, but

implements a different scoring procedure based on the number of letters correctly identified, rather than triplets of letters (Arditi 2005). The reliability and repeatability of the Mars chart were examined in normal individuals and in participants with AMD, it was demonstrated to be equal to if not better than the PR chart (Haymes et al. 2006; Thayaparan, Crossland and Rubin 2007). The Mars Letter Contrast Sensitivity test is advantageous compared to the PR chart, as it is more convenient and more appropriate to the range of contrast sensitivities in those with a visual impairment (Haymes et al. 2006; Dougherty, Flom and Bullimore 2005).

1.4.3 Reading

Reading performance is a valuable tool in diagnosing reduced visual function in AMD (Stifter et al. 2005). In individuals with AMD, reading performance and specifically reading speed is significantly reduced and associated with reduced visual satisfaction, and a reduced vision-related QoL (Stifter et al. 2005; Riusala, Sarna and Immonen 2003).

Reading is a complex task, it requires the ability to resolve the text and the capability to cognitively process and understand that which is being read. Different aspects of reading can be measured: reading acuity (near VA), critical print size and maximum reading speed. Reading speed is a particularly useful measure of reading performance. The four visual factors that affect reading speed are acuity reserve, contrast reserve, field of view and scotoma size (Whittaker and Lovie-Kitchin 1993). In an individual with visual impairment, acuity and contrast reserve typically decrease, until a level is reached that prevents fluent reading. An individual's maximum reading speed should be at least 80 wpm for sustained reading. Below this, difficulties with reading tasks and reduced satisfaction are reported (Friedman et al. 1999; Whittaker and Lovie-Kitchin 1993).

The International Reading Speed Texts (IRest) were developed as a result of the need for a standardised reading speed test across several languages. Paragraphs were

chosen over sentences, to enable a more realistic measure of reading speed. The IRest was developed in 17 different languages and showed minimal within subject variability (Trauzettel-Klosinski and Dietz 2012). The IRest has been used as an outcome measure in several studies in glaucoma (Ramulu et al. 2011; Ramulu et al. 2013) and in a study of depressive symptoms in AMD (Mielke et al. 2013). Compared to other widely used measures of reading performance, the Radner Reading Charts and MNread Reading Test, the IResT provided the most realistic measure of reading performance despite being more time consuming (Brussee, van Nispen and van Rens 2014).

1.4.4 Microperimetry

Microperimetry is comparable to standard automated perimetry (SAP) as it measures the differential light sensitivity (DLS), i.e. the minimum luminance of a white spot stimulus, superimposed upon a white background of uniform luminance, necessary to perceive the stimulus. Microperimetry is novel in that it uses an eye tracking system to correct the position of the stimulus to account for fixation losses (Markowitz and Reyes 2013). This is particularly beneficial in late AMD, in which unsteady fixation and/ or a preferred retinal locus are common (Acton and Greenstein 2013). Microperimetry also provides a real-time en-face image of the retina enabling a visualisation of the visual field outcome superimposed on to the retinal image.

In recent years, the clinical use of microperimetry has increased. In 1981, the first commercial microperimeter, the SLO 101 (Rodenstock, Ottobrunn, Germany), was used to produce scotoma maps of the macula (Timberlake et al. 1982; Mainster et al. 1982; Webb and Hughes 1981). Currently, the commercially available microperimeters include: the Nidek MP-3 (Nidek Technologies, Padova, Italy) and the Macular Integrity Assessment microperimeter (MAIA, CentreVue, Padova, Italy) (Table 1.4). These instruments have an improved dynamic range of 34dB for the MP-3 and 36dB for the MAIA, compared to 20dB for the two immediately earlier

commercially available instruments: the MP-1 (maximum stimulus luminance 400asb) and the Optos OCT SLO (Optos, Dunfermline, Scotland, UK) (400asb). The Optos combined both SD-OCT and microperimetry technology to acquire simultaneous functional and retinal structure data using a dual-imaging system. The technical specifications of the MP-3 and the MAIA can be found in Table 1.4 and a description of the MP-1 and the Optos can be found in a review by Markowitz and Reyes (2013).

	MP-3	**MAIA**
Refractive error correction (D)	-25 to +15	-15 to +10
Stimulus correction	Gaze-contingent	Gaze-contingent
Fixation monitoring method and speed	Tracks anatomic landmarks: 25Hz	Tracks each pixel of the fundal image: 25Hz
Microperimetry field of view(˚)	45	36
Background luminance (asb)	4 or 31.4	4
Stimulus attenuation (dB)	0-34	0-36
Differential luminance range (asb)	4-10,000	0.25-1000

Table 1.4 Features of two commercially available microperimeters. Modified from Markowitz and Reyes (2013)

A limitation of the current microperimeters is the lack of on-board statistical packages enabling the identification of overall and localised loss in the form of Total Deviation (TD) and Pattern Deviation (PD) probability analysis. Such analyses are similar to that which is implemented in standard perimetry (Heijl et al. 1989). TD is the difference between the measured DLS and the age matched normative database value at the corresponding location. The Mean Deviation (MD) or mean TD can also be used as a summary measure. PD adjusts the DLS values according to the overall height of the visual field and thus, shows more localised loss than TD. The majority of microperimetry studies use Mean Sensitivity (MS) as the primary outcome of microperimetry (Wu, Guymer and Finger 2016; Chandramohan et al. 2016; Hariri et al. 2016), which is less robust than pointwise analysis and also lacks probability

analysis. The establishment of a normative database allows location specific probability analysis, enabling the separation of focal defects from diffuse defects, and allowing these defects to be defined (Heijl, Lindgren and Olsson 1987a).

Whilst probability analysis is considered essential to the interpretation of standard perimetry (Flammer et al. 1983; Heijl, Lindgren and Olsson 1987a), to the author's knowledge, there is a paucity of literature in which such analysis has been applied to microperimetry. A previous study investigated normative values using the MP-1 instrument (Acton, Bartlett and Greenstein 2011). A sample of 50 healthy individuals were examined and MS in the central 10° reduced by 0.1 dB per decade (Acton, Bartlett and Greenstein 2011). Probability analyses similar to that of the Humphrey Field Analyser (HFA, Carl Zeiss Meditec, Dublin, CA) were derived from the prediction limits around the regression of DLS with age, and TD maps were generated (Acton, Bartlett and Greenstein 2011; Acton et al. 2012b; Acton et al. 2012a). In order to define abnormality, it is preferable to collect normative values specific to the study instrumentation and protocol parameters e.g. stimulus pattern, thresholding algorithm and background luminance (Acton, Bartlett and Greenstein 2011; Acton and Greenstein 2013).

A more recent study with the MAIA microperimeter, utilised computational surfaces to interpolate normative data between stimulus locations in relation to an individual's fixation (Denniss and Astle 2016). This study enabled location specific TD and PD probability analysis to be performed despite a non-foveal fixation location, which has benefits in those with unsteady/eccentric fixation associated with macular disease. Despite using strong statistical methodology, the study tested 237 stimulus locations over either 1 or 2 study visits lasting up to an hour, and these methods do not represent the typical clinical perimetric examination. Additionally, a limitation of the study is a potential learning effect in those individuals tested over two visits, where DLS results improve with experience and are most pronounced from the first to the

second visit (Wild et al. 1989; Heijl and Bengtsson 1996). Also, those with an hour testing time would be subject to the fatigue effect compared to those with shorter testing times (Hudson et al. 1994; Heijl and Asman 1995).

Further development of microperimetry in recent years has led to the adaptation of certain instruments to acquire scotopic measurements (Pfau et al. 2017). Instead of measuring largely cone function, as in ordinary 'mesopic' microperimetry, such instruments measure rod function under dark-adapted conditions (Midena and Pilotto 2017; Simunovic et al. 2016). It has been suggested that a functional deficit by scotopic microperimetry occurs earlier than that by mesopic microperimetry in early AMD (Nebbioso, Barbato and Pescosolido 2014) and intermediate AMD (Fraser et al. 2016), due to the rods being affected before the cones in the disease process (Curcio, Owsley and Jackson 2000).

Additionally, the implementation of AO technology in SLO imaging has led to further development of microperimetry measurements. AO-SLO imaging allows visualisation of the individual photoreceptors and, therefore, specific photoreceptors can be stimulated using this technology (Tuten, Tiruveedhula and Roorda 2012). However, research in this area is limited and the combined device is not commercially available, therefore, more work is required to establish its utility in AMD.

A systematic review evaluating the use of microperimetry in assessing visual function in AMD is presented in Chapter 2 and is modified from Cassels et al. (2017).

1.4.4.1 Macular Integrity Assessment microperimeter

The MAIA microperimeter became commercially available in 2009 (Figure 1.9). It is a near infrared line SLO instrument with an integrated 25Hz eye tracker, which corrects for eye movements by monitoring pixels within a fundal image. The MAIA light source is an infrared broadband super luminescent diode with a wavelength of 845nm. It has a 36˚ field of view and produces 1024 X 1024 pixel images. The MAIA has an improved dynamic range compared to that of the MP-1 instrument, however the MP-3 device has since become available with a similar dynamic range to the MAIA (Table 1.4) (Markowitz and Reyes 2013; Acton and Greenstein 2013; Acton et al. 2012a). Nevertheless, the MP-3 is limited by the lack of SLO technology and by the retinal tracking of a landmark rather than each pixel within the image. The MAIA device includes pre-defined stimulus configurations, but custom patterns may also be used.

Figure 1.9 The MAIA microperimeter with customised red filter placed on to the computerised screen (right) to avoid excessive light under dark adapted conditions.

The MAIA has the choice of two red circular fixation targets of a 1° or 12° diameter, produced by light-emitting diodes (LEDs) at 633nm. White Goldmann size III stimuli are presented onto a background of 1.27cd/m². The stimulus attenuation is 0-36dB with a maximum stimulus intensity of 318cd/m². It has three threshold estimating

strategies available: a scotoma finder supra-threshold strategy, a 4-levels-fixed supra-threshold strategy, and a 4-2 strategy.

The MAIA module software is reported by the manufacturers to contain a normative database and analysis software to enable identification of abnormality. However, the MAIA does not derive TD or PD analysis and merely displays the measured DLS, in dB, at each stimulus location. The DLS value is colour coded, using a continuous scale of colour change, to arbitrarily indicate normal, borderline and abnormal outcomes (Midena 2013) (Figure 1.10). This colour coding does not take into account the variation of DLS in the normal eye either with age, or with eccentricity (Figure 1.10). Additionally, the raw normative database values for the MAIA are currently not freely available, and a detailed methodology for derivation of the normative database is not provided in the published literature (Vujosevic et al. 2011).

A useful feature of the software includes the automated measure of fixation stability, by calculating the bivariate contour ellipse area (BCEA). The fixation positions throughout the examination are plotted on Cartesian axes and the area of the ellipse in which 63% or 95% of fixation points occur, is calculated (Figure 1.10). Fixation is also categorised as stable, relatively stable or unstable depending on the percentage of fixation points within 1° or 2° circular area representing the average centre of all fixation points (Fujii 2002). However, this method of quantifying fixation was reported to be less appropriate compared to the BCEA measure (Crossland, Dunbar and Rubin 2009).

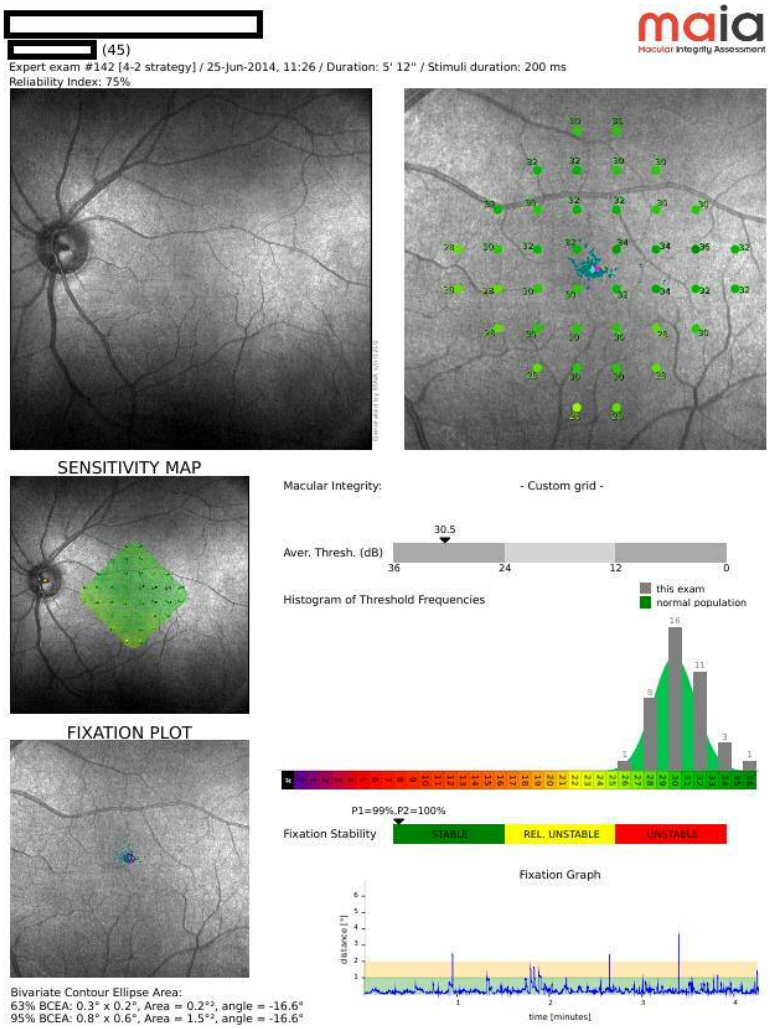


Figure 1.10 MAIA microperimetry output for a normal 45 year old individual: Infra-red MAIA image (top left) and a custom 40 location stimulus pattern (top right). The colour coding represents the different decibel values for sensitivity as shown on the frequency bar chart for the same individual (middle right). The histogram shown is that used to colour code the locations and is the same for all ages and eccentricities. The bivariate contour ellipse is overlaid on an IR image and calculated (bottom left). A fixation graph is also included to show the deviations in fixation (in degrees) during the examination (bottom right).

1.4.5 Other functional measures

A number of functional measures have been identified as potential biomarkers in AMD, including: flicker threshold (Dimitrov et al. 2011), colour threshold (Eisner et al. 1992; O'Neill-Biba et al. 2010) and dark adaptation (Dimitrov et al. 2012; Owsley et al. 2001; Owsley et al. 2007; Owsley et al. 2016).

Dark adaptation is the measurement of visual threshold recovery in the dark following presentation of a bright light that bleaches the retinal photopigment. The characteristic dark adaptation curve indicates that cones mediate the initial recovery after the bleach

and rods mediate the second stage of recovery. Rod-mediated dark adaption, cone dark adaptation and time to rod cone break are all suggested to be sensitive biomarkers for early AMD (Gaffney, Binns and Margrain 2011; Gaffney, Binns and Margrain 2013; Owsley et al. 2001; Owsley et al. 2007; Dimitrov et al. 2012).

Cone function may also be measured by the assessment of colour vision and allows for the additional assessment of the cone type affected in AMD. Blue-yellow colour vision is primarily affected in early AMD with red-green colour vision becoming affected in later stages of AMD (Cheng and Vingrys 1993; O'Neill-Biba et al. 2010).

Flicker threshold measures the highest detectable flicker rate. A sinusoidal flickering stimulus is presented at different frequencies with a fixed luminance and contrast, and the threshold is that at which the flickering stimulus appears steady. A flickering stimulus increases the retinal metabolic demand and, therefore, in AMD where the increase in metabolic demand cannot be met, the measured flicker threshold is reduced compared to healthy individuals (Dimitrov et al. 2011). Flicker threshold has the capability to detect functional deficits in early AMD compared to healthy individuals (Mayer et al. 1994; Dimitrov et al. 2012; Dimitrov et al. 2011).

To conclude, functional measures are a vital aspect of AMD clinical assessment and provide relevant information about the individual's everyday visual function. VA, CS, reading speed and microperimetry have all been shown to be sensitive to changes in AMD as a result of both treatment and progression and, therefore, are appropriate measures of visual function for individuals at all stages of AMD.

1.5 **Quality-of-life**

The World Health Organisation (WHO) states that QoL is the:

"individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" (WHOQOL 1995).

There are many aspects that affect a person's QoL including physical and mental health, social and economic situation, and education (WHOQOL 1995). This multidimensionality of QoL, suggests that change in one of these factors would be expected to affect an individual's QoL. Yet, each factor may affect QoL to a different extent depending on the individual. QoL is a highly debated topic and different aspects of QoL can be examined (Eurostat 2015). Vision-related and health-related aspects are often measured by separate questionnaires, with health-related outcomes typically sub-divided by physical and mental health. However, in reality these aspects are all intertwined (Figure 1.11).

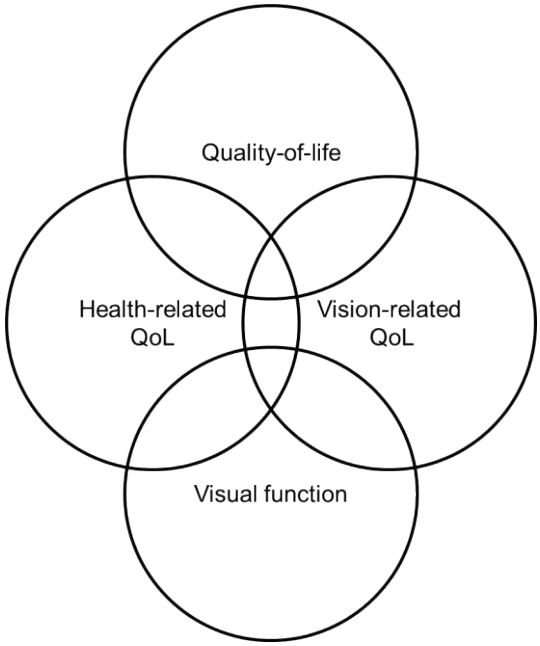


Figure 1.11 Venn diagram to illustrate the multidimensionality and overlap of QoL, health-related QoL, vision-related QoL and visual function.

1.5.1 Vision-related instruments

Visual function can be assessed by both objective and subjective methods. Objective measurements, such as VA or reading speed, are clinically important in assessing functional capabilities; however, this does not necessarily translate as the individuals 'real world' capabilities (Massof and Rubin 2001). For this reason, subjective methods, such as questionnaires, are now recommended in the assessment of visual function. Different questionnaires aim to assess separate aspects of vision and can

be referred to using different terms depending on that which is being measured. These terms include, but are not limited to vision-related QoL and visual function.

There are a large number of questionnaires or 'instruments' in optometry and ophthalmology, which assess visual function or vision-related QoL in different diseases. Each instrument is designed to measure specific aspects of visual function and vision-related QoL, either in a specific disease (e.g. glaucoma, cataract and AMD) or in a group (adult or child with low vision). It is, therefore, important to evaluate and select the most appropriate instrument available for the participants and the aims of the study (Khadka, McAlinden and Pesudovs 2013).

When evaluating these instruments, the psychometric properties, or the validity, reliability and responsiveness need to be considered (Khadka, McAlinden and Pesudovs 2013). Validity is the extent to which the instrument measures that which it was developed to measure. There are several types of validity: face, construct and criterion. Face validity refers to whether an instrument subjectively appears to measure what it is designed to. Construct validity assesses whether an instrument measures what it is designed to measure. Criterion validity can be subdivided into concurrent and predictive validity. Concurrent validity refers to how closely a new instrument correlates with an existing already validated measure. Predictive validity is the ability of an instrument to predict the results from an existing already validated measure (Bland and Altman 2002).

Reliability is the degree to which an instrument is free from random error, i.e. whether the same results are obtained a second time (Bowling and Ebradhim 2005). There are several tests for this, such as repeatability, reproducibility and internal consistency. Repeatability or test-retest reliability is the capability of an instrument to give the same measurement over a short period of time. Reproducibility is the ability to replicate an entire study. Internal consistency is usually measured by Cronbach's alpha, which calculates the correlations between items (questions) of an instrument.

Responsiveness is the ability of an instrument to detect a known change in an individual (Bowling and Ebradhim 2005).

Likert scales are commonly utilised to measure the responses for visual function instruments. Likert scales usually consist of a five point scale of answers, for example if the question was “how much difficulty do you have with watching the TV?” the answering categories might be: 0, “no difficulty”; 1, “a little difficulty”; 2, “some difficulty”; 3, “a lot of difficulty”; and 4, “unable to perform task”. The scores are then summed to give an overall score. This, however, does not take into account the difference in magnitude between the five points of the scale or the difference in difficulty between items (Elliott, Pesudovs and Mallinson 2007).

The Rasch model addresses these problems by assigning items different weightings depending on the difficulty of the item and person ability. The Rasch model was originally developed by Georg Rasch and was based upon item response theory (IRT). IRT addressed the concept that additional to items having different difficulties, people also have different abilities, and therefore, IRT scaled these accordingly (Pesudovs et al. 2007). Rasch analysis is a probabilistic logistic function that separates items and the individuals, which enables the difficulty of items and an individual’s pattern of answers to be analysed. The pattern of answers for each individual is analysed and an item difficulty rating generated accordingly. A scale based upon the individual’s responses is then produced, and compared with the other individuals. This converts ordinal raw scores into true linear scales, scored in logits, which allows for parametric statistical testing (Khadka, McAlinden and Pesudovs 2013). Additionally, Rasch analysis enables assessment of the overall fit of the items and persons to the Rasch model, which has been used to assess the validity and reliability of instruments (Massof and Rubin 2001; Pesudovs et al. 2007; Finger et al. 2008).

1.5.1.1 Age-related macular degeneration.

Age-related macular degeneration can cause difficulties with everyday activities such as self-care (Ivanoff et al. 2000) and leisure activities (Scilley et al. 2002), and also the ability to access local amenities (Hochberg et al. 2012), leading to a lack of freedom and independence (Williams et al. 1998; Bennion, Shaw and Gibson 2012). These difficulties can result in a subsequent decline in an individual's QoL (Curriero et al. 2013).

Many instruments assess different aspects of visual function and vision-related QoL including visual symptoms, socio-emotional well-being, participation in daily activities, and the effect of visual function on daily living. It is important that when measuring self-reported visual function or vision-related QoL, the chosen instrument has been validated within the intended population (Massof and Fletcher 2001). The five most commonly used instruments that have been evaluated within a population with AMD are described in the following paragraphs (Finger et al. 2008; Khadka, McAlinden and Pesudovs 2013).

1.5.1.1.1 National Eye Institute's Visual Function questionnaire

Originally, the National Eye Institute's Visual Function questionnaire (NEI VFQ) consisted of 52 items. It was designed to assess 'vision-targeted functioning' and how this influenced the vision-related QoL across a number of ocular conditions (Mangione et al. 1998). A survey of focus groups with a range of different ocular conditions was conducted, and it was concluded that to be clinically viable, the NEI VFQ would need to be shortened (Mangione 1998). The 25 item NEI VFQ (NEI VFQ-25) was one of several shorter versions (including 48, 39 and 36 items) created, which all had the same psychometric properties as the 52 item. However, these were more suitable for a clinical environment and more patient friendly (Mangione 2001; Matchar et al. 2006). The shorter versions are now widely used (Mangione 2001; Matchar et al. 2006), and the NEI VFQ-39 and the NEI VFQ-25 have been recommended for use due to a robust Rasch analysed construct (Pesudovs et al. 2010).

In CNV, the NEI VFQ-25 showed good reliability and internal consistency suggesting a good validity; however, Rasch analysis was not performed and this is a necessity in the psychometric testing of instruments (Orr et al. 2011; Khadka, McAlinden and Pesudovs 2012). In a population with low vision, the psychometric properties of the NEI VFQ-25 were assessed by Rasch analysis, and only 7 of the items were found to be sensitive to rehabilitation intervention (Stelmack, Stelmack and Massof 2002). In 2008, this was developed to produce the seven-item NEI VFQ, which was shown to have acceptable person separation reliability and sensitivity to changes after a rehabilitation intervention (Ryan, Court and Margrain 2008; Dougherty and Bullimore 2010). The floor and ceiling effects of the standard scoring of the NEI VFQ-25 were eliminated with the use of Rasch analysis, but the validity of the subscales needed reconsideration (Dougherty and Bullimore 2010). There are conflicting opinions on the use of the NEI VFQ and its various forms and subscales. A review of a number of instruments recommended several of the NEI VFQ subscales for use in a range of conditions, including refractive error and cataracts, but it was not recommended for use in AMD (Khadka, McAlinden and Pesudovs 2013).

1.5.1.1.2 Impact of Vision Impairment scale

The Impact of Vision Impairment (IVI) scale was established as a measure of vision-related QoL based upon participation in daily activities, and has been suggested as a useful approach to evaluate visual rehabilitation (Hassell, Weih and Keeffe 2000; Weih, Hassell and Keeffe 2002; Lamoureux et al. 2007b). It was developed in accordance with the WHO's statement on participation in daily activities (WHO 2001). Whereby, participation is affected by a number of factors including: eye disease, vision impairment, limitation of activities, individual characteristics and the environment (WHO 2001). The development involved consultation with focus groups, in addition to input from existing instruments (Hassell, Weih and Keeffe 2000; Weih, Hassell and Keeffe 2002). The IVI, unlike other instruments, focuses on the

individual's ability to participate within society, by assessing their visual capability in daily activities, rather than only what they are able to 'see'.

The IVI originally consisted of 32 items split into five domains: leisure and work, consumer and social interaction, household and personal care, mobility and emotional reaction to vision loss. Four of the 32 items IVI were demonstrated to deviate from the expected model when evaluated with Rasch analysis (Lamoureux et al. 2006). When these items were removed and the scoring altered, the instrument fitted to the Rasch model (Lamoureux et al. 2006). The revised 28 item IVI fitted to a three factor model divided into the subscales; "emotional well-being" (8 items), "reading and accessing information" (9 items) and "mobility and independence" (11 items) (Lamoureux et al. 2007c). The revised IVI was determined to be sensitive to changes in visual impairment when evaluating the benefit of cataract surgery in early AMD, suggesting the ability to identify changes due to treatment (Lamoureux et al. 2007a). IVI results were associated with VA, reinforcing the relationship between functional impairment and vision-related QoL (Lamoureux et al. 2007b). In AMD, the 28 item IVI fitted well to the Rasch model and was able to identify differences in the disease severity, suggesting validity in this population (Lamoureux et al. 2008). Most recently, the IVI was further shortened to produce a 'brief IVI' consisting of 15 items: 9 visual function items and 6 emotional well-being items (Fenwick et al. 2017). The aim of this shortened version was to reduce the time commitment required by the full length IVI and, therefore, reduce the burden for the participants.

In conclusion, the IVI is a vision-related QoL questionnaire that was developed to assess the effect of visual impairment on an individual's ability to participate in daily activities and society, as well as the emotional effect. It has been shown to be valid for a population with AMD, and sensitive to the severity of disease, in addition to changes due to interventions.

1.5.1.1.3 Visual Function Index

The Visual Function Index (VF-14) is an instrument that measures difficulty with visual tasks. It has fourteen items that are related to vision-specific daily activities and are scored on a Likert scale from 0 to 4; ranging from “no difficulty” to “unable to perform” respectively (Steinberg et al. 1994). It was designed for use within a population with cataracts, and when Rasch analysed within this population, there was concordance between the Rasch scores and traditional scoring (Steinberg et al. 1994; Valderas et al. 2004). The VF-14 was validated in retinal disease and AMD, in which it was found to be sensitive to changes in VA and progression of disease (Linder et al. 1999; Mackenzie et al. 2002). In late stage AMD, the VF-14 was shown to be a more useful predictor of subjective satisfaction with vision than VA (Riusala, Sarna and Immonen 2003). Rasch analysis of the VF-14 gives improved precision over Likert scoring, especially for the use in longitudinal studies (Hewitt et al. 2006; Las Hayas et al. 2011).

1.5.1.1.4 Macular Disease Quality of Life questionnaire

The Macular Disease Quality of Life (MacDQoL) instrument was originally developed to examine the impact that macular disease has on QoL (Mitchell and Bradley 2004). It was derived from a mixture of ideas from the ‘Schedule for the Evaluation of Individual QoL’ and the ‘Audit of Diabetes Dependant QoL’, then further developed using focus groups of individuals with macular disease (Mitchell and Bradley 2004). Once redundant items were removed, reducing the MacDQOL to 22 items, it was concluded that it had good face validity, construct validity, good test re-test repeatability and was sensitive to change in vision status (Mitchell et al. 2005; Mitchell et al. 2008). More recently, Rasch analysis was used to examine the psychometric properties of the MacDQOL and the answering categories were determined to have overlapping responses (Finger et al. 2012; Khadka, McAlinden and Pesudovs 2013). The instrument was also multidimensional; however, it could be split into two

subscales with simplified scoring which were psychometrically sound (Finger et al. 2012; Khadka, McAlinden and Pesudovs 2013). A more recent study performed a semi-structured interview with individuals with AMD asking questions related to the applicability of the MacDQOL instrument (Ord et al. 2015). This study concluded that the MacDQOL was relevant to those with AMD (Ord et al. 2015), however the study was limited by the lack of robust statistical analysis.

1.5.1.1.5 Daily Living Tasks Dependent on Vision

The Daily Living Dependent on Vision (DLTV-22) instrument was specifically developed as a "vision specific functional index" for individuals with AMD (Hart et al. 1999). Activities in which difficulties arise due to visual impairment were identified by individuals with AMD and healthcare professionals (Hart et al. 1999). Items were then derived from these activities and a Likert scale of responses was used (Hart et al. 1999). The psychometric properties of the DLTV-22 were improved by identifying four domains and removing redundant items (DLTV-17) (Hart et al. 2005). Additional refinement reduced the items to 11, with a 7 item subscale, which was recommended for use with an AMD population (Denny et al. 2007; Khadka, McAlinden and Pesudovs 2012).

1.5.1.1.6 Utility measurement

Utility measurements are most commonly utilised to provide an unbiased assessment of an individual's health state (Redelmeier and Detsky 1995). One method of utility measurement is the time-trade off instrument (TTO) (Brown 2000). The TTO instrument, undertaken as a health-related metric, poses two hypothetical questions; firstly, how many years the individual expects to live and secondly, how many of those years the individual would trade in return for perfect health. A utility value can then be calculated, a value of 1.0 indicates perfect health state and 0.0 indicates death (Brown 2000).

This instrument has been adapted for use with respect to vision, in which the wording of the hypothetical questions is altered to include perfect sight rather than perfect health state. This adapted TTO has been previously implemented in individuals with AMD (Brown 2000; Butt et al. 2013; Stein et al. 2003; van de Graaf et al. 2016) and is recommended for use in economic evaluations of AMD due to the association with VA (Butt, Tufail and Rubin 2017).

To summarise, there are a number of vision-related instruments that have been evaluated in a population with AMD. Three instruments are appropriate for individuals with AMD: one measuring visual function (VF-14), one measuring utility (TTO) and one measuring vision-related QoL (IVI). The VF-14 provides a subjective measurement of visual function, which has been shown to be sensitive to AMD severity. The TTO gives an unbiased assessment of the individual's visual impairment by calculating a utility value. The psychometric properties of the IVI have been examined both in a normal population and in individuals with AMD in numerous studies. Additionally, the face validity of the IVI shows a variety of items covering the three different domains, and thus, it provides a thorough assessment of vision-related QoL.

1.5.2 Health-related instruments

Physical and mental health have a larger impact on QoL than visual factors in individuals with low vision (Hernandez Trillo and Dickinson 2012), and it is therefore important to consider health-related measures when investigating vision-related QoL.

1.5.2.1 Physical health

Different chronic co-morbidities have varying effects on QoL. Since 75% of visually impaired adults have additional co-morbidities (Van Nispen et al. 2008), it is essential to take these into account when examining a population with visual impairment. As AMD is an age-related disease, additional co-morbidities are common and lead to an

increased risk of a reduced QoL (Van Nispen et al. 2009). The use of a well-established generic health instrument is necessary, as validation in different populations has already taken place and, therefore, allows for meaningful comparisons (Mangione 1998).

1.5.2.1.1 EQ-5D

The EQ-5D is a generic health status instrument, developed by the EuroQOL group. The EuroQOL group aimed to develop an instrument that was non-disease specific and standardised, but described an individual's health status (EuroQoL 1990). The EQ-5D has 5 domains: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. Each question has a three (EQ-5D-3L) or five level (EQ-5D-5L) scale of answers. This allows for the classification of 243 health states (Rabin and de Charro 2001). The EQ-5D is recommended by the National Institute for Health Care and Excellence (NICE) in the UK and is thus one of the most commonly used health status instruments in clinical practice. Furthermore, it has been utilised in clinical and economic evaluations of health care, and in population health surveys (Rabin and de Charro 2001; Clemens et al. 2014; Rencz et al. 2016). The EQ-5D is also typically included in research in AMD (Chatziralli et al. 2016; Lotery et al. 2007; Payakachat et al. 2009). The EQ-5D score is reduced in individuals with AMD compared to controls (Chatziralli et al. 2016).

1.5.2.1.2 Short Form Health Survey

The Short Form 36 Health Survey questionnaire (SF-36) is a standardised measure of health status (Garratt et al. 1993), and has been widely used to measure the impact of interventions (Garratt et al. 1993). The SF-36 has 8 dimensions that can be combined into two summary measures: physical and mental health, and has been shown to have high internal consistency, reliability and validity (Stewart 2007). The 36 item version has since been reduced to 12 items and the scoring altered to produce the 12-item Short-Form Health Survey (SF-12), which was found to be valid and

reliable in a sample of older adults (Resnick and Nahm 2001; Resnick and Parker 2001). Additionally, the SF-36 was further developed into a six-dimensional questionnaire, the SF-6D, which consists of 10 items from the original questionnaire (Brazier, Roberts and Deverill 2002). The SF-6D differs from the other two versions as it estimates a single index of health using normative database values, and can subsequently be used in economic analysis (Brazier, Roberts and Deverill 2002). The SF-36, SF-12 and SF-6D have all been utilised in AMD research (Hassell, Lamoureux and Keeffe 2006; Choudhury et al. 2016; Mathew et al. 2011; Espallargues et al. 2005) .

In conclusion, the EQ-5D and the SF-6D are both NICE recommended and have been implemented in those with AMD. However, a review by the NHS stated that the EQ-5D was the preferred health status measure by NICE, showing good responsiveness for visual disorders (Longworth et al. 2014).

1.5.2.2 Mental health

In AMD, the prevalence of depression is approximately twice as high as in the general population (Brody et al. 2001), and is also associated with reduced visual function (Rovner, Casten and Tasman 2002; Brody et al. 2001). Dissatisfaction of performance in certain daily activities has been associated with an increased risk of depression in AMD (Rovner et al. 2007). However, the presence of depressive symptoms can also be associated with greater difficulty with daily tasks in individuals with a visual impairment (Jones et al. 2009), and reduced visual function in AMD (Rovner, Casten and Tasman 2002). Social status can also affect mental health; for example in AMD, depression was less likely to occur when cohabiting (Jivraj et al. 2013). Mental well-being or positive mental health is defined as the positive aspects of an individual's everyday functioning, and is a less explored area in those with AMD. The depression instruments recommended by NICE will be briefly described and an instrument to measure well-being will also be summarised.

1.5.2.2.1 Patient Health Questionnaire-9

The Patient Health Questionnaire-9 (PHQ-9) is a well-established instrument to detect depression (Kroenke, Spitzer and Williams 2001). The 9 items are established from the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition), which describes diagnoses of major or minor depressive disorders (Association 1994). The PHQ-9 measures the symptoms of depression. A Likert scale is used to grade the symptoms from 0, “not at all” to 3, “every day”. The score is the sum of the answers and the higher the score, the more severe the depressive symptoms. The PHQ-9 is the NICE recommended instrument to measure depression severity at baseline and after treatment (Smarr and Keefer 2011).

1.5.2.2.2 Beck Depression Inventory

The Beck Depression Inventory (BDI) was developed in 1961 to measure depression objectively and to enable change to be monitored (Beck 1961). It has been adapted several times. One of the most recent versions is the BDI-II, which was developed due to the changed diagnostic criteria for depression. It is a 21 item questionnaire with a 4 category Likert scale, except for two questions that have 7 category Likert scale. The BDI-II is also one of the NICE recommended depression instruments (Smarr and Keefer 2011).

In conclusion, the PHQ-9 and the BDI are NICE recommended measures of depressive symptoms. Both instruments are well-established instruments, however the PHQ-9 is shorter than the BDI and therefore is more effective within a clinical research study.

1.5.2.2.3 Warwick-Edinburgh Mental Well-being Scale

Mental well-being can be broken down into two positive aspects; pleasure and life satisfaction (hedonic perspective) and positive cognitive functioning, healthy relationships with others and self-acceptance (eudaimonic perspective) (Ryan and Deci 2001; Berridge and Kringelbach 2011). Mental well-being is different to mental

health as it describes positive aspects of thinking and feeling, whereas mental health can include a range of conditions from excellent to poor mental health.

The Warwick-Edinburgh Mental Well-being Scale (WEMWBS) was developed in 2006 after being commissioned by Warwick and Edinburgh universities (Tennant et al. 2007). It was developed as a scale to assess positive mental health by building on existing instruments and including both aspects of well-being; hedonic and eudaimonic (Tennant et al. 2007). The development of the WEMWBS combined expert advice from many disciplines including psychiatry, public health and focus group discussions. The final instrument consisted of 14 positively worded items with 5 Likert response categories. Rasch analysis was subsequently used to evaluate the WEMWBS, and it was established to be multidimensional. Items were deleted until strict unidimensionality was obtained and 7 items remained, which became the shortened WEMWBS (SWEMWBS) (Stewart-Brown et al. 2009). Face validity of the SWEMWBS displayed bias towards eudaimonic well-being rather than hedonic, and it was concluded that the WEMWBS provided a less restricted assessment of well-being (Stewart-Brown et al. 2009).

In one recent publication in individuals with low vision, no change in WEMWBS was observed as a result of vision rehabilitation (Acton et al. 2016). However, the association between well-being and vision-related QoL has yet to be established. The already established relationship between QoL and depression in AMD (Rovner, Casten and Tasman 2002), may suggest that AMD would also be associated with a reduced level of well-being measured by the WEMWBS.

To summarise, QoL is a multidimensional concept that is difficult to define and measure. Using a combination of health- and vision-related instruments will enable a thorough evaluation of QoL. AMD is associated with a reduced vision-related QoL and the ability to understand this relationship in respect to clinical findings and health-

related measures may lead to improved identification of individuals at risk of reduced QoL within a clinical setting.

1.6 Rationale

In the evaluation of QoL and clinical outcomes in AMD, the overall aim of the thesis is to determine the factors that predict QoL in those with AMD, both at baseline and after 1 year follow-up. This section will describe the rationale behind this aim and the detailed aims of each chapter.

Age-related macular degeneration is the leading cause of sight loss in the developed world (Klein et al. 2013), and owing to an ageing population is predicted to become an increasing economic and social burden (Saxena et al. 2016; Day et al. 2011). QoL outcomes are critical to the individual and AMD has detrimental effects on an individual's QoL (Chatziralli et al. 2016), reducing independence (Wong et al. 2004), limiting activities (Scilley et al. 2002), and increasing the risk of falls and depression (Knudtson, Klein and Klein 2009; Rovner, Casten and Tasman 2002). AMD management should take these QoL changes into account. Additionally, as a result of the increasing economic burden, the ability to identify those at risk of a reduced QoL would allow more economically viable support mechanisms for those in need.

QoL is a multidimensional concept and consequently, it is influenced by a number of aspects of daily living including physical and mental health, education, and social and economic status (WHOQOL 1995). Depression is also an important predictor of QoL (Moore et al. 2005). The prevalence of depression in individuals with low vision is twice that of those with normal vision (van der Aa et al. 2015). Furthermore, it is well established that depression has a high incidence within a population with AMD (Rovner, Casten and Tasman 2002).

Clinical measures of visual function also represent a measure of the individual's everyday functioning (West et al. 2002a), and are associated with QoL in those with

AMD (Cahill et al. 2005). VA is the most established outcome measure of visual function in AMD clinical trials, yet it has been suggested that VA is not sensitive to early functional loss in AMD (Parravano et al. 2010b; Midena et al. 2007). Other common measures of visual function include assessments of reading ability and CS, which have both previously been associated with self-reported visual performance and vision-related QoL (Hazel et al. 2000; McClure et al. 2000). However, CS (measured with a letter chart) and VA are typically limited to the measurement of foveal function. A topographical measure allows a more detailed assessment of visual function and may be more valuable in a disease such as AMD, which extends across the retina. Microperimetry is such a technique, and can identify both focal and generalised functional loss. Thus, the investigation of the microperimetry outcomes relative to QoL measures may yield stronger relationships with QoL than measures such as VA, CS and reading ability.

In summary, when evaluating the factors that may predict a reduced QoL in those with AMD it is appropriate to consider clinical measures of visual function, AMD severity, metrics of depression and health status. The research presented herein will include VA, CS, reading speed and microperimetry outcomes to measure visual function, PHQ-9 to measure depressive symptoms and EQ-5D to measure health status.

It is also of interest to investigate if a change in QoL over a period of 1 year could be predicted by either the baseline measures or by the change in the same factors. Potential implications of these findings would form an evidence base for a clinical tool to identify those with a change in QoL without the need for a time-consuming questionnaire interview. This would subsequently allow clinicians to make sound management decisions with economic and social benefits, and allow resources to be directed to those who require it.

1.6.1 Thesis aims

The overall aim of this research was to investigate the relationship between clinical measures and vision-related QoL outcomes in individuals with AMD.

The detailed aims are:

- To provide a comprehensive systematic review of the current literature on the use of microperimetry as a measure of visual function in AMD.
    - This aim is addressed in Chapter 2: A systematic review evaluating the use of microperimetry in assessing visual function in age-related macular degeneration.
- To derive a pointwise age-corrected normative database with a statistical model to perform global and localised probability analyses. Two secondary aims were: to examine over three visits the characteristics of the macular visual field (MVF), from microperimetry, with respect to age and eccentricity; and to compare two different methods of deriving the normative database.
    - In Chapter 4, it was necessary to develop a robust method to analyse the outcomes of microperimetry, prior to its use in the evaluation of AMD.
- To evaluate the association between AMD-related retinal microstructure changes and microperimetry outcomes at 5° from fixation.
    - This aim is addressed in Chapter 5: The association between SD-OCT and microperimetry outcomes. The complex interrelationships between these outcomes are of interest due to their role as potential biomarkers in AMD.
- To establish the relationship between vision-related QoL, as measured by the IVI questionnaire, in individuals with AMD and the following variables: AMD severity, VA, CS, reading speed and microperimetric outcomes; additional

vision-related self-reported outcomes, assessed by VF-14 and TTO; depression (PHQ-9); health status (EQ-5D-3L); and well-being (WEMWBS).

    - Chapter 6: Vision-related quality-of-life in individuals with age-related macular degeneration directly examined the primary aim of the thesis.

- To examine the relationship between change in vision-related QoL and clinical outcomes over 1 year, in a subset of individuals with AMD. To achieve this, it was necessary to, firstly, quantify the change in vision-related QoL (IVI), clinical measures of visual function (CS, VA, reading speed and microperimetric outcomes), health status (EQ-5D), depression (PHQ-9) and well-being (WEMWBS) after a follow-up period of 1 year. Secondly, to evaluate the factors that determine change in vision-related QoL after 1 year.
    - In Chapter 7, the relationship between change in vision-related QoL and clinical outcomes benefitted from the added insight of a longitudinal evaluation of QoL, and allowed the identification of those at risk of a change over time.

Chapter 2: The use of microperimetry in assessing visual function in age-related macular degeneration

2.1 Summary

Microperimetry is a novel technique for assessing visual function and appears particularly suitable for AMD. Compared to SAP, microperimetry offers several unique features. It simultaneously images the fundus, incorporates an eye tracking system to correct the stimulus location for fixation loss, and identifies any preferred retinal loci.

A systematic review of microperimetry in the assessment of visual function in AMD identified 680 articles; of these, 56 met the inclusion criteria.

Microperimetry and AMD is discussed in relation to: disease severity; structural imaging outcomes; other measures of visual function; and evaluation of the efficacy of surgical and/ or medical therapies in clinical trials.

The evidence for the use of microperimetry in the functional assessment of AMD is encouraging. Disruptions of the ellipsoid zone band and RPE are clearly associated with reduced DLS despite the maintenance of good VA. Reduced DLS is also associated with outer segment thinning and RPE thickening in early AMD and with both a thickening and a thinning of the whole retina in CNV. However, microperimetry lacks the robust diffuse and focal loss age-corrected probability analyses associated with SAP and the technique is currently limited by this omission.

2.2 Introduction

Age-related macular degeneration is the leading cause of blindness in the developed world (W.H.O 2016) and accounts for the majority of registerable visual impairment in both the USA and the UK (Resnikoff et al. 2004; Bunce, Xing and Wormald 2010; Klein et al. 2013).

Visual acuity is the most widely used outcome measure in ophthalmic research; however, VA is insufficiently sensitive to detect the early stages of functional loss in AMD (Parravano et al. 2010b; Midena et al. 2007). Various other tests of visual function, such as dark adaptation (Owsley et al. 2001), flicker threshold (Dimitrov et al. 2011) and photostress recovery time (Neelam et al. 2009), are more sensitive than VA in detecting early functional loss in AMD; however, such tests have limited clinical utility due to their time-consuming nature (Neelam et al. 2009). There is, therefore, a need for a robust and clinically appropriate technique to assess visual function across the macula that is more indicative of visual function than VA.

Microperimetry is similar to SAP in that it measures the DLS, i.e. the minimum luminance of a white spot stimulus, superimposed upon a white background of uniform luminance, necessary to perceive the stimulus. However, microperimetry is novel in that it uses an eye tracking system to correct the position of the stimulus for any fixation loss. Such a correction is particularly appropriate in the later stages of macular disease where unsteady fixation and/ or a preferred retinal locus is common. Microperimetry offers the additional benefit of providing a real-time en-face image of the posterior pole. The latter is of value in macular disease as it enables direct comparison between the visual function outcome and the underlying fundal appearance (Acton and Greenstein 2013).

The concept of microperimetry was initially illustrated clinically in 1981 (Webb and Hughes 1981). Currently, there are two commercially available microperimeters: the

Nidek MP-3 (Nidek Technologies, Padova, Italy) and the MAIA (CentreVue, Padova, Italy). These instruments have an improved dynamic range of 34dB (differential luminance range of 4 to 10,000asb) for the MP-3 and 36dB (0.25 to 1,000asb) for the MAIA, compared to 20dB for the two immediately earlier commercially available instruments: the MP-1 (400asb) and the Optos OCT SLO (Optos, Dunfermline, Scotland, UK) (400asb). The background luminance for the MAIA is 4asb; while the MP-3 offers the option of either 4asb or 31.4asb. The technical specifications of the current and earlier microperimeters are reviewed in detail elsewhere (Markowitz and Reyes 2013). The eye-tracking systems automatically register the eye position at 25 times per second relative either to given anatomic landmarks (MP-3) or to each pixel of the fundal image (MAIA).

Mean Sensitivity is the most common outcome measure in microperimetry and is defined as the mean of the DLS obtained across all the designated stimulus locations. However, the MS is a summary measure and does not account for the decline in DLS with age. Less common, but more appropriate outcome measures for microperimetry are the TD which is defined as the difference between the DLS at a given stimulus location and the corresponding age-corrected normal value; and the MD which is defined as the weighted arithmetic mean of the TD obtained across all the designated stimulus locations. A worsening of visual function is indicated by an increasingly less positive MS and by an increasingly negative TD and MD.

Given that microperimetry is novel, and that the design features appear particularly suitable for assessing visual function in AMD, a systematic review was undertaken to critically evaluate the literature relating to the use of microperimetry for assessing visual function in AMD. The published version of this review can be found in Appendix A (Cassels et al. 2018).

2.3 Methods of literature search

The Medline, Ovid, EMBASE and Web of science databases were each searched using the search terms in Table 2.1. The search extended from 1950 (Medline only) to July 2017. The search terms were divided into two groups: population and instrument (Table 2.1). Each selected article was required to match at least one search term from each group. Additional articles were identified from the references within the publications identified by the primary search. The abstracts of articles found from the database search were independently assessed by two of the authors (NC and JA) to identify those that met the inclusion criteria.

Population		**Instrument**
Age-related Macul*		Microperimet*
AMD		Fundus controlled perimet*
ARMD	**AND**	
Macular degeneration		
Dry Macular degeneration		
Wet Macular degeneration		
Senile Macular degeneration		

Table 2.1 Terms used in the database search (=truncation: includes various word endings into search).*

Eligible articles had to include microperimetry undertaken on at least twenty eyes with AMD to provide a minimum level of evidence. All articles were required to contain the DLS outcome obtained by microperimetry. Preferred retinal location and fixation studies were excluded. Only articles that discussed microperimetry in the context of the outcome from other commercially available instrumentation were included. Conference abstracts and case reports were excluded. Studies where the whole article was not written in English were also excluded.

2.4 **Results**

The search methods identified 687 primary articles. Six additional articles were obtained from the references within the primary retrieved articles. The final number of included articles was 56 (Figure 2.1).

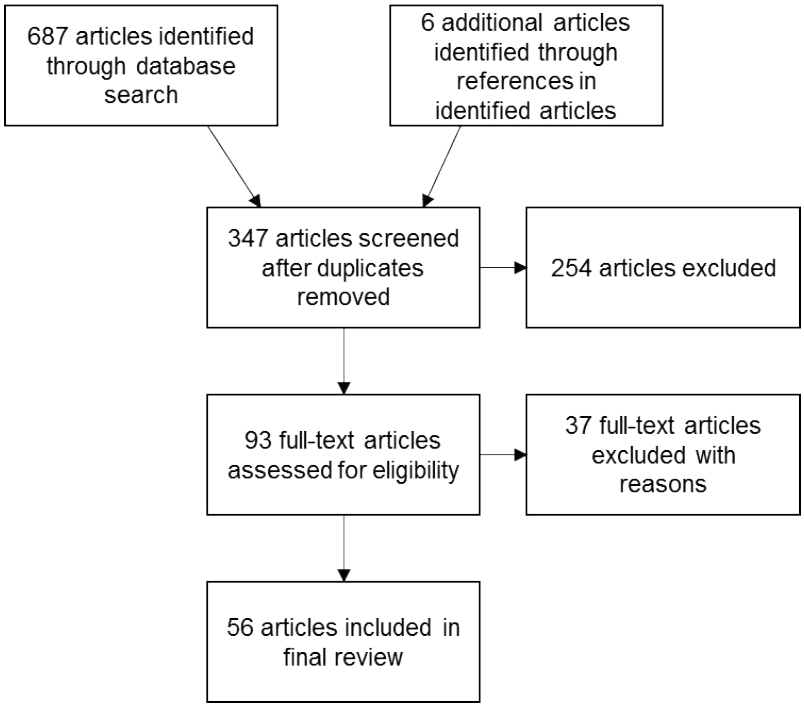


Figure 2.1 A Flow diagram demonstrating the primary identified articles and those included and excluded at each stage of the literature review. Adapted from PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis).

The review was divided into four principle areas which reflected the content of the included articles: evaluation of the efficacy of microperimetry in distinguishing between the various stages of AMD severity (6 articles); the relationship between microperimetry outcomes and structural imaging outcomes (including SD-OCT) (23 articles); the relationship between microperimetry outcomes and those of other measures of visual function (15 articles); and microperimetry outcomes in the evaluation of the efficacy of medical therapy and/ or surgical intervention in the treatment of AMD (17 articles).

2.4.1 Quality of evidence

The quality of each of the 56 included articles is described in Appendix B, which is ordered by quality of evidence. The studies were classified as either experimental or

observational. Within these two classifications, experimental studies were classified as either randomised control trial (RCT) or as non-randomised design, which will be referred to as quasi-experimental. Observational studies were classified as cross-sectional, case-controlled or case series studies. None of the included studies were cohort studies. Assessment of the quality of reporting showed that over half the articles included in this review had limitations relating to the quality of the microperimetry outcome (19 articles) and/ or to the reporting of the SD-OCT methods and analysis (12 articles). The reporting of microperimetry stimulus parameters was also generally poor, particularly in regard to the description of the stimulus program (i.e., the number, the location and the separation, of the stimuli).

The method of classification of AMD severity varied between the various studies and limited the extent of meaningful comparisons between studies. These comprised the AREDS grading system (AREDS 2001) (9 articles), the Beckman classification (Ferris et al. 2013) (10 articles), the Wisconsin Age-related Maculopathy Grading system (Klein et al. 1991) (1 articles), and the International Classification and Grading system (Bird et al. 1995) (2 articles). Consequently, the classification method utilised in each study is noted, where appropriate, throughout this review.

Similarly, the difference in the stimulus parameters and also in the dynamic range between the various microperimeters used in the various studies hinder direct comparisons of DLS between studies (Acton, Bartlett and Greenstein 2011). Microperimetry was undertaken by the Nidek MP1 or MP1-S in 30 of the 57 included articles (Giacomelli et al. 2013; Grenga et al. 2013; Dinc et al. 2008; Dunavoelgyi et al. 2011; Huang et al. 2015; Iaculli et al. 2015; Iwama et al. 2010; Kiss et al. 2009; Lazzeri et al. 2015; Mettu et al. 2011; Munk et al. 2013; Ooto et al. 2015; Ozdemir et al. 2012; Parisi et al. 2007; Pilotto et al. 2011; Pilotto et al. 2016; Sabour-Pickett et al. 2013; Sato et al. 2015; Sayegh et al. 2014; Steinberg et al. 2016; Sulzbacher et al. 2012; Sulzbacher et al. 2013; Sulzbacher et al. 2015; Takahashi et al. 2016; Weigert

et al. 2013; Amore et al. 2013; Bolz et al. 2010; Chieh, Stinnett and Toth 2008; Acton et al. 2012b; Fragiotta et al. 2017a) by the Nidek MP3 in 1 (Hariri et al. 2016), by the MAIA in 16 (Wu et al. 2015b; Wu et al. 2015c; Wu et al. 2013; Wu et al. 2015a; Wu et al. 2014c; Wu et al. 2016; Wu, Guymer and Finger 2016; Wu et al. 2014a; Alexander et al. 2012; Anastassiou et al. 2013; Chandramohan et al. 2016; Vujosevic et al. 2011; Denniss et al. 2017; Vujosevic et al. 2017; Broadhead et al. 2017), by the Optos Spectral OCT/SLO in 7 (Landa et al. 2011; Querques et al. 2012; Forte et al. 2013; Cho et al. 2013; Hautamäki et al. 2014; Hartmann et al. 2011; Hartmann et al. 2015) and by the Rodenstock SLO microperimeter in 2 articles (Ergun et al. 2003; Fujii et al. 2003). The limited dynamic range of the previously available Optos OCT SLO and Nidek MP-1 microperimeters arising from the lower maximum stimulus luminance results in ceiling and floor effects compared to the MAIA and MP-3 microperimeters (Markowitz and Reyes 2013). In particular, the presence of a floor effect can result in underestimation of the depth of the field loss. Consequently, the type of microperimeter is specified whenever the perimetric outcome is given in terms of decibels (dB).

2.4.2 Microperimetry and AMD severity

Six of the 56 included articles evaluated the efficacy of microperimetry in distinguishing between the various stages of AMD severity (Dinc et al. 2008; Vujosevic et al. 2011; Fujii et al. 2003; Wu et al. 2013; Denniss et al. 2017; Vujosevic et al. 2017).

Microperimetry with the MAIA is able to discriminate between normality and early and intermediate stages of AMD (Age-related Eye Disease Study, AREDS (AREDS 2001), grades 2 and 3 respectively), when considered both in terms of the group mean MS and of the DLS derived at individual locations (Vujosevic et al. 2011; Vujosevic et al. 2017). In the largest study of this kind to date, the group of 200 normal individuals exhibited the highest MS (mean 29.8dB; SD 1.7) whilst, within the group of 200

individuals with AMD, the MS for those with early AMD was larger (mean 24.9dB; SD 3.9) than for those with intermediate AMD (mean 21.8dB; SD 5.4) (all $p<0.001$) (Vujosevic et al. 2011). A comparable, but earlier study, of 30 individuals noted a statistically significant worsening of both the group mean MS and the group mean MD for intermediate AMD (AREDS grade 3) compared to normal individuals (Dinc et al. 2008). For both these studies, the magnitudes of the group mean MS reflected the severity of the structural classification of AMD. However, the magnitudes of the standard deviations associated with the group mean MS indicated overlap between groups. In addition, no criteria for microperimetry were given for the optimal differentiation, on an individual basis, between the AMD severities. The analysis of the DLS at each individual stimulus location enabled a localised assessment of function that was more descriptive of the AMD severity than that provided by the MS (Wu et al. 2013).

A recent study examined DLS with respect to location specific normal values, in 185 individuals with AMD, and subsequent TD and PD probability analysis was performed (Denniss et al. 2017). Within the central 5° of fixation, 95% of individuals with AMD had a TD worse than -2.0dB (measured by MAIA microperimetry), which increased to 97% at fixation (Denniss et al. 2017). This suggests that despite the common adaption of a preferred retinal loci, a significant DLS loss remains surrounding and at the PRL (Denniss et al. 2017).

The reduction in DLS varies with the location and severity of the AMD. Eyes with subfoveal nAMD that exhibit severe (absolute) localised parafoveal abnormality (0dB, as measured by an early commercially available Rodenstock SLO microperimeter; Rodenstock GmbH, Munich, Germany) manifest a normal foveal DLS enabling central fixation to be maintained (Fujii et al. 2003). The likelihood of a dense parafoveal abnormality increases as the duration of self-reported symptoms increases (Fujii et al. 2003).

In summary, the MS derived by microperimetry is reduced in those with AMD and is able to differentiate, on a group mean basis, at least, between levels of disease severity (Vujosevic et al. 2011; Dinc et al. 2008). However, the evidence is questionable as to whether microperimetry can correctly classify AMD disease severity. Characterising the reduction in DLS by location, area and depth enables the study of associations with other factors such as disease duration and maintenance of central fixation (Fujii et al. 2003).

2.4.3 Microperimetry and structural imaging modalities.

Twenty three of the 56 included articles were concerned with the relationship between visual function and retinal morphology in AMD (Forte et al. 2013; Acton et al. 2012b; Hartmann et al. 2011; Landa et al. 2011; Iwama et al. 2010; Forte et al. 2012; Ooto et al. 2015; Wu et al. 2015c; Wu et al. 2014c; Wu et al. 2015b; Pilotto et al. 2011; Iaculli et al. 2015; Sulzbacher et al. 2012; Hariri et al. 2016; Steinberg et al. 2016; Pilotto et al. 2016; Sayegh et al. 2014; Wu et al. 2016; Hartmann et al. 2015; Takahashi et al. 2016; Broadhead et al. 2017; Fragiotta et al. 2017a), most of which have used SD-OCT.

This section of the review discusses microperimetry outcomes in relation to: specific retinal layer changes; retinal pseudodrusen; GA and outer retinal tubulations (ORTs).

A typical SD-OCT horizontal line scan of an individual with AMD illustrating the retinal layers evaluated in the various studies is shown in Figure 2.2. The external limiting membrane (ELM) appears as a hyperreflective line, by SD-OCT, in the outer retina just above the ellipsoid zone (EZ). The EZ is also visible as a hyperreflective band, but is not synonymous with a single retinal anatomical feature (Tao et al. 2016). The photoreceptor outer segment layer appears below the EZ band and is visible as a

hyporeflective line. The RPE layer also appears as a hyperreflective line: it is continuous with Bruch's membrane until disease processes cause their separation.

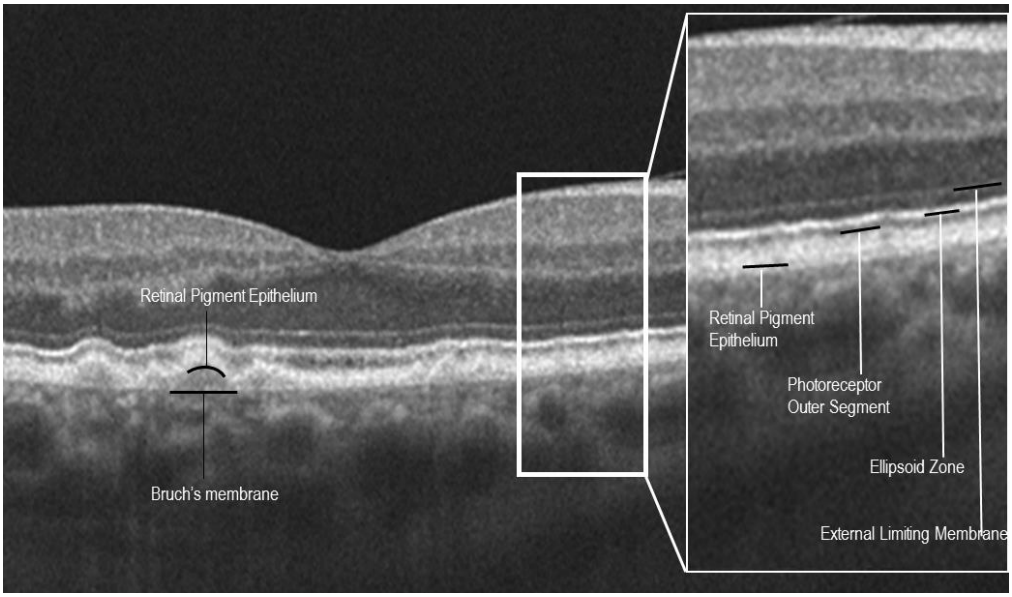


Figure 2.2 SD-OCT horizontal line scan of an eye with AMD. Right: The external limiting membrane, ellipsoid zone, photoreceptor outer segment and retinal pigment epithelium are highlighted by the three black lines which are continuous with the respective layers.

Reticular pseudodrusen represent a build-up of material below the RPE and, when viewed by SD-OCT, manifest as hyperreflective triangular shaped deposits located between the RPE and the EZ band (Figure 2.3) (Sohrab et al. 2011; Zweifel et al. 2010).

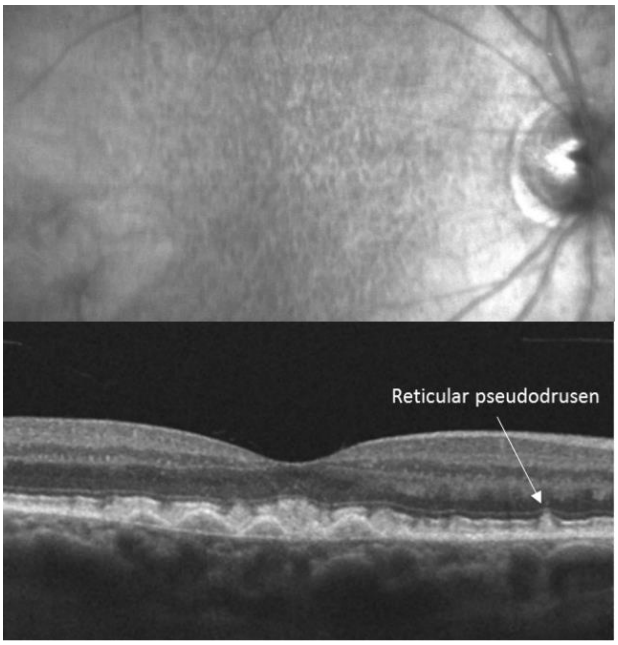


Figure 2.3 Top: Infra-red image and Bottom: SD-OCT horizontal line scan of an eye with AMD exhibiting a reticular pseudodrusen.

Geographic atrophy is the late stage of AMD and involves the loss of retinal structures including the RPE and photoreceptors, with the ensuing visibility of the underlying choroidal vessels (Figure 2.4) (Hariri et al. 2016).

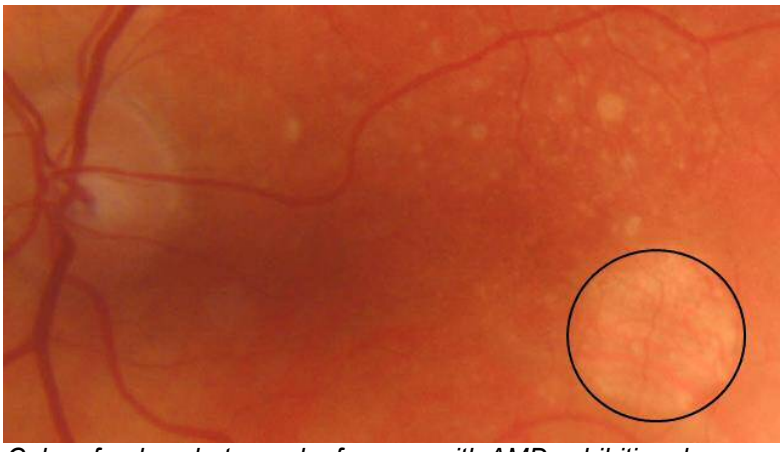


Figure 2.4 Colour fundus photograph of an eye with AMD exhibiting drusen and an area of GA (circled) with visible choroidal vessels.

Nascent geographic atrophy as defined by Wu and colleagues(Wu et al. 2015b) occurs prior to drusen-associated atrophy and has similar risk factors to GA; it can be visualised by SD-OCT but not by colour fundus photography (Wu et al. 2015b). nGA appears by SD-OCT as a breakdown of the outer plexiform layer (OPL) and inner nuclear layer (INL) accompanied with a wedge-shaped hyporeflective area in the OPL (Wu et al. 2014d). Finally, ORTs can only be visualised by SD-OCT and appear as a hyperreflective ring with a hyporeflective centre located within the outer nuclear layer (Figure 2.5).

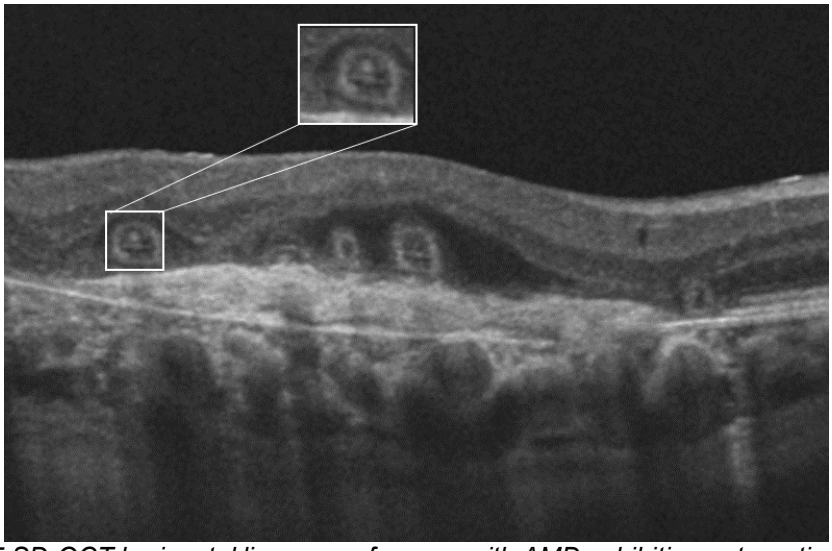


Figure 2.5 SD-OCT horizontal line scan of an eye with AMD exhibiting outer retinal tubulations (highlighted).

2.4.3.1 Retinal layers

The relationship between outer retinal layer thickness and DLS in early AMD (International Classification and Grading System (Bird et al. 1995)) has been investigated by comparing RPE and OS thicknesses at locations with and without an abnormal DLS (defined as a TD value with a probability of lying within the normal range of $p \leq 0.05$) (Acton et al. 2012b). The OS layer was thinner at locations with an abnormal TD ($p<0.01$). The OS layer thickness was also significantly correlated with both MS and MD, obtained using the MP-1 microperimeter ($r=0.62$ and $r=0.63$, respectively, both $p<0.01$) (Acton et al. 2012b). MS worsens with increased thickening of the RPE (Acton et al. 2012b; Wu et al. 2016; Wu et al. 2014c); a 10μm increase in RPE layer thickness is associated with a 0.29dB worsening of MS ($p<0.001$) obtained with the MAIA microperimeter (Wu et al. 2016).

DLS and choroidal thickness was investigated in control eyes, and eyes with early to intermediate AMD (AREDS grade 2 and 3 (AREDS 2001)) (Broadhead et al. 2017). No significant difference in choroidal thickness was present between the control and AMD groups ($p=0.36$), and no association between DLS and choroidal thickness was found in the AMD group ($p=0.08$) (Broadhead et al. 2017).

In eyes with early to intermediate AMD, the MS at locations overlying drusen is statistically significantly worse than that at adjacent locations without the presence of drusen (Hartmann et al. 2011; Iwama et al. 2010). EZ band disruption is the strongest predictor of DLS at locations with drusen (Hartmann et al. 2011) and the reduction in MS in the presence of EZ band disruption is worse than that in the presence of drusen, alone (Iwama et al. 2010). It should be noted that, in the former study, the stage of AMD was not classified; individuals exhibiting drusen (excluding nAMD) were included and, therefore, any stage of AMD may have been involved (Hartmann et al. 2011). Additionally, a more recent study investigated the predictors of DLS in individuals with intermediate AMD (Fragiotta et al. 2017a). The integrity of the EZ

band, ELM and the presence of hyperreflective foci were each associated with DLS (r=-0.45, r=-0.7 and r=-0.66, respectively) (Fragiotta et al. 2017a). However, the stage of AMD was not classified prior to the grading of SD-OCT features.

In early to late atrophic AMD, MS worsens as the EZ band disturbance increases (Landa et al. 2011; Querques et al. 2012; Wu et al. 2014c). In nAMD, a worsening of EZ band disruption and an increase in central retinal thickness are both associated with a reduction in MS (r=-0.79; p<0.001 and r=-0.51; p<0.01, respectively) (Landa et al. 2011; Sulzbacher et al. 2012). Similarly, in nAMD treated with bevacizumab, MS significantly worsened (p<0.01) with increase in EZ band disruption (Hartmann et al. 2015). The presence of nAMD, intra-retinal cysts and a focal/ localised absence either of the RPE or of the photoreceptor layer are each associated with an absolute loss of MS (<0dB) obtained with the MP-1 microperimeter (Sulzbacher et al. 2012). Sub-retinal fluid, intra-retinal fluid, PED and pseudodrusen are each separately associated with relative visual field loss (defined as 1dB to 8dB) when measured with the MP-1 microperimeter (Sulzbacher et al. 2012).

2.4.3.2 Reticular pseudodrusen

The presence of RPD in early to intermediate AMD (AREDS grade 2, 3 or 4 (AREDS 2001)) is associated with a reduction in MS out to 10° eccentricity (Ooto et al. 2015). Such an association is absent in a cohort with intermediate stage AMD (Beckman classification (Ferris et al. 2013)) (Wu et al. 2015c). MS out to 4˚ eccentricity was associated with RPD on a univariate basis; however, in a multivariate analysis incorporating age, drusen volume and pigmentary disturbance, the association was no longer present (Wu et al. 2015c). One explanation for these findings may simply be the difference in classification systems used between the two studies. In early to intermediate AMD (Beckman classification (Ferris et al. 2013)), both scotopic and mesopic group mean MSs, obtained with a modified MP-1S microperimeter, were reduced in areas of RPD (mean 12.8dB; SD 3.3 and mean 17.2dB; SD 2.5,

respectively) compared to areas without (mean 18.2dB; SD 2.2 and mean 18.4dB; SD 2.5, respectively). The scotopic MS was reduced to a greater extent than the mesopic MS (Steinberg et al. 2016). These findings suggest that, in the presence of RPD, rod photoreceptor function is the most affected. However, it is not clear whether the greater reduction in the scotopic MS was due to differences in the measurement range resulting from the two different background luminance enabling scotopic and mesopic viewing conditions. Scotopic dysfunction also correlates with outer retinal thickness in eyes with RPD: a 1μm decrease in thickness corresponded to a 0.96dB reduction in scotopic MS (Steinberg et al. 2016). In another study, the MS was also reduced in the presence of pseudodrusen in atrophy free areas of eyes with GA (Takahashi et al. 2016).

2.4.3.3 Geographic atrophy

In GA, MS has been compared between areas with and without either RPE loss and/ or photoreceptor damage (Takahashi et al. 2016). The group mean MS, obtained with the MP-1 microperimeter, was markedly lower in areas of RPE loss (mean 1.84dB; SD 2.68; $p<0.001$) and also in areas with photoreceptor damage (mean 6.57dB; SD 4.13; $p<0.001$) when compared to areas without (Takahashi et al. 2016). In GA, a thinning or an absence of the RPE, an absence of the external limiting membrane and a thickening of the EZ boundary are each associated with absolute field loss (0dB) obtained with the MP-1 microperimeter (Sayegh et al. 2014). The group mean MS, obtained with the MP-3 microperimeter, at the GA boundary is lower (mean 13.7dB; SD 4.7) than the group mean MS in the area surrounding the GA (mean 20.8dB; SD 3.8); however, the latter is lower than that in eyes without GA (mean 23.9dB; SD 2.6) ($p<0.001$) (Hariri et al. 2016). Another study utilised en-face OCT to identify GA boundaries at the choroidal and the outer retinal levels. When the MS was better than 10dB, the mean area of GA was larger at the outer retinal level than at the choroidal

level; however, the areas were similar when the MS was worse than 10dB (Pilotto et al. 2016).

In areas of nGA, the group mean MS measured by MAIA microperimetry is reduced (mean 20.4dB; SD 0.8) compared to areas without atrophy (mean 23.8dB; SD 0.7, $p<0.01$) and is greater than that obtained in areas with drusen associated atrophy (mean 16.4dB; SD 0.9; $p<0.01$) (Wu et al. 2015b). The area of drusen associated atrophy did not exhibit absolute loss as was the case in GA (Wu et al. 2015b).

The monitoring of progression of GA can be undertaken by areas of GA appear hypo-fluorescent. One study compared the outcome of MP-1 microperimetry to that from both NIR-FAF and short-wavelength FAF (Pilotto et al. 2011). The associations between severe relative loss (a DLS of not more than 5dB) and normal and hyper-fluorescence outcomes were determined for each FAF technique. It was concluded that the outcome from MP-1 microperimetry, in combination with both FAF techniques, enabled effective detection and monitoring of GA (Pilotto et al. 2011). Another study used microperimetry to evaluate SD-OCT FAF and NIR-FAF (Forte et al. 2013). As would be expected, DLS was substantially reduced in areas of GA and the imaging techniques were able to detect the presence of GA with differing capabilities. SD-OCT was considered to be the most appropriate imaging technique to examine GA (Forte et al. 2013).

2.4.3.4 Outer retinal tubulations

Outer retinal tubulations are not specific to AMD and are also seen more commonly in inherited retinal disorders such as choroideremia and retinitis pigmentosa (Goldberg et al. 2013). In AMD, they are not a typical feature and can occur in eyes with previous nAMD. The identification of ORTs is clinically important due to their misinterpretation as either intraretinal or subretinal fluid with the resultant unnecessary treatment (Iaculli et al. 2015; Zweifel et al. 2009). In a study of individuals without ORTs who were treated for nAMD, the improvement in MS,

obtained with the MP-1 microperimeter, after 12 months was less pronounced in those that developed ORTs (mean 6.31dB, SD 2.5) compared to those that did not (mean 9.89dB, SD 5.43; $p<0.01$). However, this latter study did not fully describe the stimulus parameters for the microperimetry.

In summary, focal areas of reduced DLS in AMD can be identified by microperimetry and are associated with a disruption of the EZ band and/ or changes to the RPE (Iwama et al. 2010; Landa et al. 2011; Querques et al. 2012; Wu et al. 2014c). The association between RPD and MS is equivocal. In early to intermediate AMD (AREDS 2, 3 and 4 (AREDS 2001)), the presence of pseudodrusen is associated with a reduction in MS at the macula (Ooto et al. 2015). However, there was no such association in a different cohort with intermediate AMD (Beckman classification(Ferris et al. 2013)) (Wu et al. 2015c). The differences between areas with and without pseudodrusen, for early and intermediate AMD (Beckman classification (Ferris et al. 2013)), combined, are seemingly most profound under scotopic conditions (Steinberg et al. 2016). The reduction in MS is, in general, consistent with the presence of retinal lesions apparent by OCT. In the presence of a normal retinal appearance by fundus photography, alone, microperimetry detects functional loss arising from nGA (Wu et al. 2015b; Takahashi et al. 2016; Hariri et al. 2016).

2.4.4 Microperimetry and other measures of visual function.

Fifteen included studies used microperimetry alongside other measures of visual function in individuals with AMD (Acton et al. 2012b; Munk et al. 2013; Wu et al. 2014b; Wu et al. 2015a; Ozdemir et al. 2012; Hautamäki et al. 2014; Sato et al. 2015; Amore et al. 2013; Ergun et al. 2003; Chandramohan et al. 2016; Ooto et al. 2015; Wu, Guymer and Finger 2016; Giacomelli et al. 2013; Wu et al. 2014a; Parisi et al. 2007).

In early AMD (International Classification and Grading System(Bird et al. 1995)) with distance VAs ranging from 20/20 to 20/40, the corresponding MS varied between

19.5dB (SD 0.4dB) and 14.9dB (SD 2.4dB) (Acton et al. 2012b). Similarly, in early to intermediate AMD (Beckman classification (Ferris et al. 2013)) with a distance VA better than 20/40, MS exhibited a greater reduction compared to VA and to LLVA by 3.0 and 1.9 fold, respectively (Wu et al. 2014b). A prospective longitudinal study of intermediate AMD (Beckman classification (Ferris et al. 2013)) (Wu et al. 2015a), compared two groups: those graded as progressed, defined as the development of additional structural abnormality visible by colour fundus photography, and those graded as stable with unchanged features. No deterioration from baseline in either VA or LLVA was present in either group at 12 months; however, small but statistically significant reductions in group mean MS (obtained with the MAIA microperimeter) were present in both groups (mean 0.42dB; SE 0.12 and mean 0.31dB; SE 0.10, respectively) (Wu et al. 2015a). However, it should be noted that microperimetry is only able to measure DLS to a resolution of 1dB and, therefore, the clinical significance of these findings is limited. An additional finding of this latter study was that eyes identified as improved, defined as a disappearance of structural abnormality on colour fundus photography, showed a statistically significant increase in the group mean MS (mean 1.13dB; SE 0.23, $p<0.001$) at 12 months (Wu et al. 2015a). Another study, which compared the outcomes in early AMD (AREDS grade 2 (AREDS 2001)) and in intermediate AMD (AREDS grade 3 (AREDS 2001)) to those in normal individuals, found a significant worsening in LLVA for each AMD group compared to the normal individuals ($p<0.05$) (Chandramohan et al. 2016). The reduction in LLVA was associated with a reduction in foveal DLS ($r^2=0.60$, $p<0.01$) (Chandramohan et al. 2016). In early to intermediate AMD (AREDS grade 2 and 3 (AREDS 2001)), a reduction of parafoveal MS is associated with a reduction in VA and in CS ($r=0.59$ and $r=0.35$ respectively, $p<0.01$)(Ooto et al. 2015).

In a separate study of individuals with intermediate stage AMD (Beckman classification (Ferris et al. 2013)), neither MS nor foveal DLS were associated with a

LLD, defined as the difference between VA and LLVA, or with the self-reported outcome to a 10-item night vision questionnaire. Nevertheless, LLD was significantly associated with difficulty under low luminance levels (Wu, Guymer and Finger 2016).

In individuals with nAMD who had previously received anti-VEGF therapy, MS (out to 20˚ eccentricity) was moderately correlated with both VA (r=0.54) and CS (r=0.53) separately; and to a lesser extent with reading speed (r=0.37) (all p<0.001) (Sato et al. 2015). However, in those undergoing anti-VEGF treatment, no association was present between the MS and either VA or CS (Munk et al. 2013; Hautamäki et al. 2014). Other studies have shown that both DLS and VA improve up to either 6 months (Ozdemir et al. 2012) or 12 months (Munk et al. 2013) of anti-VEGF therapy; however, the association between DLS and VA was not determined. In subfoveal CNV, an increase in the area of absolute DLS loss is associated with a decline in both reading acuity (r=0.52; p=0.01) and reading speed (r=-0.48; p=0.02) (Ergun et al. 2003).

In GA manifesting absolute loss of DLS and a central island of residual vision (foveal sparing), the MS out to 20° eccentricity was moderately associated with reading speed (r^2=0.5) (Amore et al. 2013). An improvement in reading is a major goal of visual rehabilitation; microperimetry enables additional information about the location and size of the area(s) of residual function, allowing for a realistic estimation of reading ability and the likely outcome of rehabilitation (Amore et al. 2013; Giacomelli et al. 2013).

The multifocal electroretinogram (mfERG) provides objective, topographical, electrophysiological information about central retinal function. Two studies compared microperimetry and mfERG (Parisi et al. 2007; Wu et al. 2014a). In early AMD (Wisconsin Age-related Maculopathy Grading system (Klein et al. 1991)), a significant correlation was present between the mfERG response amplitude density (N1-P1) and MS (r=0.69, p<0.01) (Parisi et al. 2007); however, there was no association for intermediate AMD (Beckman classification (Ferris et al. 2013)) (Wu et al. 2014a). This

latter study found a greater reduction in the MS than in the mfERG ($p<0.001$), suggesting that the two measures assess different aspects of retinal dysfunction (Wu et al. 2014a).

In summary, VA, CS and reading ability have, historically, been used as outcome measures in ophthalmic clinical research. Microperimetry has more recently become an additional outcome measure. MS exhibits a wide range of values in the presence of relatively good VA in early to intermediate AMD (Acton et al. 2012b) (International Classification and Grading System (Bird et al. 1995)). It is able to detect progressive improvements in AMD, consistent with colour fundus photographs, when no change is observed in VA or LLVA. There is conflicting evidence as to the strength of the associations between DLS and VA, CS and reading ability (Munk et al. 2013; Wu et al. 2014b; Wu et al. 2015a). Reading ability is an important factor when considering visual rehabilitation: microperimetry gives additional relevant information with respect to the area and location of residual function.

2.4.5 Microperimetry as an outcome measure in clinical trials of medical or surgical intervention

Microperimetry has been included as an outcome measure in 17 included articles describing clinical trials of medical and/ or surgical interventions for AMD. In individuals undergoing treatment with ranibizumab for AMD, MS, measured with the MAIA microperimeter, was at a maximum of 17dB for a central retinal thickness of 210μm. MS declined as the thickness increased, reaching a minimum of 7dB at a thickness of 320-339μm, and declined as the thickness decreased, reaching a minimum of 15dB at a thickness of <160μm (Alexander et al. 2012). However, these findings cannot be compared with other studies as both the microperimetry and the method of measuring retinal thickness were not reported. A similar finding was noted with bevacizumab therapy: MS increased following a reduction in retinal thickness (Hartmann et al. 2015) and decreased with increasing retinal thickness ($r=-0.54$,

p<0.01) (Sabour-Pickett et al. 2013). However, neither of these latter studies specified the thickness boundaries used in the retinal thickness measurements. It has been suggested that the improvement in MS occurs from the reduction in RPE lesion area with treatment rather than from a reduction in the retinal thickness, as a whole (Kiss et al. 2009).

The relationship between DLS and specific AMD morphology, as identified by SD-OCT, has been studied in previously untreated patients with nAMD who subsequently received aflibercept (Sulzbacher et al. 2015). The greatest improvement in DLS (measured with the MP-1 microperimeter), occurred 3 months after the start of therapy; areas exhibiting a reduction in either a serous PED or subretinal fluid exhibited the greatest improvement in group mean MS of 5.5dB and 4.0dB respectively (p<0.001). Areas with fibrovascular PED or with an intra-retinal cystoid space also improved, but to a lesser extent (group mean improvements 2.3dB and 1.7dB; respectively) (Sulzbacher et al. 2015). In an earlier study, DLS improved following ranibizumab therapy in previously untreated patients with nAMD. The most marked improvement occurred at stimulus locations which were associated with a reduction in subretinal fluid, intraretinal fluid or intraretinal cystoid space (Sulzbacher et al. 2013).

Although all trials of anti-VEGF therapy involving microperimetry report an improvement in DLS from baseline, the results of these studies are equivocal with respect to the duration of therapy beyond which the DLS ceases to improve. A number of studies have reported that DLS continues to improve up until 12 months, the time at which the studies ended (Cho et al. 2013; Munk et al. 2013; Sulzbacher et al. 2013; Grenga et al. 2013; Lazzeri et al. 2015). However, two studies suggest that DLS does not improve beyond that recorded after one week of treatment (Bolz et al. 2010; Kiss et al. 2009). DLS can also decline following withdrawal of anti-VEGF therapy. Individuals with stable nAMD, who ceased anti-VEGF therapy, exhibited a reduction

in DLS during the follow-up period (at least 3 visits over 7 months) when compared with those that continued to receive treatment (Alexander et al. 2012). It was speculated that the reduction in DLS may have resulted either from photoreceptor atrophy over time that was too subtle to be identified by VA or that CNV could be occurring at a subclinical level below that required by the United Kingdom NICE guidelines for an anti-VEGF injection (Alexander et al. 2012).

Two trials with an unsuccessful outcome utilised microperimetry as an outcome measure; one trial assessed the outcome of transpalpebral electrotherapy as a treatment for early to intermediate AMD (AREDS grade 2, 3 and 4(AREDS 2001)) and the another evaluated the outcome of photodynamic therapy combined with intravitreal triamcinolone as a treatment for nAMD (Dunavoelgyi et al. 2011; Anastassiou et al. 2013). Neither study found a sustained improvement in either DLS, VA or CS, following treatment.

Macular translocation surgery (MT360) involves a peripheral retinectomy of 360° at the ora serata following which the subfoveal CNV is removed and the whole retina is rotated such that the fovea is located away from the removed CNV. The retina is then reattached. In one study, VA, near VA and reading speed improved post-operatively (Chieh, Stinnett and Toth 2008). DLS was specified in terms of the median retinal sensitivity score (MRSS) obtained with the MP-1 microperimeter. The 12 month post-operative group mean MRSS was better (2.5dB, SD 4.3) in the foveal surgical area compared to the retinal area where the CNV had been removed (<0dB) (Chieh, Stinnett and Toth 2008). However, the MRSS had not been evaluated prior to surgery; therefore it is not possible to evaluate whether the surgery improved visual function. Another study found that the MRSS only improved in lesions greater than 4 disc areas (Mettu et al. 2011). However, the two studies evaluated the outcome of the translocation surgery by differing methods. The first determined the MRSS at areas of healthy retina compared to that at the surgical sites (Chieh, Stinnett and Toth 2008),

whereas the second compared the difference in the MRSS for the pre- and 12-month post-operative areas (Mettu et al. 2011).

Two RCTs examined the effect of lutein supplementation on macular pigment optical density and the subsequent effect on visual function. One RCT found that, although lutein supplementation increased the macular pigment density, there was no improvement in MS after 6 months of lutein supplementation (Weigert et al. 2013). Macular pigment density was also weakly correlated with DLS ($r = 0.25$, $p = 0.027$) (Weigert et al. 2013). The second RCT examined differing levels of lutein supplementation (10mg, 20mg and a combination of lutein with zeaxanthin) with placebo. After two years of supplementation, the group mean MS, obtained with the MP-1 microperimeter, was greater for the groups receiving 10mg (13.37dB) or 20 mg of lutein (12.55dB) compared to the control group (10.32dB, $p<0.05$) (Huang et al. 2015).

It is clear that microperimetry has the ability to detect changes in visual function arising from a variety of interventions for AMD. All studies suggest that MS improves, following anti-VEGF treatment, as retinal thickness reduces and nAMD-associated lesions improve. The extent of any such improvement in MS beyond 12 months is unknown.

2.5 Discussion

The quality of evidence varied between the 56 articles. Overall, none of the RCTs directly analysed the utility of microperimetry in the assessment of visual function in AMD but, as would be expected, evaluated a specific medical therapy using microperimetry as one of the various outcome measures. Over half of the studies included in this review were observational in design and, therefore, have a consequent risk of selection bias, information bias or confounding bias (Grimes and Schulz 2002). Many studies had limitations in the quality of reporting of the

microperimetry outcomes and/ or of the SD-OCT methods and analysis (Appendix B). Comparison between studies was also confounded by the differences in the classification systems for early and intermediate AMD. Four studies did not include the classification method (Amore et al. 2013; Giacomelli et al. 2013; Hartmann et al. 2011; Landa et al. 2011) . An additional difficulty in comparing studies arose from the differences in the dynamic range between the various microperimeters used in the studies.

The majority of studies used the summary statistic MS, which is not age-corrected, and many of the studies did not report either the number or the spatial location of the stimuli upon which the MS was based (Alexander et al. 2012; Iaculli et al. 2015; Ooto et al. 2015; Anastassiou et al. 2013; Fujii et al. 2003; Huang et al. 2015; Lazzeri et al. 2015; Mettu et al. 2011; Pilotto et al. 2011; Dinc et al. 2008; Fragiotta et al. 2017b). Only 14 of the studies analysed the DLS at each given stimulus location (Vujosevic et al. 2011; Wu et al. 2015a; Wu et al. 2015b; Wu et al. 2014c; Takahashi et al. 2016; Sulzbacher et al. 2013; Sulzbacher et al. 2015; Sulzbacher et al. 2012; Querques et al. 2012; Landa et al. 2011; Hartmann et al. 2011; Sayegh et al. 2014; Denniss et al. 2017; Vujosevic et al. 2017). From the 56 included studies, three of the studies (Acton et al. 2012b; Dinc et al. 2008; Denniss et al. 2017) utilised location-specific probability analysis of the measured DLS compared to the corresponding age-corrected normal value, as is conventional practice in SAP. Despite the latter probability analysis enabling separation of focal from diffuse defects (Heijl, Lindgren and Olsson 1987a), such an approach was only used in one of these studies (Denniss et al. 2017).

The absence of a robust statistical analysis software package for microperimetry, which separates focal from diffuse loss and which is comparable to that widely used in SAP, currently limits the technique. Such analysis would have enabled a more clinically relevant evaluation of the microperimetry outcomes, particularly their association with structure. The various microperimeter manufacturers should be

encouraged to develop such a package to enable this more comprehensive method of assessing abnormal visual function. In late stage AMD, this type of analysis would also need to be corrected for the presence for any retinal locus (Denniss and Astle 2016).

The clinical value of microperimetry has not yet been assessed against other functional biomarkers of AMD, such as flicker sensitivity and dark adaptation, known to be sensitive to AMD disease severity (Dimitrov et al. 2011; Owsley et al. 2007) Microperimetry offers detailed topographical information relative to traditional measures of foveal function such as VA and CS. In addition, microperimetry was superior to VA in detection of subtle AMD changes in a longitudinal study over one year (Wu et al. 2015a). The investigation of microperimetry in comparison with dark adaptation in early AMD would be of value and enable clearer clinical recommendations for microperimetry.

Notwithstanding the above limitations, it is clear that there is a strong association between the magnitude of the DLS and a number of classic signs associated with AMD. Disruptions of the EZ band and RPE are associated with reduced DLS despite the maintenance of good VA (Landa et al. 2011; Hartmann et al. 2015; Iwama et al. 2010; Parisi et al. 2007; Wu et al. 2014c). OS thinning and RPE thickening are both associated with reduced MS, in early AMD (Acton et al. 2012b). A thickening and a thinning of the whole retina in CNV are each associated with a reduced MS (Alexander et al. 2012; Hartmann et al. 2015; Sabour-Pickett et al. 2013).

To conclude, the current microperimetric literature is of varying quality, but has been improving in recent years. The current lack of consistency in the microperimetric techniques and in the analysis of DLS, limits the conclusions regarding the use of microperimetry in AMD. Recommendations for good clinical practice are, therefore, currently not possible; however, microperimetry provides information beyond that of VA and CS in the functional assessment of AMD. When combined with SD-OCT, it

gives a multimodal representation of AMD morphology and associated visual function. Statistical analysis software similar to that used in SAP would render microperimetry a more robust procedure. The development of a multimodal topographical classification system for all stages of AMD, based upon combined microperimetry and SD-OCT outcomes, represents an exciting prospect.

Chapter 3: Methodology

3.1 Summary

This chapter will address in detail the experimental methodology implemented in the research presented in this thesis. Firstly, the methodology for the development of a normative database using the MAIA microperimeter will be described. Secondly, the methodology for the studies that involve individuals with AMD will be presented.

3.2 Methodology for the study involving healthy individuals (development of normative database, Chapter 4)

This study was funded by Fight for Sight (grant number 1463/64).

3.2.1 Recruitment

3.2.1.1 Sample size

A sample size of 80 healthy individuals was determined on the basis of the number of individuals required by international standards to produce a perimetric normative database (ISO 12866), including an allowance for 20% of individuals who may withdraw from the study.

3.2.1.2 Inclusion and exclusion criteria

Each individual conformed to rigid inclusion criteria comprising: a refractive error of ≤5D sphere and ≤3D cylinder; VA of better than 0.10 logMAR for those aged up to 60 years, and better than, or equal to, 0.18 logMAR for those aged greater than 60 years and lenticular changes no greater than grade two in any category of the Lens Opacity Classification System (LOCS III) (Chylack et al. 1993). Exclusion criteria included glaucoma or suspect glaucoma; any severity of AMD; any previous or current ocular history of significant eye disease, trauma or surgery; history of diabetes mellitus, or systemic medication known to affect the visual field.

3.2.1.3 Recruitment

The individuals were recruited from the staff and student population at Cardiff University, and their family and acquaintances. All individuals were given information sheets regarding the study prior to the initial visit, which they attended at the School of Optometry and Vision Sciences, Cardiff University. Recruitment resulted in a cohort of 80 consecutive individuals with a median (IQR) age of 43 years (26, 65).

3.2.2 Ethics

The study adhered to the tenets of Declaration of Helsinki for research involving human participants and the protocol was approved by the School of Optometry and Vision Science Research and Audit Ethics Committee, Cardiff University. Each individual gave informed consent at Visit 1 before any procedures were performed.

3.2.3 Procedures

The individuals were required to attend three visits at the School of Optometry and Vision Sciences, Cardiff University, each visit was separated by a median (IQR) of 7 days (5, 10).

3.2.3.1 Visit 1

The initial study visit consisted of taking written consent and a standard ophthalmic examination including an ocular and medical history. VAs, anterior eye examination, non-contact tonometry (NCT) and imaging data were also performed (Figure 3.1). This was to ensure the individuals adhered to the inclusion and exclusion criteria. The first examination on the MAIA microperimeter and on the HFA 30-2 examination also took place, which were implemented in a randomised order with rest periods between them. The procedures were performed by a research assistant (AN), under the supervision and guidance of the author who was then solely responsible for the analysis.

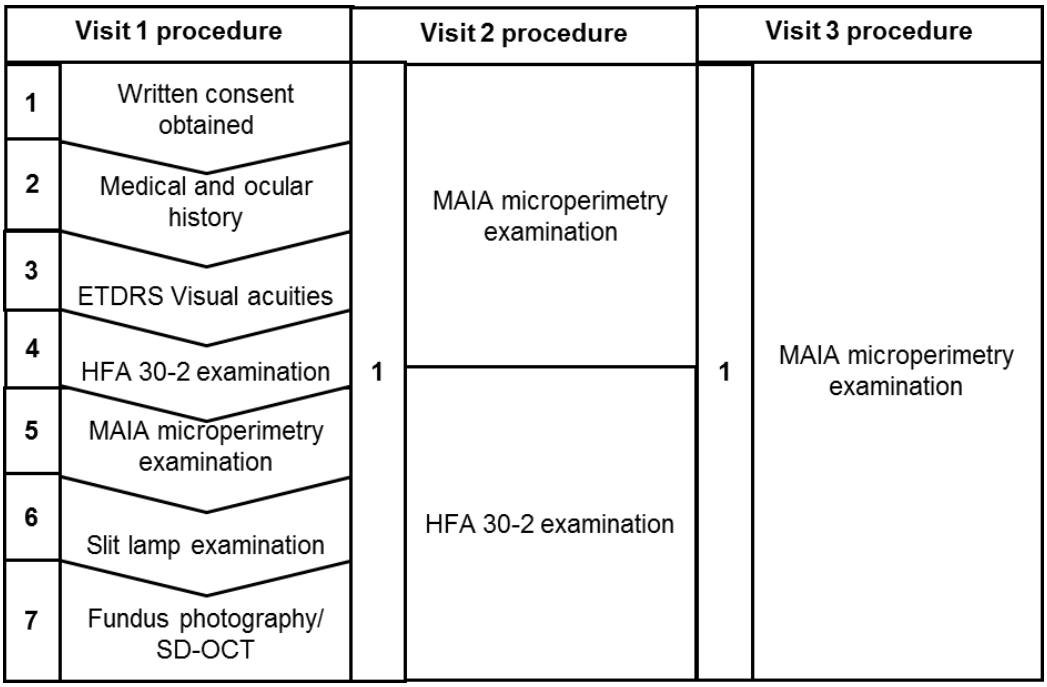


Figure 3.1 The sequence of procedures for each of the three visits, the HFA and MAIA examinations were performed in a randomised order for each individual.

3.2.3.1.1 Medical and ocular history

A comprehensive ocular history was obtained, which included previous hospital visits due to ocular-related causes, for example, diagnosed ocular conditions, or previous ocular surgery or trauma. A complete medical history was also taken including specific questions relating to diabetes, neurological conditions or systemic medication.

3.2.3.1.2 Visual acuity

Visual acuity was measured using the ETDRS LogMAR chart according to the standardised protocol (Ferris and Bailey 1996).The instructions to the individual were to read the letters on the chart from left to right and from the top to bottom. The individuals were encouraged to guess if unsure and scoring was based upon a standardised procedure in which a score of 0.1logMAR is assigned to one line and a score of 0.02logMAR is assigned to each letter (Ferris and Bailey 1996). The test was performed monocularly, with the distance refractive correction in place.

3.2.3.1.3 Anterior eye examination

A detailed anterior eye examination of both eyes by slit-lamp biomicroscopy was performed. This included grading of lens opacities and the anterior chamber angle,

using LOCS III grading (Chylack et al. 1993) and the Van Herick technique, respectively. Intraocular pressures (IOPs) were measured in both eyes, using the NT2000 non-contact tonometer (NCT, Nidek Co., Ltd., Aichi, Japan).

3.2.3.1.4 Microperimetry

MAIA microperimetry was performed on the study eye with the fellow eye occluded using an opaque patch. Prior to the examination, each individual underwent 10 minutes of adaption to a darkened room. All individuals received identical instructions. Stimuli were presented using a custom stimulus pattern (Figure 3.2), extending to an eccentricity of 7°, with an inter-stimulus separation of 2°, offset by 1° from fixation. This stimulus pattern was selected on the basis of frequency of defect maps in individuals with AMD (Acton, Gibson and Cubbidge 2012), and resembles the HFA 10-2 stimulus pattern, excluding the outermost radial locations. These stimulus locations have been previously examined in studies of individuals with AMD, but they were evaluated as part of larger grids, using different microperimeters (Meleth et al. 2011; Chen et al. 2011).

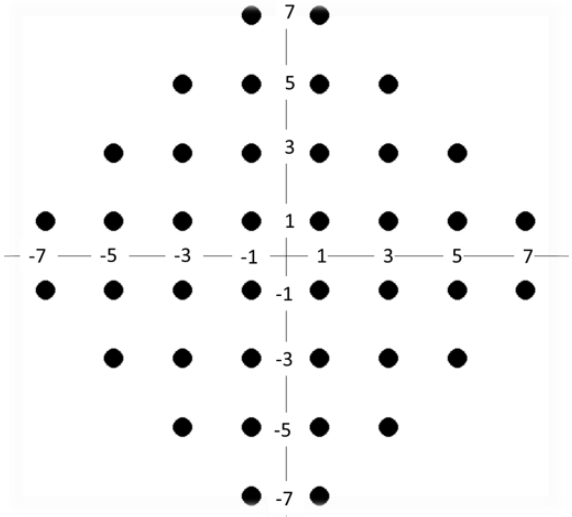


Figure 3.2 The stimulus locations used for the microperimetry examination. The inter-stimulus separation was 2° the stimuli were offset by 1° from fixation and extending to 7°.

The stimulus parameters for the MAIA microperimeter are a white Goldmann size III stimulus presented for 200ms on a uniform white background of 1.27cd/m^2 luminance. A 4-2dB threshold staircase algorithm was implemented, which uses a double crossing in 4dB and then 2dB steps. The MAIA tracks the eye position by monitoring

each pixel of the infrared retinal image at 25Hz throughout the examination. Reliability was determined by the Heijl-Krakau method (Heijl and Krakau 2009), whereby false-positive responses to a stimulus presented to the blind spot were calculated (<15% was considered acceptable). False-negative responses are not determined on the MAIA. All individuals had experience of standard perimetry, but had no experience of microperimetry.

3.2.3.1.5 Standard automated perimetry

A SAP examination was performed on the study eye using the HFA 740i (Carl Zeiss Meditec, Dublin, CA), to identify any existing visual field defects. The fellow eye was occluded using an opaque patch and all individual received identical instructions. The Program 30-2 was used, with the SITA Fast algorithm, and the Goldmann III white stimuli presented for 200ms on a white background of 10cd/m^2 luminance. The stimuli extend to an eccentricity of 30°, with an inter-stimulus separation of 6°. Fixation losses were identified by the Heijl-Krakau method and the gaze was monitored throughout the examination. False positives were identified as the number of responses when no stimulus is presented, and false negatives, as no response when a stimulus is presented at a previously visible level. A maximum criterion of 15% was considered acceptable for false positive and false negative responses, and fixation losses.

3.2.3.1.6 Imaging techniques

Colour fundus photographs and SD-OCT scans were acquired in the study eye for those over the age of 40 years. Forty-five degrees CFPs centred at the fovea (2048 x 1536 pixels) were acquired using the non-mydriatic 3D-OCT 1000 (Topcon Corp, Tokyo, Japan), which has a field angle of 45° and uses an 840nm superluminescent diode.

For the SD-OCT images, a single high-density 6mm horizontal foveal line scan consisting of 1024 A-scans was captured at the fovea, using the Cirrus HD-OCT (Carl

Zeiss Meditec, Dublin, CA). To ensure high quality images, the quality of the SD-OCT images was at least 5/10, or better.

3.2.3.2 Visit 2 and 3

The second visit consisted of the MAIA microperimetry examination and the HFA 30-2 examination, which were performed using the identical method described in Section 3.2.3.1.4 and Section 3.2.3.1.5 respectively. The third visit consisted of only the MAIA microperimetry examination.

3.3 Methodology for the studies including individuals with age-related macular degeneration (Chapter 5, 6 and 7)

3.3.1 Recruitment

3.3.1.1 Sample size

A sample size of 52 was based upon a linear multiple regression analysis to obtain an effect size of 0.4 (Mangione et al. 1999) with a power of 90% and a 0.05 probability of a Type 1 error, and a 15% allowance for individuals who may withdraw from the study. This estimate was used for the recruitment targets for the cross-sectional studies presented in Chapters 5 and 6.

For the 12 month follow-up study (Chapter 7), a separate sample calculation was necessary. A sample size of 32 was calculated, based upon a linear multiple regression analysis to obtain an effect size of 0.4 (Medeiros et al. 2015) with a power of 80% and a 0.05 probability of a Type 1 error, and a 15% allowance for individuals who may withdraw from the study.

3.3.1.2 Inclusion and exclusion criteria

The rigid inclusion criteria included VA of better than 0.6 logMAR; a refractive error of ≤5D sphere and ≤3D cylinder; lenticular changes of an average of grade 2 or better using the LOCS III (Chylack et al. 1993). Exclusion criteria consisted of glaucoma or

suspect glaucoma; previous or current history of significant eye disease other than AMD; previous eye trauma or surgery excluding phacoemulsification; systemic medications known to affect the visual field; and any systemic or neurological condition known to significantly affect visual function.

3.3.1.3 Recruitment

Individuals were recruited from the Cardiff Eye Unit at the University Hospital of Wales. Patients attending the medical retina clinic, and the nAMD clinics were recruited for the study. At these weekly clinics, the ophthalmologist (Mr Chris Blyth and/or Prof Marcela Votruba) identified those who appeared suitable based on the inclusion/exclusion criteria (see Section 3.3.1.2). These individuals were then contacted by telephone and given verbal information regarding the study. Those who were interested in participating received a written information sheet by post (Appendix C). A subsequent telephone conversation confirmed that the individuals had read the information sheet, wished to partake in the study and a date was arranged for the initial study visit.

3.3.2 Ethics

The study adhered to the tenets of Declaration of Helsinki for research involving human participants and the protocol was approved by the National Health Service South East Wales Research Ethics Committee (13/WA/0339).

3.3.3 Procedures

The individuals attended two visits at the School of Optometry and Vision Sciences, Cardiff University. A subset of individuals who attended for the initial two visits, also attended an additional follow-up visit after 1 year (Visit 3) (Figure 3.3). Visit 1 and 2

were separated by a median (IQR) of 14 days (9, 24). Visit 3 took place approximately 1 year after Visit 2, median (IQR) of 13.6 months (12.5, 14.6).

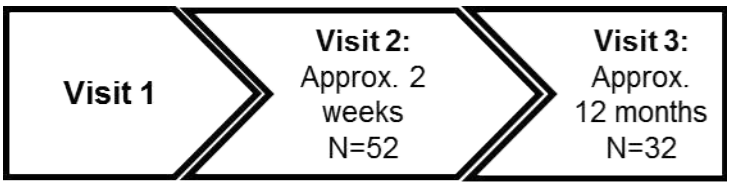


Figure 3.3 Study visit timeline.

3.3.3.1 Visit 1

The purpose of Visit 1 was to firstly confirm adherence to the inclusion and exclusion criteria by obtaining an ocular and medical history, the mini-mental state examination (MMSE) and refraction.

Secondly, a microperimetry examination was performed to reduce the perimetric learning effect at Visit 2 (Wu et al. 2013; Heijl, Lindgren and Olsson 1989). Also, SD-OCT and fundus photography images were acquired at Visit 1. The procedure for Visit 1 was identical for all individuals. Rest periods were given between tests and the test order was maintained the same for every individual (Figure 3.4). This order was chosen to minimise possible effects of fatigue (Hudson et al. 1994) on the microperimetry examination, and to avoid the bleaching effects of the slit lamp and imaging examinations prior to microperimetry. Those with AMD have reduced photoreceptor recovery after stimulation by a bright light (Curcio, Owsley and Jackson 2000).

Written consent was obtained prior to performing any examinations (Appendix D).

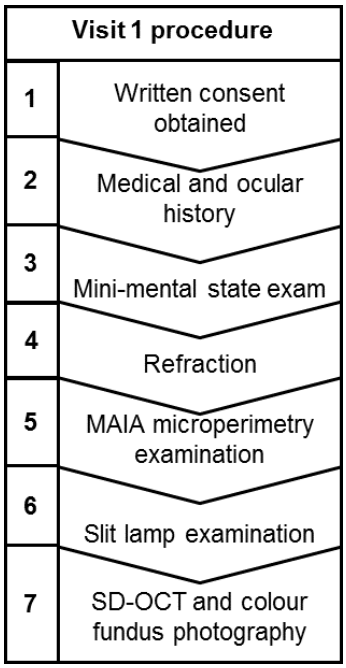


Figure 3.4 The ordered procedure for Visit 1.

3.3.3.1.1 Medical and ocular history

A structured record sheet was used to ensure commonality between the recorded responses from all individuals (Appendix E). Medical history included an open question regarding the individual's general health, an open question concerning current medications and closed questions about the presence of breathing disorders, diabetes, hearing impairment, heart conditions, hypertension and musculoskeletal conditions.

Any relevant ocular history concerning referrals to hospital eye services and any ocular diseases were recorded. More specific questions were posed relating to AMD: the type of AMD; the length of diagnosis; and the affected eye. The individual was also asked to grade their own AMD condition as early, moderate or late. The anti-VEGF injection history was also recorded. Specifically, the number of injections, the treated eye, last injection date and last appointment date.

Information about activities of daily living was also documented. This included: difficulties performing tasks such as reading, cooking and watching television; the use of visual aids (magnifiers and additional aids); sight impairment registration; and

previous access to social service. Direct questions were used to enquire about the individual's living situation and driving status. Hobbies and any current difficulties with performing these activities were noted. Fall history from the past year was also obtained. Finally, experience of visual hallucinations was probed and Charles Bonnet syndrome was explained briefly.

3.3.3.1.2 Mini-mental state examination

The shortened version of the MMSE (Schultz-Larsen, Lomholt and Kreiner 2007) is a cognitive screening tool involving 5 memory tasks (Appendix F). Firstly, three words were read aloud ("apple", "penny" and "table") and repeated until the individual had remembered the words. Three questions were then asked: "What is the day?", "What is the month?" and "What is the year?". The fourth task required the word "world" to be spelt backwards and finally the individual was asked to recall the words memorised at the beginning.

To pass the MMSE an individual was required to answer the three questions appropriately, to correctly order three letters from "world" and to repeat two words of the memorised words correctly. Those that failed the MMSE were excluded.

3.3.3.1.3 Refraction

The habitual correction was recorded and both eyes were refracted to ascertain the BCVA measured by the Snellen chart. In cases where current spectacle correction was less than 6 months old, refraction was not performed.

3.3.3.1.4 Microperimetry

The detailed protocol for MAIA microperimetry is described in Section 3.3.3.1.4. MAIA microperimetry was performed on only one eye, as this was considered a training examination for microperimetry.

3.3.3.1.5 Anterior eye examination

An examination of anterior ocular health was performed on both eyes using slit lamp biomicroscopy and included the Van Herick technique to grade the anterior chamber depth and LOCS III grading (Chylack et al. 1993).

3.3.3.1.6 Fundus photography

CFPs were obtained for both eyes, using the identical procedure described in Section 3.3.3.1.6.

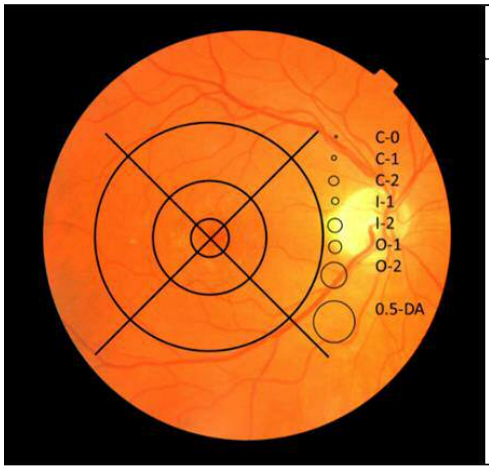
3.3.3.1.7 SD-OCT

SD-OCT images were acquired in each eye using the Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA). Volume scans were centred on the fovea with a scan angle of 20° x 20°, comprising 512 A-scans x 128 B-scans. A single high-density 6mm horizontal foveal line scan consisting of 1024 A-scans was also captured at the fovea. To ensure high quality images for grading and segmentation purposes, the quality of the SD-OCT images was at least 5/10, or better, and between 1 and 3 images were obtained. If SD-OCT was not possible due to a small pupil, one drop of Tropicamide 0.5% was instilled in each eye.

3.3.3.1.8 Colour fundus photograph grading

Colour fundus photographs were graded using the AREDS 2 classification (Danis et al. 2013), which was based on the AREDS classification system (AREDS 2001) for the use with digital photographs. CFPs were graded and classified in PowerPoint (Microsoft Office, Washington, U.S) using a digital scaling of the AREDS grid, according to the method by Danis et al. (2013) adapted for a 45° CFP. To ensure consistency of grading, each of the CFPs was resized according to the PowerPoint

equivalent size (Figure 3.5) and the grading circles were sized accordingly to ensure the correct ratios (Figure 3.5).



Grading feature	Diameter (µm)	Equivalent size in PowerPoint (cm)
Fundus photograph (45˚)	14083	16.30
Within grid	7200	8.33
Central subfield	3600	4.16
Inner subfield	1200	1.39
C-0	76	0.08
C-1	150	0.17
C-2	300	0.35
I-1	216	0.25
I-2	433	0.50
O-1	395	0.246
O-2	790	0.91
0.5-DA	1273	1.478

Figure 3.5 Left: A Colour fundus photograph of an individual with AMD with an overlay of the standard ETDRS grid and the standardised circles used for AREDs grading. Right: Table of equivalent sizes used to grade the colour fundus photographs (Adapted from Danis 2013 by [Terry, 2017])

A standard ETDRS grid was centred at the fovea for each of the images and retinal features were graded using the standard AREDS circles (Figure 3.5). Each CFP was graded for the presence of GA, drusen and pigmentation. An overall AREDs disease severity grade of 1 to 4 was assigned based upon the presence, size and location of AMD features (Table 3.1). As with AREDS 2 classification (Danis et al. 2013), history of injection was used to aid the classification of nAMD.

Once the AREDS classification had been performed, SD-OCT volume scans were used to confirm or identify the presence of intraretinal fluid, PED and other retinal features at the macula. The presence of RPD was confirmed or identified by the IR images, acquired by the MAIA microperimeter.

AREDS classification	Criteria
1	Drusen maximum size <C-0 (63µm diameter) and total area <C-1 (125µm diameter)
2	Presence of one or more of the following: •Drusen max size ≥C-0 but <C-1 •Drusen total area ≥C-1 •Pigment abnormalities consistent with AMD, defined as one or more of the following in the central or inner subfields: a) Depigmentation b) Increased pigment >C-1 c) Increased pigment present and depigmentation at least questionable
3	Presence of one or more of the following: •Drusen maximum size ≥C-1 •Drusen maximum size ≥C-0 and total area >I-2 and type is soft indistinct •Drusen maximum size >C-0 and total area >O-2 and type is soft distinct •GA within grid but none in centre of macula
4 (Late)	Presence of one or more of the following: •GA in central subfield with at least questionable involvement of centre of macula •Evidence of nAMD: a) Fibrovascular/serous PED b) Serous (or haemorrhagic) sensory retinal detachment c) Subretinal pigment epithelial haemorrhage d) Subretinal fibrous tissue e) Photocoagulation for AMD

Table 3.1. AREDS classification with criteria (AREDS 2001) © from Elsevier.

3.3.3.1.9 SD-OCT segmentation

The SD-OCT 512x128 volume scans were segmented into 10 layers (11 surfaces), using a fully automated three-dimensional segmentation algorithm (OCTSeg), a module of OCT Explorer, which is part of the Iowa Reference Algorithms (Retinal Image Analysis Lab, Iowa Institute for Biomedical Imaging, Iowa City, IA) (Garvin et al. 2009; Abràmoff, Garvin and Sonka 2010). Nine retinal layer outcomes were evaluated: the retinal nerve fibre (RNFL, boundaries 1-2), the ganglion cell layer (GCL, boundaries 2-3), the inner plexiform layer (IPL, boundaries 3-4), the inner nuclear layer (INL, 4-5), the outer nuclear (ONL, boundaries 5-6), the outer segment layer (OS, boundaries 8-10), the RPE (boundaries 10-11) and, additionally, the total

receptor layer plus RPE (boundaries 5-11) and the total retina (boundaries 1-11) (Figure 3.6).

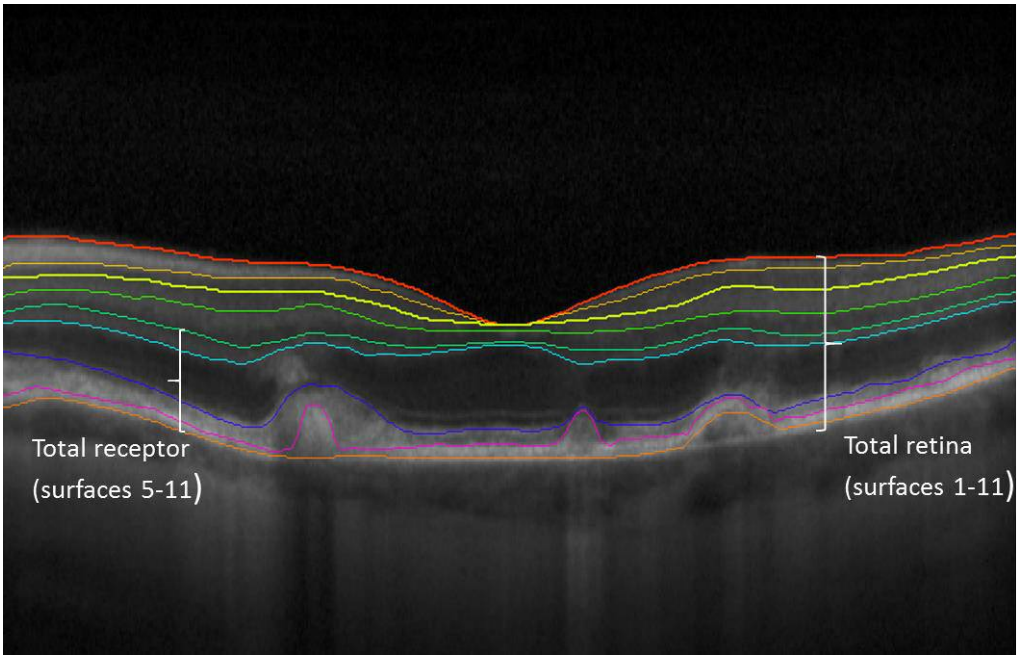


Figure 3.6 OCT Explorer segmented SD-OCT with the 8 retinal layers utilised for further analysis shown, plus the additional grouped layers of total receptor and total retina.

The pointwise retinal thickness was calculated at 40 retinal locations. Forty squares of 0.13 x 0.13mm in size, corresponding to the Goldmann III stimulus size (0.43° diameter) were identified on the en-face SD-OCT image. Stimulus sizes were converted to retinal sizes using 0.3mm equivalent to 1° (Blaker 1980; Carl Zeiss Meditec 2013; Lee et al. 2014). Each square was positioned on the en-face image, to align with the MAIA grid pattern extending to an eccentricity of 7° (Figure 3.7). This was achieved by programming coordinates for each stimulus location in the segmentation software (OCT Explorer), by writing .xml files in Notepad (Microsoft, Washington, U.S.) (Appendix G).

A second grid to account for the displacement of the retinal ganglion cell layer at the macula (Hood and Raza 2011) was applied to the thicknesses for the RNFL and GCL layers (Figure 3.7).

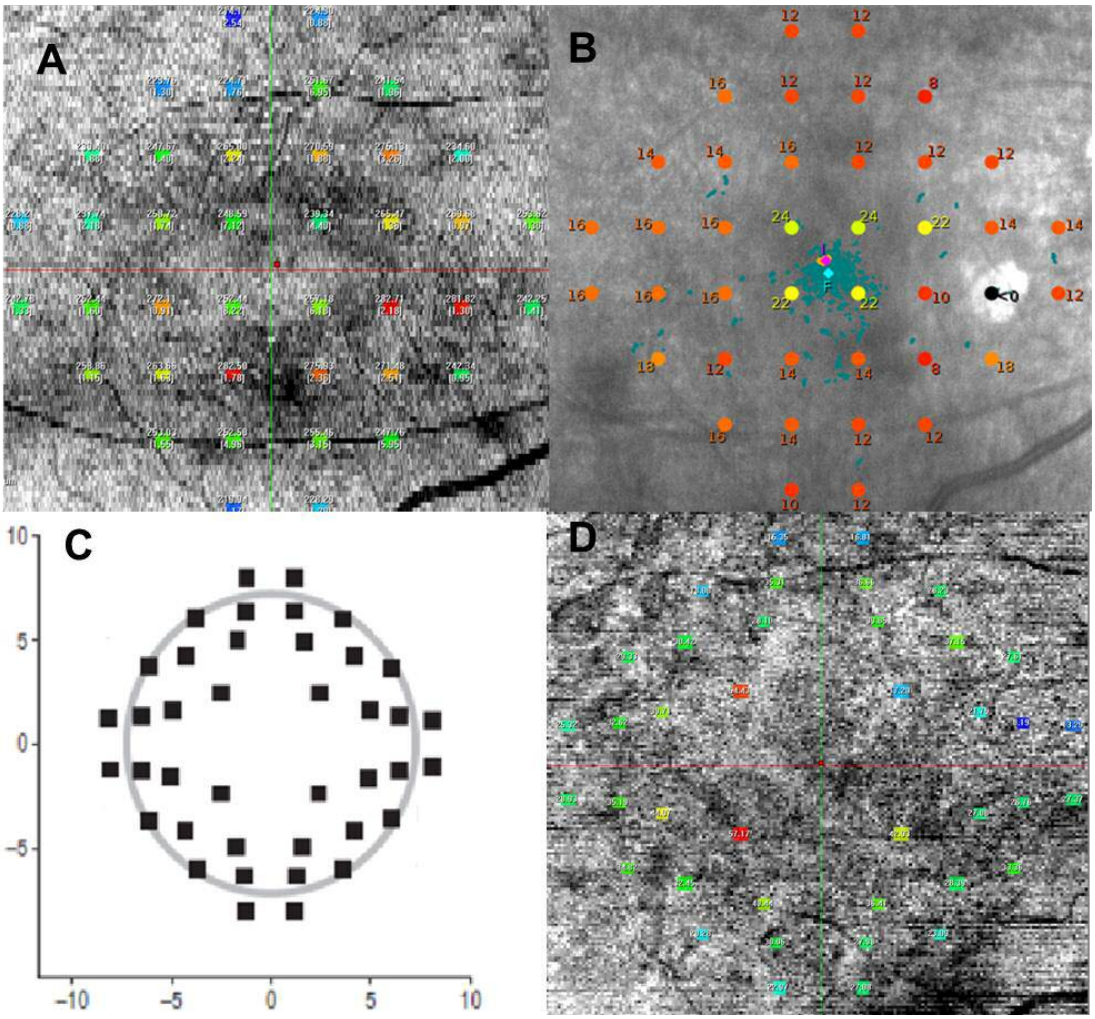


Figure 3.7 A and B: Screenshot from OCT Explorer (left) and IR image from MAIA microperimeter (right), showing the matching layout of the retinal thickness measurement locations and DLS locations. C: Realigned 40 locations in degrees from the fovea corresponding to retinal ganglion cell displacement. D: Screenshot from OCT explorer of the layout of the RNFL and GCL retinal thickness measurements.

The output of OCT Explorer takes the form of a Microsoft Excel comma separated value (.csv) file that contains the individual layer thickness for each location. From this, the mean retinal thickness outcomes at each of the stimulus locations, was calculated.

3.3.3.1.10 SD-OCT grading

SD-OCT B-scans corresponding to each of the 40 MAIA locations were examined for the presence of retinal features associated with AMD. Key retinal features associated with AMD were identified: drusen, ORTs (Figure 3.8, B), RPD (Figure 3.8, D), EZ band disruption (graded 1, 2 or 3) (Figure 3.8, A)(Wu et al. 2014c), absent RPE and/or photoreceptor layer (Figure 3.8, E), sub-retinal and intra-retinal fluid (Figure 3.8, C),

PED (fibrovascular, serous or drusenoid) and presence of fibrovascular region (Figure 3.8, C).

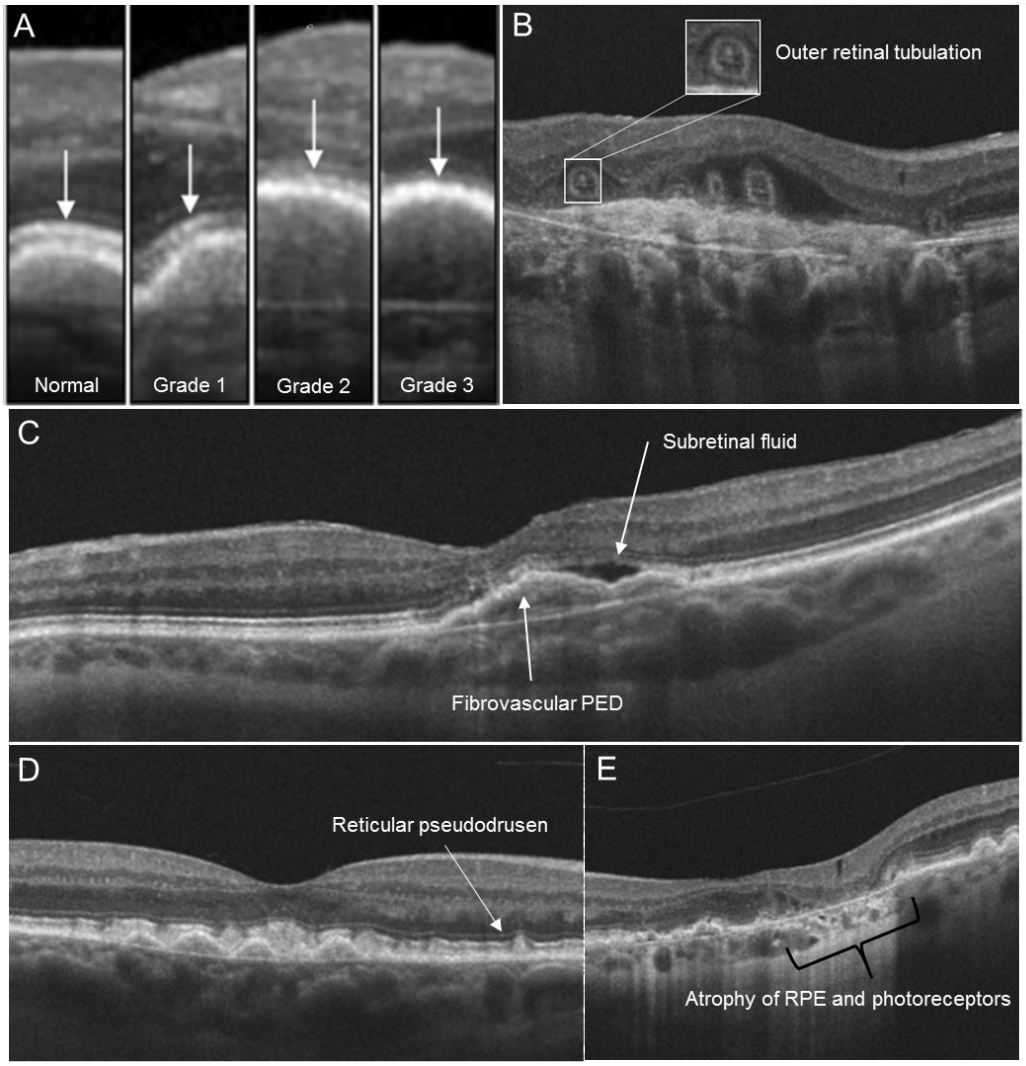


Figure 3.8 AMD associated retinal features identified by SD-OCT. A: Ellipsoid zone disruption graded from 1-3 (Wu et al. 2014c), B: Outer retinal tubulations, C: Fibrovascular PED with additional subretinal fluid, D: Reticular pseudodrusen with additional large drusen, E: Atrophy of the RPE and photoreceptor layers

3.3.3.2 Visit 2

Visit 2 was scheduled for approximately 2 weeks after the Visit 1. It consisted of VA, CS, reading speed, MAIA microperimetry and a questionnaire interview comprising a number of vision-related and health-related instruments (questionnaires). The procedure for Visit 2 was identical for all individuals. Rest periods were given between procedures and the procedure order was maintained the same for each individual

(Figure 3.9). This order was chosen to reduce the effects of fatigue in the microperimetry examination and in the questionnaire interview.

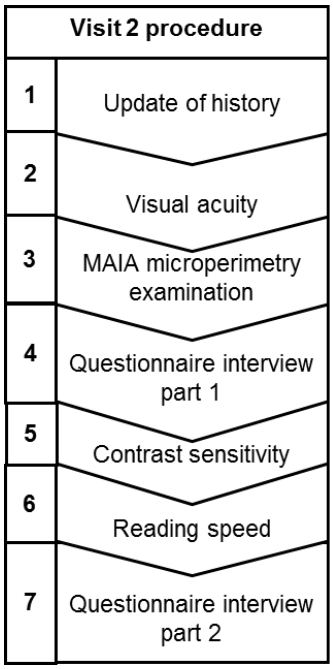


Figure 3.9 The ordered procedure for Visit 2.

At the start of Visit 2, an injection history for the two weeks between Visit 1 and 2 was recorded.

3.3.3.2.1 Visual acuity

Visual acuity was measured using the ETDRS LogMAR chart according to the standardised protocol (Ferris and Bailey 1996) using an identical method described in Section 3.2.3.1.2. The test was performed monocularly and then binocularly. This was repeated with habitual correction (VA) and best correction in place (BCVA).

3.3.3.2.2 Microperimetry

Microperimetry was performed in an identical manner to that described in Section 3.2.3.1.4 and to that in Visit 1. However, microperimetry was performed on both eyes where possible.

3.3.3.2.3 Questionnaire outcomes

Three vision-related instruments and three health-related instruments were utilised in this study. The IVI questionnaire (Lamoureux et al. 2006), the VF-14 (Steinberg et al.

1994), and the modified TTO (Brown 2000) were used to measure vision-related QoL, visual function and vision-related utility, respectively. The health-related instruments were the EQ-5D-3L (EuroQoL 1990), the PHQ-9 (Kroenke, Spitzer and Williams 2001) and the WEMWBS (Tennant et al. 2007). The primary questionnaire outcome was the IVI. The secondary outcomes were the modified TTO utility value, the VF-14, the EQ-5D-3L, the PHQ-9 and the WEMWBS. Each of the questionnaires were administered verbally and in person. The individuals could view a prompt sheet as a reminder of each of the possible Likert scale responses for the IVI, VF-14, PH-Q9 and WEMWBS (Appendix H).

The order within the questionnaire interview was the same for each individual beginning with the IVI, followed by the EQ-5D and then the WEMWBS. The individual then received a short break of between 5 and 10 minutes, in which refreshments were provided (Figure 3.10). After the break and before the next questionnaire, CS and reading speed were measured. Finally, the VF-14, followed by the PH-Q9 and concluding with the modified TTO, were administered (Figure 3.10).

1st	2nd	3rd		4th	5th	6th
IVI	EQ-5D	WEMWBS	Break	VF-14	PH-Q9	TTO

Figure 3.10 The sequence of administered questionnaires.

The IVI, VF-14 and the WEMWBS logit scores were converted into a linear scale using Rasch analysis.

3.3.3.2.3.1 ***Rasch analysis***

Rasch analysis uses item response theory to transform ordinal categories into estimates of linear interval measures, expressed in logits (Rasch 1993). It is recommended for studies that include questionnaires as it allows for parametric statistical testing (Lamoureux et al. 2008). Rasch analysis also assesses the psychometric properties of a questionnaire, including: suitable response categories; item fit; unidimensionality; differential item functioning (DIF); and the range of item difficulty to individual ability (Lamoureux et al. 2008; Rees et al. 2013).

Rasch analyses was performed according to Andrich Rating Scale model (Andrich 1978) using Winsteps software (Version 3.90.0) (Linacre 2006). The full methods to perform Rasch analyses and the associated output tables required are included in Appendix I. The psychometric properties of each questionnaire were assessed, firstly, by examining the person and item reliability and separation, where reliability estimates closer to 1 are the most reliable and separation over 2 is satisfactory (Court, Greenland and Margrain 2010). Secondly, the infit and outfit statistics were examined, which assesses how well the items measure that which the questionnaire aims to measure. Low values indicate the item correlates well with the targeted goal, values of 1.5 to 2.0 are considered as less acceptable, yet will not degrade the data, and any value greater than 2 indicated that the item is not measuring what it aims to (Court, Greenland and Margrain 2010). Thirdly, the response categories were evaluated, whereby each category required an ordered structure calibration threshold (Khadka et al. 2012). Following this, evaluation of the unidimensionality was performed, according to the infit and outfit cut-off guidelines (Smith, Schumacker and Bush 1998), whilst also taking into account the more lenient cut-offs that suggest the items are still productive for measurement (Linacre 2006). This concluded the assessment of the psychometric properties. Providing all these measures were adequate, according to the above criteria, a scoring table was produced for each questionnaire to convert raw scores to logit scores.

The logit scoring tables were constructed by combining the item measures (for each question) and the category measures (for each scoring category). The sum of these numbers provides a scoring table for each item of the questionnaire. The baseline scoring tables for each questionnaire were used to convert the raw scores, obtained at the follow-up visit, to logit scores.

3.3.3.2.3.2 ***Impact of Visual Impairment questionnaire***

The IVI is a 28 item questionnaire which utilises a Likert scale for responses (Lamoureux et al. 2006) (Table 3.2). The IVI procedure is summarised in Table 3.2 and is scored using Rasch analysis (Section 3.3.3.2.3.1) as the mean logit score for the total questionnaire and for each subscale: reading, mobility and emotional.

IVI	Questions	Response categories	Subscale
"In the past month how much has your eyesight interfered with the following activities?"	1-15	0 – not at all 1 – a little 2 – a fair amount 3 – a lot 8 – don't do for other reasons	1,3,4,6-11Reading 2,5,12-15 Mobility
"In the past month how often has your eyesight made you concerned about the following?"	16-20	0 – not at all 1 – a little 2 – a fair amount 3 – a lot 8 – don't do for other reasons	Mobility
Think about how your eyesight has made you feel in the past month"	21-28	0 – not at all 1 – a little 2 – a fair amount 3 – a lot 8 – don't do for other reasons	Emotional

Note. Reduced answering category for question 4 and 7: 0, not at all; 1, fair amount; and 2, a lot.

Table 3.2. The question wording for the Impact of Vision Impairment questionnaire with the associated response categories and subscales: mobility, emotion and reading.

Although the IVI has been Rasch analysed for AMD previously (Lamoureux et al. 2008), the published scoring system for the IVI was not established specifically for those with AMD (Lamoureux et al. 2006). Therefore, Rasch analysis for the IVI was performed within this research to produce a logit scoring table for the total score of the IVI, specifically for those with AMD. Prior to Rasch analysis, the IVI questionnaire scores were reversed and combined (Lamoureux et al. 2006), which allowed more logical interpretation, whereby a more negative logit score represents a worse vision-related QoL.

3.3.3.2.3.3 ***EQ-5D-3L***

The EQ-5D-3L instrument includes five questions with a choice of 3 responses for each question (EuroQoL 1990). The questions are related to mobility, self-care, ability to perform everyday activities, pain, and anxiety and/or depression. The individuals were required to rate each category as having no problems, 1; moderate problems, 2; or extreme problems, 3, in each case. The published country specific value sets to calculate an index (van Reenen and Oppe 2015) were used to estimate the EQ-5D index value (Rabin and de Charro 2001).

The EQ-5D also includes a visual analogue scale in which the individual was asked to rate their overall health state on the day of the visit using a scale of 0-100, with 0 being the worst imaginable health state and 100, the best.

3.3.3.2.3.4 ***Warwick-Edinburgh Mental Well-being scale***

The authors of the WEMWBS require the following copyright statement to be given when using this questionnaire:

“The WEMWBS was funded by the Scottish Government National Programme for Improving Mental Health and Well-being, commissioned by NHS Health Scotland, developed by the University of Warwick and the University of Edinburgh, and is jointly owned by NHS Health Scotland, the University of Warwick and the University of Edinburgh) (Tennant et al. 2007).

The WEMWBS includes 14 statements about positive thoughts and feelings. The individual is asked to provide the response that best describes their experience over the last two weeks (Table 3.3). The WEMWBS was scored using a Rasch analysed scoring table (Section 3.3.3.2.3.1).

WEMWBS	Questions	Response categories
"Please give the response that best describes your experiences of each over the last 2 weeks"	1-14	1 – None of the time 2 – Rarely 3 – Some of the time 4- Often 5- All of the time

Table 3.3 Warwick-Edinburgh Mental Well-Being scale question wording and the response categories.

It was necessary to undertake Rasch analysis of the WEMWBS, as a scoring table has not previously been published for individuals with AMD. The psychometric properties were assessed and a scoring table was produced.

3.3.3.2.3.5 ***VF-14***

The VF-14 consists of 14 items each with a 5 category Likert scale (Steinberg et al. 1994). The individuals were required to classify the level of difficulty experienced with 14 different tasks by means of the categories Table 3.4. If any of the questions were not relevant to the individual, they were excluded. The VF-14 was scored using a Rasch analysed scoring table.

VF-14	Questions	Response categories
"Do you have difficulty, even with glasses,…."	1-14	0- Not possible 1- a lot of difficulty 2- some difficulty 3- a little difficulty 4- no difficulty

Table 3.4 Visual function-14 question wording and response categories.

The VF-14 has been Rasch analysed in individuals with cataracts (Las Hayas et al. 2011) and with AMD (Hewitt et al. 2006), but to the authors knowledge, no scoring table has been published for individuals with AMD. Rasch analysis was, therefore, performed on the VF-14 to assess the psychometric properties and derive a scoring table for individuals with AMD.

3.3.3.2.3.6 ***PHQ-9***

The PHQ-9 consists of 9 questions relating to symptoms of depression (Kroenke, Spitzer and Williams 2001). The individual was asked "how often over the last 2 weeks

have you been bothered by any of the following problems?". The choice of responses is: 0, not at all; 1, several days; 2, more than half the days; and 3, nearly every day. The individual scores were totalled to produce the overall score, which determined the individual's level of depressive symptoms (Table 3.5).

Total score	Depression Severity
1-4	Minimal
5-9	Mild
10-14	Moderate
15-19	Moderately severe
20-27	Severe

Table 3.5 Interpretation of the Patient Health Questionnaire-9 (PHQ-9) total score to establish the severity of depressive symptoms

To identify individuals that were considered at risk of harm related to depressive symptoms, a protocol was adopted (Figure 3.11). A score of 5-27 led to the individual being offered referral to their GP, and completion of a consent form was required (Appendix J). Individuals identified as being at risk of suicide (score 2-3 on question 9 of the PHQ-9) were referred to their GP without consent being required and were excluded from the study.

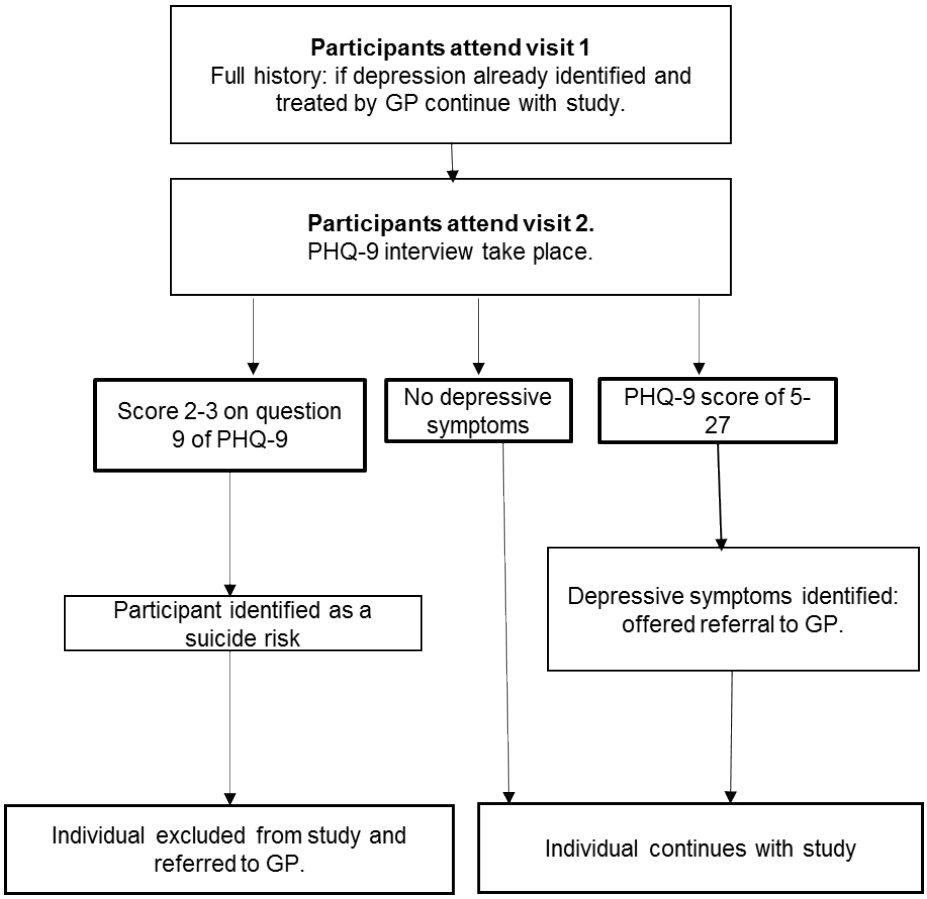


Figure 3.11 Protocol for identification of depressive symptoms from the PHQ-9

3.3.3.2.3.7 ***Modified TTO***

The modified TTO consists of two hypothetical questions (Brown 2000). Firstly: "How many years do you expect to live?" and secondly: "How many of those years would you trade for perfect vision?" A utility value was then calculated from the equation:

$$\text{Utility value} = \frac{\text{(Number of expected life years - Number of years trade-off)}}{\text{Number of expected life years}}$$

3.3.3.2.4 Contrast sensitivity

Monocular and binocular CS was measured using the Mars contrast sensitivity test (Haymes et al. 2006). Near visual correction was worn and the test undertaken at a working distance of 50cm. This was undertaken using the habitual correction and if applicable, repeated with the best correction in place. The chart was uniformly lit at an average of 85cd/m^2, measured by a photometer (LS-110; Konica Minolta., Osaka, Japan), according to the manufacturer's guidelines. Identical instructions were given, to read from left to right and top to bottom. Only a response of a letter included in the

chart was accepted. The LogCS was calculated as the LogCS value of the final correct letter minus the errors (-0.04 per incorrect letter).

3.3.3.2.5 Reading speed

The IResT (Trauzettel-Klosinski and Dietz 2012) was used to quantify reading speed binocularly. The text was held at the habitual working distance with the habitual near, and if appropriate with the best correction in place. The text was illuminated by overhead fluorescent lighting, with equal lumination (average of 85cd/m^{-2}) over the page, using the same luminance for each individual. Identical instructions were given, to read the entire paragraph of text aloud from start to finish, as quickly as possible without making corrections.

The text was initially covered and timing began when it was uncovered. The speed was measured using a stopwatch in seconds to the nearest 1/10^{th}, consistent with the researcher's reaction time. The words read incorrectly or missed were subtracted from the total number of words in the text. Reading speed in words per minute (wpm) was calculated by the equation:

$$\text{wpm} = \frac{\text{number of correctly read words}}{\text{reading time}} \times 60$$

3.3.3.3 Visit 3

Visit 3 was undertaken approximately 1 year after Visit 2 and involved the collection of follow-up outcomes in a subset of individuals. The procedure for Visit 3 was identical for all individuals, rest periods were given between tests and the test order was maintained the same for every individual (Figure 3.12).

An updated ocular and medical history was taken in the same manner as Visit 1 (Section 3.3.3.1.1). The habitual correction was recorded and both eyes were refracted, except in cases where current correction was less than 6 months old.

Monocular and binocular ETDRS VAs were recorded with both the habitual and best correction in place, as in Visit 2 (Section 3.3.3.2.1).

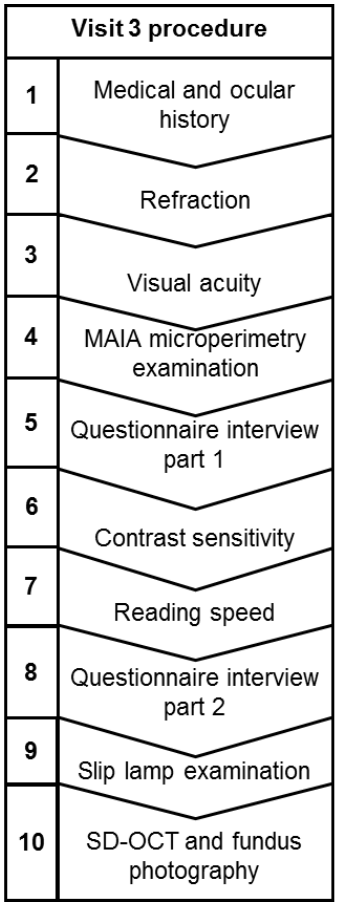


Figure 3.12 The ordered procedure for Visit 3

Microperimetry was performed using the identical protocol adopted in Visit 1, and performed on both eyes where possible (Section 3.3.3.1.4).

The questionnaire interview was performed in an identical manner to Visit 2 (Section 3.3.3.2.3).

A full anterior ocular health evaluation was performed and imaging data was collected in an identical manner to Visit 1 (Section 3.3.3.1.5 and Section 3.3.3.1.6, respectively).

This chapter described the methodology that was used for the subsequent studies presented in Chapters 4, 5, 6 and 7.

Chapter 4: Development of a normative database using the Macular Integrity Assessment microperimeter and the application in age-related macular degeneration

4.1 Summary

Purpose: The primary aim of this study was to derive a pointwise age-corrected normative database and to determine the 95%, 98% and 99% limits of normality. The secondary aims were twofold: to examine over three visits the characteristics of the macular visual field (MVF), with respect to age and eccentricity; and to compare two different methods of deriving the normative database with the addition of a clinical case study.

Methods: Sixty-five normal individuals (median age 43 years, IQR 26.0, 65.0) met the inclusion criteria and attended for three visits. The DLS for each individual was measured using a custom program (40 stimulus locations within 7° from fixation) on the MAIA microperimeter, at each of the visits. Two normative databases were derived, one using an adjusted age method (Method 1), that has previously been used with the Humphrey Visual Field Analyser, and the other using an age-specific method (Method 2) to derive the TD and PD probability levels at each of the 40 stimulus locations for each visit.

Results: Mean Sensitivity declined with age for each of the three visits ($p<0.001$). The pointwise normal DLS values and the magnitude of DLS at which the TD and PD 95%, 98% and 99% probability limits occurred for Method 1 all declined with eccentricity and increased with visit (all $p<0.05$) as did those for Method 2, which also declined with age ($p<0.05$). The pointwise values of TD and PD prediction limits

between corresponding visits were higher for Method 1 than Method 2 in all cases (all $p<0.01$).

Conclusion: The derivation of a normative database is essential for the quantification of functional deficits in AMD, detected using MAIA microperimetry. Method 2 will be employed throughout all subsequent chapters due to a robust statistical methodology.

4.2 Introduction

Normative databases for medical equipment are required to enable appropriate diagnosis and management of diseases. This chapter will develop a normative database for the MAIA microperimeter as a prerequisite for the analysis of microperimetry outcomes in individuals with AMD in the following chapters. Firstly, the relevant literature will be summarised, prior to a detailed explanation of the database derivation.

In SAP, the standard approach is to use software that incorporates normal values to allow probability analyses of the DLS results, in order to identify abnormality (Heijl et al. 1989). This includes pointwise probability analysis of TD and PD, and summary measures such as MD and mean PD (MPD). TD refers to the difference between the measured value and the corresponding age-corrected normal value at each stimulus location, with MD being the mean weighted TD and mean TD (MTD) the unweighted equivalent. PD is adjusted according to the general height of the visual field and provides information about localised loss (Heijl, Lindgren and Olsson 1987a).

The international standards for ophthalmic instruments (ISO 12866) provide a number of minimum requirements of a normative database for perimeters. Firstly, that the definition of healthy eyes must be predefined including a minimum level of VA, a maximum spherical and cylindrical optical correction and exclusion of individuals with conditions that affect the visual field. Secondly, the method of perimetric examination should be predefined including the eye to be tested, as only one eye of each subject can be included. Finally, the normative database must include at least 60 eyes, of which ten individuals are required to be younger than 30 years and ten individuals older than 60 years.

Normative databases in SAP are usually obtained across multiple research sites, with a large number of individuals (typically more than 200), who undertake perimetry on

two or more visits, where data was randomly selected from one of the visits to be included in the database (Heijl, Lindgren and Olsson 1987a). This random selection attempts to reduce the impact of the perimetric learning effect i.e. where DLS results improve with experience, and are most pronounced from the first to the second visit (Wild et al. 1989; Heijl and Bengtsson 1996). This has led to the current practice of repeating the initial perimetry examination (Wood et al. 1987; Heijl, Lindgren and Olsson 1989; Fredette et al. 2015).

Microperimetry is a relatively recent technique with two main advantages over SAP. Firstly, tracking of the fundus allows correction of unstable fixation and/or loss of fixation, which is associated with late stage AMD (Whittaker, Budd and Cummings 1988). Secondly, the DLS at each stimulus location is overlaid onto the fundus image. The MAIA (Centervue, Padova, Italy) utilises a SLO to acquire a fundal image and tracks each pixel within the image. A correction of the stimulus projection is made according to the gaze position (gaze-contingency). A full description of the technical specification of the MAIA microperimeter can be found in Chapter 1 (Section 1.4.4.1) and a review of microperimetry is presented in Section 1.4.4.

Similar to SAP, the plateauing of the learning effect after the second visit, is also evident in microperimetry as determined in a study of pointwise sensitivity on the MAIA (Wu et al. 2013). In contrast, another study found no learning effect, when examining an average index, MS (Weingessel et al. 2009). However, an average index might not be the most relevant method to analyse this due to the topographical nature of microperimetry. It is, therefore, still beneficial to have several separate examinations on different days to reduce the learning effect (Heijl and Bengtsson 1996; Wu et al. 2013).

The MAIA microperimeter does not derive TD or PD analysis and merely displays the measured DLS, in decibels, at each stimulus location. The DLS value is colour coded, using a continuous scale of colour change, to arbitrarily indicate normal, borderline

and abnormal outcomes (Midena 2013) (Figure 4.1). Although a schematic histogram of normality is presented, it does not consider the variation of DLS in the normal eye with age and with eccentricity (Figure 4.1). The lack of probability analysis, by TD and PD, may limit the ability to detect generalised and localised early functional losses in AMD and also to monitor functional deficits accurately.

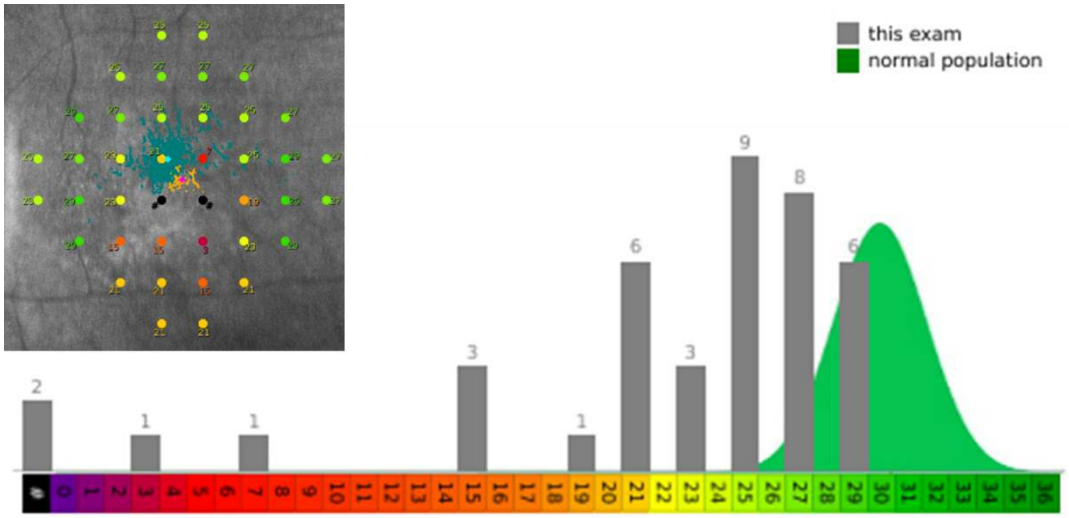


Figure 4.1 MAIA microperimetry output: 40 location stimulus pattern (top left) for an individual with AMD. The colour coding represents the different decibel values for sensitivity as shown on the frequency histogram for the same individual (bottom). The normal population distribution shown is the same for all ages and eccentricities.

DLS results and spatial characteristics in normal individuals have been previously described for the MAIA microperimeter (Vujosevic et al. 2011; Fujiwara et al. 2014). However, these studies describe MS only, did not take into account age and did not derive TD or PD probability analysis i.e. the parameters that clinicians would find most useful. Two recent studies have examined normal values of the MAIA microperimeter with respect to age (Denniss and Astle 2016; Molina-Martín, Piñero and Pérez-Cambrodí 2017). The first derived a computational model of DLS measurements enabling the derivation of TD and PD probability analyses independent of fixation (Denniss and Astle 2016). However, given the large number of stimulus locations examined, 237 locations over 1 or 2 sessions, this study did not reflect a typical perimetric situation in clinical practice. A more recent study examined median DLS values with respect to age, but did not include calculation of probability analyses

(Molina-Martín, Piñero and Pérez-Cambrodí 2017). Hence, the study presented herein will produce clinically relevant normative database values with the inclusion of probability analysis to define abnormality.

There are different methods of deriving normative databases. A long established method of normative database derivation, used for the HFA, involves the adjustment of DLS values to that of the mean age of the cohort (Bengtsson and Heijl 1999; Heijl, Lindgren and Olsson 1987a). Yet, little is known or has been published to explain the methodology and statistical reasoning behind it. Other studies have derived normative databases for microperimetry (Acton, Bartlett and Greenstein 2011) and SD-OCT (Topcon Medical Systems I 2011) using linear regression analysis. Due to the equivocal nature of the current literature, both methods will be performed and subsequently compared to establish the most appropriate method to continue forward in all future studies.

The primary aim of this study was to derive a pointwise age-corrected normative database and to determine the 95%, 98% and 99% limits of normality. The secondary aims were twofold: to examine over three visits the characteristics of the MVF, from microperimetry, with respect to age and eccentricity; and to compare two different methods of deriving the normative database with the addition of a clinical case study.

4.3 **Methods**

The cohort comprised 80 consecutive individuals with a median (IQR) age of 43 years (26, 65). The detailed methodology is presented in Chapter 3: and is summarised in Figure 4.2.

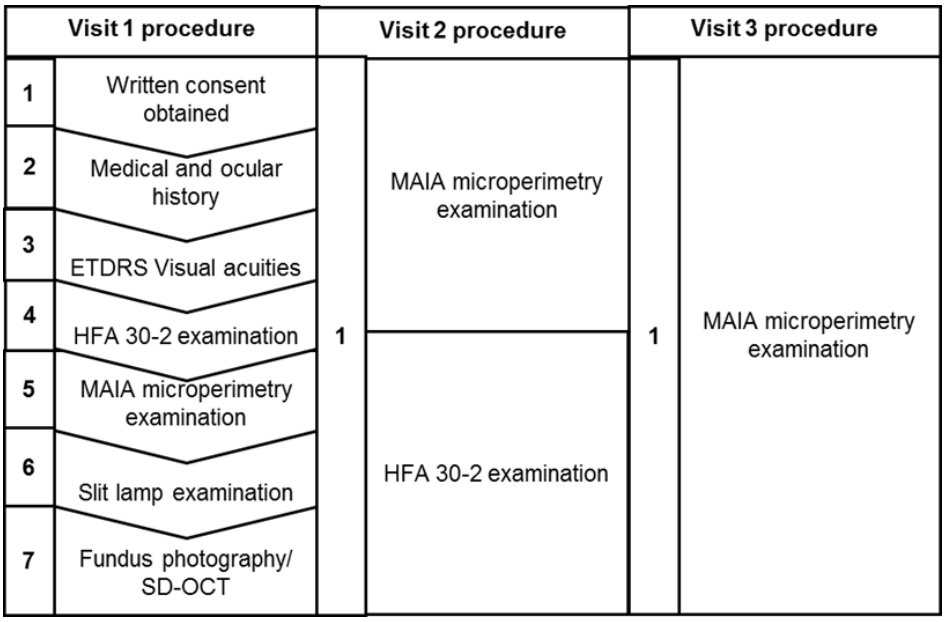


Figure 4.2 The sequence of procedures for the normative data collection. The three visits were each separated by an average of 2 weeks.

The study eye was chosen as that with the better VA, and when both eyes had equal VAs the study eye was chosen at random.

4.3.1 Analysis

4.3.1.1 Regression

MAIA DLS values from all visits were transformed to a right eye format. The distribution was examined using the Kolmogorov-Smirnov test.

Two methods of deriving a normative database were investigated in this study. Both methods required regression analysis, therefore the assumptions of linear regression were tested prior to database construction. The assumptions of linear regression are that:

- the outcome variable should have a normal distribution for each value of the predictor variable (Altman 1991).
- the variability of the outcome variable should be the same for each value of the predictor variable (Altman 1991).
- the relation between the two variables should be linear (Altman 1991).

Plotting the residuals allows subjective visual assessment of these assumptions, whilst the “gvlma” package in the open source statistical software, R (R Core Team 2017), provides statistical testing (kurtosis, skewness, heteroscedasticity and a global statistic) with p-values to ensure the assumptions are met. The relationship between age and DLS, both as a mean and for each of the 40 stimulus locations, was determined using a linear regression model and the assumptions were assessed (Altman 1991). In all 40 locations, for each visit, the assumptions were met (all p>0.05) and each plot of residuals was acceptable (Figure 4.3). Therefore, it was concluded that linear regression was an appropriate method with which to construct the normative databases.

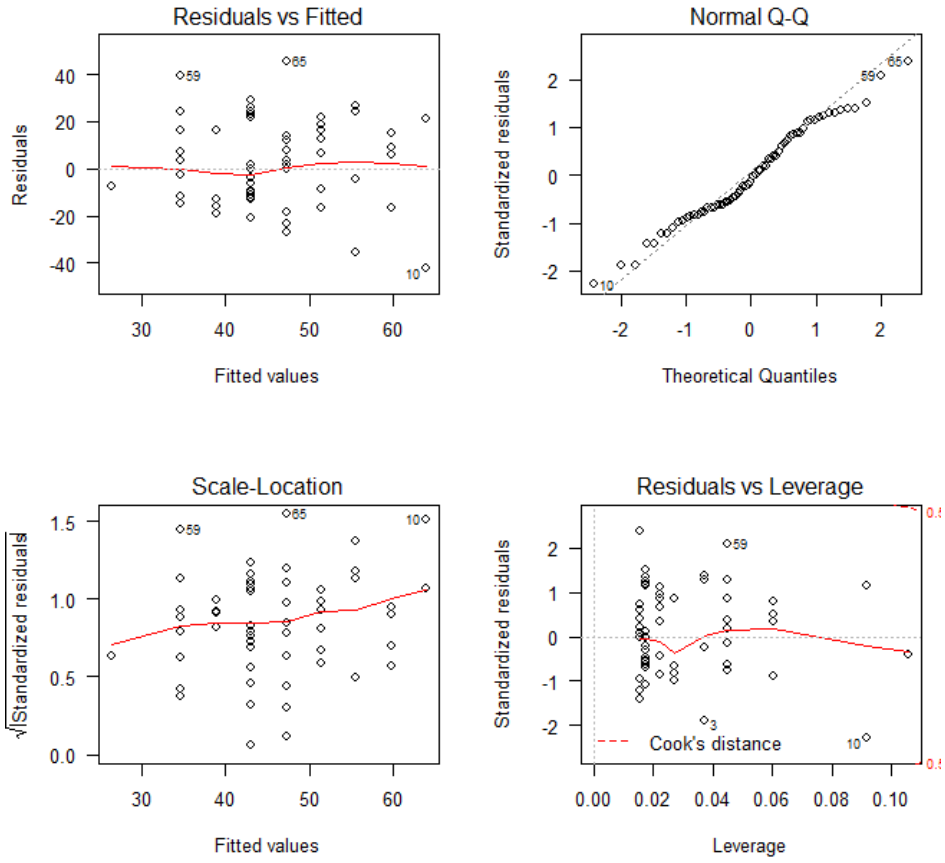


Figure 4.3 Example of residual plots for linear regression of differential light sensitivity with age for location 3 and visit 3. The residuals (top left) and standardised residuals (bottom left) plotted against the fitted values, the normal Q-Q plot (top right) and the standardised residuals plotted against the leverage (bottom right).

4.3.1.2 Database derivation

Two methods to derive the normative databases were used, the adjusted age method (Method 1) and age-specific method (Method 2). For each of these methods three databases were derived corresponding to each of the three visits (Figure 4.4).

The adjusted age method (Method 1) involves the conversion of each individual from their own age to the mean age of the cohort and subsequently the appropriate adjustment of the DLS. The age-specific method (Method 2) utilises linear regression of DLS versus age of each individual. Both databases were derived using the open source environment R (R Core Team 2015) (Appendix K).

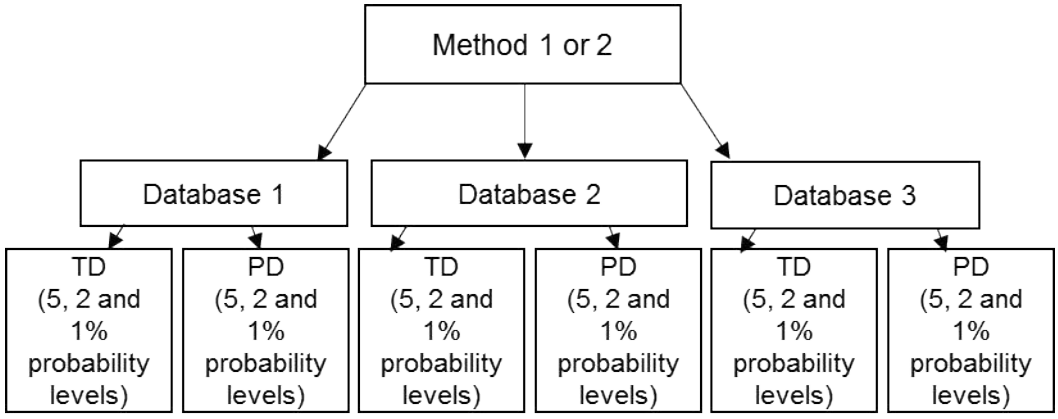


Figure 4.4 Flow diagram of derivation the normative databases for Methods 1 and 2. Three databases are derived from each of the visits and TD and PD probability analyses will be derived for each of the databases.

4.3.1.2.1 Adjusted age method (Method 1)

The rationale for the current method to calculate the prediction limits in SAP is not well documented. However, this method was used as it is similar to that used by Zeiss for the HFA normative database as can be assumed from the current literature (Bengtsson and Heijl 1999; Heijl, Lindgren and Olsson 1987a).

4.3.1.2.1.1 ***Normative database derivation***

Linear regression was used to determine the relationship between age and DLS at each stimulus location. The pointwise DLS values were then adjusted to the mean age adjusted DLS using the equation:

$$\text{Mean age adjusted DLS} = \text{DLS} + (\ 45.97 - \text{individual s age}\ \times \text{slope})$$

4.3.1.2.1.2 ***Total Deviation derivation***

Mean age (45.97 years) DLS values provide a 'normal' individual dataset for comparison with the mean age adjusted measured DLS values.

The difference between mean age DLS and the age adjusted DLS were calculated to derive the TD values, for each location. The distribution of the TD values was examined using the Shapiro-Wilk test. The TD probability limits were calculated using the 95th, 98th and 99th percentiles of the TD values at each stimulus location (Figure 4.5).

4.3.1.2.1.3 ***Pattern Deviation derivation***

The 85th percentile of the TD values across all the stimulus location, for each individual, was calculated. This was then subtracted from the mean age adjusted DLS values to produce the 85th percentile corrected DLS values for each individual. The difference between the pointwise 85th percentile corrected DLS and the mean age DLS were calculated to produce the PD values for each stimulus location. The distributions of the PD values were examined using the Shapiro-Wilk test. The PD probability limits were calculated using the 95th, 98th and 99th percentiles of the PD values at each stimulus location (Figure 4.5).

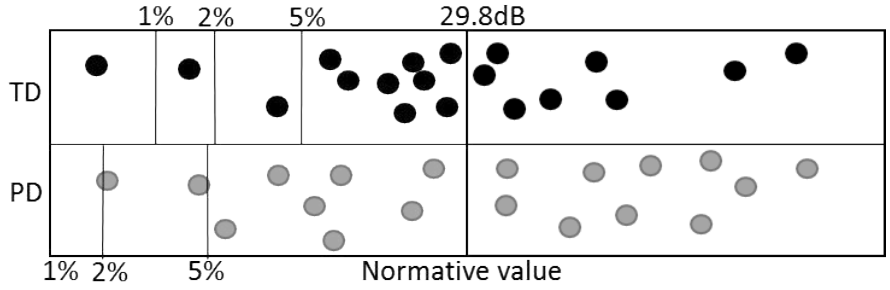


Figure 4.5 Schematic diagram of the adjusted age method (Method 1). A theoretical distribution of the TD and PD values for a single stimulus location are shown. The 5%, 2% and 1% probability limits of the normative database are derived from the 95th, 98th and 99th percentiles of the distribution.

4.3.1.2.1.4 ***Database use with clinical data***

When using this database to examine new DLS values, the measured DLS values were age adjusted. These age adjusted values were then subtracted from the mean

age DLS database values to calculate the TD values for an individual. These values were then compared to the database probability limits to identify locations exhibiting a probability value at ≤5%, ≤2% and ≤1%. The 85th percentile of the individual's TD values was then calculated and subtracted from the TD values to derive the PD values. Finally, the PD values were compared to the database PD probability limits to identify locations exhibiting a probability value at ≤5%, ≤2% and ≤1% (Figure 4.6).

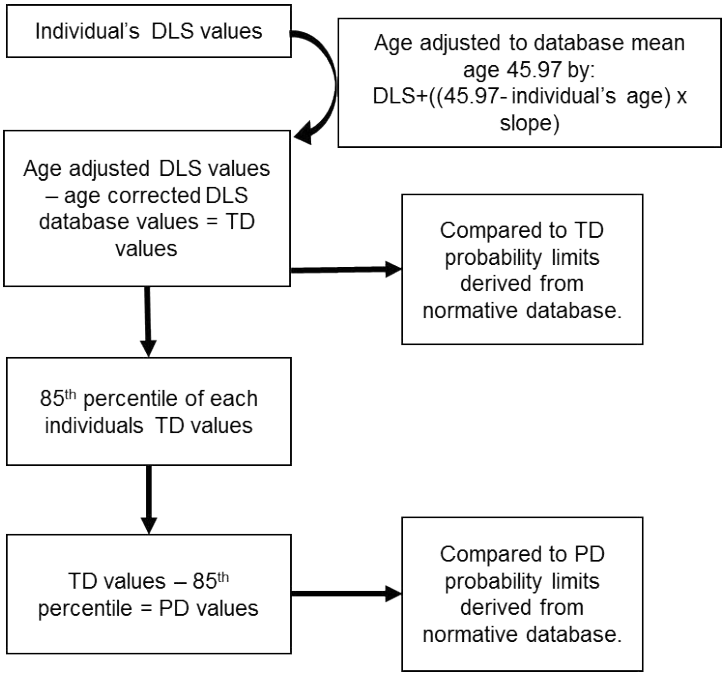


Figure 4.6 Flow diagram of the use of Method 1 database with a new individuals DLS values

4.3.1.2.2 Age-specific method (Method 2)

4.3.1.2.2.1 *Normative database derivation*

The age-specific method used regression analysis of DLS as a function of age for each of the stimulus locations to create the normative database. The linear regression line was used for the normative DLS values of the database (Figure 4.7).

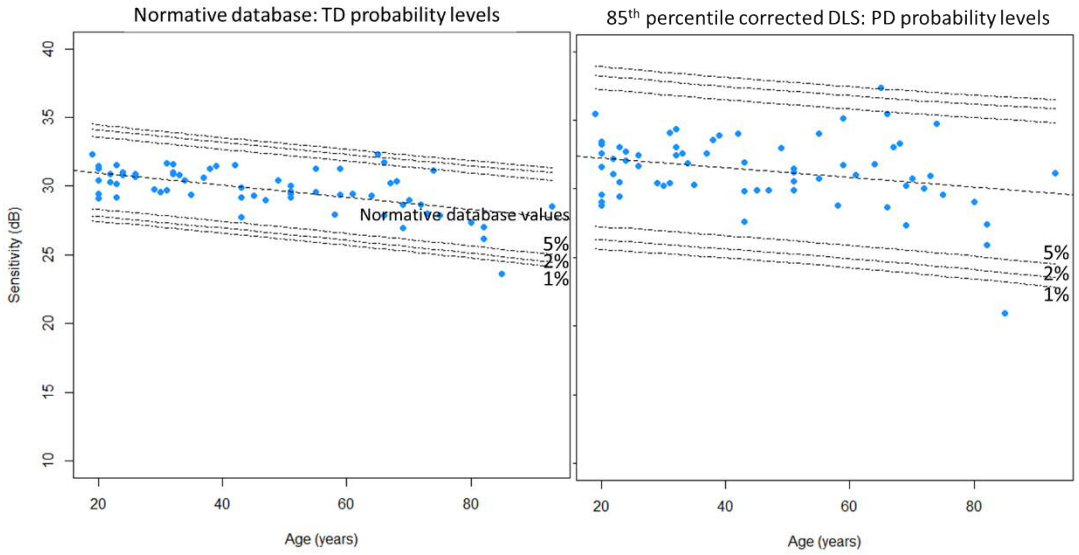


Figure 4.7 Left: Linear regression plot of differential light sensitivity (DLS) (ordinate) with age (abscissa), showing the fitted regression line which produces the normative database DLS values, the 5%, 2% and 1% prediction limits are also shown that correspond to the Total Deviation probability levels of the normative database. Right: Linear regression of 85th percentile corrected DLS values with age, showing the 5%, 2% and 1% prediction limits that correspond to the Pattern deviation probability levels.

4.3.1.2.2.2 *Total Deviation derivation*

The regression 95%, 98% and 99% prediction limits corresponded to the TD probability levels at the 5%, 2% and 1% for the normative database (Figure 4.7).

4.3.1.2.2.3 *Pattern Deviation derivation*

The 85th percentile of each individual's TD values were calculated and subtracted from the individual's DLS values to produce 85th percentile corrected DLS values. Linear regression of 85th percentile corrected DLS values with age were produced for each of the stimulus locations. The prediction levels (95%, 98% and 99%) of these were then used to derive the PD probability limits (5%, 2% and 1%) for the normative database (Figure 4.7).

4.3.1.2.2.4 ***Database use with clinical data***

When using this database to examine new DLS values, pointwise DLS values were compared to pointwise normative database values for the individual's age. The difference between the pointwise new DLS values and pointwise normative database values provides the pointwise TD values. The pointwise new DLS values were then compared to the corresponding pointwise prediction limits to derive the associated probability level. The 85th percentile of the individual's TD values was then subtracted from the TD values to derive the PD values. The PD values were then compared to the elevator corrected prediction limits to derive the pointwise PD probability level (Figure 4.8).

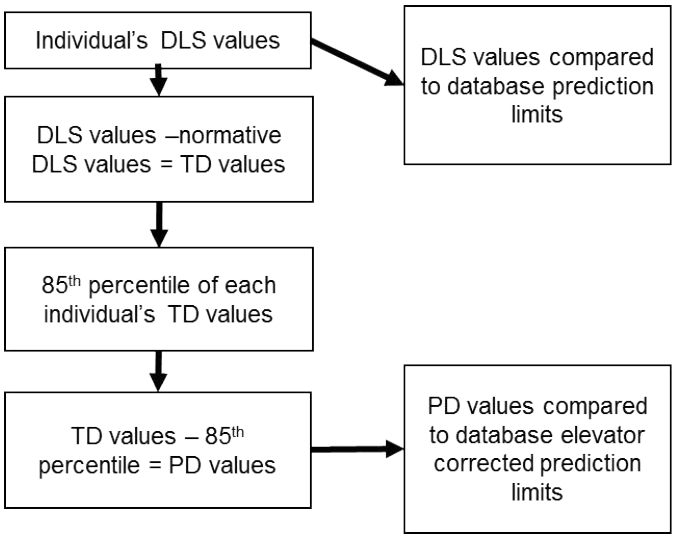


Figure 4.8 Flow diagram of the use of method 2 database with new individual's DLS values

4.3.1.3 Statistical analysis

The data was analysed using Microsoft Excel 2013, SPSS Statistical Package version 20 (SPSS, Inc., Chicago) and the open source environment R (R Core Team 2015).

To examine, over three visits, the characteristics of the MVF with age and eccentricity. The difference in the magnitude of the MS and pointwise DLS as a function of age, eccentricity and visit was analysed for Method 1 and Method 2.

For MS, a two-way repeated measures Analysis of Variance (ANOVA) with visit as a within-subject factor, and age as a between-subject factor was employed.

For pointwise DLS, eccentricity was defined in terms of four concentric annuli: within a radius of 1°, between a radius of 1° and 3°, between a radius of 3° and 5° and between 5° and 7° (Figure 4.9).

For Method 1, the DLS corresponding to the normal values, and at which 5%, 2% and 1% TD and PD prediction limits occurred were investigated using a separate two-way repeated measures ANOVA, with location and visit as separate within-subject factors. As Method 2 also included age, a separate three-way repeated measures ANOVA with location and visit as separate within-subject factors and age as a between-subjects factor was used.

A pointwise comparison of the database DLS normal values, TD and PD prediction limits (95%, 98% and 99%) between adjusted age method (Method 1) and the age-specific method (Method 2) for each of the visits was carried out using a two-tailed independent samples t-test. Significance was defined as ≤0.05 in all cases. Individual case data were also examined to visualise the difference between normative databases on a clinical level.

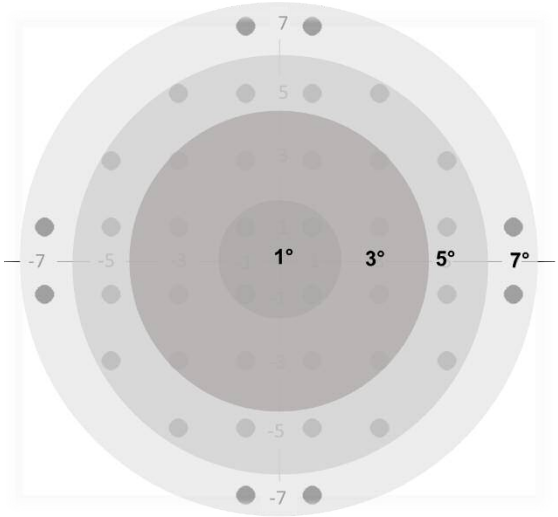


Figure 4.9 Eccentric annuli used within this study: within a radius of 1°, between a radius of 1° and 3°, between a radius of 3° and 5° and between 5° and 7°.

4.4 **Results**

The following results are presented: firstly, characteristics of the healthy individuals and the microperimetry results; secondly the analysis performed on each of the databases derived in this study (Method 1 and Method 2); finally, the comparison between the two databases with a clinical example.

4.4.1 Characteristics of healthy individuals

Five of the 80 individuals were excluded due to existing ocular co-morbidities (3 due to details from the medical history, and following ocular examination, one due to epiretinal membrane formation and one due to early AMD). A further 5 failed to complete all three visits and one was excluded due to a lens artefact in the visual field recording, resulting in a cohort of 65 individuals (38 female, 27 males).

The characteristics of the individuals, including the MAIA and HFA visual field characteristics, are presented in Table 4.1.

N=66	**Median (IQR)**
Age (years)	43.0 (26.0, 65.0)
Mean sphere (DS)	0.0 (1.4 , -2.1)
VA (LogMAR)	-0.1 (-0.1, -0.2)
IOP (mmHg)	14 (13, 17)
HFA 30-2 (dB)	
MD	-0.5 (-1.5, 0.4)
PSD	1.5 (1.3, 1.8)
MAIA Mean Sensitivity (dB)	
Visit 1	29.7 (28.4, 30.5)
Visit 2	29.8 (28.6, 30.5)
Visit 3	29.9 (29.2, 31.0)

Table 4.1 Characteristics of the healthy individuals. Median (IQR) values are presented for: age, spectacle prescription, visual acuity (VA), intra ocular pressure (IOP), Humphrey field analyser (HFA) and Macular Integrity Assessment (MAIA) microperimetry.

The measured MS declined with age for each of the three visits ($p<0.001$) (Figure 4.10), as did the measured DLS at each of the 40 locations. However, MS was not significantly different between visits ($p=0.19$). The pointwise slope values of DLS against age for each of the three visits are presented in Figure 4.11.

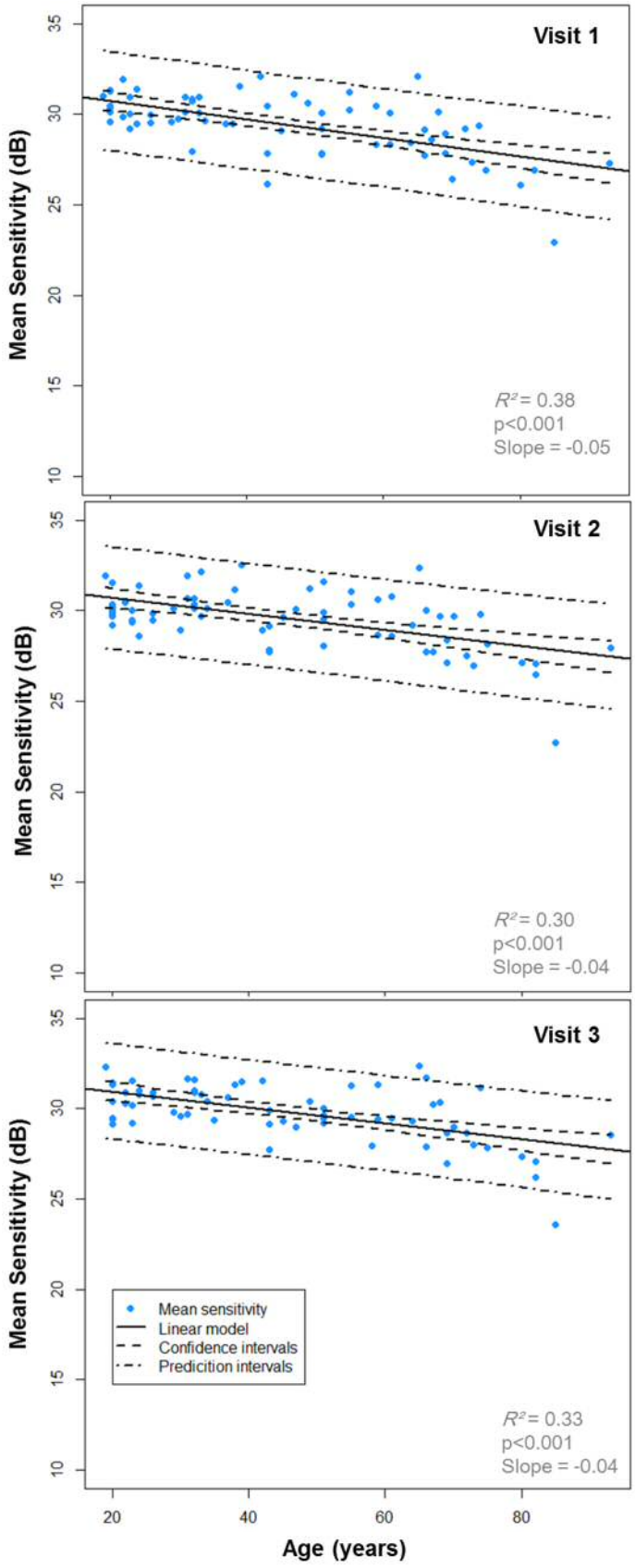


Figure 4.10 Linear regression of Mean Sensitivity (ordinate) against age (abscissa) for Visit 1 (top), Visit 2 (middle) and Visit 3 (bottom). The linear regression line (solid line), 95% confidence limits (inner curved lines) and 95% prediction limits (outer curved lines) are shown, as are the R^2, p and slope values.

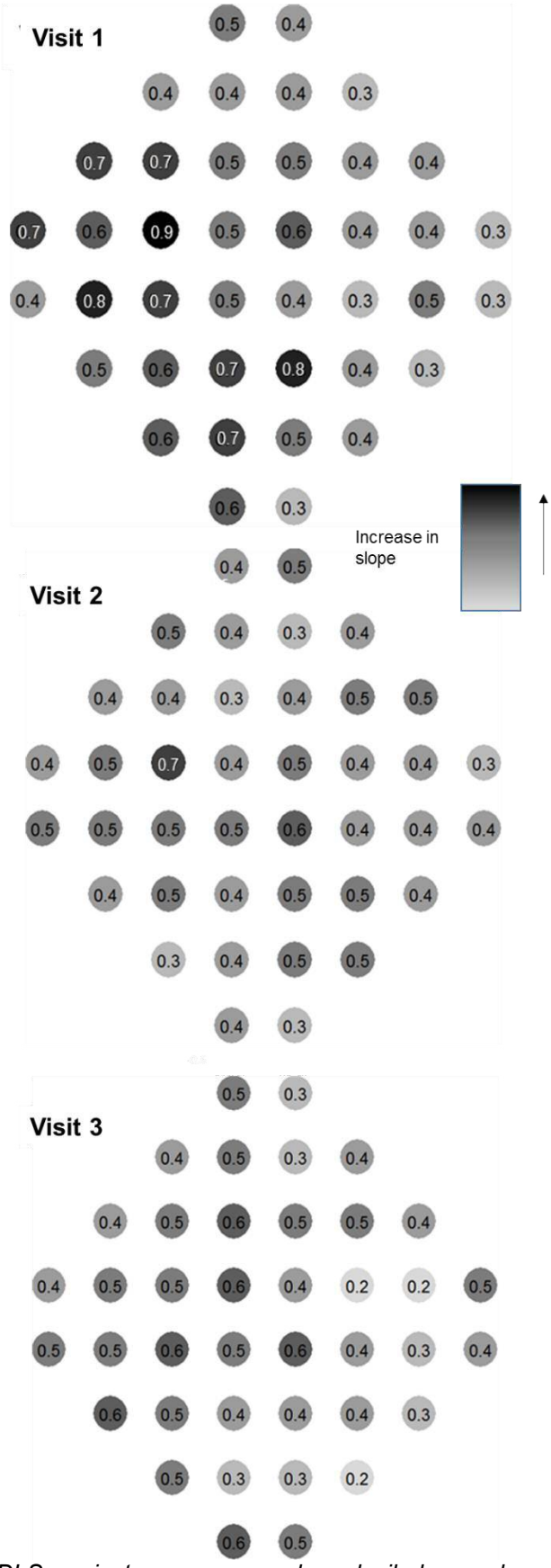


Figure 4.11 Slope of DLS against age expressed as decibels per decade of age at each stimulus location for Visit 1 (top), Visit 2 (middle) and Visit 3 (bottom). The increasingly darker colour represents an increasingly steeper slope.

4.4.2 Normative database results: Method 1

The following results describe the analysis performed on the normative database derived by Method 1 and therefore include the calculated normal DLS values and the magnitude of DLS at which the 95%, 98% and 99% TD and PD probability levels occurred.

The DLS magnitudes at which 95% TD (top) and PD (bottom) lower probability limits occurred for each visit, as a function of eccentricity, are given in Figure 4.11. The normal DLS values referenced to the mean age of 45.97 are also shown in Figure 4.12. The two graphs are ordered by eccentric annuli (1° to 7° from fixation). The normal values, TD lower limits and PD lower limits decrease from 1° to 7° from fixation. The normal values at Visit 1 were generally higher than those at Visit 2, however this difference was minimal.

The normal DLS values across all stimulus locations increased with visit ($p<0.001$) and declined with increase in eccentricity ($p<0.001$) (Table 4.2; Table 4.4). This was also the case for the magnitude of DLS at which the TD and PD 95%, 98% and 99% prediction limits occurred (Table 4.2; Table 5).

The post hoc analyses (Tukey's test) showed the increase in normal DLS values, and 95%, 98% and 99% TD and PD probability limits all consistently occurred between Visits 1 and 3 (all $p<0.01$). Similarly, post hoc Tukey's tests showed significant differences between DLS within 1° and 7° for normal DLS values and all the TD and PD probability limits (all<0.05).

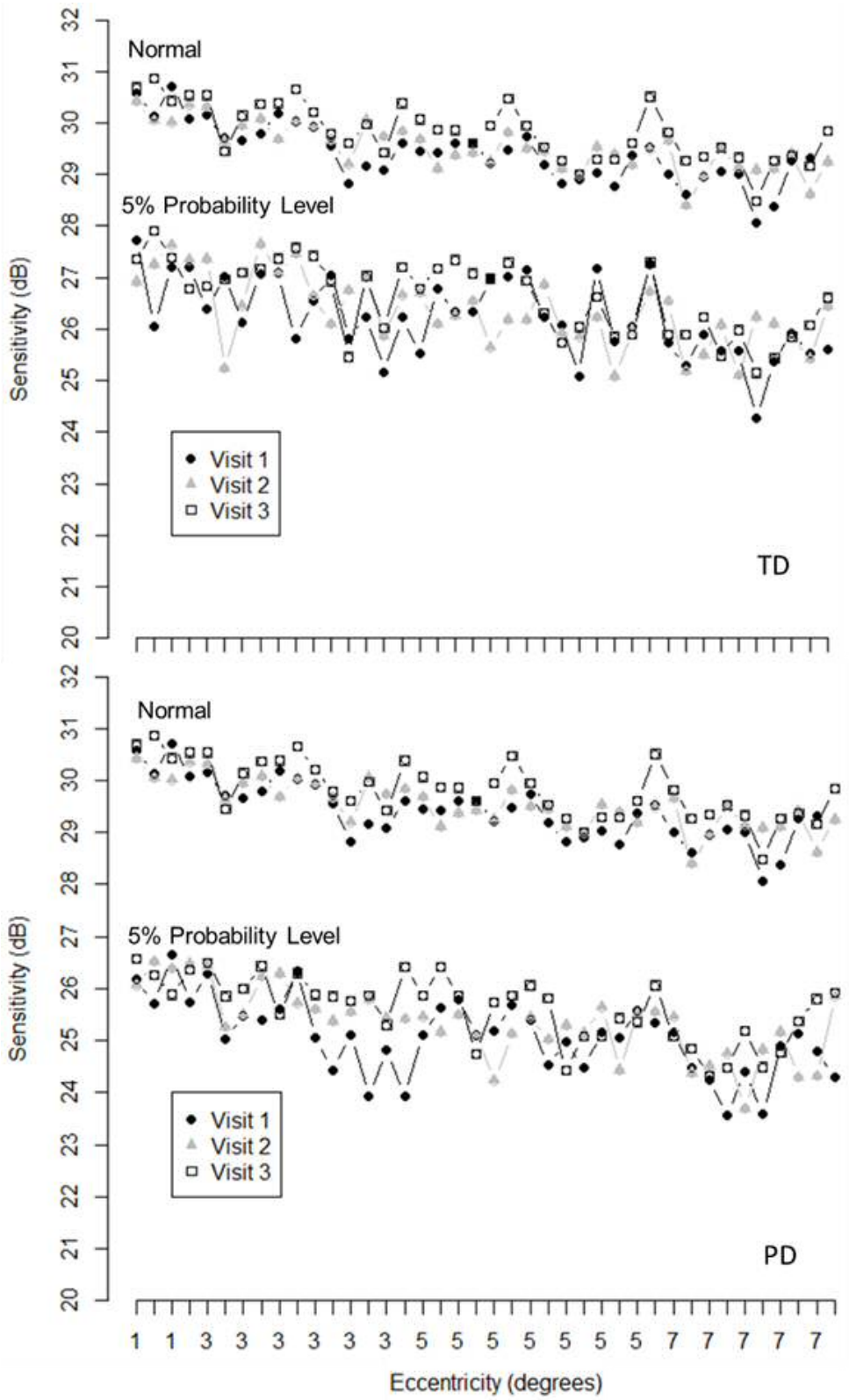


Figure 4.12 Differential light sensitivity (DLS) as a function of retinal eccentricity and 95% prediction limits for normal individuals. DLS values are presented along the ordinate and eccentricity along the abscissa. DLS values at which the 95% TD probability limit (top) and 95% PD probability limit (bottom) occurred are shown as a function of eccentricity. Eccentricity is presented by annuli (1°to 7°), ordered superior, temporal, inferior and nasal, from left to right. Data are shown for Visit 1 (filled black circle), Visit 2 (grey filled triangle) and Visit 3 (empty black square).

	df	SS	MS	F	P
Normal					
Visit	2	3.75	1.88	14.61	<0.01**
Eccentricity	3	17.63	5.88	45.86	<0.01**
95% TD					
Visit	2	3.04	1.52	4.55	0.01**
Eccentricity	3	23.58	7.86	23.52	<0.01**
95% PD					
Visit	2	28.19	14.10	35.05	<0.01**
Eccentricity	3	22.08	7.36	18.30	<0.01**

*Table 4.2 ANOVA summary table to show the variation in pointwise normal DLS values and 95% TD and PD limits with visit, eccentricity and the interaction between them. Only 95% prediction limits have been included due to similarity in results to the 98% and 99% limits. **p<0.01 and *p<0.05*

4.4.3 Normative database results: Method 2

The following results describe the analysis performed on the normative database derived by Method 2 and therefore include the calculated normal DLS values and the DLS magnitudes at which the 95%, 98% and 99% TD and PD probability levels occurred.

The TD and PD values associated with the 95% lower prediction limits at each visit as a function of eccentricity are given in Figure 4.13 and Figure 4.14, respectively. The normal DLS values are also provided for reference. In each figure, the three graphs represent different ages (25, 45 and 65 years). In all graphs both the normal values, TD lower limits and PD lower limits decrease from 1° to 7°.

The normal DLS values across all stimulus locations increased with visit (p<0.001), but decreased with increasing age (p<0.001) and eccentric annuli (p<0.001) (Table 4.3; Table 4.4). Simiarly, the magnitude of DLS at which the 95%, 98% and 99% TD and PD prediction limits occurred, also increased with visit (both p<0.001) and declined with increasing age (both p<0.001), and eccentric annuli both (p<0.001) (Table 4.3).

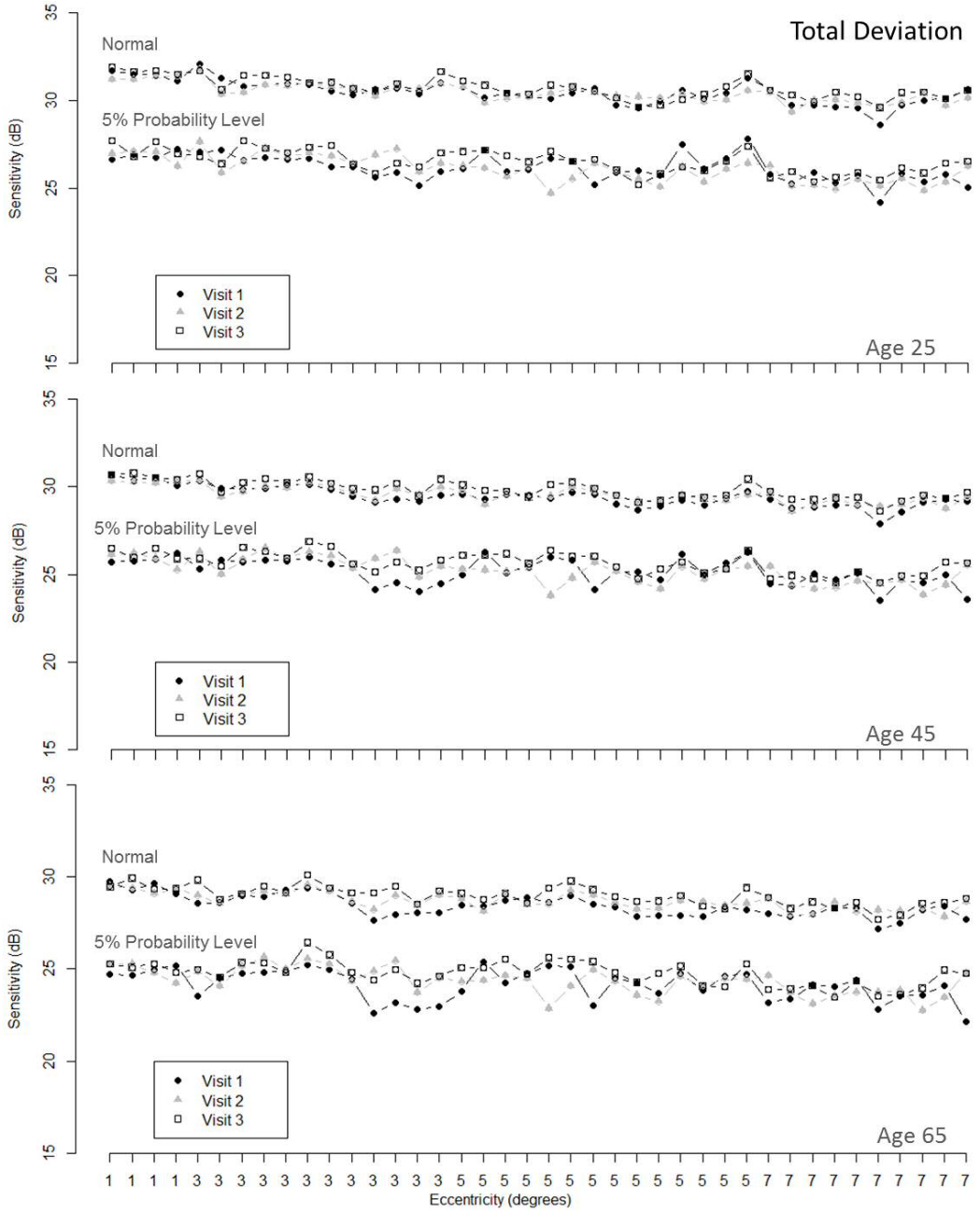


Figure 4.13 Normal DLS values, 95% TD limits (ordinate), by eccentric annuli (abscissa) for Visit 1 (black filled circles), 2 (grey filled triangle) and 3 (empty black square), for 25 year old (top), 45 year old (middle) and 65 year old (bottom).

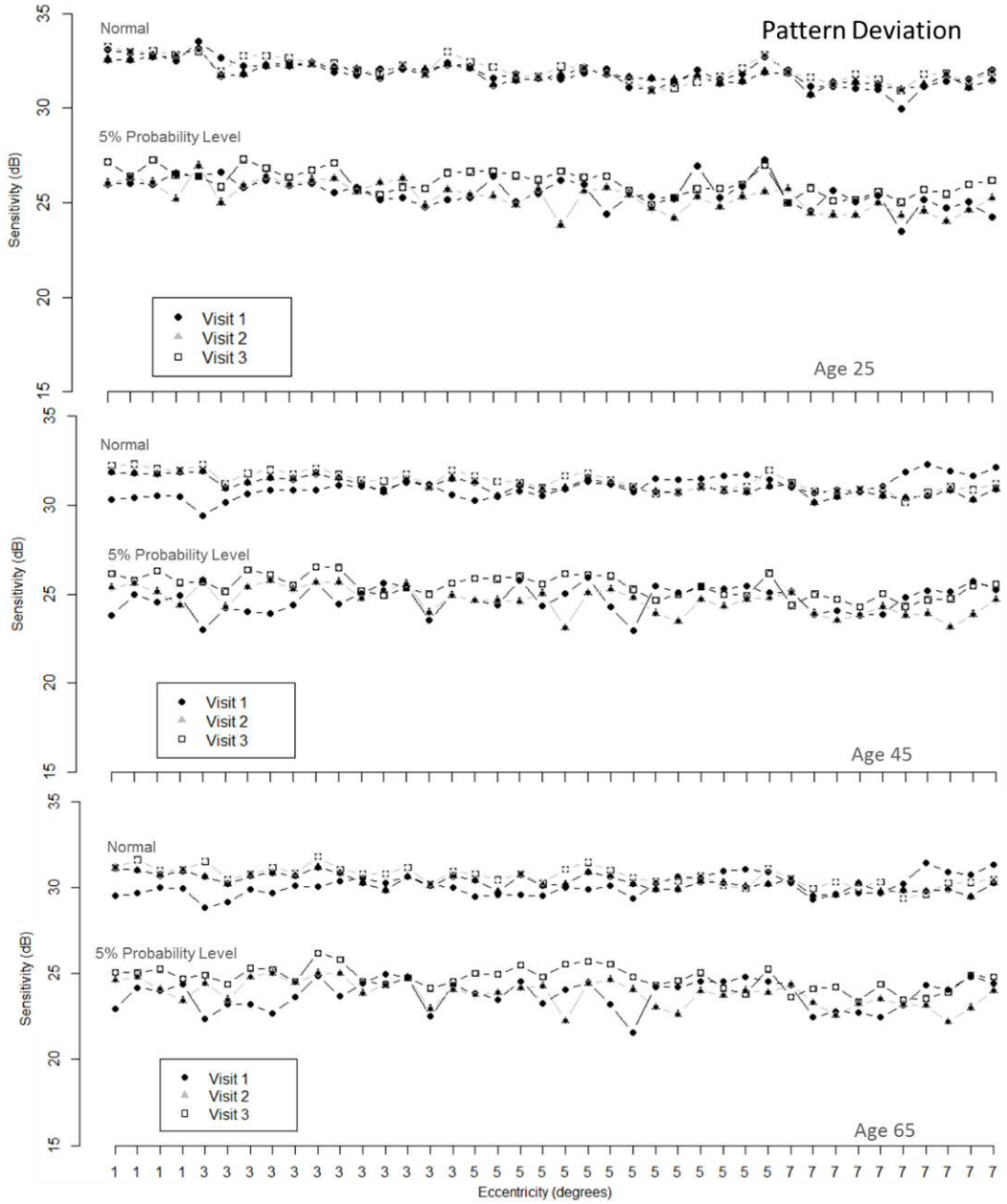


Figure 4.14 Normal DLS values, 95% PD limits (ordinate), by eccentric annuli (abscissa) for Visit 1 (black filled circles), Visit 2 (grey filled triangle) and Visit 3 (empty black square), for 25 year old (top), 45 year old (middle) and 65 year old (bottom).

The post hoc analysis (Tukey's test) for the normal DLS values and the DLS magnitude at which the 95% TD and PD probability limits occurred showed that the increase occurred between each of the visits (all $p<0.01$) and the decrease occurred between each eccentric annulus ($p<0.01$) and between each age group ($p<0.01$).

As expected, the magnitude of DLS at which the 98% and 99% TD prediction limits occurred gave similar results, whereby the magnitudes increased with visit and declined with age and eccentric annuli. Post hoc analysis (Tukey's test) results again

mimicked the results for the 95% prediction limits with the exception that no increase was present between Visit 1 and 2 for either 98% (p=0.06) or 99% limits (p=0.11).

	df	SS	MS	F	P
Normal					
Visit	2	31.63	15.82	91.65	<0.01**
Eccentricity	3	121.50	40.50	234.71	<0.01**
Age	6	719.98	120.0	695.41	<0.01**
TD 95%					
Visit	2	47.03	23.52	61.76	<0.01**
Eccentricity	3	135.49	45.16	118.60	<0.01**
Age	6	763.03	127.17	333.96	<0.01**
PD 95%					
Visit	2	128.4	64.19	145.62	<0.01**
Eccentricity	3	109.6	36.55	82.92	<0.01**
Age	6	560.8	93.46	212.04	<0.01**

*Table 4.3 ANOVA summary table of to show pointwise DLS normal values with visit, eccentric annuli and age, and the interactions between them. **p<0.01 and *p<0.05*

Similarly, 98% and 99% PD prediction limits also increased with visit (p<0.001) and declined with age (p<0.001) and eccentric annuli (p<0.001). The post hoc analysis (Tukey's test) showed comparable results in that there was no increase between Visit 1 and 2 for either the 98% (p=0.96) or 99% (p=0.85) prediction limits, there was also a decline with age present between each age group (all p<0.05). However, the decline with eccentricity was not present between the 1° and 3° annuli (p=0.15) for the 98% limit and was not present between the 1° and 3° annuli (p=0.37) and the 3° and 5° annuli (p=0.09) for the 99% limit.

4.4.4 Comparison between methods to derive the normative database

The mean normal DLS values and the mean DLS magnitude at which the TD (95%, 98% and 99%) and PD (95%, 98% and 99%) limits occurred for each of the databases (Method 1 and Method 2) were investigated for Visits 1, 2 and 3 (Table 4.4). DLS and prediction limits values at the mean age of the cohort (46 years) were greater for Method 1 than Method 2 (all p<0.01) (Table 4.4).

	Method 1			Method 2		
	V1	**V2**	**V3**	**V1**	**V2**	**V3**
Normal	29.4**	29.5**	29.8**	28.9**	29.1**	29.4**
TD 95%	26.2**	26.4**	26.6**	24.6**	24.8**	25.2**
TD 98%	25.2**	25.3**	25.7**	23.8**	24.0**	24.4**
TD 99%	24.4**	24.5**	25.0**	23.3**	23.4**	23.8**
PD 95%	25.1**	24.4	25.6**	24.3**	24.3	25.1**
PD 98%	24.1**	24.4**	24.8**	23.0**	23.0**	23.9**
PD 99%	23.6**	24.0**	24.3**	22.2**	22.1**	23.1**

*Table 4.4 Mean values of normal, TD (95%, 98% and 99%) and PD (95%, 98% and 99%) limits for each visit, for Method 1 and Method 2, at 46 years. Significant differences resulting from an independent t-test comparing the difference between visits for the values are displayed, where ** indicates p<0.01.*

Figure 4.15 shows pointwise normal DLS values and the magnitude of DLS at which the TD probability limits (95%, 98% and 99%) and PD probability limits (95%, 98% and 99%) occur for database 3 (derived from Visit 3) for both methods, arranged by eccentricity. Method 1 derived higher decibel values at the 95% TD probability limit for all locations, which indicates that defects would be detected at an earlier stage than with Method 2.

A clinical case study of an individual with AMD (recruited as part of the study described in Chapter 6) is presented in Figure 4.16 and in Figure 4.17; comprising the MAIA microperimetry output consisting of an infrared fundus image with overlaid DLS pointwise measurements, CFP, SD-OCT (Cirrus HD-OCT) horizontal line scan through the fovea, and the TD and PD probability plots derived using database 1, 2 and 3 for both Method 1 (Figure 4.16) and Method 2 (Figure 4.17).

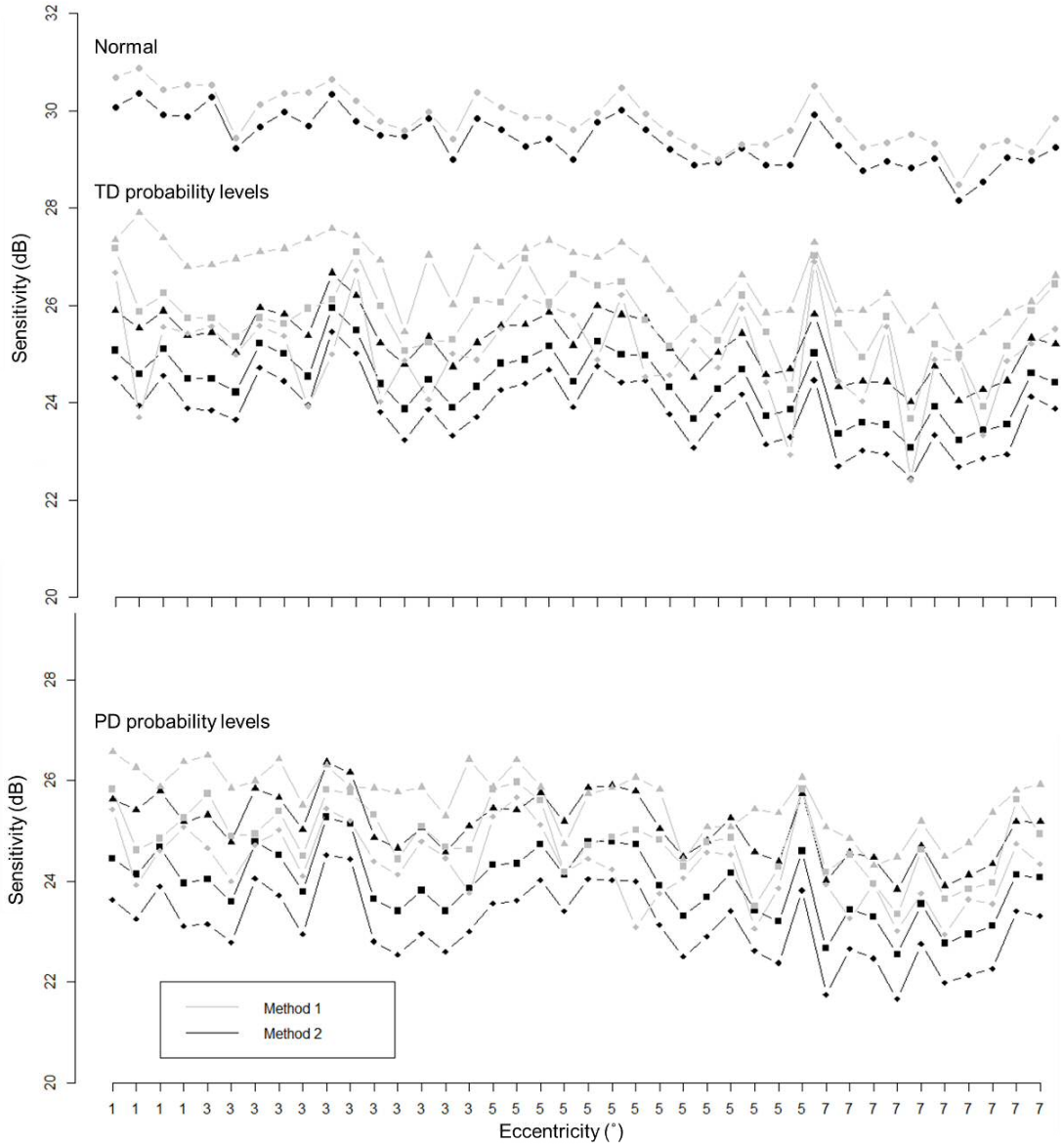


Figure 4.15 Normal DLS values and the magnitude of DLS (ordinate) at which the 95% (triangle), 98% (square) and 99% (diamond) TD probability levels (top) and 95% (triangle), 98% (square) and 99% (diamond) PD probability levels (bottom) occur, for Method 1(grey) and Method 2 (black), as a function of eccentricity (abscissa), at 46 years.

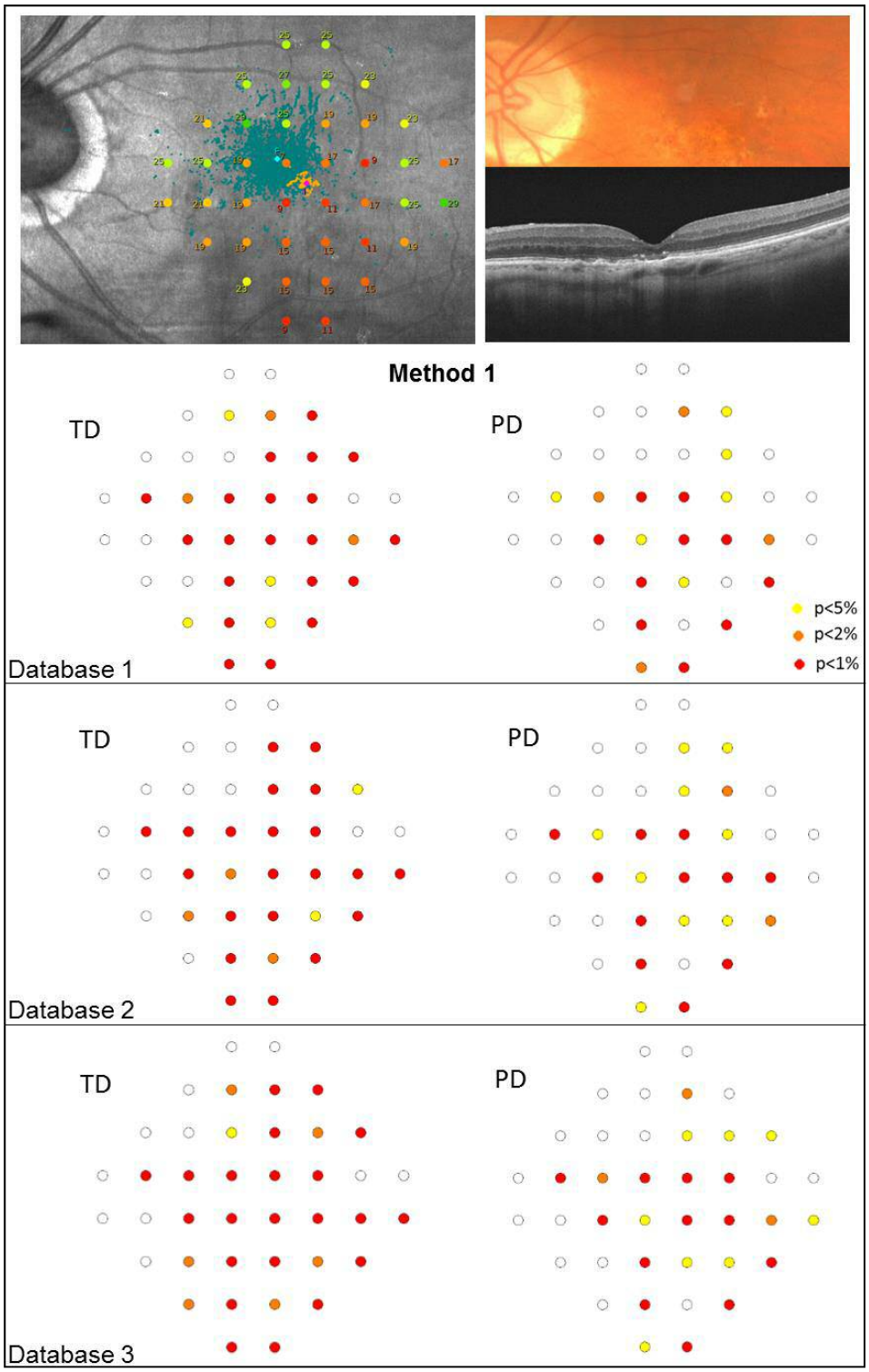


Figure 4.16 Clinical case of a 78 year old individual with AMD with the MAIA infra-red image, colour fundus photograph and SD-OCT line scan shown (top). The DLS results have been analysed with Method 1, with Visit 1 (top), Visit 2 (middle) and Visit 3 (bottom) normative databases to produce Total Deviation (TD) (left) and Pattern Deviation (PD) (right) plots with 95% (yellow), 98% (orange) and 99% (red) probability levels colour coded.

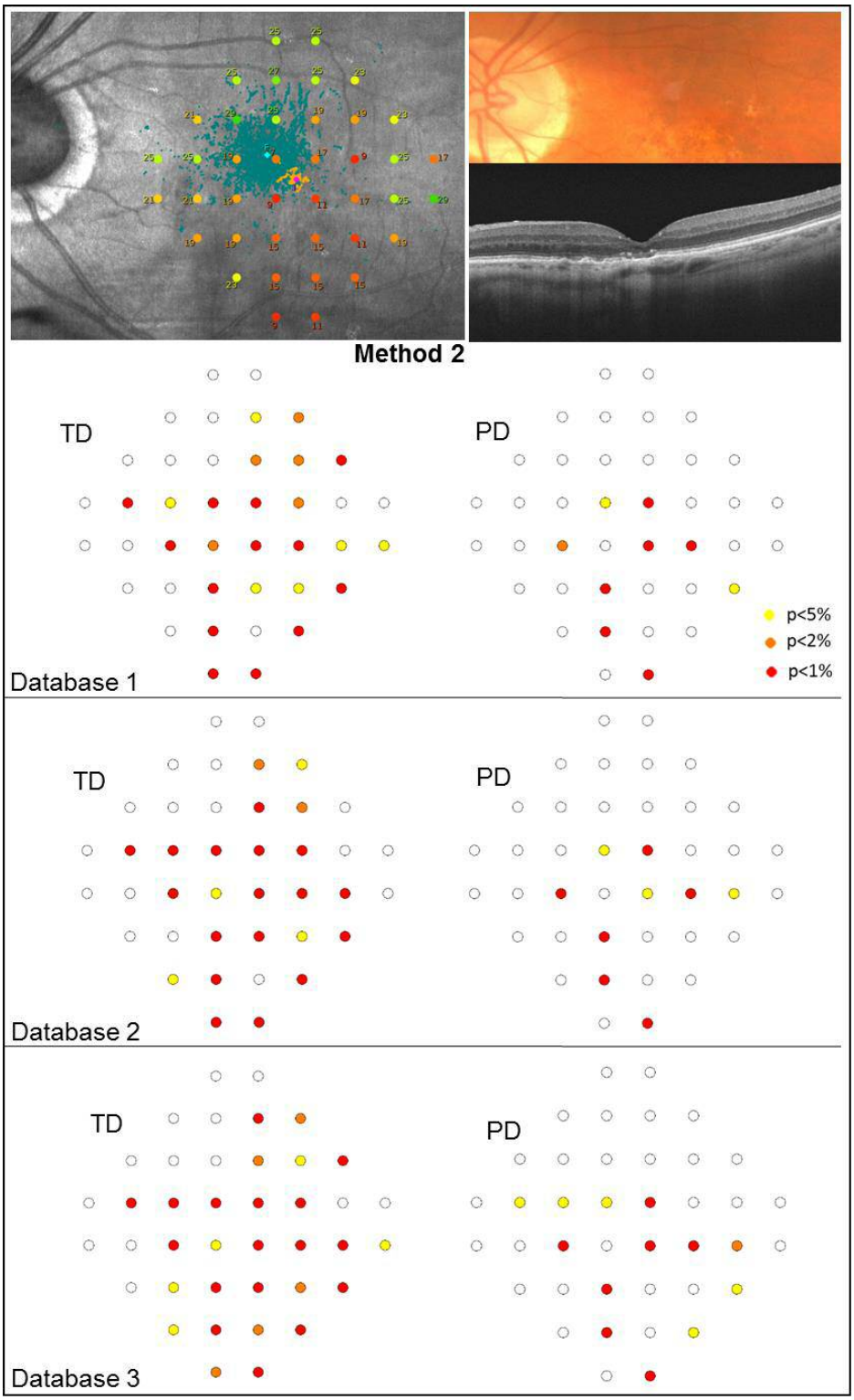


Figure 4.17 Clinical case of a 78 year old individual with AMD with the MAIA infra-red image, colour fundus photograph and SD-OCT line scan shown (top). The DLS results have been analysed with Method 2, with Visit 1 (top), Visit 2 (middle) and Visit 3 (bottom) normative databases to produce Total Deviation (TD) (left) and Pattern Deviation (PD) (right) plots with 95% (yellow), 98% (orange) and 99% (red) probability levels colour coded.

4.5 Discussion

The primary aim of this study was to derive a pointwise age-corrected normative database with a statistical model to perform global and localised probability analyses. The secondary aims were twofold: to examine over three visits the characteristics of the MVF with age and eccentricity from microperimetry; and to compare two different methods of deriving the normative database.

A linear regression model was found to be the most appropriate method to apply to the age-related decline in DLS with the MAIA (Centervue, Padova, Italy) microperimeter. This is consistent with the results of previous research on the MP-1 instrument (Midena, Vujosevic and Cavarzeran 2010; Acton, Bartlett and Greenstein 2011) and as is also the method used by convention in SAP (Heijl, Lindgren and Olsson 1987b; Flanagan et al. 1993). It is likely that including a larger proportion of individuals over the age of 70 years would influence the linearity of the model. With a larger dataset, a segmented regression model could be considered to reflect a potential worsening of the DLS with older age.

Two methods of deriving a normative database have been utilised herein. Both methods have been developed to enable probability analysis of clinical data. Method 1, the adjusted age method, is utilised by Zeiss for the HFA (Heijl, Lindgren and Olsson 1987a). Method 2, the age-specific method, used linear regression (Altman 1991) of age with DLS. It is apparent that Method 1 derives probability defects at a higher DLS value than Method 2 for each level of TD and PD probability defects. Thus, Method 2 is a more conservative method and would result in categorising fewer individuals with defects than Method 1. This difference between methods is a result of the mathematical derivation of the normal values and the associated probability limits. The normal values for Method 1 are derived using the mean age adjusted DLS values, whereas for Method 2 they are derived using the measured DLS values. The probability limits for Method 1 were derived using the distribution of the age-adjusted

individuals, and Method 2 were derived from the prediction limits of the linear regression model. These different derivation techniques have led to apparent differences in the analysis of the microperimetry outcomes. However, due to the lack of a 'gold standard' method of database derivation it is beyond the scope of this study to perform sensitivity and specificity analyses to evaluate the accuracy of defect identification between methods.

For the purpose of this thesis, a conclusion as to the most appropriate method to be taken forward for future analyses must be made. Whilst, Method 1 would lead to the detection of defects at an earlier stage, this risks the detection of a large number of false positives. Conversely, Method 2 may detect a greater number of false negatives. To the author's knowledge, the rationale and statistical reasoning behind the choice of the method of derivation used by Zeiss is not in the public domain. Method 2 is statistically appropriate for further analyses in this thesis, given the results from the tests of the assumptions of linear regression. Additionally, Method 2 accounts for the increased variability in the younger and older age groups by increasing the size of the prediction limits at these extremes. This is particularly relevant to those with AMD, given their older age. For these reasons, Method 1 will be excluded from future analysis in this thesis.

Method 2 normative DLS values and TD probability limits differ with visit, and therefore, give differing defects dependent upon the database used. The perimetric learning effect is a phenomenon whereby DLS improves with experience (Heijl, Lindgren and Olsson 1989; Heijl, Lindgren and Olsson 1987b; Wild et al. 1989). The evidence is conflicting as to the number of perimetry examinations required to extinguish this effect (Wood et al. 1987; Gardiner, Demirel and Johnson 2008; Heijl, Lindgren and Olsson 1989). Currently, in SAP research studies, visual field examinations are disregarded until the third visit (Pierre-Filho et al. 2010). Previous microperimetry literature has suggested that after Visit 2 the learning effect is no

longer present (Wu et al. 2013). However, the results from the present study suggest that the perimetric learning effect is still present at Visit 3. Therefore, to minimise the effect of learning on the normative database all further analysis in this thesis will be based on the normative database derived from the third visit.

Future research using microperimetry to investigate a larger number of visits at different intervals would enable a more thorough characterisation of the perimetric learning effect in microperimetry. Future development of normative databases that are weighted according to the visit number, could enable initial microperimetry results to be used in analysis, rather than discarded.

Consistent with previous research (Heijl, Lindgren and Olsson 1987a), in this study, the normative DLS values and the DLS values at which the TD and PD lower probability limits occurred, reduced with both eccentricity and age. The age-dependant decline of DLS reported in this study is in agreement with that for SAP (Bengtsson and Heijl 1999), for microperimetry (Acton, Bartlett and Greenstein 2011; Midena, Vujosevic and Cavarzeran 2010) and for short-wavelength automated perimetry (Bengtsson and Heijl 2003).

A strength of the study is that the method of normative data collection meets the minimum requirements of the international standards for ophthalmic equipment (ISO 12866) for the development of a normative database. The normative databases developed will allow for localised and globalised visual field loss to be defined (Heijl, Lindgren and Olsson 1987a) in AMD and other macular diseases. This will lead to more specific quantification of the functional deficit that is present in AMD (Acton, Gibson and Cubbidge 2012).

A limitation of the normative databases derived in this work is that they can only be applied to the specific stimulus locations used, in this study, to obtain the normal DLS values. Therefore, these normative databases are not appropriate for use with

different stimulus patterns or those with non-foveal fixation. Methods of interpolation can be used to overcome this limitation (Weber and Geiger 1988; Weleber et al. 2015). A recently developed normative database that implements this technique, uses computational surfaces to interpolate normative data between stimulus locations in relation to an individual's fixation (Denniss and Astle 2016). Despite this benefit, the use of computational simulation does not reflect the reality of a perimetric examination, as opposed to clinical data. Additionally, the loss of foveal fixation is most frequently associated with late AMD and associated areas of atrophic retina, which typically present with absolute scotomata i.e. DLS of <0dB and therefore lying outside of the 99% probability limits. Thus, the benefit of a normative database that accounts for loss of foveal fixation may be limited. The analyses presented in this thesis will only include those with foveal fixation in reference to TD, PD and probability analyses.

To conclude, the adjusted age method of deriving the normative database is less conservative than the age-specific method. The age-specific method is both statistically appropriate and accounts for the increased variability with age, and consequently, will be employed throughout all subsequent chapters. Database 3 will also be used in subsequent work to reduce the learning effect. The derivation of a normative database is essential for the quantification of functional deficits in AMD, detected using MAIA microperimetry. This allows for more specific assessment of the topographical nature of AMD and the associated functional outcomes with respect to vision-related quality of life.

Chapter 5: The association between microperimetry and SD-OCT outcomes

5.1 Summary

Purpose: To examine the association between AMD-related retinal microstructure abnormalities and microperimetry outcomes at 5° eccentricity from fixation.

Methods: The cohort comprised 42 participants with early to late AMD. The median age was 80 years (IQR 75, 83 years). All participants were otherwise ophthalmologically normal, with the exception of mild lens opacities. Participants underwent MAIA microperimetry (40 location 7° stimulus pattern); and volumetric imaging with the Cirrus SD-OCT (20° x 20° scan, 512 x 128 A-scans). DLS by microperimetry was referenced to a normative database (n=66). CFPs and SD-OCT images were used to classify AMD severity and identify AMD associated retinal features. Volumetric SD-OCT scans were segmented (9 boundaries, 8 retinal layers) using the Iowa Reference Algorithm (Retinal Image Analysis Lab, Iowa).

Results: The median microperimetry outcomes at 5° were: MS 23.6dB; MTD -4.6dB; MPD: -2.6dB. Forty six percent of the variance in MTD and 45% of the variance in MS was explained by the presence or absence of photoreceptor atrophy, when the AREDS classification was controlled for.

Conclusion: At a retinal eccentricity of 5° a significant proportion of the microperimetry outcomes can be explained by the presence of photoreceptor atrophy. However, this relationship is not sufficiently strong for microperimetry and SD-OCT to be interchangeable.

5.2 Introduction

A combination of morphological and visual function outcomes are commonly used in clinical trials in AMD. The success of these trials is often measured by the improvement of visual function and change in retinal features associated with AMD. This chapter will investigate the association between AMD-related retinal microstructure abnormalities and microperimetry outcomes. Prior to describing the study, the relevant functional and morphological biomarkers in AMD will be summarised.

A number of functional measures have been identified as potential biomarkers in AMD, for example: flicker threshold (Dimitrov et al. 2011; Mayer et al. 1992; Brown and Lovie-Kitchin 1987), colour thresholds (Eisner et al. 1992; O'Neill-Biba et al. 2010; Downie, Cheng and Vingrys 2014; Dimitrov et al. 2012; Holz et al. 1995) and dark adaptation (Dimitrov et al. 2012; Owsley et al. 2016; Owsley et al. 2001; Owsley et al. 2007; Gaffney, Binns and Margrain 2011; Gaffney, Binns and Margrain 2013). Furthermore, decline in visual function is associated with worsening structural AMD classification (Dimitrov et al. 2012; Acton, Gibson and Cubbidge 2012; Owsley et al. 2016; Flamendorf et al. 2015).

Microperimetry has previously been advocated as a useful biomarker in AMD (Acton et al. 2012b, Wu et al. 2014c, Fragiotta et al. 2017a). It measures DLS, whilst simultaneously imaging the fundus at 25Hz, enabling fixation losses to be monitored. Reduced DLS is associated with disruption in the RPE (Wu et al. 2014c), EZ band (Querques et al. 2012; Wu et al. 2014c) and ELM (Querques et al. 2012; Hartmann et al. 2015; Fragiotta et al. 2017a); OS thinning and RPE thickening in early AMD (Acton et al. 2012b; Wu et al. 2016); and both a thickening and a thinning of the whole retina in nAMD (Hartmann et al. 2015; Sabour-Pickett et al. 2013). These associations suggest that microperimetry has the potential to detect changes in visual function that are a result of retinal microstructure abnormalities associated with AMD.

Morphological biomarkers identified by SD-OCT have also been suggested, however these differ with stage and type of AMD. In nAMD, central retinal thickness is a common method to quantify retinal changes, but is limited by the lack of information relating to the type and depth of retinal fluid present (Schmidt-Erfurth and Waldstein 2016). Presence of intraretinal fluid (IRF) (Schmidt-Erfurth et al. 2015), subretinal fluid (SRF) (Schmidt-Erfurth et al. 2017) and PEDs (Clemens et al. 2012; Dirani et al. 2015a) are more informative biomarkers than retinal thickness (Schmidt-erfurth 2016). Recently, further potential biomarkers in nAMD have been identified: hyperreflective foci (Nagiel et al. 2015) and ORTs (Dirani et al. 2015b). The main biomarker, in research, of disease progression in early AMD is the presence of drusen (Schmidt-Erfurth et al. 2017; Dimitrov et al. 2012). Where baseline drusen volume is predictive of progression to late AMD (de Sisternes et al. 2014; Abdelfattah et al. 2016; Folgar et al. 2016). Additionally, RPD (Sivaprasad et al. 2016; Steinberg et al. 2015b) and disruption and intensity of the EZ band (Gin et al. 2017) should also be considered as biomarkers. SD-OCT also allows detailed analysis of GA (Schmitz-Valckenberg et al. 2009; Holz et al. 2014) and loss of photoreceptors is an important predictor of progression to GA (Niu et al. 2016).

The present study aims to examine the association between AMD-related retinal microstructure abnormality and microperimetry outcomes at 5° from fixation. This eccentricity was used for three reasons. Firstly, at 5° eccentricity the influence of the foveal depression on retinal layer thickness analysis will be avoided (Curcio, Owsley and Jackson 2000), as the anatomical shape of the foveal pit only extends to 2.75° (Curcio, Owsley and Jackson 2000). Secondly, mesopic microperimetry is mediated by a cone response (Simunovic et al. 2016) and, whilst the cone population peaks at the fovea, at 5° the cone density remains high at 11,600 cells/mm² (Park et al. 2013). Finally, a previous study found that visual field defects in AMD are most common within the central 5° of the visual field (Acton, Gibson and Cubbidge 2012).

In the evaluation of retinal microstructures, this study will focus on the detailed identification of AMD associated retinal features and retinal thickness measurements by SD-OCT, which have been previously suggested as potential biomarkers in AMD. With the development of automated SD-OCT segmentation software, retinal thickness measurements can be produced faster and with more accuracy. OCT Explorer will be used in the present study, which is part of the Iowa Reference Algorithm (Section 1.3.2.2) (Retinal Image Analysis Lab, IOWA Institute for Biomedical Imaging, Iowa City, IA) (Abràmoff, Garvin and Sonka 2010; Quellec et al. 2010; Antony et al. 2011; Xinjian Chen et al. 2012). This automated segmentation software segments 11 retinal layers and two choroidal layers.

5.3 Methods

A full description of the procedures and techniques used in this study can be found in Chapter 3, an overview will be presented here. Briefly, 52 individuals with AMD were recruited from Cardiff Eye Unit at the University Hospital of Wales and attended two visits at the School of Optometry and Vision Sciences, Cardiff University, in short succession. All participants were otherwise ophthalmologically normal, with the exception of mild lens opacities. Detailed inclusion and exclusion criteria are listed in Section 3.3.1.2.

At Visit 1 experimental procedures were performed to ensure the individuals met the study inclusion criteria (Section 3.3.1.2) and the imaging data (Cirrus HD-OCT and CFP using 3D-OCT 1000, Topcon) were acquired. Visit 2 involved the collection of the microperimetry data.

The test eye was chosen as the eye with a diagnosis of AMD. If both eyes had been diagnosed with AMD the test eye was chosen at random.

5.3.1 Analysis

5.3.1.1 Imaging techniques

Fundus photographs and SD-OCT images were acquired using the Topcon 3D-OCT 1000 and Cirrus HD-OCT, respectively, using the methods described in Chapter 3. In summary, a 45° colour fundus photograph, and a horizontal line scan and a 20° x 20° (512 x 128) volume scan were obtained. The colour fundus photographs were classified using the AREDS grading system (Section 3.3.3.1.8). The 512 x 128 volume scans were segmented into 10 retinal layers using OCTSeg, a fully automated segmentation algorithm, which is a module of OCT Explorer and part of the Iowa Reference Algorithms (Retinal Image Analysis Lab, Iowa Institute for Biomedical Imaging, Iowa City, IA). Of the 10 retinal layers segmented, 9 retinal layers were selected for analysis (Table 5.1) (Section 3.3.3.1.9). These 9 layers were analysed given the relevance to retinal microstructural alterations in inner and outer retinal layers (Hood et al. 2009; Acton et al. 2012b; Wu et al. 2016).

Boundaries	Retinal layers
1-2	Retinal nerve fibre
2-3	Ganglion cell
3-4	Inner plexiform
4-5	Inner nuclear
5-6	Outer nuclear
8-10	Outer segment
10-11	Retinal pigment epithelium
5-11	Total receptor plus RPE
1-11	Total retina

Table 5.1 Definition of nine retinal layers used for analysis, including single and combined layers.

Retinal thickness measurements were undertaken at the equivalent locations to the MAIA stimulus positions as described in Chapter (Section 3.3.3.1.9). For RNFL and

GCL layer thickness measures, the grid was displaced to account for the anatomical displacement of the retinal ganglion cells near the fovea (Hood and Raza 2011).

Each of the 40 locations was examined for the presence of retinal features associated with AMD (Section 3.3.3.2.10). Briefly, drusen, PEDs, ORTs, RPD, atrophy and CNV (intra- and/or sub-retinal fluid, and fibrovascular material) were recorded as either present or absent, and the EZ band integrity was also graded 0-3 (Wu et al. 2014c).

Given the anatomical shape of the fovea (Curcio, Owsley and Jackson 2000) and known frequency of defects in AMD (Acton, Gibson and Cubbidge 2012) the analysis was undertaken within the annulus at 5°, consisting of 16 stimulus locations (Figure 5.1). Both the retinal thickness and the retinal features within the 5° annulus were averaged.

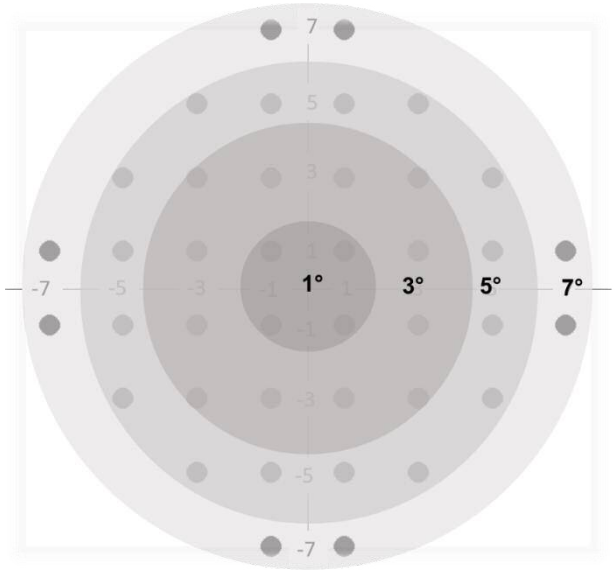


Figure 5.1 Locations within each eccentric annuli were defined as: within a radius of 1°, between a radius of 1° and 3°, between a radius of 3° and 5° and between 5° and 7°.

5.3.1.2 Microperimetry outcomes

MAIA DLS values were transformed to right eye format. MAIA DLS results for those with foveal fixation were converted into mean MTD and MPD values using the normative database developed in Chapter 4.

5.3.1.3 Statistical analysis

The approach for statistical analyses was firstly an assessment for normality (Shapiro-Wilk test), followed by a Spearman's rank correlation and lastly multiple linear regression.

A Spearman's rank correlation matrix was undertaken to demonstrate the association between all outcomes: the microperimetry outcomes (MS; MTD; MPD; number of TD defects ≥5% probability; and number of PD defects ≥5% probability), retinal features (EZ band disruption, drusen, retinal fluid, PED, atrophy and fibrovascular material) (Section 3.3.3.2.0), and retinal thicknesses (RNFL, GCL, IPL, INL, ONL, OS, RPE, total receptor and total retina) (Section 3.3.3.1.9) (Table 5.1). This process was performed to identify the variables that were not associated with microperimetry outcomes. Any predicting variables that were highly correlated with each other ($r \geq 0.8$) were not included into the same multiple regression model.

Only the strongest associations with microperimetry outcomes were then included into the multiple regression models. Each microperimetry outcome was investigated separately. Several multiple regression models including different combinations of factors were examined to find the most appropriate model to explain the variance in microperimetry outcomes from microstructural abnormalities. The multiple regression models were limited to one factor (predicting variable) per 10 participants (Altman 1991), therefore in this study, for a sample of n=47, each model should include a maximum of 4 factors. However, reducing the number of factors leads to a stronger model (Altman 1991). The assumptions of each linear regression model were examined, using the identical method described in Chapter 4 (Section 4.3.1.1). When outliers were present, but regarded as clinically significant, robust regression was utilised. Robust regression applies less weight to outliers or influential observations when estimating the regression slope (Andrews 1974).

Statistical analyses were performed using R (Version 3.2.2) and SPSS (version 20.0). A p value of ≤0.05 was considered to be statistically significant for all analyses. Bonferroni correction was not implemented in this analysis as Type 1 errors, the increased likelihood of getting a significant result by chance as a result of multiple testing, were more preferable to Type 2 errors where the actual effects may have been missed (Armstrong 2014). The descriptive statistics for all measures are presented as a median and inter-quartile range (IQR) to allow for comparison.

5.4 Results

The following results are presented: firstly, the assessment of normality results; secondly, the characteristics of the individuals with AMD; thirdly the characteristics of both the retinal features and the retinal thickness measurements; finally, the correlation and multiple regression analyses of the SD-OCT outcomes with the microperimetry outcomes.

5.4.1 Assessment of normality

Distributions were examined using the Shapiro-Wilk test and the majority of outcomes were found to have a non-Gaussian distribution ($p<0.05$), only RNFL ($p=0.06$), GCL ($p=0.6$), IPL ($p=0.3$) and INL ($p=0.7$) thicknesses were normally distributed.

5.4.2 Characteristics

Of the 52 individuals, 1 failed to complete both visits, 5 individuals were excluded due to existing co-morbidities (4 due to details from the medical history, and 1 due to high myopia), 1 was unable to perform the micrometry examination and 3 had non-foveal fixation, resulting in 42 individuals.

Forty-two individuals (25 females) with AMD met the study inclusion criteria and completed both visits. The demographic characteristics of the individuals with AMD, including the MAIA visual field characteristics at 5° eccentricity and AREDS

classification are presented in Table 5.2. Fifteen right eyes and 27 left eyes were examined.

N=42	**Median (IQR)**
Age (years)	80 (75, 83)
Rx (BVS)	0.25 (-0.25, 1.25)
MS (dB)	23.6 (20.8, 26.0)
MTD (dB)	-4.6 (-8.3, -2.3)
MPD (dB)	-2.6 (-3.9, -1.9)
Number of TD defects (≤5%)	7 (2, 12)
Number of PD defects (≤5%)	2 (0, 4)
AREDS classification	**N (%)**
1	3 (7)
2	2 (5)
3	1 (2)
4	36 (86)

Table 5.2 Characteristics of individuals with AMD including: age, refractive correction (Rx), Mean Sensitivity (MS), Mean Total Deviation (MTD), Mean Pattern Deviation (MPD), number of Total Deviation (TD) values exhibiting a probability level of worse than 5% and number of PD values exhibiting a probability level of worse than 5%.

5.4.3 AMD associated retinal microstructure characteristics

5.4.3.1 Retinal features

Retinal features were graded at 672 stimulus locations, within the 5° annulus, from 42 individuals. Of the 672 locations, 638 were successfully graded. Features could not be graded for 34 locations from 7 individuals, due to insufficient SD-OCT scan quality. These individuals were classed as partially graded, and only the locations that could be graded were included in the analysis.

Two individuals had no AMD associated retinal features present within the 5° annulus, of the 40 remaining individuals, the majority had EZ band disruption grades 1-3 (n=40) and over half were in combination with other microstructural changes (n=26) (Figure 5.2).

AMD-related retinal features were present at 350 locations (55%), at 5° eccentricity. Some locations had more than one retinal feature present at one location. Three

hundred and eight of the 638 locations had EZ band disruption, graded 1-3 (48%), with 152 of the 638 locations having grade 2 disruption (24%). In 44 and 36 of 638 locations, drusen and PEDs (serious, fibrovascular or drusenoid) were present, respectively (Table 5.3).

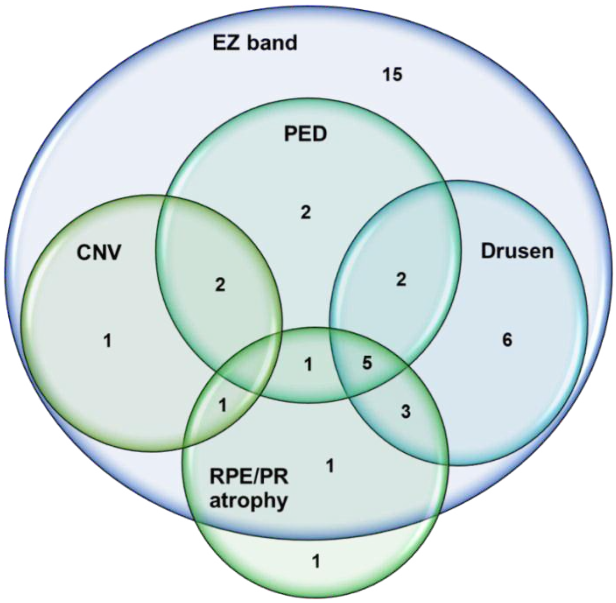


Figure 5.2 The frequency of, and the relationship between, the AMD associated retinal features within the 5˚ annulus (for n=40). Retinal features include: Ellipsoid Zone (EZ) band disruptions (grades 1-3), Choroidal neovascularisation (CNV), Drusen, pigment epithelial detachment (PED; Drusenoid, serous and fibrovascular) and retinal pigment epithelium (RPE) and photoreceptor (PR) atrophy.

N= 638	**Number of locations (%)**
Without retinal features	288 (45)
Retinal features	
EZ band grade 1	88 (14)
EZ band grade 2	152 (24)
EZ band grade 3	68 (11)
Drusen	44 (7)
Retinal fluid	4 (1)
PED	37 (6)
Atrophy	86 (14)
Fibrovascular material	9 (1)

Table 5.3 Number and percentage of total locations with and without AMD related retinal features within 5° eccentricity. More than one retinal feature was present at some locations and the sum of the percentages therefore exceeds 100%.

5.4.3.2 Retinal thickness

Three individuals were excluded from retinal thickness analysis due to the inability of the automated segmentation software to segment the volume scans. For individuals in which segmentation was successful at some, but not all locations, only thicknesses at those locations where it was successful, were included in the analysis (i.e. data was excluded from a total of 18 locations from 2 individuals). The median (IQR) of the mean retinal thicknesses at 5° eccentricity are presented in Table 5.4.

N=39	**Median (IQR)**
Retinal thicknesses (µm)	
RNFL	36.2 (32.4, 38.7)
GCL	27.1 (24.7, 30.7)
IPL	34.1 (32.6, 36.6)
INL	35.7 (32.3, 37.4)
ONL	24.1 (22.6, 26.7)
OS	30.0 (26.6, 33.6)
RPE	15.4 (14.2, 17.9)
Total receptor	161.0 (152.6, 170.0)
Total retina	294.7 (284.1, 308.6)

Table 5.4 Median (IQR) thicknesses for each retinal layer: retinal nerve fibre (RNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), outer nuclear layer (ONL), outer segment (OS) and retinal pigment epithelium (RPE), plus total receptor and total retina.

5.4.4 Association between microperimetry outcomes and retinal abnormalities

Of the associations between the AMD-related retinal features and microperimetry outcomes (Table 5.5), the strongest significant correlation was between MPD and the presence of photoreceptor atrophy ($r=-0.66$, $p<0.01$).

Of the associations between the retinal thickness measurements and the microperimetry outcomes (Table 5.6), the strongest correlation was between number of PD defects and GCL thickness ($r=0.39$, $p=0.01$).

5.4.5 Multiple linear regression

RPE atrophy and photoreceptor atrophy are anatomically closely related and were highly correlated (r=0.8, p<0.01). Therefore, of these two features only one was entered into each multiple regression model. Each multiple regression model included the AREDS grade to control for difference in severity of AMD.

The most appropriate multiple regression models are presented in Table 5.7 and all include photoreceptor atrophy as a predicting variable. All other models, which included combinations of other predicting variables (retinal features and thicknesses) were weaker. All models met the assumptions of linear regression (Section 4.3.1.1), except for the model including MPD and photoreceptor atrophy, which was performed using robust regression to avoid the influence of outliers (Table 5.7). MTD produced the strongest model with photoreceptor atrophy when AREDS grade was controlled for (R^2=0.46, p<0.01).

	Retinal features						
	EZ band	**Drusen**	**fPED**	**sPED**	**RPE atrophy**	**PR atrophy**	**CNV**
MS	-0.21 (0.25)	-0.31 (0.10)	-0.38 (0.05)	-0.01 (0.68)	-0.49 (<0.01)	-0.57 (<0.01)	-0.27 (0.08)
MTD	-0.25 (0.25)	-0.35 (0.09)	-0.41 (0.04)	0.09 (0.50)	-0.54 (<0.01)	-0.60 (<0.01)	-0.26 (0.10)
No TD defect	0.22 (0.18)	0.26 (0.11)	0.28 (0.08)	-0.07 (0.60)	0.36 (<0.01)	0.39 (<0.01)	0.32 (0.03)
MPD	-0.24 (0.16)	-0.32 (0.04)	-0.27 (0.01)	-0.04 (0.79)	-0.60 (<0.01)	-0.66 (<0.01)	-0.07 (0.30)
No PD defects	0.25 (0.14)	0.34 (0.14)	0.24 (0.12)	-0.03 (0.12)	0.58 (<0.01)	0.57 (<0.01)	0.07 (0.15)

Table 5.5 Spearman's rho values for correlations between retinal features and the microperimetry outcomes. Retinal features include: Ellipsoid zone band disruption (EZ band), Drusen, fibrovascular pigment epithelial detachment (fPED) and serous PED (sPED), RPE atrophy, photoreceptor (PR) atrophy and choroidal neovascularisation (CNV). Microperimetry outcomes included are Mean Sensitivity (MS), Mean Total Deviation (MTD), number of TD defects, Mean Pattern Deviation (MPD) and number of PD defects. P values are given in brackets and those with significance ≤0.05 are highlighted in grey.

	Retinal thicknesses								
	Total retina	**Total receptor**	**RPE**	**OS**	**ONL**	**INL**	**IPL**	**GCL**	**RNFL**
MS	0.16 (0.41)	0.26 (0.08)	-0.20 (0.52)	0.07 (0.75)	0.30 (0.03)	0.13 (0.24)	0.37 (0.01)	-0.28 (0.01)	-0.22 (0.01)
MTD	0.12 (0.50)	0.26 (0.09)	-0.21 (0.48)	0.10 (0.83)	0.33 (0.02)	0.09 (0.31)	0.30 (0.03)	-0.34 (0.01)	-0.23 (0.01)
No TD defect	-0.06 (0.82)	-0.16 (0.51)	0.18 (0.16)	-0.02 (0.36)	-0.20 (0.10)	-0.08 (0.63)	-0.27 (0.06)	0.26 (0.18)	0.17 (0.12)
MPD	0.16 (0.85)	0.29 (0.40)	-0.13 (0.61)	0.14 (0.96)	0.37 (0.02)	-0.02 (0.41)	0.25 (0.13)	-0.32 (<0.01)	-0.14 (0.04)
No PD defects	0.07 (0.25)	-0.13 (0.77)	0.08 (0.33)	-0.09 (0.24)	-0.30 (0.05)	0.16 (0.69)	-0.20 (0.15)	0.39 (0.01)	0.28 (<0.01)

Table 5.6 Spearman's rho values for correlations between retinal thicknesses and the microperimetry outcomes. Retinal thicknesses include: retinal nerve fibre layer (RNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), outer nuclear layer (ONL), outer segment layer (OS), retinal pigment epithelium (RPE), total receptor layer and total retina. Microperimetry outcomes included are Mean Sensitivity (MS), Mean Total Deviation (MTD), number of TD defects, Mean Pattern Deviation (MPD) and number of PD defects. P values are given in brackets and those with significance ≤0.05 are highlighted in grey.

Model	**Adj R^2**	**F**	**p**	**Variables in model**	**Coef**	**SE**	**t**	**p**
MS	0.45	(2,39) = 17.5	<0.01	AREDS PR	-0.10 -10.0	0.77 1.69	-0.12 -5.91	0.90 <0.01**
MTD	0.46	(2,38) = 18.3	<0.01	AREDS PR	-0.06 -10.2	0.76 1.68	-0.08 -6.03	0.94 <0.01**
No TD defect	0.24	(3,37) = 5.2	<0.01	AREDS PR CNV	-1.27 4.83 6.15	0.85 1.87 2.50	-1.48 2.59 2.45	0.15 0.01** 0.02*
MPD	*0.27*	*(2, 38) = 42.0*	*<0.01*	*AREDS PR*	*-0.44 -5.59*	*0.28 0.61*	*-1.57 -9.14*	*0.12 <0.01***
No PD defects	0.32	(2,38) = 10.5	<0.01	AREDS RPE	0.16 3.94	0.45 0.86	0.35 4.57	0.73 <0.01**

Table 5.7 Results of the multiple linear regression analysis to explain the microperimetry outcomes (Mean Sensitivity, MS; Mean Total Deviation, MTD; number of TD defects, No TD defect; Mean Pattern Deviation, MPD; and number of PD defect, no PD defects). The variables in the models are AREDS grade, photoreceptor atrophy (PR), choroidal neovascularisation (CNV) and retinal pigment epithelium (RPE) atrophy. For MPD (italicised), the model did not meet the assumptions of linear regression, therefore a robust regression model was used.

5.5 Discussion

This study examined the relationship between microperimetry outcomes and retinal microstructure features and thicknesses associated with AMD, at 5° eccentricity. The strongest models included the microperimetry outcomes, MTD and MS, and explained 46% and 45% of the variance, respectively. In both models photoreceptor atrophy was the only predicting variable. These findings can be placed in the context of known changes in AMD, in which photoreceptor death (Takahashi et al. 2016) and GA (Hariri et al. 2016) are characteristically associated with worse visual function measured by microperimetry. In another study, ELM loss caused a significant reduction in DLS and loss of RPE was able to predict the presence of absolute scotomata, in GA (Sayegh et al. 2014).

EZ band disruption occurred most commonly, at 50% of the locations, both alone and in the presence of other features. However, no relationship between EZ band disruption and microperimetry outcomes was established and this is in contrast to that found in a previous study by Landa et al. (2011). The discrepancy could be explained by the following differences in methodology. Firstly, the absence of stimulus eccentricity information in the previous study confounds comparison to the results of the present study. Secondly, the previous study is limited by the use of a polar or radial type of stimulus pattern, which lacks regular sampling in peripheral locations. Thirdly, the EZ band in the previous study was graded as either present or absent, whereas the current study graded the EZ band based on the level of disruption present. Finally, the microperimetry outcome of the previous study was MS i.e. it did not implement an age-correct normative database, unlike the probability analyses used within the present study.

Despite more moderate univariate associations between the retinal layer thicknesses and microperimetry outcomes, this variable did not reach statistical significance in the multiple regression models. Previous studies have linked microperimetry and outer

retinal layer changes: abnormal TD values were related to a thinner OS layer in early AMD (Acton et al. 2012b); abnormal MS was associated with outer retinal thinning in the presence of RPD (Steinberg et al. 2016); and abnormal MS was associated with both a thickening and a thinning of the whole retina in nAMD (Hartmann et al. 2015; Sabour-Pickett et al. 2013). Conversely, in the present study, inner retinal layer thicknesses were associated with MS, MTD, MPD and number of PD defects. Reduced inner retinal thickness is more commonly associated with glaucoma, however a number of studies have found thinning of the inner retina and of the ganglion cell complex in intermediate AMD (Rimayanti et al. 2014; Toto et al. 2017; Borrelli et al. 2017).

The relative measures used in the analyses of DLS and retinal thickness measures did not require consideration of axial length-dependant image scaling. Axial length influences the superimposition of the projected stimulus position to the fundus image. The scaling estimation for the MAIA is based solely upon spherical refractive error, as is that of the Cirrus HD-OCT, therefore magnitude of such error is negligible. Whilst correction for axial length is essential when making comparisons between retinal thickness measurements from different instruments (Terry et al. 2016), it is not considered to improve strength of structural and functional relationships in healthy individuals or in those with glaucoma (Nowroozizadeh et al. 2014).

Many of the individuals included in this study had late AMD and therefore the results do not represent the full range of AMD severities. Therefore, the incorporation of the AREDS grade is of limited value, given the marked bias (36 of 42 eyes) to grade 4. Individuals with late AMD are more likely to present with photoreceptor atrophy compared to those with early disease. The association of decreased MS in the presence of photoreceptor atrophy has been reported previously (Takahashi et al. 2016).

The identification of pointwise retinal features is a time consuming process. The development of automated segmentation software that enables retinal boundaries to be identified in the presence of lesions associated with AMD, might enable robust automated feature identification (Hussain et al. 2016). In the present study, only a small proportion of SD-OCT scans failed to be segmented, despite the presence of severe retinal layer disruptions that have been previously reported to cause segmentation error (Lee et al. 2015b; Lee et al. 2015a; de Sisternes et al. 2015). The continued improvement of automated retinal segmentation in the context of the current development of machine learning software to detect disease associated features in fundus photographs and SD-OCT images is expected to lead to automated identification of AMD associated lesions (www.moorfields.nhs.uk, 2017). Further technological advances in combined microperimetry and SD-OCT instrumentation will enable a multimodal evaluation for comprehensive diagnosis and monitoring of the disease process.

In conclusion, at 5° eccentricity, microperimetry outcomes (MS and MTD) can be explained, to a large extent, by the presence of photoreceptor atrophy. However, this relationship is not sufficiently strong for microperimetry and SD-OCT to be interchangeable.

Chapter 6: Vision-related QoL in individuals with age-related macular degeneration

6.1 Summary

Purpose: To establish the relationship between vision-related QoL and clinical, psychosocial- and health-related measures in individuals with AMD.

Methods: Forty-five individuals with AMD (27 female, 18 males) attended for two visits. Measures of visual function comprised: ETDRS distance VA; Mars Letter CS; reading speed (IReST) and microperimetry (MAIA). Vision-related QoL was assessed using the IVI; health- and psychosocial-related measures were assessed by EQ-5D-3L, PHQ-9 and WEMWBS questionnaires. Rasch analysed scoring tables were produced for the IVI and WEMWBS. Univariate regression was performed to establish the relationships between the IVI and the dependant outcomes, prior to inclusion into a multiple regression model.

Results: The median (IQR) total IVI score was 2.37 (1.70 - 3.21). The optimum multiple regression model accounted for 41% of the variance in vision-related QoL (IVI score) and comprised MTD or MS (by MAIA microperimetry) and PHQ-9 score (depressive symptoms).

Discussion: A combination of a microperimetry outcome and depressive symptom scores explained a significant proportion of variance in vision-related QoL.

6.2 Introduction

Age-related macular degeneration has detrimental effects on QoL (Williams et al. 1998), which is arguably the most important aspect to consider for these individuals. It is, therefore, beneficial to establish the clinical outcomes that can predict those at risk of a reduction in QoL due to AMD in order to enable appropriate and timely management strategies. This chapter will investigate factors that determine vision-related QoL, assessed by the IVI, in individuals with AMD. However, before describing the study in detail it is important for the reader to have a good understanding of the relevant background related to QoL and AMD, and the factors that may influence QoL such as psychosocial-related factors, visual function and health-related factors. Additionally, the questionnaires and techniques used to assess QoL and the influencing factors will be summarised.

Quality-of-life is a multidimensional concept and is influenced by many factors including physical and mental health, education, and social and economic status (WHOQOL 1995). The reduction in QoL in individuals with AMD is well-established (Cruess et al. 2007) and may be a consequence of difficulty with tasks of daily living. These include difficulties with self-care such as meal preparation and grooming (Ivanoff et al. 2000); limitations when going outside including travelling and shopping (Hochberg et al. 2012); and inability to perform leisure activities such as sewing, reading or watching the television (Scilley et al. 2002). Further consequences of AMD are an increased risk of falls (Knudtson, Klein and Klein 2009), reduction in mobility (Sengupta et al. 2015), and a decline in independence with a subsequent decrease in social interaction (Wong et al. 2004) leading to psychological and emotional distress (Bennion, Shaw and Gibson 2012; Berman and Brodaty 2006; Williams et al. 1998).

The distress associated with AMD is not, however, related to the severity of vision loss (Moore and Miller 2003). Newly diagnosed individuals will likely be distressed, whereas those who have had time to adapt to the diagnosis may be more accepting

of their situation (Bennion, Shaw and Gibson 2012). Visually impaired individuals are twice as likely to suffer from depression (Evans, Fletcher and Wormald 2007; Brody et al. 2001) and the distress caused by AMD is comparable to that caused by other severe chronic health conditions such as cancer (McDaniel et al. 1995). A cycle therefore ensues in which depression may reduce functional ability which in turn leads to problematic daily life activities and a worsening of depressive symptoms (Rovner, Casten and Tasman 2002; Cimarolli et al. 2015). The PHQ-9 is a well-established questionnaire that is recommended for use in clinical practise by NICE to measure depressive symptoms (Smarr and Keefer 2011). It has been previously implemented in low vision (Acton et al. 2016) and in AMD (Rovner et al. 2014).

Although the prevalence of depression in AMD is well known, a less investigated area is well-being. Mental well-being differs from mental health as it refers to the positive aspects of an individual's everyday functioning (Ryan and Deci 2001). There are few publications that assess well-being in a population with AMD. In one study of individuals with low vision that comprised 60% of cases with AMD, no differences in mental well-being were found between those who had received vision rehabilitation and a control group (Acton et al. 2016). However, the relationship between well-being and vision-related QoL was not assessed. Rasch analysis is undertaken by convention when examining questionnaires within medical research, as it provides a robust assessment of the psychometric properties of a questionnaire, and converts ordinal Likert scale values into a linear logit scale suitable for parametric testing (See Section 1.5). Whilst Rasch analysis has been used to validate the WEMWBS (Bass et al. 2016; Clarke et al. 2011), and Rasch scoring of the WEMWBS has been used in a cohort with low vision (Acton et al. 2016); it has not been validated in individuals with AMD. Therefore, the present study will implement Rasch analysis before exploring the relationship between well-being, as measured by the WEMWBS, and vision-related QoL.

The IVI measures vision-related QoL and is appropriate for individuals with AMD. It is based upon participation in daily activities and the emotions associated with vision impairment (Hassell, Weih and Keeffe 2000). It can be either scored as a whole questionnaire or as three subscales: mobility and independence; reading and assessing information; and emotional well-being. The psychometric properties of the IVI have been extensively examined with Rasch analysis (Lamoureux et al. 2008; Lamoureux et al. 2007c; Lamoureux et al. 2006). Previous Rasch analysis of the IVI led to a reduction in the number of items from 32 to 28 (Lamoureux et al. 2006) and to a merger of the response categories (Lamoureux et al. 2007c). The 28 item IVI has since been validated in individuals with AMD and is deemed as a suitable measure that satisfied the Rasch model (Lamoureux et al. 2008).

An unbiased assessment of an individual's visual impairment can be calculated using the TTO. The TTO was originally established to assess health status (Redelmeier and Detsky 1995) but can be adapted to measure utility values related to visual loss (Brown 1999; Brown 2000). This involves the adjustment of the questioning, so the trade-off years are replaced for 'perfect vision', rather than 'perfect health' (Brown 1999; Brown 2000).

Visual function can be measured by questionnaires and by clinical techniques. The VF-14 questionnaire measures visual function and was originally designed for use in those with cataract (Valderas et al. 2004). It has been validated in individuals with AMD (Mackenzie et al. 2002; Riusala, Sarna and Immonen 2003) and has also been subject to Rasch analysis in AMD (Hewitt et al. 2006). The VF-14 is different from the IVI in that it only measures visual function, based upon the difficulty experienced with certain daily tasks and does not include questions on emotional state.

VA, CS and reading tests are clinical measures of visual function and represent measures of foveal function. In some studies, impaired vision-related QoL was associated with reduced distance VA (Seland et al. 2011), near VA, reading speed

(Cahill et al. 2005), and CS (Hernandez Trillo and Dickinson 2012). A large impairment in vision-related QoL has been found in the presence of only a mild loss of VA (better than 6/12) (Hassell, Lamoureux and Keeffe 2006).

It is, however, important to consider that AMD can affect a wider retinal area than solely the fovea. Hence, a topographical assessment of visual function may be more useful, such as that provided by microperimetry. Two studies have examined the association between vision-related QoL and microperimetry in individuals with AMD (Meleth et al. 2011; Parravano et al. 2013). However, these two studies are limited by the lack of probability analyses of the microperimetry outcomes. The present study will evaluate microperimetry outcomes, derived by robust probability analyses, in the form of TD and PD.

When considering QoL outcomes it is also important to consider health status, as AMD commonly exists in the presence of comorbidity. In individuals with low vision, both physical and mental health were found to be associated with vision-related QoL score, and to activities of daily living (Hernandez Trillo and Dickinson 2012).

In summary, when evaluating QoL in those with AMD, it is important to consider clinical measures of visual function (VA, CS, reading tests and microperimetry), health status, depressive symptoms and well-being. Consequently, the current study aims to establish, in individuals with AMD, the relationship between vision-related QoL, as measured by the Rasch analysed IVI questionnaire, and the following variables: AMD severity, VA, CS, reading speed and microperimetric outcomes; additional vision-related self-reported outcomes, assessed by the Rasch analysed VF-14 and by the modified TTO (modified to measure vision-related utility value); depression (PHQ-9); health status (EQ-5D-3L); and well-being (Rasch analysed WEMWBS).

6.3 Methods

A detailed description of the procedures and techniques used in this chapter can be found in Chapter 3. Briefly, 52 individuals with a median (IQR) age of 79.5 years (75.0, 83.0) were recruited from the Cardiff Eye Unit at the University Hospital of Wales. They attended the School of Optometry and Vision Sciences, Cardiff University, on two occasions each separated by a median (IQR) of 14 days (9, 24).

At Visit 1, the individuals underwent examinations to ensure they met the study inclusion criteria (Section 3.3.1.2). Following this, SD-OCT scans and fundus photographs were acquired (Figure 6.1). Visit 2 involved the collection of the clinical measures of visual function (CS, VA, reading speed and microperimetry outcomes), vision-related QoL (IVI), additional vision-related questionnaires (VF-14 and modified TTO), and the health-related and psychosocial-related measures (health status, EQ-5D; depression, PHQ-9; and well-being, WEMWBS) (Figure 6.1).

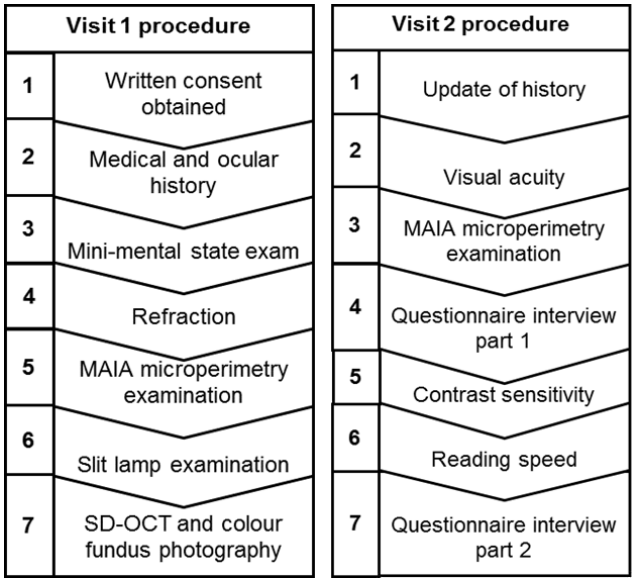


Figure 6.1 Procedures at Visit 1 and Visit 2, listed in the order performed.

Individuals with AMD who also had IOLs (n=11) were included in the analysis. The potential impact of including these individuals could be an artificial improvement in visual function in those with IOLs. However, preliminary analysis demonstrated that

there was no significant difference in the visual function measures between those with IOLs and those with a crystalline lens (independent t-test all $p>0.05$).

6.3.1 Analysis

Binocular measurements of VA, CS and reading speed outcomes were included in the analysis as they were deemed most appropriate for QoL.

6.3.1.1 Questionnaires

A detailed description of the questionnaires employed in this study, and the associated scoring procedures are provided in Chapter 3. To summarise:

6.3.1.1.1 EQ-5D

- The EQ-5D-3L index calculator was used to estimate the index score (Rabin and de Charro 2001), where a maximum value of 1 is given for perfect health and a value of 0 represents death (Dixon, Dakin and Wordsworth 2016).
- The EQ-5D also includes a visual analogue scale in which the individual is asked to rate their overall health state on the day of testing, using a scale of 0-100, with 0 being the worst imaginable health state and 100, being the best.

6.3.1.1.2 PHQ-9

- The PHQ-9 item scores were summed to produce a total score, which determines the level of depressive symptoms exhibited by the individual. A total score of 0 indicates an absence of depressive symptoms, 1-4 as minimal depressive symptoms, 5-14 as mild to moderate depressive symptoms, 15-19 as moderately severe symptoms and 19-27 as severe depressive symptoms.

6.3.1.1.3 Modified TTO

- The TTO was modified to provide a vision-related outcome (Chapter 3). The answers to the two questions were converted into a single utility value by subtracting the number of trade-off years from the number of years expected to live and then dividing by the number of years expected to live. This results

in a value between 0 and 1, where 1 represents a trade-off of all of the individual's remaining years, and 0 represents no time traded.

6.3.1.1.4 WEMWBS, IVI and the VF-14

- Rasch analysed scoring tables were produced to convert the Likert responses, for each of these questionnaires, into logit scores. The lower the logit score the worse the well-being, the vision-related QoL and the visual function, respectively.
- The overall score for each questionnaire was calculated as the sum of logit scores for all items divided by the number of questions answered.

6.3.1.2 Imaging techniques

Colour fundus photographs were graded using the AREDS classification system (AREDS 2001). SD-OCT foveal line scans were also utilised to confirm or identify PEDs, intraretinal fluid and other retinal features associated with AMD, as described in Chapter 3.

6.3.1.3 AMD severity

Participants were classified on the basis of an established binocular classification system (Aspinall et al. 2007) that included mild, moderate and severe categories. Mild is indicated by the presence of early or intermediate AMD in one or both eyes; moderate as the presence of late AMD (nAMD or GA) in one eye; and severe as the presence of late AMD in both eyes. Due to the limited numbers in the study the three classifications were combined into a binary scale to allocate individuals by mild or moderate classification (Grade 1) and by severe classification (Grade 2).

6.3.1.4 Microperimetry outcomes

The left eye DLS results were transformed into right eye format. The DLS values for those with foveal fixation were then converted into TD and PD values with corresponding probability defects using the MAIA normative database derived in the

previous study (Chapter 4). Unweighted mean TD (MTD) and mean PD (MPD) were utilised for analysis.

The best MTD approach was implemented, whereby the eye with the best MTD was used to provide a binocular estimate for microperimetry (Arora et al. 2013). Two individuals did not have foveal fixation and therefore binocular estimates were based on the eye with the best MS for these individuals. This was to avoid the interpretation of the microperimetry results based on misaligned normative values due to eccentric fixation. Further data for these individuals were excluded from all analyses that use MTD or MPD.

6.3.1.5 Statistical analyses

The approach for statistical analyses was firstly an assessment for normality (Shapiro-Wilk test), followed by a Spearman's rank correlation matrix of all outcomes variables, and lastly univariate linear regression and multiple linear regression with IVI as the dependant variable.

Correlation analysis was utilised, initially, to reduce the number of potential associations and subsequently only the significant associations were used in the univariate linear regression analysis (Armstrong, Eperjesi and Gilmartin 2005).

A Spearman's rank correlation matrix was undertaken to determine the strength of the association between all outcomes, including clinical measures of visual function, vision-related QoL, the health-related and psychosocial-related measures, age and AMD severity. This process was performed to identify the variables that were associated with vision-related QoL. When independent variables were highly correlated ($r \geq 0.8$) only one was included into each multiple regression model.

The strongest correlates of vision-related QoL were then examined by univariate regression analyses to establish the most appropriate variables to include into the final multiple regression models.

Lastly, several multiple regression models including different combinations of factors were then examined to find the most appropriate model to explain the variance in IVI score. The multiple regression models were limited to one factor per 10 participants as described in Section 5.3.1.3. The assumptions of each linear regression model were examined, as detailed in Chapter 4.

Statistical analyses were performed using the open source environment R (Version 3.2.2) and SPSS (version 20.0). A p value of ≤0.05 was considered to be statistically significant for all analyses. A Bonferroni correction was not implemented in this analysis to avoid Type 2 errors (Armstrong 2014). The descriptive statistics for all measures are presented as a median and inter-quartile range (IQR).

6.4 Results

The following results are presented: firstly, the assessment of normality and the demographic characteristics of the individuals with AMD; secondly, a summary of the Rasch analyses performed on the IVI, WEMWBS and VF-14; thirdly, the characteristics of the individuals in terms of vision-related QoL, clinical measures of visual function and health-related and psychosocial-related outcomes; and finally, the correlation, univariate regression and multiple regression analyses to explain the variance in vision-related QoL.

6.4.1 Assessment of normality

The majority of outcomes were found to have a non-Gaussian distribution (age, EQ-5D, PHQ-9, modified TTO, MS, VA, MTD, MPD and IVI, all $p<0.05$). Three outcomes had a Gaussian distribution: WEMWBS ($p=0.29$), CS ($p=0.26$) and reading speed ($p=0.42$).

6.4.2 Characteristics

Five of the 52 individuals were excluded due to existing co-morbidities (4 due to details from the medical history, and one following refraction due to high myopia), resulting in 47 individuals included in the study.

Of the 47 individuals, 2 failed to attend both visits resulting in a cohort of 45 individuals (27 female, 18 males). The characteristics of the individuals with AMD are presented in Table 6.1.

Variables	*N=45*
Age (years)	
Median age	80
IQR	75 – 83
Binocular AMD severity, n (%)	
Grade 1	19 (42.2)
Grade 2	26 (57.8)
Duration of AMD, n (%)	
<2 years	23 (51.1)
>2 years	22 (48.9)
Living, n (%)	
Alone	22 (48.9)
Spouse/family	23 (51.1)

Table 6.1 The characteristics of the 45 individuals with AMD.

6.4.3 Rasch analysis

6.4.3.1 Warwick-Edinburgh Mental Well-being Scale

The psychometric properties of the WEMWBS have not been previously examined in individuals with AMD. Firstly, the performance of the response categories were evaluated (Figure 6.2). Category 2 (“Rarely”) was identified as not having a range over which it was likely to be chosen, as it overlapped with both category 1 and 3

(Figure 6.2, left). Therefore, response options 1 and 2 were merged. Having merged these, the categories functioned well (Figure 6.2, Panel B).

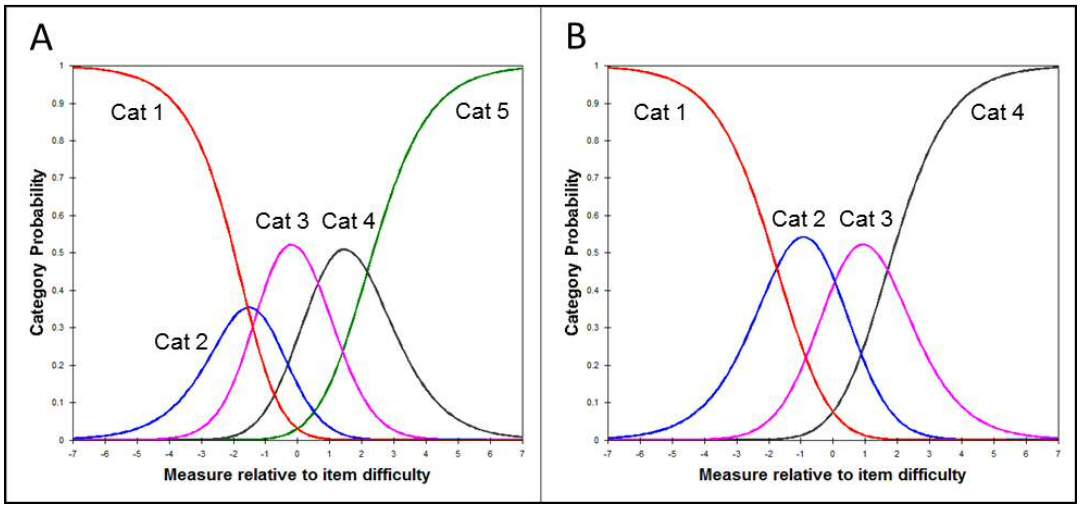


Figure 6.2 Probability curve to show the operation of the original response categories for the Warwick-Edinburgh Well-being scale (A, left) (Cat 1= "None of the time", Cat 2= "Rarely", Cat 3= "Some of the time", Cat 4= "Often", Cat 5 ="All of the time") and the improved response categories (B, right)(Cat 1="None of the time", Cat 2 = "Rarely" or "some of the time", Cat 3=" Often", Cat 4= "All of the time").

Secondly, the person fit statistics were assessed. One individual was found to have a value outside the accepted range (>1.4) (Linacre 2006) and was therefore removed from the analysis.

Figure 6.3 shows the item range from -1.8 logits to 2.0 logits. Where items at the bottom of the map (e.g. item 12 "I have been feeling loved") discriminate between those with low levels of well-being, and those at the top of the map (e.g. item 5 "I have had energy to spare") discriminate between those with high levels of well-being. On the left of the map the person ability is shown and although the items are slightly biased towards the lower levels of well-being, there is a large range of items spanning the person abilities.

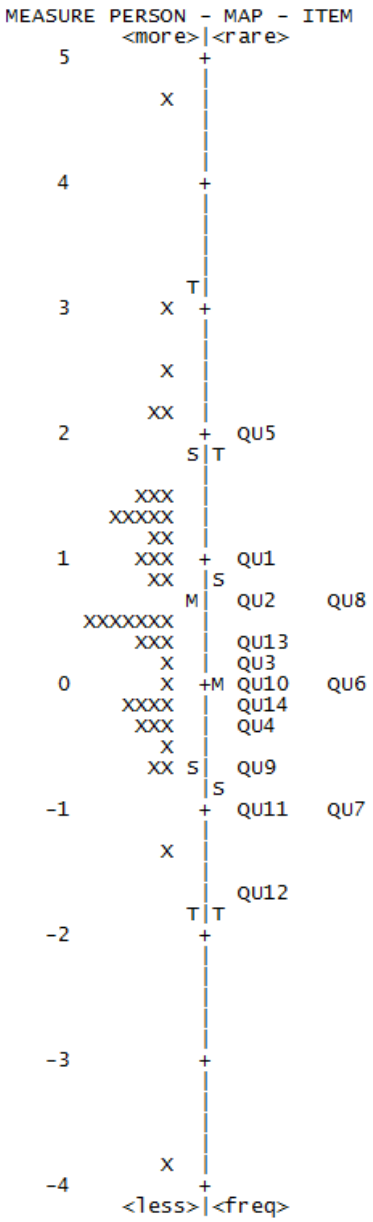


Figure 6.3 Person and item map showing the spread of item difficulty (right) with person ability (X = an individual), measured in logits (left).

Person and item reliability were both close to 1 (0.88 and 0.93 of the modelled data respectively) suggesting the estimates were accurate (Court, Greenland and Margrain 2010). Both the person and item separation were greater than 2.0 (2.75 and 3.77 respectively) and therefore reliably positioned on the Rasch scale (Court, Greenland and Margrain 2010).

The infit and outfit values from the WEMWBS were all less than 2.0 (Table 6.2). However, three items had infit values greater than 1.5, and two outfit values were over 1.5 suggesting only a modest fit with the 'well-being' concept being assessed by the questionnaire overall. Although not ideal, such fit statistics did not degrade the performance of the questionnaire and therefore it was decided to retain these items, preserving the integrity of the original questionnaire (Linacre 2006).

Item		Item difficulty (SE)	Infit (MNSQ)	Outfit (MNSQ)
1	Optimistic	0.95 (0.22)	1.37	1.71
2	Useful	0.58 (0.21)	1.26	1.18
3	Relaxed	0.22 (0.22)	0.59	0.56
4	Interested in other people	-0.31 (0.22)	1.46	1.76
5	Energy to spare	2.05 (0.23)	1.15	1.09
6	Dealing with problems well	-0.06 (0.22)	0.58	0.56
7	Thinking clearly	-0.93 (0.24)	0.79	0.74
8	Good about myself	0.58 (0.21)	0.69	0.67
9	Close to other people	-0.71 (0.23)	1.12	1.02
10	Confident	0.03 (0.22)	0.62	0.59
11	Make up my own mind	-0.93 (0.24)	0.99	1.01
12	Loved	-1.62 (0.27)	1.63	1.45
13	Interested in new things	0.26 (0.22)	1.52	1.56
14	Cheerful	-0.11 (0.22)	0.47	0.46

Table 6.2 Fit statistics (Mean-square [MNSQ] infit and outfit values) and item difficulty (in logits) for the Warwick-Edinburgh Mental Well-being scale provided by Rasch analysis.

The scoring table to covert the WEMWBS Likert scale into logit values was then calculated (Table 6.3).

		Response category			
Item		**1**	**2**	**3**	**4**
1	Optimistic	-2.01	0.03	1.89	3.87
2	Useful	-1.43	0.61	2.47	4.45
3	Relaxed	-1.21	0.83	2.69	4.67
4	Interested in other people	-1.52	0.52	2.38	4.36
5	Energy to spare	0.53	2.57	4.43	6.41
6	Dealing with problems well	0.47	2.51	4.37	6.35
7	Thinking clearly	-0.46	1.58	3.44	5.42
8	Good about myself	0.12	2.16	4.02	6.00
9	Close to other people	-0.59	1.45	3.31	5.29
10	Confident	-0.56	1.48	3.34	5.32
11	Make up my own mind	-1.49	0.55	2.41	4.39
12	Loved	-3.11	-1.07	0.79	2.77
13	Interested in new things	-2.85	-0.81	1.05	3.03
14	Cheerful	-2.96	-0.92	0.94	2.92

Table 6.3 Rasch analysed scoring table (logits) for each item of the Warwick-Edinburgh Mental Well-being scale.

6.4.3.2 Impact of Vision Impairment

Rasch analysis metrics indicated that the total IVI questionnaire had good psychometric properties. The category responses were ordered well, both the item and person reliability coefficients were high (0.94 and 0.93, respectively), as were the item and person separation ratios (4.0 and 3.6, respectively). The infit and outfit mean square values were all less than 1.5. These findings are in agreement with earlier reports on the IVI (Lamoureux et al. 2006; Lamoureux et al. 2007c). The scoring table is presented in Table 6.4.

		Response category			
Item		**0**	**1**	**2**	**3**
1	TV	-5.05	-1.46	1.96	4.06
2	Recreational activities	-5.12	-1.53	1.89	3.99
3	Shopping	-4.72	-1.13	2.29	4.39
4	Reading	-1.49	2.10	5.52	7.62
5	Visiting friends/family	-6.67	-3.08	0.34	2.44
6	Recognising/meeting	-4.85	-1.26	2.16	4.26
7	Getting information	-2.39	1.20	4.62	6.72
8	Looking after appearance	-5.71	-2.12	1.30	3.40
9	Opening packaging	-6.15	-2.56	0.86	2.96
10	Reading labels on medicines	-3.62	-0.03	3.39	5.49
11	Household appliances	-5.45	-1.86	1.56	3.66
12	Getting about outdoors	-5.09	-1.50	1.92	4.02
13	Careful to avoid falling	-4.08	-0.49	2.93	5.03
14	Travelling/transport	-5.19	-1.60	1.82	3.92
15	Steps/stairs/curbs	-4.14	-0.55	2.87	4.97
16	Safety at home	-5.77	-2.18	1.24	3.34
17	Spilling/breaking things	-5.53	-1.94	1.48	3.58
18	Safety out of home	-4.92	-1.33	2.09	4.19
19	Stopped doing things	-5.17	-1.58	1.84	3.94
20	Need help from others	-5.75	-2.16	1.26	3.36
21	Embarrassed	-6.56	-2.97	0.45	2.55
22	Frustrated	-4.66	-1.07	2.35	4.45
23	Lonely/isolated	-7.41	-3.82	-0.40	1.70
24	Sad/low	-5.55	-1.96	1.46	3.56
25	Worried about getting worse	-3.95	-0.36	3.06	5.16
26	Concerned about coping	-4.98	-1.39	2.03	4.13
27	Nuisance or burden	-6.10	-2.51	0.91	3.01
28	Interfered with life in general	-5.05	-1.46	1.96	4.06

Table 6.4 Rasch analysed scoring table (in logits) for each item of the Impact of Vision Impairment questionnaire.

6.4.3.3 VF-14

The assessment of the psychometric properties of the VF-14 highlighted an unsatisfactory overlap between the response categories and a poor fit for question 13 (outfit value= 4). It was concluded that the VF-14 was unsatisfactory for use in individuals with AMD, without significant modification. As the results from the VF-14 were not the primary outcome measure in this study, it was excluded from further analysis.

6.4.4 Characteristics of visual function and questionnaire outcomes

Descriptive statistics for the IVI, the clinical measures (VA, CS, reading speed and microperimetry) and each of the health- and psychosocial-related measures are presented in Table 6.5. Despite the proportion of individuals being classified as severe AMD (n=26), binocular VA was maintained at a high level (Table 6.5). In those with foveal fixation (n=43), the median (IQR) of the MTD was -4.5 (-1.7, -7.6) and for MPD was -2.7 (-2.1, -3.9).

The individuals had a median (IQR) of 3 (2, 4) comorbidities and were taking a median of 3 (1, 4) medications. The most common comorbidities were hearing impairments (n=29) and musculoskeletal disorders (n=26).

The EQ-5D VAS median (IQR) score was 80 (70, 87), for the EQ-5D index was 0.70 (0.66, 0.77) (Table 6.5). Self-care was the area with the least number of problems (n=4). Over half of the individuals experienced problems with pain or discomfort (n=25) (Table 6.5).

	N=45
IVI score (logits), median (IQR)	2.4 (1.7, 3.2)
Range	-1.5 – 3.9
Clinical measures, median (IQR)	
Mean sensitivity (dB)	23.7 (20.4, 26.9)
Visual acuity (logMAR)	0.1 (0.0, 0.2)
Reading speed (wpm)	158.8 (126.4, 192.6)
Contrast sensitivity (log units)	1.4 (1.2, 1.6)
EQ-5D VAS, median (IQR)	80 (70,87)
Range	9 - 100
EQ-5D index, median (IQR)	0.7 (0.7, 0.8)
Range	0.3 – 1.0
EQ-5D dimensions, n (%)	
Mobility	
Problems	24 (53.3)
No problems	21 (46.7)
Self-care	
Problems	4 (8.9)
No problems	41 (91.1)
Usual activities	
Problems	20 (44.4)
No problems	25 (55.6)
Pain/discomfort	
Problems	25 (55.6)
No problems	20 (44.4)
Anxiety/ depression	
Problems	11 (24.4)
No problems	34 (75.6)
PHQ-9 total score, median (IQR)	3 (2, 5)
Range	0 - 24
PHQ-9 depression severity, n (%)	
No depression	6 (13.3)
Minimal depression	23 (51.1)
Mild depression	14 (31.1)
Moderate depression	1 (2.2)
Severe depression	1 (2.2)
WEMWBS (logits), median (IQR)	2.3 (1.6, 3.0)
Range	-0.9 – 4.7
Modified TTO, median (IQR)	1.0 (0.8, 1.0)
Range	0.0 – 1.0

Table 6.5 Descriptive statistics for vision-related QoL (Impact of Vision Impairment, IVI) and the clinical measures of visual function and each of the health-related and psychosocial-related outcomes. For the IVI, Warwick-Edinburgh Mental Well-being Scale (WEMWBS), modified TTO and EQ-5D the higher the score the better the QoL, well-being, utility value and health status, respectively. For the PHQ-9 a higher scored indicates worse depressive symptoms.

The median (IQR) PHQ-9 total score was 3 (2, 5). Over half of the individuals had minimal or no depressive symptoms (n=29) and a third of individuals displayed only mild depressive symptoms (n=14) (Table 6.5). Three individuals were receiving treatment for depression prior to the start of the study. One individual was identified on the PHQ-9 as displaying moderate depressive symptoms and one individual as exhibiting severe depressive symptoms. Both of these individuals agreed to be referred to their GP, according to the study protocol (Section 3.3.3.2.3).

6.4.5 Correlation analysis

The correlation matrix is presented in Figure 6.4. The Spearman's rho values representing the associations between each of the clinical measures were assessed to ascertain any commonality between them. A value over or equal to 0.8 was considered as highly correlated. There was moderate correlation between all clinical measures as may be expected. The associations between MS, MTD and MPD were, unsurprisingly, high (all $r \geq 0.8$), because all were derived from the same microperimetric DLS values (Figure 6.4).

The correlations between the study outcomes and the IVI score are presented in Table 6.6. Each clinical measure, health-related and psychosocial-related measures declined with IVI score. The PHQ-9 score and the IVI score showed the strongest association ($r=-0.46$). All the clinical measures were moderately associated with IVI score, and MPD demonstrated the strongest association ($r=0.38$). Age, AMD severity and modified TTO score were not significantly correlated with the IVI score (Table 6.6).

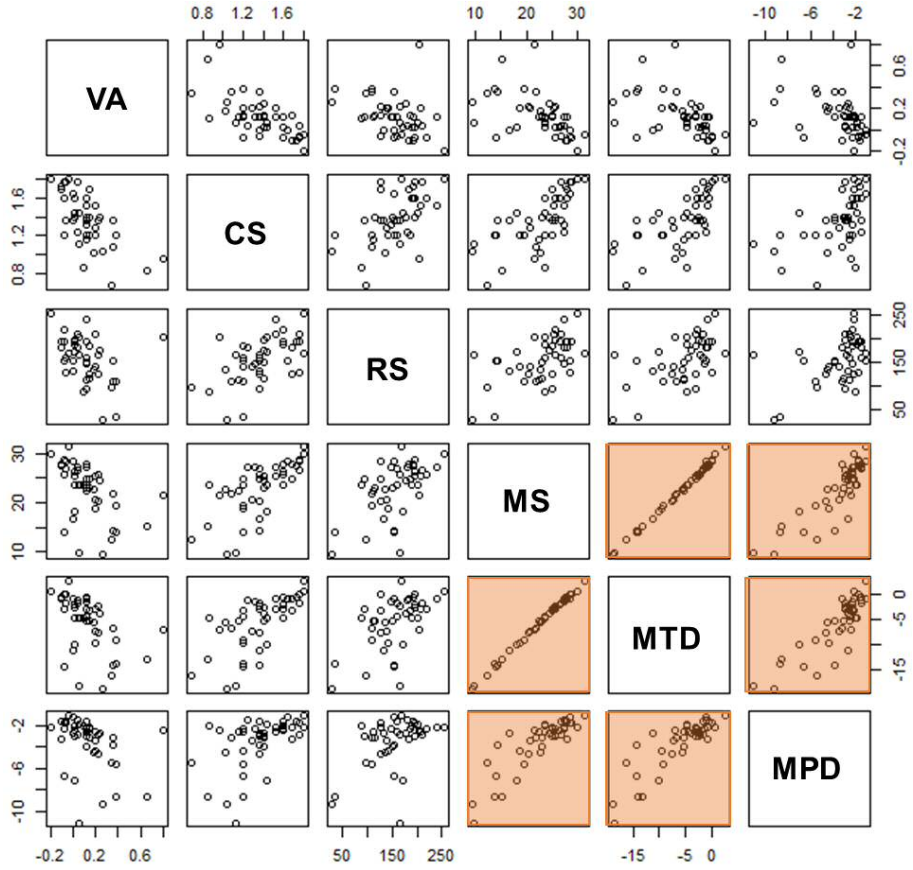


Figure 6.4.Correlation matrix for each of the clinical outcomes: visual acuity (VA), contrast sensitivity (CS), reading speed (RS), Mean Sensitivity (MS), Mean Total Deviation (MTD and Mean Pattern Deviation (MPD). The Spearman's rho values ≥0.8 are highlighted in orange.

	Rho values	p value
Age	-0.02	0.44
Visual acuity	-0.31*	0.04
Contrast sensitivity	0.36*	0.02
Reading speed	0.30**	0.01
Mean Sensitivity	0.36**	<0.01
Mean Total Deviation	0.36**	<0.01
Mean Pattern Deviation	0.38**	<0.01
AMD severity	-0.08	0.35
EQ-5D	0.35**	0.01
PHQ-9	-0.46**	<0.01
WEMWBS	0.34*	0.04
Time trade-off	0.03	0.71

*Table 6.6 Spearman's rank correlation for the association between IVI total score and clinical measures, health-related measures, age and AMD severity. * p≤0.05 and **p≤0.01*

6.4.6 Univariate linear regression

The outcomes from the univariate linear regression analysis are presented in Figure 6.5. As age, AMD severity and the modified TTO exhibited no association with IVI score, these outcomes were excluded from further analysis.

Each of the microperimetry outcomes produced identical relationships with IVI score (all R^2=0.20, $p<0.01$), confirming that only one of these should be used within the subsequent multiple regression model. From all the measures investigated, the PHQ-9 was the strongest univariate predictor of IVI score (R^2=0.21, $p<0.01$). Of the clinical measures of visual function, the microperimetry outcomes and CS produced the strongest univariate relationships with IVI score (all R^2=0.20).

Health status and well-being produced significant but weaker relationships with IVI score compared to the PHQ-9 (EQ-5D, R^2=0.14, p=0.01; and WEMWBS, R^2=0.10, p=0.04).

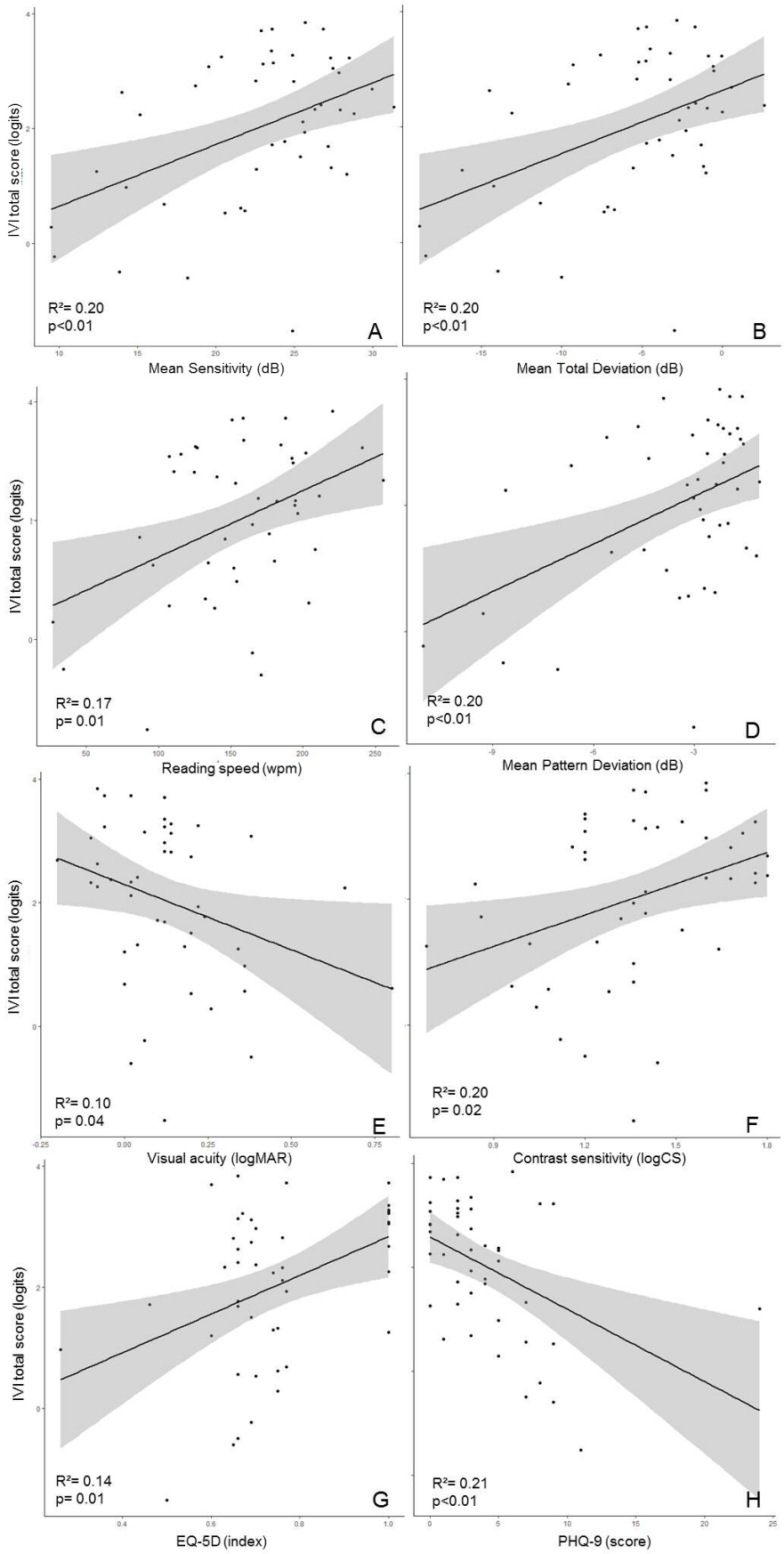


Figure 6.5 Univariate linear regression of IVI total score (ordinate) as a function of Mean Sensitivity (A), Mean Total Deviation (B), reading speed (C), Mean Pattern Deviation (D), Visual acuity (E), Contrast sensitivity (F), EQ-5D (G) and PHQ-9 (H) (abscissa). The grey shaded area represents the 95% confidence limits for linear regression.

6.4.7 Multiple linear regression

The clinical measures identified as having the strongest univariate relationships with vision-related QoL (PHQ-9, CS and the microperimetry outcomes) were examined further in combination with each other and with the other clinical, health- and psychosocial-related measures, as part of the multiple regression analysis.

Several multiple regression models, limited to a maximum of 4 predicting variables for n=45 (Section 5.3.1.3), were compared, to find the strongest model to predict total IVI score. Only one of the microperimetry outcomes was utilised within the same model due to the high correlation between them.

MTD or MS in combination with the PHQ-9 produced identical models accounting for 41% of the variance in IVI score (Table 6.7, Model A and B respectively). The model including CS and PHQ-9 accounted for 37% of the variance in IVI score (Table 6.7, Model C). None of the other clinical measures were significant within the multiple regression models.

Model	Adj R^2	F	p	Variables in model	Coef	SE	t	p
A	0.41	(2,42) = 16.0	<0.01	MTD PHQ-9	0.12 -0.15	0.03 0.04	4.11 -4.15	0.01** 0.00**
B	0.41	(2,42) = 16.0	<0.01	MS PHQ-9	0.12 -0.15	0.03 0.04	4.11 -4.15	0.01** 0.00**
C	0.37	(2,42) = 13.6	<0.01	CS PHQ-9	0.58 0.04	0.58 0.04	3.61 -4.34	0.01** 0.00**

Table 6.7 Two multiple regression models to predict the IVI total score. Model A includes Mean Total Deviation (MTD)or Mean Sensitivity (MS) and the patient health questionnaire-9 (PHQ-9) and model C includes contrast sensitivity (CS) and the PHQ-9.

6.5 Discussion

The present study investigated the relationship between vision-related QoL and clinical measures of visual function, psychosocial-related measures and health-related measures. The strongest univariate predictor of vision-related QoL was the PHQ-9, accounting for 21% of the variance. However, MS, MTD and CS all explained a similar variance of 20%.

Vision-related QoL was predicted by MS or MTD in combination with the PHQ-9. These key predictors were effective in explaining 41% of the variance in IVI score, which is twice that accounted for by the same measures univariately. This finding supports the clinical utility of microperimetry, and is consistent with the well-established links between vision-related QoL and depression in AMD (van der Aa et al. 2015; Rovner, Casten and Tasman 2002; Slakter and Stur 2005). The results reinforce our knowledge that a relationship exists between reduced visual field loss and worsened QoL (Medeiros et al. 2015). A similar variance of 42% has been previously reported in a study that predicted the activities of daily living (Activities of Daily Vision Scale) from clinical measures including VA, but did not include microperimetry outcomes (Mangione et al. 1999). By determining the clinical measures that predict vision-related QoL, these findings could have clinical implications for monitoring functional loss in individuals with AMD in the context of QoL. The combination of microperimetry outcomes and level of depressive symptoms could help identify those with a reduced vision-related QoL and, subsequently allow effective management of those most at risk.

Microperimetry outcomes were key predictors of vision-related QoL in individuals with AMD and this supports previous literature. Two previous studies examined the change in microperimetric outcomes and vision-related QoL after treatment of AMD by macular translocation surgery (Mettu et al. 2011) and photodynamic therapy

combined with Ranibizumab (Parravano et al. 2013). Only one of these assessed the association between microperimetry and vision-related QoL, whereby microperimetry was moderately correlated (r=0.35) with NEI-VFQ-25 score following macular translocation surgery, which was not the case pre-operatively (Mettu et al. 2011). However, the microperimetric outcome was limited to the median DLS and percentage non responsive locations (percentage of locations with no response to the brightest stimulus) (Mettu et al. 2011). Another study examined the comparison of vision-related QoL, between open angle glaucoma and AMD, and included SAP performed with the HFA as an outcome (Ugurlu, Karagoz and Ekin 2017). In a correlation analysis between MD values of the 10-2 visual field and total NEI-VFQ-25 score, the correlation coefficient was r=0.36. This is identical to the correlation between MTD and IVI score established in the present study (see results in Table 6.6). However, stronger associations between vision-related QoL and both VA (r=0.96), and CS (average r=0.73) were found than those in the present study.

It is also of interest that the microperimetry outcomes, MS and MTD, demonstrated stronger relationships with vision-related QoL, than VA and reading speed. This might suggest that microperimetry could replace VA and reading speed in the determination of vision-related QoL in individuals with AMD.

A further novel aspect of the current study was the application of Rasch analyses to the WEMWBS in individuals with AMD. The results of this analysis show that, after combining the response categories, the WEMWBS is a valid measurement tool, with which to quantify mental well-being in individuals with AMD. The items of the questionnaire form a valid unidimensional linear scale to measure well-being. As the WEMWBS is now validated in this cohort, further studies should establish if well-being is affected in a separate cohort of individuals with AMD. Future studies should include the assessment of well-being in a large sample of individuals with a range of AMD severities, but also in comparison with age-matched controls.

Although a large proportion of the variance in vision-related QoL was explained by the multivariate model, the unexplained variance is a consequence of the multidimensional nature of QoL, whereby other factors such as socio-economic status (e.g. household income and level of education) affect the individual's QoL. Another explanation for the moderate strength of the model is that the clinical measures utilised in this study do not reflect 'real world' scenarios and therefore the association with vision-related QoL is limited. Previous studies have measured 'real world' ability by assessing performance on tasks within a controlled environment, for example timed activities such as walking up the stairs (West et al. 2002b). Other tasks have been developed to mimic real world situations such as viewing faces, for both recognition and expression perception (Alexander et al. 1988; Vuilleumier et al. 2003) and everyday scene searching tasks (Taylor et al. 2017). These more realistic measures of visual function may lead to stronger relationships with vision-related QoL; however, due to their time consuming nature and the additional research instrumentation required, they are unlikely to be adopted in clinical practice. It is, therefore, important to make conclusions based upon instrumentation and techniques translational to AMD clinics, to enable widely applicable findings, for appropriate advice to professionals.

A limitation of the current study was the lack of age-matched controls, which limits the ability to isolate the effects of AMD on vision-related QoL. A further study including such a comparison would verify the findings from this study. Another potential limitation, was the proportion of participants with late AMD included in this study, which could have introduced bias towards a more severe vision-related QoL. Despite this, there was a range of vision-related QoL results within this study, but no relationship was found between AMD severity and vision-related QoL.

It can be argued that the aim of any AMD treatment is to improve an individual's QoL. It is not common for lengthy questionnaires to be used in clinical practice due to time

constraints. In the present study, we have identified that MTD or MS and level of depressive symptoms can explain a significant proportion of the variance in vision-related QoL. Further investigation as to whether the same clinical measures can also be used to explain the change in vision-related QoL over 1 year will be examined in the following chapter.

Chapter 7: The relationship between change in vision-related QoL and clinical outcomes: Follow-up at 1 year

7.1 Summary

Purpose: The aim of this study was twofold. Firstly, to determine if change was present in vision-related QoL, clinical measures of visual function, health status, depression and well-being outcomes at 1 year from the baseline assessment. Secondly, to evaluate the factors that determine any change in vision-related QoL at 1 year.

Methods: Twenty-nine individuals with AMD (18 female) attended a follow-up visit at 1 year. Measures of visual function comprised: ETDRS distance VA; Mars letter CS; reading speed by the IReST and MAIA microperimetry. Vision-related QoL was assessed by the IVI questionnaire, health status by the EQ-5D and depression and well-being by the PHQ-9 and WEMWBS, respectively. Univariate linear regression analysis was performed to establish the strongest predictors of any change. The predictors were then incorporated into a multiple regression model.

Results: There was no significant change over 1 year in the IVI score, EQ-5D, PHQ-9, WEMWBS, CS, reading speed or VA. Each of the microperimetry outcomes worsened over the 1 year follow-up. Baseline CS (R^2=0.36, $p<0.01$) was the strongest univariate predictors of change in IVI score, The optimum multiple regression model accounted for 43% of the change in IVI score and included baseline CS, change in reading speed and change in EQ-5D score.

Conclusion: Change in vision-related QoL over 1 year can, to a significant extent, be explained by baseline CS, changes in health status and changes in reading speed.

7.2 Introduction

The prevalence of AMD is expected to increase due to the ageing population (Owen et al. 2012) and this is likely to have significant personal, social and economic consequences (Prenner et al. 2015; Cruess et al. 2007). Current research largely concentrates on treatment and early detection of AMD, yet QoL is equally as important in terms of patient management (Yuzawa et al. 2013). The previous chapter (Chapter 6) showed that a combination of clinical outcomes and health- and psychosocial-related measures could predict, to some extent, an individual's vision-related QoL in a cross-sectional cohort with AMD. Therefore, it may be possible to predict those most at risk of vision-related QoL deterioration i.e. clinical measures of visual function and health- and psychosocial-related measures may be biomarkers for future loss of vision-related QoL.

Many have studied the factors that affect vision-related QoL in those with AMD (Coleman et al. 2010; Scilley et al. 2002; Ugurlu, Karagoz and Ekin 2017), yet fewer studies have evaluated the change in vision-related QoL over time in AMD (Markun et al. 2015; Finger et al. 2014; Yuzawa et al. 2015; van Nispen et al. 2010). Change in QoL has been adopted as an outcome measure in clinical trials in the evaluation of therapeutic and rehabilitation interventions in AMD (Markun et al. 2015; Finger et al. 2014; Yuzawa et al. 2015; van Nispen et al. 2010).

Progression from mild to severe visual impairment adversely impacts on vision-related QoL (Coleman et al. 2010). In early stages of AMD, where good VA is maintained, difficulty with everyday activities such as driving and near vision tasks are experienced, which subsequently lead to reductions in vision-related QoL (Scilley et al. 2002; Ugurlu, Karagoz and Ekin 2017).

Current AMD treatment is monitored by clinical assessment, which may include imaging and measures of visual function, but measures of vision-related QoL are

seldom considered. The identification of those with a change in vision-related QoL, could help practitioners to allocate resources more appropriately.

Microperimetric outcomes have not been previously investigated with respect to change in vision-related QoL. In glaucoma, a worsening in the binocular HFA visual field (binocular summation of the 24-2 pattern) was associated with a change in vision-related QoL (Medeiros et al. 2015). This is consistent with the results from the preceding study (Chapter 6), despite the difference between disease processes between glaucoma and AMD. In Chapter 6, it was found that microperimetric results (MS and MD) at baseline can predict, to some extent, baseline vision-related QoL and, therefore, may also be associated with change in vision-related QoL. Additionally, there is no literature examining the combination of factors that determine the change in vision-related QoL that is not a consequence of intervention.

The aim of this study was twofold. Firstly, to quantify the change (both improvement and deterioration) in vision-related QoL, clinical measures of visual function, health status, depression and well-being after a follow-up period of 1 year. Secondly, to evaluate the factors that determine change in vision-related QoL after 1 year. The clinical measures of visual function included VA, CS, reading speed and microperimetry outcomes (Chapter 3). Depressive symptoms (PHQ-9), well-being (WEMWBS), general health status (EQ-5D) and the TTO (modified to measure vision-related utility values) were also assessed (Chapter 3). Vision-related QoL was quantified using the total score of the Impact of Visual impairment (IVI) questionnaire (Chapter 3).

7.3 Methods

Each of the measures undertaken in this chapter are described in detail in Chapter 3. In brief, 52 individuals with AMD took part in a baseline assessment. Each individual attended two visits to the School of Optometry and Vision Sciences, Cardiff University,

within 14 days (9, 24). At these two visits, the vision-related QoL, clinical measures of visual function, depression, well-being and health status were collected (Figure 7.1).

Thirty-two of the 52 individuals had completed a one year cycle and, therefore, were invited to return for a follow-up visit, on a consecutive basis (see sample size calculation Section 3.3.1.1). The follow-up visit took place 1 year after the baseline visit, median (IQR) of 13.6 months (12.5, 14.6).

The follow-up visit included all of the assessments performed at the baseline visits and also consisted of an updated medical, lifestyle and living situation history (Figure 7.1) (Chapter 3).

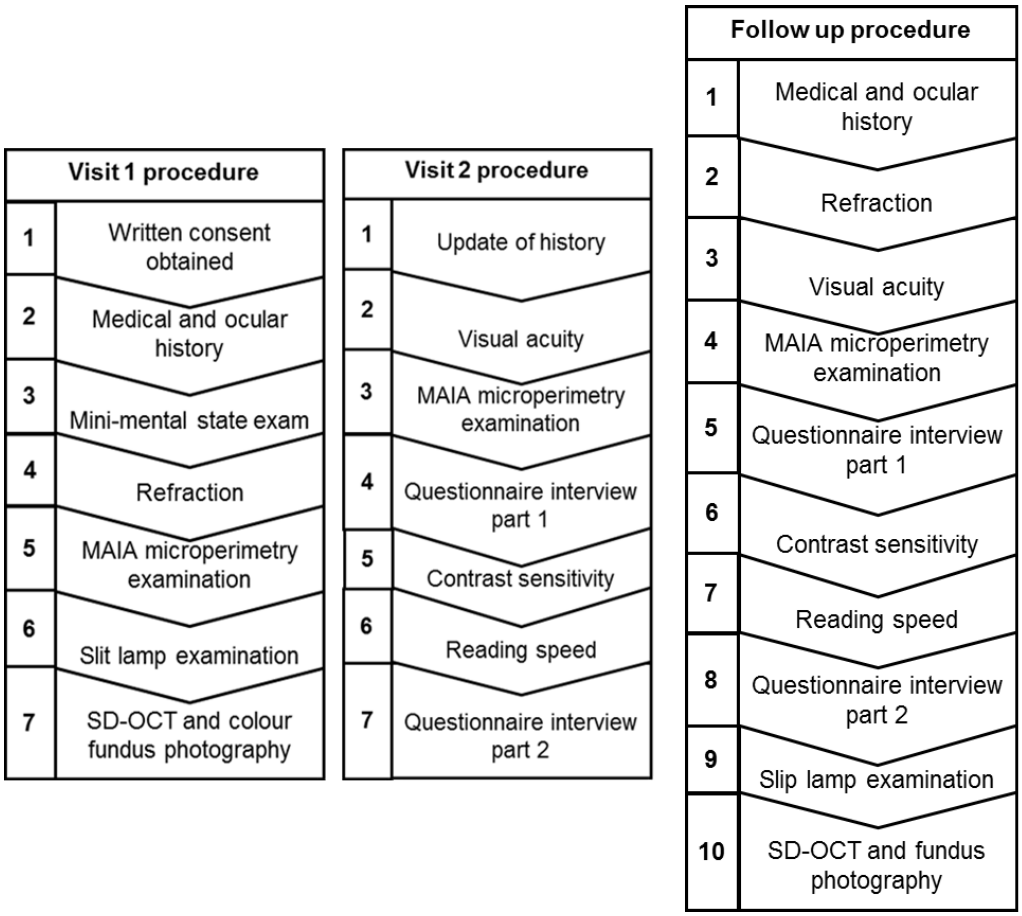


Figure 7.1 Assessments undertaken at baseline Visits 1 and 2 and the 1 year follow-up visit. Questionnaire interview part 1 consisted of IVI, EQ-5D and WEMWBS, and questionnaire interview part 2 consisted of VF-14, PHQ-9 and the modified TTO.

7.3.1 Analysis

Binocular measures of VA, CS and reading speed were used for the analysis.

7.3.1.1 Questionnaires

The WEMWBS and the IVI were assessed using the Rasch scoring tables produced in Chapter 6 (Section 6.4.3). The PHQ-9, EQ-5D and the modified TTO were scored as previously described (Section 3.3.3.2.3).

7.3.1.2 Imaging techniques

The colour fundus photographs were graded using the AREDS classification system (AREDS 2001). The SD-OCT volume scans were used to confirm and identify the presence of PEDs, intraretinal fluid and other retinal features associated with AMD (Section 3.3.3.1.8).

7.3.1.3 AMD severity

The severity of AMD was classified as mild, moderate or severe, using an established binocular classification system (Aspinall et al. 2007) (Section 6.3.1.3). Due to the limited number of individuals in the study, the three classifications were combined into a binary scale of Grade 1 mild or moderate classification, and Grade 2 severe classification.

7.3.1.4 Microperimetry

DLS results were transformed into right eye format. MAIA DLS results for those with foveal fixation were then converted into TD and PD values using the normative database developed in Chapter 4. The best MTD approach was implemented, whereby the eye with the best MTD was used to provide a binocular estimate for microperimetry (Arora et al. 2013). The microperimetry outcomes used in this analysis were MS, MTD and MPD.

7.3.1.5 Statistical analysis

The approach for statistical analyses was, firstly, an assessment for normality (Shapiro-Wilk test) of each of the variables, followed by a paired t-test between baseline and 1 year outcomes for each of the variables. A Spearman's rank correlation matrix of all variables was constructed, and lastly univariate linear regression and multiple linear regression, both with IVI as the dependent variable, were performed.

Distributions of the change in each variable were examined using the Shapiro-Wilk test for normality. Differences in measures between baseline and the 1 year follow-up were evaluated with a paired t-test for Gaussian data and the Wilcoxon test for non-Gaussian data.

A Spearman's rank correlation matrix was produced between the change in vision-related QoL and each of the baseline clinical, psychosocial-related and health-related measures, and between the change in each of the measures over the 1 year period. This process was performed to identify the significant correlations, which were further investigated with univariate linear regression, to find the strongest predictors of change in IVI score.

Any significant univariate predictors were then incorporated into a multiple linear regression. Several multiple linear regression models were developed in order to determine the strongest significant model of the change in IVI. The multiple regression models were limited to one factor per 10 participants as described in Section 5.3.1.3. The assumptions of each linear regression model were examined, as detailed in Section 4.3.1.1.

Statistical analyses were performed using R (Version 3.2.2) and SPSS (version 20.0). A p value of ≤0.05 was considered to be statistically significant. Bonferroni correction was not implemented in this analysis to avoid Type 2 errors and the loss of any real

affects within the analysis (Armstrong 2014), as detailed in Chapter 5. Descriptive data were reported using median (IQR) values.

7.4 **Results**

The following results are presented: firstly, the assessment of normality and the demographic characteristics of the individuals with AMD that attended the 1 year follow-up visit; secondly, the change in the clinical measures of visual function, vision-related QoL, depression, well-being and health status, between baseline and 1 year; and finally, the correlation, univariate regression and multiple regression analyses to explain the change in vision-related QoL.

7.4.1 Assessment of normality

The majority of outcomes were found to have a non-Gaussian distribution (change in: EQ-5D, PHQ-9, modified TTO, MS, VA, MTD and MPD, all $p<0.05$). Change in IVI was found to have a Gaussian distribution ($p=0.45$), as were change in CS ($p=0.12$), reading speed ($p=0.78$) and WEMWBS ($p=0.12$).

7.4.2 Characteristics

Of the 32 individuals, who were invited to return for the 1 year follow-up visit, 3 were unable to attend within the designated time scale of 1 year.

Twenty-nine individuals (18 females, 11 males) attended the 1 year follow-up visit. The characteristics of the 29 individuals are presented in Table 7.1. The majority of individuals had Grade 1 AMD (n = 18), and 41% were receiving treatment (n=12).

Variables	N=29
Age (years)	
Median age	78
IQR	74 – 84
Binocular AMD severity, n (%)	
Grade 1 (mild/mod)	18 (62.1)
Grade 2 (severe)	11 (37.9)
Duration of AMD, n (%)	
<2 years	14 (48.3)
>2 years	15 (51.7)
Current treatment, n (%)	
Yes	12 (41.4)
No	17 (58.6)
Living, n (%)	
Alone	12 (48.9)
Spouse/family	17 (58.6)
Number of comorbidities	
Median	3
IQR	2 – 4
Number of medications	
Median	4
IQR	1 – 6

Table 7.1 Characteristics of the 29 individuals with AMD, who attended the 1 year follow-up visit.

7.4.3 Change between baseline and the 1 year follow-up

The IVI score was not statistically different between baseline and the 1 year follow-up (paired t-test, p=0.52) (Figure 7.2). However, overall 15 people had a deterioration, 11 had an improvement and 3 had no change in IVI score between baseline and 1 year (Figure 7.3). Of those that deteriorated (below the line, Figure 7.3) 34% were not receiving treatment, and of those that had an improvement (above the line, Figure 7.3) 21% were receiving treatment.

The EQ-5D, PHQ-9, WEMWBS and modified TTO outcomes at the baseline and follow-up examination are shown in Table 7.2.

Examination of VA, CS and reading speed showed minimal change from baseline to follow up (Figure 7.4), which was not statistically significant (VA, p=0.39; CS, p=0.58; reading speed, p=0.73). Microperimetry outcomes worsened between baseline and

follow up visit, and MS and MTD worsened by a greater amount than MPD. The changes in all microperimetric outcomes were significant (all p<0.05) (Figure 7.5).

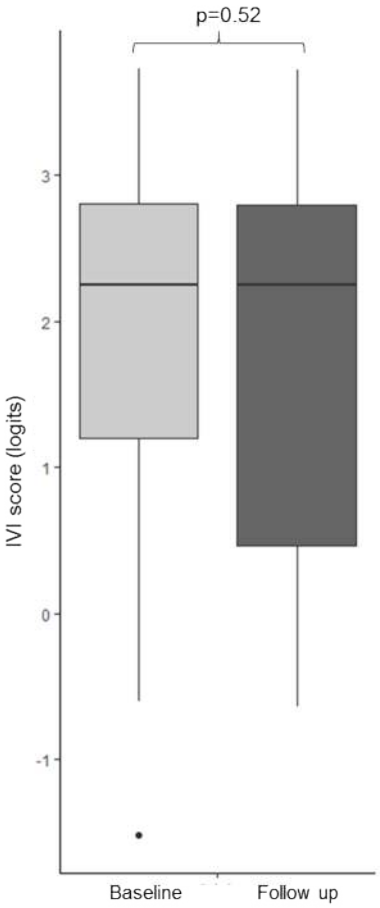


Figure 7.2 Baseline and follow up total scores for the Impact of Visual Impairment questionnaire (logits).Boxplot limits indicate the minimum, 1st quartile, median, 3rd quartile and maximum. Outliers are represented by a black circle.

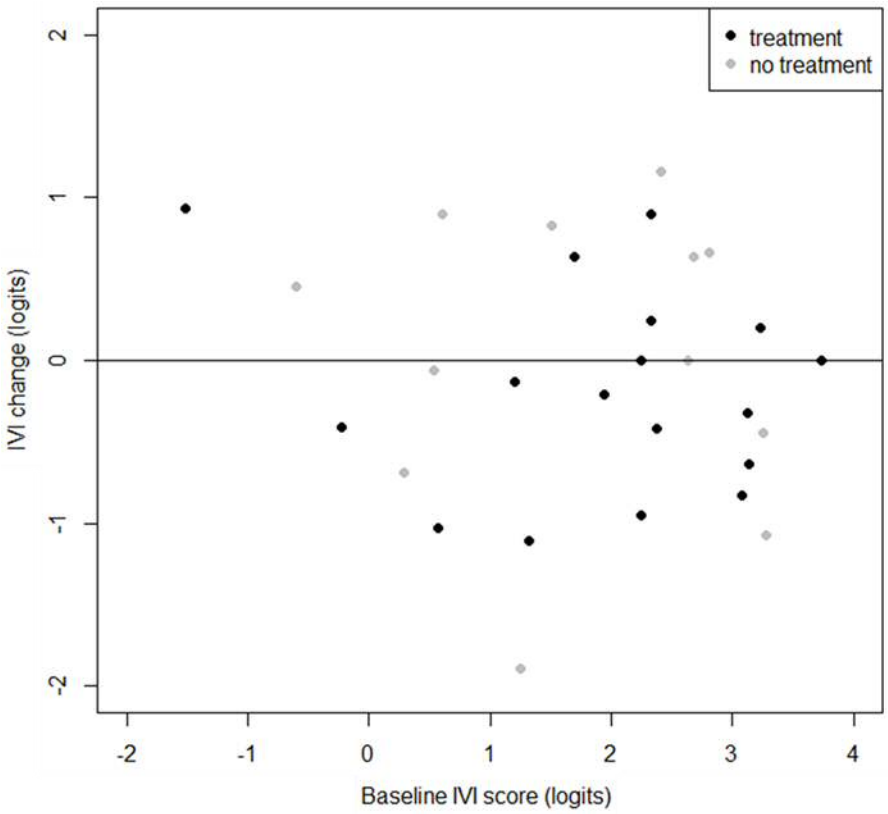


Figure 7.3 Scatter plot of change in IVI score (ordinate) as a function of baseline IVI score (abscissa), with those receiving treatment (black circle) and those not receiving treatment (grey circle) highlighted.

N=29	Baseline	Follow up	Change	p value
EQ-5D VAS, median (IQR)	80 (70, 94)	75 (60, 90)	-1.0 (-10.0, 7.8)	0.83
Range	9 - 100	45 - 100	-20.0 – 56.0	
EQ-5D index, median (IQR)	0.7 (0.7, 0.9)	0.7 (0.6, 0.8)	0.0 (-0.1,0.0)	0.06
Range	0.6 – 1.0	0.5 – 1.0	-0.2 – 0.3	
PHQ-9 total score, median (IQR)	3 (0, 7)	3 (0, 6)	0 (-2, 0)	0.39
Range	0 - 24	0 – 14	-10 – 7	
WEMWBS, median (IQR)	2.6 (1.6, 3.1)	2.0 (1.1, 3.2)	-0.3 (-0.9, 0.1)	0.27
Range	-0.9 – 4.7	0.2 – 3.9	-1.6 – 1.6	
Modified TTO, median (IQR)	1.0 (0.8, 1.0)	1.0 (0.5,1.0)	0.0 (-0.1, 0.0)	0.06
Range	0.0 – 1.0	0.0 – 1.0	-0.6 – 0.2	

Table 7.2 Median, interquartile range (IQR) and range for the baseline and follow up scores, and the median (IQR) of individual change in score for the EQ-5D, Patient Health Questionnaire (PHQ-9), Warwick-Edinburgh mental well-being scale (WEMWBS) and the modified time trade-off (TTO).

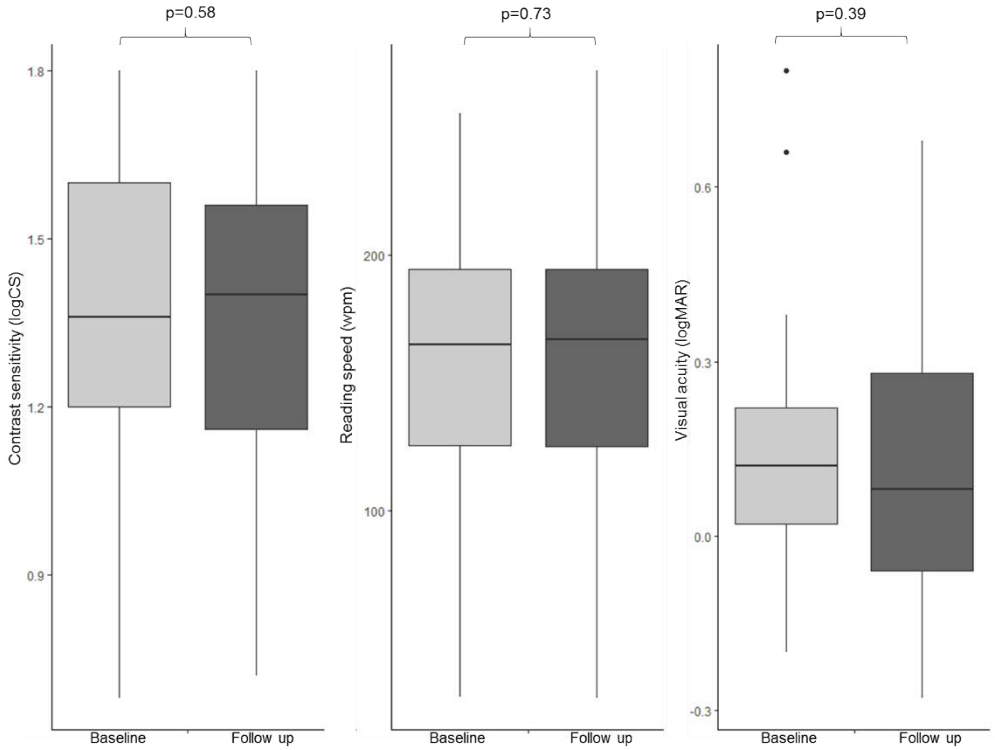


Figure 7.4 Baseline and follow up total scores for contrast sensitivity (left), reading speed (middle) and VA (right). Boxplot limits indicate the minimum, 1st quartile, median, 3rd quartile and maximum. An outlier is represented by a black circle.

7.4.4 Correlation and univariate linear regression

The Spearman's rho values for the association between change in IVI score, and baseline, and change in, clinical outcomes, health status, depressive symptoms and well-being are presented in Table 7.3. Baseline reading speed (p=0.03), CS (p<0.01), MS (p=0.02) and MTD (p=0.05) were all associated with change in total IVI score. The change in total IVI score was also significantly associated with change in VA (p=0.02), reading speed (p=0.05), MPD (p=0.03) and EQ-5D health index (p=0.03) (Table 7.3).

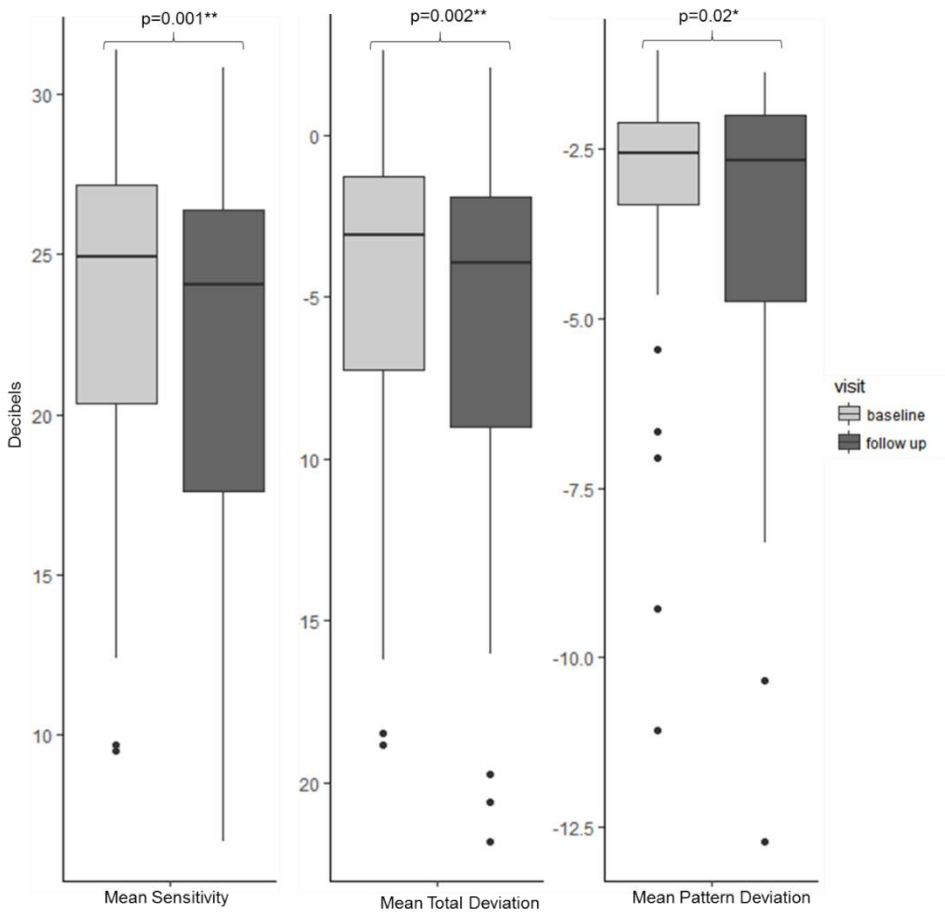


*Figure 7.5 Baseline and follow up total scores for MS (left), MTD (middle) and MPD (right). Boxplot limits indicate the minimum, 1st quartile, median, 3rd quartile and maximum, an outlier is represented by a black circle and Wilcoxon test p values * p<0.05, **p<0.01.*

	Baseline	Change
Age	-0.01	
VA	-0.36	0.45*
Reading	0.39*	-0.42*
CS	0.54**	0.05
MS	0.35*	-0.21
MTD	0.32*	-0.11
MPD	0.05	-0.47*
EQ-5D index	-0.32	0.31*
EQ-5D VAS	0.06	0.32
PHQ-9	0.12	-0.01
WEMWBS	-0.03	0.04

*Table 7.3 Spearman's rank correlation (rho values) of the associations between change in total IVI score, and baseline clinical and health-related outcomes: age, VA, reading speed, CS, MS, MTD, MPD, EQ-5D index value, EQ-5D visual analogue scale score (EQ-5D VAS), PHQ-9 and WEMWBS; as well as the association between the change in IVI score and change in the same outcome measures. *p<0.05 and **p<0.01*

The baseline and the change in depression and well-being measures were not significantly correlated with change in IVI score (both $p>0.05$). Age, AMD severity, EQ-5D visual analogue scale, and depression and well-being were not significantly correlated with change in IVI score and, therefore, were each eliminated from further analysis.

The significant associations were investigated further with univariate linear regression. Baseline CS was the strongest univariate predictor of change in IVI score ($R^2=0.36$). Baseline reading speed ($R^2=0.17$), baseline MS ($R^2=0.19$), change in reading speed ($R^2=0.14$) and change in EQ-5D score ($R^2=0.16$) were also significant univariate predictors of change in IVI score (Figure 7.6).

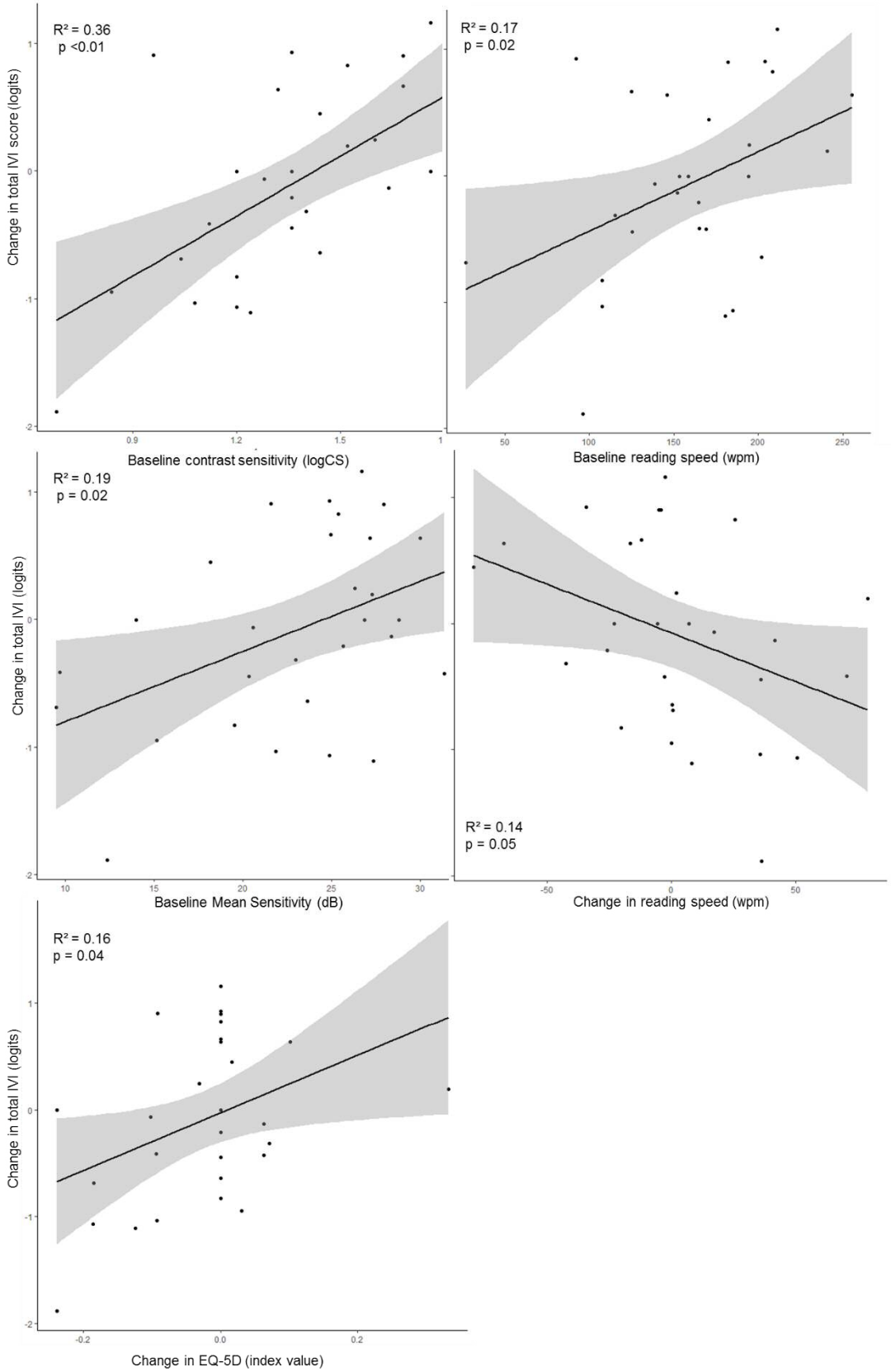


Figure 7.6 Univariate regression analysis to predict the change in total IVI score (ordinate) on the basis of baseline contrast sensitivity (top left), baseline reading speed (top right), baseline Mean Sensitivity (middle left), change in reading speed (middle right) and change in EQ-5D index value (bottom left) (abscissa). The grey shaded area represents the 95% confidence limits for linear regression.

7.4.5 Multiple linear regression analysis

Baseline CS was included in all multiple regression models, in combination with the other significant predictors of change in total IVI score. Each model was limited to a maximum of three predictors per model for n=29 (Section 5.3.1.3) (Altman 1991).

Baseline CS, change in reading speed and change in EQ-5D score were the strongest predictors of change in IVI score accounting for 43% of the variance (Table 7.4).

Model	Adj R^2	F	p	Variables in model	Coef	SE	t	p
IVI	0.43	(3,25) = 8.16	<0.01	RS change	-0.01	<0.01	-1.70	0.10
				EQ-5D change	-1.32	0.76	-1.72	0.10
				CS baseline	1.37	0.38	3.61	<0.01

Table 7.4 Multiple regression analysis to determine the predictors of the IVI total score. The following variables were included: change in reading speed (RS), change in EQ-5D and baseline contrast sensitivity (CS).

7.5 **Discussion**

The first aim of this study was to examine the change in vision-related QoL and the outcome measures over 1 year. Despite 52% of the individuals experiencing a deterioration in vision-related QoL, when examining the overall change in vision-related QoL there was no significant change at the 1 year follow-up. The microperimetry outcomes worsened significantly over the follow-up period, but all other outcome measures showed no significant change.

The second aim was to identify the factors that determine change in vision-related QoL over 1 year. CS at baseline, and change in reading speed and in EQ-5D index score can be used to identify change in vision-related QoL, in individuals with AMD. These key predictors explain a significant proportion (43%) of the variance in vision-related QoL. Interestingly, baseline CS was the strongest single predictor of change in IVI score, predicting 36% of the variance, whereby a lower CS score at baseline resulted in a worse IVI score at 1 year. This result is consistent with the concept that CS is more representative of daily visual function than VA (Owsley and Sloane 1987).

Reduced CS leads to difficulty with everyday vision-related tasks such as identifying faces, road signs and other objects (Owsley and Sloane 1987). Specifically, in those with macular disease CS is associated with vision-related QoL (Hazel et al. 2000) and the ability to perform tasks of daily living (McClure et al. 2000). However, these studies differed from the current study as they examined the association at a single time point rather than the change over 1 year.

In the present study, change in EQ-5D index score and change in reading speed both explained a proportion of the change in IVI score. The outcome for the EQ-5D is in agreement with previous findings that a change in an individual's health status affects vision-related QoL (Hernandez Trillo and Dickinson 2012). Additionally, reading ability is reduced in a high proportion of those with AMD (Crossland et al. 2007) and is also acknowledged to be of importance to those with visual impairment (Elliott et al. 1997). Reading ability has previously been associated with self-reported visual ability (McClure et al. 2000) and vision-related QoL in individuals with macular disease (Hazel et al. 2000).

To the author's knowledge, this was the first investigation to examine the association between microperimetry outcomes and longitudinal changes in vision-related QoL in individuals with AMD. The univariate model of baseline MS and change in IVI score was significant, whereby the lower the MS at baseline the larger the reduction in logit score for the IVI at 1 year. In glaucoma, more severe baseline defects were associated with greater change in vision-related QoL (Medeiros et al. 2015). However, in contrast to the current study, the change in MS predicted a change in the vision-related QoL (Medeiros et al. 2015). However, the omission of CS from the analysis of the previous study (Medeiros et al. 2015) was potentially a significant omission.

There was no relationship between baseline VA and the change in VA with vision-related QoL. This could be attributed to the large proportion of individuals receiving anti-VEGF treatment, and therefore, the increased likelihood of the maintenance of

vision over the follow-up period. Additionally, the well documented limitations of VA measurement and its lack of real world applicability may also be a further issue (Krezel, Hogg and Azuara-Blanco 2015). Moderate associations exist between change in VA and change in vision-related QoL, but these were determined over 24 months (Reeves et al. 2009), and between 10 and 15 years (Coleman et al. 2010), respectively.

It is anticipated that a long term follow-up study would confirm that individuals with the most profound change in AMD severity would be at risk of a larger reduction in IVI score (Coleman et al. 2010). The current study was limited by the size of the case series, and by the low proportion of individuals in the mild and moderate AMD severity group. The recruitment of individuals at earlier stages of the disease would provide a more even distribution of AMD severity within the case series. This would also enable more comprehensive analysis of the association between both baseline and change in AMD severity, and the change in IVI score. Additionally, the identification of those at risk of a reduction in QoL is limited given the lack of significant change in the IVI score over the one year follow up. Continuing the follow-up period for a longer period would likely yield greater change in the IVI scores and clinical measures of visual function. Such results would enable a more robust prediction of vision-related QoL change from clinical measures and more definitive clinical advice for practitioners.

This study provides evidence that change in vision-related QoL over 1 year can, to a significant extent, be explained by baseline CS. Changes in health status and reading speed over the same period of time also impact on the change in vision-related QoL. Whilst vision-related QoL is well-established as an important factor to the individual, its measurement is restricted to the use of questionnaires, which are rarely used in clinical practice. If a change in vision-related QoL can be predicted from less time-consuming clinical measures, then clinicians could use this information to identify

those who require additional or targeted assistance, such as additional support from rehabilitation services.

Chapter 8: Discussion and future work

8.1 Introduction

Vision-related QoL is arguably one of the most important factors in the management of those with AMD. Consequently, there is a clear need for an understanding of the clinical outcomes that influence vision-related QoL in order to inform management strategies. The importance of this research is further justified by the increasing prevalence of AMD, given the ageing population, and the associated economic and social burdens (Saxena et al. 2016; Day et al. 2011). The principle aim of this research was to determine the factors that predict QoL in those with AMD, both at baseline and after 12 months.

Summarised below are the major findings from each chapter, ideas for future work and the potential clinical implications.

8.2 Chapter 2: A systematic review evaluating the use of microperimetry in assessing visual function in AMD

The critical review of current literature on the use of microperimetry in assessing visual function in AMD provided promising evidence for its continued use in this disease, with the further development of implemented methodologies. AMD-related morphological changes such as disruptions of the EZ band and RPE, outer segment thinning and RPE thickening in early AMD, and retinal thickness changes in CNV are clearly associated with reduced DLS. However, there are limitations in this literature. Firstly, the lack of robust age-corrected probability analysis software in microperimetry is currently a major omission of the technique. Secondly, the quality of reporting in many studies lacks significant methodological detail, and although this has improved over time, it is a weakness of the current evidence.

8.3 Chapter 4: Development of a normative database using the Macular Integrity Assessment microperimeter and the application in AMD

The development of a pointwise age-corrected normative database for the MAIA microperimeter was a prerequisite to evaluating abnormality in AMD. The normative database enabled localised probability analysis and the consequent separation of focal from generalised functional loss, to determine abnormality by MAIA microperimetry in AMD and, subsequently, in other visual pathway diseases.

Two methods of developing a normative database were explored: the adjusted age method and the age-specific method. These methods resulted in differing outcomes from the same individuals with AMD. The adjusted age method detected defects at an earlier stage than the age-specific method. Further assessment of the sensitivity and specificity was beyond the scope of this study, but should be considered for future work. For the purpose of this thesis, the age-specific method was chosen for use in the chapters subsequent to Chapter 4, due to its appropriate statistical methodology.

8.4 Chapter 5: The association between microperimetry and SD-OCT outcomes

A secondary aim of the thesis was to examine the association between microperimetry outcomes and SD-OCT outcomes. Such an association was investigated at 5° eccentricity with respect to AMD-related microstructural changes.

Detailed topographical comparisons between microstructural changes and visual function measured by microperimetry were examined. The microperimetry outcomes (MS and MTD) were explained, to a large extent, by the presence of photoreceptor atrophy. However, this relationship was not sufficiently strong for microperimetry and SD-OCT to be interchangeable.

8.5 Chapter 6: The relationship between QoL and clinical outcomes in AMD

A primary aim was to investigate the factors that determine vision-related QoL in individuals with AMD. The microperimetry outcome, MTD, and level of depressive symptoms predicted, to a significant extent, vision-related QoL. It is already well established that depression affects QoL in AMD; however, the influence of a microperimetry outcome on QoL was a novel finding.

8.6 Chapter 7: The relationship between change in vision-related QoL and clinical outcomes: follow-up after 1 year

The investigation of the changes in clinical outcomes after 1 year and the factors that determine change in vision-related QoL over the same time period were examined. Baseline CS was the strongest univariate predictor of change in vision-related QoL. Multivariate analyses indicated change in vision-related QoL was explained by baseline CS and change in both health status and reading speed over the same period. These findings highlight the importance of CS in the consideration of vision-related QoL in those with AMD. Additionally, health status should be recognised as important in the assessment of change in vision-related QoL.

8.7 Future work

The strengths and areas in which the current research could be improved upon are summarised briefly and the potential for future work is discussed herein.

Key strengths of this thesis include: the acquisition of high quality clinical data both from healthy individuals and individuals with AMD; the implementation of a normative database in the analysis of microperimetry data; the consideration of appropriate regression techniques for each study; the use of Rasch analysis, where appropriate,

to enable robust statistical analysis of questionnaire data; the longitudinal evaluation of vision-related QoL and clinical outcomes over 1 year; and the successful recruitment, to target, of individuals with AMD.

Recruitment targets were met with respect to the sample size calculations within each of the studies of this thesis. However, the spread of individuals in the case series was limited in terms of the proportion with mild to moderate AMD. Targeted recruitment of individuals at earlier stages of the disease would provide a more evenly distributed case series. Such an extension would enable improved understanding of the relationship between clinical measures and QoL outcomes with respect to AMD severity.

Another improvement to the present research would be the extended duration of the follow-up period from a medium-term period of 1 year to a long-term period. This would be expected to yield more profound changes in vision-related QoL and clinical outcome measures, in order to examine patterns of long-term change in vision-related QoL. Such findings have the potential to validate the current results with greater statistical confidence.

8.7.1 Normative databases

Normative databases for clinical instruments are essential in the definition of abnormality. However, they are usually a costly and time consuming process to derive as a consequence of the requirement for a large number of normal individuals, usually over a number of research centres. The HFA normative database, for example, was collected over 4 sites and included over 400 visual field examinations (Heijl, Lindgren and Olsson 1987a). The study presented in Chapter 4 was a single centre study with minimal resources and, therefore, the sample size reflected this. Future normative databases could be compiled from a number of independent small scale studies to increase the sample size, which would avoid the large financial disadvantage of multicentre studies.

It is standard within the visual field literature to discard data collected from the initial visits, in an attempt to reduce the learning effect. However, an alternative approach would be to collect and derive a normative database for each visit, which takes into account the difference in variability at each visit. This would require a large number of individuals to complete examinations on a number of consecutive examinations and also at set time periods, and therefore, would be a timely and costly process. Nevertheless, with a number of independent small scale studies, the time and cost could be shared and collaborations encouraged.

8.7.2 Scotopic microperimetry

The development of scotopic microperimetry has enabled detailed research relating specifically to the rod photoreceptors (Steinberg et al. 2016; Steinberg et al. 2015a; Pfau et al. 2017). A combination of mesopic and scotopic microperimetry would enable examination of both rod and cone function with respect to retinal microstructure changes. Rods are known to be affected before cones in early AMD (Curcio, Owsley and Jackson 2000), and rod function, as measured by scotopic microperimetry, is affected in the presence of RPD (Steinberg et al. 2015a) and hard drusen (Nebbioso, Barbato and Pescosolido 2014). It would be of interest to investigate rod and cone function, by microperimetry, in a full range of AMD severities across the entire macular area, to enable the localisation of the deterioration of rod and cone function.

8.7.3 Personality types

The multidimensionality of QoL creates difficulties in determining predictors of an individual's QoL. Economic situation and years of education are commonly considered in relation to QoL (Coleman et al. 2010; Brody et al. 2001; Hernandez Trillo and Dickinson 2012). These factors, combined with the individual's overall outlook on life, could influence how the questionnaires were answered. Previous research in glaucoma suggests that personality types are associated with vision-

related QoL (Warrian et al. 2009). Personality dimensions are also determinates of QoL in systemic diseases (Weber et al. 2015; Harper et al. 2014; Boyette et al. 2014). This would be an interesting concept to investigate in those with AMD, and may account for a larger proportion of the variance in vision-related QoL.

8.7.4 Minimal important differences for quality-of-life

Measures of QoL are currently not widely used in a clinical setting due to their time consuming nature. An additional limitation is the lack of information regarding the smallest change in self-reported QoL that an individual distinguishes as important, either positively or negatively. Minimal important difference (MID) is an index that represents such a quantification (Johnston et al. 2015).

MID is based upon normal values for the questionnaire of interest (Johnston et al. 2015). The MID is compared to the disease group mean difference to give a magnitude of difference, which can be used to make clinical decisions (Johnston et al. 2016). To the author's knowledge, MIDs have not previously been studied in individuals with AMD. Such studies could inform the selection of outcomes for clinical trials in which the quantification of the effect of an intervention is required. Furthermore, in everyday clinical practice, in which management decisions are required, quantification of vision-related QoL in terms of cut-off values of "good" or "bad", would allow for more informed decisions. The availability of such information could aid the clinician in making well-informed management decisions.

8.8 **Summary**

This research has showed promising results when investigating the predictors of vision-related QoL in individuals with AMD. Baseline vision-related QoL was predicted by a microperimetry outcome and the presence of depressive symptoms. This finding is strengthened by the inclusion of robust methods of analysing microperimetry data using an age-corrected normative database. Further clinical implications are firstly,

the questionable utility of the widely used clinical measure of visual function, VA, when assessing vision-related QoL. Secondly, the results emphasise the clinical application of microperimetry and support its adoption into clinical practice. Thirdly, the findings further reinforce the emerging clinical opinion that depressive symptoms should be considered in those with AMD.

When examining change in vision-related QoL after 1 year, baseline CS was a significant predictor of change in IVI score as was, to a lesser extent, the changes in health status and in reading speed. These outcomes support previous research that highlights the importance of CS when assessing 'real world' functionality and vision-related QoL. However, CS is still not a commonly used measure within clinical environments and the results further strengthen the evidence for the increased clinical use of CS.

Overall, the findings provide an evidence base for the most clinically useful measures of visual function in identifying those with a reduced QoL or those at risk of a reduced QoL. This implies that greater importance should be placed upon CS in the clinical setting. An increased use of microperimetry would provide a clinical measure of visual function that is relevant to vision-related QoL. It is also clear that both depressive symptoms and health status are important outcome measures and both should be measured within a clinical setting.

In conclusion, this thesis has provided sufficient evidence to encourage a modification of the clinical outcome measures most relevant to vision-related QoL and most appropriate for clinical practice. Vision-related QoL can, to a significant extent, be predicted from less time-consuming clinical measures, and therefore, clinicians should use this information to aid management decisions, such as referral to rehabilitation services.

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Appendix A: Published systematic review

ARTICLE IN PRESS

SURVEY OF OPHTHALMOLOGY XXX (2017) 1–16

Available online at www.sciencedirect.com

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Survey of Ophthalmology

Major review

The use of microperimetry in assessing visual function in age-related macular degeneration

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ARTICLE INFO

Article history:
Received 20 January 2017
Received in revised form 22 May 2017
Accepted 25 May 2017
Available online xxx

Keywords:
microperimetry
age-related macular degeneration
optical coherence tomography
visual function
systematic review

ABSTRACT

Microperimetry is a novel technique for assessing visual function and appears particularly suitable for age-related macular degeneration (AMD). Compared with standard automated perimetry, microperimetry offers several unique features. It simultaneously images the fundus, incorporates an eye-tracking system to correct the stimulus location for fixation loss, and identifies any preferred retinal loci. A systematic review of microperimetry in the assessment of visual function in AMD identified 680 articles. Of these, 52 met the inclusion criteria. We discuss microperimetry and AMD in relation to disease severity, structural imaging outcomes, other measures of visual function, and evaluation of the efficacy of surgical and/or medical therapies in clinical trials. The evidence for the use of microperimetry in the functional assessment of AMD is encouraging. Disruptions of the ellipsoid zone band and retinal pigment epithelium are clearly associated with reduced differential light sensitivity despite the maintenance of good visual acuity. Reduced differential light sensitivity is also associated with outer segment thinning and retinal pigment epithelium thickening in early AMD and with both a thickening and a thinning of the whole retina in choroidal neovascularization. Microperimetry, however, lacks the robust diffuse and focal loss age-corrected probability analyses associated with standard automated perimetry, and the technique is currently limited by this omission.

1. Introduction

Age-related macular degeneration (AMD)[1] is the leading cause of blindness in the developed world[66] and accounts for the majority of registrable visual impairment in both the USA and the UK.[10,37,54] Visual acuity (VA) is the most widely used outcome measure in ophthalmic research; however, VA is insufficiently sensitive to detect the early stages of functional loss in AMD.[42,50] Various other tests of visual function, such as dark adaptation,[46] flicker threshold,[15] and photostress recovery time[44] are more sensitive than VA in detecting early functional loss in AMD; however, such tests have limited clinical utility because they are time consuming.[44] There is, therefore, a need for a robust and clinically appropriate technique to assess visual function across the macula that is more indicative than VA.

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0039-6257/$ – see front matter © 2017 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.survophthal.2017.05.007

Microperimetry is similar to standard automated perimetry in that it measures the differential light sensitivity (DLS), that is, the minimum luminance of a white-spot stimulus superimposed on a white background of uniform luminance necessary to perceive the stimulus. Microperimetry, however, is novel in that it uses an eye-tracking system to correct the position of the stimulus for any changes in fixation. Such a correction is particularly appropriate in the later stages of macular disease where unsteady fixation and/or a preferred retinal locus are common. Microperimetry offers the additional benefit of providing a real-time en-face image of the posterior pole. The latter is of value in macular disease as it enables direct comparison between the visual function outcome and the underlying fundus appearance.[2]

The concept of microperimetry was initially introduced clinically in 1981.[67] Currently, there are 2 commercially available microperimeters: the Nidek MP-3 (Nidek Technologies, Padova, Italy) and the Macular Integrity Assessment microperimeter (MAIA, CentreVue, Padova, Italy). These instruments have an improved dynamic range of 34 dB (maximum stimulus intensity of 3183 cdm^{-2}) for the MP-3 and 36 dB (318 cdm^{-2}) for the MAIA, compared with 20 dB for the 2 earlier commercially available instruments, the MP-1 (128 cdm^{-2}) and the Optos optical coherence tomography (OCT) scanning laser ophthalmoscope (SLO) (Optos, Dunfermline, Scotland, UK) (125 cdm^{-2}). The background luminance for the MAIA is 1.27 cdm^{-2}, whereas the MP-3 offers the option of either 1.27 cdm^{-2} or 10 cdm^{-2}. The technical specifications of the current and earlier microperimeters are reviewed in detail elsewhere.[40] The eye-tracking systems automatically register the eye position 25 times per second relative either to given anatomic landmarks (MP-3) or to each pixel of the fundal image (MAIA).

Mean sensitivity (MS) is the most common outcome measure in microperimetry and is defined as the mean of the DLS obtained across all the designated stimulus locations; however, the MS is a summary measure and does not account for the decline in DLS with age. Less common, but more appropriate, outcome measures for microperimetry are the total deviation (TD), defined as the difference between the DLS at a given stimulus location and the corresponding age-corrected normal value, and the mean deviation, defined as the arithmetic mean of the TD obtained across all the designated stimulus locations. A worsening of visual function is indicated by an increasingly less-positive MS and by an increasingly negative TD and mean deviation.

Given that the microperimetry is novel and that the design features appear particularly suitable for assessing visual

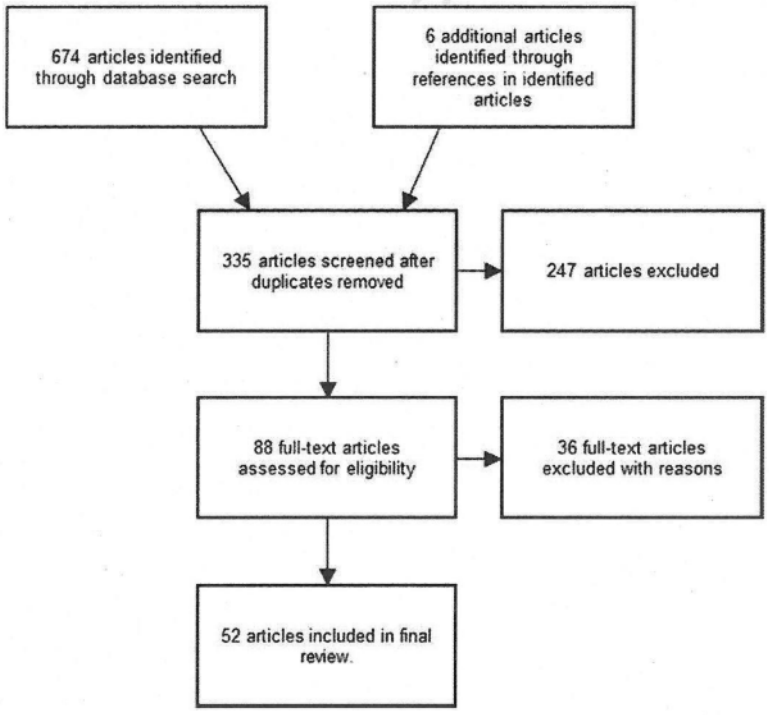

Fig. 1 – A flow diagram demonstrating the primary identified articles and those included and excluded at each stage of the literature review. Adapted from PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis).

Table 1 — Quality of evidence of the 52 included articles

Reference	Author and year	Study design	AMD identification and classification	DLS measures used	Quality of evidence
3	Acton et al, 2012	Observational: case-controlled	Early AMD: International Classification and Grading System	MS (68 locations within 10°), number of TD defects, MD, and PSD (derived from previous normative data)	High
11	Chandramohan et al, 2016	Observational: case-controlled	Early and intermediate AMD: AREDS classification (grades 2 and 3)	MS (37 locations within 5°), central MS (foveal locus and 12 locations at 1°), and percentage reduced threshold (under 25 dB)	High
18	Ergun et al, 2003	Observational: case series	nAMD: identified by FA	Size of absolute and relative scotoma	High
20	Forte et al, 2013	Observational: case series	GA: identified with color fundus photography	MS (49 locations within 3.5°), dense scotoma (0 dB), and relatively dense scotoma (<5 dB)	High
27	Harini et al, 2016	Observational: cross-sectional	Early-to-late AMD (GA): identified and classified by OCT (presence of drusen = intermediate, GA larger than 0.1 = GA)	MS (in different zones associated with GA)	High
34	Iwama et al, 2010	Observational: case series	Soft confluent drusen: International Classification and Grading System	MS (57 locations over 10°, in central 2° and at specific locations with pathomorphology)	High
43	Munk et al, 2013	Experimental: quasi-experiment (interrupted time series)	nAMD: naïve to treatment, identified with FA	MS (ETDRS grid areas), number of absolute scotoma (0 dB), severe relative scotoma (1–6 dB), mild relative scotoma (7–12 dB), and normal (>13 dB) were counted.	High
48	Ozdemir et al, 2012	Experimental: quasi-experiment (interrupted time series)	nAMD: identified with FA and OCT	MS (12 locations within 4°) and number of absolute scotoma (0 dB) from all 76 stimulus locations within 20°	High
49	Parisi et al, 2007	Observational: case-controlled	Early AMD: classified by Wisconsin Age-related Maculopathy Grading System	Central MS (4 locations within 2.5°) and paracentral MS (28 locations in annuli between 2.5° and 5°)	High
53	Querques et al, 2012	Observational: cross-sectional	Early-to-late AMD (GA): presence of soft indistinct drusen with RPE changes, and/or GA, identified with color fundus photography	MS (49 locations within 4.5°), pointwise DLS (at specific locations with pathomorphology)	High
56	Sato et al, 2015	Observational: cross-sectional	nAMD: identified by OCT and FA	MS and median DLS (29 locations within 10°)	High
57	Sayegh et al, 2014	Observational: case series	GA: identified by fundus examination	Pointwise DLS (at specific locations with pathomorphology)	High
62	Sulzbacher et al, 2015	Experimental, quasi-experiment (interrupted time series)	nAMD: naïve to treatment, identified with FA	MS (33 locations within 6°), pointwise DLS (at specific locations with pathomorphology)	High

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Table 1 – (continued)

Reference	Author and year	Study design	AMD identification and classification	DLS measures used	Quality of evidence
65	Vujosevic et al, 2011	Observational: case-controlled	Early-to-intermediate AMD: AREDS classification (stages 2–3)	MS (61 locations within 5°), K value: total number of locations <24 dB, pointwise DLS	High
68	Weigert et al, 2013	Experimental, RCT	Early-to-late AMD (GA): AREDS classification (stages 2, 3, and 4)	MS (41 locations within 6°)	High
69	Wu et al, 2013	Observational: case-controlled	Intermediate AMD: Beckman classification	MS (37 locations within 6°), pointwise DLS	High
72	Wu et al, 2014a	Observational: cross-sectional	Intermediate AMD: Beckman classification	Pointwise DLS (at specific locations with pathomorphology) and Z score (average of 2 examinations in relation to normative data)	High
70	Wu et al, 2014b	Observational: case-controlled	Intermediate AMD: Beckman classification	MS (corresponding to mfERG hexagons)	High
71	Wu et al, 2014c	Observational: cross-sectional	Intermediate AMD: Beckman classification	MS (5 locations within central 1°)	High
74	Wu et al, 2015a	Observational: cross-sectional	Intermediate AMD: Beckman classification	MS (associated with groups of AMD pathology severity) and pointwise DLS (at specific locations with pathomorphology)	High
73	Wu et al, 2015b	Observational: longitudinal case-controlled	Intermediate AMD: Beckman classification	MS (37 locations within 6°) and pointwise DLS	High
75	Wu et al, 2015c	Observational: cross-sectional	Intermediate AMD: Beckman classification	MS (25 locations within 4°)	High
76	Wu et al, 2016a	Observational: longitudinal case series	Intermediate AMD: Beckman classification	MS (37 locations within 6°), MS within EDTRS grid sections	High
77	Wu et al, 2016b	Observational: cross-sectional	Intermediate AMD: Beckman classification	MS (37 locations within 6°) and central MS (5 locations within 1°)	High
5	Amore et al, 2013	Observational: case series	AMD: with absolute scotoma and central fixation identified by microperimetry	Global MS and central MS. Size (in degrees) of central spared area (ring scotoma patients)	Medium "central vision area" DLS definition not reported AMD: not stated method AMD is classified
9	Bolz et al, 2010	Experimental: quasi-experiment (interrupted time series)	nAMD: naive to treatment	MS (foveal locus and circle of locations at 3.5°)	Medium OCT: boundaries used to define central retinal thickness not reported AMD: method nAMD is identified not stated
12	Chieh et al, 2008	Experimental: quasi-experiment	nAMD	Median DLS within surgery areas and number of areas with absolute scotoma (<0 dB)	Medium AMD: method nAMD is identified not stated
13	Cho et al, 2013	Experimental: quasi-experiment (interrupted time series)	nAMD: naive to treatment, identified by FA and/or OCT	MS (28 locations within 6°)	Medium OCT: boundaries used to define central retinal thickness not reported

17	Dunavoelgyi et al, 2011	Experimental: RCT	nAMD: naive to treatment	MS (41 locations within 6°), number of locations, and size of absolute scotoma (0 dB) and relative scotoma (<10 dB)	Medium	AMD: method nAMD is identified not stated
22	Fujii et al, 2003	Observational: cross-sectional	nAMD: identified by FA	Percentage presence of dense central scotoma (defined as having >3 locations of <0 dB within 1.5°)	Medium	Microperimetry: stimulus location pattern and stimulus details not reported
25	Grenga et al, 2013	Experimental: quasi-experiment (interrupted time series)	nAMD: naive to treatment	MS (45 locations over 10°), number of absolute scotoma locations	Medium	Microperimetry: absolute scotoma definition not reported AMD: method nAMD is identified not stated
29	Hartmann et al, 2015	Experimental: quasi-experiment (interrupted time series)	nAMD: presence of >250 μm retinal thickness, subretinal fluid or PED	MS (24 locations within 10°)	Medium	OCT: boundaries used to define retinal thickness not reported
32	Huang et al, 2015	Experimental: RCT	Early AMD: AREDS classification (grade 2)	MS (average DLS at 1°, 3°, and 5° from fixation)	Medium	Microperimetry: stimulus pattern not reported
35	Kiss et al, 2009	Experimental: quasi-experiment (interrupted time series)	nAMD: identified with FA	MS (25 stimulus locations within 7.9°), central 0°, paracentral 3.5°, and eccentric 7.9° MS and absolute scotoma size.	Medium	Microperimetry: absolute scotoma definition and mode of analysis not reported
38	Landa et al, 2011	Observational: cross-sectional	Early-to-late AMD (GA): drusen or atrophic changes, and nAMD: CNV, intraretinal/subretinal fluid and hemorrhages	MS (28 locations), pointwise DLS	Medium	Microperimetry: Stimulus degrees not reported AMD: method AMD is identified or classified not stated
41	Mettu et al, 2011	Experimental: quasi-experiment (interrupted time series)	nAMD: identified with FA	Median DLS (30 locations) and percentage nonresponse (<0 dB)	Medium	Microperimetry: stimulus degrees not reported
45	Ooto et al, 2015	Observational: cross-sectional	Early-to-late AMD (GA): AREDS classification (2, 3, or 4)	MS (29 locations within 20° and parafovea: central 9 locations)	Medium	Microperimetry: how stimulus pattern not reported
52	Pilotto et al, 2016	Observational: case series	GA: identified from fundus examination	MS and number of locations with relatively dense scotoma (≤5 dB)	Medium	Microperimetry: stimulus pattern and degrees not reported
51	Pilotto et al, 2011	Observational: cross-sectional	GA: identified from fundus examination	MS (customized grid within 8° including all areas of GA), divided into 3 groups based on MS, relative and dense scotoma rate	Medium	Microperimetry: relative scotoma definition not reported
55	Sabour-Pickett et al, 2013	Experimental: quasi-experiment (interrupted time series)	nAMD: identified with FA	MS (fixation, central 5° and all 21 locations within 16°)	Medium	OCT: retinal boundaries used were "thickness between outer most boundaries of scan" however, these are not specified.

(continued on next page)

Table 1 — (continued)

Reference	Author and year	Study design	AMD identification and classification	DLS measures used	Quality of evidence
59	Steinberg et al, 2016	Observational: case-controlled	Early or intermediate AMD with reticular pseudodrusen: Beckman classification and IR images	MS (56 locations) of areas with RPD compared with areas without (scotopic and mesopic)	Medium Microperimetry: stimulus degrees not reported
60	Sulzbacher et al, 2012	Observational: case series	nAMD: identified with color fundus photography, OCT, and FA	MS (33 locations within 6°), pointwise DLS (at specific locations with pathomorphology)	Medium Microperimetry: "central retinal sensitivity" definition not reported
61	Sulzbacher et al, 2013	Experimental, quasi-experiment (interrupted time series)	nAMD: naïve to treatment, identified with color fundus photography, OCT, and FA	MS (33 locations within 6°), pointwise DLS (at specific locations with pathomorphology)	Medium OCT: pathomorphology used within analysis not defined and method of identification not reported
63	Takahashi et al, 2016	Observational: cross-sectional	GA: identified by fundus examination	MS (57 locations within 10° and over specific areas of retinal damage)	Medium Microperimetry: stimulus pattern not reported
23	Giacomelli et al, 2013	Observational: cross-sectional	Advanced AMD	MS (19 locations over 10°)	Medium AMD: method AMD is identified or classified not stated
28	Hartmann et al, 2011	Observational: case-controlled	Early-to-late AMD (GA): presence of drusen on fundus examination	Ranked DLS threshold values and MS (28 locations within 10°), pointwise DLS overlying drusen	Medium AMD: method AMD is classified not stated
30	Hautamaki et al, 2014	Observational: cross-sectional	nAMD: naïve to treatment	MS and ranking order of DLS (28 locations within 7.5°)	Medium AMD: method AMD is identified not stated
4	Alexander et al, 2012	Experimental: quasi-experiment (interrupted time series)	nAMD: enrolled from anti-VEGF clinic	MS, macular integrity index (MAIA software)	Poor Confusing terminology (stable and unstable used to refer to both fixation and AMD status) Microperimetry: stimulus pattern, number of locations, algorithm and stimulus details not reported OCT: scan details not included and boundaries used to define retinal thickness not reported AMD: how nAMD is identified not stated
6	Anastassiou et al, 2013	Experimental: RCT	Early-to-late AMD (GA): AREDS classification (grades 2,3 and 4)	MS (37 locations within 10°)	Poor Microperimetry: stimulus pattern, algorithm and stimulus details not defined OCT: scan details not included and method of measuring retinal and choroidal thickness not reported

16	Dinc et al, 2008	Observational: case-controlled	Intermediate AMD: AREDS classification (grade 3)	MS (76 locations within 10°) and mean defect	Poor Microperimetry: mean defect derivation not reported, assumed it is from MP-1 software, stimulus pattern not reported OCT: scan details not included and boundaries used to define central retinal thickness not reported
33	Iaculli et al, 2015	Experimental: quasi-experiment (interrupted time series)	nAMD: identified by OCT and FA	MS (8°)	Poor Microperimetry: stimulus pattern and details not defined OCT: scan details not included and boundaries used to define central retinal thickness not reported
39	Lazzeri et al, 2015	Experimental: quasi-experiment (interrupted time series)	nAMD: identified with FA	MS (33 locations within 6°)	Poor Confusing terminology: both "mean central retinal sensitivity" and "mean retinal sensitivity" used; and "central retinal thickness" and "central macular thickness" both used. Difference in terms not reported. Microperimetry: stimulus pattern and details not reported OCT: scan details not included and boundaries used to define central retinal thickness not reported

AMD, age-related macular degeneration; AREDS, Age-related Eye Disease Study; DLS, differential light sensitivity; ETDRS, Early Treatment Diabetic Retinopathy Study; FA, fluorescein angiography; GA, geographic atrophy; MD, mean deviation; MS, mean sensitivity; nAMD, neovascular AMD; OCT, optical coherence tomography; PSD, pattern standard deviation; TD, total deviation.

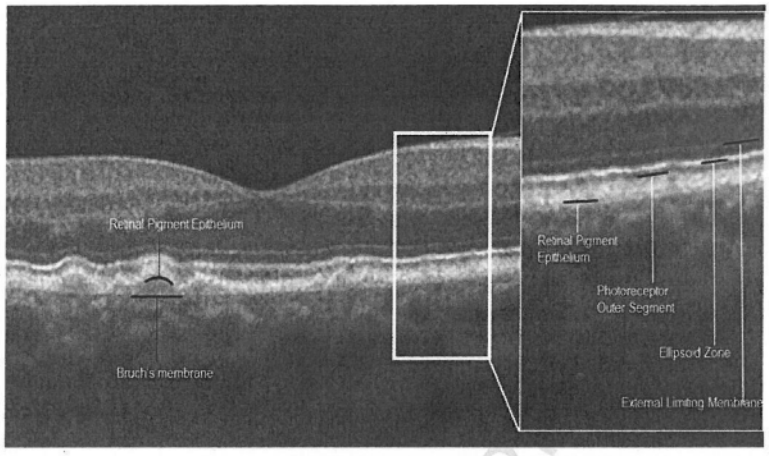

Fig. 2 – SD-OCT horizontal line scan of an eye with AMD. Right: The external limiting membrane, ellipsoid zone, photoreceptor outer segment, and retinal pigment epithelium are highlighted by the 3 black lines which are continuous with the respective layers. Left: The separation of the RPE from Bruch's membrane due to drusen. AMD, age-related macular degeneration; RPE, retinal pigment epithelium; SD-OCT, spectral-domain optical coherence tomography.

function in AMD, we undertook a systematic review to evaluate the literature relating to the use of microperimetry for assessing visual function in AMD.

2. Results

The search identified 674 primary articles. Six additional articles were obtained from the references within the primary retrieved articles. The final number of included articles was 52 (Fig. 1).

We divided our review into 4 principal areas that reflected the content of the included articles: evaluation of the efficacy of microperimetry in distinguishing between the various stages of AMD severity (4 articles), the relationship between microperimetry outcomes and structural imaging outcomes (including spectral-domain optical coherence tomography [SD-OCT]) (21 articles), the relationship between microperimetry outcomes and those of other measures of visual function (12 articles), and microperimetry outcomes in the evaluation of the efficacy of medical therapy and/or surgical intervention in the treatment of AMD (17 articles).

2.1. *Quality of evidence*

The quality of each of the 52 included articles is described in Table 1, which is ordered by quality of evidence. The studies were classified as either experimental or observational. Within these 2 classifications, experimental studies were classified as either randomized control trial (RCT) or as nonrandomized design, which will be referred to as quasi-experimental. Observational studies were classified as cross-sectional, case-controlled, or case series. None of the included studies were cohort studies. Assessment of the quality of reporting showed that over half the articles included in this review had limitations relating to the quality of the microperimetry outcome (18 articles) and/or to the reporting of the SD-OCT methods and analysis (11 articles). The reporting of microperimetry stimulus parameters was also generally poor, particularly in regard to the description of the stimulus program (i.e., the number, the location, and the separation, of the stimuli).

The method of classification of AMD severity varied between the various studies and limited the meaningful

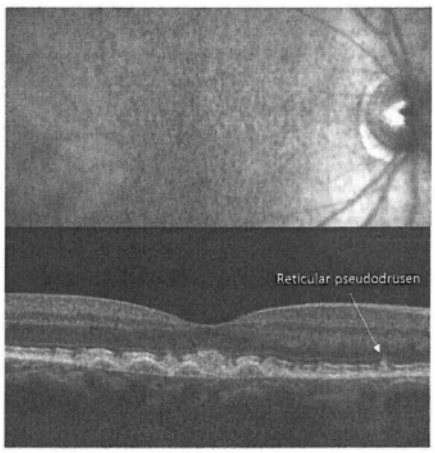

Fig. 3 – Top: IR image and Bottom: SD-OCT horizontal line scan of an eye with AMD exhibiting a reticular pseudodrusen. AMD, age-related macular degeneration; SD-OCT, spectral-domain optical coherence tomography.

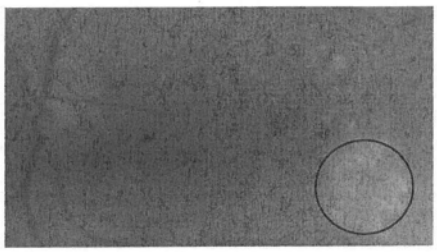

Fig. 4 – Color fundus photograph of an eye with AMD exhibiting drusen and an area of GA (circled) with visible choroidal vessels. AMD, age-related macular degeneration; GA, geographic atrophy.

comparisons between studies. These comprised the AREDS grading system[7] (7 articles), the Beckman classification[19] (9 articles), the Wisconsin Age-related Maculopathy Grading system[36] (1 article), and the International Classification and Grading system[8] (2 articles). Consequently, the classification method used in each study is noted, where appropriate, throughout this review.

Similarly, the difference in the stimulus parameters and also in the dynamic range between the various microperimeters used hinders direct comparisons of DLS between studies.[1] Microperimetry was undertaken by the Nidek MP1 or MP1-S in 29 of the 52 included articles[3,5,9,12,16,17,23,25,32–35,39,41,43,45,48,49,51,52,55–57,59–63,68] by the Nidek MP3 in 1,[27] by the MAIA in 13,[4,6,11,65,69–77] by the Optos Spectral OCT/SLO in 7[13,20,28–30,38,53] and by the Rodenstock SLO microperimeter in 2 articles.[18,22] The limited dynamic range of the previously available Optos OCT SLO and Nidek MP-1 microperimeters arising from the lower maximum stimulus luminance results in ceiling and floor effects compared with the MAIA and MP-3 microperimeters.[40] In particular, the presence of a floor effect can result in underestimation of the depth of the field loss. Consequently, the type of microperimeter is specified whenever the perimetric outcome is given in decibels (dB).

2.2. *Microperimetry and AMD severity*

Four of the 52 included articles evaluated the efficacy of microperimetry in distinguishing between the various stages of AMD severity.[16,22,65,69] Microperimetry with the MAIA is able to discriminate between normality and early and intermediate stages of AMD (Age-related Eye Disease Study, AREDS,[7] grades 2 and 3, respectively) when considered both in terms of the group mean MS and of the DLS derived at individual locations.[65] In the largest study of this kind to date, the group of 200 normal individuals exhibited the highest MS (mean 29.8 dB; SD 1.7), whereas within the group of 200 individuals with AMD, the MS for those with early AMD was larger (mean 24.9 dB; SD 3.9) than for those with intermediate AMD (mean 21.8 dB; SD 5.4—all $P < 0.001$).[65] A comparable, but earlier, study of 30 individuals found a statistically significant worsening of both the group MS and the group mean deviation for intermediate AMD (AREDS grade 3) compared with normal individuals.[16] For both these studies, the magnitudes of the group mean MS reflected the severity of the structural classification of AMD; however, the magnitudes of the standard deviations associated with the group mean MS indicated overlap between groups. In addition, no criteria for microperimetry were given for the optimal differentiation, on an

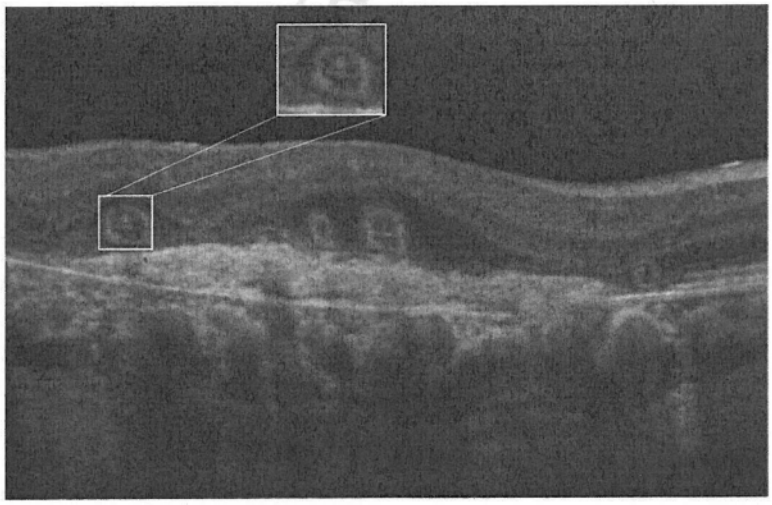

Fig. 5 – SD-OCT horizontal line scan of an eye with AMD exhibiting outer retinal tubulations (highlighted). AMD, age-related macular degeneration; SD-OCT, spectral-domain optical coherence tomography.

individual basis, between the AMD severities. The analysis of the DLS at each individual stimulus location enabled a localized assessment of function that was more descriptive of the AMD severity than that provided by the MS.[69]

The reduction in DLS varies with the location and severity of the AMD. Eyes with subfoveal neovascular AMD (nAMD) that exhibit severe (absolute) localized parafoveal abnormality (0 dB, as measured by an early commercially available Rodenstock SLO microperimeter; Rodenstock GmbH, Munich, Germany) manifest a normal foveal DLS, enabling central fixation to be maintained.[22] The likelihood of a dense parafoveal abnormality increases as the duration of self-reported symptoms increases.[22]

In summary, the MS derived by microperimetry is reduced in eyes with AMD and is able to differentiate, on a group mean basis at least, between levels of disease severity.[16,65] The evidence, however, is questionable as to whether microperimetry can correctly classify AMD disease severity. Characterizing the reduction in DLS by location, area, and depth enables the study of associations with other factors such as disease duration and maintenance of central fixation.[22]

2.3. *Microperimetry and structural imaging modalities*

Twenty of the 52 included articles were concerned with the relationship between visual function and retinal morphology in AMD,[3,20,21,27–29,33,34,38,45,51,52,57,59,60,63,72,73,75,76] most of which used SD-OCT. This section discusses microperimetry outcomes in relation to specific retinal layer changes, retinal pseudodrusen, atrophy (GA), and outer retinal tubulations (ORTs).

A typical SD-OCT horizontal line scan of an individual with AMD illustrating the retinal layers evaluated in the various studies is shown in Figure 2. The external limiting membrane appears as a hyperreflective line, by SD-OCT, in the outer retina just above the ellipsoid zone (EZ). The EZ is also visible as a hyperreflective band but is not synonymous with a single retinal anatomical feature.[64] The photoreceptor outer segment layer appears below the EZ band and is visible as a hyporeflective line. The retinal pigment epithelium (RPE) layer also appears as a hyperreflective line that is continuous with Bruch's membrane until disease processes cause their separation.

Reticular pseudodrusen represent a build-up of material below the RPE and, when viewed by SD-OCT, manifest as hyperreflective triangular-shaped deposits located between the RPE and the EZ band (Fig. 3).[58,80] GA is the late stage of AMD, with loss of retinal structures including the RPE and photoreceptors and the ensuing visibility of the underlying choroidal vessels (Fig. 4).[27] Nascent GA as defined by Wu and colleagues[74] occurs before drusen-associated atrophy and has similar risk factors to GA and can be visualized by SD-OCT but not by color fundus photography.[74] Nascent GA appears by SD-OCT as a breakdown of the outer plexiform layer and inner nuclear layer accompanied with a wedge-shaped hyporeflective area in the outer plexiform layer.[78] Finally, ORTs can only be visualized by SD-OCT and appear as a hyperreflective ring with a hyporeflective center located within the outer nuclear layer (Fig. 5).

2.3.1. *Retinal layers*

The relationship between outer retinal layer thickness and DLS in early AMD has been investigated by comparing RPE and OS thicknesses at locations with and without an abnormal DLS (defined as a TD value with a probability of lying within the normal range of $P \leq 0.05$).[3] The OS layer was thinner at locations with an abnormal TD ($P < 0.01$). The OS layer thickness was also significantly correlated with both MS and mean deviation obtained using the MP-1 microperimeter ($r = 0.62$ and $r = 0.63$, respectively, both $P < 0.01$).[3] MS worsens with increased thickening of the RPE.[3,72,76] A 10-μm increase in RPE layer thickness is associated with a 0.29 dB worsening of MS ($P < 0.001$) obtained with the MAIA microperimeter.[76]

In eyes with early-to-intermediate AMD, the MS at locations overlying drusen is statistically significantly worse than that at adjacent locations.[28,34] EZ band disruption is the strongest predictor of DLS at locations with drusen,[28] and the reduction in MS in the presence of EZ band disruption is worse than that in the presence of drusen alone.[34] Notably, in the former study, the stage of AMD was not classified. Individuals exhibiting drusen (excluding nAMD) were included and, therefore, any stage of AMD may have been involved.[28] In early-to-late atrophic AMD, MS worsens as the EZ band disturbance increases.[38,53,72] In nAMD, a worsening of EZ band disruption and an increase in central retinal thickness are both associated with a reduction in MS ($r = -0.79$; $P < 0.001$ and $r = -0.51$; $P < 0.01$, respectively).[38,60] Similarly, in nAMD treated with bevacizumab, MS significantly worsened ($P < 0.01$) with increase in EZ band disruption.[29] The presence of nAMD, intraretinal cysts, and a focal/localized absence either of the RPE or of the photoreceptor layer are each associated with an absolute loss of MS (<0 dB) obtained with the MP-1 microperimeter.[60] Subretinal fluid, intraretinal fluid, pigment epithelial detachment, and pseudodrusen are each separately associated with relative visual field loss (defined as 1 dB to 8 dB) when measured with the MP-1 microperimeter.[60]

2.3.2. *Reticular pseudodrusen*

The presence of reticular pseudodrusen in early-to-intermediate AMD (AREDS grades 2, 3, or 4[7]) is associated with a reduction in MS out to 10° eccentricity.[45] Such an association is absent in a cohort with intermediate-stage AMD (Beckman classification[19]).[75] MS out to 4° eccentricity was associated with reticular pseudodrusen on a univariate basis; however, in a multivariate analysis incorporating age, drusen volume, and pigmentary disturbance, the association was no longer present.[75] One explanation for these findings may simply be the difference in classification systems used for the 2 studies. In early-to-intermediate AMD (Beckman classification[19]), both scotopic and mesopic group mean MSs, obtained with a modified MP-1S microperimeter, were reduced in areas of reticular pseudodrusen (mean 12.8 dB; SD 3.3 and mean 17.2 dB; SD 2.5, respectively) compared with areas without (mean 18.2 dB; SD 2.2 and mean 18.4 dB; SD 2.5, respectively). The scotopic MS was reduced to a greater extent than the mesopic MS.[59] These findings suggest that, in the presence of reticular pseudodrusen, rod photoreceptor function is the most affected. It is not clear, however, whether the greater reduction in the scotopic MS was caused by differences in the measurement range resulting from the 2 different background luminances enabling scotopic and mesopic viewing conditions. Scotopic dysfunction also correlates with outer retinal thickness in eyes with reticular pseudodrusen: a 1-μm

decrease in thickness corresponded to a 0.96-dB reduction in scotopic MS.[59] In another study, the MS was also reduced in the presence of pseudodrusen in atrophy-free areas of eyes with GA.[63]

2.3.3. *Geographic atrophy*

In GA, MS has been compared between areas with and without either RPE loss and/or photoreceptor damage.[63] The group mean MS, obtained with the MP-1 microperimeter, was markedly lower in areas of RPE loss (mean 1.84 dB; SD 2.68; $P < 0.001$) and also in areas with photoreceptor damage (mean 6.57 dB; SD 4.13; $P < 0.001$) compared with areas without.[63] In GA, a thinning or an absence of the RPE, an absence of the external limiting membrane, and a thickening of the EZ boundary are each associated with absolute field loss (0 dB) obtained with the MP-1 microperimeter.[57] The group mean MS obtained with the MP-3 microperimeter at the GA boundary is lower (mean 13.7 dB; SD 4.7) than the group mean MS in the area surrounding the GA (mean 20.8 dB; SD 3.8); however, the latter is lower than that in eyes without GA (mean 23.9 dB; SD 2.6) ($P < 0.001$).[27] Another study used en-face OCT to identify GA boundaries at the choroidal and the outer retinal levels. When the MS was better than 10 dB, the mean area of GA was larger at the outer retinal level than at the choroidal level; however, the areas were similar when the MS was worse than 10 dB.[51]

In areas of nascent GA, the group mean MS measured by MAIA microperimetry is reduced (mean 20.4 dB; SD 0.8) compared with areas without atrophy (mean 23.8 dB; SD 0.7, $P < 0.01$) and is greater than that obtained in areas with drusen-associated atrophy (mean 16.4 dB; SD 0.9; $P < 0.01$).[74] The area of drusen-associated atrophy did not exhibit absolute loss as was the case in GA.[74]

Progression of GA can be monitored by fundus autofluorescence (FAF) as the areas of GA appear hypofluorescent. One study compared the outcome of MP-1 microperimetry to that from both near-infrared fundus autofluorescence and short-wavelength FAF.[52] The associations between severe relative loss (a DLS of not more than 5 dB) and normal and hyperfluorescence outcomes were determined for each FAF technique. It was concluded that the outcome from MP-1 microperimetry, in combination with both FAF techniques, allowed effective detection and monitoring of GA.[52] Another study used microperimetry to evaluate SD-OCT FAF and near-infrared fundus autofluorescence.[20] As would be expected, DLS was substantially reduced in areas of GA, and the imaging techniques were able to detect the presence of GA with differing capabilities. SD-OCT was considered to be the most appropriate imaging technique to examine GA.[20]

2.3.4. *Outer retinal tubulations*

ORTs are not specific to AMD and are seen more commonly in inherited retinal disorders such as choroideremia and retinitis pigmentosa.[24] In AMD, they are not a typical feature and can occur in eyes with previous nAMD. The identification of ORTs is clinically important as they may be misinterpreted as either intraretinal or subretinal fluid, with the resultant unnecessary treatment.[33,79] In a study of individuals without ORTs who were treated for nAMD, the improvement in MS obtained with the MP-1 microperimeter after 12 months was less pronounced in those that developed ORTs (mean 6.31 dB, SD 2.5) compared with those that did not (mean 9.89 dB, SD 5.43; $P < 0.01$). This study, however, did not fully describe the stimulus parameters for the microperimetry.

In summary, focal areas of reduced DLS in AMD can be identified by microperimetry and are associated with a disruption of the EZ band and/or changes to the RPE.[34,38,53,72] The association between reticular pseudodrusen and MS is equivocal. In early-to-intermediate AMD (AREDS 2, 3, and 4[7]), the presence of pseudodrusen is associated with a reduction in MS at the macula[45]; however, there was no such association in a different cohort with intermediate AMD (Beckman classification[19]).[75] The differences between areas with and without pseudodrusen, for early and intermediate AMD (Beckman classification[19]), combined, are seemingly most profound under scotopic conditions.[59] The reduction in MS is, in general, consistent with the presence of retinal lesions apparent by OCT. In the presence of a normal retinal appearance by fundus photography, microperimetry detects functional loss arising from nascent GA.[27,63,74]

2.4. *Microperimetry and other measures of visual function*

Fifteen included studies used microperimetry alongside other measures of visual function in individuals with AMD.[3,5,11,18,23,30,43,45,48,49,56,70,71,73,77] In early AMD (International Classification and Grading System[8]) with distance VAs ranging from 20/20 to 20/40, the corresponding MS varied between 19.5 dB (SD 0.4 dB) and 14.9 dB (SD 2.4 dB).[3] Similarly, in early-to-intermediate AMD (Beckman classification[19]) with a distance VA better than 20/40, MS exhibited a greater reduction compared with VA and to low luminance VA (LLVA) by 3.0 and 1.9 fold, respectively.[71] A prospective longitudinal study of intermediate AMD (Beckman classification[19]),[73] compared 2 groups: those graded as progressed, defined as the development of additional structural abnormality visible by color fundus photography, and those graded as stable with unchanged features. No deterioration from baseline in either VA or LLVA was present in either group at 12 months; however, small but statistically significant reductions in group mean MS (obtained with the MAIA microperimeter) were present in both groups (mean 0.42 dB; SE 0.12 and mean 0.31 dB; SE 0.10, respectively).[73] It should be noted, however, that microperimetry is only able to measure DLS to a resolution of 1 dB, and therefore, the clinical significance of these findings is limited. An additional finding of this latter study was that eyes identified as improved—defined as a disappearance of structural abnormality on color fundus photography—showed a statistically significant increase in the group mean MS (mean 1.13 dB; SE 0.23, $P < 0.001$) at 12 months.[73] Another study that compared the outcomes in early AMD (AREDS grade 2[7]) and in intermediate AMD (AREDS grade 3[7]) to those in normal individuals found a significant worsening in LLVA for each AMD group ($P < 0.05$).[11] The reduction in LLVA was associated with a reduction in foveal DLS ($r^2 = 0.60$, $P < 0.01$).[11] In early-to-intermediate AMD (AREDS grades 2 and 3[7]), a reduction of parafoveal MS is associated with a reduction in VA and in contrast sensitivity (CS) ($r = 0.59$ and $r = 0.35$, respectively, $P < 0.01$).[45]

In a separate study of individuals with intermediate-stage AMD (Beckman classification[19]), neither MS nor foveal DLS were associated with a low luminance deficit—defined as the

difference between VA and LLVA—or with the self-reported outcome to a 10-item night vision questionnaire. Nevertheless, low luminance deficit was significantly associated with difficulty under low luminance levels.[77]

In individuals with nAMD who had previously received anti-VEGF therapy, MS (out to 20° eccentricity) was moderately correlated with both VA ($r = 0.54$) and CS ($r = 0.53$) separately and, to a lesser extent, with reading speed ($r = 0.37$ all $P < 0.001$).[56] In those undergoing anti-VEGF treatment, however, no association was present between the MS and either VA or CS.[30,43] Other studies have shown that both DLS and VA improve up to either 6 months[48] or 12 months[43] of anti-VEGF therapy; however, the association between DLS and VA was not determined. In subfoveal CNV, an increase in the area of absolute DLS loss is associated with a decline in both reading acuity ($r = 0.52$; $P = 0.01$) and reading speed ($r = -0.48$; $P = 0.02$).[18]

In GA manifesting absolute loss of DLS and a central island of residual vision (foveal sparing), the MS out to 20° eccentricity was moderately associated with reading speed ($r^2 = 0.5$).[5] As an improvement in reading is a major goal of vision rehabilitation, microperimetry provides additional information about the location and size of the area(s) of residual function, allowing for a realistic estimation of reading ability and the likely outcome of rehabilitation.[5,23]

The multifocal electroretinogram provides objective, topographical, electrophysiological information about central retinal function. Two studies compared microperimetry and multifocal electroretinogram.[49,70] In early AMD (Wisconsin Age-related Maculopathy Grading system[35]), a significant correlation was present between the multifocal electroretinogram response amplitude density (N1-P1) and MS ($r = 0.69$, $P < 0.01$)[49]; however, there was no association for intermediate AMD (Beckman classification[19]).[70] This latter study found a greater reduction in the MS than in the multifocal electroretinogram ($P < 0.001$), suggesting that the 2 measures assess different aspects of retinal dysfunction.[70]

In summary, VA, CS, and reading ability have historically been used as outcome measures in ophthalmic clinical research. Microperimetry has more recently become an additional outcome measure. MS exhibits a wide range of values in the presence of relatively good VA in early-to-intermediate AMD[3] (International Classification and Grading System[8]). It is able to detect progressive improvements in AMD, consistent with color fundus photographs, when no change is observed in VA or LLVA. There is conflicting evidence as to the strength of the associations between DLS and VA, CS and reading ability.[43,71,73] Reading ability is an important factor when considering visual rehabilitation: microperimetry gives additional relevant information with respect to the area and location of residual function.

2.5. *Microperimetry as an outcome measure in clinical trials of medical or surgical intervention*

Microperimetry has been included as an outcome measure in 17 included articles describing clinical trials of medical and/or surgical interventions for AMD. In individuals undergoing treatment with ranibizumab for AMD, MS, measured with the MAIA microperimeter, was at a maximum of 17 dB for a central retinal thickness of 210 μm. MS declined as the thickness increased, reaching a minimum of 7 dB at a thickness of 320–339 μm, and declined as the thickness decreased, reaching a minimum of 15 dB at a thickness of <160 μm.[4] These findings, however, cannot be compared with other studies as both the microperimetry and the method of measuring retinal thickness were not reported. A similar finding was noted with bevacizumab therapy: MS increased after a reduction in retinal thickness[29] and decreased with increasing retinal thickness ($r = -0.54$, $P < 0.01$)[55]; however, neither of these latter studies specified the thickness boundaries used in the retinal thickness measurements. It has been suggested that the improvement in MS occurs from the reduction in RPE lesion area with treatment rather than from a reduction in the retinal thickness, as a whole.[35]

The relationship between DLS and specific AMD morphology, as identified by SD-OCT, has been studied in previously untreated patients with nAMD who subsequently received aflibercept.[62] The greatest improvement in DLS (measured with the MP-1 microperimeter), occurred 3 months after the start of therapy; areas exhibiting a reduction in either a serous pigment epithelial detachment or subretinal fluid exhibited the greatest improvement in group mean MS of 5.5 dB and 4.0 dB, respectively ($P < 0.001$). Areas with fibrovascular pigment epithelial detachment or with an intraretinal cystoid space also improved, but to a lesser extent (group mean improvements 2.3 dB and 1.7 dB, respectively).[62] In an earlier study, DLS improved after ranibizumab therapy in previously untreated patients with nAMD. The most marked improvement occurred at stimulus locations which were associated with a reduction in subretinal fluid, intraretinal fluid, or intraretinal cystoid space.[61]

Although all trials of anti-VEGF therapy involving microperimetry report an improvement in DLS from baseline, the results of these studies are equivocal with respect to the duration of therapy beyond which the DLS ceases to improve. A number of studies have found that DLS continues to improve up until 12 months, the time at which the studies ended[13,25,39,43,61]; however, 2 studies suggest that DLS does not improve beyond that recorded after 1 week of treatment.[9,35] DLS can also decline after withdrawal of anti-VEGF therapy. Individuals with stable nAMD, who ceased anti-VEGF therapy, exhibited a reduction in DLS during the follow-up period (at least 3 visits over 7 months) compared with those that continued to receive treatment.[4] It was speculated that the reduction in DLS may have resulted either from photoreceptor atrophy over time that was too subtle to be identified by VA or that CNV could be occurring at a subclinical level below that required by the United Kingdom NICE guidelines for an anti-VEGF injection.[4]

Two trials with unsuccessful outcomes used microperimetry as an outcome measure. One assessed the outcome of transpalpebral electrotherapy as a treatment for early-to-intermediate AMD (AREDS grades 2, 3, and 4[7]), and the another evaluated the outcome of photodynamic therapy combined with intravitreal triamcinolone as a treatment for nAMD.[6,17] Neither study found a sustained improvement in either DLS, VA, or CS, following treatment.

Macular translocation surgery (MT360) involves a peripheral retinectomy of 360° at the ora serata, following which the subfoveal CNV is removed and the whole retina is rotated

such that the fovea is located away from the removed CNV. The retina is then reattached. In 1 study, distance VA, near VA, and reading speed improved postoperatively.[12] DLS was specified in terms of the median retinal sensitivity score (MRSS) obtained with the MP-1 microperimeter. The 12-month postoperative group mean MRSS was better (2.5 dB, SD 4.3) in the foveal surgical area compared with the retinal area where the CNV had been removed (<0 dB)[12]; however, the MRSS had not been evaluated before surgery; therefore, it is not possible to evaluate whether the surgery improved visual function. Another study found that the MRSS only improved in lesions greater than 4 disk areas[41]; however, the 2 studies evaluated the outcome of the translocation surgery by differing methods. The first determined the MRSS at areas of healthy retina compared with that at the surgical sites,[12] whereas the second compared the difference in the MRSS for the preoperative and 12-month postoperative areas.[41]

Two RCTs examined the effect of lutein supplementation on macular pigment optical density and the subsequent effect on visual function. One RCT found that, although lutein supplementation increased the macular pigment density, there was no improvement in MS after 6 months of lutein supplementation.[68] Macular pigment density was also weakly correlated with DLS ($r = 0.25$, $P = 0.027$).[68] The second RCT examined differing levels of lutein supplementation (10 mg, 20 mg, and a combination of lutein with zeaxanthin) with placebo. After 2 years of supplementation, the group mean MS, obtained with the MP-1 microperimeter, was greater for the groups receiving 10 mg (13.37 dB) or 20 mg of lutein (12.55 dB) compared with the control group (10.32 dB, $P < 0.05$).[32]

It is clear that microperimetry has the ability to detect changes in visual function arising from a variety of interventions for AMD. All studies suggest that MS improves after anti-VEGF treatment as retinal thickness decreases and nAMD-associated lesions improve. The extent of any such improvement in MS beyond 12 months is unknown.

3. Discussion

The quality of evidence varied among the 52 articles. Overall, none of the RCTs directly analyzed the utility of microperimetry in the assessment of visual function in AMD but, as would be expected, evaluated a specific medical therapy using microperimetry as one of the various outcome measures. Over half of the studies included in this review were observational in design and, therefore, have a consequent risk of selection bias, information bias, or confounding bias.[26] Many studies had limitations in the quality of reporting of the microperimetry outcomes and/or of the SD-OCT methods and analysis (Table 1). Comparison between studies was also confounded by the differences in the classification systems for early and intermediate AMD. Four studies did not include the classification method.[5,23,28,38] An additional difficulty in comparing studies arose from the differences in the dynamic range between the various microperimeters used in the studies.

Most studies used the summary statistic MS, which is not age-corrected, and many of the studies did not report either the number or the spatial location of the stimuli on which the MS was based.[4,6,16,22,32,33,39,41,45,52] Only 12 of the studies analyzed the DLS at each given stimulus location.[28,38,53,57,60–63,65,72–74] From the 52 included studies, 2 of the studies[3,16] used location-specific probability analysis of the measured DLS compared with the corresponding age-corrected normal value, as is conventional practice in standard automated perimetry. Despite the latter probability analysis enabling separation of focal from diffuse defects,[31] such an approach was not used in these 2 studies.

The absence of a robust statistical analysis software package for microperimetry that would separate focal from diffuse loss and that is comparable to that widely used in standard automated perimetry currently limits the usefulness of the technique. Such analysis would enable a more clinically relevant evaluation of the microperimetry outcomes, particularly their association with structure. The various microperimeter manufacturers should be encouraged to develop such a package to allow this more comprehensive method of assessing abnormal visual function. In late-stage AMD, this type of analysis would also need to be corrected for the presence for any retinal locus.[14]

The clinical value of microperimetry has not yet been assessed against other functional biomarkers of AMD, such as flicker sensitivity and dark adaptation, known to be sensitive to AMD disease severity.[15,47] Microperimetry offers detailed topographical information relative to traditional measures of foveal function such as VA and CS. In addition, microperimetry was superior to VA in detection of subtle AMD changes in a longitudinal study over 1 year.[73] The investigation of microperimetry in comparison with dark adaptation in early AMD would be of value and enable clearer clinical recommendations for microperimetry.

Notwithstanding the aforementioned limitations, it is clear that there is a strong association between the magnitude of the DLS and a number of classic signs associated with AMD. Disruptions of the EZ band and RPE are associated with reduced DLS despite the maintenance of good VA.[29,34,38,49,72] OS thinning and RPE thickening are both associated with reduced MS, in early AMD.[3] A thickening and a thinning of the whole retina in CNV are each associated with a reduced MS.[4,29,55]

Table 2 – Terms used in the database search

Population	AND	Instrument
Age-related Macul[a]		Microperimet[a]
AMD		Fundus controlled perimet[a]
ARMD		
Macular degeneration		
Dry Macular degeneration		
Wet Macular degeneration		
Senile Macular degeneration		

[a] Truncation: includes various word endings into search.

4. Conclusion

The current microperimetric literature is of varying quality but has been improving in recent years. The current lack of consistency in the microperimetric techniques and in the analysis of DLS limits the conclusions regarding the use of

microperimetry in AMD. Recommendations for good clinical practice are, therefore, currently not possible; however, microperimetry provides information beyond that of VA and CS in the functional assessment of AMD. When combined with SD-OCT, it gives a multimodal representation of AMD morphology and associated visual function. Statistical analysis software similar to that used in standard automated perimetry would render microperimetry a more robust procedure. The development of a multimodal topographical classification system for all stages of AMD based on combined microperimetry and SD-OCT outcomes represents an exciting prospect.

5. Methods of literature search

The Medline, Ovid, EMBASE, and Web of Science databases were each searched using the search terms in Table 2. The search extended from 1950 (Medline only) to November 2016. The search terms were divided into 2 groups: population and instrument (Table 2). Each selected article was required to match at least 1 search term from each group. Additional articles were identified from the references within the publications identified by the primary search. The abstracts of articles found from the database search were independently assessed by 2 of the authors (N.K.C. and J.H.A.) to identify those that met the inclusion criteria.

Eligible articles had to include microperimetry undertaken on at least 20 eyes with AMD to provide a minimum level of evidence. All articles were required to contain the DLS outcome obtained by microperimetry. Preferred retinal location and fixation studies were excluded. Only articles that discussed microperimetry in the context of the outcome from other commercially available instrumentation were included. Conference abstracts and case reports were excluded. Studies where the whole article was not written in English were also excluded.

6. Disclosures

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

Acknowledgments

Nicola Cassels is in receipt of a postgraduate research studentship from Cardiff University. Jennifer Acton was also in receipt of a grant by Fight for Sight (grant number 1463/64).

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Appendix B: Quality of evidence table.

AMD: age-related macular degeneration; AREDS: Age-related Eye Disease; DLS: differential light sensitivity; ETDRS: Early Treatment Diabetic Retinopathy Study; FA: fluorescein angiography; GA: geographic atrophy; MD: Mean Deviation; MS: Mean Sensitivity; nAMD: neovascular AMD; OCT: Optical coherence tomography; PSD: Pattern Standard Deviation; TD: Total Deviation Study.

Reference	Study design	AMD identification and classification	DLS measures used	Quality of evidence
(Acton et al. 2012b)	Observational: case-controlled	Early AMD: International Classification and Grading System	MS (68 locations within 10°), number of TD defects, MD and PSD (derived from previous normative data)	High
(Broadhead et al. 2017)	Observational: case-control	Early to intermediate AMD: AREDS classification (grades 2 and 3)	DLS (13 locations: fixation and nasal, temporal, superior and inferior locations at 1˚,3˚ and 5˚)	High
(Chandramohan et al. 2016)	Observational: case-controlled	Early and intermediate AMD: AREDS classification (grades 2 and 3)	MS (37 locations within 5°), central MS (foveal locus and 12 locations at 1 °) and percentage reduced threshold (under 25dB)	High
(Denniss et al. 2017)	Observational: case-series	AMD: any manifest stage	MD and PSD (37 locations within 10˚) and Mean TD and mean PD with associated normal limits	High
(Ergun et al. 2003)	Observational: case series	nAMD: identified by FA	Size of absolute and relative scotoma	High
(Forte et al. 2013)	Observational: case series	GA: identified with colour fundus photography	MS (49 locations within 3.5°), Dense scotoma (0dB) and relatively dense scotoma (<5dB)	High
(Hariri et al. 2016)	Observational: cross-sectional	Early to late AMD (GA): identified and classified by OCT (presence of drusen = intermediate, GA larger than 0.1 = GA)	MS (in different zones associated with GA)	High

(Iwama et al. 2010)	Observational: case series	Soft confluent drusen: International Classification and Grading System	MS (57 locations over 10°, in central 2° and at specific locations with pathomorphology)	High
(Munk et al. 2013)	Experimental: Quasi-experiment (interrupted time-series)	nAMD: naïve to treatment, identified with FA	MS (ETDRS grid areas), Number of absolute scotoma (0dB), severe relative scotoma (1-6dB), mild relative scotoma (7-12dB) and normal (>13dB) were counted.	High
(Ozdemir et al. 2012)	Experimental: Quasi-experiment (interrupted time-series)	nAMD: identified with FA and OCT	MS (12 locations within 4˚) and number of absolute scotoma (0dB) from all 76 stimulus locations within 20˚	High
(Parisi et al. 2007)	Observational: case-controlled	Early AMD: classified by Wisconsin Age-related Maculopathy Grading System	Central MS (4 locations within 2.5˚) and paracentral MS(28 locations in annuli between 2.5 and 5˚)	High
(Querques et al. 2012)	Observational: cross-sectional	Early to late AMD (GA): presence of soft indistinct drusen with RPE changes, and/or GA, identified with colour fundus photography	MS (49 locations within 4.5°), pointwise DLS (at specific locations with pathomorphology)	High
(Sato et al. 2015)	Observational: cross-sectional	nAMD: identified by OCT and FA	MS and Median DLS (29 locations within 10°)	High
(Sayegh et al. 2014)	Observational: case series	GA: identified by fundus examination	Pointwise DLS (at specific locations with pathomorphology)	High
(Sulzbacher et al. 2015)	Experimental, Quasi-experiment (interrupted time-series)	nAMD: naïve to treatment, identified with FA	MS (33 locations within 6°), pointwise DLS (at specific locations with pathomorphology)	High
(Vujosevic et al. 2011)	Observational: case-controlled	Early to intermediate AMD: AREDS classification (stage 2 to 3)	MS (61 locations within 5°), K value: total number of locations <24dB, pointwise DLS	High

(Weigert et al. 2013)	Experimental, RCT	Early to late AMD (GA): AREDS classification (stage 2, 3, and 4)	MS (41 locations within 6°)	High
(Wu et al. 2013)	Observational: case-controlled	Intermediate AMD: Beckman classification	MS (37 locations within 6°), pointwise DLS	High
(Wu et al. 2014a)	Observational: case-controlled	Intermediate AMD: Beckman classification	MS (corresponding to mfERG hexagons)	High
(Wu et al. 2014b)	Observational: cross-sectional	Intermediate AMD: Beckman classification	MS (5 locations within central 1˚)	High
(Wu et al. 2014c)	Observational: cross-sectional	Intermediate AMD: Beckman classification	Pointwise DLS (at specific locations with pathomorphology) and Z score (average of 2 examinations in relation to normative data)	High
(Wu et al. 2015a)	Observational: longitudinal case-controlled	Intermediate AMD: Beckman classification	MS (37 locations within 6°) and pointwise DLS	High
(Wu et al. 2015b)	Observational: cross-sectional	Intermediate AMD: Beckman classification	MS (associated with groups of AMD pathology severity) and pointwise DLS (at specific locations with pathomorphology)	High
(Wu et al. 2015c)	Observational: cross-sectional	Intermediate AMD: Beckman classification	MS (25 locations within 4°)	High
(Wu et al. 2016)	Observational: longitudinal case series	Intermediate AMD: Beckman classification	MS (37 locations within 6°), MS within EDTRS grid sections	High
(Wu, Guymer and Finger 2016)	Observational: cross-sectional	Intermediate AMD: Beckman classification	MS (37 locations within 6°) and central MS (5 locations within 1°)	High

(Amore et al. 2013)	Observational: case series	AMD: with absolute scotoma and central fixation identified by microperimetry	Global MS and central MS. Size (in degrees) of central spared area (ring scotoma patients).	Medium 'central vision area' DLS definition not reported AMD: not stated method AMD is classified
(Bolz et al. 2010)	Experimental: Quasi-experiment (interrupted time-series)	nAMD: naïve to treatment	MS (foveal locus and circle of locations at 3.5˚)	Medium OCT: boundaries used to define central retinal thickness not reported AMD: method nAMD is identified not stated
(Chieh, Stinnett and Toth 2008)	Experimental: Quasi-experiment	nAMD	Median DLS within surgery areas and number of areas with absolute scotoma (<0dB)	Medium AMD: method nAMD is identified not stated
(Cho et al. 2013)	Experimental: Quasi-experiment (interrupted time-series)	nAMD: naïve to treatment, identified by FA and/or OCT	MS (28 locations within 6˚)	Medium OCT: boundaries used to define central retinal thickness not reported
(Dunavoelgyi et al. 2011)	Experimental: RCT	nAMD: naïve to treatment	MS (41 locations within 6˚), number of locations and size of absolute scotoma (0dB) and relative scotoma (<10dB)	Medium AMD: method nAMD is identified not stated
(Fujii et al. 2003)	Observational: cross-sectional	nAMD: identified by FA	Percentage presence of dense central scotoma (defined as having >3 locations of <0dB within 1.5°)	Medium Microperimetry: stimulus location pattern and stimulus details not reported
(Grenga et al. 2013)	Experimental: Quasi-experiment (interrupted time-series)	nAMD: naïve to treatment	MS (45 locations over 10˚), number of absolute scotoma locations	Medium Microperimetry: Absolute scotoma definition not reported AMD: method nAMD is identified not stated

(Hartmann et al. 2015)	Experimental: Quasi-experiment (interrupted time-series)	nAMD: presence of >250µm retinal thickness, subretinal fluid or PED.	MS (24 locations within 10˚)	Medium OCT: boundaries used to define retinal thickness not reported
(Huang et al. 2015)	Experimental: RCT	Early AMD: AREDS classification (grade 2)	MS (average DLS at 1, 3 and 5° from fixation)	Medium Microperimetry: stimulus pattern not reported
(Kiss et al. 2009)	Experimental: Quasi-experiment (interrupted time-series)	nAMD: identified with FA	MS (25 stimulus locations within 7.9˚), central 0˚, paracentral 3.5˚ and eccentric 7.9˚ MS and absolute scotoma size.	Medium Microperimetry: absolute scotoma definition and mode of analysis not reported
(Landa et al. 2011)	Observational: cross-sectional	Early to late AMD (GA): drusen or atrophic changes, and nAMD: CNV, intra/subretinal fluid and haemorrhages	MS (28 locations), pointwise DLS	Medium Microperimetry: Stimulus degrees not reported AMD: method AMD is identified or classified not stated
(Mettu et al. 2011)	Experimental: Quasi-experiment (interrupted time-series)	nAMD: identified with FA	Median DLS (30 locations) and percentage non response (<0dB).	Medium Microperimetry: stimulus degrees not reported
(Ooto et al. 2015)	Observational: cross-sectional	Early to late AMD (GA): AREDS classification (2,3, or 4)	MS (29 locations within 20˚ and parafovea: central 9 locations)	Medium Microperimetry: how stimulus pattern not reported
(Pilotto et al. 2011)	Observational: case series	GA: identified from fundus examination	MS and number of locations with relatively dense scotoma (≤5dB)	Medium Microperimetry: stimulus pattern and degrees not reported
(Pilotto et al. 2016)	Observational: cross-sectional	GA: identified from fundus examination	MS (customised grid within 8˚ including all areas of GA), divided into 3 groups based on MS, relative and dense scotoma rate	Medium Microperimetry: relative scotoma definition not reported

(Sabour-Pickett et al. 2013)	Experimental: Quasi-experiment (interrupted time-series)	nAMD: identified with FA	MS (fixation, central 5° and all 21 locations within 16˚)	Medium OCT: retinal boundaries used were 'thickness between outer most boundaries of scan' however, these are not specified.
(Steinberg et al. 2016)	Observational: case-controlled	Early or intermediate AMD with reticular pseudodrusen: Beckman classification and IR images	MS (56 locations) of areas with RPD compared to areas without (scotopic and mesopic)	Medium Microperimetry: stimulus degrees not reported
(Sulzbacher et al. 2012)	Observational: case series	nAMD: identified with colour fundus photography, OCT and FA	MS (33 locations within 6°), pointwise DLS (at specific locations with pathomorphology)	Medium Microperimetry: 'central retinal sensitivity' definition not reported
(Sulzbacher et al. 2013)	Experimental, Quasi-experiment (interrupted time-series)	nAMD: naïve to treatment, identified with colour fundus photography, OCT and FA	MS (33 locations within 6°), pointwise DLS (at specific locations with pathomorphology)	Medium OCT: pathomorphology used within analysis not defined and method of identification not reported
(Takahashi et al. 2016)	Observational: cross-sectional	GA: identified by fundus examination	MS (57 locations within 10° and over specific areas of retinal damage)	Medium Microperimetry: stimulus pattern not reported
(Giacomelli et al. 2013)	Observational: cross-sectional	Advanced AMD	MS (19 locations over 10°)	Medium: AMD: method AMD is identified or classified not stated
(Hartmann et al. 2011)	Observational: case-controlled	Early to late AMD (GA): presence of drusen on fundus examination	Ranked DLS threshold values and MS (28 locations within 10°), pointwise DLS overlying drusen	Medium: AMD: method AMD is classified not stated
(Hautamäki et al. 2014)	Observational: cross-sectional	nAMD: naïve to treatment	MS and ranking order of DLS (28 locations within 7.5°)	Medium: AMD: method AMD is identified not stated
(Fragiotta et al. 2017a)	Observational case-series	Intermediate AMD: Beckman classification	DLS (68 locations within 20˚)	Moderate Microperimetry: Stimulus pattern not reported

(Vujosevic et al. 2017)	Observational: longitudinal cross-sectional	Early to intermediate AMD: AREDS classification (grades 2 and 3)	MS (61 locations within 10˚), DLS within 2˚ and number of dense scotomas	Moderate OCT: ELM and IS/OS band integrity parameters not defined.
(Alexander et al. 2012)	Experimental: Quasi-experiment (interrupted time-series)	nAMD: enrolled from anti-VEGF clinic	MS, macular integrity index (MAIA software)	Poor Confusing terminology (stable and unstable used to refer to both fixation and AMD status) Microperimetry: stimulus pattern, number of locations, algorithm and stimulus details not reported OCT: scan details not included and boundaries used to define retinal thickness not reported AMD: how nAMD is identified not stated
(Anastassiou et al. 2013)	Experimental: RCT	Early to late AMD (GA): AREDS classification (grades 2,3 and 4)	MS (37 locations within 10°)	Poor Microperimetry: stimulus pattern, algorithm and stimulus details not defined OCT: scan details not included and method of measuring retinal and choroidal thickness not reported
(Dinc et al. 2008)	Observational: case-controlled	Intermediate AMD: AREDS classification (grade 3)	MS (76 locations within 10˚) and mean defect.	Poor Microperimetry: Mean defect derivation not reported, assumed it is from MP-1 software, stimulus pattern not reported OCT: scan details not included and boundaries used to define central retinal thickness not reported

(Iaculli et al. 2015)	Experimental: Quasi-experiment (interrupted time-series)	nAMD: identified by OCT and FA	MS (8°)	Poor Microperimetry: stimulus pattern and details not defined OCT: scan details not included and boundaries used to define central retinal thickness not reported
(Lazzeri et al. 2015)	Experimental: Quasi-experiment (interrupted time-series)	nAMD: identified with FA	MS (33 locations within 6˚)	Poor Confusing terminology: both 'mean central retinal sensitivity' and 'mean retinal sensitivity' used; and 'Central retinal thickness' and 'central macular thickness' both used. Difference in terms not reported. Microperimetry: stimulus pattern and details not reported OCT: scan details not included and boundaries used to define central retinal thickness not reported

Appendix C: Participant information sheet

Version 4
23/06/14

Information Booklet

for participants

Dear Sir/Madam,

Cardiff University would like to invite you to take part in our study investigating clinical tests and quality of life in macular disease. Lots of people are already helping with our research.

Before you decide, we would like you to understand why the research is being done and what it would involve for you. Please take the time to read this information sheet, feel free to talk to others about the study if you wish. Before commencing the study we will go through the information sheet with you and answer any questions you may have. Please ask us if there is anything that is not clear.

The following information booklet has two parts:

Part 1 *tells you the purpose of this study and what will happen if you take part*

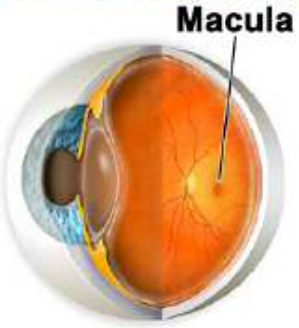
Part 2 *gives you more detailed information about the conduct of the study*

CARDIFF UNIVERSITY
PRIFYSGOL CAERDYDD

PART 1

❖ What is this study about?

Macular disease is a common eye condition that damages the macula, the part of the retina that gives us clear, central vision. This makes activities such as reading, driving and recognising familiar faces more difficult. This often leads to significant losses in quality of life and can cause an increased risk of depression.



This study seeks to determine the relationships between clinical tests and quality of life in people with macular disease, in order to gain a better understanding of how well clinical tests reflect the wellbeing of individuals with macular disease.

You have been asked to volunteer in this research because we are looking for individuals to take part in the study procedures, which include questionnaires and clinical tests, to find out the associations between these measures.

❖ What will happen to me if I take part?

1. Those who wish to take part in the study will have an **initial 40 minute appointment** with one of our team for you to ask any questions you may have and provide your consent to participating in the study. We will ask you some general questions about your health and vision and let you know if you are eligible to take part in the study. If you are eligible and wish to take part we will measure your vision, using a letter chart and carry out a visual field test using an instrument known as a microperimeter, that also takes an image of your eye. We will then go through some questionnaires, which include questions like how well you are able to do vision-related activities e.g. reading, driving and questions about your health and how you are feeling. Your questionnaire score will be looked at and if you are identified as feeling low you will be offered referral to your GP. If you are identified as being at risk of harm then you will be referred urgently to your GP.

Depending on where you were recruited, the appointments will all take place at either the Cardiff School of Optometry or Kings College Hospital, London.

2. If you willing to continue to take part, a **second appointment** will take around an hour and a half. We will carry out some standard and new clinical tests including:

   - Measuring your vision with letter and reading charts
   - Taking images and photographs of your eyes
   - Repeating the microperimetry visual field test
   - Measuring the sensitivity of the eyes after a period of time in the dark and in response to lights on a computer screen, where you will be asked to press a button.

   It may be necessary to put a drop in your eye to make your pupils larger, depending on the quality of the images we take.

Are there any risks involved?

- The drops used to enlarge your pupil are the same as those used at the opticians or eye hospital. They may make your vision temporarily a little blurred and make you sensitive to bright lights for about 6 hours. During this time we advise you not to drive or to operate any dangerous machinery. Very rarely some people can develop an adverse reaction to these drops. In **less than 1 in 20,000 people** they may cause a rise in eye pressure, known as closed angle glaucoma. The symptoms of this can include, pain, a red eye and halos around lights. In the extremely unlikely event that this should occur, you should contact us urgently on the number shown below or Cardiff University Optometrists (02920 874357). If we are unavailable then you should go straight to eye casualty for assessment and treatment with other eye drops to bring the pressure back down.
- One of the questionnaires that is being used in the study may identify depressive symptoms. In this case you will be offered referral to your GP. If it is identified that you are at risk of harm then you will be referred urgently to your GP.

3. You may be invited to take part in a third visit, 12 months later. If you wish to take part in this, it will take about 2 hours and include the same tests as the second appointment, with the addition of the same questionnaires from the first visit.

❖ **What are the possible benefits of taking part?**

The results of the study may not directly benefit you, but the information could help others. The results will help clinicians and researchers gain a better understanding of macular disease, as well as help with the design of clinical tests to include in future studies.

❖ **Do I have to take part?**

No – it is up to you whether you decide to take part or not. Participation in this study is purely voluntary. If you do decide to take part, you will be given this information sheet to keep and will be asked to sign a consent form. You can withdraw at any time without giving a reason. Please note that if you do not wish to take part in the study it will not affect your current or future care.

❖ **What if there is a problem?**

If you do have a concern about any aspect of this study, you should ask to speak to the researchers (contact details below) who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure – details can be obtained from the researchers.

NAME	EMAIL ADDRESS	ADDRESS & TELEPHONE NUMBER
Nicola Cassels	Casselsn1@cf.ac.uk	School of Optometry &Vision Sciences Cardiff University Maindy Road, Cardiff, CF24 4HQ 02920 870556
Jennifer Acton	ActonJ@cf.ac.uk	School of Optometry &Vision Sciences Cardiff University Maindy Road, Cardiff, CF24 4HQ 02920 870203

PART 2

- **What if I have any questions?**
  Please ask. We are very happy to discuss any aspect of the study. *Please do not send personal information regarding your medical status by e-mail, as this may not be a secure means of communication.*

  For independent advice, please contact the Cardiff University Optometrists, School of Optometry and Vision Sciences (02920 874357) or the Research and Commercial Division, Cardiff University (02920 875834).

- **What will happen if I don't want to carry on with the study?**
  You are free to withdraw at any time without giving a reason; however we will retain non identifiable data collected up to your withdrawal. Please note that if you do not wish to take part in the study it will not affect your current or future care.

- **What if there is a problem?**
  In the unlikely event that harm should occur as a result of negligence associated with this study, cover is provided by the Cardiff University insurance policy.

- **Will my taking part in this study be kept confidential?**
  All information collected during the study will be processed and stored securely by the researchers using password-protected systems. Your personal information will be coded and only the researchers will be able to identify you during the study. All procedures are compliant with the Data Protection Act 1998.

- **What will happen to the results of the research study?**
  The study results will be analysed and presented at national and international meetings and in scientific journals. Identities of participating volunteers will not be revealed in any resulting published material. If you wish to be provided with a summary of the research findings at the end of the study please tick the appropriate box on the consent form.

- **Who is funding and reviewing the research?**
  This study is being organised by Cardiff University in collaboration with Oxford Eye Hospital and King's College Hospital. This study was reviewed and approved by Cardiff University and the South East Wales Research Ethics Committee.

Appendix D: Participant consent form

Version 1
23/9/13

Study Title: **Quality of Life and Clinical Outcomes in Macular Disease**

Names of Researchers: Dr Jennifer Acton

Miss Nicola Cassels

Prof Victor Chong

	Please initial
1. I confirm that I have read and understand the participant information sheet dated 23/9/2013. 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 I am free to withdraw at any time without giving reason, without my medical care or legal rights being affected.	
3. I agree that my details can be used by the research team and understand that my personal details will be treated as **STRICTLY CONFIDENTIAL.**	
4. I agree to take part in the study in accordance with the terms set out in the consent form and participant information sheet.	
5. I would like to receive a summary of the research findings at the end of the study.	

Name of Patient	Date	Signature
Name of person taking consent	**Date**	**Signature**

Appendix E: Record sheet

ID					**INFO. SHEET**	Y	N
					CONSENT FORM	Y	N
DATE OF BIRTH					**GENDER**	**M**	**F**
GH					**MMSE Score**		Pass/ Fail
					Medication		
		COPD/Asthma		Musculoskeletal			
		Diabetes		Heart			
		Hearing Impairment		Hypertension			
OH					Early/Moderate/Late	Dry	Wet
					Injections (number, last one?)		
					Last appointment?		
Extra (living situation, magnifiers, hobbies and SS input)					Falls in the past year?		
					Other:		
Alone	Spouse	Friend/relative	Residential home/sheltered accom.		Visual hallucinations?		

	Focimetry		**VA (ETDRS)**		**Reading speed (wpm)**	**CS**	
OD							
OS							
Refraction and BCVA							

Anterior Eye	**OD**	**Posterior Eye**	**OD**		
	OS		**OS**		
Van Herick angle	**OD**	**IOP (mm Hg)**	**OD**	**OCT** *(✓)*	**OD**
	OS				**OS**
LOCS III grading	**OD**		**OS**	**Fundus Photograph** *(✓)*	**OD**
	OS				**OS**

MAIA 1 *(✓)*		**MAIA2** *(✓)*		**Dilation?**	
OD	**OS**	**OD**	**OS**		
Scatter (logs)		**OD**	**OS**	**Time:**	

Notes

Appendix F: The shortened version of the Mini mental state examination (Schultz-Larsen, Lomholt and Kreiner 2007).

I would like you to repeat the following three words: APPLE, PENNY, TABLE

(Repeat until the patient registers all three words)

A1	What is the day?	Correct	Yes	☐	No	☐
A2	What is the month?	Correct	Yes	☐	No	☐
A3	What is the year?	Correct	Yes	☐	No	☐
A4	Spell WORLD backwards D L R O W	Number correct		☐		

(Final cognitive screening question A5 follows the questions on visual function)

What were the 3 words that I asked you at the beginning?

1) _____
2) _____
3) _____

(apple, penny, table)

Number correct _____

Did the patient pass the cognitive screen?

Yes (1) (day, year, month correct; 3/5 WORLD; remember at least 2 words)

No (0) **Patient is ineligible**

Appendix G: Coding to obtain retinal layer thickness values at stimulus locations corresponding to the MAIA grid pattern in OCT explorer (.xml file).

```
<?xml version="1.0" encoding="UTF-8"?>
<grid>
	<version>3.0</version>
	<type>square</type>
	<unit>mm</unit>
	<region_num>40</region_num>
	<region>
		<label>1</label>
<!-- from the center of the grid -->
		<left>-0.43</left>
		<top>-2.23</top>
		<right>-0.3</right>
		<bottom>-2.1</bottom>
	</region>
	<region>
		<label>2</label>
		<left>0.3</left>
		<top>-2.23</top>
		<right>0.43</right>
		<bottom>-2.1</bottom>
	</region>
	<region>
		<label>3</label>
		<left>-1.03</left>
		<top>-1.63</top>
		<right>-0.9</right>
		<bottom>-1.5</bottom>
	</region>
	<region>
		<label>4</label>
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		<top>-1.63</top>
		<right>-0.3</right>
		<bottom>-1.5</bottom>
	</region>
	<region>
		<label>5</label>
		<left>0.3</left>
		<top>-1.63</top>
		<right>0.43</right>
		<bottom>-1.5</bottom>
	</region>
	<region>
		<label>6</label>
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		<top>-1.63</top>
		<right>1.03</right>
		<bottom>-1.5</bottom>
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	<region>
		<label>7</label>
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		<top>-1.03</top>
		<right>-1.5</right>
		<bottom>-0.9</bottom>
	</region>
	<region>
		<label>8</label>
		<left>-1.03</left>
		<top>-1.03</top>
		<right>-0.9</right>
		<bottom>-0.9</bottom>
	</region>
	<region>
		<label>9</label>
		<left>-0.43</left>
		<top>-1.03</top>
		<right>-0.3</right>
		<bottom>-0.9</bottom>
	</region>
	<region>
		<label>10</label>
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		<top>-1.03</top>
		<right>0.43</right>
		<bottom>-0.9</bottom>
	</region>
	<region>
		<label>11</label>
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		<top>-1.03</top>
		<right>1.03</right>
		<bottom>-0.9</bottom>
	</region>
	<region>
		<label>12</label>
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		<top>-1.03</top>
		<right>1.63</right>
		<bottom>-0.9</bottom>
	</region>
	<region>
		<label>13</label>
		<left>-2.23</left>
		<top>-0.43</top>
		<right>-2.1</right>
		<bottom>-0.3</bottom>
	</region>
	<region>
		<label>14</label>
		<left>-1.63</left>
		<top>-0.43</top>
```

```
        <right>-1.5</right>
        <bottom>-0.3</bottom>
</region>
<region>
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        <top>-0.43</top>
        <right>-0.9</right>
        <bottom>-0.3</bottom>
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        <right>-0.3</right>
        <bottom>-0.3</bottom>
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        <right>0.43</right>
        <bottom>-0.3</bottom>
</region>
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        <right>1.03</right>
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        <top>-0.43</top>
        <right>1.63</right>
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        <right>2.23</right>
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        <right>-2.1</right>
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        <right>-1.5</right>
        <bottom>0.43</bottom>
</region>
<region>
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        <left>-1.03</left>
        <top>0.3</top>
        <right>-0.9</right>
        <bottom>0.43</bottom>
</region>
<region>
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        <top>0.3</top>
        <right>-0.3</right>
        <bottom>0.43</bottom>
</region>
<region>
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        <right>0.43</right>
        <bottom>0.43</bottom>
</region>
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        <right>1.03</right>
        <bottom>0.43</bottom>
</region>
<region>
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        <left>1.5</left>
        <top>0.3</top>
        <right>1.63</right>
        <bottom>0.43</bottom>
</region>
<region>
        <label>28</label>
        <left>2.1</left>
        <top>0.3</top>
        <right>2.23</right>
        <bottom>0.43</bottom>
</region>
<region>
        <label>29</label>
        <left>-1.63</left>
        <top>0.9</top>
        <right>-1.5</right>
        <bottom>1.03</bottom>
</region>
<region>
        <label>30</label>
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        <top>0.9</top>
        <right>-0.9</right>
        <bottom>1.03</bottom>
</region>
<region>
        <label>31</label>
        <left>-0.43</left>
        <top>0.9</top>
        <right>-0.3</right>
```

```
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        </region>
        <region>
            <label>32</label>
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            <top>0.9</top>
            <right>0.43</right>
            <bottom>1.03</bottom>
        </region>
        <region>
            <label>33</label>
            <left>0.9</left>
            <top>0.9</top>
            <right>1.03</right>
            <bottom>1.03</bottom>
        </region>
        <region>
            <label>34</label>
            <left>1.5</left>
            <top>0.9</top>
            <right>1.63</right>
            <bottom>1.03</bottom>
        </region>
        <region>
            <label>35</label>
            <left>-1.03</left>
            <top>1.5</top>
            <right>-0.9</right>
            <bottom>1.63</bottom>
        </region>
        <region>
            <label>36</label>
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            <top>1.5</top>
            <right>-0.3</right>
            <bottom>1.63</bottom>
        </region>
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            <top>1.5</top>
            <right>0.43</right>
            <bottom>1.63</bottom>
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            <label>38</label>
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            <top>1.5</top>
            <right>1.03</right>
            <bottom>1.63</bottom>
        </region>
        <region>
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            <top>2.1</top>
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            <bottom>2.23</bottom>
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            <left>0.3</left>
            <top>2.1</top>
            <right>0.43</right>
            <bottom>2.23</bottom>
        </region>
    </grid>
```

Appendix H: Questionnaire prompt sheet

NOT AT ALL 0	HARDLY AT ALL 1	A LITTLE 2	A FAIR AMOUNT 3	A LOT 4	CAN'T DO BECAUSE OF EYESIGHT 5	DON'T DO FOR OTHER REASONS 8

IVI

NOT POSSIBLE 0	A LOT OF DIFFICULTY 1	SOME DIFFICULTY 2	A LITTLE DIFFICULTY 3	NO DIFFICULTY AT ALL 4

VF-14

NONE OF THE TIME 1	RARELY 2	SOME OF THE TIME 3	OFTEN 4	ALL OF THE TIME 5

WEMWBS

NOT AT ALL 0	SEVERAL DAYS 1	MORE THAN HALF THE DAYS 2	NEARLY EVERY DAY 3

PHQ-9

Appendix I: Rasch analysis method.

- Open Winsteps
- Import files from SPSS
- Drag and drop ID (person identification) into person and the questions into item response.
- Construct Winsteps file and save (txt file)
- Press enter, find txt file and open (enter twice) = Rasch analysis
- Gives initial summary table: check person and item reliability (close to 1) and separation (not below 2). (http://www.winsteps.com/winman/reliability.htm)
- Along top bar:
    - Diagnosis – Category function (table 3.2) (graphs - category probability curves = prettier)
    - Output tables – summary stats (table 3.1) gives same as initial table in main window broken down, gives model and real numbers.
    - Output tables – Variable map (table1) = person-item figure (ruler)
    - Output table – Item fit (tables 10-30, ordered differently) gives infit and outfit stats for items
    - Output table – Person Fit (tables 6-41) gives person infit and outfit, and measure for each person (logits).
    - Check person fit stats for 'rogue responders (output tables- person measure): misfits = model S.E >1.4. People can be removed at this point but Rasch will need to be rerun.

Interpretation of parameter-level mean-square fit statistics:	
>2.0	Distorts or degrades the measurement system
1.5 - 2.0	Unproductive for construction of measurement, but not degrading. Top end of acceptable
0.5 - 1.5	Productive for measurement.
<0.5	Less productive for measurement, but not degrading. May produce misleadingly good reliabilities and separations.

    - Output table – Scoring table (table 20) this does not allow for missing data, can only be used if all data is present.
- Scoring table (for each question and each category) = Item calibration/Item measure (table 13) + Category Measure/score at cat. (table 3.2).
    - To enter scoring table in SPSS:
        - Transform – Recode with different variable
        - Turn each category into a logit value (add extra columns)
        - Can use as a scoring table in future.

Appendix J: GP referral consent form

Study Title: **Quality of Life and Clinical Outcomes in Macular Disease**

Names of Researchers: Dr Jennifer Acton

Miss Nicola Cassels

From the questions you have answered today it has been identified that you display some depressive symptoms. We would like to offer you a referral to your GP due to these findings. Please indicate below if you consent to this referral.

I understand the statement above and consent to a referral to my GP.

Please initial ☐

Name of Patient	Date	Signature
Name of person taking consent	**Date**	**Signature**

Appendix K: R code for the use of Method 1 and Method 2 normative databases.

Method 1: TD and PD

```
newdb <- function(subject.age, sens, slope){


        agediff <- (45.97- subject.age)
        agediff2<- agediff * slope
        agediff3<- round(agediff2 + sens,2)


        }
##read in slope and AMD data
read.csv(file.choose(), header=TRUE)->amd
read.csv(file.choose(), header=TRUE)->slope


##gives new sens values
results <- as.data.frame(setNames(replicate(41,numeric(0), simplify = F), c("id", seq(1:40))))
 for (j in 1:nrow(amd)){
        results[j,1] = as.vector(amd[j,1])
                for(i in 1:40){
                results[j,i+1] <- as.matrix(cbind(newdb(amd[j,2], amd[j,i+2], slope[1,i+1])))
                        }
      names(results) <- c("id", seq(1:40))
                        }
##save new values
 write.csv(results, "newsens.csv")


###TD reports (load in new AMD)
read.csv(file.choose(), header=TRUE)->newamd
read.csv(file.choose(), header=TRUE)->slope


results <- as.data.frame(setNames(replicate(41,numeric(0), simplify = F), c("id", seq(1:40))))
```

```
for (j in 1:nrow(newamd)){
        results[j,1] = as.vector(newamd[j,1])

                for(i in 1:40){
                results[j,i+1] <- as.data.frame(newamd[j,i+1] - slope[2,i+1])
                        }
      names(results) <- c("id", seq(1:40))
                        }
##save
write.csv(results, "TD.csv")

##TD probability limits
probf<- function(td,limit)  {
  if (td < limit){report <- "Sensitivity below "
                        }
if (td ==  limit){ report <- "Sensitivity below "
                        }
if (td > limit){report <- "Sensitivity within "
                        }
                        as.data.frame(cbind(td , report))
                        }

###read AMDtd values and get report
read.csv(file.choose(), header=TRUE)->amdtd
read.csv(file.choose(), header=TRUE)->slope

 resultstd <- as.data.frame(setNames(replicate(3,numeric(0), simplify = F), c("id", "td",
"report")))
names(resultstd) <- c("id", "td", "report1")
for (j in 1:nrow(amdtd)){
        for(i in 1:40){
                data  <-  cbind(as.data.frame(cbind(amdtd[j,1],  probf(amdtd[j,i+1],
slope[3,i+1])))) ###for 95% insert slope[3,i+1] ### for 98% insert  slope[4,i+1]  for
99% insert
                names(data) <- c("id", "td", "report")
```

```
                resultstd <- rbind(resultstd, data)
        }
}

write.csv(resultstd, "IOL3HFA3tdprob0.95.csv")

 ####PD numbers
 read.csv(file.choose(), header=TRUE)->amdtd

resultsPD <- as.data.frame(setNames(replicate(41,numeric(0), simplify = F), c("id", seq(1:40))))
for(j in 1:nrow(amdtd)){
        resultsPD[j,1] =  as.vector(amdtd[j,1])
        for(i in 1:40){
                elevator <- quantile(as.numeric(amdtd[j,2:41]), .85,na.rm=TRUE)
                resultsPD[j,i+1]<-        as.data.frame(round(as.numeric(amdtd[j,i+1])-(elevator),2))
                names(resultsPD) <- c("id", seq(1:40))
                        }
                }
##save
write.csv(resultsPD, "PD.csv")

####PD probability limits
probf<- function(pd,limit)  {
if (pd < limit){report <- "Sensitivity below "
                        }
if (pd ==  limit){report <- "Sensitivity below "
                        }
if (pd > limit){report <- "Sensitivity within "
                        }
as.data.frame(cbind(pd , report))
                        }

###read AMDpd values and get report
```

```
read.csv(file.choose(), header=TRUE)->amdpd

read.csv(file.choose(), header=TRUE)->slope


 resultspd <- as.data.frame(setNames(replicate(3,numeric(0), simplify = F), c("id", "pd", "report")))

names(resultspd) <- c("id", "pd", "report1")

for (j in 1:nrow(amdpd)){

        for(i in 1:40){

                data<-cbind(as.data.frame(cbind(amdpd[j,1],probf(amdpd[j,i+1], slope[6,i+1])))) ####for 95% insert slope[6,i+1]  ###for 98% insert slope[7,i+1] ### for 99% insert  slope[8,i+1]

                names(data) <- c("id", "pd", "report")

                resultspd <- rbind(resultspd, data)

                        }

                }

 write.csv(resultspd, "IOL3HFA3pdprob0.95.csv")
```

Method 2: TD for new data

```
# Read in data

read.csv(file.choose(), header=TRUE)->Agesens

names(Agesens) <- tolower(names(Agesens))

sens.pred <- function(location, subject.age, sens, conf.level=0.98){

        #Get prediction intervals

                location.data <- lm(location ~ age)

                newdata <- data.frame(age=subject.age)

                predint <- predict(location.data, newdata, level=conf.level, interval="predict")

                td <- round(sens-predint[1],2)

                dev.neg<-round(predint[2]-predint[1],2)

                dev.pos<-round(predint[3]-predint[1],2)

        # TD probability limits

                if (td < dev.neg){report <- "Sensitivity below normal limits"

                        }

                        if (td ==  dev.neg){report <- "Sensitivity below normal limits"

                        }
```

```
                if (td > dev.pos){report <- "Sensitivity above normal limits"
                        }
                  if (td  == dev.pos){report <- "Sensitivity above normal limits"
                        }
                if (td < dev.pos && td > dev.neg){report <- "Sensitivity within normal
limits"
                        }
                as.data.frame(cbind(round(td, 2), report))
                        }
read.csv(file.choose(), header=TRUE)->amd
attach(Agesens)
#95%
results <- as.data.frame(setNames(replicate(4,numeric(0), simplify = F), c("id", "age",
"td", "report")))
names(results) <- c("id", "age", "td", "report")
for (j in 1:nrow(amd)){
        for(i in 1:40){
                data <- cbind(as.data.frame(cbind(amd[j,1], amd[j,2],
sens.pred(Agesens[,(i+2)], amd[j,2], amd[j,i+2],0.95))))
                names(data) <- c("id", "age", "td", "report")
                results <- rbind(results, data)
                        }
                }
write.csv(results, "0.95.csv")
#98%
results <- as.data.frame(setNames(replicate(4,numeric(0), simplify = F), c("id", "age",
"td", "report")))
names(results) <- c("id", "age", "td", "report")


for (j in 1:nrow(amd)){
        for(i in 1:40){
                data <- cbind(as.data.frame(cbind(amd[j,1], amd[j,2],
sens.pred(Agesens[,(i+2)], amd[j,2], amd[j,i+2],0.98))))
                names(data) <- c("id", "age", "td", "report")
                results <- rbind(results, data)
                        }
```

```
                }
write.csv(results, "0.98.csv")
#99%
results <- as.data.frame(setNames(replicate(4,numeric(0), simplify = F), c("id", "age", "td", "report")))
names(results) <- c("id", "age", "td", "report")
for (j in 1:nrow(amd)){
        for(i in 1:40){
                data <- cbind(as.data.frame(cbind(amd[j,1], amd[j,2], sens.pred(Agesens[,(i+2)], amd[j,2], amd[j,i+2],0.99))))
                names(data) <- c("id", "age", "td", "report")
                results <- rbind(results, data)
                        }
                }
write.csv(results, "0.99.csv")
```

Method 2: PD for new data

```
# Read in data
read.csv(file.choose(), header=TRUE)->Agesens
names(Agesens) <- tolower(names(Agesens))
sens.pred <- function(location, subject.age, sens, conf.level=0.98){
                location.data <- lm(location ~ age)
                newdata <- data.frame(age=subject.age)
                predint <- predict(location.data, newdata, level=conf.level, interval="predict")
                td <- round(sens-predint[1],2)
                dev.neg <-round(predint[2]-predint[1],2)
                dev.pos <-round(predint[3]-predint[1],2)
                as.data.frame(round(td, 2))
}
##save TD numbers
read.csv(file.choose(), header=TRUE)->amd
attach(Agesens)
results <- as.data.frame(setNames(replicate(42,numeric(0), simplify = F), c("id", "age", seq(1:40))))
```

```
for (j in 1:nrow(amd)){
          results[j,1] = as.vector(amd[j,1])
  results[j, 2] = amd[j,2]
                    for(i in 1:40){
                    results[j,i+2]  <-  as.data.frame(sens.pred(Agesens[,(i+2)],  amd[j,2],
amd[j,i+2]))
                              }
       names(results) <- c("id", "age", seq(1:40))
                               }
##save TD numbers
write.csv(results, "AMDTD")


###PD numbers
rm(list=ls())
read.csv(file.choose(), header=TRUE)->results


resultsPD <- as.data.frame(setNames(replicate(42,numeric(0), simplify = F), c("id",
"age", seq(1:40))))
for(j in 1:nrow(results)){
          resultsPD[j,1] =  as.vector(results[j,1])
            resultsPD[j,2] =  results[j,2]
          for(i in 1:40){
                    elevator <- quantile(as.numeric(results[j,3:42]), .85,na.rm=TRUE)
                    resultsPD[j,i+2]<-        as.data.frame(round(as.numeric(results[j,i+2])-
elevator),2))
                    names(resultsPD) <- c("id", "age", seq(1:40))
                              }
                    }
##save PD numbers
write.csv(resultsPD, "AMDPD")


###PD probability limits
read.csv(file.choose(), header=TRUE)->Agesens2
names(Agesens2) <- tolower(names(Agesens2))
sens.pd <- function(location, subject.age, pd, conf.level=0.98){
```

```
location.data <- lm(location ~ age)

newdata <- data.frame(age=subject.age)

predint <- predict(location.data, newdata, level=conf.level, interval="predict", na.action = na.exclude)

dev.neg <-round(predint[2]-predint[1],2)

dev.pos <-round(predint[3]-predint[1],2)

 if (pd < dev.neg){report <- "Sensitivity below normal limits"

}

if (pd ==  dev.neg){report <- "Sensitivity below normal limits"

}

if (pd > dev.pos){report <- "Sensitivity above normal limits"

}

if (pd  == dev.pos){report <- "Sensitivity above normal limits"

}

if (pd < dev.pos && pd > dev.neg){report <- "Sensitivity within normal limits"

}

as.data.frame(cbind(pd, report))

}

##read in saved PD data from above

read.csv(file.choose(), header=TRUE)->pd2

attach(Agesens2)

results <- as.data.frame(setNames(replicate(4, numeric(0),simplify = F), c("id", "age", "pd", "report")))

names(results) <- c("id", "age", "pd", "report")

#95%

for (j in 1:nrow(pd2)){

    for(i in 1:40){

        data <- cbind(as.data.frame(cbind(pd2[j,1], pd2[j,2], sens.pd(Agesens2[,(i+2)], pd2[j,2], pd2[j,i+2],0.95))))

       names(data) <- c("id", "age", "pd", "report")

results <- rbind(results, data)

}

}
```

```
write.csv(results, "pd95.csv")


results <- as.data.frame(setNames(replicate(4, numeric(0),simplify = F), c("id", "age",
"pd", "report")))

names(results) <- c("id", "age", "pd", "report")

#98%

for (j in 1:nrow(pd2)){

        for(i in 1:40){

                        data <- cbind(as.data.frame(cbind(pd2[j,1], pd2[j,2],
sens.pd(Agesens2[,(i+2)], pd2[j,2], pd2[j,i+2],0.98))))

                    names(data) <- c("id", "age", "pd", "report")

                results <- rbind(results, data)

                        }

                }

write.csv(results, "pd98.csv")


 results <- as.data.frame(setNames(replicate(4, numeric(0),simplify = F), c("id", "age",
"pd", "report")))

names(results) <- c("id", "age", "pd", "report")

#99%

for (j in 1:nrow(pd2)){

        for(i in 1:40){

                        data <- cbind(as.data.frame(cbind(pd2[j,1], pd2[j,2],
sens.pd(Agesens2[,(i+2)], pd2[j,2], pd2[j,i+2],0.99))))

                    names(data) <- c("id", "age", "pd", "report")

                results <- rbind(results, data)

                        }

                }

write.csv(results, "pd99.csv")
```