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Everyday visual function and the visual experience in dry age-related macular degeneration

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A Thesis submitted for the degree of Doctor of Philosophy



Division of Optometry and Visual Science

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List of Abbreviations

AMD: Age-related macular degeneration

ANOVA: Analysis of variance (ANCOVA: Analysis of covariance)

ARM: Age-related maculopathy

AT: Average threshold

BB: Big button

BCVA: Best corrected visual acuity

CFMT: Cambridge Face Memory Test

cGMP: Cyclic guanosine monophosphate

CI: Confidence interval

CNV: Choroidal neovascularisation

CS: Contrast sensitivity

DLS: Differential light sensitivity

DLTV: Daily Living Tasks Dependent on Vision Questionnaire

EQ-5D: EuroQol-5 Dimension Questionnaire

ETDRS: Early treatment in diabetic retinopathy study

FAF: Fundus autofluorescence

FDA: Food and Drugs Administration

FR: Face recognition

GA: Geographic atrophy

HDL: High density lipoprotein

IQR: Interquartile range

LOCS III: Lens Opacities Classification Scale III

LogMAR: Log minimum angle of resolution

MMAT: Mixed methods appraisal tool

MMSE: Mini Mental Status Evaluation

nAMD: Neovascular age-related macular degeneration

NEI: National Eye Institute

NEI-VFQ: National Eye Institute Visual Functioning Questionnaire

NHS: National Health Service

NICE: National Institute for Health and Care Excellence

OCT: Optical coherence tomography (SD-OCT: Spectral domain OCT, TD-OCT: Time domain OCT)

PR: Pelli-Robson

PROM: Patient reported outcome measure

QoL: Quality of life (HRQoL: Health-related quality of life)

RCT: Randomised controlled trial

RPD: Reticular pseudodrusen

RPE: Retinal pigment epithelium

SD: Standard Deviation

SE: Standard error

VA: Visual acuity (BCVA: Best corrected visual acuity)

VEGF: Vascular endothelial growth factor

WHO: World Health Organisation

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I would like to express my huge appreciation to the volunteers who have given up hours of their time, sometimes travelling halfway across the country (!), in order to participate in this research. Willing participants are absolutely vital for this type of research, but talking to them and hearing their stories often also serves as a reminder to the researcher of why patient-centred research is so important.

This work would not have been possible without the financial support of Roche Products Ltd UK and I am immensely grateful for this.

Finally, to my family: to Mum, Dad and Adam, for their constant love and inspiration, and to Elliott, whose energy and enthusiasm keep me going, thank you for being by my side throughout this PhD and always.

Declaration

The work contained in this thesis was completed by the candidate, Deanna Jayne Taylor (DJT), under the supervision of Professor David Crabb and Dr Alison Binns. It has not been submitted for any other degrees, either now or in the past. Where work contained within it has been previously published, this has been stated in the text. All sources of information have been acknowledged and references have been given. The University Librarian of City, University of London is permitted to allow the thesis to be copied in whole or in part without further reference to the author. This permission covers only single copies made for study purposes, subject to normal conditions of acknowledgement.

Abstract

Dry age-related macular degeneration (AMD) is a common eye condition, which causes progressive loss of central vision; there is currently no treatment. The five studies presented in this thesis aimed to explore different aspects of everyday visual function and the experience of living with dry AMD. In the first study, a systematic review of the literature surrounding quality of life and 'real-world' visual ability in AMD was conducted. Several domains of everyday life affected by AMD were identified; these had been investigated using a wide variety of study designs. However, only 4% of studies meeting inclusion criteria specifically investigated individuals with dry AMD. In the second and third studies, people (>60 years, logMAR binocular visual acuity of 0.7 or better) categorised with varying severities of dry AMD performed two previously validated computer-based real-world visual tasks. Comparisons for both tasks were made against a 90% normative limit for the outcome measures established in age-related peers with healthy vision. In a search task, participants were instructed to find items within digital photographs of everyday indoor and outdoor scenes. Sixty-one percent of participants with dry AMD, (including all of those with late dry AMD) exceeded the 90% normative limits for average search time; this was statistically significant (Fisher's exact test, $p < 0.0001$). In a face recognition task, participants completed a modified version of the Cambridge Face Memory Test. Percentage of correctly identified faces was used as an outcome measure. Five (17%) participants with dry AMD scored worse than the 90% limit (Fisher's exact test, $p=0.46$); four of these had fovea-involving geographic atrophy. In the fourth study, volunteers with dry AMD described their visual symptoms in an interview and were asked to comment on the realism of a photograph typically used to simulate vision in AMD. Interview transcripts underwent content analysis. The most frequently used visual symptom was blur (n=13) followed by missing part/s (n = 10) and distortion (n=7). Seventy-six percent (95% confidence interval 53 - 92%) of the participants rejected the realism of a popular image often used to portray the visual symptoms of AMD. In a fifth study, a novel test measuring mobility anxiety was introduced. Participants were shown a series of short movies of navigation through real-world mobility scenarios and were asked to press on a button during scenes which would cause them anxiety or discomfort. Pressure on the button was recorded throughout the test and this was used as an outcome measure. People with intermediate and late AMD applied more pressure to the button, on average, than those with early and no AMD (Kruskal-Wallis test, $p=0.04$). Situations involving negotiating stairs were identified as particularly problematic. To conclude, these studies spotlight the problems people with dry AMD have with visual tasks. In addition, the tests described in this thesis may have potential to be used as patient-based outcome measures for clinical trials for future treatments for dry AMD. Moreover, findings reported in this thesis may help clinicians with patient management and expectations, and should inform future patient, public and professional education about dry AMD.

Chapter 1 Introduction to thesis

The overarching aim of this PhD was to investigate patient relevant aspects of visual function and self-reported visual experience in people with non-neovascular age-related macular degeneration (AMD). In order to clarify the rationale and specific aims for the thesis, this chapter presents a summary of relevant background literature. The chapter concludes with the specific aims and outline of the thesis.

1.1 Age-related macular degeneration: an overview

1.1.1 Prevalence and impact of AMD

Age-related macular degeneration (AMD) is a potentially blinding condition, which causes progressive loss of central vision. It is the leading cause of blindness in the developed world, and is responsible for 50% of severe sight impairment registrations and 52.5% of sight impairment registrations in England and Wales (Quartilho et al., 2016). It is also the third most common cause of blindness worldwide after cataract and glaucoma (Pascolini and Mariotti, 2012). It is primarily a disease of older age; in the UK, prevalence of advanced disease is 2.4% in the population aged 50 years and older, but this increases to 4.8% for those aged ≥ 65 years and 12.2% for people aged ≥ 80 years (Owen et al., 2012). Numbers of people with AMD are set to rise as the world's population both increases and ages; 196 million people worldwide are predicted to be affected by 2020 and 288 million by 2040 (Wong et al., 2014).

A number of known risk factors are associated with AMD. According to a systematic review and meta-analysis of clinical risk factors (Chakravarthy et al., 2010), increasing age, cigarette smoking, previous cataract surgery and family history of AMD are the strongest clinical risk factors for late AMD, with consistent evidence across the literature. Additionally, high body mass index, history of cardiovascular disease, hypertension, and high plasma fibrinogen were found to have moderate associations with development of late AMD. Finally, gender, ethnicity, diabetes, iris colour, history of cerebrovascular disease, serum total, and HDL cholesterol, and triglyceride levels were found to have weak and inconsistent associations with late AMD (Chakravarthy et al., 2010). Other known risk factors include sunlight exposure (see Sui et al., 2013 for review) and diet (Carneiro and Andrade, 2017, Chong et al., 2008a, Chong et al., 2008b). Genetics are also known to play a role in the development of AMD; for example, certain variants of genes CFH, HTRA1 and ARMS2/LOC387715 are all reported to have strong associations with AMD (Chen et al., 2010),

although the exact links between genetic and environmental factors are yet to be established (Lambert et al., 2016).

Age-related macular degeneration has a substantial detrimental impact both on a personal and societal level. With respect to the individual, it is associated with reduced quality of life (QoL) (Mitchell and Bradley, 2006), increased risk of depression (Brody et al., 2001) and impaired ability to perform everyday tasks (Taylor et al., 2016, see Chapter 2). In terms of societal effects, increasing vision loss in AMD has been reported to be associated with increased assistance from caregivers, about three quarters of which was unpaid (e.g. assistance from friends or family) (Schmier et al., 2006b). There is also a substantial economic burden associated with AMD. Costs include healthcare and treatment costs (Schmier et al., 2012), lost wages (as a result of being unable to work), transportation costs (for example travel to healthcare appointments), caregiver costs, and costs incurred as a result of falls and other injuries acquired due to impaired vision (Brown et al., 2005).

1.1.2 Structure of the macula

Age-related macular degeneration is a condition that primarily affects the outer retina and associated structures within the macular region. This section provides an overview of these structures.

The macula is the part of the retina responsible for the central, most detailed part of vision. It is situated directly behind the pupil and measures approximately 6mm in diameter, corresponding to the central 20° of visual field (Klein et al., 1991). In fundus photography, it appears as a dark spot (the word 'macula' means 'spot' or stain' in Latin) in the centre of the retina, temporal to the optic disc. The fovea is the central part of the macula, measuring approximately 1.5mm in diameter, and the fovea's central point is the foveola. The fovea appears in cross-sectional imaging as a pit; this arises from eccentric displacement of intermediary neurons found in the inner layers of the retina. Surrounding the foveal pit is the foveal rim; this area is relatively thick as a result of containing the displaced neurons (Provis et al., 2013, Marshall, 1987). The visible difference in colour of the macula compared with the rest of the retina results from presence of macular pigment; lutein, zeaxanthin and mesozeaxanthin (Whitehead et al., 2006).

Photoreceptors are distributed across the whole of the retina (Curcio et al., 1990) and comprise rods, which detect visual stimuli under low lighting conditions, and cones, which detect colour and visual stimuli under brighter lighting conditions (Jackson et al., 2002). In a healthy retina, the highest density of cone photoreceptors is found at the foveola and cone density sharply decreases with increasing eccentricity from the fovea. Rod photoreceptors, which outnumber cone photoreceptors

across the retina, are not found in the fovea, but increase in density with increasing eccentricity from the fovea, reaching peak density in an ellipse at the eccentricity of the optic disc, reducing in density again towards the peripheral retina (see Figure 1.1) (Osterberg, 1935).

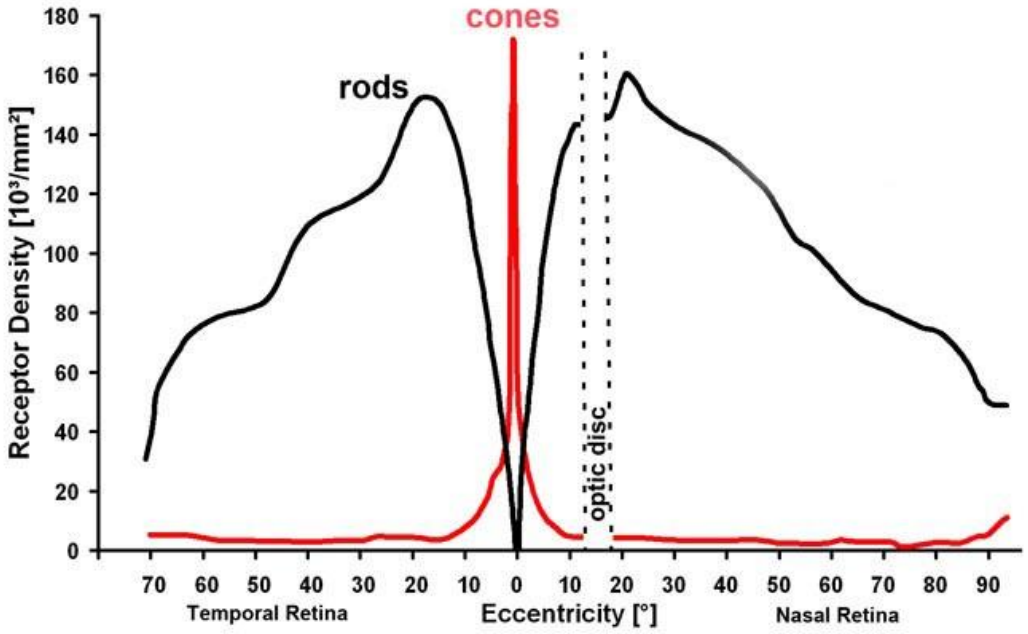


Figure 1.1: Graph showing horizontal distribution of rods and cones across the retina. Image from Osterberg, 1935, accessed from *http://webvision.med.utah.edu/*.

Whilst cone numbers remain stable, rod numbers in the parafovea decrease in normal ageing (Curcio, 2001). Photoreceptors consist of a synaptic terminal, an outer segment, an inner segment, and a cilium connecting the two segments (Kevany and Palczewski, 2010, Mustafi et al., 2009). The outer segment of photoreceptors contains photosensitive pigment (rhodopsin in rods or iodopsin in cones) (Kevany and Palczewski, 2010). These pigments are embedded within membranous discs which are configured either as invaginations of the membrane of the outer segment (cones), or as discrete discs stacked within the outer segment (rods) (Mustafi, et al., 2009). Phototransduction is the process by which light is converted into electrical nerve signals and begins when a photon of light is absorbed by the 11-cis retinal chromophore of a photopigment molecule. In rods (for which this process is better understood) this isomerises the 11-cis retinal to all-trans retinal, which initiates the breakdown of rhodopsin to metarhodopsin II and triggers a biochemical cascade which ultimately leads to closure of cyclic guanosine monophosphate (cGMP)-sensitive cation channels at the cell's plasma membrane, causing hyperpolarisation of the cell. For a detailed review of the phototransduction cascade, see Burns & Baylor (Burns and Baylor, 2001). Following phototransduction, the photoreceptor is unable

absorb further photons of light until its all-trans retinal has been regenerated into its 11-cis form and recombined with opsin. The series of reactions which then take place to facilitate this generation is known as the retinoid cycle – for review see Lamb & Pugh (Lamb and Pugh, 2004).

Directly behind the photoreceptors is the retinal pigment epithelium (RPE). This single layer of hexagonal cells is part of the blood-retinal barrier and has a vital role in the transport of nutrients and waste products into and out of the retina (Bok, 1993, Boulton and Dayhaw-Barker, 2001). This role is aided by its structure; the basement membrane forms part of the underlying Bruch's membrane, whilst the apical membrane comprises numerous microvilli which interdigitate with the tips of the photoreceptor outer segments, increasing the surface area for transport of materials (Strauss, 2005). Whilst the RPE and photoreceptors are closely apposed, there is no physical connection between the two layers. An additional role of the RPE is the pumping of fluid from this potential space between retina and RPE, in order to avoid the formation of a detachment (Marmor, 1990). The RPE also contains numerous melanin pigment granules, which absorb excess light, preventing photo-oxidative damage to the retina and reducing the effect of intraocular scattered light on image quality (Strauss, 2005, Cai et al., 2000). The RPE is also responsible for daily phagocytosis of photoreceptor outer segments, and the processing of waste materials (Kevany and Palczewski, 2010). Another key function is the isomerisation of all-trans retinol into its 11-cis configuration – a key part of the visual cycle (Lamb and Pugh, 2004). Several reviews describe the functions of the RPE and the effects of ageing and AMD on these functions in detail (Kevany and Palczewski, 2010, Mustafi et al., 2009, Curcio et al., 2000, Jackson et al., 2002, Bhutto and Lutty, 2012, Marshall, 1987, Sparrow et al., 2010).

Posterior to the RPE lies Bruch's membrane; this semi-permeable membrane separates the RPE from the blood vessels of the choroid (the choriocapillaris). The structure and function of Bruch's membrane have been reviewed in health (Booij et al., 2010) and in ageing (Guymer et al., 1999). It is acellular and consists of five layers: the basement membrane of the RPE, an inner collagenous layer, an elastin layer, an outer collagenous layer, and the basement membrane of the choriocapillaris (Booij et al., 2010). Key functions of Bruch's membrane include regulation of transport of materials between the RPE and choriocapillaris, physical support for RPE cell adhesion, and blocking cellular migration between the retina and the choroid (Booij et al., 2010, Bhutto and Lutty, 2012). The choriocapillaris, which lies posterior to Bruch's membrane, provides blood supply to the outer retina. Endothelial cells of blood vessels within the choriocapillaris are fenestrated; this is believed to aid transfer of products between blood and tissue and vice versa (Shimomura et al., 2009, Bernstein and Hollenberg, 1965).

A schematic of these layers can be viewed in Figure 1.2.

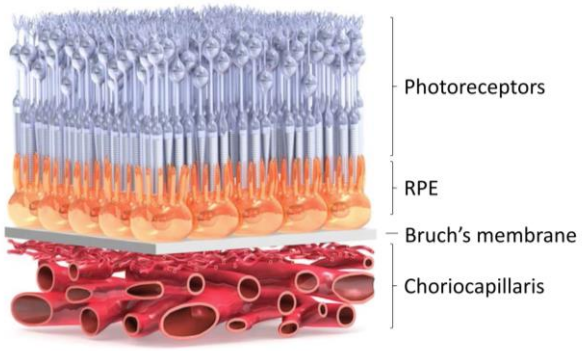


Figure 1.2: Diagram showing structure of the outer retinal layers in a healthy eye. Image adapted from *www.geographicatrophy.org*.

1.1.3 Stages of AMD

Age-related macular degeneration can be categorised into severity stages. In its early and intermediate stages, yellow/white deposits known as drusen build up beneath the RPE (Ferris et al., 2013). They may be principally classified as 'hard' drusen or 'druplets', which are small (≤63 μm) with distinct borders, or 'soft' drusen which may be larger in size and have indistinct borders. Hard drusen are believed to be a feature of normal ageing whilst soft drusen are a feature of AMD (Bird et al., 1995), although there is evidence that multiple hard drusen may be a risk factor for advanced AMD (Klein et al., 2015). Soft drusen contain proteins (apolipoprotein E, vitronectin, complement factor H) (Rudolf et al., 2008), lipids (esterified and unesterified cholesterol) (Curcio et al., 2005) and minerals (hydroxyapatite) (Thompson et al., 2015). As the disease progresses, drusen may increase in size, number or both size and number (Jager et al., 2008). Drusen may also regress; growth and regression of drusen may occur simultaneously (Smith et al., 2010). Several studies have reported regression of drusen to be a potential precursor to development of late AMD (Schlanitz et al., 2017, Yehoshua et al., 2011b, Klein et al., 2008, Toy et al., 2013). A third type of deposit associated with AMD is known as reticular pseudodrusen. These are visible on ophthalmoscopy and colour fundus photography as 'yellowish interlacing patterns' (Sarks et al., 2011). SD-OCT imaging (see section 1.2.5) reveals these to consist of hyperreflective material accumulated above the RPE, leading to the alternative term of subretinal drusenoid deposits (Zweifel et al., 2010). Several studies have found a strong relationship between reticular pseudodrusen and increased risk of progression to late AMD (Hogg, 2014, Alten and Eter, 2015).

Focal pigmentary disturbances are another feature of intermediate AMD (Ferris et al., 2013). These are described as either hyperpigmentation (clumps of grey or black pigment in or beneath the retina) or as hypopigmentation (small areas of depigmentation) (Age-Related Eye Disease Study Research

Group, 2001a). These, along with the presence of large soft drusen, are associated with an increased risk of subsequent progression to late AMD (Ferris et al., 2013). According to the Age-Related Eye Disease Study, the presence of large drusen and focal pigmentary changes in both eyes was associated with a 47% risk of 5-year progression to AMD, compared to only 0.5% risk in eyes with neither feature (Age-Related Eye Disease Study Research Group, 2005).

Late AMD may take one of two forms. In geographic atrophy (GA), areas of the macula continue to degenerate in a gradual and slowly progressive manner. In GA, RPE cell degeneration and death are believed to precede degeneration and death of neighbouring photoreceptors and choriocapillaris (Roth et al., 2004). This is viewed as sharply demarcated round or oval areas of hypopigmentation in which choroidal blood vessels are more visible than in surrounding areas (Bird et al., 1995). The pattern of geographic atrophy typically follows that of rod photoreceptor density initially, i.e. affecting parafoveal regions first, extending eccentrically, sparing the fovea (known as 'foveal sparing'), finally affecting the fovea in its end stages (Sarks et al., 1988, Sunness et al., 1999, Sunness et al., 2008).

Neovascular AMD (nAMD; wet AMD; exudative AMD) occurs as a result of growth of new blood vessels (choroidal neovascularisation; CNV) originating from the choroid, proliferating beneath or above the RPE. This is a consequence of an imbalance of angiogenic factors such as vascular endothelial growth factors (VEGFs) (Witmer et al., 2003). These blood vessels are often fragile and are susceptible to rupture and leakage, causing haemorrhages, RPE detachment and subsequent scarring (Bird et al., 1995), leading to sudden and profound vision loss.

In the UK, prevalence of GA is 1.3% (for people aged ≥ 50 years), 2.6% (≥ 65 years) and 6.7% (≥ 80 years), and prevalence of nAMD is 1.2% (≥ 50 years), 2.5% (≥ 65 years) and 6.3% (≥ 80 years) (Owen et al., 2012). Geographic atrophy comprised 53% of sight impairment registrations which were attributable to AMD in England in 2011-2012 (Bunce et al., 2015). This was a higher proportion than had been reported previously and Bunce et al suggest this may be attributable to the recent success of treatments for nAMD (see section 1.1.5).

The existing literature uses a variety of terminologies and classification systems for AMD. In this work, the recent classification proposed by the Beckman Initiative for Macular Research Committee (Ferris et al., 2013) will be used to classify AMD stage. Any non-neovascular AMD (i.e. early and intermediate AMD and GA) will be considered dry AMD. Figure 1.3 shows a flowchart of the natural history of AMD from a healthy retina to late AMD, classified according to the Beckman Classification.

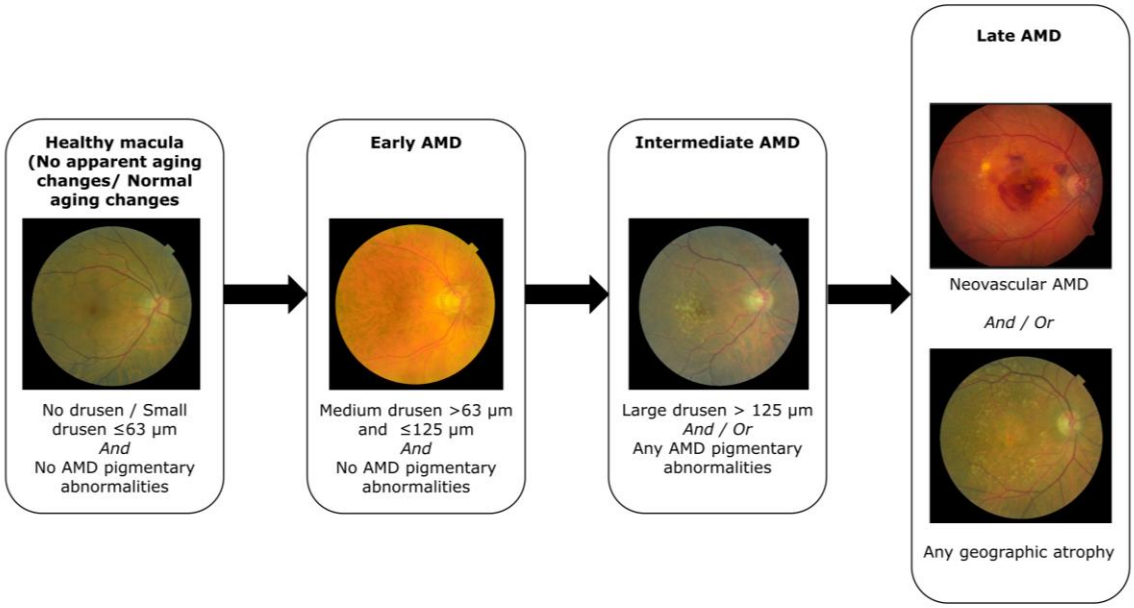


Figure 1.3: Flowchart showing photographs of retinae (right eye) at different stages in the natural history of AMD according to the Beckman Classification (Ferris et al., 2013). (Image of nAMD from National Eye Institute, National Institutes of Health. Other images belong to the author.)

1.1.4 Symptoms, detection and monitoring

Typical symptoms associated with AMD include blurred vision, distortion (often referred to as metamorphopsia), and central dark/missing areas in vision. However, much of the existing research investigating visual symptoms in AMD relates symptoms to advanced AMD and in particular to nAMD (Hessellund et al., 2012, Fine et al., 1986). Less is known about visual symptoms when disease is in its earlier stages, although there is some evidence that individuals with intermediate AMD begin to experience problems under conditions of low luminance (Wu et al., 2016). Individuals with dry AMD of varying severity were interviewed about their visual symptoms as part of this programme of research; this study is described in Chapter 5.

Age-related macular degeneration is usually identified by optometrists or ophthalmologists; early AMD may be asymptomatic and may be an incidental finding at a routine eye examination. However, a recent study (Neely et al., 2017) reported that 25% of 1,288 eyes examined with dilated fundus examination in primary care eye clinics in Birmingham, Alabama over a 31 month period whose macular health was 'normal' according to their medical record, actually had AMD. The prevalence of these undiagnosed cases was equal for patients examined by optometrists and ophthalmologists. This indicates that clinical professionals are not always able to recognise the subtle fundus features

associated with early stage disease. This is important because even in its earlier stages, although no pharmacological treatment is available, lifestyle modifications (for example stopping smoking) can be recommended to patients in order to reduce their risk of disease progression (see section 1.1.5). Patients may also be instructed to self-monitor for signs of conversion to nAMD, and advised on the appropriate course of action to take if changes are noticed in their vision. Moreover, as potential treatments do become available for dry AMD, early detection of disease may become even more crucial.

1.1.5 Treatment and management

Pharmacological treatment of AMD is currently limited to nAMD. One of the agents intrinsic to CNV formation is vascular endothelial growth factor (VEGF). The term 'VEGF' was coined by Ferrara & Henzel (1989) and is used to describe a protein which has 'selective growth promoting effects on vascular endothelial cells' (Ferrara, 2010) (thus encouraging growth of blood vessels). This may be inhibited by the introduction of VEGF inhibitors (known as anti-VEGF drugs). These are administered as intra-vitreal injections, and aim to prevent neovascularisation. The first of these to be approved by the US Food and Drug Administration (FDA) was pegaptanib in 2004. Since then, other anti-VEGF drugs have been developed and entered mainstream use for treatment of nAMD. Ranibizumab was FDA approved for use in nAMD in 2006 and mostly replaced pegaptanib in clinics due to its superior visual outcomes (Ip et al., 2008). Ranibizumab is able to halt progression of vision loss in most cases (Ying et al., 2014), and in many cases an improvement in visual function is observed (Ying et al., 2015). Bevacizumab has a similar mode of action to ranibizumab and a recent systematic review reports similar efficacy to ranibizumab and lower treatment costs (Solomon et al., 2016). At the present time, bevacizumab remains unapproved by the FDA or the National Institute for Health and Care Excellence (NICE) for use in AMD, although some clinicians choose to use this drug 'off-label'. A fourth anti-VEGF drug, aflibercept, was FDA approved in 2011. It demonstrates similar visual outcomes to ranibizumab and bevacizumab, with less frequent intra-vitreal injections required, and is now widely used (Agarwal et al., 2016, Schmidt-Erfurth et al., 2014). NICE approves the use of ranibizumab and aflibercept for the treatment of nAMD in England, where certain clinical requirements are met. For a more detailed overview of the history of the discovery of VEGF and the use of anti-VEGF drugs, see the work of Ferrara et al. (Ferrara, 2002, Ferrara, 2004, Ferrara, 2010).

Whilst no treatments currently exist for dry AMD, a number of potential therapies are currently reaching stage 2 and 3 clinical trials (Sadda et al., 2016). Several approaches to treating dry AMD are being explored. One such approach targets the complement system. This system, which is part of the

body's innate immune system, works to protect the body from invading bacteria and pathogens by means of three separate pathways. A number of genetic variants involved in the complement system have been implicated in increasing risk of AMD progression (Bradley et al., 2011, Gemenetzi and Lotery, 2016). The pathway known as the 'alternative pathway' is believed to have particular significance in AMD (Tan et al., 2016). This pathway is triggered when invaders, such as bacteria, are detected. As the proteins involved in its activation are constantly present in the blood, the system must be tightly regulated to avoid unwanted activation, which would lead to inflammation. Individuals with AMD are reported to have a genetic predisposition to a variant of a protein known as complement factor H, which is involved in regulation of the complement system (Clark et al., 2010, McHarg et al., 2015). This variant of complement factor H leads to dysregulation of the alternative pathway of the complement system, thus allowing chronic local inflammation in the macula which contributes to AMD. Because the complement system comprises part of the body's immune system, one challenge of suppressing the complement system in the attempt to treat AMD is ensuring that the treated individual is not put at risk of dangerous infections. For example, long term use of eculizumab, a drug that suppresses the complement system whose use has been explored (unsuccessfully) in dry AMD, is associated with increased risk of *Neisseria meningitides* infection (Parker, 2009). Lampalizumab (FCD4514S, Genentech/Roche, Basel, Switzerland) is another drug which specifically targets the alternative pathway of the complement system, leaving the other two pathways unaffected, thus allowing the body to continue to fight infection (Clark and Bishop, 2015). Lampalizumab is currently the subject of two phase 3 clinical trials, after a phase 2 randomised controlled trial (the MAHALO study) demonstrated reduction in GA progression compared with sham injections (Yaspan et al., 2017). However, in September 2017, Roche announced that one of these trials (Spectri; GX29185; NCT02247531) did not meet its primary endpoint (Roche, 2017).

While the approach described above is promising, one limitation is that, thus far, the therapies under investigation will, at best, reduce the progression of AMD, and will not replace diseased or lost cells and photoreceptors. One approach that addresses this issue is stem cell therapy (Olmos et al., 2015). Stem cells are unique in their ability to differentiate into RPE cells or photoreceptors under specific defined conditions and may therefore replace lost RPE cells or photoreceptors on implantation (Mu et al., 2014). However, this mode of therapy is not without risks; patients must be immunosuppressed to prevent rejection of the implant. Furthermore, the formation of tumours is common when cells do not differentiate sufficiently precisely (Garg et al., 2017, Melville et al., 2013). Nonetheless, this approach has received much attention in the literature in recent years and is the subject of several ongoing clinical trials. See Olmos et al. (2015) for an overview of stem cell therapy undergoing clinical

trials in dry AMD. Other therapies under current investigation for GA include visual cycle inhibition (aiming to reduce the accumulation of toxins in the retina), neuroprotection (preventing photoreceptor cell loss) (Holz et al., 2014) and non-pharmaceutical modification of retinal oxygen consumption (reducing outer retinal hypoxia) using low level night lighting (McKeague et al., 2014).

Aside from pharmacological treatments, a number of lifestyle modifications may be recommended to at-risk patients, based on known risk factors for the disease, several of which are modifiable (see section 1.1.1). In a robust clinical trial of more than 3000 participants, the Age-Related Eye Disease Study (AREDS) showed that daily oral dietary supplementation of antioxidants (500mg of vitamin C, 400 international units of vitamin E and 15 mg of beta carotene) plus zinc (80 mg of zinc as zinc oxide with 2 mg of copper as cupric oxide) reduced risk of progression to late AMD by 25% amongst individuals with extensive intermediate drusen, non-central GA, at least one large druse, reduced vision as a result of AMD in one eye or late AMD in one eye (Age-Related Eye Disease Study Research Group, 2001b). The second AREDS trial investigated the effects of adding carotenoids (lutein and zeaxanthin), omega-3 long-chain polyunsaturated fatty acids (docosahexaenoic acid [DHA] and eicosapentaenoic acid [EPA]), or both, and eliminating beta carotene, lowering zinc dosage, or both from the original AREDS formulation. Key findings indicated that addition of omega-3, lutein and zeaxanthin did not reduce risk of progression to late AMD above and beyond the original AREDS formulation in well-nourished individuals. However, a sub-analysis indicated that lutein and zeaxanthin may further delay disease progression in those individuals with the lowest dietary intake of xanthophylls. Furthermore, lutein and zeaxanthin may be useful as an alternative dietary supplementation to beta-carotene, which is associated with increased risk of lung cancer in smokers (Age-Related Eye Disease Study 2 Research Group, 2014).

Many individuals with AMD are advised by their eye-care practitioner to self-monitor for symptoms of conversion to nAMD with an Amsler chart. This chart, introduced by Marc Amsler (Amsler, 1947, Amsler, 1953) in the mid-twentieth century consists of horizontal and vertical black lines, forming a grid, with a central black fixation spot on a white background which covers approximately 20° of the visual field when held at 30cm (Figure 1.4). Patients are instructed to self-test monocularly with their near vision correction and to observe and report any blind spots, blurred or missing areas, or areas that appear to be wavy or distorted. Seven variations of the grid exist, with modifications such as diagonal lines to help with fixation, and a version with white lines on a black background. However, the value of this strategy in screening for nAMD has been questioned. For example, it is commonplace to notice disturbances on the Amsler grid with forms of AMD other than nAMD (Faes et al., 2014).

Conversely, visual disturbances resulting from nAMD may be masked by perceptual 'filling-in' (Crossland and Rubin, 2007); this is a well-established phenomenon whereby areas of the visual field containing scant visual stimuli appear uniform with their surrounding areas (Komatsu, 2006).

Additional management strategies for advanced AMD include low vision rehabilitation, such as low vision aids and devices, and vision training programmes (Hooper et al., 2008). Treatment for the psychological effects of AMD might include peer support, medication or counselling (Dawson et al., 2014). Finally, visual impairment registration may provide eligible individuals with financial concessions (e.g. half-price TV Licence, help with NHS costs, help with Council Tax bill and tax allowances, and free public transport) and advice (Cook et al., 2008).

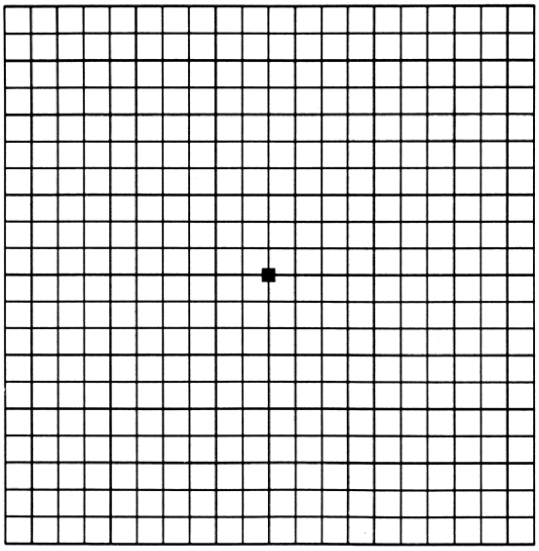


Figure 1.4: Amsler grid. Image from National Eye Institute, National Institutes of Health.

1.2 Clinical measures of visual function and retinal structures in AMD

This section introduces clinical measures of visual function and retinal imaging methods used for the assessment of AMD. A focus is placed on those techniques used in the studies presented in this thesis.

1.2.1 Visual Acuity

Visual acuity (VA), the ability of an eye to resolve detail at high contrast , is arguably the most widely known and accepted measure of visual function (McClure et al., 2000). It is traditionally measured using a high contrast letter chart, for example charts based on Snellen acuity or logMAR acuity testing (Figure 1.5). These charts typically consist of uppercase letters (or other optotypes) arranged in rows

with largest letters at the top of the chart, and progressively smaller letters going down the chart (Kaiser, 2009).

The Snellen acuity chart (Figure 1.5) is most commonly found chart in clinical practice and is widely used and accepted. This test has several important limitations (Kaiser, 2009, Bailey and Lovie, 1976). One disadvantage is the difference in the difficulty of the test depending on vision level. For example, only one letter is required to be read on the top row in order to proceed to the next difficulty level, whereas eight or more letters are available per line towards the bottom of the chart. Furthermore, the lack of letters on higher lines means that the chart is easily remembered for those with visual impairment, and there is less scope to determine the fine gradations of vision when there are only one or two letters to read. In a study comparing Snellen VA to that obtained with a chart that addresses these issues, the discrepancies between VA measurements between the two charts was much greater for those with low vision than for those with normal vision (Falkenstein et al., 2008). The ability to discriminate letters or optotypes is affected by the proximity of adjacent letters or optotypes (Flom et al., 1963); this phenomenon is known as crowding. Snellen charts are subject to differences in crowding effects as a result of the proximity of letters on each line reducing from the top of the chart (where spacing between letters is relatively wide) to the bottom (where spacing between letters is relatively narrow).

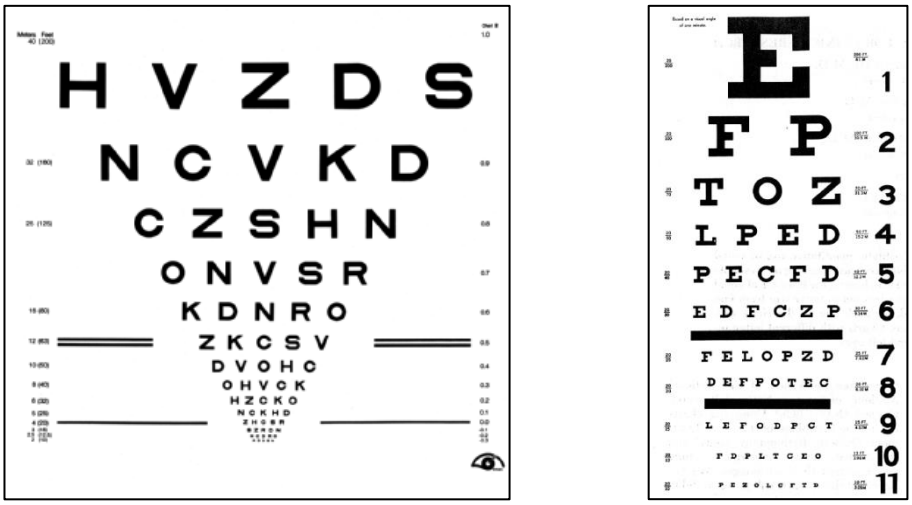


Figure 1.5: Two visual acuity charts: an ETDRS chart (left) and a Snellen chart (right). (Images from National Eye Institute, National Institutes of Health).

LogMAR visual acuity is more commonly used in research and may be measured using charts such as Early Treatment Diabetic Retinopathy Study (ETDRS) charts (Ferris et al., 1982) (Figure 1.5) or Bailey-Lovie charts (Bailey and Lovie, 1976). Their main advantage over Snellen charts is the use of equal numbers of target letters per line, equal steps between lines, equal spacing between lines and

letters across the chart, and the scoring method, which takes into account all letters read, and may be readily statistically analysed. Visual acuity is the primary and gold standard outcome measure in the vast majority of AMD clinical trials, yet its ability to detect changes in visual function in AMD is disputed in the literature. In early disease, small decreases in VA may be masked by its wide test-retest variability (Hogg and Chakravarthy, 2006). Furthermore, in late AMD, non-foveal atrophy is likely to result in reduced perceived visual function but is unlikely to result in VA reduction; foveal atrophy is likely to cause an initial VA loss while subsequent growth of atrophy extending eccentrically beyond the fovea may well be noticed by the patient but is unlikely to cause further deterioration in VA (Sadda et al., 2016, Sunness and Applegate, 2005, Sunness et al., 2007).

1.2.2 Contrast Sensitivity

While VA measures the ability to resolve detail at high contrast, contrast sensitivity (CS) is a measure of ability to resolve at differing levels of contrast (McClure et al., 2000, Hogg and Chakravarthy, 2006). A variety of tests and scoring systems have been developed; some with fixed target size/ spatial frequency and varying contrast (e.g. the Pelli-Robson chart (Pelli and Robson, 1988)), others with fixed contrast and variable spatial frequency (e.g. the Bailey-Lovie high and low contrast acuity charts (Bailey and Lovie, 1976, Brown and Lovie-Kitchin, 1989), and some which assess contrast sensitivity at a range of stimulus sizes/spatial frequencies (e.g. the Vistech chart (Ginsburg, 1984)) and the Arden grating test (Arden and Jacobson, 1978, Pesudovs et al., 2003, Corwin and Richman, 1986). One of the most widely accepted clinical tests of contrast sensitivity is the Pelli-Robson chart ((Pelli and Robson, 1988), Figure 1.6); this test consists of sixteen triplets of letters of fixed size. Triplets reduce in contrast so that the first triplet on the chart (top left) is of highest contrast and the last triplet (bottom right) is of lowest contrast and is most difficult to read. Contrast sensitivity is believed to be independently associated with several important visual tasks, for example, mobility, driving, and face recognition (Hogg and Chakravarthy, 2006, Owsley et al., 1981, Glen et al., 2012, Mones and Rubin, 2005, Rubin et al., 1994, Haegerstrom-Portnoy et al., 2000, Rubin et al., 2001, Owsley, 2003, Wood and Troutbeck, 1995, Owsley et al., 2001b, West et al., 2002).

In early to intermediate AMD, several studies have reported contrast sensitivity at high and intermediate spatial frequencies to be reduced while VA remained relatively normal (Hogg and Chakravarthy, 2006, Sjöstrand and Frisén, 1977, Kleiner et al., 1988, Stangos et al., 1995). Contrast sensitivity at all spatial frequencies is reduced in late AMD (Sunness et al., 1997, Sjöstrand, 1979).



Figure 1.6: Pelli-Robson contrast sensitivity chart. Image from http://psych.nyu.edu/pelli/pellirobson/pelli-robson.gif [accessed 22/05/18].

1.2.3 Microperimetry

In AMD, rod photoreceptor sensitivity is impaired at an early stage in the disease process, followed by subsequent loss of cone photoreceptor sensitivity later in the disease (Owsley et al., 2000, Owsley et al., 2007, Curcio et al., 2000). Peak rod sensitivity impairment is reported to occur at 2 – 4° (equivalent to ~1 mm) eccentricity from the fovea (Owsley et al., 2000). This psychophysical finding is supported by the preferential loss of parafoveal rod photoreceptors reported to occur in early AMD in histological studies (Medeiros and Curcio, 2001, Curcio et al., 1996, Curcio, 2001).

One method of measuring central retinal sensitivity is microperimetry (Webb and Hughes, 1981). This psychophysical test offers an advantage over methods such as VA and contrast sensitivity as it is able to measure retinal sensitivity (as differential light sensitivity; DLS) at multiple individual points on the retina. It differs from standard automated perimetry in that it incorporates eye tracking; this is particularly useful for assessing people with AMD, whose fixation ability can be poor. Furthermore, it captures a real-time retinal image, onto which sensitivity results are superimposed, allowing mapping of functional measures onto retinal structures (Cassels et al., 2017, Midena and Pilotto, 2017), see Figure 1.7. Various microperimeters are now commercially available, including the MAIA microperimeter (CenterVue, Padova, Italy), which was used in the study described in Chapter 6.

Changes in macular sensitivity as measured using microperimetry during the various stages of AMD have been documented in two recent reviews (Cassels et al., 2017, Midena and Pilotto, 2017). In the early stages of AMD, macular sensitivity is reduced at the location of drusen and pigmentary abnormalities (Midena et al., 2007). Once GA develops, dense scotomas may be detected using microperimetry. These often develop first in the parafovea and progress in a horseshoe shape (see Figure 1.7B), sparing the fovea until the disease reaches its end stages (Sunness et al., 1995, Sunness et al., 2008, Pilotto et al., 2011, Sayegh et al., 2014). More recently, scotopic (dark-adapted) microperimetry has been introduced (Crossland et al., 2011). This newly developed technology assesses rod function; existing studies using this modality indicate that rod function is affected to a greater extent than cone function by the presence of RPD (Steinberg et al., 2015) and hard drusen (Nebbioso et al., 2014).

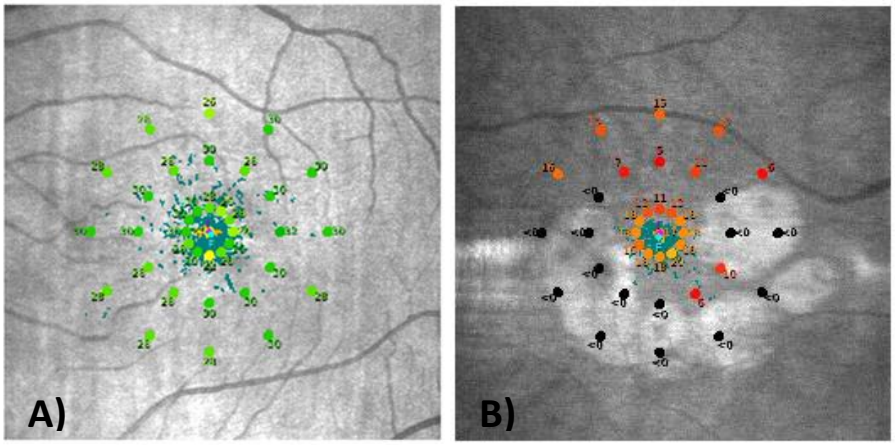


Figure 1.7: Outputs from the MAIA microperimeter (CenterVue, Padova, Italy) for two eyes; A shows a healthy macula and normal sensitivity across the macula, whilst B shows results from a macula with GA. The points are colour coded so that green represents good macular function, red represents poor macular function and black points represent areas where the patient is unable to perceive even the brightest stimuli. In B, areas of complete lack of sensitivity correspond clearly with visible areas of GA on the retinal image.

1.2.4 Other psychophysical measures of visual function

Several aspects of visual function may be assessed using psychophysical testing in AMD. These are reviewed extensively elsewhere (Neelam et al., 2009, Hogg and Chakravarthy, 2006) and are not the subject of this work. In brief however, early and intermediate AMD and GA are known have an effect on clinical and psychophysical measures of visual function, including the rate of dark adaptation (Dimitrov et al., 2008, Owsley et al., 2007, Owsley et al., 2001a), colour vision (especially blue-yellow discrimination) (O'Neill-Biba et al., 2010), and sensitivity to flickering stimuli (Mayer et al., 1992, Mayer et al., 1994). These aspects of visual function may be affected whilst VA remains near normal, and only mild retinal changes are observed.

1.2.5 Digital fundus photography

Digital fundus photography is a widely used method of imaging the retina. Fundus photography was first developed using the principles of ophthalmoscopy following the invention of the ophthalmoscope in the 19th century (Abràmoff et al., 2010). Digital fundus photography offers clear advantages over traditional film fundus photography in its ease of image accessibility and storage (Bernardes et al., 2011). Digital fundus photographs taken for the studies described in this thesis used a TRC-NW6S Non-Mydriatic Retinal Camera (Topcon medical systems Inc., Tokyo).

1.2.6 Optical Coherence Tomography

Optical Coherence Tomography (OCT) is a fairly recently developed but increasingly used technology which allows *in vivo* cross-sectional three dimensional scanning of different parts of the eye via interferometry (Huang et al., 1991). Its mode of action is similar to that of ultrasound, working on the principle of 'reflection' rather than echo. Interferometry uses the principle that the unknown distance of a sample from a light source can be measured by comparing the time delay in reflections from the sample to that of a reference beam reflected from a mirror of known distance which is attached to a reference arm. Because the various retinal structures have different reflective and light scattering properties, these may be differentiated using OCT. Initial OCT systems used time-domain OCT, which is limited in its speed and resolution ability because of its requirement for a moving reference arm. Spectral-domain OCT (SD-OCT) is implemented using a broadband light source, spectrometer and line scan camera; a Fourier transformation of the reflected spectra allows a depth scan to be calculated without movement of the reference arm (Gabriele et al., 2011, Fujimoto and Swanson, 2016). The majority of currently commercially available OCT devices use SD-OCT. OCT technologies are still developing and new techniques are emerging. For example, OCT angiography, which allows real-time non-invasive imaging of retinal blood vessels was FDA approved in 2016 (Kashani et al., 2017). Swept-source OCT uses a swept wavelength laser comprising long wavelength light (centred around 1050nm compared to 850nm wavelengths of standard SD-OCT) to allow visualisation of structures deeper than those visible using spectral domain OCT (e.g. the choroid and sclera). Ultrahigh speed imaging (100kHz axial scan rate) is used by the latest swept source OCTs to enable high resolution images to be obtained within a clinically viable timeframe (Wood et al., 2011a, Zafar et al., 2016, Ruiz-Medrano et al., 2014, Flores-Moreno et al., 2017, Park et al., 2014, Copete et al., 2014, Potsaid et al., 2010). Although it is still young, the impact of OCT

on the world of optometry and ophthalmology has been enormous, allowing detailed visualisation and measurement of retinal layers in a previously impossible non-invasive manner (Yehoshua et al., 2011a). For example, in the case of AMD, Figure 1.8 shows OCT images of a healthy macula, intermediate AMD and geographic atrophy respectively.

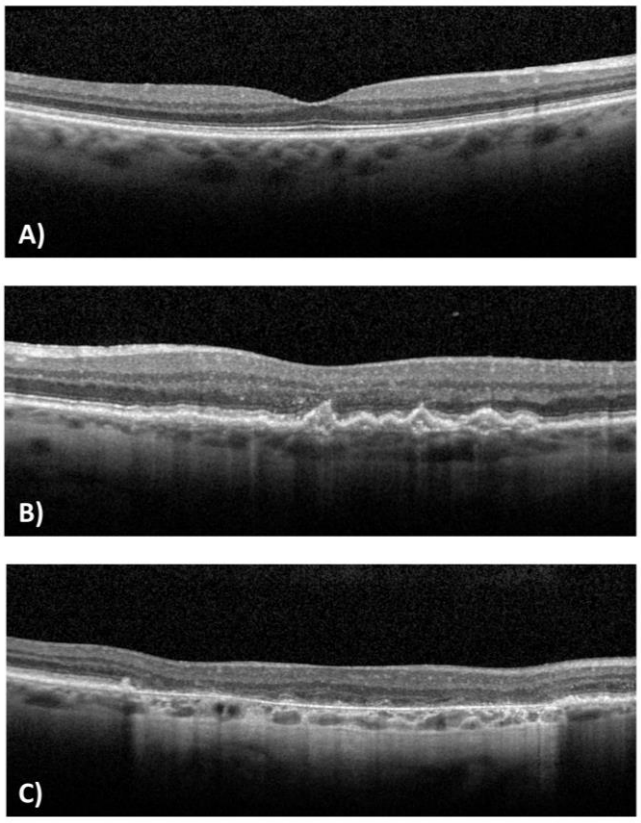


Figure 1.8: OCT scans. A shows a healthy macula, B shows a macula with intermediate AMD (soft drusen visible here as localised elevations of RPE), and C shows a macula with GA (enhanced visibility of the choroidal circulation here indicates a window defect due to loss of the heavily pigmented RPE). These scans were taken using a Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany).

1.2.7 Fundus autofluorescence

Fundus autofluorescence (FAF) is currently considered the gold standard tool for detecting GA (Schmidt-Erfurth et al., 2017). FAF works on the principle that lipofuscin, an autofluorescent material which is a by-product of photoreceptor phagocytosis, accumulates in RPE cells in normal ageing and, to a greater extent, in disease. In GA, areas of atrophy appears as clearly demarcated areas of hypo-autofluorescence surrounded by a band of hyper-autofluorescence; areas of increased autofluorescence may predict areas of future GA development (von Rückmann et al., 1997, Holz et al., 2001, Holz et al., 2007, Holz et al., 1999). FAF images for a healthy retina and for a retina with GA are shown in Figure 1.9.

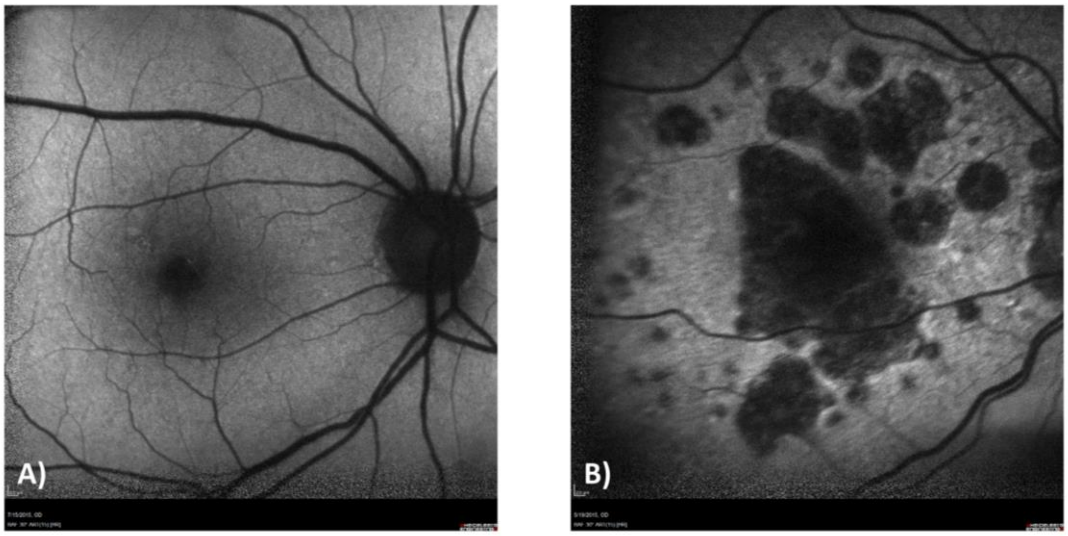


Figure 1.9: FAF images from an eye with early AMD (A) and an eye with GA (B) taken using a Spectralis (Heidelberg Engineering, Heidelberg, Germany).

1.3 Visual ability and disability

Visual disability is traditionally thought of as the loss of skills and abilities resulting from visual impairment, which in turn occurs as a result of a visual disorder (Russell et al., 2001). For example, in the case of AMD (the visual disorder), a resulting visual impairment might be reduced visual acuity, which might lead to difficulties with mobility (the visual disability). Visual disability may have consequences relating to the individual (e.g. depression), friends and family (e.g. care giving) and society (e.g. cost of low vision rehabilitation appointments). Interventions may be implemented at any stage along this continuum; for example anti-VEGF injections to treat AMD (the visual disorder), magnifiers to address reduced visual acuity (the visual impairment), white stick training to improve mobility (the visual disability) and counselling to target depression. The recent World Health Organisation International Classification of Functioning, Disability and Health (Kostanjsek, 2011) recognises the importance of personal and environmental factors on disability. Continuing the example of AMD and mobility, an example of a personal factor might be personality type, and an example of an environmental factor might be light level in a person's home. Differences in either of these factors might influence a person's level of ability or disability. Warrian et al (2010) identified a hierarchy of the overarching methods for assessing visual ability; these are:

1. Testing a person's ability – this involves observing and assessing a person actually doing a visual task and is the only direct method of assessing task performance

2. Asking the person about their ability – this might be in the form of questionnaires or through in-depth interviewing
3. Testing components of a person's ability – most traditional clinical tests of visual function fall into this category, for example, visual acuity and contrast sensitivity testing
4. Testing the factors that affect ability – in the case of AMD, this might involve grading a retinal photograph or OCT and using this result to predict visual function

The studies described in this work use computer-based surrogates of real-world tasks; this type of test permits the researcher to observe a person performing a task designed to be as similar as possible to the same task in the real-world, whilst allowing for a controlled experimental environment. A detailed review of the existing literature on visual ability and disability testing in AMD is provided in Chapter 2.

1.3.1 Visual disability as an outcome measure in clinical trials

As increasing numbers of potential therapies for dry AMD reach the stage of phase 2 and 3 clinical trials, finding appropriate outcome measures becomes ever more pertinent. A clinical endpoint should be a 'clinically meaningful measure of how a patient feels, functions, or survives' (Lesko and Atkinson, 2001). In other words, the outcome should be 'relevant to the patient' (Medeiros, 2017). Yet it has been acknowledged that traditional clinical measures, such as VA, do not reflect the patient's experience or the impact of disease on patients' lives (Denniston et al., 2014) and patient-reported outcome measures (PROMs) are now often used as secondary outcome measures in ophthalmic clinical trials (Brown et al., 2006, Rosenfeld et al., 2006, Chakravarthy et al., 2012, Krezel et al., 2015). However, discrepancies have been found between self-report and actual performance of a task (Pardhan et al., 2016, Friedman et al., 1999, McGwin et al., 1998, Hochberg et al., 2012). Moreover, perceived visual disability might be influenced by factors relating to an individual's personality (Rovner and Casten, 2001, Rovner et al., 2014). Therefore, other measures of assessing visual disability, such as those described in this work, may be more appropriate methods for assessing impact of AMD on people's day-to-day lives.

1.4 Rationale and aims of PhD

In order to provide an evidence base to support research into treatment of dry AMD, it is necessary to characterise the extent and nature of visual disability caused by the disease. This may also help improve disease awareness of AMD, and may provide important information for eye care professionals to help with management and rehabilitation of individuals with dry AMD. The use in

this PhD of novel and clinically applicable tests of visual disability with an emphasis on real-world relevance also presents new candidate outcome measures for future clinical trials of treatments for dry AMD.

The overall aim of this work, therefore, was to evaluate the difficulty that people with dry AMD (early and intermediate AMD and GA) experience with visual activities. This was achieved through a series of studies asking participants to carry out computer-based tests which simulated performance of daily activities. In addition, a further general aim was to investigate the individual experience of visual loss associated with dry AMD through asking participants to describe their visual symptoms.

Specifically, the following aims were investigated:

1) **To systematically review the literature investigating the effect of AMD on visual disability and QoL.** Different domains of everyday life affected by AMD were identified and explored, and methods for assessing these discussed. In addition, the review explored trends in specific topics within this body of literature (**see Chapter 2**).
2) **To investigate everyday visual search ability in people with dry AMD of varying severity.** Visual search is an important everyday task itself, and visual search performance is additionally believed to be a useful predictor for other daily activities, such as mobility (Fuhr et al., 2007). The hypothesis was that people with AMD would struggle more with everyday visual search tasks than age-related controls. Eye movements were recorded during the everyday search task and this was investigated as a secondary outcome measure **(see Chapter 3).**
3) **To investigate the effect of dry AMD on face recognition performance, using a validated face recognition test; the Cambridge Face Memory Test (CFMT).** The hypothesis tested was that face recognition performance is worse in people with dry AMD compared with visually healthy peers. Face recognition performance was compared between groups based on AMD severity. In addition, the value of visual acuity and contrast sensitivity as potential predictors of face recognition performance was explored. Results are discussed in the context of previous face recognition research and the implications of the results of this study for management of people with dry AMD are discussed (**see Chapter 4**).
4) **To investigate the *patient's perspective* of dry AMD.** For the study described in this chapter, individuals were interviewed about their experiences of dry AMD using semi-structured interviews. Interview transcripts were subjected to content analysis in order to derive a set of descriptors for visual symptoms of dry AMD. In addition to improving our

understanding of dry AMD from the patient's perspective, the results of this study may contribute towards patient and public education about the disease (**see Chapter 5**).

5) **To assess response anxiety with different everyday mobility situations in people with dry AMD using a novel computer-based test.** The hypothesis was that individuals with dry AMD perceive greater levels of mobility anxiety and concern than people with healthy vision. In this study, response anxiety to different everyday mobility situations was assessed. Levels of response anxiety were compared between groups of varying AMD severity, and potential predictors of mobility response anxiety were explored. In addition, anxiety levels were compared between different types of mobility situation (**see Chapter 6**).

Chapter 7 provides a brief summary of the key findings from this research and discusses these in the context of past and potential future work.

Chapter 2 How does age-related macular degeneration affect real-world visual ability and quality of life? A systematic review

2.1 Introduction

As described in Chapter 1, AMD is a highly prevalent condition which causes loss of central vision (Berdeaux et al., 2005). It is the most common cause of blindness in developed countries, and is labelled a 'priority eye disease' by the World Health Organisation (WHO) (Lamoureux et al., 2008). In the UK an incidence of 71,000 new cases of late AMD per year has been estimated (Owen et al., 2012). Incidence and prevalence are set to rise as the population ages (Wong et al., 2014).

Quality of life (QoL) is a subjective measure (Felce, 1997, Hammell, 2004) influenced by factors including expectations, relationships (WHOQoL Group, 1994), routine (Harvey, 1993), health and disability (Scaffa et al., 2008). QoL is often used interchangeably with *health status*, *functional status*, and *health-related quality of life* (Patrick and Bergner, 1990, Guyatt et al., 1993), although there are subtle differences between each of these (Patrick et al., 2011) (see Table 2.1). For the purpose of this review we use QoL to encompass these slightly different terms.

QoL is often measured using patient-reported outcome measures (PROMs), normally via a questionnaire (Clemons et al., 2003, Guyatt et al., 1986). This allows 'a better understanding of the relationship between the pathophysiology of eye disease and patient-reported functioning' (Mangione et al., 1999). Performance-based measures are another means of assessing functional ability or disability. Results from PROMs and performance-based measures may differ (Guralnik et al., 1989, Hochberg et al., 2012, Friedman et al., 1999); this review will therefore consider both.

As AMD incidence increases it is important to understand how it affects visual function and QoL. Previous large-scale systematic reviews, the most recent published over a decade ago (Berman and Brodaty, 2006, Mitchell and Bradley, 2006), concentrate on PROMs and do not describe real-world performance-based measures. More recent systematic reviews (Poku et al., 2013, Tosh et al., 2012, Pinquart and Pfeiffer, 2011, Dawson et al., 2014, Bennion et al., 2012) are much smaller scale, concentrating on only one aspect of visual ability or QoL in AMD, and again, do not consider performance-based measures. Progress in this field could be an important step towards designing appropriate strategies for monitoring disease progression, rehabilitation, justification of new treatments and designing more meaningful outcomes for clinical trials. This systematic review was conducted in order to investigate the effect of AMD on visual disability and QoL and explores trends in specific topics within this body of literature.

Table 2.1: Definitions of selected terms related to quality of life (adapted from Patrick et al. (2011))

Term	Definition
Functional status	An individual's effective ability to perform valued roles, tasks, or activities (e.g. going to work, playing sports, or housework).
Health-related quality of life (HRQoL)	Personal health status. HRQoL usually refers to aspects of our lives that are dominated or significantly influenced by our mental or physical well-being.
Quality of life (QoL)	An evaluation of all aspects of our lives, including, for example, where we live, how we live, and how we play, encompassing life factors such as family circumstances, finances, housing and job satisfaction.
Well-being	Subjective bodily and emotional states; how an individual feels; a state of mind distinct from functioning that pertains to behaviours and activities.

The work presented in this chapter forms a paper published in *BMJ Open* (Taylor et al., 2016); see list of supporting publications. The co-authors of this work are David Crabb (DC), Alison Binns (AB) and Angharad Hobby (AH). DJT and AH read and screened abstracts and full-text articles for inclusion and DJT appraised study quality. Any disagreements or uncertainties during the screening and quality appraisal process were referred to DC. DJT extracted data from articles selected for inclusion and wrote the paper, which was reviewed, edited and approved by DC and AB.

2.2 Methods

A search of the electronic databases MEDLINE, EMBASE, CINAHL, PsycINFO, PsychARTICLES and Health and Psychosocial Instruments was undertaken using keywords relating to AMD, QoL and real-world visual ability and disability (see Appendix 1 for a detailed breakdown of search terms).

Retrospective and prospective reference list searches were conducted for studies meeting eligibility criteria and relevant reviews. Eligible studies involved people diagnosed with AMD, considered an aspect of real-world visual ability or QoL as an outcome, were available in English and involved human participants only. Studies were excluded if they only considered standard clinical measures of visual function. They were also excluded if outcomes were a result of an intervention or treatment (including clinical trials) or if an abstract only was published (conference proceedings). Review articles were excluded. Two authors (DJT and AH) screened studies to assess eligibility. In the case of disagreements unresolved through discussion, a third author (DC) was consulted. Due to the extensive body of literature and existing reviews concerning the impact of AMD on reading (Kanonidou, 2011, Neelam et al., 2009), studies concerning this were excluded.

Relevant information (including study design, study population characteristics and outcomes measured) from eligible papers was entered into a data extraction table.

Quality appraisal was conducted using the Mixed Methods Appraisal Tool 2011 Version (MMAT) (Pace et al., 2012). This is a recently developed but increasingly recognised tool, with over 90 citations in the literature, including a number of high quality systematic reviews (Pieper et al., 2013, Renzi et al., 2015, Peek et al., 2014). This tool was chosen for this study because it facilitates methodological appraisal of quantitative, qualitative and mixed methods studies. Scores are based on meeting criteria, which differ according to study type. For each criterion met, a score of one is given, up to a possible total score of four for each study. For criteria which are not met, or those for which information is not given in the study, a score of zero is given. Full details of grading criteria are shown in Table 2.2.

Table 2.2: MMAT grading criteria (adapted from Pace et al. (2012))

Types of mixed methods study components or primary studies	**Methodological quality criteria**
Screening questions (for all types)	Are there clear qualitative and quantitative research questions (or objectives), or a clear mixed methods question (or objective)?
	Do the collected data address the research question (objective)? E.g. Consider whether the follow-up period is long enough for the outcome to occur (for longitudinal studies or study components).
	Further appraisal may not be feasible or appropriate when the answer is 'No' or 'Can't tell' to one or both screening questions
1. Qualitative	1.1 Are the sources of qualitative data (archives/documents/informants/observations) relevant to address the research question?
	1.2 Is the process for analysing qualitative data relevant to address the research question?
	1.3 Is appropriate consideration given to how findings relate to the context, e.g. The setting, in which the data were collected?
	1.4 Is appropriate consideration given to how findings relate to researchers' influence, e.g. Through their interactions with participants?
2. Quantitative randomised control (trials)	2.1 Is there a clear description of the randomisation (or an appropriate sequence generation)?
	2.2 Is there a clear description of the allocation concealment (or blinding where applicable)?
	2.3 Are there complete outcome data?
	2.4 Is there low withdrawal/drop-out (below 20%)?
3. Quantitative non-randomised	3.1 Are participants (organisations) recruited in a way that minimises selection bias?

	3.2 Are measurements appropriate (clear origin, or validity known, or standard instrument; and absence of contamination between groups when appropriate) regarding the exposure/intervention and outcomes?
	3.3 In the groups being compared (exposed vs. non-exposed; with intervention vs. without; cases vs. controls), are the participants comparable, or do researchers take into account (control for) the difference between these groups?
	3.4 Are there complete outcome data (80% or above), and, when applicable, an acceptable response rate (60% or above), or an acceptable follow-up rate for cohort studies (depending on the duration of follow-up)?
4. Quantitative descriptive	4.1 Is the sampling strategy relevant to address the quantitative research question (quantitative aspect of the mixed methods question)?
	4.2 Is the sample representative of the population under study?
	4.3 Are measurements appropriate (clear origin, or validity known, or standard instrument)?
	4.4 Is there an acceptable response rate (60% or above)?
5. Mixed methods	5.1 Is the mixed methods research design relevant to address the qualitative and quantitative research questions (or objectives), or the qualitative and quantitative aspects of the mixed methods question (or objective)?
	5.2 Is the integration of qualitative and quantitative data (or results) relevant to address the research question (objective)?
	5.3 Is appropriate consideration given to the limitations associated with this integration, e.g. The divergence of qualitative and quantitative data (or results) in a triangulation design?
	Criteria for the qualitative component (1.1 to 1.4), and appropriate criteria for the quantitative component (2.1 to 2.4, or 3.1 to 3.4, or 4.1 to 4.4), must be also applied)

2.3 Results

The literature search was conducted on January 6th 2015 yielding 5,712 results. An additional 15 studies were identified for inclusion from reference lists of relevant primary research studies and reviews. Reviewers were in agreement for 5,045/5,269 (95.7%) of records. Discrepancies were resolved as described previously. 123 studies were selected for inclusion. Appendix 2 summarises the characteristics and outcomes of these studies. Many studies were excluded at the record screening stage. The main reasons for this were that they did not report outcomes relating to QoL or real-world visual ability or did not include participants with AMD. Details of assessment of articles for eligibility along with reasons for excluding full-text articles are shown in the PRISMA diagram (Moher et al., 2009) in Figure 2.1.

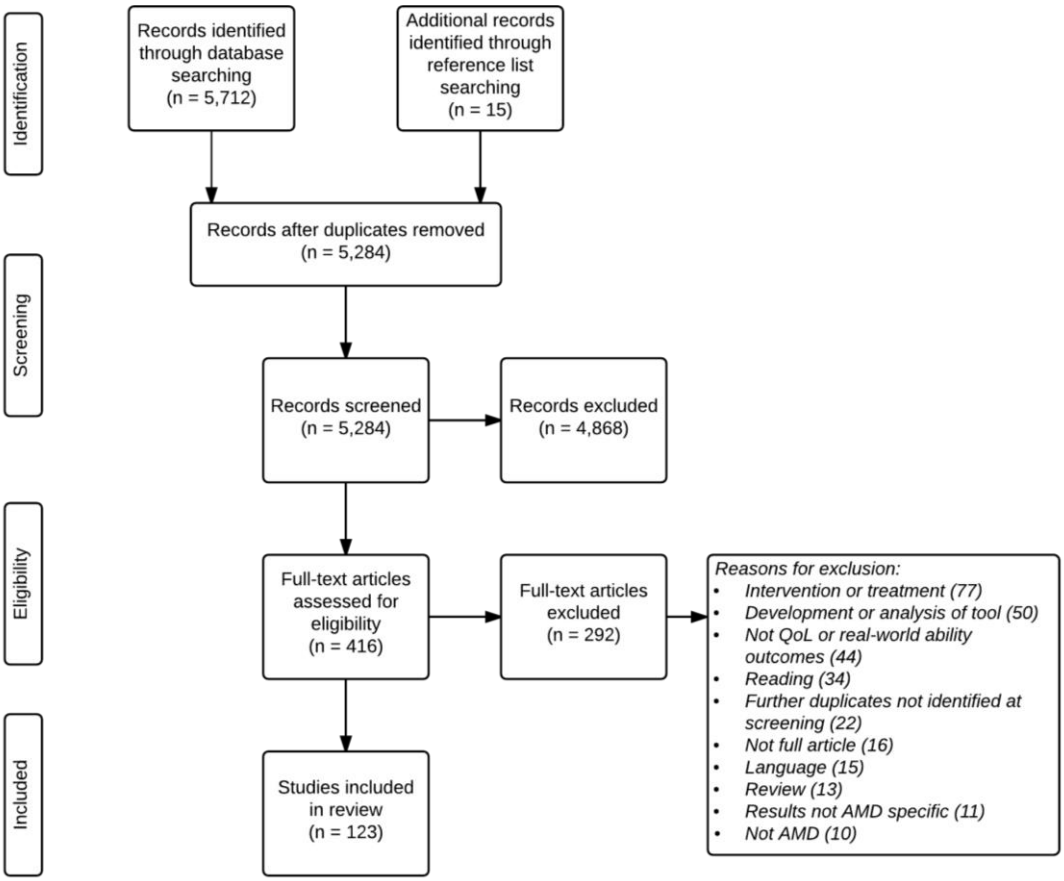


Figure 2.1: PRISMA diagram showing the study selection process

All 123 included studies underwent methodological quality appraisal using the Mixed Methods Appraisal Tool 2011 Version (MMAT) (Pace et al., 2012). Eleven studies (9%) had a score of two, thirty-three (27%) scored three and the remaining seventy-nine (64%) had a score of four. Most frequent sources of bias were related to groups not being comparable and differences between groups

not being accounted for, followed by issues regarding recruitment and sample size. Appendix 3 shows details of quality appraisal for all included studies.

Figure 2.2 shows the wide range of domains reported by studies included in this review, the most frequent of which were mobility (22% of studies) and patient-reported general visual function (17%).

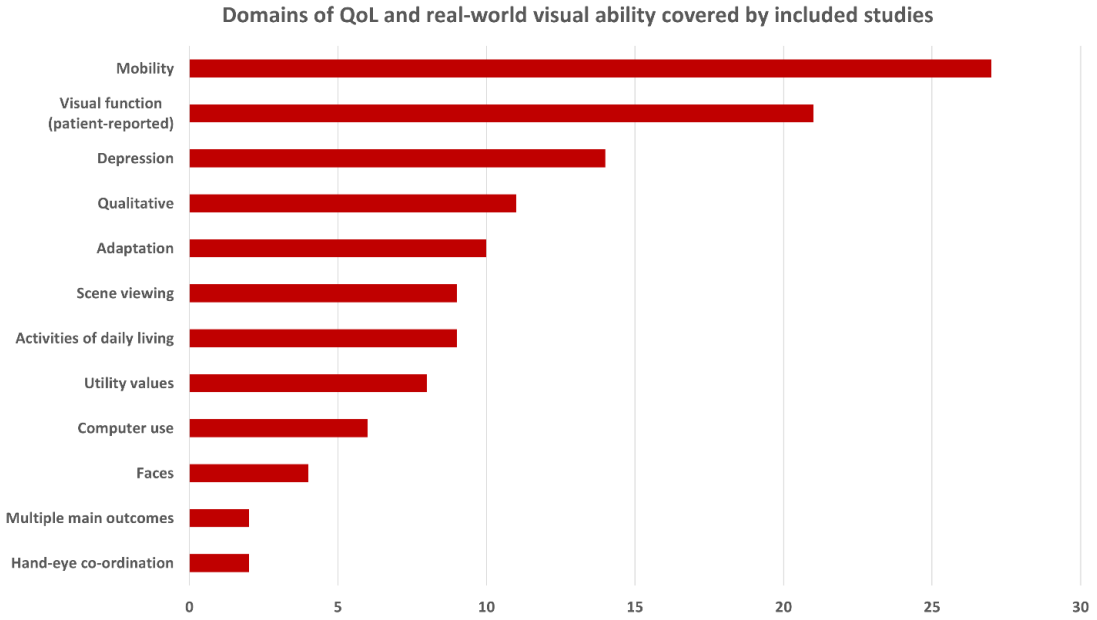


Figure 2.2: Domains of QoL and real-world visual ability covered by included studies

Below is a short description of the main findings of studies included in the systematic review. For further details of the studies, including experimental design and sample sizes see Appendix 2. The overview of the study findings is organised according to the outcome main dimension.

2.3.1 Performance based studies

2.3.1.1 Mobility

Twenty-one studies, including 1,131 people with AMD, investigating the effect of AMD on mobility performance were identified. The majority of these (n = 14) were case-control studies, followed by cross-sectional studies (n = 5), along with one cohort study and one longitudinal study.

2.3.1.1.1 Basic mobility

Individuals with AMD have been found to travel less and be less likely to drive than those with other eye diseases (Popescu et al., 2011). They are reported to have poorer balance and postural stability than non-AMD participants under a range of experimental conditions (Elliott et al., 1995, Kotecha et al., 2013, Wood et al., 2009). Binocular central scotoma size was a predictor of mobility performance in an obstacle course for people with AMD (Hassan et al., 2002).

2.3.1.1.2 Road crossing

People with AMD were equally able to detect gaps in traffic when crossing roads, but with a longer delay, reducing safety margins compared with fully-sighted controls and those with peripheral vision loss (Geruschat et al., 2011). People with AMD fixated primarily on vehicles rather than traffic lights while waiting to cross (Geruschat et al., 2006) and have been shown to make fewer head turns shortly before road crossing, preventing up-to-date road status information being gathered (Hassan et al., 2005). Overall, however, individuals with AMD were found to be similar to age-related controls in the accuracy and precision of their road crossing decisions (Hassan and Snyder, 2012).

2.3.1.1.3 Travel patterns

A uniquely designed case-control study investigated travel patterns using a cellular tracking device (Curriero et al., 2013). Amongst 65 participants with AMD, average excursion distance and span of travel reduced with VA loss.

2.3.1.1.4 Driving skills

One case-control study (Lovie-Kitchin and Brown, 1986) compared detection of traffic signals in four small groups of volunteers: young visually healthy, elderly visually healthy, age-related maculopathy (ARM; n=8, with depressed VA, fundus changes such as drusen and pigmentary changes, some central field defects and colour vision defects) and preARM (n=10, defined as having normal VA with macular drusen and/or pigment changes). People in the ARM groups had slower reaction times compared with all other groups. Interestingly, the preARM group had results outside limits set by controls, implying that real-world tasks may be affected before clinically measured function. Another case-control study (Szlyk et al., 1995) showed a group of individuals with AMD (n = 10) to perform worse than controls on an interactive driving simulator and an on-road driving test.

2.3.1.1.5 Effect of lighting conditions

Six studies assessed mobility under different lighting conditions (Spaulding et al., 1994, Spaulding et al., 1995, Alexander et al., 2014a, Alexander et al., 2014b, Brown et al., 1986, Kuyk and Elliott, 1999). People with AMD walked slowly and cautiously during both light and dark adaptation, whilst visually healthy people only behaved in this way during dark adaptation, indicating that those with healthy vision respond during dark adaptation as though their vision were impaired (Spaulding et al., 1995). People with AMD walk more cautiously, make more gait modifications whilst walking on altered surfaces (Spaulding et al., 1994) and have difficulty stepping on low contrast targets in dim light and during dark adaptation (Alexander et al., 2014a). AMD affects navigating paths under low lighting (Brown et al., 1986) and curb navigation particularly during dim lighting and dark adaptation (Alexander et al., 2014b). People with AMD performed worse on an obstacle course in dim lighting compared to well-lit conditions (Kuyk and Elliott, 1999).

2.3.1.1.6 Falls and miscellaneous

Two cross-sectional studies found that individuals with AMD have greater falls risk than those without (Szabo et al., 2008) and that fear of falling results in activity limitation (Wang et al., 2012). One case-control study (Aspinall et al., 2014) tracked eye movements and pupil diameter whilst participants watched video simulations of walking through a building. Audio records of participants reporting their journeys were also taken, and participants reported when they felt the journey to be difficult (with regards to safety, reduced confidence or uncertainty). Both groups identified similar areas as difficult, although the AMD group made more comments about this. Fixation count was higher for people in the AMD group than controls during parts of the journey identified as 'difficult' as measured subjectively, and pupil size was found to be larger throughout the journey for people with AMD, indicating increased sympathetic response.

2.3.1.2 Faces

Five studies (four case-control and one cross-sectional) including 171 people with AMD, investigating the effect of AMD on viewing faces were identified.

These studies covered a range of outcomes including familiar face recognition, facial expression discrimination and eye movements while viewing an image of a face (Alexander et al., 1988, Boucart et al., 2008b, Bullimore et al., 1991, Seiple et al., 2013, Tejeria et al., 2002). People with AMD performed better at detecting whether a face had an expression or not than on categorising the expression (Boucart et al., 2008b). In one case-control study (Alexander et al., 1988) only 26% of a

group of 100 people with AMD correctly identified the facial expression on all four photographs shown. Familiar face recognition and facial expression detection performance has been estimated to worsen with reduced luminance (Bullimore et al., 1991). One study reported significant differences in eye movements made by nine people with AMD compared to nine controls while viewing an image of the face of the Mona Lisa (Seiple et al., 2013). Findings from another study suggested self-perceived disability in face recognition does not correlate with actual face recognition performance (Tejeria et al., 2002).

2.3.1.3 Scene viewing

Nine studies investigating the effect of AMD on scene viewing were identified. These included a total of 176 participants with AMD and were all case-control studies.

People with AMD are reported to recognise isolated real-world objects better than objects in scenes, coloured images better than achromatic images (Boucart et al., 2008a), recognise an object in a scene more easily when enhanced with a border (Tran et al., 2011) and when placed on a related background, compared to an unrelated background (Boucart et al., 2013). AMD has been shown to affect processing of high spatial frequency scenes (Musel et al., 2011) and images have been shown to be more recognisable for people with AMD at lower spatial frequency bandwidths if the background is darkened (Bordier et al., 2011). In one study, researchers asked participants whether or not a real-world target was present in a scene at varying levels of contrast. Task success was found to be strongly related to contrast level (Tran et al., 2012).

People with AMD have been reported to categorise scenes as natural versus urban faster and more accurately than indoor versus outdoor, whilst no differences were found between these conditions for visually healthy people (Tran et al., 2010). In another study, participants undertook a natural versus urban scene categorisation task in which images of scenes were randomly presented in one of five locations on the computer screen (Thibaut et al., 2014). Whilst controls performed better when the image was presented centrally compared with peripheral presentation, people with AMD performed worse at all locations than controls, and did not perform better for central than peripheral presentations.

In another experiment (Tran et al., 2014) participants were presented with a view of a scene (the prime view) and asked to change the viewpoint in a computer programme representing the scene, until the viewpoint matched the prime view. Both controls (n = 13) and people with AMD (n = 19) had bias towards 'middle views' of a scene; this was more pronounced in the AMD group. Authors

hypothesised that disruption to central vision causes incorrect scene perception leading to 'false memories' of the prime view.

2.3.1.4 Computer use

Six studies investigating the effect of AMD on computer use were identified. These included a total of 57 participants with AMD. Four of these were case-control studies, whilst two were case series.

AMD may result in difficulty using computers (Jacko et al., 2000, Jacko et al., 2002, Jacko et al., 2005, Scott et al., 2002b, Scott et al., 2002a, Jacko, 2001). Performance in a basic task involving identification of commonly used computer icons was significantly associated with worsening VA, CS and colour vision defects in 18 people with AMD (Scott et al., 2002b). Other studies found that performance could also be affected by features of the graphical user interface (Jacko et al., 2000, Scott et al., 2002a, Jacko et al., 2002, Jacko, 2001), although all but one (Scott et al., 2002b) of these studies investigated only six or fewer people with AMD. People with dry AMD have been shown to benefit from auditory and haptic feedback when performing computer based tasks (Jacko et al., 2005).

2.3.1.5 Other tasks

In a case-control study of 100 people with AMD (n = 92 with nAMD), 48% were able to tell the time from a bold faced wall clock placed 1.5m away, 70% correctly identified the colour of four handkerchiefs coloured red, blue, tan and grey, and 68% correctly identified four commonly used household products when presented with well-known brands of cereal, tomato ketchup, dish detergent and milk (Alexander et al., 1988). Differences between people with (n = 10) and without (n = 10) AMD in performance of reach-to-grasp tasks have been reported in a case-control study (Timberlake et al., 2011). A further case-control study (Timberlake et al., 2013) reported that poor handwriting legibility in 8 individuals with scotomas caused by AMD may be a result of difficulty placing letters in the correct location due to inability to view the desired writing area on the page.

2.3.2 Patient reported outcomes

2.3.2.1 Patient reported visual function

Twenty-two studies investigating the effect of AMD on patient-reported general visual function were identified. These included a total of 10,877 participants with AMD. Twenty of these were cross-sectional and two were cohort studies.

The National Eye Institute Vision Function Questionnaire (NEI-VFQ) is a widely used PROM in AMD (Mitchell and Bradley, 2006). Average scores are reported to be poorer in people with AMD compared to those without (Clemons et al., 2003, Cruess et al., 2007, Soubrane et al., 2007, Lotery et al., 2007, Lin and Yu, 2012, Lopez-Miguel et al., 2013, Ruiz-Moreno et al., 2008, Seland et al., 2011) and, unsurprisingly, worse in more severe disease (Cahill et al., 2005, Clemons et al., 2003, Ruiz-Moreno et al., 2008, Seland et al., 2011). Results from studies using different tools are mostly aligned with these findings (Siaudvytyte et al., 2012, Lamoureux et al., 2011, Hassell et al., 2006, Chia et al., 2004, Esteban et al., 2008). A prospective longitudinal study investigating change in visual function in 671 women with AMD over a five year period found worse NEI-VFQ scores in those with late AMD at the beginning and end of the study and those who progressed from early to late AMD, than in those who did not progress to late AMD (Coleman et al., 2010). Two large-scale cross-sectional studies investigating 2,194 and 1,052 people with AMD found no association (Seland et al., 2011) and weak association (Maguire, 2004) between NEI-VFQ scores and early AMD, respectively, although a smaller study (n=106) using a different PROM did find impaired self-reported visual function in those with mild AMD (Hassell et al., 2006). Best and worst eye VA were found to contribute independently to NEI-VFQ scores (Berdeaux et al., 2005, Sahel et al., 2007). NEI-VFQ scores were worse in individuals with binocular compared to monocular visual loss from AMD (Dong, 2004, Marback et al., 2007), although 54 individuals with blindness in one eye reported greater emotional distress than 54 with binocular blindness, perhaps due to uncertainty regarding future disease progression (Williams et al., 1998). People with AMD who recorded a high response on a neuroticism scale self-reported worse visual function than those with average response, regardless of VA (Rovner et al., 2014).

2.3.2.2 Mobility

Seven studies investigating the effect of AMD on patient-reported mobility were identified. These included a total of 655 participants with AMD. Four of these were cross-sectional, two were cohort studies and one was a longitudinal study.

Two separate retrospective studies reported lower rates of motor vehicle collision among people with AMD compared to matched controls (McGwin Jr et al., 2013, Szlyk et al., 1995). These, and other studies (Decarlo et al., 2003, Sengupta et al., 2014), suggest that these results are observed because individuals with AMD self-regulate by changing driving habits, for example, avoiding driving at night, in unfamiliar areas or over long distances.

Higher self-reported falls rates have been reported among people with AMD compared with those without (Lotery et al., 2007, Soubrane et al., 2007, Cruess et al., 2007). Amongst people with AMD, reduced CS and VA have been associated with more self-reported falls (recorded using diaries) (Wood et al., 2011b). Older women with AMD have been reported to have almost twice the risk of injurious falls (self-reported) than those without (Szabo et al., 2010). AMD has been associated with fear of falling (van Landingham et al., 2014) and results of another PROM-based cross-sectional study suggested that limited life space and activities due to fear of falling contributes to the relationship between eye disease and depression (Popescu et al., 2012).

2.3.2.3 Utility values

Eight cross-sectional studies investigating the effect of AMD on utility values were identified. These included a total of 1,768 participants with AMD.

Utility values, a type of PROM, give quantitative expressions of preference for given health states (Mitchell and Bradley, 2006) and can be assessed using different methods. For example, *standard gamble* ascertains the risk people would be willing to take in order not to have a certain health condition and the *time trade-off* hypothetically assesses life years willing to be sacrificed in order to avoid the condition. Scores are normally presented on a scale between 0 and 1; higher scores indicate less willingness to take risks or make sacrifices to avoid a condition. Average values for AMD range from 0.60 to 0.81 (Brown et al., 2000b, Espallargues et al., 2005, Yanagi et al., 2011); people with worse vision loss from AMD score lower than those with mild loss (Brown et al., 2000b). Bass et al. (2004) used a different utility value in which individuals were first asked to rate their current vision on a scale where 0 represented complete blindness and 100 represented perfect vision. They were then asked to rate how they imagined it would feel to be completely blind, and how it would feel to have perfect vision (with their current state of general health) on a scale of 0 to 100, where this time 0 represented death and 100 represented perfect health. The latter two ratings were used as a scale on which to place the first rating. Scores were converted to a single value, yielding mean preference values for nAMD patients of 0.62 to 0.64.

Utility values allow comparisons between different health conditions. For example, values for AMD are comparable with asymptomatic HIV (0.69), mild osteoarthritis of the hip (0.69), mild and moderate angina (0.88 and 0.83), mild and moderate myocardial infarction (0.91 and 0.80), and diabetes mellitus (0.88) (Brown et al., 2003). Values reported for other eye diseases include glaucoma (0.64 to 1.0) and diabetic retinopathy (0.59 to 0.94) (Kymes and Lee, 2007). One cross-sectional study (Brown et al., 2002) compared utility values between AMD and diabetic retinopathy, and

found comparable values for equivalent levels of VA loss in each disease. Another cross-sectional study (Bansback et al., 2007) found CS to be a good predictor of utility values in 209 people with AMD.

Utility values are often established from members of the public who are given descriptions of the health condition being assessed; these tend to yield higher values than those from people with AMD (Butt et al., 2013). This is supported by results of other studies using time trade-off scores (Stein et al., 2003, Brown et al., 2000a) in which utility values were consistently overestimated by the general public, non-ophthalmic clinicians and even ophthalmologists when compared to ratings by people with AMD themselves (Stein et al., 2003, Brown et al., 2000a). These findings suggest that it may be impossible to appreciate the consequences of vision loss without having experienced them (Stein et al., 2003).

2.3.2.4 Depression

Fourteen studies investigating the effect of AMD on depression were identified. These included a total of 1,880 participants with AMD. Eight of these were cross-sectional, two were cohort studies, one was longitudinal, and one was a case report.

Associations between levels of depression and AMD have been reported in the literature (Popescu et al., 2012). Estimated prevalence rates for depression range from 11 to 44% amongst individuals with AMD (Brody et al., 2001, Eramudugolla et al., 2013, Mathew et al., 2011, Jivraj et al., 2013); the highest of these figures is two to three times the rate found in the general elderly population. In contrast, one cross-sectional study (Sun et al., 2007) found no association between AMD and depression. Discrepancies between results may arise from different tools used to assess depression in these studies, and different recruitment methods (for example, clinic-based versus population or community-based sample). Selective mortality and limiting eligibility criteria have also been suggested as reasons for not finding an association in some studies (Sun et al., 2007). Depression in AMD has been reported to be strongly correlated with increasing VA loss (Augustin et al., 2007) and to be predicted by neurotic personality type (Rovner and Casten, 2001). In other studies, depressive symptoms, even if minimal, were associated with loss of visual function regardless of VA level (Rovner and Casten, 2001, Rovner and Casten, 2002, Rovner et al., 2002, Rovner et al., 2006, Banerjee et al., 2008, Casten et al., 2002). People with AMD (n = 144) who reported poor adaptation to vision loss, especially with respect to acceptance of and compensation for vision loss, reported more depressive symptoms than those who adapted better (Tolman et al., 2005). One case report highlights risk of suicide because of AMD-related vision loss (Johnson et al., 2014); eye-care providers should be trained to identify and manage patients at risk of suicidality appropriately.

2.3.2.5 Adaptation

Ten studies investigating adaptation to AMD were identified. These included a total of 1,122 participants with AMD. Two of these were case-control, one was a cohort study, four were longitudinal and three were cross-sectional.

One longitudinal study (Schilling and Wahl, 2006) found decline in positive mood over the first two years following diagnosis, followed by an increase between the third and fifth years, with some subsequent stability. People with AMD were found to have poorer life satisfaction, greater stress (Davis et al., 1995), more emotional problems, greater social dysfunction (Cavar et al., 2014), and impaired activities of daily living over a five year period (Gopinath et al., 2014) than those without AMD.

Several studies have investigated adaptation to AMD based on Heckhausen and Schulz life-span theory of control (Heckhausen and Schulz, 1995, Wahl et al., 2003). This theory describes behavioural approaches to adapting to conditions: primary control strategies utilise resources in order to attain goals: selective primary control involves using internal resources such as time and effort, and compensatory primary control involves finding external resources in order to attain goals. Secondary control is completely independent from the outside world: selective secondary control strategies involve increasing motivational commitment toward desired goals, and compensatory secondary control involves replacing goals that are no longer attainable. Utilisation of internal resources (such as time and effort) was positively associated with ability to carry out activities of daily living, and external resource finding (such as utilising low vision services and aids) and increase of motivational commitment were positively associated with positive emotion (Wahl et al., 2003, Wahl et al., 2004). External resource finding was reported to increase shortly after diagnosis, perhaps as patients initially sought advice and support (Wahl et al., 2007). Internal resource utilisation and motivational input have been found to decrease over time amongst people with AMD, whilst external resource finding and replacement of desired goals partially increased over this time (Wahl et al., 2005). External resource finding (Schilling et al., 2013) and replacement of desired goals (Wahl et al., 2007) increased as patients lost ability to carry out activities of daily living. Variations in coping strategies, along with cognitive ability, have been reported to influence self-report of visual function (Rovner et al., 2011).

2.3.2.6 Activities of daily living

Nine studies investigating the effect of AMD on activities of daily living were identified. These included a total of 1,279 participants with AMD. Seven of these were cross-sectional, one was a case series and one was a case report.

Studies (Hochberg et al., 2012, Mathew et al., 2011) report that 39 to 45% of people with AMD require help with at least one activity of daily living. These studies and others (Cruess et al., 2007, Soubrane et al., 2007, Lotery et al., 2007) suggest that between twice as many and eight times as many people with AMD require assistance with activities of daily living compared to those without. Severity of AMD is associated with these difficulties (Mangione et al., 1999), which are unlikely to be experienced if visual function is unaffected (Knudtson et al., 2005), although night driving difficulties related to impaired scotopic sensitivity may occur whilst VA remains relatively good (Scilley et al., 2002). Activities commonly affected include meal preparation, travelling, cleaning, grooming, shopping, going out, navigating steps and pavement curbs, noticing objects, hobbies, watching TV, reading, driving (especially night driving), and using low vision devices (Mangione et al., 1999, Scilley et al., 2002, Hochberg et al., 2012, Ivanoff et al., 2000, Backman and Williams, 2002, Hassell et al., 2006). In addition, ability to carry out activities requiring visual resolution, such as reading, can distinguish those who are capable of self-care only from those who are able to care for themselves and others. Further to this, ability to carry out household chores (such as preparing food) can distinguish those who are capable of self-care and those who are not able to care for themselves (Stevenson et al., 2004).

A case study (Fletcher et al., 2008) of one patient with bilateral ring scotomas from AMD reported difficulties in 'several activities of daily living', in particular driving and following the ball when playing golf. The patient was reported to find compensatory scanning eye movements a useful way of keeping desired areas in focus.

2.3.3 Qualitative data collection methods

Eleven studies which used qualitative data from interviews, focus groups and diaries to assess how AMD affects visual disability or QoL were identified (McCloud et al., 2014, Burton et al., 2013, Moore, 2000, Moore and Miller, 2003, Moore and Miller, 2005, Owsley et al., 2006, Cimarolli et al., 2012a, Stanford et al., 2009, Kleinschmidt, 1999, Smith, 2008, Wong et al., 2004).

Several qualitative studies aimed to understand aspects of 'living with age-related macular degeneration'. McCloud et al. (2014) elucidated four themes from interviews and focus groups with

individuals living with AMD. 'Cautious optimism' was a theme amongst those who had received treatment for their AMD, 'endurance' refers to the ongoing need for invasive treatments, 'profound loss' as a result of AMD, especially in those who were unsuitable for treatment, and those for whom treatment had been unsuccessful, and all participants spoke about 'adaptation' to vision loss. Results from a semi-structured interview study by Wong et al. (Wong et al., 2004) highlights the importance of understanding the condition, social resources and the responses of society for coping successfully with AMD. Burton et al. (2013) interviewed a married couple, both suffering from AMD, together at three time points over an 18 month period, and elucidated three themes: 'disruption of vision impairment' referring to difficulties and disabilities caused by their vision loss, 'managing mutual deterioration' referring to splitting tasks between themselves and seeking external support where necessary, and 'resilience through togetherness' referring to sharing everyday tasks, utilising each other's visual strengths to counteract the other's weaknesses, and experiencing 'landmark' events together such as registering as partially sighted. Another study specifically focused on women with AMD (Moore, 2000). Three themes were identified: 'realistic awareness with steadfast positivism', 'making personal discoveries amidst enveloping losses', and 'persisting toward an unfolding way of being in the world'. This final theme refers to adapting to living with vision loss. This study was replicated in men with AMD (Moore and Miller, 2003), and central themes were identified: 'abilities and inabilities', 'cherishing of independence', 'acknowledging the progression of visual impairment', 'confronting uncertainties and fears', and 'persisting with hope and optimism'. The data from the previous two studies were then combined and re-analysed focusing exclusively on data relating to driving strategies (Moore and Miller, 2005); two central themes emerged: 'strategies used while driving', including using caution, memory, guessing, using a co-pilot, increasing the visual field (for example, by making scanning movements with the eyes) and using a visual aid, and 'strategies used to continue driving', including self-regulating driving activities, believing in driving capabilities, fulfilling desire to drive, circumventing the law, denying driving difficulties, and using visual markers. The authors highlight that these individuals were willing to go to great lengths to drive, sometimes putting themselves and others at risk. Owsley et al. (2006) conducted focus groups encouraging participants to discuss feelings and emotions about their vision. Once transcribed, interviews underwent a form of content analysis; each comment was coded as 'positive' or 'negative'. Twice as many comments made in the discussions conveyed negative compared with positive emotions. Negative comments related to feelings of frustration, fear, sadness and inadequacy, whilst positive comments related to feelings of gratitude and hope. People with each stage of AMD (early, intermediate and late) were equally likely to make positive and negative comments.

Other qualitative studies explored adjustment to visual loss from AMD. Cimarolli et al. (2012a) asked individuals about challenges relating to visual loss at three time points over the course of a two year period and observed that over the study period, functional challenges, such as using transportation, increased, whilst social challenges, such as recognising familiar faces, remained stable, and whilst psychological challenges decreased. Stanford et al. (2009) asked participants to complete diaries recording their social interactions, general health, and visual problems, along with 'happy' and 'sad' events over a twelve month period. In contrast to the previous study, this study found little or no improvement in psychosocial adjustment to AMD over the twelve months. Themes running through the diary entries were identified as personal safety issues, social interaction and isolation, loss of independence, support mechanisms, effect of disease on mood, the effects of the media and psychosocial adaptation. Kleinschmidt et al. (1999) and Smith (2008) purposely sought out participants who had successfully adjusted to their vision loss for their qualitative studies. Kleinschmidt et al. (1999) found three factors that influenced successful adjustment to vision loss: prior life experiences, internal resources and external resources. Smith (2008) reports the case of one patient who had successfully adjusted to vision loss. Themes that emerged from this interview were: attitude (acceptance, positivism, independence, altruism and faith), modification of tasks (using other senses of memory, residual vision, and assistive devices to perform everyday activities), and social support (from other individuals, low vision services, and peers with similar problems).

2.3.4 Trends

Our systematic review discovered that the literature representing the effects of AMD on QoL can be split into four categories: wet AMD only; dry AMD only; both types investigated with a breakdown and both types investigated but without a breakdown or type not reported. We show that the number of QoL and visual ability papers published in these categories is increasing over time in Figure 2.3 (before 1985 no studies had been published on the subject). This increase may simply be attributed to the increasing number of papers and journals published. Nevertheless, these studies make up a minute proportion of the body of literature on AMD as a whole; a PubMed search for articles with 'age-related macular degeneration' in their title published between 2010 and 2014 yields 2458 results, whilst only 47 papers (less than 2%) published in this time were included in this systematic review.

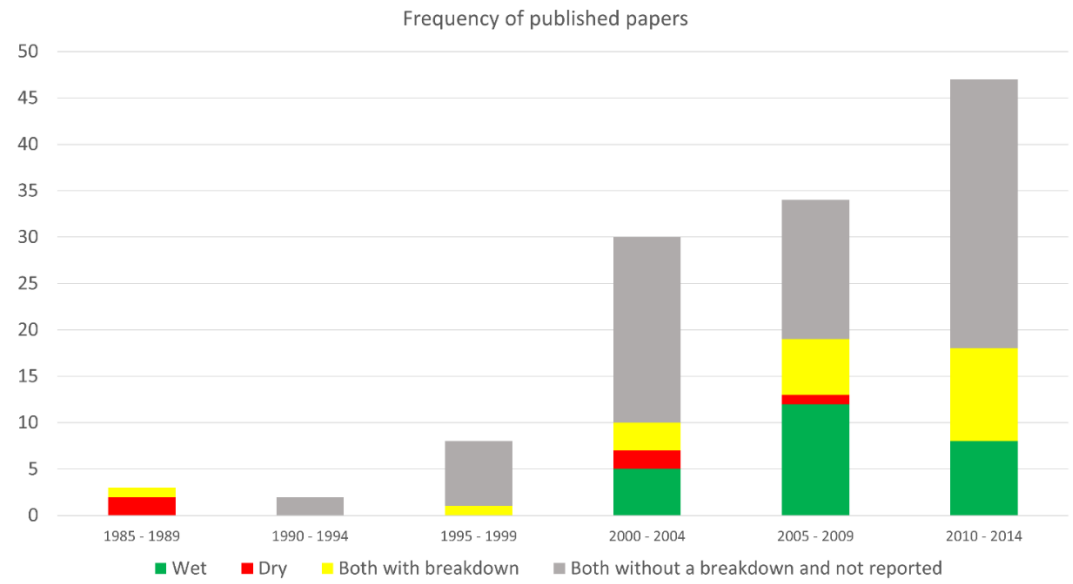


Figure 2.3: Frequency of published papers over time grouped by AMD type reported

2.4 Discussion

Our review is timely. Although smaller scale systematic reviews have been published in this field (Poku et al., 2013, Tosh et al., 2012, Pinquart and Pfeiffer, 2011, Dawson et al., 2014, Bennion et al., 2012), the most recent large-scale systematic reviews were published about ten years ago (Mitchell and Bradley, 2006, Berman and Brodaty, 2006). A more recent, non-systematic review (Yuzawa et al., 2013) cited only 30 papers. Over half of the papers included in our study were published since these other large-scale systematic reviews were conducted.

Poku et al. (2013) systematically reviewed utility values in patients with diabetic retinopathy, diabetic macular oedema and AMD in 2013 and concluded that, according to existing literature, AMD and diabetic retinopathy impact negatively on QoL, with most current research categorising by VA in patients' better-seeing eye. Tosh et al. (2012) also conducted a systematic review of preference based measures of QoL in visual disorders with similar results. Pinquart et al. (2011) conducted a meta-analysis comparing psychological well-being in people with and without visual impairment. Results suggest that psychological well-being may be affected by having visual impairment, and in particular that those with AMD are more at risk for reduced psychological well-being than those with other causes of visual impairment. Depression and anxiety amongst those with AMD was systematically reviewed by Dawson et al. (2014). Depression was found to be more prevalent amongst those with AMD than those without. Furthermore, worse disease severity was associated with increased depressive symptoms. However, similar to the results of this systematic review, wide variability was found, perhaps due to differences in sample size and tools used in included studies. Their results suggest no relationship between AMD and anxiety. Qualitative studies concerned with the experience of AMD were systematically reviewed (Bennion et al., 2012). Emerging themes centred on functional limitations, adaptation and independence, feelings about the future, interaction with health services, social engagement, disclosure, and emotional impacts.

Our review is the first to integrate PROMs and performance-based studies assessing QoL and everyday visual function in AMD. The evidence presented in this study supports previous reviews' conclusions that AMD impacts negatively on people's lives. More is now understood about some of these areas of impact, for example, the relationship between AMD and falls (Szabo et al., 2008, Wang et al., 2012, Cruess et al., 2007, Soubrane et al., 2007, Lotery et al., 2007, Wood et al., 2011b, Szabo et al., 2010, van Landingham et al., 2014, Popescu et al., 2012), and scene perception (Boucart et al., 2008a, Boucart et al., 2013, Thibaut et al., 2014, Tran et al., 2012, Tran et al., 2014, Tran et al., 2011, Tran et al., 2010, Bordier et al., 2011, Musel et al., 2011). AMD negatively affects tasks

including mobility, face recognition, perception of scenes, computer use, meal preparation, shopping, cleaning, watching TV, reading, driving and, in some cases, self-care. A large number of studies have highlighted the difficulties people with AMD may have with mobility, particularly in dim lighting (Alexander et al., 2014a, Alexander et al., 2014b, Brown et al., 1986, Spaulding et al., 1995). Large-scale studies have reported invariably that many people with AMD self-report poor visual function; this worsens with AMD severity (Clemons et al., 2003, Coleman et al., 2010, Esteban et al., 2008, Lamoureux et al., 2011, Lin and Yu, 2012, Maguire, 2004, Marback et al., 2007, Rovner et al., 2014, Ruiz-Moreno et al., 2008, Sahel et al., 2007, Seland et al., 2011, Siaudvytyte et al., 2012). There is limited evidence surrounding the issues people with AMD may have with using computers, due to the small sample sizes of the majority of studies identified (Jacko, 2001, Jacko et al., 2000, Jacko et al., 2002, Jacko et al., 2005).

A number of domains within people's lives are affected by AMD: social, emotional, and physical. Our systematic review highlights the need for eye-care providers to be aware of this research evidence, and to be able to manage these patients, whether it be referral for low vision rehabilitation or help from social or counselling services. Previous research (Stein et al., 2003, Brown et al., 2000a) has shown that people without AMD, including eye-care providers, consistently underestimate the effect of the condition and it would be interesting to discover whether public perceptions are different now, with the advent of newsworthy potential new treatments. For example, a Google search for news articles about 'age-related macular degeneration treatment' published in 2004 generates three webpages of results, whilst a search for articles on the same topic published in 2014 generates 76 webpages.

We have also identified interesting trends in the publication of studies in this field (Figure 2.3). There were no publications on QoL and visual disability in nAMD before 2000, and then there was a sudden increase; this is noteworthy and may be explained by the development of new treatments for nAMD around this time (Kim and D'Amore, 2012, Verteporfin Roundtable, 2002). These are likely to have resulted in increased interest in investigating QoL and functional impacts in order to assess both clinical and cost effectiveness outcomes of these new treatments (Espallargues et al., 2005). Few papers report the type of AMD investigated (58%, n=73) - worrying given the functional differences between the disease types, along with their differing time courses and treatments (Dawson et al., 2014). It is, however, encouraging that more recent papers that include both types are now providing a breakdown between the two. Five and 25 papers focus solely on dry AMD and neovascular AMD respectively. This is disproportionate, given that dry AMD comprises ~90% of diagnosed AMD cases (Chen et

al., 2009). In addition, 74% of included studies (n=93) do not report disease duration. As both psychological and functional effects can change over the time course of the disease, this should be an important feature on which to report and comment.

Our results are supported by other studies (Bennion et al., 2012, Dawson et al., 2014), which discuss the lack of discrimination between neovascular AMD and dry AMD in research. We spotlight this observation to be true in the majority of papers published in this field (Figure 2.3). Critically, results from studies that did discriminate between the two indicate that QoL and visual function are affected in unique ways depending on disease type. For example, one study (Banerjee et al., 2008) reported more people with nAMD than people with dry AMD suffering from depression. Another (McCloud et al., 2014) discussed the optimism that nAMD patients may feel receiving treatment, and emphasised the sense of loss that those with dry AMD may suffer from due to lack of treatment. We think these findings are interesting and more research addressing these differences is likely required (Bennion et al., 2012).

This study has limitations. First, only papers published in peer-reviewed journals were included. This is likely to have influenced the results found due to submission bias and/or publication bias. Second, the nature of this review meant that randomised control trials were excluded. Third, due to lack of translation resources, non-English language papers were excluded. Fourth, the impact of AMD on reading was not considered in this study because we felt this is a topic that is already very well reported on. For example, previous extensive reviews report reduced reading performance in AMD (Kanonidou, 2011, Neelam et al., 2009) and subsequently reading is one of the most common valued activities to be lost as a result of AMD (Mitchell and Bradley, 2006). Finally, this review aimed to investigate the effect of AMD on visual disability and QoL as reported in existing literature and to explore trends within this body of literature. As such, the review highlights what has been studied already and not necessarily what is important to individuals with AMD. Furthermore, the decision to exclude studies that relate to development of an instrument or tool meant that some studies that do highlight what is important to these individuals (e.g. Mitchell & Bradley, 2004, Hart et al., 1999, Owsley et al., 2006) were omitted. It is also worth noting that research in this field is not straightforward. For example, disentangling the effects of age alone from age-related eye disease is a challenge that often requires well defined age-matched or age-related controls. Moreover, isolating the effect of AMD when elderly people have co-morbidities is also a challenge. Still, using MMAT for our appraisal revealed most studies to have high levels of methodological quality.

2.4.1 Conclusions

Performance-based measures and PROMs have shown AMD to negatively affect QoL and visual disability; it affects many activities of daily living including, for example, mobility, driving, face recognition, scene perception and computer use. From earlier reviews we know that AMD also impacts critically on reading. Emotional impact can be severe. These impacts can differ over the time course of the disease, perhaps due to adaptation, and this should be acknowledged and investigated in future research. Future research in this field should also focus on delivering some of this research knowledge into the assessment of patients both in clinical management and clinical trials. In other words, successful clinical management of AMD should not simply be about changes on a letter chart (e.g. visual acuity or contrast sensitivity), but must equate to correct decisions about intensifying treatment when patients are at risk of developing 'visual disability'. Furthermore, our review highlights a requirement to differentiate between types of AMD, especially as new disease-type specific treatments emerge for them.

Chapter 3 Searching for objects in everyday scenes: Measuring performance in people with dry age-related macular degeneration

Visual search is an important everyday visual function. Many studies of visual search use synthetic targets and distractors. Such experiments are somewhat removed from the holistic approach needed to find a face in a crowd, search for an exit sign at an airport or locate a favourite cereal on the supermarket shelf. A recent paper by Hulleman & Olivers (2015) stated that 'item-based approaches limit the real-world applicability of results from the lab.' Two important applications of real-world visual search were given: radiology and airport security. Here we highlight search as an impaired everyday visual function in people with age-related eye disease. We speculate on how this might be best assessed with the idea of bringing visual search out of the lab and into clinical research, focusing on open angle glaucoma and AMD, two of the most common causes of visual impairment. Glaucoma is typically associated with peripheral vision loss, whilst AMD causes loss of central vision.

The work presented in this chapter features in two published papers; the literature review on visual search in age-related eye disease presented has been published in *Behavioral and Brain Sciences* (Crabb and Taylor, 2017); see list of supporting publications. The co-author on this review is David Crabb (DC). The literature review was drafted by DJT, and reviewed and edited by DC.

The main research study presented in this chapter has formed a paper published in *Investigative Ophthalmology and Visual Science* (Taylor et al., 2017); see list of supporting publications. The co-authors of this work are David Crabb (DC) and Nicholas Smith (NS). Computer programming and application development was conducted by NS. All AMD participant recruitment and data collection was conducted by DJT between May 2015 and February 2016. Comparison control data had already been collected for previous studies (Smith et al., 2012, Smith et al., 2011). Data analysis was performed by DJT with support from NS. The paper was written by DJT, and reviewed, edited and approved by all authors. Some of the work presented in this chapter has also been presented as a paper presentation at the Association for Research in Vision and Ophthalmology meeting (Seattle, WA, USA, 2016) and at EURetina (Copenhagen, Denmark, 2016); see list of supporting publications.

3.1 Introduction to visual search in age-related eye disease

Most studies of visual search in age-related eye disease have used an item-based approach (Jacko, 2001, Jacko et al., 2000), yet examples taking a more real-world approach are emerging. In one study, visual search in people with glaucoma was investigated using two computer-based tasks (Smith et al., 2011), one item-based task requiring participants to identify a target (a Landolt C) from an array of

distractors, and another more real-world task, requiring participants to find everyday items in digital photographs of indoor and outdoor scenes. Participants with glaucoma exhibited longer average search times than healthy peers for the real-world task, whilst search times were not significantly different between the two groups for the item-based task. These results support the notion that item-based search tasks are not relatable to real-world applications. When searching for targets the eyes move in patterns of *saccades* (movements of the eyes from one point to the next) and *fixations* (during which the eyes are stable, directing their gaze to a certain point). A further study (Smith et al., 2012), investigated eye movements during the same real-world visual search task and reported a reduction in saccade frequency in people with glaucoma compared with healthy peers. Furthermore, amongst participants with glaucoma, those who made more saccades per second were quicker at finding the real-world targets in photographs of everyday scenes. These results indicate that eye movement behaviour is of importance when considering visual search performance of people with age-related eye disease, and were supported by a study of similar design when detecting faces (Glen et al., 2013). These findings align with Hulleman & Olivers' (2015) proposition that fixation count is a critical factor in visual search behaviour.

Most visual search research in AMD has been conducted using optotypes in artificial arrays (for example, searching for a letter 'T' amongst distractors in the form of the letter 'L') and participants with simulated scotomas (Bertera, 1988, Coeckelbergh et al., 2002, Cornelissen et al., 2005, Geringswald et al., 2012, MacKeben and Fletcher, 2011, Murphy and Foley-Fisher, 1988, Murphy and Foley-Fisher, 1989, Kuyk et al., 2005, Geringswald et al., 2013). These approaches allow for more controlled experimental design, yet simulated scotomas may not be entirely realistic (Harvey and Walker, 2014, Schuchard et al., 1999). One method of simulating central scotoma uses contact lenses with a central opacity, which cause reduced retinal illumination, leading to worsening in visual acuity and contrast sensitivity (Butt et al., 2015). A gaze-contingent simulation of scotoma, incorporating eye tracking, is likely to provide better scotoma simulation (Butt et al., 2015); this has been used in a hazard search task in driving (Glen et al., 2015). Results were useful but simulation cannot capture the real experience of patients, where self-reported perception and description of scotoma varies enormously (Crabb et al., 2013). To our knowledge, only one study (Thibaut et al., 2016) has investigated visual search in a real-world type task in participants with AMD; this study reported individuals with AMD to exhibit higher saccade frequencies, shorter fixation durations and longer scan paths compared to those without AMD during visual search. Other papers report studies of eye movements during different types of real-world tasks. For example, Aspinall et al. (2014) found fixation count to be a useful marker of situations subjectively classed as 'difficult' by individuals with

AMD when assessing eye movement behaviour whilst watching videos of ambulatory journeys. Similarly, Geruschat et al. (2006) investigated gaze behaviour during street crossing and reported higher fixation count during more difficult/visually demanding parts of the task. Seiple et al. (2013) observed eye movements of people with AMD whilst exploring an image of a face and reported fixation count for internal facial features (eyes, nose and mouth) to be higher for controls than for individuals with AMD. All of these tasks involving visual exploration transcend the traditional 'item-based' visual search.

Studies of everyday visual search have real clinical implications. Visual search in people with visual impairment has been suggested as a predictor for mobility and performance of other daily activities (Kuyk et al., 2005). There is evidence for the effectiveness of eye movement training on visual search in congenital prosopagnosia (Schmalzl et al., 2008), following brain damage (Bouwmeester et al., 2007), and for improved visual search and mobility performance in people with visual impairment of ocular origins following repeated practice of an item-based search task (Kuyk et al., 2010, Liu et al., 2007). These types of findings could lead to interventions and alternative approaches to patient management. Potential also exists for development of tests for detecting and monitoring eye disease by using visual search using both item-based (Loughman et al., 2007) and real-world (Crabb et al., 2014) tasks.

An article published nearly 30 years ago about tumour detection using visual search (Nodine and Kundel, 1987) stated that 'detecting an object that is hidden in a natural scene is not the same as detecting an object displayed against a background of random noise.' Research in this area ought to bridge the gap between lab-based testing and the real-world. Hulleman & Olivers (2015) have made an important step towards unifying some of the theory of visual search. We anticipate this will stimulate practical studies that may lead to better understanding of visual search in people with age-related eye disease. In turn, we speculate that this will have implications for rehabilitation, and potentially lead to development of new tests for monitoring age-related eye disease.

3.1.1 Rationale for present study

Age-related macular degeneration (AMD) is the most common cause of vision impairment in the developed world (Minassian et al., 2011, Klein et al., 2011). The vast majority of people diagnosed with AMD have the 'dry' form of the disease (early and intermediate AMD, and late AMD [geographic atrophy, GA]), for which there is no available treatment to arrest progressive loss of vision. Promisingly, however, there are several potential therapies currently reaching the stage of phase

III randomised controlled trials (RCTs) (Sadda et al., 2016). So how should we be measuring treatment success in these trials? Inevitably they need to be appropriate for Food and Drugs Administration (FDA) approved functional outcomes. However, changes in traditional clinical measures such as visual acuity may not best reflect visual function in GA, because if atrophy does not involve the fovea, VA may remain relatively good, whilst visual function declines. Likewise once the fovea becomes atrophic, VA may remain stable, whilst visual function continues to decline due to enlargement of atrophy (Sunness et al., 2007, Sunness and Applegate, 2005). Importantly, imperceptible changes on a clinical chart might not matter to the patient. So, perhaps clinical measurements should be supported by secondary outcomes that more directly relate to the patient. Asking people is one way to ascertain feelings about changes in visual function, and some RCTs for neovascular AMD have used patient-reported outcome measures (Chakravarthy et al., 2012, Heier et al., 2012). Yet, discrepancies have been shown between self-reported performance of everyday visual tasks and actual performance of the task (Friedman et al., 1999, Kuyk et al., 2005, Pardhan et al., 2016). A supplementary method would be to measure performance in surrogates of real-world visual tasks that people encounter every day; an example of this idea is explored in this study.

Visual search is an important everyday task of looking for something in a cluttered visual environment. Interestingly, visual search in people with vision impairment has been shown to be a predictor for difficulties with mobility and performance of other daily activities (Kuyk et al., 2005). People with AMD certainly self-report difficulties in searching and finding things (Mangione et al., 1998, Cimarolli et al., 2012a).

An ideal surrogate of visual search performance which directly relates to patients' day-to-day lives should mimic the way in which people might search for things in the real world. This could be, for example, finding an item on a supermarket shelf, the exit sign at a bus station or an item of interest on a map. However, most visual search research in patient-based studies has been limited to using optotypes in artificial arrays (Kuyk et al., 2005, Coeckelbergh et al., 2002, MacKeben and Fletcher, 2011, Geringswald et al., 2013). Other studies concerning visual search performance of people with AMD type visual function defects seemed to be confined to simulated scotomas in people that are otherwise visually healthy (Cornelissen et al., 2005, Geringswald et al., 2012, Murphy and Foley-Fisher, 1988, Murphy and Foley-Fisher, 1989, Bertera, 1988). The latter allows for more controlled experimental design, yet simulated scotomas will never be entirely realistic (Harvey and Walker, 2014, Schuchard et al., 1999); self-reported perception of scotoma has been reported to vary enormously between patients (Crabb et al., 2013). In addition, there is a reported disconnect between visual search

performance using arrays of optotypes and search in 'real-world' scenes amongst people with eye disease (Smith et al., 2011, Hulleman and Olivers, 2015).

Eye movements have been shown to be affected in non real-world type visual search tasks in AMD (Cornelissen et al., 2005, Van der Stigchel et al., 2013). More recently, eye movements during a real-world visual exploration task have been reported to be different in patients with neovascular AMD compared with visually healthy peers (Thibaut et al., 2016).

This study, therefore, investigated the primary hypothesis that people with dry AMD perform worse than visually healthy peers on a computer-based surrogate of 'real-world' search tasks in a prospective case-control study. A secondary aim was to investigate whether eye movements during the tasks differ in people with dry AMD compared to those without.

3.2 Methods

3.2.1 Study participants

People with dry AMD were recruited from Moorfields Eye Hospital Trust, London, optometrists local to the university and the membership of the Macular Society (www.macularsociety.org). Eligibility criteria required participants to be aged ≥60 years, have sufficiently clear ocular media, adequate pupillary dilation and fixation to allow quality fundus imaging (Lens Opacities Classification System [LOCS] III grading scale (Chylack et al., 1993) of grade <3), and to have dry AMD (early/intermediate/late) in their better-seeing eye (assessed by best-corrected VA). Fellow eyes of volunteers with dry AMD were permitted to be of any AMD status because the impact of the better-seeing eye has been found to have a stronger relationship with vision related quality of life than the worse-seeing eye (Brown et al., 2001, Hirneiss, 2014, Rubin et al., 2000). Binocular VA was required to be logMAR 0.7 or better (Snellen equivalent of 6/30) as measured using an Early Treatment Diabetic Retinopathy Study (ETDRS) chart. AMD participants were excluded if they had neovascular AMD in their better-seeing eye, had any ocular or systemic diseases that could affect visual function or history of medication known to affect macular function (e.g. tamoxifen or chloroquine), or high risk of angle closure during pupillary dilation (Van Herick < Grade 2, history of angle closure or experience of prodromal symptoms of angle closure). In addition, participants were required to pass an abridged version of the Mini Mental State Evaluation (Folstein et al., 1975) which has been used in previous vision science research (McKeague et al., 2014, Margrain et al., 2012) and to have sufficient knowledge of the English language to understand the Participant Information Sheet, carry out history and symptoms questioning and understand test instructions.

Visually healthy controls were recruited from the City Sight Optometry Clinic at City, University of London. People attending this clinic for eye examinations are invited to sign-up to be contacted if they wish to be recruited for research studies for which they might be a potentially suitable participant. Eligibility criteria for controls was the same as for people with AMD except participants were required to have no AMD (or any other eye disease) in either eye, and monocular VA of logMAR 0.3 (6/12) or better.

The study was approved by Nottingham 2 National Health Service (NHS) Research Ethics Committee and was conducted according to the tenets of the Declaration of Helsinki. Written, informed consent was obtained from each participant prior to examination. Participant information was anonymised before being entered into a secure computer database.

3.2.2 Clinical examination and screening

After providing informed consent, participants underwent a series of baseline examinations to evaluate their AMD status and to ensure eligibility for participation. Structured history and symptoms were taken including questions from the EQ-5D questionnaire (Rabin and Charro, 2001) to assess general health. This questionnaire assesses self-report of five domains of life: mobility, self-care, usual activities (e.g. work, study, housework, family or leisure activities), pain or discomfort, and anxiety or depression. In the three-level version, respondents must rate their problems in each domain from a choice of three levels (Level 1 = no problems, Level 2 = some or moderate problems, Level 3 = extreme problems). Best corrected VA was determined with subjective refraction to correct the full spherical and astigmatic refractive error using a trial frame and a backlit ETDRS chart (mean luminance of 203.5 cd m^{-2}) at 4 metres (mono- and binocularly). This was scored per-letter (a logMAR score was assigned) and participants were encouraged to read down the chart until they were unable to read three out of a possible five letters on a line. Contrast sensitivity was tested with the Pelli-Robson chart at 1 metre (binocularly) with best-corrected distance prescription. This was scored per-letter (if participants read 'C' instead of 'O' or vice versa this was counted as correct (Elliott et al., 1990)).

Following the study tests, AMD participants underwent dilated fundus examination. (Control participants had already been assessed in a recent full optometric eye examination.) Lens clarity was graded using the slit lamp biomicroscope, according to the LOCS III grading scale (Chylack et al., 1993). Digital colour fundus photographs were obtained and these were used to classify and grade AMD status by the better-seeing eye (determined by VA) as early, intermediate, or late according to the Beckman classification scale (Ferris et al., 2013). This widely used scale grades macular disease status according to drusen size, pigmentary abnormalities, and presence or absence of GA or neovascular AMD. Spectral-domain OCT and fundus autofluorescence images were also taken; these, along with slit lamp indirect ophthalmoscopy, were used to support results obtained using colour fundus photographs, for example, OCT to confirm presence of nAMD, or fundus autofluorescence to confirm presence of GA.

3.2.3 Experimental procedure

This study procedure replicated one described elsewhere (Smith et al., 2012). Participants were seated at a chin rest 60 cm from a 56 cm CRT computer monitor displaying at a resolution of 1600 × 1200

at a refresh rate of 100 Hz (Iiyama Vision Master PRO 514, Iiyama Corporation, Tokyo, Japan). Optimal refractive correction for this viewing distance was determined by the operator (an optometrist; DJT) prior to testing, and participants all wore this correction mounted in a trial frame. This ensured that any effects caused by frame edges and lens size would be equivalent for each participant. Participants were tested binocularly.

Eye movements were recorded using the Eyelink II system (SR Research Ltd., Ontario, Canada). Pupil position was sampled monocularly (the chosen eye was alternated between participants). Participants rested their heads against a chin rest and a forehead bar in order to minimise head movements; the head movement detection system of the Eyelink II compensated for any head movements that did occur by adjusting the point of regard accordingly. The proprietary algorithm of the Eyelink II was used to calibrate and verify the subject's point of regard in response to prompts shown at different locations of the screen prior to starting the task, and before each individual trial drift correction was performed. When a large drift was detected, recalibration was performed.

In each trial, participants were instructed to search for a target item within a digital photograph of an everyday indoor or outdoor scene presented on the computer screen. Examples of photographs used in the study are shown in Figure 3.1. These were 40.8 cm (width) × 30.6 cm (height) subtending a half-angle of 20.3° by 14.9°. Images were chosen to represent a range of visual search tasks that people may perform in their day-to-day lives. Prior to each image being shown, instructions were displayed on the computer screen, and the operator read these instructions out loud simultaneously. A central target was then shown on a grey background and the trial would not start until the Eyelink II had detected that the participant's gaze was directed at the target. This ensured that all participants' eyes were directed towards the same location on the screen when the trial started. Three practice images were displayed first, followed by 15 test images. The 15 test images were presented in a random order. Participants were instructed to indicate verbally once the target item in the image had been detected. This was verified by the researcher (DJT) by ensuring that their gaze, as recorded by the Eyelink II was directed to the target. Search durations for each image were recorded; all search durations greater than 60 seconds were censored at this value.

The primary outcome measure for this experiment was the median search duration calculated across the 15 trials for each person. Recorded eye movement parameters, directly taken from Eyelink II, were considered to be secondary outcome measures. For each participant, a median value was calculated across the 15 trials to estimate average saccades per second, average saccadic amplitude and average fixation duration.



Figure 3.1: Examples of photographs used in this experiment. In (a) participants were asked to find the name of the street, and in (b) participants were asked to find the castle. (Images were displayed at higher resolution than shown here.)

3.2.4 Data analysis

A 90% normative reference limit was generated from the distribution of ranked median search times recorded in the visually healthy controls. This limit was estimated by a direct percentile method because the distribution of data was skewed (Schoonjans et al., 2011). Median search times for AMD participants were then specifically compared to this limit and comparisons between the AMD groups were investigated. A similar analysis was carried out for each of the three eye movement parameters. Univariate associations between median search time and VA, CS and age were explored. Formal sample size calculations were not calculated as the primary analysis was comparing results from a number of individuals with a normative reference range using the direct percentile method. However a retrospective sample size calculation using Altman's nomogram determined that a sample size of 30 (15 per group) would be sufficient to detect a clinically significant effect size of 4 seconds, at a power of 80% and significance level of 0.05. This is relevant to secondary analyses which included probability testing. Statistical analysis was carried out using SPSS Statistics 22 (IBM Corp., Somers, NY).

3.3 Results

Thirty-one people with dry AMD (84% female) with a median (interquartile range [IQR]) age of 75 (70, 79) years and 33 visually healthy controls (55% female) with a median (IQR) age of 71 (66, 75) years were eligible for this study. Participants with AMD were slightly older on average than controls (Mann-Whitney test; $p = 0.01$). Median (IQR) duration of AMD was 4 (2, 5) years. Participants had reasonable general health (ascertained by structured history and symptoms). Median (IQR) ETDRS corrected binocular LogMAR VA was 0.20 (0.18, 0.31) and -0.06 (0.12, 0) in the AMD and control groups respectively. The difference between these values was statistically significant (Mann-Whitney test; $p < 0.001$). Median (IQR) Pelli-Robson logCS values were 1.65 (1.43, 1.95) and 1.95 (1.95, 1.95) in the AMD group and controls respectively. The difference between these values was statistically significant (Mann-Whitney test; $p < 0.001$).

When stratified by the Beckman Classification according to better-seeing eye, 4, 18 and 9 people were classified as having early, intermediate and late (geographic atrophy) AMD respectively. Median (range) ETDRS (Early Treatment Diabetic Retinopathy Study) corrected binocular logMAR VA for the people with no AMD, early, intermediate and late AMD was -0.06 (-0.22, 0.08), 0.2 (0.18, 0.28), 0.19 (0.02, 0.44) and 0.38 (0.20, 0.58) respectively.

Median (IQR) search durations for participants with AMD and controls were 15.3 (11.7, 24.3) and 8.3 (6.9, 10.3) seconds respectively. Nineteen (61%) people with AMD, including all of those with late AMD, exceeded the 90% normative limits for delayed average search time set by the visually healthy controls (Figure 3.2), and this differed significantly from the number of controls exceeding this limit (n = 3) (Fisher's Exact Test, $p < 0.001$). Individual graphs showing search durations for each individual image are available in Appendix 4.

There was no statistically significant association between age and average search time in the control group (Spearman's Rho (r) = 0.05, $p = 0.54$) or the AMD group ($r = 0.22$, $p = 0.23$). Nor was there a statistically significant association between AMD duration and average search time ($r = 0.22$, $p = 0.26$). Amongst participants with AMD there were significant associations between average search time and VA ($r = 0.63$, $p < 0.001$), and CS ($r = -0.58$, $p = 0.001$).

When trials were organised by 'type', there were no statistical differences between search durations for outdoor images (n=9) compared with indoor images (n=6), (Mann-Whitney test; $p = 0.33$). Likewise, no statistical differences were found between search durations for search tasks involving reading text (e.g. 'what is the price of the yellow smoothie drink?', 'please find and read out loud the

street name') and those that did not (e.g. 'please find the hanging basket', 'how many bins are there?') (Mann-Whitney test; p = 0.45).

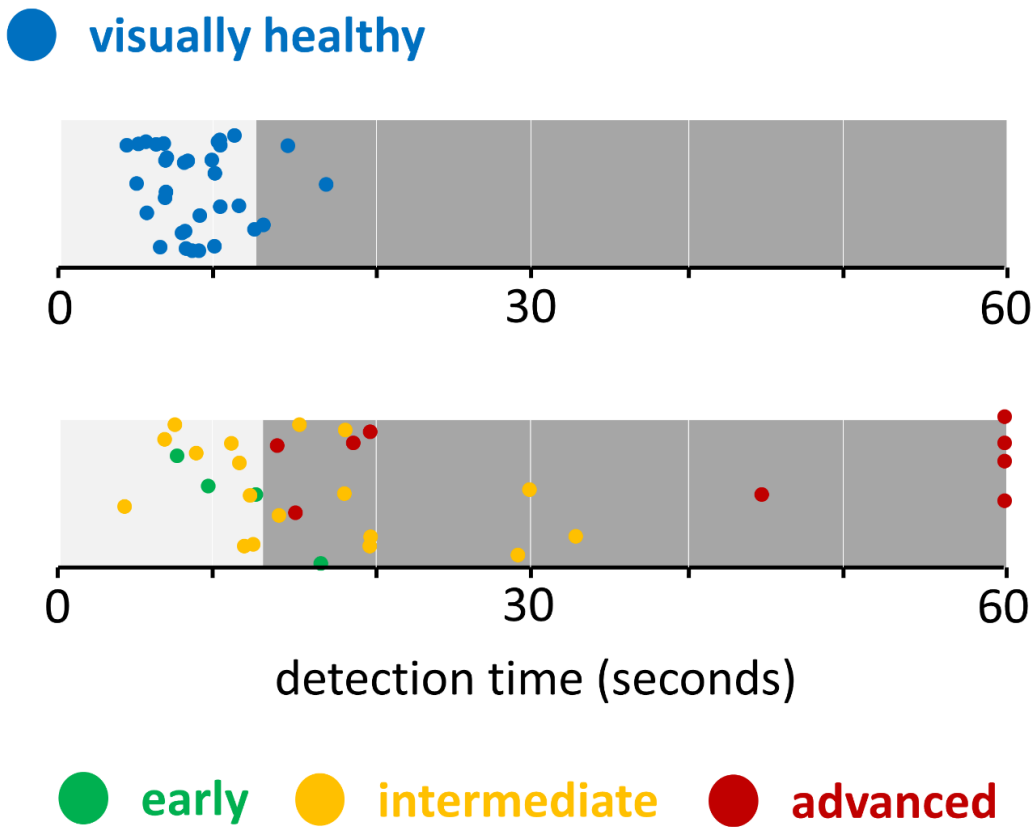


Figure 3.2: Median search durations for participants across images stratified by AMD group. The 90% normative limits set by controls are illustrated by the darker shaded area on the right of both graphs. (Some vertical jitter is added to the plotted points.)

The secondary outcome measures for this study were eye movement parameters (see Table 3.1). We found no differences between groups in fixation duration or saccades per second (Mann-Whitney test; $p > 0.05$). Yet people with AMD tended to make smaller saccades than controls and this was statistically significant (Mann-Whitney test; $p < 0.001$).

Table 3.1. Eye movement parameters expressed as median (IQR)

	AMD group (n = 31)	**Control group (n = 33)**	***p-value***
Fixation durations (ms)	288.1 (267.2, 320.7)	291.9 (268.9, 312.6)	*0.88*
Saccadic amplitude (degrees)	4.1 (3.8, 4.5)	4.89 (4.5, 5.2)	*< 0.001*
Saccades per second	2.9 (2.6, 3.1)	2.8 (2.6, 3.0)	*0.45*

Because of the difficulties some people with AMD have in foveating the target during calibration of the eyetracker, some particpants were able to achieve 'GOOD' calibration, but only 'FAIR' or 'POOR' validation during the calibration phase of the eye tracker. This is an issue that has been noted previously in people with AMD (Geringswald et al., 2013). As a result of this, we can assume eye tracking accuracy for the AMD group was poorer than for controls. When the eye movement analysis was repeated purely for those who achieved 'GOOD' calibration and validation (n = 16) compared with the 33 controls, saccadic amplitude remained significantly smaller for those with AMD than for those without ($p < 0.001$), there was no difference in fixation duration between the AMD group and controls ($p = 0.19$) and people with AMD made fewer saccades per second than those without, although the statistical significance was weak ($p = 0.04$).

Search durations and eye movement parameters did not differ significantly between males and females (Mann-Whitney test; search durations $p = 0.16$, fixation durations $p = 0.29$, saccadic amplitude $p = 0.22$, saccades per second, $p = 0.22$).

3.4 Discussion

Visual search is an important everyday task and has also been shown to be a predictor of problems with mobility and other daily activities (Fuhr et al., 2007). Existing research has focused on arrays of optotypes or examining volunteers given simulated scotomas rather than participants with ocular pathology. Other studies using real-world type tasks do not differentiate between type of age-related vision loss (Dougherty et al., 2009). In this study, we used visual search tasks based on everyday scenarios and participants with actual scotomas. Median search durations were, perhaps unsurprisingly, longer for people with AMD than for controls. The experimental effect was large: average search durations for participants were almost twice those for controls. A large number of the people with AMD, including all of those classified as having geographic atrophy in their better eye fell outside a 'normal' limit for the task. Average VA in the AMD group, although reduced, fell within the UK's legal requirements for driving and this was noteworthy. This result is consistent with previous research findings that people with AMD take longer to find targets in a visual search task than people without. Our study adds to this knowledge because we considered a group of people specifically with dry AMD of varying severity and we used realistic surrogates of an 'everyday' search task; this is likely more applicable to the real world than searching for optotypes in an array of distractors. In particular, our results highlight the burden of a diagnosis of geographic atrophy with this type of everyday task as well as showing that some people with less severe vision impairment (intermediate AMD) may have more difficulties with these sorts of activities than previously believed.

A number of theories attempt to explain extended search duration in individuals with central scotomas. It may result from the need for increased fixation durations (Murphy and Foley-Fisher, 1989, Ford et al., 1959). Yet increased fixation duration is not consistently reported across studies investigating visual search in people with central scotomas, and our study did not find a significant difference in fixation durations between the AMD group and the control group. Other studies (Thibaut et al., 2016, Crossland and Rubin, 2006) discuss the increased number of saccades that may be required to attempt to bring a target of interest onto an area of healthy retina. Our results support this idea in part; the visually healthy participants in our study made more saccades per second on average than the AMD participants during their search duration but this was only really apparent after we filtered the data by the quality of the calibration of the eye tracking experiments.

Bertera (1988) reported that search durations double for participants with an artificial central scotoma in comparison to 'no scotoma' conditions for difficult search tasks. No difference in search times was found between scotoma and no scotoma conditions for easier search tasks. In our study, the largest

proportional increase in median search durations occurred for search tasks involving finding and reading street signs, increasing search durations by five- and eight- fold (see Appendix 4). Search ability did not appear to be limited by VA in our sample; the VA of the four participants whose average search duration across all images exceeded 60 seconds ranged from 0.32 to 0.58, whilst other participants with equivalent VA recorded average search durations of as little as eleven seconds.

Cornelissen et al. (2005) found larger saccadic amplitudes amongst participants with central scotoma; conversely, other studies report no difference in saccadic amplitude between those with and those without central scotomas (Murphy and Foley-Fisher, 1989, Bertera, 1988). Crucially, these experiments were conducted using artificial scotomas, rather than people with actual vision loss. In our study, saccadic amplitudes were smaller on average amongst participants with AMD than those without; this aligns with results from a visual search study on central scotomas in people with Stargardt's disease (Van der Stigchel et al., 2013). Smaller saccadic amplitudes have also been observed during reading for people with AMD (Bullimore and Bailey, 1995). It has been suggested (Smith et al., 2012) that people with scotomas may make smaller eye movements in order to avoid their visual target falling into their scotoma.

There are limitations to this study. Although the tests were designed as surrogates of real-world tasks, performing a task at a computer screen and performing the same task in everyday life are not the same. However, we believe that this test has much better real-world applicability than search tasks conducted using arrays of optotypes. In addition, although participants were screened for cognitive defects and underwent structured history and symptoms questioning in order to ascertain reasonable levels of general health in both groups, it is possible that subtle differences in cognitive ability and general health may have had an effect on the results of this study. The participants with AMD were slightly older than the controls but only by a few years on average. Despite this, no association was found between age and average search time amongst either group. Likewise, despite the AMD group comprising more females than males, search durations and eye movement parameters did not differ between males and females. Another limitation of this study was the lack of mapping of retinal sensitivity in these patients, for example, using microperimetry. This could potentially form the basis of future work to evaluate the relationship between retinal sensitivity and visual search performance in people with dry AMD. Finally, due to poor fixation, eye tracking accuracy was worse for people with AMD than for controls. However, when the eye movement analysis was repeated including only those who performed well during the calibration phase of the test, our results remained significant.

To conclude, some people with dry AMD, particularly those with geographic atrophy, have measurable difficulties on a computer-based real-world search task beyond those observed in visually healthy peers. This is likely translatable to difficulties that these individuals may experience in their day-to-day lives; future work should investigate this further. The results of this work have important implications for the management of patients with dry AMD, particularly those who may have previously been assumed not to require the support of vision rehabilitation services. Visual search performance may also have potential to be used as a meaningful outcome measure for clinical trials for possible future treatments for dry AMD. A practically applicable version of the task we have illustrated in this study is the subject of future work.

Chapter 4 The effect of non-neovascular age-related macular degeneration on face recognition performance

4.1 Introduction

Face recognition is an important daily activity. We are believed to spend more time looking at faces than any other complex visual stimuli and this is central to social interactions (Pascalis and Kelly, 2009). Difficulties with face recognition can lead to embarrassment and anxiety in social situations which in turn can lead to social isolation (Yardley et al., 2008). People with AMD have difficulties with different aspects of face recognition. For example, in a survey of thirty people with bilateral AMD, all but one reported difficulty recognising familiar faces in the street; a third of these felt embarrassment as a result of this (Tejeria et al., 2002). In the same study, over half of respondents reported missing things in conversation because of inability to make out facial expressions. These patient-reported data are corroborated by performance-based research studies. For example, viewing distances required for recognising faces were measured to be shorter on average for people with AMD than those without (Bullimore et al., 1991). Moreover, ability to determine whether a face is expressive or not has been reported to be closely related to near reading acuity (Tejeria et al., 2002). In one study (Alexander et al., 1988), only 26% of 100 people with AMD were able to correctly identify the facial expression on four photographs of people depicting feelings like happiness, sadness and tiredness; performance in this task was related to visual acuity in the participants, with those with poorest VA performing particularly badly.

Dry AMD and neovascular AMD (nAMD) have been reported to differ in both their functional effects (Calabrèse et al., 2011) and psychological effects (McCloud et al., 2014, Banerjee et al., 2008). There is a growing interest in characterising the clinical features of different stages of dry AMD, particularly with respect to determining meaningful end points for clinical trials (Sadda et al., 2016). This interest is timely as there are several potential therapies currently reaching the stage of phase III randomised controlled trials (RCTs) for dry AMD (Sadda et al., 2016). Understanding the functional ability associated with each stage of dry AMD is a key element of this characterisation of dry AMD progression. Previous research on face recognition in AMD, however, has largely focused on people with nAMD or has not differentiated between individuals with neovascular and non-neovascular (dry) AMD (Barnes et al., 2011, Alexander et al., 1988, Tejeria et al., 2002). The aim of this study therefore, was to investigate face recognition performance in people with dry AMD of varying severity compared with visually healthy peers.

The work presented in this chapter has been submitted as a paper to *Graefe's Archive for Clinical and Experimental Ophthalmology* and is currently under final revision; see list of supporting publications. The co-authors of this work are David Crabb (DC), Alison Binns (AB) and Nicholas Smith (NS). All AMD participant recruitment and data collection was conducted by DJT between May 2015 and February 2016. Comparison control data had already been collected for previous studies (Glen et al., 2012, Glen et al., 2013). Data analysis was performed by DJT with support from NS. The paper was written by DJT, and reviewed, edited and approved by all authors. Some of the work presented in this chapter has also been presented as a paper presentation at the Association for Research in Vision and Ophthalmology meeting (Seattle, WA, USA, 2016) and at the British Congress of Optometry and Visual Science (Ulster, Northern Ireland, 2016), and as a poster presentation at Optometry Tomorrow (Birmingham, England, 2017); see list of supporting publications.

4.2 Methods

4.2.1 Participant recruitment, baseline clinical examination and ethical approval

Participant recruitment, baseline clinical examination and ethical approval were as described in sections 3.2.1 and 3.2.2.

4.2.2 Experimental testing procedure

Face recognition was measured binocularly using a modified version of the Cambridge Face Memory Test (Duchaine and Nakayama, 2006) incorporating eye tracking used in our previous research studies (Glen et al., 2012, Glen et al., 2013). This was displayed on a 22-inch monitor (Iiyama Vision Master PRO 514, Iiyama Corp., Tokyo, Japan; 1600 × 1200 pixels at 100 Hz). The monitor was placed 60cm from participants (viewing position was fixed using a head and chin rest), subtending a visual angle of 36.9° horizontally and 28.1° vertically. Images were displayed at an average luminance of 4.29 cd/m2 (SD, 1.16). On average, the faces subtended 7.4° horizontally and 11.1° vertically. The average half angle of faces was 3.7° (equivalent of 6.5 cm width half face). This is comparable to the size of a face viewed in the real-world at approximately 1 metre. Optimal refractive correction for the viewing distance was determined by the operator (an optometrist; DJT) prior to testing, and participants all wore this correction mounted in a trial frame. This ensured that any effects caused by frame edges and lens size would be equivalent for each participant.

Instructions for the test were both written in large print on the computer screen and given verbally. Trials involved a viewing phase during which participants were shown a series of faces (front, and right and left side views) for three seconds per view and a selection phase during which participants were given a forced-choice task to select which face from a set of three matched the one they had just viewed (see Figure 4.1). Responses were keyed in by the operator (DJT). Participants were allowed unlimited time during the 'selection phase'.

Following this, a montage of the six faces learnt during the preceding trials was shown (the 'review phase') and participants were asked to study them for 20 seconds. Following this, recognition of these six faces was tested, by showing participant sets of three faces and requiring them to select which one they had previously viewed (forced choice again). Overall, participants completed 51 trials.

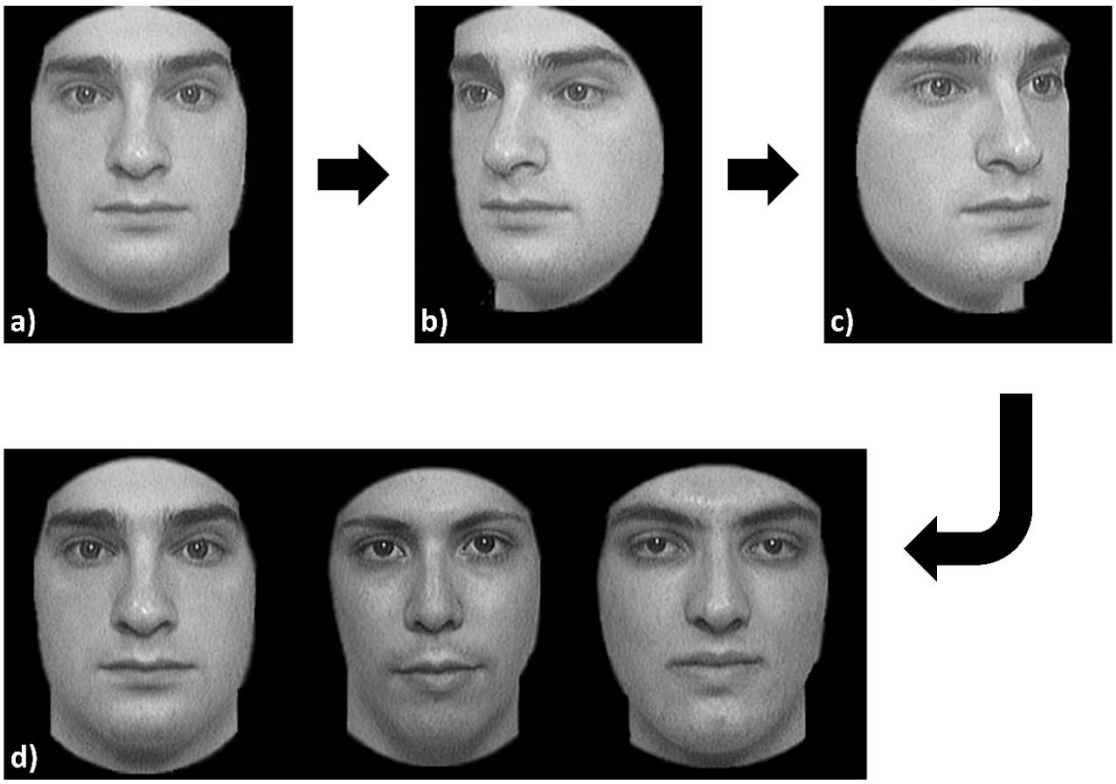


Figure 4.1: An example task from the selection phase of the CFMT. Participants were asked to familiarise themselves with a face, shown from three different viewpoints (a, b and c). Participants were then asked to tell the operator which face matched the one they had just viewed (d).

4.2.3 Analysis

Percentage of correctly identified faces across the 51 trials was used as the outcome measure (FR score) for performance for each participant. A 90% normative reference limit was generated from the distribution of ranked scores recorded in the visually healthy controls. This limit was estimated by a direct percentile method (Schoonjans et al., 2011). Scores for AMD participants were then specifically compared to this limit and comparisons were made between groups based on severity of AMD in the better-seeing eye. This was explored graphically and Fisher's exact test was used to test whether the proportion of AMD participants to fall outside this limit differed from the proportion of controls to fall outside the limit (10%). Amongst people with GA, the relationship between lesion area (as measured using Spectralis (Heidelberg Engineering, Heidelberg, Germany) Region Finder software (Schmitz-Valckenberg et al., 2011)) and presence or absence of foveal sparing and FR score were explored, again comparing scores to the normative limit set by controls. Face recognition scores

were not normally distributed (Shapiro-Wilk test; $p < 0.2$) so median scores were also calculated for each AMD severity group and comparisons were made between groups and to mean scores in the visually healthy controls using a Kruskal-Wallis test. Univariate associations between FR score and self-reported disease duration, VA, CS and age were explored. Formal sample size calculations were not calculated as the primary analysis was comparing results from a number of individuals with a normative reference range using the direct percentile method. However a retrospective sample size calculation using Altman's nomogram determined that a sample size of 30 (15 per group) would be sufficient to detect a clinically significant effect size of 10%, at a power of 80% and significance level of 0.05. This is relevant to secondary analyses which included probability testing. All statistical analysis was conducted in SPSS 22 (IBM Corp., Somers, NY).

4.3 Results

Thirty participants with AMD (87% female) with a median (interquartile range [IQR]) age of 76 (70, 79) years and thirty-four visually healthy controls (53% female) with a median age of 70 (64, 75) years took part in our study. Median (IQR) duration of AMD was 4 (2, 6) years. Participants had reasonable general health (ascertained by structured history and symptoms). Median (IQR) ETDRS corrected binocular logMAR VA was 0.22 (0.18–0.38) and –0.06 (-0.12–0) in the AMD group and controls, respectively. Median (IQR) Pelli-Robson logCS values were 1.65 (1.35–1.95) and 1.95 (1.95–1.95) in the AMD group and the control group, respectively.

When stratified using the Beckman classification according to better eye, four, seventeen and nine people were classified as having early, intermediate and late AMD (GA) respectively (Ferris, et al., 2013). Median (IQR) ETDRS corrected binocular logMAR VA according to AMD stage was 0.20 (0.19–0.26), 0.20 (0.13–0.28), and 0.36 (0.24–0.57) for people with early, intermediate, and late AMD respectively. Table 4.1 shows AMD classification for fellow eyes.

Table 4.1: AMD severity of fellow eyes according to better eye status

Classification of better-seeing eye	**Fellow eye classification**			
	Early AMD	*Intermediate AMD*	*Late AMD (GA)*	*Late AMD (nAMD)*
Early AMD	n = 4			
Intermediate AMD		n = 11	n = 3	n = 3
Late AMD (GA)			n = 8	n = 1

Five (17%) participants with AMD recorded a face recognition performance worse than the 90% limit set by controls (Figure 4.2). This number of AMD participants, as a whole sample, did not differ significantly from the number of controls falling outside the limit (Fisher's exact test, p=0.46). However, four out of the five AMD participants falling outside the 90% limit set by the controls had GA.

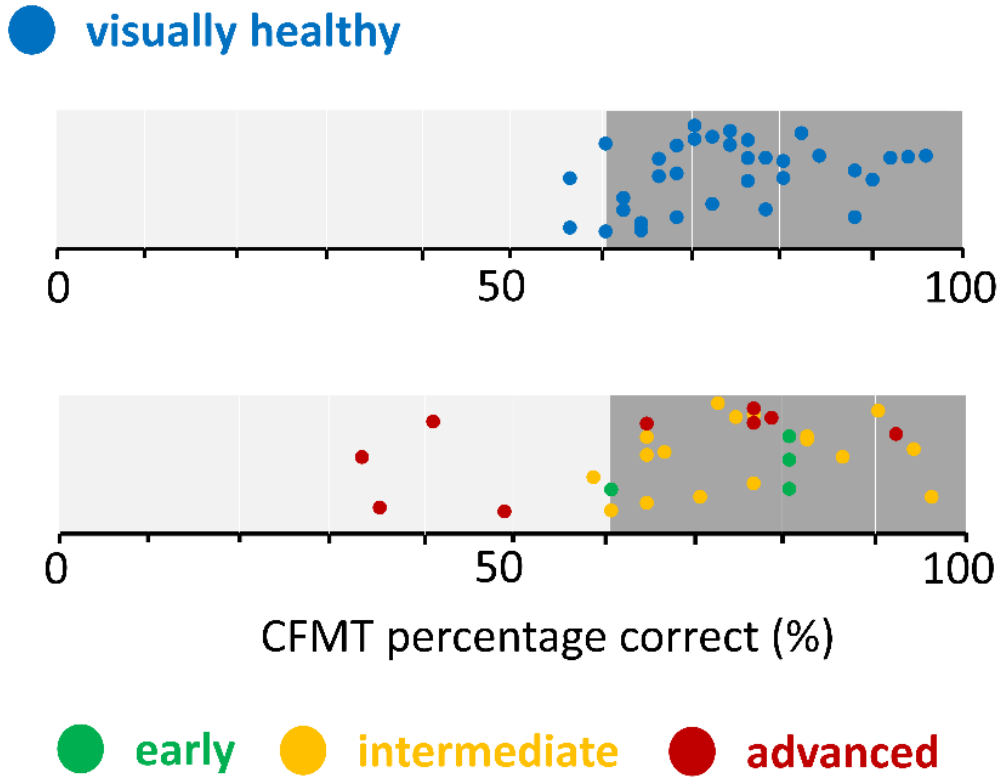


Figure 4.2: Percentage CFMT score for each participant stratified by AMD group. The 90% normative limits set by controls are illustrated by the darker shaded area on the right of both graphs. (Some vertical jitter is added to the plotted points.)

Amongst people with GA, individuals with larger GA lesion area and foveal involvement scored worse on the CFMT than people with smaller lesion area and foveal sparing (Figure 4.3). Of the four participants with GA who fell outside the normative limit for FR score set by controls, all of these had fovea-involving GA and larger lesion sizes than those who fell within the normative limit.

When considering effects across the groups, participants with GA identified fewer faces on average (median [IQR] FR score) (65% [38, 77]) than those with early (80% [66, 80]) and intermediate (75% [65, 84]) AMD and controls (74% [66, 81]); however, this difference was not statistically significant (Kruskal-Wallis; $p = 0.39$). No statistically significant differences between groups were observed when participants were grouped according to fellow eye AMD classification (Kruskal-Wallis; $p = 0.46$).

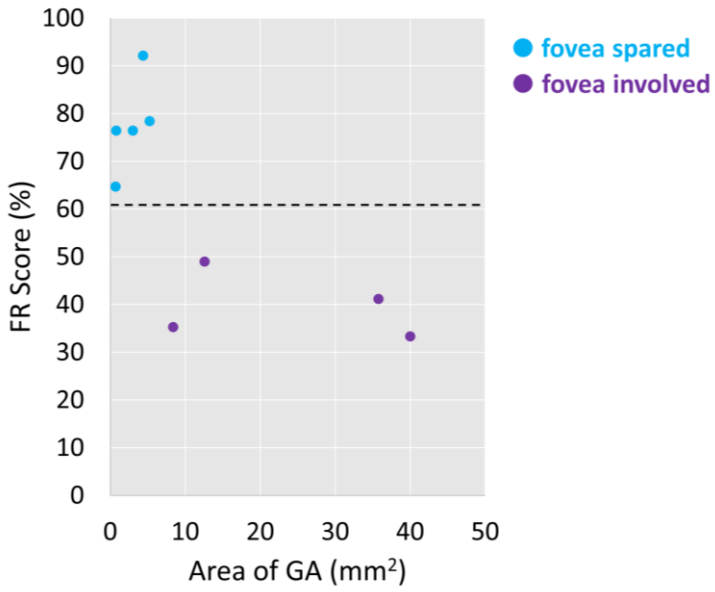


Figure 4.3: Scatter plot showing the relationship between FR score and GA lesion size amongst participants with dry AMD, colour coded according to whether foveal sparing was present or not. The dotted black line represents the 90% normative limit derived from the visually healthy controls.

Among the AMD group, there was a strong statistically significant correlation between FR score and contrast sensitivity ($r = 0.63$, $p < 0.001$), and a weaker but statistically significant correlation between FR Score and VA ($r = -0.54$, $p = 0.002$) (Figure 4.4). There was no significant correlation between AMD duration and CFMT score ($r = -0.23$, $p = 0.25$).

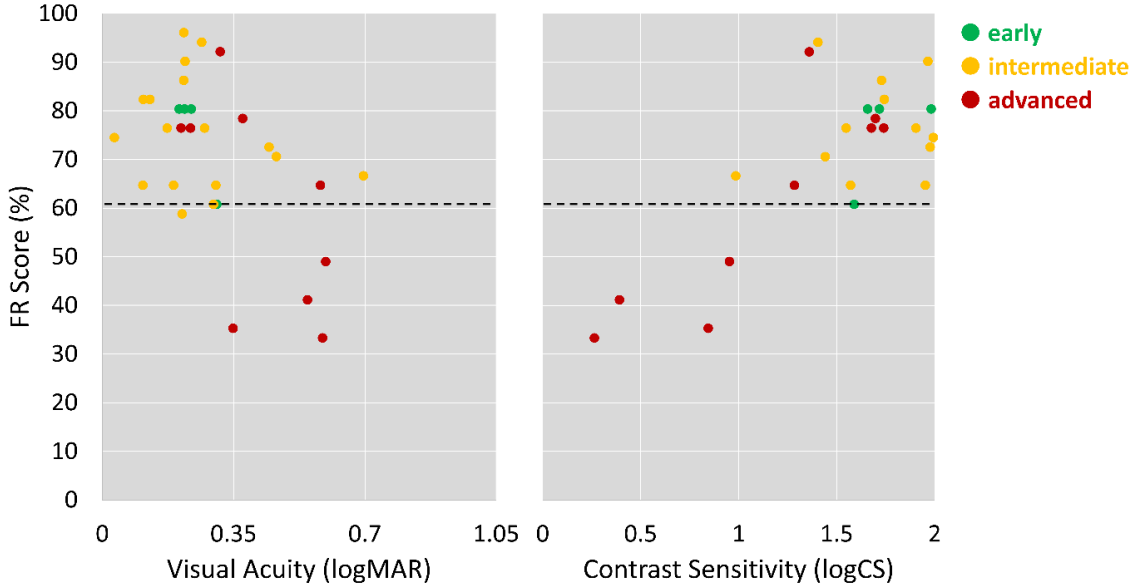


Figure 4.4: Scatter plots showing the relationship between FR score and contrast sensitivity and visual acuity amongst participants with dry AMD, colour coded according to AMD classification. The dotted black line represents the 90% normative limit derived from the visually healthy controls. (Some horizontal jitter is added to the plotted points to allow visualisation of overlapping data points.)

4.4 Discussion

We studied computer-based face recognition performance in people with a range of severities of dry AMD compared with visually healthy peers. It is well documented that people with AMD have difficulties with face recognition. Our study adds to this knowledge because it is the first study to document face recognition performance specifically in people with dry AMD. Moreover, we compared FR performance, using a validated test (Duchaine and Nakayama, 2006), in people with different stages of AMD as classified by a widely used grading scale (Ferris et al., 2013). Our results indicate that people with early or intermediate dry AMD perform as well as visually healthy peers on a controlled face recognition task. Therefore, people with dry AMD may not typically suffer from problems with recognising faces until the disease is in its later stages; those with late AMD (GA) in their least affected eye, particularly those with larger GA lesions and foveal atrophy, are likely to have difficulty recognising faces.

Our results are most comparable with a previous study we conducted in people with glaucoma. In our previous work in glaucoma using the CFMT, patients with mild and moderate glaucomatous visual field loss (Hodapp et al., 1993) were found to have similar face recognition performance to those without, whilst those with advanced glaucomatous visual field loss were found to have worse face recognition ability. Similarly, in our current study, we report that people with late dry AMD (GA) may have poorer face recognition ability, on average, than those with early and intermediate AMD and those without AMD, although in our sample this difference was not statistically significant.

The wide variation of FR scores across our results is consistent with previous work on face recognition in AMD. Barnes et al. (2011) tested a group of people with AMD with similar visual characteristics to our participants (median logMAR VA of 0.20 and CS of 1.55). A wide variability in FR scores was noted, although participants with AMD had poorer face recognition on average compared to visually healthy controls. Classification and stage of AMD was not reported. A large-scale US-based survey of people with AMD (Schmier et al., 2006a) reported a fairly even spread across response options for two of the three items on the Daily Living Tasks Dependent on Vision (DLTV) Questionnaire relating to face recognition. These items described the difficulty experienced in distinguishing a person's features across a room and distinguishing a person's features across the street. The third item on this questionnaire relating to face recognition asked respondents about difficulty in distinguishing a person's features at arm's length. A much higher proportion of respondents (61%) reported 'no difficulty at all' to this item as compared to the other items; this is relevant to our findings because

this item likely reflects difficulty under a task condition most similar to that presented by the CFMT (comparable to viewing a face at 1m). However, further comparison with our study is limited by the fact that the survey study did not report AMD stage or classification.

We showed a strong association between worsening in FR performance and worsening of measured contrast sensitivity in the people with dry AMD. Current evidence surrounding the relationship between FR performance and CS in AMD is conflicting. Some studies (Tejeria et al., 2002, Bullimore et al., 1991) report a weak relationship whilst others report a strong relationship (Barnes et al., 2011, Dinon and Boucart, 2005). Other papers have also suggested contrast sensitivity to be a more useful indicator of performance of everyday activities (Alexander et al., 1988), mobility (Wood et al., 2011b, Wood et al., 2009) and quality of life (Bansback et al., 2007) in people with AMD and in a sample of the general population (Owsley et al., 1987) than other traditional measures of visual function, certainly more useful than visual acuity alone. However, in a study investigating clinical tests perceived as most and least important by ophthalmologists (albeit almost twenty years ago), contrast sensitivity was rated consistently as one of the least important clinical tests of vision (Hart et al., 1998). Our study not only adds to the body of evidence supporting the relationship between FR performance and CS in AMD, but also supports the suggestion that CS may be a more valuable predictor of real-world visual performance than high contrast VA alone. We have also shown that foveal involvement of GA, and GA lesion area may be useful predictors for face recognition performance. This finding implies that the ability to accurately recognise faces depends highly on the fovea remaining intact and provides further evidence to support the development of treatments which may halt or slow the progression of GA before the fovea is affected, such as those currently undergoing clinical trials (Sadda et al., 2016).

Our study has limitations. Although all participants were screened for cognitive defects, it is possible that subtle differences in cognitive ability between participants may have affected the results. Another limitation of this work, and indeed of most face recognition testing, is the questionability of its real-world applicability. The CFMT was chosen for this work because of its strengths compared with other face recognition tests available at the time of testing, its wide use and acceptability (over 300 citations in peer-reviewed literature), its reliability (previous research has consistently confirmed the reliability of the CFMT [Cronbach's $\alpha > 0.8$] (Herzmann et al., 2008, Bowles et al., 2009, Wilmer et al., 2010)) and specifically its previous use in testing face recognition in eye disease (Glen et al., 2012, Glen et al., 2013). However, previous research (using different testing methodology) has found a poor relationship between perceived face recognition ability (self-reported difficulties in face

recognition reported by almost all participants in the particular study) and performance on a face recognition task (Tejeria et al., 2002). A number of theories attempt to explain these discrepancies. They may occur as a result of differing conditions in the real world, for example, differences in luminance at different times of day and indoors compared with outdoors, and differences in viewing distance (Boucart et al., 2008b, Loftus and Harley, 2005). Current face recognition testing modalities may not be sensitive enough to detect subtle differences in face recognition ability across people with eye disease of varying severity. A newer test (Logan et al., 2016) claims to have the potential to be more sensitive to subtle differences in face discrimination ability than other tests, including the CFMT. Future work might test this further.

There are other potential limitations to our findings. Our sample of cases with AMD were very slightly older, on average, than their visually healthy peers. (The 95% confidence interval for mean difference in age was 2 to 8 years.) Finally, it may be potentially viewed as a limitation that the majority (87%) of our sample of participants with AMD was female, whilst the control group was 53% female. However, the CFMT was designed with male faces specifically, as opposed to female faces or a mixture, because men and women have been shown to exhibit equal FR performance for men's faces (Duchaine and Nakayama, 2006). Therefore, we do not believe that this has influenced the results of our study.

An easily administered and shortened version of the CFMT based on our work might have a role as an outcome measure for clinical trials. Our results suggest the test would not be sensitive to changes in the early and intermediate stages of AMD but might spotlight a useful functional end point for GA progression. Results from this type of test are likely to be more meaningful to patients than traditional outcome measures such as letter charts, where changes are often imperceptible to the patient. Development of such a test is a subject of our future work.

To conclude, people with dry AMD may not suffer from problems with face recognition until the disease is in its later stages; those with late AMD (GA), particularly those with larger areas of atrophy involving the fovea, those with significantly reduced contrast sensitivity and, (to a lesser extent) visual acuity are likely to have difficulty recognising faces. This could have important implications for patients, especially when coupled with other problems associated with AMD, for example, difficulties and fears surrounding mobility (Curriero et al., 2013). The results from this study should influence both management and expectations of patients with dry AMD.

Chapter 5 Seeing it differently: self-reported description of vision loss in dry AMD

5.1 Introduction

Age-related macular degeneration (AMD) is the most common cause of visual impairment in developed countries; its prevalence is set to increase as the population ages. For example, 196 million people are estimated to have the condition by 2020 (Wong et al., 2014). The previous chapters have described how AMD impacts negatively on visual ability and quality of life. Yet, disease awareness of AMD in the public is limited. For example, a US-based study of over 2000 members of the public demonstrated only half had heard of AMD (Scott et al., 2016). Other recent studies have yielded similar results; one US-based study reported 29% of 695 members of the public surveyed to have never heard of AMD, and, perhaps more worryingly, 7% of at-risk (Caucasian non-smokers aged ≥ 60 years) and 9% of high-risk (Caucasian smokers aged ≥ 60 years) populations had never heard of AMD (Cimarolli et al., 2012b); of 385 residents of Beijing surveyed, nearly 70% were 'not at all familiar' with AMD (Zhang et al., 2017). In Singapore, awareness increased fourfold from 7% in 2006 to 28% in 2011 following awareness campaigns; however, 70% remained unfamiliar with AMD (Sanjay et al., 2014). Following awareness campaigns in Australia, awareness of AMD is reported to have increased from 47% in 2007 to 80% to 2011 (Heraghty and Cummins, 2012). Moreover, less than 20% of people with signs of AMD (most had early and intermediate AMD) were aware of their condition, in a study based in the US (Gibson, 2012). Over 99% of 181 people identified as having AMD in a Singapore-based study were unaware of their eye disease (Huang et al., 2013). Elsewhere it has been reported that many people with AMD suffering advanced visual loss are unaware aware of their scotomas (Fletcher et al., 2012).

A realistic description of visual symptoms associated with dry AMD is important for raising awareness of the condition and educating patients; this is the subject of this study.

A simple search on the internet will yield common depictions of the visual symptoms of people with AMD. Typically, this will be a photograph with a grey or black patch superimposed over its centre. A widely used example of this is the National Eye Institute (NEI) photograph of, 'A scene as it might be viewed by a person with age-related macular degeneration' (Figure 5.1). In this study, we aim to explore the accuracy of these representations with respect to the experience of people with early and intermediate AMD and pre-end stage GA. In addition, we ask individuals about their vision in order to develop a set of descriptors for visual symptoms of dry AMD.



Figure 5.1: Image frequently used for education about AMD. The image on the left shows 'normal vision' whilst the image on the right shows 'vision with AMD'. Source: https://nei.nih.gov/health/examples

The work reported in this chapter forms a paper which has been accepted for publication in *Ophthalmic and Physiological Optics* and is currently 'in press'; see list of supporting publications. The co-authors of this work are David Crabb (DC), Alison Binns (AB) and Laura Edwards (LE). Data were collected by DJT between May 2015 and February 2016, and analysed by DJT and LE. Any disagreements or uncertainties during the coding of interview transcripts were referred to DC. The paper was written by DJT and reviewed, edited and approved by all authors.

5.2 Methods

5.2.1 Images

To establish which images are used most frequently to depict the vision of people with AMD, a Google Image search was conducted independently by two of the authors (LE and DJT). The search term used was, 'vision age related macular degeneration'. The first 50 images produced by the search were evaluated and a description of the content of each image was entered into a spreadsheet.

5.2.2 Participant recruitment, baseline clinical examination and ethical approval

Participant recruitment, baseline clinical examination and ethical approval were as described in sections 3.2.1 and 3.2.2, except that only participants with AMD were included in this study.

5.2.3 Interviews and data analysis

The following questions were asked as part of a longer interview about participants' wider experiences with AMD. Interviews were recorded using an audio recorder, transcribed verbatim by an independent transcription company and transcripts were checked by the interviewer (DJT).

Participants were asked, 'When you are aware of your AMD, can you describe how it looks?' and, 'How would you describe what it is wrong or different about your vision to someone without AMD?'

This analysis of the responses was similar to that described elsewhere (Crabb et al., 2013). In brief, transcribed responses to the questions were read individually by two of the authors (LE and DJT) and words or phrases considered to be descriptors of visual symptoms were highlighted. The authors then compiled a list of individual descriptors. Where one participant used the same descriptor multiple times, this was counted as one occurrence of that descriptor. Numbers of participants to use each descriptor were then counted. A matrix was generated showing combinations of descriptors used by each participant.

Participants were then given an A4-sized page showing the NEI photograph, in both its unaltered (i.e. 'normal vision') and manipulated (i.e. 'vision with AMD') forms (Figure 5.1). They were encouraged to hold the sheet at an angle and distance to allow for optimal viewing conditions for them to see the images as clearly as possible with their habitual near correction. Participants were asked to comment on how these images tie in with their experiences. Care was taken to avoid asking the question in a leading manner.

Two of the authors (DJT and LE) independently read through the transcribed responses and assessed whether the response indicated that the image tied in with the participant's experience ('YES'), whether it did not ('NO') or if the answer was unclear ('UNCLEAR'). Any disagreements were arbitrated by another author (DC). At the time of assessment, both researchers were masked to the identities and AMD severity of participants.

5.3 Results

A Google Image search for 'vision age related macular degeneration' was conducted independently by two of the authors (DJT and LAE) on 27th March 2017. From the top 50 images produced by the search, 10 images (20%) were the NEI photo of 'A scene as it might be viewed by a person with age-related macular degeneration' (Figure 5.1). Twenty-seven (54%) were similar depictions of AMD with different photographs (i.e. a black or grey patch in the centre of an image). The remaining 13 (26%) images were mainly diagrams of the eye or textual information about AMD. Others included a photograph of a celebrity known to have AMD and a poster for macular degeneration awareness. There were no disagreements between the two independent investigators for this exercise. The Google Image search was repeated with a variety of similar phrases: 'how will age-related macular degeneration affect my vision'; 'age-related macular degeneration sight'; 'age-related macular degeneration eyesight'; 'age-related macular degeneration vision loss'; 'age-related macular degeneration symptoms'; 'how does age-related macular degeneration look'; 'what do people with macular degeneration see'. A similar array of results was observed; at least 10% (and up to 26%) of the top 50 results consistently showed the NEI image.

Twenty-nine particpants with dry AMD were interviewed about how their vision looks. The median (interquartile range [IQR]) age was 75 (70, 79) years. Median (IQR) logMAR binocular VA and Pelli-Robson CS were 0.2 (0.18, 0.36) and 1.65 (1.5, 1.95), respectively. Better and worse eye median (IQR) logMAR VA was 0.24 (0.20, 0.39) and 0.40 (0.30, 0.83) respectively. Three participants had early AMD, seventeen had intermediate AMD and nine had late AMD (GA). Some descriptions given regarding vision loss are shown in Table 5.1.

Thirty-one individual descriptors were identified. Synonyms were grouped together, creating ten descriptor groups. Synonyms used to create descriptor groups are given in Table 5.2. A large proportion of participants (45%) reported their visual symptoms in a way that implied an experience of blur. Visual distortions and missing parts of the image were also commonly reported. The most common visual symptom reported by individuals with GA was 'missing parts' (n = 6; 67% of participants with GA) whilst the most common symptom reported by people with intermediate AMD was 'blur' (n = 8; 47% of participants with intermediate AMD). Participants often reported more than one visual symptom. A matrix showing descriptors used by each participant is shown in Figure 5.2. Descriptors were considered a 'primary descriptor' if they were the initial symptom mentioned by a participant. All subsequent descriptors were considered 'secondary descriptors'. For example, one participant responded 'I've noticed letters missing from exhibitions particularly when I go… Slightly

more hazy than it was … Sometimes it's difficult to distinguish colours that are very similar'. In this instance, 'missing parts' would be the primary descriptor, 'blur' and 'colours difficult' would be secondary descriptors. Use of multiple descriptors was most common amongst people with GA. The most common primary descriptor amongst participants with intermediate AMD was blur, whilst the most common primary descriptor for those with GA was distortion.

Table 5.1: Examples of descriptions of vision loss with descriptor words/phrases in **bold**.

AMD Classification	Description of vision
GA	*'Lampposts, sort of … **bending**……As I'd gone on looking at the wall now it's got bricks in, I know I can see - they're sort of a bit **wobbly**…..I know they're straight really.'* *'It's **foggy** all the time… that's what I noticed first. I used to be saying gosh, is it **foggy** today and he'd say no, no.'* *'It's like if I'm looking at a scene, something on television or even out in the road, it's - there's **part of it missing**. There's **part of it missing** there. I can't see the whole picture anymore.'*
Intermediate AMD	*'I'm looking out from two discs that are **shimmering**, like two little suns but not as bright.. they're really **shimmering**…..like…gold.'* *'Well it's things like when I was standing on the station today, when you're looking at a long platform, it **can look a wavy line**.'*
Early AMD	*'I've lived in [the same town] for 44 years so I should know quite a lot of people but I never see them, well not never but I don't see acquaintances very well because it's a bit **blurry**.'* *'I don't draw my curtains so I look outside and I can see on the house opposite **I see two chimneys instead of one**.'*

Table 5.2: Words and phrases used to describe vision with dry AMD. Descriptions considered to be synonyms of each other were grouped together into descriptor categories.

Descriptor category	Synonyms of descriptor
Blur	*Not clear, Out of focus, Fuzzy, Foggy, Hazy, Misty, Cloud*
Distorted	*Bendy, Crooked, Wavy, Wobbly, Wiggled*
Missing part/s	*Black parts, Space, Patchy, Grey area, Words dropping from page*
Shiny area/s	*Flash, Sparkles, Spiral of light*
Double vision	
Dark	*Dull*
Colours difficult	
Speckled	
Smeary	
Bullseye	

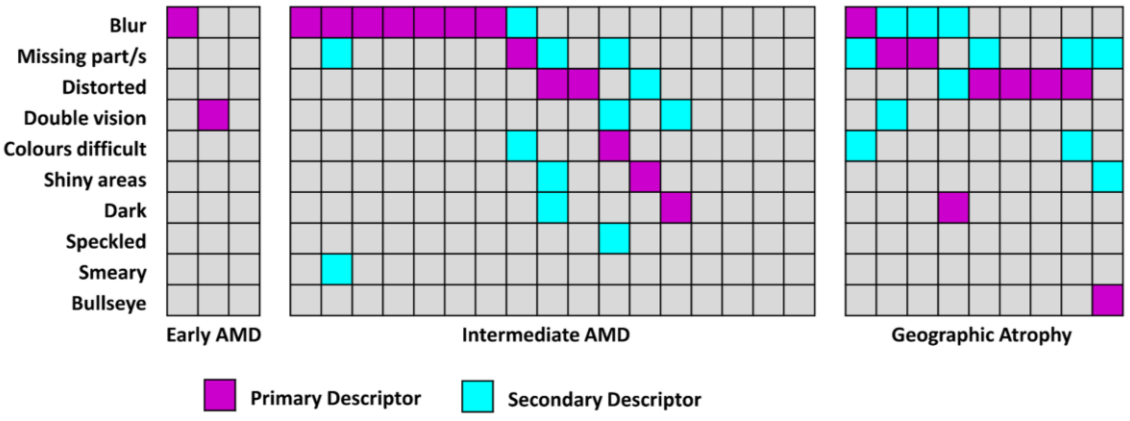


Figure 5.2: Matrix type chart showing descriptor categories reported by each participant. Each column shows descriptors from one participant. Rows are organised by frequency of occurrences for each descriptor category across all participants; 'blur' was reported most frequently, followed by 'missing part/s' and 'distorted', whilst 'speckled, 'smeary' and 'bullseye' were reported least frequently. Five columns are empty – these represent participants (one with early AMD and four with intermediate AMD) who did not report any descriptors of visual symptoms when asked.

The interviewer felt it was inappropriate to show six participants the NEI photograph because they had expressed emotional distress at the prospect of their vision worsening; this complied with the ethical aspects of the interview protocol. Two participants were unable to see either photograph adequately to make a judgement due to their poor vision. Therefore, our assessment of response to the NEI image (photo of the boys) was restricted to 21 participants (3, 11 and 7 respondents who had early, intermediate and late [GA] AMD in their better-seeing eye, respectively). Median (IQR) binocular VA and CS for these 21 participants were 0.24 (0.20, 0.36) and 1.65 (1.35, 1.90) respectively. Median (IQR) better and worse eye logMAR VA scores were 0.22 (0.2, 0.36) and 0.46 (0.32, 0.92) respectively. Example responses are shown in Table 5.3.

Table 5.3: Example responses to the NEI image for participants who positively reported the NEI image to be a good indication of their visual symptoms (top) and for those who stated that the NEI image did not represent their visual symptoms (bottom). (AMD classification shown in parentheses).

Is NEI image an accurate representation of vision with AMD?	
Yes	*'Yes….that's quite a good indication…'* (GA) *'Yes, that is it, the blurred one…'* (Intermediate AMD)
No	*'…nothing like that one…'* (Intermediate AMD) *'Well I haven't got anything at all like that…'* (GA) *'That wouldn't happen to me… the colours wouldn't be there…'* (Intermediate AMD) *'No. I don't recognise that …'* (Intermediate AMD) *'Well … absolutely not…., no relation to me at this moment… So I'm quite pleased about that.. '* (Early AMD)

Only two participants reported the image to be a good indication of their visual symptoms. One of these individuals had GA and a binocular logMAR VA of 0.32 (better eye 0.32 and worse eye 0.40) and CS of 0.75. The other individual to report the NEI image to be a good indicator of their visual symptoms had intermediate AMD and binocular logMAR VA of 0.44 (better eye 0.4 and worse eye 0.8) and CS of 1.35. Sixteen participants, representing 76% (95% confidence interval [CI] of 53-92%) of our sample, clearly stated that the image did not represent their visual symptoms. Three gave answers that were deemed to be unclear. Table 5.4 shows the summary results for different severities of AMD.

Table 5.4: Number of participants reporting the NEI photograph was an accurate representation of their vision ('Yes'), did not depict their vision ('No') and those whose responses were not clear ('Unclear'). Totals from the whole sample are represented as percentages (95% confidence intervals [CI])

Is NEI image an accurate representation of vision with AMD?			
AMD type	***Yes***	***No***	***Unclear***
All (n=21)	2	16	3
% (95% CI)	10 (1 - 30)	76 (53 - 92)	14 (3 - 36)
Early/intermediate AMD (n=14)	1	13	0
Geographic atrophy (n=7)	1	3	3

5.4 Discussion

Images showing a 'patch' of distortion or blackness in central vision surrounded by a clear periphery (Figure 5.1) are frequently used illustrators of vision with AMD. Our survey of a sample of images yielded from an internet search supports this observation – three quarters showed virtually the same basic representation. However, only a small number of our sample of people with dry AMD reported this to be an accurate depiction of their visual experience and this was a key finding from our study. Most people in our study did not think these images represented their visual symptoms. There was no strong evidence for this depiction representing visual symptoms for those with advanced dry AMD in the better-seeing eye either: only one person out of seven with geographic atrophy stated that it was clearly representative of their visual symptoms. From this study, we have also learnt that noticeable and describable vision loss is not limited to those with neovascular AMD or even just those with late AMD. This is an important finding. For instance, people in our sample with intermediate AMD provided a variety of descriptors of their visual symptoms rather than saying they were asymptomatic. Moreover, these descriptions were far more complete and varied than those implied by images that are used to depict the condition.

Our main findings are important for several reasons. First, the images we have scrutinised in this study are designed to educate the public about AMD and we have shown they are not fit for this purpose. Second, the images could be misinterpreted to be a sign of early visual changes in AMD but this clearly does not fit with the experience of people with early or intermediate AMD in our sample. Third, the visual symptoms experienced by most people with AMD are likely to be more subtle and less simplistic than those depicted in the images; this could have ramifications in individuals about misunderstanding the severity of their own condition and may in turn affect adherence to management strategies such as self-monitoring of vision and lifestyle changes to minimise risk of disease progression.

Our results show how heterogeneous descriptions of vision loss in dry AMD can be. Thirty-one individual descriptors, and ten separate descriptor groups were identified. The most frequently used descriptor, blurred vision, was only reported by half of our participants. Distortion, which is often commonly associated with neovascular AMD (Lim et al., 2012) was reported by three participants with intermediate AMD and five participants with GA in their better-seeing eye. Only two of these had unilateral neovascular AMD in their worse-seeing eye. Moreover, when participants reported multiple visual symptoms, there was no obvious pattern of symptoms commonly occurring together.

Previous research has highlighted the inaccuracy of depicting peripheral vision as being a clear surround to a patch of dysfunction in central vision; visual acuity reduces with distance from the fovea, and one paper has produced illustrations theorising what a more realistic simulation of macular disease may look like with a blurred, rather than clear periphery (Marmor and Marmor, 2010). However, the realism of these images is thrown into question when one considers the fact that we do not perceive our peripheral vision as blurred (Anstis, 1998). Other research has attempted to simulate central vision loss in AMD using contact lenses with central opacities (Butt et al., 2015). Yet this type of simulation cannot easily capture the real experience of patients, where size and depth of scotoma may vary from person to person (Schuchard et al., 1999). Whilst other studies have attempted to build realistic representations of glaucomatous visual field loss using reports from patients (Crabb et al., 2013, Hu et al., 2014), to our knowledge this has not been attempted in AMD. Reports in the literature on perceptions of vision loss in AMD tend to come from descriptions made by individual case reports (Sperduto et al., 1983, Allen et al., 2000). No studies have brought together reports from multiple patients. Fletcher and colleagues (2012) did ask a large number of people with AMD attending their initial low-vision rehabilitation evaluation whether they had experiences that led them to believe that they had defects in their field of vision. Interestingly, the majority of their patients were asymptomatic but many reported experiences of items in their vision 'disappearing'; this observation is somewhat dissimilar to the idea of a noticeable and constant disturbance in central vision as depicted in the images we have scrutinised in this study. Moreover, our results indicated 'missing parts' was a common description of the visual loss. Given the heterogeneity of the descriptors of visual symptoms reported in our study, it is perhaps unlikely that 'vision in dry AMD' can be encompassed by a single image. It may be more appropriate to develop a series of images or a dynamic representation, perhaps a series of movies or digital media, to more accurately depict vision in dry AMD. Future studies might build on this idea.

Our experimental design was a study strength because we have directly captured views from people with dry AMD. Our image search experiment illustrated the ubiquity of the NEI image. The remaining simulations of vision in AMD found using our image search were, on the whole, similar to the NEI image in that they depicted a black or grey patch in the centre of a photograph. However, there were some differences between these simulations; for example some 'scotomas' had a straight edge but the majority had a gradual fade, some retained some detail within the area of the scotoma, whilst others did not. It is possible that some of these might be better representations of visual symptoms in dry AMD than the NEI image.

One limitation of our study relates to lens opacities. Although participants were excluded if they were graded 3 or higher on any of the domains of the LOCS III scale, there is a possibility that blur caused by minimal cataract could have affected the results of the study. However, without limiting our interview to those who had undergone cataract extraction (and excluding anyone with posterior capsular opacification), it would be extremely difficult to overcome this limitation in this age-group. Moreover, only four participants had LOCS III scores of two or higher (three bilaterally for Nuclear Colour and one unilaterally for Posterior Subcapsular Cataract); none of these participants used any descriptors that had not been used by other participants with more negligible lens opacities.

Other limitations of our study are worth noting. Participants were asked to view the NEI image with their own spectacles if worn for near. There is the chance that discrepancies between 'best-corrected' subjective visual acuity and habitual near visual acuity could have affected the way in which the NEI image was perceived. However, our recruitment method meant that all participants were motivated individuals and likely to be proactive in their own eye care (for example, wearing up-to-date spectacle prescriptions). There is no evidence that wearing progressive (rather than single vision) spectacle lenses to view the image was a factor in the perception of peripheral parts of the image; no participant reported peripheral distortion on the NEI image. Furthermore, participants were allowed and indeed encouraged to hold the NEI image at an optimal viewing distance and angle to allow ideal viewing conditions and to mitigate any perceptual distortion. The NEI image was viewed binocularly in order to replicate habitual vision for participants. However, we permitted fellow eyes to be of any AMD status, and graded severity of AMD according to the better-seeing eye because the better eye is believed to have a greater impact on vision-related quality of life than the worse eye (Brown et al., 2001, Hirneiss, 2014, Rubin et al., 2000). Of course, this study does not assess vision-related quality of life, rather it assesses visual descriptors for dry AMD, for which the contribution of better eye and worse eye may not be equivalent. Future work might assess the impact of each eye's visual symptoms on binocular descriptions of vision in dry AMD.

Another key limitation is our small sample size. Our estimates of people's response to the NEI image are also restricted because it was deemed inappropriate to show some participants the photograph if they had already expressed emotional distress about their vision. Moreover, two participants were unable to see the photograph due to poor vision. It is certainly possible that these two participants could have similar visual symptoms to that depicted in the NEI image. Also, we limited our sample of participants to those with VA better than 6/30; perhaps for people with AMD and worse VA, possibly as a result of end stage GA, the NEI image is representative of how they see. This is untested

and would have to be the subject of a different study design. Despite these limitations surrounding the sample of people interviewed, the experimental effect supporting the hypothesis that typical images do not accurately depict visual symptoms for AMD was very large. For instance, and loosely speaking, the lower bound for our 95% confidence interval (53%) at least infers half of all people with dry AMD, as represented by our sample, would likely reject the image in a wider population.

To conclude, images currently used to represent vision in AMD are unrealistic for many people with dry AMD of varying severity. A wide range of descriptors is used to communicate symptoms of vision loss in dry AMD, indicating that vision loss in this condition may manifest itself in a variety of ways. These descriptions could be used to educate people about the range of possible symptoms of dry AMD and are a step towards building simulations of the view of AMD through the patient's eyes. In turn this might lead to better recognition of symptoms for people with and without the condition. The results from our study certainly suggest a need to develop more realistic images of the visual symptoms of AMD for patient and public education.

Chapter 6 Measuring dynamic levels of self-perceived anxiety and concern during mobility tasks in people with dry age-related macular degeneration (AMD)

6.1 Introduction

Mobility is crucial for day-to-day wellbeing. Increased mobility is believed to be related to improved physical and mental health (Collins et al., 2008, Sengupta et al., 2015, Shimada et al., 2010), while decreased mobility is not only associated with poor health but can also lead to social isolation and depression (Popescu et al., 2012, Wang et al., 2012). Moreover, lack of mobility may result in frailty, which contributes to a vicious cycle of ill-health and immobility (Xue et al., 2008). Age-related macular degeneration is known to have a negative impact on mobility. A recent systematic review (Taylor et al., 2016) found mobility in AMD to be the most frequent subject of published studies on visual disability in AMD. However, of these studies, only two (Brown et al., 1986, Lovie-Kitchin and Brown, 1986) focused specifically on people with dry AMD, whilst one other (Sengupta et al., 2014) considered AMD type in its analysis. Thus, the literature on mobility in dry AMD is limited.

One way of assessing mobility in eye disease is through self-report. For example, a number of previous studies have used self-report to explore the effects of AMD on driving behaviours (Szlyk et al., 1995, Decarlo et al., 2003, Sengupta et al., 2014), fall rates (Wood et al., 2011b, Szabo et al., 2010) and fear of falling (Popescu et al., 2012, van Landingham et al., 2014). A second approach involves participants performing mobility tasks in a lab-based setting, for example navigating an obstacle course (Hassan et al., 2002) or using an interactive driving simulator (Szlyk et al., 1995). In one study, eye movements and pupil diameter were measured while participants watched a video of a journey through a university whilst indicating, verbally and via button presses, sections of the journey deemed to be difficult (Aspinall et al., 2014). A third method of assessing mobility is in the 'real-world' setting, for example measuring road-crossing behaviour in the street (Geruschat et al., 2011, Geruschat et al., 2006, Hassan et al., 2005), measuring performance on an on-road driving test (Szlyk et al., 1995, Wood et al., 2016), or providing participants with cellular tracking devices (Curriero et al., 2013). Whilst these studies provide useful information about mobility in AMD, one aspect of mobility that has been paid little attention in the AMD literature is the anxiety and concern surrounding mobility. This is important because it may present a barrier to mobility tasks, resulting in the consequences of decreased mobility described above.

The aim of this study, therefore, was to assess self-perceived anxiety and concern associated with different everyday mobility situations in people with dry AMD using a novel computer-based test. In

particular, we aimed to determine the effect of AMD severity on mobility anxiety, and to assess which types of mobility situations cause the greatest amount of perceived anxiety amongst people with dry AMD compared with controls. A secondary aim of the study was to explore potential predictors of mobility anxiety.

Some of the work presented in this chapter has been presented as a paper presentation at the British Congress of Optometry and Visual Science (Plymouth, England, 2017) and as an e-poster at EURetina (Barcelona, Spain, 2017); see list of supporting publications. The co-authors of this work are David Crabb (DC), Alison Binns (AB), Pete Jones (PJ) and Nicholas Smith (NS). The videos used in the test described in this study were filmed and edited by DJT. Computer programming and application development was conducted by NS. Data were collected by DJT between March 2016 and March 2017, and analysis was performed by DJT with support from PJ, under the supervision of DC and AB.

6.2 Methods

6.2.1 Participant recruitment, baseline clinical examination and ethical approval

Participant recruitment, baseline clinical examination and ethical approval were as described in sections 3.2.1 and 3.2.2 except that all participants underwent fundus imaging (retinal photographs, fundus autofluorescence and OCT).

In addition, microperimetry for each eye was performed using the MAIA microperimeter (CenterVue, Padova, Italy). Thirty-seven points were tested over the central 10° of retina, measured using white Goldmann III targets presented for 200ms, and thresholds were calculated using the system's full threshold 4-2 staircase strategy.

6.2.2 Experimental Procedure

Participants were seated 50cm away from a Dell 23 Touch Monitor – P2314T (resolution of 1920 x 1080). Testing was carried out binocularly with participants wearing their habitual intermediate correction. In front of the monitor was a box with a big button on the top. This contained a custom-built force plate, interfaced using an Arduino Microcontroller (http://www.arduino.cc/). The test consisted of a series of eighteen short videos, shown in a randomised order. These were filmed from the point of view of someone walking through various different real-world scenarios using a GoPro Hero4 camera mounted on Feiyu Tech G4 3axis Handheld Steady Gimbal (see Figure 6.1). Figure 6.2 shows still shots from each of the eighteen movies.

The test duration was 30 minutes in total. Participants were instructed to press down on the big button with their preferred hand whenever they felt the footage to show a situation which would cause them anxiety or discomfort and to keep their hand on the button until they feel that situation has passed. A demonstration in which a cartoon face appeared to smile when the big button was not pressed, frown when the big button was fully pressed, and appeared neutral when the big button was semi pressed was shown at the start of the test and in between each of the trials. Pressure on the big button was recorded throughout the test and was recorded as amount of pressure applied to the big button at each time point during the test on a scale of 0 (no pressure) to -1 (fully pressed). Setup of the experimental procedure with still shots of the demonstration screen is shown in Figure 6.3 and with a still shot from one of the test videos in Figure 6.4.

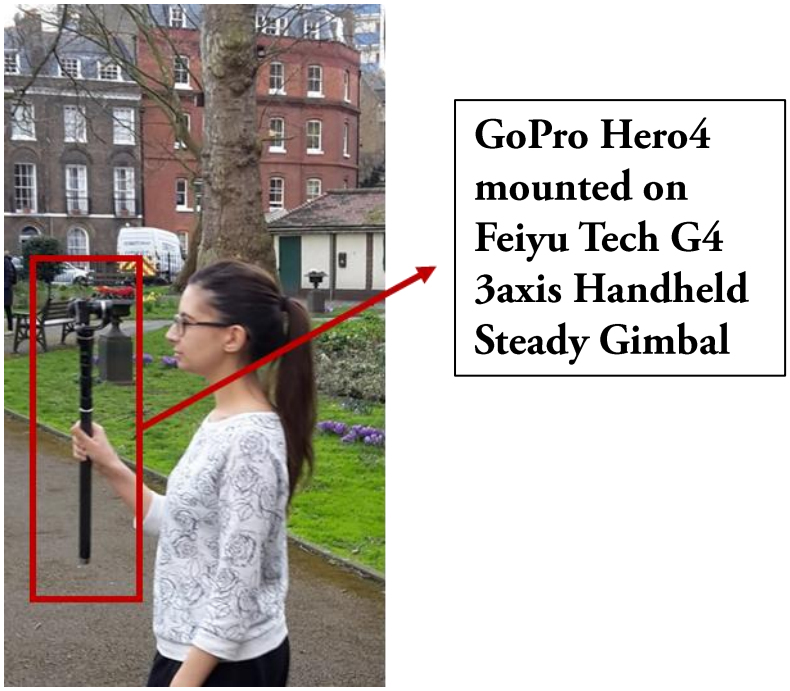


Figure 6.1: Shooting the film for the big button test. A GoPro Hero4 camera mounted on a Feiyu Tech G4 3axis Handheld Steady Gimbal was held at eye height to film various different real-world scenarios.

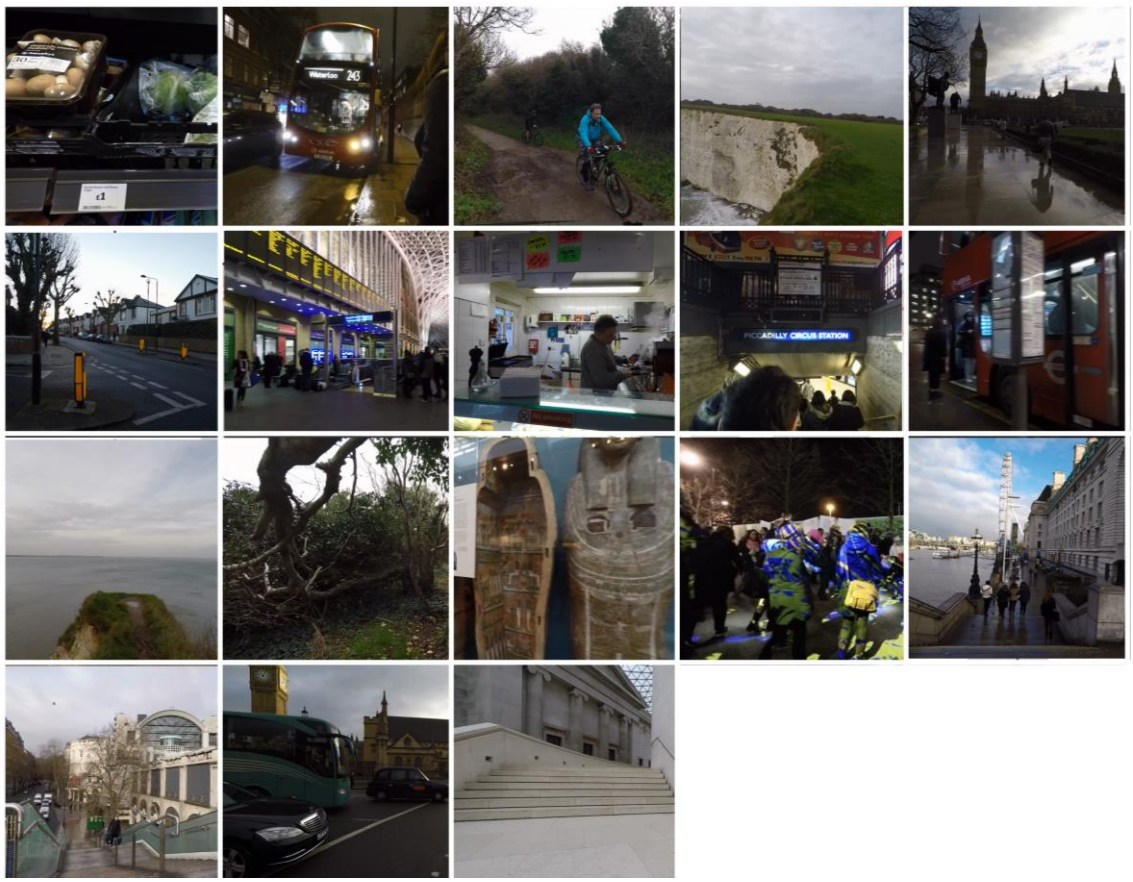


Figure 6.2: Still shots from each of the eighteen movies shown in the big button test.



Figure 6.3: Photographs of big button test setup showing demonstration screen.



Figure 6.4: Photograph of big button test setup showing test screen.

6.2.3 Data Analysis

Mean big button (BB) pressure was used as the primary outcome measure (BB response). Participants were grouped by AMD severity based on the Beckman classification in their better-seeing eye (as measured by VA). The distribution of pressure data was skewed so nonparametric tests were used to test for differences between groups. The relationship between BB response and health-related quality of life was assessed by grouping participants according to their responses to the EQ-5D questionnaire and testing for differences between these groups. Univariate associations (Spearman's Rho) between mean BB response and VA (better eye, worse eye and binocular), CS, AMD duration, average retinal sensitivity threshold (AT; better eye and worse eye) as measured by microperimetry, and age were explored.

The BB test generates a pressure trace that is aligned with time points throughout the movies to estimate response anxiety at each time during the movie. The pressure trace can be derived such that it is an average from a group of participants. Bootstrapping was used to compute confidence intervals for responses by the groups around these traces (N = 20,000; bias correct and accelerated method). These traces were examined in order to discover which types of mobility situations caused the greatest amount of response anxiety amongst people with dry AMD compared with controls. Statistical

analysis was carried out using SPSS Statistics 22 (IBM Corp., Somers, NY, USA) and Matlab R2016b (The Mathworks, Natick, MA, USA).

6.3 Results

Thirty participants completed the BB test (n = 5 no AMD, n = 3 early AMD, n = 7 intermediate AMD, n = 15 GA). There was no difference in BB response between groups based on AMD severity when not watching a video (i.e. during the demonstration phase; $p > 0.05$; Kruskal Wallis test).

6.3.1 Determining the effect of AMD severity on mobility anxiety

Median (IQR) averaged BB response across all videos for people with intermediate AMD and GA was (-0.08 [-0.19, -0.02] and (-0.07 [-0.17, -0.04]) respectively. These averages were difference to those for people with early AMD (-0.03 [-0.04, 0]) and no AMD (0.00 [-0.03, 0.00]), and this difference was statistically significant (Kruskal-Wallis; $p = 0.04$, see Figure 6.5). The median (IQR) BB response for people with intermediate AMD and GA was -0.07 (-0.17, -0.02) and the median (IQR) BB response from people with no AMD or early AMD was 0.00 (-0.04, 0.00). If we consider the quartile of each distribution with the greatest BB response then the average response across all films was more than four-fold greater in the people with intermediate AMD and GA compared to those with no AMD or early AMD.

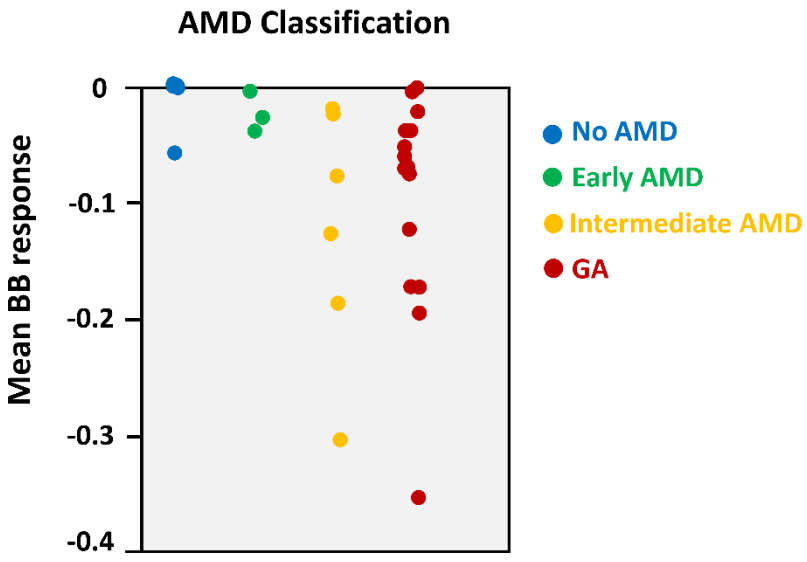


Figure 6.5: Mean BB response across all videos stratified by AMD classification (points have been horizontally jittered to avoid overlap).

6.3.2 Which types of mobility situations cause the greatest amount of response anxiety?

The pressure trace showing mean BB response at each time point across the movies for the four AMD classification groups can be viewed in Figure 6.6.

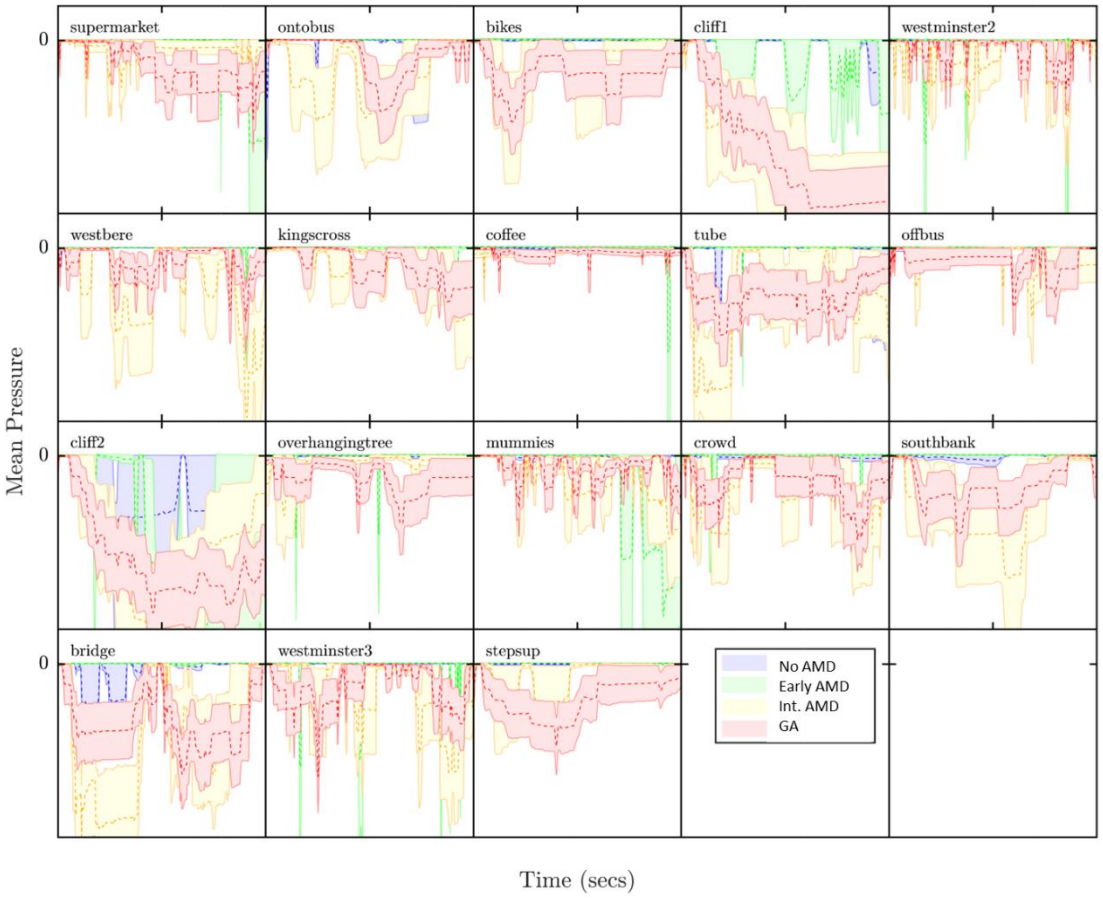


Figure 6.6: Mean (standard error [SE]) BB response (dotted line = mean; solid lines = SE) across each of the eighteen videos stratified by AMD classification according to the better-seeing eye.

From our initial analysis, it was clear that people with no AMD and early AMD showed similar BB response, and it was clear that people with intermediate AMD and GA showed similar BB response. To simplify visualisation and analysis, we therefore generated a trace grouping of no AMD and early AMD together as 'controls', and intermediate AMD and GA together (Figure 6.7). Inspection of this figure shows that within certain videos there were specific events where mean pressure for people with AMD and controls deviated significantly ($p < 0.001$; grey shaded regions of Figure 6.7; see figure legend for details). Four of these events involved walking up or down stairs; other events where these differences occurred involved avoiding cyclists on a rural path, flagging down a bus at night, navigating a crowd at night, crossing a road at night, reading a signpost with a map on it and walking along a cliff path with a steep drop on one side.

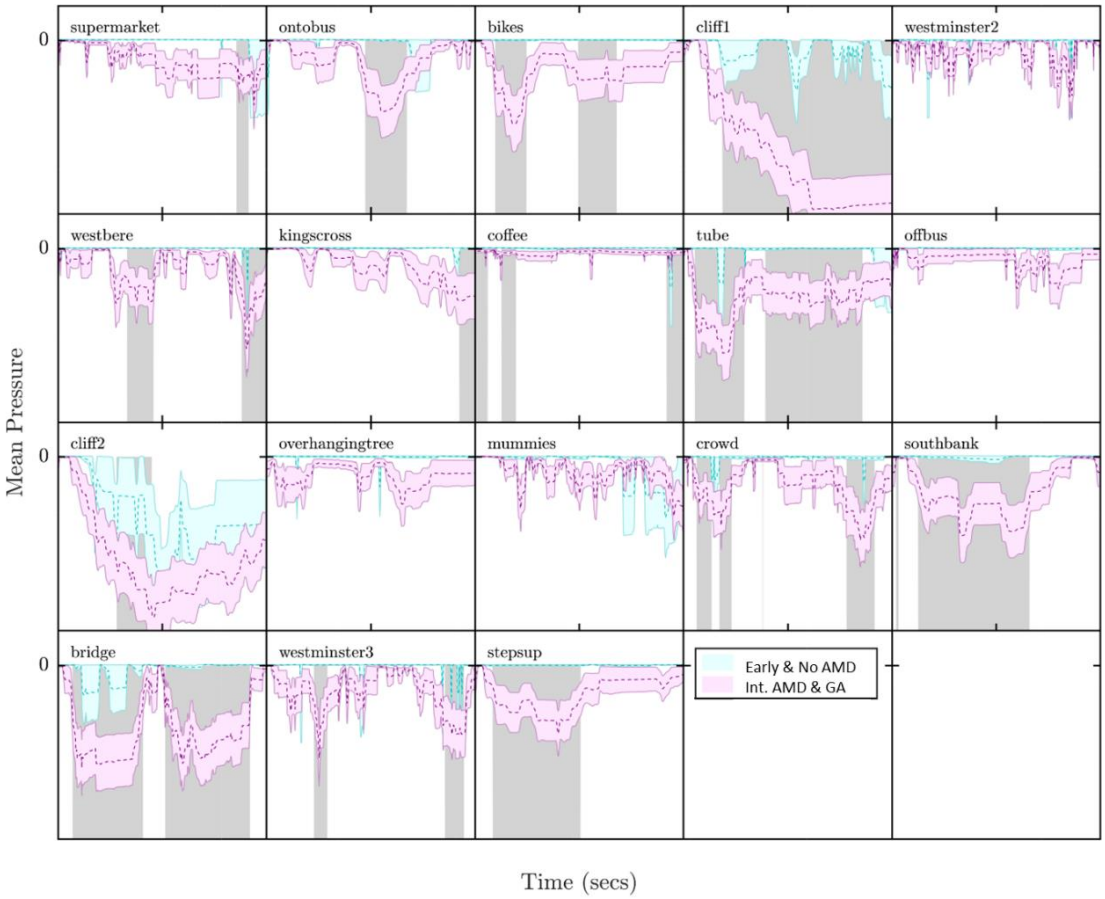


Figure 6.7: Mean (SE) BB response (dotted line = mean; solid lines = SE) for the entire duration of each of the eighteen videos shown. Grey regions on chart indicate time periods at which the difference in BB response between groups was significantly different ($p < 0.001$), i.e. situations which caused particular anxiety to individuals with dry AMD compared with controls.

6.3.3 Exploring potential predictors of mobility anxiety

Median (interquartile range [IQR]) VA scores, CS and average thresholds (AT) as measured by MAIA microperimetry for each group are shown in Table 6.1.

As shown in Figures 6.8 – 6.15, there was no significant relationship between BB response and VA (binocular, better eye and worse eye), binocular CS, MAIA average threshold (AT; better eye and worse eye), AMD duration and age (Spearman's Rho; $p > 0.05$).

Table 6.1: Summary of clinical measures expressed as median (IQR)

	Controls (early and no AMD, n = 8)	Intermediate AMD (n = 7)	GA (n = 15)	*p-value*
Age	77 (72, 80)	82 (70, 86)	75 (70, 7811)	*0.20*
Binocular VA	0.04 (-0.04, 0.18)	0.26 (0.10, 0.40)	0.32 (0.20, 0.56)	*0.01*
Better eye VA	0.10 (0.00, 0.18)	0.26 (0.20, 0.42)	0.36 (0.32, 0.60)	*< 0.01*
Worse eye VA	0.28 (0.06, 0.42)	0.58 (0.26, 1.58)	0.86 (0.40, 1.02)	*0.01*
CS	1.95 (1.65, 1.95)	1.60 (1.35, 1.65)	1.60 (1.25, 1.65)	*0.01*
Better eye AT	27.8 (26.1, 29.8)	26.5 (25.8, 27.8)	23.4 (19.0, 25.6)	*< 0.01*
Worse eye AT	27.0 (25.6, 29.5)	25.0 (23.8, 27.4)	20.4 (6.9, 23.8)	*< 0.01*
AMD Duration	11 (0, 81)	48 (34, 72)	50 (18, 78)	*0.20*

GA = Geographic atrophy

Age (years); VA = Visual acuity (logMAR); CS = Pelli-Robson contrast sensitivity (logCS); AT = MAIA microperimetry average threshold; AMD duration (months); p-values for between-group differences were calculated using a Kruskal-Wallis one-way ANOVA

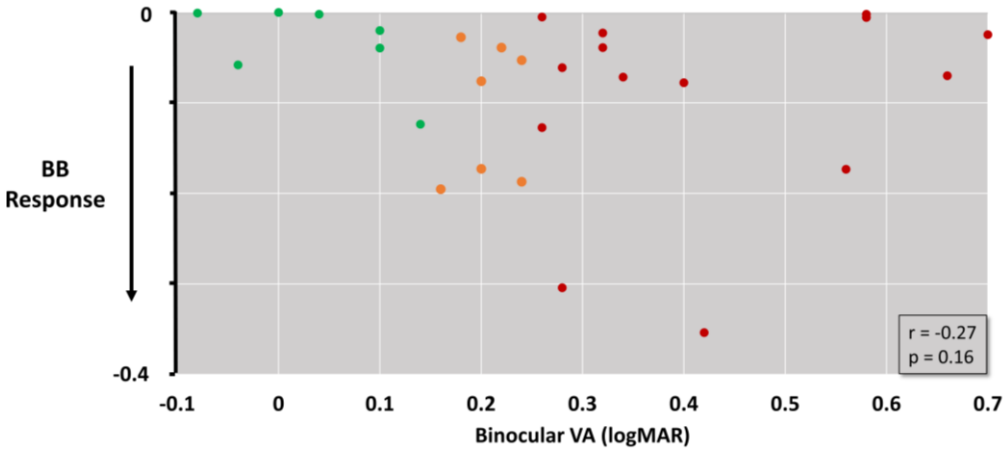


Figure 6.8: Scatter plot showing relationship between BB response and binocular VA. Points are colour coded according to AMD classification (green = early/no AMD, orange = intermediate AMD, red = advanced AMD).

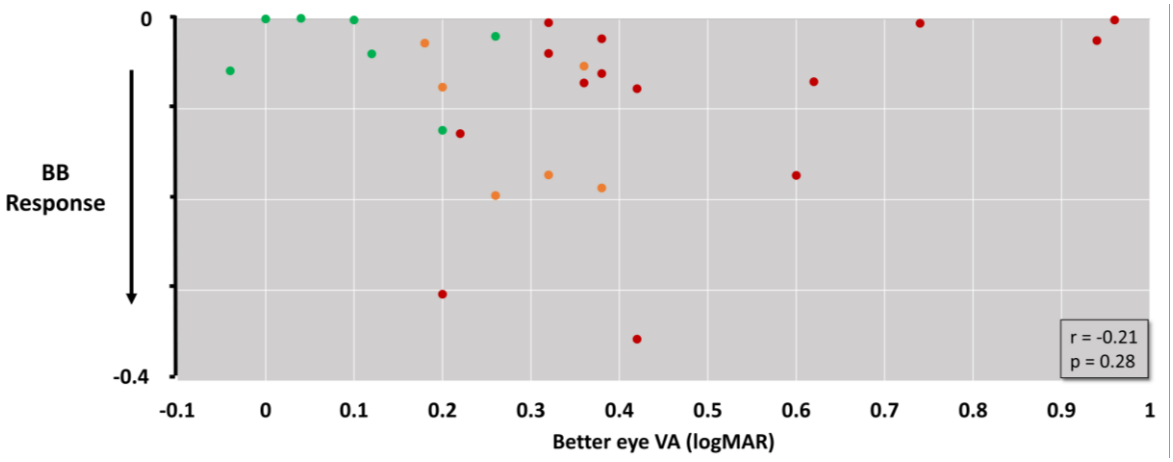


Figure 6.9: Scatter plot showing relationship between BB response and better eye VA. Points are colour coded according to AMD classification (green = early/no AMD, orange = intermediate AMD, red = advanced AMD).

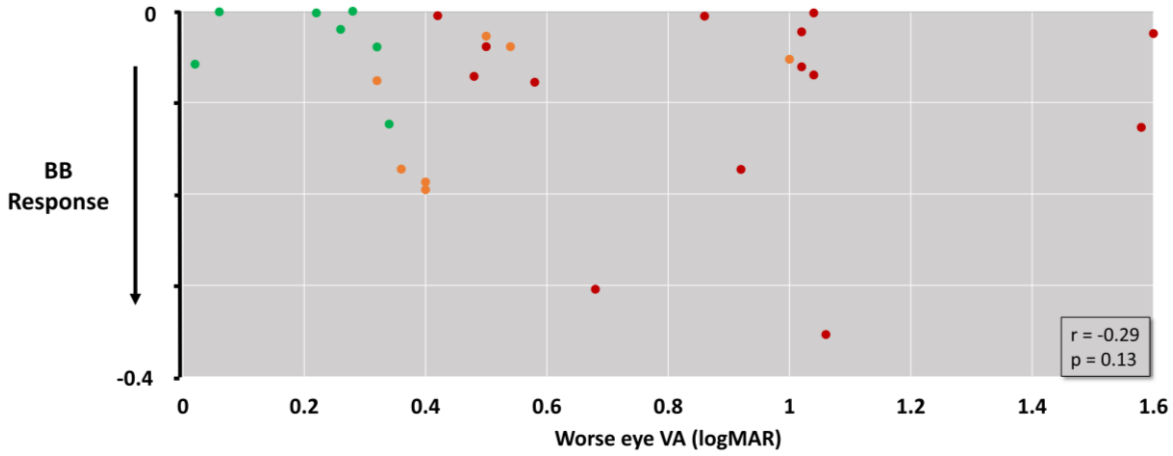


Figure 6.10: Scatter plot showing relationship between BB response and worse eye VA. Points are colour coded according to AMD classification (green = early/no AMD, orange = intermediate AMD, red = advanced AMD).

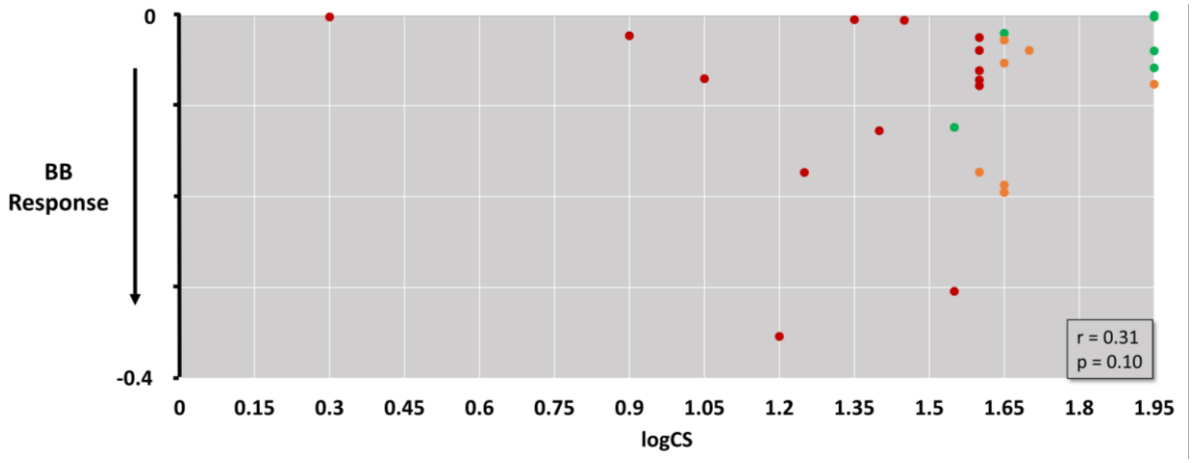


Figure 6.11: Scatter plot showing relationship between BB response and logCS. Points are colour coded according to AMD classification (green = early/no AMD, orange = intermediate AMD, red = advanced AMD).

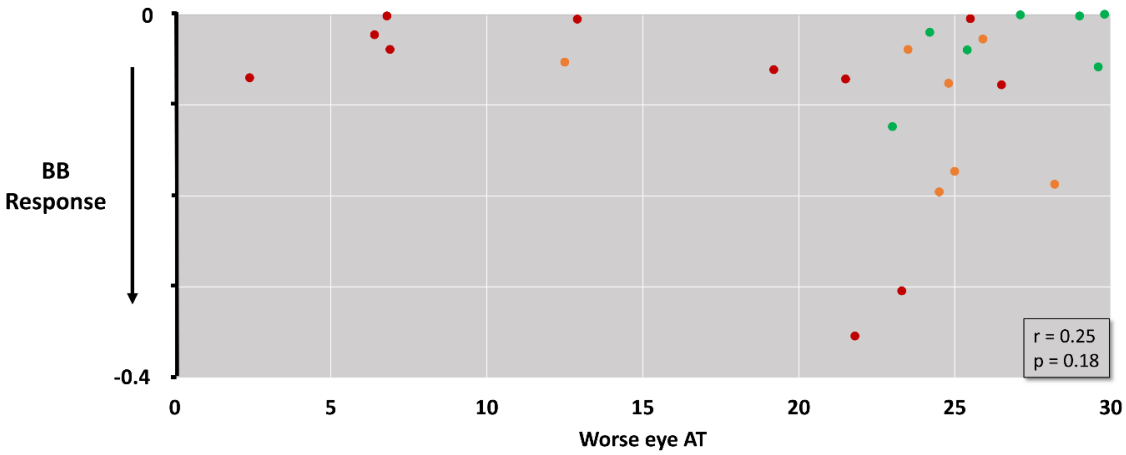


Figure 6.12: Scatter plot showing relationship between BB response and worse eye average microperimetry threshold (AT). Points are colour coded according to AMD classification (green = early/no AMD, orange = intermediate AMD, red = advanced AMD).

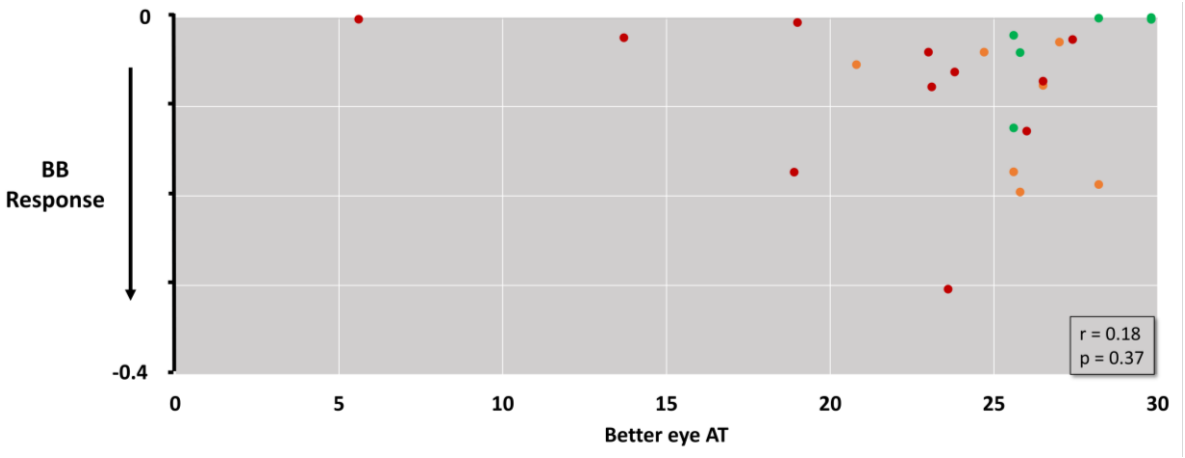


Figure 6.13: Scatter plot showing relationship between BB response and better eye average microperimetry threshold (AT). Points are colour coded according to AMD classification (green = early/no AMD, orange = intermediate AMD, red = advanced AMD).

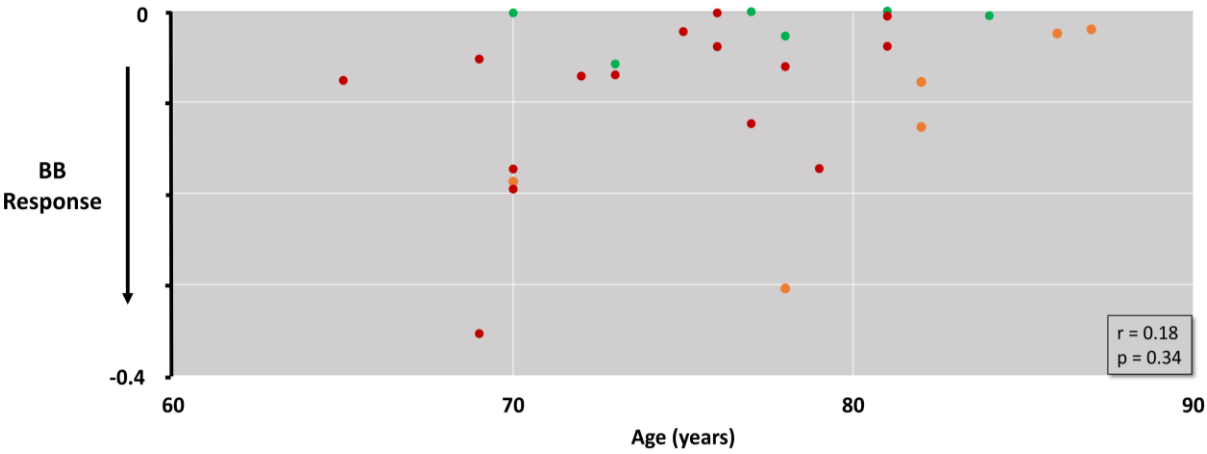


Figure 6.14: Scatter plot showing relationship between BB response and age. Points are colour coded according to AMD classification (green = early/no AMD, orange = intermediate AMD, red = advanced AMD).

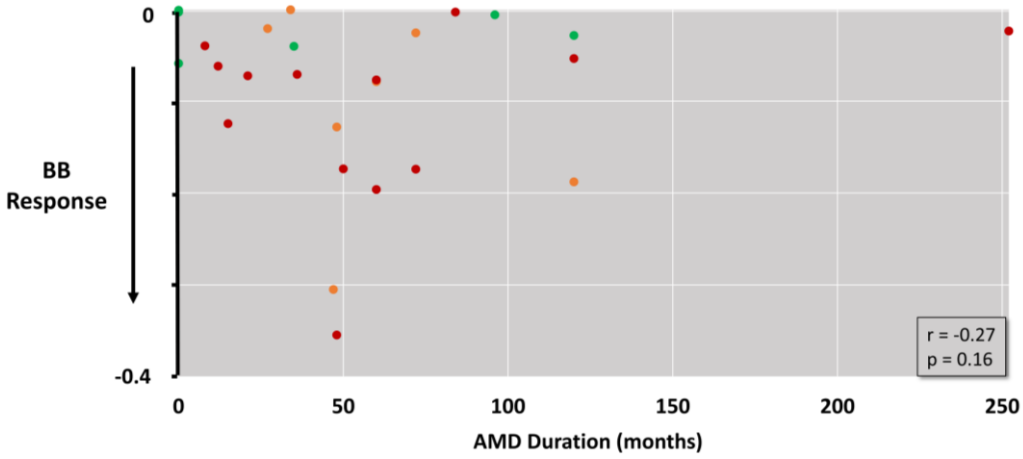


Figure 6.15: Scatter plot showing relationship between BB response and AMD duration in months. Points are colour coded according to AMD classification (orange = intermediate AMD, red = advanced AMD).

Although there were no significant correlations between BB response and clinical measures, a pattern emerged in the relationship between BB response and worse eye average microperimetry thresholds; this is demonstrated in Figure 6.16. Group A comprised of people with better average macular sensitivity as measured by MAIA microperimetry. The remaining participants with AMD were split equally between Group B (worse microperimetry scores and little to no mobility response anxiety) and Group C (better microperimetry scores and high levels of mobility response anxiety).

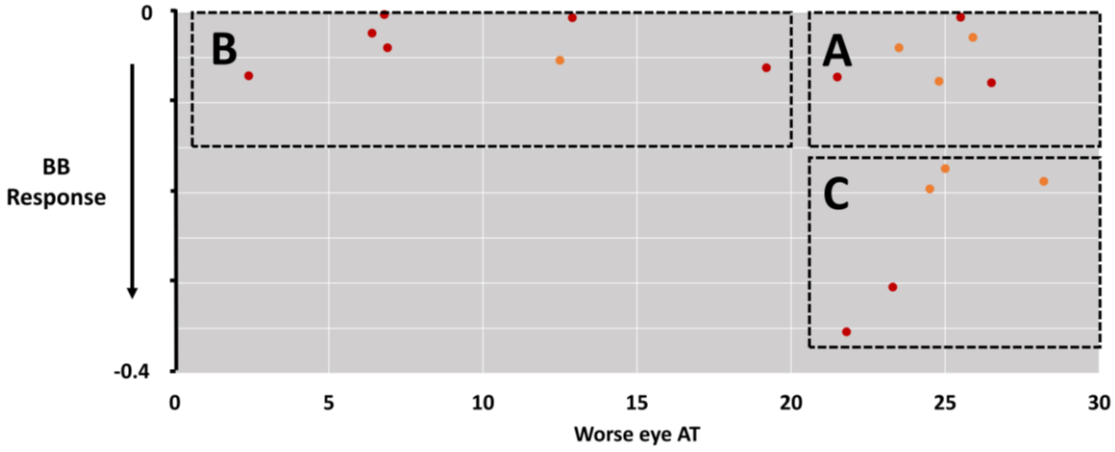


Figure 6.16: Scatter plot showing relationship between BB response and worse eye average threshold (AT) among participants with intermediate and advanced AMD (colour coded according to AMD classification [orange = intermediate AMD, red = advanced AMD]). Participants in Group A had good average macular sensitivity as measured by MAIA microperimetry. Participants in Group B had poor microperimetry scores and little to no mobility response anxiety. Those in Group C had good microperimetry scores and high levels of mobility response anxiety.

6.3.2.1 Relationship between BB response and self-reported function

All participants reported 'no difficulties' with self-care. No participants reported 'extreme difficulties' to any EQ-5D items. Participants were, therefore, grouped according to a Level 1 EQ-5D response ('no difficulties') or Level 2 ('some/moderate difficulties') for Mobility, Pain, Usual Activities and Anxiety/Depression. Results are displayed in Figure 6.17. There was no significant difference in BB response between those with Level 1 EQ-5D responses compared to Level 2 responses for Mobility, Pain or Anxiety/Depression (Mann-Whitney; $p > 0.05$). A weak statistical difference in BB response (Mann-Whitney; $p = 0.04$) between groups was observed for Usual Activities, with people who reported 'no difficulties' pressing the button slightly less, on average, than people who reported 'some difficulties'. However, after correcting for multiple testing using Bonferroni correction (p-values required to be < 0.01 to be considered significant), this difference was not statistically significant.



Figure 6.17: Box-and-whisker plots (top) show BB response grouped by EQ-5D responses. Pie charts below show proportion of Level 1 responses (no difficulties reported) compared with Level 2 responses (some difficulties reported) for each EQ-5D item.

6.4 Discussion

It is well documented that people with AMD have difficulties with mobility. This study adds to this knowledge by exploring the effect dry AMD severity has on self-perceived mobility anxiety, and assessing potential predictors of mobility anxiety. We also evaluated which types of mobility situations may cause the greatest amount of perceived anxiety for people with dry AMD. The methods used were novel; to our knowledge, mobility anxiety has not previously been assessed in this way. The primary aim of this study was to determine the effect of AMD severity on mobility anxiety. Our results suggested that individuals with intermediate and late dry AMD are more likely to experience response anxiety to mobility situations than individuals with early AMD and those without any AMD.

A further aim of this study was to assess which types of mobility situations cause the greatest amount of response anxiety. The greatest differences in BB response between groups was observed during sections of videos showing navigating up and down stairs, and for map reading, as well as for walking along a cliff top. Participants with intermediate and late dry AMD consistently had higher levels of mobility response anxiety during sections of video showing stair negotiation during multiple videos, indicating that this is a particularly troublesome task for people with AMD. This worry is not unfounded; a literature review of stair negotiation in aging (Startzell et al., 2000) reported falls on stairs to be a leading cause of accidental death, that injuries from stairs increased with age, and that perceived difficulty with stair negotiation is frequently reported amongst older people. These difficulties are likely to be exacerbated in AMD and several studies report alterations to movement and gait characteristics amongst individuals with AMD in an attempt (consciously or subconsciously) to counteract these difficulties (Alexander et al., 2014b, Spaulding et al., 1994, Wood et al., 2009).

The final aim of the study was to explore potential predictors of mobility anxiety. Our results suggest that the amount of response anxiety experienced is unlikely to be directly related to clinical measures of visual function (VA, CS and microperimetry). These results support those of Donoghue et al. (2014), who suggest that VA and CS, whilst contributing to mobility performance (as measured by the Timed Up-and-Go test (Podsiadlo and Richardson, 1991)), do not contribute to fear of falling in low vision. Of course, other measures of visual function that were not assessed as part of this study may be better predictors of the mobility response anxiety measured by BB response. This is a limitation of our study. For example, earlier research has highlighted the importance of the photostress test and cone threshold (Mathew et al., 2008), binocular central scotoma size (Hassan et al., 2002) scanning ability (a form of visual search, looking for number targets in photographs of

everyday scenes) and differential velocity threshold (the ability to discriminate between moving targets) (Kuyk et al., 1998a, Brown et al., 1986, Kuyk et al., 1998b) in predicting mobility performance measured by navigation around an obstacle course. One study (Bibby et al., 2007) reported the best predictor for self-reported mobility amongst people with low vision (attributable to a variety of causes) to be binocular visual field, followed by scanning ability, low contrast visual acuity and finally high contrast visual acuity; whilst another (Sengupta et al., 2015) reported reduced VA and CS to predict mobility restriction in people with AMD.

A surprising and intriguing finding emerged from our AMD worse eye MAIA microperimetry data. One would expect worse microperimetry results to be associated with higher levels of mobility response anxiety as measured by BB response and vice versa. Instead, participants appeared to fall into one of three groups (shown in Figure 6.16). Group A comprised (as expected) people with better average macular sensitivity as measured by MAIA microperimetry. The remaining participants with AMD were split equally between Group B (worse microperimetry scores and little to no mobility response anxiety) and Group C (better microperimetry scores and high levels of mobility response anxiety). This finding might be partially explained by those with worse visual function being unable to see the situations in the films adequately and therefore having lower levels of mobility response anxiety. However, the finding of elevated anxiety in those with relatively good visual function raises the issue of improving safety in public areas for people with fairly mild visual impairment. An alternative interpretation for this observation might relate to psychological adaptation to vision loss not explored in this study and certainly ought to be the focus of future research. Regardless of its explanation, this observation highlights the potential contribution of the worse-seeing eye to the BB response.

It was unexpected that people who reported 'no difficulties with mobility' did not differ in their BB response from those who reported 'some difficulties with mobility'. However, the EQ-5D item measures self-reported mobility *difficulty* whereas the BB test measures self-reported mobility *anxiety* with specific situations. It is also possible that a person may report no difficulties with mobility in their day-to-day life because they have self-imposed mobility restrictions (either consciously or subconsciously) which lead to avoidance of situations which might cause anxiety. Previous research has suggested that people with vision loss from AMD *do* limit activities and mobility (Wang et al., 2012, Popescu et al., 2011). The BB test may therefore show situations that these participants would not consider when rating the mobility difficulty in their day-to-day lives as these situations would be avoided in day-to-day life.

This study has made substantial progress into our understanding of the relationship between AMD and mobility-related anxiety. However, there are limitations not already mentioned which must be acknowledged. First, in an ideal world, we would have captured all possible real-world mobility situations that a person with AMD might encounter on video. However, it would be impractical to do this and show all of these videos in one sitting. Therefore, we have aimed to capture a variety of situations including daytime and night-time, urban and rural, indoor and outdoor in order to try and capture a vast array of potential scenarios, whilst keeping testing time brief enough to maintain participants' attention and limit fatigue. A second limitation of this study relates to our setting. All of our participants were volunteers who had sufficient confidence in their own mobility to travel to City, University of London to take part in the study. We therefore are likely to be underestimating the magnitude of this problem for the wider population of people with dry AMD. Future work might take a version of this test into communities in order to try and capture a wider population. A further limitation relates to our grouping for this chapter. It was clear from our initial analysis that there was little difference in BB response between no AMD and early AMD. This is in line with chapters 3 and 4 and with previous literature (for example, Lamoureux et al., 2010). On this basis, given the small sample size, early AMD and controls were grouped together for this analysis. However this might be considered a limitation, and differences in BB response between people with early AMD and controls might become apparent with a larger sample.

Physiological anxiety levels may also be measured in real-time indirectly by measuring arousal using skin conductance (Epstein and Roupenian, 1970). This method has been used in previous ophthalmic research to assess levels of anxiety during eye examinations and contact lens fitting (Margrain et al., 2003, Court et al., 2008). Future work could compare results from the BB test with real-time measurements of anxiety whilst watching the videos using this method. Further investigation into mobility anxiety might link results to personality type (Denollet, 2005) and state and trait anxiety assessed via questionnaires (Spielberger et al., 1983). There is some debate in the literature as to which type of visual field loss is more detrimental to mobility. Some studies (e.g. Subhi et al., 2017) report peripheral field loss to cause greater mobility problems, while others (e.g. Geruschat et al., 2011, Turano et al., 2004) report central visual field loss to be more problematic for mobility. This question could be addressed by replicating this study in people with peripheral visual field loss for comparison of mobility response anxiety between these two types of visual field loss.

6.4.1 Conclusions

To conclude, the big button test is a useful measure of mobility anxiety for people with dry AMD. People with intermediate and late dry AMD are likely to experience higher levels of concern or anxiety during everyday mobility tasks than people with early AMD and without AMD. The relationship between mobility anxiety and other variables such as visual function and psychological factors is likely to be complex and requires further study. The big button test highlights areas of specific concern to people with AMD; walking up and down stairs emerged as particularly troublesome. The test has the potential to be used in other eye diseases, and as a patient-based outcome measure for interventions relating to mobility. The results from this study have the potential to be useful both in patient management and in educating members of the public about the effects of AMD on everyday life.

Chapter 7 Overview of main findings and Future work

7.1 Overview of findings

The aim of this work was to investigate the difficulties that people with dry AMD experience with visual activities, and to explore visual symptoms of dry AMD. It supports the growing body of literature highlighting the negative impact of AMD on real-world tasks and quality of life. The biological basis, and therefore visual effects of dry AMD differ from nAMD. Furthermore, psychosocial impacts of the condition differ from nAMD because of its progression (gradually progressive rather than sudden) and the lack of currently available treatments. This thesis identified and addressed a prominent gap in the literature relating to the impact of dry AMD on the day-to-day lives of individuals. It adds to existing knowledge because, thus far, very little was known about the effect of dry AMD on everyday life. These findings should help clinicians with patient management and expectations, and should inform patient and public education about dry AMD.

In addition, this work suggests that rather than relying solely on traditional clinical measures of vision such as changes on 'letter charts', which may not be meaningful to patients, clinical management of patients and clinical trials should aim to consider 'real-world' measures of visual function, such as those described in this work.

In **Chapter 2**, the existing published literature in the area of visual disability and quality of life in AMD was reviewed systematically. Studies relating to various aspects of day-to-day life were identified; these included mobility, scene viewing, computer use and face recognition. Studies relating to the psychosocial aspects of AMD were also identified, for example fourteen studies examined the relationship between AMD and depression and fourteen studies explored adaptation to AMD. Only 41% of studies identified in the systematic review reported the type of AMD under investigation, and only 26% reported disease duration. This is particularly noteworthy because research shows that there are functional differences between the types of AMD, and that psychological and functional effects can change over the time course of the disease. Only 4% of included studies focused solely on dry AMD; this is disproportionate given that dry AMD is the most common form of the condition.

In the study described in **Chapter 3**, people with dry AMD were asked to find targets in everyday scenes shown on a computer screen. Visual search performance (time taken to find the targets) was compared to a 90% normative limit set by a group (n = 33) of age-related visually healthy peers. Nineteen of the thirty-one (61%) participants with AMD fell outside the 90% normative limits for average search time (Fisher's exact test, $P < 0.0001$). Eye movements of participants were

simultaneously monitored whilst the visual search task was performed and these were analysed as a secondary outcome measure. Individuals with dry AMD made smaller saccades, on average, than people without AMD; this difference remained significant when results were filtered to include only those who had performed well during the calibration of the eye tracker. The results from the study highlight the difficulties that people with this condition can have with the important task of everyday visual search, whilst their VA remains relatively good. (Median [IQR] visual acuity for the AMD group was 0.2 [0.18–0.31]). The methods used in this study also have the potential to be used as a meaningful 'real-world' outcome for clinical trials.

The work reported in **Chapter 4** investigated face recognition performance in people with dry AMD using a previously validated test, the CFMT (Duchaine and Nakayama, 2006). Results were compared between groups of varying AMD severity as well as to a group of visually healthy peers. Individuals with geographic atrophy were able to identify fewer faces on average than those with early and intermediate AMD and controls. Furthermore, all participants with fovea-involving geographic atrophy fell outside a 90% normative limit set by controls. Face recognition performance was strongly correlated with CS and, to a lesser extent (though still statistically significant), with VA. These results suggest CS may be a more valuable predictor of real-world visual performance, and certainly of face recognition performance, than high contrast VA alone in people with dry AMD. The results have implications for management and expectations of people with dry AMD.

Chapter 5 moves from performance-based tasks to self-report from patients themselves. In the study described in this chapter, participants with dry AMD were interviewed about their visual symptoms. Responses were transcribed and subjected to content analysis. Participants used a wide variety of words and phrases to describe their vision loss; these were grouped into ten descriptor categories, listed here in order of frequency of use by participants: blur, missing parts, distortion, double vision, colours difficult, shiny areas, dark, speckled, smeary, bullseye. Most participants rejected the realism of the NEI image which is commonly used to depict vision in AMD. The results of this study should inform future patient and public education about dry AMD.

In **Chapter 6**, a new test for measuring perceived anxiety related to mobility situations is described. In the test, participants are shown video clips taken from the point of regard of someone walking through various everyday scenarios. Participants' reactions are captured by pressure on a button which is pressed during scenes which would cause anxiety or discomfort in real life. The test generates a trace that can be aligned with the video clips to estimate anxiety and concern with mobility situations. Our results have shown that those with intermediate and advanced disease certainly do express greater

levels of concern or anxiety while travelling through the scenarios shown by the movie clips than those without AMD and those with early AMD; especially during situations involving climbing up or down stairs. This does not align with clinical measures which were also assessed, such as VA, CS and microperimetry, indicating that other factors may play more important roles in the relationship between dry AMD and perceived mobility anxiety.

7.2 Update to systematic review

The original systematic review literature search was conducted in January 2015. In order to identify any new and relevant work appearing since then, the search was replicated on 22nd August 2017. Besides our visual search study described in Chapter 3, an additional nineteen studies meeting inclusion criteria were identified. Six of these studies reported outcomes based on standardised, validated QoL PROMs (Choudhury et al., 2016, Nakano et al., 2016, Ugurlu et al., 2017, Paulus et al., 2017, Chatziralli et al., 2016, Fenwick et al., 2016), four reported outcomes relating to mobility (Subhi and Sørensen, 2016, Varadaraj et al., 2017, Sengupta et al., 2015, Loprinzi et al., 2015) and two described self-reports of visual ability under low luminance in dry AMD patients (Wu et al., 2016, Yazdanie et al., 2017). Others investigated performance on computer-based categorisation and identification tasks (Lenoble et al., 2015, Thibaut et al., 2016, Thibaut et al., 2015) and physical performance of everyday tasks such as food preparation (Boucart et al., 2015, Pardhan et al., 2015) and a reach-to-grasp task (Pardhan et al., 2017). One study described coping mechanisms in AMD (Schilling et al., 2016). Of all of these studies, only four did not report AMD type under study, although others reported that both types were included but did not break down results by type. Five investigated nAMD only and three (including the two about vision under low luminance levels) investigated dry AMD only. Six studies reported disease duration.

7.3 Ideas for future work

The studies reported in this thesis go some way towards understanding the impact of dry AMD on the day-to-day lives of those people living with it. Yet it also raises a number of issues which have the potential to be addressed in future research. Specific ideas relating to each individual project are discussed in the preceding chapters; the following ideas arise from the body of work as a whole:

Chapter 3 demonstrated that individuals with dry AMD take longer, on average, to search for items in everyday scenes, as presented on a computer setup. A different aspect of everyday visual search, which is becoming increasingly important, is the ability to search for an image within an array of other images; this is necessary for navigation of computers, tablets and smartphones, using a machine

to buy train tickets, checking in at an airport, using self-checkout at a supermarket or even ordering food at some restaurants for example. This is different from searching for an item within an everyday scene and the effect of dry AMD on performance of this task may differ from the performance characteristics described in **Chapter 3**. We have therefore designed a new computer-based visual search test to investigate performance of people with dry AMD of varying severity on this type of search task. The computer application for this test was developed by Wei Bi (WB) with design advice from DJT and support from Nicholas Smith (NS). In this test, participants are shown an image of an object in the centre of the touch screen monitor for 0.5 seconds, they are then required to find this image from an array of 50 different objects shown on the screen and to touch the object on the screen once it has been found (see Figure 7.1). The test is performed binocularly, with habitual refractive correction for a viewing distance of 50cm. Chin and head position are not fixed, in order for the test to be as naturalistic as possible for participants, although viewing distance is constantly monitored by the operator and participants are reminded to try not to move closer to or further away from the screen. Two main outcome measures are considered: accuracy of test performance, i.e. whether the correct target was selected from the array of images displayed, and search duration, i.e. time taken to locate the object and touch the screen. We speculate that results may differ from those observed in **Chapter 3** because of the difference in the nature of the task. For example, contextual clues that may assist with searching for objects in everyday scenes are not present in this type of task, making it more difficult. On the other hand, because it is a matching task, clues in the shapes and colours of objects may assist in the performance of this task.

One important aspect of everyday visual function which was not fully investigated as part of this work was the effect dry AMD on multi-tasking. In daily life, it is quite common to be required to attend to two or more tasks at a time, and it is thought that the ability to do this may decline with age (Verghese et al., 2002, Prado et al., 2007) and with vision loss (Kotecha et al., 2013). One task that particularly requires visual attention to multiple visual stimuli is driving. This is the subject of another future study. This study also used a computer application developed by WB with design advice from DJT and support from NS. In part one of this test (Figure 7.2), participants are shown a dynamic scene of a road in which they are approaching a hazard sign (the 'target' sign). This may be on either side of the road. They are asked to look at the sign, and as soon as they have identified what the sign is showing to press the space button. The screen then shows four different road signs and participants must select which is the target sign by touching the screen. Six practice trials are shown before the test starts. All signs used are from the Highway Code. In part two of the test (Figure 7.3), participants are again shown a dynamic scene of a road. They are advised that this will be very similar to the

previous task, however, two signs will be shown instead of one, a target image, and a distractor. The signs may be on either side of the road, and the target may be the upper or the lower sign. Participants must press the space button as soon as they have identified what is being shown on the signs. As before, they will then be shown a screen with four different signs, one of which will match one of the signs from the road scene - this must be selected by touching the screen. The main outcome measures for parts one and two are percentage of correctly identified signs, time taken to identify signs and the size of the target signs when identified. Comparisons between performance for part one and part two will be made using paired tests for each of these outcome measures. We expect participants to perform worse on part two than part one, and we expect performance to decline with increasing AMD severity. We also speculate that the difference in performance between parts one and two may be greater for individuals with dry AMD than those without, as a result of the increased difficulty these individuals may experience with visual attention.

Thus far, 50 eligible participants have been tested (by DJT) for both the search study and the road signs study described above.



Figure 7.1: An example trial from the new everyday search task. Participants are shown the top image (the target object) for 0.5 seconds. They are then instructed to find the target object from an array of 50 images of objects (bottom image). The target object for this trial has been highlighted in red.



Figure 7.2: Example trial from part one of the road sign identification test. Participants must press the space button once they have identified the sign shown in the road scene (left). They must then select this sign from a choice of four shown on the touch screen monitor (right).

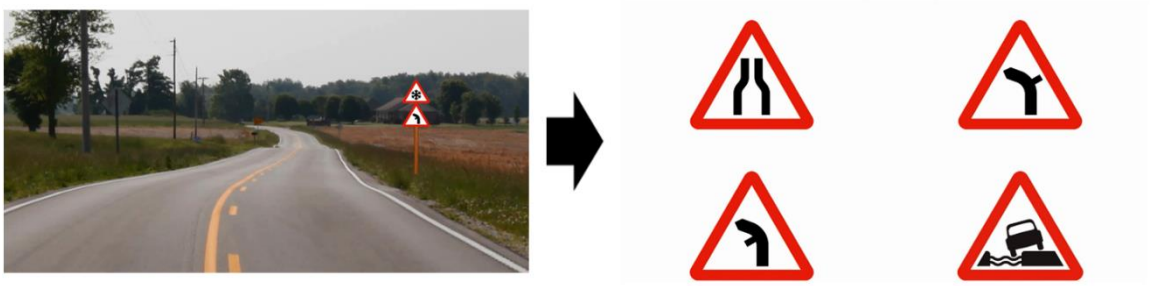


Figure 7.3: Example trial from part two of the road sign identification test. Participants must press the space button once they have identified both of the signs shown in the road scene (left). They must then select which one of the four signs shown on the touch screen monitor match one of the signs from the road scene (right).

For all of the studies reported in this thesis, a VA cut-off was set at 0.7 logMAR. This level was set because we believed participants falling outside this level of vision would be unable carry out the tasks required as part of these studies, indeed, a few participants meeting these criteria struggled with the tasks set. However, this does mean that study results are generalisable only to those who meet these criteria. Future work ought to focus on real-world visual ability in those with more advanced vision loss – this would require different study designs.

As dry AMD is a gradually progressive condition, participants must adapt to some extent over time and this might affect visual ability. Whilst data regarding disease duration was collected for these studies, it was not the main focus; studies specifically focusing on the effect of disease duration on visual ability in dry AMD might more carefully recruit participants with varying disease durations, or assess people with dry AMD longitudinally.

The tests carried out as part of these studies were conducted binocularly, in order to be as close to the 'real life' experience as possible. Future work might conduct similar tests monocularly, in order to assess the contribution of each individual eye to test performance.

Future work might aim to further establish links between location of vision loss related to AMD and visual performance on everyday tasks. These locations could be ascertained by microperimetry. Results would be useful in predicting the type of activities likely to be affected depending on location of vision loss, and visual rehabilitation.

Individuals with AMD are known to have difficulties with vision under different lighting conditions; for example, glare recovery and dark adaptation may both be prolonged in AMD. Future work might assess the impact of altering the lighting conditions these tests (i.e. surrogates of everyday tasks) are performed under, for example under low light levels, or following exposure to glare.

Although all participants were screened for cognitive defects using the abridged MMSE, it is possible that subtle differences in cognitive ability between participants could have affected the results. Furthermore, there have been suggestions in the literature that AMD and cognitive function may be linked (Baker et al., 2009, Clemons et al., 2003, Lindekleiv et al., 2013, Lindekleiv et al., 2012, Wong et al., 2002). Future work might use more extensive cognitive tests in order to disentangle this potentially complex relationship.

Finally, we have suggested that the tests described in this work have the potential to be used in clinical trials for possible future treatments for dry AMD and other conditions; it would be useful to compare performance of these tasks pre- and post- treatment to further test their suitability for outcomes of clinical trials.

List of supporting publications

Peer-reviewed manuscripts

Taylor, D.J., Hobby, A.E., Binns, A.M. and Crabb, D.P., 2016. How does age-related macular degeneration affect real-world visual ability and quality of life? A systematic review. *BMJ Open*, 6(12), e011504.

Crabb, D. P. and **Taylor, D.J.**, 2017. Searching for unity: Real-world versus item-based visual search in age-related eye disease. *Behavioral and Brain Sciences*. Cambridge University Press, 40.

Taylor, D.J., Smith, N.D. and Crabb, D.P., 2017. Searching for Objects in Everyday Scenes: Measuring Performance in People With Dry Age-Related Macular Degeneration: Everyday Visual Search in Dry AMD. *Investigative Ophthalmology & Visual Science*, 58(3), 1887-1892.

Taylor, D.J., Edwards, L.A., Binns, A.M., and Crabb, D.P. (In Press). Seeing it differently: self-reported description of vision loss in dry AMD. *Ophthalmic and Physiological Optics.*

Taylor, D.J., Smith, N.D., Binns, A.M., Crabb, D.P. (Under Review). The effect of non-neovascular age-related macular degeneration on face recognition performance. *Graefe's Archive for Clinical and Experimental Ophthalmology.*

Conference presentations

British Congress of Optometry and Visual Science – BCOVS 2017 – Plymouth, England – paper presentation
Measuring dynamic levels of anxiety and concern during mobility tasks in people with dry age-related macular degeneration (AMD)
***Deanna J. Taylor**, Pete Jones, Nicholas Smith, Alison Binns, David Crabb*

The 17th Congress of the European Retina, Macula and Vitreous Society – EURETINA 2017 Annual Meeting – Barcelona, Spain – e-poster presentation
A novel test for measuring dynamic levels of anxiety and concern during mobility tasks in people with dry age-related macular degeneration (AMD)
***Deanna J. Taylor**, Pete Jones, Nicholas Smith, Alison Binns, David Crabb*

The College of Optometrists' annual conference – Optometry Tomorrow 2017 – Birmingham, England – poster presentation
Let's face it - Another everyday problem for people with late stage dry age-related macular degeneration
***Deanna J. Taylor,** Nicholas Smith, David Crabb*

The Association for Research in Vision and Ophthalmology- ARVO 2016 Annual Meeting – Seattle, WA, USA – paper presentation
Searching for objects in everyday scenes and recognising faces: measuring performance in people with dry age-related macular degeneration (AMD).
***Deanna J. Taylor**, Nicholas Smith, Alison Binns, David Crabb*

The 16th Congress of the European Retina, Macula and Vitreous Society – EURETINA 2016 Annual Meeting – Copenhagen, Denmark – paper presentation
Searching for objects in everyday scenes in dry age-related macular degeneration (AMD)
***Deanna J. Taylor**, Nicholas Smith, David Crabb*

British Congress of Optometry and Visual Science – BCOVS 2016 – Ulster, Northern Ireland – paper presentation
Everyday visual search and face recognition in dry age-related macular degeneration (AMD).
***Deanna J. Taylor**, Nicholas Smith, Alison Binns, David Crabb*

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Appendix 1 Keywords used in literature search for systematic review (Chapter 2)

("age related macular degeneration" or "age related maculopathy" or AMD or ARMD or "geographic atrophy" or nAMD)

AND

("quality adj1 life" or QoL or "vis* function" or "vis* dysfunction" or "vis* ability" or "vis* disability" or function* or performance or "real world" or everyday or "daily living" or "daily life" or behaviour or "independent living" or "well being" or wellbeing or "self concept" or "personal satisfaction" or "patient satisfaction" or depress* or anxiet* or "psychological impact" or reading or searching or shopping or falls or driving or mobility or "face recogni*" or "face detecti*" or "facial recogni* or facial detecti*" or ADL or IADL)

Appendix 2 Data extraction table for systematic review (Chapter 2)

Study	Study Design	Domain of main outcome	Study objectives	Study population	Key outcome(s) measured	Key results	MMAT Score
Alexander et al (1988)	Case-control	**MU**	To describe the ability of a group of patients with AMD and low VA to perform a few simple visual tasks.	100 people with AMD (92% nAMD, duration not stated), and 11 visually healthy controls aged between 70 and 80 (no mean given).	Ability to: tell time, distinguish colours, household products and facial expressions.	48% could tell time at 1.5m 70% were able to identify correctly four colours 32% were unable to correctly identify four household products 26% correctly identified facial expressions on four photographs	4
Alexander et al (2014a)	Case-control	**M**	To determine how AMD and changes in ambient light affect the control of foot placement while walking	10 people with AMD (mean age 82.7, SD 7.4, type and duration of AMD not stated) and 11 visually healthy controls (mean age 74.1, SD 6.6).	Performance of precision walking task.	AMD subjects walked significantly slower than controls in dim lighting but not in normal lighting or after a sudden light reduction.	4
Alexander et al. (2014b)	Case-control	**M**	To determine how AMD and changes in ambient light affect ability to negotiate a curb while walking.	10 people with AMD (mean age 82.7, SD 7.4, type and duration of AMD not stated) and 11 visually healthy controls (mean age 74.1, SD 6.6).	Performance of curb negotiation task.	Curb ascent: People with AMD walked slower regardless of lighting condition. In sudden reduction of light condition, people with AMD took longer to initiate movement than controls. Curb descent: In dim and sudden reduction of light condition people with AMD used more 'shuffle steps' than controls (slowly inching foot towards curb edge before stepping down).	3
Aspinall et al (2014)	Case-control	**M**	To examine gaze function and pupil diameter during navigation in patients with AMD	34 people with AMD (mean age 80, SD 6.6, type and duration of AMD not stated) and 23 visually healthy controls (mean age 76, SD 8.0).	Behaviour (comments, button presses, fixation count and duration, and pupil diameter) while watching a movie clip of a journey through a university building.	Comments similar in both groups but reported more frequently by AMD group. Button presses similar in both groups. Fixation count was higher in AMD group during parts of the journey identified as 'difficult'. Pupil diameter greater in AMD group throughout task.	3

Augustin et al (2007)	Cross-sectional	**D**	To estimate the prevalence rates of depression and anxiety in patients with wet age-related macular degeneration (AMD) and the relationship with visual acuity and to develop a simple algorithm for depression screening.	336 people with nAMD (mean age 77, average time since diagnosis 2.3 years).	Hospital Anxiety and Depression Scale (HADS).	Prevalence of depression varied from 0% in the best VA group, to 7.6% in the worst VA group. Total depression scores strongly associated with VA loss, whilst total anxiety scores not associated with VA loss. Responses to 2 HADS items ('I still enjoy things I used to enjoy', and 'I can enjoy a good book or radio or television program') identified 95% of severely to moderately depressed patients.	4
Backman & Williams (2002)	Case series	**ADL**	Not stated implicitly. Authors interested in providing information to people with AMD on the causes and effects of the condition.	52 people with AMD (type not stated, duration of 5 years or less for 34 participants) aged between 42 and 95 (no mean given).	National Eye Institute Visual Functioning Questionnaire (NEI-VFQ). Activities of Daily Vision Scale (ADVS).	Difficulties reported with driving, navigation, facial recognition, noticing objects around them or on a crowded shelf, reading, watching TV, doing hobbies and using low vision aids. Relatively less difficulties were reported with personal tasks such as dressing, personal grooming and socialising. Most tried to maintain privacy and independence.	2

Banerjee et al (2007)	Cross-sectional	**D**	To estimate depression in patients with AMD and study the relationships among depression, VA and disability.	53 people with AMD (10 nAMD, 43 dry AMD, mean duration of 44 months for depressed group and 59 for non depressed group), mean age 69 (SD 8.65).	Depression and disability measures: fourth edition of Diagnostic and Statistical Manual of mental disorders (DSM-IV), Geriatric Depression Scale (GDS), Structured Clinical Interview for DSM-IV Axix -I Disorders, Clinical Version (SCID-CV), World Health Organisation Disability Assessment Schedule-II (WHODAS-II) and Daily Living Tasks dependent on Vision scale (DLTV).	26% of participants met DSM-IV criteria for diagnosis of depressive disorder. Depressed participants had greater levels of disability than non-depressed participants.	4
Bansback et al (2007)	Cross-sectional	**U**	To determine whether contribution of contrast sensitivity explains HRQoL and health utilities over and above that of VA.	209 people with AMD (80% nAMD, 20% dry AMD, mean duration of 3.7 years), aged between 43 and 96 (mean 80, SD 7.5).	Standard vision tests and VF-14, health utilities index (HUI3) and time trade-off (TTO).	Contrast sensitivity appears to be better related to HRQoL and health utility than VA.	3
Bass et al (2004)	Cross-sectional	**U**	To measure the preference value that patients with subfoveal CNV assigned to their health and vision status, in order to improve understanding and awareness of the impact of subfoveal choroidal neovascularisation (CNV) on health-related quality of life.	792 people with nAMD (duration not stated), median age 75.	Preference value scale designed by authors.	People with poorer VA and greater evidence of dysfunction had lower preference value scores.	4

Berdeaux et al (2005)	Cross-sectional	**V**	To evaluate relative impact of best and worst eye on vision-related QoL in patients suffering from AMD.	114 people with nAMD (duration not stated), mean age 76.5.	NEI-VFQ 39	Worst eye VA and best eye VA contributed independently to vision related QoL.	4
Bordier et al (2011)	Case-control	**S**	To examine further the effect of background attenuation on the bandwidth for image recognition in macular pathology, specifically to test if the bandwidth advantage for segmented images is specific to observers with AMD or if the phenomenon can also be demonstrated in the central vision of young and older observers; whether this phenomenon is present in the normal peripheral visual field.	14 people with AMD (9 with nAMD, 3 with dry AMD and 2 not recorded, mean age 82, SD 5.4, duration not stated), 20 older controls (mean age 72, SD 7.7), and 13 young controls (mean age 25, SD 3.2).	Image recognition task with progressively low-pass filtered images, presented in order of increasing bandwidth; half the series were presented with a darkened background.	The critical bandwidth for image recognition was reduced by darkening image background for younger and older control groups as well as those with AMD. People with AMD tended to recognise more images at full bandwidth if their background was darkened.	2
Boucart et al (2008a)	Case-control	**S**	To investigate how photographs of real-world scenes are perceived by people with low vision.	15 people with AMD (8 nAMD and 7 with dry AMD, duration not stated) aged between 71 and 91 (mean 80), and 11 controls aged between 70 and 82 (mean 77).	Recognition task comparing coloured versus achromatic scenes, and isolated objects versus objects within scenes.	Colour versus achromatic images task: controls performance was equivalent for colour and achromatic pictures, whilst colour facilitated performance in people with AMD. Isolated objects versus objects within scenes: control performance was equivalent under both conditions, people with AMD categorised isolated objects more accurately than those within scenes.	2
Boucart et al (2008b)	Case-control	**F**	To evaluate the capabilities of AMD pxs to recognise facial emotion in novel faces.	17 people with AMD (9 nAMD, 8 dry AMD, duration not stated) aged between 71 and 91 (mean 80), and 6 controls aged between 69 and 80 (mean 75).	Tasks detecting whether a face had an expression or not, and categorising facial expressions as happy/angry/neutral.	People with AMD performed worse than controls when categorising whether faces had expressions or not, but performed similarly to controls when categorsing expressions.	4

Boucart et al (2013)	Case-control	**S**	To investigate whether contextual information provides additional cues in cases of image degradation due to impaired central vision, and whether people with AMD are able to explicitly associate an object and its background.	22 people with nAMD (duration not stated) aged between 61 and 87 (mean 78, SD 7), and 18 controls aged between 64 and 89 (mean 76, SD 5).	Object detection task: identifying an object set on a background that is either conistent with its context or not. Congruency task: determining whether foreground object is consistent with background.	People with AMD performed better when target object was consistent with background, but performed no better than chance in congruency task.	3
Brody et al (2001)	Cross-sectional	**D**	To examine the prevalence of depressive disorders in community dwelling adults with advanced AMD and the relationship in this population between depression, VA, number of comorbid medical conditions, disability caused by vision loss as measured by NEIVFQ and SIPV and SIP.	151 people with both types of AMD (no breakdown or duration reported) with a mean age of 80.	Structured clinical interview (SCID-IV), geriatric depression scale, NEI-VFQ, vision specific sickness impact profile (SIPV) and sickness impact profile 68 (SIP).	32.5% of participants met the SCID-IV criteria for depressive disorder; this rate is twice that found in community dwelling elderly.	4
Brown et al (1986)	Case-control	**M**	To investigate whether mobility performance can be predicted from measures of visual function.	10 people with dry AMD (duration not stated) aged between 61 and 80 (mean 72), and 8 controls aged between 62 and 70 (mean 67).	Path navigation under different luminance levels.	People with AMD performed worse than controls in the lowest light condition, but there was no significant difference between the groups in higher light conditions. Vision variables, such as VA, can be used to predict mobility performance, such as average speed.	3
Brown et al (2000)	Cross-sectional	**U**	To ascertain utility values associated with AMD and varying degrees of visual loss.	72 people with AMD (16 with bilateral dry AMD, 25 with nAMD, and 31 with dry or nAMD, duration of 1 year or less (49%) or longer than 1 year (51%)) aged between 54 and 85 (mean 74).	Utility values: time trade-off and standard gamble.	Substantial decreases in utility values were found amongst people with AMD, these were worse with progressive VA loss; those with milder VA loss were willing to trade 11% of remaining lifetime, whilst those with the most severe VA loss were willing to trade 60% of their remaining lifetime in return for perfect vision in each eye.	4

Brown et al (2002)	Cross-sectional	**U**	To compare the quality of life in patients with VA loss occurring secondary to diabetic retinopathy (DR) with VA loss occurring secondary to ARMD.	263 people with both types of AMD (no breakdown, mean duration of VA loss 2.1 years (SD 2.2), mean age 73.2 (SD 9.8)), , 354 people with DR (mean duration of VA loss 2.5 years (SD 4.0), mean age 62 (SD 11.8)).	Time trade-off (TTO).	QoL is similar for equivalent levels of VA in DR and AMD.	4
Bullimore et al (1991)	Case-control	**F**	To quantify the level of face recognition impairment in ARM subjects by comparing face recognition ability with several clinical tests of visual function: contrast sensitivity for both gratings and edge targets, grating acuity, letter chart acuity and word reading acuity.	15 people with AMD (type and duration not reported), aged between 62 and 96, and 4 controls aged between 62 and 75.	Facial identity recognition and expression recognition task.	Face recognition performance was most closely related to word-reading acuity and least closely related to contrast sensitivity. In advanced AMD, identity recognition performance was poorer than facial facial expression recognition.	2
Burton et al (2015)	Qualitative	**Q**	To investigate the experiences of an older couple living together with AMD and explore how Galvin and Todres' conceptual framework can be used to make sense of their experiences.	Two people (a married couple) both with AMD (one with dry AMD diagnosed 22 years ago, and one with unilateral dry and nAMD diagnosed recently).	Open ended questions about diagnosis, daily activities, retationships and thoughts about the future.	Three themes identified: disruption of vision impairment, managing mutual deterioration and resilience through togetherness.	2

Butt et al (2013)	Cross-sectional	**U**	To test if utility values for health states associated with AMD elicited directly from patients were different from those calculated from public tariffs.	58 people with AMD (79% nAMD, mean duration 7 years (SD 6.2)), mean age 84 (SD 6.5).	Generic-preference based HRQoL questionnaires (EQ-5D and SF-6D), TTO and visual analogue scale (VAS).	Utility values from people with AMD were significantly worse than those derived from public tariffs.	3
Cahill et al (2005)	Cross-sectional	**ADL**	To determine the QoL of patients with bilateral severe AMD before macular translocation with 360^0 peripheral retinectomy.	70 people with bilateral nAMD (mean duration of vision loss in second eye 13.5 weeks (SD 11.2), mean age 76 (SD 5.7).	NEI-VFQ 25 and SF-12.	Certain activities assessed by NEI-VFQ (general vision, distance tasks, near tasks, dependency, role difficulties, mental health, social function) worsened with increasing age and duration of vision loss, and improved with better VA and reading speed. Vision-related QoL in this group appears to be similar to people with low vision but worse than people without eye disease and people with AMD of varying severity.	4
Casten et al (2002)	Cross-sectional	**D**	To examine relationships among vision impairment, depression, and disability among older people with AMD.	114 people with AMD (type and duration not reported), mean age 80 (SD 6.4).	Center for Epidemiological Studies- Depression scale (CES-D).	43% of participants met criteria for syndromal depression. These participants had worse vision-specific and general function.	4
Cavar et al (2014)	Case-control	**A**	To determine the relationship between the risk factors (age, obesity, hypertension, hyperlipidemia, smoking, consumption of alcohol and drugs, positive family history, and exposure to sunlight), coping with stress, psychological well-being and ARMD.	40 people with AMD (type and duration not reported) and 63 controls aged between 55 and 84 (mean 64, SD 9.8)	Questionnaire on general information, Coping Experience to Problems (COPE) questionnaire, General Health Questionnaire (GHQ).	People with AMD scored poorer in the COPE questionnire than the control group; this difference was significant for 'emotions' subscale. People with AMD scored significantly poorer than controls for 'social dysfunction' subscale of GHQ.	4

Chia et al (2004)	Cross-sectional	**V**	To assess the impact of visual impairment on health-related quality of life (HRQoL) in an older population and compare it with the impact of major medical conditions.	3154 people (population based), 99 of whom had AMD (type and duration not reported), aged between 49 and 98 (mean 66.7).	SF-36.	People with AMD and people with cataracts scored worse on SF-36 than those without visual impairment. No significant differences was found between scores for people with AMD and scores for people with cataract.	4
Cimarolli et al (2012)	Qualitative	**Q**	To provide an in-depth assessment of challenges faced by older adults with recent vision loss and to determine changes in the nature of these challenges over time for the purpose of informing the design of vision rehabilitation services.	364 people with AMD (type and duration not reported), mean age 82.8 (SD 6.3).	Interviews conducted at baseline, one year and two years. Open ended interview questions assessing challenges faced due to vision loss in 3 domains: functional, social and psychological.	Over 2 years, functional challenges increased (reflecting the progressive nature of AMD), social challenges remained stable, and psychological challenges decreased (reflecting adjustment to psychological challenges).	3
Clemons et al (2003)	Cohort	**V**	To describe the vision-targeted, health-related quality of life, measured with the NEI-VFQ in pxs with ARMD, cataract, or reduced VA; to determine the relationship between NEI-VFQ subscale scores and clinical measures of visual function; and to assess the internal consistency and reliability of the NEI-VFQ subscales.	4077 people with both types of AMD (no breakdown and duration not reported), mean age 74 (SD 5).	NEI-VFQ.	Overall scores and subscale scores worsened with increasing severity of AMD.	4

Coleman et al (2010)	Cohort	**V**	To assess vision-specific quality of life, based on abbreviated surveys derived from the NEI-VFQ in a cohort of US women who participated in the Study of Osteoperotic Fractures.	671 women with AMD (90 with nAMD) and 1003 women without AMD aged between 65 and 92 (mean 78.2, SD 3.6) at end of study.	NEI-VFQ conducted at start and end of study (5 years apart).	NEI-VFQ scores showed greatest declines in people who progressed from early or no AMD to late AMD between visits, and shows who had late AMD at both visits.	3
Cruess et al (2007)	Cross-sectional	**V**	To assess the burden of nAMD in the Canadian population.	67 people with nAMD (duration not reported) aged between 58 and 90 (mean 78.8, SD 7.6), and 99 controls aged between 50 and 87 (mean 61.7, SD 8.5).	NEI-VFQ, EQ-5D, HADS, health care resource utilisation.	People with nAMD reported worse visual function and wellbeing, more depressive symptoms, higher need for assistance with activities of daily living, and higher falls rates than controls. No difference in anxiety symptoms was found between the groups.	4
Curriero et al (2013)	Case-control	**M**	To determine whether decreased VA from age-related macular degeneration and visual field loss from glaucoma are associated with restricted travel patterns in older adults.	60 people with both types of AMD (no breakdown and duration not reported), mean age 74.4 (SD 5), 74 people with glaucoma (mean age 70.5, SD 5.3) and 59 controls (mean age 69.6, SD 5.2).	Participants' travel patterns were recorded using a cellular tracking device.	Although no significant difference was found in travel patterns between the groups, when comparing people with AMD and controls, average excursion size and span decreased by about a quarter of a mile per line of better eye VA loss.	4
Davis et al (1995)	Case-control	**A**	To study psychosocial adjustment to ARMD by comparing responses of subjects with the condition to controls on 4 psychosocial scales: life satisfaction, daily hassles, social support, and self-esteem.	30 people with AMD (type not reported, mean duration of vision loss 9.5 years, range 3-44) aged between 67 and 96 (mean 81.4, SD 6.5) and 30 age-matched (±3 years) controls.	Modified Life Satisfaction Index-Well-Being (LSI-W), modified Social Support Scale (SSS), Revised Feelings of Inadequacy Scale (RFIS), revised Hassles Scale (HS) and Self-Care Assesment Schedule Scale (SCAS).	People with AMD reported worse life satisfaction, social support, and severity of hassles, but not self-esteem, self-care, frequency or intensity of hassles.	3

Decarlo et al (2003)	Cross-sectional	**M**	To characterize the driving habits of persons with age-related maculopathy who present to a low-vision rehabilitation clinic and to examine how driving status relates to vision-specific health-related quality of life.	126 people with AMD: 96 non-drivers (50% nAMD, mean duration 6 years, SD 4, mean age 80, SD 7) and 30 drivers (53% nAMD, duration 5 years, SD 4, mean age 76, SD 7).	Driving Habits Questionnaire, NEI-VFQ and Life Space Questionnaire.	Of the non-drivers, 85% has ceased due to vision. Of the current drivers, only 23% met state vision standard for driver licensure. Over 50% of the drivers had difficulty with, or avoided driving in rain, at night, on motorways, in heavy traffic or during rush hour because of their vision.	4
Dong et al (2004)	Cross-sectional	**V**	To describe the effect of subfoveal choroidal neovascularisation on HRQoL of pxs at enrollment in 2 RCTs; to examine the relation of VA to HRQoL; to compare HRQoL scores between participants with unilateral and bilateral CNV independent of other characteristics.	789 people with nAMD (duration not reported) with either new subfoveal CNV (median age 77) or predominantly haemorrhagic CNV (median age 79).	NEI-VFQ, SF-36, HADS, SST Vision Preference Value Scale.	Participants reported poor visual function as measured by NEI-VFQ. Better eye VA was strongly associated with NEI-VFQ scores.	4
Elliott et al (1995)	Case-control	**M**	To investigate changes in mobility with loss of visual capacity, to determine correlates of mobility performance and to suggest possible rehabilitation strategies for improved orientation and mobility training for individuals with low vision.	16 people with AMD (type and duration not reported), mean age 73.9 (SD 7.4) and 19 controls (mean age 69.1 (SD 5.5).	Balance control during normal standing, and while input from the kinesthetic (by standing on foam) and/or visual systems (by closing eyes) were disrupted.	No significant difference was found between between ARM group and controls in normal standing condition and eyes closed condition (i.e. when one or less system disrupted). This suggests that in normal standing condition, kinesthetic and vestibular systems compensate for lack ofl information from visual system in people with AMD. However, when input from kinesthetic system significantly disrupted (i.e. by standing on foam), there is too much to disruption to compensate for and the balance control of people with AMD was significantly poorer than controls.	4

Eramudugolla et al (2013)	Cross-sectional	**D**	To examine the prevalence of co-morbid age-related eye disease and symptoms of depression and anxiety in late life, and the relative roles of visual function and disease in explaining symptoms of depression and anxiety.	Community-based sample of 662 people aged between 70 and 95, 19 with AMD alone (type and duration not reported) and 51 with co-morbid eye diseases.	Goldberg Anxiety and Depression Scales (GADS).	People with eye disease reported depressive symptoms more than those without and people with multiple eye diseases were more likely to report higher levels of depressive symptoms.	3
Espallargues et al (2005)	Cross-sectional	**U**	To estimate health status utility values in patients with age-related macular degeneration associated with visual impairments, by using preference-based measures of health.	209 people with AMD (79% nAMD, mean duration 43.9 months, SD 38.7) aged between 43 and 96 (mean 79.6, SD 7.5).	Visual function index (VF-14), EQ-5D, SF-6D, HUI-3 and TTO.	HUI-3 had larger and more significant correlations with visual function tests and VF-14 than any of the other preference-based measures.	2
Esteban et al (2007)	Cross-sectional	**V**	To estimate the prevalence of visual impairment (VI) in a population sample of older adults of the province of Cuenca, Spain and to evaluate the impact of VI on HRQoL in this population group.	1,144 people (population based sample, unclear how many with AMD), aged between 65 and 97 (mean age 73.7).	VF-14 and SF-12.	VF-14 scores decreased with each level of VA loss. Visual impairment, cataract and diabetic retinopathy predicted VF-14 score in both genders, late ARM predicted VF-14 score in females.	3
Fletcher et al (2008)	Case report	**ADL**	Not explicitly stated.	One person with nAMD in one eye and dry AMD in one eye (duration not reported) aged 79.	Case report.	The patient had extensive vision loss from nAMD in one eye and a ring scotoma from geographic atrophy in his other eye. Despite maintaining sufficient VA to meet standards for driving, he had ceased driving , and reported difficulties with reading, writing, and following the ball in golf.	2

Geruschat et al (2006)	Case-control	**M**	To assess the gaze behaviour of the visually impaired during the activity of crossing the street and to compare this with gaze behaviour among those who are fully sighted; whether a person's crossing strategy (revealed by the time of crossing relative to the status of the traffic light) can be determined from gaze behaviour.	9 people with AMD (type and duration not stated) aged between 71 and 86 (mean 78.7, SD 6), 12 people with glaucoma aged between 42 and 76 (mean 63.9, SD 12.7), and 12 controls aged between 23 and 79 (mean 58.6, SD 24.1).	Gaze tracked as participants crossed at two unfamiliar intersections.	For controls, street crossing behaviour corresponded with gaze behaviour: those who crossed with the traffic lights fixated on the lights and those who crossed early fixated on vehicles. People with eye disease (AMD or glaucoma) fixated on vehicles, regardless of crossing strategy.	2
Geruschat et al (2011)	Case-control	**M**	To evaluate the effect of 2 types of vision loss (central or peripheral) on the ability to detect gaps in traffic.	10 people with AMD (type and duration not reported), mean age 80 (SD 8.3), 9 people with glaucoma and 8 with retinitis pigmentosa (mean age 56, SD 16), and 14 controls (mean age 68, SD 12.5).	Traffic gap detection task.	No difference was found between the 3 groups in identification of crossable gaps in traffic, however, road crossing latency and safety margins were worst for people with AMD.	3
Gopinath et al (2013)	Cohort	**A**	To assess the prospective association between AMD and impaired activities of daily living (ADL) among a large cohort of older adults.	761 people aged 60+ (age not reported), 94 of whom had AMD (type and duration not reported).	Older American Resources and Sources (OARS) ADL scale.	Having AMD increased risk of developing impaired ADL over a 5 year period.	4
Hassan & Snyder (2012)	Case-control	**M**	To determine whether street crossing decisions of subjects with AMD were as accurate and precise as those made by young and older subjects with normal vision.	13 people with AMD (type and duration not reported), mean age 78.7 (SD 7.5), 20 older controls (mean age 79.1, SD 7.9), and 20 younger controls (mean age 25.3, SD 2.2).	Street crossing decision making precision and accuracy.	Street crossing precision was not significantly affected by age or mild central vision loss. Street crossing accuracy was affected by age but not by mild central vision loss.	3

Hassan et al (2002)	Case-control	**M**	To investigate the effects of ARMD on mobility performance and to identify the vision determinants of mobility in subjects with ARMD.	21 people with AMD (type and duration not reported) aged between 66 and 87 (mean 79.7, SD 5.3), and 11 controls aged between 66 and 86 (mean 77.1, SD 6.7).	Walking speed and number of obstacle contacts made on 79m indoor mobility course.	People with AMD did not exhibit poorer performance (speed and contact with obstacles) than controls on the mobility course. The most significant predictor of mobility performance was size of binocular central scotoma.	4
Hassan et al (2005)	Case-control	**M**	To compare head movement behavious of visually impaired pedestrians with fully sighted pedestrians at two types of complex intersections: a plus intersection and a roundabout. To evaluate how many visually impaired subjects relative to fully sighted subjects demonstrated head movement behaviour consistent with maximising safety as following street crossing safety recommendations set forth by National Highway Traffic Safety Administration.	11 people with AMD (type and duration not reported), median age 79.5 (IQR 71.3-83.8), 10 people with glaucoma (median age 63.2, IQR 52.7-72.3), and 12 controls (median age 69.8, IQR 40.1-78.1).	Head movement behaviour as approaching and crossing at cross junction and roundabout.	More people with visual impairment showed less safe head movement behaviour than controls.	3
Hassell et al (2006)	Cross-sectional	**V**	To describe the impact of age-related macular degeneration on quality of life and explore the association with vision, health and demographic variables.	106 people with AMD (type not reported, median duration 2 years).	Impact of Vision Impairment questionnaire (IVI).	People with AMD reported at least 'a little' concern on 23 of the 32 IVI items.	4

Hochberg et al (2012)	Cross-sectional	**ADL**	To determine if glaucoma and/or AMD are associated with disability in instrumental activities of daily living (IADLS).	47 people with AMD (type and duration not reported), median age 75.1 (IQR 70.9-78.3), 84 people with glaucoma (median age 70.6, IQR 66.4-74.5) and 60 controls (median age 69.4, IQR 65.2-72.8).	IADL disability questionnaire.	44.7% of people with AMD reported disability in one or more IADLs, compared with 25% of people with glaucoma and 18.3% of controls; the most frequently reported IADL diabilities were meal preparation, grocery shopping, and travelling.	4
Ivanoff et al (2000)	Cross-sectional	**ADL**	To describe disability in activities of daily living and how it relates to visual impairment, focusing on AMD.	617 people, all aged 85, 143 of whom had AMD (type and duration not reported).	ADL questionnaire.	People with visual impairment (with and without AMD) reported more disability in ADLs than those without visual impairment; risk of developing ADL disability increased with deterioration in VA (weak relationship indicates people adapt to impairment).	3
Jacko et al (2000)	Case-control	**C**	To characterise the search and selection strategies of computer users with AMD.	5 people with AMD (type and duration not reported) aged between 63 and 83 (mean 77).	Computer icon matching task.	Icon size and number of icons affect icon identification time.	3
Jacko et al (2001)	Case-control	**C**	To derive empirical knowledge of the visual search strategies of computer users who have AMD.	5 people with AMD (type and duration not reported) aged between 63 and 83 (mean 77) and 5 young controls aged between 22 and 32 (mean 26.2).	Eye movements recorded as participants perform computer icon matching task.	Differences in strategies used appear to exist between people with AMD and people without AMD; background colour, number of icons and icon size can affect the interactions.	2

Jacko et al (2002)	Case-control	**C**	To derive empirical knowledge of the visual search strategies of computer users who suffer from AMD; to compare the search and selection strategies of AMD and fully sighted users.	5* people with AMD (type and duration not reported) aged between 63 and 83 (mean 77) and 5 young controls aged between 22 and 32 (mean 26.2). *1 person with AMD did not complete the task.	Computer icon matching task.	Icon size, number of icons and background colour affected task performance. Scan time was longer for people with AMD, but scan length did not differ between the groups.	2
Jacko et al (2005)	Case-control	**C**	To examine the effect of AMD on the performance of older adults when completing a simple compuer-based task.	6 people with dry AMD and 6 controls all aged between 62 and 80 (mean 73.3).	Drag-and-drop task with multimodal feedback.	People with AMD exhibited less efficient drag-and-drop performance than people without AMD. Non-visual feedback (alongside visual feedback), especially auditory feedback, improved task performance in those with and without AMD.	3
Jivraj et al (2013)	Cross-sectional	**D**	To identify the point prevalence of depressive symptoms, QoL impairment, and demographic parameters associated with depression in patients with AMD attending a retina clinic in Edmonton, Alberta.	94 people with AMD (7 with dry AMD, 46 with unilateral nAMD, and 41 with bilateral nAMD, mean duration 4.1 years (SD 3.5), mean age 80.4 (SD 6.8).	Centre for Epidemiological Studies Depression Scale (CES-D) and NEI-VFQ.	21.3% of participants exhibited severe symptoms of depression. NEI-VFQ scores worsened with worsening severity of AMD. Significant differences in some NEI-VFQ subscale scores were found between depressed and non-depressed participants.	4
Johnson et al (2014)	Case report	**D**	Not explicitly stated.	One 80 year old with a 'multi-year history' of nAMD.	Case report.	This patient stated during her ophthalmological evaluation that she 'wanted to die' and reported suicidal plans. These were not noted in patient records or discussed with another eyecare professional at the time. Later on, the clinician phoned the patient and discussed suicide prevention.	3

Kleinschmidt (1999)	Qualitative	**Q**	To explore successful adjustment to vision loss from the perspectives of those who have accomplished it.	12 people with AMD (type not reported, mean duration 6.7 years) aged between 68 and 93 (mean 79.6).	Open ended questionnaire.	The meaning of 'good adjustment' is described as 'a positive view of ability to function and, more generally, a positive attitude or outlook'. Themes were identified as prior life experiences, internal and external resources.	3
Knudtson et al (2005)	Cross-sectional	**ADL**	To examine the associations of measures of quality of life (Medical Outcomes Study Short Form Health Survey SF-36) and functional activities (ADL, IADL and visual function) in persons with and without age-related eye diseases.	2,670 people (number with AMD not clear due to missing information, type and duration not reported) with no eye disease (n=1,444, mean age 64.4), any eye disease unilaterally (n=426, mean age 70.4), or bilateral eye disease (n=641, mean age 75.7).	Interview including Medical Outcomes Study Short Form Health Survey (SF-36), activities of daily living (ADL) and instrumental activities of daily living (IADL) and visual function questionnaires.	SF-36 scores were poorer for people with age-related eye disease, and poorer for those with bilateral disease than unilateral disease. These scores appear to be explained by visual acuity and comorbid conditions rather than the presence of eye disease in itself.	4
Kotecha et al (2013)	Case-control	**M**	To investigate the effects of a secondary task on standing balance in pxs with glaucoma or AMD compared with age-similar control subjects.	12 people with AMD (type and duration not reported), mean age 72.2 (SD 5.3), 12 people with glaucoma (mean age 69.2, SD 4.3), 12 controls (mean age 66.2, SD 6.4).	Posturography under 2 standing conditions (eyes open on a firm surface and a foam-rubber surface) and during 2 tasks (quiet standing and whilst undertaking a mental arithmetic task).	Performing concurrent task whilst standing inccreased postural instability in all groups; this appeared to be worse in AMD group compared with control group in both standing conditions.	4
Kuyk & Elliott (1999)	Case-control	**M**	To determine the effects of reducing light level on mobility performance in persons with ARMD and how performance relates to measures of visual sensory and perceptual function.	41 people with AMD (type and duration not stated), mean age 72.8 (SD 6.09).	Mobility performance under photopic and mesopic lighting conditions on a laboratory obstacle course and 2 real-world courses, an indoor hallway and an outdoor residential route.	Reducing light level increased time taken to complete courses and the number of errors made within the courses. Visual field and contrast sensitivity were more important predictors of obstacle course performance.	4

Lamoureux et al (2011)	Cross-sectional	V	To assess to impact of early and late age-related macular degeneration on vision-specific functioning in Singapore Malays.	3,252 people, 182 of whom had AMD (type and duration not reported) aged between 40 and 80 years.	Modified VF-11 scale.	Late AMD was associated with poor self-reported visual function, whilst early AMD, drusen or RPE abnormalities were not independently associated with self-reported visual function.	4
Lin & Yu (2012)	Cross-sectional	V	To evaluate the relationship between visual impairment and HRQoL by identifying factors that affect the EQ-5D index score and the VFQ global scores, and to determine whether VFQ-25 and EQ-5D scores are correlated.	318 people, 51 of whom had AMD (type and duration not reported), median aged 74 (IRQ 66-79).	NEI-VFQ and EQ-5D.	Correlation between the two questionnaires was weak-moderate. Scores for both increased with improvement in VA and mean deviation (MD).	4
Lopez-Miguel et al (2013)	Cross-sectional	V	To evaluate the patient-reported outcomes in AMD patients by using instruments for eliciting health status and vision specific issues.	34 people with AMD (type and duration not reported) aged between 70 and 92 (mean 82.5, SD 5.2).	NEI-VFQ and SF-12.	Self-reported visual function is severely affected in people with AMD. Results from this study are comparable with those from other studies using NEI-VFQ.	4
Lotery et al (2007)	Cross-sectional	V	The International AMD Burden of Illness Study aimed to document the humanistic and economic impacts of NV-AMD through a simultaneous assessment of patients and a similar group of subjects not affected by the disease in five countries. This article reports the humanistic burden of NV-AMD and related resource utilisation in patients and controls from the UK cohort included in the international study.	75 people with nAMD (duration not reported) aged between 60 and 92 (mean 79.6, SD 6.4) and 91 controls aged between 50 and 86 (mean 65.3, SD 8.5).	NEI-VFQ, EQ-5D, HADS, health care resource utilisation (HRU).	People with AMD had poorer self-reported visual function and wellbeing, higher depression scores and greater need for assistance with activities of daily living than controls.	4

Lovie-Kitchin & Brown (1986)	Case-control	**M**	To determine the effect of age and ARM on the ability to perceive and react to red lights that simulated red traffic signals.	8 people with dry AMD (duration not reported) aged between 70 and 85 (mean 76.5), 10 people with preARM (normal visual acuity with retinal drusen and/or macular pigment changes) aged between 56 and 73 (mean 64.6), 11 older controls aged between 59 and 66 (mean 63.5) and 10 younger controls aged between 19 and 37 (mean 27.6).	Reaction times to red lights of same size and chromaticity as traffic signals under photopic and mesopic conditions and with central and eccentric fixation.	People with AMD had slower reaction times to the lights than the older controls, and people with preARM had results between those of these two groups (i.e. slower than the older controls but faster than people with AMD).	3
Maguire et al (2004) Complications of Age-Related Macular Degeneration Prevention Trial Research Group.	Cross-sectional	**V**	To describe characteristics of participants in the Complications of Age-Related Macular Degeneration Trial (CAPT) at baseline and to investigate associations among visual function, fundus features and vision-related quality of life.	1052 people with dry AMD (duration not reported), mean aged 71 (SD 7.6).	NEI-VFQ.	NEI-VFQ scores were associated with measures of visual function but not with fundus features.	4
Mangione et al (1999)	Cross-sectional	**ADL**	To describe the influence of age-related maculopathy on visual functioning and health-related quality of life.	201 people with AMD (64% dry both eyes, 31% unilateral nAMD and 5% bilateral nAMD), duration not reported), mean age 71 (SD 10).	Interview including ADL scale and SF-36.	Severity of nAMD was associated with poorer ADL scores, and was most significant for near vision and driving related activities. SF-36 scores were not significantly correlated with AMD severity. Self-reported visual function was more accurately represented by VA than by observed clinical severity.	3

Marback et al (2007)	Cross-sectional	**V**	To evaluate the quality of life for persons affected by AMD that results in monocular or binocular legal blindness.	54 people with monocular legal blindness resulting from AMD (type and duration not reported, aged between 51 and 87, mean 74.6, SD 7.3), 54 people with binocular blindness resulting from AMD (type and duration not reported, aged between 54 and 87, mean 75.6, SD 6.3) and 40 controls aged between 50 and 81 (mean 65.7, SD 7.6).	NEI-VFQ.	Both visual impairment groups had poorer NEI-VFQ scores than the control group; those with binocular blindness scored worse than those with monocular blindness.	4
Mathew et al (2010)	Cross-sectional	**D**	To examine QoL and associated factors in people with AMD.	145 people with AMD (type and duration not reported), mean age 78 (SD 7.7) and 104 controls, mean age 78.1 (SD 5.8).	Goldberg Anxiety and Depression scale (GAD), Medical Outcomes Study Short Form (SF-36) and questions relating to assistance required for activities of daily living.	People with AMD scored worse than controls on GAD scale and SF-36, and more people with AMD required assistance with at least one activity of daily living than controls.	4
McCloud et al (2014)	Qualitative	**Q**	To understand people's experience with AMD in light of new treatment successes.	34 people with AMD (6 with dry AMD and 28 with nAMD, 7 with duration less than 2 years, and 27 with duration longer than 2 years.	Focus groups or single in-depth interviews.	Four major themes emerged: cautious optimism, enduring, adaptation and profound loss.	4
McGwin Jr et al (2013)	Cohort	**M**	To examine asssociations between Motor Vehicle Collision involvement and AMD prescence and severity.	142 people with AMD (type and duration not stated) and 63 controls, mean age 72.7 (SD 6.8).	Motor Vehicle Collision rates (from state records) and Driving Habits Questionnaire.	Motor Vehicle Collision rates highests for controls, declining for those with early and intermediate AMD, and then increasing for those with advanced AMD (although noted that sample size for advanced AMD group significantly smaller than other groups).	4

Moore & Miller (2003)	Qualitative	**Q**	To gain an understanding of the experience of severe visual impairment from the perspective of older men with macular degeneration.	8 people with AMD (type not reported, duration of 6 months to 25 years) aged between 68 and 87.	Unstructured, nondirective interview. Participants asked 'Tell me about your experience of living everyday with changes in your vision due to macular degeneration?' and asked to discuss thoughts until nothing more to say.	Six central themes emerged: abilities and inabilities, cherishing of independence, creating strategies, acknowledging the progression of visual impairment, confronting uncertainties and fears, and persisting with hope and optimism.	2
Moore & Miller (2005)	Qualitative	**Q**	To present findings from a secondary analysis that explored the driving strategies used by older adults diagnosed with macular degeneration.	16 people with AMD (type not reported, duration of 6 months to 25 years) aged between 63 and 87 years.	Secondary analysis of qualitative data. Participants initially asked 'Tell me about your experience of living everyday with changes in your vision due to macular degeneration?'. All data relating to driving were retrieved for analysis.	Two central themes were identified: strategies used while driving (using caution, using memory, guessing, using a copilot, increasing visual field, and using a visual aid) and strategies used to continue driving (self-regulating driving activities, believing in driving capabilities, fulfilling desire to drive, circumventing the law, denying driving difficulties, and using visual markers).	2
Moore (2000)	Qualitative	**Q**	To uncover the meaning of severe visual impairment to older women diagnosed with macular degeneration.	8 people with AMD (type not reported, duration for first eye between 6 months and 20 years, duration for second eye 6 months to 12 years) aged between 63 and 85 (mean 75.4)	Unstructured, nondirective interview. Participants asked 'Tell me about your experience of living everyday with changes in your vision due to macular degeneration?' and asked to discuss thoughts until nothing more to say.	Three central themes emerged: embracing a realistic awareness with steadfast positivism, making personal discoveries amidst enveloping losses, and persisting toward an unfolding way of being in the world.	4

Musel et al (2011)	Case-control	**S**	To investigate the residual abilities in AMD patients to process spatial frequencies in natural environments.	Experiment 1: 12 people with nAMD (duration not reported), mean age 75 years (SD 6) and 12 controls, mean age 76 (SD 7). Experiment 2: 10 people with nAMD (duration not reported), mean age 72 (SD 6) and 10 controls, mean age 72 (SD 6).	Ability to categorise indoor vs. outdoor scenes at high spatial frequency (HSF) and low spatial fequency (LSF).	Experiment 1: People with AMD made more no-reponses to categorise HSF than LSF scenes, irrespective of scene category.They also had longer reaction times to categorize HSF than LSF scenes but only for indoor scenes. Experiment 2: People with AMD made the pattern of errors as in Experiment 1, and this time took longer to categorise HSF than LSF scenes, regardless of scene category.	4
Owsley et al (2006)	Qualitative	**Q**	To identify content areas characterising emotional issues faced by persons with AMD.	53 people with AMD (type and duration not reported) in 6 focus groups.	Focus groups followed by telephone interview 6 months later.	Twice as many comments conveyed negative emotions (for example frustration, fear, sadness and inadequacy) than positive emotions (for example gratitude and hope).	4
Popescu et al (2011)	Cross-sectional	**M**	To comprehensively examine several measures of mobility performance (such as life space, balance, TUG, driving status, falls) in people with one of three common age-related conditions (AMD, Fuch's corneal dystrophy and glaucoma) compared to a control group. To determine whether any relationships between eye disease and mobility were primarily explained by VA, CS or visual field.	68 people with AMD (type and duration not reported), mean age 82.6 (SD 5.8), 49 people with Fuchs' corneal dystrophy, mean age 79.4 (SD 7.3), 82 people with glaucoma, mean age 76.5 (SD 7.4), and 73 controls, mean age 72.8 (SD 4.6).	Life Space Assessment questionnaire, one-legged balance test, TUG, Geriatric Depression 15-Item Scale and questions about current driving status and use of public transport, falls and fall-related injuries.	People with AMD had the lowest life-space scores and were least likely to drive.	4

Popescu et al (2012)	Case-control	**MU**	To examine the relationship between patients with different types of visually impairing eye disease and depression. To examine whether reduced mobility mediated these relationships.	81 people with AMD (type and duration not reported), mean age 82.4 (SD 5.9), 55 people with Fuchs' corneal dystrophy, mean age 79.1 (SD 7.2), 91 people with glaucoma, mean age 76.4 (SD 7.6) and 88 controls, mean age 73.1 (SD 4.5).	Life Space Assessment questionnaire, Geriatric Depression 15-Item Scale, participants asked if they limited activities due to fear of falling.	78 people in the cohort met criteria for depression. All of the eye disease groups were more likely to be depressed than the control group; AMD and Fuchs' corneal dystrophy had the strongest relationships with depression. The relationship between eye disease and depression appeared to be mediated by limited life space and activities due to fear of falling.	4
Rovner & Casten (2001)	Cohort	**D**	To investigate incidence rate of depression and its risk factors and consequences in a 6 month longitudinal study.	51 people with bilateral nAMD, second eye onset 6 weeks prior to first interview, mean age 81.3 (6.4).	CES-D Scale, Neuroticism, Extraversion, Openness Five Factor Inventory (NEO-FFI) Forms S and R for participants and informants (family members) respectively, Functional Vision Screening Questionnaire.	Baseline rate of depression was 23% and 6 month incidence rate was 28%. Self-rated and informant-rated neuroticism were strongest risk factors for depression. People who developed depression were more likely to become disabled in visual function, regardless of change in VA.	4
Rovner & Casten (2002)	Longitudinal	**D**	To investigate the interrelationships of disease severity, disability and depression and focus on loss of valued activities as an emblematic disabling consequence of AMD.	51 people with bilateral nAMD, second eye onset 6 weeks prior to first interview, mean age 81.3 (6.4).	CES-D Scale, Index of Affective Suffering (IAS), Revised NEO-FFI Form S, questions about activity loss.	Loss of valued activities appeared to mediate the relationship between VA and affective suffering.	4
Rovner et al (2002)	Cohort	**D**	To report the prevalence rate of depression in older patients with recent vision loss due to AMD and to describe the effect of depression on self-reported vision function during 6 months.	51 people with nAMD, onset within 6 weeks, mean age 81.3 (SD 6.4).	CES-D Scale, Functional Vision Screening Questionnaire, Community Disability Scale.	33% of participants were depressed at baseline; these participants had worse VA and greater disability than nondepressed participants. Decline in self-reported visual function was predicted by increase in depressive symptoms over time, regardless of VA changes or medical status.	4

Rovner et al (2006)	Cross-sectional	**D**	To evaluate the impact of minimal depression on subjective and objective visual function measures in AMD.	206 people with nAMD, onset within 6 months, mean aged 81.2 (SD 5.8).	Structured Interview Guide for Hamilton Depression Rating Scale, NEI-VFQ, Social Problem-Solving Inventory (Short Form) and performance-based visual function (Melbourne Low Vision Index: writing mock cheque, pouring water and identifying lifesize pictures of common household objects).	Minimally depressed participants had worse self-reported visual function and worse problem-solving skills than those who were not depressed.	4
Rovner et al (2011)	Longitudinal	**D**	To investigate the effect of coping strategies, depression, physical health and cognition on NEI-VFQ scores obtained at baseline in a sample of older patients with AMD enrolled in the Improving Function in AMD trial.	241 people with AMD (type and duration not reported), mean age 82.8 (SD 6.9).	Patient Health Questionnaire-9 (PHQ-9), Animal Fluency Test, NEI-VFQ and Optimisation in Primary and Secondary Control Scale (OPS).	Better scores on the cognitive task were associated with less perceived difficulties with visual fucntion.	4
Rovner et al (2014)	Cross-sectional	**V**	To determine whether personality traits influence self-reported functional vision in patients with AMD.	182 people with AMD (type and duration not reported), mean age 84.1 (SD 6.7).	NEI-VFQ, PHQ-9 and revised NEO-FFI.	Visual acuity and neuroticism were independently associated with self-reported difficulty with distance and near activities.	4
Ruiz-Moreno et al (2008)	Cross-sectional	**V**	To describe the impact of bilateral nAMD on patients' functioning, health related QoL and overall economic burden of the disease.	89 people with nAMD aged between 53 and 92 (mean 76.2) and 96 controls aged between 50 and 88 (mean 61.9).	NEI-VFQ, EQ-5D and HADS.	People with nAMD had significantly worse NEI-VFQ scores than controls; these scores decreased significantly with decline in VA.	4
Sahel et al (2007)	Cross-sectional	**V**	To assess the impact of best-eye and worst-eye VA on HRQoL and utility in patients with wet AMD.	360 people with nAMD (mean duration 2.3 years) aged between 51 and 96 (mean 77, SD 8).	NEI-VFQ, Macular Disease Quality of Life (MacDQoL) Scale and HUI3.	Best-eye VA and worst-eye VA each correlated independently with QoL.	4

Schilling et al (2006)	Longitudal	**A**	To explore adaptation of positive affect (PA) and negative affect (NA) under the health condition of AMD with a research design based on a 1 year observation period with 5 measurement points conducted in 3 month intervals.	90 people with AMD (type not reported, mean duration 45.5 months, SD 37.9), mean age 79.5 (SD 6.6).	Positive and Negative Affect Schedules (PANAS).	Positive affect appears to decline over first 2 years of disease, stabilising after this, ending in constant decline after about 6 years. Negative affect appeared to be more stable across measurement occasions.	4
Schilling et al (2013)	Longitudinal	**A**	By use of a vision-specific control strategy assessment applied to AMD individuals over 2 years, to add empirical evidence of change to the life-span theory of control by providing a detailed description of the observed change dynamics in control.	364 people with AMD (type and duration not reported), aged between 65 and 98 (mean 83) at baseline.	Vision specific version of Optimisation in Primary and Secondary Control Scale (OPS), OARS Multidimensional Functional Assessment Questionnaire and CES-D.	Compensatory primary control increased as activities of daily living deteriorated, until a point was reached at which compensatory primary control plateaued. All other strategies declined as activties of daily living deteriorated.	4
Scilley et al (2002)	Cross-sectional	**ADL**	To determine whether early ARM is associated with visual difficulty in daily activities beyond the difficulty that would be expected based on normal retinal aging; to determine whether scotopic sensitivity and VA are associated with visual difficulties in these older adults.	92 people with dry AMD (duration not reported) grouped by status of fellow eye: VA in fellow eye 20/60 or better median age 71 (IQR 66-75), VA in fellow eye worse than 20/60 median age 75 (IQR 69-83), and 55 controls, median age 68 (IQR 57-74).	Scotopic light sensitivity, Activities of Daily Vision Scale (ADVS).	Self-reported difficulty in activities was highest in those with early ARM and poor vision in fellow eye, followed by early ARM and better vision in fellow, then controls. Self-reported difficulty in night driving was linked to scotopic sensitivity impairment.	4
Scott et al (2002a)	Case series	**C**	To investigate the impact of visual function parameters on computer task performance in patients with AMD.	18 people with AMD (12 bilateral nAMD, 1 bilateral dry, 5 unilateral nAMD with dry AMD in the fellow eye, duration not reported) aged between 67 and 89 (mean 81, SD 6).	Computer icon identification tasks.	VA, contrast sensitivity and colour vision defects were strongest predictors of computer task performance.	4

Scott et al (2002b)	Case series	**C**	To investigate the impact of graphical user interface screen features on computer task performance in patients with age-related macular degeneration.	18 people with AMD (type and duration not reported).	Computer icon indentification tasks where size of icons, set size and background colour were varied.	Icon size and set size were significantly associated with computer task accuracy.	4
Seiple et al (2013)	Case-control	**F**	Based on the evidence of abnormal eye movements by patients with AMD, to explore whether abnormal fixation patterns occur when these patients view an image of a face.	9 people with AMD (7 nAMD, 2 dry AMD, duration not reported) aged between 61 and 87 (mean 75) and 9 controls.	SLO of fundus movements recorded while participants viewed an image of a face.	People with AMD fixated less on interal facial features (eyes, nose and mouth) and more on external features than controls. Controls made fewer and shorter saccades than AMD group.	3
Seland et al (2011)	Cross-sectional	**V**	To determine the prevalence of visual impairment (VI) in populations 65 years or older from six European countries and describe the association with vision-related QoL.	4,166 people, QoL data available for 4,133 of these (2,194 with AMD, type and duration not reported), mean age 73.2 (SD 5.6).	NEI-VFQ.	QoL scores were strongly associated with VA and prescence of bilateral AMD; scores were lowest in those with late AMD, and were not related to early AMD.	4
Sengupta et al (2014)	Cross-sectional	**M**	To determine if central vision loss is associated with driving cessation, driving restriction, or other-driver preference.	64 people with AMD (47% dry AMD, 53% nAMD, duration not reported), mean age 74.8 (SD 4.98) and 58 controls (mean age 69.8, SD 5.29).	Salisbury Eye Evaluation Driving Study questionnaire, driver preference ascertained and Geriatric Depression Scale Short Form.	One in four people with AMD had stopped driving; driving cessation became more common with worse VA and contrast sensitivity. Of those who continued to drive, people with AMD were significantly more likely to prefer someone else to drive, and to self-regulate driving (avoiding night driving, unfamiliar areas and long distances).	4
Siaudvytyte et al (2012)	Cross-sectional	**V**	To evaluate the quality of life in persons affected by AMD.	70 people with AMD (type and duration not reported), mean age 68 (SD 8.9) and 70 controls, mean age 61 (SD 5.3).	HADS and Vision Functioning Questionnaire.	People with AMD scored worse than controls on HADS and Vision Functioning Questionnaire; differences were found between binocular and monocular AMD for self-reported performances of certain activities (near and far vision, colour vision and social functioning).	3

Smith (2008)	Qualitative	**Q**	To elucidate how a woman with AMD adapted to the challenges that she faced in performing everday activities.	1 person aged 81 with nAMD of 4 year duration.	Questions about adaptations made in day-to-day life.	Three themes emerged: attitude (acceptance, positivism, independence, altruism and faith), modification of tasks (using other senses or memory, residual vision, and assistive devices to perform everyday activities), and social support (help from other, the blindness system and peers).	3
Soubrane et al (2007)	Cross-sectional	**V**	To describe the burden of bilateral nAMD on patient-reported functioning and health resource utilisation.	401 people with nAMD (duration not reported) aged between 53 and 95, mean 78.1 (SD 6.9) and 471 controls aged between 50 and 88, mean 63.8 (SD 8.4).	NEI-VFQ, EQ-5D, HADS, HRU and specific questions to assess occurrence of accidents and falls, and related falls and fractures.	People with AMD reported worse vision-related functioning and wellbeing, more anxiety and depression, and higher falls rates and requirement for assistance with activities of daily living than controls.	4
Spaulding et al (1994)	Case-control	**M**	To evaluate gait adaptations to altered surface characteristics and high and low ambient light conditions by subjects with ARM.	20 people with AMD (type and duration not reported), mean age 73.9 (SD 7.2) and 20 controls, mean age 70.3 (SD 5.5).	Walk along 6 metre path, along which 1 of 3 altered surfaces (compliant, uneven or shiny) were encountered.	People with AMD walked more cautiously than controls when walking on altered surfaces and made adjustments above and beyond those made by controls in order to maintain safe mobility.	4
Spaulding et al (1995)	Case-control	**M**	To evaluate the gait responses of individuals with low vision compared to those of normal visioned individuals when their vision is challenged by extreme levels of light.	19 people with AMD (type and duration not reported), mean age 73.9 (SD 7.2) and 20 controls, mean age 70.3 (SD 5.5).	Walk along flat, unobstructed path immediately after light level changed.	People with AMD walked slower and more cautiously than controls regardless of light level. People with AMD kept their head low during high light, whilst both groups kept their head low during low light.	3
Stanford et al (2009)	Qualitative	**Q**	To describe longitudinally the psychosocial adjustment to visual impairment of patients with age-related macular degeneration.	226 people with AMD (type and duration not reported), mean age 81.6.	Weekly diaries in which participants were instructed to record social interaction, general health status and visual problems along with details of 'happy' and 'sad' events.	Over 12 months, vision related to daily life appeared to decline with little or no adjustment to AMD.	4

Stein et al (2003)	Cross-sectional	**U**	To evaluate the quality of life of patients with AMD through the use of utility evaluation, and assess whether clinicians and healthy volunteers appreciate the impact of AMD on HRQoL.	115 people with AMD (type and duration not reported), mean age 75.1 (SD 7.92), 142 members of the general public, mean age 44.3 (SD 13.32) and 62 clinicians, mean age 29 (SD 7.32).	TTO.	Significant differences were found between people with AMD (grouped in mild, moderate and severe) and members of the general public and clinicians who were instructed to assume that they had each severity of AMD, with people without AMD underestimating impact of AMD on patients. People with severe AMD had lower utility scores than those with mild AMD.	4
Stevenson et al (2004)	Cross-sectional	**ADL**	To study the relation between visual impairment and ability to care for oneself or a dependent in older people with AMD.	199 people with AMD (type and duration not reported), mean age 74 (SD 9).	SF-36, Daily Living Tasks Dependent on Vision (DLTV) questionnaire and questionnaire about ability to care for self and others.	Ability to care self and others strongly related to self-reported visual functioning and QoL.	4
Sun et al (2007)	Cross-sectional	**D**	To examine the association between AMD and depressive symptoms.	2,194 people, 367 with AMD (type and duration not reported), mean age 78.4.	CES-D.	No association was found between AMD and depressive symptoms.	4
Szabo et al (2008)	Cross-sectional	**M**	To determine whether older women with exudative AMD are at greater risk of falls.	115 people with nAMD (mean duration 26 months) aged between 70 and 92 (mean 81.3) and 54 controls aged between 71 and 88 (mean 77.5).	Fall risk index score from short form physiological profile assessment (PPA) including CS, proprioception, quadriceps strength, simple reaction time and postural sway, interview to evaluate behavioural risk factors for falling, physical activities scale for the elderly (PASE), fear of falling quantified using activities-specific balance confidence (ABC) scale, NEI-VFQ.	People with AMD had greater fall risk than comparison cohort; this risk increased with age.	4

Szabo et al (2010)	Cohort	**M**	To determine whether older women with nAMD are at an increased risk of falls or injurious falls.	114 people with nAMD (duration not stated) aged between 70 and 92 (mean 81.2) and 132 controls aged between 70 and 92 (mean 76.3).	Physical activities scale for the elderly (PASE), Barthel index evaluated independent activities of daily living and mobility, ABC scale, NEI-VFQ.	People with AMD fell twice as often (falls per year) than controls, and had almost twice the risk of injurious falls than controls.	4
Szlyk et al (1995)	Case-control	**M**	To determine the effects of age and central vision loss on driving skills.	10 people with AMD (type and duration not reported), mean age 75.7 (SD 4.5), 11 elderly controls, mean age 71 years (SD 8.3) and 29 young controls aged between 19 and 62, mean age 38.9 (SD 12.4).	Interactive driving simulator, on-road driving test and self-reported frequency of real-world accident and convictions for traffic violations.	Although people with AMD performed worst on the driving simulator and the on-road driving test, they were involved in less real-word accidents and had less convictions for traffic violations than controls, perhaps due to risk aversion.	3
Tejeria et al (2002)	Cross-sectional	**F**	To explore relations between tasks of familiar face recognition (FFR) and discrimination of face expression difference (FED), perceived disability in face recognition and standard clinical measures of visual function; to determine to what extent performance in the face recognition tasks can be improved using a bioptic device.	30 people with AMD (type and duration not reported) aged between 66 and 90 (mean 81.5).	FFR: identification of images of famous people. FED: discrimination of facial expression. Self-rated disability in FR questionnaire.	Self-rated disability did not correlate with performance on either FR task, although questionnaire item on familiar face recognition did correlate with FFR performance. FFR was related most closely to distance VA. FED was most closely related to continuous text reading acuity.	4
Thibaut et al (2014)	Case-control	**S**	To compare scene gist recognition in central and in peripheral vision in people with central vision loss and normally sighted age-matched observers.	21 people with nAMD (duration not reported) aged between 66 and 89 (mean age 79, SD 5.7) and 15 controls aged between 66 and 83 (mean age 74.6, SD 6).	Natural vs. urban scene categorisation task with images presented randomly at one of 5 spatial locations on screen.	People with AMD showed poorer performance than controls at all spatial locations; whilst controls performed better for images presented in central locations than those presented peripherally, people with AMD did not.	3

Timberlake et al (2011)	Case-control	**H**	To investigate changes in reach-to-grasp movement dynamics and to relate those changes to the characteristics of subjects' preferred retinal loci, scotomas, and VAs.	10 people with AMD (type and duration not reported), mean age 81.4 and 10 controls, mean age 78.3.	Reach and grasp task.	People with AMD showed longer hand movement duration, lower maximum velocities and longer visual reaction times than controls. Maximum grip aperture (of block) decreased with increasing PRL area, and visual reaction time increased with decreasing VA.	4
Timberlake et al (2013)	Case-control	**H**	To elucidate the roles of the fovea in normally sighted individuals and the fPRL in those with macular scotomas from AMD in handwriting; and to determine whether the pen tip retinal location is the same as the fingertip retinal location during tracing.	8 people with AMD (type and duration not reported) aged between 74 and 88 (mean age 80.3) and 7 controls aged between 74 and 89 (mean 78.7).	Word writing task while observing hand, pen and text in a SLO.	Poor handwriting performance in people with macula scotomas appears to be due to difficulties placing letters in appropriate location due to reduced VA and scotoma obscuration of the location.	3
Tolman et al (2005)	Cross-sectional	**A**	To examine psychosocial adaptation to vision loss and its relationship to depressive symptomatology in legally blind older adults with ARMD.	144 people with AMD (type and duration not reported) aged between 65 and 95 (mean age 81.58, SD 6.24).	Short Portable Mental Status Questionnaire (SPMSQ), short form of Geriatric Depression Scale (GDS-SF), Adaptation to Vision Loss (AVL) scale).	People with AMD who reported poor adaptation to vision loss also reported more depressive symptoms than those who reported more successful adaptation.	4
Tran et al (2010)	Case-control	**S**	To assess the scene gist recognition in eyes with AMD and to study the relationship between scene recognition and macular function.	27 people with AMD (17 with nAMD and 10 with dry AMD, duration not reported) aged between 59 and 91, mean 79 (SD 7.5) and 17 controls, mean age 74 (SD 8.5).	Scene categorisation task (natural vs. urban and indoor vs. outdoor).	Performance amongst people with AMD was poorer than that of controls.	3
Tran et al (2011)	Case-control	**S**	To investigate impairment in discriminating a figure from its background and to study its relation to VA and lesion size in patients with nAMD.	17 people with nAMD (duration not reported) aged between 60 and 92 (**mean reported as 77 and 81 at different parts of article**) and 17 controls, mean age 74.5 (SD 7.2).	Object discrimination task.	People with AMD performed worse than controls; people with AMD detected the target best when it was isolated from its background.	3

Tran et al (2012)	Case-control	**S**	To investigate to effect of contrast on scene perception in people with AMD and to examine the relationship between task performance and macular function.	19 people with nAMD (duration not reported) aged between 59 and 91, mean 79 (SD 8) and 16 controls aged between 65 and 85, mean 75 (SD 8.5).	Detection of an animal in a natural scene at varying levels of contrast.	People with AMD showed a larger deterioration in performance at lower contrast levels than controls.	3
Tran et al (2014)	Case-control	**S**	To investigate the effect of AMD on memory for spatial representations in realistic environments.	19 people with AMD (12 with nAMD and 7 with dry AMD) aged between 59 and 91, mean 79 (SD 8) and 13 controls aged between 59 and 81, mean 73.	Matching viewpoint of scene to that of initially presented scene.	Both people with AMD and controls showed systematic biases toward middle view of range; this bias was stronger for people with AMD.	4
van Landingham et al (2014)	Cross-sectional	**M**	To determine if AMD and AMD-related vision loss are associated with fear of falling.	65 people with AMD (type and duration not reported), median age 75.9 (IQR 71.9-78.3) and 60 controls, median age 69.4 (IQR 65.2-72.8).	University of Illinois at Chicago Fear of Falling Questionnaire.	AMD, VA and CS were associated with fear of falling; relationship was stronger for VA and CS than for AMD.	4
Wahl et al (2003)	Cross-sectional	**A**	To examine whether there are differences in control strategies as in basic versus expanded outcomes between visually impaired adults and unimpaired older adults; and to examine the kind of relations that exist between control strategies and basic versus expanded outcomes in visually impaired older adults.	90 people with AMD (type and duration not reported), mean age 79.5 (SD 6.6) and 35 controls, mean age 72.2 (SD 9).	OPS, PANAS, AVL, Scales of Psychological Well-Being and ADL/IADL competence assessed.	People with AMD had higher levels of compensatory primary control tha controls; large differences were found between ADL/IADL competence between those with AMD and those without.	4

Wahl et al (2004)	Cross-sectional	**A**	To examine the effect of primary and secondary control on 3 major outcomes experienced by visually imapired older adults: functional ability, adaptation to vision loss and positive affect.	90 people with AMD (type and duration not reported) aged between 61 and 93 (mean 79.5).	OPS, modified Multilevel Assessment Instrument, AVL and PANAS.	Selective primary control was positively related to ADL/IADL ability. Compensatory primary control and selective secondary control were positively related to positive affect. ADL/IADL ability was related to adaptation to vision loss.	4
Wahl et al (2005)	Longitudal	**A**	To test the assumption that: the experience of AMD places limits on exerting what the life span theory of control has coined selective control and compensatory control efforts should gain in importance over time.	90 people with AMD (type and duration not reported), mean age 79.5.	OPS, modified Multilevel Assessment Instrument and PANAS.	Selective control strategies decreased over time. Higher selective control at earlier timepoint predicted higher functional ability and positive affect at later timepoint.	4
Wahl et al (2007)	Longitudal	**A**	To apply the life-span theory of control proposed by Heckhausen and Schulz to study the change in use of control strategies related to AMD.	90 people with AMD (type not reported, mean duration 49.6 months, SD 46.4 at start of study).	OPS, self-reported time since diagnosis and modified Multilevel Assessment Instrument.	Compensatory primary control increased shortly after diagnosis. Increase in compensatory secondary control was related to functional loss in IADLs.	4
Wang et al (2012)	Cross-sectional	**M**	To determine whether patients with age-related eye disease are more likely to limit their activities due to a fear of falling.	93 people with AMD (type and duration not reported, mean age 83, SD 6), 57 people with Fuchs' corneal dystrophy (mean age 79, SD 7), 98 people with glaucoma (mean age 77, SD 8) and 97 controls (mean age 73, SD 5).	Self-reported falls in the past year, Life Space Assessment questionnaire, one-legged balance test, Geriatric Depression Scale and participants asked if limited activities due to fear of falling.	Up to one half of people with eye disease reported activity limitation due to fear of falling, compared with 16% of controls.	4
Williams et al (1998)	Cross-sectional	**V**	To demonstrate the impact of AMD on QoL, emotional distress, and functional level.	86 people with AMD (type not reported, mean duration 5.9 years, SD 6.2) aged between 63 and 91 (mean 78.7, SD 6.3).	Quality of Well-Being (QWB) scale, Profile of Mood States (POMS) and IADL Index.	People with AMD had worse QoL, greater psychological distress and greater disability in carrying out activities of daily living than that of other elderly samples.	4

Wong et al (2004)	Qualitative	**Q**	To conduct in-depth individual interviews to explore a range of issues and perspectives, making sense of individual experiences, and to understand the specific needs of people with ARMD.	15 people with AMD (type not reported, duration of 6 months to 7 years) aged between 60 and 85 (mean 77).	In-depth semi-structured interviews with questions asked about participants' experience with AMD within broader social and psychological context.	Limitations associated with AMD depended on visual impairment. Understanding the condition, social resources and responses of society can all affect a person's ability to cope.	3
Wood et al (2009)	Case control	**M**	To assess the postural stability and gait characteristics of adults with ARM and to identify the visual factors associated with postural stability and gait in this clinical population.	80 people with AMD (type and duration not reported) aged between 59 and 95 (mean 77.18, SD 6.89).	Postural sway assessment, gait assessment and physical function questionnaire.	Poorer visual function was associated with postural instability and gait adaptations, such as shorter steps steps, wider stance, slower walking speed and more time with both feet on the ground.	4
Wood et al (2011)	Longitudinal	**M**	To better understand the prospective injury risk from falls and non-fall-related causes over a 12-month follow-up period in a sample of older adults with a range of levels of visual impairment due to AMD.	76 people with AMD (type and duration not reported) aged between 59 and 95 (mean 77, SD 6.9).	Falls and injury diary.	Increasing visual impairment was associated with higher incidence of falls and injuries.	4
Yanagi et al (2011)	Cross-sectional	**U**	To investigate utility values associated with bilateral AMD among Japanese elderly patients and the imapct of the disease in their QoL using preference-based techniques.	50 people with nAMD (duration not reported) aged between 59 and 91 (mean 75.9).	Time trade-off and standard gamble.	AMD causes substantial deterioration in utility values; TTO values correlated with better eye VA.	4
Domains of main outcomes: A = Adaptation, ADL = Activities of Daily Living, C = Computer use, D = Depression, F = Faces, H = Hand-eye coordination, M = Mobility, MU = Multiple, Q = Qualitative, S = Scene viewing, U = Utility values, V = Visual function (patient-reported)							

Appendix 3 Quality appraisal for studies included in systematic review (Chapter 2)

For full details of grading criteria, please refer to Table 2 in Chapter 2.

Study	Study type	MMAT Criterion				MMAT Score
		1	2	3	4	
Alexander et al (1988)	Case series (Quantitative descriptive)	Yes	Yes	Yes	Yes	4
Alexander et al (2014a)	Case-control (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Alexander et al (2014b)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Can't tell	Yes	3
Aspinall et al (2014)	Case-control (Quantitative non-randomised)	Yes	Yes	Can't tell	Yes	3
Augustin et al (2007)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Backman & Williams (2002)	Case series (Quantitative descriptive)	No	Can't tell	Yes	Yes	2
Banerjee et al (2007)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Bansback et al (2007)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	No	3
Bass et al (2004)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Berdeaux et al (2005)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Bordier et al (2011)	Case-control (Quantitative non-randomised)	Can't tell	Yes	Can't tell	Yes	2
Boucart et al (2008a)	Case-control (Quantitative non-randomised)	No	Yes	No	Yes	2
Boucart et al (2008b)	Case-control (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Boucart et al (2013)	Case-control (Quantitative non-randomised)	Yes	Yes	Can't tell	Yes	3
Brody et al (2001)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Brown et al (1986)	Case-control (Quantitative non-randomised)	Can't tell	Yes	Yes	Yes	3
Brown et al (2000)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Brown et al (2002)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Bullimore et al (1991)	Case-control (Quantitative non-randomised)	Yes	Yes	Can't tell	Yes	3
Burton et al (2015)	Qualitative	Yes	Yes	No	No	2

Butt et al (2013)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Can't tell	Yes	3
Cahill et al (2005)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Casten et al (2002)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Cavar et al (2014)	Case-control (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Chia et al (2004)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Cimarolli et al (2012)	Qualitative	Yes	Yes	No	Yes	3
Clemons et al (2003)	Cohort (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Coleman et al (2010)	Cohort (Quantitative non-randomised)	Yes	Yes	Yes	No	3
Cruess et al (2007)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Curriero et al (2013)	Case-control (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Davis et al (1995)	Case-control (Quantitative non-randomised)	Yes	Yes	No	Yes	3
Decarlo et al (2003)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Dong et al (2004)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Elliott et al (1995)	Case-control (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Eramudugolla et al (2013)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	No	3
Espallargues et al (2005)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Can't tell	No	2
Esteban et al (2007)	Cross-sectional (Quantitative non-randomised)	Yes	No	Yes	Yes	3
Fletcher et al (2008)	Case report (Quantitative descriptive)	No	No	Yes	N/A	2
Geruschat et al (2006)	Case-control (Quantitative non-randomised)	No	Yes	Yes	No	2
Geruschat et al (2006)	Case-control (Quantitative non-randomised)	No	Yes	Yes	Yes	3
Gopinath et al (2013)	Cohort (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Hassan et al (2002)	Case-control (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Hassan et al (2005)	Case-control (Quantitative non-randomised)	Yes	Yes	Can't tell	Yes	3

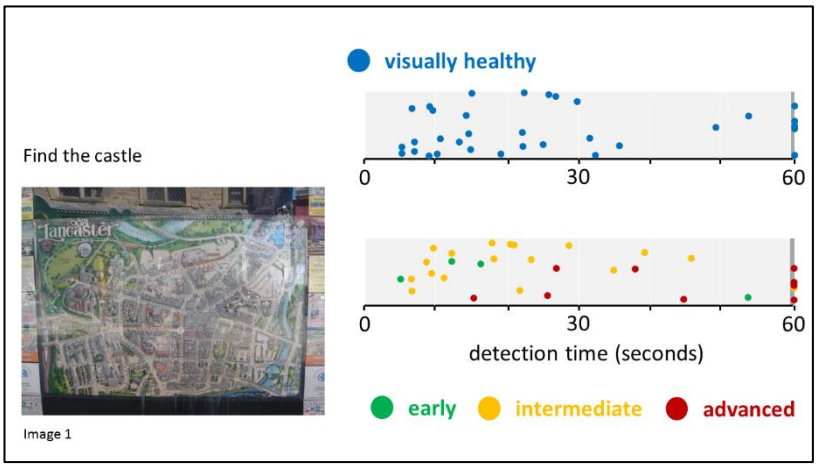
Hassan & Snyder (2012)	Case-control (Quantitative non-randomised)	No	Yes	Yes	Yes	3
Hassell et al (2006)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Hochberg et al (2012)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Ivanoff et al (2000)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Can't tell	Yes	3
Jacko et al (2000)	Case-control (Quantitative non-randomised)	Yes	Yes	Can't tell	Yes	3
Jacko et al (2001)	Case-control (Quantitative non-randomised)	No	Yes	No	Yes	2
Jacko et al (2002)	Case-control (Quantitative non-randomised)	No	Yes	No	Yes	2
Jacko et al (2005)	Case-control (Quantitative non-randomised)	Yes	Yes	Yes	Yes	3
Johnson et al (2014)	Case report (Quantitative descriptive)	Yes	No	Yes	N/A	3
Jivraj et al (2013)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Kleinschmidt et al (2013)	Qualitative	Yes	Yes	Yes	No	3
Knudtson et al (2005)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Kotecha et al (2013)	Case-control (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Kuyk & Elliott (1999)	Case-control (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Lamoureux et al (2011)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Lin & Yu (2012)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Lopez-Miguel et al (2013)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Lotery et al (2007)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Lovie-Kitchin & Brown (1986)	Case-control (Quantitative non-randomised)	Yes	Yes	No	Yes	3
Maguire et al (2004) Complications of Age-Related Macular Degeneration Prevention Trial Research Group.	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Mangione et al (1999)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	No	3
Marback et al (2007)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4

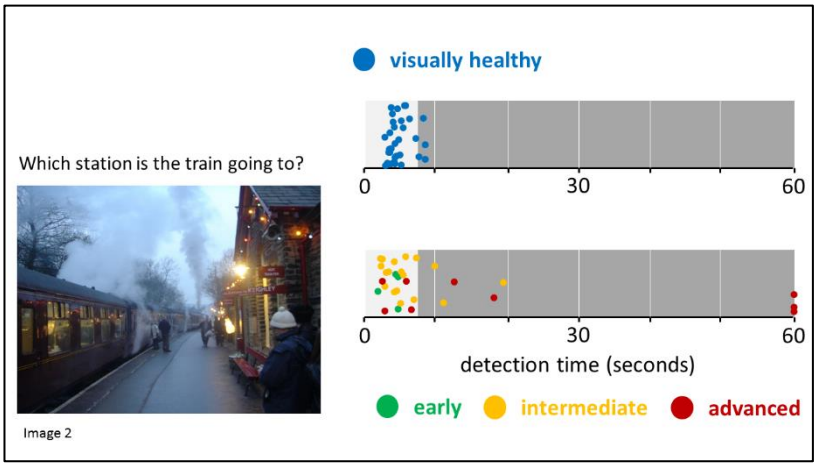
Mathew et al (2010)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
McCloud et al (2014)	Qualitative	Yes	Yes	Yes	Yes	4
McGwin Jr et al (2013)	Cohort (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Moore (2000)	Qualitative	Yes	Yes	Yes	Yes	4
Moore & Miller (2003)	Qualitative	Yes	Yes	No	No	2
Moore & Miller (2005)	Qualitative	Yes	Yes	No	No	2
Musel et al (2011)	Case-control (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Owsley et al (2006)	Qualitative	Yes	Yes	Yes	Yes	4
Popescu et al (2011)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Popescu et al (2012)	Case-control (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Rovner & Casten (2001)	Cohort (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Rovner & Casten (2002)	Longitudinal (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Rovner et al (2002)	Cohort (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Rovner et al (2006)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Rovner et al (2011)	Longitudinal (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Rovner et al (2014)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Ruiz-Moreno et al (2008)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Sahel et al (2007)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Schilling et al (2006)	Longitudinal (Quantitative descriptive)	Yes	Yes	Yes	Yes	4
Schilling et al (2013)	Longitudinal (Quantitative descriptive)	Yes	Yes	Yes	Yes	4
Scilley et al (2002)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Scott et al (2002a)	Case series (Quantitative descriptive)	Yes	Yes	Yes	N/A	4
Scott et al (2002b)	Case series (Quantitative descriptive)	Yes	Yes	Yes	Yes	4
Seiple et al (2013)	Case-control (Quantitative non-randomised)	Yes	Yes	Can't tell	Yes	3
Seland et al (2011)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4

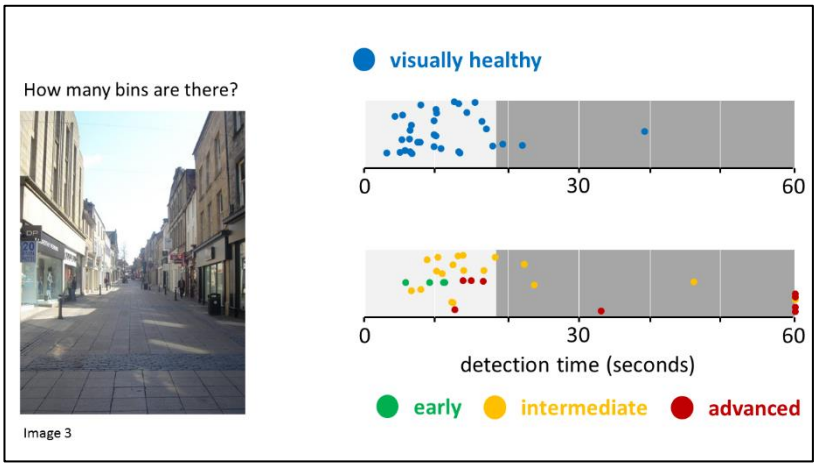
Sengupta et al (2014)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Siaudvytyte et al (2012)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	No	Yes	3
Smith (2008)	Qualitative	Yes	Yes	No	Yes	3
Soubrane et al (2007)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Spaulding et al (1994)	Case-control (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Spaulding et al (1995)	Case-control (Quantitative non-randomised)	Yes	Yes	Can't tell	Yes	3
Stanford et al (2009)	Qualitative	Yes	Yes	Yes	Yes	4
Stein et al (2003)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Stevenson et al (2004)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Sun et al (2007)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Szabo et al (2008)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Szabo et al (2010)	Cohort (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Szlyk et al (1995)	Case-control (Quantitative non-randomised)	Yes	Yes	Can't tell	Yes	3
Tejeria et al (2002)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Thibaut et al (2014)	Case-control (Quantitative non-randomised)	Yes	Yes	No	Yes	3
Timberlake et al (2011)	Case-control (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Timberlake et al (2013)	Case-control (Quantitative non-randomised)	No	Yes	Yes	Yes	3
Tolman et al (2005)	Cross-sectional (Quantitative descriptive)	Yes	Yes	Yes	Yes	4
Tran et al (2010)	Case-control (Quantitative non-randomised)	Yes	Yes	Can't tell	Yes	3
Tran et al (2011)	Case-control (Quantitative non-randomised)	Yes	Yes	Can't tell	Yes	3
Tran et al (2012)	Case-control (Quantitative non-randomised)	Yes	Yes	Can't tell	Yes	3
Tran et al (2014)	Case-control (Quantitative non-randomised)	Yes	Yes	Can't tell	Yes	3
van Landingham et al (2014)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4

Wahl et al (2003)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Wahl et al (2004)	Cross-sectional (Quantitative descriptive)	Yes	Yes	Yes	Yes	4
Wahl et al (2005)	Longitudinal (Quantitative descriptive)	Yes	Yes	Yes	Yes	4
Wahl et al (2007)	Longitudinal (Quantitative descriptive)	Yes	Yes	Yes	Yes	4
Wang et al (2012)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Williams et al (1998)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Wong et al (2004)	Qualitative	Yes	Yes	No	Yes	3
Wood et al (2009)	Case-control (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4
Wood et al (2011)	Longitudinal (Quantitative descriptive)	Yes	Yes	Yes	Yes	4
Yanagi et al (2011)	Cross-sectional (Quantitative non-randomised)	Yes	Yes	Yes	Yes	4

Appendix 4 Search durations for each individual image (Chapter 3)



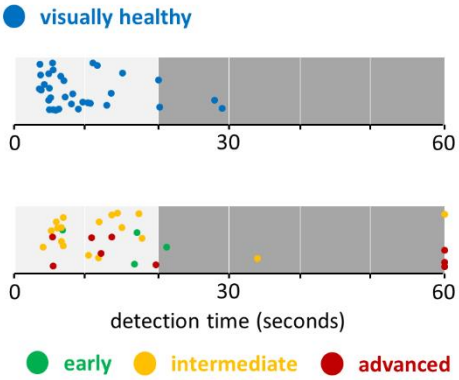




How much is a bottle of regular Coca Cola?



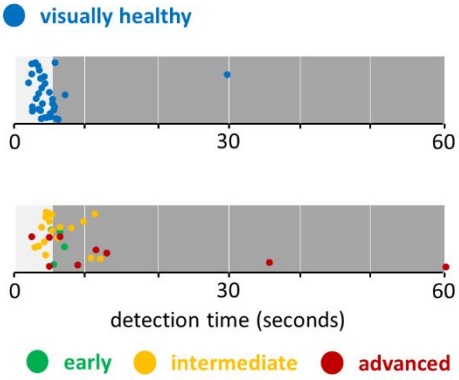
Image 4



Find the hanging basket



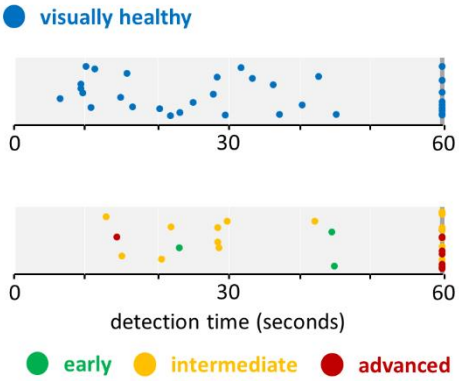
Image 5



How much is the Fimbles cake mix?



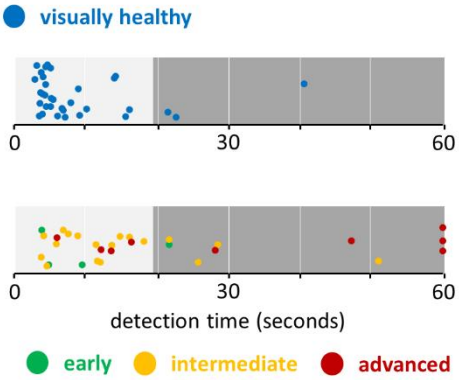
Image 6



Locate McDonalds



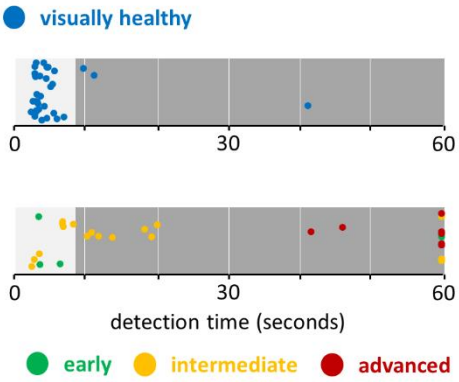
Image 7



Find and read out
loud the street name



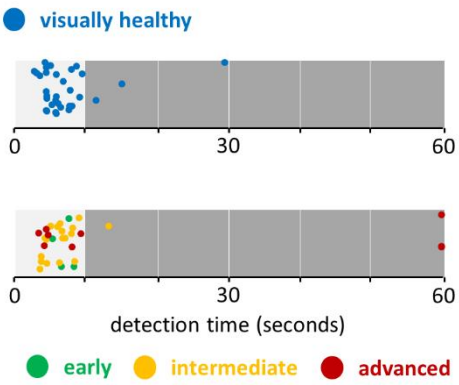
Image 8



What is the price of the yellow
smoothie drink?



Image 9



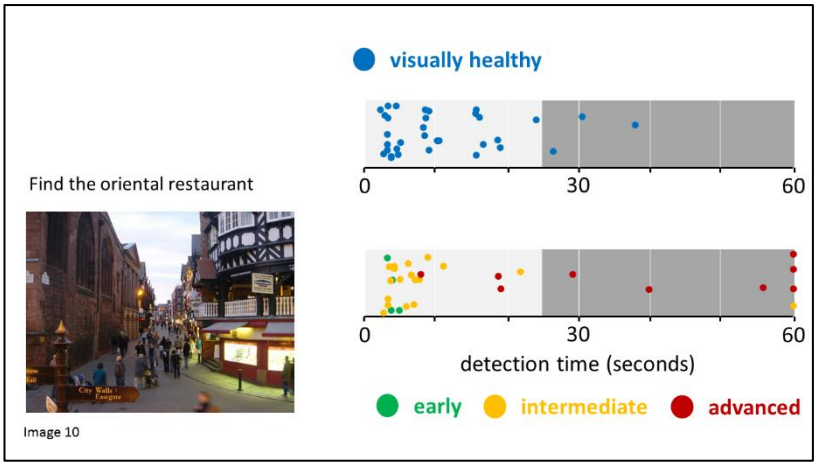


Image 10

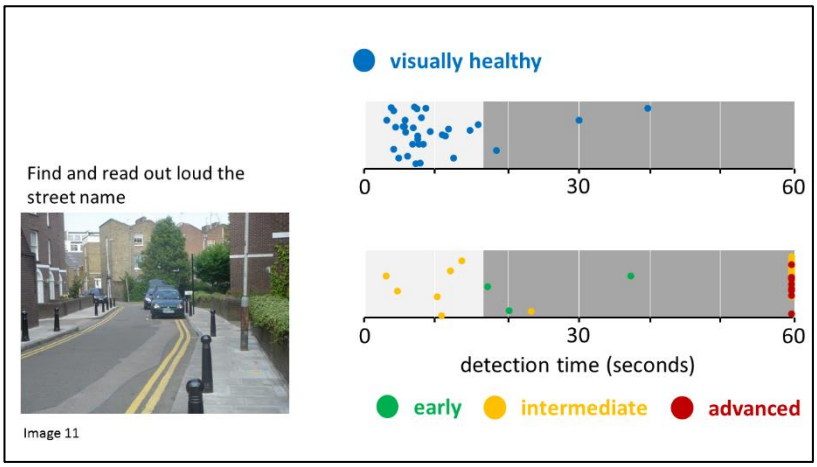


Image 11

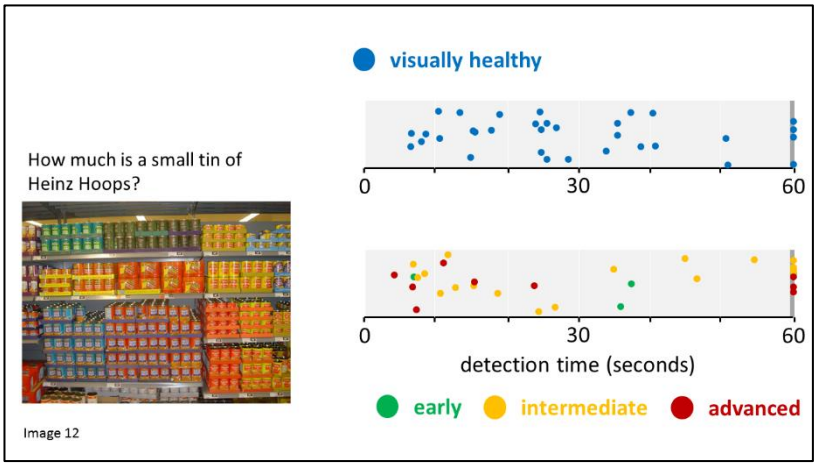
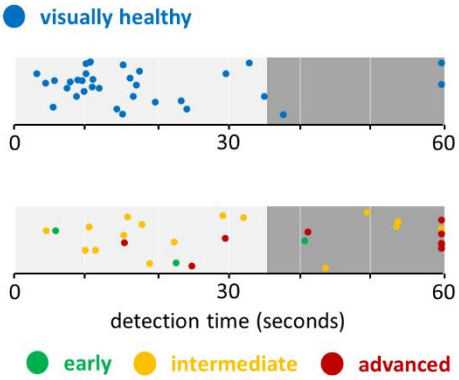


Image 12

Find the Butchers sign



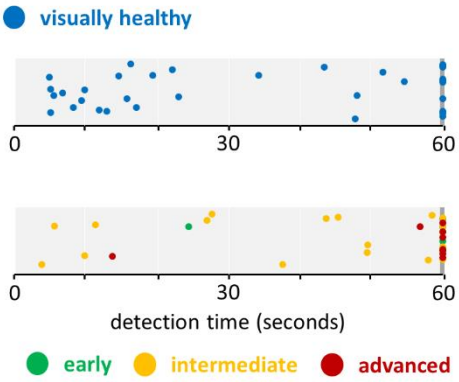
Image 13



Find the sign for the WC (toilet)



Image 14



What is the price of a loaf of Kingsmill Square Medium Cut?



Image 15

