RISK FACTORS FOR LATE PRESENTATION OF CHRONIC GLAUCOMA

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STATEMENT OF ORIGINALITY AND CONSENT

The work presented in the present thesis embodies original research carried out by the author as a contribution to the science and clinical practice of ophthalmology.

I consent to this thesis being made available for consultation, photocopying and for use through other libraries either directly or via the British Lending Library.

PUBLICATIONS AND PRESENTATIONS ARISING FROM THE THESIS

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To Helen

Risk factors for late presentation of chronic glaucoma

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CHAPTER 1: BACKGROUND.

1.1 WHAT IS GLAUCOMA?

The word glaucoma is derived from the Greek *glaukos* meaning of a dull greyish green colour - descriptive of the appearance of advanced acute glaucoma.

The umbrella term 'glaucoma' consists of a group of diseases that are characterised by a variable combination of elevated intraocular pressure (IOP), optic disc abnormalities and characteristic visual field defects.

The first main sub-division is into acute and chronic types. Acute angle closure glaucoma occurs when the IOP rises very quickly (hours) producing ocular pain and an immediate reduction in visual acuity. The angle referred to is the area of the eye where aqueous humour drains and if this is blocked a sudden pressure rise ensues. The chronic glaucomas usually have a rise in IOP but this occurs over a longer period of time (months and years) and tends not to be as high (although it can reach very high levels) as in the acute form. This means that, until the very late stages, chronic glaucoma tends to be asymptomatic.

Chronic glaucoma can be divided into open and closed angle types, the closed angle form tends to be much more insidious than the acute closed angle form and may or may not produce symptoms. More commonly, the chronic glaucomas have an open drainage angle and are then called the open angle glaucomas. These are further sub-divided into primary and secondary types. The secondary types are so called because aqueous drainage is hampered by some mechanism -which may be pigment in pigmentary glaucoma, amyloid like material in pseudoexfoliation or abnormal blood vessels in rubeotic glaucoma.

Primary open angle glaucoma (POAG) is the commonest type of glaucoma in many parts of the World – especially Europe and the United States of America and is, therefore, the most studied of all the glaucomas. Despite this, the mechanism of optic nerve damage in POAG has not been fully elucidated. The classical theory of all glaucomas is that raised IOP damages the optic nerve and so produces characteristic changes in the visual field. Unfortunately, and especially in POAG, this is not always true. In some individuals, raised IOP causes field loss, while in others with the same IOP level, no field loss occurs – this latter situation is termed ocular hypertension (OHT). The concept of 'raised IOP' came from population studies that calculated the mean IOP for the sample population and found that two standard deviations above this was 21mmHg - thus the concept of raised pressure is a statistical one. In reality, typical glaucomatous cupping and field loss occur at pressures under 21mmHg and this group of open angle glaucomas was previously named low tension but it is now termed normal tension glaucoma (NTG).

1.2 THE EPIDEMIOLOGY OF GLAUCOMA.

This work is concerned with 'symptomless glaucomas' constituting POAG, NTG, pseudoexfoliation (PXF), pigmentary glaucoma and some chronic angle closures. The reason for calling them symptomless is because the progression of visual field loss in them is often not noticed by the patient until it is extremely constricted -sometimes only when central vision is reached. It may be argued that these conditions are symptomatic prior to this and I will discuss this later, but those glaucomas that are likely to manifest themselves in their early stages e.g. acute angle closure or rubeotic glaucoma were specifically excluded from the study. For this reason, unless otherwise stated, the term glaucoma can be assumed to mean of the chronic type (although not necessarily open angle) in the remainder of the text.

1.2.1 Glaucoma prevalence

Glaucoma prevalence rates vary in different studies and this is summarised in Table 1.1.

The studies with the highest prevalences -the Baltimore Eye Study (BES) [1], Barbados[2] and the St Lucia[3] studies were the only studies to contain Black subjects. The BES found a prevalence of glaucoma of 1.7% for whites and 7.3% for blacks.

The studies with the lowest prevalence rates - the Ferndale[4], Dalby[5] and Bedford[6] were also those that had the lowest upper limit of age for study subjects. The prevalence of POAG increases with age [7, 1, and 8] and any population study that has an upper age limit will find a lower overall prevalence compared to those without an age limit. The Roscommon study[7] had a peak prevalence of glaucoma of 3.20% in the 70-79 age group, the BES also had a peak prevalence in the same age group of 2.85% while the Beaver Dam[8] study had a prevalence of 4.7% in the over 75 age group.

The majority of the major studies have failed to show a differing prevalence for males and females[9]. The Barbados study [2] did show an small excess risk for males.

Table 1.1

STUDY	ROSCOMMON	BEAVER DAM	BALTIMORE (WHITES)	BALTIMORE (BLACKS)	FERNDALE	DALBY	ICELAND	BARBADOS	ST.LUCIA	BEDFORD
AGE RANGE STUDY	>50	43-84	>40	>40	40-75	55-69	>50	40-84	>30	40-75
PREVALENCE POAG (%)	1.87	2.1	1.7	7.3	0.43	0.86	1.91	7.9	8.8	0.71
PREV ACAG (%)	0.09	0.4			0.09					0.17
PREV PXF (%)	1.33				0.22	0.07				

1.2.2 Glaucoma incidence

Data on glaucoma incidence is sparser than that on prevalence, with estimates varying from 1 in 1000 to 1 in 100[10]. Leske *et al*[11] calculated an incidence of 0.08/1000 per year for those in their forties to 1.46/1000 per year for those in their eighties. The Bedford survey [6] had an average annual incidence rate of 0.048%, while Armaly[12] gave a figure of 0.025%.

The above figures are all estimates and were calculated from age-specific prevalences. They also take these prevalences from white populations and are therefore very likely to be underestimates. It is likely in the future, as the big prevalence studies revisit their populations (especially those who had normal examinations), that we will get a much more accurate idea of glaucoma incidence.

1.3 RISK FACTORS FOR DEVELOPING GLAUCOMA

There is a long list of risk factors that have been proposed for glaucoma, but a number of factors have been studied more extensively. The vast majority of the work has been done on POAG and most of the risk factors pertain to this. However, these factors generally hold true for the other types of chronic glaucoma and where they do not it will be indicated in the text.

1.3.1 Demographic risk factors

Age.

As seen from the prevalence and incidence figures discussed above, increasing age is a risk factor for glaucoma. In fact, this risk has been found in every study that has examined age on a population basis [10]. It is consistent across the studies, the magnitude is uniformly large, with prevalence rates four to ten times higher in the oldest age group compared to the baseline (usually subjects in their forties) [4,13,1]. Prevalence rates rise from 0.7% in the under 40's to 4.8% of the over 60's[14].

Gender.

The Ferndale [4], Baltimore[1], Beaver Dam[8] and Roscommon[7] studies failed to show a significant gender difference for rates of glaucoma. Some studies have shown a slight increase risk for females[13] while others have shown the reverse[2,5].

Overall, it seems unlikely that gender is a significant risk factor for developing glaucoma.

Ethnic origin.

It was long suspected that individuals of African, African-American and African-Caribbean origin were at higher risk of POAG but it is only relatively recently that this has been proved by large-scale population studies.

The Baltimore eye study [1], indicated a four fold excess prevalence in blacks compared to whites, the St Lucia[3] study found a prevalence of 8.8%. More recently the London African Caribbean eye survey[15] showed a relative risks for glaucoma in Haringey blacks compared to Roscommon whites of 3.7 and the Barbados Eye Study found a prevalence of POAG in Blacks of 7% and in those of mixed race of 3.3%[2]. Case-control studies also show a higher risk for Black subjects. Wilson *et al*[16] finding an adjusted odds ratio of 6.8 in Blacks compared to Whites.

Not only is there a higher prevalence of POAG amongst Blacks but there is evidence that the onset of the disease is at a younger age. Freund[17] described a large number of glaucoma patients in their 20's, Degazon [18] found the average age of glaucoma patients in Jamaica was 10 years less than the American average. Wilson *et al*[19] study found that the average age at presentation for Blacks was 49.5 years while for whites it was 59.8 and this was statistically significant.

Of course, earlier diagnosis does not necessarily indicate earlier onset of the disease but the studies are so consistent that it seems likely that there is a younger onset.

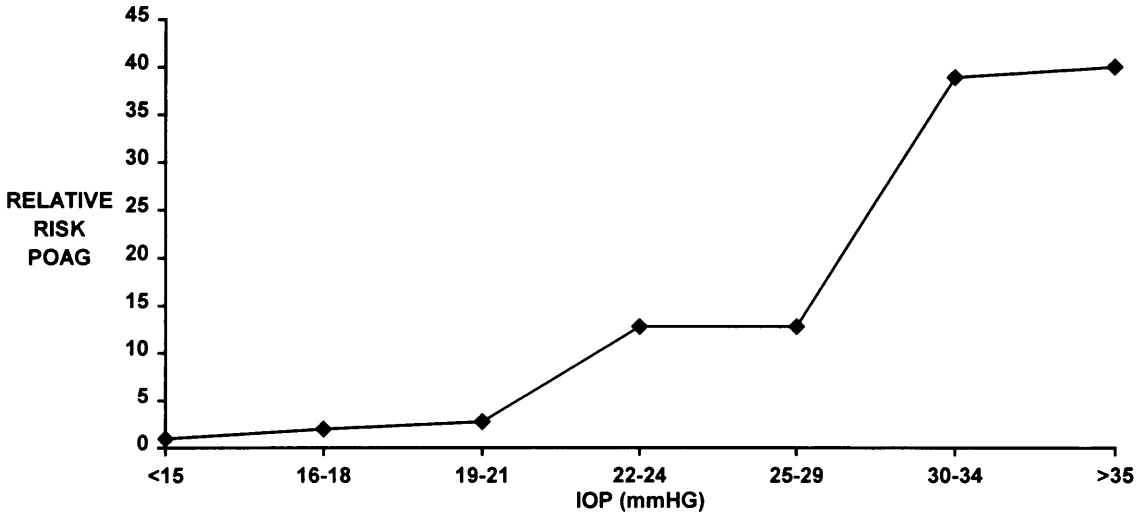
1.3.2 Ocular risk factors.

Intraocular pressure.

Although there is little doubt that raised IOP is a major risk factor for glaucoma, it is not the *sine qua non* that it was once thought to be.

There is strong evidence that IOP is intimately associated with glaucoma and even when one excludes IOP from the definition for glaucoma, IOP is strongly related to the cross-sectional prevalence and longitudinal risk of glaucoma[10]. The prevalence of glaucoma rises with IOP levels[20] and this is illustrated in Fig 1.1: -

Figure 1.1. The risk of Primary Open Angle Glaucoma at varying levels of intra ocular pressure (from Sommer et al[20]).

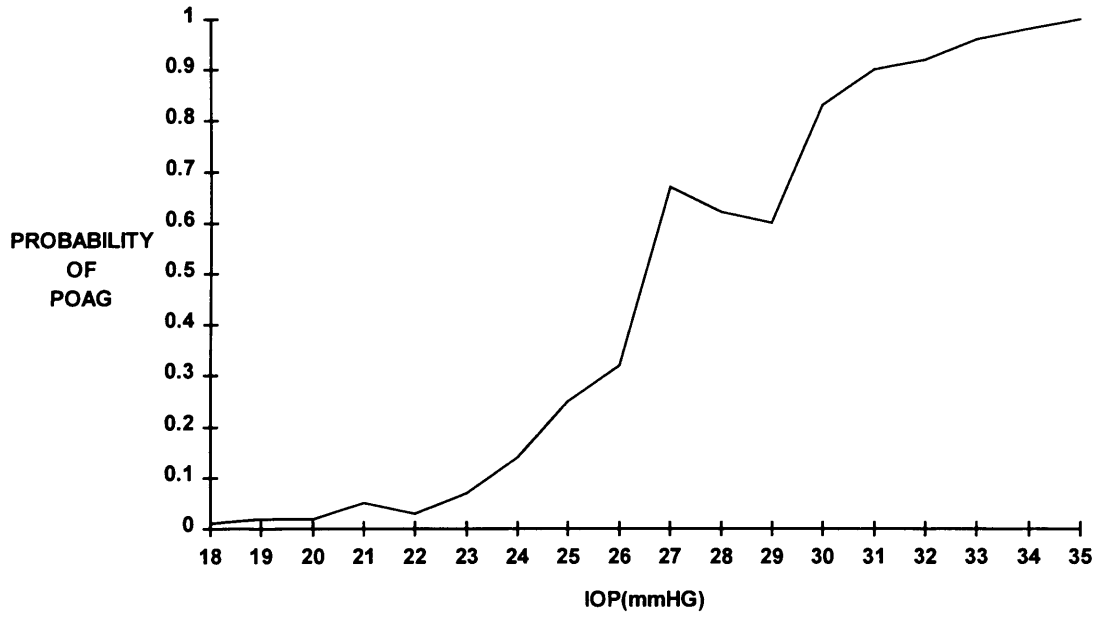


Further evidence comes from individuals with asymmetric IOP's who lose field in the eye with the higher IOP - this can occur when one IOP is high e.g. post-trauma or when both are within the 'normal' limit of 21 but asymmetrical[65].

Looking more closely at Fig 1.1 it can be seen that the relative risk of glaucoma begins to rise from 16mmHg onwards, not from 21. Population studies have indicated that the prevalence of glaucoma associated with high intraocular pressure is relatively rare and that normal or marginally raised IOP is much more common[22].

Whilst there is a threshold of IOP above which glaucomatous damage appears inevitable, below this we cannot be so sure. Fig 1.2 from Davanger *et al*[23] illustrates this point:-

Figure 1.2. The probability of POAG at varying levels of IOP (from Davenger et al[23]).



At an IOP of 35mmHg the probability of glaucoma is around 1, but at an IOP of around 27 the probability is only 0.5, thus 50% of those with this IOP would not progress to glaucoma. These figures are drawn from a clinic based population rather than population based and should be extrapolated with caution (See section 1.3.2).

In summary, although there is little doubt that IOP is a major risk factor for glaucoma, unless the pressure exceeds 34mmHg we cannot set a limit of IOP at which we can say an eye will or will not sustain field loss. To quote Alfred Sommer "The important point is that there is little scientific basis for the traditional distinction between 'high' and 'low' tension glaucoma. The relationship between IOP and glaucoma is a continuum....Patients with an IOP in the high teens are already at increased risk"[21].

Implicit in this is that there must be some other factor or factors that act with the particular pressure in an eye to produce characteristic glaucomatous changes.

Optic nerve head.

The optic nerve head is that part of the optic nerve visible within the eye and is where the ganglion cell axons exit the eye. Since the invention of the ophthalmoscope, the appearance of the optic nerve has been used to diagnose and follow the progress of glaucoma.

Glaucomatous discs exhibit characteristic changes most prominent of which is a backward bowing of the nerve commonly known as cupping. However, as well as being a marker for the disease it is also felt that the structure of the optic nerve head can make an individual more or less susceptible to glaucoma.

There are two main theories regarding the mechanism of optic nerve damage. The first is the mechanical (IOP-related) mechanism in which it is suggested that the pressure has a direct effect on the lamina cribosa of the nerve[24]. The lamina cribosa has been shown to be weaker superiorly and inferiorly and these are the areas at which glaucomatous damage first appears[24]. IOP may have a direct effect on the ganglion cell axons as they pass through the lamina cribosa and this effect occurs

where the axons are relatively unsupported. Variations in support of the ganglion cell axons may explain differing susceptibility at different IOP levels.

An alternative theory is the vasogenic mechanism of damage in which it is felt that changes within the microcirculation of the optic disc capillaries are responsible for glaucomatous changes[24]. Abnormal optic nerve, retinal and ophthalmic artery blood flow have been shown in patients with POAG although their exact role in the pathogenesis of damage has not been fully elucidated.

Epidemiological studies have also implicated disc variation as a risk factor for glaucoma. Hart *et al*[25] found that vertical and horizontal cup/disc ratio correlated positively with subsequent visual fields loss. The Collaborative Glaucoma study[14] also indicated that a high horizontal cup/disc ratio was a risk factor for field defects.

As mentioned previously, the risk of POAG is much greater in Black patients, but there are no differences in their IOP levels compared to Whites [20, 26]. What has been shown is that black patients have larger discs (and therefore cups) than whites [21] and that discs with bigger cups seem more susceptible to further damage.

Myopia.

Myopia has long been associated with an increased risk of POAG. Wilson *et al*[27] found a two fold excess prevalence of myopia in patients with POAG, Perkins [28] found an odds ratio of five while one study [29] only showed an increased risk only in those with more than five dioptres of myopia. The Casteldaccia eye study[30] showed a greater prevalence of glaucoma amongst myopes of greater than 1.5D and Daubs and Crick [31] showed a similar relationship.

It is important to realise that risk factors such as myopia (and diabetes and systemic hypertension) are subject to selection bias. Myopes are more likely to have regular ophthalmic/optometric reviews and therefore be diagnosed as having

glaucoma. This means they tend to be over-represented in the glaucoma clinic. The other problem with myopia is that myopic discs can sometimes be very difficult to assess for glaucoma and can even produce visual field changes that mimic glaucoma.

Hypermetropia.

Increasing hypermetropia leads to an increased risk of angle closure glaucoma. Hypermetropic eyes tend to be small and have a shallow anterior chamber, which can lead to progressive angle closure. Shallow anterior chambers themselves are associated with high IOP [30].

1.3.3 Systemic risk factors

Diabetes.

A large number of studies have implicated diabetes as a risk factor for POAG. Katz and Sommer[32] found a risk of 2.8 of having POAG if the subject was diabetic, Wilson *et al*[16] found an association -as did the Casteldaccia eye study[30].

As with myopia, there is a definite 'hospital bias' to these associations - diabetic patients have an increased level of medical and ophthalmic surveillance and so will be more likely to have their glaucoma diagnosed. Any hospital-based study of glaucoma will inevitably show more diabetic patients than would be expected from population based studies. Consequently, when we look at population based studies [14,33,10] the effect of diabetes as a risk factor disappears.

Systemic Hypertension.

Studies of the role of blood pressure (BP) in glaucoma are, like diabetes, subject to hospital bias. A number of studies have related height of BP to IOP[34,10, 35] but it has been harder to find an association between BP and POAG.

As simply comparing blood pressure in individuals with and without glaucoma seemed unable to provide a definitive answer, Baltimore Eye Study investigators [34]

calculated vascular perfusion pressure in their subjects - this being the blood pressure (systolic, diastolic or mean) minus the IOP- and showed that the lower the diastolic perfusion pressure the higher the prevalence of POAG. In fact, subjects with diastolic perfusion pressures below 30mmHg had an age adjusted risk of POAG six times higher than those with pressures of 50mmHg or greater.

A further refinement of this hypothesis was indicated by the fact that younger patients with raised BP had a lower risk of POAG than the age matched normal population, while the older subjects had a higher risk than their age matched controls. Thus it is presumed that optic nerve blood flow in the early stages of hypertension is very good but as time goes by secondary changes occur in the blood vessels, reducing blood flow.

These secondary changes also mean that blood vessel autoregulation is lost and with it the ability to respond to low diastolic perfusion pressures.

This theory is an exciting one and it appears that BP and glaucoma are related, although further evidence is needed.

1.3.4 Genetic Risk Factors

There is little doubt that a positive family history of glaucoma puts an individual at increased risk of glaucoma. The magnitude of this risk varies with different studies, estimates have varied from 13% to 47% of POAG cases being familial [36], there is a five to 20 times risk in those with a family history[37]. It is uncommon, but both autosomal dominant and recessive pedigrees have been described [29].

It is important to be aware that family history studies can by affected by hospital bias and this may explain the widely differing prevalence rates seen in different studies. Patients who have relatives with glaucoma are more likely to seek

glaucoma testing and thus end up in the clinic (glaucoma case-finding and 'screening' will be discussed at the end of this chapter).

The Baltimore eye survey provides figures for this risk factor based on unbiased population surveys [37]. They too found that family history was an important risk factor for POAG, but less so than in clinic based studies. Odds ratio of POAG for those with siblings with the disease was 3.69, parents with POAG 2.17 and for those with children with POAG the odds ratios was 1.12.

The true extent of the genetic risk of glaucoma is best assessed with twin study data. Using this method, Teikari found the heritability of chronic open angle glaucoma was around 13%[67].

1.3.5 Other proposed risk factors

Cigarette Smoking.

Although addressed in a number of studies, smoking has not been shown to be a risk factor for glaucoma in most studies. Wilson *et al* [16] did suggest a relative increase in risk of POAG in current smokers, but there are no other studies that back this up. Katz and Sommer[32], Stewart *et al*[38] or Ponte *et al*[30] could not show an effect of smoking. Perhaps most convincingly the Beaver Dam study[39] , which is the largest of all these studies, could not show any relationship between smoking and risk of POAG.

Alcohol Intake.

A number of studies have linked alcohol consumption to the risk of glaucoma. Katz and Sommer[32] found an association between glaucoma and alcohol use, but only amongst whites. There was a similar finding in the Framingham study [40].

Once again, it seems likely that non-population studies will be biased - heavy drinkers having more contact with health services. Thus when we look at a population

survey like the Beaver Dam [39], we find no suggestion of a relationship between alcohol and glaucoma.

Socioeconomic factors.

As Leske and Rosenthal [36] suggest it would seem likely that by influencing access to adequate medical care (including the use of screening services[*sic*]) income, educational level and socioeconomic class would have an effect on the occurrence of glaucoma.

There has been little work done on this aspect, Bjornsson [41] found a higher prevalence of glaucoma in outdoor manual workers than in indoor workers (the latter having a higher income). Similarly, Packer [42] found a higher rate of glaucoma in manual labourers compared to clerical workers, although this was not controlled for race.

Tielsch *et al* [43], looked at socioeconomic status and visual impairment among urban Americans and found an association between lower socioeconomic status and visual impairment.

1.4 GLAUCOMA EXAMINATION AND REFERRAL

All the patients in this study were recruited and seen in the United Kingdom thus this section describes the glaucoma detection and referral system found in this country.

The destination of all referrals is to the hospital eye service (HES) (apart from an unknown number of private referrals) but the vast majority originates from optometrists, general practitioners or from patients referring themselves to Eye Casualty departments.

1.4.1 Optometrist referral

When a glaucoma suspect is seen in the HES and has been referred from an optometrist the chain of events is usually fairly typical. It is possible to break it down into three components: -

i. An individual's decision to visit an optometrist (whether for glaucoma testing or not) – usually for a sight test.

ii. The attending optometrist must perform the appropriate glaucoma tests.

iii. The individual has to be referred to the HES.

Discussing each of these in detail: -

i. Initial optometric consultation.

It is uncommon for someone to attend an optometrist requesting a 'glaucoma test' and the usual reason is for a routine sight test. The sight test can be used as a marker for the proportion of the population who are being examined for glaucoma. Reliable data on the number of sight tests undertaken in this country has been hard to come by until the General Household Survey began collecting sight test related ophthalmic data in 1991[44].

The General Household survey (GHS) is a survey of the population in private households (conducted by the OPCS) in Great Britain each financial year. The sample size is between 23,000 and 24,000 people per year, and in the past four years, sections on use of spectacles, contact lenses and attendance for sight testing have been included[44]. The survey is conducted by interviewers cold-calling in the defined geographical areas (using telephone directories) and conducting an interview with willing participants – the response rate figure is not available in the published document. Although the survey technique has flaws, the large sample size is an advantage and the GHS is probably the best indicator of sight test usage in the UK.

Although it has been suggested that there is a tendency for people to underestimate the time since their previous sight test [45], the crude percentage of sight testing in the population has increased over the survey period from 27% in 1990-91 to 32% in 1993-94 (not age standardised). The percentage of women having sight tests has been consistently higher than of men. In the most recent survey (1993-94) 34% {95 % CI: (33 %, 35%)} of women had sight tests in the previous twelve months compared with 28% (28 %, 29 %) of men.

As shown by the figures in section 1.2.1, the incidence of glaucoma rises with age. The GHS data, however, show that the likelihood of sight testing does not show the same trend. There is an increase from 28 % of those aged 25-34 having sight tests to 40 % of those aged 45-54, but thereafter a decrease, so that 37 % of those over 65 reported having had a sight test in the previous year. The peak is likely to be due to presbyopia - (the need for reading glasses) which usually starts in the fifth decade but stabilises by the seventh. Those over 65 are less likely to need an increase in the power of their reading correction and so have less incentive to seek sight testing. The GHS data also reveal differences between socioeconomic groups in sight test uptake. The highest percentages of sight testing are found in those classed as professional, with 39 % of professional men and 40 % of professional women compared with 22 % of the unskilled men and 29 % of unskilled women. Stratification shows that this difference between the upper and lower social scales is not accounted for by age [46].

ii. Glaucoma examination by optometrists.

The International Glaucoma Association (IGA) has undertaken extensive work on this topic and have conducted a large prospective survey examining various aspects of testing performed by optometrists. There are some potential biases in their

figures in that the study was conducted by visiting a sample of optometrists premises and asking what glaucoma testing equipment that they had and which ones they used and on what groups of patients. It seems possible that the figures actually are a reflection of what the optometrist feels they should do rather than what they actually do.

If an optometrist chooses to test a patient for glaucoma they may use IOP measurement (tonometry) which is either contact or non-contact, ophthalmoscopy of the optic disc or may test the patients visual fields (perimetry). The IGA figures indicated that 90% of optometrist's practices surveyed had a tonometer[47] but that 10-15% of practices did not use them[47]. 55% of the survey respondents only routinely tested patients aged over 50. 80% of all practices were found to have a working field screener and around 10% used them -with the vast majority only in patients in which there was reason for suspicion e.g. abnormal discs or a family history of the disease. Ophthalmoscopy was performed by all the optometrists surveyed whatever the circumstances [47].

Vernon and Henry produced similar figures in their study of optometric practices in Nottingham by sending a questionnaire to practices listed in the telephone directory. This study could have been subject to some of the same biases as the IGA survey and the results were similar with all optometrists performing ophthalmoscopy and 92% performing tonometry. 8% performed fields routinely, 19% did not do fields and the remainder only when the other tests indicated it. Other studies have more or less agreed with these figures [49,50].

Pitts-Crick and Tuck [51] calculated that optometrists who routinely used tonometry detected over twice as much glaucoma as did those who relied mainly on ophthalmoscopy. Those who also used perimetry in high-risk patients detected over

three times as many glaucoma. Therefore, it would appear that perimetry is the most sensitive method of glaucoma screening and the Baltimore Eye Survey figures bear this out. They calculated that IOP measurements only identified half of all patients in need of treatment, perimetry two thirds while combining IOP, perimetry, cup analysis and history of risk factors had an 83% sensitivity[21].

To produce a 100% glaucoma detection rate would be ideal, but for an optometrist to perform all three tests on each customer would be expensive, time consuming and probably not acceptable to a large proportion of customers. It is also likely that there will be a high price to pay in the hospital eye service with a large number of false positive referrals. Thus it is really those patients at higher risk of glaucoma that need time and resources concentrated on them. It is only recently, with large scale population surveys that we are getting an idea of the true risk factors for glaucoma.

iii. Referral to the HES.

Sheldrick *et al* [52] found that 99% of patients with a suspicion of glaucoma were referred via optometrists, however, only 32% of these were shown to have glaucoma. Harrison *et al*[50] found that 82% of glaucoma referrals were from optometrists but 20% did not have glaucoma, while Brittain *et al*[53] found that 72% were referred from optometrists and of these, 33.7% showed no evidence of glaucoma. All these figures were derived from clinic based surveys of referral letters and the outcome of the subsequent clinical examination. It is important to bear in mind that because glaucoma can be a difficult disease to diagnose in one visit, these figures could represent either under or over estimate of the accuracy of optometrists glaucoma diagnoses.

We can see that the vast majority of glaucoma referrals to hospital are from optometrists but that the rate of inappropriate referrals is high. Studies have shown that the main source of inappropriate referrals is from practitioners who simply do ophthalmoscopy or tonometry[51,52]. There is however little published information regarding false positives produced by optometrists routinely checking visual fields but this is an area that is likely to become increasingly important as more practices purchase field analyzers.

1.4.2 General practitioners and referral.

Glaucoma referrals from General Practitioners are much less common than from optometrists and show much less diagnostic accuracy. This is not surprising as very few GP' s have the equipment or training to accurately diagnose glaucoma. Although, when questioned, most possess an ophthalmoscope, disc analysis is one of the least specific methods of diagnosis[54].

Brittain *et al* [53], found that of all GP's referrals to the eye clinic that they studied 23.7% of patients had a presumptive diagnosis of glaucoma but 74.1% had no subsequent evidence of glaucoma. Steinmann [55] showed only 18% of GP's were correct in their diagnosis, Sheldrick *et al*[52] found only 1% of glaucoma patients referred to an eye department came from GP's.

It has been suggested that the GP is in an ideal position to 'screen' for glaucoma analogous to the manner that they opportunistically check blood pressure [56]. Others have felt that this screening should be undertaken in tandem with an optometrist [50] and this would appear to be the most productive and cost effective method [57,58].

The majority of referrals from optometrists in this country are initially sent to the GP with hospital referral occurs from there [26] - this allows the GP to maintain a

central role in the patients care. This arrangement has been criticised by Kljakovic *et al*[59] who found that this led to a delay in referral for 16% of their patients. They suggest that optometrists should be able to refer directly to the HES.

1.4.3 Other sources of referral

This mode of referral is small and unlikely to be in significant numbers. For example, Brittain *et al* [53] found that 1.5% of the patients in their study were picked up in the Eye Casualty department and one patient came from the diabetic clinic. MacKean and Elkington [60] found that 5% of there patients came via this route and 3% from other clinics.

1.4.4 Screening and glaucoma

Screening is a term often loosely applied to a number of clinical situations ranging from examination of an individual (e.g. blood pressure measurement) to Government organised, comprehensive, population testing e.g. the cervical smear programme. This looseness of definition creates problems in the understanding and application of screening[61,62].

To improve this understanding, it has been suggested that the word screening should be restricted to the presumptive identification of individuals in a defined population at risk likely to be affected by an asymptomatic or sub-clinical condition who can benefit by being further investigated[63]. Thus true screening involves the entire population who are at risk being identified and offered an examination. Opportunistic plasma lipid testing by a General Practitioner is not true screening but examining the fundi of all diabetics in the practice is.

At first glance it would seem that glaucoma is a disease that should be screened for. It has a long pre-symptomatic phase and the blindness resulting from

glaucoma is particularly severe in that it is bilateral and involves all the visual field. However important prerequisites for screening are not met by glaucoma[22].

There is a lack of a true understanding of the natural history of the disease and there is no agreed policy on who to treat and how. Further, there is a lack of good evidence of the efficacy of treatment of glaucoma and without randomised controlled trials we do not know for sure if pressure reducing treatment prolongs visual field survival.

The other problem with screening for glaucoma is the lack of a robust screening test. Taken individually, intraocular pressure (IOP) measurement, optic disc assessment and visual field testing have low sensitivity and poor positive predictive value[22]. Using an IOP of above 21mmHg as a screening test for glaucoma will mean that not only will 50% of those with glaucoma not be identified but that the hospital eye service will be burdened with a large number of ocular hypertensives who will never require treatment.

Although optic disc assessment can have high sensitivity and specificity[66], it is often found to be poor predictor of glaucoma. The mode of examination/level of training of the observers is usually the limiting step rather than optic disc examination itself [68]. Variations in disc and cup size and poor agreement between observers making it a poor screening tool.

Visual field testing is the best single screening tool for glaucoma - although it is detecting the disease *after* functional damage has occurred. It produces problems in that it is time consuming, results can depend on patient (rather than disease) variability and requires expensive equipment[64]. However, the development of low cost techniques e.g. the Damato Campimeter [69] and more sensitive techniques.

At present a combinations of all three tests provides the highest validity (the degree to which a measurement measures what it purports to measure). No country has a formal screening programme for glaucoma for the reasons outlined above. In the UK the majority of glaucoma suspects are identified by optometrists during routine sight tests but this relies on people attending for regular sight tests (and there is evidence that those at greatest risk of glaucoma are also those who are least likely to attend for sight testing) and the optometrist examining for glaucoma. Concentrating on high risk groups such as the elderly, African Caribbean's and those with a family history would improve the sensitivity but still does not justify a nationwide screening programme[46].

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CHAPTER 2: STUDY RATIONALE.

2.1 THE EPIDEMIOLOGY OF GLAUCOMA BLINDNESS

Glaucoma is the second leading cause of blindness in the world after cataract. It has been calculated that there will be 6.7 million blind from the disease by the year 2,000[1]. Amongst the industrialised nations it is regularly the second or third commonest cause of blindness, Table 2.1 illustrates the percentage of those who are registered blind from glaucoma in published studies:-

Table 2.1

STUDY	THOMPSON	GHAFOUR	SORSBY	ACLIMANDOS	GREY	HILLER	FRAMINGHAM
YEAR PUB	1989	1983	1966	1988	1989	1975	1980
COUNTRY	ENGLAND	SCOTLAND	ENGLAND	ENGLAND	ENGLAND	USA	USA
% REG GLAUCOMA	13	14.6	13	14	13	11.4	15.3

Although the figures are consistent, they all come from blind registration data which can have a number of flaws. Firstly, they are commonly regarded as an underestimate of the visually handicapped [9] because not all those eligible are seen by an ophthalmologist and when there is on-going treatment, ophthalmologists may be reluctant to register patients -who themselves often refuse registration in order to avoid being stigmatised. Secondly, fluctuations in the figures may not be caused by a true improvement in treatment or increase in disease prevalence[10].

Population estimates of glaucoma blindness are much less prone to the biases mentioned above. The Roscommon survey found a prevalence of blindness amongst their subjects of 7.3%[11] and the BES found 4.4%[12] but higher in Blacks at 7.9%. Black patients do seem at a greater risk of blindness than whites, Hiller and Khan found a rate of glaucoma blindness seven times higher for non-whites [7] and amongst African-Americans glaucoma is the top cause of Blind registration [13]. The difference persists in all age groups and both sexes[14], however, few studies have

addressed the potential modifier of socioeconomic status, ethnic origin and blindness from glaucoma

The incidence of glaucoma blindness (per year) in three studies is shown below in Table 2.2:-

Table 2.2

AGE RANGES	SORSBY	ACLIMANDOS
0-15	0.25	0.17
16-64	0.48	0.52
65-74	8.23	9.1
75+	25.25	46.97

AGE RANGES	HILLER (WHITE)	HILLER (NON-WHITE)
20-44	0.9	7.6
45-64	8.8	131.4
65-74	35	388
75-84	97	577
85+	261	747

The table indicates a marked increase in blind registrations from glaucoma with increasing age - consistent with the increased incidence and prevalence of the disease and its natural history.

It can also be seen from Hiller and Kahns' study [7] that the incidence for non-whites is much higher. This fits in with the American "Model Reporting Area for Blindness Statistics"[7] which showed that the average age of registration of blindness due to glaucoma for non-whites was 62 years but for whites was 70 years.

2.2 WHY DO SOME PEOPLE GO BLIND FROM GLAUCOMA?

The blindness statistics given above inevitably lead to the question why do some people go blind from glaucoma and others do not. This was a question asked in a seminal paper by W. Morton Grant and Joseph F. Burke in 1982[15] but apart from this there has been little work on this topic.

Grant and Burke suggested that there were two reasons that may cause an individual to become blind from their glaucoma:-

1. They present so late in the course of their disease that treatment is either too late or only effective for a short period of time.

2. Presentation is in an earlier phase of the disease but treatment is inadequate or ineffective.

The latter of these two findings is undoubtedly extremely important and underpins our current treatment strategies, with a wealth of literature devoted to it, but is outside the remit of this present work. It is the other finding of the Grant and Burke study is the one that this study was designed to look at in more depth.

2.2.1 How common is late presentation?

Grant and Burke [15] examined the records of 750 patients (i.e. a hospital based study) who had been registered blind at the Massachusetts Eye and Ear infirmary over the previous ten years. This revealed 128 individuals registered from glaucoma alone - of these 25 were blind in both eyes on presentation and 17 in one eye. Thus around one third of patients were blind in one or both eyes on presentation.

Sheldrick *et al* [16] found that 19% of new referrals to an eye clinic showed advanced field loss in their worse eye. Perkins [17] in the Bedford survey, judged that 28.7% of his sample were certified as blind because of late presentation while Miller and Karseras [18] found that of the 34 glaucomatous patients registered blind at Moorfields eye hospital over a three year period 14 (41%) were as a result of late presentation. MacKean and Elkington[19] found that 59 out of 191 patients (31%) presenting to their clinic had advanced field loss in one or both eyes, similarly Gillie[20] found that 26.5% of his patients presented with advanced field loss.

2.2.2 Why does late presentation matter?

The studies indicate that late presentation is a significant problem, but what evidence is there that late presentation predisposes to blindness?

Wilson *et al* [21] looked at risk factors for rate of progression of glaucomatous visual field loss in 57 known glaucoma patients and found that initial visual field was the strongest determinant of rate of further visual field loss. In fact patients in their study deteriorated 11.7 times faster in the eyes with more advanced loss on the initial field.

Grant and Burke [15] found, when they looked at the pre-treatment condition of eyes that went blind from glaucoma compared to those that did not (over a 20 year period), that the blinded eyes were more likely to present with disc cupping and visual field defects. They concluded that eyes with a visual field defect at the start of treatment were more likely to progress to blindness than eyes in which treatment is started at the stage where there is no field loss.

Studies such as that of Grant and Burke, that compare the decline of patients with 'early' and 'late' glaucoma must be interpreted with some caution. If early glaucoma is defined as patients with no field loss or only classified using one set of fields then it is possible to include patients without glaucoma in the early group. Not surprisingly this will exaggerate the effect of advanced field loss on subsequent blindness. Thus only figures from studies that have a rigorous definition of early glaucoma should be considered.

Frähauf *et al* [22] who also did a 20 year retrospective study, but only used patients with definite field loss, found that progressive field loss was more common in those not diagnosed and treated until they had reached a more advanced stage.

Hart and Becker[23] divided glaucomatous visual field deterioration into three phases:-

1. First or sub-threshold phase- this is mainly inferential, but there is histological evidence that a significant number of ganglion cells are lost before visual field defects occur.

2. The second or threshold phase is one in which the earliest visual field defects occur.

3. Once past threshold, the third stage is manifest glaucoma.

Using this classification, they found that by the time phase three had begun, the susceptibility of remaining nerve fibres was very high and that there was a high probability of extensive progression within the next ten years. They also found that this progression occurred in spite of only marginally elevated IOP.

Mikelburg *et al* [24] measured scotoma mass of fields and compared them to the rate of subsequent decline. They found that when scotoma mass was small (i.e. early disease) rate of visual field loss was slow but when the scotoma mass was large, more rapid progression of visual fields occurred.

Miller and Karseras [18] stated that from their series glaucoma is more benign in patients with considerable visual reserve.

It would appear that there is good evidence that late presentation (i.e. substantial field loss) is a significant risk factor for subsequent glaucoma blindness. There is also a biological plausibility underpinning this in that the less axons a nerve has the less it can lose without significant field changes. It has also been shown that discs with larger cups are more susceptible to the mechanical stress created by IOP than are discs with little or no cupping [64]. From an epidemiological point of view

studies of apparent higher risk of blindness in those with more advanced visual fields can be subject to length bias and this will be discussed in Chapter 5.

2.2.3 Does early presentation reduce the risk of subsequent blindness?

It would appear that late presentation represents a high risk for glaucomatous blindness but does the converse hold i.e. does early presentation give an individual a chance of reducing or avoiding visual loss from glaucoma?

As discussed in section **1.3.2**, IOP is a major risk factor for glaucoma and that while previously it was a *sine qua non* for glaucoma this is no longer so. One of the reasons for the importance of IOP as a risk factor is that, at the present time, it is the only one that we can manipulate. That reduction of IOP slows the rate of glaucomatous visual field loss is a tenet that most ophthalmologists believe. In practice -and in the context of early presentation- it is very important as it is the mechanism that will allow for long-term survival of the field. This being so, what is the evidence that reducing IOP reduces visual field loss? Vogel *et al* [26] summarise the situation well "the evidence (that control of IOP will exert a favourable influence on progression of glaucoma) is mainly inferential and anecdotal, but it is compelling to the degree that clinicians feel that it would be unethical not to attempt this form of treatment". Thus randomised clinical trials of treatment versus non-treatment of glaucoma are ethically difficult and we must try to gain evidence in more circuitous ways.

Jay and Murdoch[25] produced an important paper concerning visual field loss if IOP was not treated. They calculated the age at diagnosis of patients who presented with mild field loss and compared it with the age of those who presented with a field that was almost extinguished. IOP was divided into three groups, 21-25mmHg, 26-30mmHg and >30mmHg and they calculated that if someone had an IOP in the lower

group of 21-25mmHg then the approximate time to blindness was 14.4 years. In the moderate group (26-30) it was 6.5 years while at pressures over 30 it was a little as 2.9 years. It is important to note that this time course is only in eyes with some damage already and that as, the authors admit, there are some limitations to the study -including the hospital based nature of the patients, that other risk factors were not taken into account and there are is an assumption that visual field decline is at the same rate between individuals.

Jay and Murdochs' paper indicates that the higher the IOP the more rapid the visual field loss and other studies have concurred with this. Vogel *et al* [26] looked at 747 patients with POAG in a hospital eye clinic and found that the higher the IOP on detection of the glaucoma, the worse the visual field was and they felt that this supported the argument for controlling IOP. Hart *et al* [23] found that mean IOP was directly related to amount of field loss and Kass *et al* [27] had similar findings. Hovding and Aasved [28] found that patients with PXF (who tend to run higher pressures than POAG) ran a higher risk of glaucomatous damage. Wilson *et al* [21], found that the risk of progression of field loss in their subjects was increased by a factor of 2.7 for IOP's over 21 compared to those under this figure. Because all these studies are hospital clinic based there is always the possibility that differential referral (e.g. patients with more advanced field loss had symptoms and went for a sight tests or that optometrists were more likely to refer patients with higher IOP's) could be responsible for some of the findings. Wilensky *et al* [29], in a rare prospective study, found that an IOP of greater or equal to 25mmHg to be an important prognostic indicator of subsequent glaucomatous field loss.

So the evidence that increasing IOP increases field loss in glaucoma although not conclusive does seem consistent. That does not necessarily tell us that lowering

the IOP reduces visual field loss - although it would be reasonable to infer. Jay and Allen [30], when they looked at the benefit of early trabeculectomy versus medical management of glaucoma found that the surgical group - who had a lower IOP than the medically treated group- had a significantly better field after 2.6 and 4.6 years. Putting their three studies together they estimated that the time from the earliest demonstrable field loss to end stage disease in each group was as follows [25]:-

IOP at diagnosis>25mmHg	1. Untreated	3.6years of field survival
"	2. Unsatisfactory treatment	10years "
"	3. Optimum treatment	38years "

Unsatisfactory treatment is medical treatment that reduces the IOP but not consistently, optimum treatment is a sustained reduction in IOP, the former finding indicates that even some lowering of IOP has an effect on prolonging visual field survival.

Kass *et al* [27] compared the normal fellow eye of patients who had bilateral raised IOP but glaucomatous loss only in the other eye. They found that treatment of this fellow eye did not protect it from the development of visual field loss unless the IOP was reduced to 24mmHg or less on more than 50% of measurements.

Vogel *et al*[26] found that if the IOP was reduced to 14-16mmHg with treatment, as compared to patients with treated IOP's of 22, there was double the rate of field loss of the latter group. There are numerous other papers that show reductions in IOP reduce the risk of further glaucomatous damage [7,31,32]. Interestingly, what both Odberg[33] and Mao *et al*[34] found was that in the patients who had their IOP maintained below 16mmHg, progression was much less than in those who ranged

from the high teens to the low twenties. As Alfred Sommer writes [32],"while the data are less than ideal, it is likely that by significantly lowering IOP one can effectively reduce the rate of optic nerve destruction. The relationship, however, is not simply linear- a small or even a modest reduction in IOP may provide little or no clinically significant benefit."

Although it can be misleading to extrapolate ocular hypertension data to glaucomatous patients it can tell us something about the relationship between IOP and glaucoma. Becker and Morton [35] showed that topical adrenaline (which lowers IOP) reduced the risk of conversion to glaucoma. Similar results were shown for Timolol drops [36].

That reduction of IOP is not the only factor involved in preventing further optic nerve damage is obvious from the fact that a significant number of individuals will progress despite seemingly adequate IOP control, that those with IOP under 21 can progress to blindness and that black patients have been shown to have the same IOP levels as white patients but glaucoma that progresses more rapidly [37].

In conclusion, adequate reduction of IOP seems to reduce the rate of visual field decline in most patients and is therefore likely to prevent progression to blindness. This fact along with the knowledge that those who present with advanced glaucoma are not uncommon and are at high risk of blindness is the rationale for studying the reasons for late presentation.

2.3 WHY DO SOME PEOPLE PRESENT LATE?

The available evidence points to late presentation being a risk factor for blindness from glaucoma, but what are the risk factors for late presentation?

Reviewing the literature reveals a large number of studies stressing the importance of late presentation but few that mention the possible reasons why patients have presented late. From these few and from the knowledge of the pathogenesis of glaucoma noted previously, it is possible to construct a set of hypotheses that may help to explain differences in the stage of disease at presentation to the HES.

2.3.1 Age

Increasing age is strongly associated with in an increased incidence and prevalence of glaucoma [38]. Incidence of new registrations for glaucoma blindness rise steeply in the over 70's[39] as the incidence of other sensory and motor handicaps increase. It would appear reasonable to hypothesise that increasing age would be a risk factor for late presentation - the elderly represent the largest number of people with the condition, they have had a longer period of time for the disease to progress and may have problems with access to testing.

2.3.2 Ethnic origin

There is little in the literature regarding any ethnic groups apart from African-Caribbeans and African-Americans as compared to Caucasians with glaucoma. However, there is good evidence that blacks do present later in the disease [7] and have an excess prevalence of glaucoma blindness [40]. Wilson *et al* [41] retrospectively compared black and white males with glaucoma and found that disk damage and visual field loss at initial diagnosis appeared to be worse in the eyes of blacks. They also noted that at initial diagnosis blacks were younger than whites allowing not only a longer period for glaucomatous damage to occur but also means that optometrists who use age as an indicator of when to screen for glaucoma [42] may well miss the younger black sufferers. We can see that it is not only older age

than may be a risk factor for late presentation but also those under 40 may well not be being screened.

Wilensky *et al* [29] suggested that blacks, because of socioeconomic reasons, do not seek medical care until their glaucoma is more advanced although they presented no evidence for this. There is though, evidence that compared to age matched white patients, black patients present later in the course of other diseases - including prostate cancer [43,44], breast cancer [45] and colorectal cancer [46]. Similarly there is evidence that African-American populations utilise health-screening services less than white patients [47]. Wells and Horm [45] showed that the racial differences of stage at presentation disappeared if socioeconomic class was accounted. Similarly, the BES identified an association between race and blindness which was reduced, but not eliminated, after adjustment for socioeconomic factors [48].

In summary, we can hypothesise that blacks may be at greater risk of late presentation than whites because:-

1. They appear to have an earlier onset of the disease.
2. The time course between early disease and blindness is shorter [41].
3. They may have a reduced contact with medical services.

2.3.3 Use of optometry services

As discussed previously, there are three steps from optometric attendance to hospital visit, each step could influence a person's stage of diagnosis. These steps are:-

i. An individuals decision to visit an optometrist (whether for glaucoma testing or not).

ii. The attending optometrist must perform one or all of the appropriate glaucoma tests.

iii. The individual has to be referred to the HES.

The first two steps are the more important in determining late presentation as failure of referral, although it does happen, is unlikely to be common.

If an individual never attends an optometrist then it is not unreasonable to suppose their chances of presenting late with glaucoma are high. Conversely, frequent attendance at the optometrist may be thought to confer an increased likelihood of earlier presentation (assuming glaucoma is tested for). Therefore we can hypothesise that the longer the interval since the individual visited an optometrist the higher their risk of being a late presenter.

Whether an optometrist tests for glaucoma is obviously going to have a major bearing on presentation. Those people who do not have a glaucoma examination at the optometrists would be at greater risk of late presentation than those individuals who had at least one of the appropriate tests. Pitts-Crick and Tuck [22] calculated that tonometry by optometrists detected twice as many glaucomas as just ophthalmoscopy, while perimetry increased this to three times as many detected. Thus it may be that late presenters who did attend optometrists are less likely to have been examined for glaucoma or, if they are examined, are less likely to have the full range of glaucoma tests compared to the earlier presenters.

2.3.4 Social Deprivation

It has long been known that socioeconomic factors influence the access to adequate medical care as well as patient compliance with treatment [49] and this extends to screening services. Loehrer *et al* [50] found that late presentation of various cancers was directly related to lower socioeconomic status and felt this was

due to both risk promoting lifestyles and beliefs about cancer based on incomplete or erroneous information. Other studies have confirmed the link between later presentation of cancers and social deprivation including breast [45], colorectal [46] and skin [51].

It has also been shown that lower socioeconomic status is associated with poor uptake of screening services in mammography [52] and cervical smears [52].
The relationship between increased mortality and morbidity and social deprivation is well-documented [53,54] and it has been shown that many screening services fail to serve the socially deprived.

As far as eye disease is concerned, Smith *et al* [55], looked at the relationship between social deprivation and age at presentation of amblyopia. They found that the more deprived children were much more likely to present late with anisometropic amblyopia. One aspect of the Baltimore Eye Study looked at Socioeconomic Status and Visual Impairment Among Urban Americans [48] and they found that lower status was associated with higher rates of visual impairment.

It seems reasonable to extrapolate the above to glaucoma detection and hypothesise that those of lower socioeconomic status are less likely to attend for regular sight testing and therefore to present later in the course of the disease.

Measurement of deprivation.

The content and derivation of measures of deprivation has been the subject of much debate in Public Health circles [54]. There are now a number of deprivation indices available with the Townsend index [54] and Jarman score [56,57] devised for use specifically in the context of health to seek to explain variations in health indicators in terms of material deprivation [54]. Although it has been suggested that the Townsend score is a better indicator of material disadvantage [143], the Jarman

score correlates more highly than the Townsend index with hospital use variables particularly those of the elderly [54]. Also the Townsend index does not include scores for London so the Jarman index may be more useful in this study.

Underprivileged Area Score. The Jarman score (or index) or Underprivileged area score (UPA) is a measure of deprivation as it affects primary care services [56,57]. It came about in the 1970's when the difficulties of general practitioner services in inner cities were brought to light.

Areas (usually inner city) containing high concentrations of elderly people, single parents, overcrowded households, ethnic minorities and unemployed were known to have a significant effect on mortality and morbidity patterns and use of GP services. To target primary care resources on areas of greatest need a method of identifying these areas was required. 10% of all GP's in the UK were surveyed and asked to weight a range of factors according to the degree which they increased the pressure of services in their area. The average weightings given by the GP's were then calculated for each factor and the results were:-

1. Elderly living alone 6.62
2. One-parent families 3.01
3. Children under 5 4.64
4. Social class V 3.74
5. Unemployed 3.34
6. Overcrowded households 2.88
7. Moved house within year 2.68
8. Born in Commonwealth 2.50

Using Census data, the proportion of individuals with these factors in each Electoral Ward can be calculated and then by weighting it according to the variables

shown above, a UPA score can be produced for any ward. UPA scores can vary from minus 50 to plus 70 with a higher score indicating a higher level of deprivation.

The UPA score produces an overall measure of deprivation for the ward in which the patient lives and can easily be calculated if the patients postcode is known. While this measure is extremely useful as a blanket indicator of social deprivation it does make generalisations about individuals. Slogett and Joshi [53] found that an assessment of *individual* deprivation could be made using four factors:-

1. Access to a car.
2. Living alone.
3. Occupational class.
4. Type of accommodation.

As well as being useful indicators of individual socioeconomic status, these factors could contribute to late presentation themselves. For example, access to a car may be very important to some individuals who are unable to travel independently to their optometrist.

2.3.5 Education level

Although this is closely linked to socioeconomic status, it can be independent of it and may be an important factor determining time of presentation in its own right. A study on breast cancer in the USA found that the better educated patients were more likely to have undergone mammography [58] and a similar study on prostate cancer and stage of presentation showed later presentation in the less well educated group [43].

The Baltimore Eye Study investigators looked at educational levels in their study and found that years of schooling were inversely associated with the prevalence of blindness and visual impairment [48].

Unless an individual has ocular symptoms, attendance at an optometrist every 2-3 years is only likely to occur if that individual understands the need for regular sight testing. Vernon and Henry [59] found that 67% of the patients they surveyed knew what glaucoma was. Using educational level as a very rough indicator of knowledge of glaucoma and its asymptomatic nature we can hypothesise that those who present late with glaucoma are more likely to have left full time education at a younger age than the earlier presenters.

2.3.6 Intraocular pressure.

Jay and Murdoch suggested that high (>30mmHg) can lead to blindness within 3 years [25] and that the higher the IOP is the speedier the field loss. It would thus be reasonable to speculate that the higher the IOP at presentation the greater the risk of late presentation. Included in this would be those glaucomas that tend to have higher IOP's - i.e. PXF and CACG, may, by the same token, be at greater risk of presenting late.

The converse to the above is NTG where the pressure does not rise above 21mmHg. The danger with this is that optometrists who only test with tonometry are going to miss these patients. So although the patient has regular sight tests, NTG may be in danger of being missed until disc cupping becomes very marked or perimetry is performed. Thus an IOP under 21mmHg may also be a risk factor for late presentation.

2.4 EFFECT MODIFIERS

Effect-measure modification refers to variation in the magnitude of a measure of exposure effects across levels of another variable. This variable, across which the effect measure itself varies, is called an effect modifier[63]. It is different from confounding which is an effect of an extraneous variable that wholly or partially

accounts for the apparent effect of the study exposure or that masks an underlying true association. An apparent association between an exposure and disease may actually be due to another variable.

The difference between an effect modifier and a confounder is that confounding is a bias that the investigator hopes to prevent or remove from the effect estimate while an effect modifier is a property of the effect of the study. It is therefore part of the results rather than a bias to be avoided.

There are a number of effect modifiers that could potentially influence the hypotheses discussed above:-

2.4.1 Use of Medical Services

Individuals who are high users of medical services e.g. the disabled or chronically ill are often of low socioeconomic status and might be expected, from the hypothesis regarding social deprivation, to be more likely to be late presenters. However, as we have seen from hospital based studies those with greater than normal contact with medical care e.g. diabetics or hypertensives, tend to be over-represented in glaucoma studies [60].

When the BES investigators looked at self-reporting of poor health and prevalence of visual impairment [48], they found little association between blindness and use of health care services -although this was not specifically regarding glaucoma blindness.

Poor health seeking behaviour and risk promoting lifestyles have been associated with late presentation [50] in various cancers. Thus, although those of lower socioeconomic status may be more likely to present late with advanced field loss this effect may be modified by their higher use of medical services.

2.4.2 Family History

Similarly, it would appear possible that a family history of glaucoma could act as a effect modifier of any of the above hypotheses. Although we know from population based studies [61] that the familial risk of glaucoma is not as high as hospital based studies and in view of the possibility of under or over-reporting of cases, it is currently difficult to get good estimates of the size of the genetic effect in glaucoma. However, family history is something that many new patients seem aware of and it seems likely that anyone with a family history will have a greater understanding of the need for regular sight testing. Further, the optometrist is more likely to perform the appropriate examinations on those with a family history [42].

It would seem likely that a positive family history of glaucoma could be a powerful incentive for regular sight testing and therefore earlier presentation and may therefore be a effect modifier

2.4.3 Ocular factors

Presbyopia.

Although this is not a risk factor as such, it may well be a determinant of presentation (and therefore could in fact be thought of as a true confounder rather than as an effect modifier). Presbyopia is the need for reading glasses usually starting in the fifth decade and stabilising by the seventh. This means that those over 65 are less likely to need an increase in the power of their reading correction and so, unless some other pathology intervenes, have less incentive to seek sight testing. This may be another factor contributing to late presentation in older age.

Other ocular pathology.

Cataract has long been associated with glaucoma [62] and it would appear that glaucoma is a powerful and independent risk factor for the development of cataract.

Thus we might hypothesise that because the cataract will produce symptoms it will allow detection of the underlying glaucoma. But this could of course work the other way - that the developing cataract prevents ophthalmoscopy and perimetry and therefore detection of the glaucoma.

2.5 STUDY HYPOTHESES AND AIMS

The aims of this work is to ascertain why some people present in the early stages of glaucoma while others present with almost complete field loss in one or both eyes. The reason that late presentation is so important is that it is a major risk factor for blindness but also is, at least theoretically, a factor that could be modified. Without adequate knowledge of the elements that go into causing later presentation this modification could not occur. The remainder of the thesis represents an attempt to define these elements and is in effect an attempt to answer the hypotheses listed below. Conducting the study in this fashion reduces the risk of not obtaining the requisite information and defines the research question more precisely [60].

To summarise the hypotheses discussed above, late presentation of chronic glaucoma is more likely to occur:-

1. With increasing age of the study subjects.
2. In African-Caribbean and African subjects than Caucasians.
3. The longer the interval has been since the subject has visited an optometrist.
4. In those who are more socially deprived - as measured by UPA score, occupational classification, housing tenure, social isolation and access to a car.
5. In those who left full-time education earlier.
6. In those with higher IOP's at presentation.

Potential modifiers of these hypotheses that need investigation are:-

1. Individuals with frequent access to medical services

2. Those with a family history of glaucoma.

3. Those with visual or other ocular symptoms not related to their glaucoma.

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CHAPTER 3: PATIENTS AND METHODS.

3.1 CASE-CONTROL STUDIES

When looking into the causation of disease, a longitudinal study is most useful. However, when the particular disease is of low incidence, large and lengthy studies may be required to give adequate statistical power. An alternative to this is the case-control study in which cases and controls are compared with respect to existing attributes or exposures thought to be relevant to the development of the condition or disease under study [1].

Glaucoma is a disease of low incidence in the population and late presentation of it has an even lower incidence -so that it is well suited to the case-control format. For this study, the method has other advantages -including its usefulness in diseases of long latency and the fact that it allows investigation of multiple potential causation factors [1,2,3].

The study is not looking into the causes of glaucoma - when the cases would be patients with glaucoma and the controls would be those free of the disease - but into differences in presentation of the disease. Thus the particular 'condition' that the cases have is late presentation while the controls are free of it - but both have glaucoma. The ratio of the odds of the condition in exposed individuals relative to the unexposed will provide estimates of the odds ratio of late presentation versus early presentation for each group.

It was mentioned previously that some studies that have compared early and late glaucoma may be flawed regarding wrong classification of early glaucoma. This study avoids this flaw as both cases and controls have glaucoma.

3.1.1 The Case-Control method in the evaluation of screening.

The use of the term screening in relation to glaucoma was discussed in Chapter 1, however the term 'optometric screening' is often used to describe the examination of patients by optometrist for glaucoma but, in fact, this examination does not fulfil the definition of screening and is perhaps more accurately described as opportunistic surveillance or case-finding. However, for the purposes of this study, it is useful to think of sight tests as screening events (like BP measurements by a GP) to allow comparison with some of the (non-ophthalmic) literature that use the case-control method to evaluate the usefulness of screening measures.

A randomised control trial is the best method of studying the efficacy of screening [2] -one group of individuals are offered screening and the other group not. If randomisation is complete (and the potential for certain biases is recognised in the design of the study) the problems of lead time and length bias (see section 5.5) can be eliminated. This is something that cannot be done using the case-control method.

For practical purposes it would be unethical to exclude people from the non-screened group - and difficult to get fully informed volunteers. The other difficulty is that studies must enroll a large number of screened and non-screened subjects in order to achieve enough power to identify even a moderate effect of screening [3]. In order to get over these problems, case-control studies have been used to evaluate the success of early detection programs e.g. cervical and breast cancer programs[2].

Although it has obvious advantages in evaluating screening, the case-control method has been criticised in this role. Connor *et al* [2] feel that there is a self-selection bias i.e. because screening is offered to all, those that have chosen to be screened have been self-selected (which is consistent with the findings of this present study). Weiss [3] notes that there is considerable potential for confounding in case-control studies of screening efficacy in that the presence of risk factors for an illness leads an individual to seek screening (such as family history and glaucoma). A further problem is that those who have received a screening test are more likely to have received the same test in the past.

Bearing in mind the reservations noted above using the case-control method to assess the efficacy of glaucoma 'screening' is probably the best method - for both logistical and ethical reasons.

3.2 STUDY DESIGN

3.2.1 Definitions of Cases and Controls

Cases were defined as having:-

Visual field loss that was consistent with a known pattern of glaucomatous loss (e.g. arcuate scotomas) was compatible with the patients disc changes and in which there was no suggestion of other optic nerve pathology (e.g. defects crossed the horizontal mid-line) within five degrees of fixation and beyond 30 degrees in one or both eyes.

Glaucoma of any chronic type i.e. Primary open angle, pseudoexfoliative, normal tension, chronic angle closure, aphakic or pigment dispersion.

Two consecutive fields (threshold or suprathreshold) confirming the loss except where field loss was so advanced that perimetry was not possible

Patients who had more than one third fixation losses, false positives, or false negatives on their initial field test were not enrolled for the study. Fields were almost exclusively with the Humphrey 24-2 or 10-2 threshold strategies. The grey scale was used to identify glaucomatous defects as long as the reliability indices were acceptable (see below).

A cup disc ratio greater than 0.8 in one or both eyes.

Controls were defined as having:-

Visual field loss that was consistent with a known pattern of glaucomatous loss, was compatible with the patients disc changes and in which there was no suggestion of other optic nerve pathology (e.g. defects crossed the horizontal mid-line), but no absolute scotomas within 20 degrees of fixation in either eye.

Glaucoma of any chronic type -as above.

Two consecutive fields confirming the loss

Patients who had more than one third fixation losses, false positives, or false negatives on their initial field test were not enrolled for the study. Fields were almost exclusively with the Humphrey 24-2 or 10-2 threshold strategies.

A cup disc ratio assessed as greater than 0.5 or there was a difference of greater than 0.2 between the discs.

To enable the study to be conducted prospectively and to minimise the problems of recall bias, patients were recruited after the first field. If, during follow-up, visual fields 'improved' to the extent that the patient no longer met the above criteria they were removed from the study.

The reason for using these criteria were as follows:-

Fields.

The field criteria were a modification of those used by Jay and Allan [5] in the Early Trabeculectomy trial. They had a five-stage classification of visual field changes, with stages four and five being absolute defects within five degrees of fixation and stage one early relative defects. Thus those in stage four or five in their study are the late presenters (equivalent to the cases in this study) and the early presenters (the controls) are stage one but with no scotomas within 20 degrees of fixation -to ensure a definite difference between case and controls.

Both cases and controls had typical glaucomatous loss e.g. arcuate scotomas, nasal steps and with no other obvious ocular cause. The AGIS trial defined this latter criterion as determined by clinical examination in which there is no sign of corneal opacity, pupil miosis, cataract, optic nerve head anomaly, retinal defect or retrobulbar problem that might cause the defect [6].

Discs.

Initially disc quantification was not part of the case-control criterion but following the pilot study it was added. The pilot study is more fully described in section 3.2.3 and was published as a paper (Appendix 1). It was noted in the pilot study that all fields that had a persistent defect (i.e. in more than one field test) within five degrees of fixation also had an estimated cup disc ratio of greater than 0.8. Similarly the controls who had persistent defects always had a cup disc ratio of more than 0.5 or, if they did not, had an estimated difference of at least 0.2 between the two discs. Thus disc cupping was added to the criteria for the main study.

Glaucoma diagnosis.

As discussed previously, the study is not about any type of glaucoma in particular, but is concerned with those types that can be symptomless until blindness i.e. the chronic glaucomas. Because POAG is by far the commonest type in this country it will predominate but PXF, NTG, pigmentary and aphakic glaucomas tend to be asymptomatic and are therefore included. Chronic angle closure can lead to typical symptoms such as haloes and pain in the evenings but patients who reported these symptoms were not included in the study. Patients whose narrow angles were found on gonioscopy were included.

3.2.2 Sample Size

It is important to calculate the number of subjects required when planning the study so that the study will have enough power. In practice, most case-control studies use all eligible cases arising within the defined period which is usually enough for the study's primary objective, but may preclude sub-group analysis.

The sample size estimation depends on the specification of two parameters - the relative frequency of exposure among controls in the target population and a hypothesised relative risk associated with exposure that would have sufficient public health importance to warrant its detection [1]. For this study, if a relative risk of 0.5 is taken to be important with 80% power and 95% confidence intervals, then all that is needed is the frequency of exposure in the target population. The exposure in question is (optometric) glaucoma testing and a figure of around 70% per two years has been found for the total population over 40 years of age [7]. Combining these variables gives an estimated sample size of 104 cases and 104 controls - which is the minimum required in order for the 80% power.

3.2.3 The pilot study.

Performing a pilot study prior to the main study can be very informative [1,8]. It is really a feasibility study to allow for any last minute alterations in design - to see how easy it will be achieve reasonable numbers of cases or to show flaws in the control selection or that some study questions are poorly worded.

The pilot study associated with this study was submitted as a paper in its own right [9] and is printed in full in *Appendix 1*. It involved a retrospective notes analysis when patients were divided into cases or controls (with the criteria shown above) using their visual field on presentation. As much information as possible was extracted from the notes and the results are summarised in the *Appendix 1* tables. Because the study relied on notes review it is open to criticism (discussed in the paper), but it did lead to some very useful pointers to the main study:-

1. The pilot study indicated that to recruit an adequate number of patients (as calculated above), in the year that the patients were to be collected, would be difficult if only one recruiting centre was to be used.

2. As explained above, the pilot indicated that disc cupping could be used as criteria for assigning case-control status. Cases had cupping of >0.8, controls of greater than 0.5.

3. The pilot study indicated the information that could be found in the notes, for example the patients post code and age were universally found while other details like occupation or race were much more patchy.

4. The results of the pilot indicated that increasing age, males, African-Caribbean origin, presenting IOP and being referred from a source other than an optometrist were risk factors for late presentation. These were significant

even after adjustment for key modifiers and were very useful pointers to the adjustments that were required in the main study.

3.3 STUDY EXECUTION

Patients were recruited for the study between August 1995 and July 1996 and during this time period 110 cases and 110 controls were questioned. The results of the power calculation shown above necessitated more than one centre would be required to achieve adequate power. There were three main eye units that cases and controls were drawn from:-

1.Moorfields Eye Hospital.

This included the main hospital in Central London and the outreach clinics in Tottenham, Potters Bar, Barking and Bow. These centres represent a mixture of inner city and urban populations and differing races and socioeconomic groups.

2. Harold Wood Hospital.

This is a District General Hospital in Essex serving an overwhelmingly White population with relatively good incomes.

3. Sunderland Eye Infirmary.

Sunderland is an area with highs and lows of income but negligible ethnic mix.

To avoid biasing the results towards one particular centre i.e. one centre may produce a large number of cases but few controls and vice-versa for a different centre, numbers of cases and controls were matched for each area. This does have the disadvantage that any differing regional effects (e.g. socioeconomic) will be missed by this method.

3.3.1 Recruitment

For a patient to be recruited they were required to be:-

1. A new patient i.e. no previous diagnosis of glaucoma made in the HES.

2. Have glaucoma.

The first criteria was fulfilled by recruiting subjects from new patient clinics and primary care services. At Moorfields (MEH) all new patients are seen in the Primary Care Clinic (PCC) or Casualty department, in the outreach clinics the new patients are seen in the PCC service at the appropriate Hospitals. During the time period of the study, the majority of patients that had a tentative diagnosis of glaucoma (from the GP or optometrists letter) were directed to be seen by myself in the PCC at MEH. If they fitted the criteria listed above they had the study explained to them and asked if they would mind being telephoned and asked some questions regarding their general health and lifestyle.

All the patients from Tottenham and Harold Wood hospitals were personally recruited in the same way. However there was also a cohort of patients who I did not see personally - those whose glaucoma was diagnosed as an incidental finding by another PCC doctor and those from outreach clinics I did not attend. The notes of all these patients came to a central point at MEH after they had been seen and so identification of appropriate patients was simple. With Moorfields Ethics Committee approval, these patients were sent a letter explaining the purpose and method of the study and that they would be telephoned in the forthcoming week. If they did not want to take part in the study they had the opportunity to say this when telephoned and the interview would immediately be terminated.

The Sunderland patients were all seen by a Consultant Ophthalmologist sub-specialising in glaucoma. The criteria for cases or controls were the same and patients were consented when first seen and the examination findings were sent to me (including a copy of the fields).

All suitable patients had there details entered on a form shown in Appendix 2 whether they were seen by me, seen in Sunderland or if only the notes were seen.

The second requirement for recruitment was a diagnosis of glaucoma. Glaucoma is a diagnosis often made over time and can be very difficult to definitively diagnose on a first visit. IOP changes from hour to hour and it is well recognised that visual field testing has a learning effect with the first field usually being the worst but subsequent ones appearing to approve. The purpose of the study was to identify *new* patients and then question them regarding their possible risk factors. Repeating visual fields over six to nine months would mean that these patients would no longer be newly presenting and that their memories of the exposures in question would be even less reliable.

To gain a balance between recruiting true glaucoma patients (and to make sure the patients were assigned their case or control status correctly) and extracting reliable information from the patients a number of checks were used:-

1. Many of the cases were obvious e.g. small central islands of field and advanced cupping.
2. Those with IOP's over 30mmHg (and fulfilled the criteria) have a very high likelihood of glaucoma [10].
3. The pilot study, because it was a medical records review, had the advantage of a number of successive fields being present. As mentioned in section **3.2.1** this showed that cupping estimated at >0.8 for cases and >0.6 for controls indicated that the visual fields continue to show the appropriate defect even after the learning effect of a number of fields.
4. All the patients who were recruited in the study had their notes reviewed, by me, after they had made there first visit to the glaucoma clinic. If either the

visual fields or the optic disc assessment were then outside the study criteria the patients were excluded at that stage. The same process occurred for the Sunderland patients.

The fact that no patients had to be excluded at this stage indicated that initial glaucoma diagnosis and case-control assignment were reasonably accurate.

3.3.2 Patient Interviews.

Once the patients had been identified as potentially suitable for the study they had their medical details, ophthalmic findings, address and telephone number taken from the notes and entered in the 'Notes Questionnaire' form seen in *Appendix 2*. To ascertain the other risk factors required interviewing of the patient. To avoid bias, the interviewer was masked to the case or control status of the patient. The interviews were conducted by telephone, usually to a home number -or in a small number of patients at their work.

The patients seen in clinic gave verbal consent to be telephoned and were all telephoned within ten days of being seen in the clinic. Those patients who were identified via their notes and then written to, were not contacted within one week of the letter being sent to ensure that they had received it. When the patients were telephoned they were initially asked if they remembered being informed of the study or had received a letter explaining it. This gave them an opportunity to withdraw from the study if they so wished. In fact no patients verbally consented or contacted by letter declined to take part in the study.

The interviewer proceeded to ask the patients the questions listed in *Appendix 3* 'Patient Questionnaire'. The patient questionnaire was divided into three different sections:-

Section A

Questions 1,2 and 4 double-checked age and post-code.

Question 3 was about Ethnic origin and used the same categories that have been used in the population census forms.

Question 5 pertained to Employment group. When telephoned, each patient was asked about there present occupation and this was later converted to one of the occupational categories explained below. If the patient was retired, unemployed or long term sick this was noted and the occupation they had performed for the major part of their working life was entered. For married women who themselves had never worked their husbands occupation was entered.

The employment classification was taken from the Standard Occupational Classification (SOC) which was devised by the Employment Department Group and the OPCS [11]. Volume two of the manual consists of a detailed alphabetical index of job titles giving the SOC group to which each is assigned. To assist coding, guidance notes are provided within this volume so that location of the correct entry is much easier. There are six categories used:-

I Professional occupations

II Managerial and Technical occupations

IIIN Skilled occupations – non-manual

IIIM Skilled occupations – manual

IV Partly skilled occupations

V Unskilled occupations

Question 6 like the BES [12] enquired about age at leaving full time education.

Question 7 was regarding type of accommodation of the patients and again the categories were taken from those found in the Census form.

Question 8 and 9 asked if the patient lived alone and if they had access to a car.

Section B.

This was concerned with medical details of the patient.

Question 1 asked how often the patient visited their GP. The choices the patients were given were as shown in *Appendix 3*.

Question 2 asked if the patient had ever smoked and if so for how long. This allowed the packs per day and years smoked to be calculated.

Question 3 is related to alcohol consumption and is taken from the Stress and Health questions of the Civil Servants Study[13].

Question 4 concerns family history of glaucoma. If the patient did have a FH they were asked to give details and these were categorised as:-

i. Those with one or more second degree relatives with glaucoma.

ii. One first degree relative.

iii. More than first degree relative.

Section C.

This section was concerned with the patients optometrist and history of screening. The visit to the optometrist who initiated the referral visit (if the patient was referred by this source) was known from the notes review and was

rechecked during the telephone interview. One of the study hypotheses was that the earlier presenters had visited an optometrist more recently than late presenters. It is important to realise that this requires knowledge of optometric visits *prior* to the visit that resulted in hospital referral. Thus the first question in Section C was when did you last visit an optometrist (apart from a referral visit)?

Taking five years as a cut-off, if the patient had not visited the optometrist within five years they were asked the reasons why (**question 2**). This cut-off comes from the Jay and Murdoch [3] calculation that certain patients can go blind within three years. Also most optometrists would send sight test reminders to patients every two to three years, so that five years or more would involve missing at least one reminder.

The third question in Section C was concerned with why the individual visited the optometrist who had referred them to the HES. Although chronic glaucoma is classically symptomless Grant and Burke [14], found that 'most' of their patients who presented with advanced loss in one or both eyes had experienced symptoms that, they felt, may have heralded impending visual loss. Unfortunately, they did not have a comparison group for this who may well have had a similar symptoms. If symptoms were the initiator of attendance at the optometrist there nature was ascertained by question four. No matter how often an individual is consulting an optometrist, if during the consultation glaucoma testing is not performed that individual is likely to be at increased risk of late presentation. Thus question eight is concerned with what the patient remembers of their optometric examination (again, prior to the visit that initiated the referral). A number of options were given to jog the patients

memory about the examination. **Questions five and six** are along similar lines, enquiring if a patient recently changed to the optometrist who referred. The reasoning behind this being that if the patient was regularly seeing an optometrist who was not screening it is only by changing there optometrist that they have the possibility of having their glaucoma picked up.

Question seven in Section C looked at the financial aspect of sight testing and if those people who pay for their eye tests are more likely to present late than those who are eligible for free tests.

The data from Section C has the potential for errors and biases and this will be discussed more fully in Chapter Six.

3.4 DATA COLLECTION AND ANALYSIS

The forms shown in Appendices 3 and 4 were filled in by hand. The data was entered into *Quattro Pro for Windows*, which is a spreadsheet program that also allows statistical analysis. Once the data had been entered in its raw form it was converted into numbered codes to make analysis possible.

For the UPA score, the post codes for all the patients were sent to the Department of Primary Care and General Practice at the Imperial College School of Medicine at St. Mary's. The scores were calculated there and returned and this was entered in the spreadsheet.

The data were analysed using *STATA* [15] to investigate the effects of each study factor on the risk of being a late presenter. Odds ratio is defined as odds of disease in exposed persons divided by the odds of disease in unexposed persons [8], the 'disease' in question is advanced glaucoma. Thus the odds of the disease for those

exposed and those not, is the number with the disease (the number of new cases during a specified period of time) divided by those without the disease (the controls). The odds ratio is then these two odds divided by each other. To summarise:-

	LATE PRESENTER		
	Yes	No	Odds disease
EXPOSURE			
Yes	A	B	A/B
No	C	D	C/D

Odds ratio = A/B / C/D (= AD/BC)

For each study factor (exposure) deciding which odds to use as a baseline was determined either because its selection appeared to give the most meaningful results or because it contained the greater number of observations and hence its choice favoured precision.

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CHAPTER 4: RESULTS.

4.1 INTRODUCTION

The study was undertaken over a nine-month period from August 1995 to July 1996 and stopped when 110 cases and controls were collected. None of the patients who fitted the study criteria declined to take part in the study and there was no loss of patients during the study.

Of the 110 cases and 110 controls, the numbers collected from each centre is shown in Table 4.1:-

Table 4.1

CENTRE	CASES	CONTROLS
CITY ROAD	54	54
TOTTENHAM	4	4
POTTERS BAR	4	4
BARKING	8	8
BOW	13	13
HAROLD WOOD	16	16
SUNDERLAND	11	11
TOTAL	110	110

The results of the study are presented in Tables **4.2, 4.3, 4.4, 4.5** and **4.6**. The first part of this chapter gives these results in relation to the study hypotheses outlined in Chapter 2, the second part presents the results of the potentially effect modifiers variables while the remainder of the chapter presents the results collected that were not from the *a priori* hypotheses.

Table **4.2** is the study factors by case-control status excluding the data regarding SES which is presented separately in Tables **4.5** and **4.6**. Table **4.3** shows the estimates of the effect of each study factor on late presentation – the factors adjusted for are explained in the section below. Table **4.4** is a partial correlation matrix of study factors.

Table **4.5** shows the socioeconomic characteristics of the study population and table **4.6** the unadjusted and adjusted estimates of the effects of these socioeconomic factors on the risk of late presentation.

Table 4.2: Study factors by case control status

Study Factor		Controls n1	Cases n2	All n1 + n2	patients % of total
Age	<= 40	8	9	17	8
	41 - 50	16	6	22	10
	51 - 60	26	7	33	15
	61 - 70	27	27	54	25
	71 - 80	29	47	76	35
	81 - 90	4	14	18	8
	median	63 (52, 71)	72 (63, 78)	67	(55, 75)
Sex	Male	54	60	114	52
	Female	56	50	106	48
Ethnicity	Caucasian	98	73	171	78
	African Caribbean	6	29	35	16
	Asian	6	8	14	6
Type of glaucoma	POAG	83	72	155	71
	PXF	0	15	15	6
	Normal Tension	21	6	27	12
	Aphakic	0	2	2	1
	Pigmentary	4	1	5	2
	Traumatic	1	2	3	1
	Chronic Angle Closure	0	13	13	6
IOP median (IQR)	right eye	22.5 (20, 26)	27 (22, 35)	24	(22,30)
	left eye	23 (20, 26)	28 (23, 34)	25	(22,30)
	max	30 (25, 38)	25 (22, 27)	26	(23, 31.5)
Medical problems	Hypertension	18	21	39	18
	Diabetes mellitus	5	4	9	4
	CVA	1	4	5	2
	Ischaemic Heart Disease	1	2	3	1
	Hypertension & Diabetes	1	3	4	2
	Respiratory diseases	5	7	12	5
	Thyroid	4	7	11	5
	Nil significant	75	62	137	64
Family History of Glaucoma	No	62	93	155	71
	Second Degree Relative	9	5	14	6
	First Degree Relative	23	8	31	14
	More Than One First Degree Relative	16	4	20	9
Referral Source	Optometrists with correct diagnosis	100	63	163	74
	Other	10	47	57	26
Last visit to optometrist (years)before referral	1	27	12	39	18
	2	45	23	68	31
	3	16	10	26	12
	5	12	15	27	12
	6	0	1	1	1
	10	5	23	28	13
	> 10 or never	5	26	31	14

Table 4.3: Estimates of the effect of each study factor on late presentation

Study Factor		OR	95 % CI	adj OR*	95 % CI
Age	<= 40	1			
	41 - 50	0.33	(0.09, 1.27)	0.79	(0.09, 6.99)
	51 - 60	0.24	(0.07, 0.85)	0.15	(0.02, 1.25)
	61 - 70	0.89	(0.30, 2.65)	1.01	(0.15, 6.90)
	71 - 80	1.44	(0.50, 4.15)	1.82	(0.30, 11.06)
	81 - 90	3.11	(0.72, 13.44)	2.97	(0.30, 29.35)
Sex	Male	1			
	Female	0.8	(0.47, 1.36)	1.23	(0.53, 2.85)
Ethnicity	Caucasian	1		1	
	African Caribbean	6.49	(2.56, 16.44)	2.47	(0.63, 9.72)
	Asian	1.79	(0.60, 5.38)	0.81	(0.12, 5.67)
Type of Glaucoma	POAG	1	-	1	-
	PXF	∞	(4.98, ∞)	-	-
	NTG	0.33	(0.13, 0.87)	3.04	(0.63, 14.70)
	Aphakic	∞	(0.32, ∞)	-	-
	Pigmentary	0.29	(0.03, 2.67)	1.55	(0.03, 85.12)
	Traumatic	2..33	(0.21, 26.27)	0.18	(0.00, > 200)
	Chronic Angle Closure	∞	(4.25, ∞)	-	-
Maximum IOP		1.17	(1.11, 1.24)	1.20	(1.11, 1.28)
Medical Problems	No	1			
	Yes	1.43	(0.82, 2.49)	1.01	(0.43, 2.35)
Family History of Glaucoma	No	1			
	Second Degree Relative	0.36	(0.12, 1.13)		
	First Degree Relative	0.23	(0.09, 0.54)		
	> 1 First Degree Relative	0.16	(0.05, 0.51)		
	Yes (combining last 3 above)	0.23	(0.12, 0.44)	0.29	(0.12, 0.74)
Referral Source	Optometrists & correct diagnosis	1			
	Other	7.46	(3.52, 15.82)	4.53	(1.52, 13.48)
Last visit to optometrist (years) before referral		1.29	(1.18, 1.41)	1.25	(1.10, 1.42)

* adjustment made for, maximum IOP at presentation, family history, referral source and number of years before last visit to optometrist

Table 4.4: Partial Correlation Matrix of study factors

	Case	Age group	Sex	Ethnicity	Glau Type	Max IOP	Med Probs	Fam Hist	Ref Source
Age group	0.24								
Sex	-0.05	0.06							
Ethnicity	0.21	-0.25	0.04						
Glau Type	0.17	0.00	-0.02	0.04					
Max IOP	0.46	0.09	-0.11	0.05	0.08				
Med Probs	0.08	0.27	0.15	0.02	0.06	0.08			
Fam Hist	-0.32	-0.11	0.08	-0.07	-0.06	-0.12	-0.07		
Ref Source	0.3	-0.04	0.02	0.28	0.14	0.15	0.1	-0.07	
Last visit	0.43	0.02	-0.16	0.34	0.06	0.20	-0.11	-0.15	0.31

Table 4.5: Socioeconomic Characteristics of the Study Population

Study Factor		Controls n1	Cases n2	All n1 + n2	patients % of total
UPA score	median (IQ range)	21.3 (6.12, 37.44)	29.5 (9.00, 42.21)	25.3 (7.83, 8.29)	
Live alone?	Yes	40	40	80	36
	No	70	70	140	64
Access to car?	Yes	73	48	121	55
	No	37	62	99	45
Occupational Group	I	5	0	5	2
	II	27	1	28	13
	III	56	42	98	45
	IV	12	29	41	19
	V	10	38	48	22
Age when leaving full-time education (years)	<=12	4	17	21	6
	13	0	1	1	1
	14	45	69	114	52
	15	18	5	23	10
	16	21	13	34	15
	17	2	1	3	1
	18	19	4	23	10
	>18	1	0	1	1
Accommodation	Owner	70	41	111	51
	Private rental	8	10	18	8
	LA rental	32	59	91	41

Table 4.6: Unadjusted and adjusted estimates of the effects of socioeconomic factors on the risk of late presentation

Study Factor		Odds Ratios	Confidence Intervals	Adjusted OR*	Confidence Intervals
UPA	per ten unit increase	1.16	(1.01, 1.33)	0.98	(0.82, 1.16)
Live alone?	Yes	1		1	
	No	1	(0.58, 1.73)	1	(0.58, 1.73)
Access to car?	Yes	1		1	
	No	2.55	(1.48, 4.40)	1.86	(1.00, 3.49)
Occupational Group (baseline, gp V)	I				
	II	0.01	(0.00, 0.08)	0.02	(0.00, 0.16)
	III	0.20	(0.09, 0.44)	0.27	(0.09, 0.80)
	IV	0.64	(0.24, 1.67)	0.95	(0.26, 3.46)
	V	1		1	1
Age when leaving full-time education (years)	< = 14	1		1	
	> 14	0.21	(0.117, 0.38)	0.23	(0.11, 0.50)
Accommodation	Owner	1		1	1
	Private rental	2.13	(0.78, 5.84)	1.28	(0.41, 4.07)
	LA rental	3.15	(1.77, 5.61)	2.08	(1.08, 4.01)

*** Adjusted for referral source, family history of glaucoma, number of years since last visited an optometrist and maximum IOP (ie larger of left IOP and right IOP) at presentation.**

4.2 STATISTICAL ANALYSIS

The data were analysed by a medical statistician using *STATA*© to investigate the effects of each study factor on the odds of being a late presenter. Estimates of the odds ratios (OR) of being a late presenter with approximate 95 % confidence intervals, by study factors were computed by logistic regression. In each case the first category (unless otherwise stated) of each categorical study factor was used as a baseline either because its selection appeared to give the most meaningful results or because it contained the greater number of observations and hence its choice favoured precision. Factors significant at univariate level were entered into a multivariate model but subsequently dropped if not statistically significant in this model - this will be referred to as model I. Unadjusted and adjusted odds ratios are presented - adjustment being made for all factors found to be statistically significant in model I.

4.3 RESULTS OF HYPOTHESES

4.3.1 Age and late presentation

The results shown in Table **4.2** indicate that the vast majority (60%) of patients in the study were between 61 and 80 years of age, with the lowest numbers occurring under 40 (8%) and over 80 (8%). This is expected, as glaucoma has a low prevalence in the under 40's and the total number of patients in the general population over 80 is lower even though the glaucoma incidence and prevalence rates are at their highest.

Because the data are skewed, the mean of the ages will be strongly influenced by outlying values thus the median is a better calculation of the central tendency. The median age of the controls was 63 with an interquartile range of 52 to 71years, while that of the cases was 72 years with a range of 63,78.

Table **4.3** contains the results of the univariate analysis and reveals a trend of increasing odds of late presentation with increasing age. However, it can also be seen that the CI's are wide and cross unity - suggesting that this is partly due to the small numbers in each sub-group.

Using the rationale discussed in the statistical analysis section above, when the OR is adjusted for the trend remains, but again the Confidence Interval's (CI's) are wide. Late presenters tend to be older than earlier presenters and there is a trend of later presentation with increasing age although this was not statistically significant.

4.3.2 Ethnic origin and late presentation

The study allowed for 13 ethnic categories as shown on the patient questionnaire in *Appendix 3*. White British patients represented by far the largest group. In comparison, most of the other categories were very small. To make the analysis more meaningful, White British and European numbers were combined to form the Caucasian group. Black Caribbean and Black African patients were combined to form the African-Caribbean group. Indian, Pakistani, Bangladeshi and Other Asian (Sri Lankans) were combined to form the single Asian group.

The results of this combination are shown in Table **4.2** with 78% of patients in the study classified as white, 16% as Black and 6% as of Asian origin.

Univariate analysis indicates that those of African-Caribbean origin have a risk of late presentation of over six times that of Caucasians with wide but statistically significant CI's. Asian patients have a risk of 1.79 but this was not statistically significant [0.6,5.38].

When adjustment is made for the factors shown at the base of Table **4.3**, the African-Caribbean risk is reduced to 2.47 and the statistically significance is lost. Table **4.5** indicates that the main study factors that influence this adjustment are

referral source (less African-Caribbean patients came from a correctly diagnosing optometrist than did Caucasian patients) and number of years since last visiting an optometrist (Caucasian patients tended to have a sight test more recently).

4.3.3 Sight testing and late presentation

Although initially the patients were placed into four 'referral categories': -

1. From a GP with a presumptive diagnosis of glaucoma.
2. From a GP with no mention of glaucoma in the referral letter
3. From an optometrist with a presumptive diagnosis of glaucoma
4. From an optometrist with no mention of glaucoma in the referral letter

In practice, no patients were found who fitted into Category 1 and therefore categories 2 and 4 were combined. This left two categories, those who had been referred to the HES with a tentative diagnosis of glaucoma and those who had been referred for another reason and in which there was no suggestion of glaucoma.

Table **4.2** shows that 74% of the patients were correctly referred from an optometrist with a correct diagnosis of glaucoma while the remaining 26% had been referred from a GP or optometrist with no mention of glaucoma. The OR for late presentation if the patient had not been referred with the correct diagnosis was 7.46 [3.52,15.82]. After adjustment this remained statistically significant with an OR of 4.53 [1.52,13.48].

Table **4.2** also shows that the majority (49%) of patients has attended for a sight test within the two years prior to their referral. Conversely, 27% of patients had not had a sight test for ten or more years. Of those patients who had had a sight test within two years 72 of the patients were controls compared to 35 of the cases.

Table **4.3** shows that for every increase in year since the last visit to an optometrist, the OR of late presentation increase by 1.29[1.18, 1.41] and this remains after adjustment at 1.25 [1.10,1.42].

4.3.4 Socioeconomic status and late presentation

Tables **4.5** and **4.6** are concerned with the results of the questions regarding the patient's socioeconomic status and late presentation.

General deprivation measure (UPA score)

Table **4.5** presents the socioeconomic characteristics of the study population. The median (inter-quartile range) UPA score overall was 25.3 [7.83,38.29]. The median score for controls was 21.3 [6.12,37.44] and for cases was 29.5 [9.00, 42.21]. As discussed in the method section, the higher the UPA score is the greater the deprivation in those areas.

As far as individual deprivation indices are concerned 36% of the patients lived alone and just over half (55%) had access to a car. Equal numbers of cases and controls lived alone but more controls had access to a car than did cases (73 controls compared with 48 cases).

Occupational classification.

As discussed in Chapter 3, once occupation had been ascertained, it was converted to one of the standard occupational classification categories. When this was being done it was obvious that the job descriptions given by the patients were not detailed enough to reliably separate non-manual from manual in class III, therefore these categories were joined to for a single class III comprising both groups.

The majority of patients (45%) were in SOC group III (manual or non-manual) with only 2% being recorded as group I and 22% were placed in group V. No cases were found in group I but there were 38 in group V compared with 10 controls.

For those currently not at work 85% were retired, 9% unemployed and 7% classified themselves as long term sick.

Accommodation

The accommodation categories that can be seen in the patient questionnaire in *Appendix 3* are taken from those used in the Census. In practice the numbers in the study were too small to allow representation of a number of the categories. Three main categories were thus formed: -

1. Owner-occupied.
2. Privately rented (furnished and unfurnished combined).
3. Local authority rental.

Approximately one half (51%) of the patients were owner-occupiers, 8% rented property privately and 41% were in council housing. No patients from non-permanent accommodation, sheltered accommodation or institutions were found.

Table **4.6** shows the estimated effect of each socioeconomic factor on late presentation. The factors adjusted for are the same as those in Table **4.3**.

The OR of late presentation can be seen to increase with higher UPA score (i.e. higher level of deprivation) and for every 10 unit increase in UPA score there is an increase in the OR of 1.16[1.01,1.33]. After adjusting for the factors shown, this OR is reduced and the CI's cross unity (0.98[0.82, 1.16]).

After adjustment the data provide some evidence of an association between the odds of late presentation and having access to a car. Patients without access to cars are estimated to be 1.86 [1.00,3.49] times more likely to be late presenters than patients with access to cars after adjustment for modifiers.

The data in Table **4.6** show evidence of a trend of increasing risk of late attendance with increasing SOC. Patients of group II had an OR of 0.01[0.00,0.08] of

late presentation while a patient of group V had an OR of 1. This trend persists after adjustment.

There is a similar relationship between housing tenure and late presentation. Those living in local authority accommodation are more than three times more likely to present late than those who are owner-occupiers and this is statistically significant. These odds are reduced after adjustment to 2.08[1.08,4.01] but remain statistically significant. Although those in privately rented accommodation do appear to be at increased risk of late presentation from the OR the CI's cross unity.

4.3.5 Educational level and late presentation.

Table **4.5** shows that the majority of patients (52%) left full-time education at the age of 14 and given the overall age of the patients this is as expected. Only 6% of subjects left school at age 12 or less and they were more likely to be cases (17 patients) than controls. Only one patient had stayed on in full-time education over the age of 18 and this patient was a control.

Because of the small numbers in most of the sub-groups, the categories were combined to form two groups – those who left full-time education at the age of 14 or less and those who had left after 14. Those who had left at less than 14 were nearly five times as likely to be late presenters and this was little changed even after adjustment.

4.3.6 IOP and late presentation

Table **4.2** indicates the presenting IOP for cases and controls right and left eyes. The data were skewed therefore the median IOP is shown. Cases tended to have higher IOP's with a median of 27mmHg and 28mmHg for right and left respectively compared to controls at 22.5 and 23mmHg.

The table also indicates 'max IOP' which represents the greater of the right and left IOP's at presentation. From this the OR of late presentation is calculated to be increased by 1.17 [1.11,1.24] per unit increase in mmHg of IOP at presentation. After adjustment this figure is little changed at 1.20 [1.11,1.28] per unit increase. Thus higher presenting IOP is associated with late presentation.

Related to presenting IOP is the type of glaucoma the patient has. Most patients had POAG (71%), 12% of patients were labeled as possible normal tension glaucoma (NTG) at the first visit, 6% as pseudoexfoliative glaucoma (PXF) and 6% as chronic angle closure glaucoma (CACG).

Multivariate analysis indicates that those glaucomas that tend to be associated with high IOP's (PXF and CACG) are more likely to be associated with late presentation. So that there were in fact no controls for PXF and CAC glaucomas - giving infinitely high odds ratios. NTG suspects had OR's of 0.33[0.13,0.87] before adjustment and 3.04[0.63,14.70] after. The NTG results are hugely modified by adjustment and very large change in effect appears to be because of the small numbers in this group.

4.4 RESULTS OF POTENTIAL EFFECT MODIFIERS

4.4.1 Use of medical services

There were a number of factors examined in this category that may have modified the results.

Medical history

This was taken from the GP's referral letters and confirmed with the patient interview. The different diagnoses are grouped as shown in Table **4.2**, 64% of subjects had no significant medical problem, the commonest diagnosis amongst those with

ongoing medical treatment was hypertension with 18%, then respiratory disease (5%), thyroid disease (5%) and diabetes (4%).

Because of the small numbers in the disease groups two groups were formed for the analysis – those with and those without medical problems. Univariate analysis showed a slightly higher odds of late presentation for those with ongoing medical problems of 1.43[0.82,2.49] and adjustment reduced this further to 1.01[0.43, 2.35].

GP attendance

The result for this category is not shown in the tables. The vast majority of patients (92%) put themselves in the category of visiting their GP a 'few times a year'. Only one patient said they visited the doctor at least once a week and the remainder (8%) went around once a month.

Not surprisingly, no category of GP attendance had a significant odds ratio, those who attended a few times a year did have an OR of 1.99 but this was lost with adjustment.

Alcohol consumption

The actual numbers in each group shown in the Patient Questionnaire were small and to make the analysis more meaningful, two groups were formed consisting of: -

1. Those who drank equal to or more than once a week, which was the 'regular' group.
2. The 'rarely' group consisted of those who drank no more than twice a month.

The regular group comprised 66% of the patients and the rarely group the other 34%. Those in the rarely group had an OR of 0.59 compared with those who

drank regularly but this was not significant. There was a similar result when adjustment took place.

Smoking

The median **packs** per day by number of years was the same for cases and controls with both having a median of 10. The standard deviations were both 0-30.

Because the median amount smoked was equal for cases and controls two categories were formed to investigate the odds - those who had *ever* smoked and those who had *never* smoked. The OR and adjusted OR were almost identical so that smoking seemed to have no influence on late presentation.

4.4.2 Family history

The results shown in Table **4.2** indicate that 71% of the study patients had no FH, 6% had one or more second-degree relatives with glaucoma, 14% had a single first degree relative and 9% had more than one first degree relative.

Table **4.3** shows the results of the univariate analysis and generally shows a statistically significant trend ($p<0.0001$) of a decreased OR the 'greater' the family history of glaucoma. Thus those with more than one first degree relative with glaucoma are over six times less likely to be late presenters than those who have no family history of glaucoma.

Again, because of small numbers, multivariate analysis was performed using combined groups of those with no family history and those with any family history. This again showed that family history was protective with an adjusted OR of 0.29[0.12,0.74] for those with any family history.

4.4.3 Ocular factors

Ocular pathology

This pertains to any ocular pathology that was felt to be significant enough to reduce the patients vision beyond 6/12. 70% of patients had no significant pathology aside from their glaucoma, 18% had significant cataract, 5% had age related macular degeneration (AMD) and 4% had a significant corneal abnormality. All these patients were able to perform some type of field and had cup:disc ratios consistent with the field loss.

Patients with visually significant cataract (not shown in table **4.5**) did have a greater risk of later presentation but after adjusting for age this effect disappeared. The numbers of patient with other significant ocular pathology were not large enough to allow analysis. Because the numbers were small, those patients with (non-glaucomatous) ocular pathology were combined and compared to those without. This showed that those with no other pathology had an OR of 0.27 compared to those with, but when adjusted for age this lost its significance and would appear to be mainly a function of the older age of the patients who presented late.

Refraction.

This was taken from the optometrist's letter or was checked when seen in the clinic. Because the patients did not all come from an optometrist or have there refraction checked in clinic it is rather patchy data (only 34% had written evidence of refractive status). Most of the patients were hypermetropic with 45%; myopes accounted for 20%.

Compared to emmetropia, the OR of myopes presenting late was 0.56 but this protective effect was not significant nor was the adjusted OR. The adjusted OR for hypermetropia was 0.62 but again this was not significant.

4.5 OTHER RESULTS

This final part of the chapter gives the results of a number of ancillary questions that the patients were asked that were not related to the main hypotheses and were not thought of as being potential effect modifiers. They are mainly related to sight testing.

Gender and late presentation

The study consisted of 52% males and 48% females. Univariate analysis suggested a slight protective effect for women (OR 0.8) but this was not statistically significant and the effect was lost in the adjustment.

The results do not indicate a gender difference in the risks of late presentation.

Reasons for visiting referral optometrist

The subjects were asked why they had gone to the optometrist who referred them (whether or not they were correctly referred).

57% went because of symptoms

29% went as part of a routine visit.

Of those who went with symptoms, 72 were cases and 53 controls which is a significant difference (p=0.002). When those patients who said that they had gone to the optometrist because of symptoms were asked the nature of those symptoms 84% attended because of visual changes, with the vast majority feeling that their glasses needed altering. Of the remaining 16%, the vast majority went either because of headaches or because they felt that things 'weren't quite right'.

Those patients who had gone to their optometrist on a routine visit were far more likely to be controls than cases - 42 versus 2 ($p<0.0001$).

Recently change of optometrist

50% of those patients who regularly attended their optometrist (defined as those who had attended within the previous five years) had recently changed their optometrist to the one who had referred them.

29% of patients had been forced to change their optometrist for a variety of reasons including the patient moving, the optometrist shop closing or the optometrist retiring and/or dying. 18% of the patients had changed because they were unhappy with the glasses their previous optometrist had prescribed. 46% of patients simply fancied a change, with a proportion of these had been influenced by media advertising.

Only 8% of the patients had changed optometrist because they wanted a glaucoma test, which their current optometrist did not provide. It is worth noting that all these patients were controls.

Those patients who had changed their optometrist to the one who had referred them had slightly higher odds of presenting late than those who had not but the OR and adjusted OR for this were not significant.

Those patients who had *not* visited an optometrist within five years were asked the reason why. 89% did not see the need to have a regular eye test, only 6% did not go because of cost or mobility problems.

Equal numbers of cases and controls paid for their eye tests.

Tests performed by the optometrists

According to the optometrists referral form the IOP was measured by 63% of these optometrists, there was a comment regarding the disc from 90% of them although only 34% performed fields of any type.

It is worth noting that the optometrist who referred controls checked IOP, discs and fields roughly 50% more than the optometrist who referred cases.

When the patients were questioned directly, none of the cases ever remembered having a visual field test performed (except at the visit that resulted in their referral) while 20% of the controls did.

CHAPTER 5:DISCUSSION.

This chapter discusses the results presented in Chapter 4. The first section is a summary of the pilot study; this is followed by discussion of the hypotheses, confounders and some of the supplementary results. The chapter finishes with a discussion of some of the biases of the study, conclusions and suggestions for further study.

5.1 THE PILOT STUDY

The paper published from the results of the pilot can be found in *Appendix 1*. The pilot study was limited to data that could be collected reliably from the notes. Some of the results will be discussed in later sections but in summary, patients who presented with advanced visual field loss were more likely to be: -

- Male
- Of African-Caribbean origin
- Older
- Not been referred to the HES by an optometrist with a diagnosis of glaucoma
- Have a higher presenting IOP

.....than those presenting with early field loss.

From these results, it was speculated that whether an individual presents late in the course of their glaucoma is likely to be a function of the rapidity of their visual field deterioration and the frequency of their sight tests. An individual with a rapid decline may lose significant field even with two yearly sight tests - unless tested during an early, but detectable phase of the disease. Conversely, an individual with a slowly declining field but who does not attend for sight testing for some years (or does not have a glaucoma examination during their sight tests) is at risk of late presentation for

a different reason. It always important to put these results in the context of length bias – a bias which can afflict any study that deals with glaucoma progression. This bias will be discussed more fully later in the chapter.

Those patients with rapid decline are likely to be those with higher presenting IOP [1] whereas the reasons why patients do not attend for regular sight tests is likely to be multi-factorial.

5.2 HYPOTHESES OF THE MAIN STUDY

James Schlesselman [2] defines a research question as "a list of hypotheses that can be tested, at least within the limitations of the methods available to study the issue. A hypothesis is a predictive statement about relationship between independent and dependent variables."

The hypotheses for this study presented in Chapter 2 will be discussed in light of the results.

5.2.1 Age and late presentation

Both the main and pilot studies suggest an increased risk of late presentation with increasing age. However, even though the median age of the cases was 72 years and that of the controls was 63, when the age groups were divided up, the CI's crossed unity. The pilot study did find a statistically significant rise in OR of late presentation with increasing age.

The loss of significance in the main study may well be due to the small groups formed as there is a trend of increasing OR with increasing age. In retrospect it would have been more informative to record age as continuous variable in both the pilot and the main study.

There may be a number of reasons why the elderly may be at more risk of late presentation: -

1. Rates of sight testing decline over the age of sixty [3]. The results of this study has shown the importance of regular sight testing in glaucoma detection.

2. The elderly tend to have problems with mobility either through purely physical problems or social isolation. More controls had access to a car (73) than did cases (48) and it would be interesting to know if there was any reason for this difference e.g. the cases had had more accidents.

3. Cost. Unless in an exemption category for free sight tests (see *Appendix 4*) the fee has to be paid. A previous study has indicated that the cost of a sight test may be prohibitive[4]. Many of the elderly do not have large incomes or savings and may well feel sight testing (which is itself a small proportion of the cost of glasses) to be an unnecessary luxury. Having said this only 6% of those in the study stated cost as a reason for not visiting their optometrist (although all these were cases).

4. The need for reading glasses (presbyopia) reaches a peak in the fifth but stabilises by the seventh decade. Unless there is a significant reduction in vision from another cause e.g. cataract or AMD, there will be no incentive to attend for sight testing. This is borne out by the fact that 89% of study patients who did had not attended their optometrist for five years gave the reason as "not seeing the need".

5.2.2 Ethnic origin and late presentation

Univariate analysis revealed a risk of late presentation for those of African-Caribbean origin of more than six and this was consistent with the pilot study findings. However, after adjustment (see table 4.6) the OR was reduced to 1.79 (which was not statistically significant). The partial correlation matrix shown in table

4.4, shows that the major adjustment was for differences in sight testing rates between African-Caribbean's and Caucasians.

These results are consistent with previous studies of black patients presenting later in the disease[5] and may go some way to explaining the higher rates of glaucoma blindness in the black population[6].

It has previously been suggested that the socioeconomic differences between Blacks and Whites account for the differing stages of presentation of glaucoma [7]. This study does not support this, correcting for socioeconomic status still leaves Black patients at a much higher risk of presenting late. The fact that African-Caribbean patients were much less likely to have been referred from an optometrist and were much less likely to have had a sight test in the previous five years was the main reason why they had a much higher OR of late presentation than equivalent Caucasian patients. In other words the major component of the excess risk of African-Caribbean's presenting with advanced glaucoma is explained by variations in patterns of sight testing.

The results of this study did not indicate a higher risk of late presentation in the (heterogeneous) Asian population studied, although the total number was small.

5.2.3 Sight testing and late presentation

The hypothesis for this part of the study was that the longer the interval since the individual visited an optometrist the higher their risk of being a late presenter. The results of the study were consistent with this hypothesis and showed an OR of late presentation increased by 1.25 for every year since the patients last visited an optometrist.

The other important finding of both the main and pilot study was that early presenters were much more likely to have been referred by an optometrist who had

correctly diagnosed glaucoma. This suggests that patients who attend for sight tests and are examined for glaucoma are more likely to be early presenters.

The question of what examinations the optometrist is performing is a difficult one to answer. Asking the patients what tests they remembered having had done at the optometrist at their previous visit has obvious flaws, although the controls consistently remembered having more tests performed at the optometrist. This is discussed at the end of this chapter.

The study results provide (indirect) evidence that visiting an optometrist reduces the risk of late presentation.

5.2.4 Socioeconomic status and late presentation

The hypothesis was that those who are more socially deprived (general and specific measures) are more likely to present late and the results seem to generally support this.

General deprivation as measured by UPA score showed a higher median score for cases and an increase in OR with an increase in score – although this was not quite significant after adjustment. The specific deprivation indicators – standard occupational classification, access to a car and type of housing all showed an association between socioeconomic status and late presentation. The results show a consistent trend of late presentation with lower socioeconomic status even when factors such as age and race are accounted for.

As discussed in Chapter 2, lower socioeconomic group has been associated with delay in presentation of various cancers, later presentation in amblyopia and lower use of screening services. It has been speculated that there may be a number of reasons for this:-

i. Inadequate knowledge about the disease and ignorance of preventative health measures and screening techniques [8,9].

ii. Inaccurate beliefs about the disease[9].

iii. Cost of screening.[10]

iv. Less contact with medical services[9].

Cost does not seem to have been a major factor for the patients in our study as only five give this as a reason for not visiting their optometrist regularly (although it is interesting to note that these were all cases). There are however 'hidden' costs to screening such as time off work and transport costs that were not asked about.

The other possible reason that needs consideration is that long term material deprivation may lead to more rapidly progressive and aggressive disease. The links between raised cortisol, ocular hypertension and glaucoma[11] provide some support for a psychosocial mechanism mediated by altered hypothalamic-pituitary-adrenal function[12]. Thus the possible "length bias" which could be an important determinant of both case and control status might be driven by pathological mechanisms linked to social status.

It is important to recognise that it may not only be IOP that determines the rate of ganglion cell loss and that there are many other possible influences – some of which may also be related to related to material deprivation. This is more fully discussed in the paper 'Deprivation and late presentation of glaucoma' which is reproduced in *Appendix 6*.

5.2.5 Education level and late presentation

The results indicated that leaving school at 14 or less was associated with around a five times higher risk of late presentation compared to those who left school

after the age of 14. This is consistent when adjusted for important confounders i.e. age, race and socioeconomic status.

The findings are in keeping with the studies discussed in Chapter 2 -such as those that found an association between late presentation of breast and prostate cancer and lower educational levels[8,9]. It is presumed, in these studies, that the effect is because of poorer knowledge of the disease and ignorance of the need for screening in those who have had less formal education. The study has highlighted the importance of regular sight testing in the early detection of glaucoma and if the individual is not aware of this is more likely to be a late presenter. Better education tends to result in positive health seeking behaviour and the better educated therefore tend to be healthier.

5.2.6 IOP and late presentation

The hypotheses discussed above are likely to have their influence on stage of presentation via their effect on sight testing rate but it might be expected that IOP has a direct effect on visual field. In Chapter 2 the evidence that higher presenting IOP's can result in rapid field loss was highlighted [1]. The results of this study indicate a higher median IOP in cases, and the odds of late presentation increase with higher IOP at presentation. Similarly those types of glaucoma associated with high IOP's such as CACG and PXF are strongly associated with late presentation (in fact no CACG's presented early).

The pilot study findings are in agreement with this and high IOP appears to have an important association with late presentation.

Whether a patient with NTG tends to present late or early is not answered by this present study. Neither the pilot nor main study indicated that NTG was either less (because of its slow deterioration) or more (because it is more difficult for the

optometrist to diagnose) likely to present late. The NTG results should be interpreted with some caution, as the study categorises patients on presentation and those whose pressure rises at subsequent visits may move out of the NTG diagnosis. Although the NTG patients were followed up at their next clinic visit this is too short a follow up time.

5.3 EFFECT MODIFIERS

Three potential effect modifiers were identified at the start of this study.

5.3.1 Use of medical services and late presentation

None of the indicators of medical services use were found to be associated with late or early presentation. It was felt that those with regular contact with medical services may have increased the opportunities they would have had for having a glaucoma examination but this appeared not to be so. This may reflect the difficulties of diagnosing glaucoma in Primary Care.

In particular, patients with hypertension and diabetes may tend to present relatively early in the course of their glaucoma, as they are more likely to undergo fundoscopy by GP's and/or optometrists. However the results showed roughly equal numbers in both groups, although the total number in both groups was small.

5.3.2 Family history and late presentation

Patients who report a positive FH of glaucoma more than one third more likely to present early in the course of their disease. The stronger the FH was, the lower the risk of late presentation.

This is as expected with those who have a knowledge of the disease being more likely to seek testing, are more likely to have pressures from family members to be tested and are more likely to be tested for glaucoma when visiting an optometrist[13]. Those with a FH of glaucoma are also eligible for government

payment of eye tests and as few patients gave cost as a reason for not having sight tests it may be that an incentive is being offered to a group who are already highly motivated to seek sight testing.

5.3.3 Ocular symptoms and late presentation

The results did not indicate that patients with visual symptoms were important modifiers of the results. Visually significant pathology such as cataract or AMD was not over-represented in cases or control group and similarly there was no statistically significant effect for different refraction.

It is interesting to note that more cases went to the optometrist because of symptoms prior to referral. Other authors have suggested that patients with advanced glaucoma, but no immediate threat to fixation, seem to suffer from non-specific ocular and visual symptoms[13].

5.4 OTHER STUDY FINDINGS

To quote Schlesselman once more "Even within the confines of a study designed to address a narrowly specified hypothesis, one may want to gather data on factors that may provide new leads regarding other potential causes of the study disease". There are a number of further pieces of information that have come out of this study.

Gender

The main study did not show any male-female difference in late presentation although the pilot study did show that there was a small protective effect for women. This is compatible with the literature which does not show a consistent difference in prevalence or incidence of glaucoma between males and females or that one group tends to present with earlier disease. The concept that women are more likely to have positive health seeking behaviour than men is not borne out by the results.

Optometry data

The results from this part of the study show that more cases went to the optometrist because they were in some way symptomatic. This could be because they were aware of field change or because they had not had a sight test for some years. In fact when questioned, most felt that 'their glasses needed changing' although again this is subjective and may simply be their way of expressing their feeling that 'something was wrong'. Either way it illustrates the importance of visual symptoms in prompting sight testing and this is also shown by the fact that 89% of all participants did not see the need for regular sight testing.

Change of optometrist did not seem to be an important factor in stage of presentation – although of the 8% who did change because they wanted a glaucoma test, all were controls. Cost does not seem to have a major influence on attendance for sight testing as very few patients gave this as a reason for non-attendance. This could be due to the fact that those on income support get free sight tests or simply that the study patients were too embarrassed to admit this as a reason to the interviewer.

The crude method of ascertaining what tests the optometrist was performing, indicated that optometrist referring controls were more likely to have performed and commented on IOP, discs and fields than those referring cases. Although this is obviously prone to some inaccuracies, it is consistent with data collected by Pitts-Crick and Tuck[13].

Similarly, more control patients remembered having visual field testing at previous optometrist visits than did the cases. The results suggest that cases may be more likely to come from optometrists who are not performing the full range of glaucoma tests.

5.5 BIASES AND IMPRECISIONS

Bias is the systematic error in design, conduct or analysis of a study that results in a mistaken estimate of an exposure's effect on the risk of disease. There are some biases specific to this study as well as the biases that result from using a Case-control method [18,19]– this was discussed in Chapter 3.

5.5.1 Selection bias

This study has an intrinsic problem in that it relies on newly presenting patients. While this means that the patients have a better recall of their optometric visit it does raise a question over the diagnosis of glaucoma. As mentioned previously, glaucoma can be a difficult diagnosis to make on a first visit and often repeat testing is required.

To reduce this bias the patients had their notes reviewed after their follow-up appointment and, in fact, no patients were excluded when this was done. It seems unlikely that those patients who fitted the field and disc criteria on two separate visits would later not fit these criteria. This is however a limitation of the study design and it is possible that a small number of cases and controls were incorrectly classified.

The data regarding 'time since last sight test' also has a potential flaw. Comparing the frequency of sight tests between late and early presenters may not be comparing like with like i.e. it compares those with early disease and those who have possibly had disease for some years. What would be very useful to know is the frequency of sight tests in late presenters in the early stages of *their* disease. In reality, because of the differing progression rates of the disease it is impossible to say when someone's early stage of disease was. What in fact the frequency of recent sight tests figure represents is an overall impression of the individuals sight testing history i.e.

the presumption is that if they had not had a sight test for some years then this was a proxy for poor sight testing prior to this.

Another possible source of bias could have occurred with the separation of normal tension and high tension glaucomas (and it is questionable whether such a separation is in itself valid). As well as the potential error of one off readings, it is artificial to separate those with IOP over 21mmHg from those with IOP under 21mmHg – especially as IOP was expressed as a continuous variable. The risk of late presentation of those with NTG has not been properly addressed by this study and the results should be interpreted very cautiously.

A further bias may have occurred because not all the patients were examined by myself i.e. all the Sunderland patients and some of the Moorfields patients. All these patients did fit the inclusion criteria and continued to do so when reviewed by the other ophthalmologists and a copy of all their fields was seen by me. The cup disc ratio although a very subjective measurement, when used in conjunction with fields rather than as a criterion on its own, was useful in separating cases and controls.

The fact that more than one centre was used in this study makes it more likely that the patients represented the general population (i.e. there was external validity). Equal numbers of cases and controls came from each hospital and no centre effect could be found (data not shown). What this does remove from the study is the ability to look at differing rates and causes of late presentation in the different areas – for example the influence of social deprivation and late presentation in Sunderland as compared to Essex. This may be a fruitful area for research in the future.

Both cases and controls had glaucoma and there were equal numbers of each. This reduces self-selection, differential surveillance and differential referral biases

from the study. So although this study was hospital-based rather than population-based, it is valid because both cases and controls came from the same source.

One further, potential weakness of the study is that it only addresses access to the NHS. There was only one case from SOC I/II which might indicate that those from higher social groups with advanced disease may seek private health care. It is not possible to know the extent to which this selection bias lead to an over-estimation of the effect of individual social deprivation. The fact that there were 33 controls from the higher SOC suggests that this source of bias is unlikely to be serious, but it is an aspect of the study that is of concern as there are no reliable estimates of how many new glaucoma patients are seen outside the NHS.

5.5.2 Information bias

A problem in a study of this nature is the potential for recall bias. While this is obviously not a problem for occupation, housing etc. it is when details of past optometric events are asked about.

Similarly, data regarding past medical history is subject to possible recall bias. The information was taken from the GP's letter if possible, from the patient in the clinic and was rechecked when the patient was telephoned. Both these sources are open to bias and for more accurate information the patients' GP would have had to be contacted directly. As this was not a major part of the study this was not performed.

The section regarding other ocular pathology was also prone to bias in that it depended on the opinion of the examiner as to whether the pathology was worth noting. It may also be that a cataract present in a severely cupped disc would not be felt to be worth noting, but in a younger control would be of more significance.

The most important source of information bias in this study was the potential for the patients to be aware of their case or control status. In fact some patients did tell

the interviewer that they had been told in the clinic that they were "in the early stages of glaucoma" or had "a lot of damage". There is little that can be done about this source of bias but the number appeared to be very small.

To avoid further bias, the interviewer was masked ask to the patients case or control status - although as noted above on a small number of occasions, the patient did give information regarding the severity of their glaucoma.

5.5.3 Length and lead time biases

The effect of length and lead time biases are an important problem in the study. First of all however, it is important to be clear what the term 'late presenter' means. It is, in this present study, simply a description of a patient who has presented to the HES for the first time with advanced visual field loss. Thus, it does not distinguish between patients who have had a very rapid (2-3 years[1]) visual field decline from those who have had a slower decline. This means that late presenters, although lumped together under one category, may have had glaucoma for quite different periods of time (in theory this may also be true for the early presenters). The evidence suggests glaucomas do not progress at the same rate e.g. Jay and Murdoch inferred faster progression at higher IOP [1,15] and a number of studies indicate faster progression with more advanced disease [14,16]. It is difficult to conceive a case-control method that could separate these subjects into rapid and slower field loss – it may be possible with a cohort study but this would need to be conducted over a period of some years and would require large numbers to show a difference in outcome between the groups.

Many glaucoma studies- especially those looking at outcomes, are likely to be affected by length and lead time bias and this is comparable with studies looking at survival rates for some Cancers.

Length bias occurs when survival is apparently longer for a disease simply because the disease was picked up at an earlier stage rather than because of a true increase in survival (this could account for the observation that persons who present late are more likely to go blind and conversely, those who present early are apparently less likely to become blind).

Patients whose disease is discovered by screening appear to survive longer than do patients who are treated after development of the symptoms [20]. There may be one or more of three reasons why this is seen[21]:-

1. Early treatment is beneficial and leads to prolonged life – a good example of this would be early cervical cancer.
2. The patients whose disease is detected by screening gain lead time i.e. the diagnosis of their disease is earlier than the time the clinical diagnosis would have occurred. This is lead time bias and is when apparent survival is greater because the disease is diagnosed earlier than normal rather than because of the treatment.
3. Screening programmes may identify cases that are destined to have a benign course irrespective of lead time or true benefit of early treatment. This is an example of length bias as apparent survival is mainly due to a slower rate of disease progression rather than to any intervention.

Although this work pertains mainly cancer survival it is easy to see how it applies to chronic glaucoma – both length and lead time problems. Rather than death, the end-point in glaucoma is blindness and like many cancers e.g. bronchial or pancreatic, symptoms occur only in the very late stages in glaucoma.

This study has indicated that regular sight testing is associated with earlier presentation of glaucoma, but all it may be showing is the lead time that the individual gains from an optometrist diagnosing their glaucoma. To know if this lead time is

worth gaining we need to know if our interventions truly slow the progress of the disease. Our only glaucoma intervention at present is IOP lowering and we still await definitive evidence that this is beneficial – hopefully we will soon have this evidence from studies such as the Swedish Early manifest Glaucoma Trial.

The rapidity of visual field loss appears to be extremely variable[1,20] and this is where the potential for length bias comes in. Some individuals probably have a visual field that declines very quickly (and therefore have a much higher risk of being late presenters) whilst others have a much slower field decline. The latter group may not in fact be in any danger of going blind within their life-span. Although we do not as yet know what all the factors are that influence the speed of visual field decline it would appear, as has been discussed previously, there is evidence that the rapidity of visual field loss is related to the height of the IOP. So that the higher the IOP the faster the loss of visual field - this current study concurs with this as late presentation was associated with higher presenting IOP.

It follows that if studies confirm the importance of lowering IOP on field survival then attempting to find patients in the earlier stages of disease will be worthwhile. This study indicates that the regular sight testing is likely to reduce the rate of glaucoma blindness. It does not however, address the issue of the increased number of false positives that an increase in sight testing would bring to the HES.

5.6 CONCLUSIONS

Glaucoma is a disease of major public health significance affecting at least 2% of the population over the age of 40. Despite new medical and surgical strategies to control IOP, blindness registration continues to account for 10-15% of blind registrations[24]. At an individual level, this causes a particularly profound and disabling visual loss[6].

The basis of this study is that patients who present with advanced field loss in one or both eyes are at greater risk of subsequent blindness and, because of this, it is worth trying to identify the characteristics of those who present late. In summary, the important findings of this study can be summarised as:-

1. **Increasing age is associated with an increased risk of late presentation.**
2. **The apparent increased risk of late presentation in African-Caribbean's is mainly due to less frequent sight tests.**
3. **Late presenters were less likely to have been referred from an optometrist with a presumptive diagnosis of glaucoma and less likely to have had a sight test within the previous five years. Regular sight testing reduces the risk of presenting with advanced glaucoma.**
4. **Measures of material deprivation such as Jarman Index, Occupational classification, housing tenure and having access to a car were all associated with late presentation.**
5. **The earlier a subject had left full-time education the greater the risk of late presentation.**
6. **The higher the IOP at initial examination in the HES the greater the risk of late presentation.**
7. **Subjects with a reported family history of glaucoma were more likely to present early.**

At the end of the pilot study it was suggested that late presentation was a function of frequency of sight testing and rapidity of visual field decline. It has been consistently stated in this study, that this latter factor is probably related to the height

of the IOP but that it is important to remember that other factors age, ethnic origin or even socioeconomic status may be having an influence on the rate of the decline. Until further factors have been elucidated, the other side of the equation that has been suggested by this study – frequency of sight testing – seems more likely to be the common pathway that explains the late presentation risk of the groups described above.

5.7 SUGGESTIONS FOR FURTHER STUDY

This present study is unique in that it was designed to look at why patients with glaucoma present with advanced glaucoma and as far as we know is the first study in the world to specifically address this issue. There are a number of strengths and weaknesses in the study and a number of areas where further studies are required.

1. Because the study is unique it needs to be repeated in an attempt to confirm the results. This repetition may take the form of a case-control study again or could possibly be performed as a (large) cohort study. The strengths and weaknesses of the case-control study have already been outlined already but produced a relatively inexpensive method of looking at a range of risk factors. The case-control criteria were robust when field criteria were combined with disc criteria and this has been a useful finding of the study. The importance of avoiding any overlap between cases and controls was addressed and it is unlikely that misclassification occurred.

   If the study were to be repeated a much larger number of cases and controls from a wider geographical distribution could be used i.e. a National Case-Control study. This would allow both a larger range of risk factors to be looked at (see below) and could be designed to allow comparisons between different regions in the UK.

A randomised control trial of screened versus non-screened (the screening being in the form of say an optometrist or ophthalmic nurse examining a defined population) would be technically possible. However to find a difference in outcomes (such as blindness rates) would require a very long study time and large numbers of subjects. Both of these factors tend to be prohibitively expensive. The case-control method, despite its problems, is a very useful technique in studies such as this one.

2. Because a variety of risk factors were looked at the number of sub-groups for analysis was very small. Ideally the study should be repeated with much larger numbers or, alternatively, certain groups could be targeted e.g. Asians or African-Caribbean's for separate studies using the same format. There may well be important findings in these groups that were missed in this study because of the small numbers. One of the most important areas for further study is the relationship between material deprivation and late presentation. This is a new finding in glaucoma, but is well recognised in other areas of medicine and it is important to try to replicate this result. The actual mechanism that causes those of lower SES to present with more advanced cancers or glaucoma is not known and may be an intrinsic problem of being poor or because of health risk behaviour. Future studies, using a similar format, could concentrate on socioeconomic variables in those with and without glaucoma to see if those who are deprived are more likely to develop glaucoma rather than not having it picked up until a later stage.
3. The format of this study i.e. cases and controls with the same disease but of different stages would be suitable for other types of eye disease. This has been recognised and there are currently studies of late presentation of diabetic

retinopathy and retinal detachment underway at Moorfields using this method. One interesting aspect of the study that will be pursued is a comparison of the results of the retrospective study with the main studies prospective identification of cases and controls to see if the different methods of collecting patients had a direct effect on the results.

4. There are a number of assumptions in this study, one of which is that those who present late are at much greater risk of subsequent blindness. This seems plausible for reasons outlined in Chapter 2 , but it is important to go back to these patients to see how many have been (or fulfil the criteria for) blind or partially sighted registration. This will be done for the patients who were involved in the retrospective study as they have been in the HES much longer and as they are all from one Hospital collecting the information will be logistically simpler.
5. A further assumption of this study that has been alluded to already in this chapter and that is the relationship between IOP level and visual field decline. The arguments for this assumption have been discussed but there is no doubt that studies looking directly at the role of IOP in glaucoma are essential. It is the results of these studies that will tell us whether early treatment of IOP slows visual field decline or that we are simply observing a good example of length bias.
6. Although this study has shown that visiting an optometrist protects against late presentation it cannot address the issues of false positives. It is unacceptable for an optometrist to ensure a high sensitivity by referring all glaucoma suspects - both from the individual patients point of view and from an economic point of view. More studies are required that address the issue of cost-effectiveness of optometric services as well as their effectiveness in diagnosing glaucoma. A study

is currently underway at Moorfields and funded by the Department of Health that is looking at the issue of false positive referrals.

7. It is important to remember that the controls in this study even though they are 'early presenters' have lost at least 30% of their retinal ganglion cells[23]. This means that it is important to continue to look for reliable and consistent mechanisms of identifying early disease. It seems unlikely that subjective tests such as perimetry will be the answer to this but there is hope that techniques such as laser scanning ophthalmoscopy of the disc or nerve fibre layer analysis will improve our diagnostic accuracy in the future.
8. The true nature of the disease entity that is glaucoma remains elusive. Little is known of the natural history of the disease, we do not have a screening test that allows us to reliably separate those with the disease from those without and we remain unsure of the effectiveness of our interventions.

For these reasons it is difficult to make strong recommendations to reliably avoid glaucoma blindness. However, in the meantime, the results of this study can allow us to target those groups that are at risk of blindness because of their risk of late presentation.

There may be a number of methods that can be targeted in these groups:-

i. Frequency of sight testing. Individuals should be encouraged to have a regular sight test – at least every three years but ideally every two. Encouragement may take the form of :-

a. *Financial* – this is the current method used. Certain groups (see Appendix 4) have their sight test fee paid by the government. Family history of glaucoma is one reason for a free test, yet the results show that this is a group who

tend to attend for sight tests and therefore present to the HES with early disease. The results also indicate that attendance for sight testing is not solely due to the financial incentive.

It is likely that persons over the age of 65 will be entitled to free sight tests in the near future, however a group with an even higher risk of late presentation - the African-Caribbean's are unlikely to get the same incentive.

Those on low income are also entitled to a free test, but again this does not seem to be enough of an incentive to encourage those of low socioeconomic status to attend. This may be due to lack of awareness of the need for regular testing or the fear of having to purchase a new pair of spectacles each time they have a sight test.

b. *Health Education* – in conjunction with free sight tests there needs to be ongoing health education initiatives that stress the need for regular sight tests with or without visual symptoms (and that the visit does not necessarily mean purchasing an expensive pair of glasses). This study has shown that 83% of patients did not realise that regular sight testing was advisable.

As well as a general campaign consisting of media advertising (which could be partly funded by the Optometry chains) and posters in GP and clinic waiting rooms, a greater pick-up could be gained from targeting populations at greatest risk of late presentation . For example, using Community centres and leaders in areas where there is a large African-Caribbean population or posters in Elderly day centres.

Most campaigns that suggest regular sight tests at the present time are run by charities such the RNIB or Fight for Sight and these make a valuable contribution.

However, a dedicated Government funded scheme may be necessary to get the sight testing message to as wide a group of people as possible.

ii. Rapidity of visual field decline

At present, the only method we may have of altering the visual field decline is by reducing the IOP – either medically or surgically. It has been suggested that the only type of glaucoma optometrists need to look for is that associated with high IOP's as this is the only type that benefits from treatment [22]. While this concept makes a number of assumptions (e.g. it assumes that IOP is consistently high in an individual), it may well pick up those patients who are at risk of blindness in the short to medium-term. If nothing else, optometrists should be taking the IOP on all patients over the age of 40 and especially in the groups at high risk of late presentation.

iii. Standard of optometric examination

There is little point encouraging people to attend for regular sight tests if they are not going to be examined for glaucoma. At the present time there is an *ad hoc* system dependent on the discretion of the optometrist. It is in impractical to expect all patients to have tonometry, ophthalmoscopy and perimetry at each visit and so guidelines are required to help the optometrist identify high-risk patients and perform the appropriate examinations. Certain groups of patients are well known to be at risk of having glaucoma and optometrists are often well aware of this, what this present study does is to highlight patients who may be at risk of presenting with advanced disease and the *College of Optometrists* may want to take this into account when setting standards of practice for optometrists in the future.

There are an increasing number of post-graduate courses for optometrists to improve their skills in diagnosing glaucoma. This is likely to be a good thing in that more glaucoma will be diagnosed at an earlier stage and, hopefully without the added burden of false positives.

Once again it is important to reiterate that ongoing assessment of the cost-effectiveness of sight testing and glaucoma examination is essential. Although late presentation is a tragedy for the individual its importance must be put in context of eye services, indeed health services, for the whole population.

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Appendix 1: Pilot study results.

A RETROSPECTIVE ANALYSIS OF RISK FACTORS FOR LATE PRESENTATION OF CHRONIC GLAUCOMA.

Abstract

Background Why some individuals present to the ophthalmologist in the early stages of chronic glaucoma but others present with very advanced visual field loss is a question which has received little attention. This study is an attempt to identify some basic characteristics of people who present with late glaucoma.
Methods A retrospective case-control study by medical record review was employed. 100 cases and 100 controls were identified from the notes of patients presenting to Moorfields Eye Hospital glaucoma service between July 1993 and July 1995. Cases were defined as new patients presenting with absolute field loss within five degrees of fixation and a cup disc ratio of greater than 0.8 in one or both eyes. Controls were new patients with no absolute field loss within 20 degrees in either eye, but otherwise typical glaucomatous field loss and a cup disc ratio of greater than 0.5 or a difference of 0.2 or more between the discs.
Results. The ethnic origin, sex, referral source, presenting IOP and age of the subjects studied were independently associated with late presentation. An African Caribbean patient is estimated to be four and a half times more likely to attend with advanced field loss than a Caucasian patient of similar age, sex, IOP and referral source (adj OR: 4.55, 95% CI [1.57, 13.18]). A female patient is estimated to be one third (0.34, [0.15, 0.74]) as likely to attend late than a male patient of the similar age, IOP, ethnic origin and referral source. A patient referred via any source other than an optometrist with the correct diagnosis is estimated to be greater than four times (4.32 [1.89, 9.88]) more likely to be a late attender than a patient of the same sex, ethnicity and similar age but referred with a diagnosis of glaucoma. There was a trend of increasing odds of late presentation increasing age over 40 years (adj. OR per ten years, baseline 40-49 yrs 1.68 [1.22, 2.20]). A patient whose presenting IOP is 21-25 mmHg is estimated to be a quarter (0.24, [0.09, 0.64]) as likely to attend with advanced field loss than a patient of the same ethnic origin, sex, age, referral source but with presenting IOP of greater than 31 mmHg
Conclusions These data strongly suggest that certain subgroups of patients with glaucoma are likely to be at greater risk of presenting with advanced and irremediable field loss.

INTRODUCTION

Despite extensive research and new treatments, glaucoma remains a major cause of blindness in the developing and developed world. Risk factors for the development of glaucoma have been extensively investigated but those for glaucoma blindness have received little attention.

A number of workers have shown that patients who present with advanced glaucoma are at a substantial risk of blindness [1,2,3]. Grant and Burke found that eyes with a visual field defect at the start of treatment were more likely to progress to blindness than eyes in which treatment is started at the stage where there is no field loss (although whether all the patients in the second group had glaucoma is difficult to ascertain) [1]. Wilson *et al* looked at risk factors for rate of progression of glaucomatous visual field loss in 57 patients and found that initial visual field was the strongest determinant of rate of further visual field loss [4]. Patients in their study deteriorated 11.7 times faster in the more advanced eyes. Mikelburg *et al* measured scotoma mass of fields and compared them to the rate of subsequent decline [5]. They found that when scotoma mass was small (i.e. early disease) rate of visual field loss was slow but when the scotoma mass was large, rapid linear progression of visual fields occurred. Miller and Karseras stated, that from their series, glaucoma is more benign in patients with considerable visual reserve [6].
These studies suggest that late presentation is a considerable risk factor for glaucoma blindness.

PATIENTS AND METHODS

All patients referred from the Primary Care Clinic at Moorfields Eye Hospital to the Glaucoma service between July 1993 and July 1995 who had not previously been diagnosed as having chronic glaucoma were identified.

For simplicity, the first 100 consecutively identified cases and 100 controls that fitted the criteria were used . This study was a pilot, an objective of which was to provide estimates for use in sample size calculations in subsequent work.

Cases were defined as typical glaucomatous field loss *within* five degrees of fixation but beyond 30 degrees in one or both eyes. The glaucoma could be of any chronic type as long as field loss was present. There had to be at least two consecutive fields confirming loss and a cupped disc ratio of more than 0.8. The only exception to this was when the field loss was so advanced that field testing was not possible. Fields (Henson or Humphrey) were excluded if there were more than 20% fixation losses or false positives errors were more than 33% [7].

Controls had typical glaucomatous field loss but *no* absolute scotomas within 20 degrees of fixation in either eye (therefore there was no doubt as to their glaucoma status). The glaucoma could be of any chronic type as long as field loss was present. There had to be at least two consecutive fields confirming this loss and a cup disc ratio of greater than 0.5 must be present or a difference of more than 0.2 must have been noted. Fields (Henson or Humphrey) were excluded if there were more than 20% fixation losses or false positives errors were more than 33%.

For each case and control the following information was extracted from the notes:-

1. Basic data - age, sex and ethnic origin.
2. Referral source of the patient - this was initially divided into four groups:-
   - i. From optometrist with a presumptive diagnosis of glaucoma.
   - ii. From an optometrist but with no mention of glaucoma in the referral letter
   - iii. From a General Practitioner with a presumptive diagnosis of glaucoma
   - iv. From a General Practitioner with no mention of glaucoma in the referral letter

   In practice, a more meaningful comparison was between those patients referred with a presumptive diagnosis of glaucoma from their optometrist and those who had come from other sources (i.e. ii,iii and iv combined).
3. Type of glaucoma diagnosed by ophthalmologist.
4. Intraocular pressure (IOP) at presentation.
5. Other significant ocular pathology present
6. Presence of systemic disease e.g. hypertension, diabetes.
7. Family history of glaucoma.

The data were analysed using STATA[8] to investigate the effects of each study factor on the odds of being a late presenter. Estimates of the odds of being a late presenter with approximate 95 % confidence intervals, by study factors were computed by logistic regression. In each case the first category of each study factor was used as a baseline, either because its selection appeared to give the most meaningful results or because it contained the greater number of observations and hence its choice favoured precision. Unadjusted and adjusted odds ratios are presented - adjustment being made for factors found to be statistically significant in the univariate models. A chi-square test for trend was conducted to assess departure from linearity in the apparent trend of increasing odds of late presentation with increasing age.

RESULTS

Table 1 shows the characteristics of the study population. The majority (73.5%) of patients were over 60 years and similar numbers of men and women were studied. More than half of the study patients were Caucasian (61 %), 13.5% were African Caribbean and 9% were Asian. 12.5% of the group did not have their ethnic origin recorded in their notes. The majority of patients (68%) had been referred to the Hospital Eye Service by optometrists with a presumptive diagnosis of glaucoma. The remaining 32% had either come from their GP or from their optometrist but without a diagnosis of glaucoma mentioned in the referral letter. 41.5 % of patients studied had a presenting IOP of greater than 31 mm Hg, only 7 % had an IOP of less than 21 mmHg at presentation. The most common glaucoma diagnosis made by the ophthalmologist was primary open angle glaucoma (POAG). 78% of the patients were diagnosed with POAG compared with 9 % chronic angle closure (CACG) and 6 % each of pseudoexfoliation (PXF) and normal tension glaucoma (NTG). Most patients (83%) had no other significant ocular pathology mentioned in the notes and 59.5% were generally in good health. 29% of the patients had a family history of glaucoma mentioned in their notes.

Table 2 shows the estimated effect of each study factor on late presentation. These data provide strong evidence of independent associations between late presentation and the age, sex, ethnic origin, referral source and presenting IOP of the study patient. We estimate a trend of increasing odds of late presentation with increasing age over 40 years (adj OR: 1.68 [1.22, 2.20]) in sufferers of the same sex, ethnic and IOP group and referral source. A woman is estimated to be one third (0.34 [0.15, 0.74]) as likely to be a late presenter than a man of the same ethnic, group, referral source and similar age and presenting IOP. These data provide strong evidence of association between ethnicity and late presentation that is not explained by differences in age, sex, IOP or referral source. An African Caribbean patient is estimated to be four and a half times (4.55 [1.57, 13.18]) more likely to present with advanced loss than a Caucasian patient of the same sex and referral source and similar age and IOP. These data suggest also that Asian patients may be at slightly increased odds of late presentation than the Caucasian patients, although numbers were small and the confidence interval includes the unity of no association. Referral source is shown by these data to be strongly associated with late presentation. A patient referred via any source other than an optometrist with the correct diagnosis is estimated to be greater than four times (4.32 [1.89, 9.88]) more likely to be a late attender than a patient so referred of the same sex, ethnicity and similar age and IOP. These data provide evidence too of association between presenting IOP and field loss. Estimated at greatest odds of late presentation are patients with presenting IOP of greater than 31 mm Hg. A patient with a presenting IOP of 21-25 mmHg is estimated to be a quarter (0.24[0.09, 0.64]) as likely to attend with advanced field loss as a patient with presenting IOP of greater than 31 mmHg but of the same sex, age, ethnic origin and referral source.

These data provide little evidence of association between late presentation and any of the other factors studied, but this may well be a consequence of the low power associated with a pilot study of this size.

DISCUSSION

There have been a number of hospital-based studies that have estimated the proportion of glaucoma patients that present with substantial visual field loss. Grant and Burke calculated that one third of the patients who had become blind from glaucoma had done so before they had sought medical attention for their eyes [1]. Elkington *et al* and Sheldrick *et al* gave respectively figures of 33% and 20 % presenting late. [9,10] The West of Ireland population-based study found that 10% of people with glaucoma were severely visually impaired at first examination. [11]

It is of note that of these, only Grant and Burkes' study included non-Caucasian patients and that their estimate of late presentation was greater than the other studies. Our data suggest that patients of African Caribbean origin are over four times more likely to present late than comparable Caucasian patients. There are a number of possible reasons for this including a more rapid disease progression, earlier onset of disease (which is also when glaucoma testing is less likely during routine sight testing) and poorer access/uptake of eye care services [12, 13,14].

Our results provide strong evidence of an association between age and late presentation,. The risk of late presentation appears to increase linearly with increasing age over 40 years. This seems plausible since both the prevalence and incidence of glaucoma rise with age -as does the incidence of blind registrations from glaucoma [15]. Other factors such as difficulties with mobility and social isolation can reduce access to sight (and therefore glaucoma) testing may also contribute to the later presentation.

In Britain, the optometrist plays a pivotal role in glaucoma detection. One study showed that 90 % of glaucoma patients are referred to hospital on the basis of abnormal findings by an optometrist [10]. Our results estimate that a patient who has not been correctly referred to the hospital by an optometrist is over four times more likely to be a late presenter than a comparable patient who has. Patients referred from optometrists with a diagnosis of glaucoma are more likely to be in the earlier stages of the disease. This suggests that late presenters attend optometrists who do not test for glaucoma, or more probably, late presenters are people who tend not to go for regular sight tests.

We estimate that women are more likely to present in the early stages of glaucoma than men of similar age, presenting IOP, ethnic origin and referral source. There is no firm evidence of a difference in the prevalence of glaucoma in men and women.[12] Glaucoma is not known to be a more rapidly progressive disease in men so the most plausible explanation for the earlier presentation of women is

that their rate of sight testing (and general use of all preventative health services) is higher and this is supported by evidence from the General Household Survey [16].

Whether an individual presents late in the course of their glaucoma is likely to be a function of the rapidity of their visual field deterioration and the frequency of their sight tests. An individual with a rapid decline can lose significant field even with two yearly sight tests - unless tested during an early, but detectable phase of the disease. Conversely, an individual with a slowly declining field but who does not attend for sight testing for some years (or does not have a glaucoma examination during their sight tests) is at risk of late presentation for a different reason.

Individuals with rapid field loss are likely to be those with higher IOP's [2]. The influence of rapidity of field loss on late presentation is thus supported by our study in that we estimate that patients with presenting IOP's of greater than 31 mm Hg are at greatest risk of late presentation. Further support for this is that patients with PXF and CACG appear at greater risk of late presentation, although the confidence intervals are wide -reflecting the small numbers.

NTG might be expected to be associated with late presentation since detection relies on visual field analysis by the optometrist or recognition of suspicious discs rather than raised IOP. One survey showed perimetry was only performed by 10% of optometrists [12]. Our data do not support this, suggesting perhaps that visual field deterioration is slower in NTG patients than other types of glaucoma. It is important to treat the NTG data with some caution as the numbers are small.

Our data provide little evidence of any association between late presentation and other pathology - be it systemic or ocular. Patients with cataract do appear to be slightly albeit not statistically significantly at greater risk of late presentation but we would advise cautious interpretation since 'significant' cataract was only defined as mention of lens opacity in the clinical notes and was thus highly subjective.

Family history is well recognised as a risk factor for glaucoma and one might well expect it to be protective against late presentation because of increased awareness of the condition and eligibility for free sight tests. Our data are consistent with a weak protective effect although this was not statistically significant - perhaps a reflection of recall bias.

There are a number of potential biases in the study, the first of which is that it relied on information taken from medical notes. In some cases this was incomplete- for example, the ethnic origin of the patient, and in others it may have been inaccurate - for example, systemic disease. Another potential bias in the study could have arisen because case/control status was decided from the notes prior to the other information being extracted -which may have influenced the subsequent collection of information. Whilst plausible, consideration should be given as to whether these observed associations might be due to residual confounding or perhaps bias. Whilst this study has enabled adjustment for several potential confounders, bias due to unmeasured confounders such as socioeconomic status cannot be excluded.

As mentioned above, late presentation is a function of rapidity of visual field loss and frequency of sight testing. It is not possible in this pilot study to assess the relative influence of these two determinants in the risk factors that have been isolated but in the prospective study currently being undertaken this will be possible. The prospective study will also remove the bias of medical record review and be able to look at a far greater range of potential risk factors.

CONCLUSIONS

These data provide strong evidence that the risk of a patient over 40 years with chronic glaucoma presenting to the hospital eye service with advanced visual field loss is independently associated with sex, age, ethnic origin, referral source and presenting IOP. Certain subgroups of patients with glaucoma are likely to be at greater risk of permanent visual impairment.

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Table 1: Study factors by Case/Control Status

Study Factor		No. of Controls	No. of Cases	Total no. of patients (percentages)
Age (years)	40-50	15	8	23 (11.5%)
	51-60	19	11	30 (15.0%)
	61-70	38	26	64 (32.0%)
	71-80	26	41	67 (33.5%)
	81-90	2	13	15 (7.5%)
	91 +	0	1	1 (0.50%)
Sex	Male	47	58	105 (52.5%)
	Female	53	42	95 (47.5%)
Ethnic Origin	Caucasian (British)	77	45	122 (61%)
	African Caribbean	8	19	27 (13.5%)
	Asian	9	9	18 (9%)
	Caucasian (Other European)	2	6	8 (4%)
	Not ascertained	4	21	25 (12.5%)
Referral Source	Optometrist with correct diagnosis	85	51	136 (68%)
	Other	15	49	64 (32%)
Presenting IOP(mmHg)	> 31	26	57	83 (41.5 %)
	26 - 30	31	25	56 (28%)
	21 - 25	34	13	47 (23.5%)
	< 21	9	5	14 (7%)
Glaucoma Diagnosis	POAG	84	72	156 (78%)
	PXF	2	10	12 (6%)
	Chronic angle closure	6	12	18 (9%)
	Normal Tension	7	5	12 (6%)
	Other	1	1	2 (1%)
Ocular Pathology	Nil Significant	91	75	166 (83%)
	Cataract	3	15	18 (9%)
	AMD	3	3	6 (3%)
	CRVO/BRVO	3	1	4 (2%)
	Corneal problem	0	4	4 (2%)
	Uniocular/Amblyopic	2	0	2 (1%)
Systemic Disease	Generally in Good Health	60	59	119 (59.5%)
	Hypertension	23	29	52 (26%)
	Diabetes	6	5	11 (5.5%)
	Other chronic diseases	8	5	13 (6.5%)
	Hypertension and diabetes	3	2	5 (2.5%)
Family History	Nil	67	75	142 (71%)
	Glaucoma in 1st or 2nd degree relative	33	25	58 (29%)

Table 2: Estimates of the effect of each study factor on late-presentation.

Study Factor		Odds of being a late presenter	95% CI	OR	95% CI	Adj. OR**	95%CI
Age	40-50	0.53	(0.23,1.26)	1			
	51-60	0.58	(0.28,1.22)	1.09	(0.35,3.38)		
	61-70	0.68	(0.42,1.23)	1.28	(0.48,3.46)		
	71-80	1.58	(0.97,2.58)	2.96	(1.10,7.95)		
	81-90	6.50	(1.47,28.80)	12.19	*(2.19,67.95)		
	91 +						
Per ten years							
	Baseline 40-50 years			1.68	(1.28,2.20)	1.78	(1.22,2.60)
Sex	Male	1.23	(0.84,1.81)	1			
	Female	0.79	(0.53,1.19)	0.64	(0.37,1.12)	0.34	(0.15,0.74)
Ethnic Origin	Caucasian (British)	0.58	(0.41,0.84)	1			
	African Caribbean	2.38	(1.04,5.43)	4.06	(1.65,10.04)	4.55	(1.57,13.18)
	Asian	1.00	(0.40,2.52)	1.71	(0.63,4.63)	1.22	(0.36,4.11)
	Caucasian (Other European)	3.00	(0.61,14.86)	5.13	(0.99,26.52)	2.01	(0.26,15.61)
Referral Source	Optometrist with correct diagnosis	0.60	(0.42,0.85)	1			
	Other	3.27	(1.83,5.83)	5.44	(2.77,10.68)	4.32	(1.89, 9.88)
Presenting IOP(mmHg)	> 31			1			
	26 – 30			0.37	(0.18, 0.74)	0.43	(0.18, 1.03)
	21 – 25			0.17	(0.08, 0.38)	0.24	(0.09, 0.64)
	< 21			0.25	(0.08, 0.83)	0.36	(0.08, 1.66)
Glaucoma Diagnosis	POAG	0.86	(0.63,1.17)	1			
	PXF	5.00	(1.10,22.82)	5.83	(1.24,27.49)	3.47	(0.62, 19.50)
	Chronic angle closure	2.00	(0.75,5.33)	2.33	(0.83,6.53)	2.48	(0.69, 8.90)
	Normal Tension	0.71	(0.23,2.25)	0.83	(0.25,2.74)		
Ocular Pathology	Nil Significant	0.82	(0.61,1.12)	1			
	Cataract	5.00	(1.45,17.27)	6.06	(1.69,21.75)	4.20	(0.93, 19.00)
	AMD	1.00	(0.20,4.96)	1.21	(0.24,6.19)	0.72	(0.10, 5.11)
Systemic Disease	Generally in Good Health	0.98	(0.69,1.41)	1			
	Hypertension	1.26	(0.73,2.18)	1.28	(0.67,2.47)	0.76	(0.32, 1.81)
	Diabetes	0.83	(0.25,2.73)	0.85	(0.25,2.93)	0.46	(0.09, 2.25)
	Other chronic diseases	0.63	(0.20,1.91)	0.64	(0.20,2.06)	0.28	(0.06, 1.37)
	Hypertension and diabetes	0.67	(0.11,3.99)	0.68	(0.11,4.20)		
Family History	Nil	1.19	(0.81,1.56)	1			
	Glaucoma in 1st or 2nd degree relative	0.76	(0.45,1.27)	0.68	(0.37,1.25)	0.86	(0.37, 2.04)

* Test against departure from linearity: Chi-sq (3 df) 4.39, p=0.222

** Adjusted for age, ethnic origin, referral source and presenting IOP

APPENDIX 2

NOTES QUESTIONNAIRE

A).DEMOGRAPHIC DETAILS

1.NAME.....

2. ADDRESS.....

.....

.....

3. POST CODE.....

4. TELEPHONE NUMBER.....

5. BEST TIME TO RING.....

6. PERSON TO SPEAK TO (IF NOT PATIENT).....

7. AGE.....

8. SEX M/F

9. ETHNIC ORIGIN (PLEASE RING)

WHITE BRITISH	PAKISTANI
AFRICAN-CARRIBEAN	BANGLADESHI
INDIAN	WHITE EUROPEAN
CHINESE	

B).REFERRAL DETAILS

10. REFERRAL SOURCE

OPTOMETRIST

GP |

INCIDENTAL FINDING FROM OPTOMETRIST > GO TO NEXT

INCIDENTAL FINDING FROM GP | SECTION

11. OPTOMETRIST LETTER SENT? Y/N

12. HIGHEST IOP FOUND BY OPTOMETRIST

RIGHT..... LEFT.....

13. IOP METHOD OF OPTOMETRIST

NON-CONTACT

CONTACT

NOT MENTIONED

14. DISC COMMENT? Y/N

15. FIELDS PERFORMED? Y/N

TYPE THRESHOLD

SUPRA-THRESHOLD

CONFRONTATION

NOT KNOWN

16. REFRACTION

RIGHT..... LEFT.....

17. VISUAL ACUITY

RIGHT..... LEFT.....

C).EXAMINATION FINDINGS

18. DIAGNOSIS

POAG	CHRONIC ANGLE CLOSURE
PXF	FUCHS
PIGMENTARY	NORMAL TENSION
APHAKIC	TRAUMATIC

19. HIGHEST IOP FOUND

RIGHT..... LEFT.....

20. FIELD RESULT(RING MORE THAN ONE IF NECCESSARY)

GRADE 1(CONTROL) RIGHT

GRADE 4/5 (CASE) LEFT

21. DISC ASSESSEMENT

RIGHT..... LEFT.....

22. OTHER SIGNIFICANT OCULAR PATHOLOGY? Y/N

CATARACT	AMBLYOPIA
ARMD	LOSS OF EYE
VEIN OCCLUSION	
CORNEAL OPACITY	

23. SYSTEMIC DISEASE

GENERALLY IN GOOD HEALTH

HYPERTENSION

DIABETES

COAD

OTHER (DETAILS)

24. FAMILY HISTORY EYE DISEASE Y/N

GLAUCOMA IN FIRST DEGREE RELATIVE

GLAUCOMA IN SECOND DEGREE RELATIVE

RELATIVE REGISTERED BLIND

OTHER

APPENDIX 3

PATIENT QUESTIONNAIRE

A. DEMOGRAPHIC DETAILS

1.NAME.....

2.AGE.....

3.ETHNIC ORIGIN

White British	White European
Black Caribbean	Black African
Black-other	Indian
Pakistani	Bangladeshi
Chinese	Other Asian
White Non-European	Irish
Other	

4.POSTAL CODE.....

5.EMPLOYMENT GROUP.(Present occupation or occupation during most of life).....

Retired/Unemployed/Long term sick

6.WHAT AGE DID YOU LEAVE FULL TIME EDUCATION?

....

7.TYPE OF ACCOMODATION.

Owner occupier	Non-permanent accomodation
Rented privately furnished	Sheltered accomodation
Rented privately unfurnished	Institution
Rented with job or business	
Rented from LA	

8.DO YOU LIVE ALONE? Y/N

9.DO YOU HAVE ACCESS TO A CAR Y/N

B. MEDICAL DETAILS

1.MEDICAL ATTENDENCE

How often do you see your GP?	**At least once a week**
	At least once a month
	A few times a year
	Very rarely

2.SMOKING Y/N/EX PACKS A DAY.....

YEARS SMOKED.....

3.ALCOHOL In the past twelve months have you taken an alcoholic drink?

Twice a day or more	Once or twice a month
Daily or almost daily	Special occasions only

Once or twice a week No

4.FAMILY HISTORY GLAUCOMA Y/N

One or more second degree relatives

One first degree

More than one first degree

C.OPTOMETRIC SCREENING.

1.WHEN DID YOU LAST VISIT AN OPTICIAN, APART FROM THE REFERRAL VISIT?

Within the last year

Within the last 2 years

Within the last 3 years

Within the last 5 years

Within the last 6 years

Within the last 10 years

More than 10 years

Never previously

2.REASON FOR NOT VISITING WITHIN 5 YEARS?

Cost

Forgot and not reminded

Forgot but reminded

Did not see the need

Mobility problems

3.REASON FOR VISITING OPTOMETRIST WHO REFERRED:-

Symptoms

Optometrist reminder

Routine attendance without reminder

Appendix 4: Sight test exemption categories (at the time of the study)

Aged over 40 years with a first degree relative with glaucoma.

Diabetics

Those on Income support

Complex spectacle prescriptions

Registered Blind or Partially Sighted

Under 16 years of age and those in Full-time education

Appendix 5.

RISK FACTORS FOR LATE PRESENTATION OF CHRONIC GLAUCOMA.

Purpose: To identify the risk factors for first presenting to the Hospital eye clinic with advanced glaucomatous visual field loss.
Methods: This was a hospital-based, case-control study involving patients newly diagnosed with glaucoma at first presentation to one of three Ophthalmic Departments in the United Kingdom. Patients with a previous history of ocular hypertension or any documented suspicion of glaucoma(within the Hospital Eye Service) were excluded.
Results: Occupational group, presenting IOP, family history of glaucoma, method of referral to hospital and the number of years before the last visit to an optometrist were found to be independently associated with late presentation. We estimate a linear trend of increasing odds of late attendance with increasing Standard Occupational Classification with those in managerial (II) and skilled (III) groups estimated to be respectively 0.02 [0.00, 0.16] and 0.27 [0.1, 0.8] as likely to attend with advanced glaucomatous field loss as unskilled (V) people with similar presenting IOP, family history, referral route and time since last optometrist visit. The data strongly suggest an association between IOP and advanced field loss at presentation. We estimate a 1.2 [1.12, 1.28] increase in the odds of late presentation per unit increase in mmHG after adjustment for the other mentioned factors. People with a family history of glaucoma are estimated to be almost one third (adj OR: 0.29 [0.12, 1.28]) as likely to present with advanced field loss than those with no family history. People referred via any source other than an optometrist with the correct diagnosis (of glaucoma) are estimated to be four and a half times (adj OR: 4.53 [1.52, 13.48]) more likely to be late attenders than patients so referred but similar with regards to other mentioned factors. These data provide strong evidence, too, that the greater the number of years since last visiting an optometrist the greater the likelihood of first presenting with advanced glaucomatous visual field loss (adj OR per year: 1.25 [1.10, 1.42]).
Conclusions: These data strongly suggest that certain subgroups of individuals with glaucoma are at greater risk of presenting with advanced and irremediable field loss.

INTRODUCTION

Glaucoma is a disease with major public health implications. It is known to afflict approximately 2 % of Caucasians aged 40 or more and at least four times this in African American's and African Caribbean's[1]. Populations are ageing and the increase in the prevalence of glaucoma with increasing age has been well documented[1,2].

Despite new medical and surgical strategies to control intraocular pressure, blindness registration from glaucoma continues to increase and glaucoma remains the second or third most common cause of blindness in the world[3,4].

Why do individuals become blind from glaucoma? Grant and Burke[5] have suggested that there are two reasons why this occurs:-

1. People present late in the course of the disease - when the rate of field loss is increased and there is less field left to lose.
2. People present early but receive sub-optimal treatment.

Published work on the first of these reasons -late presentation- is scarce. This study was conducted to redress this and attempts to identify the factors that put an individual at risk of presenting to the hospital eye service with advanced glaucomatous visual field loss.

METHODS

This was a hospital-based, case-control study with recruitment at three independent Eye Departments in the United Kingdom (see Appendix). Patients were eligible for study if they were diagnosed with glaucoma according to the criteria listed below when *first examined* by an ophthalmologist at one of the three sites. Any patients with a previous history of glaucoma, ocular hypertension, or of being a glaucoma suspect (made by an ophthalmologist or optometrist) were excluded from the study. All fields were also examined by one author (SF) to ensure consistency of case definition.

Eligibility criteria for recruitment to study

To be considered for the study all patients had:-

1.Visual field loss that was consistent with a known pattern of glaucomatous loss (eg arcuate scotomas), was compatible with the patients disc changes and in which there was no suggestion of other optic nerve pathology (eg defects crossed the horizontal mid-line)

2. Glaucoma of any chronic type i.e. Primary open angle, pseudoexfoliative, normal tension, chronic angle closure, aphakic or pigment dispersion.

3. Two consecutive fields (threshold or suprathreshold) confirming the loss except where field loss was so advanced that perimetry was not possible

4. Patients who had more than one third fixation losses, false positives, or false negatives on their initial field test were not enrolled for the study. Fields were almost exclusively with the Humphrey 24-2 or 10-2 threshold strategies.

If the patients fitted these criteria then a decision was made as to whether they could be cases or controls based on visual field and optic disc anomalies:-

Cases were defined as having:-

Fulfilling the above criteria but with the field loss being within five degrees of fixation and beyond 30 degrees in one or both eyes and with a cup disc ratio greater than 0.8 in the same eye.

Controls were defined as having:-

Fulfilling the above criteria but with the visual field having no absolute scotomas within 20 degrees of fixation in either eye and a cup disc ratio assessed as greater than 0.5 or a difference of greater than 0.2 between the discs.

In an attempt to minimise the problems of recall bias, patients were recruited after the first field. If, during follow-up, visual fields 'improved' to the extent that the patient no longer met the above criteria they were removed from the study. Six patients were excluded on this basis, each after their second visual field. The disc parameter criteria were shown, by pilot study, to be sensitive indicators of cases and controls.

Basic demographic, referral and ophthalmic information was collected at the initial consultation and suitable patients were consented for further evaluation. These patients were then telephoned by an interviewer masked to their case/control status - who validated demographic data and asked a series of standard questions regarding socioeconomic status, general medical health and attendance and use of sight testing (i.e. optometrists) services.

For each patient identified as eligible for the study, information on the following was collected:-

- Age when first assessed by the ophthalmologist.
- Sex.
- Ethnic origin - Caucasian (all those from the UK and Ireland).
  -African/African Caribbean.
  -Asian (from the Indian Subcontinent).
- Coexisting ocular or medical pathology.
- IOP - the standard Goldman tonometer reading at initial examination.
- Frequency of sight testing. In the UK the majority of glaucoma patients have their referrals to the Hospital Eye Service (HES) initiated by optometrists in commercial practice. Optometrists do not usually refer directly to an ophthalmologist but via the patients General Medical Practitioner (GP) who then formally refers them to the HES. It is rare for a GP to have the expertise or equipment necessary to test for glaucoma themselves. By review of referral letters and telephone confirmation, two principal referral sources were identified:-
  1. From an optometrist with a diagnosis of ?glaucoma.
  2. From an optometrist but with no mention of glaucoma in the referral letter, or from the GP directly without being prompted by an optometrists findings (and therefore without a diagnosis of glaucoma).
- The patients occupational group was classified using the Standard Occupational Classification outlined in *Table 1*. If the patient was retired, unemployed or suffering from long-term illness, the occupation they had performed for the major part of their working life was entered. For married women who had never worked their husbands occupation was entered as per SOC guide-lines[6].

In practice, groups IIIN and IIIM were difficult to distinguish using the information collected and a pooled category III was used.

The research followed the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of Moorfields Eye Hospital.

STATISTICAL ANALYSES

Power calculations were employed to determine the sample size. 110 cases and 110 controls were recruited to enable an 80% chance of detecting as statistically significant at the 5% level, a doubling in the odds of late presentation in a factor present among 10% of the controls.

The data were analysed using STATA [7] to investigate the effects of each study factor on the odds of being a late presenter. Estimates of the odds ratios (OR) of being a late presenter with approximate 95 % confidence intervals, by study factors were computed by logistic regression. In each case the first category (unless otherwise stated) of each categorical study factor was used as a baseline either because its selection appeared to give the most meaningful results or because it contained the greater number of observations and hence its choice favoured precision. Factors significant at univariate level were entered into a multivariate model but subsequently dropped if not statistically significant in this model - this will be referred to as model I. Unadjusted and adjusted odds ratios are presented - adjustment being made for all factors found to be statistically significant in model I.

RESULTS

The study was undertaken over a nine month period from September 1996 to May 1997 and stopped when 110 cases and controls were collected. None of the patients who fitted the study criteria declined to take part in the study and there was no loss of patients during the study.

Table 2 shows the characteristics of the study population. The median (inter-quartile range: IQR) age of controls was 63 (52, 71) years and of cases was 72 (63,78) years. Similar numbers of men and women were studied. Most of the patients recruited were Caucasians, 35 were of African or African Caribbean origin and 14 were of Asian origin. The most common diagnosis was primary open angle glaucoma (POAG) followed by normal tension glaucoma (NTG), 15 patients were diagnosed with pseudoexfoliative glaucoma (PXF) and 13 as chronic angle closure glaucoma (CACG). The median (IQR) IOP in right eyes was 24 (22, 30) mm Hg and 25 (22, 30) mm Hg in left eyes. The median (IQR) maximum IOP (ie the higher of the right and left IOP's at presentation) was 26 (23, 31.5) mm HG. The majority of subjects had no significant ongoing medical problems of those who reported problems, systemic hypertension was the most common problem reported. Most subjects gave no family history of glaucoma. 31 subjects had a single first degree relative with glaucoma, 14 had a second degree relative with glaucoma and 20 gave a history of having two or more first degree relatives with glaucoma. The majority of patients were referred from optometrists with a presumptive diagnosis of glaucoma. *Table 2* also shows that most of subjects had visited an optometrist no more than five years prior to the referral visit. 31 subjects had either never seen an optometrist or had not seen one for more than ten years.

Tables 2 and 3 show the estimated effect of each study factor on late presentation. The data provide strong evidence of independent associations between late presentation and the model I variables : occupational group, maximum measured IOP, family history, referral source and time since last visit to optometrist of the study patient.

We estimate a linear trend of increasing odds of late attendance with increasing occupational group. Patients of managerial (II) and skilled (group III) occupations are estimated respectively to be 0.02 [0.02, 0.16]and 0.27 [0.1, 0.8] as likely to attend with advanced glaucomatous field loss as patients of unskilled occupations but similar with regards IOP, family history, referral source and time since last visit to an optometrist. The statistical non-significance of the other occupational OR estimates may be a reflection of low power - only 15 % of patients being of groups I and II.

Maximum IOP (ie the greater of the right and left IOP's) at presentation was shown by these data to be strongly associated with the odds of presenting with advanced field. We estimate a 1.2 [1.11, 1.28] increase in the odds of late presentation per increased unit mmHg after adjustment for model I factors.

The stronger the patients family history the lower their odds of late presentation. Overall, a patient with a family history of glaucoma is estimated to be almost one third (0.29 [0.12, 0.74]) as likely to attend with advanced field loss than a patient with no family history but of the same occupational group, IOP, referral source and similar time since last visit to an optometrist.

Referral source is shown by these data to be strongly associated with late presentation. A patient referred via any source other than an optometrist with the correct diagnosis is estimated to be

four and a half times (4.53 [1.52, 13.48]) more likely to be a late attender than a patient so referred but similar with regards to other model I variables. These data provide strong evidence that the greater the number of years since last visiting an optometrist the greater the likelihood of being a late attender. (adj OR per year : 1.25 [1.10, 1.42]).

Univariate analysis suggested a strong association between ethnic origin and late attendance - estimating that individuals of African Caribbean origin are greater than six times more likely to be late attenders than Caucasian patients. Ethnic origin was not, however, statistically significant, in the multivariate model. Inspection of a partial correlation matrix of all study factors revealed moderate correlation between ethnic origin, referral source and number of years since last visit to an optometrist. Much of the apparent effect of ethnicity on late presentation appears to be due to less frequent sight testing. However the statistical non-significance may well be a consequence of relatively low power.

These data provide little evidence of association between late presentation and any of the other factors studied

DISCUSSION

A number of workers have shown that patients who present with advanced glaucoma are at a substantial risk of blindness[5,8-12]. Grant and Burke[5] found that eyes with a visual field defect at the start of treatment were more likely to progress to blindness than eyes in which treatment is started at the stage where there is no field loss (although whether all the patients in the second group had glaucoma is difficult to ascertain). Wilson *et al*[8] looked at risk factors for rate of progression of glaucomatous visual field loss in 57 patients and found that initial visual field was the strongest determinant of rate of further visual field loss. Patients in their study deteriorated 11.7 times faster in the more advanced eyes. Mikelburg *et al*[12] measured the scotoma mass of fields and compared them to the rate of subsequent decline . They found that when scotoma mass was small (i.e. early disease) rate of visual field loss was slow but when the scotoma mass was large, rapid linear progression of visual fields occurred.

Thus there is good (if inferential) evidence that late presentation (i.e. substantial field loss) is a significant risk factor for subsequent glaucoma blindness. There is also a biological plausibility underpinning this in that the less axons a nerve has the less it can afford to lose without significant field changes.

The other important aspect of late presentation that needs addressing is the extent of the problem. Late presentation may be important to the individual but does it occur in significant numbers?

There have been a number of studies that have estimated the proportion of glaucoma patients that present with substantial visual field loss. Grant and Burke(5) calculated that one third of the patients who had become blind from glaucoma had done so before they had sought medical attention for their eyes. Elkington *et al*(13) gave a figure of 33% presenting late, the West of Ireland(14) study found 10% of those with glaucoma were severely visually impaired at first examination, while Sheldrick *et al*(15) had a figure of 20% in their study. The published evidence would seem to indicate that late presentation of glaucoma is an important and not uncommon risk factor for blindness. This study was an attempt to elucidate the risk factors for this late presentation.

It was suggested in our pilot study that whether an individual presents late in the course of their glaucoma is likely to be a function of the rapidity of their visual field deterioration and the frequency of their sight tests[16]. An individual with a rapid decline could lose significant field even with two yearly sight tests - unless tested during an early, but detectable phase of the disease. Conversely, an individual with a slowly declining field but who does not attend for sight testing for some years (or does not have a glaucoma examination during their sight tests) is at risk of late presentation for a different reason. The pilot study did find evidence to support this, but the findings were limited by the retrospective nature of the data collection. Do the results of this present study support the results of the pilot study?

Consistent with our earlier pilot study, these data provide strong evidence ($p < 0.05$) of an association between maximum IOP at presentation and the odds of late presentation. There is evidence in the literature that higher IOP's lead to more rapid visual field loss (and thus increased likelihood of late presentation). David *et al*[17], Hart *et al*[18] and Armaly *et al*[19] all found more rapid visual field loss at higher levels of IOP. Jay and Murdoch[20] calculated that for pressures of 21 to 25 mmHg untreated disease was likely to progress from early field changes to end stage in around 14 years while for pressures over 30mmHg this interval was as short as 3 years.

Related to this are the results from the category of glaucoma diagnosis. *Tables 2* and *3* show that patients with Pseudoexfoliative glaucoma and chronic angle closure were in fact all cases (giving infinite odds ratios). As these conditions are usually associated with higher IOP's than POAG this is a further indication that those with higher IOP's are more likely to present late.

Our results support the concept that those expected to have had a rapid visual field decline (i.e. those with higher presenting IOP's) are at risk of presenting with advanced visual field loss. Are the results also consistent with the alternative reason for patients presenting late - that of infrequent sight testing?

In the UK, the optometrist plays a pivotal role in glaucoma detection. One study showed that 90% of glaucoma patients are referred to hospital on the basis of abnormal findings by an optometrist (15). Our results estimate that a patient who has *not* been correctly referred to the hospital by an optometrist was four and a half times more likely to be a late presenter than a comparable patient who was. This result is very similar to that found in the pilot study(16).

Referral source appears to be an important factor in early presentation -with patients referred from optometrists with a diagnosis of glaucoma more likely to be in the earlier stages of the disease. This suggests one of two things -that late presenters attend optometrists who do not test for glaucoma, or more probably, late presenters are people who tend not to go for regular sight tests.

The evidence for the latter interpretation is the finding that the risk of late presentation is proportional to the number of years since the patient last visited an optometrist with an adjusted OR per year of 1.25 [1.10,1.42]. Thus those who attend for regular sight tests are more likely to present in the early stages of glaucoma. Although this may seem self evident, there is little published evidence with regard to the protective effect of regular sight testing

These results do lend weight to the concept that those who do not have regular sight tests are at greater risk of late presentation. However the results contain a number of potential confounders.

Socioeconomic status (as measured by occupational categories) was shown to be strongly associated with the risk of late presentation with those of highest SES estimated to be at lowest risk of presenting late. Corroborating evidence for this comes from *The General Household Survey (GHS): Analysis of Ophthalmic data 1990-91 to 1993-94* which was published in July 1995[21]. This was a nationwide survey of private households in the UK, with a sample size of between 23,000 and 24,000 people per year. In the years noted above, questions were included on use of spectacles, contact lenses and attendance for sight testing. The GHS data indicate that the highest percentage of those who attended for regular sight testing were in occupational groups I and II with the lowest in group IV and V and this is consistent with our figures which indicate a lower risk of late presentation in these groups.

It has long been known that socioeconomic factors influence the access to adequate medical care as well as patient compliance with treatment [22] and this extends to screening services. Loehrer *et al*[23] found that late presentation of various cancers was directly related to lower socioeconomic status. They felt this was due to both risk promoting lifestyles and beliefs about cancer based on incomplete or erroneous information. Other studies have confirmed the link between later presentation of cancers and social deprivation including breast[24], colorectal [25] and skin[26]. It has also been shown that lower socioeconomic class is associated with poor uptake of screening services in mammography[27] and cervical smears [27].

As far as eye disease is concerned, Smith *et al*[28], looked at the relationship between social deprivation and age at presentation of amblyopia. They found that the more deprived children were much more likely to present late with anisometropic amblyopia. The Baltimore Eye Study(BES) looked at Socioeconomic Status and Visual Impairment Among Urban Americans[29] and they found that lower status was associated with higher rates of visual impairment.

The finding in this present study that higher SES was associated with a reduced risk of late presentation is largely but not completely explained by differences in sight testing rates. Even when sight testing is adjusted for, as in *Table 3*, the difference in SES remains, indicating there may well be other differences between the groups.

Family history of glaucoma was also found to be an important determinant of stage of presentation. Those who reported a family history were one third as likely to present late as those who did not and the more members of the family with glaucoma the more likely the patient was to present early. The reason for this result is may be two fold -firstly those with a positive FH are more likely to appreciate the need for regular sight testing passed on from other members of the family. Secondly, in the UK, all first degree relatives of glaucoma sufferers are encouraged to have regular sight tests by providing free sight test provided by the NHS.

Individuals of African Caribbean origin were found, in the univariate model, to have a much greater risk of late presentation than Caucasians -a result consistent with the pilot study. However this risk was not statistically significant after adjustment. As described in the results section, this appears to be related to a lower attendance for sight testing in the African Caribbean subjects.

While there is no evidence that there was any statistical difference between the IOP of African Caribbean's and Caucasians -this does not rule out a faster rate of visual field loss. Lower

socioeconomic status, which is an important confounder, shows some correlation with ethnic origin and is probably a further reason for a lower rate of sight testing (and therefore late presentation).

Wilensky *et al*[30] suggest that African Americans, because of socio-economic reasons, do not seek medical care until their glaucoma is more advanced -although they present no evidence to support this. There is, however, evidence that, compared to age matched white patients, black patients present later in the course of certain diseases -including prostate cancer [31,32], breast cancer [33] and colorectal cancer [34]. Similarly, there is evidence that African-American populations utilise health screening services less than white patients [35]. Wells and Horm[33] showed that the racial differences of stage at presentation disappeared if socio-economic class was accounted. Similarly, the BES identified an association between race and blindness which was reduced, but not eliminated, after adjustment for socioeconomic factors [29].

The results from this present study would seem to indicate that poor uptake of sight testing is an important risk factor for African Caribbean patients presenting to the HES with advanced glaucomatous field loss.

Our pilot study(16) found a strong, linear relationship of increasing age and increasing risk of late presentation. This is un surprising as prevalence and incidence of glaucoma increase with age, while the GHS indicated a reduction in the likelihood of sight testing in those over the age of 65 in the UK. Although not statistically significant, the results of this present study do show a general trend of increasing risk of late presentation with age with or without adjustment.

The pilot study also indicated that men were more likely to present late than women. Although there is a small protective effect for women in the present study this is lost after adjustment, and again, is not statistically significant.

Patients who gave a history of concurrent medical problems (the assumption being that they had an increased involvement with medical services and thus were more likely to be tested for glaucoma) were not found to present with earlier glaucoma than those who did not report any problems.

There are a number of potential biases in this study. Recall bias could be problem with regard to the data on previous sight test - this information is related to the optometrist visit *prior* to the visit that resulted in referral (if the patient had been referred from an optometrist) - which may have been some time before-hand. This bias is however, reduced because the subjects recruited were unaware of their own case/control status.

It is important to note that the data regarding IOP are one-off measurements on first examination in the HES and, with later regression to the mean, the individual IOP's could be different in subsequent examinations - although this is less likely to affect the overall median IOP. The nature of this study required that patients were recruited at initial presentation and this means prolonged follow-up of the patients has not yet occurred - for this reason, the findings regarding the normal tension glaucoma group (Table 3) should be interpreted with caution as some of the patients may have converted to POAG after longer follow-up or phasing .

Using three different sites in the study to recruit patients is unlikely to have introduced any bias into the results as the patients were chosen with standard criteria shown above. Using three geographically distinct centres (and using equal numbers of cases and controls from each centre) reduces the probability that the results are due to one unrepresentative centre.

In conclusion, published evidence indicates that late presentation of glaucoma appears to be associated with risk of subsequent blindness. This study has found that the risk factors for late presentation itself are higher IOP, infrequent attendance for sight testing and lower socioeconomic status. Conversely, a positive family history is likely to be associated with earlier presentation.

Appendix

The current system for glaucoma detection in the UK relies almost exclusively with optometrists in private practice. A patient requiring a sight test will attend an optometrist who will, if he suspects glaucoma, refer the patient to their General Medical Practitioner (GP)with the intention of onward referral to an ophthalmologist in the Hospital Eye Service(HES). Although an optometrist cannot refer a patient directly to the HES, the GP may. It is very rare for the GP to have the expertise or equipment to examine for glaucoma which is the reason the vast majority of referrals originate with the optometrist.

Participating centres in this study:- Moorfields Eye Hospital, London. Sunderland Eye Hospital, Sunderland. Harold Wood Hospital, Essex.

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Table 1 : Standard Occupational Categories

I	Professional occupations
II	Managerial and Technical occupations
IIIN	Skilled occupations - manual
IIIM	Skilled occupations - non-manual
IV	Partly skilled occupations
V	Unskilled occupations

Table 2: Study factors by case control status

Study Factor		Controls n1	Cases n2	OR	95 % CI
Age	<= 40	8	9	1	
	41 - 50	16	6	0.33	(0.09, 1.27)
	51 - 60	26	7	0.24	(0.07, 0.85)
	61 - 70	27	27	0.89	(0.30, 2.65)
	71 - 80	29	47	1.44	(0.50, 4.15)
	81 - 90	4	14	3.11	(0.72, 13.44)
	Median	63(52,71)	72 (63,78)		
Sex	Male	54	60	1	
	Female	56	50	0.8	(0.47, 1.36)
Ethnicity	Caucasian	98	73	1	
	African Caribbean	6	29	6.49	(2.56, 16.44)
	Asian	6	8	1.79	(0.60, 5.38)
Occupational Group	I	5	0	0	(0.00, 0.26)
	II	27	1	0.01	(0.00, 0.08)
	III	56	42	0.20	(0.09, 0.44)
	IV	12	29	0.64	(0.24, 1.67)
	V	10	38	1	
Type of Glaucoma	POAG	83	72	1	-
	PXF	0	15	∞	(4.98, ∞)
	Normal Tension	21	6	0.33	(0.13, 0.87)
	Aphakic	0	2	∞	(0.32, ∞)
	Pigmentary	4	1	0.29	(0.03, 2.67)
	Traumatic	1	2	2..33	(0.21, 26.27)
	Chronic Angle Closure	0	13	∞	(4.25, ∞)
IOP median (IQR)	right eye	22.5 (20, 26)	27 (22, 35)		
	left eye	23 (20, 26)	28 (23, 34)		
	max IOP	25 (22, 27)	30 (25,38)	1.17	(1.11, 1.24)
Medical problems	Hypertension	18	21		
	Diabetes mellitus	5	4		
	CVA	1	4		
	Ischaemic Heart Disease	1	2		
	Hypertension & Diabetes	1	3		
	Respiratory diseases	5	7		
	Thyroid	4	7		
	Nil significant	75	62		
Combining	No			1	
	Yes			1.43	(0.82, 2.49)
Family History of Glaucoma	No	62	93	1	
	Second Degree Relative	9	5	0.36	(0.12, 1.13)
	First Degree Relative	23	8	0.23	(0.09, 0.54)
	More Than One First Degree Relative	16	4	0.16	(0.05, 0.51)
	Any Family History (combining last three categories)			0.23	(0.12, 0.44)
Referral Source	Optometrists with correct diagnosis	100	63	1	
	Other	10	47	7.46	(3.52, 15.82)
Last visit to optometrist (years)before referral	1	27	12		
	2	45	23		
	3	16	10		
	5	12	15		
	6	0	1		
	10	5	23		
	> 10 or never	5	26		
Last visit to optometrist (years) before referral				1.29	(1.18, 1.41)

Table 3: Estimates of the effect of each study factor on late presentation

Study Factor		adj OR*	95 % CI
Age	<= 40		
	41 - 50	0.79	(0.09, 6.99)
	51 - 60	0.15	(0.02, 1.25)
	61 - 70	1.01	(0.15, 6.90)
	71 - 80	1.82	(0.30, 11.06)
	81 - 90	2.97	(0.30, 29.35)
Sex	Male	1	
	Female	1.23	(0.53, 2.85)
Ethnicity	Caucasian	1	
	African Caribbean	2.47	(0.63, 9.72)
	Asian	0.81	(0.12, 5.67)
OccupationalGroup	I	0	-
	II	0.02	(0.00, 0.16)
	III	0.27	(0.10, 0.80)
	IV	0.95	(0.26, 3.46)
	V	1	
Type of Glaucoma	POAG	1	-
	PXF	-	-
	NTG	3.04	(0.63, 14.70)
	Aphakic	-	-
	Pigmentary	1.55	(0.03, 85.12)
	Traumatic	0.18	(0.00, > 200)
	Chronic Angle Closure	-	-
Maximum IOP		1.20	(1.11, 1.28)
Medical Problems	No	1	
	Yes	1.01	(0.43, 2.35)
Family History of Glaucoma	No		
	Second Degree Relative		
	First Degree Relative		
	> 1 First Degree Relative		
	Yes (combining last 3 above)	0.29	(0.12, 0.74)
Referral Source	Optometrists & correct diagnosis	1	
	Other	4.53	(1.52, 13.48)
Last visit to optometrist (years) before referral		1.25	(1.10, 1.42)

* adjustment made for occupational group , maximum iop, family history, referral source and number of years before last visit to optometrist

Appendix 6.

DEPRIVATION AND LATE PRESENTATION OF GLAUCOMA.

Objectives. To identify socioeconomic risk factors for first presenting to an NHS ophthalmologist with advanced glaucomatous visual field loss by comparing with a group who present with early loss.
Design. Hospital-based case-control study with prospective identification of cases and controls.
Setting. Three Hospital Eye Departments in England.
Subjects. Consecutive patients newly diagnosed with glaucoma (n=220). Cases were those presenting with advanced glaucoma (n=110), controls were those with early glaucoma (n=110). Patients with a previous history of ocular hypertension or any documented suspicion of glaucoma (within the Hospital Eye Service) were excluded.
Results. Median underprivileged area scores were higher in cases (29.5.{Interquartile range 9.0, 42.2}) than controls (21.3 {6.1, 37.4}) p=0.035. Cases were more likely than controls to be of lower Occupational class (age and referral centre adjusted Odds Ratio compared with Group I/II, for Group III 20.1 {95% CI 2.6, 155} for Group IV/V 86.0 {11.0, 674}), to be without access to a car (adjusted OR 2.2. {1.2, 4.0}), to have left full time education at age 14 or less (adjusted OR 7.5 {2.3, 24.7}), and to be tenants rather than owner-occupiers (adjusted OR for local authority tenants 3.2 {1.7, 5.8}, private tenants 2.1 {0.7, 5.8}). The effects of deprivation were partly accounted for by self-report of family history of glaucoma and time since last visit to an optometrist and lack of an initial diagnosis of glaucoma by an optometrist.
Conclusions. Area and individual level deprivation were both strongly associated with late presentation of glaucoma. Existing evidence shows that late presentation is an important risk factor for subsequent blindness. Deprived groups thus appear to be at greater risk of going blind from glaucoma. Deprivation may be associated with more aggressive disease as well as later presentation to the Eye Service.

Introduction

Glaucoma is a disease with major public health significance accounts for 13% of all new blind registrations annually [1]. It affects approximately 2% of Europeans aged 40 or more and some four times this proportion in African Americans and African Caribbean's [2]. The European and North American populations are ageing, and as glaucoma prevalence is strongly linked with age [3,4], the number of persons blinded by the disease is set to increase.

End-stage glaucoma causes a particularly profound and irreversible visual loss, but population studies show that only 50% of glaucoma sufferers are diagnosed and treated at any one time [5].

Late presentation, when visual field loss threatens central vision, is an important risk factor for glaucoma related blindness [6]. Research into determinants of presenting with advanced glaucoma is scarce and therefore this case-control study was designed to determine both social and demographic risk factors as well as ocular and biological factors (presented elsewhere[7]). This paper reports on the role of area deprivation and several measures of socioeconomic status in the stage of presentation of glaucoma in the Hospital Eye Service. A link between deprivation and advanced glaucomatous visual field loss at first presentation would provide evidence for systematic inequity of access to effective hospital care [8].

Method

A prospective hospital-based case-control study with recruitment at three independent Eye Departments in England (Moorfields Eye Hospital, London; Sunderland Eye Hospital, Sunderland; Harold Wood Hospital, Essex) was conducted between September 1996 and May 1997. Patients were eligible for study if they were diagnosed with glaucoma according to the case/control criteria described below when *first examined* by an ophthalmologist. Those with a previous definite or possible diagnosis of glaucoma or ocular hypertension were not eligible. The optic disc criteria were shown, by pilot study, to be good indicators of disease severity [9]. Intraocular pressure was obtained from the standard Goldman tonometer reading at initial examination.

A sample size calculation showed that 110 cases and 110 controls were required to provide 80% power to detect a doubling in the odds of late presentation in a factor present among 10% of controls at the 5% level of statistical significance (two tailed test).

The study was conducted prospectively, to reduce selection and recall bias, by recruitment after the first of two visual field tests and this gave a consecutive series of cases and controls. After patients gave their informed consent they were telephoned by a trained interviewer masked to their case/control status. The interviewer validated demographic data and asked a series of standard questions regarding socioeconomic status (occupational class, car access and housing tenure),

educational level (age at leaving full time education), ethnic origin (White European, African/African-Caribbean and Asian), use of general medical services, and attendance and use of sight testing (optometric) services. There were no losses to follow up.

The referral of the majority of glaucoma patients to the Hospital Eye Service in the UK is initiated by optometrists. Optometrists refer the patient to their General Practitioner who then refers them to the Hospital Eye Service. Review of referral letters with telephone confirmation identified two principal referral sources: from an optometrist with, or without, a diagnosis of possible or probable glaucoma, or from the GP directly without an optometrist's referral and therefore without a diagnosis of glaucoma.

Case-control criteria:-

CASES

1. Visual field loss consistent with a pattern of glaucomatous loss e.g. arcuate scotomas, residual temporal island, compatible with the patients disc changes and in which there was no suggestion of other optic nerve pathology (e.g. defects crossed the horizontal mid-line), within five degrees of fixation and beyond 30 degrees in one or both eyes.
2. Glaucoma of any chronic type i.e. primary open angle, pseudoexfoliative, normal tension, chronic angle closure, aphakic or pigment dispersion.
3. Two consecutive fields (threshold or suprathreshold) confirming the loss except where field loss was so advanced that field testing was not possible.
4. The cup disc ratio was assessed as being greater than 0.8 in the eye(s) with the field loss.

CONTROLS

1.Visual field loss consistent with a pattern of glaucomatous loss, compatible with the patients disc changes and in which there was no suggestion of other optic nerve pathology (e.g. defects crossed the horizontal mid-line), but no absolute scotomas within 20 degrees of fixation in either eye.
2. Glaucoma of any chronic type as above.
3. Two consecutive fields (threshold or suprathreshold) confirming the loss.
4. The cup disc ratio was assessed as being greater than 0.5 or there was a difference of greater than 0.2 between the discs.

Patients were excluded who had problems performing the visual field test, defined as more than one third fixation losses, false positives, or false negatives on Visual field analysis.

Deprivation measures

Jarman's Underprivileged Area (UPA) score was used to index area deprivation [10]. The score is based on GP derived weightings of the effects of eight census variables on workload in primary care. The variables (GP ratings in brackets) are Ward percentages of households with: elderly living alone(6.62), one-parent families (3.01), children under 5 (4.64), social class V (3.74), unemployed (3.34), overcrowded households (2.88), moved house within year (2.68), born in Commonwealth (2.50). The UPA score is calculated by linking individual post-codes with census data.

Four factors were used to measure individual deprivation [11]: occupational class, housing tenure, access to a car and living alone. The Standard Occupational Classification (SOC) assigns job titles to one of six categories [12]. Occupational categories are: I Professional, II Managerial and technical, IIIN Skilled non-manual, IIIM Skilled manual, IV Partly skilled manual, V Unskilled manual. Retired, unemployed or long term sick participants were assigned by their previous main occupation. Married women outside the labour market were classified to their husbands' occupation. Participants were combined into three groups: I/II, III, IV/V.
Housing tenure was classified in three groups: owner-occupier, private tenant and local authority tenant. In this study access to a car is not likely to be confounded by fitness to drive since all participants were newly diagnosed at entry.

Statistical analyses

The effect of each socioeconomic factor on the likelihood of presenting with advanced glaucomatous field damage was estimated with unconditional logistic regression using Stata [11]. We previously showed that late presentation was associated with: referral type (not referred by an optometrist with a diagnosis of possible/probable glaucoma), family history (protective), and time since last visit to an optometrist [7]. These factors were treated as covariates in this analysis.

Results

Table 1 summarises demographic and glaucoma-related characteristics of the study sample. Table 2 presents socioeconomic characteristics by case-control status. The Jarman score is presented as median (interquartile range), the higher the score, the greater the area deprivation. The majority of participants were in SOC group III. Just over a third lived alone and just over half had access to a car.

Most participants left full time education aged 14. Half were owner-occupiers, and 41% were in council housing.

Table 3 shows the age-adjusted odds of late presentation for each deprivation measure before and after three adjustments. Lower socioeconomic status and education level is linked with late presentation, though for UPA score this relation is weak. Living alone was not a risk factor. Additional adjustment for Hospital in the age-adjusted models had a negligible effect on the Odds Ratio therefore the age-adjusted models are not shown. Precision of the risk estimates for occupational status is poor because there is only one case in Group I/II. Ethnicity, added to model II, accounted for about a quarter of the log odds of late presentation associated with education level and council tenancy. Taking account of family history of glaucoma, time since last attending an optometrist and referral source further reduces the odds of late presentation although that associated with occupational group remained significant.

Discussion

This study provides strong evidence for an association between lower socioeconomic status and late presentation of glaucoma. Those who presented with more advanced field loss had higher UPA scores, lower occupational status, lower education level, were less likely to have access to a car, and were more likely to be tenants. As in cancer, presenting with advanced glaucoma is associated with a poor prognosis[6,14,15].

The inverse association between socioeconomic status and late presentation can be interpreted in two ways. First, socially patterned differences in health seeking behaviour are likely to operate. This was so for the reported use of optometry services in the General Household Survey (1991-1994) [16]. Regular sight testing was associated with higher social class and in this present study greatly reduced the risk of presenting late.

Second, long term deprivation may lead to more rapidly progressive and aggressive disease. The links between raised cortisol, ocular hypertension and glaucoma[17] provide some support for a psychosocial mechanism mediated by altered hypothalamic-pituitary-adrenal function[18]. Thus the possible "length bias" which could be an important determinant of both case and control status might be driven by pathological mechanisms linked to social status.

We have previously reported a strong association between African-Caribbean ethnic origin and late presentation [7]. The Baltimore Eye Study showed African Americans to be at significantly increased risk of visual impairment [19] but, in our study sample, ethnic origin did not account for the excess of cases in the lower occupational groups (table 3).

Our study adds to the sparse evidence that low social position is linked with increased risk of chronic eye disease and extends it to include glaucoma. It has been shown previously late presentation with amblyopia in childhood is linked with deprivation [20], and that adult urban Americans of lower social status have higher rates of visual impairment [19]. Further, lower socioeconomic class is associated with poor uptake of mammography and cervical screening [21] and social deprivation has been linked to later presentation of cancers including breast[22], colorectal [23] and skin[24].

Early detection of glaucoma is clearly desirable but the means to achieve this on a population basis remains problematic. Not only is there a lack of a single adequate screening tool (currently an NHS Technology Assessment research priority) but it is not clear how the test can be delivered to those most in need[25]. Optometrists are encouraged by their Council to perform diagnostic testing for glaucoma on all who present for routine sight testing over the age of forty. This places a strain on both optometrists and the Hospital Eye Service as a result of false positive referrals[26]. A final problem, the lack of good evidence for the effectiveness of lowering intraocular pressure, is being dealt with in Sweden (Early manifest Glaucoma Trial, www.nei.nih.gov).

This hospital based case-control study is valid because it analyses factors for late presentation to hospital. A weakness of our study is that it only addresses access to the NHS. There is only one case from SOC I/II which might indicate that those from higher social groups with advanced disease may seek private health care. We cannot know the extent to which this selection bias lead to an over-estimation of the effect of individual social deprivation. The fact that there were 33 controls from the higher social strata suggests that this source of bias is unlikely to be serious.

To our knowledge, this study is the first to report that hose with the least material and psychosocial resources to cope with blindness are at substantially higher risk of glaucomatous visual loss. Equity of access to effective health care is an enduring principle of the NHS [27]. Our results suggest that glaucoma should be included among conditions targeted in policy aimed at reducing social inequalities in health.

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Table 1: Demographic characteristics of the study sample

Study factor		patients % of total
Age (years)	<= 40	8
	41 – 50	10
	51 – 60	15
	61 – 70	25
	71 – 80	35
	81 – 90	8
	Median (IQR)	67 (55, 75)
Sex	Male	52
	Female	48
Ethnicity	White	78
	African Caribbean	16
	Asian	6
IOP median (IQR)	right eye	24 (22,30)
	left eye	25 (22,30)
	max	26 (23, 31.5)
Family History of Glaucoma	No	71
	Second Degree Relative	6
	First Degree Relative	14
	More Than One First Degree Relative	9
Referral Source	Optometrists with correct diagnosis	74
	Other	26
Last visit to optometrist before referral (years)	1	18
	2	31
	3	12
	5	12
	6	1
	10	13
	> 10 or never	14

IQR=interquartile range

Table 2: Socio-economic characteristics by case:control status

Study Factor		Controls	Cases	% of total
UPA score	median (IQ range)	21.3 (6.1, 37.4)	29.5 (9.0, 42.2)	
Live alone?	Yes	40	40	36
	No	70	70	64
Access to car?	Yes	73	48	55
	No	37	62	45
Occupational Group	I	5	0	2
	II	27	1	13
	III	56	42	45
	IV	12	29	19
	V	10	38	22
Age when leaving full-time education (years)	<=12	4	17	6
	13	0	1	1
	14	45	69	52
	15	18	5	10
	16	21	13	15
	17	2	1	1
	18	19	4	10
	>18	1	0	1
Housing tenure	Owner	70	41	51
	Private rental	8	10	8
	LA rental	32	59	41

Table 3: Unadjusted and adjusted estimates of the effects of socio-economic factors on the risk of late presentation

				Model I		Model II		Model III	
Study Factor		Odds Ratio	95% Confidence Interval	OR	95% CI	OR	95% CI	OR	95% CI
UPA	per ten unit increase	1.16	(1.01, 1.33)	1.02	(1.01, 1.04)	1.01	(1.0, 1.03)	1.01	(0.99, 1.03)
Live alone?	Yes	1							
	No	1.00	(0.58, 1.73)	1.00	(0.56, 1.77)	1.03	(0.55, 1.94)	0.84	(0.41, 1.71))
Access to car?	Yes	1							
	No	2.55	(1.48, 4.40)	2.22	(1.24, 3.96)	1.58	(0.83, 3.00)	1.16	(0.56, 2.40)
Occupational Group	I & II	1							
(baseline, gp V)	III	24.0	(3.15, 183)	20.1	(2.60, 155)	35.0	(3.56,	27.2	(2.92, 253)
	IV & V	97.5	(12.6, 755)	86.0	(11.0, 673)	103	344) (10.5, 1027)	73.4	(7.67, 703)
Age when leaving	>= 14	1							
full-time education	< 14	5.18	(1.69, 15.87)	7.47	(2.26, 24.7)	4.39	(1.01, 19.0)	3.20	(0.58, 17.7)
Housing tenure	Owner	1							
	Private rental	2.13	(0.78, 5.84)	2.06	(0.73, 5.83)	2.16	(0.69,	1.32	(0.38, 4.63)
	LA rental	3.15	(1.77, 5.61)	3.16	(1.73, 5.77)	2.44	6.79) (1.27, 4.71)	1.58	(0.75, 3.30)

Model 1 = adjusted for age and centre
Model II - adjusted for age, centre and ethnicity
Model III = adjusted for age, centre, ethnicity, family history of glaucoma and time since last visit to an optometrist