Epidemiology of eye disease in the UK:

The Bridlington Eye Assessment Project

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(i) Candidate Information

Epidemiology of eye disease in the UK: The Bridlington Eye Assessment Project

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(iii) Acknowledgments

The Bridlington Eye Assessment project was conceived and instigated by Dr Jonathon Hillman and Dr Hamish MacNab (GPs) in collaboration with Prof. Stephen Vernon and with the assistance of Mrs Sheila MacNab (BEAP Manager), Linda Sanderson (Receptionist), the nursing staff, and Mr S Brown, Mrs J Button, Mr G Langton, and Mr M Kunz (Optometrists). Mr J Bapty, Mr N Connell, Mr P Jay, and Mrs G Poole acted as charity trustees. Prof. David Crabb and Dr Haogang Zhu conceived and developed the novel shape analysis tools. Prof. Harmindar Dua acted as my university supervisor and Alison Adair provided secretarial support locally, frequently going above and beyond to help. The work on Age related macula degeneration was written in collaboration with Dr Craig Wilde and features as part of both candidates' theses. Dr Wilde graded all photographs and wrote the first draft of the manuscript, while I prepared and integrated the relevant study databases and performed the statistical analysis. Both of us contributed to writing the final draft. I am especially grateful to Dr Hillman, whose selfless and tireless contribution to the town and project was evident from interactions with all those I encountered while in Bridlington. Professor Stephen Vernon provided excellent advice and insight throughout and I am especially grateful for his unwavering kindness, care and thoughtfulness without which I would have found it impossible to complete this work.

(iv) Dedication

This work is bittersweet in that it has acted a backdrop to some of the most difficult times I have faced. This includes the death of both my parents and my short marriage and divorce. While these events are near universal and loom small on the scale of human tragedy, for me, they cut deep and remain indelibly associated with this work. At times it has provided me with comfort and escape, while at others I have felt its heavy weight across my shoulders. It has shaped me as much as I have shaped and managed its swathes of data in an effort to extract something of value. It is for my father who was always the consummate academic and would be proudest of its completion, for my mother who kept it in context, for my former wife, Nadine, who saw its value and for my son whose arrival heralded its completion. Regardless of whether or not it is accepted, its completion represents a triumph over many of my own demons, including procrastination and disorganisation. It has allowed me the opportunity of working with some remarkable individuals including Professor's Vernon and Crabb and of attending fabled institutions across the world, for which I will always be grateful.

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(vii) Abstract

Purpose;

To determine the prevalence of and impact of eye disease in an elderly population and the diagnostic accuracy of a novel artificial intelligence algorithm for the detection of glaucoma

Design;

population based, cross sectional study

Participants;

3549 Caucasian individuals over the age of 65 years

Methods:

A directed general and ophthalmic history was obtained from all subjects. Slit lamp eye examination including applanation tonometry and dilated examination of the fundus was performed by one of four specially trained optometrists and supplemented with fundus photography, visual field testing and Heidelberg Retinal Tomography (HRT). Those with reduced vision, raised intraocular pressure, visual field defects or other abnormalities were referred for further assessment by a consultant ophthalmologist and followed longitudinally until a definitive diagnosis was made. All diagnoses of glaucoma were made retrospectively using at least 5 years of longitudinal data to determine status at incident examination. All fundus photographs were reviewed by a single ophthalmologist for signs of age related macula degeneration (AMD) and other retinal disease. HRT outputs were analysed using the device's proprietary software which produced results for normative based Moorfield's regression analysis (MRA) and the shape analysis tool Glaucoma Probability Score (GPS).

We used a bespoke Matlab based machine learning classifier to providing two further measures based on shape analysis which were termed shape abnormality score (SAS) and abnormal disc score (ADS).

Statistical Analysis: Outcomes and associations were explored using t-tests, chi-squared tests and Mantal Haenzel methods. Linear and logistic regression was used for multivariate analysis. Agreement was measured using kappa, intraclass correlation coefficient and concordance correlation coefficient and plotted using Bland Altman plots. Covariate effects on diagnostic performance were examined using a combination of maximum likelihood probit models and bootstrap analysis. All data analysis was performed using Stata v14

Results;

Cataract; Significant lens opacities were present in 45% of individuals of whom 12% went on to have cataract surgery. Women were 29% more likely to have significant cataract than men. 9.5% of eyes showed signs of previous cataract surgery of which 17% either required or had received treatment for subsequent posterior capsular opacification. In the absence of thresholds for surgery 18 cataract operations per thousand (95% CI 14 – 23) were required for those aged 65-75 years old. For those over 75 years, 76 cataract operations per thousand (95% CI 66 – 86) were required

AMD; Geographic atrophy (grade 4a) occurred in 2.5%, and neovascular AMD (grade 4b) in 1.8% of eyes. Prevalence increased with age with grade 4 (advanced) AMD in 2.2% of those aged 65–69 years, 15.8% for those aged 85–90 years, and 21.2% for over 90 years. There was significant asymmetry between eyes of individuals with advanced AMD ($P<0.001$). After correction for age and co-pathology, those with advanced AMD in the better eye were 4 times more likely to be disattisified with their vision.

Glaucoma; For tests with a specificity of > 90% for new OAG, intraocular pressure was the least sensitive (48%), while clinical CDR ≥ 0.7 was the most sensitive (76%) test. Optometric impression showed the best specificity (98%) with acceptable sensitivity (51%) but may have been subject to verification bias since final diagnosis was based on clinical impression albeit with the reference to longitudinal results. Because of the low relative prevalence of new glaucoma, the test specificity of 98% still resulted in referral of nearly twice as many false positives as new patients with glaucoma. There was moderate agreement between individual optometrists and the HRT in measuring CDR but wide limits of agreement precluding effective comparison between approaches.

Of the disc based measures, SAS and optometric assessment were found to be the most specific but MRA showed the best overall performance. In our subgroup analysis, we found a drop in sensitivity for detection of new disease by HRT using automated shape analysis and by optometrist using Jonas cirteria. MRA performed well across all groups and showed similar sensitivity in detection of new and previously diagnosed glaucoma.

Chapter 1 Introduction

1.1 Introduction to epidemiology of eye disease

Sense organ disease, including eye disease and hearing loss is the most common cause of disability in the elderly and the second leading cause of disability worldwide[1]. Globally there are 1.3 billion (18%) of individuals with some form of visual impairment[2]. Approximately 80% of this is thought to be avoidable[3].

Uncorrected refractive error, cataract, glaucoma and macula degeneration are the major causes. In 2015, it was estimated that there were 36 million blind individuals worldwide. There were 217 million with severe visual impairment and 189 million with mild visual impairment. Estimates for the number of individuals with presbyopia varies from 1.1 to 1.8 billion[4,5] with 826 million thought to be functionally disabled due to a lack of available correction for near vision[5]

Given the sheer scale of the issue, a descriptive epidemiological approach is necessary and offers a number of clear advantages. It facilitates planning, it allows intelligent use of resources, it helps to describe disease in a useful and relevant way, it provides clues to its aetiology and it can be used to assess the impact of preventative measures and treatment at a population level.

1.2 Historical population based surveys of eye disease in the UK

The importance of recording blindness and visual impairment has been understood in the UK since antiquity. An entry in the Domesday book from the 11th century notes that 'In Warsop [near Mansfield], a certain blind man owns one oxgang in alms of the King'[6]. Medical references are rare in this context and the entry demonstrates both the relevance of the infirmity and the need for provision for those affected.

In 1843, an article in the Provincial Medical Journal, (the forerunner of the BMJ), noted that 'there are few diseases in the whole range of surgery to which the statistical method is more readily applicable than to cataract'[7]. The report went to enumerate frequency by age group in a clinic based sample of 67 individuals, concluding that 'cataract is of rare occurrence before the age of manhood, but begins to show itself frequently between the ages of 50 and 70. The few number of cases which occur after this latter period is explained by small number of individuals who attain a very advanced age.' The importance of age stratification and attrition bias in the very elderly remains a pertinent issue in modern reports.

From 1851, a column denoting whether the individual was blind, or deaf and dumb was included in the UK national census, along with name, age, sex, marital status, occupation, place of birth and relationship to the head of the household. The health column was expanded in 1871 to distinguish between

blindness and deafness and to add codes for 'imbeciles, idiots and lunatics' which at the time were separate categories for intellectual impairment[8] without the modern pejorative associations. In 1911, the age at which the infirmity occurred was added[9]. In 1920 the Blind Persons Act led to the creation of a separate register along with statutory benefits for registrees[10] and these questions were discontinued from the national census.

The first modern reports of registration statistics were compiled by Arnold Sorsby in 1950. He initially analysed a sample of 19,149 blind registration certificates (B.D.8) for the years 1933 - 1943 drawn from the population of around 76,000 registrants in England. Despite the large sample size, the initial survey was thought to be confounded by a failure to account for individuals who had since died, as well as other limitations. A further study of all new registrations made between 1948 – 1950 was subsequently performed and 19,673 further certificates examined. Results were stratified by age and sex and reported the frequency and percentages for individuals with the same cause and with a different cause for blindness in each eye. Cataract, Senile Macular Degeneration (SMR), Glaucoma and Myopia were the most common reasons for registration[11].

One of the earliest population based cross sectional surveys of glaucoma was performed for the medical research council (MRC) in 1963 by Hollows and Graham. They used an established cohort from the Rhonda Valley in South Wales aged 45-75, originally recruited to study the prevalence of various lung

diseases in miners. The investigators performed direct ophthalmoscopy and tonometry on 4,231 participants as well as Friedman visual field testing on every third subject. They reported results for rates of chronic simple, low tension, angle closure, secondary and congenital glaucoma. The authors noted that 'the diagnosis of chronic simple glaucoma is often loosely applied and the definition we use has the consent of tradition and its strict application would prevent additional confusion in the already chaotic literature of glaucoma epidemiology'. Low tension glaucoma was divided into confirmed and unconfirmed depending on whether the pressure was subsequently raised. The diagnosis of 'chronic simple glaucoma' required '(a) Glaucomatous cupping of the optic disc, (b) Visual field defects of the following types: (i) Seidel; (ii) Bjerrum; (iii) Roenne's nasal step; (iv) Tubular, (c) Pressure above or equal to, or known to have been above or equal to, 21mmHg and (d) An anterior chamber angle free of abnormal mesoderm and unobstructed by the root of the iris'[12]. They also measured facility of aqueous outflow on those with raised pressure in an effort to sort the 'ocular hypertensive sheep from the pre-glaucomatous goats'. There were 6 (0.28%) individuals with chronic simple glaucoma out of 39 (0.8%) with glaucoma and 397 (8.6%) individuals with ocular hypertension. Only 30% of those with field loss were 'under medical care'[12]. A further sample was drawn from this cohort in 1965 to investigate the association between diabetes and cataract[13]. At the time, no association was found.

The WHO program for the prevention of blindness was established in 1978 and led to the creation of Global Databank on blindness which has since become the evidence base for the development of global priorities in eye health. The first estimates of global blindness were based on reports of member states of the and heavily underestimated the prevalence. Subsequent estimates organised by region and based on survey data have improved the reliability of the data and feed in to the annual world health report[14].

Acquisition of evidence on the magnitude and causes of visual impairment and eye care services and to identify priorities and monitor progress remains the first (1) objective of the Global Action Plan for universal eye health, along with the (2) the development and implementation of integrated national eye health policies and (3) multi-sectoral engagement and effective partnership[3]. Of particular challenge, has been the acquisition of data in resource poor environments. To some extent, this has been addressed through the development of the Rapid Assessment of Avoidable Blindness (RAAB) methodology by the International Centre for Eye Health (ICEH) at the London School of Hygiene and Tropical Medicine (LSHTM).

1.3 Rapid Assessment of Avoidable Blindness (RAAB)

Rapid assessment of avoidable blindness (RAAB) surveys were developed to perform a robust, quick and relatively inexpensive determination of the causes blindness in a population with a special focus on the cataract surgical coverage, barriers to uptake of cataract surgery and outcomes after cataract surgery[15]. Briefly, a sampling frame is identified and divided into approximately 50-100 clusters. Field teams consisting of a local guide, an ophthalmic assistant and an ophthalmologist screen around 50 individuals per day within a single cluster. Distance acuity is measured in all individuals using a tumbling E chart. Those with an acuity of 6/12 or worse are tested with a pinhole and examined by an ophthalmologist to determine the main cause visual loss. Quality control is maintained through the use of trial registries, standardised methodologies, double data input and standardised computer software for analysis and reporting[16]. This approach has been very successful in the developing world, with over 300 RAAB surveys performed but it has been less successful in developed countries[17] where comprehensive eye surveys are still preferred. It is limited by its emphasis on anterior segment disease and cataract and away from diseases such as diabetic retinopathy and glaucoma where individuals can retain good acuity despite having relatively advanced disease.

1.4 Definition of visual impairment

The International Classification of Diseases 11 (2019) classifies vision impairment into two groups, distance and near presenting vision impairment[18].

Category	**Presenting distance visual acuity**	
	Worse than:	**Equal to or better than:**
0 No vision impairment		6/12 5/10 (0.5) 20/40
1 Mild vision impairment	6/12 5/10 (0.5) 20/40	6/18 3/10 (0.3) 20/70
2 Moderate vision impairment	6/18 3/10 (0.3) 20/70	6/60 1/10 (0.1) 20/200
3 Severe vision impairment	6/60 1/10 (0.1) 20/200	3/60 1/20 (0.05) 20/400
4 Blindness	3/60 1/20 (0.05) 20/400	1/60* 1/50 (0.02) 5/300 (20/1200) or counts fingers (CF) at 1 metre
5 Blindness	1/60* 1/50 (0.02) 5/300 (20/1200)	Light perception
6 Blindness	No light perception	
9	Undetermined or unspecified	
Category	**Presenting near visual acuity**	
	Worse than N6 or M 0.8 with existing correction	

Table 1.1 ICD-11 Classification of visual impairment

This classification is based on recommended by the Resolution of the International Council of Ophthalmology (2002)[19] and the Recommendations of the WHO Consultation on “Development of Standards for Characterization of Vision Loss and Visual Functioning" (September 2003)[20]. Of note is the change in ICD 11 from ‘best corrected’ to ‘presenting’ vision, emphasising both the important and widespread lack of appropriate correction in some regions.

The guidance recommends the use of the linear ETDRS scale as the de facto standard but, oddly, the criteria are reported in terms of the traditional snellen metric, decimal and US imperial scales. This is of concern because they do not necessarily have common linear equivalents. For example, the cut off for moderate visual impairment approximates to logMAR 0.5 but the precise value varies depending on the scale chosen, i.e. 6/18 snellen, 0.3 decimel and 20/70 US imperial correspond to logMAR 0.48, 0.52 and 0.54 respectively[21].

Having a clear value for moderate visual impairment is arguably of greater importance than for mild visual impairment or normal vision and it is especially troubling that corresponding values lie on either side of the logMAR cutoff value of 0.5 when rounded to 1 decimal place (dp).

If an investigator wishes to identify individuals with moderate or severe visual impairment, they could choose to include those with a logMAR acuity *greater* than 0.5 **or** *greater than or equal to* 0.5, since logMAR 0.48 will capture acuities that are *greater than or equal to* 0.5.

This is especially apparent in international comparisons. Recent studies in the UK have classified individuals with logMAR acuity 0.5 as visual impaired, while in the Blue Mountains[22] and Beaver dam eye study, only those with a vision of 20/80 (equivalent to logMAR acuity 0.6) were considered to have moderate visual impairment. To add further confusion, both studies used a 70 letter ETDRS scoring system which has since been superseded by a 100 letter system[23]. More recent studies in Australia[24] and the US[25] have largely ignored this issue by using thresholds of <20/40 (6/12) and <20/200 (6/60) for mild and severe visual impairment respectively and avoid reference to moderate visual impairment.

This inclusion / exclusion of individual with logMAR acuity 0.5 is potentially an important source of variability. Within BEAP 130 (3.7%) of individuals had a presenting acuity of exactly 0.5 in either eye, though only 31 (0.9%) had a presenting acuity of 0.5 in the better seeing eye.

1.5 Determination of the prevalence of visual impairment

Traditionally, the prevalence of visual impairment has been determined through the use of comprehensive cross-sectional surveys and cohort studies. In these, either the entire population or clustered sample is examined by eye professionals. This have been regarded as the most useful, reliable and generalizable sources of data but are often impractical or difficult to perform in the developing world and have been largely augmented by newer methodologies, including Rapid Assessment of Avoidable Blindness (RAAB) surveys which have improved the ease and speed at which reliable information can be acquired around the world.

Information can be also obtained from other sources, including hospital and pharmacy statistics, insurance records, census data and general health surveys. To be valid, the survey should meet the following criteria; (1) it should have a clearly defined population from which it draw's its sample, (2) it should use random sampling methods in order that the results can be generalised to the wider population, (3) the population should representative and not deliberately enriched with high risk individuals, (4) the sample should be large enough to provide a 95% confidence interval of the prevalence of the disease under investigation and (5) clear cut descriptions of the sampling process, the definition, the enumeration procedures, examination protocol and the data analysis should be clear from the methodology[14].

1.6 Describing causes of blindness

Description of the sampling frame and population demographic is of particular importance in eye disease as blindness can be regarded as a function of age. Different definitions, different approaches to examination and physiological differences between populations can also introduce bias and limit the generalizability of results. Finally, difference in nomenclature and categorisation can introduce additional variation and each disease has its own idiosyncrasies.

This is well illustrated by the various grading schemes for cataract and the considerable overlap with cataract and presbyopia and refractive shift. Studies on macular degeneration are often based on imaging alone without regard to acuity and there are wide variations in the assessment and definition of glaucoma. In some surveys, glaucoma is not even considered to be an avoidable cause of blindness[26].

1.7 Classifying co-pathology

Where there are multiple causes of sight loss in an individual, the convention adopted by WHO is that the cause 'most easily preventable or curable' should be described[14]. This approach is pragmatic as it focuses on maximising the benefits of treatment but is unhelpful in determining the contribution of co-pathology which is not uncommon. It is also possible to describe causes 'by eye' instead of 'by person' or the number of individuals with the same or different causes in each eye, which was the original approach taken by the medical research council in the 1950s[11]. A variation of the this method is to report the cause in each person but to assign a weighting to each cause where it is different in each eye, as was performed in the Andhra Pradesh eye study[27]. The multiple options and permutations add complexity to reporting and make comparisons across studies more difficult.

1.8 Blindness registration

In the UK, individuals can be registered as sight impaired (SI) / partially sighted or severely sight impaired (SSI) / blind with statistics are collated nationally. The most recent report from 2013, listed AMD as the largest cause, accounting for around half of registrations. This was followed by glaucoma which was responsible for 11% of SSI and 7% of SI certificates[28]. A key limitation of this data is that registration is voluntary and the criteria open to interpretation with poor intra- and inter-observer agreement among ophthalmologists[29]. Hospital based studies have shown a high proportion of eligible individuals remain unregisterd[30]. In addition, the requirement for binocular loss leads to an underestimation of prevalence, particular in diseases where the central acuity is retained till relatively late.

Within BEAP, blindness / partial sight registration were criterion for exclusion, despite this, ten individuals attended and answered 'yes' when asked if they were registered as partially sighted or blind. The registration status was doubtful in two (with macular degeneration) as they retained good acuities. In total, there were six with macular degeneration, one with myopic degeneration, one with glaucoma and one with diabetic retinopathy and one with 'other / unspecified macula disease'. This is broadly in line with what would be expected from reports of national registration data. Registration statistics for the population around the time of the study were obtained and used to estimate the disease specific total prevalence of visual impairment for the study population.

1.9 Other metrics of visual function

Visual acuity is the most common metric reported in ophthalmology but comprises only one aspect of visual function. It is also subject to variation from environmental factors, such as lighting and crowding. A decrease in luminance will lead to a decrease in acuity and this drop is disproportionately larger in the elderly[31].

Other aspects of visual function are often more relevant than acuity alone. Reduced contrast sensitivity impairs mobility[32] and the presence of glare adversely affects driving performance, especially at night[33]. The presence of the visual field defects is associated with an increased risk of a motor vehicle accident, while surprisingly, a reduction in visual acuity below the legal standard is not[34]. Similarly, reduced depth perception is a greater risk factor for falls than a drop in acuity[35].

Comprehensive evaluation of visual function has been previously attempted in an overseas population based setting. The Salisbury eye project assessed the contrast and glare sensitivity, stereo-acuity and visual fields of 2520 elderly subjects. Visual acuity was measured in normal and low luminance and these metrics were compared against self reported disability as measured using the Activities of Daily Vision Scale (ADVS) questionnaire[36]. Each metric was independently associated with disability. The project was also notable for performing objective assessments of visual function on participants. These

included tests of mobility involving rising from chair, walking and negotiating stairs, tests of daily living such as inserting a key in a lock and a plug in a wall as well as measurements of reading speed and facial recognition[37]. They found it was possible to determine cut-off points for each disability but they reported that these cut-offs varied according to the task. This led them to conclude that it would be inappropriate and unhelpful to select a single arbitrary threshold.

1.10 Visual function questionnaires and patient reported outcomes

Objective evaluation of function is not always practical or desirable and determination of subjective patient reported visual function and quality-of-life through the use of surveys or screening questions is helpful in determining levels of disability and the impact of treatment. A large number of questionnaires have been developed for this purpose. These include the Visual Functioning Index (VFI / VF-14), the Vision-related Quality of Life Core Measure 1 (VCM1), the Visual Functioning Questionnaire (VFQ-25), the Glaucoma Symptom Scale (GSS) and the Glaucoma Quality of Life – 15 (GQL-15) survey. A number of the longer questionnaires also have corresponding short versions which seek reduce the time taken to administer them by omitting unnecessary questions while minimising information loss.

These questionnaires focus on the subject's ability to complete everyday tasks and be divided into those that aim to determine general visual function and those specifically developed to assess the impact of a particular disease. Some

also include questions on the individual's subjective perception of disease and their health status.

The Glaucoma Quality of Life – 15 (GQL-15) / Glaucoma Activity Limitation (GAL-9) score assesses an individual's ability to adapt to changes in lighting and their navigational vision. These metrics are commonly associated with the peripheral visual field defects seen in glaucoma but are not always associated with a decrease in visual acuity[38]. The glaucoma symptom scale (GSS) assesses irritation and redness as well as visual symptoms including halos and blurring, commonly associated with the use of glaucoma eye drops[39].

The VF-14 includes 14 questions on the subject's ability to perform 14 vision related tasks. These include driving, reading, playing sports and board games, cooking and navigating. Tasks are assessed on a 5 point scale ranging from 'no difficulty' to 'unable to perform task'[40]. The Vision-related Quality of Life Core Measure 1 (VCM1) consists of 10 questions on subjective perception vision and it's impact; how embarrassed, lonely, sad or worried they feel about their vision, how much it impacts on their life and prevents them from doing things that they enjoy[41]. The VFQ-25 is the short version of the 51 question National Eye Institute Visual Functioning Questionnaire[42]. As with the VF-14 it includes questions on activities but in addition to these it contains questions on the individual's subjective perception of their experience, similar to the VCM1; it assesses how subjects would rate their sight, whether they worry about it and whether they are limited by it. It has been widely adopted and used as part of a

wider effort to improve patient participation in decision making and care, which has been accompanied by the development of standardised frameworks or developing and reporting patient reported measures and outcomes[43]. As with any reseach tool, there is a risk of confusion if a patient believes that they are being asked to communicate information to their clinical team rather than to collate and aggregate information at health service level.

Despite their utility, the application of even the short versions of these questionnaires is not always practical, particularly in large population based studies or when applied to frail or elderly populations or those with low vision. Participants are more likely to supportive of instruments that are short, practical and useful and are wary of forms that are long or have the appearance of a bureaucratic excercise[44]. In some population based surveys, just one or two question will be devoted to vision and visual function. These can either be an endpoint in themselves and / or as a sifting tool to trigger a further more detailed enquiry.

1.11 Prevalence of visual impairment in the UK

A literature search was performed using the keywords blindness OR low vision AND UK or England or Wales or Scotland or Ireland. The terms ‘blindness’ and ‘low vision’ were selected and mapped to unrestricted top level MeSH terms. These were combined with geographic indicators (UK / England / Scotland / Ireland) which were again mapped to top level MeSH domains. The large number of international projects undertaken by UK based researchers precluded the use of free text searches for the UK and its constituent countries. Articles were searched using the PubMed interface of the MEDLINE database.

The following search term was used; ((("Blindness"[MeSH Terms] OR "Vision, Low"[MeSH]))) AND (((((("ireland"[MeSH]) OR "wales"[MeSH]) OR "scotland"[MeSH]) OR "england"[MeSH]) OR "united kingdom"[MeSH]).

The search retrieved 421 records, which were filtered by title and abstract. References pages of relevant articles and books were also examined along with reports and proceedings from the ‘grey literature’. Studies included in the WHO Global Vision Database were identified separately. Each abstract was reviewed for relevance with the theme of visual impairment. Studies on blind certification and registration were excluded as were hospital based / case controls type studies which defined the sampling frame by the presence or absence of disease. After exclusion of duplicates and relevant papers: 11 studies identified for full review and subsequent inclusion. These are listed in table 1.2 below.

1.12 Prevalence of subjective visual impairment

In the MRC Trial of the Assessment and Management of Older People in the Community, 32,990 individuals aged 75 years and older registered in one of 106 general practices were screened using a questionnaire administered either by post or by a lay interviewer or by a nurse. Depending on randomisation, the participants went on to have a further assessment that was either universal in the 'universal' arm or triggered by items on the screening questionnaire in the 'triggered' arm. All subjects were asked to grade how easily 'they were able to read newsprint' on a three-point scale; "no difficulty," "a little difficulty," and "a lot of difficulty". They found that between 8-11% of subjects reported 'a lot of difficulty seening'[45]. Subjects undergoing a detailed assessment also had their vision acuity tested at 3m. The investigators found that there was similar proportion; 1742 (12.5%) people in the universal detailed assessment arm, had a presenting acuity worse than 6/18 as those who had reported subjective visual impairment[46].

The English Longitudinal Study of Ageing (ELSA) assessed self-rated eyesight in 6634 participants with a mean age 65.0±9.2 years by asking 'Is your eyesight (using glasses or corrective lenses; if you use them) excellent/very good/good/fair/ or poor'. Subjects were also asked 'How good is your eyesight for seeing things at a distance, like recognising a friend across the street' and 'How good is your eyesight for seeing things up close, like reading ordinary newspaper print'.

They performed a cross sectional analysis of the association between self reported eyesight and physical activity, which they categorised by both frequency and intensity. They found 700 (11%) of individuals reported that they had 'fair–poor' vision and that these subjects were over twice as likely to be physically inactive as the those who reported having excellent vision[47].

The 1958 British birth longitudinal cohort comprises everyone born in Britain in 1 week in 1958. At age 44, participants the habitual and pinhole corrected distance acuity, near vision and stereoacuity of participants was measured and they were asked to complete the VCM1 questionnaire. Out of the 8600 responders, 79 (0.9%) had VCM1 scores that suggested 'more than a little concern' about vision. However, a large proportion of these had normal / near normal visual acuities and there was some confounding with individuals with poor vision less likely to complete the VCM1 instrument[48].

In the EPIC Norfolk cohort study, monocular logMAR acuity and determined self reported vision was measured in 8405 individuals with a mean age of 68.6 years. They found that poor self reported vision was associated with falls independent of acuity. Self reported vision was determined using the question; 'How good is your eyesight for seeing things at a distance, like recognising a friend from across the street (wearing lenses or glasses if you usually wear them) ?'[49]. This is similar to the approach taken within the Bridlington project, where participants were simply asked whether they were 'happy with their vision', with responses coded as as 'yes / no'.

1.13 Prevalence of objective visual impairment

Within the Bridlington study, after the exclusion of 10 participants who stated that they were partially sighted, there were 143 (4.0%) individuals with a presenting acuity (unaided or with regular spectacle correction) of logMAR 0.5 – 1.0 in the better eye, there were 5 (0.1%) with an acuity of worse than 1.0 in the better eye out of the remaining 3539 subjects.

Visual acuity was also measured in a number other UK population-based studies, including the Child Health and Education Study (CHES)[50], National Diet and Nutrition Survey (NDNS)[51], European Eye Study – Belfast cohort (EUREYE)[52], Melton Mowbray[53], Inner London[54], North London[55] and the UK Biobank[56] studies. These are listed as in table 1.2 below along with crude prevalence estimates for moderate and severe visual impairment. The most recent report from the vision loss expert group using data from the World Health Organisation global vision databank includes age-adjusted estimates and temporal trends for the UK and other countries but rely predominantly on studies from older studies with only one study from this century included in their latest published estimates[2]. An updated meta-analysis based on the above systematic review was performed.

1.14 Meta analysis

A random effects model was used for all the meta-analyses and was stratified by inclusion or exclusion from the Global Vision Databank. Data were displayed graphically in Forest plots, with point estimates of prevalence along with 95% confidence intervals (CI) for each study. Standard weighting was applied according to study size but was not displayed graphically on the Forest plots because of the varying order of magnitude between study participant numbers. I^2 statistic values were calculated to quantify degree of heterogeneity among studies, where values of 25–50% represented moderate heterogeneity and values of >50% large heterogeneity each study on the overall prevalence was assessed. The use of Egger's or Begg's tests for publication bias was not applied as heterogeneity was expected within the sample due metholodogical differences between studies. All analyses were conducted using Stata version 14 (StataCorp), using the 'metan', 'metareg' and 'metaprop' software commands. Metaprop was used for the majority of the analysis as it is specifically designed for binomial data, allowing computation of 95% confidence intervals using the score statistic and the exact binomial method, incorporating the Freeman-Tukey double arcsine transformation of proportion, as well as allowing the within-study variability to be modelled using the binomial distribution[57].

Detailed statistics on the number of adults and children registered, as being blind or partially sighted in 2016/17 were obtained from summary datasets complied by NHS Digital from the triennial SSDA 902 return submitted by Local

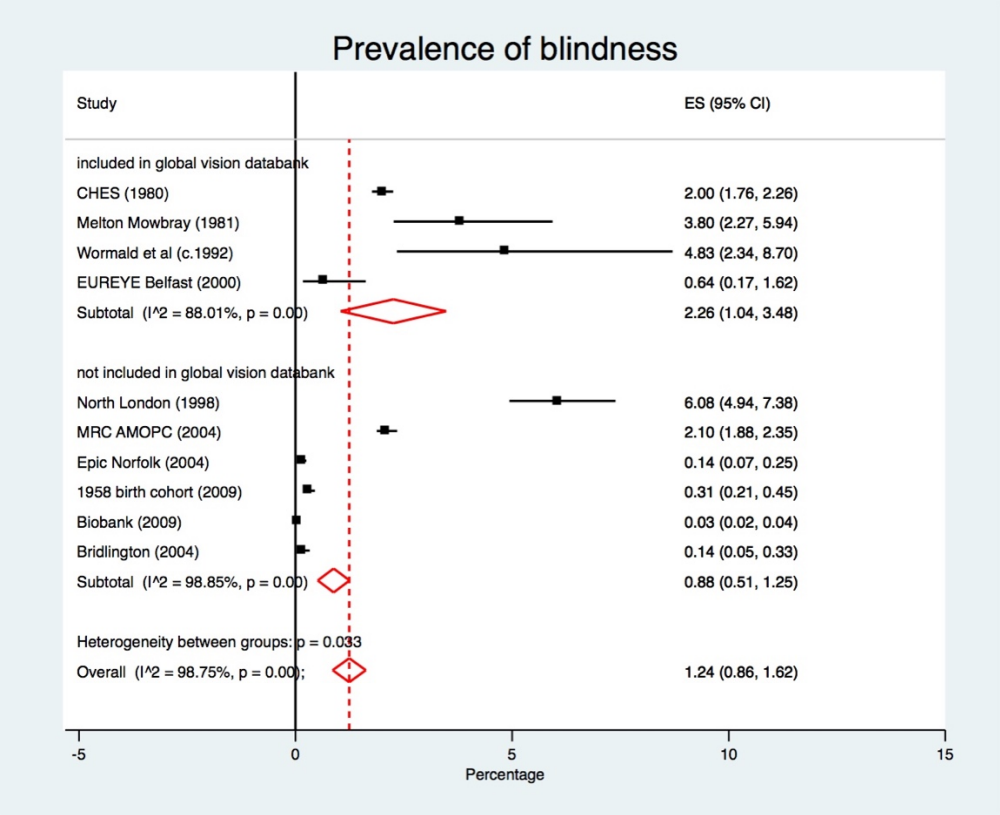
Authorities[58]. These were compared against ONS population statistics for England for mid-2016[59] to derive an estimate of the prevalence of blind / partial sight registration in individuals 65 years and older to serve as a comparator to the study data.

Of note is the high rates of blindness in some of the older studies. This is most likely due to classification artefact rather than advances in treatment. In both the CHES and Melton Mowbray older studies, individuals with a visual acuity of 6/60 were considered blind, while in more modern studies, only individuals with vision worse than this are included. The majority of studies reported vision in the better eye as a surrogate for presenting binocular acuity but the North London study only reported rates for the worse eye, explaining the high rates of visual impairment reported. However higher rates were also seen in the other London based study and it is difficult to discount the possibility that these are linked to higher levels of deprivation. Conversely, very low rates were seen in the UK Biobank study. Despite the high number of participants, the study was limited by a healthy cohort effect with high levels of recruitment of generally well subjects. While this does not limit the use of this cohort to identify longitudinal trends and associations, it does hamper generalisation to the wider population for the determination of prevalence of disease[60]. Rates of blindness were similar between the EPIC Norfolk and Bridlington eye studies but the higher rates of moderate vision impairment seen in the Bridlington cohort likely reflect the old average age of participants in the Bridlington study.

Study	Sampling method	Mean Age	Age range	Year	Number
CHES	birth cohort	10.5	10-11	1980	12,853
Melton Mowbray	population		75+	1981	474
Wormald et al	GP practice 50% random		65+	c.1992	207
NDNS	random postcode		65+	1994	1,362
EUREYE Belfast		73.2	65+	2000	629
North London	GP 2 stage cluster		65+	1995	1,547
MRC AMOPC	GP cluster randomised	81.3	75+	2004	14,600
Epic Norfolk	population	68.6	48-92	2004	8,317
1958 birth cohort	birth cohort	44.5	44-45	2009	9,253
Biobank	population<25mi test centre (5%)	56.8	40-73	2009	112,314
Bridlington	population	75	65-100	2004	3,539
CVI register	ONS / NHS data		65+	2016	55,268,067

Study	moderate vi	severe vi	mvi %	svi %	mvi cut-off	svi cut-off
CHES	900	257	7.0	2.0	≥ 6/24	≥ 6/60
Melton Mowbray	122	18	25.7	3.8	> 6/18	≥ 6/60
Wormald et al	16	10	7.7	4.8	> 6/18	> 6/36 (b1)
NDNS	119		8.7		> 6/18	
EUREYE Belfast	4	4	0.6	0.6	> 0.48	> 1.3 (3/60)
North London	273	94	17.6	6.1	> 6/18	> 6/60
MRC AMOPC	1504	307	10.3	2.1	≥ 0.5	≥ 1.4 (3/60)
Epic Norfolk	46	12	0.6	0.1	6/18-6/60	> 6/60
1958 birth cohort	98	29	1.1	0.3	0.5-1.0	≥ 1.01
Biobank	727	32	0.6	0.03	0.5-1.0	≥ 1.10
Bridlington	143	5	4.0	0.1	0.5-1.0	> 1.0
CVI register	108230	98850	0.20	0.18		

Table 1.2 Summary of UK studies on prevalence of visual impairment



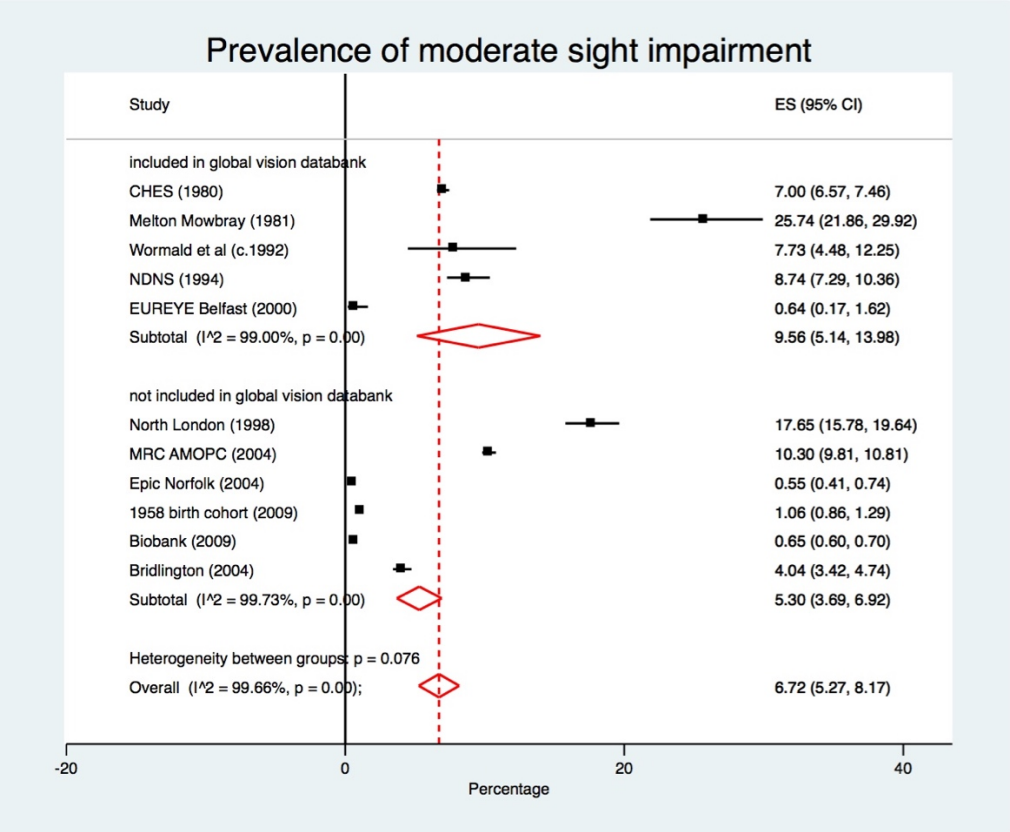


Figure 1.1 Forest Plots of the prevalence of (a) blindness and (b) moderate visual impairment in UK population based studies including summary estimates

1.15 Cataract

Cataract is the most common cause of blindness in Europe[61] and worldwide[62] and the most common reason for surgery in the UK[63]. Surgical capacity for cataract has increased substantially in recent years but there is substantial geographic variation in operation rates within the UK[64] and continued debate over adequate provision of care[65]. Accurate prevalence data is therefore critical for proper health planning.

Population studies have previously described cataract prevalence in the UK. Reidy et al, reported 30% prevalence of significant cataract in 1547 patients from North London using LOCS 2 grading but without specifying their diagnostic criteria[66] as well as a gender effect of similar size to our own. The Melton Mowbray Eye study reported an overall prevalence of 11% using LOCS 3 grading but examined a younger population of 560 individuals. Their rates for their older age groups were similar to BEAP[67].

Frost et al examined visual related quality of life and subjective visual satisfaction as well as lens grade in order to better estimate which individuals would go on to have cataract surgery[68]. They examined 1078 individuals and estimated 0-19 cataract operations per thousand would be those required for those aged 65-74. This rose to 24-89 operations per thousand for those aged over 75 years.

International comparisons are more complex. In addition to the demographic differences between populations, comparisons between studies are complicated by the use of different scoring systems and the lack of a single definition for ‘significant cataract’. Levels of severity can vary substantially with different grading methods[69] though systems have been proposed to convert scores[70,71] and standardise definitions between studies[72].

The Beaver Dam[73] and Blue Mountain[74] studies were of similar size to our study population (n>3000). Both used the Wisconsin grading system and reported similar rates of late cataract to BEAP but lower rates of previous surgery. This is not unexpected, as the threshold for cataract surgery has fallen with time[75]. The Skövde Cataract study[76] examined 565 individuals using LOCS 3 grading. They reported lower rates of significant cataract using similar criteria but excluded pseudophakes from their analysis.

1.16 Glaucoma

Glaucoma is the leading worldwide cause of irreversible blindness, attributable to at least 2% of reported visual impairment and 8% of blindness[77]. It's impact is underestimated through underreporting in the presence of significant catarct[78]. Extrapolation from glaucoma prevalence surveys have suggested that it may be responsible for twice as many cases of blindness and affects 60 million people worldwide. This is projected to rise to 80 million by 2020[78]. It is the second leading cause of blindness in the UK (after macular degeneration) and was responsible for 684 cases or 8 % of severe sight impairment registrations in 2008[79]. This issue of under reporting is compounded by the absence of a clear definition and the consequent lack of generalizable results, leading to wider problems with collation of data on prevalence and burden of disease[80].

The disease is routinely assessed through examination of the optic nerve, visual field and intraocular pressure. Assessment of the optic nerve is a measure of structure while visual field tests are a measure of function. Following diagnosis, a target intraocular pressure (IOP) will often be set and structural and functional assessment made at regular intervals. In the presence of worsening optic nerve appearance or deteriorating visual field function, a clinician will normally employ medical or surgical interventions to either achieve the target pressure set at the commencement of treatment or revise down the target pressure if it is thought that the target pressure has been set too high.

The pathogenesis of glaucoma can usefully be considered from a biomechanical view point. It is known that in glaucoma, cells in the trabecular meshwork and within the optic nerve head, including retinal ganglion cells, are all altered through pressure sensitive mechanisms. The extracellular matrix, cell membrane, cytoskeleton, and nucleus, are closely interconnected and respond to mechanical forces in a variety of ways including cross linking and alteration of gene expression [81]. At a cellular level this leads to compartmentalised retinal ganglion cell damage at the level of the lamina cribrosa, resulting in apoptosis and eventual cell death[82].

From the clinical perspective , glaucoma is conventionally defined as "a characteristic optic neuropathy, which derives from various risk factors including increased intraocular pressure'[83]. This definition evolved over the 20th century[84] and continues to be subject to scrutiny, not least due to the subjectivity inherent in the description of the optic disc and the lack of a functional correlate. The inclusion of intraocular pressure (IOP) is also controversial since it is neither necessary nor sufficient for functional loss.

A better definition for prevalence studies has been proposed comprising of 3 levels of evidence for diagnosis; 1. Veritcal cup disc ratio (VCDR) or VCDR asymmetry >97.5th percentile of the normal population together with a visual field defect compatible with glaucoma, 2. A severely damaged optic disc (VCDR >99.5th percentile of the normal population) in a patient in whom a reliable visual field was not obtainable and 3. A patient with no view of optic disc who

has an IOP >99.5th percentile of the normal population or evidence of previous glaucoma filtration surgery[85]. While this approach confines the diagnosis to those with a measurable functional deficit, it relegates assessment of the optic disc to a single parameter and ignores confounders of assessment such as race and disc size[86].

Each of the tests described has its own diagnostic characteristics and comparison is further complicated by the choice of reference standard employed. There have been some attempts to amalgamate the existing data and one meta-analysis of 40 studies comprising 48 000 patients seemed to suggest that IOP measurement is the most specific test, VF analysis the most sensitive and optic nerve head examination lies somewhere in between[87]. This analysis is limited by different definitions of glaucoma, different approaches to visual field and optic nerve examination, and by physiological differences between study populations. What is noticeable regarding the tests described and their confidence limits is the is the lack of overlap between ranges emphasising that the 3 variables are measuring different parameters in very different ways. Even within a single modality differences can often arise. A good example is the differences between results from ophthalmoscopy and disc photography[87].

Amalgamating results over time or combining results from different tests is intuitively a more robust method to guard against false positives and some attempts have been made to automate this processes, notably through the use

of Bayesian methods to create structure function maps[88] to raise pre-test probability and highlight biological concordance.

Assessment of the optic nerve head and visual fields can therefore be seen as broad surrogates for retinal ganglion cell count and function while measurement of IOP is a relatively crude gage of the biomechanical forces involved. It is therefore unsurprising that correspondence of each of tests, particularly the structural and functional changes varies greatly between individuals.

1.17 Screening / Case finding in Glaucoma

Despite the high prevalence of glaucoma in the elderly and the significant morbidity associated with late diagnosis, there is currently no screening program in the UK for glaucoma. The Wilson and Junger criteria for screening suggest that to implement such a program a disease should be well understood with a suitable and economical test and treatment, together with an identifiable latent stage and an agreed policy on who to treat[89].

With regard to glaucoma, there remain important uncertainties in all of these areas. Population based screening is not thought to be economically viable, though there is some evidence to justify targeted screening of selected groups such as those with a family history or African ancestry[90]. However, even in high risk populations, trials of screening have been hampered by poor uptake of testing and treatment with one study reporting just 69% of individuals screened positive for visual field defects went on to attend for further evaluation[91].

As a consequence, detection in the UK relies on case finding by community optometrists with sight tests freely available to everyone over 60 years as well as to those over 40 years who have a family history of glaucoma.

The current guidance from the college of College of Optometrists mandate internal eye examination during routine assessments, consisting at a minimum of direct ophthalmoscopy on an undilated eye[92]. In those at risk of glaucoma,

the guidance recommends assessment of the optic nerve head, applanation tonometry and threshold perimetry, repeated where necessary to obtain a meaningful result[93].

A 2008 Survey[94] of optometrists comprising 1264 of 1875 eligible practices reported the use a wide a range of methods to examine each of these parameters, with 25% of respondents performing direct ophthalmoscopy alone; the minimum standard set by the college of optometrists. At the other extreme 7% reported direct access to sophisticated imaging equipment including HRT, OCT and GDx. Intraocular pressure (IOP) measurement using applanation methods was performed by only 16% of optometrists with the majority (79%) using non-contact methods.

The use of non contact tonometery is permissible within the college guidance with the proviso that borderline results be rechecked with an applanation tonometer. The use of surveys to report patterns of behaviour is limited by selection and reporting bias with a tendency of more conscientious practitioners to respond to the survey and to report idealised rather than actual behaviour. In particular, optometrist will over report the frequency of which they will routinely perform IOP measurement and visual field assesment[95]. One way to overcome this is to employ a standardised patient to undergo an eye examination and recall or record the questions they were asked and the tests they performed.

In one study of routine optometric practice, an anonymous standardised patient actor was presented to 100 different optometrists[96]. The investigators found that 95% optometrists checked the actor's fundus and intraocular pressure while 35% went on to perform a visual field test as well. The purpose of one of my analysis is to determine whether this approach which focuses on examination of the optic nerve head combined with measurement of intraocular pressure is an adequate method to screen for open angle glaucoma.

1.18 Visual Field Defects

Visual field tests are important in the diagnosis of eye disease and useful indicators of function. Visual field loss has been independently associated with decreased quality of life[97–99] and an increase in falls[97,100–102]. Field tests are routinely used in the diagnosis of glaucoma where field loss is synonymous with functional change[103] and in the application of driving standards where an intact peripheral field is a key determinant of fitness to drive[104,105].

Assessing the prevalence of visual field loss within a population as well as the limitations of a common method of testing is important for health planning and disease prevention. Prevalence[97,106–110] and incidence data[111–113] have been described in previous population based studies but comparisons between studies are difficult because of demographic differences between study populations as well as wide variation in modes of testing.

The aim here is to describe the prevalence and cause for visual field loss within an elderly Caucasian population using a testing method in common use.

1.19 Intraocular Pressure

Normal intraocular pressure in healthy young adult is thought to be 12 +/- 2 mmHg, and it increases by 1 mm Hg per decade after 40 years of age[114]. There is significant diurnal variation[115] as well as a large overlap between intraocular pressures in the normal population and in those with glaucoma[90]. The use of intraocular pressure in defining disease seems initially attractive since reducing IOP in individuals with raised pressure is known to delay or prevent the onset of glaucoma[116] and to reduce the rate of progression in those with established diseease[117]. However, population based studies have shown the majority of patients with glaucoma have a screening pressure below 21 mmHg[118] and a significant proportion have a 24 hour peak IOP of less than 21mmHg[119]. There also does not appear to be any practical limit below which glaucoma cannot be said to occur. In addition, the effect of intraocular pressure on the optic nerve head appears can be modified by a complex mechanism involving of a number of biomechanical parameters within the eye[120] and structures adjacent to it[121]. Despite this, a sample of papers from the 1980s and early 90s, showed 20% of studies in Ophthalmology, American Journal of Ophthalmology, and Archives of Ophthalmology used intraocular pressure as the sole criterion for diagnosis[122].

IOP is classically measured using the Goldmann applanation tonometer (GAT) although use of non-contact and dynamic contact tonometers has been described in epidemiological studies[123,124]. This Goldmann tonometer is seen as the reference standard and infers IOP from the force required to flatten

(applanate) a predetermined area of the central cornea[125] . Unsurprisingly, readings can be affected by a number of corneal parameters including changes in central corneal thickness (CCT), structure and curvature. The influence of corneal thickness on glaucoma and IOP measurement has gained prominence since the OHTS study[126] and is based on the assumption that thinner corneas will be more deformable and will therefore record artificially low pressures. Other possibilities are that corneal thinning is an elastic response to rises in IOP[127] or that those with thin corneas have larger and potentially more susceptible optic discs[128]. While broad categorisation of CCT may be useful in helping to predict risk of conversion to glaucoma[126] in those with ocular hypertension it cannot be used to calculate a 'corrected value' of IOP[129]

A number of alternatives to applanation tonometry exist, some of which have been used population based studies. The Pascal Dynamic Contour Tonometer uses the priniciple of contour matching to reduce the influence of cornea on measurement by using a curved tonometer head with a piezo-electric sensor mounted inside. The device avoids active deformation of the cornea during measurement and the pressure is transmitted across the head and detected by the sensor directly. In one study involving over 2000 participants, the Pascal was found to be less affected by CCT than GAT but more affected by corneal curvature. Both the GAT and Pascal are limited by the need to instill topical anaesthetic eye drops prior to measurement as well as problems of cross contamination and infection control[130].

By contrast, non-contact tonometers (NCT) avoid these issues and appear more popular among optometrists[94]. One population based study reported a sensitivity and specificity of 92% for the NCT but a positive predictive power of only 14% due to the low pre-test probability of disease. The study was limited by its inclusion of a lower limit for IOP within the definition of disease[123].

The Ocular Response Analyser is a type of non contact tonometer that provides an corrected measurement of IOP based on a biomechanical properties of the cornea termed corneal hysteresis (CH). CH appears to be more important than CCT in determining inaccuracies in applanation tonometry[131]and biomechanical parameters derived from the ORA explain more of the interindividual variation in Goldmann IOP than CCT alone[132]. CH tends to be lower in those with glaucoma[133], particularly 'normal tension' glaucoma[134] and unlike CCT it has been correlated with visual field progression[135]. Corrected intraocular pressure reading from the ocular response analyzer have been shown to improve discrimination in normal tension glaucoma when compared to GAT[136].

Recent experience in the UK has highlighted the difficulties in setting an IOP criteria for institution of monitoring / treatment, particularly where these criteria are applied within the community. Physiological variation in intraocular pressure together with differences in methods of measurement compounded by a failure to account for potential confounders had led to an increase in false positive referrals[137,138] with secondary effects on service provision.

1.20 Cup to Disc Ratio

Optic neuropathies, including glaucoma lead to changes to the optic nerve head which are visible at the slit lamp[139] and which normally precede visual field loss[140]. Current consensus is that the optic nerve should be assessed at least once a year in patients with primary open angle glaucoma (POAG) and clinical examination supplemented with photos and perhaps other form of imaging[141].

Clinical measurement of the Cup to Disc ratio (CDR) is especially useful. It is the most accurately assessed disc parameter[142] and each increment increase is independently associated with a 10% increase in the risk of subsequent visual field loss[143]. It is commonly used in the diagnosis of glaucoma, normally in combination with tonometry and perimetry although in the absence of these tests, variations in CDR beyond the 99.5th percentile are by themselves sufficient for diagnosis[144]. It is also less prone to the physiological variability inherent in intraocular pressure[145] and visual field measurement[146].

Despite its utility, accurate measurement of CDR is not without difficulty. Clinical assessment is dependant on disc size and subject to significant inter[147] and intra-observer[148,149] variability and these problems extend to evaluation of disc photographs[150–152]. Automated imaging appears to be more consistent[153,154] but varies systematically to subjective clinical measures[155–161].

Due to its central role in diagnosis, accurate estimation of the difference between methods and individuals is important both for clinical evaluation and for epidemiological research.

The purpose of this analysis is to compare clinical estimates of CDR performed by optometrists at the slit lamp with those derived semi-automatically from HRT within an epidemiological population.

1.21 The Heidelberg Retinal Tomograph

The Heidelberg retinal tomograph (HRT) is a semi-automated confocal scanning laser ophthalmoscope, which utilises a 675 nanometer monochromatic diode laser as its light source. Two oscillating mirrors are used to reflect an image fixed at 15 x 15 degree on to a luminance detector. The confocal aperture limits the depth of from which reflected light is received and scans are therefore made up of a series of 2 dimensional sections.

A 3 dimensional image is generated from a set of these 2 dimensional sections with the height on the z axis calculated as the point of maximum relative luminance from the series. By progressively moving the aperture in towards the eye throughout the scan between 16 - 64 individual 2-dimensional confocal planes are aquired, each with a lateral resolution of 384 x 384 (approx 150 000 pixels).

The first plane is focused at the level of the posterior vitreous and sections are generated at a set distance of 62.5 microns apart until no further reflectance images can be usefully obtained. Relative luminance between each section is compared for each of the 150 000 pixel points on a composite 2 dimensional grid and a relative pixel height is assigned for each point depending on the interpolated point of maximum reflectance along the z-axis (optical axis). This point of maximum reflectance is thought to correspond to the position of the internal limiting membrane (of Elsnig). The theoretical resolution of HRT is

limited by the optics of the eye and is thought to consist of a transverse resolution of 10 microns with an axial resolution of 300 microns per pixel. The latest fourier domain OCTs are approaching similar levels of transverse resolution with superior axial resolution. Each scan sequence is repeated three times and 3 similar height values calculated for each of the 150,000 pixels within the 2 dimensional grid.

A geometric mean of the 3 values [personal communication with D Crabb] is assigned to each point. The standard deviation of each group of 3 height values is calculated. This is repeated for all 150 000 pixels within the 2 dimensional grid and a geographic average of the all 150 000 standard deviations is derived and termed mean pixel height standard deviation. This is the most common measure of image quality but is limited by differences in disc morphology since pixel that occur around the disc edge where there is often a wide variation in height are more likely to have a higher standard deviation if the cup has a large gradient rather than a gently sloping rim.

Given that a single wavelength of light is used, composite raw data is presented as a grey scale with marked variations in height outlined in darker shades. Output from the luminance detector is presented as a separate image utilising false colour imaging to help differentiate structures with varying levels of reflectance.

A 2 dimensional interactive grid is also provided as part of the standard output screen with a cross sectioning of the height contour along the z axis presented for each corresponding point underlying the placement of the cursor. This can help the operator to identify the relative heights of different points presented on the 2 dimensional image.

These maps allow a subjective interpretation of the position of the neuroretinal rim and cup in order for the operator to to manually mark the inner border of the edge of the scleral canal of elsnig as a pre-requisite for use of the automated diagnostic algrorithms that are provided as standard within the machine software. Once the neuroretinal rim has been outlined a reference plane 50 micrometers posterior the maculopapular bundle is defined automatically with structure anterior to this point defined as rim and structures posteriorly or distal to this defined as cup.

Delineation of the neuroretinal rim was performed by a single experienced trained operator (Ali Poostchi) using a standard 5 step methodology.

1.22 The Bridlington Eye Assesment Project

The original remit of this report was to describe the prevalence and cause of visual loss within the Bridlington Eye Assessment Project (BEAP) cohort, in a similar manner to other large epidemiological studies. A variety of approaches have been taken previously. In Blue Mountain Eye Study, the cause of visual loss was identified by a single ophthalmologist at the time of examination[162]. The Rotterdam and EPIC- Norfolk studies retrospectively reported outcomes on a small selected subset of patients identified as suffering severe sight impairment[163,164]. Investigators in the North London Eye Study simply identified disease, described it's prevalence and inferred sight loss from its presence, with causes grouped in to non-mutually exclusive categories[165]

Within BEAP, all three approaches are, to some extent, possible but describing causes of visual loss in selected subset of patients with reduced acuity or disease prevalence in the whole population are the preferred options. It is possible to describe study outcomes as reported by the examining optometrists and ophthalmologists (as in the North London Study) but it is difficult to confidently attribute causation and simply describing disease prevalence may result in undue weight been given to common outcomes of variable significance i.e. drusen / cataract. While important, categorization by visual acuity also has limitations. Visual acuity is not a universal surrogate for visual function and is

often preserved until relatively late in diseases such as glaucoma, where loss of function from visual field loss can be more significant in the early stages.

The first part of this analysis broadly describes the demographics of the population of interest and the prevalence of known major causes of vision loss; cataract, age related macular degeneration and glaucoma. The diagnosis of glaucoma varies substantially according to the criteria applied[166] and this section examines the diagnostic accuracy of the various tests and combinations of tests as applied within the project. Finally, we examine the diagnostic accuracy of a machine learning classifier designed to differentiate between normal and glaucomatous optic discs based on HRT outputs.

Chaper 2 Methodology

2.1 Background

The Bridlington Eye Assessment Project was conceived and organized by Prof SA Vernon (Consultant Ophthalmologist, Queen's Medical Centre, Nottingham) and Dr J Hillman and Dr H MacNab (General Practitioners, Bridlington) with the dual aims of identifying causes of visual loss in the elderly population and reducing the associated morbidity within the study group.

The project was well received within the community and received substantial 'grass roots' support both in terms of fundraising and awareness[167] along with broader support in the form of unrestricted grants from national and international donors.

The project is an epidemiological cross sectional survey of individuals over 65 years of age registered with two primary care surgeries comprising of 30 general practitioners within the town of Bridlington. The town was deemed especially suitable as it contained a predominantly elderly population with little migration.

The study methodology was first described when reporting the results of HRT evaluation of the optic nerve head in normal subjects[168].

2.2 Subjects

Subjects were systematically invited to attend examination in ascending numerical order of postal code. At the first visit, history and visual acuity were recorded by a study nurse and a full eye examinations was performed by one of four specially trained optometrists.

The study included all individuals over 65 years of age, registered with a General Practitioner and normally resident within the town of Bridlington. Those known to be bed-bound or demented, registered as blind or partially sighted or moving in or out of the area were excluded.

A subset of 46 individuals not eligible for the main study was recruited as pilot to test the study methods and the optometrist received periodic general feedback from the lead hospital and lead investigator over the course of the study. Subjects were enrolled between November 5, 2002 and 29th March 2006.

Informed consent was obtained from all participants, and ethics approval for study methodology was granted by Scarborough and North East Yorks Ethics Research Committee (Ref PB/RH/02/288). All methods adhered to the tenets of the Declaration of Helsinki guidelines for research in human subjects.

2.3 Medical History

At the initial assessment, data was acquired using a standard pro-forma detailing the history and examination. This is reproduced in Appendix 1.

Subjects were specifically asked if they lived alone, if they drove, if they wore reading glasses, when they last saw their own optician and if they were happy with their vision. They were asked if they had ever been registered as blind or partially sighted and if they were on a waiting list for eye surgery or if they had previously undergone any eye surgery and if so, what type and in which eye.

They were asked if they if they had glaucoma, if they instilled glaucoma drops or if they had undergone prior glaucoma surgery and if they had a family history of glaucoma. They were also asked asked if they had diabetic retinopathy or macular degeneration in either eye.

The presence or absence of other ophthalmic and relevant medical problems including diabetes, hypertension and previous stroke was also recorded.

2.4 Examination

Uncorrected, corrected, and pinhole logMAR acuities were obtained using Bailey-Lovie no. 4 Chart (National Vision Research Institute of Australia, Carlton, Victoria, Australia).

Slit lamp examination was performed by the study optometrist and comprised of structured anterior segment exam, including the cornea, anterior chamber and lens. The examining optometrist was asked to make an assessment of the anterior chamber depth and dilate the subject if felt safe to do so. Gonioscopy was performed on those with narrow angles on van Herick testing.

Following dilation, the vitreous and fundus, including optic disc, macula and periphery were examined using a 90 dioptre indirect lens and the optometrists were asked to record whether they felt that the optic disc appeared normal or abnormal according to criteria outlined by Jonas et al[169,170].

Imaging was obtained using a high-resolution digital fundus camera (TRC NW6S; Topcon, Tokyo, Japan) and confocal scanning laser ophthalmoscope (HRT II software ver. 1.4.1.0; Heidelberg Engineering GmbH).

2.5 Intraocular pressure & Visual Fields

Intraocular pressure was measured using a calibrated Goldmann Applanation Tonometer (GAT). The patient was positioned at the slit lamp following instillation of 1 drop of combined Minims Proxymetacaine hydrochloride 0.5% w/v & Fluorescein sodium 0.25% w/v to each eye. The tonometer dial was initially set to 10 mmHg and the prism applied to the cornea. The dial was slowly increased until the inner edge of the fluorescein mires met at diastole. In patients known to have astigmatism of greater than 3 dioptres the prism meridian was adjusted in line with manufacturer instructions. Where there was any uncertainty over the reading, a further two readins were taken twice and the average of the three results recorded. CCT measurement was performed by ultrasound pachymetry (Tomey SP-3000 Pachymeter, Tomey Corporation, Nagoya, Japan).

A Henson perimeter (Henson Pro 5000) with software version 3.1.4 (Tinsley Instruments, Croydon, UK) was used visual field testing in all participants. A single-stimulus, supra-threshold, central 26-point test was presented and this was automatically extended to a 68-point test if a defect was detected. The software automatically classified outputs as normal, suspicious or abnormal. For the purposes of this analysis, any defect including those classified as suspicious were treated as abnormal. The visual field output from the first visit was available during hospital follow up and normally supplemented with results from a full threshold Henson test.

Results from the screening visit and hospital follow up, including visual field printouts and fundus images were reviewed by a single fellowship trained glaucoma subspecialist (SAV) who classified the defects and acted as final arbiter. Where a defect disappeared on repeat testing or where no clear cause for was found, it was classified as a test artefact. In all other cases, the cause was identified and recorded.

It was deemed impractical to mask the optometrists to IOP readings but they were asked not to examine the output of the visual field test prior to their assessment of the optic disc. Similarly, all referral decisions were made prior to completion of fundus imaging and automated diagnostic outputs from the HRT were not available during data acquisition.

2.6 Optometrist training

Each optometrist spent 3 days receiving individual clinic based from a single fellowship trained glaucoma sub-specialist (SAV). Training comprised of both talks and slit lamp teaching with a special emphasis on disc assessment and identification of glaucoma. Similar interventions have been described elsewhere for the purpose of improving optometric detection of glaucoma either in the community[171] or through community based referral schemes[172].

2.7 Hospital referral

Those with new or unexplained ocular pathology including raised intraocular pressure or a visual field defect were automatically referred or re-referred to the hospital eye service for further assessment. Patients sent to the hospital eye clinics were seen by a senior ophthalmologist at least once and outcomes were recorded at each visit in a prospective longitudinal manner until a definitive diagnosis had been established. Subjects already under the care the hospital eye service were identified as such and the outcomes similarly recorded.

Following the initial optom visit, 822 (23%) subjects were referred and 215 (6%) were re-referred to the hospital eye service for assessment. 331 (9%) were referred to their own optometrist for early refraction because they had reduced vision thought likely to respond to optical correction. 2058 (58%) were discharged to their own optometrist for routine review and 100 (3%) were referred to their GP.

Hospital attendance records were examined to minimize loss to follow up, either from protocol breaches, where no outcome was recorded, where patients should have been referred but were not or where they were referred via alternative pathways. In addition to the 1035 patients referred/re-referred to the hospital eye service, records of a further 215 were examined.

Data from hospital outcomes was copied to the study administrator following hospital visits and hospital records were reviewed 5 years following the end of study recruitment. Much of this work was unfunded and so pragmatic approach was taken to acquire the relevant information in collaboration with the medical records department in Bridlington Hospital. Temporary accreditation was provided to a single investigator (Ali Poostchi) who was able to retrieve data from a variety of paper based and electronic sources held within the project database and the records department of Bridlington and Scarborough Hospitals.

Where data from secondary examination was not available in an individual who was referred or eligible to be referred as part of the study protocol, the results of the original optometric examination including fundus photos but excluding HRT images were reviewed by a panel of 3 ophthalmologists (Craig Wilde, Ali Poostchi and Stephen Vernon) and opinion given on the information available. Where there was a lack of consensus, the opinion of the most senior ophthalmologist (SAV) was used.

2.8 Data types

4 types of information were acquired at the initial visit; directed history and slit lamp examination, visual field test output from Henson Pro, HRT images of the optic nerve head and fundus photographs.

A paper pro forma was used to record findings from the history and examination. Visual field output from both eyes was printed on a single sheet of A4 paper and attached to the subject's pro-forma with an electronic copy retained on the machine.

HRT images were stored electronically as e2e files, while Fundus photographs were saved as jpeg images. For patients referred to hospital, a separate outcome sheet was used to report findings from the hospital visit. This was sent to the study administrator along with a copy of the clinic letter.

2.9 Electronic data entry

Data from pro-formas was transcribed on to an excel worksheet by a single investigator dedicated to the task with a single row used to record entries for each study participant. Entry fields were unrestricted and any input was valid. Unclear or questionable entries on the pro-forma were reviewed by a single fellowship trained glaucoma subspecialist (Matthew Hawker) before being entered. The original data file was titled BEAPrawdata.xls

Records from hospital follow up were subsequently acquired and entered by other project collaborators. Changes made to subsequent iterations of the study databases were not performed in a consistent manner and could not be confidently tracked subsequently, despite extensive attempts to do so. Following several failed attempts to identify, standardise and track these changes, a decision was made to discard these databases and outputs. The original excel spreadsheet which recorded outcomes from the initial study visit as well limited information from hospital visits was used as a template and a bespoke coding system developed and applied to consistently categorise results from hospital visits. Free text entries remained available where outcomes defied clear categorisation. Data from hospital visits and other sources was entered initially from paper records held locally and subsequently from records held in variety of formats in Bridlington and Scarborough.

Modifications to this new research file were tracked through 10 versions to improve consistency of reporting and to facilitate import in to statistical software (Stata versions 12 and 14). Subsequent modifications including data cleaning and recoding were made using Stata do file codes which were far easier to track and audit. A copy of the version log is reproduced in Appendix 2.

The original data set included of 128 observations on 3590 individuals. This comprised of 98 variables obtained from initial optometric assessment and 30 variables describing subsequent assessment within the hospital eye service, if applicable. This was expanded to 155, then later 165 observations, when it was judged necessary to recode hospital outcomes as described to improve accuracy and minimize attrition. In addition to the core dataset, a sub-analysis of images obtained from fundus photographs and HRT led to the identification of additional variables. Work by another researcher (Craig Wilde) undertaken to determine the prevalence of macula degeneration led to the creation of 23 variables, while analysis of HRT output yielded approximated 150 separate outputs.

Where records were derived from other databases and subsequently combined, records were matched against first name, surname, study number and date of birth before integration. Mismatches were identified and resolved prior to integration and rechecked after merging files.

2.10 Data validation

Data validation checks were performed at every stage to identify and minimise duplication and input errors. Following entry of the first batch of proformas (>200 records), manual checks were performed on 10% of records and revealed a transcription error rate of 1%.

Following completion of database entry, a range checks were performed to identify errors. These included identification and review of outlier data, symmetry checks and cross tabulation of related variables. Examples of this included examination of CCT values below 400 or above 650 micrometers, comparison of average values and ranges between left and right eyes and cross tabulating medication use and diagnosis to ensure patients who reported use of drops had a diagnosis attributed to them.

Wherever possible, automated methods were used to categorise and recode the data in preference to manual coding. This generally involved the generation of new variables from existing data using set criteria, e.g. categorisation of age groups using the following stata code;

```
egen agegrp=cut(examage), at(65,70,75,80,85,105) label
```

This line of code takes the variable for age at time of the examination (examage) from which it generates a new categorical variable (agegrp) which codes the participants into the following age categories, 65-70, 70-75, 80-85, 85-105.

The advantage of this approach is that it avoids transcription errors. The disadvantage is that an error in the analysis code is then propagated through the whole dataset. To avoid this, validation checks were performed following the generation of each new variable, e.g. after generation of variable 'agegrp', the minimum and maximum values were compared with the following stata code;

```
table agegrp, contents(freq min examage max examage)
```

This line of code generates the following table;

agegrp	Freq.	min(examage)	max(examage)
65-	860	65.01027	69.99863
70-	1,089	70.00684	74.98152
75-	830	75.0089	79.98905
80-	548	80.01643	84.97741
85-	227	85.00753	100

table 2.1 minimum and maximum values for age at examination in each age group category

Coding was performed in Stata by default as the programme was more flexible and more capable than excel and allowed the generation of code / programme files which could be used to track, modify and reproduce changes to the both the database code and analysis code with ease. By contrast, manual coding generally involved the creation of a new column in excel where data from

various sources including sometimes the spreadsheet would be entered. This was much more difficult to audit. Occasionally there was some overlap between methods and this allowed for direct comparison between them.

For example, both manual and automated coding were applied to categorisation of AMD entries for worst eye. In the manual method, a new column labelled ‘worst eye AMD’ was created in excel immediately after the two columns for right and left eye AMD grade. A single investigator (CW) looked at the codes for the right and left eye and entered the value for the worst of the two eyes in the ‘worst eye AMD column’. In the automated method, stata code was simply written used generate the variable ‘wrott’ which was defined as the worst of the value of two eyes where AMD for at least one eye was available.

Out of 3536 entries, 71 were found to be discordant between the two methods. When checked, all 71 discrepancies were attributed to human error during data entry, corresponding to a manual error rate of 2%.

Participants who attended the screening visit on more than one occasion were identified by cross checking self reported duplicated visits (10), first names and surnames (7) and dates of births (6). 46 duplicated study numbers were identified using these methods and duplicates removed.

2.11 Inclusion criteria

The original study protocol excluded individuals under the age of 65, as well as those who were bed bound or in residential care and those registered partially sighted or blind. Despite this, a number of ineligible individuals were examined and entered into the excel spreadsheet either as test subjects or exclusion failures. While age criteria was applied during data analysis, it was subsequently not felt useful to exclude those who had been registered partial sighted / blind for all analysis. After removing those under 65 years (31 subjects) and those who attended more than once (7 subjects), 3549 unique subjects remained eligible for analysis.

2.12 Missing data

For the initial optometric visit, basic demographic data, i.e name, gender, date of bith, date of examination and study number was available for all individuals.

For other variables, observations were not recorded for between 0.08% (Lids normal right) and 2.08% (Left post sub caps grade) of participants. Very limited data was available for the first 30 subjects but no real pattern was detected for the other missing data points.

Visual acuity was measured unaided, with glasses and with pinhole. A very small proportion of individuals did not have any measurement of visual acuity (right eye 0.2%, left eye 0.62%) but a much larger proportion (30% right and left) did not have a pinhole acuity.

Wherever possible and appropriate, complete case analysis was performed though imputation for missing values was considered.

2.13 Cataract

Lens grading: The lens was assessed by the examining optometrist at the slit lamp following dilation and graded according to LOCS3 system with reference to standardised photographs[173]. The optometrists performing the grading had been trained and assessed to be competent by an experienced consultant ophthalmologist experienced in the use of the LOCS grading system (SAV). Lens opacities were graded on a decimilised scale in 0.1 increments which ranged from 0-5.9 for Cortical and Posterior Subcapsular changes and from 0 - 6.9 for Nuclear Colour / Opalescence.

Criteria for Significant Cataract: To determine what grade of cataract could be considered significant, we reviewed the status at the study visit of all eyes selected for surgery and determined the mean LOCS 3 grade for each subtype when it occurred in the absence of significant grades of other types of cataract. We found the average grade of 'pure' clinically significant cataract to be 4.2 for nuclear sclerosis, 2.9 for cortical and 1.7 for posterior subcapsular cataract. Significant cataract was therefore defined as ≥ 1 of the following lens scores; nuclear sclerosis > 4, cortical > 3 or posterior subcapsular ≥ 2. Among all individuals with significant cataract involving one or more subtypes, we found that age, visual acuity and perceived dissatisfaction with vision were predictors for referral for surgery

2.14 Photographic grading for AMD

Note; Age Related Macular Degeneration This section was completed in collaboration with Dr Craig Wilde (CW), who performed the initial literature review, image grading and drafted the manuscript, in press. The candidate (AP) performed a second literature review, managed the study database, integrated it with the image grading dataset, performed the exploratory and main statistical analysis and made critical revisions to the published manuscript from which this section is adapted.

A single ophthalmologist (CW) trained in image grading at the Central Angiographic Reading Facility (CARF), Belfast performed grading all photographs using definitions and grids as described in the International Classification System for AMD[174].

Grading was masked with the grader unaware of the age, sex and medical history of subjects. A circle with a diameter of 6000μm is centred on the fovea and features of ARM and AMD are recorded. The grid consists of 3 concentric circles with radii of 500, 1500 and 3000μm, with 4 radial lines angled at 45 and 135 that divide the grid into 9 subfields. Drusen were categorised by size, homogeneity and outline[174]. Pigmentary irregularities were classed as hyperpigmented or hypopigmented or both. GA was defined as a sharply demarcated area of RPE loss that was at least 175μm in diameter that was roughly round or oval in shape, with at least two of the following features: scalloped edges, visible choroidal vessels that are more prominent than in the surrounding areas and well defined margins in-keeping with the clarity of the

fundus photograph. Eyes were deemed to have nAMD if within the grid there was: definite RPE detachment, haemorrhagic or serous and /or subretinal or sub-RPE haemorrhages not associated with any other vascular lesion and/or intraretinal, sub-retinal or sub-RPE glial tissue and/or subretinal or sub-RPE neovascular membrane as characterised by a grey/yellowish discolouration. If any of these features occurred directly adjacent to and contiguous with the optic disc then it was described as peripapillary choroidal neovascularisation (CNV). All questionable lesions and all lesions that were graded as GA, nAMD or peripapillary CNV were reviewed by a fellowship trained retinal sub-specialist with expertise in image grading (WMA). Where conflicts in grading occurred, images were sent to CARF for arbitration grading. Where the possibility of other diease, including diabetic retinopathy, pathological myopia, chorioretinitis or previous therapeutic laser existed, this took precedence and the eye was not graded as having AMD. The Rotterdam grading system has been described previously and consists of five exclusive stages (0-4). For quality control, 1 in 10 right eye images from the BEAP database were randomly selected and sent to the CARF in Belfast for secondary masked grading by a certified grader.

Grade	Description
0a	Normal-no signs of AMD at all
0b	<10 hard drusen <63µm in size
1a	≥10 hard drusen or any soft distinct drusen ≥63µm
1b	Pigmentary abnormalities only, or with hard drusen 63µm in size, no soft drusen
2a	Soft distinct drusen ≥125µm in size or reticular drusen only
2b	Soft distinct drusen ≥63µm in size with pigmentary abnormalities
3	Soft indistinct drusen ≥ with pigmentary abnormalities
4a	Geographic atrophy
4b	Neovascular AMD
4c	Peri-papillary neovascular CNV
7	Other macular disease
8	No image available
9	Ungradable image

table 2.2 Modified Rotterdam AMD grading scale

2.15 Diagnosis of Glaucoma

Glaucoma was defined in three ways;

1. Incident clinical diagnosis by Hospital Eye Service
2. Enhanced retrospective diagnosis at time of first study visit, with the benefit of hindsight from longitudinal results, and
3. ISGEO definition;

Category (1) CDR ≥ 97.5th percentile + glaucomatous VF defect

Category (2) CDR ≥ 99.5th percentile + no field

Category (3) no field / disc view but other evidence

The International Society for Geographical and Epidemiological Ophthalmology (ISGEO) classify glaucoma according to three levels of evidence[175];

Category 1 indicates structural and functional damage with CDR or CDR asymmetry > 97.5th percentile and a definite visual field defect consistent with glaucoma, or a neuroretinal rim width reduced to <0.1 CDR (between 11 to 1 o'clock or 5 to 7 o'clock) that also showed a definite visual field defect consistent with glaucoma

Category 2 described patients who had advanced structural damage (CDR / CDR asymmetry > 99.5th percentile) with field loss unproven due to an inability to complete the field test.

Category 3 diagnosis describing patients who are unable to complete a field test and in whom there is no view of disc but who have; (A) VA <3/60 and the IOP >99.5th percentile, or (B) VA <3/60 and evidence of glaucoma filtering surgery, or records confirming glaucomatous visual morbidity.

In previous surveys, the 97.5th and 99.5th percentile values have been equivalent to CDR 0.7 and 0.7-0.8 respectively. The corresponding values for CDR asymmetry range from 0.15-0.2 for the 97.5th percentile and 0.3-0.32 for the 99.5th percentile. Within BEAP, estimation of the vertical cup to disc ratio was performed at the slit lamp by the examining optometrist, who also assessed whether the disc appeared abnormal according to the criteria developed by Jonas et al[169,170]. The 97.5th percentile values for all eyes with a normal screening field was CDR 0.75 and CDR asymmetry 0.3. The corresponding 99.5th percentile values were CDR 0.8 and CDR asymmetry 0.5

The hospital diagnosis of glaucoma was made following an outpatient visit by a fellowship trained consultant ophthalmologist with access to the optometrist visit proforma but not the HRT / fundus imaging. The enhanced retrospective diagnosis of glaucoma was made using data from the incident optometric examination together with longitudinal results from the subsequent hospital visits. There were 345 individuals who were deemed to be at risk and who were followed for a median of 5.2 years. This diagnosis was made by a panel of 3 ophthalmologists including a senior glaucoma subspecialist (SAV) who acted as final arbiter.

2.16 Shape Abnormality Score and Abnormal Disc Score

We developed a MATLAB based machine learning classifier to help differentiate between normal and abnormal optic discs based on validated datasets from Manchester and Halifax. We have described this software previously[176] but briefly the program transforms morphological features of the optic disc from the HRT datafile (e2e) into a wavelet coefficient. Principal component analysis is then used to identify the features that best discriminate between disc types, assigning common patterns to an image space. When applied to a novel disc image, the program uses a Gaussian process to classify the disc as either normal or abnormal and assigns a probability to each possibility. The program also produces a probabilistic score of disc abnormality based on how similar or dissimilar the image under consideration is to the features it recognises as defining a normal or abnormal optic disc. We termed this output, the Abnormal Disc Score (ADS) since it described variation from what could be considered to be a typical normal or typical pathological optic disc.

2.17 Statistical Analysis

Outcomes were initially examined graphically and through the use of summary tables. Associations between groups were explored through the use of unpaired t-tests for continuous variables and chi squared for discrete. Where necessary, results were stratified using Mantal Haenzel methods.

For continuous outcomes, linear regression was used for multiple variable analysis, while logistic regression was used for categorical outcomes. Both models were computed using a step wise approach with each relevant additional variable added sequentially and the model re-checked for change.

The use of generalized linear mixed models (GLMM) and population-average (marginal) modelling using the Generalized Estimating Equations (GEE) approach has been advocated by some[177] and was considered but is limited by it's analytical complexity[178]. A key advantage of these is that they can be used to model both fixed and random effects, as well as marginal effects. They have flexible framework in specifying parameter distribution and are capable of handling unbalanced data. The advantage of using linear / logistic regression is that they are easier to use and can be cross checked against simpler models. They also make comparisons to previous studies more straight forward. A sensitivity analysis on the cataract data showed only a modest improvement in the precision of confidence intervals that was not offset by scope for error in

model specification. We adopted the convention of previous epidemiological studies in reporting results by person rather than eye[178].

To facilitate comparisons between HRT and optometrist assessment, we examined unadjusted CDR as a continuous variable and CDR rounded to 1 dp as a categorical variable. CDR is conventionally measured and reported to 1 decimal place (dp). Despite this, approximately 10% of clinical measurements were recorded to 2dp (invariably +/- 0.05). Measurements made with the HRT were also recorded to 2dp but along a continuous linear scale.

We used interclass correlation coefficient (ICC) and Lin's concordance correlation coefficient to measure agreement between continuous variables and calculated weighted kappa for categorical variables. Results for ICC were subsequently omitted due to similarity with concordance correlation coefficient which was judged to be a more robust measure[179].

Direct assessment of inter – rater agreement between optometrists was not possible because each optometrist saw a different group of patients. However, the groups seen by each optometrist were similar and we were able to compare clinical and automated CDR assessment using the HRT across the 4 optometrists. Results for right and left eyes were calculated separately and found to be broadly similar. Results for right eye only are presented for the HRT analysis.

To facilitate comparison of crude measures we recoded GPS probabilities in to categories using the conventional cutoffs of <0.28 for normal scans, 0.28-0.65 for borderline results and >0.65 for abnormal results. Cutoffs for SAS were chosen to facilitate comparison with other measures and were selected after examination of unadjusted ROC curves. SAS results of <0.3 were considered normal, 0.3 – 0.71 were classed as borderline and >0.7 were considered abnormal. Original continuous outputs were used for all other analysis.

We used the method described by Alonzo and Pepe to examine covariate effects on receiver operating characteristic (ROC) curves[180] using nonparametric methods to explore single covariate effects and parametric methods for the final model. Maximum likelihood Probit analysis was used to identify significant covariates and to graph covariate effects on ROC curves in the final adjusted model. Bootstrap methods were used to estimate linear covariate effects and to derive bias corrected confidence intervals for the adjusted Areas Under the Curve (AUC). All data was analysed with Stata v14 (Stata Corp, Tx).

Chapter 3 Results

3.1 Non-Attenders

Information on the age, gender and Jarman score of individuals within the sampling frame who did not participate in the project but were eligible to do so was retained.

On average, these individuals were 2 years older, (75 vs 73yrs), with a slightly reduced average Jarman score (-3.92 vs -1.75) corresponding to slightly higher levels of deprivation, which was judged to be clinically insignificant. The age difference was significant for younger ages but disappeared in groups over 80yrs old.

Age is one the variables used to calculate Jarman score and so the weak association between attendance and deprivation, as measured by the Jarman score could have been confounded by the age difference between groups.

However, the association persisted after correcting for age using both Mantel-Haenszel estimates and logistic regression, with an adjusted odds ratio of 0.99 (95% CI 0.987-0.994, $p<0.001$).

There were no significant differences in gender between groups.

3.2 Subjects, Age and Gender

After removing those under 65 years (31 subjects) and those who attended more than once (7 subjects), 3549 unique subjects remained eligible for analysis. The study population had an average 75yrs (sd 6yrs, range 65-100yrs) and a slight female preponderance 56:44.

35 (1%) of patients were waiting for treatment from the eye department at the time of examination

Within BEAP, blindness / partial sight registration was a criterion for exclusion, despite this, when asked if they were registered partially sighted or blind, 10 (0.3%) individuals reported that they were partially sighted, 3 were unsure and 3500 stated that they were not.

The registration status was doubtful in two (with macular degeneration) as they retained good acuities. In total, there were six with macular degeneration, one with myopic degeneration, one with glaucoma and one with diabetic retinopathy and one with 'other / unspecified macula disease'.

3.3 Optometrist Visit Outcome and Data Available

table 1.1a Disposal decision by study optometrist versus number of data sources for each individual					
	Number of secondary data sources available				
Disposal	0	1	2	3	Total
No outcome reported	14	12	0	0	26
%	53.85	46.15	0	0	100
Routine review by own optom in 12m	1,975	76	4	0	2,055
%	96.11	3.7	0.19	0	100
Referred to own optom for early refraction	311	20	0	0	331
%	93.96	6.04	0	0	100
Referred to Hospital Eye Service	29	742	48	3	822
%	3.53	90.27	5.84	0.36	100
Re-referred to the Hospital Eye Service	14	172	26	3	215
%	6.51	80	12.09	1.4	100
Referred to GP	89	10	1	0	100
%	89	10	1	0	100
Total	2,432	1,032	79	6	3,549
%	68.53	29.08	2.23	0.17	100

Table 1.1b Data source versus subsequent attendence in Bridlington Hospital					
Secondary data sources	Outcome Code	No further HES visits	Post study visit	Total	
BEAP Outcome Form	1	46	639	685	
	%	6.72	93.28	100	
Letters retrieved by secondary investigator (	2	2	107	109	
	%	1.83	98.17	100	
Printed letters retrieved seperately	3	7	94	101	
	%	6.93	93.07	100	
Hospital Notes	4	1	71	72	
	%	1.39	98.61	100	
Hosptial electronic records	5	7	241	248	
	%	2.82	97.18	100	
No activity found	6	120	7	127	
	%	94.49	5.51	100	
Various sources following protocol failure	7	4	8	12	
	%	33.33	66.67	100	

table 3.1 Outcomes of screening visit and data sources for hospital visits.

The table above displays a summary of patient disposals following the end of the initial study visit and sources of information on study participants. This included, hospital notes, hospital letters, electronic copies of records and study outcome pro-formas

3.4 Last visit to own optometrist

More than half the population had seen their own optometrist within the last year but 5% had not seen one within 5 years and 14 individuals stated that they had never seen an optometrist. Other results are listed in table 3.2

			agegrp			
visitoptom	65-	70-	75-	80-	85-	Total
<1yr	433	555	476	328	138	1,930
	51.18	51.72	57.91	60.52	61.06	55
1-2yr	259	325	216	143	54	997
	30.61	30.29	26.28	26.38	23.89	28.41
2-5yr	105	139	104	49	24	421
	12.41	12.95	12.65	9.04	10.62	12
>5yrs	49	54	26	22	10	161
	5.79	5.03	3.16	4.06	4.42	4.59
Total	846	1,073	822	542	226	3,509
	100	100	100	100	100	100
tab visitoptom agegrp, col						

table 3.2 last visit to own optometrist by age group

3.5 Living alone

Participants were questioned regarding their home circumstance and 1109 (32%) of subjects reported that they lived alone. There was some speculation that it might be possible to infer home circumstance from subject surnames. This was attempted for the purposes of cross validation and potentially to facilitate cluster analysis with each household treated as a separate cluster but the large number of common surnames e.g Smith, Walker, Taylor, etc... precluded any meaningful result. 796 subjects had unique surnames and 986 had surnames that were duplicated once only. The remainders were duplicated more than once.

3.6 Diabetes, Hypertension and Stroke

358 (10%) of individuals reported that had been diagnosed with diabetes. 2 subjects stated that they were borderline diabetic and 1 reported that he was still under investigation. These 3 subjects were recoded as 'missing'.

The majority of subjects had type 2 diabetes with only 2 individuals having been diagnosed with type 1 diabetes (personal communication with J Hillman). The prevalence of self reported hypertension was 48% and the prevalence of previous stroke was 9%. As expected, the prevalence of both increased with age.

		Age group				
	65-	70-	75-	80-	85-	Total
Diabetes						
No	759	980	742	496	205	3,182
%	88.67	90.24	89.83	91.01	91.11	89.94
Yes	97	106	84	49	20	356
%	11.33	9.76	10.17	8.99	8.89	10.06
Total	856	1,086	826	545	225	3,538
	100	100	100	100	100	100
Hypertension						
No	509	569	388	250	97	1,813
%	60.09	52.98	47.26	46.13	43.5	51.7
Yes	338	505	433	292	126	1,694
%	39.91	47.02	52.74	53.87	56.5	48.3
Total	847	1,074	821	542	223	3,507
	100	100	100	100	100	100
Previous Stroke						
No	794	992	737	477	190	3,190
%	93.63	92.45	89.55	87.68	84.44	90.81
Yes	54	81	86	67	35	323
%	6.37	7.55	10.45	12.32	15.56	9.19
Total	848	1,073	823	544	225	3,513
	100	100	100	100	100	100

table 3.3 self reported of diabetes, hypertension, previous stroke by age & sex

3.7 Past Ophthalmic History

		Age group				
	65-	70-	75-	80-	85-	Total
Glaucoma						
No	827	1,046	794	510	204	3,381
%	97.99	97.21	96.71	93.75	90.27	96.3
Yes	17	30	27	34	22	130
%	2.01	2.79	3.29	6.25	9.73	3.7
Total	844	1,076	821	544	226	3,511
	100	100	100	100	100	100
AMD						
No	835	1,050	789	503	212	3,389
%	98.93	98.68	96.45	93.32	95.07	97.16
Yes	9	14	29	36	11	99
%	1.07	1.32	3.55	6.68	4.93	2.84
Total	844	1,064	818	539	223	3,488
	100	100	100	100	100	100
Diabetic Retinopathy						
No	842	1,069	819	542	224	3,496
%	99.64	99.44	99.76	99.63	99.12	99.57
Yes	3	6	2	2	2	15
%	0.36	0.56	0.24	0.37	0.88	0.43
Total	845	1,075	821	544	226	3,511
	100	100	100	100	100	100

table 3.4 Age stratified prevalence of self reported glaucoma, AMD and diabetic retinopathy (DR)

3.8 Refractive error

There was near universal use of glasses with 97% of the population reporting their use for reading and 79% of the population reported their use for distance correction. Vision with and without glasses ranged from -0.2 to count fingers.

3.9 Subjective self reported satisfaction with vision

When asked if they were 'happy with their vision' 24% of subjects said that they were not. Vision in the better eye in this group ranged from -0.2 to CF, with average vision of 0.23 compared to 0.12 in subjects who were happy ($p<0.001$).

Satisfaction of vision is a key dependant variable which was used within logistic regression analysis to assess the impact of cataract and AMD on subjective quality of life.

3.10 Visual Acuity

Purpose; to describe the prevalence of visual impairment

Visual acuity was measured unaided, with glasses and with pinhole. Average best acuity unaided or with glasses in right eyes was 0.27, (sd 0.56, range -0.3 to NPL) and 0.28 for left eyes (sd 0.59, range -0.3 to PL), this improved to 0.2 for both right and left when excluding those with vision worse than Logmar 1.0. When excluding those who were subsequently referred for early refraction, this improved further to 0.19 for both eyes. Similar results were obtained when we used the geometric mean to minimize the effect of extreme values. We calculated geometric average acuity of 0.21 for both right and left.

The average best-corrected acuity when including pinhole vision was 0.14 in both right and left eyes (in those with vision of 1.0 or better).
As expected, visual acuity was found to worsen with both increasing age and lens opacities.

1546 individuals had an unaided / aided with glasses vision of 6/12 or worse in either eye and 624 individuals had a vision of 6/12 or worse in their better eye, of whom 324 had vision between 6/12 and 6/15 in their better eye. Of the remaining 300, 36 were thought to have reduced vision due to uncorrected optical error and were referred to their own optometrists for early refraction.

		right eye				
		normal	mild	moderate	blind	Total
left	normal	2,013	293	105	66	2,477
eye	mild	302	235	91	22	650
	moderate	113	97	108	18	336
	blind	35	19	17	5	76
	Total	2,463	644	321	111	3,539

table 3.5 Visual impairment (VI) by eye using WHO ICD-11classification

	freq	%
normal	2,927	82.71
mild	464	13.11
moderate	143	4.04
blind	5	0.14
Total	3,539	100

table 3.6 Visual impairment (VI) by person using better eye

	freq	%
Cataract	66	44.59
Refractive error	22	14.87
Posterior capsular opacification	5	3.38
Geographic Atrophy (dry AMD)	9	6.08
neovascular AMD (wet AMD)	7	4.73
Corneal scar	2	1.35
Macular hole	2	1.35
Glaucoma	1	0.68
Other	34	22.97
Total	148	100

table 3.7 Cause of visual impairment (VI) by person using better eye

3.11 Cataract

Purpose; to describe the prevalence of cataract and relevant associations

Prevalence Tables and Graphs

Rates of significant cataract and previous surgery are presented in table 1. The proportion of individuals who had undergone surgery prior to the study rose steeply after the age 80 (figure 3.1). Age stratified prevalence rates for LOCS 3 grade rounded to the nearest positive integer are presented in table 3.8.. The average density of all types of cataract increased with age but appeared to plateau after the age of 80 (figure 3.2).

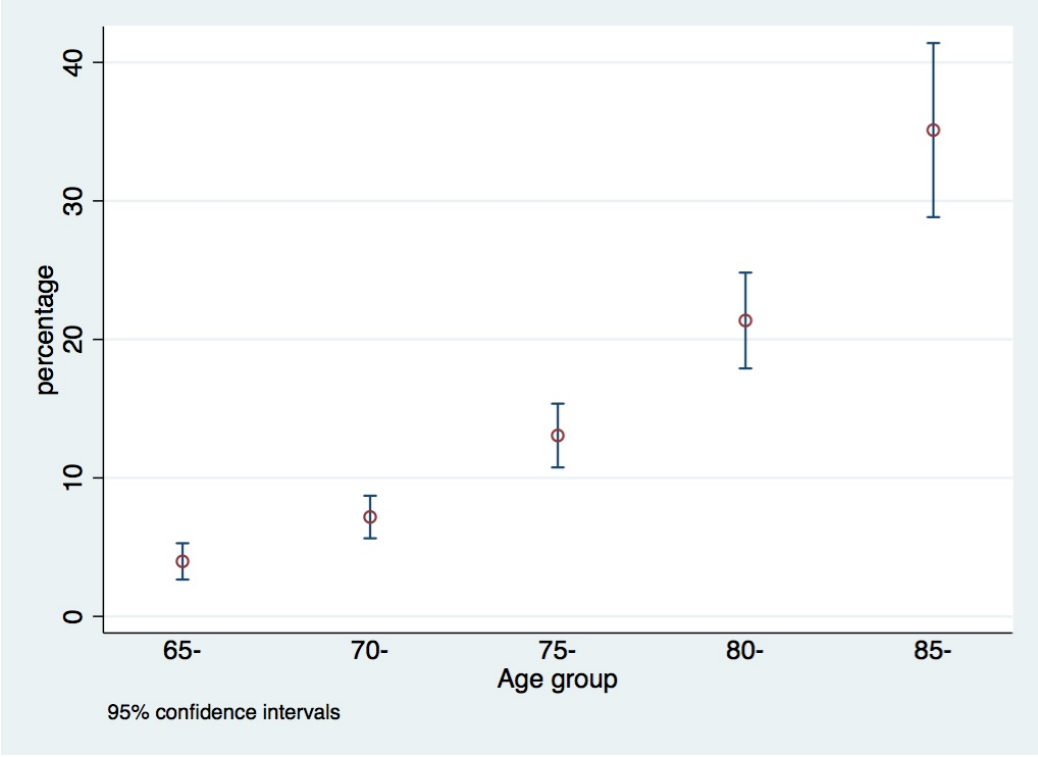


figure 3.1 proportion of individuals who have undergone previous surgery

All eyes	mean VA	sd VA	standar error VA	lower 95% ci	upper 95% ci	median vision	N(StudyNu~r)	%
non significant lens opacity	0.19	0.43	0.01	0.18	0.21	0.12	4078	57.7
significant cataract	0.39	0.67	0.01	0.37	0.42	0.24	2314	32.8
pco +	0.42	0.76	0.07	0.28	0.57	0.24	104	1.5
pco ++	0.70	1.30	0.25	0.21	1.18	0.25	28	0.4
pco +++	0.74	0.58	0.21	0.33	1.15	0.73	8	0.1
peripheral opacification	0.32	1.01	0.17	-0.01	0.66	0.10	35	0.5
central lens clear / post yag	0.19	0.23	0.03	0.14	0.25	0.14	70	1.0
clear lens	0.32	0.65	0.03	0.26	0.38	0.20	412	5.8
aphakic	1.69	2.05	0.65	0.42	2.96	0.31	10	0.1
ACIOL	0.43	0.24	0.17	0.10	0.76	0.43	3	0.0
							7062	100.0
VA < CF eyes	mean VA	sd VA	standar error VA	lower 95% ci	upper 95% ci	median vision	N(StudyNu~r)	
non significant lens opacity	0.15	0.18	0.00	0.14	0.16	0.1	4,010	58.4
significant cataract	0.27	0.21	0.00	0.27	0.28	0.22	2,214	32.2
pco +	0.27	0.24	0.02	0.22	0.32	0.22	99	1.4
pco ++	0.26	0.16	0.03	0.20	0.32	0.22	25	0.4
pco +++	0.56	0.31	0.12	0.33	0.79	0.7	7	0.1
peripheral opacification	0.16	0.20	0.03	0.09	0.22	0.1	34	0.5
central lens clear / post yag	0.19	0.23	0.03	0.14	0.25	0.14	70	1.0
clear lens	0.22	0.22	0.01	0.20	0.25	0.2	399	5.8
aphakic	0.15	0.17	0.07	0.02	0.29	0.15	6	0.1
ACIOL	0.43	0.24	0.17	0.10	0.76	0.43	2	0.0

table 3.8 Average Vision for all eye (corrected and uncorrected), prevalence of significant cataract defined as LOC3, nuclear ≥ 4, corticol ≥ 3, psc ≥ 2

agegrp	right eye	left eyes	either eye	ee std err.	ee low 95% ci	ee high 95%	totals
65-	136	155	200				843
%	16.39	18.61	23.72	1.47	20.89	26.74	
70-	275	284	370				1,037
%	27.09	27.57	35.68	1.49	32.76	38.68	
75-	331	344	430				763
%	45.03	46.3	56.36	1.80	52.75	59.91	
80-	265	275	330				468
%	59.82	60.98	70.51	2.11	66.15	74.61	
85-	128	121	149				169
%	80	79.61	88.17	2.48	82.32	92.62	
Total	1,135	1,179	1,479				3,280
%	35.66	36.74	45.09	0.87	43.38	46.81	

table 3.9 prevalence of significant cataract defined as LOC3, nuclear ≥ 4, corticol ≥ 3, psc ≥ 2 excluding past cataract surgery

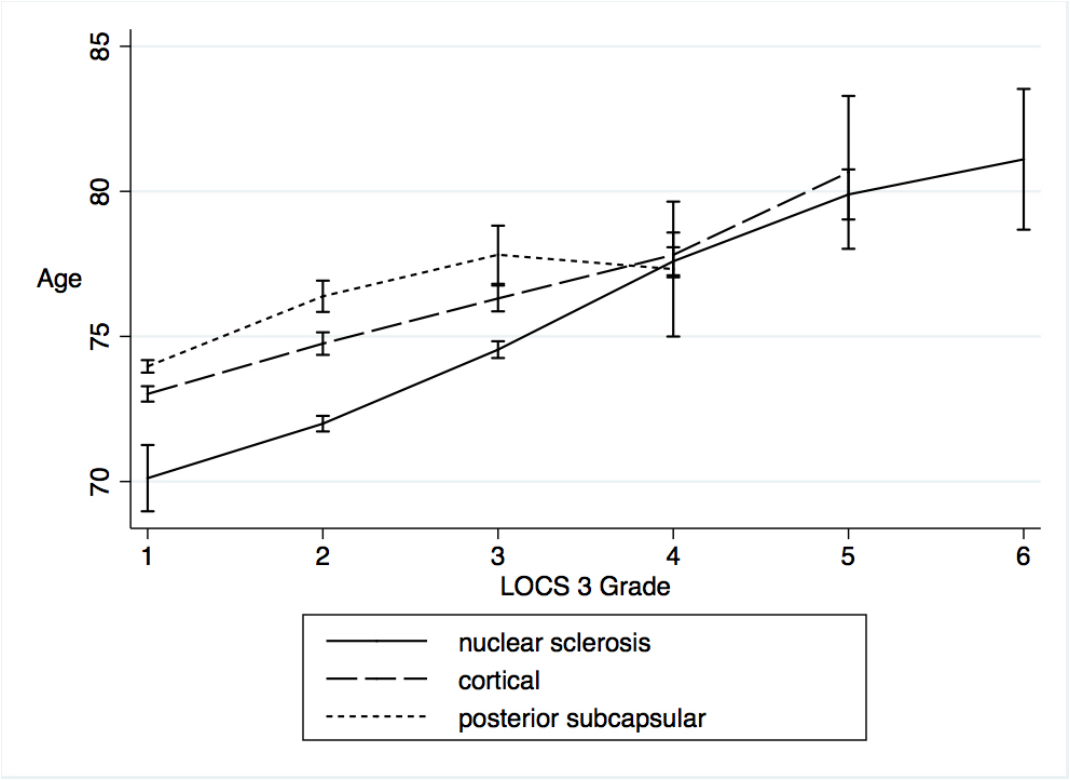


figure 3.2 age vs average LOCS 3 grade

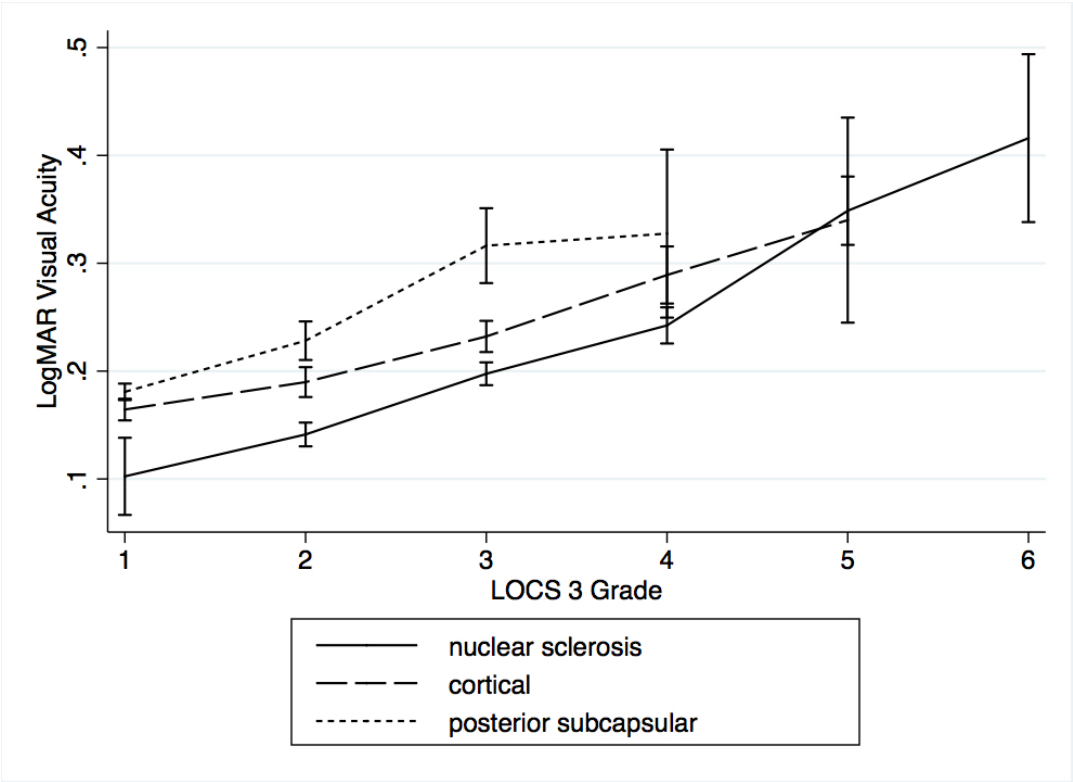


figure 3.3 LogMAR visual acuity vs average LOCS 3 grade

Selection for surgery

Following the initial visit 222 individuals were referred for consideration of cataract surgery. Of these, 141 were offered cataract surgery by the treating consultant. In addition, 80 individuals referred for other reasons were found to have clinically significant lens opacities. Of all those offered surgery 181 (82%) agreed to intervention, with a total of 272 cataract operations performed as a direct or indirect consequence of the study visit. After excluding 18 eyes with logMAR vision > 1.5. The average pre-operative acuity of eyes that underwent surgery was logMAR 0.43 (95% CI 0.41 – 0.46). The median age of patients selected for surgery was 79.

Cataract surgery on 'non-cataract' referrrals

Grades of nuclear sclerosis and posterior subcapsular cataract were similar among all eyes that were selected for surgery regardless of whether they were referred to the hospital eye service for cataract or for other reasons. In the univariate analysis, grades of cortical cataract were significantly higher (p=0.006) in those referred by the optometrist specifically for cataract surgery compared to those that were offered surgery after attending the HES for other reasons. However, this effect became less obvious following adjustment for age and sex (p=0.09).

Optometrist Variation

There was some variation in rates of referral. Within the adjusted model, one optometrist was found to be significantly more likely to refer than the other three (see table 3.10). We did not find that excluding the results from that optometrist made a substantial difference to our results and so data from all four assessors was included in the final model. There was a weak associtation between significant cataract and a recent optometrist assessment but this disappeared within the adjusted model.

Predictors of which individuals were referred for cataract surgery					logistic d_cat i.sct i.sad exa	
	Odds Ratio	Stand Error	z	P>|z|	95% Conf Inteval	
significant cataract	63.84	32.87	8.07	0.00	23.27	175.13
dissatisfied with vision	3.14	0.50	7.25	0.00	2.30	4.28
exam age	1.08	0.01	5.98	0.00	1.06	1.11
female gender	1.10	0.18	0.60	0.55	0.80	1.51
Acuity in better eye	1.26	0.11	2.54	0.01	1.05	1.50
optom 1	1.51	0.33	1.92	0.06	0.99	2.31
optom 2	0.98	0.23	-0.10	0.92	0.61	1.56
optom 3	3.31	0.77	5.13	0.00	2.10	5.22
_cons	0.00	0.00	-11.24	0.00	0.00	0.00
Predictors of having a significant cataract in either eye					logistic sct examage i.genc	
scat	Odds Ratio	Std. Err.	z	P>z	[95% Conf.	Interval]
age at exam	1.16	0.01	19.95	0.0000	1.15	1.18
female gender	1.29	0.10	3.23	0.0010	1.10	1.50
vision in better eye	1.57	0.13	5.26	0.0000	1.33	1.86
_cons	0.00	0.00	-20.72	0.0000	0.00	0.00
Predictors of having undergone previous cataract surgery in either eye					logistic pseudo5 examage	
pseudo5	Odds Ratio	Std. Err.	z	P>z	[95% Conf.	Interval]
pseudo 5 = prev surgery						
age at exam	1.14	0.01	14.33	0.0000	1.12	1.16
female gender	1.15	0.13	1.28	0.1990	0.93	1.44
DM	1.97	0.31	4.28	0.0000	1.45	2.69
vision in the better eye	0.99	0.08	-0.13	0.8970	0.84	1.16
_cons	0.00	0.00	-17.13	0.0000	0.00	0.00

table table 3.10 logistic regression models of associations with referral for surgery, significant cataract and having undergone previous cataract surgery

Previous surgery

There were 415 patients who had evidence of previous lens surgery, including 255 who had undergone surgery in both eyes. 7 individuals were aphakic including 3 with bilateral aphakia. There were 3 individuals with an ACIOL present in one eye. The remaining 405 (98%) were pseudophakic with posterior chamber implants. After correcting for age, we found that visual acuity was significantly better in operated eyes compared to those with significant lens opacities OR=8, $p<0.0001$ (95% CI 4.3 – 14.8) but not significantly different from eyes with non-significant lens opacities (p=0.8).

Bilateral vs Unilateral Surgery

Individuals who had undergone previous surgery in only one eye were on average 2 years younger (p=0.002) than those who had had bilateral surgery. Pinhole vision was better in those with bilateral pseudophakia (OR 1.5 95% CI 1.1-2.1, p=0.02) after correcting for age. Unaided / spectacle acuity was similar between groups (p=0.61) with average logMAR acuity of 0.14 in better eyes. Satisfaction with vision (p=0.60), gender ratios (p=0.64) and the presence of screening visual field defects (p=0.50) were similar between groups. The average nuclear grade was similar between phakic contralateral eyes of those referred for cataract surgery (mean ns=3.40 (n=69) and contralateral eyes of unilateral pseudophakes ns=3.45 (n=157).

Recollection of previous surgery

Prior to examination, subjects were asked if they had undergone any previous eye surgery and, if so, to state laterality and type of surgery. Recollection was good with pseudophakic /aphakic inidividuals correctly recalling previous surgery in 98% of right eyes and 96% of left eyes. Recollection of the type of surgery was reasonable with ‘cataract’ or related terms being correctly recalled for 86% of right eyes and 81% of left eyes among those found to be pseudophakic at the slit lamp.

Posterior Capsular Opacification

Posterior capsular opacification (PCO) was recorded with respect to severity and location. Evidence of previous capsulotomy was inferred when the capsule was described as ‘clear centrally’ and correlated with recollection of previous laser. 70 patients fulfilled these criteria. Following the initial study visit, 16 inidividuals were referred to the HES for assessment of PCO of whom 9 went on to have treatment. 29 individuals referred to HES for other reasons also underwent YAG capsulotomy for PCO with 44 eyes of 38 individuals treated in total. Other results are summarised in table 3.8

Cataract and Gender

The relationship between cataract and gender is outlined below

	Female Gender			Male Gender		
Age	Beaver	Blue Mounta	BEAP	Beaver	Blue Mounta	BEAP
65-			227			184
%	26.8	23.6	22.86	20.1	19.1	21.6
75-			367			229
%	57.5	57.6	54.45	42.9	48.4	45.44
85-			77			51
%		83.8	78.57		56.5	82.26
Total			671			636
			38.02			22.43

table 3.11 Prevalence of significant cataract in right eyes excluding past cataract surgery

table 3.12 Age stratified prevalence LOC- 3 grades

	Right nuclear grade							Right cortical grade							Right posterior subcapsular grade						
agegrp	1	2	3	4	5	6	Total	agegrp	1	2	3	4	5	Total	agegrp	1	2	3	4	5	Total
65-	37	413	313	57	7	3	830	65-	533	156	113	25	1	828	65-	732	72	18	2	0	824
	4.46	49.76	37.71	6.87	0.84	0.36	100		64.37	18.84	13.65	3.02	0.12	100		88.83	8.74	2.18	0.24	0	100
70-	14	356	475	147	21	2	1,015	70-	524	245	179	59	6	1,013	70-	843	130	32	8	0	1,013
	1.38	35.07	46.8	14.48	2.07	0.2	100		51.73	24.19	17.67	5.82	0.59	100		83.22	12.83	3.16	0.79	0	100
75-	5	166	323	181	51	9	735	75-	276	191	191	68	7	733	75-	555	126	44	6	1	732
	0.68	22.59	43.95	24.63	6.94	1.22	100		37.65	26.06	26.06	9.28	0.95	100		75.82	17.21	6.01	0.82	0.14	100
80-	1	60	191	128	49	14	443	80-	142	99	129	62	10	442	80-	304	98	29	5	4	440
	0.23	13.54	43.12	28.89	11.06	3.16	100		32.13	22.4	29.19	14.03	2.26	100		69.09	22.27	6.59	1.14	0.91	100
85-	1	5	52	62	33	7	160	85-	46	29	49	29	7	160	85-	97	37	20	5	1	160
	0.62	3.12	32.5	38.75	20.62	4.38	100		28.75	18.12	30.63	18.12	4.38	100		60.62	23.12	12.5	3.12	0.62	100
Total	58	1,000	1,354	575	161	35	3,183	Total	1,521	720	661	243	31	3,176	Total	2,531	463	143	26	6	3,169
	1.82	31.42	42.54	18.06	5.06	1.1	100		48	22.67	20.81	7.65	0.98	100		79.87	14.61	4.51	0.82	0.19	100

	Left nuclear grade							Left cortical grade							Left posterior subcapsular grade						
agegrp	1	2	3	4	5	6	Total	agegrp	1	2	3	4	5	Total	agegrp	1	2	3	4	5	Total
65-	34	390	341	57	8	3	833	65-	513	174	113	26	3	829	65-	731	76	13	2	3	825
	4.08	46.82	40.94	6.84	0.96	0.36	100		61.88	20.99	13.63	3.14	0.36	100		88.61	9.21	1.58	0.24	0.36	100
70-	13	366	480	145	22	4	1,030	70-	504	279	169	70	4	1,026	70-	852	139	26	9	1	1,027
	1.26	35.53	46.6	14.08	2.14	0.39	100		49.12	27.19	16.47	6.82	0.39	100		82.96	13.53	2.53	0.88	0.1	100
75-	2	161	349	181	45	5	743	75-	266	205	194	68	8	741	75-	559	133	35	9	0	736
	0.27	21.67	46.97	24.36	6.06	0.67	100		35.9	27.67	26.18	9.18	1.08	100		75.95	18.07	4.76	1.22	0	100
80-	2	58	206	129	46	9	450	80-	127	106	138	67	12	450	80-	301	106	34	6	2	449
	0.44	12.89	45.78	28.67	10.22	2	100		28.22	23.56	30.67	14.89	2.67	100		67.04	23.61	7.57	1.34	0.45	100
85-	1	5	51	63	29	3	152	85-	33	38	52	21	8	152	85-	95	33	17	5	2	152
	0.66	3.29	33.55	41.45	19.08	1.97	100		21.71	25	34.21	13.82	5.26	100		62.5	21.71	11.18	3.29	1.32	100
Total	52	980	1,427	575	150	24	3,208	Total	1,443	802	666	252	35	3,198	Total	2,538	487	125	31	8	3,189
	1.62	30.55	44.48	17.92	4.68	0.75	100		45.12	25	20.83	7.88	1.09	100		79.59	15.27	4	0.97	0.25	100

3.12 Age related macular degeneration

Purpose; to describe the prevalence of AMD

There were 3473 attendees who had gradable photographs in at least one eye. Overall, 95% of photographs were gradable, of which 98% were of a gradable standard in at least one eye. The mean age of individuals with gradable photographs was 75 years (SD 5.9), with 55.8% being female. Excluded participants had an older mean age of 77.7 years (SD 6.1) and were more likely to be female (66%).

Interobserver variability was assessed using Kappa, using the cut-offs proposed by Landis and Koch. There was substantial agreement between CARF and CW, with 76% agreement (kappa=0.69, SE 0.03, $p<0.001$) and excellent agreement between CW and WMA, with 86% agreement (kappa=0.82, SE 0.04, $p<0.001$). There was good agreement between raters across all grades of AMD but limited by the low number of higher grades. The combined kappa for all 3 raters for all categories was 0.71. [Cohen's kappas ≥ 0.80 represent excellent agreement, coefficients between 0.61 and 0.80 represent substantial agreement, coefficients between 0.41 and 0.61 moderate agreement and <0.41 fair to poor agreement.]

Prevalence rates were similar between the right and left eyes (table xxx) and between genders. Nearly 40% of subjects had no or minimal (<10 small hard

drusen <65μm in size) signs of ARM/AMD in their worse eye (grade 0). Individual eyes were more likely to be grade 0, with approximately 50% of eyes having no significant ARM. When graded for the worse eye however, a higher prevalence of grade 1 (41.2%) occurred as shown in table 2. Prevalence rates for the worse eye were: 12.7% for grade 2 and 2.8% for grade 3; GA or nAMD (grade 4 AMD) was diagnosed in 158 persons, giving a prevalence of 4.6%. For the worse eye, GA (grade 4a) was more prevalent (2.4%) than nAMD (grade 4b) (1.9%). Peri-papillary CNV (4c) was an infrequent finding, with prevalence for the worse eye of 0.3%.

Subjects aged 65 to 69 years, 44.6% had grade 0 AMD in their worse eye, but in the over 90 year age group only 15.2% of subjects had no or minimal morphological changes evident. The prevalence of grade 4 AMD increased from 2.3% in the 65-69 year age group, to 15.7% for individuals aged 85-90 years. The highest prevalence of disease (21.2%) was in the over 90 years' age group.

There was some co-linearity between eyes but disease asymmetry was common. Of the 84 persons with GA in at least one eye, 28 subjects (0.81%) had bilateral GA. There were a total of 65 persons having nAMD in at least one eye. Bilateral disease was present in 13 subjects (0.37%), indicating that nAMD was more likely to be a unilateral finding when compared to GA. Fifteen (15) people (0.43%) had GA in one eye and nAMD in the other, while one individual had GA in one eye and a peripapillary membrane in the other. Bilateral AMD (either 4a, 4b or 4c) occurred in 57 people overall (1.6%).

Visual acuity was well maintained at LogMAR 0.2 or better for most eyes with the early stages of ARM. Even in eyes with GA, (grade 4a) vision was maintained at a mean of 0.76 and 0.78 in the right and left eyes respectively. There was significant variation in vision, ranging from excellent (LogMAR 0.0) to counting fingers, depending on the exact location of the degeneration. As expected, eyes with nAMD (Grade 4b) had the worse vision on average; with a mean Log MAR BCVA of 2.09 and 2.12 in the right and left eyes respectively.

There was no association of AMD grade with gender ($p=0.55$), the presence of diagnosed hypertension ($p=0.513$), or diabetes mellitus ($p=0.882$). A history of a previous stroke did show a trend but for the left eye only ($p=0.055$). As the right eye showed no trend ($p=0.318$) the significance of this finding is uncertain and it may reflect chance.

The proportion of the population with self-perceived dissatisfaction increased with grade but was most apparent in those with grade 4 disease. It appears that a significant number of participants with the more advanced grades of ARM/AMD still considered their vision to be satisfactory, with 60.5% and 41.5% of subjects with known GA and nAMD stating they were happy with their vision. As the grade of ARM/AMD increased in severity the percentage of subjects happy with their vision decreased from 77.8% (Grade 0) to 41.5% for grade 4b. There was an inverse trend with dissatisfaction and age at the earlier stages of

ARM/AMD (Stage 0-1), with the younger age groups being more dissatisfied with their vision compared to older subjects with the same stage of disease.

Individuals previously certified as visually impaired were excluded from the study but it was felt possible to estimate the proportion of certified individuals by estimating the proportion of certified individuals within the sampling frame.

In the UK, between 1999-2000, there were 7561 certifications for blindness (severe sight impairment) due to AMD registered nationally[181]. This represented 42% of all registrations for blindness in those aged 65-74years old, increasing to 66% and 74% of all registrations in those aged 74-84 years and 85 years and older, respectively.

The 2001 census reported that there were 9.4 million individuals over the age of 65 years living in the UK [182]. From this, we can infer that the national incidence of certification for blindness due to AMD was approximatedly 0.08% just prior to our study. This is broadly inline with our results.

Population data for individual districts was also available from the census. There were 7986 individuals aged 65 years and older living in Bridlington in 2001. Information on certification for sight impairment within the town of Bridlington was provided by the East Riding social service department [personal communication]. They reported that there were 138 individuals over the age of 65 years certified as severe or partially sight impaired at the start of the study.

If we assume that the national age specific incidence data is stable and representative, we can predict that 75 of these individuals would have been certified as sight impaired due to AMD. We can use this to derive an approximate population prevalence of 0.94% of sight registration due to AMD for those aged 65 years and older living within the town of Bridlington.

Grade	Right Eye	Left Eye
0	1687 (50.5)	1731 (51.2)
1	1136 (34.0)	1115 (33.0)
2	341 (10.2)	340 (10.1)
3	66 (2.0)	89 (2.6)
4a	66 (2.0)	63 (1.9)
4b	38 (1.1)	40 (1.2)
4c	5 (0.1)	4 (0.1)
Total	3339 (100)	3382 (100)

table 3.13: BEAP AMD grading results for right eye and left eye. Freq (%).

Grade	Females	Males
0	736 (54.6) ***38.0%***	611(45.5) ***39.8%***
1	791 (55.3) ***40.8%***	639 (44.7) ***41.6%***
2	258 (58.4) ***13.3%***	184 (41.6) ***12.0%***
3	61 (63.5) ***3.1%***	35 (36.5) ***2.3%***
4a	48 (57.1) ***2.5%***	36 (42.9) ***2.3%***
4b	39 (60.0) ***2.0%***	26 (40.0) ***1.7%***
4c	5 (55.5) ***0.3%***	4 (44.4) ***0.3%***
Total	1938 (55.8)	1535 (44.2)

table 3.14: Sex distribution of worse eye Rotterdam AMD grade. Freq (%) with gender stratified prevalence ***in bold italics***.

	Age, years						
AMD score	65-69	70-74	75-79	80-84	85-90	≥90	Total
0	378 (44.6)	454 (42.5)	289 (35.8)	168 (31.6)	53 (28.8)	5 (15.2)	1347 (38.8)
1	370 (43.7)	475 (44.4)	337 (41.7)	189 (35.5)	51 (27.7)	8 (24.2)	1430 (41.2)
2	69 (8.1)	105 (9.8)	113 (14.0)	107 (20.1)	39 (21.2)	9 (27.3)	442 (12.7)
3	11 (1.3)	14 (1.3)	26 (3.2)	29 (5.5)	12 (6.5)	4 (12.1)	96 (2.8)
4a	9 (1.1)	16 (1.5)	21 (2.6)	18 (3.4)	18 (9.8)	2 (6.1)	84 (2.4)
4b	9 (1.1)	4 (0.4)	19 (2.4)	19 (3.6)	10 (5.4)	4 (12.1)	65 (1.9)
4c	1 (0.1)	1 (0.1)	3 (0.4)	2 (0.4)	1 (0.5)	1 (3)	9 (0.3)
Total	847 (100)	1069 (100)	808 (100)	532 (100)	184 (100)	33 (100)	3473 (100)
P-value	<0.001						

table 3.15: Age distribution by worse eye Rotterdam AMD score. Freq (%)

	Right eye			Left eye			Worse eye		
AMD grade	N	Mean (SD)	95% CI	N	Mean (SD)	95% CI	N	Mean (SD)	95% CI
0	1687	73.9 (5.5)	73.7-74.2	1731	74.2	73.9-74.5	1347	74.2 (5.6)	73.9-74.5
1	1136	74.7 (5.5)	74.4-75.0	1115	74.5	74.2-74.8	1430	74.4 (5.5)	74.1-74.7
2	341	78.0 (6.5)	77.3-78.7	340	77.6	77.0-78.3	442	77.3 (6.3)	76.7-77.9
3	66	79.2 (6.8)	77.5-80.9	89	79.3	77.8-80.8	96	78.9 (6.8)	77.6-80.3
4a	66	79.9 (6.8)	78.2-81.6	63	79.8	78.1-81.6	84	79.4 (6.8)	77.9-80.6
4b	38	80.6 (6.0)	78.6-82.6	40	79.4	77.3-81.6	65	79.6 (6.6)	77.9-81.2
4c	5	76.2 (6.5)	68.1-84.2	4	76.1	63.7-88.5	9	78.9 (7.8)	73.0-84.9
Total	3339	75.0 (6.9)	74.7-75.1	3382	74.9	74.7-75.1	3473	75.0 (5.9)	74.8-75.2

table 3.16 Mean age distribution of Rotterdam grades.

	Vision perceived as satisfactory by study subject	
AMD score	No, Freq (%)	Yes, Freq (%)
0	295 (22.2)	1033 (77.8)
1	285 (20.3)	1116 (79.7)
2	114 (26.0)	325 (74)
3	32 (34.4)	61 (65.6)
4a	32 (39.5)	49 (60.5)
4b	38 (58.5)	27 (41.5)
4c	3 (33.3)	6 (66.7)
Total	799 (23.4)	2617 (76.6)

table 3.17 Subject self-perception of vision as being satisfactory, with corresponding AMD grades.

	Right eye BCVA (LogMAR)		Left eye BCVA (LogMAR)	
AMD Grade	Freq	Mean (SD)	Freq	Mean (SD)
0	1687	0.15 (0.26)	1725	0.16 (0.34)
1	1136	0.14 (0.24)	1113	0.16 (0.37)
2	340	0.20 (0.30)	340	0.21 (0.31)
3	66	0.27 (0.18)	89	0.30 (0.49)
4a	63	0.76 (1.18)	63	0.78 (1.28)
4b	38	2.09 (1.65)	39	2.12 (1.73)
4c	5	0.16 (0.11)	4	0.34 (0.15)

table 3.18 Summary of the association of right eye and left eye best corrected visual acuity (BCVA) with AMD grade

		Age, years						
	AMD score	65-69	70-74	75-79	80-84	85-90	≥90	Total
Beaver Dam Eye Study	Late AMD (4a and 4b)	1.4		≥75: 7.2				1.6 (ages 43-86)
The Blue Mountains Eye Study	Late AMD (4a and 4b)	0.7		5.4		≥85: 18.5		1.9 (≥49 years)
The Irish Longitudinal Ageing Study (TILDA)	4a Males	0.3		≥75: 1.6				0.6 (in over 50 years population)
	4a Females	0.2		≥75:1.0				
	4b Males	0.2		≥75: 1.1				
	4b Females	0.2		≥75: 1.0				
EUREYE	4a Males	0.51	0.56	1.91	≥80y: 1.39			1.2
	4a Females	0.11	0.95	1.18	≥80y: 5.75			
	4b Males	0.38	1.40	2.63	≥80y: 5.56			2.3
	4b Females	0.92	1.42	2.17	≥80y: 10.50			
BEAP	4a	1.1	1.5	2.6	3.4	9.8	6.1	2.4
	4b	1.1	0.4	2.4	3.6	5.4	12.1	1.9
	4c	0.1	0.1	0.4	0.4	0.5	3	0.3
	Total	2.3	2.0	5.4	7.4	15.7	21.2	4.6

table 3.19: A comparison between reported prevalence of AMD grades (in either eye), across age-groups and gender. Values are percentages.

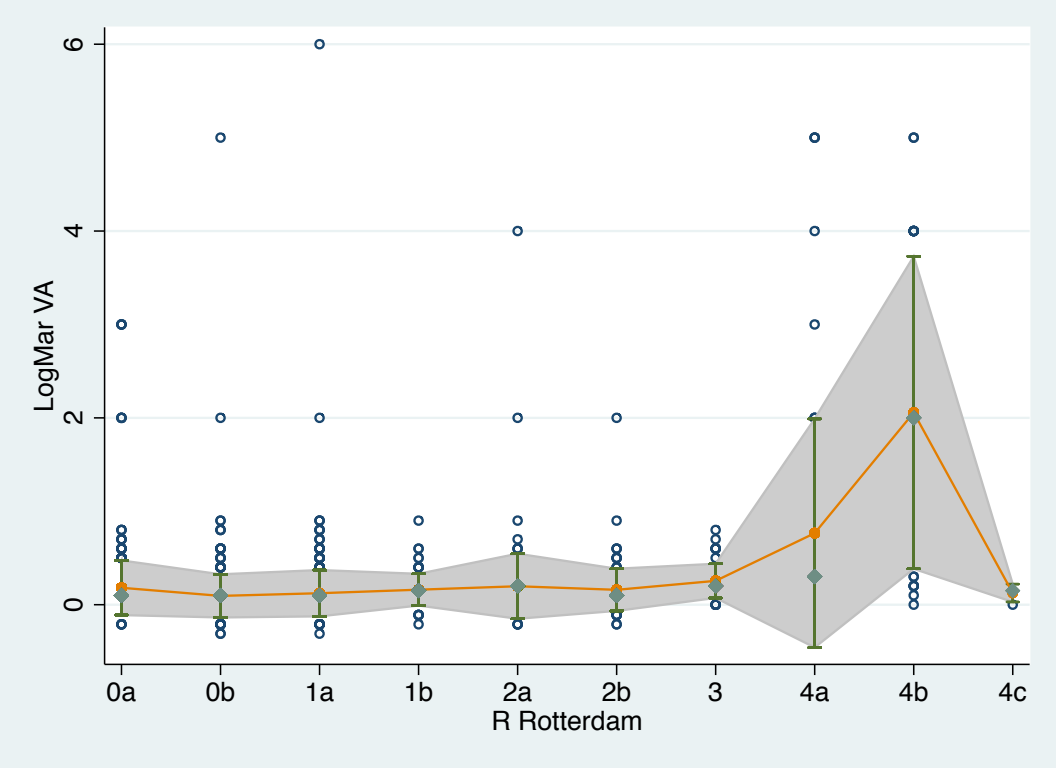


figure 3.4 mean (yellow) visual acuity against right Rotterdam grade with median (green diamond), standard deviations (grey) and outliers (circles) shown

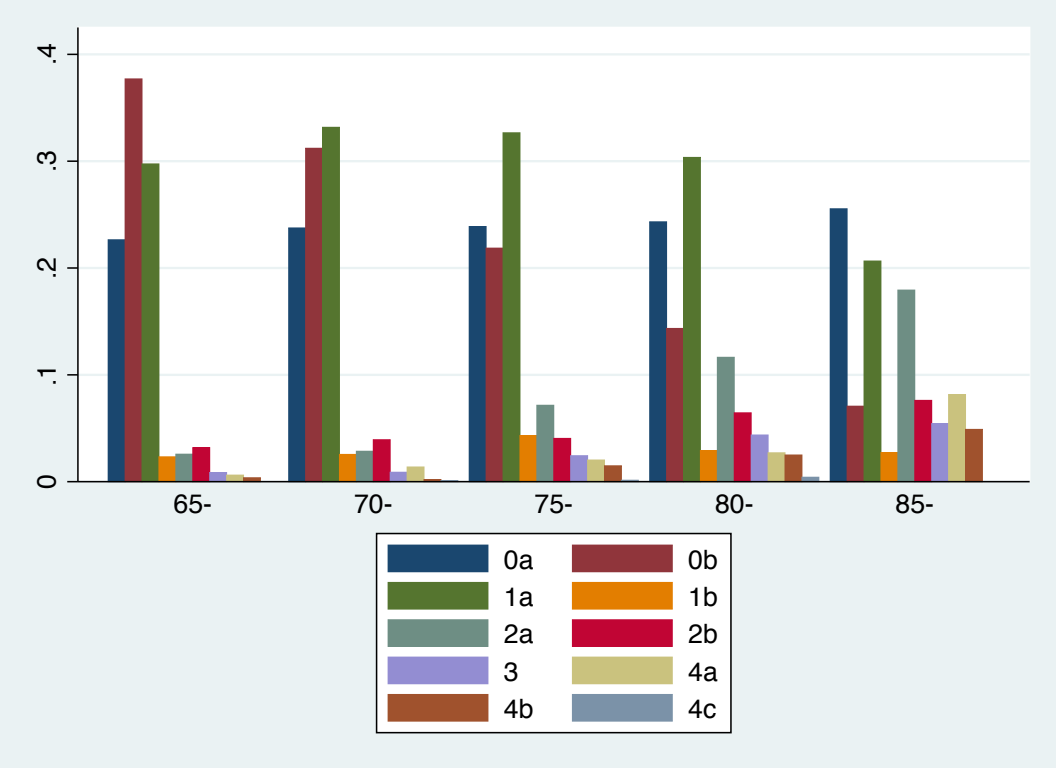
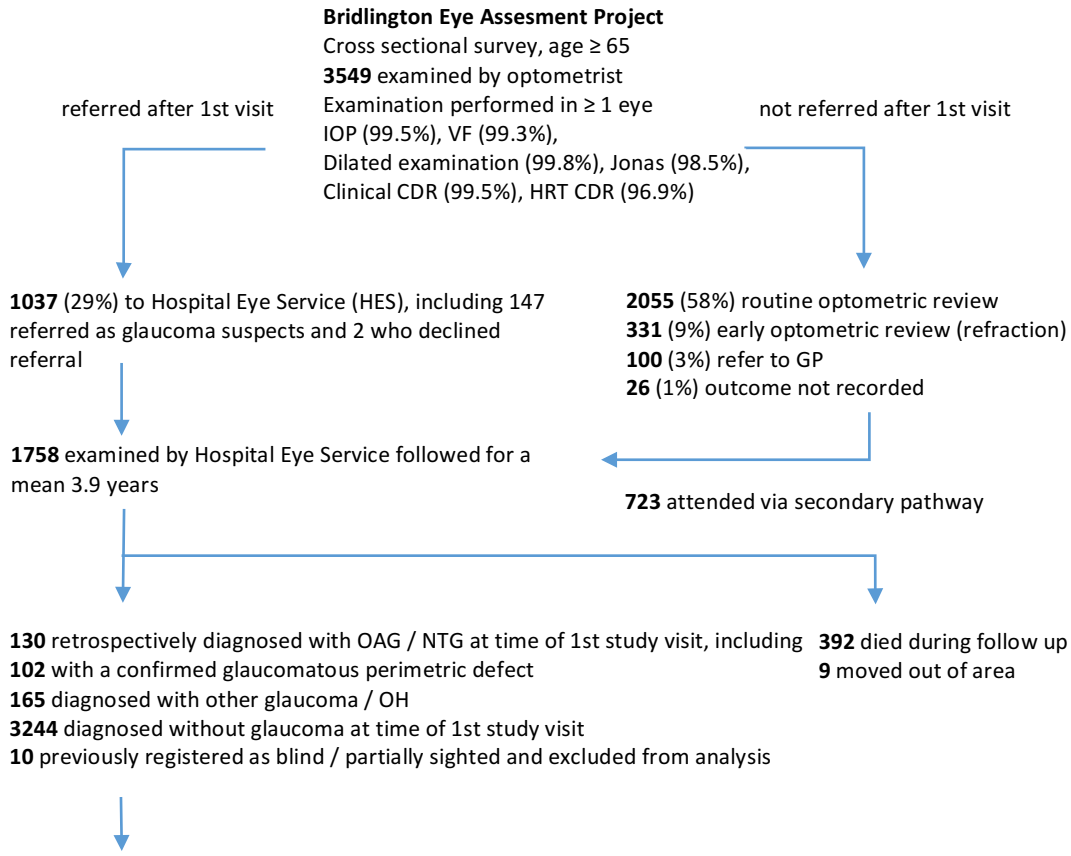


figure 3.5 prevalence of AMD grade by age in right eyes (percentage on x-axis)

3.13 Glaucoma

Purpose; to describe the prevalence of Glaucoma



	number	crude %	adjusted %	low 95% ci	up 95% ci
OAG	109	3.1	3.5	2.8	4.2
NTG	17	0.5	0.5	0.3	0.8
Suspect	28	0.8	0.7	0.5	1
ACG	12	0.3	0.4	0.1	0.6
Narrow Angles	17	0.5	0.5	0.2	0.8
2ndry glaucoma	7	0.2	0.2	0.1	0.4
Other disc path	100	2.8	2.8	2.2	3.3
ISGEO Category 1	76	2.1	2.6	2	3.2
ISGEO Category 2	17	0.5	0.6	0.3	1
ISGEO Category 3	3	0.1	0.1	0	0.2

table 3.20 Crude and Adjusted prevalence of Glaucoma

3549 eligible individuals attended the screening visit and 1037 were referred or re-referred to the hospital eye service for a secondary examination, including 147 referred as glaucoma suspects. No glaucoma suspect refused referral but 2 patients with a suspicion of macula degeneration declined to hospital referral. The majority (55%) had seen an optometrist within the last year. Intraocular pressure, Cup to Disc ratio Visual fields results were reported in 99% of participants.

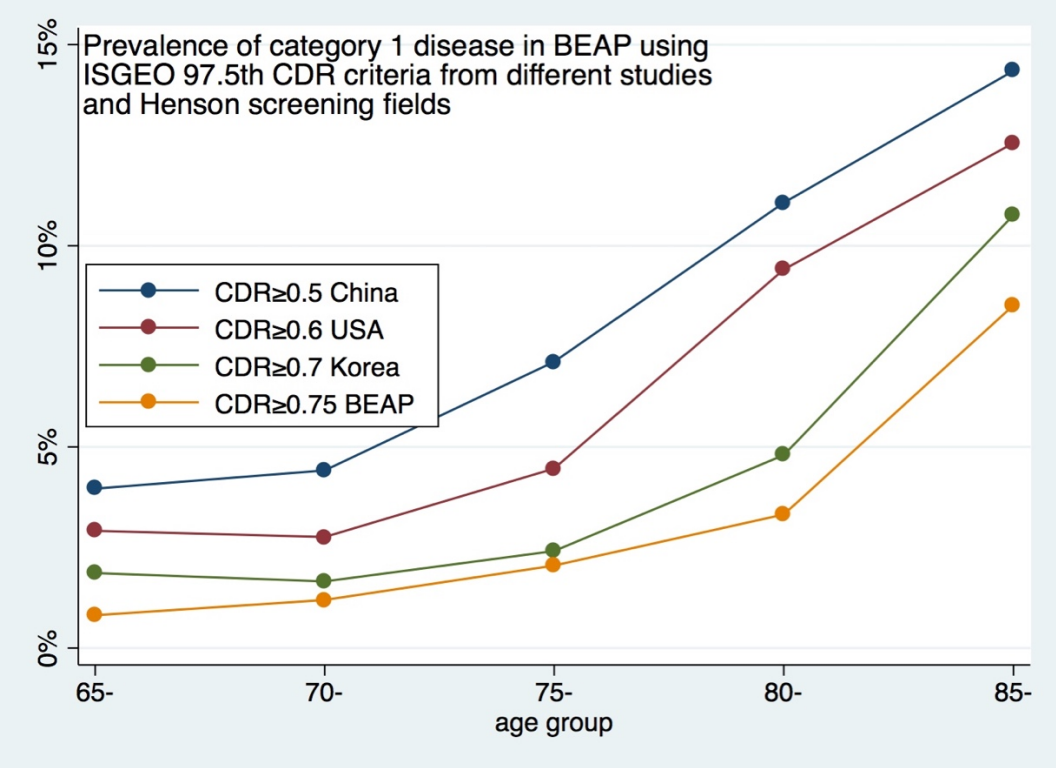
One was referred with drusen and the other with a small macula haemorrhage. Neither was thought to have any evidence of glaucoma. 9 individuals were known to have moved from the area during the course of follow up. 1 was not referred for secondary examination, 2 had a single visit to the hospital eye service. The remaining 6 were followed for a mean of 2.4 years before loss to follow up. In the 5 years following the last screening visit, 1499 study patients were seen by the hospital eye service. Of these, 25% were discharged following a single visit while the remainder were followed for mean of 3.9 years (range 7 days – 8.9 years). Incident glaucoma was defined retrospectively with reference to pressure, fields and fundus photos from the initial visit but within the context of results from subsequent hospital visits.

15% (534) of individuals reported a family history of glaucoma in a first or second degree relative. The majority of associations were with a female relative. The presence of glaucoma in a mother / sister was described in 332 (69%) of

cases. This trend persisted in those diagnosed with glaucoma with over half of those with OAG / NTG reporting glaucoma in their mother / sister.

3.7% (130) of individuals reported a personal history of glaucoma. Individuals were questioned regarding previous eye surgery, including laser. Previous trabeculectomy was reported by 18 individuals (Right 7, Left1, Both 10), while 15 others recalled unspecified surgery for glaucoma (Right 3, Left 2, Both 10). 2897 (82%) reported no surgery in either eye.

In total 131 patients were diagnosed as having primary open angle or normal tension glaucoma at the time of the initial study visit, including 56 previously undiagnosed individuals. The mean age at diagnosis of new patients was 78 yrs (range 65 – 93 yrs). A perimetric defect was present at screening or within the first 3 visits to the hospital eye service in 44 patients. The remaining 12 patients were diagnosed with pre-perimetric glaucoma.



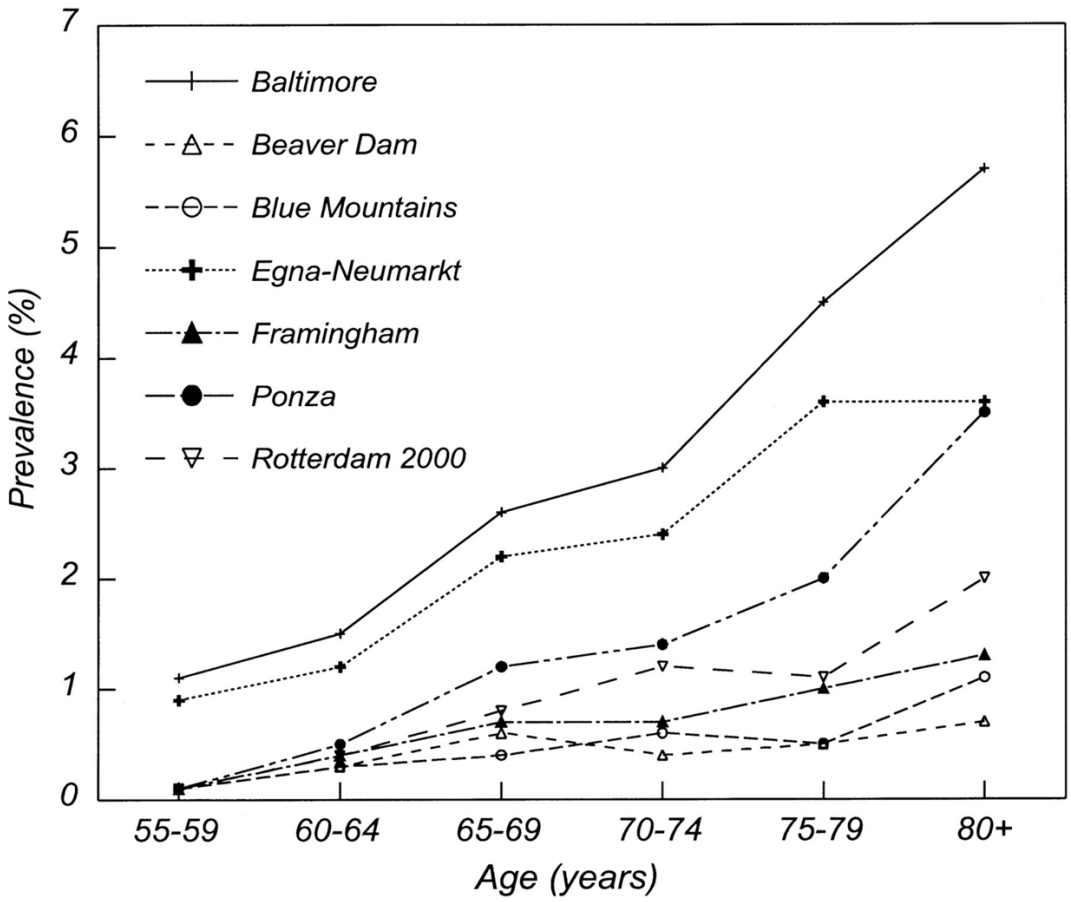


figure 3.6 (a) Prevalence using ISGEO criteria (b) Wolfs et al, IOVS 2000 note the marked variation pre & post introduction of ISGEO criteria

Time	mean	sd	min	max	N
8	13.5	0.7	13	14	2
9	16	2.9	7	26	914
10	16.1	3	8	28	864
11	16.3	3	9	28	1011
12	16.2	3.1	9	27	529
13	15.6	2.9	8	25	326
14	15.9	2.9	8	26	1033
15	15.8	3.1	5	33	982
16	15.9	3	5	25	520
17	16	2.5	12	21	92
18	16.3	5.3	10	29	12
Total	16	3	5	33	6285
	mean	sd	min	max	Number
Female	16.1	2.8	8	33	3527
Male	15.8	3.2	5	28	2777
Diabetes					
No	16	3	5	33	5646
Yes	16.3	3.1	9	29	642
Hypertension					
No	16.2	2.9	5	28	3207
Yes	15.8	3	5	33	3027

table 3.21 outcomes of intraocular pressure testing

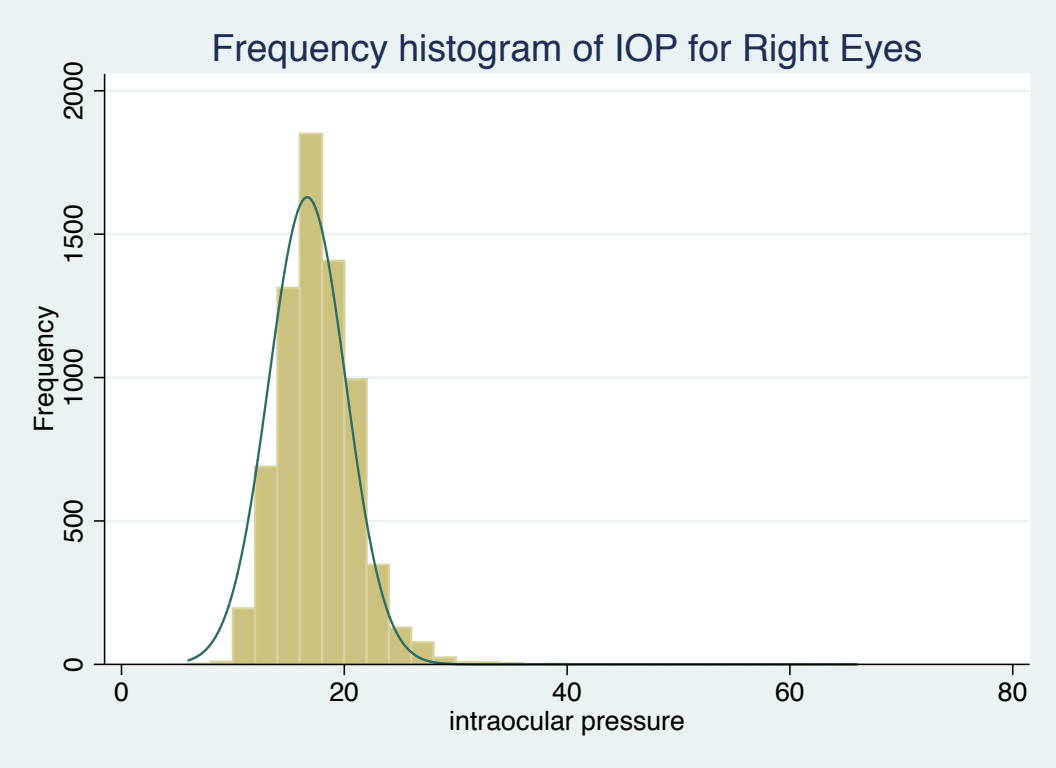


figure 3.6 frequency histogram of IOP for right eyes

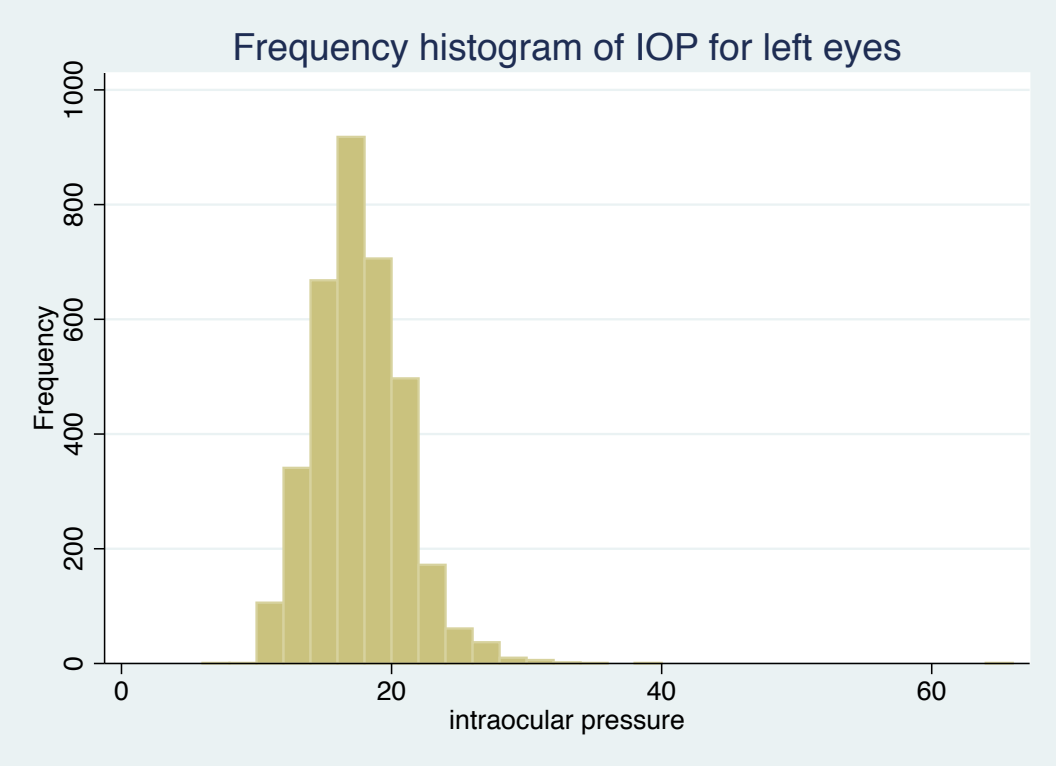


figure 3.7 frequency histogram of IOP for left eyes

table 4.2.1a results of Henson screening fields for both eyes									
		VF LE							
	VF RE	normal	abnormal	not performed	total				
	normal	2,903	183	30	3,116				
	abnormal	168	205	8	381				
	not performed	19	8	25	52				
	total	3,090	396	63	3,549				
table 4.2.1b Causes of reproducible VF defects									
	normal on retest	artefact	cataract/pco	macula	other disc	retrochiasmal	adenexal	other	glaucoma
65 -	55	71	7	24	18	10	7	6	25
75 -	40	70	15	72	19	16	13	0	50
85 -	3	17	5	19	3	1	2	1	21
total	98	158	27	115	40	27	22	7	96
table 4.2.1c Macula subtypes									
	mac_amd	mac_rvo	mac_erm	mac_myo ma	c_hole	mac_RD	any macula		
65 -	11	5	4	6	1	3	29		
75 -	40	19	6	2	7	7	79		
85 -	16	3	1	1	1	1	22		
total	67	27	11	9	9	11	130		
table 4.2.1d Disc subtypes									
	tilt	myopia	ppa	atrophy	any (except glaucoma)				
65 -	6	6	5	4	19				
75 -	9	3	3	9	22				
85 -	2	1	1	2	6				
total	17	10	9	15	47				

table 3.22 results of visual field tests

Of those with a glaucotomous perimetric defect, 32% of new patients had a normal VF field at the screening visit, compared to 13% of patients with a previous diagnosis of glaucoma. Mean intraocular pressure at presentation was 21 mmHg (range 12 – 33 mmHg). 40% of patients with new (Hypertensive) OAG had normal intraocular pressure at their screening visit. By definition, all normal tension patients had a normal pressures recorded at screening and subsequently. Vertical Cup to Disc ratio (CDR), as assessed by the optometrist at the slit lamp was 0.7 (range 0.2 – 0.9)

New OAG / NTG	IOP ≥ 21	95% CI		HRT vert CDR ≥ 0.7	95% CI		Optom CDR ≥ 0.7	95% CI	
Prevalence Pr(A)	1.70%	1.3 - 2.21		1.70%	1.3 - 2.22		1.70%	1.3 - 2.21	
Sensitivity Pr(+A)	47.30%	33.7 - 61.2		70.40%	56.4 - 82		76.40%	63 - 86.8	
Specificity Pr(-N)	91.60%	90.6 - 92.5		88.70%	87.5 - 89.8		90.80%	89.7 - 91.8	
ROC area (Sens. + Spec.)/2	0.694	62.8 - 76.1		0.795	73.4 - 85.7		0.836	77.9 - 89.3	
Odds ratio LR(+)/LR(-)	9.76	5.7 - 16.7		18.7	10.40 - 33.50		31.9	17.10 - 59.50	
Positive predictive value Pr(A+)	8.87%	5.88 - 12.7		9.74%	6.99 - 13.1		12.60%	9.22 - 16.6	
Negative predictive value Pr(N-)	99%	98.6 - 99.3		99.40%	99.1 - 99.7		99.60%	99.2 - 99.8	
	IOP => 21			hrtvcdr2			highest optom CDR		
New OAG / NTG	Pos.	Neg.	Total	Pos.	Neg.	Total	Pos.	Neg.	Total
OAG / NTG	26	29	55	38	16	54	42	13	55
Normal	267	2,908	3,175	352	2,765	3,117	292	2,882	3,174
Total	293	2,937	3,230	390	2,781	3,171	334	2,895	3,229

New OAG / NTG	JONAS	95% CI		VF abnormal	95% CI		Referred as g	95% CI	
Prevalence Pr(A)	1.70%	1.2 - 2.16		1.70%	1.3 - 2.2		1.70%	1.3 - 2.2	
Sensitivity Pr(+A)	66%	51.7 - 78.5		56.40%	42.3 - 69.7		65.50%	51.4 - 77.8	
Specificity Pr(-N)	93.90%	93 - 94.7		86.40%	85.2 - 87.6		98.10%	97.6 - 98.5	
ROC area (Sens. + Spec.)/2	0.8	73.5 - 86.4		0.714	64.8 - 78		0.818	75.4 - 88.1	
Odds ratio LR(+)/LR(-)	30	16.80 - 53.50		8.22	4.81 - 14.10		97.2	53 - 178	
Positive predictive value Pr(A+)	15.40%	11 - 20.8		6.68%	4.58 - 9.35		37.10%	27.5 - 47.5	
Negative predictive value Pr(N-)	99.40%	99 - 99.6		99.10%	98.7 - 99.4		99.40%	99.1 - 99.6	
	jonas positive in either eye			VF abnormal in either eye			Referred as glaucoma suspects		
New OAG / NTG	Pos.	Neg.	Total	Pos.	Neg.	Total	Pos.	Neg.	Total
OAG / NTG	35	18	53	31	24	55	36	19	55
Normal	192	2,958	3,150	433	2,757	3,190	61	3,129	3,190
Total	227	2,976	3,203	464	2,781	3,245	97	3,148	3,245

table 3.23 diagnostic accuracy of different tests for glaucoma

Of the 3549 right eyes available for analysis, optometrists reported CDR values for 3520 (>99%), while HRT images were obtained for 3386 (>95%). In addition, 459 HRT images were excluded due to unacceptable variability during image acquisition, defined as a mean pixel height standard deviation > 50um. A further 620 HRT images produced a CDR output of zero. Excluding these images had a limited effect on calculations of agreement and so they were included in the final models except where stated below.

Bland Altman plots showing the difference between clinical and automated CDR against the average of both methods are shown in figure 3.9. HRT appeared to underestimate small CDR and overestimate large CDR compared to clinical measurement.

This effect was accentuated by classification of 18% CDR values as zero by the HRT. This is evident as a cluster of negative points for low average values of CDR (figure 3.9a). Excluding these points reduced the gradient of the regression line but the effect was still observable (figure 3.9b).

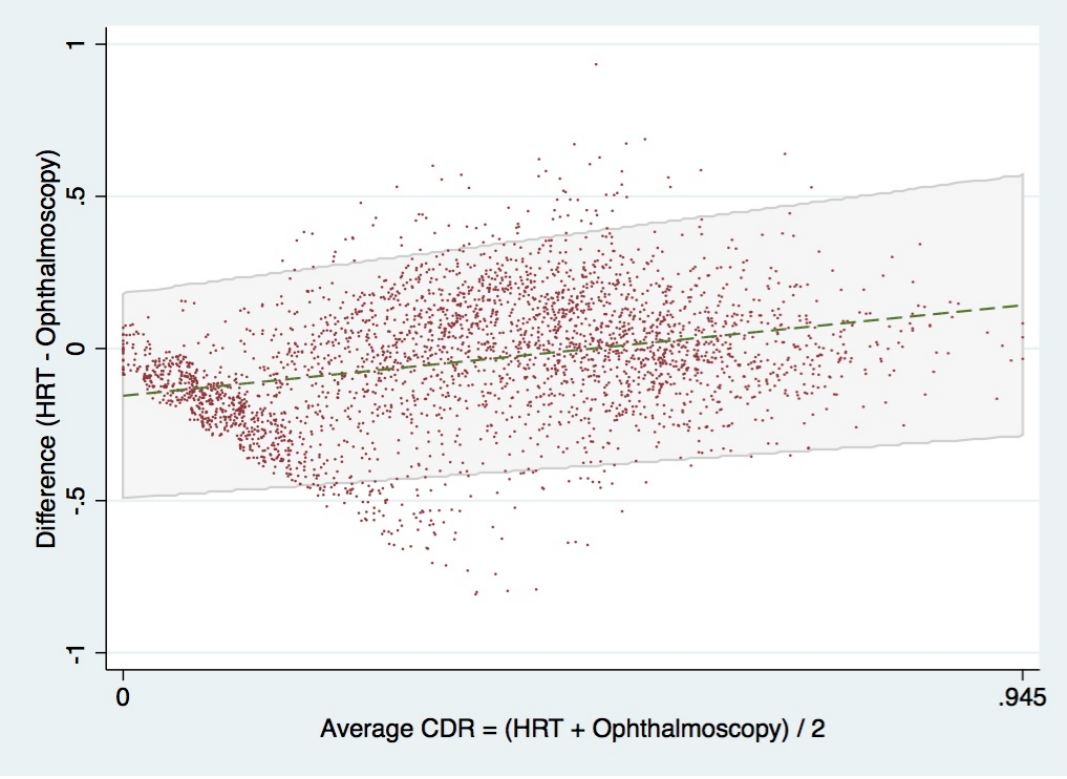


figure 3.9 Bland Altman plot of average CDR

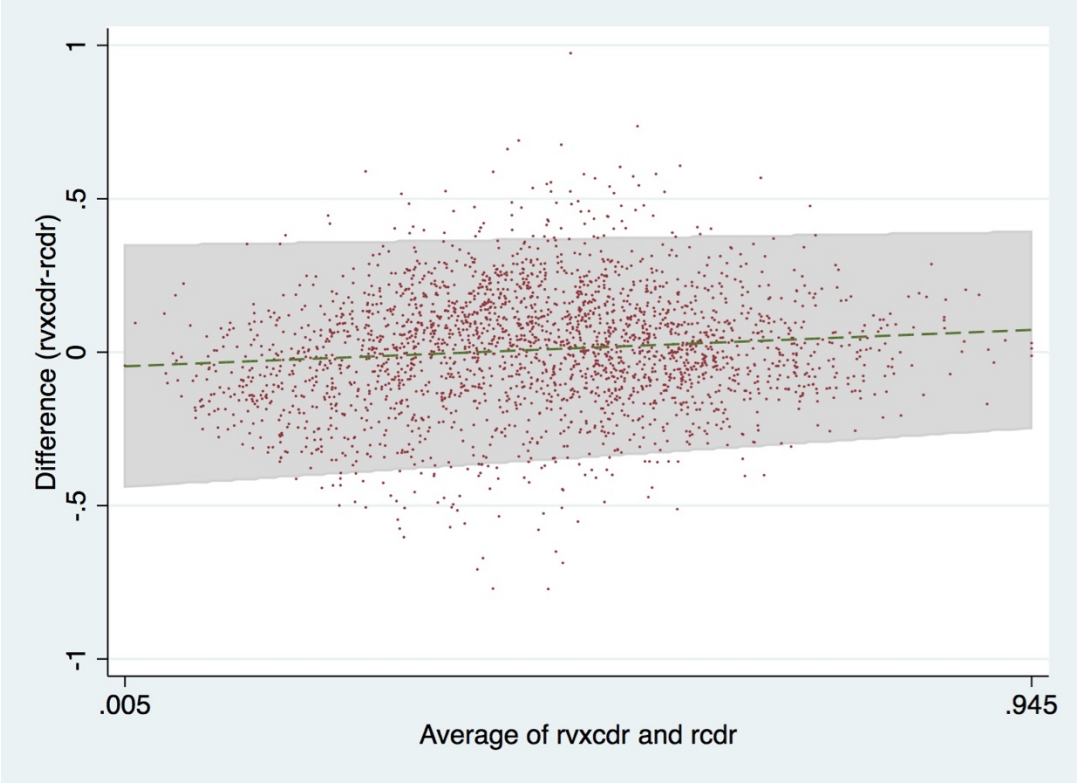


figure 3.9 Bland Altman plot of average CDR with HRT zero outputs excluded

After excluding those with glaucoma and adjusting for age and sex, we found no significant difference in HRT derived measures of CDR between groups. However, we found significant differences in clinical assessment between the 4 optometrists. When compared to the most conservative assessor, the difference in average clinical CDR ranged from 1-16%.

	rho_c	SE(rho_c)	Obs
Right eyes			
HRT linear cdr vs vertical cdr	0.782	0.005	3329
Optom CDR vs HRT Linear CDR	0.573	0.011	3319
Optom CDR vs HRT Vertical CDR	0.556	0.011	3376
Left eyes			
HRT linear cdr vs vertical cdr	0.796	0.005	3324
Opt CDR vs HRT Lin CDR	0.572	0.011	3302
Opt CDR vs HRT Vert CDR	0.554	0.011	3371
concord lcdr lvxcdr			
	Agreement	Expected Agree	Kappa
Right			
HRT linear cdr vs vertical cdr	88.51%	73.64%	0.564
Opt CDR vs HRT lin CDR	85.98%	77.93%	0.3647
Opt CDR vs HRT vert CDR	83.04%	73.10%	0.3695
Left			
HRT linear cdr vs vertical cdr	88.93%	73.76%	0.578
Opt CDR vs HRT lin CDR	85.85%	77.88%	0.3606
Opt CDR vs HRT vert CDR	83.30%	73.44%	0.3711
kap lxcdr lvxcdr2, wgt(w)			
Intraclass correlations , Two-way mixed-effects model, Consistency of agreeme			
Right eyes			
HRT linear cdr vs vertical cdr			
	ICC	[95% Conf. Int]	
Individual	0.84	0.83	0.85
Average	0.91	0.91	0.92
ICC=0.00: F(3328.0, 3328.0) = 11.33	Prob > F = 0.000		
n=3329			
Optom CDR vs HRT Linear CDR			
Individual	0.60	0.58	0.62
Average	0.75	0.73	0.77
ICC=0.00: F(3318.0, 3318.0) = 3.99	Prob > F = 0.000		
n=3319			
Optom CDR vs HRT Vertical CDR			
Individual	0.56	0.54	0.58
Average	0.72	0.70	0.74
ICC=0.00: F(3375.0, 3375.0) = 3.55	Prob > F = 0.000		
n=3376			

table 3.24 measures of agreement of CDR

In the right eye analysis, 224 (6.3%) of eyes were excluded due to the presence of other other types of disc pathology including other forms of glaucoma. In the worst eye analysis, 165 (4.7%) individuals were excluded for the same reason. Tabulated outcomes for each test are listed in table 3.25. The study optometrists failed to record a result for 0.9% of individuals and 1.5% of right eyes. SAS performed the best of the HRT measures, providing an output for every HRT scan, omitting a result for just 1.9% of individuals and 3.7% of right eyes. GPS performed the worst, failing to produce an output for 3.3% of individuals and 8.4% of right eyes.

Unadjusted results for the performance of each tests against our reference standard of arbitrated ophthalmologist assessment are listed in table 3.26, which shows test outcomes when borderline results were classed as normal, optimising specificity. The change in sensitivity and specificity when treating borderline results as normal or abnormal is shown in the crude ROC curves (figure 4.7.1) and include analysis of right eyes (figure 4.7.1a) and worst eyes (figure 4.7.1b) and the effect on all four tests when the threshold for a positive result is reduced from ‘abnormal’ to ‘abnormal or borderline’.

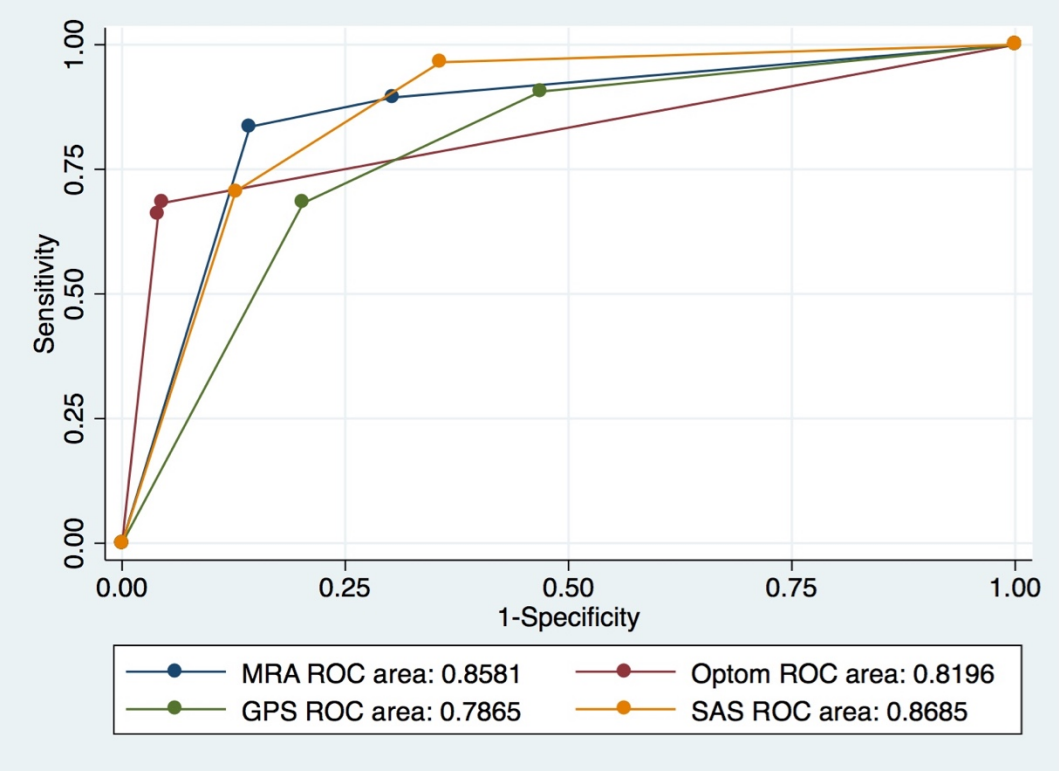


figure 3.11 Unadjusted ROC curve for right eyes

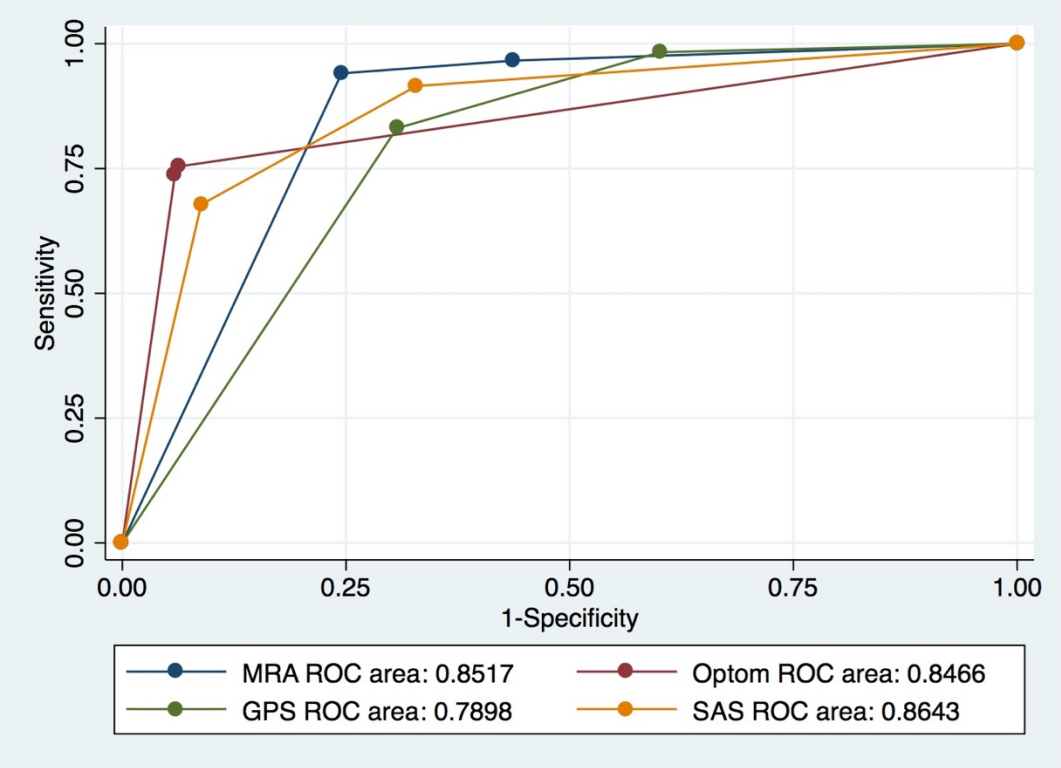


figure 3.12 Unadjusted ROC curve for worst eyes

We found that the change in classification had a minimal effect on clinical assessment using Jonas criteria due to the relatively low number of eyes (<1%) that the study optometrists recorded as borderline. There was some improvement in MRA sensitivity in right eyes when borderline results were classed as abnormal but for the worst eye of each individual we found a negligible improvement in test sensitivity against a large loss in test specificity. Overall MRA was the most sensitive test although results for SAS did surpass those for MRA in the single eye analysis when borderline results were classed as normal. A similar improvement in sensitivity was seen with GPS but was associated with an unacceptable fall in specificity to below 50%.

MRA results were similar for individuals and eyes with previously diagnosed and newly diagnosed glaucoma. For other tests, there was a reduction in sensitivity when we examined results for newly diagnosed glaucoma separately. This was most obvious in the clinical assessment of right eyes by optometrists with a 13.2% reduction in sensitivity for newly diagnosed glaucoma. A similar but less pronounced reduction in sensitivity for newly diagnosed glaucoma was seen with SAS (9.2%) and GPS (8.4%).

table 4.7.1a test outcomes worst eyes					
Optom worst eye	Normal	Borderline	Abnormal	Unclassified	Total
Normal	3,024	15	187	27	3,253
%	92.96	0.46	5.75	0.83	100
OAG / NTG	29	4	95	3	131
%	22.14	3.05	72.52	2.29	100
Total	3,053	19	282	30	3,384
%	90.22	0.56	8.33	0.89	100
MRA worst eye					
Normal	1,796	601	777	79	3,253
%	55.21	18.48	23.89	2.43	100
OAG / NTG	4	3	117	7	131
%	3.05	2.29	89.31	5.34	100
Total	1,800	604	894	86	3,384
%	53.19	17.85	26.42	2.54	100
SAS worst eye					
Normal	2,151	764	280	58	3,253
%	66.12	23.49	8.61	1.78	100
OAG / NTG	10	30	86	5	131
%	7.63	22.9	65.65	3.82	100
Total	2,161	794	366	63	3,384
%	63.86	23.46	10.82	1.86	100
GPS worst eye					
Normal	1,255	925	970	103	3,253
%	38.58	28.44	29.82	3.17	100
OAG / NTG	2	19	101	9	131
%	1.53	14.5	77.1	6.87	100
Total	1,257	944	1,071	112	3,384
%	37.15	27.9	31.65	3.31	100
table 4.7.1b test outcomes right eyes					
Optom Right eyes	Normal	Borderline	Abnormal	Unclassified	Total
Normal	3,033	14	124	46	3,217
%	94.28	0.44	3.85	1.43	100
OAG / NTG	31	2	70	5	108
%	28.7	1.85	64.81	4.63	100
Total	3,064	16	194	51	3,325
%	92.15	0.48	5.83	1.53	100
MRA Right eyes					
Normal	2,146	481	453	137	3,217
%	66.71	14.95	14.08	4.26	100
OAG / NTG	9	6	85	8	108
%	8.33	5.56	78.7	7.41	100
Total	2,155	487	538	145	3,325
%	64.81	14.65	16.18	4.36	100
SAS Right eyes					
Normal	1,998	718	386	115	3,217
%	62.11	22.32	12	3.57	100
OAG / NTG	4	24	72	8	108
%	3.7	22.22	66.67	7.41	100
Total	2,002	742	458	123	3,325
%	60.21	22.32	13.77	3.7	100
GPS Right eyes					
Normal	1,571	781	603	262	3,217
%	48.83	24.28	18.74	8.14	100
OAG / NTG	8	20	62	18	108
%	7.41	18.52	57.41	16.67	100
Total	1,579	801	665	280	3,325
%	47.49	24.09	20	8.42	100

table 3.25 HRT test outcomes

Worst Eye, all open angle glaucoma								
	Optometrist		MRA		SAS		GPS	
Prevalence Pr(A)	3.80%	3.2 - 4.52%	3.80%	3.1 - 4.47%	3.80%	3.2 - 4.5%	3.70%	3.1 - 4.44%
Sensitivity Pr(+A)	74.20%	65.7 - 81.5%	94.40%	88.7 - 97.7%	79.40%	71.2 - 86.1%	82.80%	74.9 - 89%
Specificity Pr(-N)	94.20%	93.3 - 95%	75.50%	74 - 77%	80.90%	79.5 - 82.2%	69.20%	67.6 - 70.8%
ROC area (Sens. + Spec.)/2	0.842	80.4 - 88%	0.849	82.8 - 87.1%	0.801	76.5 - 83.7%	0.76	72.5 - 79.5%
Observations	3354		3298		3321		3272	
Likelihood ratio (+) Pr(+A)/Pr(+N)	12.8	10.8 - 15.2	3.85	3.58 - 4.15	4.15	3.7 - 4.65	2.69	2.44 - 2.96
Likelihood ratio (-) Pr(-A)/Pr(-N)	0.274	0.204 - 0.367	0.0748	0.0364 - 0.154	0.255	0.181 - 0.359	0.249	0.168 - 0.367
Odds ratio LR(+)/LR(-)	46.8	30.7 - 71.2	51.6	24.4 - 109	16.3	10.5 - 25.2	10.8	6.74 - 17.3
Positive predictive value Pr(A+)	33.70%	28.2 - 39.5%	13.10%	10.9 - 15.5%	14.10%	11.6 - 16.8%	9.43%	7.75 - 11.3%
Negative predictive value Pr(N-)	98.90%	98.5 - 99.3%	99.70%	99.4 - 99.9%	99%	98.5 - 99.3%	99%	98.5 - 99.4%
Worst eye, new open angle glaucoma								
Prevalence Pr(A)	1.60%	1.2 - 2.15%	1.70%	1.3 - 2.22%	1.70%	1.3 - 2.24%	1.70%	1.3 - 2.2%
Sensitivity Pr(+A)	64.20%	49.8 - 76.9%	94.40%	84.6 - 98.8%	60%	45.9 - 73%	77.40%	63.8 - 87.7%
Specificity Pr(-N)	94.40%	93.5 - 95.2%	75.60%	74 - 77.1%	91.40%	90.3 - 92.3%	69.30%	67.6 - 70.9%
ROC area (Sens. + Spec.)/2	0.793	72.7 - 85.8%	0.85	81.8 - 88.2%	0.757	69.1 - 82.2%	0.733	67.6 - 79.1%
Observations	3218		3171		3192		3145	
Likelihood ratio (+) Pr(+A)/Pr(+N)	11.5	8.96 - 14.7	3.86	3.53 - 4.22	6.95	5.44 - 8.86	2.52	2.16 - 2.94
Likelihood ratio (-) Pr(-A)/Pr(-N)	0.38	0.265 - 0.544	0.0735	0.0245 - 0.221	0.438	0.317 - 0.605	0.327	0.199 - 0.538
Odds ratio LR(+)/LR(-)	30.2	17 - 53.7	52.5	17.3 - 159	15.9	9.17 - 27.4	7.7	4.07 - 14.6
Positive predictive value Pr(A+)	16.10%	11.4 - 21.8%	6.27%	4.71 - 8.17%	10.90%	7.59 - 14.9%	4.14%	2.99 - 5.57%
Negative predictive value Pr(N-)	99.40%	99 - 99.6%	99.90%	99.6 - 100%	99.20%	98.8 - 99.5%	99.40%	99 - 99.7%
Right, all open angle glaucoma								
Prevalence Pr(A)	3.10%	2.6 - 3.8%	3.10%	2.6 - 3.81%	3.10%	2.5 - 3.79%	3%	2.4 - 3.62%
Sensitivity Pr(+A)	68%	58 - 76.8%	85%	76.5 - 91.4%	72%	62.1 - 80.5%	68.90%	58.3 - 78.2%
Specificity Pr(-N)	96.10%	95.4 - 96.7%	85.30%	84 - 86.5%	87.60%	86.3 - 88.7%	79.60%	78.1 - 81%
ROC area (Sens. + Spec.)/2	0.82	77.5 - 86.6%	0.851	81.6 - 88.7%	0.798	75.3 - 84.2%	0.742	69.4 - 79.1%
Observations	3274		3180		3202		3045	
Likelihood ratio (+) Pr(+A)/Pr(+N)	17.4	14 - 21.6	5.78	5.13 - 6.51	5.79	4.96 - 6.75	3.38	2.89 - 3.95
Likelihood ratio (-) Pr(-A)/Pr(-N)	0.333	0.252 - 0.442	0.176	0.11 - 0.28	0.32	0.233 - 0.438	0.391	0.287 - 0.532
Odds ratio LR(+)/LR(-)	52.1	33.3 - 81.6	32.9	18.9 - 57	18.1	11.6 - 28.3	8.64	5.5 - 13.6
Positive predictive value Pr(A+)	36.10%	29.3 - 43.3%	15.80%	12.8 - 19.2%	15.70%	12.5 - 19.4%	9.32%	7.22 - 11.8%
Negative predictive value Pr(N-)	98.90%	98.5 - 99.3%	99.40%	99.1 - 99.7%	99%	98.5 - 99.3%	98.80%	98.3 - 99.2%
Right, new open angle glaucoma								
Prevalence Pr(A)	1.30%	0.96 - 1.79%	1.40%	1 - 1.87%	1.40%	1 - 1.86%	1.30%	0.91 - 1.76%
Sensitivity Pr(+A)	54.80%	38.7 - 70.2%	83.70%	69.3 - 93.2%	62.80%	46.7 - 77%	60.50%	43.4 - 76%
Specificity Pr(-N)	96.20%	95.4 - 96.8%	85.20%	83.9 - 86.5%	87.60%	86.4 - 88.7%	79.60%	78.1 - 81%
ROC area (Sens. + Spec.)/2	0.755	67.8 - 83.1%	0.845	78.9 - 90.1%	0.752	67.9 - 82.5%	0.701	62.1 - 78%
Observations	3173		3086		3107		2956	
Likelihood ratio (+) Pr(+A)/Pr(+N)	14.3	10.3 - 19.8	5.67	4.85 - 6.64	5.06	3.95 - 6.49	2.96	2.27 - 3.87
Likelihood ratio (-) Pr(-A)/Pr(-N)	0.47	0.337 - 0.656	0.191	0.0969 - 0.376	0.425	0.288 - 0.626	0.496	0.334 - 0.736
Odds ratio LR(+)/LR(-)	30.4	16.2 - 56.8	29.7	13.4 - 65.8	11.9	6.42 - 22.1	5.97	3.13 - 11.4
Positive predictive value Pr(A+)	16.10%	10.5 - 23.1%	7.42%	5.25 - 10.1%	6.63%	4.42 - 9.51%	3.72%	2.37 - 5.52%
Negative predictive value Pr(N-)	99.40%	99 - 99.6%	99.70%	99.4 - 99.9%	99.40%	99 - 99.7%	99.40%	98.9 - 99.6%

table 3.26 diagnostic performance of HRT and optometrist disc assessment

Table 4.7.3a Diagnostic performance of each individual test against reference standard for worst eyes					
New OAG / NTG	Obs	Area	Std. Err.	95% CI	
worst eye optom	3,087	0.79	0.03	0.73	0.86
worst eye mra	3,087	0.85	0.02	0.82	0.88
worst eye sas (category)	3,087	0.85	0.02	0.80	0.90
worst eye gps (category)	3,087	0.77	0.02	0.72	0.81
All OAG/NTG	Obs	Area	Std. Err.	95% CI	
worst eye optom	3,211	0.85	0.02	0.81	0.89
worst eye mra	3,211	0.85	0.01	0.83	0.87
worst eye sas (category)	3,211	0.86	0.02	0.83	0.90
worst eye gps (category)	3,211	0.79	0.01	0.76	0.82
Table 4.7.3b Diagnostic performance of each individual test against reference standard for right eyes					
Right eye New OAG / NTG	Obs	Area	Std. Err.	95% CI	
right optom	2,893	0.77	0.04	0.69	0.85
right mra	2,893	0.85	0.03	0.79	0.91
right sas (categorical)	2,893	0.84	0.03	0.79	0.89
right gps (categorical)	2,893	0.74	0.04	0.66	0.82
Right eye all OAG / NTG	Obs	Area	Std. Err.	95% CI	
right optom	2,977	0.82	0.03	0.77	0.87
right mra	2,977	0.86	0.02	0.82	0.90
right sas (categorical)	2,977	0.87	0.01	0.84	0.90
right gps (categorical)	2,977	0.79	0.02	0.74	0.83
Table 4.7.3c Diagnostic performance of each individual test against reference standard for right eyes (result					
Right eye all OAG / NTG adjusted	Obs	Area	Bootstrap Std. Err.	95% CI (bias corrected)	
right optom	2,977	0.76	0.04	0.69	0.83
right mra	2,977	0.84	0.03	0.78	0.89
right sas (continuous)	2,977	0.83	0.03	0.78	0.88
right gps (continuous)	2,977	0.79	0.03	0.73	0.84
right sas (categorical)	2,977	0.84	0.02	0.79	0.88
right gps (categorical)	2,977	0.76	0.03	0.71	0.81

table 3.27 HRT / Optom Area Under the Curve (AUC) results for (a) unadjusted worst eyes, (b) unadjusted right eyes, (c) covariated adjusted right eyes

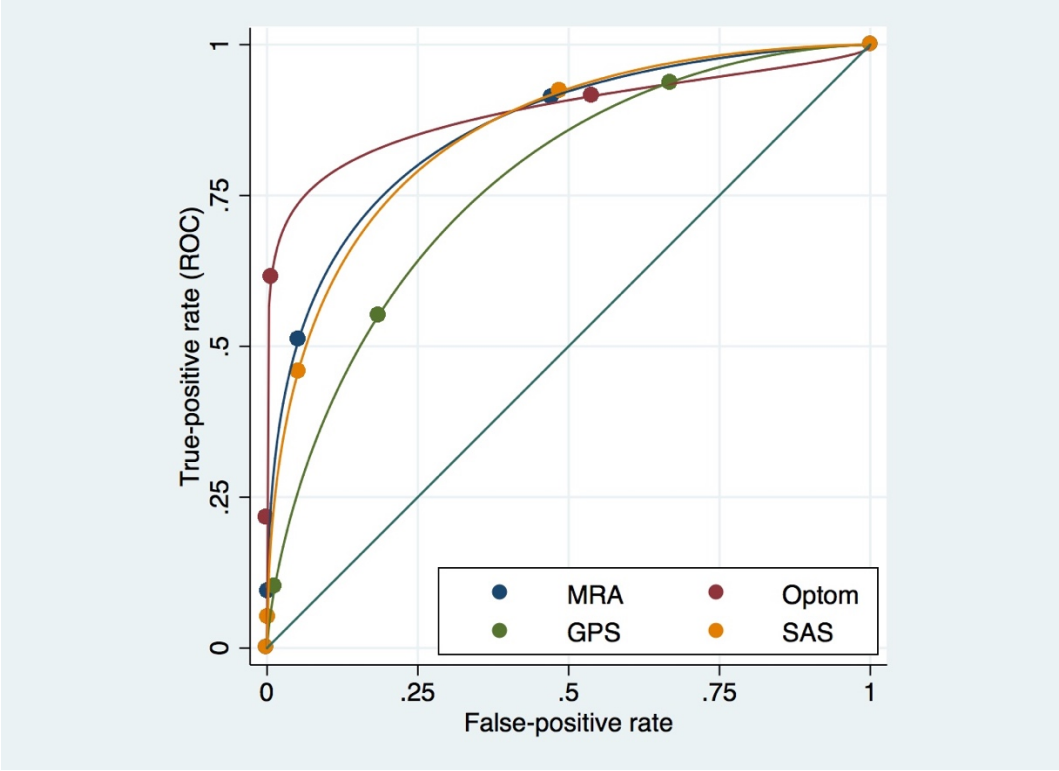


figure 3.13 Covariate adjusted ROC curve for right eyes with conventional cutoffs marked

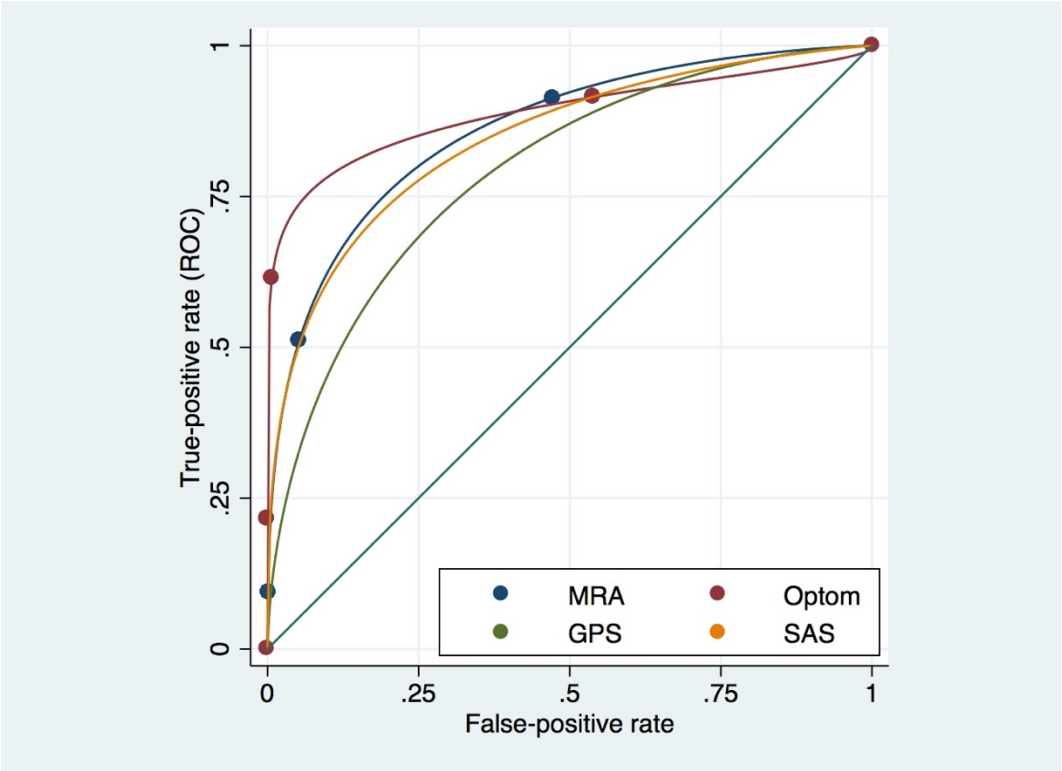


figure 3.14 Covariate adjusted ROC with continuous data (SAS / GPS)

For MRA, we found that ADS and MPHSD were significant covariates of both sensitivity and specificity within the Probit Maximum likelihood model. Disc area had a significant effect on test specificity ($p<0.001$) but not sensitivity ($p=0.86$). Age and lens opacity as measured by LOCS3 score were also significant covariates in the univariate analysis but were omitted from the final model due to colinearity with MPHSD. A similar but less obvious effect was seen with the other HRT measures. For optometrist assessment ADS, MPHSD and Disc Area as measured by HRT were associated with a significant effect on specificity but not sensitivity. ROC curves adjusted for these covariate effects are shown in figure 4.7.2. Probit analysis was used to examine the effect of different cutoffs for ADS (figure 3.15) and MPHSD (figure 3.16) on adjusted ROC curves.

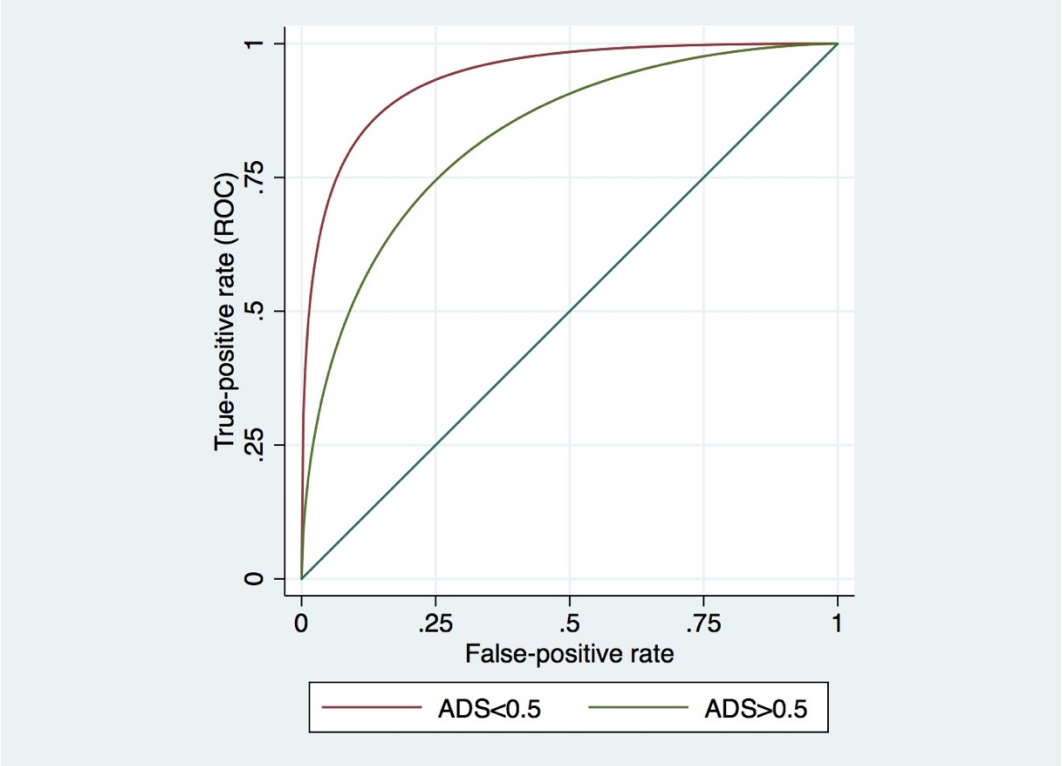


figure 3.15 Covariate adjusted ROC stratified by ADS

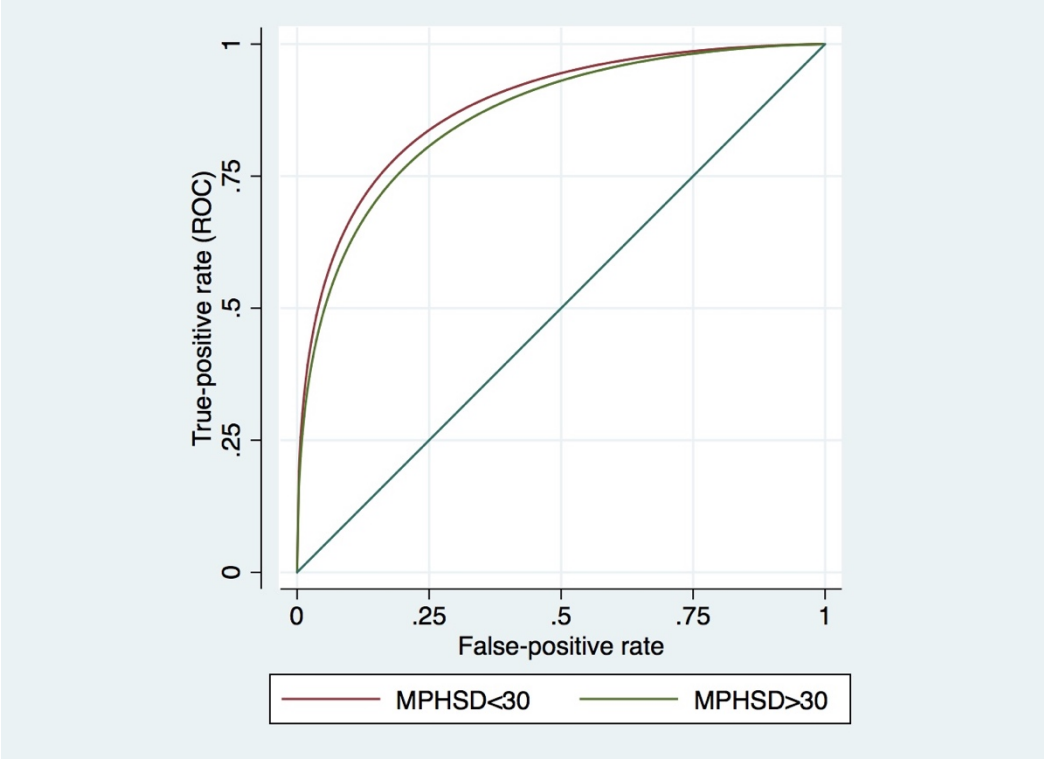


figure 3.16 Covariate adjusted ROC stratified by MPHSD

Chapter 4 Discussion

4.1 Cataract

To our knowledge, this is the first epidemiological study to report the population prevalence of untreated PCO and the first to demonstrate a difference in acuity between those who have had cataract surgery in one or both eyes versus those who have not had cataract surgery.

4.2 Previous cataract surgery

In our population 9.5% of eyes showed evidence of previous lens surgery. We found that pinhole acuity was significantly better in those who undergone bilateral cataract surgery. We did not find any difference in unaided / spectacle acuity (in the better eye), field defects or satisfaction with vision between those who had surgery in one or both eyes. At the time of the study there were no restrictions on second eye surgery and it is likely that those who had undergone unilateral surgery did so because they had good vision in the other eye or because their other eye had limited visual potential. This could have respectively increased or decreased the strength of the association we observed. Previous studies have suggested that one of the demonstrable benefits of bilateral surgery is a reduction in falls [183], Others include improvements in stereoacuity[184] and visual related quality of life[185]. These metrics were beyond the scope of this study.

4.3 Posterior Capsular Opacification

We found that 10% of pseudophakic eyes had evidence of previous capsulotomy. When we included eyes that underwent treatment as a result of the study, the capsulotomy rate for our population increased to 17%. We may have overestimated rates of previous capsulotomy as there will have been some overlap between those who had previous laser and those in who were found to have opacification naturally confined to the periphery. However, there was an opportunity to record this separately and those who were identified as having a 'clear central lens' at examination were significantly more likely to have recalled previous laser (OR=31, 95% CI 17-59, $p<0.001$) when interviewed than other groups, suggesting that our assessment was robust.

The population based design removes the risk of loss to follow up inherent in hospital based cohort studies but limits the opportunity to include lens factors[186] in our analysis. [The market shift from round to sharp edge optics will hopefully have limited the importance of this]. Conversely, the decision to use a treatment based definition of PCO will have reduced our figures but will make them more applicable when planning treatment provision. The rates we describe appear in line with lower estimates of previous reports which place the cumulative probability of PCO at 17-25% at 3 years and 18-38% after 5yrs[187,188]. Crucially, the rates of treated and treatable PCO did not appear to vary with age suggesting that within our populations adequate mechanisms exist to identify and treat this complication.

4.4 Cataract and Gender

After adjusting for age, we found that women were 30% more likely to have cataract than men. This relationship was significant for nuclear and cortical cataract in either eye but not for posterior subcapsular changes.

The prevalence is cataract has been shown to vary with age, gender and race[189] and our results are consistent with the Beaver Dam[73] and Skovde[76] eye studies which both showed higher rates of nuclear and cortical opacities in Caucasian women compared to men. In the Blue Mountain[74] study only cortical cataract varied with gender and a weak protective effect from hormone replacement therapy was also seen[190]. Estrogen receptors are present in the lens and in vitro studies have suggested that they have a role in the formation of cataract[191]. Differences can also be attributed to barriers to surgery for women which have been reported in both developing[192] and developed countries[193]. However, this did not appear to be a factor in our population, since women were found to have a higher rate of previous surgery than men. The difference persisted after adjusting for age but did not reach conventional levels of statistical significance.

4.5 Age and Cataract

We noticed a marked rise in previous surgery with age but a plateau in average lens density around the age of 80. (table 2) as an increasing prevalence of the denser grades is found in the 85 and over group.The median age of those selected for surgery was 79, which is similar to the results from the UK national dataset which reported a median age for first eye cataract surgery of 77 years[63]. The small difference is probably related to our exclusion of individuals under 65 yrs. It maybe that intervention is simply less likely in this group or that the environmental and genetic factors that determine cataract act mainly before the age of 80 and that those who survive beyond this age have a lower than expected incidence of cataract along with better general health. Prospective follow up would be needed to explore this further.

4.6 Vision and Cataract Surgery

There was a strong relationship between mean acuity as measured by a high contrast chart and lens grade for all types of cataract but considerable variation in the range of acuity for each grade. This may be one of the reasons why only a small proportion of those with significant cataract went on to have surgery. We found that subjective satisfaction with vision was the most important predictor of those with significant cataract who went on to have surgery. The relationship between driving status and incident surgery was also explored but we found no clear association. Similarly, within the adjusted model there was no clear association between significant cataract and time since the last visit to their own optometrist. While we would have expected more undiagnosed cataract in those who had not seen an optometrist in some time, it is equally possible that individuals who had noticed a deterioration in their vision due to progressive cataract would be more likely to have seen their own optometrist recently.

Cataract surgery was offered to a number of patients who had been referred to the HES for other reasons. In most cases (54%) they had been referred to the HES with unexplained visual field defects. This is consistent with reports of cataract as an important cause of visual field defects[108] along with our own analysis of the cause of visual field defects within this population.

4.7 Other Studies on Cataract

Population studies have previously described cataract prevalence in the UK. Reidy et al, reported 30% prevalence of significant cataract in 1547 patients from North London using LOCS 2 grading but without specifying their diagnostic criteria[66] as well as a gender effect of similar size to our own. The Melton Mowbray Eye study reported an overall prevalence of 11% using LOCS 3 grading but examined a younger population of 560 individuals. Their rates for their older age groups were similar to our population[67]. Frost et al examined visual related quality of life and subjective visual satisfaction as well as lens grade in order to better estimate which individuals would go on to have cataract surgery[68]. They examined 1078 individuals and estimated 0-19 cataract operations per thousand would be those required for those aged 65-74. This rose to 24-89 operations per thousand for those aged over 75 years. Within our population, 18 operations per thousand were performed for those 65-75 years and 76 (95% CI 66 – 86) cataract operations per thousand for those over 75 years. This was similar to the upper range of their estimates. We would argue that our results are more generalizable both because or our larger sample size and because we did not use surrogate measures but instead recorded which patients underwent surgery as a direct result of the study visit.

International comparisons are more complex. In addition to the demographic differences between populations, comparisons between studies are complicated by the use of different scoring systems and the lack of a single definition for

'significant cataract'. Levels of severity can vary substantially with different grading methods[69] though systems have been proposed to convert scores[70,71] and standardise definitions between studies[72].

The Beaver Dam[73] and Blue Mountain[74] studies were of similar size to our study population (n>3000). Both used the Wisconsin grading system and reported similar rates of late cataract to our own but lower rates of previous surgery. This is not unexpected, as the threshold for cataract surgery has fallen with time[75]. The Skövde Cataract study[76] examined 565 individuals using LOCS 3 grading. They reported lower rates of significant cataract using similar criteria but excluded pseudophakes from their analysis.

By presenting age stratified unadjusted results for our population we have tried to allow for subsequent aggregation while minimising information loss. We have used a pragmatic definition of significant cataract based on the average results of patients selected for surgery by experienced surgeons. While our definition could be influenced by both patient and surgeon subjectivity, it is similar to consensus derived criteria[72] and our results are in line with other large population based studies. Using this definition, we diagnosed over a third of our population with significant cataract of which just 12% underwent surgery, with an uptake rate of 82% amongst those offered surgery. 9.5% of eyes showed signs of previous cataract surgery of which 17% either required or had received treatment for subsequent posterior capsular opacification. The results of this study will assist healthcare planners organise cataract services for the elderly.

4.8 Age related Macular Degeneration

The size of this study is a key strength along with standard approach to grading. It is the largest population-based study of AMD in the elderly in the UK to date and includes a large number of participants over 80 years old. The use of fundus photography provides clear advantages over studies that rely on hospital records or registration data and the use of dilation enhances the probability the we were able to detect of early disease. The attendance rates are comparable to other studies[194–197] which is reassuring given the older average age of our population.

The prevalence of advanced AMD (grade 4) in the over 65 year population was 4.6%, which is higher than the figures reported in other comparable UK based studies, including the EUREYE (3.8% in the Belfast arm) and the Speedwell study (0.5%) but similar to the figure of 4.8% calculated by Owen et al who standardised the results of a meta-analysis on Caucasian populations to ONS data for the UK population[198], though prevalence in older individuals was higher in the Bridlington population. Similarly, in the Rotterdam study, in those over 85 years old, the prevalence of late AMD was 11.1% compared to 15.7% in Bridlington. As far as we are aware, this analysis is the first to determine the prevalence of grade 4c AMD (peripapillary CNV) in the UK.

Disease asymmetry was present in 64% of participants. Registration statistics only identify those with binocular loss and are likely to miss these individuals unless they have sight loss from other causes in their other eye.

We found that dissatisfaction with vision increased with grade and was more common in elderly participants. It is likely this was confounded by other visual and non-visual comorbidities. The elderly are at increased risk from falls and can be disproportionately affected by changes to their vision

A key limitation is the use of non-stereoscopic photographs, making it difficult to identify subtle pigment epithelial detachments (PED), leading to an underestimation of the prevalence of nAMD. We feel that this unlikely as in active diease, other signs such as retinal haemorrhages or gliosis which would normally have been present. While the exclusion of individuals registered as sight impaired will have led to an underestimation of the prevalence of AMD, we were able to capture the likely proportion excluded through the use of local registration data.

In conclusion, this analysis provides contemporary data for prevalence rates of different stages of AMD in a UK population. It shows that the disease is common and often asymmetric.

4.9 Visual Field Defects

There was a 10% prevalence of visual field loss in individuals, over 65 years old. Test sensitivity was 70% for patients with a final diagnosis of open angle or normal tension glaucoma and specificity was 92% for reproducible loss. Glaucoma was the single biggest attributable cause of field loss, followed by AMD. The presence of cataract was a significant risk factor for field loss within a logisitic regression model. The increase in field defects with increasing age is a common finding across studies but estimates of prevalence vary and comparison are complicated by the absence of a universal definition for field defects or standard mode of testing.

There are 2 other studies that have sought to identify the cause and relative frequency of field defects in a population based setting. In the Rotterdam study, a 56 point suprathreshold Humphrey field test was performed on 6250 individuals, over 55 years old. Field loss was verified with a second suprathreshold test and Goldmann kinetic perimetry was performed on those with consistent loss or unreliable results[97]. In the Beijing study a single frequency doubling test was performed in 4350 subjects over the age of 40 years[108]. Glaucoma was the leading cause of field loss in the Rotterdam study and was responsible for 27% of field defects, compared to 23% in the Beijing study. 50% of visual field defects were unexplained in the Beijing study and cataract, followed by glaucoma, was the single leading cause, responsible for

26% of field defects. In both studies, the leading causes were diagnoses of exclusion and did not necessarily represent positive findings.

The Rotterdam study reported a prevalence of field loss of 3% in those aged 55-64 years, rising to 19% in those over 85 years old. The Beijing study reported a slightly higher prevalence of 5.3% in those aged 40-49 years, rising to 25.4% in those over 70 years old. In Beaver Dam study of individuals 43-84 years old, 20% of subjects failed the initial 26 point Henson screening test. The prevalence of glaucoma was 2.1% glaucoma in their population[199]. In the Melbourne study, VF loss in 16-17% of eyes was reported in using a mixed protocol of suprathreshold and threshold Humphrey field tests[107]. In the Baltimore eye study, 26% individuals over 40 years old, failed Humphrey Full field 120 suprathreshold test, of which 36% went on to have an abnormal Goldmann field. Test sensitivity for detection of glaucoma was 52% at a specificity of 90%. 16% of glaucoma in the study was pre-perimetric[200]. In the Tajimi study, 9% of individuals aged 40-92 years had an abnormal FDT result. They reported a sensitivity of 56% for detecting glaucoma with specificity of 93%[109]. In a study of 10 000 drivers, Johnson et al reported an overall prevalence of 3.3% for field loss in those over 16 years, rising to 13% in those of 65 years. Within their sample, 0.6% had a history of glaucoma, of whom 35% had detectable field loss[110].

The overall prevalence of field loss of 15.5% in the Beijing study while the Rotterdam study reported a much lower prevalence of 6%. Much of this

difference can be explained by the use of multiple tests. In the Rotterdam study, around half the individuals who failed the first suprathreshold screening test had a normal second test and only 37% of those with 2 negative screening tests had a detectable defect on Goldmann perimetry. In the Baltimore Eye Study where 36.3% of individuals with an abnormal Humphrey Full Field 120 had a defect on Goldmann perimetry[200]. Similarly in the OHTS study, two thirds of individuals with 2 consecutive abnormal test had a normal subsequent test[201]. A specificity of 94% has previously been reported for the Henson perimeter when used in population screening [202]. This is in line with our results and compares favourably to 80-96% for frequency doubling perimetry[109,203,204]. Use of frequency doubling perimetry for population screening is currently limited by its relatively low sensitivity[109,204].

The choice of Henson perimetry seems reasonable. Henson perimeters are the most common perimeters in use among community optometrists in the UK[205]. The device has been validated previously for population screening for glaucoma[202] and has been used in other epidemiological studies[199,206,207]. We adopted a suprathreshold strategy with automatic extension of the test where any point was missed. Where a defect detected the patient was referred for a hospital assessment with further testing. Visual field results can be variable and it is likely we may will have missed some subtle defects. Ideally, we would have peformed at least 2 threshold visual field tests in all participants but this would not have been practical. While a significant proportion of those diagnosed with glaucoma had normal screening fields it is not possible to infer a test sensitivity

from this because we did not test everyone twice. Comparisons are further complicated by the variability inherent in field testing[208] and uncertainty over structure function relationships in glaucoma in those with glaucomatous optic neuropathy but normal fields[103].

The presence of cataract is known to interfere with both white-on-white and frequency doubling perimetry[209] though the effect is variable. In this study, there was a strong association between field loss and cataract within our logisitc regression model (OR 3.5, 95 % CI 2.7-4.7, p<0.0001) but field defects were rarely attributed directly to cataract because of the inherent subjectivity in doing so. Instead, they were normally classified as test artefacts. The Beijing study classified cataract as the cause of visual field defects where significant lens opacities were present along with a normal fundus appearance. Using the same criteria, we would have obtained similar results from our population. In the Blue mountain study, loss of 5 or more points was seen in up to 22% of patients with cataract[210] but there was no association with sectoral field loss and after adjusting for age and other confounders the association between cataract and points lost disappeared[211].

In conclusion, in this population based study we have shown that the Henson perimeter performs within acceptable limits for detecting field loss and that glaucoma remains the single most important cause of field defects in all age groups. Visual field testing is a useful tool detection of eye disease as it allows direct identification of those with important aspect of functional visual loss.

4.10 Optometrists Screening

This is the first study to examine the use of optometrists to screen for glaucoma in an epidemiological population. For tests with a specificity of > 90% for new OAG, intraocular pressure was the least sensitive (48%), while clinical CDR ≥ 0.7 was the most sensitive (76%). Optometric impression showed the best specificity (98%) with acceptable sensitivity (51%) but may have been subject to verification bias since final diagnosis was based on clinical impression albeit with the reference to longitudinal results. Because of the low relative prevalence of new glaucoma, the test specificity of 98% still resulted in referral of nearly twice as many false positives as new patients with glaucoma.

The absence of an established gold standard test requires a number of alternative approaches to assess the utility of screening tests for glaucoma. These include confirmation of disease at follow-up, stratification according to treatment and comparison against other tests or combinations of tests[212]. Our use of a robust epidemiological population, longitudinal diagnosis, stratification of disease groups and pragmatic approach to treatment are all strengths of this study.

An important limitation is that we are unable the exclude the possibility undiagnosed glaucoma, particularly in those not referred on to the hospital for a secondary examination. Despite this, we think the probability of false negatives is low. The population had good optometric surveillance with over half of

individuals having seen an optometrist within the last year. Hospital records were available for just under half of the population and we used multiple methods to ensure outcomes were available irrespective of both the mode of referral and the choice of secondary / tertiary provider. The population as a whole demonstrated minimal migration and attrition beyond mortality commensurate with an elderly population.

4.11 Screening with Intraocular pressure

The low sensitivity of intraocular pressure for diagnosis of glaucoma is consistent with previous epidemiological studies[213,214] and reviews[87,212]. IOP is known to fluctuate dynamically and this variability poses an important challenge to diagnosis and treatment[145]. Even, when confining our analysis to new untreated individuals with high pressure disease, we found that 40% recorded a normal pressure in both eyes at the screening visit. Our results are near identical to those from the Baltimore Eye Study[213] and are better than those from the Blue Mountain[214] and Rotterdam Eye Studies[166] (see table 4.4.2). The poorer results in these studies can be explained by the lower age and thereby lower disease prevalence in their population, the inclusion of treated individuals on IOP lowering medication in the Blue Mountain study, analysis by eye rather than by individual and lack of distinction between normal and high tension glaucoma.

Study	Population	Visual field	Sensitivity	Specificity	IOP	Sensitivity	Specificity
BEAP	3549	Henson pro 5000 26 / 68 point suprathreshol	56	86	GAT ≥ 21 mmHg	47	92
Baltimore	5308	Dicon suprathreshold	50	83	GAT > 21 mmHg	47	92
Blue Mountain	3654	Humphrey suprathreshold 30-2 76 point mod	47	83	GAT > 22 mmHg	14	98
Rotterdam	6576	Humphrey suprathreshold 24-2 56 point test	27	83	GAT > 21 mmHg	11	98
Meta-Analysis (Burr et al)	10200 / 20308	Various	71	85	GAT > 21 mmHg	46	95

table 4.1 comparison with other population based studies

4.12 Screening with Cup to Disc Ratio

In her meta-analysis, Burr et al identified 7 studies reporting test accuracy for ophthalmoscopy, including 4 population based studies. At the most common cut-off of CDR > 0.7, they reported an overall estimate of sensitivity of 60% and specificity of 94 %. At CDR > 0.7 our sensitivity was only 44% with a specificity of 96%. We found that a cut-off of CDR ≥ 0.7 offered a better trade off between sensitivity and specificity. Optic disc appearance is arguably the measure least prone to short term physiologic fluctuation and CDR was the most promising single test we identified but consistent subjective evaluation remains challenging. Spry et al compared results of ophthalmoscopy between community optometrists and ophthalmologists in research clinics and ophthalmologists in routine hospital clinics and found poor agreement in measurements of CDR between all 3 groups with adjusted inter-class correlation coefficients ranging from 0.46 to 0.54. The absolute mean difference they reported, ranged from 0.1 to 0.15 but they described wide tolerance limits of up to 40% of the range of values[215]. Conversely, Theodossiades and Murdoch reported that CDR was the most accurately assessed disc parameter, achieving a mean kappa of 0.84 when comparing results of direct ophthalmoscopy between 8 optometrists and an ophthalmologist[142]. We found that application of Jonas criteria was a more specific test but only achieved moderate sensitivity. The usefulness of ISNT rule when applied on its own is questionable[216] but it does provide a useful starting point for subjective evaluation of the optic nerve.

Glaucoma is normally identified through case finding by optometrists. Screening programs have been considered but the low prevalence, lack of a single screening test and uncertainties over the cost and impact of disease mean that age based screening is currently not viable[217]. Screening of high risk groups may, however, be cost effective[218] because of the higher prevalence of disease and therefore higher pre-test probability of a positive result. The use of multiple tests is another way of enriching the population, artificially raising the prevalence and reducing the absolute number of false positives with a trade off of against additional cost and complexity for the additional testing. The feasibility of multiple testing during community screening by optometrists has been examined and found to enhance specificity without loss of sensitivity[219] and to help stratify population according to the risk of visual loss[220]. We found that referral as a glaucoma suspect by the examining optometrist was the most specific predictor of new glaucoma and showed reasonable sensitivity. This is most likely because the optometrist will have formed their opinion based on the outcomes of multiple tests in a similar way to the diagnosing ophthalmologist.

We would therefore caution that this result may have been influenced by verification bias, not least because the study optometrists were responsible for referring patients for a secondary examination. As far as possible, our protocol was designed to account for and minimise this types of bias. A raised pressure or abnormal field resulted in automatic referral to the hospital eye service and where there was any uncertainty over the cause, the results were reviewed by a single senior ophthalmologist (SAV) both to identify missed glaucoma and to

identify false positive diagnoses of glaucoma that were not supported by longitudinal results.

It is reassuring that reliable results were obtained by the study optometrists following short but directed training but it is likely that this training will have influenced our results and limited generalizability. Optometrist with some exposure to hospital clinics are known to discriminate more reliably between photographs of normal and glaucomatous optic nerves[221], and ophthalmic assistants have been shown to have better agreement with ophthalmologists when screening for glaucoma in a hospital setting compared to screening in the community[222].

In conclusion, we found that no single test had sufficient sensitivity or specificity to screen for glaucoma but that assessment by trained optometrists following multiple tests achieved high specificity (98%) with an acceptable level of sensitivity (66.5%).

4.13 Agreement between clinical and automated measures of CDR

To my knowledge, this is the first study to compare CDR estimates by optometrists to those obtained from an automated instrument. We found moderate agreement between individual optometrists and the HRT with concordance correlation coefficients ranging between 0.49 – 0.63. The average differences between each optometrist and the HRT was small but there were wide limits of agreements which included between 76-86% of values within the scale of measurement. This effectively precludes comparison between measures since one method cannot usefully be used to predict the other. The HRT also failed to provide usable images in nearly a third of subjects, with 13% of images excluded due to low quality and 18% due to zero outputs.

This was similar to results from the population based study by Perera et al who compared slit lamp estimates of CDR by ophthalmologists using an eye piece graticule to results from OCT and HRT. They reported a 'differential performance threshold effect' with HRT producing zero outputs compared to non-zero outputs from OCT for 10% of images[160]. When when compared to clinical assessment, the found that HRT appeared to underestimate CDR at low values and overestimate higher values. We noted a similar effect but found that when we excluded the zero outputs from the analysis this effect was substantially reduced though still detectable.

When comparing clinical CDR assessment with HRT, they reported limits of agreement of up to 0.54, which suggest closer agreement than we found in our study. The mean CDR in both populations was similar but our population had a larger standard deviation for clinical measurements. Possible explanations beyond the wider spread, include their use of a younger population, differences in ethnicity, differences in training and the use of an eyepiece graticule. The hospital based study by Jayasundera et al[159] compared results from ophthalmoscopy by a single glaucoma subspecialist to HRT and reported 95% limits of agreement of 0.64, which is similar to our overall result of 0.66 in this study. Zangwill et al[161] also reported measures of agreement similar to our own. They compared results from 3 ophthalmologists to results from an earlier version of the HRT device and found agreement, as measured by kappa ranging from 0.21 – 0.55. The weighted kappas in our study between the 4 optometrists and the HRT ranged from 0.25 – 0.44.

4.14 Confounders of HRT and Clinical Assessment

Calculation of HRT stereometric parameters, including CDR, requires manual placement of contour line at the inner margin of Elschnig's ring. These parameter estimates are dependent on both the contour line and more importantly, the position of the reference plane , which is conventionally situated 50um below the retinal surface at the approximate location of the papillomacula bundle (350-356°)[223].

Anatomic landmarks visible on ophthalmoscopy do not always correspond to the confocal images acquired by the HRT and studies comparing stereophotographs and HRT have shown significantly smaller CDR estimates from photos[224,225]. Disc size is another known confounder of CDR measurement[226] and a number of studies have attempted to mitigate its effect by using it to stratify their results[159,160]. We did not deem this necessary since we while reference plane height and rim volume were predictive of a greater difference between clinical assessment and HRT, disc area was not.

Reference plane height and cup shape measures were other HRT parameters that were, perhaps unsurprisingly, predictive of a larger difference between methods. We also found our novel analysis tool to be the best single predictor of a difference between clinical and HRT assessment. The Abnormal disc score (ADS) Clinical assessment is known to be affected by disc shape and colour but these factors are less important with adequate stereopsis[227] which is easily

achieved during a dilated examination at the slit lamp in the majority of cases. Overall, the agreement between HRT and clinical assessment was at best, moderate but it performed far better than the semi-automated topographic methods used in the only other population based study of CDR agreement of which we are aware. The Rotterdam study reported low levels of agreement with kappa 0.18[228] when comparing CDR derived from monocular direct and indirect ophthalmoscopy to semi automated analysis of transparencies derived from stereoscopic fundus photography.

4.15 Optometrist Variability in determining CDR

The other use of the HRT in this study was as a reference standard against which the variability of the 4 optometrists in this study could be indirectly assessed. We found average variations of between 0.01 – 0.14, similar to those of Spry et al who compared results of ophthalmoscopy between community optometrists and ophthalmologists in research clinics and ophthalmologists in routine hospital clinics and found absolute mean differences ranging from 0.1 to 0.15 but wide tolerance limits of up to 40% of the range of values[215]. The variability in CDR measurement within the group of four optometrists and between the optometrists and the automated measure suggest that caution should be used when applying CDR criteria in epidemiological studies. The combination of perimetry and CDR measurement as suggested for category 1 epidemiological diagnosis[85] seems reasonable but risks under reporting disease particularly where visual field defects are combined with conservative assessments of CDR. It may be possible to predict discordance between clinical and automated assessment by identifying which types of discs are the most difficult to interpret through the use of a machine learning classifier imbedded within the program software.

4.16 Performance of Current and Novel HRT diagnostic algorithms

SAS and optometric assessment were found to be the most specific measures but MRA showed the best overall performance. In our subgroup analysis, we found a drop in sensitivity for detection of new disease by HRT using automated shape analysis and by optometrist using Jonas cirteria. MRA performed well across all groups and showed similar sensitivity in detection of new and previously diagnosed glaucoma. New patients had lower rates of perimetric disease and it is possible that RNFL changes were detected by MRA before morphological changes to the disc had occurred. It is also possible that our results were influenced by expectation bias. Participants were directly questioned about any personal or family history of glaucoma as well as any past or current treatment for eye disease prior to examination. The study optometrists were not masked to these results and it is possible that this extra information could have influenced detection of previously diagnosed disease. However, this does not explain the drop in sensitivity for both GPS and SAS and so it is unlikely that the decrease in sensitivity was due to expectation bias alone.

4.17 Glaucoma Probability Score (GPS)

GPS computes the probability of glaucoma based on 3 disc and 2 Retinal Nerve Fibre Layer (RNFL) parameters. It compares the data acquired from the scan against two previously computed models of a normal and abnormal disc and determines which model the scan fits best, producing a probabilistic score that the disc is glaucomatous. The main advantage of GPS over MRA is that it does require user input to delineate the disc margin and is not affected by inter and intra-observer variability during this process[229]. The methodology of GPS is also intuitively similar to that employed during clinical examination

It has been shown to be comparable to subjective evaluation of disc photographs in identifying early disease and predicting change[230] but comparisons against MRA have produced mixed results, perhaps due to the susceptibility of GPS to covariate effects. Both measures are known to be affected by disc size and disease severity[231] but MRA appears to be better at detecting more advanced disease[232,233] and less influenced by disc size. GPS is also more likely to fail to classify small discs or falsely classify large discs as abnormal[231,233–236]. Middle GPS scores are also less reproducible than extreme values[237,238]. Within this study, GPS performed poorly compared to SAS, both in direct measures and it's failure to provide an output for a large proportion of subjects.

4.18 Mean pixel height standard deviation & abnormal disc score

Mean pixel height standard deviation (MPHSD) and abnormal disc score (ADS) and Disc size had the most important covariate effects, influencing all HRT and clinical measures. MPHSD is is a measure of intra-scan variability and while it is commonly used as a surrogate for scan quality it has previously been correlated with age and glaucoma[239]. It is intuitively likely that an excavated glaucomatous disc will exhibit more topographical variability at the margins than would be seen in a gently sloping healthy rim. Similarly an increase in MPHSD can been seen in smaller disc[240] as proportionally they will have more variable edge points than in larger discs.

A relationship between rim area and image quality as measured by MPHSD has been reported within population based setting[241]. Image quality is known to affect HRT reproducibility[242] and the detection of structural change between scans[243] This effect is pronounced and can determine the number of examinations required to identify progression[244]. But image quality has so far not been shown to affect diagnostic accuracy in discriminating between healthy and glaucomatous discs using the MRA[245].

Within BEAP, MPHSD was significantly higher in the patients with open angle or normal tension glaucoma patients compared to rest of the cohort but not when compared to controls matched for age, sex and lens opacity in scans with MPHSD < 50. Sung et al also reported a higher average MPHSD in their case

control study of glaucoma and normal patients (25 vs 22 um), though this was not statistically significant[245]. In a mixed model we found that age, disc area and image quality were all significant co-variates of GPS score though the effect from image quality was not seen when excluding scans with MPHSD<30.

The overall effect of MPHSD and disc area on diagnostic performance appeared limited compared to the marked effect of stratification by ADS score (figure 3a). ADS was developed as a predictor of MRA misclassification and our results validate are the first validation of its use. As well providing a threshold beyond which scans cannot be usefully interpreted using current methods, qualitative review of the image outputs suggests that it may have a role in the systematic classification of disc phenotypes and identification of those less suited to automated analysis.

The major strength of this study is the population based design and it's use of longtitudanol results to provide a retrospective diagnosis[246]. The development and testing of other machine learning classifiers for disc assessment have been reported previously[247–250] but in line with GPS and MRA, they majority of these reports are based on case control or hospital based cross sectional studies., where the use of imperfect comparators can lead to artificially high results for sensitivity and specificity[251,252] Case-controls also have higher specificities[251].

While this approach can yield useful insight in to a population of interest it remains unrepresentative of the use of these algorithms as a screening tool

within an unselected population. Systematic reviews[90,253] have been attempted to improve generalizability but in general they provide ranges of estimates and summary measures instead of identifying sources of heterogeneity. It is difficult to see how we can usefully interpret the weighted effect of disparate results they report.

The use of HRT in unselected[239,254–256] and high risk populations[257,258] has been described previously. We found a higher sensitivity for MRA at similar levels of specificity than those reported by Healey et al in the Blue Mountain and in contrast to Saito et al[255] we found that MRA outperformed GPS. We would attribute these differences to both demographic and ethnic differences between populations. Healey et al noted how shifting analysis from eye to individual increased sensitivity and reduced specificity by doubling the opportunities for a true or false positive diagnosis. We noticed a similar effect but found MRA was less affected than other measures.

We previously described an analysis based on division of the data by size quartiles[259] and by asymmetry[260]. In fact, multiple different criteria can be used to select out different patterns or identify particular groups. We would, however, argue that this approach is to be preferred both because it utilises all data available from the scans and allows the it to categorised in it's own terms through features that differentiate it from other shapes. This approach can easily be adapted to other imaging techniques but it remains to be seen how it fares when faced with novel disc phenotypes.

Chapter 5 Concluding Remarks

The success of any research project can be broadly described in terms of it's ability to define a problem and reduce uncertainty. This is particularly true of epidemiological research where it is especially challenging to apply a robust test or criteria to a large heterogeneous sample.

The definition of cataract as an opacification of the lens is inherently subjective and the development of an evidence based approach to previously arbitrary criteria is an important outcome, along with the novel findings of improved pinhole acuity in the better eye following bilateral surgery and the first population based reports of the prevalence PCO / YAG capsulotomy following cataract surgery.

The work on AMD provides important insight in to disease asymmetry, providing a more complete picture of disease that appears underrepresented by sight impairment registration. As the last large population based study in the pre 'anti-VEGF' era, our results also provide important insight into the impact and natural history of disesase.

The discordance between structure and function and the limitations of current testing methods are evident from sections on glaucoma, both from its length and wide variety of statistical approaches that have been required to reduce or at least define the uncertainty inherent in testing methods of testing. A major

problem with diagnosis in glaucoma is that it can describe a group of different pathological processes acting on a group of heterogeneous phenotypes. The methods we describe for HRT appears to be a useful tool to categorise disc types and stages of pathology. It is likely that they can be easily adapted to OCT to help breakdown this mixed problem into its smaller component parts.

References

1. GBD 2015 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Lond. Engl.* **388**, 1603–1658 (2016).
2. Bourne, R. R. A. *et al.* Magnitude, temporal trends, and projections of the global prevalence of blindness and distance and near vision impairment: a systematic review and meta-analysis. *Lancet Glob. Health* **5**, e888–e897 (2017).
3. *Universal eye health: a global action plan 2014-2019.* (World Health Organization, 2013).
4. Bourne, R. R. A. *et al.* Prevalence and causes of vision loss in high-income countries and in Eastern and Central Europe in 2015: magnitude, temporal trends and projections. *Br. J. Ophthalmol.* **102**, 575–585 (2018).
5. Fricke, T. R. *et al.* Global Prevalence of Presbyopia and Vision Impairment from Uncorrected Presbyopia: Systematic Review, Meta-analysis, and Modelling. *Ophthalmology* **125**, 1492–1499 (2018).
6. James, R. R. *Studies in the history of ophthalmology in England: prior to the year 1800*. (Cambridge University Press, 2013).
7. Maunoury, M. & Thore. Remarks on Cataract: From the Clinique of M. Roux, Paris. *Prov. Med. Surg. J.* **s1-5**, 303–307 (1843).
8. Huey, E. B. *Backward and feeble-minded children : clinical studies in the psychology of defectives, with a syllabus for the clinical examination and testing of children*. (Warwick and York, Inc, 1912).
9. Archives, T. N. The National Archives - Homepage. *The National Archives*
10. Tate, R., Smeeth, L., Evans, J., Owen, C. & Rudnicka, A. *The Prevalence of Visual Impairment in the UK: A Review of the Literature*. (RNIB, 2005).
11. Sorsby, A. *The causes of blindness in England / by Arnold Sorsby.* (HMSO, 1953).
12. Hollows, F. C. & Graham, P. A. Intra-ocular pressure, glaucoma, and glaucoma suspects in a defined population. *Br. J. Ophthalmol.* **50**, 570–586 (1966).
13. McGuinness, R. Association of diabetes and cataract. *Br Med J* **2**, 416–418 (1967).
14. *Epidemiology of eye disease*. (Imperial College Press ; Distributed by World Scientific, 2012).
15. Kuper, H., Polack, S. & Limburg, H. Rapid assessment of avoidable blindness. *Community Eye Health* **19**, 68–69 (2006).
16. Mactaggart, I., Limburg, H., Bastawrous, A., Burton, M. J. & Kuper, H. Rapid Assessment of Avoidable Blindness: looking back, looking forward. *Br. J. Ophthalmol.* bjophthalmol-2019-314015 (2019). doi:10.1136/bjophthalmol-2019-314015
17. Németh, J. *et al.* Feasibility of the rapid assessment of avoidable blindness with diabetic retinopathy module (RAAB+DR) in industrialised countries: challenges and lessons learned in Hungary. *Ophthalmic Epidemiol.* **25**, 273–279 (2018).
18. World Health Organization. *International statistical classification of diseases and related health problems.* (2019).

19. International Council of Ophthalmology. Visual Standards, Aspects and Ranges of Vision Loss. (2002).
20. WHO Programme for the Prevention of Blindness and Deafness. Consultation on development of standards for characterization of vision loss and visual functioning : Genveva, 4-5 September 2003. (2003).
21. National Electrical Manufacturers Association (NEMA). RR.2 Reference Tables For Equivalent Visual Acuity Notations. Available at: http://dicom.nema.org/DICOM/2013/output/chtml/part17/sect_RR.2.html. (Accessed: 22nd September 2019)
22. Attebo, K., Mitchell, P. & Smith, W. Visual acuity and the causes of visual loss in Australia. The Blue Mountains Eye Study. *Ophthalmology* **103**, 357–364 (1996).
23. Beck, R. W. *et al.* Visual acuity as an outcome measure in clinical trials of retinal diseases. *Ophthalmology* **114**, 1804–1809 (2007).
24. Foreman, J. *et al.* The Prevalence and Causes of Vision Loss in Indigenous and Non-Indigenous Australians: The National Eye Health Survey. *Ophthalmology* **124**, 1743–1752 (2017).
25. Chan, T., Friedman, D. S., Bradley, C. & Massof, R. Estimates of Incidence and Prevalence of Visual Impairment, Low Vision, and Blindness in the United States. *JAMA Ophthalmol.* **136**, 12–19 (2018).
26. Neena, J., Rachel, J., Praveen, V., Murthy, G. V. S. & for the RAAB India Study Group. Rapid Assessment of Avoidable Blindness in India. *PLoS ONE* **3**, e2867 (2008).
27. Dandona, L. *et al.* Blindness in the Indian state of Andhra Pradesh. *Invest. Ophthalmol. Vis. Sci.* **42**, 908–916 (2001).
28. Quartilho, A. *et al.* Leading causes of certifiable visual loss in England and Wales during the year ending 31 March 2013. *Eye Lond. Engl.* **30**, 602–607 (2016).
29. Guerin, E., Bouliotis, G. & King, A. Visual impairment registration: evaluation of agreement among ophthalmologists. *Eye* **28**, 808–813 (2014).
30. Barry, R. J. & Murray, P. I. Unregistered visual impairment: is registration a failing system? *Br. J. Ophthalmol.* **89**, 995–998 (2005).
31. Richards, O. W. Effects of luminance and contrast on visual acuity, ages 16 to 90 years. *Am. J. Optom. Physiol. Opt.* **54**, 178–184 (1977).
32. Marron, J. A. & Bailey, I. L. Visual factors and orientation-mobility performance. *Am. J. Optom. Physiol. Opt.* **59**, 413–426 (1982).
33. Kimlin, J. A., Black, A. A. & Wood, J. M. Nighttime Driving in Older Adults: Effects of Glare and Association With Mesopic Visual Function. *Invest. Ophthalmol. Vis. Sci.* **58**, 2796–2803 (2017).
34. Kotecha, A., Spratt, A. & Viswanathan, A. Visual function and fitness to drive. *Br. Med. Bull.* **87**, 163–174 (2008).
35. Nevitt, M. C., Cummings, S. R., Kidd, S. & Black, D. Risk factors for recurrent nonsyncopal falls. A prospective study. *JAMA* **261**, 2663–2668 (1989).

36. Rubin, G. S. *et al.* The Association of Multiple Visual Impairments with Self-Reported Visual Disability: SEE Project. *Invest. Ophthalmol. Vis. Sci.* **42**, 64–72 (2001).

37. West, S. K. *et al.* How does visual impairment affect performance on tasks of everyday life? The SEE Project. Salisbury Eye Evaluation. *Arch. Ophthalmol. Chic. Ill 1960* **120**, 774–780 (2002).

38. Khadka, J. *et al.* Reengineering the Glaucoma Quality of Life-15 Questionnaire with Rasch Analysis. *Invest. Ophthalmol. Vis. Sci.* **52**, 6971–6977 (2011).

39. Lee, B. L. *et al.* The Glaucoma Symptom Scale. A brief index of glaucoma-specific symptoms. *Arch. Ophthalmol. Chic. Ill 1960* **116**, 861–866 (1998).

40. Steinberg, E. P. *et al.* The VF-14. An index of functional impairment in patients with cataract. *Arch. Ophthalmol. Chic. Ill 1960* **112**, 630–638 (1994).

41. Frost, N. A. *et al.* Development of a questionnaire for measurement of vision-related quality of life. *Ophthalmic Epidemiol.* **5**, 185–210 (1998).

42. Mangione, C. M. *et al.* Development of the 25-list-item National Eye Institute Visual Function Questionnaire. *Arch. Ophthalmol.* **119**, 1050–1058 (2001).

43. Dean, S. *et al.* "The patient is speaking": discovering the patient voice in ophthalmology. *Br. J. Ophthalmol.* **101**, 700–708 (2017).

44. Somner, J. E. A. *et al.* Moving from PROMs to POEMs for glaucoma care: a qualitative scoping exercise. *Invest. Ophthalmol. Vis. Sci.* **53**, 5940–5947 (2012).

45. Smeeth, L. *et al.* Randomised comparison of three methods of administering a screening questionnaire to elderly people: findings from the MRC trial of the assessment and management of older people in the community. *BMJ* **323**, 1403–1407 (2001).

46. Evans, J. R., Fletcher, A. E., Wormald, R. P. L. & MRC Trial of Assessment and Management of Older People in the Community. Causes of visual impairment in people aged 75 years and older in Britain: an add-on study to the MRC Trial of Assessment and Management of Older People in the Community. *Br. J. Ophthalmol.* **88**, 365–370 (2004).

47. Smith, L. *et al.* Physical inactivity in relation to self-rated eyesight: cross-sectional analysis from the English Longitudinal Study of Ageing. *BMJ Open Ophthalmol.* **1**, e000046 (2017).

48. Rahi, J. S., Cumberland, P. M. & Peckham, C. S. Visual impairment and vision-related quality of life in working-age adults: findings in the 1958 British birth cohort. *Ophthalmology* **116**, 270–274 (2009).

49. Yip, J. L. Y. *et al.* Visual acuity, self-reported vision and falls in the EPIC-Norfolk Eye study. *Br. J. Ophthalmol.* **98**, 377–382 (2014).

50. Stewart-Brown, S. & Butler, N. Visual acuity in a national sample of 10 year old children. *J. Epidemiol. Community Health* **39**, 107–112 (1985).

51. van der Pols, J. C. *et al.* Visual acuity measurements in a national sample of British elderly people. *Br. J. Ophthalmol.* **84**, 165–170 (2000).

52. Seland, J. H. *et al.* Visual impairment and quality of life in the older European population, the EUREYE study. *Acta Ophthalmol. (Copenh.)* **89**, 608–613 (2011).

53. Gibson, J. M., Lavery, J. R. & Rosenthal, A. R. Blindness and partial sight in an elderly population. *Br. J. Ophthalmol.* **70**, 700–705 (1986).

54. Wormald, R. P., Wright, L. A., Courtney, P., Beaumont, B. & Haines, A. P. Visual problems in the elderly population and implications for services. *BMJ* **304**, 1226–1229 (1992).

55. Reidy, A. *et al.* Prevalence of serious eye disease and visual impairment in a north London population: population based, cross sectional study. *BMJ* **316**, 1643–1646 (1998).

56. Cumberland, P. M., Rahi, J. S. & UK Biobank Eye and Vision Consortium. Visual Function, Social Position, and Health and Life Chances: The UK Biobank Study. *JAMA Ophthalmol.* **134**, 959–966 (2016).

57. Nyaga, V. N., Arbyn, M. & Aerts, M. Metaprop: a Stata command to perform meta-analysis of binomial data. *Arch. Public Health* **72**, 39 (2014).

58. Registered Blind and Partially Sighted People, England 2016-17. *NHS Digital* Available at: https://digital.nhs.uk/data-and-information/publications/statistical/registered-blind-and-partially-sighted-people/registered-blind-and-partially-sighted-people-england-2016-17. (Accessed: 6th October 2019)

59. UK Population 2017 - Office for National Statistics. Available at: https://www.ons.gov.uk/aboutus/transparencyandgovernance/freedomofinformationfoi/ukpopulation2017. (Accessed: 6th October 2019)

60. Fry, A. *et al.* Comparison of Sociodemographic and Health-Related Characteristics of UK Biobank Participants With Those of the General Population. *Am. J. Epidemiol.* **186**, 1026–1034 (2017).

61. Bourne, R. R. A. *et al.* Prevalence and causes of vision loss in high-income countries and in Eastern and Central Europe: 1990-2010. *Br. J. Ophthalmol.* **98**, 629–638 (2014).

62. Pascolini, D. & Mariotti, S. P. Global estimates of visual impairment: 2010. *Br. J. Ophthalmol.* **96**, 614–618 (2012).

63. Day, A. C., Donachie, P. H. J., Sparrow, J. M., Johnston, R. L. & Royal College of Ophthalmologists' National Ophthalmology Database. The Royal College of Ophthalmologists' National Ophthalmology Database study of cataract surgery: report 1, visual outcomes and complications. *Eye Lond. Engl.* **29**, 552–560 (2015).

64. Keenan, T., Rosen, P., Yeates, D. & Goldacre, M. Time trends and geographical variation in cataract surgery rates in England: study of surgical workload. *Br. J. Ophthalmol.* **91**, 901–904 (2007).

65. Coronini-Cronberg, S., Lee, H., Darzi, A. & Smith, P. Evaluation of clinical threshold policies for cataract surgery among English commissioners. *J. Health Serv. Res. Policy* **17**, 241–247 (2012).

66. Reidy, A. *et al.* Prevalence of serious eye disease and visual impairment in a north London population: population based, cross sectional study. *BMJ* **316**, 1643–1646 (1998).

67. Hall, A. B., Thompson, J. R., Deane, J. S. & Rosenthal, A. R. LOCS III versus the Oxford Clinical Cataract Classification and Grading System for the assessment of nuclear, cortical and posterior subcapsular cataract. *Ophthalmic Epidemiol.* **4**, 179–194 (1997).

68. Frost, A. *et al.* The population requirement for cataract extraction: a cross-sectional study. *Eye Lond. Engl.* **15**, 745–752 (2001).

69. Tan, A. C. S. *et al.* Cataract Prevalence Varies Substantially with Assessment Systems: Comparison of Clinical and Photographic Grading in a Population-Based Study. *Ophthalmic Epidemiol.* **18**, 164–170 (2011).

70. Hall, A. B., Thompson, J. R., Deane, J. S. & Rosenthal, A. R. LOCS III versus the Oxford Clinical Cataract Classification and Grading System for the assessment of nuclear, cortical and posterior subcapsular cataract. *Ophthalmic Epidemiol.* **4**, 179–194 (1997).

71. Wong, W. L. *et al.* Cataract conversion assessment using lens opacity classification system III and Wisconsin cataract grading system. *Invest. Ophthalmol. Vis. Sci.* **54**, 280–287 (2013).

72. Congdon, N. *et al.* Prevalence of cataract and pseudophakia/aphakia among adults in the United States. *Arch. Ophthalmol.* **122**, 487–494 (2004).

73. Klein, B. E., Klein, R. & Linton, K. L. Prevalence of age-related lens opacities in a population. The Beaver Dam Eye Study. *Ophthalmology* **99**, 546–552 (1992).

74. Mitchell, P., Cumming, R. G., Attebo, K. & Panchapakesan, J. Prevalence of Cataract in Australia: The Blue Mountains Eye Study. *Ophthalmology* **104**, 581–588 (1997).

75. Taylor HR, Vu HV & Keeffe JE. VIsual acuity thresholds for cataract surgery and the changing australian population. *Arch. Ophthalmol.* **124**, 1750–1753 (2006).

76. Ostberg, A., Löth, A., Gustafson, D. & Lindblom, B. Skövde cataract study: I. Prevalence of lens opacities in a Swedish community. *Ophthalmology* **113**, 970–975 (2006).

77. Pascolini, D. & Mariotti, S. P. Global estimates of visual impairment: 2010. *Br. J. Ophthalmol.* **96**, 614–618 (2011).

78. Quigley, H. A. The number of people with glaucoma worldwide in 2010 and 2020. *Br. J. Ophthalmol.* **90**, 262–267 (2006).

79. Bunce, C., Xing, W. & Wormald, R. Causes of blind and partial sight certifications in England and Wales: April 2007–March 2008. *Eye* **24**, 1692–1699 (2010).

80. Kroese, M. Primary open angle glaucoma. The need for a consensus case definition. *J. Epidemiol. Community Health* **57**, 752–754 (2003).

81. Clark, A. F. The Cell and Molecular Biology of Glaucoma: Biomechanical Factors in Glaucoma. *Invest. Ophthalmol. Vis. Sci.* **53**, 2473–2475 (2012).

82. Whitmore, A. V., Libby, R. T. & John, S. W. M. Glaucoma: thinking in new ways-a rôle for autonomous axonal self-destruction and other compartmentalised processes? *Prog. Retin. Eye Res.* **24**, 639–662 (2005).

83. Van Buskirk, E. M. & Cioffi, G. A. Glaucomatous optic neuropathy. *Am. J. Ophthalmol.* **113**, 447–452 (1992).

84. Shields, M. B. & Spaeth, G. L. The Glaucomatous Process and the Evolving Definition of Glaucoma. *J. Glaucoma* **21**, 141–143 (2012).

85. Foster, P. J., Buhrmann, R., Quigley, H. A. & Johnson, G. J. The definition and classification of glaucoma in prevalence surveys. *Br. J. Ophthalmol.* **86**, 238–242 (2002).

86. Samarawickrama, C., Hong, T., Jonas, J. B. & Mitchell, P. Measurement of Normal Optic Nerve Head Parameters. *Surv. Ophthalmol.* **57**, 317–336 (2012).

87. Mowatt, G. *et al.* Screening tests for detecting open-angle glaucoma: systematic review and meta-analysis. *Invest. Ophthalmol. Vis. Sci.* **49**, 5373–5385 (2008).

88. Zhu, H., Crabb, D. P., Fredette, M.-J., Anderson, D. R. & Garway-Heath, D. F. Quantifying discordance between structure and function measurements in the clinical assessment of glaucoma. *Arch. Ophthalmol.* **129**, 1167–1174 (2011).

89. Wilson JM & Jungner YG. Principles and practice of screening for disease. (1968).

90. Burr, J. M. *et al.* The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation. *Health Technol. Assess. Winch. Engl.* **11**, iii–iv, ix–x, 1–190 (2007).

91. Mansberger, S. L., Edmunds, B., Johnson, C. A., Kent, K. J. & Cioffi, G. A. Community Visual Field Screening: Prevalence of Follow-Up and Factors Associated With Follow-Up of Participants With Abnormal Frequency Doubling Perimetry Technology Results. *Ophthalmic Epidemiol.* **14**, 134–140 (2007).

92. College of Optometrists. B2: The routine eye examination. (2012).

93. College of Optometrists. D3: Examining patients at risk from glaucoma. (2012).

94. Myint, J., Edgar, D. F., Kotecha, A., Murdoch, I. E. & Lawrenson, J. G. A national survey of diagnostic tests reported by UK community optometrists for the detection of chronic open angle glaucoma. *Ophthalmic Physiol. Opt.* **31**, 353–359 (2011).

95. Theodossiades, J., Myint, J., Murdoch, I. E., Edgar, D. F. & Lawrenson, J. G. Does optometrists' self-reported practice in glaucoma detection predict actual practice as determined by standardised patients? *Ophthalmic Physiol. Opt. J. Br. Coll. Ophthalmic Opt. Optom.* **32**, 234–241 (2012).

96. Shah, R. *et al.* Glaucoma detection: the content of optometric eye examinations for a presbyopic patient of African racial descent. *Br. J. Ophthalmol.* **93**, 492–496 (2009).

97. Ramrattan, R. S. *et al.* Prevalence and causes of visual field loss in the elderly and associations with impairment in daily functioning: the Rotterdam Study. *Arch. Ophthalmol.* **119**, 1788–1794 (2001).

98. McKean-Cowdin, R. *et al.* Severity of visual field loss and health-related quality of life. *Am. J. Ophthalmol.* **143**, 1013–1023 (2007).

99. Kulkarni, K. M., Mayer, J. R., Lorenzana, L. L., Myers, J. S. & Spaeth, G. L. Visual field staging systems in glaucoma and the activities of daily living. *Am. J. Ophthalmol.* **154**, 445-451.e3 (2012).

100. Coleman, A. L. *et al.* Binocular visual-field loss increases the risk of future falls in older white women. *J. Am. Geriatr. Soc.* **55**, 357–364 (2007).

101. Haymes, S. A., Leblanc, R. P., Nicolela, M. T., Chiasson, L. A. & Chauhan, B. C. Risk of falls and motor vehicle collisions in glaucoma. *Invest. Ophthalmol. Vis. Sci.* **48**, 1149–1155 (2007).

102. Freeman, E. E., Muñoz, B., Rubin, G. & West, S. K. Visual field loss increases the risk of falls in older adults: the Salisbury eye evaluation. *Invest. Ophthalmol. Vis. Sci.* **48**, 4445–4450 (2007).

103. Malik, R., Swanson, W. H. & Garway-Heath, D. F. 'Structure-function relationship' in glaucoma: past thinking and current concepts. *Clin. Experiment. Ophthalmol.* **40**, 369–380 (2012).

104. Owsley, C. & McGwin Jr., G. Vision and driving. *Vision Res.* **50**, 2348–2361 (2010).

105. van Rijn, L. J. *et al.* Prevalence of impairment of visual function in European drivers. *Acta Ophthalmol. (Copenh.)* **89**, 124–131 (2011).

106. Rubin, G. S. *et al.* A comprehensive assessment of visual impairment in a population of older Americans. The SEE Study. Salisbury Eye Evaluation Project. *Invest. Ophthalmol. Vis. Sci.* **38**, 557–568 (1997).

107. Taylor, H. R., Livingston, P. M., Stanislavsky, Y. L. & McCarty, C. A. Visual impairment in Australia: distance visual acuity, near vision, and visual field findings of the Melbourne Visual Impairment Project. *Am. J. Ophthalmol.* **123**, 328–337 (1997).

108. Wang, Y., Xu, L. & Jonas, J. B. Prevalence and causes of visual field loss as determined by frequency doubling perimetry in urban and rural adult Chinese. *Am. J. Ophthalmol.* **141**, 1078–1086 (2006).

109. Iwase, A. *et al.* Performance of frequency-doubling technology perimetry in a population-based prevalence survey of glaucoma: the Tajimi study. *Ophthalmology* **114**, 27–32 (2007).

110. Johnson, C. A. & Keltner, J. L. Incidence of visual field loss in 20,000 eyes and its relationship to driving performance. *Arch. Ophthalmol.* **101**, 371–375 (1983).

111. Czudowska, M. A. *et al.* Incidence of glaucomatous visual field loss: a ten-year follow-up from the Rotterdam Study. *Ophthalmology* **117**, 1705–1712 (2010).

112. Wang, Y. X. *et al.* Five year incidence of visual field loss in adult Chinese. The Beijing Eye Study. *PloS One* **7**, e37232 (2012).

113. Leske, M. C. *et al.* Nine-year incidence of open-angle glaucoma in the Barbados Eye Studies. *Ophthalmology* **114**, 1058–1064 (2007).

114. Martin, X. D. Normal intraocular pressure in man. *Ophthalmol. J. Int. Ophtalmol. Int. J. Ophthalmol. Z. Für Augenheilkd.* **205**, 57–63 (1992).

115. Pointer, J. S. The diurnal variation of intraocular pressure in non-glaucomatous subjects: relevance in a clinical context. *Ophthalmic Physiol. Opt.* **17**, 456–465 (1997).

116. Kass, M. A. *et al.* The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Arch. Ophthalmol.* **120**, 701–713; discussion 829-830 (2002).

117. Heijl, A., Bengtsson, B., Hyman, L. & Leske, M. C. Natural history of open-angle glaucoma. *Ophthalmology* **116**, 2271–2276 (2009).

118. Sommer, A. *et al.* Relationship Between Intraocular Pressure and Primary Open Angle Glaucoma Among White and Black Americans: The Baltimore Eye Survey. *Arch. Ophthalmol.* **109**, 1090–1095 (1991).

119. Wang, N. L. *et al.* A Population-Based Assessment of 24-Hour Intraocular Pressure among Subjects with Primary Open-Angle Glaucoma: The Handan Eye Study. *Invest. Ophthalmol. Vis. Sci.* **52**, 7817–7821 (2011).

120. Sigal, I. A. An Applet to Estimate the IOP-Induced Stress and Strain within the Optic Nerve Head. *Invest. Ophthalmol. Vis. Sci.* **52**, 5497–5506 (2011).

121. Wang, N. *et al.* Orbital Cerebrospinal Fluid Space in Glaucoma: The Beijing iCOP Study. *Ophthalmology* (2012). doi:10.1016/j.ophtha.2012.03.054

122. Bathija, R., Gupta, N., Zangwill, L. & Weinreb, R. N. Changing definition of glaucoma. *J. Glaucoma* **7**, 165–169 (1998).

123. Vernon, S. A., Jones, S. J. & Henry, D. J. Maximising the sensitivity and specificity of non-contact tonometry in glaucoma screening. *Eye Lond. Engl.* **5 (Pt 4)**, 491–493 (1991).

124. Francis, B. A. *et al.* Effects of corneal thickness, corneal curvature, and intraocular pressure level on Goldmann applanation tonometry and dynamic contour tonometry. *Ophthalmology* **114**, 20–26 (2007).

125. Goldmann, H. & Schmidt, T. Über Applanationstonometrie. *Ophthalmol. J. Int. Ophtalmol. Int. J. Ophthalmol. Z. Für Augenheilkd.* **134**, 221–242 (1957).

126. Gordon, M. O. *et al.* The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. *Arch. Ophthalmol.* **120**, 714–720; discussion 829-830 (2002).

127. Johnson, C. S. *et al.* Role of corneal elasticity in damping of intraocular pressure. *Invest. Ophthalmol. Vis. Sci.* **48**, 2540–2544 (2007).

128. Pakravan, M., Parsa, A., Sanagou, M. & Parsa, C. F. Central corneal thickness and correlation to optic disc size: a potential link for susceptibility to glaucoma. *Br. J. Ophthalmol.* **91**, 26–28 (2007).

129. Park, S. J. K., Ang, G. S., Nicholas, S. & Wells, A. P. The effect of thin, thick, and normal corneas on Goldmann intraocular pressure measurements and correction formulae in individual eyes. *Ophthalmology* **119**, 443–449 (2012).

130. Smith, C. A. & Pepose, J. S. Disinfection of tonometers and contact lenses in the office setting: are current techniques adequate? *Am. J. Ophthalmol.* **127**, 77–84 (1999).

131. Mollan, S. P. *et al.* Accuracy of Goldmann, ocular response analyser, Pascal and TonoPen XL tonometry in keratoconic and normal eyes. *Br. J. Ophthalmol.* **92**, 1661–1665 (2008).

132. Kotecha, A., Elsheikh, A., Roberts, C. R., Zhu, H. & Garway-Heath, D. F. Corneal thickness- and age-related biomechanical properties of the cornea measured with the ocular response analyzer. *Invest. Ophthalmol. Vis. Sci.* **47**, 5337–5347 (2006).

133. Sullivan-Mee, M. *et al.* Ocular Response Analyzer in subjects with and without glaucoma. *Optom. Vis. Sci. Off. Publ. Am. Acad. Optom.* **85**, 463–470 (2008).

134. Shah, S., Laiquzzaman, M., Mantry, S. & Cunliffe, I. Ocular response analyser to assess hysteresis and corneal resistance factor in low tension, open angle glaucoma and ocular hypertension. *Clin. Experiment. Ophthalmol.* **36**, 508–513 (2008).

135. Congdon, N. G., Broman, A. T., Bandeen-Roche, K., Grover, D. & Quigley, H. A. Central corneal thickness and corneal hysteresis associated with glaucoma damage. *Am. J. Ophthalmol.* **141**, 868–875 (2006).

136. Morita, T. *et al.* Intraocular pressure measured by dynamic contour tonometer and ocular response analyzer in normal tension glaucoma. *Graefes Arch. Clin. Exp. Ophthalmol.* **248**, 73–77 (2009).

137. Shah, S. & Murdoch, I. E. NICE - impact on glaucoma case detection. *Ophthalmic Physiol. Opt. J. Br. Coll. Ophthalmic Opt. Optom.* **31**, 339–342 (2011).

138. Vernon, S. A. *et al.* Community optometrist referral of those aged 65 and over for raised IOP post-NICE: AOP guidance versus joint college guidance--an epidemiological model using BEAP. *Br. J. Ophthalmol.* **95**, 1534–1536 (2011).

139. Jonas, J. B., Budde, W. M. & Panda-Jonas, S. Ophthalmoscopic evaluation of the optic nerve head. *Surv. Ophthalmol.* **43**, 293–320 (1999).

140. Sommer, A., Pollack, I. & Maumenee, A. E. Optic disc parameters and onset of glaucomatous field loss. I. Methods and progressive changes in disc morphology. *Arch. Ophthalmol. Chic. Ill 1960* **97**, 1444–1448 (1979).

141. Singh, K., Lee, B. L., Wilson, M. R. & Glaucoma Modified RAND-Like Methodology Group. A panel assessment of glaucoma management: modification of existing RAND-like methodology for consensus in ophthalmology. Part II: Results and interpretation. *Am. J. Ophthalmol.* **145**, 575–581 (2008).

142. Theodossiades, J. & Murdoch, I. What optic disc parameters are most accurately assessed using the direct ophthalmoscope? *Eye Lond. Engl.* **15**, 283–287 (2001).

143. Quigley, H. A. *et al.* Risk factors for the development of glaucomatous visual field loss in ocular hypertension. *Arch. Ophthalmol. Chic. Ill 1960* **112**, 644–649 (1994).

144. Foster, P. J., Buhrmann, R., Quigley, H. A. & Johnson, G. J. The definition and classification of glaucoma in prevalence surveys. *Br. J. Ophthalmol.* **86**, 238–242 (2002).

145. Sit, A. J. Continuous monitoring of intraocular pressure: rationale and progress toward a clinical device. *J. Glaucoma* **18**, 272–279 (2009).

146. Heijl, A., Lindgren, A. & Lindgren, G. Test-retest variability in glaucomatous visual fields. *Am. J. Ophthalmol.* **108**, 130–135 (1989).

147. Spry, P. G. *et al.* The Bristol Shared Care Glaucoma Study: reliability of community optometric and hospital eye service test measures. *Br. J. Ophthalmol.* **83**, 707–712 (1999).

148. Ford, M. & Sarwar, M. Feautres of a Clinically Normal Optic Disc. *Br. J. Ophthalmol.* **47**, 50–52 (1963).

149. Hitchings, R. A., Genio, C., Anderton, S. & Clark, P. An optic disc grid: its evaluation in reproducibility studies on the cup/disc ratio. *Br. J. Ophthalmol.* **67**, 356–361 (1983).

150. Abrams, L. S., Scott, I. U., Spaeth, G. L., Quigley, H. A. & Varma, R. Agreement among optometrists, ophthalmologists, and residents in evaluating the optic disc for glaucoma. *Ophthalmology* **101**, 1662–1667 (1994).

151. Tielsch, J. M., Katz, J., Quigley, H. A., Miller, N. R. & Sommer, A. Intraobserver and interobserver agreement in measurement of optic disc characteristics. *Ophthalmology* **95**, 350–356 (1988).

152. Varma, R., Steinmann, W. C. & Scott, I. U. Expert agreement in evaluating the optic disc for glaucoma. *Ophthalmology* **99**, 215–221 (1992).

153. Balasubramanian, M., Bowd, C., Weinreb, R. N. & Zangwill, L. M. Agreement between the Heidelberg Retina Tomograph (HRT) Stereometric Parameters Estimated Using HRT-I and HRT-II. *Optom. Vis. Sci. Off. Publ. Am. Acad. Optom.* **88**, 140–149 (2011).

154. Sung, V. C. T., Bhan, A. & Vernon, S. A. Agreement in assessing optic discs with a digital stereoscopic optic disc camera (Discam) and Heidelberg retina tomograph. *Br. J. Ophthalmol.* **86**, 196–202 (2002).

155. Arthur, S. N. *et al.* Agreement in assessing cup-to-disc ratio measurement among stereoscopic optic nerve head photographs, HRT II, and Stratus OCT. *J. Glaucoma* **15**, 183–189 (2006).

156. Durmus, M., Karadag, R., Erdurmus, M., Totan, Y. & Feyzi Hepsen, I. Assessment of cup-to-disc ratio with slit-lamp funduscopy, Heidelberg Retina Tomography II, and stereoscopic photos. *Eur. J. Ophthalmol.* **19**, 55–60 (2009).

157. Correnti, A. J., Wollstein, G., Price, L. L. & Schuman, J. S. Comparison of optic nerve head assessment with a digital stereoscopic camera (discam), scanning laser ophthalmoscopy, and stereophotography. *Ophthalmology* **110**, 1499–1505 (2003).

158. Greaney, M. J. *et al.* Comparison of optic nerve imaging methods to distinguish normal eyes from those with glaucoma. *Invest. Ophthalmol. Vis. Sci.* **43**, 140–145 (2002).

159. Jayasundera, T., Danesh-Meyer, H. V., Donaldson, M. & Gamble, G. Agreement between stereoscopic photographs, clinical assessment, Heidelberg retina tomograph and digital stereoscopic optic disc camera in estimating vertical cup:disc ratio. *Clin. Experiment. Ophthalmol.* **33**, 259–263 (2005).

160. Perera, S. A. *et al.* Cup-to-Disc Ratio From Heidelberg Retina Tomograph 3 and High-Definition Optical Coherence Tomography Agrees Poorly With Clinical Assessment. *J. Glaucoma* **25**, 198–202 (2016).

161. Zangwill, L., Shakiba, S., Caprioli, J. & Weinreb, R. N. Agreement between clinicians and a confocal scanning laser ophthalmoscope in estimating cup/disk ratios. *Am. J. Ophthalmol.* **119**, 415–421 (1995).

162. Attebo, K., Mitchell, P. & Smith, W. Visual acuity and the causes of visual loss in Australia. The Blue Mountains Eye Study. *Ophthalmology* **103**, 357–364 (1996).

163. Khawaja, A. P. *et al.* The EPIC-Norfolk Eye Study: rationale, methods and a cross-sectional analysis of visual impairment in a population-based cohort. *BMJ Open* **3**, e002684–e002684 (2013).

164. Klaver, C. C., Wolfs, R. C., Vingerling, J. R., Hofman, A. & de Jong, P. T. Age-specific prevalence and causes of blindness and visual impairment in an older population: the Rotterdam Study. *Arch. Ophthalmol. Chic. Ill 1960* **116**, 653–658 (1998).

165. Reidy, A. *et al.* Prevalence of serious eye disease and visual impairment in a north London population: population based, cross sectional study. *BMJ* **316**, 1643–1646 (1998).

166. Wolfs, R. C. W. *et al.* Changing Views on Open-Angle Glaucoma: Definitions and Prevalences—The Rotterdam Study. *Invest. Ophthalmol. Vis. Sci.* **41**, 3309–3321 (2000).

167. Town pioneers eye tests for the world. Available at: http://www.bridlingtonfreepress.co.uk/news/town-pioneers-eye-tests-for-the-world-1-1719210. (Accessed: 1st December 2016)

168. Vernon, S. A. Laser Scanning Tomography of the Optic Nerve Head in a Normal Elderly Population: The Bridlington Eye Assessment Project. *Invest. Ophthalmol. Vis. Sci.* **46**, 2823–2828 (2005).

169. Jonas, J. B., Gusek, G. C. & Naumann, G. O. Optic disc, cup and neuroretinal rim size, configuration and correlations in normal eyes. *Invest. Ophthalmol. Vis. Sci.* **29**, 1151–1158 (1988).

170. Jonas, J. B., Budde, W. M. & Lang, P. Neuroretinal rim width ratios in morphological glaucoma diagnosis. *Br. J. Ophthalmol.* **82**, 1366–1371 (1998).

171. Theodossiades, J., Murdoch, I. & Cousens, S. Glaucoma case finding: a cluster-randomised intervention trial. *Eye Lond. Engl.* **18**, 483–490 (2004).

172. Henson, D. B., Spencer, A. F., Harper, R. & Cadman, E. J. Community refinement of glaucoma referrals. *Eye* **17**, 21–26 (2003).

173. Chylack, L. T. *et al.* The Lens Opacities Classification System III. The Longitudinal Study of Cataract Study Group. *Arch. Ophthalmol. Chic. Ill 1960* **111**, 831–836 (1993).

174. Bird, A. C. *et al.* An international classification and grading system for age-related maculopathy and age-related macular degeneration. The International ARM Epidemiological Study Group. *Surv. Ophthalmol.* **39**, 367–374 (1995).

175. Foster, P. J., Buhrmann, R., Quigley, H. A. & Johnson, G. J. The definition and classification of glaucoma in prevalence surveys. *Br. J. Ophthalmol.* **86**, 238–242 (2002).

176. Zhu, H., Poostchi, A., Vernon, S. A. & Crabb, D. P. Detecting abnormality in optic nerve head images using a feature extraction analysis. *Biomed. Opt. Express* **5**, 2215–2230 (2014).

177. Ying, G., Maguire, M. G., Glynn, R. & Rosner, B. Tutorial on Biostatistics: Statistical Analysis for Correlated Binary Eye Data. *Ophthalmic Epidemiol.* **25**, 1–12 (2018).

178. Fan, Q., Teo, Y.-Y. & Saw, S.-M. Application of Advanced Statistics in Ophthalmology. *Invest. Ophthalmol. Vis. Sci.* **52**, 6059–6065 (2011).

179. Chen, C.-C. & Barnhart, H. X. Assessing agreement with intraclass correlation coefficient and concordance correlation coefficient for data with repeated measures. *Comput. Stat. Data Anal.* **60**, 132–145 (2013).

180. Alonzo, T. A. & Pepe, M. S. Distribution-free ROC analysis using binary regression techniques. *Biostat. Oxf. Engl.* **3**, 421–432 (2002).

181. Bunce, C. & Wormald, R. Causes of blind certifications in England and Wales: April 1999-March 2000. *Eye Lond. Engl.* **22**, 905–911 (2008).

182. Swan, J. 2011 Census: Population Estimates for the United Kingdom, 27 March 2011. *Office for National Statistics* (2012). Available at: http://www.ons.gov.uk/ons/rel/census/2011-census/population-and-household-estimates-for-the-united-kingdom/stb-2011-census--population-estimates-for-the-united-kingdom.html. (Accessed: 3rd October 2015)

183. Meuleners, L. B., Fraser, M. L., Ng, J. & Morlet, N. The impact of first- and second-eye cataract surgery on injurious falls that require hospitalisation: a whole-population study. *Age Ageing* **43**, 341–346 (2014).

184. Foss, A. J. E. *et al.* Falls and health status in elderly women following second eye cataract surgery: a randomised controlled trial. *Age Ageing* **35**, 66–71 (2006).

185. Frampton, G., Harris, P., Cooper, K., Lotery, A. & Shepherd, J. The clinical effectiveness and cost-effectiveness of second-eye cataract surgery: a systematic review and economic evaluation. *Health Technol. Assess. Winch. Engl.* **18**, 1–205, v–vi (2014).

186. Buehl, W. & Findl, O. Effect of intraocular lens design on posterior capsule opacification. *J. Cataract Refract. Surg.* **34**, 1976–1985 (2008).

187. Ando, H., Ando, N. & Oshika, T. Cumulative probability of neodymium: YAG laser posterior capsulotomy after phacoemulsification. *J. Cataract Refract. Surg.* **29**, 2148–2154 (2003).

188. Schaumberg, D. A., Dana, M. R., Christen, W. G. & Glynn, R. J. A systematic overview of the incidence of posterior capsule opacification. *Ophthalmology* **105**, 1213–1221 (1998).

189. Leske, M. C., Connell, A. M., Wu, S. Y., Hyman, L. & Schachat, A. Prevalence of lens opacities in the Barbados Eye Study. *Arch. Ophthalmol. Chic. Ill 1960* **115**, 105–111 (1997).

190. Kanthan, G. L. *et al.* Exogenous oestrogen exposure, female reproductive factors and the long-term incidence of cataract: the Blue Mountains Eye Study. *Acta Ophthalmol. (Copenh.)* **88**, 773–778 (2010).

191. Zetterberg, M. & Celojevic, D. Gender and cataract--the role of estrogen. *Curr. Eye Res.* **40**, 176–190 (2015).

192. Lewallen, S., Mousa, A., Bassett, K. & Courtright, P. Cataract surgical coverage remains lower in women. *Br. J. Ophthalmol.* **93**, 295–298 (2009).

193. Smirthwaite, G., Lundström, M., Albrecht, S. & Swahnberg, K. Indication criteria for cataract extraction and gender differences in waiting time. *Acta Ophthalmol. (Copenh.)* **92**, 432–438 (2014).

194. VanNewkirk, M. R. *et al.* The prevalence of age-related maculopathy: the visual impairment project. *Ophthalmology* **107**, 1593–1600 (2000).

195. Vingerling, J. R. *et al.* The prevalence of age-related maculopathy in the Rotterdam Study. *Ophthalmology* **102**, 205–210 (1995).

196. Akuffo, K. O. *et al.* Prevalence of age-related macular degeneration in the Republic of Ireland. *Br. J. Ophthalmol.* **99**, 1037–1044 (2015).

197. Bressler, N. M., Bressler, S. B., West, S. K., Fine, S. L. & Taylor, H. R. The grading and prevalence of macular degeneration in Chesapeake Bay watermen. *Arch. Ophthalmol. Chic. Ill 1960* **107**, 847–852 (1989).

198. Owen, C. G. *et al.* The estimated prevalence and incidence of late stage age related macular degeneration in the UK. *Br. J. Ophthalmol.* **96**, 752–756 (2012).

199. Klein, B. E. *et al.* Prevalence of glaucoma. The Beaver Dam Eye Study. *Ophthalmology* **99**, 1499–1504 (1992).

200. Katz, J. *et al.* Automated suprathreshold screening for glaucoma: the Baltimore Eye Survey. *Invest. Ophthalmol. Vis. Sci.* **34**, 3271–3277 (1993).

201. Keltner, J. L. *et al.* Normal Visual Field Tests Following Glaucomatous Visual Field Endpoints in the Ocular Hypertension Treatment Study (OHTS). *Arch. Ophthalmol.* **123**, 1201–1206 (2005).

202. Vernon, S. A., Henry, D. J. & Jones, S. J. Calculating the predictive power of the Henson field screener in a population at risk of glaucomatous field loss. *Br. J. Ophthalmol.* **74**, 220–222 (1990).

203. Tatemichi, M. *et al.* Performance of glaucoma mass screening with only a visual field test using frequency-doubling technology perimetry. *Am. J. Ophthalmol.* **134**, 529–537 (2002).

204. Francis, B. A. *et al.* Population and high-risk group screening for glaucoma: the Los Angeles Latino Eye Study. *Invest. Ophthalmol. Vis. Sci.* **52**, 6257–6264 (2011).

205. Myint, J., Edgar, D. F., Kotecha, A., Murdoch, I. E. & Lawrenson, J. G. A national survey of diagnostic tests reported by UK community optometrists for the detection of chronic open angle glaucoma. *Ophthalmic Physiol. Opt.* **31**, 353–359 (2011).

206. Reidy, A. *et al.* Prevalence of serious eye disease and visual impairment in a north London population: population based, cross sectional study. *BMJ* **316**, 1643–1646 (1998).

207. Coffey, M. *et al.* Prevalence of glaucoma in the west of Ireland. *Br. J. Ophthalmol.* **77**, 17–21 (1993).

208. Sample, P. A. *et al.* Identifying glaucomatous vision loss with visual-function-specific perimetry in the diagnostic innovations in glaucoma study. *Invest. Ophthalmol. Vis. Sci.* **47**, 3381–3389 (2006).

209. Kook, M. S. *et al.* Effect of cataract extraction on frequency doubling technology perimetry. *Am. J. Ophthalmol.* **138**, 85–90 (2004).

210. Ivers, R. Q., Optom, B., Macaskill, P., Cumming, R. G. & Mitchell, P. Sensitivity and specificity of tests to detect eye disease in an older population. *Ophthalmology* **108**, 968–975 (2001).

211. Ivers, R. Q., Mitchell, P. & Cumming, R. G. Lack of association between localized cataract and visual field loss: the Blue Mountains Eye Study. *Aust. N. Z. J. Ophthalmol.* **25**, 193–198 (1997).

212. Moyer, V. A. Screening for Glaucoma: U.S. Preventive Services Task Force Recommendation Statement. *Ann. Intern. Med.* **159**, 484–489 (2013).

213. Tielsch, J. M. *et al.* A Population-based Evaluation of Glaucoma Screening: The Baltimore Eye Survey. *Am. J. Epidemiol.* **134**, 1102–1110 (1991).

214. Ivers, R. Q., Macaskill, P., Cumming, R. G. & Mitchell, P. Sensitivity and specificity of tests to detect eye disease in an older population. *Ophthalmology* **108**, 968–975 (2001).

215. Spry, P. *et al.* The Bristol Shared Care Glaucoma Study: reliability of community optometric and hospital eye service test measures. *Br. J. Ophthalmol.* **83**, 707–712 (1999).

216. Morgan, J. E. *et al.* The accuracy of the inferior>superior>nasal>temporal neuroretinal rim area rule for diagnosing glaucomatous optic disc damage. *Ophthalmology* **119**, 723–730 (2012).

217. Burr, J. *et al.* Is it worthwhile to conduct a randomized controlled trial of glaucoma screening in the United Kingdom? *J. Health Serv. Res. Policy* **19**, 42–51 (2014).

218. Vaahtoranta-Lehtonen, H. *et al.* Cost effectiveness and cost utility of an organized screening programme for glaucoma. *Acta Ophthalmol. Scand.* **85**, 508–518 (2007).

219. de Vries, M. M., Stoutenbeek, R., Müskens, R. P. H. M. & Jansonius, N. M. Glaucoma screening during regular optician visits: the feasibility and specificity of screening in real life. *Acta Ophthalmol. (Copenh.)* **90**, 115–121 (2012).

220. Vernon, S. A., Henry, D. J., Cater, L. & Jones, S. J. Screening for glaucoma in the community by non-ophthalmologically trained staff using semi automated equipment. *Eye Lond. Engl.* **4 (Pt 1)**, 89–97 (1990).

221. Hadwin, S. E. *et al.* Assessment of optic disc photographs for glaucoma by UK optometrists: the Moorfields Optic Disc Assessment Study (MODAS). *Ophthalmic Physiol. Opt. J. Br. Coll. Ophthalmic Opt. Optom.* **33**, 618–624 (2013).

222. Sinha, S. K. & Astbury, N. Evaluation of the effectiveness of ophthalmic assistants as screeners for glaucoma in North India. *Eye Lond. Engl.* **25**, 1310–1316 (2011).

223. Roff, E. J., Hosking, S. L. & Barnes, D. A. The influence of contour line size and location on the reproducibility of topographic measurement with the Heidelberg Retina Tomograph. *Ophthalmic Physiol. Opt. J. Br. Coll. Ophthalmic Opt. Optom.* **21**, 173–181 (2001).

224. Hoffmann, E. M. *et al.* The Heidelberg retina tomograph ancillary study to the European glaucoma prevention study: study design and baseline factors. *Acta Ophthalmol. (Copenh.)* **91**, e612-619 (2013).

225. Zangwill, L. M. *et al.* The confocal scanning laser ophthalmoscopy ancillary study to the ocular hypertension treatment study: study design and baseline factors. *Am. J. Ophthalmol.* **137**, 219–227 (2004).

226. Garway-Heath, D. F., Ruben, S. T., Viswanathan, A. & Hitchings, R. A. Vertical cup/disc ratio in relation to optic disc size: its value in the assessment of the glaucoma suspect. *Br. J. Ophthalmol.* **82**, 1118–1124 (1998).

227. Lichter, P. R. Variability of expert observers in evaluating the optic disc. *Trans. Am. Ophthalmol. Soc.* **74**, 532–572 (1976).

228. Wolfs, R. C., Ramrattan, R. S., Hofman, A. & de Jong, P. T. Cup-to-disc ratio: ophthalmoscopy versus automated measurement in a general population: The Rotterdam Study. *Ophthalmology* **106**, 1597–1601 (1999).

229. Garway-Heath, D. F. *et al.* Inter- and intraobserver variation in the analysis of optic disc images: comparison of the Heidelberg retina tomograph and computer assisted planimetry. *Br. J. Ophthalmol.* **83**, 664–669 (1999).

230. Alencar, L. M. *et al.* Comparison of HRT-3 glaucoma probability score and subjective stereophotograph assessment for prediction of progression in glaucoma. *Invest. Ophthalmol. Vis. Sci.* **49**, 1898–1906 (2008).

231. Oddone, F. *et al.* Exploring the Heidelberg Retinal Tomograph 3 diagnostic accuracy across disc sizes and glaucoma stages: a multicenter study. *Ophthalmology* **115**, 1358–1365, 1365.e1–3 (2008).

232. Gabriele, M. L. *et al.* Comparison of parameters from Heidelberg Retina Tomographs 2 and 3. *Ophthalmology* **115**, 673–677 (2008).

233. Ferreras, A. *et al.* Diagnostic ability of the Heidelberg Retina Tomograph 3 for glaucoma. *Am. J. Ophthalmol.* **145**, 354–359 (2008).

234. Harizman, N. *et al.* Detection of glaucoma using operator-dependent versus operator-independent classification in the Heidelberg retinal tomograph-III. *Br. J. Ophthalmol.* **90**, 1390–1392 (2006).

235. Burgansky-Eliash, Z. *et al.* Glaucoma detection with the Heidelberg retina tomograph 3. *Ophthalmology* **114**, 466–471 (2007).

236. Coops, A., Henson, D. B., Kwartz, A. J. & Artes, P. H. Automated Analysis of Heidelberg Retina Tomograph Optic Disc Images by Glaucoma Probability Score. *Invest. Ophthalmol. Vis. Sci.* **47**, 5348–5355 (2006).

237. Strouthidis, N. G., Demirel, S., Asaoka, R., Cossio-Zuniga, C. & Garway-Heath, D. F. The Heidelberg retina tomograph Glaucoma Probability Score: reproducibility and measurement of progression. *Ophthalmology* **117**, 724–729 (2010).

238. Yoshioka, N., Wong, E., Kalloniatis, M. & Zangerl, B. Repeatability of Heidelberg Retinal Tomography 3 and effect of alignment algorithm on glaucoma suspects. *Clin. Exp. Optom.* (2016). doi:10.1111/cxo.12408

239. Healey, P. R., Lee, A. J., Aung, T., Wong, T. Y. & Mitchell, P. Diagnostic accuracy of the Heidelberg Retina Tomograph for glaucoma a population-based assessment. *Ophthalmology* **117**, 1667–1673 (2010).

240. Chauhan, B. C., LeBlanc, R. P., McCormick, T. A. & Rogers, J. B. Test-retest variability of topographic measurements with confocal scanning laser tomography in patients with glaucoma and control subjects. *Am. J. Ophthalmol.* **118**, 9–15 (1994).

241. Zheng, Y. *et al.* Determinants of image quality of Heidelberg Retina Tomography II and its association with optic disc parameters in a population-based setting. *Am. J. Ophthalmol.* **151**, 663–670 (2011).

242. Strouthidis, N. G. *et al.* Factors affecting the test-retest variability of Heidelberg retina tomograph and Heidelberg retina tomograph II measurements. *Br. J. Ophthalmol.* **89**, 1427–1432 (2005).

243. Saarela, V., Falck, A., Airaksinen, P. J. & Tuulonen, A. The sensitivity and specificity of Heidelberg Retina Tomograph parameters to glaucomatous progression in disc photographs. *Br. J. Ophthalmol.* **94**, 68–73 (2010).

244. Owen, V. M. F., Strouthidis, N. G., Garway-Heath, D. F. & Crabb, D. P. Measurement variability in Heidelberg Retina Tomograph imaging of neuroretinal rim area. *Invest. Ophthalmol. Vis. Sci.* **47**, 5322–5330 (2006).

245. Sung, K. R. *et al.* Scan quality effect on glaucoma discrimination by glaucoma imaging devices. *Br. J. Ophthalmol.* **93**, 1580–1584 (2009).

246. Medeiros, F. A., Zangwill, L. M., Bowd, C., Sample, P. A. & Weinreb, R. N. Use of progressive glaucomatous optic disk change as the reference standard for evaluation of diagnostic tests in glaucoma. *Am. J. Ophthalmol.* **139**, 1010–1018 (2005).

247. Asaoka, R. *et al.* Combining multiple HRT parameters using the 'Random Forests' method improves the diagnostic accuracy of glaucoma in emmetropic and highly myopic eyes. *Invest. Ophthalmol. Vis. Sci.* **55**, 2482–2490 (2014).

248. Townsend, K. A. *et al.* Heidelberg Retina Tomograph 3 machine learning classifiers for glaucoma detection. *Br. J. Ophthalmol.* **92**, 814–818 (2008).

249. Mardin, C. Y. *et al.* New glaucoma classification method based on standard Heidelberg Retina Tomograph parameters by bagging classification trees. *J. Glaucoma* **12**, 340–346 (2003).

250. Zangwill, L. M. *et al.* Heidelberg retina tomograph measurements of the optic disc and parapapillary retina for detecting glaucoma analyzed by machine learning classifiers. *Invest. Ophthalmol. Vis. Sci.* **45**, 3144–3151 (2004).

251. Lijmer, J. G. *et al.* Empirical evidence of design-related bias in studies of diagnostic tests. *JAMA* **282**, 1061–1066 (1999).

252. Medeiros, F. A. *et al.* The effects of study design and spectrum bias on the evaluation of diagnostic accuracy of confocal scanning laser ophthalmoscopy in glaucoma. *Invest. Ophthalmol. Vis. Sci.* **48**, 214–222 (2007).

253. Michelessi, M. *et al.* Optic nerve head and fibre layer imaging for diagnosing glaucoma. *Cochrane Database Syst. Rev.* **11**, CD008803 (2015).

254. Ohkubo, S., Takeda, H., Higashide, T., Sasaki, T. & Sugiyama, K. A pilot study to detect glaucoma with confocal scanning laser ophthalmoscopy compared with nonmydriatic stereoscopic photography in a community health screening. *J. Glaucoma* **16**, 531–538 (2007).

255. Saito, H., Tsutsumi, T., Araie, M., Tomidokoro, A. & Iwase, A. Sensitivity and specificity of the Heidelberg Retina Tomograph II Version 3.0 in a population-based study: the Tajimi Study. *Ophthalmology* **116**, 1854–1861 (2009).

256. Khawaja, A. P. *et al.* Laser scanning tomography in the EPIC-Norfolk Eye Study: principal components and associations. *Invest. Ophthalmol. Vis. Sci.* **54**, 6638–6645 (2013).

257. Banister, K. *et al.* Can Automated Imaging for Optic Disc and Retinal Nerve Fiber Layer Analysis Aid Glaucoma Detection? *Ophthalmology* **123**, 930–938 (2016).

258. Harasymowycz, P. J., Papamatheakis, D. G., Fansi, A. K., Gresset, J. & Lesk, M. R. Validity of screening for glaucomatous optic nerve damage using confocal scanning laser ophthalmoscopy (Heidelberg Retina Tomograph II) in high-risk populations: a pilot study. *Ophthalmology* **112**, 2164–2171 (2005).

259. Hawker, M. J., Vernon, S. A., Tattersall, C. L. & Dua, H. S. Linear regression modeling of rim area to discriminate between normal and glaucomatous optic nerve heads: the Bridlington Eye Assessment Project. *J. Glaucoma* **16**, 345–351 (2007).

260. Hawker, M. J., Vernon, S. A., Tattersall, C. L. & Dua, H. S. Detecting glaucoma with RADAAR: the Bridlington Eye Assessment Project. *Br. J. Ophthalmol.* **90**, 744–748 (2006).

Appendices

Study No. 2601

THE BRIDLINGTON EYE ASSESSMENT PROJECT (B.E.A.P.)

DATA ENTRY FORM

Today's date 27.4.05

Date of birth [redacted]

Name [redacted] G.P. name [redacted]

PREVIOUS MEDICAL HISTORY

Diabetes yes / (no) 10% yes.
Hypertension (on Rx) (yes) / no
Previous stroke yes / (no)

PREVIOUS OPHTHALMIC HISTORY

Specs for distance (yes) / no

Specs for reading (yes) / no

Happy with vision ? (yes) / no

Last visit to optometrist within last yr / (1-2yrs ago) / 2-5yrs ago / >5 yrs ago

Registered Partially sighted or Blind yes / (no)

	Right eye	Left eye
Lazy eye ?	yes / (no)	yes / (no)
Past Eye Operations (state)	NONE TOO BIG TO	NONE SUMMARISE ?
Known glaucoma	yes / (no)	yes / (no)
Using glaucoma drops	yes / (no)	yes / (no)
Diabetic retinopathy	yes / (no)	yes / (no)
Macular degeneration	yes / (no)	yes / (no)

SOCIAL HISTORY

Lives alone (yes) / no
Drives yes / (no)
Glaucoma in brother / sister / child / or parent yes / (no)
On waiting list for eye surgery yes / (no)

Study No. 2601

ANTERIOR SEGMENT EXAM

	Right eye		Left eye	
if abnormal state why			S Ptosis	
Lids normal	(Yes)	No	Yes	(No)
Cornea clear	(Yes)	No	(Yes)	No
Previous cataract surgery	Yes	(No)	Yes	(No)
IOP	17 mmHg		18 mmHg	
	at 235 am/pm		at 235 am/pm	
Corneal thickness	486 microns		481 microns	
Safe to dilate	(Yes)	No	(Yes)	No

VISUAL ACUITY

	Right eye	Left eye
Unaided	+0.3	+0.36
With glasses	+0.26	+0.34
With pinhole	+0.2	+0.32

VISUAL FIELD

	Right eye		Left eye	
Performed	(Yes)	No	(Yes)	No
26 point screen normal	(Yes)	No	(Yes)	No
if extended normal	Yes	No	Yes	No

+3.50

LENS ASSESSMENT

	Right eye	Left eye
Nuclear Colour (NC)	C3	C3
Cortical (C)	C4	C4
Post subcap (P)	P1	P1

Study No. 2601

OPTIC DISC ASSESSMENT

	Right eye	Left eye
Assessment possible	(Yes) No	(Yes) No
Jonas normal	(Yes) No	(Yes) No
Vertical C/D ratio	4/10	4/10.
Other disc abnormality	Yes (No)	Yes (No)
If yes - state		

MACULA

	Right eye	Left eye
Normal	(Yes) No	(Yes) No
ARMD present	Yes (No)	Yes (No)
ARMD subtype (pigmentary, drusen, disciform)		
Other macula abnormality (state)		

OTHER RETINA

	Right eye	Left eye
Normal	(Yes) No	(Yes) No
If no state why		

	Right eye	Left eye
HRT scan performed	(Yes) No	(Yes) No
If no (give reason)		
Retinal photos done	(Yes) No	(Yes) No
If no (give reason)		

Study No.....

DISPOSAL (circle one only)

1 To routine optometrist review

2 For early refraction at own optometrist (good chance of significantly better vision)

3 To ophthalmologist (new referral)

4 Back to ophthalmologist (already under active review)

5 To G.P.

If to ophthalmologist, choose why (may be more than one)

1 New glaucoma / glaucoma suspect

2 Cataract

3 ARMD

4 Diabetic retinopathy

5 Other retinal

6 Undiagnosed field defect

7 Unexplained visual loss

8 Lid / adnexal problem

9 Other (state)

Form completed by _____

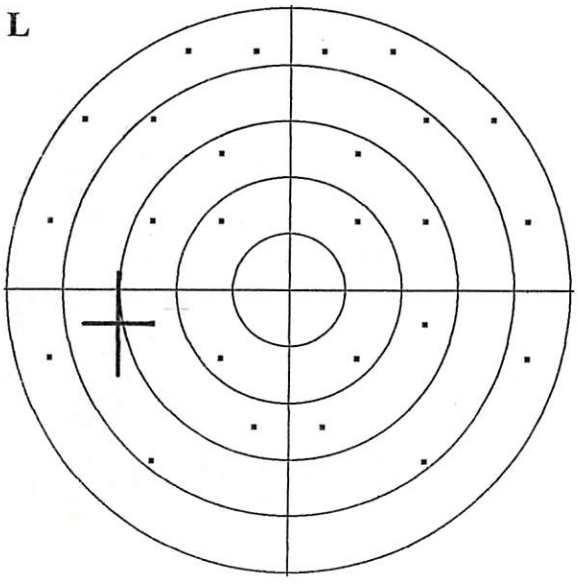
Single stimulus, suprathreshold, central 25 degrees.

Family Name	[redacted]
First Name	[redacted]
Birth Date	[redacted]
Record Num	2601

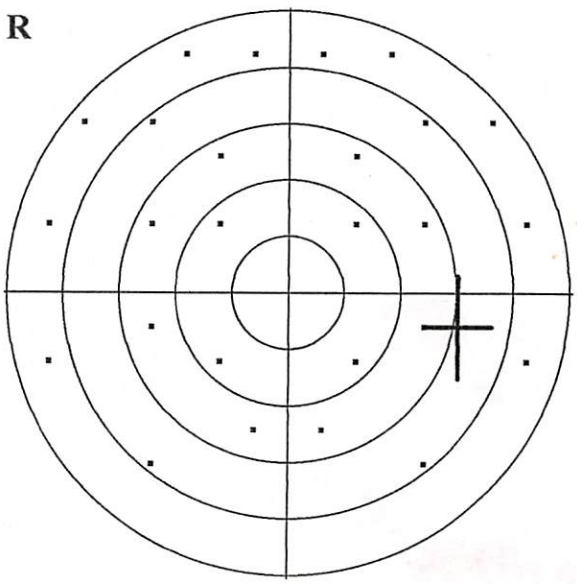
Test date 27/04/05

RxR / **RxL** +3.50

L



R



5 dB
8 dB
12 dB

Threshold	**34 dB**
Total Missed/Presented	**0/26**
Superior Missed/Presented	**0/16**
Inferior Missed/Presented	**0/10**
False Positives	**4/5**
False Negatives	**0/1**

Threshold	**32 dB**
Total Missed/Presented	**0/26**
Superior Missed/Presented	**0/16**
Inferior Missed/Presented	**0/10**
False Positives	**0/2**
False Negatives	**0/3**

Raw Data File Created on 27th March 2007

Modified on 8th December 2011

1. Original headings ammended and abbreviated

2. New columns added (sheet 2)

Note: in practice, optoms were referring suspicious discs e.g 68

4 subsequent iteration of the modified Raw file have since been created.

Modified 1 was the recoding of data completed in Bridlington

Modified 2 added the remaining data source 5 (electronic letters) patients that were not completed in Bridlington

Modified 3 was the final version completed prior to coding alert 7 (VF defect but not seen) patients by SAV

Modified 4 is the version with assessment of those with VF defect not seen / not referred to HES

Modified 5 is the version with Modification of disc assesment and VF

Modified 6 is reviewing patients with glaucoma

Re-categorisation of IOP and CCT was completed in version 3, outliers were rechecked for IOP (<8 and > 30 mmHg) and for CCT (<425 and > 650 um)

In version 4 the following null reading were recoded to blank

IOP Blepharospasm
177
326
783
1356
1446
1485
2433
3177
3544

IOP Unable
228
424
1662
1707

1732
2755
3049
3549
3566

CCT Blepharospasm
783
1446
3177
3544

CCT Unable
23
24
176
228
1166
1732
2108
2755
3549
3049
3124
3348 631

29th April and 13th May attended rooms with SAV and determined cause of VF defect in those not referred or seen in hospital

3. Optic discs reclassified - those with flat / minimal cups classified as 0.0

Discs with pluses and minuses (e.g 0.1+ ignored)

Descriptors moved to adjacent columns

Cross check - compared to Modified Raw file version 4 and columns subtracted

NB When using paste special multiply function to convert all entries to number format, blanks were converted. This needs to be corrected by comparing versions 4 and 5

16th June

Modified 6 has been ammended and blanks reclassified as 0.0 have been returned to blank
Modified 7 start of VA and Cataract reclassification
3255 R 3.0 - actually 0.3 then 0.44
846 ua r hm l 0.8, gl r+L -0.1

16
3141 l ua
3220 l ua

Modified 8 is prep for stata
Modified 9 is change recode missing VA from 99 to blank, removed 1792 506 duplicate
Blank category added to VFCause to help stata identify clear columns

Went back to version 7 - modified (a) is Prof Vernon's reclassification of all abnormal hospital fields

28th July

Modified 8 is BCVA recoded to remove formulae errors.
BCVA still needs to be checked for VA <-0.2
Recoded classification 2 + 3,4,7 i.e artefact + BRVO etc...
Disciforms coded in to 1

Notes section modified to fill in gaps for missing VF cause subtypes
Consider rechecking 2138 with prof to re-check classification
Also please check 1516 for description of field defect

2nd November

Cataract data cleaned
=countif(D:D,D2)>1
PCIOL 7.0 pco + 7.1 pco ++ 2 pco +++ 3 periph pco 7.4 clear central / post yag 7.5 clear / all clear 7.6 aphakic 7.7 ACIOL 7.8

7062 lens assessments in **3538** (99.7%) individuals
4078 (58%) eyes showed no significant opacity
2314 (33%) eyes had significant opacities
657 (9.3%) eyes had PCIOL
10 (0.14%) eyes had ACIOL
3 (0.04%) eyes were Aphakic

referred after 1st visit

not referred after 1st visit

1037 (29%) individuals sent to Hospital Eye Service (HES), including
222 referred for consideration of cataract surgery

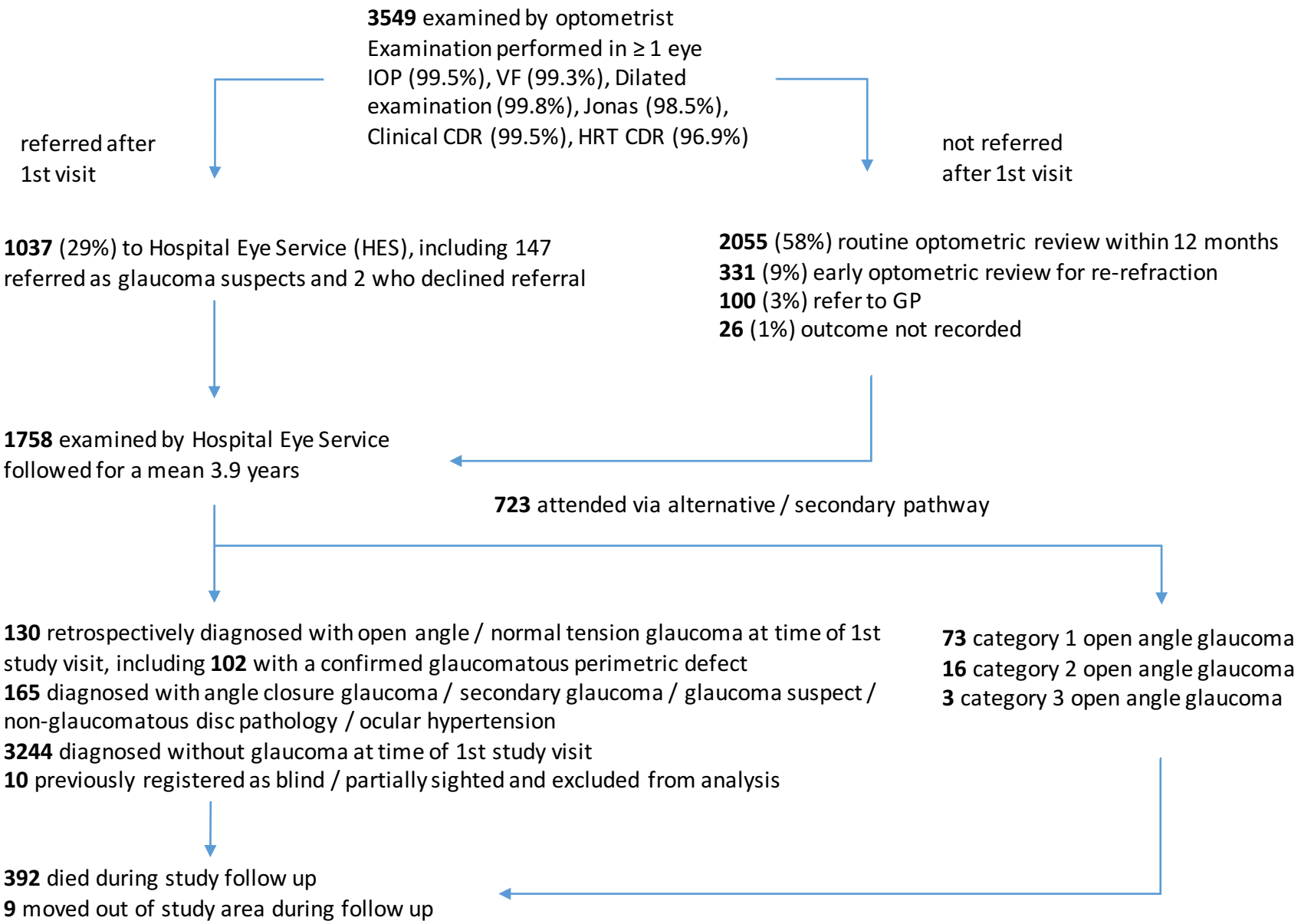
2055 (58%) individuals sent for routine optometric review within 12 months
331 (9%) early optometric review for re-refraction
100 (3%) referred to GP
26 (1%) outcome not recorded

1758 individuals examined by Hospital Eye Service followed for a mean 3.9 years, including
123 referred for cataract surgery agreed to proceed (55% uptake)
62 referred for other reasons agreed to cataract surgery

723 individuals attended via alternative / secondary pathway

272 cataract operations in **185** individuals
44 YAG Capsulotomies in **38** individuals
392 died during study follow up
9 moved out of study area during follow up

Appendix A3(a) Lens Assesment and flow



Appendix A3(b) Glaucoma Assesment and flow

Appendix 4

Publications related to the Bridlington Eye Assesment Project

1. Prevalence of optic disc haemorrhages in an elderly UK Caucasian population and possible association with reticular pseudodrusen-the Bridlington Eye Assessment Project (BEAP): a cross-sectional study (2002-2006).
Wilde C, **Poostchi A**, Narendran R, MacNab HK, Hillman JG, Alexander P, Amoaku WM, Vernon SA.
Eye. 2019 Apr;33(4):580-586

2. Prevalence of peripapillary choroidal neovascular membranes (PPCNV) in an elderly UK population-the Bridlington Eye assessment project (BEAP): a cross-sectional study (2002-2006).
Wilde C, **Poostchi A**, Mehta RL, Hillman JG, MacNab HK, Messina M, Monaco G, Vernon SA, Amoaku WM.
Eye. 2019 Mar;33(3):451-458

3. Prevalence of reticular pseudodrusen in an elderly UK Caucasian population-The Bridlington Eye Assessment Project (BEAP): a cross-sectional study (2002-2006).
Wilde C, **Poostchi A**, Mehta RL, Hillman JG, MacNab HK, Messina M, Morales M, Vernon SA, Amoaku WM.
Eye. 2018 Jun;32(6):1130-1137

4. Prevalence of age-related macular degeneration in an elderly UK Caucasian population-The Bridlington Eye Assessment Project: a cross-sectional study.
Wilde C, **Poostchi A**, Mehta RL, MacNab HK, Hillman JG, Vernon SA, Amoaku WM.
Eye. 2017 Jul;31(7):1042-1050. doi: 10.1038/Eye..2017.30. Epub 2017 Mar 10.

5. Detecting abnormality in optic nerve head images using a feature extraction analysis.
Zhu H, **Poostchi A**, Vernon SA, Crabb DP.
Biomed Opt Express. 2014 Jun 11;5(7):2215-30.

6. Community optometrist referral of those aged 65 and over for raised IOP post-NICE: AOP guidance versus joint college guidance--an epidemiological model using BEAP.
Vernon SA, Hillman JG, Macnab HK, Bacon P, van der Hoek J, Vernon OK, Bhargarva A.
Br J Ophthalmol. 2011 Nov;95(11):1534-6.

7. Observer agreement using the Heidelberg retina tomograph: the Bridlington Eye Assessment Project.
Hawker MJ, Ainsworth G, Vernon SA, Dua HS.
J Glaucoma. 2008 Jun-Jul;17(4):280-6.

8. The relationship between central corneal thickness and the optic disc in an elderly population: the Bridlington Eye Assessment Project.
Hawker MJ, Edmunds MR, Vernon SA, Hillman JG, MacNab HK.
Eye. 2009 Jan;23(1):56-62. Epub 2007 Oct 19.

9. Linear regression modeling of rim area to discriminate between normal and glaucomatous optic nerve heads: the Bridlington Eye Assessment Project.
Hawker MJ, Vernon SA, Tattersall CL, Dua HS.
J Glaucoma. 2007 Jun-Jul;16(4):345-51.

10. Detecting glaucoma with RADAAR: the Bridlington Eye Assessment Project.
Hawker MJ, Vernon SA, Tattersall CL, Dua HS.
Br J Ophthalmol. 2006 Jun;90(6):744-8.

11. Specificity of the Heidelberg Retina Tomograph's diagnostic algorithms in a normal elderly population: the Bridlington Eye Assessment Project.
Hawker MJ, Vernon SA, Ainsworth G.
Ophthalmology. 2006 May;113(5):778-85.

12. Asymmetry in optic disc morphometry as measured by heidelberg retina tomography in a normal elderly population: the Bridlington Eye Assessment Project.
Hawker MJ, Vernon SA, Ainsworth G, Hillman JG, MacNab HK, Dua HS.
Invest Ophthalmol Vis Sci. 2005 Nov;46(11):4153-8.

13. Laser scanning tomography of the optic nerve head in a normal elderly population: the Bridlington Eye assessment project.
Vernon SA, Hawker MJ, Ainsworth G, Hillman JG, Macnab HK, Dua HS.
Invest Ophthalmol Vis Sci. 2005 Aug;46(8):2823-8.