Primary open angle glaucoma case finding in a UK community

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I, Michelle Pui Yan Chan, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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ABSTRACT

Glaucoma is a leading cause of irreversible blindness in the UK, and generates the sixth largest share of NHS outpatient attendances. There are inadequacies in the current system of primary open angle glaucoma (POAG) case-finding and its referral to the hospital eye service (HES). Half the cases are undiagnosed, while a large proportion of referrals for raised intraocular pressure (IOP) (>21mmHg) do not have glaucoma. No diagnostic test exists with both sufficient sensitivity and specificity suitable for population-wide glaucoma screening.

The EPIC-Norfolk Eye Study is a cross-sectional ophthalmic survey. This thesis aims to explore the characteristics of POAG, the risk factors for undiagnosed POAG, to re-examine the IOP referral threshold, and to evaluate the diagnostic performances of optic disc imaging in population screening.

Among the 8623 participants, 4.2% had glaucoma and 3.7% had POAG. A large number were glaucoma suspects (7%) and ocular hypertensives (10%). POAG was strongly associated with higher corneal compensated IOP (IOPcc) and lower corneal hysteresis, which could become useful metrics in disease management. 34% of POAG cases were previously undiagnosed, the risk factors were having normal tension rather than high tension glaucoma, lower pre-treatment IOP and smaller cup/disc ratio. This suggests an over-reliance on IOP in diagnosis and the need to re-focus on disc assessment.

The upper limit of IOP distribution (mean+2 standard deviations) in the study was 23.6mmHg. Increasing the referral threshold to >24mmHg could cut HES referrals by up to 67%. IOP used alone is ineffective in diagnosing POAG. HRTII and GDx-VCC used in combination generated high sensitivities and specificities in glaucoma screening, but would be costly and impractical to implement. The individual normative values of HRTII and GDx-VCC generated low sensitivities but high specificities (>97.0%), and could be useful in excluding glaucoma on a population scale. These findings can help transform glaucoma care in the UK.

IMPACT STATEMENT

Results from the EPIC-Norfolk Eye Study have had a significant impact on national policy on glaucoma management, as well as generating findings that help inform the future direction of glaucoma care. In addition, data in this thesis challenged the conventional referral threshold of >21mmHg by examining the IOP distribution in the cohort, which found the upper limit of distribution to be approximately 24mmHg using Goldmann-correlated IOP (IOPg). This data were presented to the NICE committee in 2017. As a result, in the updated NICE guidelines published in November 2017, 24mmHg was adopted as the new IOP referral threshold for further investigation and diagnosis of chronic open angle glaucoma and related conditions.[1] Specifically, it recommended that IOP should be measured with Goldmann applanation tonometer and confirmed on repetition, and that referral decision should not be based solely on IOP measurements using non-contact tonometry. The recommended treatment threshold for ocular hypertension has also been simplified from the previous threshold of >21-25 mmHg depending on age and central corneal thickness in the 2009 guidelines, to ≥24mmHg applicable to all patients if they are deemed to be at risk of visual impairment within their lifetime. The recommendations have also been disseminated by the Royal College of Ophthalmologists and the College of Optometrists to their members. The NICE changes are expected to reduce the number of false positive referrals to the HES, freeing resources from already over-stretched glaucoma clinics.

The study's glaucoma diagnosis and IOP distribution (Chapter 7) was published in the British Medical Journal in October 2017, [2] and the accompanying editorial highlighted the flaw in screening for glaucoma using IOP alone, describing it as "an outdated concept that should be abandoned".[3] The analysis of risk factors associated with undiagnosed POAG (Chapter 6) found that having NTG and lower IOP were the most important risk factors, as well as having lower cup/disc ratio, and hence less severe optic disc changes. This highlights the overall message that over reliance on IOP in glaucoma detection is detrimental, and is linked to glaucoma being missed, while more careful assessment of the optic discs in screening for glaucoma is crucial. This is an important practical learning point that needs to be enforced in the training of all eye care professionals.

PERSONAL CONTRIBUTION

The EPIC Norfolk cohort study was established in 1993. I started the work presented in this thesis in 2011, when the Third Health Check was nearing the end of its recruitment process, and subjects were undergoing the screening eye examination. My role in the study involved the extraction, cleaning, curation and analysis of eye data, and the processes involved to generate the glaucoma diagnosis. Specifically, my direct contribution included:

- Extraction of visual fields from the Humphrey's field analyzer hard drive.
- Processing all visual fields into an analyzable form suitable for Stata software.
- Cleaning and analysis of visual field data using statistical programming to identify patients who match the definition of a glaucomatous field.
- Extracting, processing and cleaning of data from participants' examination at the Norfolk & Norwich University Hospital eye clinic into an analyzable form suitable for Stata software.
- Writing the protocol for visual field analysis.
- Writing the protocol for optic disc grading from fundus photos.
- Calibrating the fundus camera using a model eye.
- Conceptualizing, designing, and executing the Glaucoma Diagnosis Refinement process as described in Chapter 4 to generate the final glaucoma diagnosis.
- All statistical and data analyses presented in this thesis were performed by myself alone.

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ABBREVIATIONS

3HC	Third health check
AS-OCT	Anterior segment optical coherence tomography
AUC	Area under curve
BCVA	Best corrected visual acuity
CCT	Central corneal thickness
CDAR	Cup to disc area ratio
CDR	Cup to disc ratio
CH	Corneal hysteresis
CI	Confidence interval
CRF	Corneal resistance factor
DCT	Dynamic contour tonometer
DFA	Discriminant function analysis
DH	Disc haemorrhage
EPIC	European Prospective Investigation of Cancer study
ENES	EPIC-Norfolk Eye Study
FCC	Fixed corneal compensator
FDT	Frequency doubling technology
GAT	Goldmann applanation tonometer
GCC	pre-macular ganglion cell complex
GCIPL	ganglion cell within the inner plexiform layer
GDx-VCC	Scanning laser polarimetry with variable corneal compensator
GHT	Glaucoma hemifield test, a metric of the Humphrey's automated perimetry
GP	General practitioner
GPS	Glaucoma probability score
GWAS	Genome-wide association study

LASIK	Laser in situ keratomileusis
LCDR	Linear cup to disc ratio
LDF	Linear discriminant function
LogMAR	Logarithm Minimal Angle of Resolution
HES	Hospital Eye Service
HTG	High tension glaucoma
HRT	Heidelberg Retinal Tomography
IOP	Intraocular pressure
IOPcc	Corneal-compensated intraocular pressure
IOPg	Goldmann-correlated intraocular pressure
ISGEO	International Society for Geographical and Epidemiological Ophthalmology
IQR	Interquartile range
MD	Mean defect
MRA	Moorfields Regression Analysis
NCT	Non-contact tonometer
NFI	Nerve fibre indicator
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NNUH	Norfolk and Norwich University Hospital NHS Foundation Trust
NRR	Neuroretinal rim
NTG	Normal tension glaucoma
OAG	Open angle glaucoma
OCT	Optical coherence tomography
OHT	Ocular hypertension
ONH	Optic nerve head
OR	Odds ratio
ORA	Ocular Response Analyzer non-contact tonometer
PAC	Primary angle closure

PACG	Primary angle closure glaucoma
POAG	Primary open angle glaucoma
PPA	Parapapillary atrophy
PSD	Pattern standard deviation
RDAR	Rim to disc area ratio
RGC	Retinal ganglion cells
RNFL	Retinal nerve fibre layer
ROC	Receiver operating curve
RPE	Retinal pigment epithelium
SAP	Standard automated perimetry
SD	Standard deviation
SD-OCT	Spectral domain optical coherence tomography
SLP	Scanning laser polarimetry
SITA	Swedish Interactive Threshold Algorithms
UK	United Kingdom
VA	Visual acuity
VCDR	Vertical cup to disc ratio
VF	Visual field

PUBLICATIONS

Publications generated directly from the work described in this thesis:

1. Chan MPY, Broadway DC, Khawaja AP*,* Yip JLY, Garway-Heath DF, Burr JM, Luben R, Hayat S, Dalzell N, Khaw KT, Foster PJ*.*
   Glaucoma and intraocular pressure in EPIC-Norfolk Eye Study: cross sectional study. *BMJ* 2017;358:j3889

   BMJ Editorial
   Jampel HD. Screening for glaucoma using intraocular pressure alone. *BMJ* 2017;158:j4160

Publications generated during the time of research:

2. Chan MP, Grossi CM, Khawaja AP*,* Yip JL, Khaw KT, Patel PJ, Khaw PT, Morgan JE,Vernon SA, Foster PJ.
   Associations with Intraocular Pressure in a Large Cohort: Results from the UK Biobank. *Ophthalmology* 2016;123(4):771-82.

3. Kapetanakis VV, Chan MP, Foster PJ, Cook DG, Owen CG, Rudnicka AR. [Joint first authors]
   Global variations and time trends in the prevalence of primary open angle glaucoma (POAG): a systematic review and meta-analysis. *Br J Ophthalmol.* 2016; 100(1):86-93

4. Khawaja AP, Chan MP, Yip JL, Broadway DC, Garway-Heath DF, Luben R, Hayat S, Matthews FE, Brayne C, Khaw KT, Foster PJ.
   Retinal nerve fiber layer measures and cognitive function in the EPIC-Norfolk Cohort Study. *Invest Ophthalmol Vis Sci*. 2016;57(4):1921-6.

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12. Khawaja AP, Chan MP, Hayat S, Broadway DC, Luben R, Garway-Heath DF, Sherwin JC, Yip JL, Dalzell N, Wareham NJ, Khaw KT, Foster PJ.
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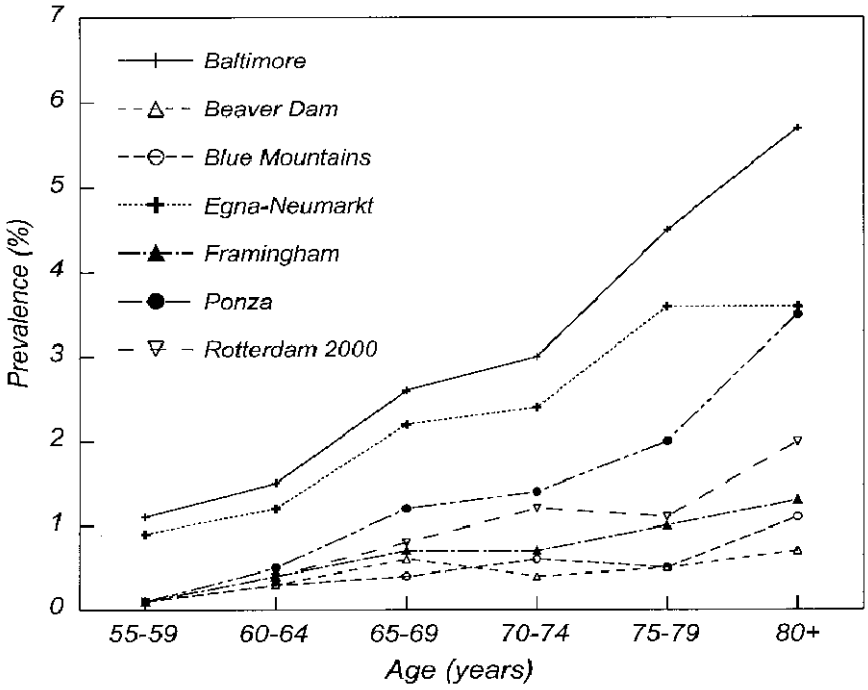
CHAPTER 1 INTRODUCTION

1.1 Epidemiology of Glaucoma

1.1.1 Definitions of Glaucoma

Glaucoma encompasses a group of diseases. Its definition often includes progressive structural & functional damage to the optic nerve, resulting in optic disc cupping and associated reproducible visual field defect, not consistent with other diseases. However, no explicit, widely-accepted set of definitions exists that clearly defines a case of glaucoma and excludes other diseases. Many published population studies use different criteria for optic disc cupping, degree of visual field defect, and some also include a criterion for raised IOP. This has led to great variability in the reporting of glaucoma risk factors, and prevalence data can vary by up to six fold in the older age groups (**Figure 1.1**).[4]

Figure 1.1 Variations of open-angle glaucoma (OAG) prevalence in the Rotterdam study when criteria of OAG from other population studies were applied to the Rotterdam data (reproduced with permission) [4]



For the purpose of cross-sectional population study reporting, Foster *et al* for the International Society for Geographical and Epidemiological Ophthalmology (ISGEO) proposed a set of guidelines for defining & classifying glaucoma.[5] It adopts a population's 97.5th & 99.5th percentile in cup-to-disc ratios as the statistical cutoff for normality, and proposed three different levels of evidence for glaucoma, based on the availability of disc and visual field evidence of optic neuropathy. The ISGEO criteria are used as a framework for reporting population glaucoma prevalence data.

1.1.2 Classification of Glaucoma

Glaucoma can be classified as primary or secondary, and the mechanism is divided into open-angle and closed-angle glaucoma, which are essentially different conditions with separate mechanisms, risk factors and management requirements. The focus of this research study is on primary open-angle glaucoma (POAG), the most common type of glaucoma in the UK and the western world.

The definition of POAG includes that of glaucoma, in the presence of open anterior chamber angle on gonioscopy and the absence of a secondary cause. POAG is subdivided into normal tension glaucoma (NTG) and high tension glaucoma (HTG) to reflect the spectrum of variable sensitivities to raised intraocular pressures in different people. NTG is POAG without elevation of IOP, defined as untreated IOP of <21mmHg[6,7] although some clinical studies also allowed IOP up to <24mmHg.[8]

1.1.3 Prevalence & Incidence of Primary Open-Angle Glaucoma

The number of people affected by glaucoma worldwide was estimated as 64.3 million in 2013, with the prevalence of POAG highest in Africa and the prevalence of primary angle closure glaucoma (PACG) highest in Asia.[9] The number of people with POAG is estimated to be 44 million by two separate meta-analyses,[9,10] and is predicted to increase to between 65.5 million [10] and 76 million [9] in 2020. OAG accounts for 68% of all glaucoma cases.[9] There is a considerable wealth of prevalence data of OAG from European, African-American and Asian-derived populations, but information is still lacking from African, Middle Eastern and South American countries. Case definitions of OAG vary significantly, but the prevalence among adults aged >40 years is generally around 1-3%.[11]

Data on the incidence of OAG is much less commonly reported. From the few cohort studies with a follow-up period, OAG incidence is reported as 0.1-0.2% per year in

European populations,[11] and a meta-analysis reported pooled estimates of 0.03% per year in those aged 40 and 0.18% per year in those aged 70;[12] the Barbados Eye Study reported incidence of 0.5% per year among its Black participants.[13]

1.1.4 Risk Factors for Primary Open-Angle Glaucoma

Age, sex and ethnicity

Increasing age is a well-established risk factor for POAG. Population surveys such as the Baltimore Eye Survey,[14] the Vision Impairment Project in Melbourne,[15] the Rotterdam Eye Study,[16] and a study in Roscommon, west of Ireland,[17] showed the prevalence of POAG increases with age. The risk of POAG increases with age across all ethnic groups. For each decade increase in age, risk increases greatest in Hispanics (by 2.3 times), followed by Whites (doubles), South Asians (by 1.7 times), followed by Black and South Asians (by 1.6 times), and South East and Eastern Asians (by 1.5 times).[10] The pooled estimate of POAG is 4.2% among Black populations, 2.1% in White populations, and 1.4% in Asian populations.[18]

Men were found to have a higher risk of glaucoma than women in two recent meta-analyses. After adjusting for ethnicity, age and other design factors, the odds ratio of OAG was 1.37 [10] and 1.30 [9] for men compared to women.

Intraocular pressure

Intraocular pressure (IOP) is a strong and well-established risk factor for POAG, a finding supported by many different types of evidence. In cross-sectional population studies, the prevalence of POAG increases with IOP level, such as in the Baltimore Eye Study,[14] the Framingham Eye Study[19] and the Tajimi Study.[20] In longitudinal studies, higher IOP predicted OAG development. The 9 year follow-up of the Barbados Eye Study reported a thirteen-fold relative risk in developing OAG in those with baseline IOP of >25mmHg compared to those with IOP ≤17mmHg, even though half of OAG cases are normal tension glaucoma.[21] The 5 year follow-up study of the Visual Impairment Study in Melbourne also confirmed increased IOP was associated with the risk of POAG development.[22]

Treating ocular hypertension was shown prospectively to reduce the risk of developing POAG in the Ocular Hypertension Treatment Study. With the goal of reducing IOP by >20%, the rate of suspected POAG development can be reduced from 9.5% to 4.4% after 5 years.[23] IOP reduction in glaucoma patients has been shown to reduce the rate of glaucoma visual field progression in three randomized treatment trials: the Advanced

Glaucoma Investigation Study (laser then trabeculectomy vs trabeculectomy then laser),[24] the Early Manifest Glaucoma Trial (laser and topical beta blocker vs placebo),[25] and the UK Glaucoma Treatment Trial (topical latanoprost vs placebo).[26] Finally, a meta-analysis estimated that IOP>26mmHg presents a 13 times higher relative risk of developing OAG than those with lower IOP.[12]

Nevertheless, the use of the conventional ocular hypertension threshold of >21mmHg to stratify glaucoma risk is seen as outdated,[27] as the value of 21mmHg corresponds to two standard deviations above a population's mean IOP,[28,29] and as such is a statistical construct rather a true threshold for increased OAG risk. There is no evidence to support that glaucoma risk increases significantly at >21mmHg.[14]

Central corneal thickness and corneal biomechanics

Corneal biomechanics is thought to be related to the pathophysiology of glaucoma, possibly as an indication to the structural properties of the scleral and lamina cribrosa, and therefore the vulnerability of the optic nerve to pressure forces.

Central corneal thickness (CCT) has long been known as a source of error in the accuracy of IOP measured with the Goldmann applanation tonometer (GAT).[30,31] Thick CCT will lead to over-estimation of true IOP, while thin CCT will lead to under-estimation.[30] However, thinner CCT has shown to be an independent risk factor that predicted POAG development in the 9 year follow-up of the Barbados Eye Study,[32] the Early Manifest Glaucoma Treatment Study,[33] and the Ocular Hypertension Treatment Study (OHTS).[34] The OHTS quantified that participants with CCT <555 μm had a 3 fold greater risk of developing OAG than those with CCT >588 μm in 5 years.[34] Thinner CCT was also shown to be associated with more severe Advanced Glaucoma Intervention Study (AGIS) disease score.[35] However, not all researchers were convinced by the interpretation of CCT as an independent risk factor, as thin CCT could be related to falsely low IOP, and therefore the risk of OAG could actually be mediated by high IOP.[36] CCT is also thinner in Black compared to White subjects,[37,38] and could indicate a lower IOP that mediated a higher risk of glaucoma.[39]

Corneal hysteresis (CH) is a measure of the cornea's ability to absorb and dissipate energy, and is measured by the Ocular Response Analyzer, a non-contact tonometer. It is emerging as an additional risk factor for POAG. Lower CH was associated with structural parameters of HRT and GDx-VCC [40] and OCT disc parameters.[35] Low CH was also found to be associated with a greater rate of visual field progression in longitudinal studies of glaucoma patients.[41-43] There is evidence that CH is more

important than CCT, explaining a larger degree of the variation of VF progression then CCT,[43] and in some studies, CCT was found to be not related to VF progression in glaucoma while CH was.[41,42]

Myopia

Another ocular risk factor that has been consistently shown is myopia. The proportion of OAG among myopes is consistently higher than non-myopes in cross-sectional studies after adjusting for age and sex,[44-46] and myopia is related to higher baseline IOP.[45] The Beijing Eye Study found a dose-response relationship, as high myopia (≤ 6D) is associated with higher frequency of glaucoma than moderate and low myopia.[44] The pooled relative risk of OAG among myopes compared to non-myopes is estimated as 1.88.[12] Nevertheless, this figure could be an over-estimation, as glaucoma is inherently difficult to diagnose among myopes. This is due to the morphology of myopic discs, which can be small and tilted. The presence of parapaillary atrophy can also cause non-progressive visual field defects that are difficult to differentiate from glaucomatous field defects.

Diabetes

The role of diabetes in the risk of developing OAG is unclear. While cross-sectional studies show a higher prevalence of glaucoma among diabetics,[47-49] and a meta-analysis of cross-sectional and case-controlled studies show that diabetic patients are at significant higher risk of developing OAG (pooled odds ratio of 1.50),[50] incidence studies [32,51] and some cross-sectional studies [52,53] found no link between diabetes and OAG.

Family history

Family history of glaucoma is often self-reported and can be difficult to verify, and as such is prone to recall bias and inaccuracies. Studies using self-reported family history of glaucoma in a first degree relative found the odds ratio of having OAG as 1.92,[54] while a meta-analysis shows that it is associated with a 3 fold excess age-adjusted risk.[12] However, the Baltimore Eye Survey, which ascertained family history of glaucoma by interviewing the relatives, shows that age-adjusted associations of OAG were higher in siblings than parents, and children of the patient.[55]

Genetics

Genes that contribute to adult-onset POAG and NTG have been identified through genome-wide association studies (GWAS) in European and Asian populations.[56-60] The loci are associated with a range of biological processes, such as cytokine signaling,

lipid metabolism, membrane biology, extracellular matrix as well as mitochondrial function. Genome-wide meta analysis on IOP and optic disc parameters has also been useful in discovering novel loci which were subsequently validated in their association with POAG.[61,62]

1.1.5 Burden of Primary Open-Angle Glaucoma

The burden of POAG can be far-reaching. To the individual, even mild visual field loss can cause significant morbidity, and it is also a common cause of certifiable visual impairment. To the health care system and society, it incurs substantial direct financial costs from medical and surgical treatment, as well as indirect costs from lost earnings and productivity.

Visual impairment

Glaucoma is the second most common cause of irreversible blindness (VA in better eye <3/60) after macular degeneration worldwide, according to a systematic analysis of data between 1990-2020.[63] In England and Wales, POAG is the second most common cause of registered blindness (8%) and partial sightedness (7%) after age-related macular degeneration,[64] while similar trends are found in Ireland [65] and West of Scotland.[66] The true burden of visual morbidity is likely to be even higher as many patients who are eligible for registration are not registered.[67]

The probability of blindness from treated OAG has been estimated as 14.6% in one eye and 6.4% for both eyes after 15 years in one study,[68] while another study estimates the risk of blindness as 27% in at least one eye and 9% for both eyes after 20 years' follow-up.[69] Late presentation – with either advanced field loss or blindness at presentation - is a major risk factor for glaucoma blindness,[68-70] as well as poor compliance with medication,[68,70] fluctuations in IOP and presence of exfoliation syndrome.[70] In turn, the factors associated with late presentation with advanced chronic glaucoma in the UK include lower occupational class, lack of family history, higher IOP on presentation, Afro-Caribbean race, being referred by sources other than optometrists, being male, and increasing age.[71,72]

Loss in quality of life & functional disability

Visual field loss negatively impacts a person's health related quality of life (HRQoL). It is significantly reduced even with mild visual field loss of between -2dB and -6dB of median deviation in either the worse or better seeing-eye compared to those without

any visual field defects.[73] The loss in HRQoL is worse with any central visual field loss than unilateral or bilateral peripheral field loss.[74]

The reasons for the loss of HRQoL stem from difficulty with driving, vision-related dependency and vision-related mental health issues.[73] Specifically, glaucoma is associated with slower reading,[75] reduced mobility performance such as walking speed,[76] and increased risk of a motor vehicle collision.[77] Glaucoma patients also suffer from increased risk of falls by two to four folds.[78] [79]

Financial burden

The financial burden ascribed to glaucoma arises largely from direct medical costs, such as the cost of ocular hypotensive medication, outpatient & inpatient hospital care. It also incurs direct non-medical costs from transportation and government purchase programs, and indirect costs due to loss of productivity & earnings.[80]

In both Australia and the USA, the annual direct medical costs attributed to glaucoma is ranked third among visual disorders (behind the costs of cataracts and refractive error), costing A$144.2 million and US$2.9 billion respectively.[81,82] The projected mean cost per patient treated for POAG specifically varies greatly between countries: in the UK it is US$1337, in the US is $2111, while other European countries range from $708 in Germany to $1963 in Spain.[83] This cost increases with the stage of disease measured by visual field defect and baseline IOP.[83,84]

1.1.6 Open-Angle Glaucoma Case Detection in the UK

Currently, glaucoma is diagnosed by screening and opportunistic case finding in the UK. This relies on individuals presenting to an eye care professional, usually a community optometrist, to be examined, and for any glaucoma suspects to be referred to ophthalmologists for definitive diagnosis and management. Individuals aged >60, those aged >40 years with a first degree family history of glaucoma, and those advised by an ophthalmologist to be at risk of glaucoma are eligible for a free NHS optician's eye test.[85]

Role of community optometrists

Community optometrists play an integral role in providing the initial assessment of suspected glaucoma cases in the UK. They account for 95% of referrals made to secondary ophthalmic care, and 55% of these referrals have a final diagnosis of glaucoma, glaucoma suspect or ocular hypertension.[86]

The College of Optometrists has published guidelines on the minimum standards of a basic optometrists' examination, which includes visual acuity and direct ophthalmoscopy without pupil dilation, but not IOP measurement or anterior chamber depth assessment.[87] For patients considered to be at risk of POAG, additional tests should include optic nerve head assessment, IOP measurement, anterior chamber depth assessment, and central visual field assessment using perimetry.[88] Patients who are deemed at risk from glaucoma include those with raised IOP, optic disc suggestive of glaucoma, symptoms of loss of peripheral vision, Afro-Caribbeans, those with first degree relatives of glaucoma, age over 40, use of topical or systemic steroids, anterior chamber capable of closure, and the people of South or East Asian descent for PACG. [88] Optometrists should refer asymptomatic glaucoma suspects to a hospital eye department if any of the criteria listed in Table 1.1 is satisfied.

Table 1.1 Guidance on the referral of asymptomatic glaucoma suspects by community optometrists
(issued by the College of Optometrists and the Royal College of Ophthalmologists) [89]

Optic disc signs consistent with glaucoma in either eye.
IOP in either eye >21mmHg
A visual field defect consistent with glaucoma in either eye.
A narrow anterior drainage angle on van Herick testing consistent with a significant risk of acute angle closure within the foreseeable future
Signs often associated with glaucoma (e.g. pigment dispersion or pseudoexfoliation)

Limitations of current opportunistic case finding

Eye surveys conducted in developed Western countries show that half of glaucoma cases are previously undiagnosed.[16,90] The figure is closer to 70-80% in Poland,[91] Brazil,[92] Japan [93] and urban cities such as London and Los Angeles,[94,95] indicating the inadequacy in the current methods of community case finding.

The limitations of opportunistic case funding are as follows:

- Most glaucoma cases are asymptomatic and progression is usually insidious, hence affected patients are unaware of their condition
- It relies on patients' awareness of glaucoma and its risk factors
- It may not capture the at risk groups for glaucoma
- Despite clear guidelines on referral to the hospital eye service for glaucoma suspects, the examination protocol by optometrists is not standardized
- There is no consensus on the most accurate tests to screen for OAG

- Access to optometrists depends on variation on local NHS provision and funding, as well as individual factors such as mobility, physical frailty, and socio-economic deprivation.

Glaucoma referral pathway

A large number of referrals to the HES are made by optometrists for suspected glaucoma, and 30% of those are for ocular hypertension. There are over a million glaucoma-related outpatient visits every year in the English HES,[96] and they account for the sixth largest share of NHS outpatient attendances after general medical examination, breast cancer, schizophrenia, prostate cancer and joint pain.[97]

To enhance the quality of referral and avoid over burdening the HES, the Royal College of Ophthalmologists published its guidance on commissioning for glaucoma care, which included intermediary services to refine the referrals.[98] This includes "repeat measure" services, which repeat the measurement of parameters related to the diagnosis, such as IOP or visual fields. "Referral refinement" is a two-tier assessment in which the initial abnormality found in screening is validated by a second assessment. "Enhanced case finding" is a newly introduced to provide enhanced examination such as slitlamp indirect biomicroscopy or Goldmann applanation tonometry.

The potential for mass screening of POAG

Since opportunistic case finding for POAG has limited effectiveness, the question arises whether OAG will be better detected through a population-wide screening programme, although it is currently not recommended. The aim of screening would be to detect early OAG, either pre-symptomatic disease or unrecognized early visual field changes, before visual morbidity sets in.

The UK National Screening Committee (NSC) has set out a list of criteria to assess the suitability of a screening programme,[99] which were adopted from Wilson & Jungner's original publication.[100] They appraise the condition, the test, the treatment options, and the effectiveness and appropriateness of a programme. OAG satisfies the criterion of being an important health condition, with a well-understood natural history that offers the chance to intervene at a pre-symptomatic stage.[101] There is evidence that treatment of early disease– either with medication, laser or surgery – is effective in slowing the progression of OAG.[8,25] However, OAG does not satisfy the criteria of having a suitable screening test, nor is the optimal parameters of a screening programme – including target population, screening tests, personnel, screening interval

– established. It is therefore difficult to assess the effectiveness and acceptability of an OAG screening as a whole at the present time.

Several analyses were performed to assess the likely cost-effectiveness of an OAG screening programme using different models in the UK and in Finland.[12,102,103] This depends on many variables, including the prevalence of OAG in the screened population, the sensitivity and specificity of the screening tests in, the costs of treating the screened positive cases, the savings from prevention of visual morbidity in those treated, and the costs of establishing and running the programme.

One UK study published in 1997, concluded that screening those aged 40-59 could be economical, as long as it costs no more than US$850 to detect a new case.[102] A study in Finland concluded that screening could be cost-effective in older age groups.[103] A more detailed systematic review in the UK concluded that population screening will not be effective, but target screening of high-risk groups such as those with a family history or those of Black ethnicity, may be.[12]

1.2 Optic Disc and Visual Field Changes in Glaucoma

1.2.1 Structure of the Retinal Nerve Fibre Layer and the Optic Nerve Head

The retina consists of ten sub-layers (**see Fig 1.2**). The retinal nerve fibre layer (RNFL) and the internal limiting membrane make up the inner layer of the retina. The RNFL consists of highly ordered parallel axonal fibres of the retinal ganglion cells (RGC) as well as astrocytes and blood vessels. Axons of the RGC from the temporal retina follow an arcuate course around the macula resulting in a horizontal raphe temporal to the macula. Axons from the fovea run directly to the temporal edge of the optic nerve head and form the papillo-macular bundle. An approximate 1.2 to 1.5 million axons converge at the optic nerve head (ONH) and bend to exit the eyeball at the posterior scleral foramen. The optic nerve head - or the optic disc - is therefore the anterior end of the optic nerve. **Fig 1.3** illustrates the anatomy of the optic nerve.

The ONH measures approximately 1.76mm in its horizonal diameter, 1.92mm vertically,[104] and is slightly tilted. It is bounded by the Elschnig ring, the visible scleral surrounding the scleral foramen through which the optic nerve travels. The Elschnig ring therefore corresponds to the outer margin of the neuroretinal rim of the optic nerve head.

The neuroretinal rim (NRR) of the ONH is its outer ring, consisting of nerve fibre bundles. The central depression, the cup, does not contain axons, but is occupied by retinal vessels and connective tissue. It is defined by the level at which the nerve fibres bend towards the lamina cribrosa. The ONH is slightly vertically oval while the cup is slightly horizontally oval. Lamina cribrosa is the fine mesh structure in the inner two thirds of the sclera across the scleral foramen. It provides mechanical support to the nerve fibre bundles. The axons usually become myelinated posterior to the lamina cribrosa as they become covered by meningeal sheaths.

Figure 1.2 Illustration showing the layers of the retinal (left) and the specific neuronal components (right)
(reproduced with permission) [105]

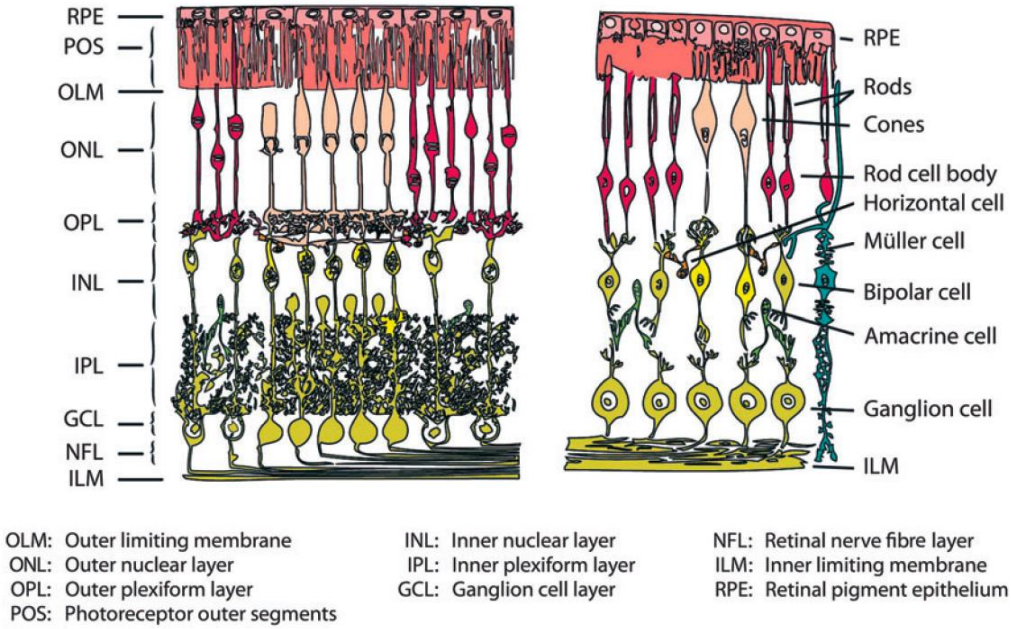
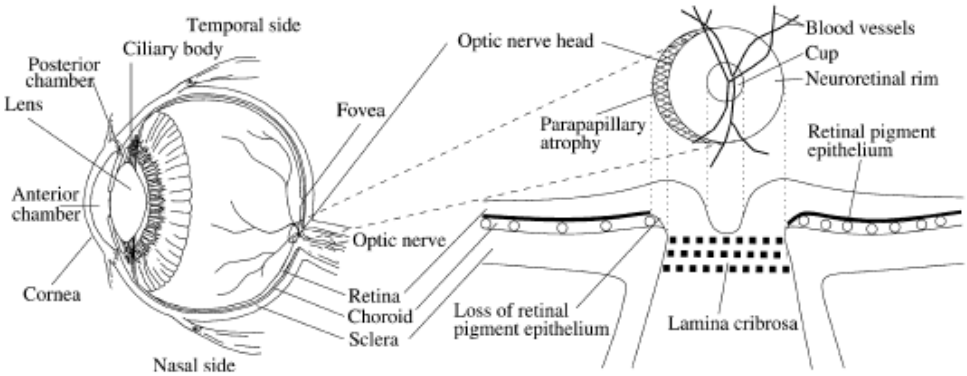


Figure 1.3 Basic anatomy of the eye and the optic nerve head
(reproduced with permission) [106]



1.2.2 Histopathology of the Glaucomatous Optic Nerve Head

Glaucoma is characterized by the loss of retinal ganglion cells by apoptosis, and it is preceded by axonal injury at the level of the lamina cribrosa,[107] where anterograde and retrograde axonal transport is disrupted. It has been shown by Quigley that at least 40% of RGC loss at the ONH occurs before definite visual field loss is detectable on perimetry.[108]

In addition to RGC loss, the characteristic excavation of the cup in glaucoma is caused by remodelling of the ONH surrounding tissues. This remodelling is specific to glaucoma and is not seen in other mechanisms of optic neuropathies. It is believed that the remodelling occurs as a response to mechanical stresses caused by IOP. The relative compliance and stiffness of the lamina cribrosa and the parapapillary sclera may contribute to the susceptibility of the ONH to IOP stresses, resulting in axonal injury and glaucoma, and may explain why glaucoma can occur at a wide range of IOP levels. This is supported by findings that greater axonal cell death occurs in areas of the ONH with greatest deformity.[107] A reduction in lamina cribrosa thickness,[109,110] posterior bowing and sliding of the lamina insertion,[111] and larger lamina pore size [112] are changes which can be seen in glaucoma.

1.2.3. Pathogenesis of Glaucoma

The primary insult in glaucoma is traditionally believed to be a combination of mechanical stress from raised IOP (described above), and vascular dysregulation leading to ischaemia of the ONH. Both mechanisms contribute to oxidative stress in the axons of the RGC, ultimately leading to apoptosis. However, many clinical cases remain inexplicable on this basis.

Raised IOP

Raised IOP is postulated to result from impaired aqueous drainage due to changes in the trabecular meshwork (TM) and Schlemm's canal. The TM has been shown to exhibit cytoskeletal changes,[113] altered cellularity [114] and changes in extracellular matrix. The Schlemm's canal endothelium shows loss of giant vacuoles, reduced pore size and density on the wall of the canal.

Vascular theory

Intact vascular autoregulation is needed to ensure adequate and stable ONH perfusion regardless of blood pressure or IOP. Dysfunction in autoregulation is believed to cause reduced and unstable ONH perfusion, leading to ONH ischaemia.

This is thought to be particularly important in the pathogenesis of NTG. NTG is associated with migraines,[115,116] sleep apnoea [117] and peripheral vascular abnormalities.[118,119] The rate of central field progression in NTG is greater in patients with lower heart-rate variability, a marker of autonomic dysfunction, then patients with higher heart-rate variability.[120] Nocturnal hypotension is a risk factor for visual field progression in NTG.[121-123] In particular, excessive dips in noctural BP by >20%, or minimal dips by <10%, are both regarded as pathological signs of vascular dysregulation, and are associated with a greater risk of progression than those whose noctural BP dips within a physiological range (10-20%).[123]

Nevertheless, IOP is still implicated in the aetiology of NTG, and reducing IOP is still the main treatment modality in NTG.[8] The Collaborative Normal Tension Glaucoma Study showed that IOP reduction by 30% was associated with stability of visual fields in 80% of patients. [124] However, with the knowledge of the vascular risk factors on NTG, optimizing the management of these patient's vascular conditions, and monitoring 24-hour blood pressure to detect nocturnal dips are extra facets of managing NTG.

1.2.4 Morphology of the Optic Nerve Head in Glaucoma

The thinning and loss of the NRR in glaucoma results in cupping- enlargement of the cup. Several recognized features are detectable on fundoscopy **(see Fig 1.4).** These features are often mixed, but one pattern might predominate.

ISNT rule and vertical cup/disc ratio

The contour of the NRR in the healthy, non-glaucomatous eye is encapsulated by the "ISNT" rule. The rim is widest at the inferior rim (I), followed by the superior rim (S), the nasal rim (N), and it is narrowest at the temporal rim (T). One of the earlier and subtler changes is the violation of the ISNT rule, whereby the vertical rim widths become thinner than the horizontal rim widths, and the cup becomes vertically oval. This is also conceptualized as increase in the vertical cup-to-disc ratio (CDR) **(see Fig 1.4b**)**.** However, CDR needs to be interpreted in relation to the disc diameter, as CDR increases with disc diameter, and an increased CDR may be physiological rather than

glaucomatous.[125] CDR asymmetry between the two eyes suggests the cupping is not physiological.

Notching

The thinning of the NRR can be focal, whereby a notch (see **Fig 1.4c**) in the rim or localized rim loss is seen, or global, as the NRR is thinned concentrically. The lamina cribrosa can collapse focally in extreme cases of focal rim thinning, leading to an acquired disc pit, recognizable as a local depression on the disc.

Blood vessels

The retinal vessels that emanate from the optic disc also show characteristic appearances as a result of NRR thinning. Bayoneting describes sharp bends in the vessels at the NRR, and baring of the vessels is the hanging of blood vessels away from the underlying NRR that has eroded away.

Parapapillary atrophy

Parapapillary atrophy (PPA) is the thinning of the retinal layers and retinal pigment epithelium (RPE) around the optic nerve **(see Fig 1.4d).** It can be divided into the inner beta zone, which is the pale area of visible sclera and choroidal vessels around the peripapillary scleral ring, and the outer alpha zone, with areas of hyper or hypopigmentation of the RPE. PPA has been shown to be larger and occurred more often in glaucomatous eyes than non-glaucomatous eyes.[126] The size of the PPA and the size of the beta zone (relative to the disc area) predict the development of glaucoma,[127] and the progression of PPA may be an early glaucomatous finding among ocular hypertensives.[128]

Disc haemorrhages in glaucoma

Disc haemorrhages (DH) (**Fig 1.4e**) are well known phenomena in glaucoma**.** They usually occur on the inner Elschnig ring on the RNFL as linear feathery-shaped splinter haemorrhages, or round in deeper retinal layers. In the OHTS study, the occurrence of DH increased the risk of developing POAG 3.7-fold in a multivariate analysis, and the cumulative incidence of conversion to POAG in 8 years was 13.6% among eyes with DH compared to 5.2% in eyes without DH.[129] Patients with NTG have a particularly high incidence of recurrent DH of up to 67%.[129] DH is also an independent risk factor predictive of POAG in the 13 year follow-up of OHTS.[130] Nevertheless, the majority (86.7%) of eyes in OHTS with DH did not develop POAG. The other causes of DH include diabetes mellitus, posterior vitreous detachment, and anterior ischaemic optic neuropathy.

Parapapillary RNFL loss in glaucoma

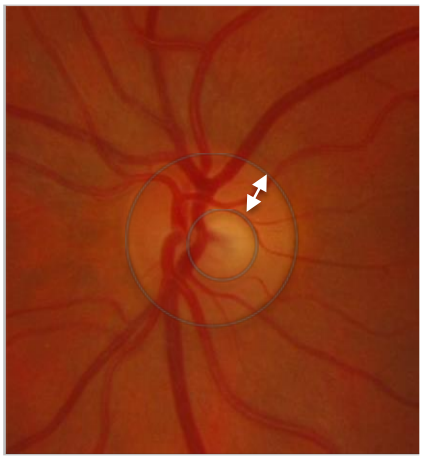
On fundoscopy using red-free illumination, the RNFL can be seen as silver striations. In glaucoma, focal thinning of the RNFL can be seen as slits or wedges of dark bands in the retina, originating from the optic disc radiating and broadening towards the periphery. Generalized thinning of the RNFL can be more difficult to detect, but the retinal vessels will stand out in relief against a dull, matt background of retina.

Myopic discs

Myopia is a risk factor for glaucoma. The axial elongation in myopic eyes often results in smaller, tilted discs with crescent formation,[131] which make these discs difficult to assess for glaucoma. Moreover, the tilt can be responsible for non-progressive[132] as well as progressive visual field loss.[131]

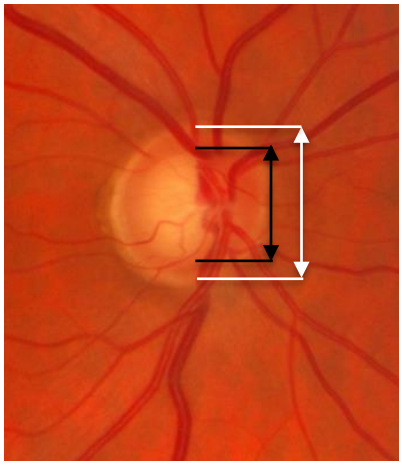
Figure 1.4 Disc photographs of the optic nerve head

a) A normal, non-glaucomatous optic disc, with margins of the disc (outer ring), cup (inner ring), and the neuroretinal rim (arrow) highlighted.



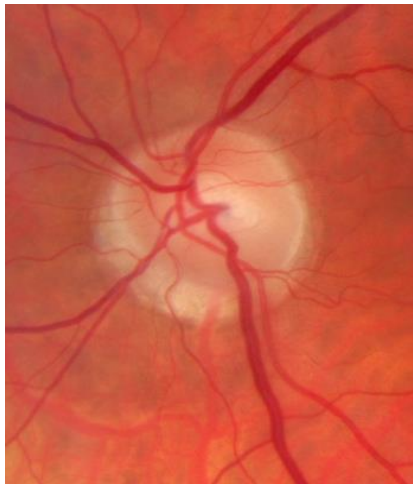
b) Enlarged cup to disc ratio, showing the vertical disc diameter (white arrow) and cup diameter (black arrow)

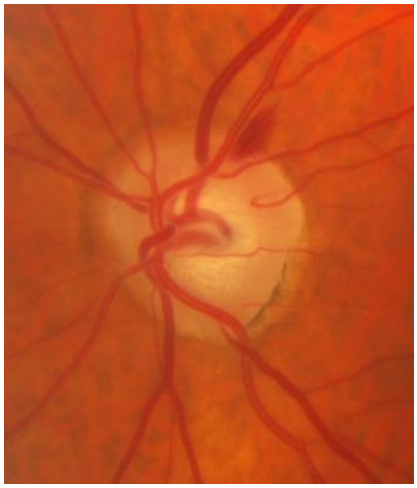
c) Disc notching (arrow)



d) Parapapillary atrophy

e) Disc haemorrhage





1.2.5 Visual Field Changes in Glaucoma

Normal visual field

A healthy, non-glaucomatous eye can detect stimuli 60° superiorly**,** 70° inferiorly, 60° nasally and 100° temporally from central fixation. The "hill of vision" is a three-dimensional graphic representation of differential light sensitivity at different positions in the visual field, which is greatest in the fovea and declines toward the periphery.

Patterns of glaucomatous field loss

Patterns of localized field defects are common in glaucoma, and they correlate with the anatomical arrangement of the RNFL. Arcuate scotomas occur early in the disease, as the arcuate fibres are susceptible to early damage, possibly because they are in the watershed junction of the vascular supply from adjacent ciliary vessels. Inferior fibres are more vulnerable, so superior arcuate scotomas develop first.[133] Early arcuate scotomas obey the horizontal midline and terminate at the nasal horizontal meridian, which reflect how the superior and inferior arcuate fibres terminate at the horizontal raphe. Nasal steps result as the loss of nerve fibre bundles are asymmetrical in the superior relative to the inferior hemifields. In two separate studies examining the evolution of field defects, nasal step was found to be the most common initial field defect, occurring as the first defect in 50% of eyes.[133,134] Diffuse field loss can also occur in early disease due to diffuse RGC loss. Temporal wedges occur due to the loss of the nasal fibres, and they do not obey the horizontal midline. Nasal fibres and the papillomacular bundle are more resistant to glaucomatous loss, so central vision and a temporal island is usually preserved until late in the disease.

Hart *et al* described the evolution of field defects on Goldmann kinetic perimetry through the stages of glaucoma, and have observed the following order of field loss.[133]

1) Nasal step defect
2) Temporal wedge defect
3) Arcuate scotoma
4) Paracentral defect 10–20° from the blind spot
5) Arcuate defect with peripheral breakthrough
6) Generalised constriction (tunnel vision)
7) Severe visual field loss with temporal sparing
8) Total loss of field.

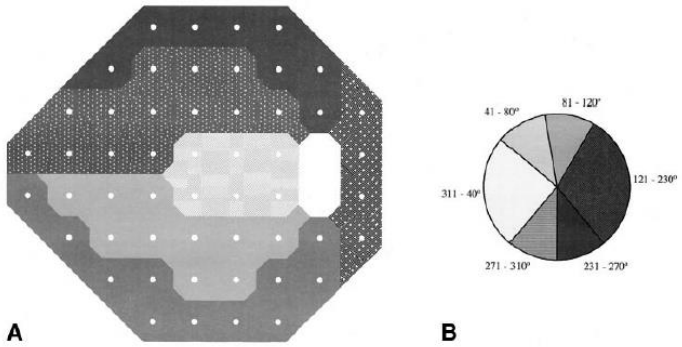
1.2.6 Structure-Function Relationship in Glaucoma

There is good evidence of a correlation between optic disc changes and visual field loss in glaucoma. Linear correlation between quantitative optic disc parameters by planimetry, particularly between optic disc rim area and standard automated perimetry (SAP) mean defect in glaucoma patients have been demonstrated.[135,136] Correlation is also found using alternative methods of disc assessment, such as the scanning laser ophthalmoscopy's disc parameters, which are found to correlate with SAP visual field indices[137,138] and with short wavelength automated perimetry indices.[139] Scanning laser polarimetry (GDx-VCC [140]) and OCT measured parapapillary RNFL thickness [141,142] were all correlated with SAP.

Spatial relationship

The anatomical relationship between the ONH and the corresponding points on the Humphrey's 24-2 field was mapped by Garway-Heath *et al* using RNFL photographs.[143] They showed that the superior and inferior poles of the ONH are the most densely sampled in the visual field (**Fig 1.5**). This means early glaucoma will be easier to diagnose, since thinning of the neuroretinal rim at the poles is often the earliest sign of glaucoma.

Figure 1.5 Anatomical relationship between the optic nerve head and the Humphrey's 24-2 visual field
(reproduced with permission)[143]



Temporal relationship

Quigley demonstrated that at a histological level, at least 40% of RGC loss at the ONH occurs before definite visual field loss is detectable on perimetry.[107] Many clinical studies have since demonstrated that quantitative disc changes on disc photography occur before visual field changes on standard automated perimertry, such as the prospective Structure and Function Evaluation Study.[144] In the Early Manifest

Glaucoma Treatment Trial, 86% of patients who progressed did so on fields alone, 0.7% progressed on disc alone, and 13% progressed concurrently.[25] The European Glaucoma Prevention Study found similar results, with 64% progressed on visual fields and 42% on disc criteria.[145] However, different results were found in the OHTS, with 55% ocular hypertensives who converted to OAG did so with optic disc end points, 44% reached VF end points, and 1% reached VF and disc changes end points concurrently.[34] HRT measured disc changes also predicts subsequent VF progression.[146] With HRT rim area is used as the optic disc parameter, it is noted that progression by VF occurred at least as frequently as progression by HRT rim area among ocular hypertensives.[147]

1.2.7 Defining Glaucoma

Glaucoma is characterized by progressive structural and functional damage to the optic nerve, but there is no universally agreed universal set of diagnostic criteria. The difficulty lies with the fact that disc and field damage is continuous, and many different features constitute a glaucomatous field or disc. Wolfs *et al* highlighted the varied criteria for POAG that exist among cross-sectional population studies. Some studies used clearly defined and repeatable quantitative criteria in CDR and CDR asymmetry, while others simply defined glaucoma as the presence of glaucomatous disc and congruous field defect.[148] However it has been shown in the European Optic Disc Assessment Trial, whereby ophthalmologists in 11 European countries were asked to grade a standard set of optic disc photos for glaucoma, even among experts there was great variability in accuracy and agreement in diagnosis.[149] Older studies also incorporated a minimum IOP criterion of >20-22mmHg for glaucoma – such as the Ponza Glaucoma Study, Visual Impairment Study, the Beaver Dam Eye Study, and the Egna-Neumarkt Study - which we now widely regarded to be flawed and leads to missed cases.

Defining the glaucomatous optic disc

It is common to define a glaucomatous disc quantitatively by CDR or CDR asymmetry. (**see Table 1.2**) In 2002, ISGEO proposed the first set of disc criteria that use the 97.5th or 99.5th centile of the populations' CDR distribution to define the upper limits of "normal", that is eyes without a glaucomatous visual field defect.[5] The CDR cut off therefore varies for different populations. The ISGEO criteria has since been widely adopted by many population studies.[20,150-152] The principle of using the 97.5th centile to define "normality" has been validated in a study using data from the Rotterdam study.

The optimum CDR cutoff point associated with glaucomatous field loss as determined in regression analysis was 97.0th centile (95% CI, 95.5-98.5th centile).[153]

Table 1.2 Examples of optic disc criteria for definite glaucoma adopted by population surveys

Study	Disc criteria
Baltimore Eye Survey [154]	CDR ≥0.8 or CDR asymmetry ≥0.3
Barbados Eye Study [155]	CDR ≥0.6 or CDR asymmetry ≥0.2
Beaver Dam Eye Study [156]	CDR ≥0.8 or CDR asymmetry ≥0.2
Blue Mountains Eye Study [90]	CDR ≥0.7 or CDR asymmetry ≥0.3
Framingham Eye Study [157]	CDR ≥0.6 or CDR asymmetry ≥0.2
Ponza Glaucoma Study [158]	CDR ≥0.5 or CDR asymmetry ≥0.2
Rotterdam Study [4]	CDR ≥0.7 or CDR asymmetry ≥0.2 or NRR<0.1
Thassaloniki Eye Study [159]	Thinning or notching of disc, or CDR asymmetry >0.2
Visual Impairment Project [15]	CDR ≥0.7 or CDR asymmetry ≥0.3

Defining the glaucomatous visual field

Hodapp, Parrish and Anderson described a set of glaucoma visual field criteria in 1993, which set the precedence of identifying focal field loss based on a cluster of 3 contiguous points of depression.[160] The criteria have been widely adopted by many studies. The original criteria below were based on the Humphrey 's 30-2 full threshold strategy field, but a 24-2 field version has been developed, such as the one used in ISGEO (**Table 1.3**).

Table 1.3 Criteria defining the glaucomatous visual field

Hodapp-Parrish-Anderson Criteria for Glaucomatous Field
• GHT "outside normal limits" on at least 2 occasions, *or* • A cluster of three or more non-edge points in a location typical for glaucoma, all of which are depressed on the pattern deviation plot at p<5% level and one of which is depressed at a p<1% level on two consecutive fields, *or* • A corrected pattern standard deviation (CPSD) that occurs in less than 5% of normal fields on two consecutive fields.
ISGEO Criteria for Glaucomatous Field
• GHT "outside normal limits" *and* • A cluster of three contiguous points at the 5% level on the pattern deviation plot

Categories of diagnosis

More than one glaucoma definition has been developed in some studies to allow for participants who could not perform visual fields, or when the optic disc cannot be

visualized. The ISGEO criteria detailed below (**Table 1.4**) uses three broad categories, and more stringent disc criteria (CDR >99.5th centile for normal population) when visual field is missing, or allows poor vision in the context of advanced disc cupping and missing field to be diagnostic.

Table 1.4 ISGEO criteria for diagnosis of glaucoma in cross sectional prevalence surveys

Diagnostic Category		Diagnostic Criteria
Category 1 diagnosis (structural & functional evidence)	1A	CDR ≥ 97.5th percentile for the normal population, and definite glaucomatous visual field defect
	1B	CDR asymmetry ≥ 97.5th percentile for the normal population, and definite glaucomatous visual field defect
	1C	NRR width reduced to ≤ 0.1 CDR (between 11-1 o'clock or 5-7 o'clock), and definite glaucomatous visual field defect
Category 2 diagnosis (advanced structural damage with unproved field loss)	2A	No visual fields data (persons unable to perform field due to poor vision), and CDR ≥ 99.5th percentile for the normal population
	2B	No visual fields data (persons unable to perform field due to poor vision), and CDR asymmetry ≥ 99.5th percentile for the normal population
Category 3 diagnosis (optic disc not seen, field test impossible)	3A	VA <3/60 and IOP > 99.5th percentile
	3B	VA <3/60 and the eye shows evidence of filtering surgery or medical records confirming glaucomatous visual morbidity
Glaucomatous visual field		The Glaucoma Hemifield Test "outside normal limits", and A cluster of three contiguous points at the 5% level on the pattern deviation plot, using the threshold test strategy with the 24-2 test pattern of the Zeiss-Humphrey field analyser 2

CDR cup to disc ratio; NRR neuroretinal rim; VA visual acuity; IOP intraocular pressure

1.3 Examination and Imaging in Glaucoma

Diagnostic tests for POAG involve the assessment of the optic nerve head for structural changes, assessment of functional loss with visual field testing, and measurement of IOP. A range of tests are being used by optometrists and ophthalmologists, depending on the availability of equipment and the skills of the examiner. The National Institute of Clinical Excellence (NICE) guidelines recommend that in examining a person with suspected POAG, the tests should include: Goldmann

applanation tonometry (GAT), central corneal thickness measurement, gonioscopy, optic nerve assessment with pupil dilation using slitlamp biomiscroscopy, and standard automated perimetry using central threshold testing.[1] Optic nerve head imaging with stereo photography or with optical coherence tomography (OCT) at diagnosis for baseline documentation is also recommended.

Automated methods of optic nerve head structural assessment, namely optic nerve head ophthalmoscopy (Heidelberg retinal tomography, HRT), scanning laser polarimetry (GDx-VCC) and OCT are available in some Hospital Eye Service departments, but were previously not recommended by NICE in the 2009 guidelines due to a lack of evidence of their effectiveness over slitlamp fundoscopy with stereo-photograph.[161] However, the 2017 updated guidelines now recommend the used of OCT. HRT and GDx-VCC will be described in detail below as they are used in the research described in this thesis.

A comprehensive Health Technology Assessment report of diagnostic tests for POAG concluded that most tests (including frequency doubling technology, ophthalmoscopy, Goldmann applanation tonometry, and standard automated visual field testing) report a specificity of at least 85%, although there is no single test or combinations of tests that are superior to all others due to the lack of high quality comparative evidence.[162]

1.3.1 Tonometry

While IOP is not a diagnostic criterion for glaucoma, it is the only modifiable risk factor, and IOP reduction is the mechanism of glaucoma treatment. A tonometer therefore needs to be accurate, repeatable, safe and easy to use. There are many different types of tonometers available both clinically and for research use.

Goldmann applanation tonometer

Applanation tonometry is based on the Imbert-Fick principle, which states that the pressure inside an ideal dry, thin-walled sphere equals the force necessary to flatten its surface divided by the area of flattening. Goldmann applanation tonometer (GAT) is the gold-standard instrument in clinical practice. It requires instillation of topical anaesthesia and fluorescein prior to use. The tonometer, which is mounted on a slit lamp, is advanced until the prism touches the cornea, and the two semiciruclar miers are aligned by dialling the tonometer which indents the cornea. When first introduced in 1957, Goldmann and Schmidt stressed that there will be measurement errors due to

variations in corneal thickness and stiffness.[163] It has since been shown that thin CCT leads to under-estimation of true IOP, while a thick cornea over-estimates IOP, and corneal curvature also affects the accuracy of GAT measurements.[31]

Hand-held applanation tonometers

Hand-held applanation tonometers, such as the Perkins and Kowa tonometers, use the same principle as GAT and similar tonometer prisms. They are useful substitutes for GAT when patients cannot be examined on the slit lamp due to mobility or positional problems.

Non-contact tonometer

The non-contact tonometer (NCT) uses a jet of air to indent the cornea. The NCT is favoured by optometrists,[164] as its use does not require topical aneasthesia nor direct contact with the cornea, therefore avoids the potential -albeit small - risks of corneal trauma and infection transmission with direct applanation tonometers. In a systematic review of studies that directly examined agreement of tonometers with GAT, NCTs have shown to have the least amount of variability, with the difference in IOP of only 0.2mmHg on average compared to GAT.[165] However in practice, the accuracy of NCT has been shown to be lower at high IOP levels.[166]

Ocular Response Analyzer

The Ocular Response Analyzer (ORA) is the tonometer used in the current study. It was introduced in the last decade as an innovative non-contact air-puff which measures corneal biomechanics. It measures the air pulse pressure at which the cornea is applanated (P1) by the air puff, and the pressure at which it regains its original shape (P2), and these two pressures provide useful information about the biomechanical properties of the cornea. The ORA generates two IOP metrics – IOPg which is calibrated against GAT, and IOPcc, which is derived by modelling the IOP of patients who have had LASIK to limit the difference before the IOP measured before and after the surgery.[167] IOPcc is therefore designed to be less influenced by corneal biomechanics. The difference between P1 and P2 is corneal hysteresis, which represents the property of the cornea to absorb and dissipate energy, and is shown to be an independent risk factor of POAG. Corneal resistance factor was derived as another measure of the biomechanical properties but is relatively unaffected by IOP and is more strongly associated with CCT than CH.[168] ORA is increasingly being used in clinical practice

Rebound tonometer (Icare)

The Icare is a portable rebound tonometer. It uses a disposable tip which has a 1.8mm plastic ball on a stainless steel wire which springs forward and makes contact with the cornea. The deceleration of the ball is more rapid if the IOP is high and slower if the IOP is low. Icare is the only contact tonometer that does not require topical anaesthesia, and is portable, quick to use and well-tolerated. It is therefore particularly suited for examining children. The Icare ONE Home model is developed for self tonometry.[169] The various Icare models show high agreement with GAT.[170-174]

Tono-Pen

The Tono-Pen is a portable hand held contact tonometer. It requires topical anaesthesia but its main advantage is that it can be used with the patient in any position.

Dynamic contour tonometer

The Pascal dynamic contour tonometer (DCT) is a slit lamp mounted applanation tonometer. It uses a unique contour matching principle, whereby the cornea matches the contour of the tonometer tip, which has a concave contact surface, and that greatly reduces errors on IOP from corneal biomechanical factors.[175] The DCT takes 100 measurements per second over a 5-8 second period, and therefore also generates a measure of the ocular pulse amplitude. DCT measurements have been shown to be less affected by CCT than GAT,[176-178] and in one study they also show superior reproducibility compared to GAT and ORA.[179]

Agreement of tonometers with GAT

Cook *et al* published a systematic review on the agreement of a range of tonometers with GAT as the reference.[165] NCT measurements were closest to GAT. NCT over-estimated GAT by 0.2mmHg (95%CI -0.1 to 0.6mmHg), and 66% of the measurements were within 2.0mmHg from GAT. Hand held applanation tonometers produced the next best agreement with GAT, and achieved 59% of measurements within 2.0mmHg of GAT, and it underestimated GAT by 1.2mmHg (95% -2.8 to 0.4mmHg). ORA IOPg – which is used extensively in this thesis – over-estimated GAT by 1.5mmHg (95% CI 0.9 to 2.2mmHg), and had greater variability, with only 46% of measurement falling within 2.0mmHg from GAT. Overall, however substantial variability in measurements within and between studies, even for studies of GAT measurements.

Table 1.5 Summary of different tonometers currently available

Tonometer	Set up	Mechanism	Use/ Benefits
Goldmann applantion tonometer (GAT)	Slitlamp mounted	Applanation	Gold standard in clinical use.
Perkins	Hand held	Applanation	Useful in patients who cannot be examined on the slitlamp
Non contact tonometers	Hand held / table mounted	Pneumo	No anaesthesia required, most commonly used among optometrists
Ocular response analyzer (ORA)	Table mounted	Pneumo	No anaesthesia required. Able to measure corneal hysteresis and corneal independent IOP.
Icare	Hand held	Rebound	No anaesthesia require, easily tolerated & portable. Gold standard in paediatric clinical use.
Tono-Pen	Hand held	Contact	Able to be used regardless of patient's position.
Dynamic contour tonometer	Slitlamp mounted	Contour matching	Contour matching eliminates measurement error from cornea. Used mainly in research.

1.3.2 Pachymetry

When GAT was first introduced in 1957, Goldmann and Schmidt stressed that there will be measurement errors due to variations in corneal thickness and stiffness.[163] It has since been shown that thin CCT leads to under-estimation of true IOP while thick cornea over-estimates, and corneal curvature also affects the accuracy of GAT measurements [31] Algorithms to correct the IOP measurements for CCT have been developed [180-184] although their precision have been discounted.[185,186] Nevertheless, CCT is widely regarded as an independent predictor of POAG development.[34,35,187,188] Pachymetry to measure CCT thickness is therefore important for risk stratification in glaucoma and for determining in whom to start treatment in ocular hypertensives.[161]

1.3.3 Gonioscopy and anterior chamber depth assessment

Gonioscopy

Gonioscopy is the gold standard technique for examining the anterior angle, and is an important part of the glaucoma examination. A gonio lens is applied to the cornea after topical anaesthesia, and the angle is examined on the slitlamp under dark conditions. The depth of the angle is classified depending on the angle structures visible, and hence the risk of angle closure. A "wide open" angle corresponds to seeing all angle

structures including the ciliary body and the risk of closure is minimal, while an occludable angle is judged to have at least 2 quadrants of irido-trabecular meshwork contact where trabecular meshwork is not visible, and the eye is at risk of acute angle closure attack. Occludable angles may necessitate preventative treatment such as laser peripheral iridotomy [189-191] or lens extraction in the presence of raised IOP (primary angle closure) or glaucoma (primary angle closure glaucoma).[192]

Other useful observations on gonioscopy include: heavy pigmentation of the trabecular meshwork in pigment dispersion syndrome, Sampaolesi line which is pigmentation anterior to the Schwalbe's line, in either pigment dispersion syndrome or pseudoexfoliation syndrome, angle recession, iris or angle neovascularisation. All these signs indicate possible secondary causes for open angle glaucoma.

Van Herick test

Assessment of anterior chamber depth with the van Herick classification is a non-contact method to assess the risk of angle closure [193] A narrow beam on the slitlamp off set at 60° is used to examined the temporal peripheral cornea and anterior chamber at the limbus. The anterior chamber depth is compared to the corneal thickness. If the ratio is 1:1, then angle closure is very unlikely. If the anterior chamber depth is ¼ of the corneal thickness, then angle closure is possible.

Anterior segment optical coherence tomography (AS-OCT)

AS-OCT is an automated imaging technique that generates high resolution cross-sectional images of the anterior segment from angle to angle. Unlike gonioscopy, which is a subjective assessment that requires an experienced examiner and contact with the cornea using a gonio lens, AS-OCT is non-invasive and simple to perform, and the images have good repeatability.[194] The images allow quantitative measurements and comparisons for changes. The images can be further analysed with different software for more detailed measurements for the angle that is useful in research.[195]

1.3.4 Automated Perimetry

Automated perimetry rather than manual perimetry is the preferred choice of visual field testing for detecting and monitoring glaucoma, as it provides sensitive, reproducible and quantitative results. It detects the patient's threshold visual sensitivity in multiple points within the visual field. The light intensity of the target increases with each stimulus until the patient detects it and registers their response with the response

button. The threshold sensitivity is determined traditionally using a “staircase algorithm”, which presents stimuli in large steps or increments of light intensity, to rapidly bracket the range of the estimated threshold. It then reverses the light sensitivity in smaller increments to efficiently identify the threshold. The results are compared to an age-correlated database of normative sensitivity values. The Humphrey Field Analyzer (Carl Zeiss Meditec) and the Octopus perimeter (Haag-Streit Diagnostics) are the most popular models in clinical practice.

Standard automated perimetry

Standard automated perimetry (SAP) is the most widely used perimetry in the clinical management of glaucoma. It measures the threshold sensitivity of 50-80 defined points within the visual field under standardized conditions, typically using a white stimulus, presented for 0.2 seconds against a white background. The size target is variable but a Goldmann Size III target is the standard. Examination of the central 24-30° area around fixation is usually adopted. Different test strategies can be used which vary in the sensitivity and the length of test. Threshold testing is the current standard for SAP in glaucoma management. It determines the dimmest stimulus which can be detected 50% of the time. Suprathreshold testing uses a target brighter than threshold testing of pre-determined intensity. It does not determine the precise sensitivity of each location, and is designed to screen for moderate to severe field defects.

The Swedish Interactive Threshold Algorithm (SITA) is a test strategy developed in 1997 for the Humphrey Field Analyzer with the aim of shortening the test time, and improving patient tolerability without reducing data quality.[196] It uses mathematical modelling to predict the patient’s response based on their previous responses in surrounding test locations, and presents a stimulus of an intensity close to the predicted threshold. A shorter version, SITA Fast was developed using an algorithm that accepts a lower accuracy of results. [197] Compared to full threshold testing, SITA Standard is 50% faster, and SITA Fast only takes 34% of the full threshold’s test time.[198,199] Both strategies achieved low test-retest variability [198] and excellent sensitivities (SITA standard 92%, SITA Fast 85% in detecting mild glaucoma, 100% for both in detecting advanced glaucoma) and specificities (96%).[200] SITA has since been adopted as the standard test strategy by most clinicians.

Short wavelength automated perimetry

Short wavelength automated perimetry (SWAP) uses a blue target (larger Goldmann Size V target lit with a 440nm interference filter), on a yellow background. SWAP can

diagnose glaucoma [201,202] and detect progression [203] earlier than SAP , as it isolates and tests a small specific subpopulation RGC which are sensitive to blue stimuli that are lost early in the disease. SAP in comparison, tests all RGC subpopulations.

Frequency doubling technology perimetry

Frequency doubling technology (FDT) perimetry uses a low spatial frequency sinusoidal grating at a target that undergoes high temporal frequency counterphase flicker. This preferentially tests the function of a subset of sparsely spaced of RGC, the M cells, which is different from SAP, and may allow glaucoma to be diagnosed earlier. FDT is a compact, transportable perimeter, and can tolerate refractive errors up to 6D as the targets are larger than SAP. It is much faster to perform than even the SITA-Fast strategy on SAP to complete.[204] It detects visual field loss associated with a range of conditions such as cataract, retinal and neurological diseases. Its main use in glaucoma is as a screening tool using its screening strategies.

FDT using its full threshold strategy has been shown to have lower intra and inter test variability compared to SAP.[205] Abnormalities detected by FDT were predictive of future onset and location of SAP field defects among glaucoma suspects in longitudinal study.[206,207] Cross-sectional studies have shown Matrix FDT is comparable to or better than SAP in its discriminatory power for glaucomatous VF defects.[208,209]

1.3.5 The Zeiss Humphrey's Visual Field Analyzer

Figure 1.6 shows the printout of a SAP performed on a Humphrey's Field Analyzer. Information printed on top include the patient's name, date of birth and age, refractive error correction, test strategy, duration of test, and reliability indices. Sensitivities across the visual field are displayed graphically in several maps. Summary indices for overall performance is provided by the mean deviation, pattern standard deviation, and the Glaucoma Hemifield Test.

Reliability indices

Fixation losses, false positive and false negative rates give an impression of the patient's reliability. Fixation is monitored by a gaze tracker throughout the test, and a video tracker allows the examiner to observe fixation externally. Manufacturer's guideline states that fixation losses >20% and false positives >15% are deemed unreliable, and is indicated with "XX" next to the result.[210] However, poor reliability

indices could be due to poor vision or advanced field loss, and do not necessarily invalidate the test.

Numerical threshold map - shows the raw estimated threshold (dB) at every test location.

Grey scale map – is a graphical representation of the numeral thresholds

Numerical total deviation map – shows the point-wise difference between the measured thresholds and the age-corrected normal values.

Numerical pattern deviation map – shows the thresholds corrected for diffuse sensitivity losses (such as due to media opacities), hence highlighting focal field losses.

Probability maps – provide the statistical significance ($p<5\%$, $p<2\%$, $p<1\%$, $p<0.5\%$) for the values on the total deviation and standard deviation maps. For example, a probability of <0.5% means the deviation from normal at that location occurs in <0.5% of the normal population.

Global Index - Mean deviation (MD)

The MD is the average difference in the patient's threshold sensitivities compared to the normal expected values for the patient's age. It is useful as a quantitative measure for the overall sensitivity of the field, the more negative the MD, the more depressed the field loss. MD is accompanied by a p value to indicate the probability of the normal population having an MD larger than the patient's.

Global Index - Pattern standard deviation (PSD)

PSD is a measure irregularities in the patient's hill of vision by comparing to the hill of vision of the age-matched normal. A low PSD indicates a smooth hill of vision, and a high PSD indicates an irregular hill, which could be due to true field irregularities or variability in patient's response.

Visual Field Index (VFI)

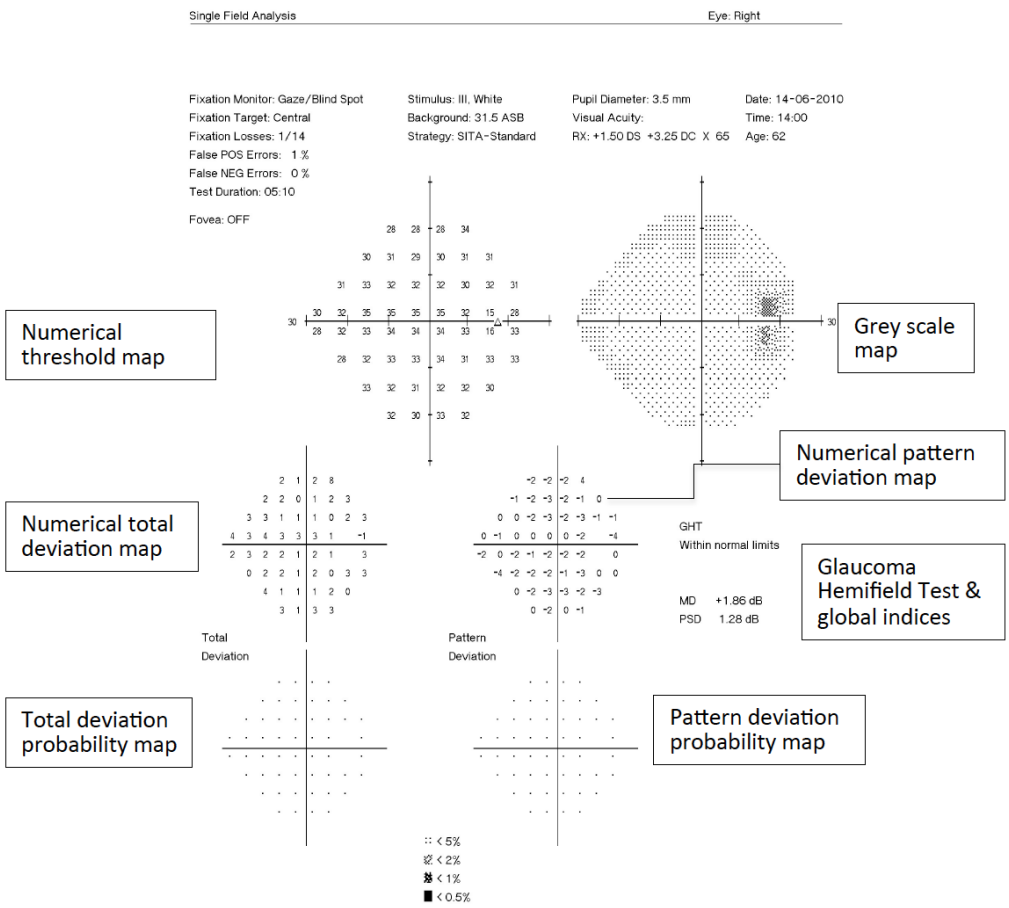
VFI is a measure of the subject's overall visual function compared to an age-adjusted normal population. It refers to the proportion of the field on the 24-2 test pattern which

is depressed relative to the age-adjusted normal hill of vision at the 5% level or worse in the Pattern Deviation plot.

Glaucoma Hemifield Test (GHT)

The GHT is a classification of the likelihood of glaucoma based on known patterns of glaucomatous visual loss. The field is divided into 5 corresponding mirror image zones above and below the horizontal midline. The thresholds of each mirror image zone pairs are compared and evaluated against the normal database. The result is a printed message of either “within normal limits”, “borderline”, or “outside normal limits”. In addition, “general depression of sensitivity” appears if the sensitivity of the field is depressed to a level seen in fewer than 0.5% of the normal age-matched population, while “abnormally high sensitivity” appears when the sensitivity is higher than fewer than 0.5% of the normal population, indicating perhaps a “trigger happy” or unreliable patient.

Figure 1.6. An example of a Humphrey's 24-2 visual field test printout



1.3.6 Disc Photography & Planimetry

Monoscopic and stereoscopic photography

Disc assessment using colour monoscopic and stereoscopic photography is an important method to document the ONH appearance which is comparable to the view seen on slitlamp fundoscopy, and serial photos is useful for detecting progression. Stereo photography is achieved by taking two simultaneous photos with a spatial shift, and viewing them through a stereo-viewer to achieve a three- dimensional appreciation of disc morphology. This is particularly useful for delineating the margins of the NRR and the optic cup, and hence rim loss, compared to the two dimensional view of monoscopic photos. Clear media and pupil dilation will help produce high quality images in disc photography. Stereo-photographs are recommended by NICE,[161] the European Glaucoma Society,[211] and the American Academy Ophthalmology [212] for baseline ONH documentation, and they were used in the OHTS and EMGTS as a valid tool to document the ONH to detect progression.

Planimetry is the measurement of ONH dimensions on disc photographs for quantitative assessment, which is often done with computed assistance on digital photos. Stereo photos are often used in conjunction to visualize the margins of the disc and cup.

The main limitation of disc photography is that it is a subjective assessment. In the Glaucomatous Optic Neuropathy Evaluation (GONE) project, inter-observer agreement among fellowship trained glaucoma specialists in estimating glaucoma likelihood with stereo photos (weighed kappa 0.59) is similar to the results with mono photos (weighed kappa 0.61), although mono photos showed poorer inter-observer agreement in the assessment of cup depth.[213]

Among general ophthalmologists in Europe, stereo photos' performance in diagnosing glaucoma has a sensitivity of 75%, specificity of 87%, and overall accuracy of 81%, although stereo photos underperformed compared to machine classifiers with HRT and GDx.[149]

1.3.7 Scanning Laser Ophthalmoscopy (HRT)

The Heidelberg Retinal Tomography (HRT) scanning laser ophthalmoscopy is an automated imaging technique which assesses ONH morphology and parapapillary RNFL. **Figure 1.7** shows the output of an HRT II scan**.**

Principles of operation

The HRT uses a rapid scanning 670nm diode laser beam, which focuses using two oscillating mirrors and scans the fundus. The laser is reflected from the surface of the retina and optic nerve. A luminance detector measures the light reflected from each point in the retina after the light passes through a confocal pinhole. The pinhole limits the depth from which the reflected light reaches the detector at a set focal plane on the retinal or optic nerve surface. A two dimensional image is thus generated. The depth of the focal plane is automatically adjusting by shifting the confocal aperture to acquire multiple optical sections through the tissues, ultimately creating a layered three-dimensional image.

The reflectance image and the topographic image

The HRT II acquires a series of 16 to 64 optical sections in depth at intervals of 1/16mm, and images tissues up to a depth of 4mm. The image field is 15°x15°, with a density of 384x384 pixels. Both a reflectance and a topographical image are generated. A reflectance image, which is a false-colour image based on the reflectance of the tissues, areas of high reflectance, such as the base of the optic cup appearing brighter. The result is an image appearing like a fundus photograph. The topographic image is generated based on the height of the surface contour of the tissues. It is also a false-colour image, with deeper structures appearing lighter and elevated structures appearing darker.

The contour line and the reference plane

After the image is taken, a contour line needs to be drawn manually by the operator to outline the optic disc margin. This is done either on the reflectance or the topographic image, by placing 3-6 points on the margin, and a circle is completed automatically.

Once the contour line is drawn, HRT then defines the reference plane, an imaginary plane parallel to the retinal surface. The default plane is set at 50μm below the contour line at the temporal disc margin, and is the approximated location of the papillomacular

bundle, which is assumed to remain stable as glaucoma progresses. The reference plane is used to calculate the height and cross sectional area of the nerve fibre layer. Within the scleral ring, space that is above the plane is defined as the neuroretinal rim, and place below is the cup. Parameters that are independent of the reference plane include the disc area, height variation contour and cup shape measure.

Quantitative measures

The HRT provides a range of stereometric parameters, based on a normative database of 349 White subjects.

Discriminant function analysis (DFA)

Rather than using single HRT parameters, combinations of parameters used together in the form of DFA have been shown to improve diagnostic performance compared to single parameters. Several DFA have been devised by modelling combinations of HRT measurements and weighing each variable separately. Notable discriminant functions were published by Mikelberg,[214] Bathija,[215] Burk,[216] Mardin,[217] and Iester.[218] The HRT II software provides the DFAs of Mikelberg and Burk. All of these DFAs made use of cup shape measure as a variable, while Iester used a sector based formula and adjusted for varying sector size.

These DFA have all proven to be more effective than cup shape measure alone in diagnosing glaucoma.[219,220] Comparing these five DFAs directly, Mikelberg and Bathija resulted in the best diagnostic performance in small discs, Iester performed best for medium disc size.[219]

Moorfields Regression Analysis (MRA)

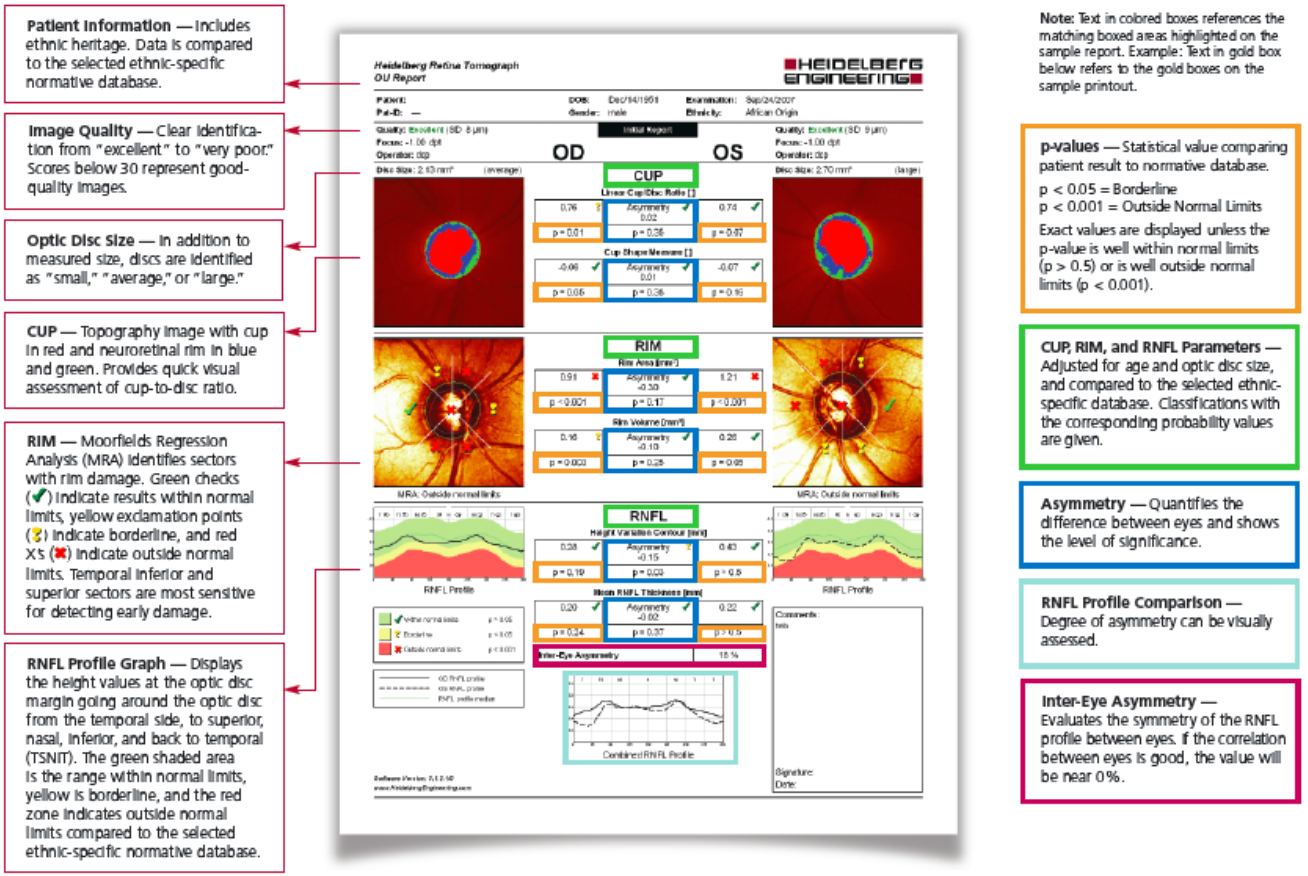
The MRA is a statistical algorithm-based analysis that classifies each disc into three categories: within normal limits, borderline, or outside normal limits. It uses linear regression of NRR area and CDR, taking into account the prior knowledge that NRR area varies with ONH size,[221] and that NRR area may decline with age.[222] Its range of normal values were generated from a database of 112 “hyper normal” white subjects who had normal visual fields, intraocular pressure <21mmHg, visual acuity better than 20/40, a refractive error less than 6 dioptres ametropia, and no history of diabetes, ocular surgery, glaucoma or first degree family history of glaucoma, or on systemic beta blocker medication. A particular advantage of the MRA is it provides analysis by sector, therefore allowing the clinician to compare the results to the visual fields.

Reproducibility of HRT stereometric measurements

Reproducibility of HRT results is important clinically. It serves to ensure that progression of glaucoma can be judged with reliability, and that the results will not vary significantly between tests and between observers. In a study by Iester *et al* on the original version of HRT, the parameters that showed the least inter-observer variation were: cup shape measure, maximum cup depth, height contour variation, and mean height contour, possibly because these parameters were most independent of the outlining of the disc margin.[223] Volume below surface, volume below reference plane, volume above surface and volume above reference plane, as expected showed the greatest variability due to their reliance on the disc margin. By having available a stereo-photo to aid the drawing of the disc contour, some observers produced less inter-observer variation.

Similarly, works by Strouthidis *et al* on HRT II showed that parameters with the least test-retest variability were rim area measurement and mean cup depth.[224] They were influenced most by reference height differences and image quality. By using a different reference plane set at 320μm posterior to the reference ring in the image, rather than the standard reference plane set at 50μm posterior to the contour line, and choosing higher quality images, test-retest reliability improved.[225]

Figure 1.7. An example of a HRT II scan printout
(reproduced from manufacturer's manual) [226]



Performance of HRT II in diagnosing glaucoma

The performance of HRT II in differentiating normal and glaucoma subjects have been reported in many case-control studies using the linear discriminant functions (LDF) and MRA. **Table 1.3** summarizes the main studies and their findings.

Comparison of HRT with other diagnostic tests

HRT is more sensitive than visual field in detecting change, and can detect changes before confirmed field changes.[227] In the European Optic Disc Assessment Trial, which compared the diagnostic accuracy of glaucoma specialists (using stereo disc slides), HRT and GDx-VCC in discriminating between healthy and glaucomatous eyes, HRT MRA and GDx NFI outperformed every clinician in its diagnostic accuracy (80.5% clinician, 93.2% NFI, 89.8% MRA), while a large variability in diagnostic accuracy and agreement was demonstrated among clinicians.[149]

Disc size

Optic disc size is well known to affect disc parameters. For HRT stereometric parameters, sensitivity and specificity were found to be lower with unusually small discs (disc area <2mm^2) compared to disc size of 2-3mm^2 and larger discs of >3mm^2. [218] Ford *et al* found the performance of Mikelberg and Burk LDF, but not Bathija LDF were significantly influence by disc size, with larger discs (>2.1mm^2) tended to be classified with a higher sensitivity but lower specificity than small disc areas (<1.73mm^2) [228]

Performance of HRT in population setting

The HRT has been tested in population mass screening settings.

In the Singapore Malay Eye Study, three algorithmns: Mikelberg, Burk and Bathija discriminant functions, as well as MRA were examined.[229] It found only moderate sensitivities of 31.5%, 42.7%, 45.2% respectively for the three discriminant functions, at specificity of 95%. The Blue Mountain Eye Study in Australia examined the performance of MRA in HRTII in diagnosing glaucoma among 1644 participants. [230] MRA sensitivity was 64.1%, specificity 85.7%. Particular strength of the study was all participants underwent visual field testing. Data from both eyes were used. Single eye analyses overestimated specificity and underestimated sensitivity compared to data from both eyes. Ramdas *et al* examined the use of HRT 3 in the Rotterdam Study data, and found that disc adjusted LCDR is the best suitable variable to develop normative values for diagnosing glaucoma on a population scale, as it showed the highest sensitivity (35%) at a defined high specificity level of 97.5%.[231]

From a different point of view, The Bridlington Eye Assessment Project examined the ability of HRT II to exclude glaucoma by studying its specificity in a series of 459 normal eyes of elderly participants (aged 66-89 years). It found that specificity deteriorated significantly with larger disc size, and male had significantly larger cups than females. This unexpected problem arose because the HRT normative database was developed on younger subjects. [232]

Table 1.6 Summary of case-control studies examining diagnostic performance of HRT II in differentiating normal and glaucoma subjects.

Study	Model	Glaucoma severity	Test classifier Outcome
Mikelberg, 1995 [214]	HRT	Early glaucoma	Mikelberg LDF (89% sens, 87% spec)
Uchida, 1996 [233]	HRT	Glaucoma	Cup shape measure (83%77%) Cup/ disc area ratio (AUC 0.94) Uchida's LDF (86 93%)
Bathija, 1998 [215]	HRT	Early glaucoma	Bathija LDF (62% sens, 94% spec)
Burk, 1998 [216]	HRT	Glaucoma	Burk LDF (74.1% sens, 85.9% spec)
Mardin, 1999 [217]	HRT	Pre-perimetric glaucoma	Mardin LDF (42.2% sens at 95% spec 83.6% spec at 95% sens)
Wollstein, 2000 [234]	HRT	Early glaucoma	MRA (84.3% sens, 96.3% spec)
Miglior, 2001[235]	HRT	Glaucoma	Mikelberg LDF (80% sens, 65% spec)
Iester, 2002 [220]	HRT	Glaucoma	Sectorial formula LDF (precision 82%) Bathija LDF (79%) Mikelberg LDF (74%) Cup shape measure (64%)
Ford, 2003 [228]	HRT II	Glaucoma	Mikelberg LDF (39% sens at 95% spec) Burk LDF (55% sens at 95% spec) Bathija LDF (44% sens at 95% spec) MRA (ONL) (78% sens, 81% spec) MRA (borderline) (58% sens, 96% spec)
Medeiros, 2004 [236]	HRT II	Glaucoma	Bathija LDF (AUC 0.86) Mikelberg LDF (AUC 0.83) VCDR (AUC 0.83) Cup/disc area ratio (AUC 0.81) Rim/disc area ratio (AUC 0.81)

AUC-area under curve, sens-sensitivity, spec-specificity, LDR – linear discriminant function

HRT-3 & Glaucoma Probability Score (GPS)

HRT-3, the latest operational software, was released in 2008. It has a larger normative database than HRT II, and includes non-white ethnicity, including 215 African Americans, 100 Indians. In addition, a new parameter, the GPS, is included. It is generated from a mathematical model that includes 10 parameters of the ONH

morphology.[237] A two dimensional surface of the ONH shape can therefore be modelled without the manual delineation of the optic disc rim.

1.3.8 Scanning Laser Polarimetry

Principles of operation

A scanning laser polarimeter (SLP) is a confocal scanning laser ophthalmoscope with an integrated ellipsometer that measures retardation. The SLP measures thickness of the RNFL. It does so by measuring the birefringence of the axons to the RNFL, which by their different orientations creates a phase shift in the birefringence, which proportional to the thickness of the RNFL. **Figure 1.8** shows the printout of a GDx-VCC scan.

A polarized light beam of 790nm is split by the instrument's polarizer into two components before entering eye. The light then falls onto the retinal surface and double crosses the RNFL. The two components then travel at different velocities, creating a retardation, which is proportional to the thickness of the RNFL.[238,239]

Variable corneal compensation

The lens and cornea in the anterior segment of the eye are also birefringent. The SLP compensates for that by isolating and neutralizing the birefringence. The earlier model of SLP, the Nerve Fiber Analyzer has a fixed corneal compensator (FCC), which assumes that the corneal polarization axis and magnitude (15° and 60nm) is the same in all subjects. However, studies showed that to be inadequate and produced erroneous results. [240-242] The variable corneal compensator (VCC) was developed, which customized the retardation for individuals by measuring the macular area's birefringence as a control. The uncompensated image from the macular produces a bow-tie pattern, which is a result from the combined anterior segment and RNFL birefringence, while the radial birefringence of the Henle's fibre layer provides information about the residual birefringence, as the layer guarantees uniform minimal birefringence. The uncompensated image is then analyzed to determine the magnitude and axis of the anterior segment birefringence. The SLP using VCC compared to the FCC, provided improved ability to discriminate normal and glaucoma subjects,[241,243,244] and the RNFL thickness also showed improved correlation with visual fields.[245] The latest model of SLP, the GDx-VCC, uses the VCC.

Fundus image

The GDx-VCC contains a number of graphical and numerical results. The fundus image is a reflectance image generated from the light reflected directly from the retinal surface. It is presented as a false colour image of the optic disc and parapillary area. A calculation circle represents the location where the subsequent RNFL is based. The fundus image is useful in the assessment of image quality and the centration of the ONH.

Nerve fibre layer map

This shows a reflectance image of the distribution of the RNFL thickness. Warmer colours represent thicker and more regular RNFL, while cooler colours represent thinner areas. A healthy eye will display an “hourglass” distribution of warmer colours superior and inferiorly, and cooler colours nasally and temporally. In glaucomatous eyes, retardation is typically lost especially supero-temporally and infero-temporally to the ONH.

Deviation map & normative values.

The deviation map analyses the nerve fibre layer maps compared to age-matched and ethnicity-matched normative values from the GDx-VCC database, and provide a colour-coded significance scale based on the probability of the area being abnormal. The comparative database comprises of 540 normal eyes and 271 glaucoma eyes, from individuals aged 18-89 years. The ethnic breakdown is reported as 70% Caucasian, 18% African American, and 12% Asian. The definition of normality was eyes with IOP <22mmHg, non-glaucomatous optic disc (CDR asymmetry<0.2, no rim thinning, notching, excavation or RNFL defect), and normal visual fields.

TSNIT plot

The plot represents the RNFL thickness plot along the measurement circle (TSNIT-temporal-superior-nasal-inferior-temporal), showing also the age and ethnic-based normal ranges of the RNFL thickness throughout. Both eyes’ plot are shown together to aid detection of asymmetry.

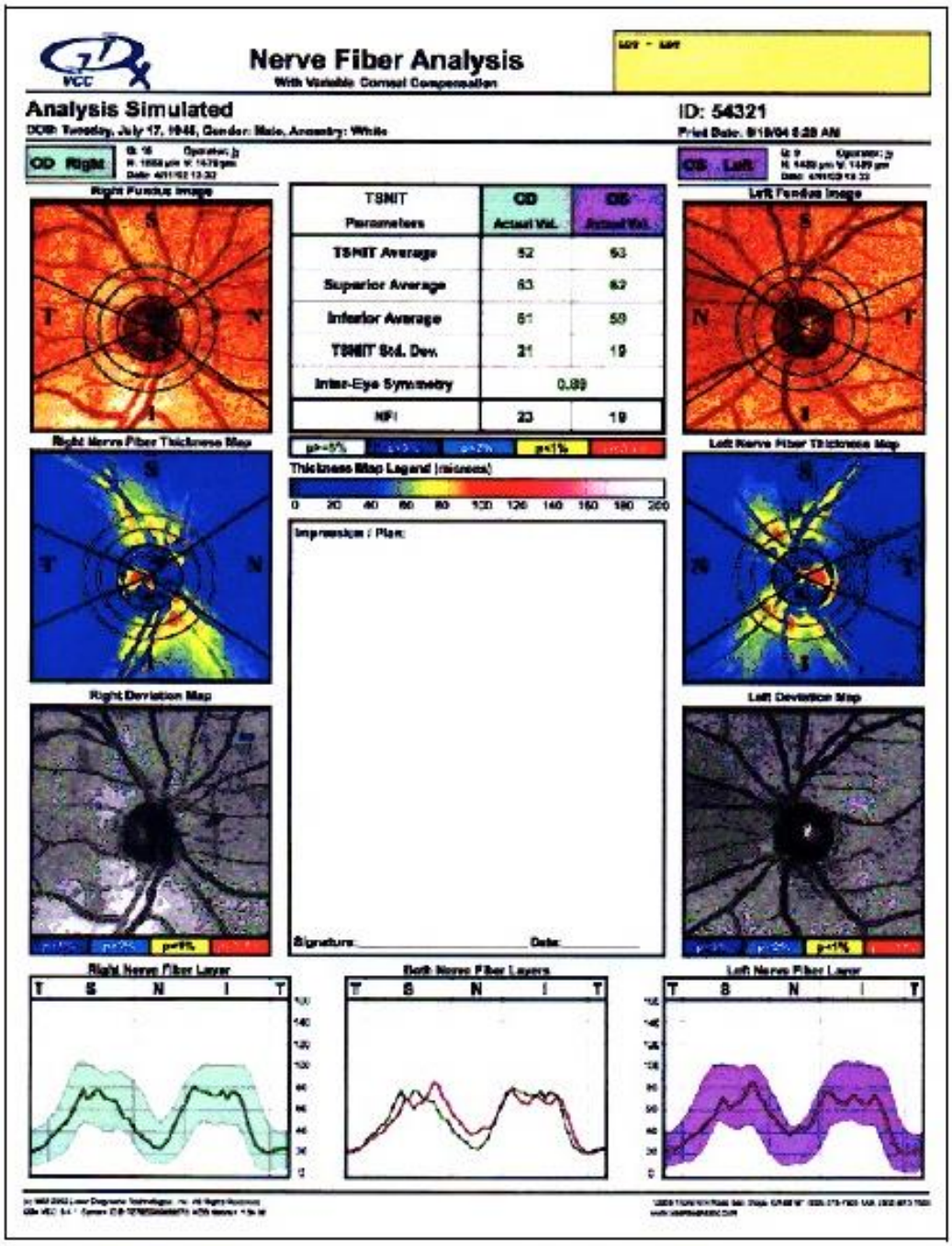
RNFL summary parameters

The GDx-VCC provides a few key parameters. TSNIT average, superior average, and inferior measures compare the RNFL thickness within the calculation circle to the normative database. The TSNIT standard deviation refers to the amplitude of the TSNIT curves – flatter curves with lower standard deviation could represent a loss of

integrity of the superior and inferior RNFL bundles. Inter-eye asymmetry is an indicator of symmetry of the TSNIT profiles between both eyes. All of these parameters are colour coded on a significance scale based on the probability of the value being abnormal

The Nerve Fibre Indicator (NFI) is a global measurement based on a form of neural network analysis. It analyses the entire RNFL and provides a single number to represent the integrity of the RNFL as a whole.
0-30: Within normal limits
31-50: Borderline
51-100: Outside normal limits.

Figure 1.8. An example of a GDx-VCC scan printout
(reproduced from manufacturer's manual) [246]



Performance of GDx-VCC in diagnosing glaucoma

Many studies have published the performance of the earlier versions of SLP. The table below refers to the main studies on the performance of the GDx-VCC in case-control settings in differentiating normal and glaucomatous eyes. There is good correlation between GDx-VCC and visual fields.[140,247]

Table 1.7 Summary of main studies that reported the diagnostic performance of GDx-VCC

Study	Glaucoma severity	Results (AUC)
Da Pozzo, 2005 [248]	Glaucoma	NFI 0.938 TSNIT average 0.897
Da Pozzo, 2006 [249]	Early glaucoma	NFI 0.870 Superior average 0.817 TSNIT average 0.789
Reus, 2004 [250]	POAG vs normal	NFI 0.98 Superior average 0.94 TSNIT average 0.93 Inferior average 0.92
Reus, 2004 [251]	Pre-perimtric glaucoma	All classifiers -significant difference between pre-perimetric glaucoma eyes and healthy control eyes
Badalà, 2007 [252]	Early glaucoma	NFI AUC 0.92 Superior average 0.88 TSNIT DF 0.85
Medeiros, 2004 [236]	70% early glaucoma	NFI AUC 0.91

AUC-area under curve, sens-sensitivity, spec-specificity

1.3.9 Optical Coherence Tomography

Principle of operation

Optical coherence tomography (OCT) is the most advanced and rapidly evolving imaging modality in ophthalmology. It is commonly used in clinical practice to diagnose and monitor glaucoma. It produces high resolution cross-sectional images of the retina using infrared light reflected from the scanned tissues to discriminate the retinal layers. A large number of scans are taken per second (400 A-scans/sec in time domain OCT, 52,000 A-scans/sec in spectral domain OCT) and a composite image is generated. Time domain OCT (TD-OCT) such as the Stratus OCT, is the older generation of device although its use in glaucoma has been well investigated. The latest generation is the spectral domain OCT (SD-OCT). It has a much faster image acquisition speed, and therefore can acquire scan patterns with a higher density scans, resulting in higher axial resolution of <5μm as compared to TD-OCT devices (approximately 10 μm). SD-

OCT allows retinal structure previously indistinguishable on the TD-OCT, such as the ganglion cell layer to be imaged.

OCT parameters used in glaucoma

The two groups of parameters most commonly used in glaucoma detection are parapapillary RNFL thickness and ONH parameters. A newer parameter available in the SD-OCT is the pre-macular ganglion cell complex (GCC). It refers to the three innermost retinal layers – the RNFL, ganglion cell layer, and the inner plexiform layer - which are believed to be preferentially affected in glaucoma. [253] Using automated segmentation software, the SD-OCT can quantify individual layers of the macular RNFL (mRNFL), ganglion cell-inner plexiform layer (GCIPL), and the GCC, which is the total thickness of mRNFL and GCIPL.

The measurements are compared to a normative database and the results presented in formats similar to HRT and GDx printouts, such as thickness maps, infrared derived image maps, and colour-coded maps on the probability of the results being within the normative limits.

Diagnostic performance of OCT in detecting glaucoma

To date, most published work on the diagnostic ability of OCT centred on the RNFL thickness. TD-OCT shows good reproducibility in measuring RNFL thickness. [254] It is effective in differentiating glaucomatous and normal eyes, and its performance is similar to HRT and GDx. [255-258] SD-OCT ‘s GCIPL and GCC have been shown to effective in differentiating healthy and glaucomatous eye, with areas under curve over 0.90 in receiver operating characteristic plot analyses. [259-261]

1.4 Treatment of Primary Open Angle Glaucoma

1.4.1 Principles of Treatment

The ultimate goal of glaucoma treatment is to maintain the patient's visual function and related quality of life, at a sustainable cost. Lowering IOP is the only proven method of treatment in POAG to slow down the rate of progression.[262] The aggressiveness of treatment and hence the target IOP, will depend on the stage or severity of glaucoma, rate of glaucoma progression, the untreated IOP, the age and life expectancy of the patient, the presence of additional prognostic factor such as ethnicity, myopia, or thin CCT. The choice of treatment will depend on patient's tolerance and preferences, the likely gain or preservation of quality of life from maintaining visual function, balanced against the likely side effects or risks of treatment.

Treatment ladder

The treatment ladder for POAG usually starts with topical ocular hypotensive agents, as they are non-invasive and relatively low risk, although they do have some side effects. Treatment usually starts with monotherapy, and additional drops can be added when there is disease progression, although treatment non-compliance needs to be excluded. Laser selective trabeculoplasty can be considered as first line treatment in patients with high tension glaucoma who wants to avoid drops, or are intolerant of them. Surgical treatment is usually reserved when maximum tolerable topical treatment fails to prevent disease progression, although it is often offered earlier in patients who present with advanced disease, and are at greater risk of visual loss.

1.4.2 Evidence of Randomized Controlled Clinical Trials

Several seminal clinical trials generated the evidence that influenced the treatment of POAG. Their main findings are summarized below.

Ocular Hypertension Treatment Study (OHTS) [34]

The aim was to determine whether treating ocular hypertensives (IOP 24mmHg-32mmHg in one eye, 21-32mmH in other eye) has been effective in preventing the development of OAG. It compared treatment (with topical agents, target of reducing IOP by >20% or IOP<24mmHg) vs no treatment. The rate of conversion to suspected POAG was 4.4% in the treatment group and 9.5% in the observation group in 5 years,

concluding that treating ocular hypertension was effective in reducing the risk of POAG by 50%.

European Glaucoma Prevention Study (EGPS) [145]

The aim was same as OHTS, to determine whether lowering IOP in ocular hypertensives (IOP 22-29mmHg) prevents or delays the development of POAG. Treatment (topical dorzolamide) was compared to no treatment. The results showed no statistically significant treatment between the two groups. The reasons EGPS and OHTS showed different results was explained by the high attrition rate of EGPS participants, and that the EGPS placebo group also had significant and consistent IOP reduction [263]

Early Manifest Glaucoma Treatment Trial (EMGT) [25]

The aim was to compare immediately IOP lowering (laser trabeculoplasty and topical betaxolol) vs no treatment or late treatment in early POAG. It showed that a 25% decrease in IOP reduced the risk of glaucoma progression by 50%, and the risk of progression decreased by 10% with every 1mmHg of IOP reduction, thereby confirming that treating early POAG was probably beneficial in most cases.

Collaborative Initial Glaucoma Treatment Study (CIGTS) [264]

The aim was to compare the effectiveness of medical therapy vs filtration surgery (trabeculectomy with or without 5FU) as the initial treatment in newly diagnosed POAG patients. Surgery achieved greater IOP reduction (by 48%) than medical treatment (by 35%), and there was greater IOP variation in the medical group. [264] AT 8 years, significant visual field progression (reduction in MD by 3dB) occurred in 21% of the surgical group and 25 % in the medical group. Initial quality of life was worse in the surgical group. The risks of surgery include 1.1% developed endophthalmitis after 5years, and twice as many cataract surgery than the medical group. Subsequent analysis of risk factors of progression supported early surgical treatment for patients who presented with more advanced disease with the possible exception of diabetics patients. [265]

Collaborative Normal Tension Glaucoma Study (CNTGS) [124]

The aim was to determine whether lowering IOP in NTG could prevent glaucoma progression. It compared treatment (medical/ surgical/laser treatment, aiming for 30% reduction of IOP from baseline) vs no treatment in normal tension glaucoma (IOP<21mmHg).[124] Progression measured by disc or field changes, was seen in 12%

of treated eyes vs 35% of controls. The study concluded that treating NTG by lowering IOP is effective in slowing progression.

Advanced Glaucoma Intervention Study (AGIS) [266,267]

The aim was to compare laser treatment (argon laser trabeculoplasty ALT) vs filtration surgery (trabeculectomy) in the treatment of advanced glaucoma whose IOP was uncontrolled on topical treatment. Patients were randomized between two regimens:

- ATT: ALT first, then trabeculectomy if needed, and then a second trabeculectomy if needed.
- TAT: Trabeculectomy fist, then ALT if needed, and then a second trabeculectomy if needed.

An early key finding from AGIS is that reducing IOP slows down visual field loss. After 7 years, IOP reduction was greater in the TAT group, and the cumulative probability of failure of the first treatment was greater in the ATT group. Race had an important effect on the results. In the 10 year follow-up report, black subjects in either arm of the study had the same proportion of visual field decline, while white subjects who started with ALT did worse and had a higher proportion of visual field decline than those who started with trabeculectomy.[266] Younger age and higher initial IOP were risk factors for failure for both ALT and trabeculectomy.[267] Taking into account all the findings, the overall conclusion from this study is that for advanced glaucoma, ALT should be the first treatment in patients with limited life expectancy regardless of race, while trabeculectomy should be the treatment of choice for otherwise healthy white subjects.

While the technique and success of trabeculectomy has since improved with the use of antimetabolites, and ALT has largely been substituted by SLT, AGIS' continuing influence on glaucoma management is the understanding that lower IOP slows down progression regardless of treatment modality, and that disparate treatment outcomes are associate with race.

1.4.3 Medical Therapy

Several classes of topical treatment are currently available. Factors that will influence the choice include effectiveness of the drug, dosing frequency, adverse effects and cost.

Prostaglandin analogues (e.g. latanoprost, bimatoprost, travaprost, tafluprost)
Prostaglandin analogue is the first line recommended monotherapy according to NICE guidelines, as it is the most efficacious. Its once a night dosing frequency makes it convenient and aids compliance. Its main side effects are hyperaemia, lengthening of eye lashes, darkening of the iris and periocular skin and orbital fat atrophy.

Beta blockers (e.g. timolol, betaxolol, carteolol, levobunolol)
Beta blockers are the second most efficacious class of drops. They suppress aqueous production. Timolol is frequent used in fixed combinations with prostaglandin analogues, carbonic anhydrase inhibitors, or with brimonidine. Beta blockers are the best locally tolerated drops, with few experiencing redness or ocular discomfort. However, they cause a range of significant systemic side effects, such as bronchoconstriction, fatigue, bradycardia, drop in blood pressure, dizziness, falls, and erectile dysfunction. Some of these side effects can be avoided with cardiac selective beta 1 blockers such as betaxolol and by performing punctal occlusion to reduce systemic absorption through the nasal epithelium. Beta blockers should be avoided in asthmatics, elderly patients, and some believe in NTG as they could reduce optic nerve perfusion and worsen the glaucoma.

Carbonic anhydrase inhibitors (e.g. brinzolamide, dorzolamide)
Carbonic anhydrase inhibitors (CAI) decrease aqueous production. Topical agents are instilled twice daily. They can cause local side effects such as irritation and temporary blurred vision as they come in a suspension. They can also cause bitter taste in the mouth, nausea, gastrointestinal effects or headaches. Oral or intravenous CAI is used in very high IOP levels due to its large hypotensive effect and rapid onset of effect. It is usually reserved in acute IOP spikes, such as during acute angle closure attack or post intraocular surgery, or for refractory IOP seen in secondary glaucoma. Systemic CAI is often poorly tolerated and cause fatigue, malaise, numbness and tingling of extremities, potassium depletion, gastrointestinal symptoms, and even renal dysfunction, renal calculi and blood dyscrasias.

Alpha agonist (e.g. brimonidine, apraclonidine)
Alpha agonists reduce aqueous production. They are used as second or third line therapy due to their side effect profile, including high incidence of hyperaemia and allergy. Brimonidine is associated with depression, and apraclonidine is contraindicated in unstable cardiac conditions.

Rho-kinase inhibitors

Rho-kinase inhibitors are a new class of topical agents which reduce IOP by increasing aqueous outflow at the level of the trabecular meshwork. Phase 3 clinical trials are now complete, and the drug has gained its first global approval in Japan.[268-270]

Ocular surface disease and preservatives

Ocular surface disease is a common side effect with long-term topical treatment due to the preservative benzolkalonium choride. Redness, irritation, blepharitis and corneal epitheliopathy vary in seriousness, and is an important reason for patient non-adherence. Preservative-free preparations of most classes of drugs are available but are more costly than the normal preparations.

Treatment non-adherence

Non-adherence to topical glaucoma treatment has been shown to affect 50% of patients 75% of the time.[271] It leads to reduced treatment effectiveness and increased costs. Reasons for non-adherence in glaucoma could be drug-related (side effects, dosing regimen), patient related (poor knowledge of glaucoma and visual loss, ethnicity, stage of disease), provider related (poor communication), and environmental related (financial cost to patient).[272] Practical strategies to improve adherence include simplifying drug regimen, education of patients, and the use of reminder devices and automated telephone services.[273]

1.4.4 Laser Treatment

Selective laser trabeculoplasty

Selective laser trabeculoplasty (SLT) is an effective method to reduce IOP in POAG and OHT as well as pseudoexfoliative and other types of secondary open angle glaucoma. Its efficacy is reported to be 6.9-35.9% reduction in IOP in 12 months in a meta-analysis.[274] Its works by causing selective photothermolysis by targeting melanin in the trabecular meshwork cells to increase aqueous outflow, while sparing adjacent cells and tissues and maintaining trabecular meshwork architecture. This contrasts with the effects of argon laser trabeculoplasty (ALT), the predecessor of SLT, which destroys cells in the meshwork and may include normal viable tissue. The effects of SLT decreases with time, but it can be safely repeated in the future, a major advantage over ALT. SLT can be used as a primary treatment in treatment-naive patent, or in conjunction with topical therapy.

Cyclophotocoagulation

Cyclophotocoagulation of the ciliary body is a destructive procedure which damages the secretory ciliary epithelium and reduces aqueous production. It can be delivered in several modalities. The effect diminishes when the epithelium regenerates, and treatment is often repeated. Trans-scleral cyclophotocoagulation (TSCPC) is very effective in achieving low IOP, but is usually reserved in refractory glaucoma as a final treatment option due to its risk of hypotony, visual loss and phthisis bulbi. Endoscopic cyclophotocoagulation (ECP) is delivered with an intraocular endolaser probe under direct visualization, and its main indication is in patients who are undergoing phacoemulsification as it can be done as a combined procedure.

1.4.5 Glaucoma Surgery

When medical and laser treatment are insufficient to prevent progression or lower IOP to a satisfactory level, surgery is indicated. Trabeculectomy and aqueous shunt insertion (tube surgery) are the two most commonly performed glaucoma surgery and have the longest history and the most accumulated evidence. Minimally invasive surgical techniques introduced in the last decade are gaining traction as quicker and less invasive surgical options.

Trabeculectomy

Trabeculectomy is a guarded filtration surgery. An alternate route for aqueous drainage is created through a sclerostomy and partial thickness scleral flap, and aqueous drains under the conjunctiva forming a bleb, into the subtenons space. Scarring is the main cause of failure. The adjunctive use of antimetabolite agents 5-flurouracil (5FU) or mitomycin C (MMC) during surgery is now routine and is effective in improving success rates,[275,276] although MMC has largely superseded 5FU. Sight-threatening complications include hypotony and endophthalmitis. The Moorfields Safer Surgery System is a set of surgical strategies widely adopted that aims to reduce post-operative complications and surgical failure.[277]

Aqueous shunt ("tube") surgery

Tube surgery involves the insertion of an aqueous shunt (tube) that connects the anterior chamber and the subtenons space. Different types of tubes are available such as the Baerveldt, Molteno and the Ahmed valved shunts. It is the surgical treatment of choice in secondary glaucoma (eg uveitic and rubeotic glaucoma) which are likely to fail with trabeculcectomy due to their risk of scarring, or after failed trabeculectomy.

The Tube vs Trabeculectomy Study is a multisite randomized controlled trial that compares the safety and efficacy of Baerveldt tube surgery and trabeculectomy with MMC in patients with prior cataract surgery. It found the two surgical techniques both effective in producing sustained IOP reduction, comparable in the proportion of patients with IOP <14mmHg after 5 years, and comparable in the number of adjunct topical agents.[278] Early post-operative complications occurred more frequently after trabeculectomy, but there were no differences in the rate of late post-operative complications or serious complications.

Minimally invasive glaucoma surgery (MIGS)

In the last few years, a range of new glaucoma drainage devices were introduced as less invasive surgical alternatives than trabeculectomy or tube surgery. The proposed benefit of MIGS is shorter surgical and recovery time, fewer serious post-operative complications and better patient tolerance. They work by either removing or stenting the Schlemm's canal (eg Trabectome, iStent, Hydrus microstent), draining into the subconjunctival space (XEN gel implant, InnFocus microshunt), or draining into the suprachoroidal space (CyPass microstent). There is evidence that they may be effective in lowering IOP or reducing the topical medication burden in glaucoma cases in 12 months. [279-282] However, long-term results, cost-effectiveness and benefits to quality of life of these devices are still to be demonstrated. The CyPass microstent was voluntarily withdrawn by its manufacturer in August 2018 due to safety concerns over results from its 5 year follow-up COMPASS-XT study, which showed a higher rate of corneal endothelial cell loss in those treated with CyPass and cataract extraction compared to those who underwent cataract extraction alone.[283]

CHAPTER 2: AIMS

Glaucoma and glaucoma suspects account for the sixth largest share of NHS outpatient attendances in England, after general medical examination, breast cancer, schizophrenia, prostate cancer and joint pain. [97] A large proportion of those are referrals for raised IOP using the conventional threshold of 21mmHg, which is associated with a low diagnostic yield for glaucoma.[284-286] At the same time, it is estimated from Western population surveys that 50% of POAG cases are undetected in the community. [16,90,154,159] There are also no "ideal" set of diagnostic tests in glaucoma that provides adequate sensitivity and specificity on a population level.[12] This underscores the need for better case-finding strategies in the community which can reduce false positive referrals, but targets the potentially undiagnosed cases, and improve diagnostic accuracy. The EPIC-Norfolk Eye Study is the most recent large-scale ophthalmic survey in the UK since 1998.[94]

The aims of the thesis are to use the data available in the study to address the diagnostic challenges above.

1. To describe the characteristics of POAG in the study population
   - To explore the associations of POAG
   - To explore the associations of previously undiagnosed POAG

2. To explore the validity of IOP referral thresholds using the IOP distribution in the study
   - To examine the effects on referable cases to the HES and missed glaucoma cases if different IOP referral thresholds were used.

3. To investigate the performance of disc photography, scanning laser polarimetry (GDx-VCC) and scanning laser ophthalmoscopy (HRT II) in glaucoma case finding in a community setting
   - To assess whether combination of test measures can enhance case finding performance

CHAPTER 3: METHODS - STUDY DESIGN

3.1 EPIC-Norfolk Study

The European Prospective Investigation of Cancer (EPIC) study is an on-going prospective, pan-European multi-cohort study. It was designed mainly to investigate the dietary and lifestyle determinants of cancer risks. The EPIC-Norfolk cohort was established in the rural & urban areas around the city of Norwich, Norfolk, UK. [287] The study was carried out with the approval of the East Norfolk & Waverney NHS Research Governance Committee (2005EC07L), and the Norfolk Research Ethics Committee (05/Q0101/191), in accordance with the principles of Declaration of Helsinki.

Three phases of in-depth health checks, as well as two follow-up health questionnaires have been completed since recruitment (Table 3.1). There is a wealth of information already available on the social, anthropometric, psychosocial, lifestyle and biological measures of the participants. EPIC-Norfolk is particularly useful in examining the determinants of health & chronic diseases.

3.1.1 Baseline subject recruitment

Participants were recruited at a baseline survey between 1993-1997 from 35 collaborating general practitioner surgeries in rural areas and market towns of Norfolk as well as the city of Norwich. Invitations were sent to 77,630 people aged 40-79 years, and 30,445 men and women consented to the baseline study. **Table 3.1** summarizes the timeline of the subsequent phases of EPIC-Norfolk.

Table 3.1 Timeline and participant numbers at different phases of the EPIC-Norfolk Study

Time form baseline	Phase	Numbers approached	Numbers consented
Baseline (1993-97)	Baseline health check	77,630	30,445
3 years	Second health check	27,399	19,560
13 years	Third health check	18,380	8,623
21 years	Fourth health check	on going	on going

3.2 The Third Health Check (3HC)

The latest completed phase of EPIC-Norfolk is the third health check (3HC), which took place between 2004-2011. The focus for data collection was visual health, cognition, skin ageing and physical activity performance. It was the first time eye examination was performed in EPIC-Norfolk.

3.2.1 Subject Recruitment

All surviving baseline participants of EPIC-Norfolk were invited to take part in the 3HC, except those who had previously refused, and the participants from four general practices who were not contactable. Recruitment of the 3HC occurred between 2004-2011. In total, 18380 people were invited, 8623 (46.9%) consented to both physical examination and health questionnaire, and 2374 (12.9%) consented to the questionnaire only.

Compared to other eye surveys in the world, the response rate of EPIC-Norfolk is much lower. Of those who were invited, the percentage who completed the examination were 79.2% in the Baltimore Eye Survey,[288] 82% in the Los Angeles Latino Study,[148] 82.4% in the Blue Mountains Eye Study,[90] and 80% in the Rotterdam Study.[16] A possible explanation of the low response rate of EPIC-Norfolk is that the parent EPIC study had been on-going for over a decade, and the participants' enthusiasm has waned over time.

3.2.2 Full Participants vs Partial and Non-Participants

Only the 8623 full participants who consented to both physical examination and the questionnaire were included in the analyses of this thesis. Comparison in the demographics between this group and the other 9761 invitees (who either did not consent to the 3HC or only consented to the questionnaire) is summarized in **Table 3.2**

The full participants were significantly younger and had a smaller proportion of women than the partial and non-participants. They were also generally more affluent, with a higher proportion belonging to the higher social classes, had higher educational achievements, and lived in less deprived areas.

Table 3.2 Comparison of full participants and the partial and non-participants in the EPIC - Norfolk 3HC.

	Full participants	Partial & non-participants	p value *
n	8623	9761	
Age, years	68.5 (68.3, 68.7)	71.9 (71.7, 72.1)	<0.001
Sex (% female)	55.2%	58.0%	<0.001
Social class [a]			
Professional/ managerial	49.9%	35.0%	<0.001
Skilled manual/ non-manual	36.6%	44.0%	
Semiskilled/ unskilled	13.5%	21.1%	
Education level			
Degree level	17.6%	8.8%	<0.001
O levels/ A levels	56.1%	46.2%	
No qualifications	26.3%	45.1%	
Townsend deprivation index [b]	-2.26 (-2.30, -2.21)	-1.80 (-1.94, -1.84)	<0.001

Mean (95% CI) shown for age and Townsend deprivation index.
[a] Registrar-General's social class by occupation
[b] Townsend deprivation index- a lower score indicates less deprivation
* Comparison between the responders and non-responders by T test for continuous variables or chi square test for categorical variables.

3.3 The EPIC-Norfolk Eye Study

The eye and vision component of the 3HC is officially known as the EPIC-Norfolk Eye Study (ENES). It is a nested cross-sectional observational study nested within the EPIC-Norfolk Study. It was established with the aims of studying glaucoma, diabetic retinopathy and age-related macular degeneration in the cohort.

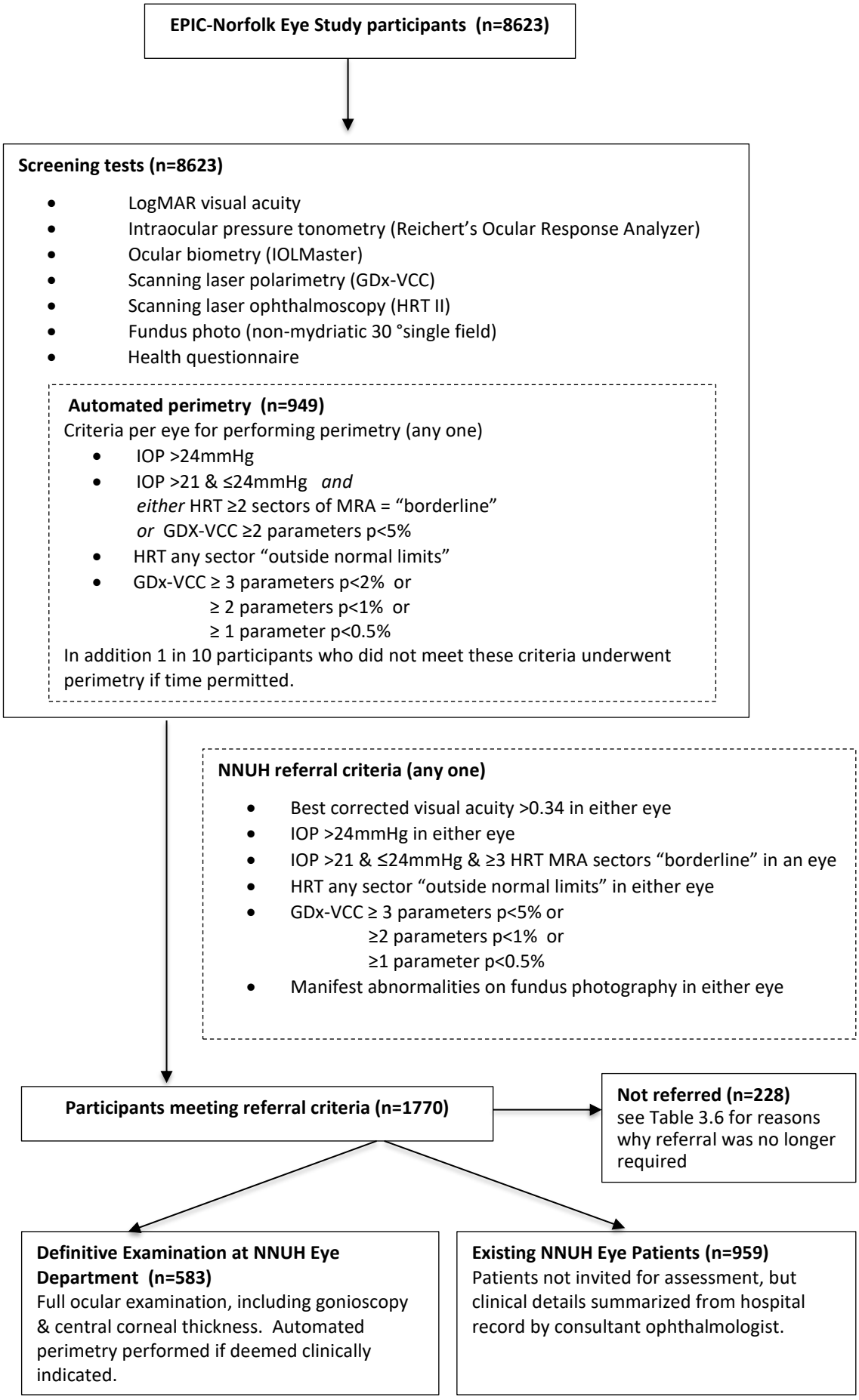
3.3.1 Study Design

All participants of 3HC underwent a screening eye test in the EPIC research clinic. **Figure 3.1** summarizes the flow of participants through ENES and the tests undertaken. Data were reviewed weekly and participants with abnormal results were referred to the Eye Department of the Norfolk & Norwich University Hospital (NNUH), according to criteria drawn up mainly to capture glaucoma cases. They then underwent a full ocular examination and received further management by a consultant glaucoma specialist. For participants who met the referral criteria, but were already known patients of the NNUH Eye Department, a summary was made of their clinical records.

3.3.2 Sample Size

For continuous outcome measures, the study is powered to detect a difference of 10% of SD, with 90% power at a 5% significance level (e.g. 0.36 mmHg for IOP, or 0.02 for HRT linear cup-to-disc ratio). For case-control analyses of primary open-angle glaucoma, using an estimated projection of 132 ‘ definite’ cases, the study provides 90% power at a 5% significance level to detect an odds ratio of 1.83, assuming an exposure prevalence of 25% in the controls.

Figure 3.1 Diagram to summairze the flow of participants through the EPIC-Norfolk Eye Study



3.3.3 Health and Lifestyle Questionnaire

The 3HC health and lifestyle questionnaire was administered to all participants. It incorporates the following validated questionnaires: the Health and Life Experiences Questionnaire (HLEQ),[289] the Physical Activity Questionnaire (EPAQ2),[290] and the Food Frequency Questionnaire (FFQ).[291-294] The 3HC questionnaire covers the following broad areas.

- Basic demographics and employment status
- Lifestyle (including smoking, alcohol, physical activities, social activities)
- Health, wellbeing and medical history (including general wellbeing, vision, hearing, mental and emotional health, mobility and physical capabilities)
- Current medication history

Specifically, 8 questions relate to eyes and vision listed in **Table 3.3**.

Table 3.3 Eye and vision questions in the 3HC health and lifestyle questionnaire

Question	Response choices
Do you wear glasses/contact lens? If yes, for what reason?	Yes/ No/ Don't know Distance/ Reading Distance and reading/ Others
If you wear glasses/contact lenses for reading, at what age?	Yes/ No / Don't know
Do you have any other problems with your eyesight? If yes, please indicate what they are.	
How good is your eyesight for seeing things at a distance, like recognising a friend across the street?	Excellent Very good Good Fair Poor
How good is your eyesight for seeing things up close, like reading ordinary newspaper print (using glasses or corrective lens if you usually wear them)?	
Have you ever had an eye operation? If yes, please specify.	Yes / No/ Don't know
Do you have a relative with eye disease or eye problems? If yes, please specify.	
Are you having any treatment or medication (e.g. eye drops) for any eye conditions? If yes, please specify.	

3.3.4 Screening Tests

8623 participants consented to and underwent a series of tests and measurements in the EPIC research clinic. All the tests were completed during a single 120-minute study

visit, of which the eye tests took 40 minutes. The tests were administered by trained research technicians. Intensive periods of staff training and validation were undertaken before the project started. Refresher training was provided at least annually. All eye tests were performed without pupil dilation. **Table 3.4** below lists the eye tests performed and the instruments used.

Table 3.4 Screening eye tests performed in the EPIC-Norfolk Eye Study

Test	Instrument model (manufacturer)
Visual acuity	LogMAR chart (Precision Vision, LaSalle, Illinois, USA)
Refraction	Humphrey Auto-Refractor 500 (Humphrey Instruments, San Leandro, California, USA)
Ocular biometry	IOLMaster V.4 (Carl Zeiss Meditech Ltd, Welwyn Garden City, UK)
Tonometry	AT555 Non-Contact Tonometer (Reichert, New York, USA) Ocular Response Analyzer (ORA, Reichert, New York , USA; software V3.01)
Scanning laser polarimetry	GDx-VCC (Zeiss, Dublin, California, USA)
Scanning laser ophthalmoscopy	Heidelberg Retinal Tomograph II (Heidelberg Engineering, Heidelberg, Germany)
Fundus photography	TRC-NW6S nonmydriatic retinal camera and IMAGEnet Telemedicine System (Topcon Corporation, Tokyo, Japan)
Automated perimetry	Humphrey 750i Visual Field Analyzer (Carl Zeiss Meditech Ltd, Welwyn Garden City, UK)

Visual acuity (VA)

Monocular VA was measured using a LogMAR (Logarithm of the Minimum Angle of Resolution) chart (chart 1) on a light box under standard illumination. The participant's usual distance refractive correction was worn and the test was carried out at 4 metres (or 2 metres then 1 metre if unable to read any letters). The test was terminated when the participant was able to read ≤ 3 letters on a line and testing repeated using pinhole-correction if participants were unable to read 3 letters on the 0.3 line. Standard letter-by-letter scoring was used to derive LogMAR VA. If a participant failed to read any letters at 1 m, further testing comprised counting fingers at 30 cm, followed by hand movements at 30 cm, followed by perception of light using a handheld torch.

Refractive error

Refractive error was measured using a Humphrey Auto-Refractor 500.

Ocular dimensions

Biometry was conducted using non-contact partial coherence interferometry (IOL Master). For each eye, five measurements of axial length, three measurements of corneal curvature and one measurement of anterior chamber depth were taken. Axial length measurements were repeated if flagged as >0.1 mm different to the others.

Tonometry & corneal biomechanics

IOP of the first 443 participants were measured using an AT555 non-contact tonometer (Reichert, New York, USA), a fully automated, table mounted, air-puff tonometer. Three readings were taken for each eye, and repeated if measurements were flagged as suspect (>5mmHg different to the other two). For subsequent participants, IOP was measured using the Ocular Response Analyzer, an air-puff table-mounted tonometer that also measures corneal biomechanics. Three readings were taken per eye following a demonstration puff. ORA measurements with a poor quality pressure waveform were repeated.

Retinal nerve fibre layer (RNFL) imaging

Scanning laser polarimetry (GDx-VCC, Zeiss, Dublin, California, USA) assesses the peripapillary RNFL. Spherical equivalent values derived from the autorefractor were inputted. A corneal scan was taken, followed by the RNFL scan. If the macular ellipse for corneal compensation was not well centred, it was modified accordingly. If an RNFL scan was not of sufficient quality (quality score<7), it was repeated once.

Optic nerve head topography

Scanning laser ophthalmoscopy (Heidelberg Retinal Tomograph II) was used to assess optic nerve head topography. The participant's keratometry results were entered prior to scanning. If the image quality was poor (topographic standard deviation >40μm) a repeat scan was undertaken. Contours around the disc margins were manually drawn and subsequently checked by an ophthalmologist, and redrawn if necessary. The HRT software was subsequently updated to Glaucoma Module Premium Edition (software V.3.1) and data exported following this. These data are equivalent to HRT3-derived parameters.

Fundus photography

One colour digital photograph of the fundus was taken of each eye using a TRC-NW6S non-mydriatic retinal camera and IMAGEnet Telemedicine System (Topcon Cooperation, Tokyo, Japan) with a 10 megapixel Nikon D80 camera (Nikon Corporation , Tokyo, Japan). The photos were centred on the macula but included the optic disc. They were graded for glaucoma, age-related macular degeneration, diabetic retinopathy. Details of optic disc grading are described below.

For those participants who did not have fundus photos taken, but were known patients of the NNUH eye department, digital fundus photos held at the NNUH as part of their clinical management were use instead, and were subjected to the same grading protocol for glaucoma.

Automated perimetry (visual fields)

Visual field tests were performed in all participants meeting pre-determined criteria listed in **Figure 3.3**, designed to capture likely glaucoma cases. Only the eye(s) that met the criteria were tested. In addition, 1 in 10 sequential participants not meeting the criteria were also tested in both eyes if time permitted. A central 24-2 Swedish Interactive Testing Algorithm (SITA) threshold algorithm on a Humphrey 750i Visual Field Analyzer was used. Auto-refractor results were entered and the trial lens calculated.

3.3.4 Fundus Photo Analysis for Glaucoma

The digital fundus photos were analysed at the Moorfields Eye Hospital Reading Centre for glaucoma by computer-assisted planimetry. The measurements were performed by a single grader (NP), who was masked to the participants' details except their study identification numbers. The measurements were performed using Photoshop CS5 software, on one computer terminal at the Moorfields Reading Centre. Grading for all image types was independent. If the grader could not complete the grading or was unsure of their responses, she can select the image for adjudication by a senior grader or clinician. **Table 3.5** lists the features that were being graded or measured.

Intra-grader reliability

Periodically, 3% of images were re-graded with a minimum time interval of 14 days between the gradings. The 3% sample was randomly generated from the patient's ID numbers. The temporal drift in grading was also assessed by re-grading a set of 50 images at 6 monthly intervals.

Optic Disc Planimetry

The digital images were first graded for photo quality according to the scale described below. Images of quality of ≥5 were discarded from the analyses. The following parameters were measured using the software's measuring tool: vertical disc diameter, cup diameter, and superior rim thickness. The cup/disc ratio and inferior rim thickness (disc diameter-cup diameter- superior rim thickness) were then calculated.

Table 3.5 List of features graded on digital fundus photos by the Moorfields Grading Centre

Feature	Definition
Photo quality	
Excellent	Publication quality images with suitable field position, image clarity and outstanding focus
Good	Crisp focus with sharply defined retinal details. Possible to see the ends of larger vessels approaching the foveal avascular zone.
Fair	Less well focussed. More difficult to determine when the ends of the larger vessels approaching the foveal avascular zone terminate.
Poor but main features still gradable	Image is less well focussed and unclear. Subtle retinal details might be missed but major disease characteristics still gradable.
Ungradable	Poor quality images where retinal vessels are not seen.
Wrong field definitions but some features gradable	It may be possible to grade for main features on a good quality image, where not the whole field of interest is visible.
Missing photo	No image supplied for that eye.
Disc parameters measured	
Vertical disc diameter	Distance between the superior and inferior disc margins along the vertical axis.
Vertical cup diameter	Distance between the superior and inferior cup margins along the same vertical plane as the disc diameter.
Superior neuro-retinal rim thickness	Distance between the superior disc margin and the superior cup margin along the same vertical plane.
Disc haemorrhage	Presence of haemorrhage on the optic disc area.
Cannot grade (obscured feature)	
Cannot grade (poor image quality)	

Calibration of photo image size

The disc dimensions were measured in units of pixels. To convert the measurements to real image size, the camera's magnification and the participant's refractive error need to be taken into account.

To calibrate the measured image size to millimeters, a model eye with modifiable axial length and a fixed optic disc size was used. Photos were taken of the model eye's optic disc with the same fundus camera used in the study, at 30° and 45° fields of view, at a wide range of refractive errors (spherical equivalence) which included the range of the

participants. The photos were graded by NP using the same protocol as that of the study images. Calculations showed that the image magnification remains the same through the full range of refractive error of the participants. Magnification factors were calculated for images of 30° and 45° fields and used to calculate the real sizes of optic disc features.

3.3.5 Referral for Definitive Examination

Test results from the eye examination at the EPIC research clinic were reviewed weekly and participants with abnormal results were referred to the Eye Department of the Norfolk & Norwich University Hospital (NNUH) for definitive examination, according to criteria drawn up mainly to capture glaucoma cases, but also anyone with reduced visual acuity and manifest abnormalities on fundus photos. (see **Figure 3.1**). Those referred then underwent a full ocular examination and received further management by a Consultant glaucoma specialist, Prof David Broadway (DB). For participants who met the referral criteria but were already known patients of the NNUH Eye Department a summary was made of their clinical records by DB in the form of a clinical letter.

Check for missed referrals

At the close of the 3HC in December 2011, participants' test results were checked to ensure all those who met referral criteria were referred to NNUH. Out of the 1770 who met the referral criteria, 254 (14.4%) participants had not been referred. Their records were examined in conjunction with their test results. Referral was subsequently deemed unnecessary in 228 subjects due to the reasons listed in **Table 3.6**, the most common being known amblyopia that explained the participant's reduced visual acuity. The remaining 26 participants were contacted by phone by the Principal Investigator to discuss the abnormal test results. Twelve participants agreed to attend NNUH, while three declined. Eleven participants were not contactable, so a letter was sent detailing the situation and inviting them to contact us or get themselves referred via their GP or optometrist.

Table 3.6 Reasons referral to NNUH was no longer required among 228 participants who met the referral criteria.

Reason (>1 reason may apply to each participant)	**Participant n**
Patient deceased	16
Patient had since been referred by GP or optometrist	49
Known patient to NNUH eye department	38
Known amblyopia to explain reduced visual acuity	58
Known eye pathologies that explained abnormal findings	39
Mild reduced visual acuity but otherwise normal test findings and fundus photo.	19
Mild intraocular pressure elevation but otherwise normal test findings and fundus photo.	30
Mild HRT or GDx abnormalities with otherwise normal test findings and fundus photo.	17

3.3.6 Definitive Examination

The definitive eye examination was performed at the NNUH eye department, by Professor David Broadway (DB), a fellowship-trained glaucoma specialist. The assessment included eliciting the full ocular and medical history, family history of glaucoma, and social history including whether patient drives or not. The examination included: Snellen visual acuity, Goldmann applanation IOP, central corneal thickness with a pachymeter, gonioscopy (documented according to Shaffer grading) and dilated fundus examination. Visual fields (Humphrey Visual Field Analyzer II, Carl Zeiss Meditech Ltd, Welwyn Garden City, UK) were performed on all participants, unless it was already done as part of the screening test, although repeated fields were performed if deemed clinically necessary. The process of arriving at the glaucoma diagnosis is detailed in Chapter 4.

3.3.7 Summary Letters for Known Patients

For 959 participants who met the referral criteria but were already known patients of the NNUH Eye Department, either as a previous or current patient, their NNUH notes were retrieved and summarized in a letter by the consultant ophthalmologist (DB) with the information listed below. All visual fields in file were also photocopied and included for inspection.

- Past and current ophthalmic history, including investigations, interventions, diagnoses and treatment.
- Glaucoma diagnosis status. If this was not mentioned specifically in the patients' clinical records (e.g. if patient was seen for other conditions), then

documentation of a healthy optic disc in the notes was taken as evidence for no glaucoma.

- Visual acuity
- Central corneal thickness
- Optic disc and visual field findings

3.3.8 Data Extraction

Screening test results

All data from the screening test were recorded onto a proforma by the staff who administered the test. Data from the proforma were entered onto a database by trained EPIC research staff. For machine-based tests (auto-refraction, biometry, ORA tonometer, HRT and GDx-VCC), the data were downloaded directly from the machines' hard drives.

Definitive examination & summary letters

Data on the definitive examination proforma and the summary letters were entered manually into a computer database by an ophthalmologist (MC). Any unstated or unclear diagnoses, or diagnoses that appeared to contradict the findings and management described in the letters were queried, and clarified by DB in further written communication. Data closest to the date of the participants' screening test was selected for entry to the database.

Screening visual fields

Screening visual fields were all performed on a single Humphrey Fields Analyser in the EPIC research clinic dedicated to the sole use of the study. The fields were downloaded form the machine's hard drive and stored digitally as TIFF images. An ocular character reader software was used to transcribe and separate all the data (including each data point of the total and pattern deviation plots) by Dr. Hao-Gang Zhu at Moorfields Eye Hospital, London.

Visual fields from definitive examination & summary letters

Data from the photocopied visual fields were recorded manually into a separate database by an ophthalmologist. Data points from the pattern deviation probability plot were also included. Only one field per eye was recorded, and only fields performed within 12 months (before or after) of a participant's date of screening test were eligible. If more than one field is eligible, then the one with the higher accuracy indices was chosen, irrespective of the results of the field test.

3.4 Statistical Analysis

All statistical analysis in this thesis is performed using Stata SE 13.1 statistical software (StataCorp, College Station, Texas, USA).

3.5 Conclusion

The EPIC-Norfolk study is an established pan-European multi cohort epidemiological study. Nestled within it is the EPIC-Norfolk Eye Study, established in 2004 when eye data was collected for the first time among its remaining participants. The response rate for the EPIC-Norfolk Eye Study is 46.9%, much lower compared to other eye surveys across the world, which report response rates of about 80%. This chapter detailed the recruitment, tests and examinations of the participants through the EPIC-Norfolk Eye Study, the focus of which was geared towards generating a glaucoma diagnosis for the participants.

CHAPTER 4: METHODS - GLAUCOMA DIAGNOSIS

This chapter describes the definitions used to define glaucoma and related diagnoses, and the refinement process used to detect false positives, false negatives, and counter incomplete data, to reach the final glaucoma diagnosis for each participant.

4.1 Diagnostic Definitions

4.1.1 Glaucoma

Table 4.1 summarizes the pre-determined definitions used to reach the initial and final diagnoses in the study. Both structural and functional deficit was needed for the diagnosis of glaucoma. It was defined as the presence of a glaucomatous optic disc, and either a matching visual field defect or non-specific visual field loss, with no other explanations for the disc and field appearances. A glaucomatous disc was defined as one with focal (notching) or diffuse neuro-retinal rim thinning, and may possess, though not necessary for the definition, additional characteristic features such as bared circumlinear vessels, disc haemorrhages or nerve fibre layer defects.

We adopted the ISGEO's definition of glaucomatous field, defined as having both Glaucoma Hemifield Test "outside normal limits" and three contiguous points on the pattern deviation plot at <5% or worse on a reliable field. This definition suited the 24-2 fields strategy used in this study. Only visual fields with all reliability indices (false positive, false negative and fixation losses) <33% were used. While these are the manufacturer's recommendation for clinical diagnosis, and have been adopted by several population based studies,[16,151,295] many visual fields on a population level are not expected to meet these reliability standards, and some population studies adopt a looser standard.[20] Repetition of the field abnormality was not required, as very few participants had repeated fields done unless they were known patients of the NNUH.

The differentiation of high tension and normal tension open-angle glaucoma (HTG and NTG) was based on evidence either on examination or in the records of persistently elevated untreated IOP >21mmHg on at least two separate occasions, or a one-off measurement above 24mmHg. Diurnal IOP phasing was performed in the NNUH for newly diagnosed open-angle glaucoma cases to ascertain their maximum IOP.

For patients previously treated with trabeculectomy or aqueous shunt operations, a diagnosis of glaucoma was not automatically granted, but followed the same definitions above, as these operations were sometimes performed for the sole indication of uncontrolled IOP.

4.1.2 Secondary Glaucoma

Secondary glaucoma was defined as the presence of glaucomatous disc and field changes with known secondary cause(s). Pseudoexfoliative and pigmentary glaucoma were classified as secondary glaucoma in this study. If accurate visual field testing was impossible due to poor vision, then a glaucomatous disc alone will satisfy the definition. If visibility of the optic disc was poor, then elevated IOP>24mmHg on more than two occasions in the presence of a known secondary cause for glaucoma will suffice.

4.1.3 Glaucoma Suspect & Ocular Hypertension

A glaucoma suspect was an eye with features of early or minor glaucomatous disc features, associated with a normal visual field or the absence of visual field data. Ocular hypertension (OHT) was defined as an eye with evidence of untreated IOP >21mmHg on at least two separate occasions, but with no evidence of glaucomatous disc or field changes.

4.1.4 Narrow Angle Spectrum

Definitions of the spectrum of narrow drainage angle conditions were based on the widely accepted definitions [5,296,297] which was summarized in the World Glaucoma Association publication. [298] Primary angle closure suspect (PACS) was defined as an eye with posterior trabecular meshwork invisible on gonioscopy for ≥180° of the drainage angle. Primary angle closure (PAC) was defined as PACS with peripheral anterior synechiae (PAS) on gonioscopy, and/or IOP ≥ 21mmHg. Primary angle closure glaucoma (PACG) was defined as the presence of PAC and disc and field changes which satisfied the definition of glaucoma. In this study, eyes which had previously undergone laser peripheral iridotomies with no current evidence of glaucoma were classified as PAC.

While “narrow angles” was not a commonly accepted diagnostic entity in the literature, in this study, it was used to label any eyes with at least two quadrants of the drainage

angles at Shaffer grade 2 (only the trabecular meshwork but not the scleral spur visible) or narrower, but did not satisfy the PACS definition. This label allows such participants to be identified in the diagnostic refinement process when false negatives were being sought (see section 4.4 Diagnostic refinement and final diagnosis).

4.1.5 Normal Eyes

Eyes which were examined in the NNUH following referral were classified as “normal” in terms of glaucoma if they did not possess features of glaucomatous disc or field, had open angles on gonioscopy, and their IOP did not meet the criteria for OHT.

For participants who met the referral criteria but were known patients of the NNUH eye department, their notes were examined by DB to ensure the examination closest (at least within 12 months) to their date of screening test did not possess features of glaucomatous disc or field changes, and their IOP did not meet criteria for OHT. However, gonioscopy might not have been performed if the participants were seen for other conditions, and hence PACS or PAC could be missed. If the participants’ NNUH notes did not provide any documentation of IOP and optic disc examination, then their diagnosis was recorded as “not recorded”.

Participants who did not meet the initial referral criteria were automatically labelled as “normal - rest of cohort”. Participants who met the referral criteria but were unable or unwilling to attend the definite examination were labelled as “not recorded”.

Table 4.1 Definitions used to derive glaucoma diagnosis for each eye

Diagnosis	Definition
Glaucomatous disc	Focal (notching) or diffuse neuro-retinal rim thinning.
Glaucoma	Glaucomatous disc & matching VF defect or non-specific VF loss, in the absence of other pathologies that could explain the findings
Glaucoma suspect	Early or minor glaucomatous disc changes associated with normal VF or missing VF, or glaucomatous visual changes associated with normal disc appearance.
Open angle	The posterior trabecular meshwork visible for at least 180° on gonioscopy
Primary open angle glaucoma (POAG)	Glaucoma in the presence of open anterior angles with no known secondary causes
High tension glaucoma (HTG)	Glaucomatous eye with open angles, and IOP >24mmHg on one occasion, or >21mmHg on at least two separate occasions or diurnal IOP phasing
Normal tension glaucoma (NTG)	Glaucomatous eye with open angles, and IOP ≤21mmHg on at least two separate occasions or on diurnal IOP phasing
Secondary glaucoma	Eyes with glaucomatous disc changes (and field changes if visual field tests were possible) and a known secondary causes. If the optic disc view was poor, then IOP>24mmHg on more than two occasions in the presence of a known secondary cause for glaucoma will suffice.
Ocular hypertension (OHT)	IOP >21mmHg on at least two separate occasions in the presence of open angles, without evidence of glaucoma or glaucoma suspect
Primary angle closure suspect (PACS)	Eyes with ≥180° of the posterior trabecular meshwork not visible on gonioscopy.
Primary angle closure (PAC)	PAC with IOP >21mmHg or peripheral anterior synaechiae (PAS) on gonioscopy, with no evidence of glaucomatous disc changes. Participants with existing peripheral iridotomies were classified as PAC in the absence of glaucomatous disc or field changes
Primary angle closure glaucoma (PACG)	PAC with evidence of glaucomatous disc and field changes
Narrow angles	Eyes with ≥180° of the angle judged as Shaffer classification's grade 2, with only the trabecular meshwork but not the scleral spur visible.
Normal	Eyes with no evidence of glaucomatous disc or field changes, had open angles on gonioscopy, and IOP did not meet criteria for OHT.
Not recorded	Participants who met referral criteria but did not attend definitive examination.

Only visual fields with reliability indices (false positive, false negative, and fixation losses) all <33% were considered. VF visual fields; IOP intraocular pressure

4.2 Initial Diagnosis

After participants underwent the definitive examination at the NNUH, an initial glaucoma diagnosis was given by Prof David Broadway (DB), consultant ophthalmologist at NNUH who has a specialist interest in glaucoma. **Table 4.2** below summarizes the diagnosis for each eye.

Table 4.2 Initial glaucoma diagnosis by eye as generated by Prof David Broadway

Diagnoses	Right eye		Left eye	
	n	%	n	%
Normal	799	9.3	790	9.2
POAG	146	1.7	142	1.7
NTG	128	1.5	124	1.4
PACG	28	0.3	26	0.3
Secondary OAG	14	0.2	12	0.1
Suspect OAG	425	4.9	433	5.0
OHT & Suspect OAG	41	0.5	46	0.5
Suspect ACG	20	0.2	20	0.2
Secondary OHT / OAG suspect	1	0.0	3	0.0
OHT	79	0.9	79	0.9
PAC	26	0.3	28	0.3
Narrow angles	39	0.5	39	0.5
Narrow angle/PAC	0	0.0	1	0.0
Not recorded	24	0.3	27	0.3
Normal –rest of cohort (not met referral criteria)	6853	79.5	6853	79.5
Total	8623	100	8623	100

4.2.1 Caveats of Initial Diagnosis

The initial diagnosis was likely to have missed glaucoma cases in several sources:
- Glaucoma cases might not be captured by the referral criteria.
- A large proportion of those who met referral criteria did not have visual field testing at any point in the study (619 right eyes, 637 left eyes). These were patients known to NNUH and therefore did not receive a definitive examination, but had their letters summarized. Visual field testing would not have been done if not indicated clinically, and glaucoma cannot be diagnosed without a visual field.

4.3 ISGEO Diagnosis

The ISGEO diagnostic scheme was applied to provide an objective glaucoma diagnosis which uses pre-defined 97.5th and 99.5th centile of CDR among the normal population to define the glaucomatous disc. Since 1125 (13%) participants did not have fundus photos taken, the ISGEO diagnosis cannot reliably be used for the entire study. Its use was limited only to identifying any potential missed cases among the initial diagnoses. Any cases which were not diagnosed as glaucoma in the initial diagnosis but met the ISGEO glaucoma criteria would then undergo full diagnostic verification. Details of the ISGEO diagnostic scheme are summarized in Chapter 1, section 1.2.7.

4.3.1 Distribution of CDR in the "Normal Population"

A glaucomatous disc in ISGEO is defined by the 97.5th or 99.5th centiles of the CDR, CDR asymmetry and IOP among people with normal visual function. The definition of normal visual function was not specified in the scheme, but in this study, it was taken as participants who had a reliable visual field with Glaucoma Hemifield Test "within normal limits". Both sources of visual fields (EPIC research clinic and NNUH clinic) were considered, and if both fields were available, then they must be both "within normal limits". A reliable field was defined as having the reliability indices fixation losses, false positive, and false negative all <33%.

In this study, 449 right eyes and 423 left eyes in 665 participants met the criteria of "normal visual function". The mean of both eyes' values were used if both met the criteria of normal visual function. **Table 4.3** below shows the 97.5th and 99.5th percentile values for CDR, CDR asymmetry and IOPg.

Table 4.3 Percentile values for cup/disc ratio (CDR), cup/disc ratio asymmetry and Goldmann-correlated intraocular pressure (IOPg) in eyes with normal visual function

	n (person)	97.5th	99.5th
CDR	535	0.64	0.70
CDR Asymmetry	163	0.18	0.29
IOPg	656	27.8	32.5

4.3.2 ISGEO Diagnosis Applied to the EPIC-Norfolk Eye Study

Applying the ISGEO diagnostic scheme, 24 right eyes and 30 left eyes were diagnosed as glaucoma. **Table 4.4** and **table 4.5** below show the diagnosis per eye and per person.

Table 4.4. ISGEO glaucoma diagnosis (per eye) applied to the EPIC-Norfolk Eye Study

	Right eye				
Left eye	Category 1A	Category 1B	Category 2B	Normal	No disc photo
Category 1A	4	0	0	6	0
Category 1B	1	0	0	8	0
Category 2B	0	0	1	10	0
Category 3B	0	0	0	0	1
Normal	3	5	11	7448	0
No disc photo	0	0	0	0	1125

Table 4.5 ISGEO glaucoma diagnosis (per person) applied to the EPIC-Norfolk Eye Study *

ISGEO diagnosis	**n (persons)**	**%**
Category 1 glaucoma	27	0.3
Category 2 glaucoma	22	0.3
No glaucoma right eye, no left disc photo	601	7.0
No glaucoma left eye, no right disc photo	261	3.0
No glaucoma either eye	6353	73.7
No disc photo either eye	1359	15.8
Total	8623	100

* If the two eyes fall under categories 1 & 2 of glaucoma diagnosis, then the person is counted as having category 1 glaucoma

4.4 Diagnosis Refinement & Final Diagnosis

A diagnosis refinement process was undertaken with the aims of detecting false positive and false negative cases among the initial diagnosis, to ensure that the diagnostic definitions described in section 4.1 were followed, and to allow missing data to be properly handled. **Figure 4.1** summarises the process to refine the initial diagnoses. In brief, all cases initially diagnosed by DB as glaucoma and all cases identified by ISGEO as glaucomatous would undergo a full diagnosis verification

process (see section **4.4.1**). Cases which were initially diagnosed as glaucoma suspect, having narrow angle sepctrum or OHT, as well as all those diagnosed initially as normal would have their test results (visual fields, disc photos and HRT II, GDx-VCC) screened by myself (MC) to identify possible glaucoma cases. (see section **4.4.2-4.4.4**). Any cases suspected to have glaucoma will undergo full diagnosis verification.

4.4.1 Full Diagnosis Verification

All glaucoma cases underwent full diagnosis verification by Prof Paul Foster (PF), consultant ophthalmologist who specialises in glaucoma. Disc photos, visual fields, and summary letters from NNUH were reviewed. In the absence of disc photos, HRT or GDx-VCC images were used purely as a substitute of a disc image. HRT or GDx-VCC results otherwise did not influence diagnosis.

Glaucomatous visual field was necessary for a diagnosis of glaucoma to be made. To counter the large number of participants with no VF test done, exception was made if there was advanced disc cupping, then glaucoma was diagnosed in the absence of visual fields, although not in the presence of a normal field. If a visual field test result was described in the NNUH summary letters, that information was also counted when making a decision on the participants' diagnosis.

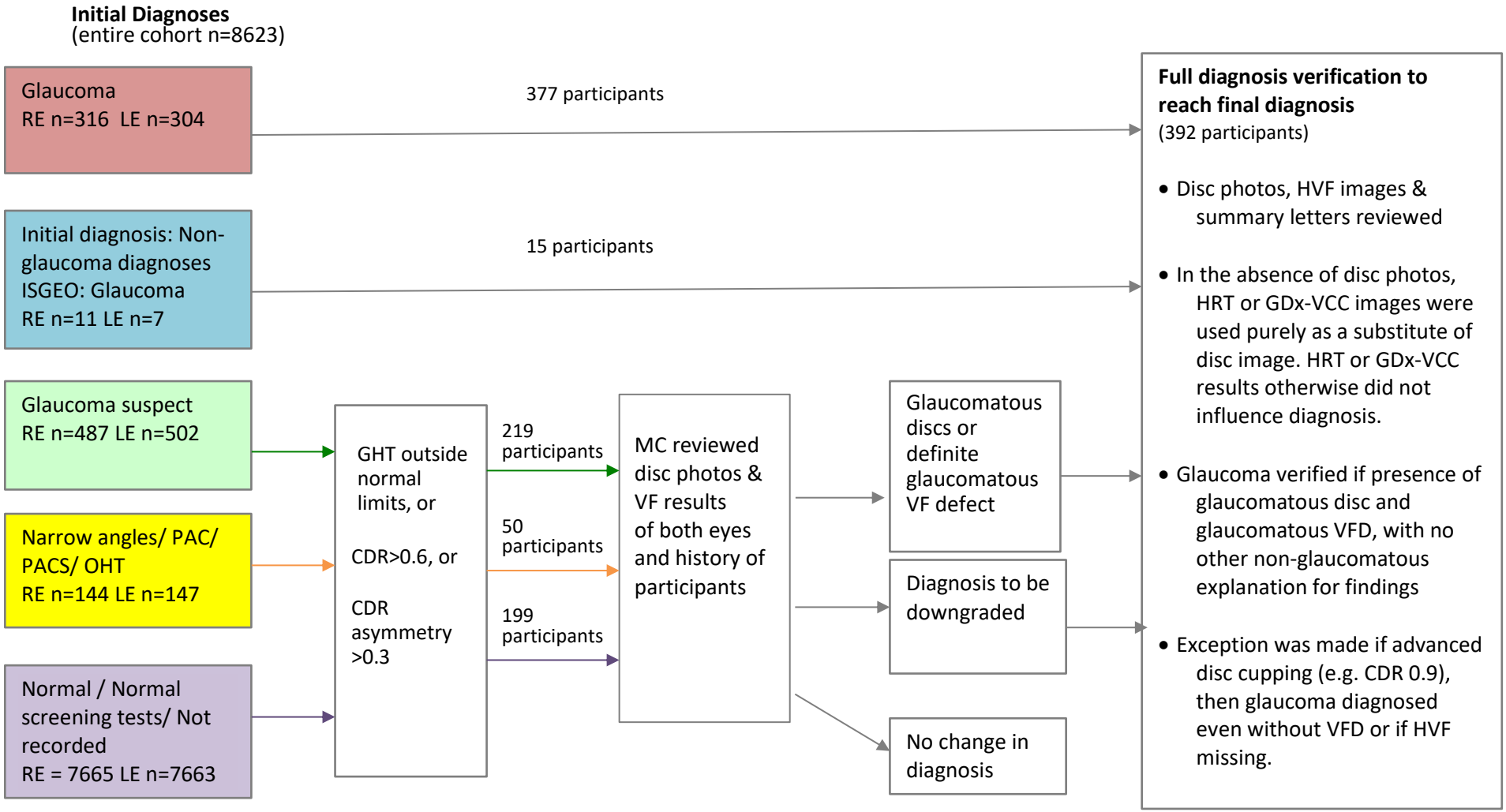


Figure 4.1 Diagnosis refinement pathway to verify initial & ISGEO diagnoses to reach the final glaucoma diagnosis

4.4.2 Detecting False Negatives

False negative cases were sought among eyes which had an initial diagnosis of "normal". They comprise of the following groups:
- Those who underwent definitive examination and were cleared.
- Those who did not meet the referral criteria after the screening tests.
- Those who were known NNUH patients but did not have a glaucoma diagnosis.

False negatives were also sought among those diagnosed as any of: glaucoma suspects, OHT, PAC, PACS or narrow angles, as they already possess risk factors for glaucoma.

Within these groups, anyone with an abnormal visual field (GHT outside normal limits) or a suspicious disc (CDR>0.6 or inter-eye CDR asymmetry >0.3) were identified. The participants' disc photos and visual field results were reviewed by an ophthalmologist (MC), in conjunction with other details such as comments in their NNUH summary notes. Any discs judged to be glaucomatous, or anyone with a definitive glaucomatous field defect then underwent full diagnosis verification by PF. Diagnoses of glaucoma suspects could also be downgraded to "normal" if they were judged to possess normal discs and fields.

4.4.3 Outcome of Diagnosis Refinement

A total of 860 participants were identified for diagnosis refinement. Both eyes were reviewed in the process even if only one eye satisfied the criteria for diagnosis refinement. The reasons for their inclusion in this process are summarized in **Table 4.6** below. The outcome of the refinement process is summarized in **Table 4.7**. The diagnosis remained the same for the majority of eyes (75.8% right eyes, 75.0% left eyes). More eyes had their diagnosis downgraded (13.3% right eyes, 13.0 left eyes) than upgraded (8.9% right eyes, 9.2% left eyes).

Table 4.6 Reasons for the 860 participants undergoing glaucoma refinement

Reasons for diagnosis refinement	**n (person)**	**%**
Glaucoma cases in initial diagnosis	377	43.8
Initial diagnosis- normal, ISGEO – glaucoma	15	1.7
OAG suspects or OHT/Suspects	219	25.5
PAC or OHT or narrow angles	50	5.8
No glaucoma by initial and ISGEO diagnosis	136	15.8
No glaucoma in rest of cohort	63	7.3
Total	860	100

Table 4.7. Changes from initial to final diagnoses for the 860 eyes that underwent diagnosis refinement. Non-glaucoma refers to diagnosis of either PAC, OHT, or narrow angles.

Comparison of initial and final diagnoses		**Right eye**		**Left eye**	
		n	**(%)**	**n**	**(%)**
Diagnosis unchanged		651	75.7	643	74.8
Downgraded	From Glaucoma	89	10.3	79	9.2
	From Suspect to Non-glaucoma	2	0.2	6	0.7
	From Suspect to Normal	25	2.9	30	3.5
	From Non-glaucoma to Normal	2	0.2	1	0.1
	Subtotal	118	13.7	116	13.5
Upgraded	To Glaucoma	36	4.2	34	4.0
	From Normal to Non-glaucoma	2	0.2	0	0
	From Normal to Suspect	31	3.6	39	4.5
	From Non-glaucoma to Suspect	6	0.7	9	1.0
	Subtotal	75	8.7	82	9.5
Altered	Change of glaucoma mechanism	14	1.6	11	1.3
	Change of suspect mechanism	1	0.1	6	0.7
	Change of diagnosis within non-glaucoma groups	1	0.1	2	0.2
	Subtotal	16	1.9	19	2.2
	Total	860	100	860	100

The false positive rates for glaucoma ("downgraded from glaucoma") is 10.2% and 8.8% for right and left eyes respectively. The false negative rates for glaucoma ("upgraded to glaucoma") is 4.3% and 3.6% for right and left eyes. Most false positive cases had their diagnosis changed to suspects (**Table 4.8**), usually due to the lack of visual field evidence of glaucomatous changes. Most false negatives glaucoma cases were upgraded from initial diagnosis as suspect.

Table 4.8. Detailed breakdown of the changes for cases with an initial diagnosis of glaucoma and a final diagnosis of glaucoma.
R=right eye, L=left eye

	Final Diagnosis				
	Glaucoma	**Suspect**	**PAC/OHT/ Narrow angles**	**Normal**	**Total**
Initial diagnosis of glaucoma	R 227 (71.8%)	R 77 (24.3%)	R 4 (1.3%)	R 8 (2.5%)	R 316 (100%)
	L 225 (74.0%)	L 65 (21.4%)	L 5 (1.6%)	L 9 (3.0%)	L 304 (100%)
	Initial Diagnosis				
	Glaucoma	**Suspect**	**PAC/OHT/ Narrow angles**	**Normal**	**Total**
Final diagnosis of glaucoma	R 227 (86.0%)	R 33 (12.5%)	R 1 (1.1%)	R 3 (0.4%)	R 264 (100%)
	L 225 (87.5%)	L 29 (11.3%)	L 1 (0.4%)	L 2 (0.8%)	L 257 (100%)

4.4.4 Missing Data

1126 participants did not have disc photos taken during the initial screening examination. For 157 subjects who were known to NNUH eye department, we were able to identify disc photos taken during the course of their clinical management at the hospital which were +/- 12 months from their date of check, and therefore contemporaneous with their data. Those photos were subjected to the same grading protocol as the other images. Overall, 7654 (88.8%) subjects had disc photos available for analysis.

During the glaucoma diagnosis refinement process, the reflectance images from the HRT and GDx-VCC printouts were used as substitutes for missing disc photos. The images provided the examiners (MC and PF) an impression of the disc as being glaucomatous or not, and the summary statistics in the HRT and GDx-VCC printout were not taken into consideration, nor were measurements of disc parameters such

(e.g. cup diameter, disc diameter) performed. The images were used only if the examiners felt the quality was sufficient to confidently diagnose the disc as glaucomatous or not. To counter missing visual fields, detailed description of test results in the NNUH summary letters written by avid bwere used as substitutes. If no substitution were available to verify the diagnosis, then the diagnosis remained unchanged.

Table 4.9 and **Table 4.10** summarize the use of substitutions for missing disc photos and visual fields in the diagnosis refinement process. For the majority of cases disc photos (91.5% right eyes, 88.6% left eyes) and visual fields (80.1% right eye, 80.6% left eye) were available. Substitutes were used in 7.2% right eyes and 9.7% of left eyes for missing disc photos, and 10.2% right eye and 9.7% left eyes for missing visual fields. Only <2% of eyes had no substitutes for missing disc photos, while almost 10% of cases had no substitutes for missing visual fields.

Table 4.9 Disc photo availability in the diagnosis refinement process

	Right eye	**(%)**	**Left eye**	**(%)**
Disc photo available	787	91.5	762	88.6
HRT/GDx as substitute	62	7.2	83	9.7
No disc/HRT/GDx photos	11	1.3	15	1.7
Total	860	100	860	100

Table 4.10 Visual field data availability in the diagnosis refinement process

	Right eye	**(%)**	**Left eye**	**(%)**
VF available	689	80.1	693	80.6
Letter description as substitute	88	10.2	83	9.7
No VF or letter description	83	9.7	84	9.8
Total	860	100	860	100

4.5 Inter-Observer Agreement in Optic Disc Assessment

4.5.1 Background

Optic disc assessment by four separate individuals (NP, DB, MC and PF) contributes to the final glaucoma diagnosis. It is important to establish the degree of agreement among them as a quality control measure, to ascertain any systematic biases in grading, and that the final glaucoma diagnoses were robust.

NP is a professional image grader from the Moorfields Image Grading Centre was the sole and official grader of disc images in this study. DB is a consultant glaucoma ophthalmologist. He examined the participants in NNUH and formulated the initial glaucoma diagnoses. MC is an ophthalmologist with an interest in glaucoma and re-examined approximately 10% of disc images by grading discs into glaucoma/suspect/ no glaucoma to identify possible false positives or false negatives in the initial diagnoses. PF is a consultant glaucoma ophthalmologist. He re-examined the images identified by MC as possibly requiring a change of diagnoses and adjudicated the final changes in conjunction with visual field data and the participants' history. PF also reviewed all records of those initially diagnosed as glaucoma and formulated the final glaucoma diagnosis.

4.5.2 Aims

1. To detect any systematic differences in NP's measurements of disc dimensions from measurements by DB, MC and PF.
2. To ascertain the agreement in grading of optic disc glaucoma status by MC, DB and PF.

4.5.3 Methods

The four graders independently graded a set of 45° digital disc photos from the study, masked to any of the participants' details. The official disc grading from the study was used as NP's grading. A total of 209 photos were selected to include a wide range of cup/disc ratios, disc sizes and photo qualities. They also included glaucomatous and suspect discs, discs with haemorrhages, as well as discs that could be inherently difficult to assess such as tilted, crowded discs, and discs of irregular shape. The

features used for selection were based on NP's observations. **Table 4.11** summarizes the characteristics of the photos selected for grading.

Table 4.11 Selection of digital disc photos used for intra-observer grading assessment

Reason for photo selection	Number of photos
Glaucomatous disc	36
Suspicious disc	35
CDR <0.3	15
CDR 0.3-0.4	15
CDR 0.4-0.5	14
CDR 0.5-0.6	14
CDR 0.6-0.7	15
CDR 0.7-0.8	15
Vertical disc diameter <2 pixels	5
Vertical disc diameter 2-2.5 pixels	4
Vertical disc diameter >2.5 pixels	5
Photo quality grade 4 (poor but main features still gradable)	9
Disc haemorrhage	7
Parapapillary atrophy	10
Unusual disc morphology (e.g. crowded/tilted/oval/irregular contour)	10
Total	209

CDR Vertical cup/disc ratio

All grading was performed using the same software as the one used to grade the study photos (Adobe Photoshop CS5 Extended version 12, Adobe Systems Incorporated). The graders were asked to measure the vertical disc diameter, vertical cup diameter, and superior rim thickness using the software's measuring tool. Cup/disc ratio was calculated as the measured vertical cup diameter/ vertical disc diameter. The graders were also asked to give an overall glaucoma diagnosis based on the disc appearance as no glaucoma / suspect/ or glaucoma.

4.5.4 Statistical Analysis

Agreement in disc measurements was assessed with Bland-Altman plots and Lin's concordance correlation coefficient (ρ_c). Agreement in disc glaucoma grading was assessed with unweighted kappa coefficient. Generally accepted interpretations of Lin's concordance correlation coefficient and kappa's statistic are as follows: 0.81-0.99 almost perfect agreement, 0.61-0.80 substantial agreement, 0.41-0.60 moderate agreement, 0.21-0.40 fair agreement, 0.01-0.2 slight agreement, and <0 less than chance agreement.[299]

4.5.5 Results

Agreement in disc dimension measurements

Table 4.12 shows the results in disc dimension measurements. Agreement among the four graders in vertical disc diameter and cup diameter was “almost perfect” (ρ_c 0.79-0.95 disc diameter, 0.73-0.90 cup diameter). Agreement in superior rim thickness was less, in the “moderate” to “substantial” range (ρ_c 0.41-0.73), In particular, it was the agreement between NP & PF (ρ_c 0.41), PF & DB (ρ_c 0.49), and MC & PF (ρ_c 0.55) that fell in the moderate range, indicating that PF’s superior rim thickness measurements were the anomaly compared to the other three graders, and the measurements were thinner than the other graders by 0.14-0.20 pixels on average.

Agreement in CDR (ρ_c 0.54-0.83), which was calculated from the disc and cup diameters, was generally lower than the agreement for either disc or cup diameters. This was because CDR was a derived variable, and so the disagreement between graders was mathematically multiplied.

For every dimension measured, the agreement between NP and PF was the weakest, while the agreement between MC and DB was the strongest. Overall, there was no evidence that NP’s measurements were consistently different from the other graders.

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Table 4.12 Inter-observer agreement in measurements of disc dimensions by the four graders on a selection of 209 disc photos

Agreement in vertical disc diameter				
Grader A	**Grader B**	**ρ_c (95% CI)**	**Mean difference (grader A-grader B),** pixels	**Bland Altman 95% limits of agreement**
NP	PF	0.79 (0.75,0.83)	0.14	-0.14, 0.42
NP	DB	0.84 (0.81,0.88)	0.11	-0.14. 0.37
NP	MC	0.87 (0.84,0.90)	0.07	-0.19, 0.14
PF	DB	0.95 (0.94,0.96)	-0.03	-0.19, 0.14
MC	DB	0.95 (0.93, 0.96)	0.04	-0.13, 0.21
MC	PF	0.93 (0.91, 0.95)	0.07	-0.11, 0.24

Agreement in vertical cup diameter				
Grader A	**Grader B**	**ρ_c (95% CI)**	**Mean difference (grader A-grader B),** pixels	**Bland Altman 95% limits of agreement**
NP	PF	0.73 (0.68,0.79)	-0.25	-0.67, 0.18
NP	DB	0.84 (0.80,0.87)	-0.11	0.34, 0.47
NP	MC	0.84 (0.81,0.88)	-0.10	0.34,0.47
PF	DB	0.85 (0.81,0.88)	0.13	-0.26, 0.52
MC	DB	0.90 (0.88, 0.93)	-0.02	-0.39, 0.36
MC	PF	0.83 (0.79, 0.87)	-0.15	-0.56, 0.27

Agreement in superior rim thickness				
Grader A	**Grader B**	**ρ_c (95% CI)**	**Mean difference (grader A-grader B),** pixels	**Bland Altman 95% limits of agreement**
NP	PF	0.41 (0.34, 0.47)	0.20	-0.04, 0.43
NP	DB	0.71 (0.65, 0.78)	0.05	-0.22, 0.31
NP	MC	0.73 (0.67, 0.79)	0.06	-0.15, 0.28
PF	DB	0.49 (0.42, 0.56)	-0.15	-0.44, 0.13
MC	DB	0.73 (0.67, 0.79)	-0.02	-0.28, 0.25
MC	PF	0.55 (0.48, 0.62)	0.14	-0.08, 0.36

Agreement in vertical cup/disc ratio				
Grader A	**Grader B**	**ρ_c (95% CI)**	**Mean difference (grader A-grader B),** pixels	**Bland Altman 95% limits of agreement**
NP	PF	0.54 (0.47, 0.60)	-0.14	-0.33, 0.05
NP	DB	0.73 (0.67, 0.78)	-0.08	-0.26, 0.10
NP	MC	0.76 (0.70, 0.81)	-0.06	-0.25, 0.13
PF	DB	0.74 (0.69, 0.80)	0.06	-0.11, 0.24
MC	DB	0.83 (0.79, 0.88)	-0.02	-0.19, 0.16
MC	PF	0.70 (0.64, 0.76)	-0.08	-0.27, 0.11

ρ_c Lin's concordance correlation coefficient.
NP-Nisha Patel, grader; PF Paul Foster, consultant ophthalmologist; DB David Broadway, consultant ophthalmologist; MC Michelle Chan, ophthalmology trainee

Table 4.13 Inter-observer agreement in glaucoma grading (no glaucoma/ suspect/ glaucoma) on a selection of 290 disc photographs.

Grader A	Grader B	Kappa	95% CI
NP	PF	0.39	(0.33-0.45)
NP	DB	0.38	(0.36-0.45)
NP	MC	0.38	(0.34-0.45)
PF	DB	0.41	(0.37-0.44)
MC	DB	0.64	(0.58-0.69)
MC	PF	0.55	(0.50-0.62)

Table 4.14 Combinations of glaucoma grading between pairs of graders on a selection of 209 disc photographs.

		A over-estimates B			B over-estimates A			Agree	Total
Grader A		GL	GL	Sus	Sus	No	No		
	Grader B	Sus	No	No	GL	GL	Sus		
NP	PF	26	3	7	2	11	33	127	209
NP	DB	8	4	8	19	14	29	127	209
NP	MC	15	4	7	16	20	20	127	209
PF	DB	4	2	18	42	1	16	123	209
MC	DB	11	2	8	16	1	11	160	209
MC	PF	34	2	8	3	0	15	147	209

No=no glaucoma, Sus= glaucoma suspect, GL= glaucoma

Agreement in disc grading for glaucoma

The agreement in grading for glaucoma on a three-point scale was only "fair" to "moderate" among the graders (kappa 0.38-0.64) (see **Table 4.13)**. From **Table 4.14** it can be seen that DB overestimated the severity of glaucoma status compared to all three other graders. PF underestimated the severity compared to DB and MC. Agreement between MC & PF and MC & DB were both high. Agreement between PF and DB was only 0.41 (95%CI 0.37-0.44). NP under-estimated glaucoma status compared to all 3 other graders, and there were more large differences in grading (normal vs glaucoma) with NP and the other three graders

4.5.6 Discussion

The purpose of studying the agreement between the 4 graders' assessment of the optic disc from disc photos was to evaluate the potential biases in the glaucoma diagnostic process in the study. Inter-observer differences could arise from demarcation of the disc and cup margins, made more challenging on monoscopic photos. The judgment of whether a disc is glaucomatous or not is also a subjective practice.

The selection of the photos for grading had a heavy slant on glaucoma cases, with 48% of the photos selected for cases of glaucoma, suspect, or for CDR>0.6. This was designed to test at greater depth, the graders' ability to differentiate between glaucoma and normal discs. The results showed that DB tended to over estimate the glaucoma diagnoses while PF tended to under-estimate. While there is no gold standard in glaucoma diagnosis, and judgments on the diagnostic accuracies of individual graders could not be made, it does mean that the final diagnoses were likely to be less severe than the initial diagnoses. Since DB formulated the initial diagnosis in the study, the overall false negative diagnostic rate would be limited. MC showed good agreement with both PF and MC. MC facilitated the diagnosis by identifying intermediary cases that needed further verification, this process was therefore unlikely to be subject to any major differences from the initial or final diagnoses.

NP under-estimated glaucoma status compared to all 3 other graders, and there were more large differences in her grading from the other three graders. This is likely due to the fact that unlike NP who is an optometrist, all three other graders were ophthalmologists with an interest in glaucoma, and were more likely to agree due to professional training. They were also more experienced in making diagnostic judgments about discs. Nevertheless, since NP's glaucoma grading was not used in the diagnostic process, this finding has no implication on the study's glaucoma diagnosis.

Comparison to other studies

Our study found the agreement among the graders in disc and cup diameter measurements to be substantial (ρ_c, 0.73-0.95), rim thickness measurement to be moderate to substantial (0.41-0.74), CDR to be moderate (ρ_c 0.54-0.83), and the glaucoma status to be moderate (kappa 0.38-0.64). Our results are similar to many other studies which examined the inter-observer agreement among expert graders from stereo photos, which showed substantial agreement in vertical [300] and horizontal CDR, [300] as well as disc parameter measurements. [301] The European Optic Disc

Assessment Trial showed good inter-observer agreement among 243 glaucoma specialists in their glaucoma diagnosis based on stereo photos. [149] Agreement in glaucoma progression from serial stereo photos is generally worse, with studies showing only fair to moderate agreement. [302,303] The Glaucomatous Optic Neuropathy Evaluation project described a comprehensive analysis on the agreement among 22 glaucoma specialists and fellows in various aspects of disc assessment on both monoscopic and stereo photos, including diameter and cup measurements, CDR estimation, glaucoma likelihood, as well as presence of pallor, disc haemorrhage and parapapillary atrophy. [213] It found agreement in glaucoma likelihood to be moderate and vertical CDR to be substantial. In particular, it showed that monoscopic photos did not lead to lower levels of inter-observer agreement compared to stereo photos in the assessment of any disc characteristics, which is reassuring to our study.

4.6 Conclusion

This chapter described how the final glaucoma diagnosis for each participant in the study was generated through a rigorous process that ensures its accuracy. The final glaucoma diagnosis is of immense importance, as it is used in all subsequent analyses in the thesis.

The chapter discussed the definitions used to define glaucoma and related conditions in the study, and how, through a diagnostic refinement process, the initial data from the study was double-checked to limit false positive and false negative cases in the final glaucoma diagnosis. The judgment of clinicians and technicians who were involved in evaluating the data to generate the glaucoma diagnosis was also assessed, and no major disagreement between them that could bias the diagnosis was found.

CHAPTER 5: RESULTS - COHORT PROFILE & DESCRIPTIVE EPIDEMIOLOGY

This chapter will describe the demographics of the participants and examine how representative the 3HC cohort is to the UK general population. Eye and visual test results and data availability will be summarized to serve as a reference to the later chapters.

5.1 Participant Demographics

A total of 8623 participants were examined in the 3HC, 3861 (44.8%) were men and 4762 (55.2%) were women. Their age ranges from 48.4 to 92.2 years, and the mean age was 68.7 years (95%CI 68.5-68.9 years).

Table 5.1 Age and sex distribution of the participants in the 3HC.

Age, years	Men n (%)	Women n (%)	Total n (%)
48-59	398 (4.6)	666 (7.7)	1064 (12.3)
60-64	879 (10.2)	1257 (14.6)	2136 (24.8)
65-69	799 (9.3)	985 (11.4)	1784 (20.7)
70-74	762 (8.8)	832 (9.6)	1594 (18.5)
75+	1023 (11.9)	1022 (11.9)	2045 (23.7)
Total	3861 (44.8)	4762 (55.2)	8623 (100)

5.1.1 Age

Compared to the populations of Norfolk and the UK (**Figure 5.1**), the 3HC cohort had a higher proportion of those aged 60-80 years, and a significant under representation of the 45-55 age group and the oldest group aged ≥ 85.

5.1.2 Sex Distribution

Overall, there were slightly more women (55.2%) than men in the 3HC. Compared to the Norfolk and UK population, the 3HC cohort had a higher proportion of women under 70 years, but a higher proportion of men aged ≥ 85. The sex distribution in the general population in both Norfolk and the UK shows an increasing proportion of women with rising age, probably a reflection of longer life expectancy in women, but the 3HC had a reverse trend of decreasing proportion of women with age (**Figure 5.2**).

Figure 5.1 Age distribution of the EPIC-Norfolk 3HC cohort compared to the population of Norfolk & the UK.
(Source: 2014 mid-year population estimates in the UK, Office for National Statistics)

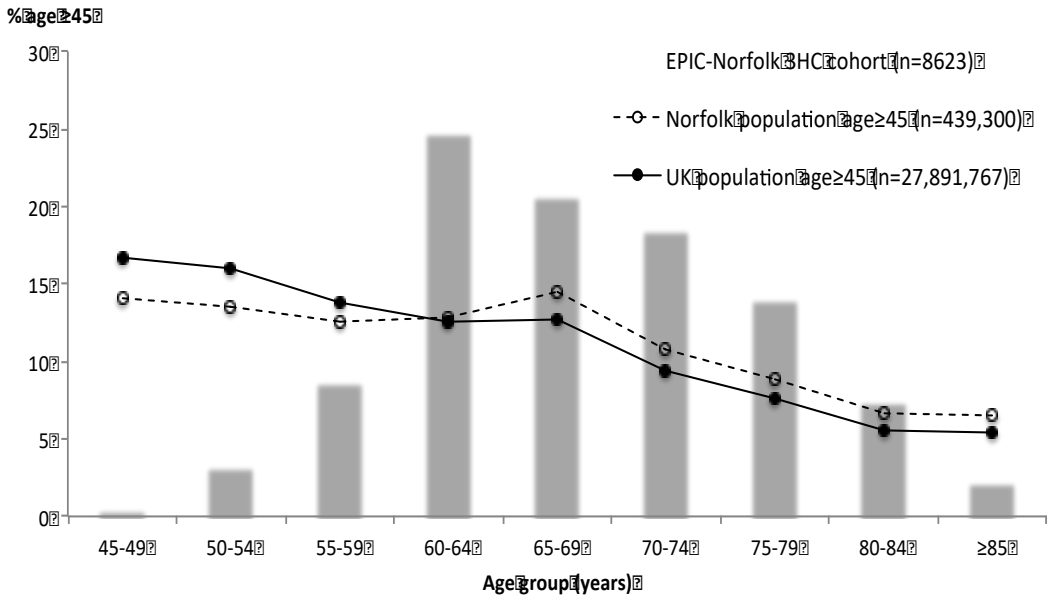
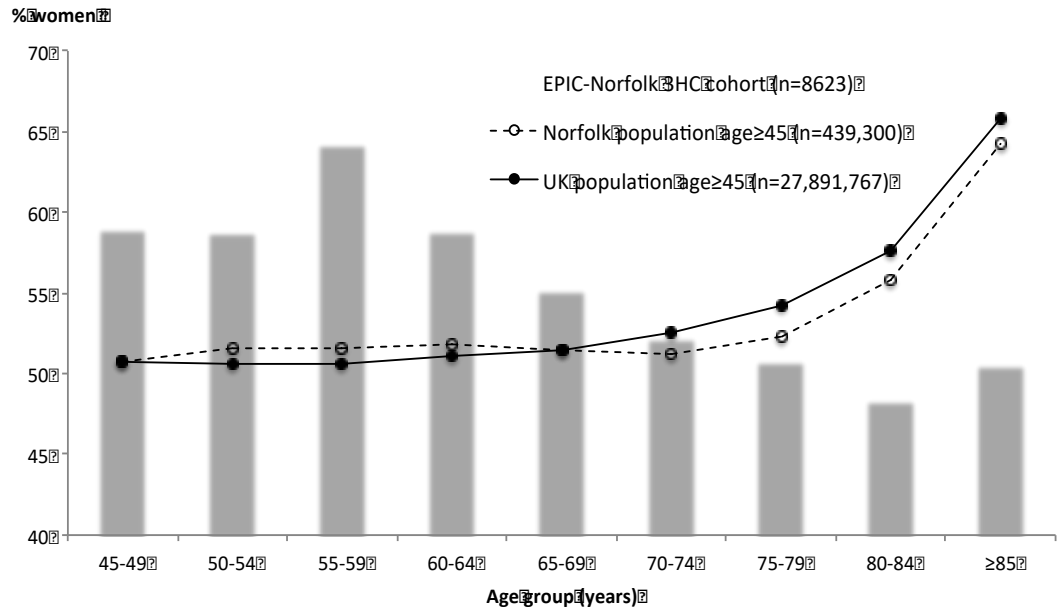


Figure 5.2. Sex distribution of the EPIC 3HC cohort compared to the population of Norfolk and the UK.
(Source: 2014 mid-year population estimates in the UK, Office for National Statistics)



5.1.3 Ethnicity

Table 5.2 shows the ethic makeup of the 3HC cohort compared to the population of Norfolk and UK. Note that data for Norfolk and UK includes residents of all ages, while the 3HC cohort only includes adults aged above 45. Non-responses or inconsistent responses were edited by imputation in the UK population estimates, while missing data were documented as a separate category in the 3HC.

White was the majority ethnic group in the 3HC cohort, Norfolk and the UK, although the percentage was greater in 3HC and Norfolk at 99.4% and 96.5% compared to 87.2% in the UK population. The 3HC had a far smaller proportion of all ethnic minority groups (Blacks, Asians, Chinese, others) compared to Norfolk and the UK. Overall, the 3HC cohort was less ethnically diverse than the general Norfolk or UK population.

Table 5.2 Ethnicity of 3HC participants compared to the population of Norfolk & the UK

Ethnicity	EPIC 3HC (age 48+)		Norfolk (all ages)	UK (all ages)
	n	%	%	%
White	8571	99.4	96.5	87.2
Black	6	0.07	0.5	3.0
Asians	5	0.06	1.1	6.2
Indian	3	0.03	0.5	2.3
Pakistani	2	0.02	0.1	1.9
Bangladeshi	0	0	0.1	0.7
Others	-	-	0.5	1.4
Chinese	3	0.03	0.4	0.7
Others	13	0.15	1.4	2.9
Non-responder	25	0.29	-	-
Total	8623	100	100	100

Source: 2014 mid-year population estimates in the UK, Office for National Statistics

5.1.4 Employment Status

Table 5.3 shows the employment status of the cohort. As expected for the older age of the cohort, the majority of the participants have retired from their main occupation (74.4%), although 6.1% still retained a paid job; 19.7% were in paid employment, and 1.8% were not retired and not in paid employment.

Table 5.3 Employment status of the 3HC participants

Employment status	n	%
Retired	6417	74.4
No paid job	5875	61.1
Paid job	530	6.1
Not retired	1861	21.6
No paid job	154	1.8
Paid job	1696	19.7
Missing data	345	4.0
Total	8623	100

5.1.5 Education level

The majority of participants have some form of educational qualification (73.7%) (**Table 5.4**)**.** Most have obtained A levels (44.2%), and 17.5% have higher education. Nevertheless, over a quarter (26.3%) have no formal qualification. Overall, the younger participants were better qualified than the older participants, as the percentage with no formal qualification increases with age, and the percentage with higher education decreases with age.

Table 5.4 Highest educational attainment by age group of the 3HC participants

Age, years	Educational level					
	No formal education	O level	A level	Higher education	Non responder	Total
	n (%)					
48-59	169 (15.9%)	162 (15.2%)	462 (43.4%)	271 (25.5%)	0	1064 (100%)
60-64	449 (21.0%)	270 (12.6%)	1016 (47.6%)	401 (18.8%)	0	2136 (100%)
65-69	447 (25.1%)	238 (13.3%)	780 (43.7%)	319 (17.9%)	0	1784 (100%)
70-74	491 (30.8%)	194 (12.2%)	684 (42.9%)	224 (14.1%)	1 (0.05%)	1594 (100%)
75+	713 (34.9%)	162 (7.9%)	868 (42.4%)	301 (14.7%)	1 (0.05%)	2045 (100%)
Total	2,269 (26.3%)	1,026 (11.9%)	3810 (44.2%)	1516 (17.6%)	2 (0.02%)	8623 (100%)

5.1.6 Social Class

Social class for each participant was recorded using the Registrar-general's social classes by occupation (**Table 5.5**). Most participants in the 3HC had a managerial occupation and belonged to social class II (40.7%). The next largest group was skilled manual workers (class IIIM). The distribution of the social classes remains similar across different age groups.

Comparative data from the 2011 UK census data for usual residents in Norfolk and the UK are presented in **Table 5.6**. It shows social classification applied per person according to the Registrar-Gereral's social classication, a robust and detailed classification derived in 2005 to better reflect occupation and social advantage in the modern society.[304] **Figures 5.3A and 5.3B** plot the data for 3HC, UK and Norfolk using comparable scaling. It is apparent that the distribution of the social classes are similar between 3HC and regional and national data, with the largest numbers in the managerial classes, followed by those in the interim social classes, and the smallest numbers in the lowest social class.

Table 5.5 The Registrar-general social class by age group for 3HC participants

Age, years	Social Classes by Occupation							
	I	II	III N	III M	IV	V	Missing data	Total
	n (%)							
48-59	109 (10.2%)	444 (41.7%)	161 (15.1%)	210 (19.7%)	111 (10.4%)	21 (2.0%)	8 (0.8%)	1064 (100%)
60-64	186 (8.7%)	896 (42.0%	301 (14.1%)	459 (21.5%)	233 (10.9%)	45 (2.1%)	16 (0.8%)	2136 (100%)
65-69	130 (7.3%)	743 (41.7%)	245 (13.7%)	384 (21.5%)	220 (12.3%)	45 (2.5%)	17 (1.0%)	1784 (100%)
70-74	138 (8.7%)	608 (38.1%)	280 (17.6%)	324 (20.3%)	188 (11.8%)	39 (2.5%)	17 (1.1%)	1594 (100%)
75+	187 (9.1%)	820 (40.1%)	389 (19.0%)	376 (18.4%)	202 (9.9%)	49 (2.4%)	22 (1.1%)	2045 (100%)

Social classes by occupation: I professional, II managerial, III N skilled non-manual, III M skilled manual, IV semi-skilled, V un-skilled work.

Table 5.6 NS-SEC (National Statistics: Social-economic Classification) for the UK and Norfolk

Social-economic class	UK (%)*	Norfolk (%)*
1. Higher managerial, administrative and professional occupations	12.8	10.9
2. Lower managerial, administrative and professional occupations	21.7	21.1
3. Intermediate occupations	10.1	9.4
4. Small employers and own account workers	12.1	14.4
5. Lower supervisory and technical occupations	8.6	9.9
6. Semi-routine occupations	12.7	14.4
7. Routine occupations	12.0	12.9
8. Never worked and long-term unemployed	4.0	2.8
L14.1 Never worked	2.5	1.5
L14.2 Long-term unemployed	1.5	1.3
Not classified (including L15 Full-time students)	2.0	1.3
Total	100	100

*Percentage of all usual residents aged 16+

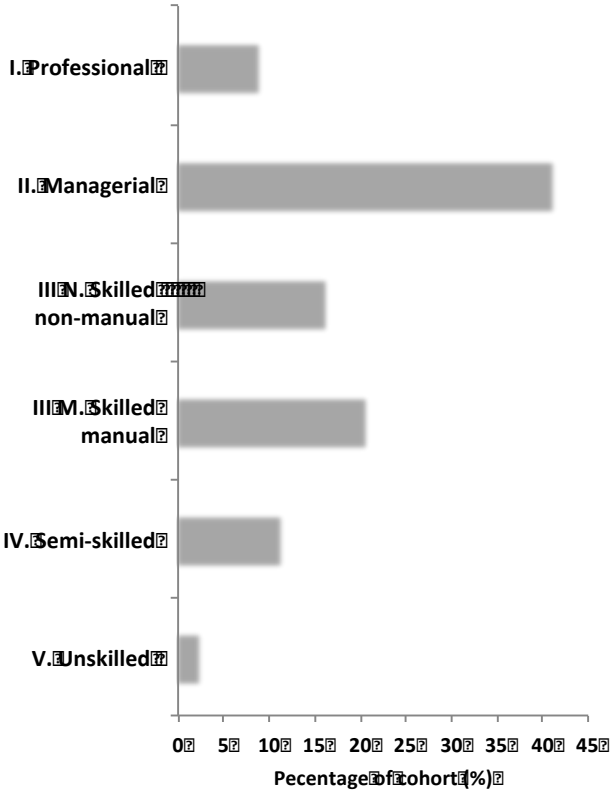


Figure 5.3A Social classes of the 3HC participants by the Registrar-General's Classification by Occupation

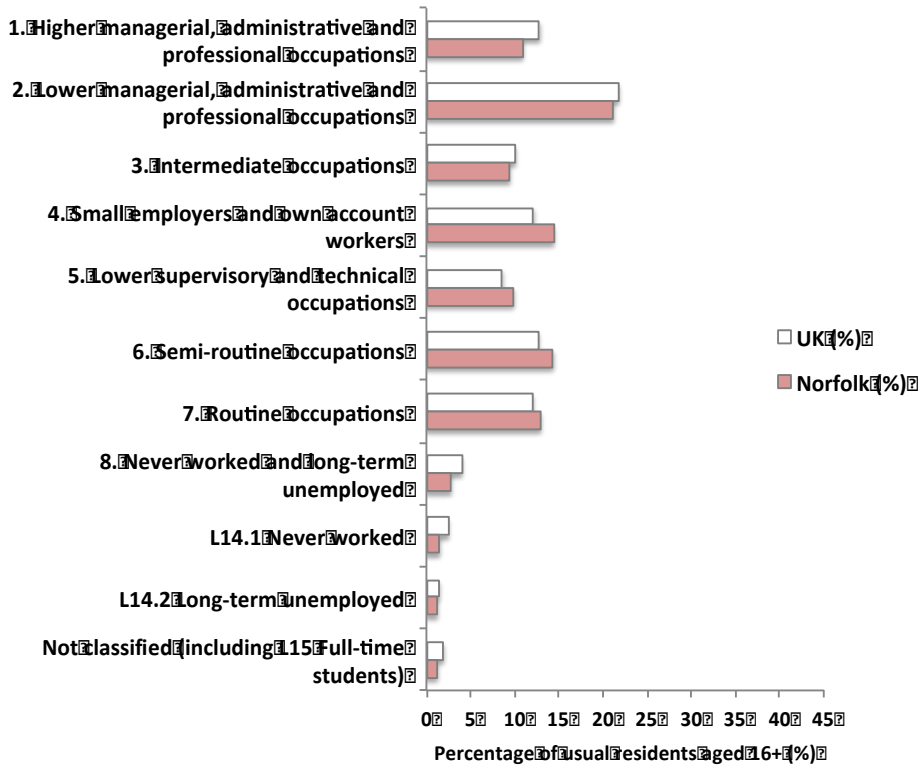


Figure 5.3B Social classes of the usual residents (aged ≥16) of Norfolk & the UK according to the National Statistics-Socio-economic Classification.

5.1.7 Discussion

The EPIC 3HC cohort described in this thesis is different from the broader population of Norfolk and the UK in age and sex distribution. The 3HC cohort is older, with 74.4% already retired, and has a larger proportion of women. Its ethnic makeup is similar to that of Norfolk and the UK with a large White majority, although it is less ethnically diverse.

About three quarters of the population have formal educational qualifications of at least O levels. The social structure of the 3HC cohort is largely similar to that of Norfolk and the UK with the largest numbers in the managerial classes, and the smallest numbers in the lowest social class.

5.2 Eye and Visual Parameters of the EPIC-Norfolk Eye Study

This section will provide a brief report on data availability for all the eye tests and provide a brief description of the data.

5.2.1 Visual acuity

LogMAR visual acuity was measured in 8564 (99.3%) participants (**Table 5.7**).
The mean best corrected acuity (BCVA) for right eyes were 0.05 (Snellen equievalent between 6/6 -6/7.5, 95% CI 0.05-0.06) and left eyes were 0.04 (95%CI 0.04-0.05). Only 29 participants (0.3%) had BCVA consistent with visual impairment (LogMAR >0.48, Snellen equivalent <6/18) in their better seeing eye.

Table 5.7 Best corrected visual acuity of the 3HC cohort

Best corrected visual acuity		Right eye	Left eye
LogMAR	Snellen equivalent	n (%)	
≤0.0	≤6/6	3478 (40.3%)	3841 (44.5%)
<0.3	>6/12	4494 (52.1%)	4097 (47.5%)
≥0.3 to <0.5	≤6/12 to >6/18	386 (4.5%)	394 (4.6%)
≥0.5 to <0.8	≤6/18 to >6/36	72 (0.8%)	70 (0.8%)
≥0.8 to <1.0	≤6/36 to >6/60	29 (0.3%)	25 (0.3%)
≥1.0	≤6/60	56 (0.7%)	68 (0.8%)
Visual acuity not available		108 (1.3%)	128 (1.5%)
Total		8623(100%)	8623 (100%)

5.2.2 Biometry, Refraction and Lens status

Biometry was performed in 8033 (93.2%) participants and refraction in 8513 (98.7%) participants. **Table 5.8** shows the different measurements obtained. The mean axial length was 23.6mm (95% CI 23.5-23.6 mm) for right eyes and 23.5mm (95% CI 23.49-23.54mm) for left eyes.

Refraction was performed in 8508 (98.7%) participants. The mean spherical equivalent was +0.15D (95% CI +0.10 to +0.20D) for right eyes and +0.20D (95% CI +0.15 to +0.25D). Over 27% left and right eyes were emmetropic (**Table 5.9**). The lens status was known in 100% participants. 852 (9.6%) right eyes and 824 (9.6%) left eyes were pseudophakic. 315 (36.5%) participants were pseudophakic in one eye and 680 (7.9%) participants in both eyes.

8449 (98.0%) participants answered the question on the health questionnaire “Do you wear glasses or contact lenses?” and 8213 participants answered “yes”.

Table 5.8 Biometry of the 3HC cohort

Axial length (mm)	**n**	**Range**	**Mean (95%CI)**	**Median (IQR)**
Right eye	7976	16.1- 32.1	23.6 (23.5- 23.6)	23.5 (22.8-24.2)
Left eye	7905	14.3- 32.4	23.5 (23.49- 23.54)	23.4 (22.8-14.1)
Anterior chamber depth (mm)				
Right eye	7784	1.4- 6.6	3.14 (3.13- 3.15)	3.1 (2.8- 3.4)
Left eye	7796	1.7- 5.7	3.18 (3.17- 3.19)	3.1 (2.9- 3.4)
Mean corneal curvature (Dioptre)				
Right eye	7185	37.2- 51.2	43.7 (43.6- 43.7)	43.7 (42.7-44.7)
Left eye	7143	35.1- 50.9	43.7 (43.7- 43.8)	43.7 (42.8-44.7)

Table 5.9 Refractive error of the 3HC cohort

Spherical equivalent (D)	**Classification**	**Right eye**	**Left eye**
		n(%)	
≥ +6.00	High hyperopia	51 (0.6%)	55 (0.6%)
+0.51 to +5.99	Hyperopia	3816 (44.3%)	3875 (44.9%)
-0.50 to +0.50	Emmetropia	2402 (27.9%)	2377 (27.6%)
-5.99 to -0.49	Myopia	2019 (23.4%)	1998 (23.2%)
≤-6.00	High myopia	188 (2.2%)	173 (2.0%)
not available	-	147 (1.7%)	145 (1.7%)

5.2.3 Intraocular Pressure and Corneal Biomechanics

8343 (96.6%) participants had IOP measured. The first 443 (5.1%) participants in the study had measurement with the AT555 tonometer (an automated, table mounted, air-puff tonometer), and all subsequent participants had measurements with the Reichert ORA tonometer. The ORA also measures corneal hysteresis and corneal resistance factor. **Figure 5.4** plots the distribution of the cohort's Goldmann-correlated IOP (IOPg), corneal-compensated IOP (IOPcc), corneal hysteresis and corneal resistance factor. Details of the cohort's IOP distribution and its relationship with glaucoma is described in Chapter 7.

CCT measurement was only available in the NNUH clinic, where participants with abnormal results in the initial screening tests were referred. Among the 1770 participants who attended the NNUH clinic, 1411 (79.7%) had CCT measured. **Table 5.10** summarizes the IOP and corneal biomechanical properties of the 3HC

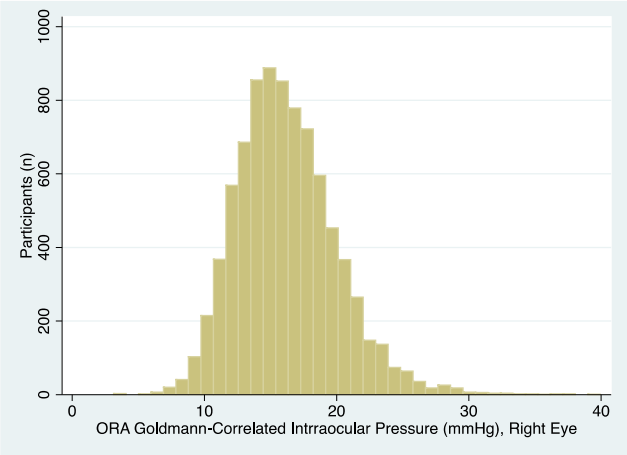
Table 5.10 Intraocular pressures and corneal biomechanical parameters of the 3HC participants

	n	Range	Mean (95% CI)	Median (IQR)
AT555 IOP				
Right eye	440	9.7-28.1	14.5 (14.2-14.9)	13.7 (11.7-16.7)
Left eye	443	8.3-33.7	14.7 (14.4-15.1)	14.0 (12.0-17.0)
ORA IOPg				
Right eye	8343	3.1 - 39.9	16.2 (16.1 -16.3)	15.9 (13.6-18.4)
Left eye	8315	3.7 - 45.6	16.3 (16.2 -16.4)	16.0 (13.7-18.5)
ORA IOPcc				
Right eye	7903	0.0- 59.0	17.2 (17.1-17.3)	16.8 (14.6-19.3)
Left eye	7872	0.0 -46.0	17.3 (17.3 - 17.4)	17.0 (14.8-19.5)
ORA corneal hysteresis				
Right eye	7903	0.0, 21.7	9.93 (9.9, 10.0)	10.0 (8.9-11.0)
Left eye	7872	2.4, 30.0	9.87 (9.8, 9.9)	9.9 (28.8-10.9)
ORA corneal resistance factor				
Right eye	7903	0.0 -21.2	10.2 (10.2, 10.3)	10.2 (9.1-11.4)
Left eye	7872	3.5 - 30.1	10.2 (10.2, 10.3)	10.1 (9.0-11.3)
Central corneal thickness (mm)				
Right eye	1411	351-690	554.1 (552.2-556.1)	552 (528-580)
Left eye	1409	421-678	556.1 (554.1-558.1)	554 (530-581)

IOP Intraocular pressure; ORA Ocular Response Analyzer tonometer; IOPg Goldmann-correlated intraocular pressure; IOPcc Corneal-compensated intraocular pressure

Figure 5.4 Graphs showing distribution of the cohort's ORA measurements
a) Goldmann correlated IOP (IOPg), b) corneal compensated IOP (IOPcc), c) corneal hysteresis, and d) corneal resistance factor

a)



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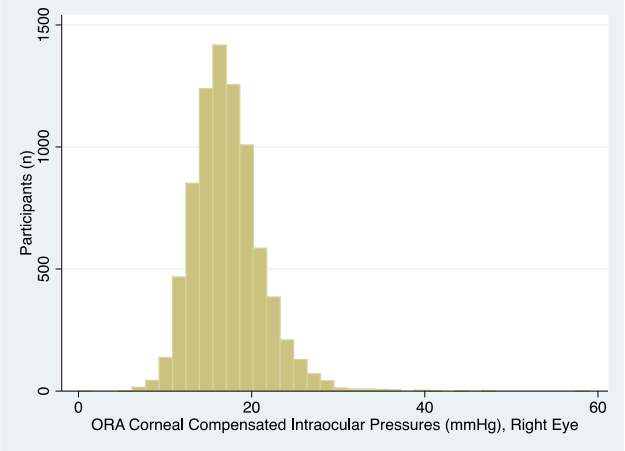

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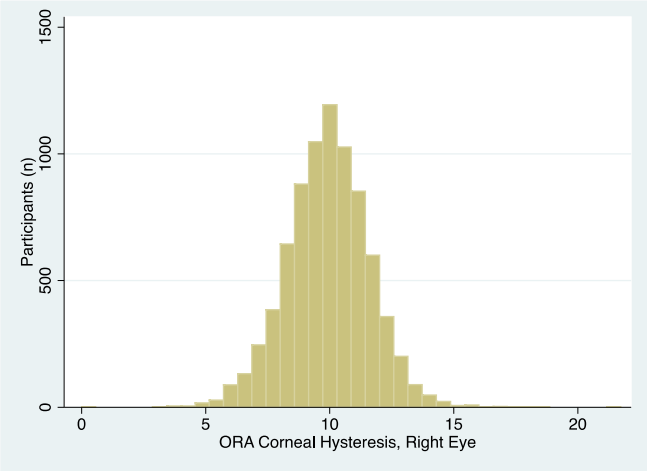

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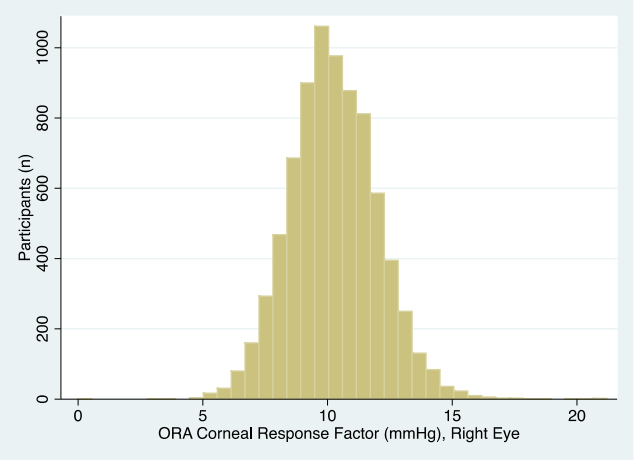


5.2.4 Visual Field (VF) Tests

A total of 3344 VF tests for 1459 (16.9%) participants were performed. 1444 participants met the criteria for VF testing (see Chapter 3, **Figure 3.3**), and 1100 received the test (76.2%). The criteria also stipulated that 1:10 random participants who didn't meet the list of abnormal results in IOP, HRT or GDx-VCC should also have VF testing, and only 359 out of the 7179 participants (5.0%) of those had a VF test.

1349 fields (949 participants) were done in the EPIC clinic as part of the screening examination, and 1995 fields (1039 participants) were done in the NNUH clinic, for participants referred there after abnormal findings in their screening tests, or for existing patients of the NNUH. 1169 participants (13.6%) had VF in both eyes, and 290 participants (3.4%) had VF in one eye only.

Table 5.11 Reliability indices of visual field tests done in EPIC clinic and the NNUH clinic

	EPIC clinic (n=1349)	NNUH clinic (n=1995)
Fixation losses <33.3%	71.7%	92.4%
False positive <33.3%	99.3%	99.8%
False negative <33.3%	99.4%	99.6%
Overall reliable field * (% fields done at that site)	71.8%	92.0%
Overall analyzable field (% fields done at that site)	71.8%	77.4%

NNUH Norfolk & Norwich University Hospital
*Overall reliable field = all three indices were <33.3%. Overall analyzable field = when fields were reliable and performed contemporaneous to their EPIC screening test date.

Table 5.11 summarizes the reliability indices of the visual fields done in the EPIC and NNUH clinics. VFs were deemed reliable if all three indices (fixation losses, false positives and false negatives) measured below <33.3%. A test was deemed analyzable if, in addition to being reliable, it was also performed within one year from the date of the screening examination at the EPIC clinic, such that the visual field test would be contemporaneous to all other examination parameters.

A smaller proportion of EPIC field tests than NNUH fields had fixation losses of <33.3% (71.7% vs 92.4%), which in turn lowered the overall proportion of reliable fields in EPIC. This could be because many of the participants were doing field tests for the first time in the EPIC clinic, while many NNUH fields were done on existing patients who have had previous fields done. The staff could also be better at instructing patients to maintain fixation in NNUH than EPIC clinic. Overall, the proportion of analyzable fields in NNUH (77.4%) was higher than in the EPIC clinic (71.8%).

Table 5.12 Glaucoma Hemifield Test results of visual fields done in EPIC clinic and the NNUH clinic in the 3HC

Glaucoma Hemifield Test	EPIC clinic n(%)		NNUH clinic n(%)	
	RE	LE	RE	LE
Within normal limits	250 (51.4%)	225 (46.6%)	406 (52.5%)	400 (51.9%)
Outside normal limits	153 (31.5%)	177 (36.6%)	225 (29.1%)	244 (31.6%)
Borderline	66 (13.6%)	64 (13.3%)	129 (16.7%)	111 (14.4%)
Borderline/ General reduction in sensitivity	4 (0.8%)	3 (0.6%)	3 (0.4%)	3 (0.4%)
General depression of sensitivity	13 (2.7%)	13 (2.7%)	8 (1.0%)	8 (1.0%)
Abnormally high sensitivity	0 (0%)	1 (0.2%)	2 (0.3%)	5 (0.6%)
Total	486 (100%)	483 (100%)	773 (100%)	771 (100%)

Table 5.12 shows the Glaucoma Hemifield Test (GHT) results. Half of all tests were "within normal limits", and that proportion is similar for both EPIC fields (46.4-51.4%) and NNUH fields (51.9-52.5%) fields. This reflects the fact that many participants had repeat VF tests in both clinics, as the criteria for having VF test in the EPIC clinic is very similar to the criteria for referral for NNUH. It also reflects the small number of other non high-risk participants having field test done in the EPIC clinic.

5.2.5 Disc Photos

A total of 7654 subjects (88.8%) had disc photos taken in either eye (7652 had photos in both eyes). 7497 subjects' photos were taken as part of the EPIC study; for 157 subjects who were known NNUH ophthalmic patients, the disc photos held on their records that were contemporaneous with their date of 3HC were used in the analysis. The quality of the photos taken in the EPIC study clinic and NNUH clinic were comparable: 94% of EPIC photos and 95% of NNUH photos were gradable (**see Table 5.13**).

5.2.6 Scanning Laser Ophthalmoscopy (HRT II)

8064 (93.5%) participants had HRT II scans taken. 76.2% of the scans had a topography standard deviation ≤ 40μm, the cutoff usually used to defined scans of adequate quality. 62-63% of scans had MRA results "within normal limits" (**Table 5.14**). Detailed analysis of the diagnostic ability of is presented in Chapter 8.

Table 5.13 Image quality of disc photos taken in the EPIC & NNUH

	EPIC photos		NNUH photos	
	Right eye	**Left eye**	**Right eye**	**Left eye**
Excellent (publication quality)	5 (0.1%)	2 (0.03%)	4 (2.5%)	1 (0.6%)
Good	2,107 (28.1%)	1,594 (21.3%)	122 (77.7%)	123 (79.4%)
Fair	3,904 (52.1%)	3,872 (51.7%)	19 (3.2%)	18 (11.6%)
Poor, but main features are still gradable	1,007 (13.4%)	1,212 (16.2%)	5 (3.2%)	5 (3.2%)
Ungradable	371 (5.0%)	556 (7.4%)	5 (3.2%)	5 (3.2%)
Wrong field definition but some features are gradable	24 (0.3%)	29 (0.4%)	0	0
Photo missing from file	79 (1.1%)	232 (3.1%)	2 (1.3%)	3 (1.9%)
Total	7497 (100%)	7497 (100%)	157 (100%)	155 (100%)

Table 5.14 HRT Moorfields Regression Analysis results among the 3HC participants

	Right eye	**Left eye**
Within normal limits	4753(60.7%)	4720 (60.1%)
Borderline	1586 (20.3%)	1659 (21.1%)
Outside normal limits	1493 (19.1%)	1481 (18.8)%
Total	7832 (100%)	7860 (100%)

5.2.7 Scanning Laser Polarimetry (GDx-VCC)

7943 (92.1%) participants had GDx-VCC scan performed. 79.2% of scans had quality score ≥7, a cutoff usually used to define scans of adequate quality for analysis. The mean nerve fibre indicator score (NFI) was 19.7 (95% CI 19.4-19.9) for right eyes and 19.0 (95% CI 18.8-19.3) for left eyes. The diagnostic ability of GDx-VCC is analysed in Chapter 8.

5.2.8 Self-Reported Eye Conditions

Health questionnaire was administered to all participants, and 8501 participants (98.6%) answered the eye-related questions listed below (**Table 5.15**). 20.9% of the cohort reported problems with their eyesight, 16.7% reported previous eye operations, 10.1% reported having some treatment for eye conditions, and 61.4% were aware of a family history of eye problems.

Table 5.15 Eye-related questions asked in the Health Questionnaire among the participants in the 3HC

Questions	Yes	No	Don't know	Missing data
	number of participants (% of cohort)			
Do you wear glasses or contact lenses?	8213 (95.9%)	236 (2.7%)	52 (0.6%)	122(1.4%)
Do you have any problems with your eyesight?	1804 (20.9%)	2090 (70.6%)	607 (7.1%)	122 (1.4%)
Have you ever had an eye operation?	1430 (16.6%)	6517 (75.6%)	91 (1.1%)	585 (6.8%)
Do you have a relative with eye disease or eye problems?	1973 (61.4 %)	5298 (61.4%)	767 (8.9%)	585 (6.8%)
Are you having any treatment or medication (e.g. eyedrops) for any eye conditions?	870 (10.1%)	7052 (81.8%)	116 (1.3%)	585 (6.8%)

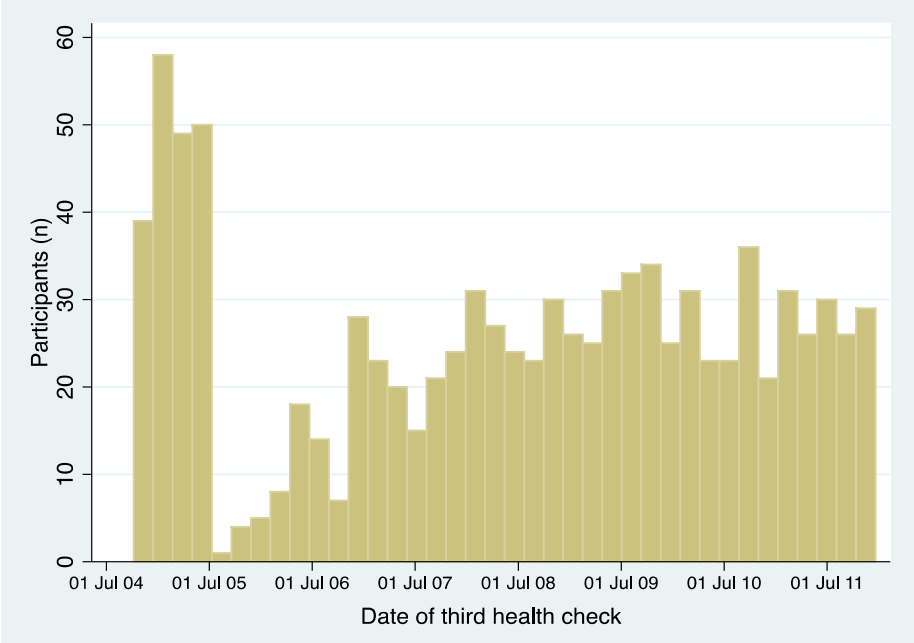
Questions	Excellent	Very good	Good	Fair	Poor	Missing data
	number of participants (% of cohort)					
How good is your eyesight at distance recognizing friends across the street? (using glasses or corrective lens if you usually wear them)?	1513 (17.6%)	3470 (40.2%)	2524 (29.3%)	738 (8.6%)	229 (2.7%)	123 (1.4%)
How good is your eyesight at seeing things close up (using glasses or corrective lens if you usually wear them)?	2440 (28.7%)	3490 (40.5%)	2008 (23.3%)	435 (5.0%)	91 (1.1%)	123 (1.4%)

5.2.9 Discussion

Overall, there is a high percentage (92.1%-99.3% participants) of data available for all ocular parameters. The main exceptions were disc photos (88.8%) and VF test (16.9%). The reasons for missing disc photos were analyzed examining the dates of the testing, and it is clear from **Figure 5.5** that there was a period in the start of the study when many photos were missed. This could be due to mechanical problems with capturing or saving the images. Staff was also known to not save any poor quality images in the beginning, although that had subsequently been discovered and rectified with further training. However, it is possible that in cases where the images were clearly unusable, most likely due to the presence of cataracts without pupil dilation, images were still not saved, contributing to missing data.

The test with the highest rate of missing data is VF test. This is explained by the protocol of only testing those deemed at risk of glaucoma and an additional 1:10 other participants, as VF tests on all participants would be unfeasibly time-consuming and costly. Nevertheless, there is a short fall of expected VF test done, with only 76% of those meeting the criteria having the test, and 5% instead of 10% of the rest of the cohort having a VF test. This deviation from the testing protocol was mainly due to time pressure, although individual reasons for missing the test were not documented. Since VF testing demands a high degree of concentration and coordination, it is possible that VF was attempted but abandoned in some participants who could not complete the test.

Figure 5.5 The dates of examination for participants whose disc photos were missing



5.3 Conclusion

This chapter described the demographics of the EPIC-Norfolk Eye Study participants, their basic eye and vision tests results, and the completeness of the data. Compared to the general UK and Norfolk populations, the study participants were older, with a higher proportion of women, and were ethnically less diverse, although their social status were similar. There was a high percentage of data availability for most ocular parameters, expect disc photos and visual fields, which will likely affect the diagnostic accuracy of glaucoma in the study. These basic characteristics of the study participants will influence the subsequent analyses in the thesis, and will be discussed in further detail.

CHAPTER 6: GLAUCOMA IN THE EPIC-NORFOLK EYE STUDY

6.1 Background

Glaucoma prevalence data have been reported from populations in the USA,[14,95] Australia,[90,305] Europe[16,91,159] and South East Asia.[20,151,306,307] However, recent data from the UK is lacking, with the latest published cross-sectional population glaucoma survey being one from a rural population in the West of Ireland in 1993,[17] and a survey from north London in 1998.[94] EPIC-Norfolk will provide the most up-to-date glaucoma data in a UK population.

The risk factors of POAG had been extensively studied in many publications, The well-established factors include increasing age,[14-17] raised IOP,[14,16,20,90,91,151,159,305,306] myopia,[12,44-46] and positive family history.[55] There is also evidence of corneal biomechanical factors such as CCT [34,35,187,188] and corneal hysteresis [35,40-43] as independent risk factors have been shown in many studies, but no study had examined this relationship on a population level. EPIC-Norfolk will be the first study that examines the relationship of corneal biomechanical factors and glaucoma on a population level.

Undiagnosed glaucoma is a sizeable yet hidden public health problem. Eye surveys conducted in developed Western countries show that at least half of glaucoma cases are previously undiagnosed.[16,90] Published studies have described the clinical features and risk factors of undiagnosed glaucoma.[308-310] The Barbados Eye Study found poorer education level at baseline in the undiagnosed group compared to the diagnosed group,[308] while the Thessaloniki Study found that previously undiagnosed patients are more likely to have not seen an eye doctor in the past year [309] Similarly both the Barbados Eye Study [308] and the Visual Impairment Project [310] showed undiagnosed patients sought eye care less frequently in the past year, with the source of eye care more likely to be an optometrist rather than an ophthalmologist.[308 310] There are also reasons to suspect the clinical features and severity of glaucoma may differ between previously diagnosed and undiagnosed glaucoma patients. The features shown to be significant for undiagnosed glaucoma are: smaller vertical cup to disc ratio (VCDR), a negative family history of glaucoma,[309] presence of visual field detect,[310] and in the Barbados Eye Study 9 year-follow-up, lower mean baseline IOP and baseline hyperopia.[308] This chapter will therefore aim to examine the risk factors associated with

previously undiagnosed POAG, focusing on the severity of disease, as well as physical or social barriers to eye care access.

6.2 Aims

1. To describe the clinical features of glaucoma subjects and glaucomatous eyes.
2. To study the risk factors for primary open angle glaucoma
3. To study the risk factors for previously undiagnosed primary open angle glaucoma

6.3 Methods

6.3.1 Glaucoma Diagnosis

Details of how glaucoma diagnosis was reached have been described in full in Chapter 4 “Methods-Glaucoma Diagnosis”. Characteristics of glaucoma diagnosis were reported per person and per eye. Glaucoma diagnosis per person was obtained by taking the clinically more serious diagnosis of either eye, in the following hierarchy (most serious to least serious): glaucoma, glaucoma suspect, ocular hypertension, narrow angle spectrum (primary angle closure, primary angle closure suspect and narrow angles), and normal.

6.3.2 Associations of Primary Open Angle Glaucoma

Participants with POAG in either eye were compared with those without glaucoma in either eye using logistic regression modelling, with the dependant variable coded as 0=subjects without glaucoma and 1=subjects with primary open angle glaucoma in either eye.

The factors studied were decided *a priori* to include demographic and socio-economic factors (sex, age, social group and education level), ocular factors (IOPg, IOPcc, corneal hysteresis (CH), corneal resistance factor (CRF), and axial length), family history of glaucoma, diabetes, and anthropometric factors which have been linked to intraocular pressure (height, weight, body mass index, weight height ratio, systolic blood pressure, diastolic blood pressure). Diabetes status was ascertained using GP and hospital records and diabetes registers. CCT was not included in the analysis, as it was only measured in at risk subjects who were referred to the NNUH, and so the rate of missing data is high among non-glaucoma subjects.

Statistical analysis

To best represent the association with glaucoma, the higher value of either eye for IOPg, IOPcc, and axial length, and the lower value of either eye for CH and CRF were used for each subject.

Variables were first examined in univariable regression, and factors that were significantly associated with POAG ($p<0.05$) were included in the final multivariable model. IOPg, IOPcc, CH and CRF in either eye showed collinearity (variance inflation factor>10) and were substituted in separate multivariable models but using the same co-variates to allow the models to be comparable. Pseudo R^2 of the four models were compared to see how much the models account for the variance of POAG.

Sensitivity Analysis

The association of POAG with CH and CRF is likely to be falsely enhanced by including subjects who were on pressure-lowering drops or had glaucoma surgery. The analysis was therefore repeated by excluding POAG cases that were previously diagnosed before the study, and controls who were on pressure-lowering drops in either eye.

Pre-treatment IOP and its imputation

To allow unbiased comparison of IOP levels between the two groups, the pre-treatment IOP was used for participants who have had pressure-lowering treatment. Pre-treatment IOP is defined as the highest IOP (GAT) documented in the patient's hospital records before any IOP-lowering treatment (drops or surgery) was instigated. For those who have had IOP-lowering treatment but the pre-treatment IOP was unavailable, the pre-treatment IOP was imputed.

Among the entire EPIC-Norfolk Eye Study, 301 (34.9%) right and 299 (34.7%) left eyes were on pressure-lowering treatment, defined as being on pressure-lowering medication and/or having undergone glaucoma surgery, irrespective of their glaucoma diagnosis. In 126 right and 131 left eyes, the pre-treatment IOP was available. The ratio of pre-treatment/current study IOP was 0.740 (95%CI 0.70-0.78) in the right eye and 0.747 (95%CI 0.71-0.79) in the left eye (**Table 6.1**), and the mean ratio was 0.744. To impute the pre-treatment IOP level for eyes whose pre-treatment IOP is unknown, the current study IOPg was divided by 0.744.

Table 6.1. Documented pre-treatment IOP and current study IOP levels for the subjects whose pre-treatment IOP were available.

	Documented pre-treatment IOP (mmHg)	Study IOPg (mmHg)	Pre-treatment IOP / Current IOP
		mean (95% CI)	
Right eye (n=126)	25.1 (24.1-26.0)	17.8 (16.9-18.7)	0.740 (0.70-0.78)
Left eye (n=131)	25.3 (24.3-26.4)	18.1 (17.2-18.9)	0.747 (0.71-0.79)

6.3.3 Associations of Previously Undiagnosed Primary Open Angle Glaucoma

Logistic regression was used to analyse the risk factors for previously undiagnosed POAG, with the dependent variable coded as 0=subjects with known POAG and 1= subjects with previously undiagnosed POAG. Factors that were significant ($p<0.05$) in the univariable analysis were included in the multivariable model except for collinear variables. The factors examined (**Table 6.2**) include socioeconomic, demographics and ocular factors that could affect a subject's likelihood of seeking eye care, such as presence of low visual acuity, previous cataract surgery, other eye problems, high refractive error, or wearing glasses/ contact lens. Physical and economic factors that could present a barrier to eye care access, such as financial difficulty, physical frailty, and poor health status were also included. Cup/disc ratio (CDR) and CDR asymmetry were multiplied by 10 in the regression models to allow the odds ratio to be analysed per 0.1 increase in CDR.

Table 6.2. List of potential risk factors for previously undiagnosed primary open angle glaucoma examined in the study

Socio-demographic factors	
	age, sex
	social class by occupation
	highest educational qualification
	employment status
	self-reported financial status
Ocular risk factors	
	glaucoma type
	maximum Goldmann-correlated IOP (IOPg) of either eye
	higher cup/disc ratio on disc photos of either eye
	CDR asymmetry
	axial length
Proxy factors for eye care seeking behaviour	
	self reported family history of glaucoma (in any blood relation)
	self-reported glasses/ contact lens wear
	self-reported eyesight problem
	previous cataract surgery in either eye
	maximum absolute refractive error of either eye
	worse visual acuity of either eye
	self reported health status (excellent or very good/ good/fair/ poor)

6.4 Results

6.4.1 Glaucoma Diagnosis

Table 6.3 and **Table 6.4** show the glaucoma diagnosis by eye and by person. Out of the 8623 participants in the EPIC-Norfolk cohort, 363 (4.2%) had glaucoma in either eye, 314 had POAG (3.6%), 607 (7.0%) were glaucoma suspects, 863 (10.0%) were ocular hypertensives, 54 (0.6%) had narrow angle spectrum. Twenty-three participants (0.3%) had no recorded diagnosis, as they declined or were unable to undergo definitive eye examination after failing the screening tests.

A large number of eyes (n=1082,12.5%) were classified as glaucoma suspects. The majority of these (887 eyes) were classified based on the presence of glaucomatous discs only, and 134 had glaucomatous discs with ocular hypertension (mean IOPg >21mmHg).

The majority of people with glaucoma had POAG (86.5%), with an equal proportion of high pressure (50.0%) and normal pressure glaucoma (50.0%). Among the 363

glaucoma cases, 55.9% of cases were bilateral. 242 glaucoma cases (66.6%) were previously known, and 66.3% of POAG cases were previously known. The prevalence of all cause glaucoma and POAG increased with age for both men and women (**Figure 6.1, Table 6.5)**, and the prevalence was higher among men (5.2%) then women (3.4%) (X^2 p<0.0001). **Figure 6.2** shows that the prevalence of POAG (who were not on IOP treatment) increases with IOP.

Table 6.6 summarizes the ocular characteristics of the 523 glaucomatous eyes. The majority of them were already on glaucoma drops at the date of examination (66.8%). Their median IOPg was 16.7mmHg (IQR 6.7mmHg) and the median IOPcc was 19.0 mmHg (IQR 6.2mmHg). The median central corneal thickness was 545μm (IQR 48μm). The majority of glaucomatous eyes had good best corrected visual acuity (BCVA) of LogMAR<0.3 (84.3%), 4.2% had severe visual impairment of BCVA ≥1.0 (**Table 6.7**). One glaucomatous eye had no vision recorded as it was eviscerated. The median vertical CDR on disc photos of the glaucomatous eyes was 0.52 (IQR 0.2), and the majority of glaucomatous eyes had vertical CDR <0.6. A large proportion did not have CDR available: 81 (15.5%) of glaucomatous eyes had photos which were ungradable, and 27 (5.2%) had no disc photos taken, but all glaucoma patients were examined physically and the diagnosis made on clinical disc assessment. Formal visual field assessment was not feasible in 28 eyes due to poor vision. Most of these participants had secondary glaucoma which was diagnosed by advanced disc cupping and uncontrolled IOP.

Table 6.3 Glaucoma diagnosis per eye

Glaucoma diagnosis	Right eye		Left eye	
	n	% (95% CI)	n	% (95%CI)
Normal	7091	82.2 (81.4-83.0)	7061	81.9 (81.1-82.7)
Primary open angle glaucoma	236	2.7 (2.4-3.0)	230	2.7 (2.3-3.0)
High tension glaucoma	121	1.4 (1.2-1.6)	121	1.4 (1.2-1.6)
Normal tension glaucoma	115	1.3 (1.1-1.5)	109	1.3 (1.1-1.5)
Primary angle closure glaucoma	20	0.2 (0.1-0.3)	17	0.2 (0.1-0.2)
Secondary glaucoma	9	0.1 (0.03-0.2)	11	0.1 (0.03-0.2)
Subtotal with glaucoma	265	3.1 (2.7-3.5)	258	3.0 (2.6-3.4)
Suspect OAG	444	5.2 (4.7-5.7)	443	5.1 (4.6-5.6)
OHT & Suspect OAG	67	0.8 (0.6-1.0)	67	0.8 (0.6-1.0)
Suspect ACG	27	0.3 (0.2-0.4)	28	0.3 (0.2-0.4)
Secondary OHT/OAG suspect	2	0.02 (0-0.06)	4	0.1(0.03-0.2)
Subtotal glaucoma suspects	540	6.3 (5.8-6.8)	542	6.3 (5.8-6.8)
OHT	641	7.4 (6.8-8.0)	670	7.8 (7.2-8.4)
PAC	27	0.3 (0.2-0.4)	32	0.4 (0.3-0.5)
Narrow angles	36	0.4 (0.3-0.5)	34	0.4 (0.3-0.5)
Not recorded	23	0.3 (0.2-0.4)	26	0.3 (0.2-0.4)
Total	8623	100	8623	100

OAG open angle glaucoma; ACG angle closure glaucoma; OHT ocular hypertension; PAC primary angle closure

Table 6.4 Glaucoma diagnosis per person

Glaucoma diagnosis *	n	% (95% CI)
Normal	6,713	77.9 (77.0-78.8)
Glaucoma	363	4.2 (3.8-4.6)
HTG	157	1.8 (1.5-2.1)
NTG	157	1.8 (1.5-2.1)
PACG	29	0.3 (0.2-0.5)
Secondary glaucoma	20	0.2 (0.1-0.3)
Glaucoma suspect	607	7.0 (6.5-7.5)
Ocular hypertension	863	10.0 (9.4-10.6)
Narrow angles spectrum	54	0.6 (0.4-0.8)
Not recorded	23	0.3 (0.2-0.4)
Total	8623	100

* More severe diagnosis of either eye used, in the following order (most severe to least severe) - glaucoma, glaucoma suspect, ocular hypertension, narrow angles spectrum (primary angle closure, primary angle closure suspect), normal, diagnosis not recorded

Table 6.5 Glaucoma per person by age and sex

Age (yrs)	All Cause glaucoma				Primary open angle glaucoma			
	Men		Women		Men		Women	
	n	% of age group (95%CI)	n	% of age group (95%CI)	n	% of age group (95%CI)	n	% of age group (95%CI)
<55	1	0.8 (0.6-1.0)	1	0.5 (0.4-0.6)	1	0.8 (0.6-1.0)	1	0.5 (0.4-0.6)
55-60	4	1.5 (1.2-1.8)	5	1.0 (0.8-1.2)	4	1.5 (1.2-1.8)	5	1.0 (0.8-1.2)
60-65	20	2.3 (2.0-2.6)	19	1.5 (1.2-1.8)	16	1.8 (1.5-2.1)	15	1.2 (1.0-1.4)
65-70	34	4.3 (3.9-4.7)	22	2.2 (1.9-2.5)	27	3.4 (3.0-3.8)	21	2.1 (1.8-2.4)
70-75	50	6.6 (6.1-7.1)	42	5.0 (4.5-5.5)	44	5.8 (5.3-6.3)	31	3.7 (3.3-4.1)
75-80	43	7.2 (6.7-7.7)	30	4.9 (4.4-5.4)	39	6.6 (6.1-7.1)	26	4.3 (3.9-4.7)
80+	48	11.2 (10.5-11.9)	44	10.8 (10.1-11.5)	44	10.5 (9.9-11.1)	41	10.1 (9.5-10.7)
Total	200	5.2 (4.7-5.7)	163	3.4 (3.0-3.8)	175	4.5 (4.1-4.9)	140	3.0 (2.6-3.4)

Figure 6.1 Prevalence of primary open angle glaucoma by age and sex within the cohort
(error bars represent 95% CI)

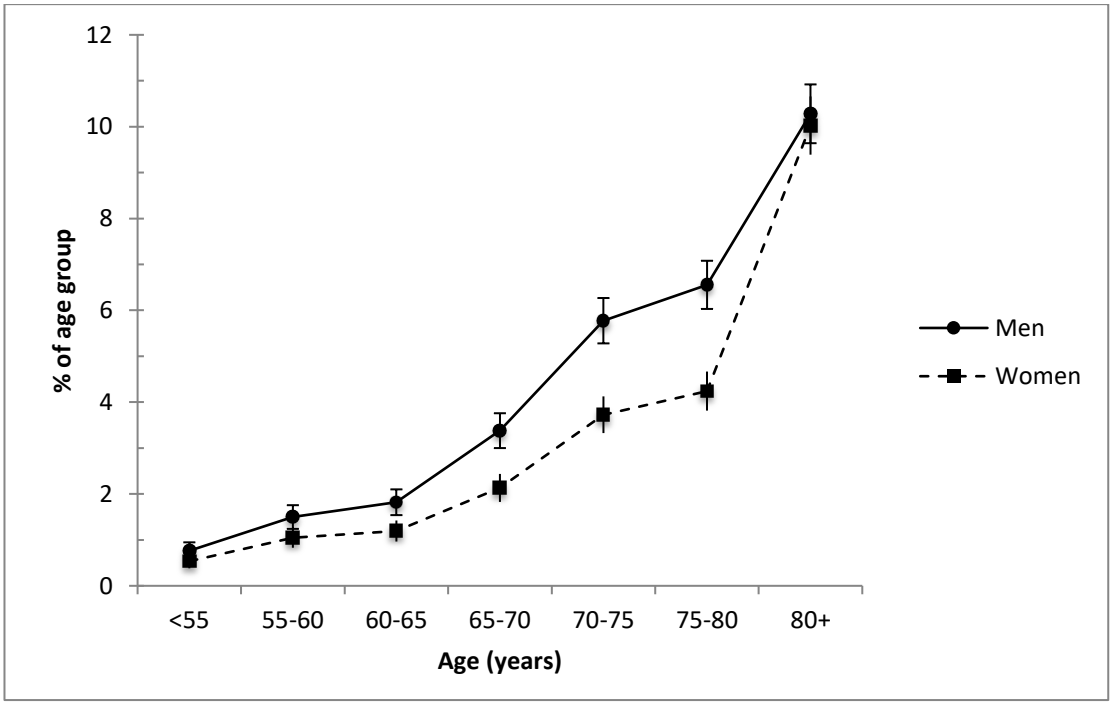


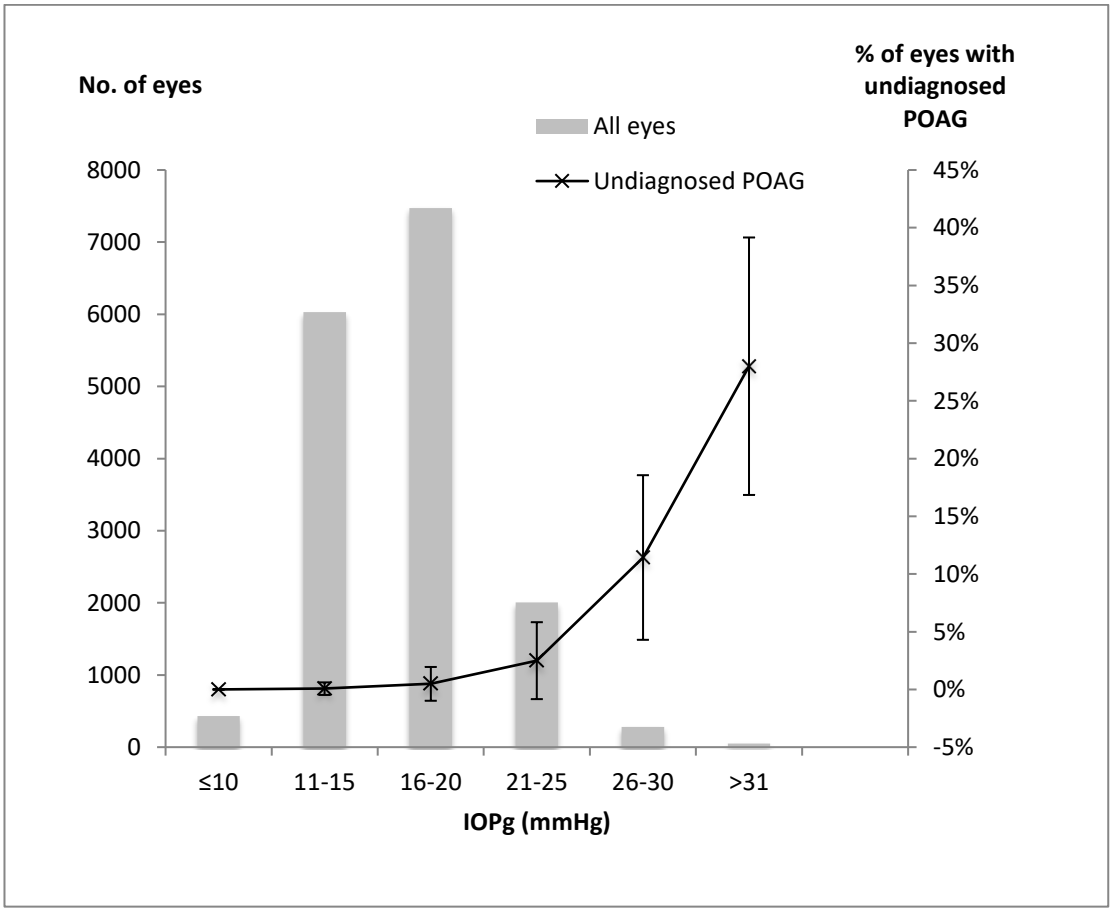
Table 6.6 Ocular characteristics of the 523 glaucomatous eyes

	n	% or median (IQR)
Laterality		
Right eye	265	50.7 %
Left eye	258	49.3%
On glaucoma drops?		
Yes	354	66.8%
No	176	33.4%
Lens status		
Phakic	382	73.0%
Pseudophakic	141	27.0%
IOPg (mmHg)	491	16.7 (13.8, 20.5)
IOPcc (mmHg)	464	19.0 (16.1, 22.3)
Corneal hysteresis (mmHg)	464	8.7 (7.7, 10.1)
Corneal resistance factor (mmHg)	464	9.7 (8.3, 11.0)
Central corneal thickness (μm)	439	545 (520, 568)
Axial length (mm)	470	23.8 (23.1, 24.6)
Cup/disc ratio (disc photo)	415	0.5 (0.4, 0.6)
<0.3	14	2.7%
≥0.3-0.49	168	32.1%
≥0.5-0.59	126	24.1%
≥0.6-0.69	61	11.7%
≥0.7-0.79	41	7.8%
≥0.8	5	1.0%
Disc photo ungradable for CDR	81	15.5%
No disc photo	27	5.2%
HVF Mean deviation (dB)	340	-3.3 (-5.9, -1.42)
HVF Glaucoma Hemifield Test		
Outside normal limits	265	50.7%
Borderline	31	5.9%
Borderline/ general reduction of sensitivity	5	1.0%
General reduction of sensitivity	6	1.2%
Abnormally high sensitivity	1	0.2%
Within normal limits	29	5.5%
Visual fields availability		
VF done in study	337	64.4%
VF done in NNUH	158	30.2%
VF not done – unable	28	5.4%
HRT Moorfields regression analysis global results	223	42.6%
Outside normal limits		
Borderline	113	21.6%
Within normal limits	122	23.3%
No HRT results	65	12.4%
GDx-VCC Nerve Fibre Indicator	491	34 (23, 49)
GDx-VCC TSNIT average thickness (μm)	491	50.2 (44.3, 55.6)

Table 6.7 Best corrected visual acuity of the 523 glaucomatous eyes

Best corrected visual acuity		n (%)
LogMAR	Snellen equivalent	
<0.3	>6/12	441(84.3%)
≥0.3 to <0.5	≤6/12 to >6/18	49 (9.4%)
≥0.5 to <0.8	≤6/18 to >6/36	8 (1.5%)
≥0.8 to <1.0	≤6/36 to >6/60	2 (0.4%)
≥1.0	≤6/60	22 (4.2%)
Visual acuity not available		1 (0.2%)
Total		523 (100%)

Figure 6.2 Prevalence of undiagnosed and untreated POAG increases with IOP level in the cohort
(error bars represent 95% CI)



6.4.3 Associations for Primary Open Angle Glaucoma

The logistic regression compared subjects with POAG in either eye (n=314) and the 8237 subjects who did not have glaucoma in either eye, although it included subjects who were glaucoma suspects, OHT, or had eyes in the narrow angle spectrum and healthy eyes. The 23 participants in the cohort who did not have a glaucoma diagnosis (see **Figure 6.2**) were excluded form the analysis. **Table 6.8** shows the univariable logistic regression results. The significant factors in the univariable regression were: older age, male sex, lower educational attainment, positive family history of glaucoma, pseudophakia in either eye, greater IOPg or IOPcc, lower CH or CRF, longer axial length and greater waist height ratio.

Table 6.9 shows the multivariable regression results. After adjusting for covariates, the factors significantly associated with POAG were: older age (OR 1.96-2.21/decade, p<0.0001), positive family history of glaucoma (OR 3.00-3.43, p<0.0001), higher IOPg (OR 1.08/mmHg, p<0.0001), higher IOPcc (OR 1.11/mmHg, p<0.0001), lower CH (OR 0.72/mmHg, p<0.0001), lower CRF (OR 0.86/mmHg, p<0.0001) and longer axial length (OR 1.28-1.32/mm, p<0.0001). Being pseudophakic was associated with OAG (OR 1.74-1.86, p<0.0001). Sex was no longer associated with POAG in the multivariable model after adjustment for axial length. The pseudo R^2 values were higher for models using CH (13.7%) and IOPcc (13.2%) then IOPg (12.1%) or CRF (11.6%).

The multivariable regression was repeated in **Table 6.10** by excluding subjects already on pressure-lowering treatment as sensitivity testing to limit bias towards CH and CRF (0=controls not on pressure lowering drops, 1=newly diagnosed POAG cases). The same factors remained significantly associated with POAG except CRF (OR 1.01, 95%CI 0.89-1.15), while the effects of CH was attenuated, as its pseudo R^2 (7.6%) now fell behind that of IOPcc (8.9%) and IOPg (8.4%), indicating that IOPcc and IOPg explained a greater proportion of the variance of POAG than CH. Being pseudophakia in either eye was also no longer significant in the sensitivity testing (OR 1.00, p-values 0.57-0.64), as a smaller proportion of newly diagnosed POAG cases were pseudophakic (15.0% of newly diagnosed POAG cases vs 29.9% of all POAG cases).

Table 6.8 Univariable logistic regression model of primary open-angle glaucoma subjects vs subjects without glaucoma in either eye
(0=No glaucoma 1= primary open-angle glaucoma) * Higher IOPg, IOPcc, axial length, and lower CH, CRF of either eye

Characteristics		**POAG** n=314	**No glaucoma** n=8234	**Odds ratio (95% CI)**	**p value**
		median (IQR) or %			
Age, years		74.4 (68.7-80.2)	67.8 (62.6-74.3)	1.09 (1.08,1.11)	<0.0001
Sex	Male	55.4%	44.3%	1.00	
	Female	44.6%	55.7%	0.64 (0.51, 0.80)	<0.0001
Social group					
Professional/ Managerial		50.0%	49.8%	1.00	
Skilled manual/Non-manual		36.3%	36.5%	1.00 (0.78,1.27)	0.98
Semi-skilled/ Unskilled		13.7%	13.7%	1.02 (0.72, 1.43)	0.92
Education level					
No formal qualifications		26.2%	30.3%	1.00	
O levels		12.0%	8.3%	0.60 (0.38,0.93)	0.02
A levels		44.0%	48.7%	0.96 (0.74, 1.24)	0.75
Degree		17.8%	12.7%	0.63 (0.43, 0.90)	0.01
Family history of glaucoma	No	68.8%	86.9%	1.00	
	Yes	31.2%	13.1%	3.02 (2.31,3.95)	<0.0001
* IOPg (mmHg)		17.6 (14.9-21.5)	16.7 (14.4-19.2)	1.09 (1.06, 1.12)	<0.0001
* IOPcc (mmHg)		20.1 (17.5-23.1)	17.8 (15.6-20.2)	1.14 (1.11, 1.16)	<0.0001
* CH (mmHg)		8.2 (7.9-9.4)	9.5 (8.4-10.5)	0.65 (0.60, 0.71)	<0.0001
* CRF (mmHg)		9.2 (7.7-10.5)	9.8 (8.7-10.9)	0.83 (0.77, 0.89)	<0.0001
* Axial length, mm		23.9 (23.2-24.8)	23.5 (22.9-24.3)	1.31 (1.21, 1.43)	<0.0001
Pseudophakia in either eye	No	70.1%	89.3%	1.00	
	Yes	29.9%	10.7%	3.54 (2.75, 4.55)	<0.0001
Diabetic	No	97.5%	95.9%	1.00	
	Yes	2.6%	4.1%	0.62 (0.30, 1.25)	0.18
Height, cm		167.8(160-173.6)	165.8 (159.6-173.0)	1.01 (0.99, 1.02)	0.30
Weight, kg		72.5 (64.6-83.6)	73.3 (64.3-83.2)	1.00 (0.99, 1.01)	0.84
Body mass index, kg/m^2		26.3 (23.9-28.9)	26.3 (24.0-29.1)	0.98 (0.96, 1.01)	0.197
Waist height ratio		0.91 (0.86-0.96)	0.90 (0.83-0.95)	23.4 (2.9, 51.0)	0.001
Systolic BP, mmHg		138.3(128.5-147.5)	136.0 (125.5-146.5)	1.01 (1.00, 1.01)	0.005
Diastolic BP, mmHg		77.5 (70.5-84)	77.5 (72-84)	1.00 (0.99, 1.01)	0.61

Table 6.9 Multivariable logistic regression models of primary open-angle glaucoma subjects (n=314) vs those without glaucoma in either eye (n=8234)

(0=No glaucoma 1= primary open-angle glaucoma)

	Model 1 with IOPg (n=6921)		**Model 2 with IOPcc** (n=6921)		**Model 3 with CH** (n=6921)		**Model 4 with CRF** (n=6921)	
	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p
Age, decade	2.21 (1.83, 2.67)	<0.0001	2.13 (1.76, 2.58)	<0.0001	1.96 (1.62,2.37)	<0.0001	2.07 (1.71, 2.50)	<0.0001
Sex Male	1.00		1.00		1.00		1.00	
Female	0.73 (0.51, 1.03)	0.07	0.76 (0.54,1.08)	0.13	0.83 (0.58,1.17)	0.28	0.75 (0.53,1.06)	0.11
Education level								
No qualifications	1.00		1.00		1.00		1.00	
O levels	0.76 (0.46, 1.27)	0.30	0.75 (0.45, 1.25)	0.27	0.76 (0.46, 1.28)	0.31	0.79 (0.47, 1.31)	0.36
A levels	1.08 (0.79, 1.48)	0.63	1.10 (0.80, 1.51)	0.57	1.11 (0.81, 1.53)	0.52	1.10 (0.80, 1.51)	0.56
Degree	0.64 (0.41, 1.00)	0.05	0.65 (0.41, 1.02)	0.06	0.67 (0.42, 1.04)	0.08	0.65 (0.41, 1.01)	0.06
Family history of glaucoma No	1.00		1.00		1.00		1.00	
Yes	3.10 (2.32,4.15)	<0.0001	3.00 (2.24,4.02)	<0.0001	3.20 (2.39, 4.29)	<0.0001	3.43 (2.56,4.58)	<0.0001
* ORA variable, mmHg	IOPg		IOPcc		CH		CRF	
	1.08 (1.05, 1.11)	<0.0001	1.11 (1.08,1.14)	<0.0001	0.72 (0.67, 0.79)	<0.0001	0.86 (0.80,0.93)	<0.0001
* Axial length, mm	1.30 (1.18, 1.43)	<0.0001	1.28 (1.16,1.41)	<0.0001	1.28 (1.16,1.41)	<0.0001	1.32 (1.20,1.46)	<0.0001
Pseudophakia in either eye No	1.00		1.00		1.00		1.00	
Yes	1.85 (1.32, 2.59)	<0.0001	1.86 (1.32, 2.61)	<0.0001	1.79 (1.28, 2.52)	<0.0001	1.74 (1.24, 2.44)	<0.0001
Waist height ratio	0.69 (0.08, 5.65)	0.73	0.76 (0.09 6.25)	0.80	0.84 (0.10, 6.94)	0.87	0.62 (0.08, 5.07)	0.66
Systolic BP, mmHg	1.00 (0.99, 1.00)	0.33	0.99 (0.99,1.00)	0.20	1.00 (0.99,1.01)	0.48	1.00 (0.99,1.01)	0.96
Pseudo R^2	12.1%		13.2%		13.7%		11.6%	

* Higher IOPg, IOPcc, axial length, lower CH, CRF, worse visual acuity of either eye.

Table 6.10 Multivariable logistic regression models of primary open-angle glaucoma subjects previously undiagnosed (n=107) vs those without glaucoma in either eye but not on pressure lowering treatment (n=8146)

(0=No glaucoma 1= primary open-angle glaucoma)

	Model 1 with IOPg (n=6696)		**Model 2 with IOPcc** (n=6696)		**Model 3 with CH** (n=6696)		**Model 4 with CRF** (n=6696)	
	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p
Age, decade	1.98 (1.47, 2.66)	<0.0001	1.90 (1.41, 2.56)	<0.0001	1.81 (1.35, 2.44)	<0.0001	1.96 (1.46, 2.64)	<0.0001
Sex Male	1.00		1.00		1.00		1.00	
Female	0.59 (0.34, 1.05)	0.07	0.62 (0.35,1.09)	0.10	0.64 (0.36,1.13)	0.12	0.58 (0.33,1.01)	0.06
Education level								
No qualifications	1.00		1.00		1.00		1.00	
O levels	0.71 (0.32, 1.56)	0.39	0.70 (0.32, 1.54)	0.37	0.75 (0.34, 1.64)	0.47	0.75 (0.34, 1.64)	0.48
A levels	0.91 (0.55, 1.51)	0.72	1.92 (0.56, 1.53)	0.76	0.95 (0.58, 1.58)	0.86	0.94 (0.57, 1.55)	0.81
Degree	0.51 (0.25, 1.07)	0.08	0.52 (0.25, 1.08)	0.08	0.54 (0.26, 1.12)	0.10	0.52 (0.25, 1.09)	0.08
Family history of glaucoma No	1.00		1.00		1.00		1.00	
Yes	2.04 (1.22, 3.39)	0.01	2.03 (1.22, 3.38)	0.01	2.25 (1.36, 3.72)	<0.0001	2.33 (1.41,3.85)	<0.0001
* ORA variable,	IOPg		IOPcc		CH		CRF	
mmHg	1.11 (1.06, 1.16)	<0.0001	1.11 (1.07,1.16)	<0.0001	0.81 (0.71, 0.92)	<0.0001	1.01 (0.89, 1.15)	0.89
* Axial length, mm	1.36 (1.17, 1.58)	<0.0001	1.35 (1.16,1.57)	<0.0001	1.37 (1.18,1.59)	<0.0001	1.41 (1.21,1.63)	<0.0001
Pseudophakia in either eye No	1.00		1.00		1.00		1.00	
Yes	0.84 (0.43, 1.64)	0.62	0.85 (0.44,1.66)	0.64	0.83 (0.42, 1.61)	0.58	0.83 (0.43, 1.60)	0.57
Waist height ratio	0.67 (0.02, 20.6)	0.82	0.71 (0.02, 21.8)	0.84	0.73 (0.02, 22.6)	0.86	0.56 (0.02, 17.1)	0.74
Systolic BP, mmHg	1.00 (0.99, 1.02)	0.64	1.00 (0.99,1.02)	0.70	1.01 (0.99,1.02)	0.38	1.01 (0.99,1.02)	0.31
Pseudo R^2	8.4%		8.9%		7.6%		6.6%	

* Higher IOPg, IOPcc, axial length, lower CH, CRF, worse visual acuity of either eye.

6.4.4 Associations of Previously Undiagnosed Primary Open Angle Glaucoma

Among the 314 POAG cases, 207 (65.9%) were known cases and 107 (34.1%) were previously undiagnosed. The mean age of the 314 participants were 74.2 years, (range 49-90 years) and 45% were female. **Table 6.11** shows the univariable logistic regression results comparing known POAG to previously undiagnosed POAG cases (0=known POAG, 1=previously undiagnosed POAG). The factors associated with previously undiagnosed POAG in the univariable regression were: younger age, higher social class (professional/ managerial vs skilled manual/non-manual occupation), being currently employed, having NTG rather than HTG, lower pre-treatment IOP, lower CDR, negative family history of glaucoma, reporting no problems with eyesight, being phakic rather than pseudophakic in either eye, and higher absolute refractive error.

In the final multivariable model (**Table 6.12**), subjects with newly diagnosed POAG compared to those with a known diagnosis were more likely to have: NTG rather than HTG (OR 8.05, 95%CI 2.19-29.6, p=0.002), a lower pre-treatment IOP (OR 0.78/mmHg, 95%CI 0.69-0.89, p<0.0001), a smaller CDR (OR 0.54 per 0.1CDR, 95%CI 0.31-0.93, p=0.03), and to have reported no problems with their eyesight (OR 0.02, 95%CI 0.01-0.08, p<0.0001).

Table 6.11 Univariable logistic regression of previously diagnosed vs previously undiagnosed primary open angle glaucoma
(0=diagnosed 1=undiagnosed)

Characteristics median (IQR) or %		**Previously diagnosed (n=207)**	**Previously Undiagnosed (n=107)**	**Odds Ratio (95% CI)**	**p value**
Age, years		72.8 (67.0-78.4)	75.4 (70.3-81.0)	0.96 (0.93,0.99)	0.008
Sex	Male	52.2%	61.7%	1.00	
	Female	47.8%	38.3%	0.68 (0.42,1.09)	0.15
Social class	Professional/Managerial	48.3%	53.3%	1.00	
	Skilled (manual/non manual)	41.6%	25.7%	0.57 (0.33,0.98)	0.04
	Semi-skilled/ Unskilled	10.1%	21.0%	1.84 (0.93,3.63)	0.08
Education	No qualifications	30.4%	29.9%	1.00	
	O levels	7.3%	10.3%	1.44 (0.59,3.50)	0.42
	A levels	48.8%	48.6%	1.01 (0.59,1.74)	0.96
	Degree	13.5%	11.2%	0.84 (0.38, 1.88)	0.68
Currently employed?	No	89.3%	79.8%	1.00	
	Yes	10.7%	20.2%	2.12 (1.10,4.06)	0.02
How often do you not have enough money for basics?	Never	63.9%	65.7%	1.00	
	Seldom/Sometimes	36.1%	34.3%	0.93 (0.56, 1.54)	0.77
OAG type	HTG	69.1%	15.9%	1.00	
	NTG	30.9%	84.1%	11.8 (6.52,21.5)	<0.0001

HTG=High tension glaucoma; NTG Normal tension glaucoma

(continue) Table 6.11

Characteristics median (IQR) or %		**Previously diagnosed**	**Previously Undiagnosed**	**Odds Ratio (95% CI)**	**p value**
* IOPg (mmHg)		19.3 (15.5-22.0)	17.2 (14.7, 20.7)	1.03 (0.99,1.08)	0.18
* Pre-treatment IOP (mmHg)		24.0 (20.6, 28.0)	19.3 (15.5,22.0)	0.82 (0.77, 0.86)	<0.0001
* Axial length (mm)		23.9 (23.2, 25.1)	23.9 (23.1, 24.8)	1.12 (0.94,1.34)	0.21
Worse LogMAR visual acuity of either eye		0.08 (0.0- 0.26)	0.14 (0.02, 0.30)	0.86 (0.39, 1.89)	0.70
* Disc photo CDR x10		5.0 (4.4, 5.7)	5.5 (4.7, 6.4)	0.74 (0.58, 0.94)	0.02
CDR asymmetry x10		0.6 (0.2,1.1)	0.7 (0.4, 1.1)	0.74 (0.48, 1.15)	0.19
Family history of glaucoma	No	64.0%	77.7%	1.00	
	Yes	36.0%	22.3%	0.51 (0.29, 0.91)	0.02
Wears glasses/ contact lenses?	No	2.5%	0.96%	1.00	
	Yes	97.6%	99.0%	2.59 (0.30, 22.4)	0.39
Do you have any problems with eyesight?	No	11.5%	75.5%	1.00	
	Yes	88.5%	24.5%	0.04 (0.02, 0.08)	<0.0001
Pseudophakic in either eye	No	62.3%	85.1%	1.00	
	Yes	37.7%	15.0%	0.29 (0.16, 0.53)	<0.0001
* Absolute refractive error (D)		1.81(0.75, 2.63)	1.25 (0.63, 2.25)	1.16 (1.01, 1.33)	0.03
Self reported health status	Excellent/very good	37.4%	33.0%	1.00	
	Good	44.2%	47.2%	1.21 (0.71, 2.05)	0.48
	Fair	16.5%	15.1%	1.04 (0.51, 2.12)	0.93
	Poor	1.9%	4.7%	2.75 (0.70, 10.9)	0.15

* higher value of either eye. IOPg Goldmann-correlated IOP

Table 6.12 Multivariable regression of previously diagnosed vs previously undiagnosed primary open angle glaucoma
(0=diagnosed 1=undiagnosed)

Characteristics		**Odds Ratio (95% CI)**	**p value**
Age, years		0.98 (0.90, 1.06)	0.55
Social class	Professional/ Managerial	1.00	
	Skilled (manual/ non-manual)	0.50 (0.15,1.70)	0.27
	Semiskilled/unskilled	4.25 (0.94,19.3)	0.06
Currently employed?	No	1.00	
	Yes	0.87 (0.15, 4.94)	0.88
OAG type	HTG=0	1.00	
	NTG=1	8.05 (2.19, 29.6)	0.002
* Pre-treatment IOP (mmHg)		0.78 (0.69, 0.89)	<0.0001
* Disc photo CDR x10		0.54 (0.31,0.93)	0.03
Family history of glaucoma	No	1.00	
	Yes	0.56 (0.16, 1.93)	0.36
Do you have any problems	No	1.00	
with eyesight?	Yes	0.02 (0.01, 0.08)	<0.0001
Pseudophakia in either eye	No	1.00	
	Yes	0.47 (0.12, 1.80)	0.27
* Absolute refractive error (D)		1.18 (0.90, 1.55)	0.24

* higher value of either eye

6.5 Discussion

6.5.1 Glaucoma Diagnosis and Comparison with Other Studies

Glaucoma prevalence data have been reported from populations in the US,[14,95] Australia,[90,305] Europe [16,91,159] and South East Asia.[20,151,306,307] However, recent data from the UK is lacking. The last published cross-sectional population glaucoma survey was one from a rural West of Ireland in 1993 [17], and a survey from north London in 1998. [94] EPIC-Norfolk provides the most up-to-date reporting on glaucoma frequency and characteristics in a UK population. There are fundamental differences between the EPIC-Norfolk participants and the local population of Norfolk, as the study participants were not sampled systematically, but recruited by inviting all adults aged >40 from GP practices. The response rate was also low, with 46% of the invited subjects undergoing an eye examination, compared to other ophthalmic epidemiological surveys which report response rate of around 80%.[16,90,148,288] Apart from differences in age and sex composition, EPIC-Norfolk participants were likely to be less deprived and were potentially healthier due to the volunteer nature of the study. The glaucoma cases derived from the cohort therefore may not be representative of the local or national population, likely being less afflicted by disease, and possibly having a different pattern of disease than the broader UK population.

Nevertheless, results in this study are consistent with many established trends in glaucoma epidemiology. Our predominant glaucoma type was POAG, a consistent finding among European populations.[9,311] The prevalence of POAG in the study increased with age and IOP. The frequency of all cause glaucoma in the cohort was 4.2%, and 3.7% for POAG. This echoed findings from a meta-analysis in 2014, whereby the prevalence of glaucoma (POAG and PACG) for Europeans aged 40-80 years was 2.93%(95%CI 1.85-4.40%), and the prevalence of POAG was 2.51% (95% CI 1.54-3.89%).[9] In another meta-analysis published in 2006, the pooled prevalence of POAG for white population was of 2.1% (95%CI 1.6-2.7).[18] The EPIC cohort is older than many study cohorts, and hence the higher prevalence is not surprising.

Among those who were undiagnosed and not on treatment, our study found that 84% had NTG. This percentage is higher than expected for a mainly Caucasian population. Rotterdam Study reported 39% of their undiagnosed OAG as having IOP <21mmHg,[16] and Thessaloniki Eye Study reported 59%.[159] In fact, our figure is comparable to studies of Asian populations, where proportion of NTG is known to be higher (Singapore Malay Eye Study 86.4%,[307] Tajimi Study 95%[20]). This is probably due to the

fact that our study population is not representative of the UK general population. Comparison of prevalence figures derived from this study may not be appropriate.

We found 66% of POAG cases in the cohort to be previously diagnosed. This was higher than surveys of mainly Caucasian populations, which reported figures of 49% in the Blue Mountain Eye Study,[90] 40% in Melbourne's Visual Impairment Study, 49.5% in the Thessaloniki Eye Study,[159] 47% in the Rotterdam Eye Study,[16] and 50% among the white subjects in the Baltimore Eye Survey.[154] Glaucoma is detected by opportunistic case finding in the UK and relies on patients presenting to an eye care professional, usually a community optometrist, and then referred to ophthalmologists for definitive diagnosis and management. The higher rate of previously known glaucoma found in this study could reflect either better health care access among the study participants due to recruitment bias, or perhaps a generally more effective health care provision in Norfolk. However, one cannot discount the possibility that some participants who are known glaucoma patients were motivated to take part by an enthusiasm to have additional eye testing, causing response bias.

A striking finding in the study was the large number of glaucoma suspects (7%) and ocular hypertensives (10%). Collectively they represent a large number of potential referrals to the Hospital Eye Services (HES), many of whom will remain under observation for up to 5 years.[161] This is reflected on the existing burden to the HES, whereby ocular hypertension accounts for 30-45% of the referrals it receives.[284,285] Coupled with the fact that glaucoma is a chronic disease that needs regular and long-term follow-up, it is no wonder that glaucoma and glaucoma suspect account for the sixth largest share of NHS outpatient attendances.[97]

6.5.2 Sources of Under-Reporting of Glaucoma

There were several sources of under-reporting for glaucoma diagnosis in this study. Only 18% of study subjects had visual field done, and a lack of routine field test in a population study had been shown in a meta-analysis as a study design factor that led to under-diagnosis.[10] According to the Ocular Hypertension Treatment Study, a randomized controlled trial comparing observation vs treatment with anti-hypertensive drops in preventing POAG conversion among ocular hypertensives, 30-40% of subjects who converted did so by reaching the study's visual field end point before optic disc end points.[23] However, in our study, both disc and field abnormalities were the pre-requisite of glaucoma diagnosis, which is a well-established definition used in most population cross sectional studies.[16,19,95,151,154,155] An exhaustive refinement

process had been undertaken to uncover glaucomatous discs among those whose initial screening examination did not generate sufficient abnormal results to meet the referral criteria for a definitive exam. In a small number of participants deemed high risk for glaucoma, HRT and GDX reflectance images were used as a substitute for disc photos to allow the examiner to gain an impression whether the disc was glaucomatous or not, and this could lead to error in diagnosis. For those in whom no substitutes for disc photos were available, we expect a small number of cases of glaucoma to have been missed. The number of narrow angle spectrum phenotypes (e.g. primary angle closure, primary angle closure suspects) are also likely to be underestimated as gonioscopy or anterior chamber depth assessment on slitlamp were not part of the screening test, although those with PACG should not have been missed, as they would have been detected from their disc and field abnormalities, and received a full slitlamp examination including anterior angle assessment.

6.5.3. Associations of Primary Open Angle Glaucoma

The risk factors for POAG have been widely examined in many publications. The present analysis confirmed some well-established associations: older age, greater axial length, increasing IOP and a positive family history of glaucoma. Out of the ORA variables, IOPg, IOPcc and CH were strongly associated with POAG, but not CRF.

IOP and biomechanics in POAG

The association of POAG with GAT IOP is supported by a large body of evidence that established its role as the major modifiable risk factor of OAG. In population studies, glaucoma prevalence increases with IOP,[14,19,20] a finding echoed by this study. In longitudinal population cohorts,[312] [22] higher IOP was a risk factor for incidence and progression of POAG. In therapeutic trials, lowering IOP among ocular hypertensives reduced the risk of OAG development (albeit by a modest amount, and within the IOP range 24-32mmHg)[23,26] and lowering IOP in established glaucoma cases slowed down visual field progression.[24] [25] [26] None of these studies, however, used ORA IOP metrics. Ours is the first population-based study that demonstrated an association of POAG with IOPg and IOPcc.

Our finding that IOPcc explained a greater degree of variance in POAG than IOPg indicates the potential usefulness of IOPcc over IOPg or possibly even GAT IOP, a hypothesis that has been supported by other non-population based studies. In patients with asymmetric OAG severity, the worse eye was associated with higher IOPg, IOPcc, lower CH and CRF, but no difference in GAT IOP and CCT.[313] In another study of NTG

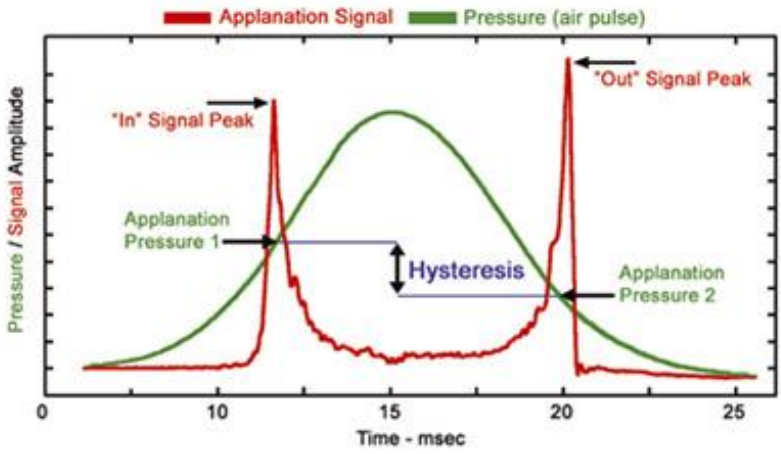
patients, higher IOPcc, lower CH, and larger difference between IOPcc and GAT IOP predicted more rapid VF deterioration, indicating that GAT IOP underestimated the "true" IOP.[314] In the UK Biobank study, a large-scale cohort study of over 110,000 participants with IOPcc and IOPg data, the two measurements showed different directions of associations with certain biological parameters, such as height, diabetes, smoking and ethnicity, indicating that they plausibly reflect different biological features.[39]

CH was found to be significantly associated with POAG. Hysteresis is hypothesised to reflect the collagen properties and in particular the lamina cribrosa and peripapillary sclera, and the susceptibility of the ONH to IOP stresses. The importance of CH in POAG has been emerging for some years. Lower CH was associated with structural parameters of HRT and GDx-VCC (in a publication based on our present EPIC-Norfolk data)[40] and OCT disc parameters.[35] Low CH was also found to be associated with a greater rate of visual field progression in three separate longitudinal studies of glaucoma patients.[41-43] Lower CH has been linked to other types of glaucoma such as primary angle closure glaucoma,[315] congenital,[316,317] and pseudoexfoliative glaucoma.[318] Treatment with prostaglandin analogue has been shown to increase CH independent of its effect on IOP lowering.[319]

It is not entirely clear how the four ORA metrics are related. IOPg is an average of applanation pressure 1 (P1) and applanation pressure 2 (P2), while IOPcc is derived by modelling P1 and P2 to limit the difference before and after LASIK surgery and has, therefore, limited influence from corneal biomechanics. CH is derived as the difference between P1 and P2.[320] CRF is defined as P1-kP2, whereby k is a constant that is determined in an analysis of the relationship between P1, P2 and CCT. CRF therefore is a measure relatively unaffected by IOP and is more strongly associated with CCT than CH.[168] It would have been useful to have CCT measurements in the present study to further understand the relationship between OAG and the ORA metrics, and to answer the question whether CCT was truly an independent risk factor of glaucoma. However, CCT was only measured in at risk subjects and so the rate of missing data was very high among non-glaucoma subjects and thus not included in the analysis.

The fact that IOPcc and CH explained the greatest degree of variance of OAG could imply that these two metrics have the potential to become useful in the management of glaucoma, such as risk stratification or even monitoring of treatment and disease progression.

Figure 6.3 Ocular Response Analyzer applanation signal and pressure waveform
(reproduced from www.reichert.com)



Age

Older age has been shown by population surveys in Baltimore,[14] Melbourne,[15] west of Ireland,[17] and Rotterdam[16] as a risk factor for POAG. A meta-analysis of all surveys published between 1966-2014 showed that for each decade increase in age, the odds ratio of developing OAG was 1.99 in white populations,[10] which was similar to our finding of OR of 1.96-2.21 per decade of age.

Sex

Sex was not shown to be associated with POAG in our study, although several meta-analysis have shown men to be 1.30 to 1.37 times more likely than women to have OAG after adjusting for age, race, and study design.[9,10,18] In the univariable analysis, male gender was significantly associated with OAG, but the association between male sex and POAG became insignificant after adjusting for axial length. The mean axial length of men is longer than women in this study (T-test, $p<0.0001$), with a mean difference of 0.55mm (95%CI 0.50-0.60). This suggests that the observed higher risk of POAG among men in other studies could be due to men having longer axial length, a major risk factor of POAG. This is the first study to suggest that axial length explains the sex differential in POAG.

Family history

Family history of glaucoma was a strong risk factor in the present study, increasing the odds of having POAG by 2-3 folds. Family history was ascertained as any self-reported history of glaucoma among any blood relative, irrespective of whether they were first or

second degree relatives. The history was not confirmed by hospital records nor by clinical examination of the relatives and, therefore, could be inaccurate. Nevertheless, our findings are in agreement with results from the Baltimore Eye Survey, which ascertained family history of glaucoma by interviewing the relatives and showed that the age-adjusted risk of OAG was highest in siblings (OR 3.69), then parents (OR 2.17), and lastly children (OR 1.12).[55]

Myopia

Myopia is a well-established risk factor for POAG. The proportion of POAG among myopes has been shown to be consistently higher than for non-myopes in cross-sectional studies after adjusting for age and sex,[44-46] and myopia has been found to be related to higher baseline IOP.[45] The pooled relative risk of OAG among myopes compared to non-myopes has been estimated to be 1.88.[12] The Beijing Eye Study found a gradient in the relationship, since high myopia (≤ 6D) was associated with a higher frequency of glaucoma than moderate and low myopia.[44] The OHTS study, however, did not find that myopia as a baseline risk factor predicted OAG, when myopia was defined as a refractive error <-1D. In this study, we used axial length rather than refractive error as a continuous variable for myopia to avoid the irrelevance of refractive error among pseudophakic patients. We found that for every 1mm increase in axial length, the odds of having POAG increased by 1.35-1.41 fold.

6.5.4 Associations of Previously Undiagnosed Primary Open Angle Glaucoma

Among the social, economic and ocular factors examined, the only ones associated with undiagnosed POAG were: having NTG rather than HTG, lower pre-treatment IOP, smaller CDR, and reporting no eyesight problems. NTG was the risk factor with the greatest effect, and was associated with an 8-fold increase in odds ratio. With the additional finding that IOP was lower among undiagnosed POAG cases, this points to an over-reliance on IOP level to exclude glaucoma. IOP has been shown to be an ineffective tool for glaucoma case finding in the EPIC-Norfolk Eye Study, and no single IOP level provides both high sensitivity and specificity in glaucoma diagnosis.[2] This should serve as an important learning point for all ophthalmic clinicians to avoid missed glaucoma cases.

The smaller the vertical CDR on disc photography, the more likely the POAG to be undiagnosed. This supports the notion that less severe disease was more easily missed. In addition, CDR does not adequately capture features of a glaucomatous

disc, and other features such as focal rim loss, nerve fibre layer defects, and disc haemorrhages could be overlooked. These features may also be difficult to spot unless the pupil is dilated, which may not happen on a routine eye test.

Several factors were examined that could reflect a participant's access or likelihood to seek eye care. The only significant factor associated with undiagnosed POAG was answering no to the question "do you have problems with your eyesight", while worse acuity of either eye was not related. This indicates that it was the self-perception of good eyesight, and by implication, a lesser likelihood to visit an optometrist, rather than actual visual function, that led the POAG to be undiagnosed. Nevertheless, the participants with existing glaucoma might have perceived their eyesight as being worse than those with undiagnosed glaucoma, as they had a known eye condition, or the use of eyedrops or having had eye surgery diminished their visual function. Wearing glasses or contact lenses was not a significant factor, most likely because 98% of the cohort wore glasses, and it was not effective in discriminating those with previously diagnosed and undiagnosed POAG.

One question that has been explored in published studies was whether visits to eye care professionals is important in facilitating the discovery of glaucoma. Late presentation of glaucoma with advanced field defect has been known to be associated with the number of years since last optometrist visit.[71] The Thessaloniki Study found that previously undiagnosed patients were more likely to not have seen an eye doctor in the past year.[309] Similarly both the Barbados Eye Study[308] and the Melbourne Visual Impairment Project [310] showed previously undiagnosed patients sought eye care less frequently in the past year, with the source of eye care more likely to be an optometrist rather than an ophthalmologist.[308,310] However, these findings are potentially confounded by the fact that diagnosed glaucoma patients would already be under the care of an ophthalmologist, so a prospective study is required to adequately answer that question. Currently in the UK, POAG is diagnosed by opportunistic case finding, relying on patients presenting to an optometrist for an eye test, and referral made to the Hospital Eye Service under the National Health Service if glaucoma is suspected. Those most at risk of glaucoma –aged 60 and those aged >40 with a positive family history of glaucoma in a first degree relative – can get the optician's eye test for free, and so there is no financial barrier to the diagnosis of glaucoma among those at risk. In EPIC-Norfolk, 67% of all glaucoma cases were previously diagnosed, which is higher than the 50% reported in most Western population studies. However, our findings that patients with self-reported good eyesight were more likely to have undiagnosed POAG supports the need to improve the public's awareness of glaucoma, that it is an

asymptomatic but potentially blinding condition, in order to improve their likelihood of being tested for the condition.

An ancillary finding in this study of methodological importance was the pre-treatment/ current study IOP ratio. Among eyes which were on pressure-lowering treatment, the ratio of pre-treatment IOP/ current IOP was found to be 0.744, indicating a general IOP reduction by approximately 26% with glaucoma treatment – both surgical and medical - on a population level. This is comparable to a meta-analysis on the pressure-lowering effects of single agent topical medications in clinical trials, which reported a mean reduction of 23-33%. [321] This has been adopted by genome-wide association studies as an average 30% reduction, and was used empirically to impute missing pre-treatment IOP by dividing the study IOP by 0.7.[61,322,323] Our results are useful in validating this method of imputing IOP on a population level, whereby the precise glaucoma treatment is much less well defined than clinical trials.

In conclusion, the most important healthcare implication from this analysis is the need for eye care professionals to focus on careful assessing the optic disc, and avoid being falsely reassured by a lower level of IOP in glaucoma case finding. There is also a suggestion that raising public awareness of glaucoma can help reduce undiagnosed glaucoma.

6.6 Conclusion

The EPIC-Norfolk Eye Study is the largest and most up to date glaucoma survey in the UK. This chapter presented the key analyses of this thesis. It included the glaucoma diagnosis of the study participants, the demographics, ocular and systemic factors associated with POAG, and the risk factors that might explain why POAG could be undiagnosed in some participants.

While many findings were consistent with other published studies, we found a higher prevalence of NTG among than other Caucasian studies, and a higher proportion previously diagnosed glaucoma patients. This reflects how our study population is different from the UK general population, and direct comparisons or inference of prevalence figures will not be appropriate.

The factors found to be associated with POAG were older age, greater axial length, increasing IOP and a positive family history of glaucoma. Out of the ORA variables,

IOPg, IOPcc and CH were strongly associated with POAG. CH and IOPcc hold promise as useful parameters in glaucoma management.

Among the risk factors for previously undiagnosed POAG, having NTG rather than HTG was the strongest predictor. Lower pre-treatment IOP, smaller CDR, and reporting no eyesight problems were also related to undiagnosed glaucoma. Collectively these factors point towards an over-reliance on IOP in glaucoma case finding, and that less abnormal looking optic discs in glaucoma, and perhaps a lack of awareness of glaucoma can lead to the disease being missed.

CHAPTER 7: REDEFINING THE INTRAOCULAR PRESSURE REFERRAL THRESHOLD

7.1 Background

Elevated intraocular pressure (IOP) is the most significant risk factor for OAG development [21,324] and progression [325], and it is the only risk factor that is modifiable.[25,34] There has long been controversy over the clinical convention of an IOP criterion of > 21mmHg used to define ocular hypertension (OHT), indicating an increased risk of glaucoma,[27] even though around 50% of glaucoma cases present in the "normal" range of <21mmHg.[326] The figure of 21mmHg corresponds to two standard deviations (SD) above a population's mean IOP. It was originally reported in a Welsh survey using Goldmann applanation tonometry (GAT) in 1966.[28] It was the non-glaucomatous populations' mean IOP ± two SDs (10-21mmHg). Measurements below 21mmHg therefore encompass 97.5% of the populations' values, assuming the IOP distribution to be Gaussian. As such, "ocular hypertension", which is currently defined as IOP >21mmHg without signs of glaucoma, represents an IOP above the statistical upper limit of the population's distribution, rather than a true threshold for OAG risk. Nevertheless, the use of IOP>21mmHg for referrals to exclude glaucoma has become a deeply entrenched practice, accounting for 30-45% of all referrals made to the hospital eye service in the UK,[284,285] while glaucoma and glaucoma suspects account for the sixth largest share of NHS outpatient attendances in England, after general medical examination, breast cancer, schizophrenia, prostate cancer and joint pain.[97]

It is questionable whether this OHT threshold value is relevant in modern case-finding practice, especially when referral decisions from community optometrists to the Hospital Eye Service (HES) are made on non-contact tonometry (NCT) measurements.[164] In addition, the population distribution of IOP and the corresponding mean plus two SD criterion vary with geography and ethnicity.[14,159,327] In the UK, central to the debate is the official guideline issued by the Royal College of Ophthalmologists to community optometrists in 2010, recommending the referral of any patient with an IOP>21mmHg, without any additional risk factors.[328] Goldmann applanation tonometry (GAT) was the recommended choice of tonometer since it offers greater accuracy, but if non-contact tonometry (NCT) measurements were used, the recommendations specified that an average of four readings should be taken. The recommendations

resulted in a surge of referrals to the by over a third [329] without any increase in the absolute numbers of glaucoma or glaucoma suspects diagnosed.[286]

For these reasons, there is a need to re-examine the population's upper limit of IOP distribution. In this chapter, the mean+2SD and the 97.5th centile value for IOP measured with the ORA, which is an NCT, will be determined among non-glaucomatous participants. The effect of varying IOP referral thresholds on the potential referable numbers to the HES, and the effects on missed glaucoma diagnosis at different IOP thresholds will be explored.

7.2 Aims

1. To replicate the OHT threshold in the EPIC-Norfolk cohort by defining the mean IOP + two SDs and the 97.5th centile values by age and sex, among participants who did not use ocular hypertensive drops or had glaucoma in either eye.

2. To examine the effect on projected numbers of referable cases to the Hospital Eye Service in England and Wales if the IOP referral thresholds (highest from either eye) were altered.

3. To estimate the effects on missed glaucoma diagnosis if the OHT thresholds were changed.

4. To assess the diagnostic performance of IOP alone in differentiating between glaucoma and non-glaucoma eyes.

7.3 Methods

All participants had three IOP measurements for each eye made. The first 544 participants had it measured with the AT555 NCT, and all subsequent participants had IOP measured with the Ocular Response Analyzer NCT (ORA; Reichert Corporation; Philadelphia) with software version 3.01 as it became available in the study. Three IOP measurements were taken successively. For ORA measurements the mean IOPg and the single IOPg measurement with the highest waveform score (best signal value) were obtained. The IOP referral thresholds were obtained using the the higher IOP of either eye to reflect normal clinical practice. Projected numbers of referable cases were based on 2014 population estimates for England and Wales.[330]

Area under curve (AUC) for IOP performance

The performance of IOP in differentiating glaucoma and non-glaucomatous eyes was examined using area under receiver operator characteristic curves (AUC). For subjects who have had glaucoma treatment, their pre-treatment IOP was used, which is defined as the highest IOP (GAT) documented in the patient's NNUH records before any IOP-lowering treatment (drops or surgery) was instigated. For those who have had IOP-lowering treatment but the pre-treatment IOP was unavailable (180 right eyes, 172 left eyes), the pre-treatment IOP was imputed by dividing the current study IOPg by 0.744 (see Chapter 6, Methods 6.3.2).

7.4 Results

7.4.1 Study Participants and Defining the Study's OHT thresholds

Out of 8623 participants in the cohort, 8,343 had IOP measured (7,958 with ORA, 443 with AT555 NCT), 243 used ocular hypotensive eyedrops in either eye, and 363 had glaucoma in either eye. Among the participants who had ORA IOP measured and did not use ocular hypotensive eyedrops or have glaucoma in either eye (n=7544), their mean age was 68.4 years (range 48-92 years), 56.1% of participants were female and 99.7% were white. Compared to the 1966 Rhondda Valley Welsh population and the 2014 England and Wales population estimates, the study population was older (**Table 7.1, Figure 7.1**).

Figure 7.2 shows the distribution of ORA-IOPg in right eyes. IOPg (mean of three values, right eye) followed an approximately Gaussian distribution, with a right skew and an exaggerated peak (skewness 0.70, kurtosis 4.5). The mean IOP was 16.2mmHg (95% CI 16.1-16.3mmHg, SD 3.8mmHg). Two SDs above the cohort's mean IOP was 23.9mmHg. Even after using different IOP metrics and regardless of the laterality of the eye, the mean+2SD remained at approximately 24mmHg, higher than the current "historical" threshold of 21mmHg (**Table 7.2**). Among the 424 normal study subjects who had tonometry with the AT555, the mean +2SD was 21.5-21.6mmHg. Since the IOP distribution was skewed, the 97.5th centile provides a more appropriate estimate of the upper limit of the IOP distribution. This measured 24.1-24.6mmHg with ORA-IOPg, and 22.7-23.4mmHg with the AT555 NCT (**Table 7.2**). For each five-year age group and for both men and women, the mean +2SD IOP value consistently measured above 21mmHg (**Figure 7.3**), ranging between 22.8-24.6mmHg in men and 22.6-24.3mmHg in women.

Table 7.1. Comparison of study demographics: EPIC-Norfolk Eye Study, 1966 Rhondda Valley Wales Study and the 2014 population estimates of England and Wales

	EPIC-Norfolk Eye Study	1966 Rhondda Valley, Wales	2014 England & Wales (age 45+)
n	7544	4091	24,702,316
% female	56.1	n/a	52.1
Age range, yrs	48-92	40-74	>45
Mean age (men), yrs	69.1	55.1	61.7
Mean age (women), yrs	67.8	55.6	63.1

Figure 7.1 Age and sex distribution for the participants in the EPIC-Norfolk Eye Study and the 1966 Rhondda Valley Study

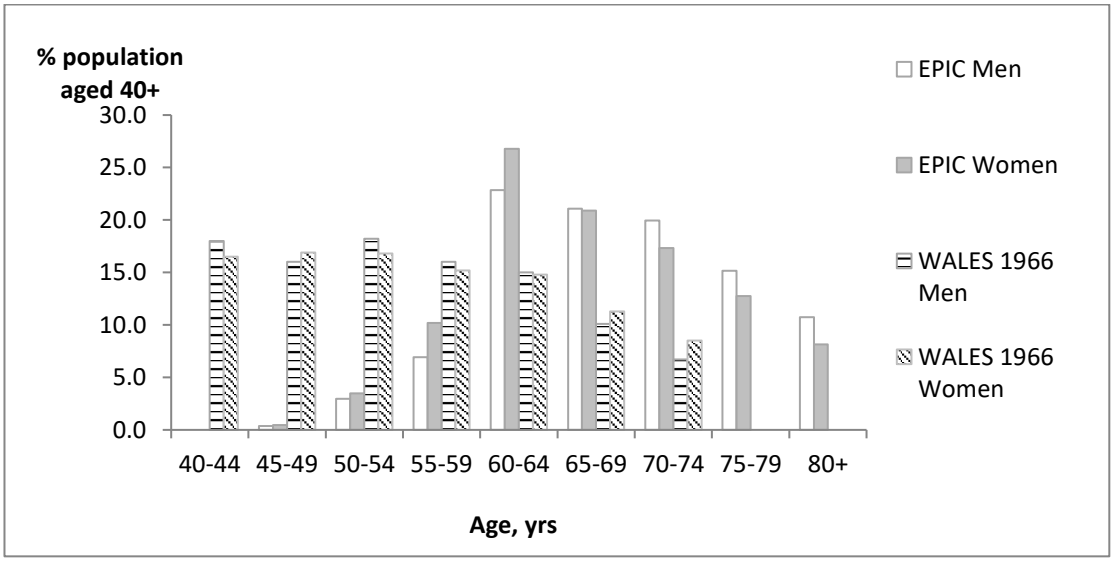


Figure 7.2 Distribution of ORA-IOPg among non-glaucomatous participants who did not use ocular hypotensive agents (n=7544)
The distribution approximates a Gaussian distribution, but has an exaggerated central peak and a modest right skew.

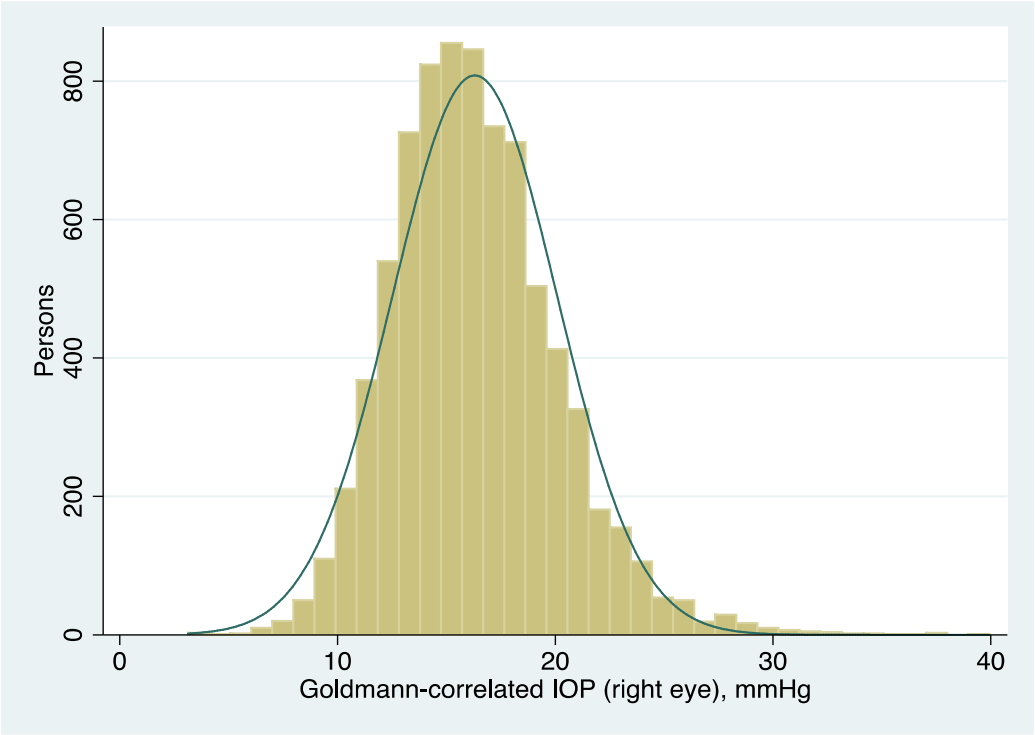
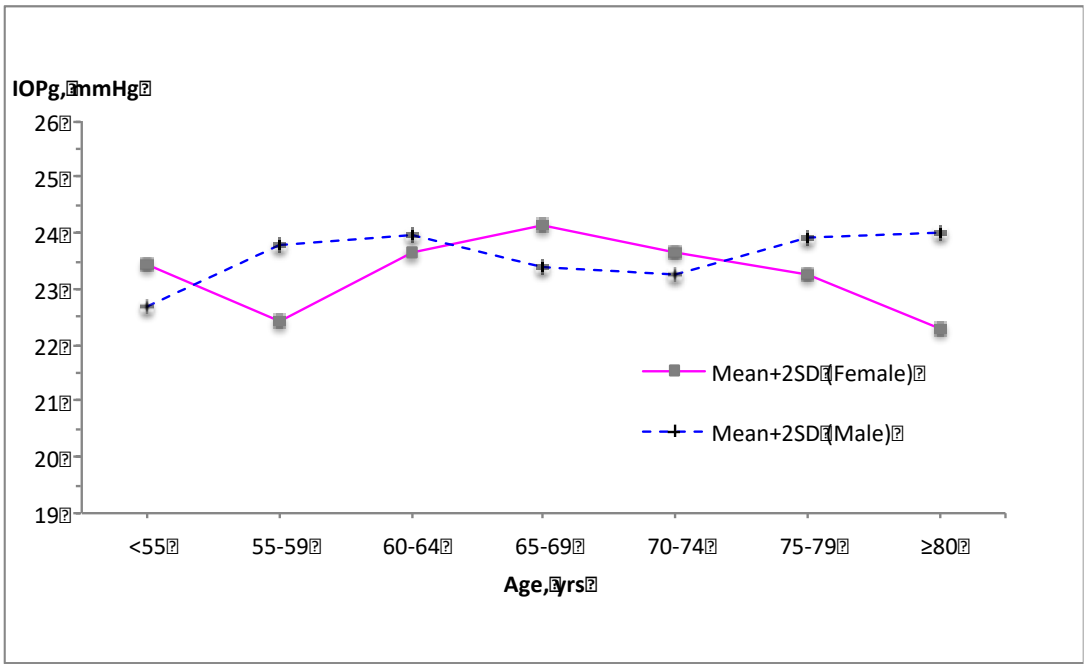


Table 7.2 Summary of the IOP measurements in participants who did not use ocular hypotensive drops or have glaucoma in either eye
The upper limits of IOP distribution (mean+2SD or 97.5th centile) are consistently higher than the historical threshold of 21mmHg.

IOP measurement	Mean (95%CI)	SD	Mean +2SD	97.5th centile
		mmHg		
ORA-IOPg mean of three readings				
right eye (n= 7493)	16.2 (16.1-16.3)	3.7	23.6	24.1
left eye(n=7467)	16.3 (16.2-16.4)	3.7	23.6	24.4
ORA-IOPg best signal value				
right eye (n=7493)	16.0 (15.9-16.1)	3.8	23.6	24.4
left eye (n=7467)-	16.1 (16.0-16.2)	3.8	23.7	24.6
AT555 mean of three readings				
right eye (n=421)	14.5 (14.2-14.9)	3.5	21.5	23.4
left eye (n=424)	14.7 (14.4-15.1)	3.4	21.6	22.7

Figure 7.3 Mean+2SD IOP values vary across the age groups and for both sexes in the study participants.



7.4.2 Impact of Varying the IOP Referral Thresholds on Referral Burden

The number of potential referable cases to the HES will vary if different IOP thresholds were used. To estimate the referable cases, the higher IOP of either eye (IOPg or AT555 values) were used to reflect clinical practice. **Table 7.3** shows the distribution of participants by their higher IOP of either eye at different IOP thresholds. In total, 13.9% participants had maximum IOP measurements above 21mmHg, which is equivalent to approximately 3.42 million people when projected to the age-adjusted population of England and Wales (**Table 7.4**). If the referral threshold were to increase from >21mmHg to >24mmHg, the number of referable subjects based on IOP could be reduced by 67.0%, or 2.29 million people. Even a modest increase of the threshold to >22mmHg or >23mmHg would bring a substantial reduction in the referable numbers by 31.1% and 52.3%, respectively.

Table 7.3. Percentage of participants by age at different IOP thresholds using the higher IOP of either eye

Age, yrs	Mean IOP (95% CI), mmHg	Participants (% age group)					
		≤21 mmHg	>21 mmHg	>22 mmHg	>23 mmHg	>24 mmHg	>25 mmHg
45-49 (n=36)	15.9 (14.7-17.0)	88.9	11.1	8.3	2.8	0.0	0.0
50-54 (n=270)	16.6 (16.2-17.0)	89.3	10.7	7.8	4.8	3.7	3.0
55-59 (n=727)	16.6 (16.4-16.9)	90.5	9.5	5.9	3.7	2.9	2.1
60-64 (n=2090)	17.3 (17.1-17.4)	86.1	13.9	9.3	6.7	4.6	3.6
65-69 (n=1745)	17.3 (17.1-17.5)	84.6	15.4	10.8	8.0	5.4	3.6
70-74 (n=1546)	17.1 (16.9-17.3)	85.3	14.7	9.8	6.6	4.6	3.3
75-79 (n=1154)	17.0 (16.8-17.2)	86.2	13.8	10.3	6.7	4.2	3.0
80-84 (n=598)	16.9 (16.8-17.2)	86.8	13.2	9.2	6.7	5.0	3.7
≥85 (n=177)	16.7 (16.1-17.4)	83.6	16.4	11.3	6.8	5.6	4.0
Total (n=8343)	17.1 (17.0-17.2)	86.1	13.9	9.6	6.6	4.6	3.3

Table 7.4 Impact of varying the IOP referral threshold on referable numbers from 21mmHg by extrapolating EPIC-Norfolk data to England and Wales 2014 population estimates.

IOP referral thresholds	EPIC (n)	UK persons (millions)*	Change in persons eligible for referral	
			%	persons (million) *
>21mmHg	1157	3.42	-	-
>22mmHg	797	2.36	-31.1	-1.07
>23mmHg	552	1.63	-52.3	-1.79
>24mmHg	382	1.13	-67.0	-2.29
>25mmHg	276	0.82	-76.1	-2.61

*applied to age-matched 2014 population estimates of England and Wales [330]

7.4.3 Impact of Changing the IOP Referral Threshold on Glaucoma Detection

The effect of raising the IOP referral threshold would mean missing some glaucoma cases. **Table 7.5** shows the higher IOP of either eye among glaucoma cases and suspects in the cohort. Among the newly diagnosed glaucoma cases, up to 81.0% cases had IOP ≤24mmHg, and 65.3% had IOP ≤21mmHg, hence an extra 16% new glaucoma cases could be missed if the referral threshold was raised from 21mmHg to 24mmHg. Among the newly diagnosed glaucoma suspects, up to 84% suspects could be missed compared to 71% if the referral threshold was raised from 21mmHg to 24mmHg, a 12% increase.

Table 7.5 IOP levels among glaucoma cases and glaucoma suspects in the cohort

Higher IOP of either eye, mmHg	All cause glaucoma		Glaucoma suspects	
	New diagnosis (% of total)	Known diagnosis (% of total)	New diagnosis (% of total)	Known diagnosis (% of total)
≤21mmHg	79 (65.3%)	164 (67.8%)	419 (71.4%)	88 (55.0%)
≤22mmHg	86 (71.1%)	173 (71.5%)	449 (76.5%)	94 (58.8%)
≤23mmHg	94 (77.7%)	182 (75.2%)	475 (80.9%)	100 (62.5%)
≤24mmHg	98 (81.0%)	191 (78.9%)	492 (83.8%)	112 (70.0%)
≤25mmHg	103 (85.1%)	202 (85.1%)	511 (87.1%)	120 (75.0%)
Not measured	1 (0.8%)	15 (6.2%)	16 (2.8%)	8 (5.0%)
Total	121 (100%)	242 (100%)	587 (100%)	160 (100%)

7.4.4 AUC for IOP performance in Diagnosing Glaucoma

Documented pre-treatment GAT IOP was available for 126 right and 131 left eyes, and pre-treatment IOP was imputed for the remaining eyes which already had IOP-lowering treatment (180 right and 172 left eyes). The overall “pre-treatment IOP” used in the AUC analysis therefore consists of pre-treatment IOP (GAT) for 306 right eyes and 303 left eyes, but the study IOP (IOPg or IOP measured with the AT555 tonometer) for the remaining eyes. The “study IOP” consists of IOPg or AT555 IOP.

The AUC analysis was performed to test the ability of IOP in differentiating glaucoma and non-glaucoma eyes (**Table 7.6**). The AUC using the study IOP was 0.57 (95%CI 0.53-0.61) for the right eye and 0.56 (95%CI 0.52-0.60) in the left eye. However, the

AUC using the right eye pre-treatment IOP was 0.78 (95%CI 0.75-0.82), which was statistically greater than the AUC using the right eye study IOPg (0.57, 95%CI 0.53-0.61, p<0.0001). The same trend was found comparing the left eye pre-treatment IOP (AUC 0.77, 95%CI 0.74-0.81) and the left eye study IOP (AUC 0.56, 95%CI 0.52-0.60 p<0.0001).

The diagnostic performance of IOPg and IOPcc were also compared using the study IOPg and IOPcc, since no pre-treatment IOPcc was available. The AUC of IOPcc was greater than IOPg in both eyes (p<0.0001), indicating it has overall greater diagnostic accuracy.

Table 7.6 Performance of different IOP metrics in differentiating between glaucoma and non- glaucomatous eyes

IOP used in AUC analysis	n	IOP mean (95% CI)	AUC (95%CI)	p value
Study IOP (RE)	8343	16.2 (16.1-16.3)	0.57 (0.53-0.61)	0.0001
Pre-treatment IOP (RE)	8343	16.5 (16.4-16.5)	0.78 (0.75-0.82)	
Study IOP (LE)	8343	16.3 (16.2-16.4)	0.56 (0.52-0.60)	0.0001
Pre-treatment IOP (LE)	8343	16.6 (16.5-16.6)	0.77 (0.74-0.81)	
Study IOPg (RE)	7903	16.3 (16.2-16.4)	0.57 (0.53-0.61)	0.0001
Study IOPcc (RE)	7903	17.2 (17.1-17.3)	0.64 (0.60-0.68)	
Study IOPg (LE)	7872	16.4 (16.3-16.5)	0.56 (0.52-0.61)	0.0001
Study IOPcc (LE)	7872	17.3 (17.3-17.4)	0.64 (0.60-0.68)	

Figure 7.4 and **Table 7.7** show the sensitivity and specificity of glaucoma detection at different IOP thresholds using pre-treatment IOP. As the referral threshold increases, the sensitivity of glaucoma detection (if based on IOP alone) decreases, and poor (<75%) for IOP levels between 19-26mmHg, regardless of the additional refining parameters of age and sex. Specificity on the other hand, increases with IOP, from 86% at 21mmHg to 91% at 22mmHg, and reached 96% at 24mmHg. Nevertheless, there was no one single IOP level that afforded both high sensitivity and specificity, and therefore IOP alone was not adequate for glaucoma screening if used as the only criteria.

Figure 7.4 Sensitivity and specificity of IOP in detecting all cause glaucoma in the cohort

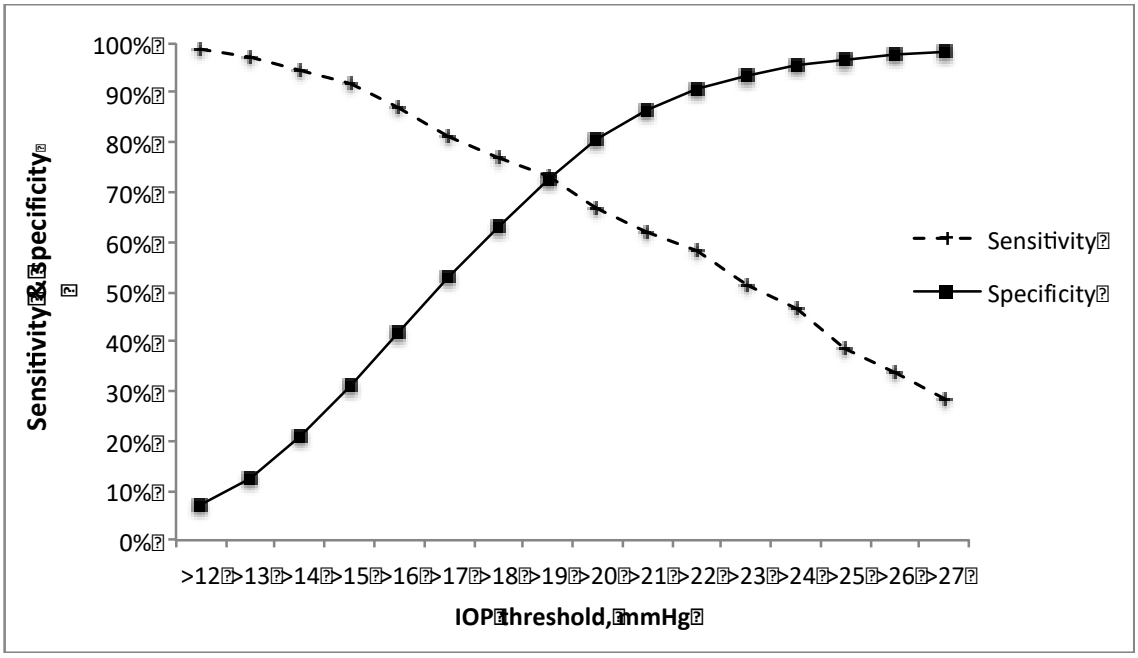


Table 7.7 Sensitivity and specificity of all cause glaucoma detection at different IOP thresholds

IOP mmHg	Sensitivity (%)							Specificity (%)						
	Overall	Age				Male	Female	Overall	Age				Male	Female
		<65	≥65	<70	≥70				<65	≥65	<70	≥70		
>19	73.2	68.0	74.1	71.4	74.0	75.9	70.0	72.6	73.7	71.9	72.4	72.9	73.2	72.2
>20	67.0	60.0	68.2	62.9	68.8	69.2	64.4	80.4	81.6	79.7	80.5	80.3	79.8	80.9
>21	62.0	56.0	63.0	58.1	63.6	63.6	60.0	86.3	87.4	85.6	86.4	86.2	85.1	87.2
>22	58.3	52.0	59.3	56.2	59.2	60.0	56.3	90.7	91.6	90.1	90.7	90.6	89.8	91.4
>23	51.3	48.0	51.8	50.5	51.6	53.3	48.8	93.5	94.3	93.0	93.5	93.6	92.7	94.2
>24	46.5	44.0	46.9	47.6	46.0	48.2	44.4	95.5	96.0	95.2	95.4	95.7	94.9	96.0
>25	38.3	34.0	39.0	40.0	37.6	38.0	38.8	96.7	96.8	96.6	96.7	96.7	96.1	97.1
>26	33.5	30.0	34.1	35.2	32.8	32.3	35.0	97.6	97.5	97.6	97.6	97.5	97.1	97.9

7.5 Discussion

7.5.1 Principal Findings and Comparison with Other Studies

This study is the first to our knowledge to attempt to re-visit the definition of the historical OHT threshold using data to explore the IOP distribution of a large White UK population measured with NCT. All methods used to replicate the OHT threshold in the study yielded values higher than 21mmHg. The historical threshold of 21mmHg was derived from the now antiquated Schiötz tonometry measurements, while the upper limit GAT measurement from the same 1966 study was actually 22mmHg.[28] Using the Reichert ORA, the mean+2SD in this study was 23.6mmHg. For a smaller subset of subjects using the AT555 conventional NCT, the value was 21.5-21.6mmHg, similar to the 1966 study results. However, using the 97.5 centile to allow for the right skew in the data, the threshold was 22.7-23.7mmHg.

One of the reasons for the higher OHT threshold in this study could be population-specific factors related to genetics, lifestyle and environmental influences. Secondly, it could be the large SD of our IOP measurements. Compared to the IOP reported in other population studies for white populations measured with GAT (**Table 7.8**), the SD of EPIC-Norfolk data was the highest, indicating the largest spread of values, even though our mean IOP was similar to other studies. This was most likely due to our use of NCT rather than GAT.

This leads to the question whether results derived from NCT can be applied to GAT, and vice versa. A meta-analysis examining the agreement between GAT and various tonometers demonstrated great variation.[165] The 95% limits of agreement between GAT and conventional NCT were 0.2mmHg (-3.8 to 4.3mmHg), and between GAT and ORA IOPg was 1.5mmHg (-3.9 to 7.0mmHg). Considerable inter and intra-observer variability was also noted for measurements with GAT, suggesting that it may not be a reliable reference standard tonometer. Since most optometrists use NCT rather than GAT in making referrals, our data will actually be more relevant than GAT results. In practice, the UK optometric bodies recommended the use of any “reliable and consistent” tonometer to reach referral decisions, but recommended an average of four NCT measurements to improve accuracy.[328] Joint guidelines from the College of Optometrists and the Royal College of Ophthalmologists, on the other hand, recommended the use of GAT where possible,[89] and have urged the commissioning of an IOP re-measuring service in the community using GAT.[331]

Table 7.8 IOP distribution reported by population surveys of white subjects

Study location	n	Age, yrs	% women	Tonometer	IOP, mmHg	
					Mean (SD)	Mean + 2SD
EPIC-Norfolk	7544	48-92	56.1	ORA NCT	16.2 (3.7)	23.6
EPIC-Norfolk	443	48-86	50.8	AT555 NCT	14.6 (3.6)	21.7
Baltimore[326]	2913	>40	n/a	GAT	17.2 (3.4)*	23.9*
Thessaloniki, Greece[159]	2554	>60	47.1	GAT	15.3 (3.5)	22.3
Beaver Dam[332]	4926	43-86	57.0	GAT	15.3 (3.4)	22.1
Rhonda Valley, Wales[28]	1873	40-75	53.8	GAT	15.9 (2.9)*	21.6*
Rhonda Valley, Wales[28]	1873	40-75	53.8	Schiötz	14.6 (3.0)*	20.5
Blue Mountain, Australia[333]	3654	>49	56.7	GAT	16.0 (2.6)	21.2

ORA Ocular Response Analyzer, GAT Goldmann applanation tonometry, NCT non-contact tonometry, n/a not available.
* Values for non-glaucomatous subjects only

The purpose of incorporating pre treatment and imputed IOP in part of this analysis was to avoid under estimating IOP's ability to differentiate between glaucoma non-glaucoma cases, especially since a large proportion (66%) of the glaucoma cases in this cohort were previously diagnosed and already on treatment. As expected, pre-treatment IOP was better than study (treated) IOPg in identifying glaucoma cases, and the increase in AUC is significant. This occurs despite NTG accounting for 50% of POAG cases. However, an AUC of 0.74, pre treatment IOP is still not enough to be used as a stand alone parameter for glaucoma screening, and no single IOP level provides both adequate sensitivity and specificity. As shown in chapter 6, the greatest risk factor for undiagnosed IOP is having NTG so over reliance on IOP in glaucoma detection can be detrimental. Our results also showed that IOPcc had a significantly greater AUC than IOPg in its diagnostic ability. This corroborate with results in chapter 6 (see section 6.5.3) whereby IOPcc explained a greater degree of variance in POAG than IOPg and suggests IOPcc could be a more useful metric in glaucoma management.

The assumption made with imputation is that treatment would be effective and consistently reduce IOP by 74% - the average drop in IOP seen in cases in which the data was available. There is also error induced by incorporating GAT pretreatment IOP within a dataset of otherwise ORA IOPg to generate the "pre treatment IOP".

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7.5.2 Implications of raising the ocular hypertension threshold

Our data suggest that the current OHT threshold – the threshold for HES referrals - could be increased. As a crude estimate, an increase to >24mmHg, would see a substantial drop in the number of referable subjects by 67.0%. The largest contribution to this reduction came from the younger age group of 45-49, the majority of whose IOP measured less than 21mmHg but all of which fell below 24mmHg. The highest mean IOP was found in the ages 60-70 years, which also accounted for a large reduction. Even a modest increase of the threshold to >22mmHg or >23mmHg would lead to a reduction of 31% and 52% of the population meeting the referral criteria. However, in practice, the actual reduction is expected to be less, since our estimates assume 100% of cases would present themselves to an optometrist. Nevertheless, what this demonstrates ostensibly is that a small increase in IOP threshold could lead to potentially large savings to the NHS by cutting referrals, and most of those referrals would be unnecessary, false positive referrals in the first place, as the specificity of glaucoma case-finding improves with a higher IOP threshold.

On the other hand, the clinical implications of such a change need to be examined. The purpose of identifying ocular hypertensives in the community is to identify those at risk of converting to glaucoma, determine their need for follow-up and initiation of topical ocular hypotensive therapy.[161] According to 2009 NICE guidelines, the IOP at which treatment is considered for ocular hypertension starts at 25mmHg, the exact level depending on other factors (age, central corneal thickness). Therefore increasing the referral threshold up to 24mmHg is unlikely to have a detrimental effect of missed treatment.

For the secondary purpose of OAG case-finding, the sensitivity of detection would reduce with a higher IOP threshold, and our data estimate 16% of undiagnosed glaucoma cases could be missed if the referral threshold was raised from >21mmHg to >24mmHg. However, this needs to be reconciled with the fact that no single IOP value provides a good trade-off between sensitivity and specificity of OAG detection, a finding in this study which mirrored results from the Baltimore Eye Survey.[14] This reinforces the principle that IOP alone should not be used as a screening tool for glaucoma without considering other risk factors such as family history, central corneal thickness, as well as optic disc and visual field findings.

In summary, data from this study on the EPIC-Norfolk cohort indicate that the IOP referral threshold of >21mmHg could be inappropriate for current practices.

In light of our data and the well-recognised weakness of IOP as the sole case finding tool for glaucoma, policy makers should consider increasing referral thresholds where IOP is the only ocular abnormality identified.

Influencing Practice Changes: Update to NICE Guidelines

Glaucoma diagnosis and IOP distribution from the EPIC-Norfolk Eye Study was published in the British Medical Journal in October 2017[2], and the accompanying editorial highlighted the flaw in screening for glaucoma using IOP alone, describing it as “an outdated concept that should be abandoned”. [3]

In addition, data from this analysis were presented to the NICE committee in 2017. In the updated NICE guidelines published in November 2017, 24mmHg was adopted as the new IOP referral threshold for further investigation and diagnosis of chronic open angle glaucoma and related conditions.[1] Specifically, it recommended that IOP should be measured with GAT and confirmed on repetition, and that referral decision should not be based solely on IOP measurements using non-contact tonometry. The recommended treatment threshold for OHT has also been simplified from the previous threshold of >21-25mmHg depending on age and CCT in the 2009 guidelines, to ≥24mmHg applicable to all patients if they are deemed to be at risk of visual impairment within their lifetime. The recommendations have also been disseminated by the Royal College of Ophthalmologists and the College of Optometrists to their members.

7.6 Conclusion

The historical use of IOP>21mmHg as the definition of OHT and the threshold for referring patients to the HES to exclude glaucoma is well-known to be associated with a high false positive rate. This chapter used the data from the EPIC-Norfolk Eye Study to challenge this threshold by examining the upper limit of IOPg distribution in the study population, using the 97.5th centile value as well as the 2 standard deviations above the population’s mean. That figure was found to be approximately 24mmHg. The findings in this chapter has since been used to influence national policy, and the NICE guidelines have now adopted >24mmHg as the limit for referral to the HES.

CHAPTER 8: OPTIC DISC IMAGING TESTS PERFORMANCE IN GLAUCOMA DETECTION

8.1 Background

Population-based screening for glaucoma is an attractive idea. It has so far not shown to be cost-effective for several reasons.[12] One main obstacle is the lack of appropriate diagnostic test(s) that provide sufficient sensitivities and specificities. HRT and GDx-VCC have the potential to be useful screening tools due to the objectivity of the results, the ease of operation, and their non-invasiveness, and proven effectiveness in case-control studies. Their performances in differentiating glaucoma discs from normal subjects in experimental case-control studies have already been proved to be superior to experts. [149] However, their use in a mass screening setting has not been tested. This chapter will test the diagnostic performance of HRT and GDx-VCC classifiers together with other parameters that could improve the diagnostic yield. It will also test their performance in detecting early and advanced glaucoma.

97.5th centile value is often adopted as the reference upper normative limit of a continuous variable within a population,[153] and the ISGEO glaucoma diagnostic criteria use the 97.5th centile vertical cup/disc ratio of a non-glaucomatous population to define the upper limits of a healthy disc.[5] This chapter will test the diagnostic ability of the 97.5th or 2.5th centiles for variables, depending whether they show a positive or an inverse correlation with glaucoma.

8.2 Aims

To evaluate the diagnostic ability of disc photo measurements, HRT II and GDx-VCC to detect glaucoma in a population screening setting, and to find the optimum screening test combinations and cut-off values.

8.3 Methods

8.3.1 Screening Scenarios

The abilities of disc photo measurements, HRT II and GDx-VCC to discriminate between glaucoma cases from controls were tested using area under receiver operator characteristics curves (AUC) under three screening scenarios. **Table 8.1** summarizes the inclusion criteria for the three glaucoma classes (all cause, early, moderate and advanced glaucoma) and the control pairs. Stages of glaucoma were defined by visual field mean defect (MD) cutoffs according to Hodapp-Parrish and Anderson.[160]

A: All glaucoma vs rest of cohort (non-glaucoma cases)

B: Early glaucoma (visual field MD >-6dB) vs rest of cohort (non-glaucoma cases)

C: Moderate to advance glaucoma (visual field MD ≤-6dB) vs rest of cohort (less advanced glaucoma and non-glaucoma cases). Glaucomatous eyes with no visual field data were not included in the control group in this scenario, as their severity cannot be verified.

Table 8.1 The screening scenarios and the glaucoma and control pairs used to test the diagnostic abilities of disc photo measurements, HRT II and GDx-VCC.

Diagnosis	Visual field (MD)	A		B		C	
		GL	CTRL	GL	CTRL	GL	CTRL
No glaucoma	Not specified						
Early glaucoma	>-6dB						
Moderate glaucoma	-6dB to -12dB						
Advanced glaucoma	<-12dB						

Scenario A: Glaucoma eyes vs eyes in the rest of the cohort
Scenario B: Early glaucoma eyes (MD ≥ -6dB) vs eyes without glaucoma
Scenario C: Moderate to advanced glaucoma eyes (MD <-6dB) vs eyes in the rest of the cohort. Glaucomatous eyes with no visual field data were not included in the control.
GL-glaucoma, CTRL - control

8.3.2 List of Classifiers

Table 8.2 shows the list of disc photos, HRT II and GDx-VCC classifiers being tested for their diagnostic performance.

Table 8.2 List of disc photos, HRT II and GDx-VCC classifiers being tested for their diagnostic performance

Abbreviation	Description
Disc photo measurement	
Vertical CDR	Vertical cup/disc ratio
Vertical SDR	Vertical superior rim/disc ratio
HRT	Overall Moorfields Regression Analysis
MRA overall-1	1 = within normal limits /borderline/outside normal limits
MRA overall -2	2 = within normal limits / borderline & outside normal limits
MRA overall-3	3 = within normal limits & borderline / outside normal limits
	Global Moorfields Regression Analysis
MRA global-1	1 = within normal limits /borderline/outside normal limits
MRA global-2	2 = within normal limits / borderline & outside normal limits
MRA global-3	3 = within normal limits & borderline / outside normal limits
Horizontal CDR	Horizontal cup/disc ratio
Vertical CDR	Vertical cup/disc ratio
Cup-disc area ratio	Cup area/ disc area ratio
Rim-disc area ratio	Rim area / disc area ratio
Linear CDR	The square root of the cup/disc area ratio
Rim area (mm^2)	Area of the neuroretinal rim, enclosed by the contour line and located beneath the reference plane
Disc area (mm^2)	Are enclosed within the contour line
Cup area (mm^2)	Area of the optic cup, enclosed by the contour line and located beneath the reference plane
Rim volume (mm^2)	The volume of the neuroretinal rim, defined as the volume enclosed by the contour line and located above the reference plane.
Cup volume (mm^3)	The volume of optic cup, defined as the volume enclosed by the contour line and located beneath the reference plane.
Mean cup depth (mm)	Mean depth of the optic cup.
Cup shape measure	A measure of the skewness of the frequency distribution of depth values within the contour line and below the curved surface of the retina. It is an indicator of the overall shape of the cup.
Height variation contour	This is the difference in height between the most elevated and depressed point. This parameter decreases when nerve fibre loss occurs diffusely but increases with development of a localized nerve fibre defect.
Mean RNFL thickness	Mean retinal nerve fibre layer thickness along the contour line
RNFL cross sectional area (mm^2)	Total retinal nerve fibre layer cross sectional area along the contour line
CLM temporal- superior	Contour line modulation (temporal to superior sector). The difference between the mean height of the retinal surface along the contour line in the temporal quadrant and the temporal-superior quadrant
CLM temporal- inferior	Contour line modulation (temporal to inferior sector) The difference between the mean height of the retinal surface along the contour line in the temporal quadrant and the temporal-inferior quadrant
FSM DF	FSM Frederick S. Mikelberg discriminant function
RB DF	Reinhard Burk discriminant function
GDX-VCC NFI	Nerve fibre indicator. This is an artificial intelligence algorithm derived ordinal number (1-100), and relates the likelihood that RNFL map is abnormal
Average RNFL thickness (µm)	Average retinal nerve fibre layer thickness
Superior RNFL thickness (µm)	Average RNFL thickness in the superior 120 degrees.
Inferior RNFL thickness (µm)	Average RNFL thickness in the inferior 120 degrees.
Nasal RNFL thickness (µm)	Average RNFL thickness in the nasal 70 degrees.
Temporal RNFL thickness (µm)	Average RNFL thickness in the temporal 50 degrees.

8.3.3 Choice of Classifiers

For disc photo measurements, only CDR and superior rim/ disc ratio were tested. True disc parameters such as disc diameter or superior rim thickness were not used, as some photos were taken using different fundus cameras which were not available for calibration.

All HRT and GDx-VCC variables were tested. Only HRT II scans with topographical score of ≤40 and GDx-VCC scans with quality score ≥7 were used in the analysis. Right eye data were used in the analysis and left eye values were used for sensitivity analysis.

For Moorfields Regression Analysis (MRA), the global and overall results were tested. Different methods of categorising the MRA were tested to see if the diagnostic performance changes:
1 – as three categories: within normal limits/ borderline/ outside normal limits
2 – as two categories: within normal limits vs borderline or outside normal limits
3 – as two categories: within normal limits or borderline vs outside normal limits

8.3.4 Effects of Optic Disc Size on HRT Classifiers

Optic disc size is known to affect classifiers involving cup/disc ratios as well as some HRT discriminant functions.[218,234] HRT disc area was stratified into small (<1.5mm^2), medium (1.5-2.0mm^2), and large (>2.0mm^2). The effect of disc area on the area under receiver operating curve (AUC) of vertical cup/disc ratio (VCDR), linear cup/disc ratio (LCDR), rim/disc area ratio (RDAR), MRA overall, MRA global results, Reinhard Burk discriminant function (RB) and Frederick S. Mikelberg discriminant function (FSM) were tested (**Table 8.3**) by comparing the AUC at different disc areas (X^2 test with Bonferroni correction). There were no significant differences between the AUC of small disc areas with either medium or large disc areas (p=1.00 for all). Therefore all subsequent analyses were not adjusted for disc size.

Table 8.3 Effects of disc area on the performance of HRT classifiers in diagnosing all cause glaucoma vs non-glaucoma subjects

HRT classifier	HRT disc area		
	Small <1.5mm^2 n=1221	**Medium** 1.5-1.9mm^2 n=2832	**Large** ≥2.0 mm^2 n=1983
Vertical CDR	0.905 STD	0.930 p=1.00	0.895 p=1.00
Linear CDR	0.828 STD	0.911 p=1.00	0.911 p=1.00
Horizontal CDR	0.769 STD	0.804 p=1.00	0.788 p=1.00
Rim disc area ratio	0.834 STD	0.912 p=1.00	0.878 p=1.00
MRA global	0.760 STD	0.790 p=1.00	0.803 p=1.00
MRA overall	0.796 STD	0.894 p=1.00	0.838 p=1.00
RB discriminant function	0.839 STD	0.870 p=1.00	0.792 p=1.00
FSM discriminant function	0.831 STD	0.884 p=1.00	0.877 p=1.00

AUC of each HRT classifier in diagnosing glaucoma were compared to the standard (STD)

8.3.5 AUC and Sensitivity at 95% Specificity

The diagnostic abilities of disc photo measurements, HRT II and GDx-VCC were first explored using area under receiver operator characteristics curves (AUC) for all classifiers, as well as the sensitivity at 95% specificity for continuous classifiers. The sensitivity at 95% specificity was chosen to reflect the importance of having low false positive rate in a screening scenario.

For classifiers which have an inverse relation with glaucoma, characterized by inverted receiver operating curves (ROC) that fall below the diagonal, the AUC under the diagonal is used.

Table 8.4 Disc photo, HRT and GDx-VCC classifiers that show an inverse relation with glaucoma

Disc photo measurements	Vertical superior rim/disc ratio
HRT	rim disc area ratio
	rim area
	mean RNFL thickness
	RNFL cross sectional area
	contour line modulation (temporal to superior sector)
	contour line modulation (temporal to inferior sector)
	FSM discriminant function
	RB discriminant function
GDx-VCC	average RNFL thickness
	superior RNFL thickness
	inferior RNFL thickness
	nasal RNFL thickness

8.3.6 Testing Classifiers in Combination & Determining the Optimum Combination

The classifiers that yielded the top three highest AUC for each screening scenario were identified. They were tested in combination with each other and with age to explore whether the AUC improved. Only two classifiers were tested in each combination. Logistic regression modelling - with the dependent variable being each of the three screening scenarios and the covariates the classifiers – was used to construct the combination models, and the AUC for each model was calculated.

The top three pairs of classifiers that yielded the highest AUC for each screening scenario were identified. Their AUCs were compared using chi square test with Bonferroni correction for multiple comparisons. For each screening scenario, the

combination(s) of classifiers with AUC that was statistically significantly higher ($p<0.05$) than others was identified at the end of the process as being the optimum combination.

8.3.7 Sensitivities And Specificities Of The Optimum Combinations

For the optimum combination(s) of classifier for each screening scenario, the sensitivities and specificities were explored in order to find the optimum cutoff values. The cutoffs were altered stepwise, one classifier at a time, to find the value that generates the highest sensitivity at high specificity.

8.3.8 The Normative Values And Their Diagnostic Performance

The normative value for each continuous classifier was ascertained among "normal" participants. It was defined as either the 97.5th centile or 2.5th centile of the distribution for continuous classifiers, depending on whether it increases or decreases with the likelihood of glaucoma respectively. Receiver operator curve (ROC) for each classifier in differentiating glaucomatous vs normal right eyes was plotted. If the ROC curve was inverted, then 2.5th centile was used as the normative cut-off, if not inverted, the 97.5th centile value was used. For HRT MRA classifiers, "outside normal limits" was used as the normative cutoff.

The "normal" population was defined as those who met all these criteria in the right eye:
- No glaucoma diagnosis
- Normal visual field test result –the eye must have a visual field "within normal limits" on the Glaucoma Hemifield Test that is reliable, and contemporaneous (within 12 months) with their HRT, GDx-VCC scans and disc photography

The sensitivities and specificities for each normative value (>97.5th centile value or <2.5th centile value) in detecting glaucoma were calculated for the three screening scenarios.

8.4 Results

8.4.1 Baseline Characteristics and Data Availability

There were 265 glaucomatous right eyes in the study, 122 had early glaucoma and 38 had moderate to advance glaucoma as categorized by their visual fields, and there were 8358 non-glaucoma participants. The all cause glaucoma group therefore was composed largely of early glaucoma eyes. **Table 8.5** summarizes the characteristics of the three glaucoma groups and the non-glaucoma group, **Table 8.6A** and **Table 8.6B** describe their disc photo measurements, HRT and GDx-VCC values and data availability. Primary open angle glaucoma (HTG, NTG) were the most common diagnoses in every glaucoma group.

The median visual field defect (MD) was -3.1dB for all glaucoma eyes, -2.1dB in the early glaucoma group, -10.9dB in the moderate/advance group, and -0.97dB in the non-glaucoma group. Visual field availability was much lower among the non-glaucoma eyes (13.8%), as the criteria for performing them were based on abnormalities in initial screening examination. However, 105 glaucomatous right eyes (39.6%) did not have visual fields done and could not be categorized into either early or moderate-advanced groups, and were also excluded from the control group in the screening scenario where the moderate-advanced glaucoma group was compared to the rest of the cohort of less severe glaucoma or eyes without glaucoma.

The availability of ungradable disc photos was low (6.5-10.5%) among the four groups compared to the 22.5-38.9% of ungradable HRT scans and 19.8-37.3% of ungradable GDx-VCC scans. This could be due to disc photos being graded manually and therefore a greater tolerance of substandard images were allowed as long as the disc and cup margin could be delineated, while HRT and GDx-VCC scans demand greater image quality for all the stereometric parameters to be defined. A greater proportion of glaucomatous eyes had ungradable HRT or GDx-VCC scans than normal subjects, which was expected, explained possibly by older age of the glaucomatous groups and therefore prevalence of cataracts.

Overall, the availability of analyzable visual fields were low (66.8% of all glaucoma eyes, 13.8% of non-glaucomatous eyes), which reflects the fact that visual fields were not performed as a routine for all subjects.

8.4.2 AUC and Sensitivity with Single Classifier

Table 8.7 explores the AUC for all classifiers under the three screening scenarios, and their sensitivity at 95% specificity. Overall, HRT classifiers performed better than GDx-VCC in glaucoma detection. HRT VCDR was the best performing classifier across all three screening scenarios (AUC 0.91-0.96), and HRT LCDR and RDAR were joint second best for detecting all cause glaucoma (AUC 0.90) and early glaucoma (AUC 0.88). The third best performing classifiers were HRT Frederick S. Mikelberg discriminant function (FSM) and HRT cup area in detecting early glaucoma (AUC 0.87). To detect moderate/advance glaucoma, HRT Reinhard Burk discriminant function (RB) was second best (AUC 0.94); the third best were: GDx-VCC nerve fibre indicator (NFI), LCDR and RDAR (AUC 0.93).

At 95% specificity, sensitivities were generally higher for detecting moderate/advance glaucoma than early glaucoma. However, the sensitivities were generally low, between 40.3%-54.5% for the top three classifiers in detecting early glaucoma, and 42.7%-62.9% in detecting all cause glaucoma.

For MRA, the original three-tier categorization (within normal limits/ borderline/ outside normal limits) performed better then the two tier categories, when borderline was merged with either within normal limits or outside normal limits.
The three-tier category was used in all subsequent analysis.

8.4.3 AUC of Two Classifiers in Combination

The performance of classifiers in combination (**Table 8.8**) was explored using permutations of the top performing classifiers identified in table 8.4 (VCDR, LCDR, cup/disc area ratio (CDAR), RDAR, cup area, FSM, RB, and NFI). Adding age improved the AUC for all classifiers, but using combinations of machine classifiers yielded the highest AUC. The top three combinations for the different screening scenarios all involved combining a HRT classifier with GDx-VCC NFI.

VCDR+NFI, CDAR+NFI and RDAR+NFI were ranked first or second best combination in all screening scenarios. LCDR + NFI was ranked first for detecting moderate/advanced (AUC 0.989), second for detecting all cause glaucoma (AUC 0.952), and third for early glaucoma (AUC 0.932). Other high performing combinations include cup area + NFI, which was third in detecting all cause glaucoma (AUC 0.945) and moderate/advance glaucoma (AUC 0.986). FSM+NFI and RB+NFI performed well

in detecting moderate/advance glaucoma, being ranked second (AUC 0.988) and third (AUC 0.986) respectively.

8.4.4 Optimum Combinations and Cutoff Values

The best performing pairs for each screening scenario were listed in **Table 8.9**. They were not statistically different from each other in their AUC.

The optimum cutoff values were ascertained by altering each classifier value stepwise. The values that provided the highest sensitivity at high specificity were deemed the optimum. Details of this process are shown in the **Appendix. Table 8.10** summarizes the sensitivities and specificities of the optimum values.

Overall, high sensitivity and specificity were achieved with these cutoff values, with many combinations achieving 100% sensitivity at high specificity of at least 98%. In detecting all cause glaucoma, the combination of cup area >1.4 + NFI>45 achieved the highest specificity of 98.22%, and 100% sensitivity. For early glaucoma, CDAR>0.70 + NFI>45 and RDAR <0.30 + NFI>45 both achieved specificity of 98.96% at 100% sensitivity. For moderate/ advance glaucoma, CDAR>0.80 + NFI>45 and RDAR <0.20 + NFI>35 achiever specificity of 99.77% and 100% sensitivity

8.4.5 Normative Values and their Diagnostic Performance

A total of 565 right eyes met the criteria of normality. The normative value for each classifier and their diagnostic ability is summarized in **Table 8.11.** Specificity was high (97.0-100%) for the normative values under all three screening scenarios, indicating a negative result is useful in excluding glaucoma. Sensitivities were low for all screening scenarios. For the three classifiers with the highest sensitivities, their sensitivities range between 47.8-51.6% in detecting all cause glaucoma, 26.5-29.7% in detecting early glaucoma, and 17.0-19.2% in detecting moderate/ advance glaucoma.

8.4.6 Sensitivity Testing with Left Eye Data

The analysis was repeated using left eye data. The AUC for the classifiers in singles and in pairs was generated for the left eye, and results of both eyes were compared. The two eyes showed a high degree of correlation. Spearman rank correlation for the AUC between left and right eyes for all test classifiers listed in **Table 8.12** are: 0.94

(p<0.0001) in detecting all cause glaucoma, 0.95 (p<0.0001) in detecting early glaucoma, and 0.89 (p<0.0001) in detecting moderate/late glaucoma.

Table 8.5 Characteristics of the glaucoma and non-glaucoma groups (right eyes)

	No glaucoma	All glaucoma	Early glaucoma	Moderate & advance glaucoma
n	8353	265	122	38
Age, yrs	62.6 (6.6)	74.1 (12.1)	72.3 (10.2)	73.4 (11.3)
Sex, % female	55.5%	46.4%	46.7%	34.2%
Glaucoma type				
POAG	-	45.7%	36.1%	55.3%
NTG	-	43.4%	52.5%	34.2%
PACG	-	7.6%	11.5%	7.9%
Secondary	-	3.4%	0%	2.6%
Visual field loss (MD), dB	-0.97 (2.6)	-3.1 (5.2)	-2.1 (2.5)	-10.9 (5.4)
Refraction, D	0.38 (2.13)	0.0 (2.25)	0.25 (2.75)	0.0 (1.50)
Axial length, mm	23.4 (1.37)	23.8 (1.66)	23.8 (1.96)	23.9 (1.29)
Analyzable visual fields	13.8%	66.8%	100%	100%
Disc photos available	88.6%	96.2%	98.4%	100%
% photos ungradable	6.5%	7.5%	6.7%	10.5%
HRT scans available	91.0%	88.3%	93.4%	94.7%
% HRT scans ungradable	22.5%	36.5%	32.5%	38.9%
GDx-VCC scans available	92.1%	94.9%	93.4%	89.5%
% GDx-VCC scans ungradable	19.8%	37.3%	36.0%	23.5%
Both HRT % GDx-VCC scans available	84.5%	83.8%	87.7%	84.2%
% both scans ungradable	10.6%	24.8%	19.6%	6.3%

Age, visual fields, refraction and axial length shown are median (IQR) values.
Visual fields were included in the analysis if reliability indices (false positive, false negative, fixation losses) were <33% and performed within 1 year of the date of check.
Disc photos were deemed ungradable if photos were of inadequate quality for discs to be graded for glaucoma.
HRT scans were ungradable if topography standard deviation was >40µm.
GDx-VCC scans were ungradable if quality score was < 7.

Table 8.6A Description of HRT classifiers for the glaucoma and non-glaucoma groups

Classifier		No glaucoma (n=8358)		All glaucoma (n=265)		Early glaucoma (n=122)		Moderate-advance glaucoma (n=38)	
		n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)
HRT									
Overall MRA	WNL	3768	63.9	5	5.2%	4	5.2%	0	0%
	Borderline	1247	21.2	24	20.8%	16	20.8%	2	9.1%
	ONL	878	14.9	114	74.0%	57	74.0%	20	90.9%
Global MRA	WNL	5142	87.3	43	36.4%	28	36.4%	6	27.3%
	Borderline	586	9.9	39	31.2%	24	31.2%	3	13.6%
	ONL	165	2.8	61	32.5%	25	32.5%	13	59.1%
Linear CDR		5763	0.47 (0.23)	143	0.67 (0.14)	77	0.67 (0.14)	22	0.74 (0.19)
Horizontal CDR		5893	0.45 (0.29)	143	0.65 (0.23)	77	0.65 (0.23)	22	0.69 (0.24)
Vertical CDR		5893	0.38 (0.43)	143	0.67 (0.16)	77	0.67 (0.16)	22	0.79 (0.13)
Rim-disc area ratio		5893	0.79 (0.21)	143	0.55 (0.19)	77	0.55 (0.19)	22	0.47 (0.27)
Rim area (mm^2)		5893	1.37 (0.42)	143	1.12 (0.31)	77	1.12 (0.31)	22	0.96 (0.51)
Disc area (mm^2)		5893	1.81 (0.55)	143	2.14 (0.47)	77	2.14 (0.47)	22	1.97 (0.60)
Cup area (mm^2)		5893	0.37 (0.44)	143	0.93 (0.58)	77	0.93 (0.58)	22	1.02 (0.71)
Rim volume (mm^3)		5893	0.33 (0.17)	143	0.22 (0.14)	77	0.22 (0.14)	22	0.14 (0.12)
Cup volume (mm^3)		5893	0.05 (0.12)	143	0.21 (0.32)	77	0.21 (0.32)	22	0.25 (0.25)
Mean cup depth (mm)		5893	0.18 (0.12)	143	0.29 (0.14)	77	0.29 (0.14)	22	0.23 (0.08)
Cup shape measure		5893	-0.18 (0.09)	143	-0.09 (0.06)	77	-0.09 (0.06)	22	-0.08 (0.11)
Height variation contour		5893	0.36 (0.12)	143	0.32 (0.15)	77	0.32 (0.15)	22	0.30 (0.14)
Mean RNFL thickness (mm)		5893	0.23 (0.09)	143	0.18 (0.07)	77	0.18 (0.07)	22	0.11 (0.09)
RNFL cross sectional area (mm^2)		5893	1.07 (0.43)	143	0.9 (0.32)	77	0.9 (0.32)	22	0.57 (0.46)
CLM temporal- superior		5893	0.17 (0.09)	143	0.15 (0.13)	77	0.15 (0.13)	22	0.12 (0.14)
CLM temporal-inferior		5893	0.15 (0.10)	143	0.09 (0.12)	77	0.09 (0.12)	22	0.02 (0.11)
FSM discriminant function		5893	1.28 (2.1)	143	-0.86 (1.7)	77	-0.86 (1.7)	22	-1.60 (2.7)
RB discriminant function		5893	1.07 (1.0)	143	0.14 (1.0)	77	0.14 (1.0)	22	-0.65 (1.1)

Table 8.6B Description of disc photo measurements and GDx-VCC classifiers for the glaucoma and non-glaucoma groups

Classifier	No glaucoma (n=8358)		All glaucoma (n=265)		Early glaucoma (n=122)		Moderate-advance glaucoma (n=38)	
	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)
Disc photo measurements								
Vertical CDR	7153	0.39 (0.12)	236	0.53 (0.2)	112	0.53 (0.14)	34	0.54 (0.18)
Vertical SDR	7153	0.28 (0.07)	236	0.22 (0.08)	112	0.21 (0.09)	34	0.21 (0.12)
GDx-VCC								
Nerve fibre indicator	6164	19.0 (11.0)	156	35.0 (28.0)	73	28.0 (24.0)	26	45.5 (29.0)
Average RNFL thickness (μm)	6164	56.4 (7.8)	156	49.5 (10.9)	73	51.3 (13.1)	26	45.2 (13.0)
Superior RNFL thickness (μm)	6164	65.6 (11.0)	156	52.7 (15.2)	73	57.3 (14.8)	26	48.3 (13.1)
Inferior RNFL thickness (μm)	6164	65.6 (11.6)	156	57.1 (16.6)	73	59.6 (17.4)	26	54.8 (14.8)
Nasal RNFL thickness (μm)	6164	42.1 (12.5)	156	38.1 (10.3)	73	38.5 (10.4)	26	34.4 (8.5)
Temporal RNFL thickness (μm)	6164	29.5 (12.5)	156	32.6 (16.1)	73	33.8 (17.1)	26	30.2 (16.0)

Table 8.7 Area under curve and sensitivity (at 95% specificity) for disc photo measurements, HRT and GD-VCC in different diagnostic settings

Classifier	All glaucoma		Early glaucoma		Moderate & advance glaucoma	
	AUC (95% CI)	Sens (%)	AUC (95% CI)	Sens (%)	AUC (95% CI)	Sens (%)
Disc photo measurements						
Vertical CDR	0.80(0.76-0.83)	39.8	0.82(0.78-0.86)	42.5	0.81	47.1
Vertical SDR	0.77(0.74-0.81)	25.1	0.79(0.74-0.83)	30.0	0.75(0.65-0.84)	30.1
HRT						
MRA overall-1	0.87(0.85-0.89)	-	0.86(0.82-0.89)	-	0.90(0.88-0.93)	-
MRA overall -2	0.80(0.79-0.82)	-	0.79(0.77-0.82)	-	0.82(0.81-0.82)	-
MRA overall-3	0.82(0.79-0.86)	-	0.80(0.75-0.85)	-	0.88(0.81-0.94)	-
MRA global-1	0.81(0.77-0.85)	-	0.77(0.71-0.82)	-	0.82(0.72-0.93)	-
MRA global-2	0.79(0.75-0.82)	-	0.75(0.70-0.81)	-	0.80(0.70-0.89)	-
MRA global-3	0.70(0.66-0.74)	-	0.65(0.60-0.70)	-	0.78(0.67-0.88)	-
Linear CDR	0.90(0.88-0.93)	52.4	0.88(0.84-0.92)	48.1	0.93(0.89-0.97)	63.6
Horizontal CDR	0.82(0.79-0.85)	33.6	0.80(0.75-0.84)	28.6	0.84(0.76-0.91)	40.9
Vertical CDR	0.92(0.90-0.94)	62.9	0.91(0.88-0.94)	54.5	0.96(0.92-0.99)	81.8
Cup-disc area ratio	0.90(0.88-0.93)	53.1	0.88(0.84-0.92)	49.4	0.93(0.90-0.97)	63.6
Rim-disc area ratio	0.90(0.88-0.93)	62.0	0.88(0.84-0.92)	52.5	0.93(0.90-0.97)	79.4
Rim area	0.79(0.75-0.83)	27.7	0.74(0.68-0.80)	12.3	0.87(0.80-0.95)	59.6
Disc area	0.68(0.64-0.72)	10.5	0.70(0.64-0.75)	10.4	0.60(0.48,0.71)	7.2
Cup area	0.88(0.86-0.91)	42.7	0.87(0.83-0.90)	40.3	0.89(0.84,0.95)	40.9
Rim volume	0.81 (0.77-0.84)	32.8	0.76(0.71-0.81)	26.1	0.92(0.87-0.96)	68.5
Cup volume	0.83(0.80-0.86)	36.4	0.82(0.77-0.84)	39.0	0.84(0.78-0.91)	36.4
Mean cup depth	0.77(0.74-0.81)	25.9	0.79(0.74-0.84)	29.9	0.72(0.63-0.80)	18.2
Cup shape measure	0.85(0.82-0.88)	42.0	0.84(0.80-0.89)	33.8	0.82(0.74-0.91)	36.4
Height variation contour	0.41(0.36-0.46)	7.5	0.46(0.39-0.53)	7.5	0.39(0.26-0.52)	1.8
Mean RNFL thickness	0.75(0.71-0.79)	22.3	0.70(0.65-0.76)	14.6	0.89(0.83-0.94)	56.2
RNFL cross sectional area	0.70 (0.65-0.74)	15.5	0.64(0.58-0.70)	10.2	0.88(0.82-0.94)	61.7
CLM temporal- superior	0.66 (0.61-0.71)	10.3	0.59(0.52-0.66)	4.9	0.74(0.63-0.82)	18.9
CLM temporal- inferior	0.73(0.69-0.78)	11.3	0.70(0.63-0.76)	11.3	0.90(0.84-0.95)	64.6
FSM DF	0.88(0.85-0.91)	56.0	0.86(0.82-0.90)	48.9	0.90(0.85-0.96)	69.4
RB DF	0.84(0.87-0.81)	38.1	0.80(0.76-0.85)	33.1	0.94(0.89-0.98	72.8
GDx-VCC						
Nerve fibre indicator	0.83(0.80-0.87)	48.1	0.77(0.72-0.83)	34.2	0.93(0.88-0.98)	73.1
Average RNFL thickness	0.76(0.71-0.80)	7.5	0.68(0.60-0.75)	6.1	0.82(0.72-0.92)	16.2
Superior RNFL thickness	0.80(0.76-0.84)	23.2	0.73(0.67-0.80)	20.5	0.89(0.81-0.96)	41.1
Inferior RNFL thickness	0.73(0.68-0.78)	4.3	0.66(0.59-0.74)	4.1	0.76(0.64-0.88)	0.3
Nasal RNFL thickness	0.64(0.60-0.69)	12.7	0.61(0.55-0.49)	14.8	0.74(0.66-0.82)	37.2
Temporal RNFL thickness	0.57(0.52-0.61)	3.0	0.59(0.51-0.66)	2.7	0.54(0.42-0.66)	1.2

Sens: sensitivity
Key: AUC results ranked for each screening scenario

1st	2nd	3rd

Table 8.8 Area under curve for combinations of the best performing classifiers

Classifier combination		All cause glaucoma	Early glaucoma	Moderate advance glaucoma
		AUC		
Linear CDR		0.901	0.878	0.930
Linear CDR	Age	0.912	0.891	0.942
Vertical CDR		0.922	0.910	0.958
Vertical CDR	Age	0.929	0.920	0.962
Cup-disc area ratio		0.901	0.881	0.932
Cup-disc area ratio	Age	0.915	0.896	0.945
Rim-disc area ratio		0.903	0.881	0.932
Rim-disc area ratio	Age	0.915	0.896	0.945
Cup area		0.882	0.843	0.891
Cup area	Age	0.897	0.866	0.900
FSM		0.881	0.862	0.903
FSM	Age	0.896	0.880	0.899
RB		0.840	0.803	0.937
RB	Age	0.853	0.820	0.940
GDx NFI		0.832	0.773	0.928
GDx NFI	Age	0.845	0.778	0.930
Linear CDR	Vertical CDR	0.919	0.905	0.955
Linear CDR	Cup-disc area ratio	0.901	0.878	0.929
Linear CDR	Rim-disc area ratio	0.901	0.878	0.929
Linear CDR	Cup area	0.902	0.878	0.935
Linear CDR	FSM	0.904	0.882	0.930
Linear CDR	RB	0.911	0.888	0.960
Linear CDR	GDx NFI	0.952	0.932	0.989
Vertical CDR	Cup-disc area ratio	0.922	0.908	0.957
Vertical CDR	Rim-disc area ratio	0.922	0.908	0.957
Vertical CDR	Cup area	0.922	0.910	0.957
Vertical CDR	FSM	0.923	0.912	0.956
Vertical CDR	RB	0.924	0.912	0.967
Vertical CDR	GDx NFI	0.953	0.944	0.988
Cup-disc area ratio	Rim-disc area ratio	0.903	0.881	0.932
Cup-disc area ratio	Cup area	0.904	0.881	0.938
Cup-disc area ratio	FSM	0.906	0.886	0.933
Cup-disc area ratio	RB	0.914	0.893	0.962
Cup-disc area ratio	GDx NFI	0.953	0.933	0.989
Rim-disc area ratio	Cup area	0.904	0.881	0.938
Rim-disc area ratio	FSM	0.906	0.886	0.933
Rim-disc area ratio	RB	0.914	0.893	0.962
Rim-disc area ratio	GDx NFI	0.953	0.933	0.989
Cup area	FSM	0.904	0.888	0.918
Cup area	RB	0.907	0.893	0.953
Cup area	GDx NFI	0.945	0.927	0.986
RB	MRA	0.911	0.889	0.959
RB	GDx NFI	0.899	0.864	0.986
FSM	GDx NFI	0.929	0.903	0.988

AUC results ranked for each screening scenario	1st	2nd	3rd

Table 8.9. Comparison of combinations of tests in detecting glaucoma under different screening scenarios.
A) all cause glaucoma vs rest of cohort B) early glaucoma vs rest of cohort without glaucoma C) moderate/advance glaucoma vs rest of cohort.
AUC were compared using chi-square test with Bonferroni correction.

A. All cause glaucoma vs rest of cohort

Classifier		**Corrected AUC**				
VCDR	NFI	0.919 STD	0.919 p=1.00	0.919 p=1.00	0.919 p=1.00	0.919 p=1.00
CDAR	NFI	0.922 p=1.00	0.922 STD	0.922 p=1.00	0.922 p=1.00	0.922 p=0.008
RDAR	NFI	0.922 p=1.00	0.922 p=1.00	0.922 STD	0.922 p=1.00	0.922 p=0.008
LCDR	NFI	0.922 p=1.00	0.922 p=1.00	0.922 p=1.00	0.922 STD	0.922 p=0.08
Cup	NFI	0.912 p=1.00	0.912 p=0.008	0.912 p=0.008	0.912 p=0.08	0.912 STD

B. Early glaucoma vs rest of cohort without glaucoma

Classifier		**Corrected AUC**			
LCDR	NFI	0.909 STD	0.909 p=1.00	0.909 p=1.00	0.909 p=1.00
VCDR	NFI	0.911 p=1.00	0.911 STD	0.911 p=1.00	0.911 p=1.00
CDAR	NFI	0.910 p=1.00	0.910 p=1.00	0.910 STD	0.910 p=1.00
RDAR	NFI	0.910 p=1.00	0.910 p=1.00	0.910 p=1.00	0.910 STD

C. Moderate/advance glaucoma vs rest of cohort

Classifiers		**Corrected AUC**						
VCDR	NFI	0.962 STD	0.962 p=1.00	0.962 p=1.00	0.962 p=1.00	0.962 p=1.00	0.962 p=1.00	0.962 p=1.00
LCDR	NFI	0.966 p=1.00	0.966 STD	0.966 p=1.00	0.966 p=1.00	0.966 p=1.00	0.966 p=1.00	0.966 p=1.00
CDAR	NFI	0.968 p=1.00	0.968 p=1.00	0.968 STD	0.968 p=1.00	0.968 p=1.00	0.968 p=1.00	0.968 p=1.00
RDAR	NFI	0.968 p=1.00	0.968 p=1.00	0.968 p=1.00	0.968 STD	0.968 p=1.00	0.968 p=1.00	0.968 p=1.00
Cup	NFI	0.965 p=1.00	0.965 p=1.00	0.965 p=1.00	0.965 p=1.00	0.965 STD	0.965 p=1.00	0.965 p=1.00
RB	NFI	0.969 p=1.00	0.969 p=1.00	0.969 p=1.00	0.969 p=1.00	0.969 p=1.00	0.969 STD	0.969 p=1.00
FSM	NFI	0.967 p=1.00	0.967 p=1.00	0.967 p=1.00	0.967 p=1.00	0.967 p=1.00	0.967 p=1.00	0.967 STD

STD (standard) indicates the combination which is being compared to.

Table 8.10 Optimal combinations of classifiers and the sensitivity and specificity at the optimum cutoff values

see Appendix for full details of derivation of optimum combinations and cutfoff values

Optimum combinations	Optimum cutoff values	Sensitivity (%)	Specificity (%)
All glaucoma			
VCDR+NFI	VCDR >0.80 + NFI >45	92.86	98.28
LCDR+ NFI	LCDR>0.85 + NFI>45	100	98.16
RDAR +NFI	RDAR <0.30 + NFI>45	100	98.18
CDAR + NFI	CDAR>0.70 + NFI >45	100	98.18
Cup area + NFI	Cup >1.4 + NFI>45	100	98.22
Early			
LCDR+ NFI	LCDR>0.85 + NFI>45	100	98.94
CDAR + NFI	CDAR>0.70 + NFI>45	100	98.96
RDAR+NFI	RDAR <0.30 + NFI>45	100	98.96
VCDR+NFI	VCDR >0.80 + NFI >45	83.33	99.03
Moderate/advance glaucoma			
VCDR +NFI	VCDR >0.80 + NFI >55	40.00	99.81
LCDR+ NFI	LCDR>0.90 + NFI>30	100	99.76
CDAR + NFI	CDAR>0.80 + NFI>45	100	99.77
RDAR+NFI	RDAR <0.20 + NFI>35	100	99.77
FSM+NFI	FSM<-5.5 + NFI >45	100	99.75
Cup+ NFI	Cup >1.50 + NFI >45	42.86	99.79
RB+ NFI	RB<-1.6 & NFI >45	40.00	99.77

Table 8.11 The normative cut-off values of the classifiers and their sensitivity and specificity tested under three diagnostic scenarios

Classifier	Normative cutoff	All cause glaucoma		Early glaucoma		Moderate/ advance glaucoma	
		Sens (%)	Spec (%)	Sens (%)	Spec (%)	Sens (%)	Spec (%)
Disc photo measurements							
Vertical CDR	>0.64	46.4	97.2	29.7	98.7	10.3	99.7
Sup rim-disc ratio	<0.14	44.3	97.3	23.5	98.7	13.1	99.7
HRT							
Overall MRA	ONL	12.9	99.0	6.4	99.5	2.1	99.96
Overall MRA	Borderline	6.1	99.9	3.3	99.9	1.0	99.9
Global MRA	ONL	27.0	98.6	11.5	99.0	6.4	99.8
Global MRA	Borderline	11.8	99.2	6.1	99.5	2.0	99.9
Linear CDR	>0.77	51.6	98.1	29.6	98.9	17.0	99.8
Horizontal CDR	>0.92	21.3	97.8	7.5	98.8	4.8	99.7
Vertical CDR	>0.82	48.0	98.0	25.7	98.9	18.2	99.8
Rim-disc area ratio	<0.41	47.8	98.2	26.5	98.9	15.5	99.8
Cup-disc area ratio	>0.59	10.6	97.9	3.7	98.8	1.8	99.7
Rim area	<0.71	39.2	97.9	18.4	98.8	19.2	99.8
Disc area	>3.11	3.2	97.6	1.6	98.7	0.0	99.6
Cup area	>1.60	39.5	97.9	18.8	98.8	11.1	99.7
Rim volume	<0.09	28.0	97.1	10.0	98.6	11.1	99.6
Cup volume	>0.54	6.5	99.6	3.6	99.8	1.1	99.95
Mean cup depth	>0.43	25.5	97.8	14.6	98.8	0.0	99.6
Cup shape measure	>0.01	37.8	97.9	25.8	98.8	6.1	99.7
Height variation contour	>0.58	3.50	97.7	0.7	98.7	1.42	99.7
Mean RNFL thickness	<0.04	15.6	97.0	5.3	98.6	6.6	99.6
RNFL cross sectional area	<0.15	15.8	97.0	7.7	98.6	3.7	99.6
CLM temp- superior	<0	15.8	97.0	5.9	98.6	6.9	99.6
CLM temp -inferior	<-0.05	23.6	97.1	12.7	98.7	7.4	99.6
FSM	<-3.19	29.8	97.1	15.4	98.6	9.3	99.6
RB	<-0.87	29.4	97.2	15.3	98.7	9.0	99.6
GDx-VCC NFI	>46.0	32.9	97.5	13.6	98.7	7.8	99.7
Average RNFL thickness	<42.7	41.0	97.3	14.0	98.7	13.2	99.7
Sup RNFL thickness	<44.6	35.4	97.2	10.5	98.6	13.2	99.7
Inf RNFL thickness	<45.4	35.3	97.2	8.3	98.6	9.1	99.6
Nasal RNFL thickness	<28.1	7.0	97.1	2.8	98.6	1.2	99.6
Temp RNFL thickness	>57.6	4.0	97.0	1.8	98.6	1.5	99.6
RNFL standard dev	<11.0	26.0	97.2	10.5	98.7	7.5	99.6

Key: Sensitivities ranked for each screening scenario | 1st | 2nd | 3rd |

Normative cutoff is either the <2.5th centile value or >97.5th centile value of the normal population who had no glaucoma and had normal visual fields

Table 8.12 Comparison of right & left eye results: the best performing pairs of classifiers and their area under curve and rank in each diagnostic setting

Combination of classifiers		All cause glaucoma		Early glaucoma		Moderate/ advance glaucoma	
		RE	LE	RE	LE	RE	LE
VCDR	NFI	1st 0.953	1st 0.966	1st 0.944	2nd 0.961	2nd 0.988	2nd 0.980
CDAR	NFI	1st 0.953	2nd 0.964	2nd 0.933	1st 0.963	1st 0.989	1st 0.987
RDAR	NFI	1st 0.953	2nd 0.964	2nd 0.933	1st 0.963	1st 0.989	1st 0.987
LCDR	NFI	2nd 0.952	3rd 0.963	3rd 0.932	2nd 0.961	1st 0.989	1st 0.987
Cup	NFI	3rd 0.945	4th 0.955	4th 0.927	3rd 0.953	3rd 0.986	4th 0.970
FSM	NFI	4th 0.929	10th 0.940	8th 0.903	4th 0.948	2nd 0.988	5th 0.969
VCDR	RB	5th 0.924	5th 0.947	6th 0.912	5th 0.942	4th 0.967	3rd 0.971
RB	NFI	24th 0.899	26th 0.864	23rd 0.921	22nd 0.922	3rd 0.986	5th 0.969

Screening scenario	* Spearman rank correlation coefficient between left and right eye AUC
All cause glaucoma	0.94 (p<0.0001)
Early glaucoma	0.95 (p<0.0001)
Moderate/ advance glaucoma	0.89 (p<0.0001)

* includes all single and pairs of classifiers listed in Table 8.6
p value for null hypothesis that the left and right eye AUC ranks are independent.

8.5 Discussion

8.5.1 Principle Findings

The main aim of this chapter is to examine the effectiveness of disc photo measurements, HRT and GDx-VCC on detecting glaucoma discs in an unselected population. Different screening scenarios – for early and moderate/late glaucoma – were tested, as the diagnostic performance and the best performing classifier will likely alter depending on disease severity. The different screening strategies will also answer different public health needs –to detect the 50% of OAG that are undiagnosed in the community, or to detect late glaucoma to prevent visual loss.

Overall, the HRT classifiers VCDR, LCDR, CDAR, RDAR were the best performing parameters in both screening for early or late glaucoma. VCDR is the cup/disc diameter ratio at the vertical axis, RDAR and CDAR are ratios of the rim area and cup area respectively against the optic disc area, while LCDR is the square root of CDAR, therefore represents an average cup/disc diameter ratio. The reason these classifiers perform well could be because they are ratios and not absolute measurements, and therefore takes into account the large variation in disc morphology in an unselected population. VCDR in particular was the best performing single classifier in all three screening scenarios, which reflects how vertical cup/disc ratio is a cardinal clinical sign used in diagnosing glaucoma by clinicians. Horizontal CDR did not perform as well which may reflect the fact that inferior & superior rims are the first to thin in glaucoma.

Disc photos' vertical CDR, in contrast, was a far less effective classfier than the HRT ratio classifiers. This might reflect the inherent inaccuracies of human disc assessment compared to machine classifiers. In the European Optic Disc Assessment Trial, which compared the diagnostic accuracy of glaucoma specialists (using stereo disc slides), HRT and GDx-VCC in discriminating between healthy and glaucomatous eyes, HRT MRA and GDx-VCC NFI outperformed every clinician in its diagnostic accuracy (80.5% clinician, 93.2% NFI, 89.8% MRA), while a large variability in diagnostic accuracy and agreement was demonstrated among clinicians.[149]

NFI was the best performing GDx-VCC parameter, which was a consistent finding in many studies.[236,248-250,252] On its own, it only ranked 7th for detecting all cause glaucoma and 9th for early glaucoma among all classifiers, but adding NFI to most HRT classifiers significantly improved their performances, and produced the best performing combinations in all screening scenarios. This reflects the fundamental difference

between disc morphology and RNFL assessment, and that a combined approach requiring abnormality in both tests was a more robust method to diagnose glaucoma. NFI performed much better at detecting moderate/late glaucoma (AUC 0.93, ranked 3rd) than early or all cause glaucoma, and this could mean RNFL changes it detected occurred later in disease.

Among published studies, the best performing HRT classifiers have variably been reported as FSM, Bathija discriminant function, and cup shape measure in case control studies. In studies that included both HRT and GDx-VCC, NFI have been shown to be the best classifier by Badala *et al*[252] and Medeiros *et al*,[334] although both also found OCT to be better than either HRT or GDx-VCC classifiers. However, clinic-based case control studies results cannot be extrapolated to screening in an unselected population. The two groups in a case-control setting are more clearly different, while an unselected population will include a large number of subjects with uncertain diagnosis, and include a large variation in disc sizes, difficult to grade discs, small, myopic, and tilted discs.

In a mass screening setting, the Singapore Malay Study compared four HRT classifiers: Mikelberg, Burk and Bathija discriminant functions, as well as MRA in a Malay population, and found the best classifiers in order were MRA, Bathija, Mkibelberg, and Burk discriminant functions.[229] The Rotterdam Study showed that disc adjusted LCDR was the best classifier among all HRT parameters.[231] There were no studies on the performance of HRT and GDx-VCC in a mass screening setting with which to compare our findings, however, like the Rotterdam Study, which studied all HRT classifiers rather than a selected few, we found HRT ratio classifiers the most effective in differentiating glaucoma from normal eyes.

8.5.2 Application to Mass Screening

An ideal screening test should have both high sensitivity and specificity. The normative values found using the 2.5th or 97.5th centile values of the normal subjects produced high specificities of at least 97.0% but low sensitivities. The sensitivities were lower for moderate/late glaucoma than early glaucoma, indicating that these normative thresholds capture mainly healthy rather than glaucomatous eyes, and as such, were not suitable for detecting glaucoma. They would however, be suitable for excluding glaucoma. At a specificity of 97%, 3% of true glaucoma will be missed. The definition of a “normal population” is open to interpretation. Apart from having normal visual fields and optic discs, the GDx-VCC manufacturer’s normative database also required normal subjects to have IOP <22mmHg, CDR asymmetry of <0.2, and visual acuity of

at least 20/40; for the HRT normative database, subjects also had less than 6 dioptres refractive error, no history of diabetes, ocular surgery, glaucoma or first degree family history of glaucoma, and not be on systemic beta blocker medication.[335] In this analysis, we did not adopt such strict criteria, but defined “normal” as not having glaucoma, instead of being “hyper-normal”, as our aim is to describe the distribution of phenotypes in the non-glaucoma population. This also explains why our normative thresholds have relatively low diagnostic sensitivities but high specificities.

With two classifiers in combination, and using cutoff values that were higher than the normative values, sensitivities were much improved. For each screening scenario, there was at least one combination of NFI with an HRT classifier that produced sensitivity of 100% and specificity of above 98%. However, the main obstacle to putting that into practice in a real screening programme would be the high proportion (37%) of HRT and GDx-VCC scans that were of inadequate quality among glaucoma subjects. Of the glaucoma subjects who had both HRT and GDx-VCC scans performed, 24.8% had inadequate quality for both scans.

HRT and GDx-VCC are increasingly being substituted by OCT in clinical practice. OCT has the distinct economical advantage of having multiple uses as it also images the macula and retina. OCT bears some similarity to GDx-VCC as it images para-papillary RNFL thickness, and its performance is comparable to HRT and GDx-VCC.[255-258] In addition it images the premacular ganglion cell complex which has also shown to be effective in glaucoma detection.[259-261] In principle, it is possible that OCT used in combination with HRT or GDx-VCC may also produce high sensitivity and specificity just like HRT and GDx-VCC did.

8.5.3. Limitations

There are several limitations to our findings. While neither disc photo measurements, HRT nor GDx-VCC results were used in reaching the final glaucoma diagnoses, HRT and GDx-VCC were used in the identification of high risk individuals for full examination (see Chapter 2 Methods), while disc photos CDR was used to identify possible missed cases in the referral refinement process (see Chapter 3 Glaucoma Diagnosis Methods). This could have led to biases that improved the performance of these tests. Secondly, not all subjects underwent visual field test by design of the study. Only 13.8% of non-glaucoma subjects and 66.8% of all cause glaucoma subjects had visual field done. This would lead to a bias of possible undetected glaucoma subjects in the non-glaucoma group.

8.6 Conclusion

This chapter examined the abilities of different optic disc imaging modalities – disc photography, GDX-VCC and HRT II – in diagnosing glaucoma in an unselected population setting. Each available test parameters for the three modalities were included, and their abilities do detect glaucomatous eyes in different screening scenario were thoroughly tested. The aim was to find the single test or combinations of tests in detecting glaucoma, which may be useful in population-based glaucoma screening. The best performing individual test paramteres were the HRT cup/disc ratios, but when combined with the NFI of GDX-VCC, high sensitivities and specificities were achieved. However, the need for adequate quality scans in two imaging modalities, as well as the cost incurred of running two devices, means this finding is unlikely to be adopted in practice.

CHAPTER 9: DISCUSSION

This thesis has set out to explore the characteristics of POAG and the issues around its detection in the community through the data available in the EPIC-Norfolk Eye Study, a nested cross-sectional study of the EPIC-Norfolk cohort.

9.1 Study Design and Impact on Glaucoma Diagnosis

Choice of glaucoma definition

The definition of glaucoma used in this study was the conventional, widely-accepted definition as the presence of structural and functional evidence of glaucomatous optic neuropathy (judged on disc photography). The ISGEO diagnostic criteria, designed for population surveys and based on the 97.5th and 99.5th centile of the population's CDR, was not used. This is due to the large number of missing of disc photos in the study. The ISGEO principle was however, applied as an extra method to identify potential missed diagnosis in the glaucoma refinement process.

Missing data and the impact on diagnosis

Missing data is unavoidable in studies on a population scale. The low rate of data availability for disc photos (89%) and visual fields (17%) were of particular concern. The paucity for disc photos was believed to be due to poor quality images not being saved in the early stages of the study. VF by design, was performed only in a proportion of subjects, proposed to be all those who failed the initial screening test, plus an extra 1:10 of random participants. Both these factors are likely to cause under-diagnosis of glaucoma. Nevertheless, a rigorous multi-stage, largely objective process was used in generating glaucoma diagnosis, involving screening for high risk individuals, diagnosis after clinical examination by consultant glaucoma specialist, and a final refinement process to scrutinize all diagnosed cases by a second glaucoma consultant, and to detect potential missed cases. The potential for missed glaucoma cases has been minimized as much as possible.

How representative is the EPIC-Norfolk data?

The EPIC-Norfolk study population is different and not totally representative from the general population of Norfolk and the UK, due to the method of recruitment and the low

response rate. They differ in sex and age distribution, and EPIC-Norfolk participants are possibly healthier, and better educated about health due to the volunteer nature of recruitment. For these reasons, the estimates of glaucoma generated in this study were not used to predict the wider population's prevalence of POAG. Nevertheless, the subsequent key findings on corneal biomechanics and glaucoma, the over-reliance of IOP in glaucoma detection, and the diagnostic performance of imaging technologies are unlikely to be significantly biased as a result. In fact, the EPIC-Norfolk Eye Study is important as the most current eye study in the UK. Its value lies in the large participant number (8623), and the wealth of ophthalmic and non-ophthalmic data, from which generated many findings and publications.

9.2 Role of Intraocular Pressure in Glaucoma Case Detection

The role of IOP in glaucoma case detection was brought under scrutiny by the results in Chapters 6 and 7. Having NTG rather than HTG was shown to be the most powerful risk factor for undiagnosed POAG, as well as lower pre-treatment IOP, suggesting there has been an over reliance on IOP to exclude glaucoma in the community. The conventional referral threshold of >21mmHg was challenged by examining the IOP distribution in the cohort, which found the upper limit of distribution (mean+2SD or 97.5th centile) to be approximately 24mmHg using ORA IOPg or 22mmHg using NCT. While this does not completely replicate the original Hollows and Graham study, in which the threshold of 21mmHg was derived based on GAT data on a Welsh population, this results support increasing the IOP referral threshold. The burden of false positive referrals will be reduced significantly by a modest increase. While OAG cases could be missed with a higher threshold, IOP on its own is not diagnostic of glaucoma, and the importance of relying on optic disc assessment to detect or rule out glaucoma is particularly relevant in this argument. By increasing the threshold to no more than 25mmHg, those who might need IOP lowering treatment for ocular hypertension and who have healthy, non-glaucomatous discs will not be missed. These findings were presented to the NICE committee, and were influential in changing national policy. In the latest updated NICE guidelines published in November 2017, the IOP referral threshold is increased to >24mmHg, and the threshold for commencing treatment for OHT has also been simplified to >24mmHg, if the patient is deemed likely to lose vision in their lifetime.[1]

9.3 Relationship of Corneal Biomechanics in POAG

To our knowledge, the EPIC-Norfolk Eye Study is the first large-scale population study that reports the relationship of ORA metrics (IOPg, IOPcc, CH and CRF) and glaucoma diagnosis. In Chapter 6, we demonstrated a strong association of POAG with higher IOPg, IOPcc and lower CH, but not with CRF. In Chapter 7, IOPcc was shown to have a greater AUC than IOPg in differentiating glaucomatous and non-glaucomatous eyes. IOPcc and CH could be potentially useful new parameters in glaucoma management. In particular, the logistic model with IOPcc showed the greatest variance among the four ORA metrics, slightly higher than the model with IOPg.

IOPcc and CH actually reflect very different aspects of corneal biomechanics. IOPcc is an IOP metric that is calibrated to be independent of corneal influence, while CH is a measure of the cornea's ability to absorb and dampen stresses. Lower CH is hypothesized to reflect an inability of the lamina cribrosa to withstand physical stresses from varying IOP, and is therefore a measure of pathogenesis importance. IOPcc could be the IOP measure that is more reflective of "true" IOP and free of the measurement error inflicted by different CCT, and therefore potentially more useful than IOPg or GAT IOP.

The findings from Chapter 6 should prompt further research into how IOPcc and CH change in glaucoma, how they can best be used in predicting or managing glaucoma, and whether they have the potential to be the next "modifiable risk factor".

9.4 The Role of Automated Imaging Detecting Glaucomatous Discs in a Population Setting

As demonstrated in previous chapters, there is a need to improve the accuracy of detecting glaucomatous discs in the community to reduce the number of undiagnosed glaucoma cases, which is 40% in this study and 50% in other European population studies. The use of imaging technology in detecting glaucomatous discs in a population setting is explored in Chapter 8. These devices carry the advantages of being automated, independent, reproducible, and non-invasive. When considering their use in a population screening, there are several important considerations: the severity of glaucoma that needs to be detected (early vs advanced disease), the choice of classifier (e.g. cup/disc ratio, HRT-MRA, GDx-NFI), the choice of a specific cut-off value, the diagnostic performance of the chosen test and chosen cutoff value, and

ultimately the cost effectiveness and practicality of applying the test on a general population.

We found that HRT's cup/disc ratio classifiers provide the best diagnostic abilities out of all the classifiers tested when used on their own, and were superior to cup/disc ratio from manual grading of disc photos, with AUC >0.90. When combined with GDx-VCC's NFI, the AUC increase to 0.93-0.99. By accounts of our results, both high sensitivity and specificity are achievable in screening for both early or moderate/advance disease, but it requires using two classifiers in combination – an HRT cup/disc ratio with GDx's NFI, which can generate sensitivity of 100% and specificity of 98%. However, these results are based on cut-off values generated specifically in this study, and would need to be tested in another independent population. Their performance in a population screening scenario is unknown, and is likely to be poorer.

In comparison, the performances of in-built machine classifiers, such as the MRA, produces high specificity (>99%) but low sensitivity (<13%) in diagnosing all cause glaucoma. Normative values (<2.5th centile or >97.5th centile of the study population's value) for HRT cup/disc ratios also produce high specificities of 98%, but sensitivities were only approximately 50% for diagnosing all cause glaucoma. However, the high specificities of both the MRA and HRT normative values can be potentially put to good use in excluding normal individuals from further investigation. In particular, the MRA could be particularly useful as no specific numeral cutoff value would need to be chosen as its results are already divided into three distinct categories.

Based on our findings, the main limitations of using the disc imaging devices on a population level is that two devices are required to produce both high sensitivities and specificities, which would be too costly. It also means that only 75% of the study participants produce scans of high adequate qualities for both tests. These would need to be properly assessed in an economic model.

New imaging technology, notably the OCT, is now widely available. While HRT and GDx-VCC are still widely used, they are at risk of being superseded, as OCT has the practical advantage of also imaging the retina, and most ophthalmic units would therefore only require one machine for both their retina and glaucoma practices. A Health Technology Assessment report directly compared the performance of HRT-MRA, HRT-GPS, GDx and OCT in diagnosing glaucoma in 950 patients who were referred to the hospital eye service for suspected glaucoma.[336] It found that HRT-MRA provided the highest sensitivity (87%) but lowest specificity (65%), while GDx had the

lowest sensitivity (35%) but the highest specificity (97%); HRT GPS and OCT results were intermediate. It found that combining two imaging tests only improved the results marginally. It also showed these tests useful in ruling in or ruling out glaucoma when used in combination with IOP and visual acuity assessment as a triage test. However, only the triage tests using HRT-MRA were cost-effective. Adopting this composite triage of tests is relatively inexpensive (<£30) including tonometry and visual acuity testing.[336] It would be cost-effective compared with current practice of seeing all community referrals by a clinician.

While automated imaging in glaucoma is years ahead of other ophthalmic conditions, the technology in retinal disease imaging is catching up. Software developed to grade diabetic retinopathy from fundus images shows comparable sensitivity to human graders and sufficient specificity for it to be used as alternatives to manual graders.[337] A more exciting development is the latest use of artificial intelligence and deep learning, which is able to "learn" to distinguish abnormal retinal OCT images from training images, and make referral recommendations that equals or exceeds that of experts on a range of sight threatening retinal diseases.[338] Glaucoma imaging seem ripe to be the next target for deep learning, and we may look forward to accurate machine-based automated glaucoma diagnosis that may outperform current existing machine classifiers in OCT, HRT or GDx-VCC.

Overall, based on our results, optic disc imaging technology has the potential to improve the diagnosis of glaucomatous disc on a population scale. Further independent verification of their performance in a different population and careful economic analysis is required.

9.5 Limitations of Study

A fundamental limitation of the study, as mentioned earlier, is that the participants do not fully represent the local Norfolk or the UK population. This stems from the recruitment process, which recruited the surviving participants of the parent EPIC-Norfolk cohort, rather than cluster sampling of the local population to derive a study population that is representative in age and sex strata of the UK population.

In the study design, it would have been immensely useful if all participants had undergone visual field test by default, rather than a subset of individuals with abnormal screening tests. While it will be more time consuming and costly, visual field defect is

part of the glaucoma definition, so the resultant glaucoma diagnosis dataset will have fewer missed cases.

In analyzing the association of glaucoma and corneal biomechanics in Chapter 6, the limited availability of central corneal thickness data only among those at risk of glaucoma means it cannot be included in the study without causing bias. The inclusion of central corneal thickness measurement in every participant as part of their baseline screening test will be crucial in answering the question, how the different corneal biomechanical factors such as hysteresis and corneal thickness interact, and their roles as markers or risk factors of glaucoma. It will be particularly statistically powerful if present in such a large dataset.

Finally, a decision in the basic design of the study to use GDx-VCC and HRT rather than OCT as the disc imaging modality, means the data in the study is now almost obsolete as GDx-VCC and HRT are rarely used now. With hindsight, these two imaging modalities were already widely used clinically at the time, while OCT was an emerging technology in glaucoma imaging. The study is more likely to be relevant and to discover new findings if a younger imaging technology was used. On the other hand, the choice of ORA tonometry, at the time a relatively little-used tonometer, is a rather inspired decision on hindsight. With the subsequent explosion of corneal biomechanics studies and the increasing dominance of ORA in clinical practice, novel findings were discovered in this study.

9.6 Implications to Future Glaucoma Care in the UK

The thesis confirmed the incongruity in current POAG detection – a large burden of glaucoma suspects and ocular hypertensives (16% of study population), while 34% of POAG cases are undiagnosed. There is currently a significant capacity issue in the HES, which is unable to meet the demand for timely glaucoma appointments, putting patients at risk of visual loss.[339,340] With an ageing population, the pressures on the hospital glaucoma service is only going to increase, with more people expected to be referred, and more requiring screening, monitoring and treatment. The tariff for seeing follow-up glaucoma patients is also being driven down. The priorities of glaucoma care in the future will be to meet these demands while providing safe, efficient and timely care at a lower cost.

In response to these challenges, new models of care have been developed in recent years. They aim to improve the quality of referrals (such as referral refinement, enhanced case-finding, and repeat measurement service), and to triage and risk stratify existing HES patients so those with complex or unstable glaucoma can be reviewed in ophthalmologists-led clinics, while glaucoma suspects or low-risk stable glaucoma patients who can be monitored remotely in virtual clinics or in community based clinics.

This thesis has identified possible solutions to the current HES challenges. NICE has now raised the IOP referral threshold in response to our results, which should reduce the burden of false positive referrals from the community, The findings that smaller CDR is associated with undiagnosed glaucoma means the quality of referrals can be improved by focusing on optic disc assessment. This can be achieved through better training of optometrists and ophthalmologists in identifying glaucomatous discs, and maybe using automated imaging technology as a useful adjunct. However, while our data show that HRT combined with GDx-VCC produce excellent diagnostic performance in identifying glaucomatous discs, how that can be adopted in a screening programme that is cost effective, and avoids the pitfall of generating unnecessary referrals to the NHS, remains a challenge.

9.7 Future Direction

The work presented in this thesis raises questions that will merit further research and investigation. One of them is how corneal biomechanical measurements can be used in the management of glaucoma. At the moment, CCT is the only corneal bioemechanical metric widely used clinically to risk stratify patients, but it is still debatable whether it is truly an independent risk factor of glaucoma, or whether it is merely reflecting the under-measurement of IOP. Fundamentally, we do not understand how CCT, corneal hysteresis, IOPg and IOPcc are interrelated, how they alter with time, and with treatment.

Ultimately we need longitudinal studies and interventional trials to examine the natural history of these metrics, specifically, how they change with age, with glaucoma progression, and with pressure-lowering treatment. This will allow us to untangle their relative roles in glaucoma, and identify the metrics most useful in risk stratification and in monitoring glaucoma.

The idea of mass screening for glaucoma has been explored in several studies in the past, but the lack of an effective screening test is a major hurdle. OCT has now surpassed HRT or GDx as the optic disc imaging of choice. Its use in other areas of ophthalmology, particularly in retina, means research into OCT and the investment to improve this technology continue to grow rapidly. It is therefore reasonable to assume that OCT will be the main glaucoma imaging modality for the foreseeable future. It will therefore be useful to examine the clinical effectiveness of using of OCT in glaucoma mass screening, and economic modelling of a screening programme that includes its use.

A promising development in future glaucoma care is the possibility of using AI to screen optic disc images. The hope is for it to effectively identifying low risk glaucoma suspects who do not further monitoring, allowing them to be discharged, while also ensuring high risk individuals are not missed. Genetic testing is another area that holds great potential. Private companies already offer off–the-shelf DNA kits and DNA analysis services that are widely used in ancestry tracing, but they also offer health screening. These range from screening for inherited diseases such as breast cancer, cystic fibrosis, and sickle cell anaemia, to quantifying risks to conditions such as Alzheimers, Parkinson’s and age-related macular degeneration. Screening for individuals at risk of POAG may allow more targeted monitoring of glaucoma suspects, thereby freeing the need for low risk individuals from further monitoring.

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APPENDIX: Derivation of optimum combinations and cutoff values for HRT II and GDX-VCC classifiers

This appendix describes the method used to derive the optimum combination of test cutoffs that was used in **Chapter 8, section 8.4.4**.

A1.1 Determining the best performing pair of classifier

The pairs of test classfiers with the highest AUC were determined in **Chapter 8, section 8.4.4 (Table 8.10)** for each screening scenario. They were: VDR+NFI, CDAR +NFI RDAR NFI, LCDR+NFI, cup+NFI, RB+NFI, and FSM+NFI. To directly compare their diagnostic abilities and hence their AUC, multiple logistic regression modelling (e.g. 1= eyes with glaucoma vs 0= eyes with no glaucoma) was used to compare the AUC for these pairs of classifiers, for the three screening scenarios (detecting all cause glaucoma vs rest of cohort, early glaucoma vs rest of cohort without glaucoma, and moderate/advance glaucoma vs rest of cohort). The results in **Table 1** show that no particular pair of classifier was significantly better than another (p=1.00 for all comparisons). Therefore in the subsequent section, the optimum cutoff value for every pair of classifiers will be explored.

A1.2 Exploring the optimum cutoff value

The optimum cutoff values for the pairs of classifiers were ascertained by altering each classifier value stepwise (see **Tables 2A-2C**). The values that provided the highest sensitivity at high specificity were deemed the optimum and were highlighted in yellow the tables. The optimum values are summarized in **Chapter 8, table 8.8.**

Appendix Table 1 Comparison of combinations of tests using multiple logistic regression modelling in detecting glaucoma different screening scenarios

A) All cause glaucoma vs rest of cohort

Classifier		**Corrected AUC**				
VCDR	NFI	0.919 STD	0.919 p=1.00	0.919 p=1.00	0.919 p=1.00	0.919 p=1.00
CDAR	NFI	0.922 p=1.00	0.922 STD	0.922 p=1.00	0.922 p=1.00	0.922 p=0.008
RDAR	NFI	0.922 p=1.00	0.922 p=1.00	0.922 STD	0.922 p=1.00	0.922 p=0.008
LCDR	NFI	0.922 p=1.00	0.922 p=1.00	0.922 p=1.00	0.922 STD	0.922 p=0.08
Cup	NFI	0.912 p=1.00	0.912 p=0.008	0.912 p=0.008	0.912 p=0.08	0.912 STD

B) Early glaucoma vs rest of cohort without glaucoma

Classifier		**Corrected AUC**			
LCDR	NFI	0.909 STD	0.909 p=1.00	0.909 p=1.00	0.909 p=1.00
VCDR	NFI	0.911 p=1.00	0.911 STD	0.911 p=1.00	0.911 p=1.00
CDAR	NFI	0.910 p=1.00	0.910 p=1.00	0.910 STD	0.910 p=1.00
RDAR	NFI	0.910 p=1.00	0.910 p=1.00	0.910 p=1.00	0.910 STD

C) Moderate/advance glaucoma vs rest of cohort

Classifiers		**Corrected AUC**						
VCDR	NFI	0.962 STD	0.962 p=1.00	0.962 p=1.00	0.962 p=1.00	0.962 p=1.00	0.962 p=1.00	0.962 p=1.00
LCDR	NFI	0.966 p=1.00	0.966 STD	0.966 p=1.00	0.966 p=1.00	0.966 p=1.00	0.966 p=1.00	0.966 p=1.00
CDAR	NFI	0.968 p=1.00	0.968 p=1.00	0.968 STD	0.968 p=1.00	0.968 p=1.00	0.968 p=1.00	0.968 p=1.00
RDAR	NFI	0.968 p=1.00	0.968 p=1.00	0.968 p=1.00	0.968 STD	0.968 p=1.00	0.968 p=1.00	0.968 p=1.00
Cup	NFI	0.965 p=1.00	0.965 p=1.00	0.965 p=1.00	0.965 p=1.00	0.965 STD	0.965 p=1.00	0.965 p=1.00
RB	NFI	0.969 p=1.00	0.969 p=1.00	0.969 p=1.00	0.969 p=1.00	0.969 p=1.00	0.969 STD	0.969 p=1.00
FSM	NFI	0.967 p=1.00	0.967 p=1.00	0.967 p=1.00	0.967 p=1.00	0.967 p=1.00	0.967 p=1.00	0.967 STD

STD Standard to which the tests are compared

Appendix Table 2A Exploring the sensitivities and specificities of different cutoffs for differentiating all cause glaucoma vs the rest of cohort.

(The values providing the highest sensitivity at high specificity are highlighted in yellow)

Classifiers	Sens (%)	Spec (%)	Classifier	Sens (%)	Spec (%)
Rim-disc area ratio + NFI			**Cup Area+ NFI**		
NFI>45 + RDAR <0.20	100	98.07	NFI >45 + Cup >1.0	64.00	98.34
NFI>45 + RDAR <0.25	100	98.14	NFI >45 + Cup >1.2	77.78	98.30
NFI>45 + RDAR <0.30	100	98.18	NFI >45 + Cup >1.4	100	98.22
NFI>45 + RDAR <0.35	85.71	98.26	NFI >45 + Cup >1.5	100	98.22
NFI>45 + RDAR <0.40	87.50	98.30	NFI >45 + Cup >1.6	100	98.20
RDAR <0.30 + NFI>35	90.00	98.20	Cup >1.4 + NFI>35	73.68	98.30
RDAR <0.30 + NFI>40	90.00	98.20	Cup >1.4 + NFI>40	81.25	98.28
NFI>45 + RDAR <0.30	100	98.18	Cup >1.4 + NFI>45	100	98.22
RDAR <0.30 + NFI>50	100	98.12	Cup >1.4 + NFI>50	100	98.18
RDAR <0.30 + NFI>55	100	98.09			
Vertical CDR + NFI					
NFI>46 + VCDR >0.65	77.14	98.57			
NFI>46 + VCDR >0.70	83.33	98.53			
NFI>46 + VCDR >0.75	88.00	98.46			
NFI>46 + VCDR >0.80	92.86	98.28			
NFI>46 + VCDR >0.85	87.50	98.16			
VCDR >0.80 + NFI >35	82.35	98.3			
VCDR >0.80 + NFI >40	82.35	98.3			
VCDR >0.80 + NFI >45	92.86	98.28			
VCDR >0.80 + NFI >50	91.67	98.24			
VCDR >0.80 + NFI >55	90.00	98.20			
Cup-disc area ratio +NFI					
NFI>45 + CDAR >0.6	87.50	98.30			
NFI>45 + CDAR >0.65	85.71	98.26			
NFI>45 + CDAR >0.70	100	98.18			
NFI>45 + CDAR >0.75	100	98.14			
NFI>45 + CDAR >0.80	100	98.07			
CDAR>0.70 + NFI >35	90.00	98.20			
CDAR>0.70 + NFI >40	90.00	98.20			
CDAR>0.70 + NFI >45	100	98.18			
CDAR>0.70 + NFI >50	100	98.12			
HRT Linear CDR + NFI					
NFI >45 + LCDR>0.70	80.95	98.36			
NFI >45 + LCDR>0.75	88.24	98.32			
NFI >45 + LCDR>0.80	86.67	98.28			
NFI >45 + LCDR>0.85	100	98.16			
NFI >45 + LCDR>0.90	100	98.03			
LCDR>0.85 + NFI>35	87.50	98.16			
LCDR>0.85 + NFI>40	87.50	98.16			
LCDR>0.85 + NFI>45	100	98.16			
LCDR>0.85 + NFI>50	100	98.09			
LCDR>0.85 + NFI>55	100	98.07			

Appendix Table 2B Exploring the sensitivities and specificities of different cutoffs in differentiating early glaucoma vs rest of cohort without glaucoma

(The values providing the highest sensitivity at high specificity are highlighted in yellow)

Classifier	Sensitivity (%)	Specificity (%)
Linear CDR + NFI		
NFI >45 + LCDR>0.70	54.55	99.03
NFI >45 + LCDR>0.75	75.00	99.03
NFI >45 + LCDR>0.80	71.43	99.01
NFI >45 + LCDR>0.85	100.00	98.94
NFI >45 + LCDR>0.90	No +	98.90
LCDR>0.85 + NFI>35	66.67	98.96
LCDR>0.85 + NFI>40	66.67	98.96
LCDR>0.85 + NFI>45	100	98.94
LCDR>0.85 + NFI>50	100	98.94
LCDR>0.85 + NFI>55	100	98.94
Rim-disc area ratio + NFI		
NFI>45 + RDAR <0.25	100	98.94
NFI>45 + RDAR <0.30	100	98.96
NFI>45 + RDAR <0.35	66.67	99.01
NFI>45 + RDAR <0.40	71.43	99.03
RDAR <0.30 + NFI>35	75	98.99
RDAR <0.30 + NFI>40	75	98.99
RDAR <0.30 + NFI>45	100	98.96
RDAR <0.30 + NFI>50	100	98.94
RDAR <0.30 + NFI>55	100	98.94
Vertical CDR + NFI		
NFI>46 + VCDR >0.65	57.89	99.15
NFI>46 + VCDR >0.70	66.67	99.13
NFI>46 + VCDR >0.75	72.73	99.09
NFI>46 + VCDR >0.80	83.33	99.03
NFI>46 + VCDR >0.85	80.00	99.01
VCDR >0.80 + NFI >35	62.50	99.03
VCDR >0.80 + NFI >40	62.50	99.03
VCDR >0.80 + NFI >45	83.33	99.03
VCDR >0.80 + NFI >50	83.33	99.03
VCDR >0.80 + NFI >55	83.33	99.03
VCDR >0.80 + NFI >60	80.00	99.01
Cup-disc area ratio +NFI		
NFI>45 + CDAR >0.60	71.43	99.03
NFI>45 + CDAR >0.65	66.67	99.01
NFI>45 + CDAR >0.70	100	98.96
NFI>45 + CDAR >0.75	100	98.94
CDAR>0.70 + NFI>35	75.00	98.99
CDAR>0.70 + NFI>40	75.00	98.99
CDAR>0.70 + NFI>45	100	98.96
CDAR>0.70 + NFI>50	100	98.94

Appendix Table 2C Exploring the sensitivities and specificities of different cutoffs in differentiating moderate/ advance glaucoma vs rest of cohort

(The values providing the highest sensitivity at high specificity are highlighted in yellow)

Classifiers	Sens (%)	Spec (%)	Classifiers	Sens (%)	Spec (%)
Linear CDR + NFI			**Cup-disc area ratio + NFI**		
NFI >45 + LCDR>0.60	16.22	99.85	NFI>45 + CDAR >0.60	36.36	99.81
NFI >45 + LCDR>0.65	16.00	99.81	NFI>45 + CDAR >0.65	40.00	99.81
NFI >45 + LCDR>0.70	26.67	99.81	NFI>45 + CDAR >0.70	66.67	99.81
NFI >45 + LCDR>0.75	33.33	99.81	NFI>45 + CDAR >0.75	75.00	99.79
NFI >45 + LCDR>0.80	36.36	99.81	NFI>45 + CDAR >0.80	100	99.77
NFI >45 + LCDR>0.85	60.00	99.78			
NFI >45 + LCDR>0.90	100	99.76	CDAR>0.80 + NFI>35	100	99.77
			CDAR>0.80 + NFI>40	100	99.77
LCDR>0.90	66.67	99.66	CDAR>0.80 + NFI>45	100	99.77
LCDR>0.90 + NFI>30	100	99.76	CDAR>0.80 + NFI>50	100	99.75
LCDR>0.90 + NFI>35	100	99.76			
LCDR>0.90 + NFI>40	100	99.76	**RB discriminant + NFI**		
LCDR>0.90 + NFI>45	100	99.76	NFI>45 & RB <-1.8	40.00	99.77
LCDR>0.90 + NFI>50	100	99.74	NFI>45 & RB <-1.6	40.00	99.77
			NFI>45 & RB <-1.5	33.33	99.77
Cup area + NFI			NFI>45 & RB <-1.0	15.38	99.77
NFI>45 + Cup >0.50	12.28	99.87			
NFI>45 + Cup >1.00	20.00	99.81	RB<-1.6 & NFI >35	40.00	99.77
NFI>45 + Cup >1.30	30.77	99.81	RB<-1.6 & NFI >40	40.00	99.77
NFI>45 + Cup >1.50	42.86	99.79	RB<-1.6 & NFI >45	40.00	99.77
NFI>45 + Cup >1.60	42.86	99.79	RB<-1.6 & NFI >50	25	99.75
NFI>45 + Cup >1.70	25.00	99.75			
			Rim-disc area ratio + NFI		
Cup >1.60 + NFI >35	37.50	99.79	NFI>45 + RDAR <0.20	100	99.77
Cup >1.60 + NFI >40	42.86	99.79	NFI>45 + RDAR <0.25	75	99.79
Cup >1.60 + NFI >45	42.86	99.79	NFI>45 + RDAR <0.30	66.67	99.81
Cup >1.60 + NFI >50	40.00	99.77	NFI>45 + RDAR <0.35	40	99.81
Cup >1.60 + NFI >55	40.00	99.77	NFI>45 + RDAR <0.40	36.36	99.81
Vertical CDR + NFI			RDAR <0.20	66.67	99.67
NFI>45 + VCDR >0.65	17.14	99.85	RDAR <0.20 + NFI>35	100	99.77
NFI>45 + VCDR >0.70	20.00	99.85	RDAR <0.20 + NFI>40	100	99.77
NFI>45 + VCDR >0.75	24.00	99.85	RDAR <0.20 + NFI>45	100	99.77
NFI>45 + VCDR >0.80	35.71	99.83	RDAR <0.20 + NFI>50	100	99.75
NFI>45 + VCDR >0.85	12.50	99.75			
			FSM discriminant + NFI		
VCDR >0.80 + NFI >40	35.29	99.85	NFI>45 + FSM <-3.0	33.33	99.79
VCDR >0.80 + NFI >45	35.71	99.83	NFI>45 + FSM <-4.0	50.00	99.77
VCDR >0.80 + NFI >50	33.33	99.81	NFI>45 + FSM <-4.5	50.00	99.77
VCDR >0.80 + NFI >55	40.00	99.81	NFI>45 + FSM <-5.0	50.00	99.75
VCDR >0.80 + NFI >60	37.5	99.79	NFI>45 + FSM <-5.5	100	99.75
			FSM<-5.5 + NFI >45	100	99.75
			FSM<-5.5 + NFI >55	100	99.75
			FSM<-5.5 + NFI >65	100	99.75
			FSM<-5.5 + NFI >70	100	99.75
			FSM<-5.5 + NFI >75	100	99.76

Glaucoma and intraocular pressure in EPIC-Norfolk Eye Study: cross sectional study

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ABSTRACT

OBJECTIVES

To report the distribution of intraocular pressure (IOP) by age and sex and the prevalence of glaucoma.

DESIGN

Community based cross sectional observational study.

SETTING

EPIC-Norfolk cohort in Norwich and the surrounding rural and urban areas.

PARTICIPANTS

8623 participants aged 48-92 recruited from the community who underwent ocular examination to identify glaucoma.

MAIN OUTCOME MEASURES

Prevalence and characteristics of glaucoma, distribution of IOP, and the sensitivity and specificity of IOP for case finding for glaucoma.

RESULTS

The mean IOP in 8401 participants was 16.3 mm Hg (95% confidence interval 16.2 mm Hg to 16.3 mm Hg; SD 3.6 mm Hg). In 363 participants (4%), glaucoma was present in either eye; 314 (87%) had primary open angle glaucoma. In the remaining participants, glaucoma was suspected in 607 (7%), and 863 (10.0%) had ocular hypertension. Two thirds (242) of those with glaucoma had previously already received the diagnosis. In 76% of patients with newly diagnosed primary open angle glaucoma (83/107), the mean IOP was under the threshold for ocular hypertension (21 mm Hg). No one IOP threshold provided adequately high sensitivity and specificity for diagnosis of glaucoma.

CONCLUSIONS

In this British community, cases of glaucoma, suspected glaucoma, and ocular hypertension represent a large number of potential referrals to the hospital eye service. The use of IOP for detection of those with glaucoma is inaccurate and probably not viable.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Glaucoma is the leading cause of irreversible blindness in the world and the second most common cause of registered blindness in England and Wales

The management of glaucoma, suspected glaucoma, and ocular hypertension accounts for a considerable amount of NHS outpatient resources

While the prevalence of glaucoma has been reported in many population studies worldwide, there are no recent data for the UK

WHAT THIS STUDY ADDS

This study provides the most current data on prevalence and type of glaucoma in a British community and identified a large number of people with ocular hypertension and suspected glaucoma

The large number of people with confirmed glaucoma and intraocular pressure under the threshold for ocular hypertension (21 mm Hg) reinforces the weakness of reliance on this for detection of glaucoma

Introduction

Glaucoma is the leading cause of irreversible blindness in the world[1] and the second most common cause of registered blindness in England and Wales.[2] It comprises a group of ocular diseases of progressive damage to the optic nerve, with characteristic structural changes to the optic disc and visual field defects.[3] Glaucoma and suspected glaucoma combined account for the sixth largest share of National Health Service (NHS) outpatient attendances in England, after general medical examination, breast cancer, schizophrenia, prostate cancer, and joint pain.[4] The most common type of glaucoma among white people is primary open angle glaucoma (POAG); primary angle closure glaucoma (PACG), which results from occlusion of aqueous humour outflow, is more common among Asian people.[5] Secondary glaucoma results from a diverse range of ocular and systemic conditions. Raised intraocular pressure (IOP) is the major modifiable risk factor for primary open angle glaucoma,[6-8] but around half of people with glaucoma present with IOP below 21 mm Hg, which is the threshold for ocular hypertension (raised IOP without any evidence of glaucoma).[9] The EPIC-Norfolk Eye Study, initiated in 2004, is the most recent large scale eye survey in the UK. We examined the prevalence and characteristics of glaucoma and distribution of IOP in the study participants.

Methods

The European Prospective Investigation of Cancer (EPIC) study is a pan-European multi-cohort study designed to investigate the lifestyle determinants of risk of cancer. The EPIC-Norfolk cohort was established in the city of Norwich and the surrounding rural and urban areas, in the eastern English county of Norfolk, in 1993-97.[10] A total of 30 445 men and women aged 40-79 were recruited at a baseline survey from the databases of 35 general practices. The predominant ethnicity of the cohort was white, and it included individuals across the range of socioeconomic status and educational achievements. The EPIC-Norfolk Eye study was carried out in 2004-11, when ophthalmic data were collected from 8623 participants.[11]

The first 443 sequential participants had IOP measured with a non-contact tonometer (AT555, Reichert Corporation, Philadelphia, PA, USA). In the remaining participants IOP was measured three times in each eye with the ocular response analyser (ORA) non-contact analyser (Reichert Corporation, Philadelphia, PA, USA) with software version 3.01. This flattens the cornea with a jet of air and uses an electro-optical system to measure the air pressures at which the cornea flattens both inwards and outwards. The average of the two pressure values are calibrated linearly against the Goldmann applanation tonometer (GAT) to provide a Goldmann-equivalent IOP measurement (IOPg, mm Hg).[12]

A systematic review showed that among 12 studies that directly compared the agreement between IOPg and GAT, the mean difference between the two (IOPg–GAT) is 1.5 mm Hg (95% predicted interval −0.6 mm Hg to 3.7 mm Hg).[13]

The glaucoma status of the participants was determined from a systematic examination that included visual acuity, tonometry, and assessment of the optic nerve head (Heidelberg Retina Tomograph II) and the peripapillary nerve fibre layer with scanning laser polarimetry (GDx VCC, Zeiss, Dublin, CA, USA). A 24-2 central threshold visual field test (Humphrey 750i Visual Field Analyzer, Carl Zeiss Meditech, Welwyn Garden City, UK) was performed in those participants with abnormal findings on HRT or GDx VCC and in one in 10 with normal findings. Those with abnormal findings who met a set of predefined criteria designed to detect glaucoma were referred to the eye department of the Norfolk and Norwich University Hospital for a definitive eye examination by a consultant ophthalmologist with a specialist interest in glaucoma (DCB). A detailed description of the study design has been published previously.[11] Glaucoma was defined as the presence of characteristic structural abnormalities of the optic disc and visual field loss, with no other explanations for the disc and field appearances. The differentiation between high tension and normal tension glaucoma was based on IOP level before glaucoma treatment started. Suspected glaucoma was defined as the presence of early or minor glaucomatous disc features, associated with a normal visual field or the absence of visual field data. Ocular hypertension was defined as IOP >21 mm Hg with no features of glaucoma in the optic disc or visual field. Specific quantitative methods and principles for diagnosis of primary open angle glaucoma and suspected primary open angle glaucoma followed the diagnostic principles from the International Society of Geographical and Epidemiological Ophthalmology (ISGEO).[3] To limit false positive or false negative results, another consultant glaucoma ophthalmologist (PJF) reviewed all examination findings and history in a subset of high risk participants. Figure 1 shows the flow of participants through the study and the diagnostic process. We determined glaucoma diagnosis per person by taking the clinically more serious diagnosis of either eye in the following hierarchy (most serious to least serious): glaucoma, suspected glaucoma, ocular hypertension (IOP >21 mm Hg), narrow angle spectrum (primary angle closure, primary angle closure suspect and narrow angles), and normal.

Statistical analysis

The IOP reported for the cohort was the mean of the mean IOP in the left and right eyes, with the ORA IOPg or the AT555 NCT values. We calculated sensitivities and specificities of IOP for glaucoma detection from the ability of various IOP thresholds to differentiate between participants with all cause glaucoma in either eye and those with no glaucoma in either eye. The reporting of this study conformed to the STROBE statement.[14] All statistical analyses were performed with STATA (Stata/SE 13.1, StataCorp, College Station, TX).

Results

There were 8623 participants in the EPIC-Norfolk Eye Study, with a mean age of 68.7 (range 48-92), and over half (55%) were women. Compared with the population estimates for Norfolk and for the UK, the study population was older and had a decreasing proportion of women with age, which is opposite to the Norfolk

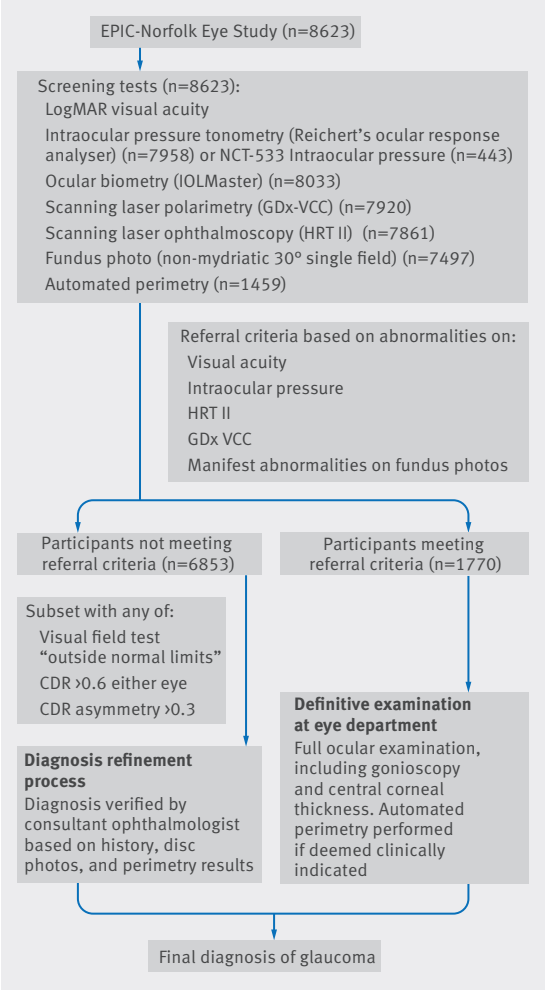

Fig 1 | Flow of participants through EPIC-Norfolk study

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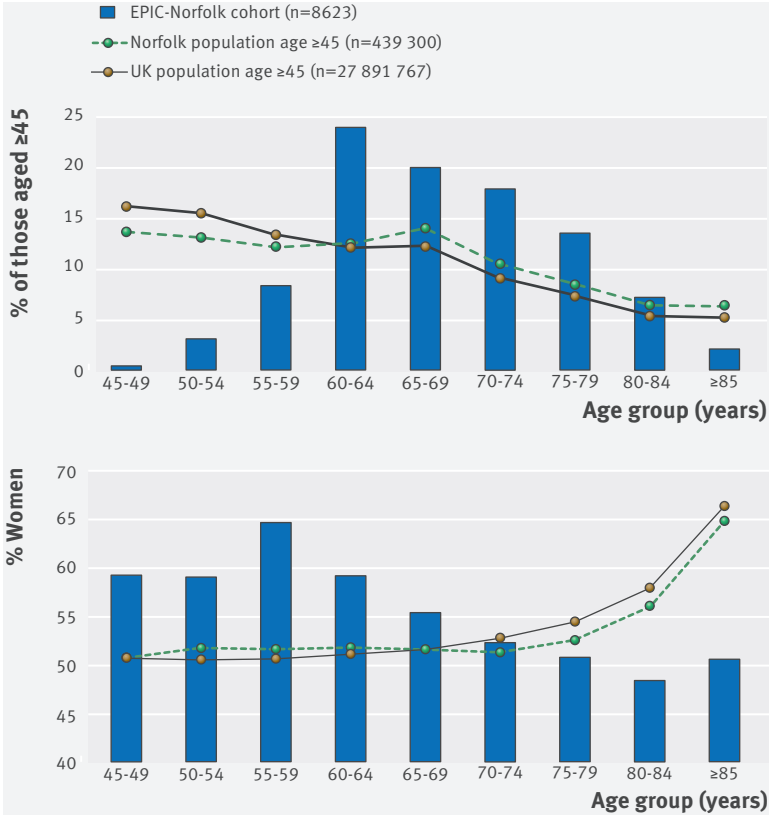

Fig 2 | Age and sex distribution of EPIC-Norfolk 3HC cohort compared with population of Norfolk and UK (2014 mid-year population estimates[15])

and UK population's trend of an increasing proportion of women with age (fig 2). Nearly all participants were white (99.4%), compared with 96.5% and 87.2%, respectively, in Norfolk and the UK.[15]

Tables 1 and 2 show the glaucoma diagnosis by eye and by person. A total of 363 participants (4.2%, 95% confidence interval 3.8% to 4.6%) had glaucoma in either eye, 314 had primary open angle glaucoma (3.6%, 3.3% to 4.0%), 607 (7.0%) had suspected glaucoma, 863 (10.0%) had ocular hypertension (untreated IOP >21 mm Hg), and 54 (0.6%) had narrow angle spectrum. Twenty three participants (0.3%) had no recorded diagnosis as they declined or were unable to undergo definitive eye examination after abnormal results on the screening tests. Table 3 breaks down glaucoma by type in the 363 affected men and women. Most people with glaucoma had primary open angle glaucoma (86.5%), with an equal proportion of high pressure and normal pressure glaucoma. Out of the 523 eyes affected by glaucoma, formal visual field assessment was not feasible in 28 because of poor vision. Most of these participants had secondary glaucoma, which was diagnosed by advanced disc cupping and uncontrolled IOP.

Among the cases of glaucoma, 242 (66.6%) were previously known, and 66.3% cases of primary open angle glaucoma were previously known. The prevalence of glaucoma in the study population increased with age and was higher in men than in women (table 4).

Table 1 | Diagnosis of glaucoma by eye in 8623 men and women aged 48-92 in EPIC-Norfolk cohort. Figures are numbers (percentage) of participants

Diagnosis	Right eye	Left eye
Normal	7091 (82.2)	7061 (81.9)
Primary open angle glaucoma	236 (2.7)	230 (2.7)
High tension glaucoma	121 (1.4)	121 (1.4)
Normal tension glaucoma	115 (1.3)	109 (1.3)
Primary angle closure glaucoma	20 (0.2)	17 (0.2)
Secondary glaucoma	9 (0.1)	11 (0.1)
Subtotal with glaucoma	265 (3.1)	258 (3.0)
Suspected open angle glaucoma	444 (5.2)	443 (5.1)
Ocular hypertension and suspected open angle glaucoma	67 (0.8)	67 (0.8)
Suspected angle closure glaucoma	27 (0.3)	28 (0.3)
Secondary ocular hypertension /suspected open angle glaucoma	2 (0.0)	4 (0.1)
Subtotal suspected glaucoma	540 (6.3)	542 (6.3)
Ocular hypertension	641 (7.4)	670 (7.8)
Primary angle closure	27 (0.3)	32 (0.4)
Narrow angles	36 (0.4)	34 (0.4)
Not recorded	23 (0.3)	26 (0.3)
Total	8623 (100)	8623 (100)

Table 2 | Diagnosis of glaucoma in 8623 men and women aged 48-92 in EPIC-Norfolk cohort. Figures are numbers (percentage) of participants

Diagnosis*	No (%) of participants
Normal	6713 (77.9)
Glaucoma	363 (4.2)
Suspected glaucoma	607 (7.0)
Ocular hypertension	863 (10.0)
Narrow angle spectrum	54 (0.6)
Unrecorded	23 (0.3)
Total	8623 (100)

*More serious diagnosis of either eye used, from (most serious to least serious): glaucoma, suspected glaucoma, ocular hypertension, narrow angle spectrum (primary angle closure, primary angle closure suspect), normal, diagnosis not recorded.

Table 3 | Type of glaucoma in 363 men and women aged 48-92 with glaucoma in EPIC-Norfolk cohort. Figures are numbers (percentage) of participants

Diagnosis	No (%) of participants
Primary open angle glaucoma	314 (86.5)
High tension glaucoma	157 (43.3)
Normal tension glaucoma	157 (43.3)
Primary angle closure glaucoma	29 (8.0)
Secondary glaucoma	20 (5.5)
Total (all glaucoma)	363 (100)

Table 4 | Glaucoma by age and sex in 363 men and women aged 48-92 with glaucoma in EPIC-Norfolk cohort. Figures are numbers (percentage of age group)

	All cause glaucoma		Primary open angle glaucoma	
Age (years)	Men	Women	Men	Women
<55	1 (0.8)	1 (0.5)	1 (0.8)	1 (0.5)
55-60	4 (1.5)	5 (1.0)	4 (1.5)	5 (1.0)
60-65	20 (2.3)	19 (1.5)	16 (1.8)	15 (1.2)
65-70	34 (4.3)	22 (2.2)	27 (3.4)	21 (2.1)
70-75	50 (6.6)	42 (5.0)	44 (5.8)	31 (3.7)
75-80	43 (7.2)	30 (4.9)	39 (6.6)	26 (4.3)
≥80	48 (11.2)	44 (10.8)	44 (10.5)	41 (10.1)
Total	200 (5.2)	163 (3.4)	175 (4.5)	140 (3.0)

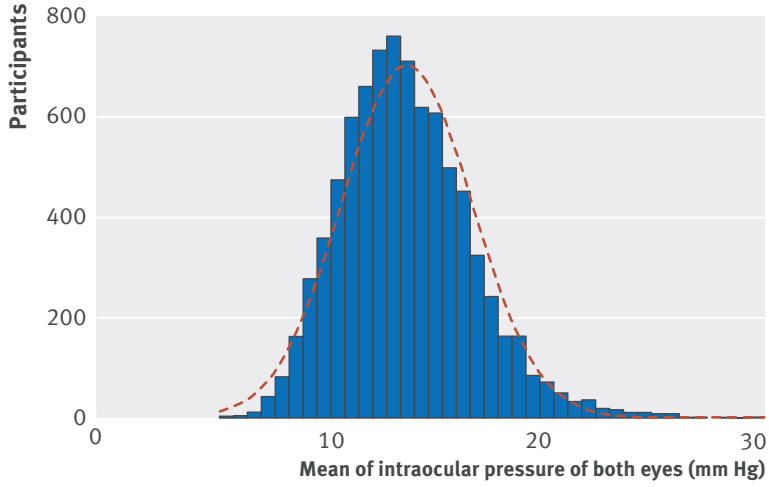

Fig 3 | Distribution of IOP in EPIC-Norfolk population (n=8401). Distribution approximates Gaussian distribution but has exaggerated central peak and modest right skew

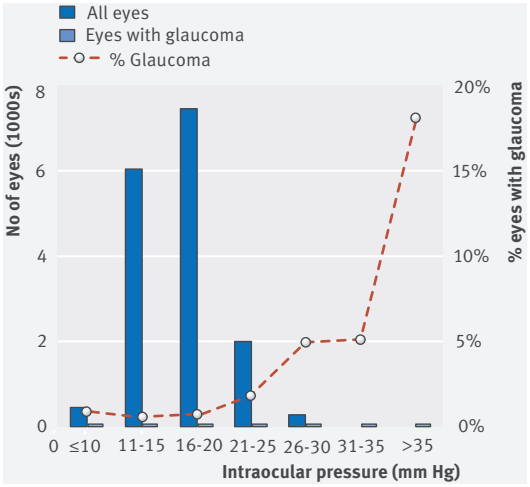

Fig 4 | Intraocular pressure for all eyes and eyes with glaucoma in EPIC-Norfolk cohort

IOP was measured in 8401 participants (7958 with ORA, 443 with AT555 NCT), 243 of whom used ocular hypotensive eye drops in either eye. Figure 3 shows the distribution of mean IOP of both eyes, which followed an approximately Gaussian distribution, with a right skew and an exaggerated peak. The cohort mean IOP was 16.3 mm Hg (95% confidence interval 16.2 mm Hg to 16.3 mm Hg; SD 3.6 mm Hg). Table 5 shows the distribution of IOP by age and sex. The mean IOP for glaucomatous eyes was 16.7 mm Hg (17.1 mm Hg to 18.1 mm Hg; range 4.0-45.6 mm Hg), and the percentage of eyes with glaucoma increased with IOP (fig 4). Of the 107 patients with a new diagnosis of primary open angle glaucoma, 76% (81) had mean IOP below 21 mm Hg.

Table 6 and figure 5 show the sensitivity and specificity of glaucoma detection at different IOP thresholds. Overall, sensitivity was poor at all levels shown, regardless of the additional refining parameters of age and sex, and there was no one single level that afforded both high sensitivity and specificity.

Discussion

In this large population based study, we found that intraocular pressure was not a sensitive or specific indicator of glaucoma. This is the most current large scale population study reporting glaucoma epidemiology in the UK. We found many participants with suspected glaucoma or ocular hypertension, confirming a large potential referral burden to the NHS. IOP has also been shown to be a poor case finding test for glaucoma.

Principal findings and comparison with other studies

Data on prevalence of glaucoma have been reported from populations in the US,[16 17] Australia,[18 19] Europe,[20-22] and South East Asia.[23-26] Recent data from the UK, however, is lacking, with the last published cross sectional population surveys being one from rural west of Ireland in 1993[27] and another from north London in 1998.[28]

There were differences between the participants from EPIC-Norfolk and the local population of Norfolk as the study participants were not sampled systematically but recruited by inviting all adults aged >40 from GP practices. Apart from differences in age and sex composition, EPIC-Norfolk participants were less likely to live in deprived areas and were potentially healthier because of the volunteer nature of the study. The people with glaucoma identified in the cohort might therefore not be fully representative of the local or national population and are probably an underestimation of the true numbers. Nevertheless, results in this study corroborated many established trends in glaucoma epidemiology. The predominant type in our cohort was primary open angle glaucoma, a consistent finding among European populations.[529] The prevalence increased with age, which is its strongest known risk factor.[30] The prevalence of all cause glaucoma in those aged 48-92 was 4.2% (95% confidence interval 3.8% to 4.6%) and 3.7% (3.3% to 4.0%) for primary open angle glaucoma. This echoed findings from a meta-analysis in 2014, in which the prevalence of glaucoma (primary open angle glaucoma and primary angle closure glaucoma) for Europeans

Table 5 | Distribution of mean intraocular pressure (IOP)* by age and sex in 8623 men and women aged 48-92 in EPIC-Norfolk cohort

	Men		Women	
Age group (years)	No of patients	IOP mm Hg (95% CI)	No of patients	IOP mm Hg (95% CI)
<55	128	15.9 (15.4 to 16.5)	185	15.7 (15.2 to 16.2)
55-<60	262	15.8 (15.4 to 16.3)	473	15.9 (15.6 to 16.2)
60-<65	857	16.4 (16.2 to 16.7)	1240	16.5 (16.3 to 16.6)
65-<70	790	16.2 (15.9 to 16.4)	969	16.7 (16.5 to 17.0)
70-<75	746	16.3 (16.0 to 16.5)	808	16.3 (16.1 to 16.6)
75-<80	570	16.0 (15.7 to 16.4)	591	16.2 (15.9 to 16.4)
≥80	402	16.0 (15.6 to 16.4)	380	15.8 (15.5 to 16.2)
Total	3755	16.2 (16.1 to 16.3)	4646	16.3 (16.2 to 16.4)

*Mean IOP of both eyes.

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Table 6 | Sensitivity and specificity for detection of all cause glaucoma at different thresholds of intraocular pressure (IOP)

	Sensitivity (%)							Specificity (%)						
		Age							Age					
IOP mm Hg	Overall	<65	≤65	<70	≥70	Men	Women	Overall	<65	≤65	<70	≥70	Men	Women
>19	45.0	36.7	46.3	45.6	44.7	49.2	39.7	73.2	74.1	72.6	72.8	73.6	73.7	72.7
>20	36.3	26.5	37.9	34.0	37.3	42.4	28.9	81.0	82.0	80.3	80.9	81.0	80.5	81.3
>21	30.0	24.5	30.9	28.2	30.7	35.1	23.7	86.9	87.7	86.4	86.8	87.0	85.8	87.7
>22	25.4	22.5	25.8	23.3	26.2	30.4	19.2	91.2	91.9	90.7	91.1	91.3	90.3	91.9
>23	20.5	18.4	20.8	20.4	20.5	24.6	15.4	94.0	94.5	93.8	93.8	94.5	93.2	94.7
>24	16.7	18.4	16.4	16.5	16.8	20.9	11.5	96.0	96.2	95.9	95.7	96.4	95.4	96.5
>25	12.1	12.2	12.1	10.7	12.7	16.2	7.1	97.1	97.0	97.2	96.9	97.5	96.6	97.6
>26	7.8	8.2	7.7	6.8	8.2	11.0	3.9	98.0	97.8	98.1	97.8	98.3	97.5	98.4

aged 40-80 was 2.93% (1.85% to 4.40%) and the prevalence of primary open angle glaucoma was 2.51% (1.54% to 3.89%).[5] In another meta-analysis, published in 2006, the pooled prevalence of primary open angle glaucoma in white people was 2.1% (1.6% to 2.7%).[31]

In our cohort, two thirds of those with primary open angle glaucoma had previously received the diagnosis. This is the highest reported figure from a major community based study. Previous reported figures include 49% in the Blue Mountains Eye Study,[18] 50% in Melbourne's Visual Impairment Study,[19] 50% in the Thessaloniki Eye Study,[22] 47% in the Rotterdam Eye Study,[20] and 50% among white people in the Baltimore Eye Survey.[32] Glaucoma is a largely asymptomatic disease, with insidious onset. In most industrialised countries, it is detected by opportunistic case finding and relies on people being examined by an eye care professional. In the UK, this would usually be a community optometrist. People with suspected glaucoma are then referred to ophthalmologists for definitive diagnosis and management. The higher rate of previously known glaucoma cases in EPIC-Norfolk than in other studies could reflect either better access to healthcare among the study participants because of recruitment bias or generally more effective provision of healthcare in the UK, with universal access and free eye tests for those aged over 60 in the NHS.

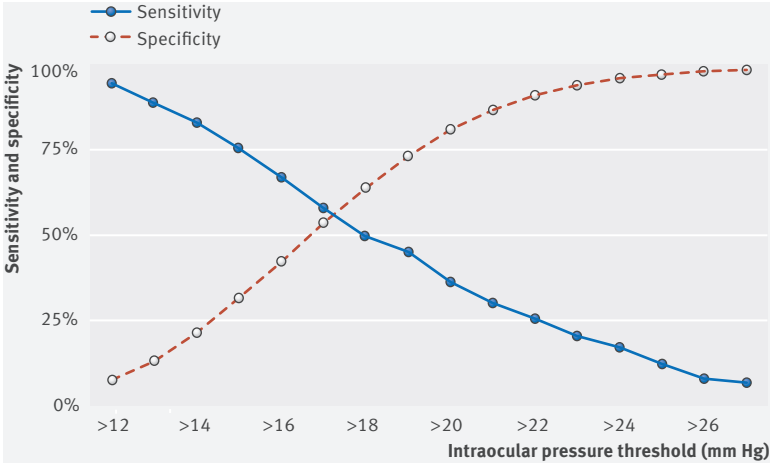

Fig 5 | Sensitivity and specificity for detection of all cause glaucoma in EPIC-Norfolk cohort

A striking finding in the study was the large number of people with suspected glaucoma (7%) and ocular hypertension (10%). Collectively they represent a large number of potential referrals to the hospital eye services, many of whom remain under observation for up to five years.[33] This is reflected by the existing burden in hospital eye services, whereby ocular hypertension accounts for 30-45% of the referrals it receives.[34 35] Coupled with the fact that glaucoma is a chronic disease that needs regular and long term follow-up, it is no wonder that glaucoma and suspected glaucoma account for the sixth largest share of NHS outpatient attendances.[4]

While raised IOP is the strongest risk factor after age for primary open angle glaucoma,[30] our data reiterate that no single IOP level provides sufficiently high sensitivity and specificity for detection of glaucoma, as shown in figure 3, mirroring results from the Baltimore Eye Survey.[16] This reinforces the principle that IOP alone without optic disc examination or a visual field test is not an effective screening tool for glaucoma.

Limitations of study

There were several sources of under-reporting of a diagnosis of glaucoma in this study. Only 18% of participants underwent visual field testing. A meta-analysis showed that lack of routine field testing in a population study was a study design factor that led to underdiagnosis.[36] In our study, however, both disc and field abnormalities were prerequisites of diagnosis, supporting well established diagnostic principles used in most population cross sectional studies.[17 20 23 32 37 38] We used a multimodal optic disc examination to uncover glaucomatous damage and determine who was referred for a definitive exam. We therefore expect that few cases of glaucoma would have been missed. The number of cases of narrow angle spectrum is also likely to be underestimated, as gonioscopy or anterior chamber depth assessment on slit lamp were not part of the screening test, although those with primary open angle glaucoma should not have been missed because of that as all glaucoma suspects underwent a full examination.

Conclusion

In conclusion, this study confirms the high prevalence of glaucoma and suspected glaucoma in the UK.

We have reported the IOP distribution among the population and among those with glaucoma, confirming its poor case finding performance. These findings will be useful in the planning of ophthalmic services in the UK and help to revaluate the use of IOP in making referrals from the community to the hospital eye services.

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Contributors: MPYC analysed and interpreted the data and drafted the manuscript. PJF and DCB contributed to the conception and design of the study and to data collection. APK and JLYY contributed to data collection and interpretation. DGH contributed to the conception and design of the study and to data interpretation. JMB contributed to data interpretation. RL contributed to the design of the study and to data management. SH contributed to the design of the study. ND contributed to the design of the study and to data acquisition. KTK contributed to the conception and design of the study and to data interpretation. All authors read and critically revised the manuscript and approved the final manuscript. MPYC and PJF are guarantors.

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Ethical approval: The work was approval by the East Norfolk and Waverney NHS research governance committee (2005EC07L) and the Norfolk research ethics committee (05/Q0101/191).

Data sharing: Requests for data sharing/access should be submitted to the EPIC Management Committee via Mrs Shabina Hayat (sah63@medschl.cam.ac.uk). Applications will be judged on a case by case basis, determined by the scientific merit, in line with MRC guidelines (https://www.mrc.ac.uk/publications/browse/mrc-policy-and-guidance-on-sharing-of-research-data-from-population-and-patient-studies/).

Transparency: The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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