

INVESTIGATION OF RISK FACTORS THAT PRECEDE
PRIMARY OPEN ANGLE GLACOMA.

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ABSTRACT

Primary open angle glaucoma (POAG) is characterized by progressive degeneration of the retinal ganglion cells, resulting in optic nerve atrophy with visual field defects. The biological basis of POAG is not fully understood.

This thesis covers two studies. The aims for Study 1 were to investigate the risk factors of glaucoma in a population aged 18 years to 40 years. These were investigated by a retrospective study of intraocular pressure measurements and optic nerve assessments (cup to disc ratio) in two groups. One group had a family history of glaucoma and a second group was without a family history of glaucoma. The aims for Study 2 were to investigate whether the risk factors for primary open angle glaucoma were present many years before glaucoma develops. These were investigated with a retrospective review of intraocular pressure measurements and optic nerve measurements in participants who subsequently developed primary open angle glaucoma.

Each study collected anonymised retrospective data from community optometry clinics for extraction and analysis of data on intraocular pressure measurements and optic nerve assessments. Study 1 collected one data entry per case. Study 2 collected ten years of historical data from each clinical visit from clinical records of participants prior to their diagnosis/treatment of glaucoma. This data spanned 33 years. For each glaucoma record, data for a similar period were obtained from a case-matched control record.

The results for Study 1 are that mean intraocular pressure measurements and optic nerve head assessments in young adults aged between 18 years and 40 years did not differ significantly in cases with a family history of glaucoma compared with a group without. For Study 2, the correlations of intraocular pressure and optic nerve cup to disc ratio indicate an increase in values over a 10-year duration for cases that subsequently developed glaucoma as compared to case-matched controls. Analyses conducted at 5 and 10-year time points for mean intraocular pressure and median optic nerve cup to disc ratios prior to POAG diagnosis were statistically significantly different ($p < 0.05$). Visual field data were

collected for all the cases and descriptive data showed that pre-diagnosed cases had more reported suspicious visual field defects.

The principle findings of this thesis are that there are pre-glaucomatous changes up to ten years before glaucoma diagnosis and that this may have considerable relevance for models of glaucoma aetiology. It also highlights the important role that community optometrists play in guarding the borders between pre-glaucoma and glaucoma.

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LIST OF TERMS

Anterior Chamber Angle	The anterior chamber angle is the junction formed by the scleral-corneal junction, the ciliary body and the peripheral iris (Leung & Weinreb 2011).
Aqueous Humour	Clear, colourless fluid that fills the anterior and posterior chambers of the eye. It contributes to the maintenance of the intraocular pressure. It is formed in the ciliary processes, flows into the posterior chamber, then through the pupil into the anterior chamber and leaves the eye through the trabecular meshwork passing to the canal of Schlemm (Millodot & Laby 2002).
Angle Closure Glaucoma	See Glaucoma.
Glaucoma	“The term glaucoma encompasses a number of diseases in which there is a progressive loss of retinal ganglion cells (RGC) with corresponding visual field loss that results in a characteristic “cupped” appearance in the optic nerve head. Glaucoma results in an irreversible loss of visual field, usually starting in the periphery, and sometimes affecting the central visual field first, but leading to varying degrees of visual disability and, in a small but significant proportion of patients, blindness” (Barton & Hitchings 2013).
Hypermetropia	Hypermetropia is a refractive condition in which images of distant objects are focused in behind the retina; thus, vision is blurred (Millodot & Laby 2002).
Intraocular Pressure	The internal pressure of the fluid contained within the eye (NICE 2017).
Lamina Cribrosa	Where axons of retinal nerve cells exit to form the optic nerve (Tan et al. 2018).
Myopia	Myopia is a refractive condition in which images of distant objects are focused in front of the retina; thus, distance vision is blurred (Millodot & Laby 2002).
Normal Tension Glaucoma (NTG)	In NTG, IOP is below 21.0mmHg, yet has an open anterior chamber and there are glaucomatous optic nerve changes and visual field defects. (Shields 2008).
Ocular Hypertension (OHT)	Elevated IOP (greater than 21.0mmHg) in one or both eyes in the absence of clinical evidence of optic nerve damage, visual field defect or other pathology (College of Optometrists 2016).
Open Angle Glaucoma (OAG)	See Glaucoma.
Ophthalmologist	A medical doctor with specialist qualification in conditions that affect the eye and orbit, including diagnosis, management and surgery.
Ophthalmoscopy	A technique to describe examination of the optic nerve, retinal, ocular media using an ophthalmoscope or with slit lamp bio-microscopy.
Optical Coherence Tomography	Device that uses the principle of low-coherence interferometry to produce cross sectional images of ocular tissues (Fujimoto et al. 1995).

Optometrist	A healthcare professional with specialist training and expertise in conditions of the eye, especially measurement of vision and refractive error, prescription and dispensing of spectacles and contact lenses.
Pre-Perimetric Glaucoma	Glaucomatous optic nerve changes and/or nerve fibre layer defect, with no visual field defect caused by glaucoma. (Sawada et al. 2017)
Primary Closed Angle Glaucoma	Primary closed angle glaucoma is defined as an occludable drainage angle and features indicating that trabecular obstruction by the peripheral iris has occurred (European Glaucoma Society 2017).
Primary Open-Angle Glaucomas	Primary open-angle glaucoma (POAG) is a chronic progressive optic neuropathy with characteristic morphological changes at the optic nerve head and retinal nerve fibre layer in the absence of other ocular disease or congenital anomalies. Progressive retinal ganglion cell death and visual field loss are associated with these changes (European Glaucoma Society 2017).
Secondary Glaucoma	Secondary glaucomas are a heterogeneous group of conditions, in which elevated IOP is the leading pathological factor causing glaucomatous optic neuropathy. Most forms of secondary glaucoma like uveitic or traumatic glaucoma have complex pathomechanisms including both an open or closed angle (European Glaucoma Society 2017)
Slit Lamp Bio-Microscope	A microscope that projects a narrow beam of light that allows examination of the structures of the eye (Walters 2006).
Tonometry	A test to measure intraocular pressure using an instrument called a tonometer (NICE 2017).
Van Herick Method	A non-contact approach for estimating angle width using the slit-lamp beam to compare the depth of the peripheral anterior chamber depth to the thickness of the cornea (Van Herick et al. 1969).
Visual Field	The extent of space in which objects are visible to an eye in a given position (Millodot & Laby 2002).

LIST OF ABBREVIATIONS

ACA	Anterior Chamber Angle
AH	Aqueous Humour
BMC	Slit lamp biomicroscopy
CC	Case-matched control
CI	Confidence Interval
COAG	Chronic Open Angle Glaucoma
CVF	Computerised Visual Field
GAT	Goldmann Applanation Tonometry
HES	Hospital Eye Services
ICO	Information Commissioner's Office
INSTRUM	Instrument
IOP	Intraocular Pressure
L IOP AV	Left Intraocular Pressure Average
L SER	Left Spherical Equivalent Refraction
LVA	Left Visual Acuity
NICE	National Institute for Health and Care Excellence
NHS	National Health Service
NTG	Normal Tension Glaucoma
OCT	Optical Coherence Tomography
OHT	Ocular Hypertension
ONH	Optic Nerve Head
ONHVL	Optic Nerve Head Vertical Left
ONHVR	Optic Nerve Head Vertical Right
OR	Odds Ratio
PG	Pre-diagnosis glaucoma
PPG	Pre-perimetric Glaucoma
POAG	Primary Open-Angle Glaucoma

R IOP AV	Right Intraocular Pressure Average
RGC	Retinal Ganglion Cells
RNFL	Retinal Nerve Fibre Layer
R SER	Right Spherical Equivalent Refraction
RVA	Right Visual Acuity
S.D	Standard Deviation
SPSS	Statistical Package for the Social Sciences
VH	Van Herick
VF	Visual Field

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1. INTRODUCTION

1.1 BACKGROUND

Primary open angle glaucoma (POAG) is characterized by progressive degeneration of the retinal ganglion cells, resulting in characteristic visual field defects, that reflect optic nerve atrophy, with a distinctive clinical appearance (Gemenetzi et al. 2012). A typical glaucomatous optic nerve will have localised nerve loss and generalised enlargement of the optic cup (European Glaucoma Society 2017). A diagnosis of POAG is a life-changing commitment for the patient and health service, and POAG has profound public health implications. It is a condition that contributes globally to severe visual impairment and blindness (Murray & Lopez 2013; WHO 2017).

The biological basis of POAG is not fully understood (Weinreb et al. 2014). Numerous studies have investigated the risk factors (Prum et al. 2016), which include elevated intraocular pressure, increasing age, family history, race and myopia (Hirani et al. 2012).

Guidelines on glaucoma diagnosis and management were introduced in 2009 and were re-issued in November 2017 by the National Institute of Clinical Excellence. (NICE 2017). The introduction of the NICE guidelines increased the absolute number of patients detected with glaucoma and has resulted in more patients being diagnosed with early disease (de Silva et al. 2013). Case-finding and referral for glaucoma is conducted mostly by optometrists (Lawrenson 2013).

The aims for this thesis are to provide information about intraocular pressure and optic disc cupping by comparing with control groups (a) a population at risk of glaucoma owing to family history (Study 1); and (b) a population who subsequently went on to develop glaucoma (Study 2).

This chapter will introduce the function of the eye and the structures of the eye which are pertinent to glaucoma. Following this, the chapter will review glaucoma, concentrating on POAG and the assessments which are used for its detection and management.

1.2 STRUCTURE AND FUNCTION OF THE EYE

A schematic diagram of the eye is shown in Figure 1.2-1. The diagram presents the structures of the eye that will be referred to in this thesis. A simple description of the function of the eye is to convert light to an electrical signal and all the preliminary image analysis in the retina (Tovee 1996). After light is captured by the eye, it is refracted (partially focussed) by the cornea and passes through an aperture called the pupil. There are chambers positioned anterior and posterior to the pupil. Each of these chambers contain aqueous humour (AH) (Section 1.2.4).

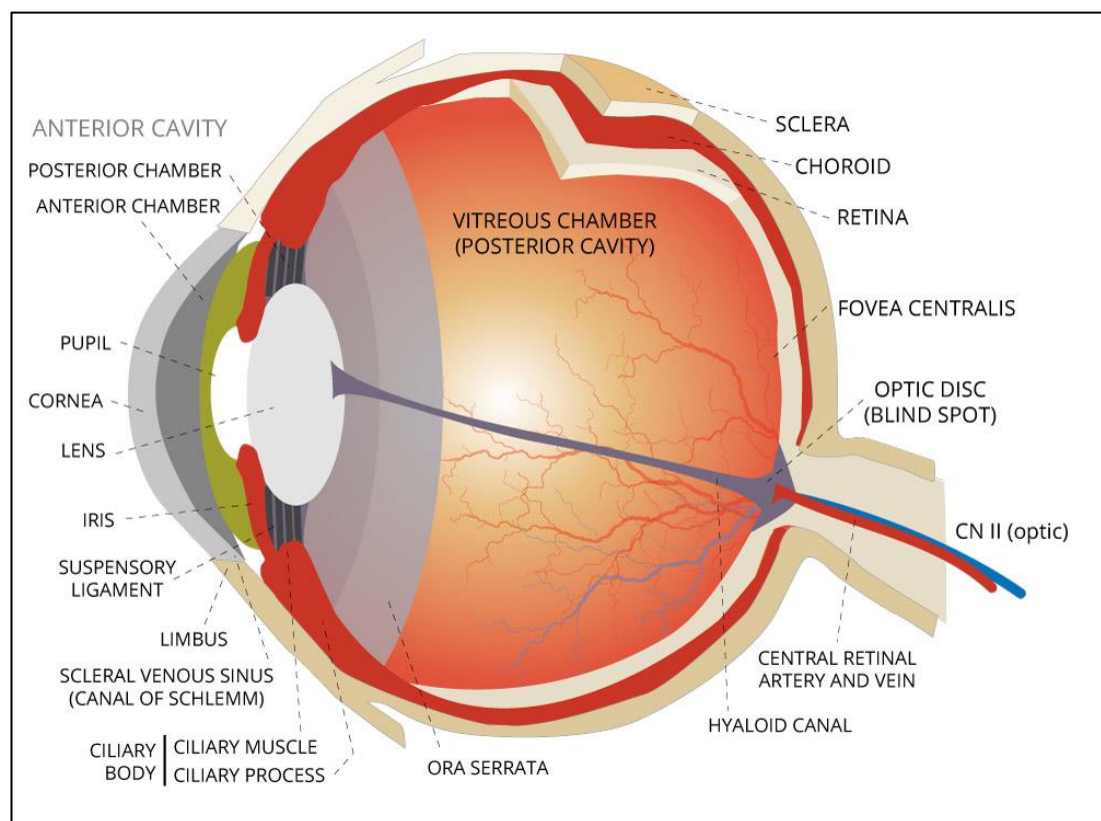


FIGURE 1.2-1 Illustration of the human eye (sagittal view).

The anterior chamber is the space between the iris and the cornea. The posterior chamber is the anatomical portion of the eye posterior to the iris and anterior to the lens and vitreous face. The largest component of the eye is the vitreous chamber, which makes up more than two-thirds of the volume of the eye (5-6 ml) and contains the vitreous gel (Murthy et al. 2014;

Stamer et al. 2008). Light passes through the vitreous before reaching the back of the eye. It is then transformed into a neural signal by specialised receptor cells at the retina. The retina is the photosensitive layer that contains neural elements that are involved in processing visual information (Field & Chichilnisky 2007). The neural signal is modified in the retina, before travelling onto the brain via the optic nerve (Tovee 1996; Nuschke et al. 2015; Heitmancik & Nickerson 2015).

The eyeball is composed of three concentric layers. The outermost layer consists anteriorly of the transparent cornea and the opaque sclera posteriorly. The cornea meets the sclera at a region known as the limbus or corneoscleral junction (Forrester et al. 2015). The cornea, together with the sclera forms a tough fibrous envelope that protects the ocular tissues (Forrester et al. 2015). The sclera becomes thin and sieve-like at an area called the lamina cribrosa. This is where the axons of retinal nerve cells exit to form the optic nerve (Tan et al. 2018).

The middle layer of the globe is called the uvea; it consists of the choroid, ciliary body and iris. The uvea is highly vascular and serves a nutritive and supportive function. The inner layer of the globe is the retina.

1.2.1 CORNEA

The cornea constitutes the main refractive element of the eye (Kamma-Lorger et al. 2010) and covers the anterior one sixth of the total surface area of the globe (Dawson et al. 2009). The sclera covers the remaining five sixths (Dawson et al. 2009). The cornea is composed of six layers: corneal epithelium, anterior limiting lamina, corneal stromal (substantia propia), Dua's layer, posterior limiting lamina (Descemet's membrane) and the corneal endothelium (Dua et al. 2013). The thickness of the central part of the cornea (central corneal thickness/CCT) has mean values between 427 to 620µm, with a maximal difference between eyes of 42µm (Wolfs et al. 1997).

1.2.2 LIMBUS

The limbus is the zone between the cornea and the sclera. This area contains the pathways for aqueous humour outflow (Section 1.2.4). The limbus also functions to maintain nourishment of the peripheral cornea and is a repository of stem cells (Michael Van Buskirk 1989).

1.2.3 ANTERIOR CHAMBER & ANTERIOR CHAMBER ANGLE (ACA)

In this section, the anterior chamber, the anterior chamber angle (ACA) and intraocular pressure will be described. These three components work in conjunction. Physical viewing of the anterior chamber will allow for its angle to be viewed simultaneously. The anterior chamber is anterior to the cornea and posterior to the iris diaphragm and the pupil (Figure 1.2-2). The anterior chamber angle consists of Schwalbe's line, Schlemm's canal and trabecular meshwork, scleral spur, anterior border of the ciliary body and the iris (Liu et al. 2011). The depth of the ACA can vary; it is deeper in those who do not have a natural lens (aphakia) or a replacement intraocular lens (pseudophakia). There is a relationship between refractive error and the depth of the ACA; being greater in those with eyes with a longer axial length of the eye (myopia) and shallower in those who have a smaller axial length (hypermetropia) (Liu 2008).

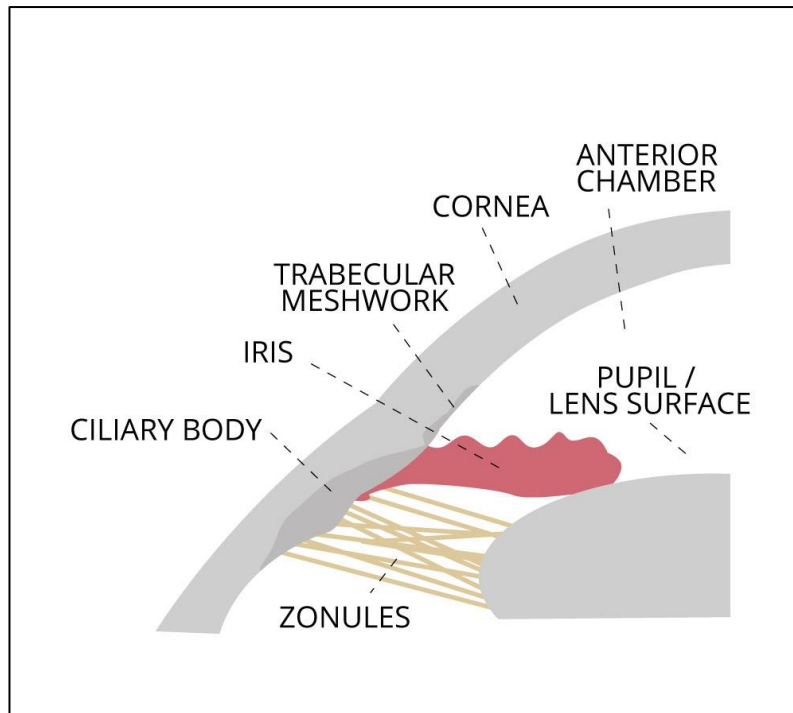


FIGURE 1.2-2 Positioning of the anterior chamber: it is situated anterior to the cornea and posterior to the iris diaphragm and the pupil.

1.2.4 AQUEOUS HUMOUR

Aqueous humour is a transparent fluid that circulates from the posterior to the anterior chamber of the eye. Its transparency allows for optical clarity (Stamer et al. 2008). The major components of AH are organic and inorganic ions, carbohydrates, glutathione, urea, amino acids and proteins, oxygen, carbon dioxide and water (Goel et al. 2010). The anterior and posterior chamber fluids are similar in chemical composition (Kinsey 1953).

The circulation of AH supplies nutrients and oxygen and removes metabolic wastes from the anterior intraocular tissues such as cornea, crystalline lens and trabecular meshwork. AH also facilitates the local immune responses during inflammation and infection (To et al. 2002; Wax et al. 2014). AH inflates the globe and creates an intraocular pressure (IOP) for normal optical functioning of the eye.

1.2.4.1 CILIARY EPITHELIUM

AH is secreted by the ciliary epithelium; this covers the surface of the ciliary body and has a non-pigmented side and a pigmented side (To et al. 2002). The inner layer abuts to the aqueous side or vitreous body (To et al. 2002).

Ion transporters are most commonly concerned with epithelial secretion and have been found to be more numerous at the anterior region (pars plicata) than the posterior region (pars plana) of the ciliary body (To et al. 2002). This suggests that the pars plicata is the primary site of AH formation (Ghosh et al. 1991).

Transport from the posterior chamber to the anterior chamber is uni-directional and achieved by three inter-dependent mechanisms (Civan & Macknight 2004). These processes are diffusion, ultrafiltration and active transport.

1.2.4.2 DIURNAL VARIATION

Diurnal variations have been observed with AH turnover rates, reflecting the pattern known as circadian rhythm. AH flow is normally about 3.0 μ l/min in the morning, 2.4 μ l/min in the afternoon, and drops to 1.5 μ l/min at night (Wilensky 1991). The fluid volume of the anterior chamber can be completely changed over a period of 100 min (Pascale et al. 2012).

1.2.4.3 AQUEOUS HUMOUR ABSORPTION/OUTFLOW

There are two outflows for AH from the eye: the conventional and non-conventional outflows (Figure 1.2-3). Each of these has a different physiological mechanism (Goel et al. 2010) and each shall be described in turn.

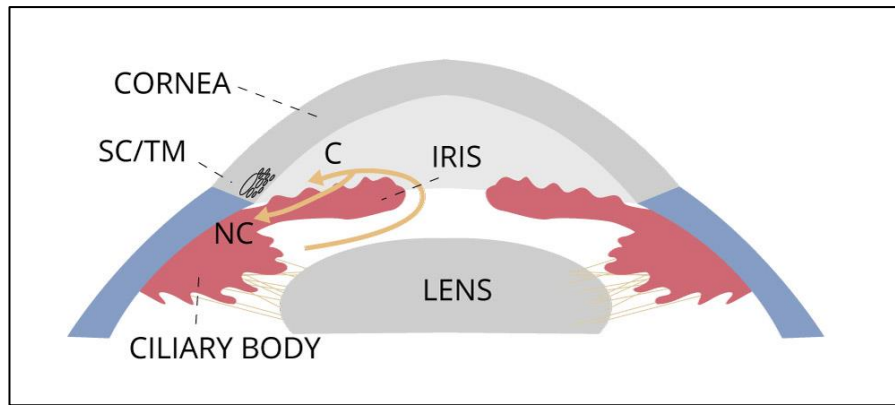


FIGURE 1.2-3 Aqueous humour is secreted by the ciliary body and moves through the pupil, around the iris. a pressure gradient directs it toward the SC lumen (red arrow). This is termed the conventional pathway (C). The non-conventional pathway (NC) involves the drainage of aqueous through the fibres of the ciliary body into the supraciliary and suprachoroidal spaces.

1.2.4.3.1 CONVENTIONAL ROUTE OF AQUEOUS HUMOUR OUTFLOW

The conventional route for AH outflow is pressure dependent and utilises the trabecular meshwork. The trabecular meshwork is an area of connective tissue located at the anterior chamber angle. It contains endothelium-lined spaces (intertrabecular spaces) through which AH passes to the Schlemm's canal (Millodot & Laby 2002). Schlemm's canal is in the form of a circular duct, in the deep part of the limbus (Dvorak-Theobald 1934) (Figure 1.2-3). Outflow from the trabecular meshwork has been described as a series of linear springs that allow Schlemm's canal to change with the proportion of AH filtering through (Johnson & Kamm 1983; Acott et al. 2014).

1.2.4.3.2 NON-CONVENTIONAL ROUTE OF AQUEOUS HUMOUR OUTFLOW

The non-conventional route is not pressure dependent but has been reported to be pressure insensitive rather than pressure independent (Johnson et al. 2017). This process uses uveoscleral outflow (Figure 1.2-3) (Alwaird & Longmuir 2008). Approximately 10% of AH outflow is thought to be via a non-conventional route, although this is an unclear determination (Pederson & Toris 1987). AH is said to enter connective tissue between the muscle bundles, through the suprachoroidal space, and out through the sclera (Ascher 1954; Bill & Hellsing 1965; Alm & Nilsson 2009).

1.3 INTRAOCULAR PRESSURE

The integrity of the eye and the structures that mediate vision are dependent on intraocular pressure (IOP) (Kelly & Farrell 2017). IOP is maintained primarily by change in the aqueous humour outflow resistance, which is located within the connective tissue (cribiform meshwork) of the trabecular meshwork and the inner wall of Schlemm's canal (Acott & Kelley 2008; Johnson 2006). Maepae and Bill (1992) showed that in monkey eyes, nearly 90% of the outflow resistance was in the subendothelial region of Schlemm's canal. There is stable inflow for aqueous humour, unless high pressures are achieved (Brubacker 1991). As discussed in Section 1.2.4.3, AH outflow is primarily through the conventional route but also occurs through the non-conventional route.

Several population studies have collectively shown that IOP measurements differ little between genders (Armaly 1965; Hollows & Graham 1966; Bankes et al. 1968; Kahn et al. 1977; Klein et al. 1992). Each study found some indication of increasing pressure with age and that this age effect was lost or at least weakened at the oldest ages (Armaly 1965; Hollows & Graham 1966; Bankes et al. 1968; Kahn et al. 1977; Klein et al. 1992). Table 1.3-1-1 shows that between the ages of 40 years and 86 years, mean IOP values have been measured between 14.7mmHg and 17.5mmHg for females and between 15.0mmHg and 17.4mmHg for males.

Epidemiologic studies have shown the mean measurement of IOP to be approximately 16.0mmHg, with a standard deviation of 3.0mmHg (Colton & Ederer 1980). More recent research from a UK bio data bank, states that the mean IOP in a majority Caucasian population with a mean age of 57 years, to be 15.7mmHg (Chan et al. 2016). There is limited normative data on the range of IOP in people under the age of 40 years.

An estimated 50% of people with glaucoma present with IOP below 21.0mmHg (Chan et al. 2016) suggesting that there is no value of IOP that can be used to differentiate as safe or unsafe (Liu & Allingham 2017).

IOP is a dynamic variable that follows a circadian rhythm (Liu et al. 2011). Animal studies have shown IOP can fluctuate as much as 10.0mmHg day to day and hour to hour (Crawford-

Downs et al. 2011). The time at which IOP peaks, appears to be usually in the morning hours (Liu et al. 2011). The diurnal fluctuation is an important consideration in glaucoma but very little is known how the eye responds to these fluctuations (Downs 2015). IOP can have a wide variability throughout a 24-hour period due to activity, nocturnal elevation, physiologic body position, and individual variability of response to topical medications (Sit & Liu 2009; Orzalesi et al. 1999; Khawaja et al. 2014).

TABLE 1.3-1-1 Summary of (IOP) intraocular pressure from population studies. Age measured in years. IOP measured in mmHg. S.D.=standard deviation

Study	Gender	Age range/years	IOP mmHg	S.D
Armaly 1965	Female	50-59	16.0	3.1
	Female	80-86	14.7	3.3
	Male	43-49	15.0	2.9
	Male	80-86	15.5	3.3
Hollows and Graham 1966 UK Study	Female	40-74	16.6	2.9
	Male	40-74	15.9	2.9
Banks et al. 1968 Bedford Glaucoma Study	Female	Under 40	14.9	2.9
	Female	40-49	15.5	2.4
	Female	50-59	15.7	2.4
	Female	60-69	15.9	2.5
	Female	70-79	16.0	2.5
	Female	80+	15.4	2.6
	Male	Under 40	15.3	2.5
	Male	40-49	15.4	2.5
	Male	50-59	15.7	2.6
	Male	60-69	15.6	2.6
	Male	70-79	15.4	2.6
	Male	80+	15.1	3.2
Kahn et al. 1977 Framingham Study	Female	52-64	16.8	3.4
	Female	64-74	17.5	4.4
	Female	75-85	17.3	5.3
	Male	52-64	16.6	3.4
	Male	64-74	17.4	4.4
	Male	75-85	17.4	4.9
Klein et al. 1992 Beaver Dam Study	Female	43-86	15.5	3.3
	Male	43-86	15.3	3.4
Chan et al. 2016 Norfolk	Female	48-92	16.3	3.6
	Male	48-92	16.2	3.6

1.4 RETINA

1.4.1 RETINAL STRUCTURE

The retina is the innermost lining of the eye and becomes part of the central nervous system. It is a thin, transparent structure that during embryo development, originates from the inner and outer layers of the optic cup. The layers of the retina from outer to inner retina are: retinal pigment epithelium (RPE) and its basal lamina, rod and cone inner and outer segments, external limiting membrane, outer nuclear layer (nuclei of the photoreceptors), outer plexiform layer, inner nuclear layer, inner plexiform layer, ganglion cell layer, nerve fibre layer (axons of the ganglion cells) and the internal limiting membrane (Cheng et al. 2006). There are key areas of the retina which provide orientation for observing the retina. The posterior pole or central retina (area centralis) is a 5-6mm diameter circular zone of retina situated between the superior and inferior temporal arteries. The macula lutea is a 1.5mm diameter area in the posterior pole and is positioned 3mm lateral to the optic disc. The fovea centralis (fovea) is a central 0.35 mm wide zone in the macula, consisting of a depression surrounded by slightly thickened margins (Sundaram et al. 2016). This is where cone receptors are concentrated at maximum density to the exclusion of rods (Hendrickson & Drucker 1992). The optic disc lies 3mm medial to the centre of the macula (fovea). There are no normal retinal layers at the optic disc and it is the area where ganglion cell axons from the retina pierce the sclera to enter the optic nerve. The central retinal vessels emerge at the centre of the optic disc and radiate out to supply the retina. The peripheral retina is the remainder of the retina outside the posterior pole and it is rich in rods. The ora serrata is the anterior margin of the sensory retina (Sundaram et al. 2016).

For descriptive purposes, the retina is divided into nasal and temporal halves by a vertical line through the fovea. The optic nerve head (ONH) is often used as the central point to describe the retina as having supero- and infero-nasal and supero- and infero-temporal quadrants.

Figure 1.4-1 presents a direct observation of the human retina as would be seen by an optometrist or ophthalmologist or on a direct photograph.

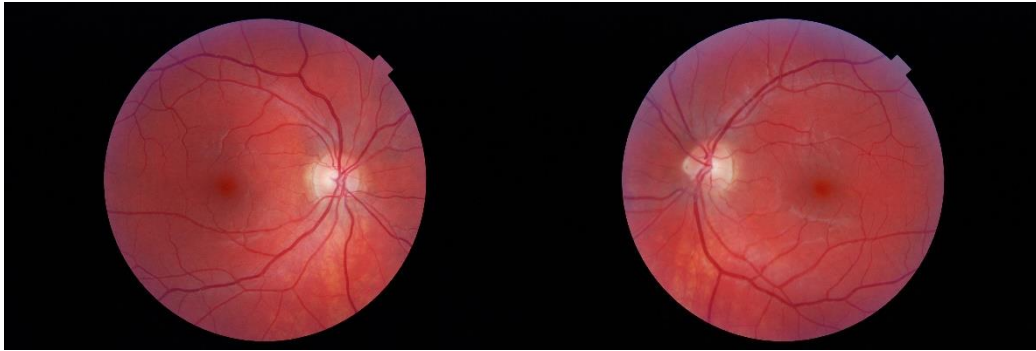


FIGURE 1.4-1 Retinal photographs of right eye (left image) and left eye (right image). showing healthy physiological optic nerve, retinal arteries and veins and macula.

1.4.2 RETINAL FUNCTION

Light striking the retina initiates a cascade of chemical and electrical events that ultimately trigger nerve impulses. The retina utilises five types of retinal nerve cells to carry out this process; these are shown in Figure 1.4-2. These nerve cells are the photoreceptors which detect light; the interneurons (horizontal, bipolar and amacrine cells) process the output of the photoreceptors and the retinal ganglion cells (RGC) axons convey visual information to the rest of the brain through the optic nerve (Purves et al. 2001; Sanes & Masland 2015).

1.4.2.1 PHOTORECEPTORS

The receptor layer (which lies underneath the retinal pigment epithelial layer) (Figure 1.4-2) holds two types of light-sensitive photoreceptors; the rods and cones. Cones are centred at the fovea and mediate vision under typical daytime bright (photopic) conditions and provide high-acuity colour vision (Curcio et al. 1990). Rods mediate vision under dark (scotopic) conditions and provide only low-acuity monochrome vision (Tovee 1996). There are on average 91 million rods in the human retina and 4.5 million cones. The density of the rods is much greater than the cones throughout most of the retina, except for the fovea. The fovea is a highly specialised region of the central retina where cone density increases almost 200-fold (Purves et al. 2001). The extreme centre 300 μm of the fovea (the foveola), is cone saturated and rod-free (Purves et al. 2001). The layers of cell bodies and retinal blood vessels that overlie the

photoreceptors in other areas of the retina are displaced around the fovea which allows for less light scatter and superior acuity (Purves et al. 2001).

The ONH is the channel connecting the neurosensory retina to the visual cortex (Calkins et al. 2017). Travelling from the eye, the ONH travels through the orbit and the optic canal to then form the optic chiasm. Topographically, this is divided into the intraocular part and the retrobulbar portion. The retinal ganglion cell layer, the retinal nerve fibre layer, and the ONH make up the intraocular portion (Wilczek 1947; Minckler 1986; Gala 2015).

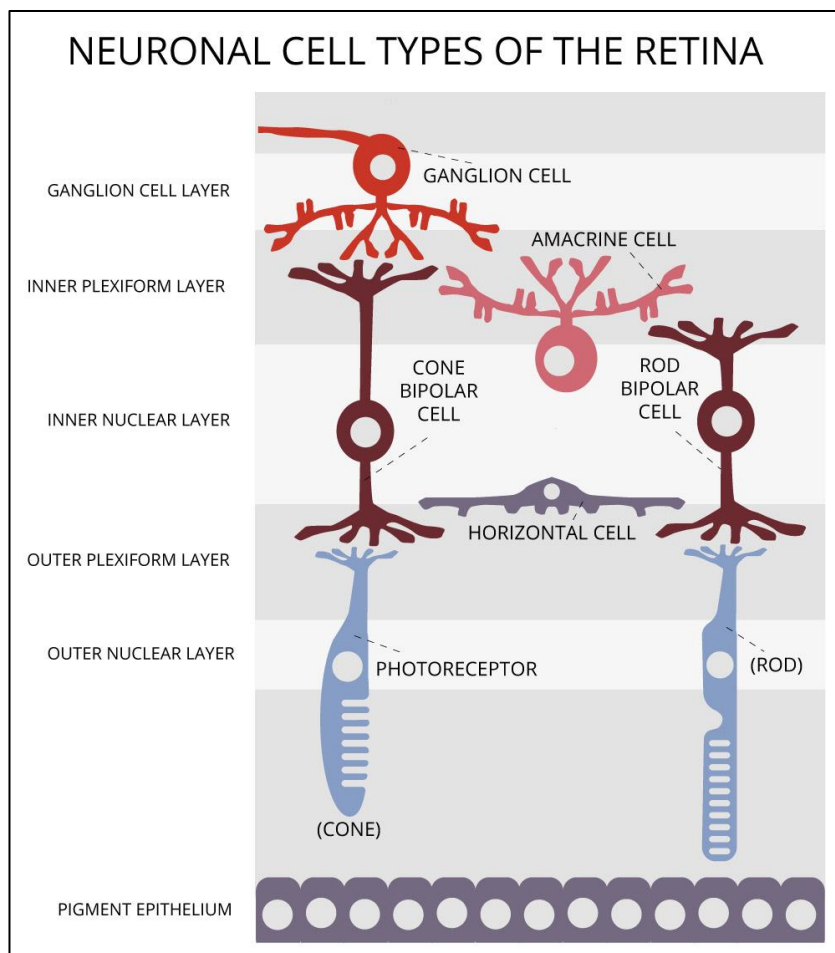


FIGURE 1.4-2 Schematic diagram to show the course of retinal ganglion cells to the optic nerve. (Adapted from Carreras et al. 2014).

1.4.2.2 RETINAL GANGLION CELL LAYER

Retinal neurons are stacked in five alternating layers (Figure 1.4-2). The cell bodies of the retinal neurons are in the inner nuclear, outer nuclear, and ganglion cell layers, and the processes and synaptic contacts of them are in the inner plexiform and outer plexiform layers (Purves et al. 2001; Sanes & Masland 2015). The retinal ganglion cells represent the final output neurons of the retina (Pascale et al. 2012).

1.4.2.3 RETINAL NERVE FIBRE LAYER

The retinal nerve fibre layer (RNFL) comprises ganglion cell axons, astrocytes, retinal vessels and Müller cell processes (Jonas & Schiro 1993). Within the nerve fibre layer, ganglion cell axons complete a 90° turn and proceed toward the optic nerve head, where they ultimately exit the eye (Radius 1987). The axons of the ganglion cells nasal to the ONH run directly towards it, while those of the ganglion cells in the temporal fundus describe an arcuate course around the fovea (Vrabect 1966; Jonas & Schiro 1993). This region is called the temporal raphe (Huang et al. 2015). At the fovea, the ganglion cells divide into a superior temporal and an inferior temporal group. The course of the RGC axons are demonstrated in Figure 1.4-3.

RNFL thickness has been reported to be on average 100 µm (Alasil et al. 2013; Budenz et al. 2007). The RNFL thickness increases from the fundus periphery to the optic disc (Jonas et al. 1993). The arrangement of the thickness of the RNFL corresponds to the arrangement of the intrapapillary neuro-retinal rim (Dichtl et al. 1999; Jonas et al. 1993; Varma et al. 1996) (Section 1.4.2.3). RNFL thickness values starting from the thickest quadrant inferiorly to the thinnest quadrant temporally: inferior quadrant (~126µm), superior quadrant (120 µm), nasal quadrant (80 µm), and temporal quadrant (~70 µm SD 10.8) (Alasil et al. 2013; Budenz et al. 2007). In healthy eyes, thinner RNFL measurements were associated with older age; being Caucasian, versus being either Hispanic or Asian; or being more myopic (Alasil et al. 2013). For every decade of increased age, mean RNFL thickness reduces by approximately 1.5 µm

(95% CI 0.24-0.07) (Alasil et al. 2013). There has been no relationship found between gender and RNFL thickness or right versus left (Mwanza et al. 2012; Budenz et al. 2007).

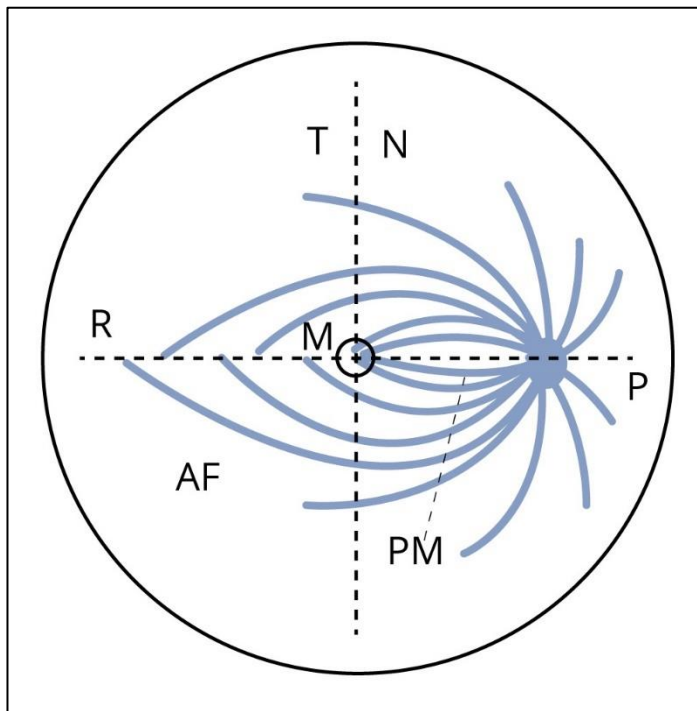


FIGURE 1.4-3 Schematic diagram of the optic nerve fibres of the right eye seen from the front (M, macula; P, optic disc; R, retinal raphe; PM, papillomacular fibres; AF, arcuate fibres; T,temporal side; N, nasal side). (Adapted from Millodot 2009).

1.4.3 OPTIC NERVE HEAD

The retinal ganglion cell axons leave the eye through an area called the posterior scleral foramen, which is like a funnel (Jonas et al. 1993). With ophthalmoscopy view, the internal surface of the posterior scleral opening is the optic nerve head (ONH) (Jonas et al. 1993). The ONH is surrounded by the peripapillary scleral ring of Elschnig as shown in Figure 1.4-5.

1.4.3.1 PERIPAPILLARY SCLERAL RING OF ELSCHNIG

The intrapapillary region of the ONH is delineated by a white, often circular band surrounding the optic disc and separating the intrapapillary optic disc region from the para-papillary area. This is called the peripapillary scleral ring of Elschnig; its size can range from 0.68 to 4.42mm² (Jester et al. 2005).

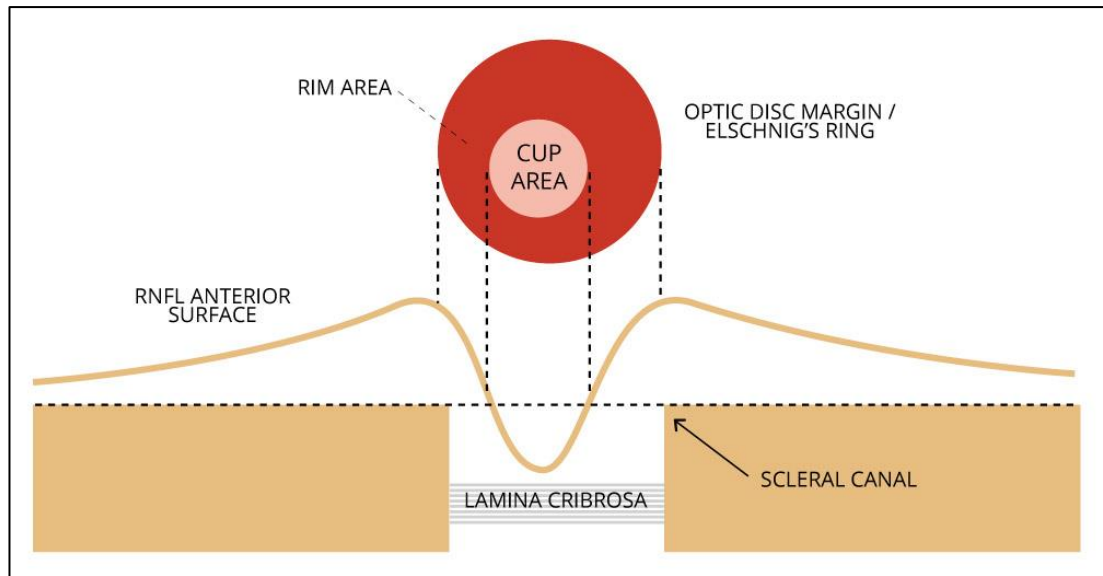


FIGURE 1.4-4 Schematic diagram of the optic nerve head. the disc rim is the area contained between the disc edge and the cup edge. the cup edge is where the surface of the nerve fibre layer intersects the imaginary plane established by the inner margin of the scleral ring. (Adapted from Moya et al. 1999).

1.4.3.2 OPTIC DISC SHAPE AND SIZE

The optic disc is slightly vertically oval with the vertical diameter having been shown to be on average about 9 % larger than the horizontal diameter (Jonas et al. 1988; Quigley et al. 1990). The interindividual variability of the ONH size is influenced by the size of the peripapillary scleral ring of Elschnig; the ONH size can range in area from 1.15 to 4.94 mm² (Iester et al. 2005). The area of the ONH, as well as its vertical diameter, is on average 12 % larger in individuals of Black race than those of White race (Radius et al. 1981; Quigley et al. 1990; Oliveira et al. 2007). On average, optic nerve size in females has been shown to be smaller than those in males (Quigley et al. 1990). Larger ONH and optic discs have more optic nerve fibres than do smaller discs (Quigley et al. 1990).

1.4.3.3 OPTIC CUP

The intrapapillary ring (the area inside the peripapillary scleral ring), consists of the neuroretinal rim (Section 1.4.3.5) and the optic cup (Section 1.4.3.3) (Jonas & Naumann 1993). Measurement of the optic cup can be achieved with imaging systems but is more commonly estimated with observation. The estimation is made by comparison of the cup with the size of

the disc and given as the ratio of the vertical diameter of the cup to the vertical diameter of the disc (vertical cup/disc ratio or CDR) (Weismann et al. 1973; Hitchings & Spaeth 1976; Tielsch et al. 1988; Varma et al. 1992). There is a wide variation in the size of the cup in the normal population due to a physiological relation between optic disc size and cup size (Zangwill et al. 1995; Teal et al. 1972; Bengtsson & Krakau 1992). Larger cup size is associated with large optic discs with the opposite being said for smaller optic nerve and cupping (Nixon et al. 2017; Garway-Heath et al. 1998). In healthy eyes, cupping between the two eyes is mostly symmetrical in over 96% of normal subjects (European Glaucoma Society 2017).

1.4.3.4 CUP-DISC RATIOS

The cup to disc ratio (CDR) in normal eyes is significantly larger horizontally than vertically (Jonas et al. 1988; Samarawickrama et al. 2012). CDR have been shown to have a mean of 0.39 horizontally and 0.34 vertically with normal healthy adults (Jonas et al. 1988). On average, CDR measurements have been reported to be larger in patients with African descent compared to Indian, Asian and Caucasian (Samarawickrama et al. 2012).

1.4.3.5 NEURO-RETINAL RIM

The neuro-retinal rim is the intrapapillary equivalent of the retinal nerve fibres and optic nerve fibres; it is one of the main targets for clinical assessment of the optic nerve (Jonas et al. 1999; European Glaucoma Society 2017). On direct observation, the neuro-retinal rim is the area resulting from subtraction of the cup from the disc area (Jonas et al. 1988). The neuro-retinal rim width follows the pattern of inferior, superior, nasal and temporal in order of thickness ($I > S > N > T$) (Poon et al. 2017). This is in line of the RNFL thickness (Section 1.4.2.3). There is high correlation for interocular symmetry for neuro-retinal rim width and RNFL thickness (Li et al. 2013).

1.4.3.6 LAMINA CRIBROSA

The lamina cribrosa is a mesh-like structure in the scleral canal of the optic nerve head; it is composed of overlapping and branching collagenous beams (Wilczek 1947; Anderson 1969; Emery et al. 1973). The collagenous beams form pores through which the retinal ganglion cell (RGC) axons and retinal blood vessels pass. Part of the lamina cribrosa can be visible at the base of the optic cup when viewed by a direct ophthalmoscope (Figure 1.4-5) (Park & Ritch 2011). Girkin et al. (2017) report that the lamina cribrosa has conflicting functions as it also needs to provide structural support to the ONH by withstanding IOP related mechanical strain but also having to provide an open pathway for retinal ganglion cell axons to leave the eye. The retrobulbar portion of the optic nerve starts at the posterior end of the lamina cribrosa.

1.4.3.7 RETROBULBAR OPTIC NERVE

The retrobulbar portion of the optic nerve is subdivided into three parts. These are the intraorbital part, the intracanalicular portion and the prechiasmatic intracranial portion. The retrobulbar section joins the contralateral optic nerve to form the optic chiasma, where the nasal fibres from each optic nerve decussate and temporal fibres do not decussate (Wilczek 1947; Gala 2015).

1.4.4 BLOOD SUPPLY TO THE RETINA AND OPTIC NERVE

The central retinal artery arises from the ophthalmic artery in the optic canal. It passes forward in the centre of the optic nerve accompanied by the central retinal vein. The large retinal arterial branches travel in the RNFL beneath the inner limiting membrane. Each of its four major branches supplies a sector of the retina (Forrester et al. 2015). The central retinal artery supplies all the retina apart from the photoreceptors. On occasion, a cilioretinal artery is also observed on the retina; this is a small artery from the choroid which can follow from the edge of the optic disc onto the retina (Hayreh 2015). The photoreceptors receive their metabolic supply from the choroid (Foulds 1990).

The vasculature system of the optic nerve is supplied from branches of both the central retinal artery and posterior ciliary arteries (Yu et al. 2017). The most anterior part of the ONH is said to be supplied by the retinal arterioles; in some cases, the temporal region is supplied by the posterior ciliary artery (Hayreh 2001). The circle of Haller and Zinn is formed by short posterior ciliary arteries and the lamina cribrosa is supplied either directly or from this circle. The optic nerve behind the lamina cribrosa (the retrolaminar region) is supplied from branches of the circle of Haller and Zinn and branches from the central retinal artery (Hayreh 1985; Hayreh 2001).

There are individual variations in the blood supply of the optic nerve head due the anatomical pattern of blood supply, the pattern of posterior ciliary artery circulation and blood flow (Hayreh 1985). One suggested reason for the variation in the blood flow in the eye is change in intraocular pressure (Hayreh 1985). Acute IOP spikes can reduce blood flow to the retina, choroid and optic nerve in healthy volunteers (Findl et al. 2000) with suggestion that there can also be interference with delivery of chemicals from the brain to the retina (Quigley et al. 2000).

1.4.5 VISUAL FIELD

One approach to assessing visual function is to measure the visual field (Fontenot Chair et al. 2017). The visual field is that portion of space in which objects are visible at the same moment during steady fixation of gaze in one direction (Grill-Spector 2003). The visual field holds a historic definition given by Harry Moss Traquair (1875-1954) of “an island of vision in a sea of darkness”(Grzybowski 2009). Figure 1.4-5 presents this description diagrammatically and shows how the shores represent the extent of the visual field and the height of the island above sea level denotes sensitivity (Johnson et al. 2000). The normal extent of the visual field for a bright stimulus is furthest temporally measuring 100 degrees, followed by 75 degrees inferiorly and 60 degrees both superior and nasal.

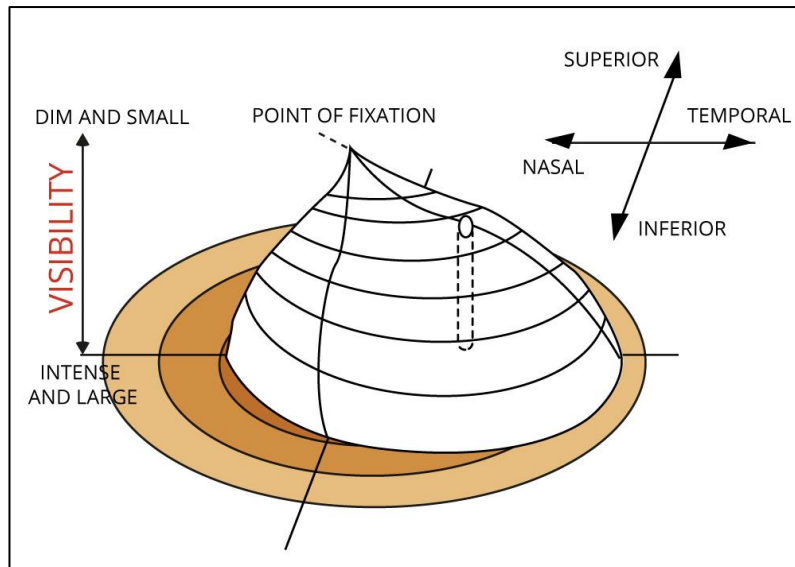


FIGURE 1.4-5 Schematic representation of an island of vision in a sea of darkness. (Adapted from www.ssc.education.ed.ac.uk/resources).

The first part of the introduction has described structures of the eye and described visual function. The main structures of the eye described in the anterior segment were the cornea and anterior chamber which lead to an understanding of intraocular pressure. The posterior segment of the eye reviewed the retina, optic nerve and visual field have also been described. Understanding these structures will aid understanding processes of development of glaucoma. The following section will introduce glaucoma and its classification and then continue to discuss glaucoma classification, diagnosis and treatments.

1.5 GLAUCOMAS

The most important characteristic of the glaucomatous process is change in the appearance of the disc from its former state. Spaeth (1993)

This section will provide an overview of primary open angle glaucoma. It will review the definition and classification of glaucoma. Its prevalence and incidence will be considered, followed by the criteria used for primary open angle case finding in the UK. Current literature on the pathogenesis of POAG will be reviewed as will treatment strategies.

The glaucomas refers to a group of conditions with heterogeneous causes that result in damage to the optic nerve head and loss of visual field (NICE 2017; Kansal et al. 2018). Their uniting clinical feature is optic neuropathy (Casson et al. 2012). All glaucomas have clinically visible changes at the ONH which include focal or generalised thinning of the neuro-retinal rim, excavation and enlargement of the optic cup, neurodegeneration of retinal ganglion cell axons and deformation of the lamina cribrosa (European Glaucoma Society 2017; Casson et al. 2012). These changes lead to a corresponding diffuse and localised retinal nerve-fibre bundle pattern visual field loss. Change in visual field and visual acuity may not be detectable in early stages but progression can lead to irreparable loss of vision (Casson et al. 2012).

1.6 CLASSIFICATION OF GLAUCOMAS

Glaucoma is classified as open or closed with this differentiation being directed from the structure and function of the anterior chamber angle. An open anterior chamber angle will allow drainage of aqueous humour; a closed angle will create a forced block. (Figure 1.6-1). Open and closed angle glaucomas are further classified by being either primary or secondary.

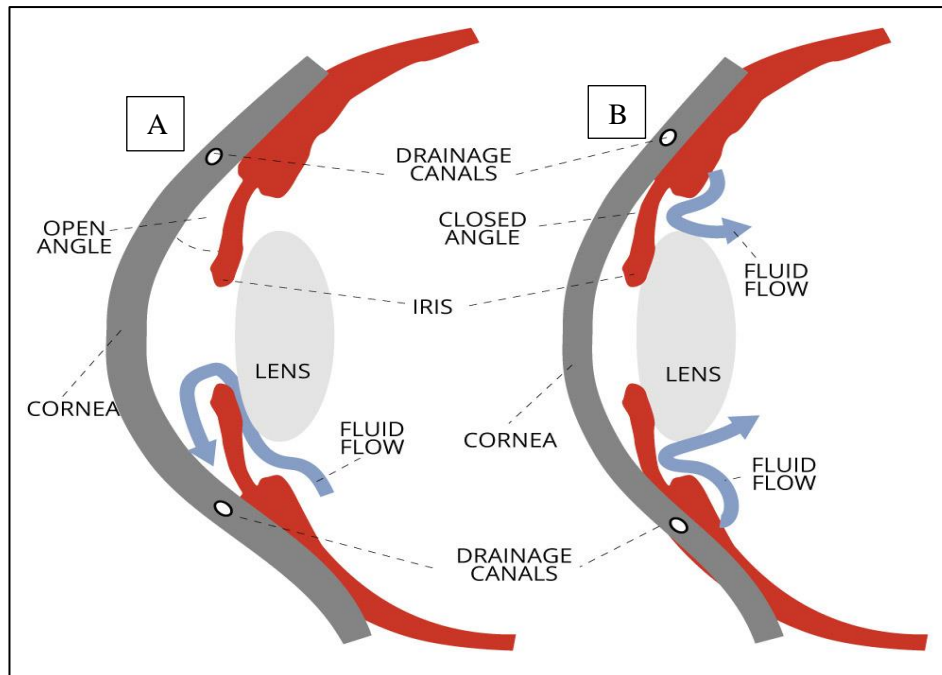


FIGURE 1.6-1 Schematic diagram to show an (A) open anterior chamber and (B) closed anterior chamber angle. (Adapted from Glaucoma Research Foundation 2010).

Primary open angle glaucomas are usually bilateral and are caused by increased resistance to the outflow of aqueous humour or to the closure of the anterior chamber with no known ocular or systemic association. Primary closed angle closure glaucomas are usually unilateral and caused by disorders of the iris, the lens, and retro-lenticular structures. Pupillary block is the most common mechanism of angle closure and is caused by resistance to aqueous humour flow from the posterior to anterior chambers at the pupil (Weinreb et al. 2014). Primary closed angle glaucoma may be chronic or acute but these are beyond the scope of this thesis and will not be reviewed.

Secondary glaucomas are asymmetric or unilateral and associated with disorders that cause decreased aqueous humour outflow. Combined-mechanism glaucoma can appear in a patient with open-angle glaucoma who develops secondary angle closure from other causes but is uncommon (Lee & Fantes 2003). Open-angle glaucoma is classified as primary when no anatomically identifiable underlying cause of the events that led to outflow obstruction and IOP elevation can be found.

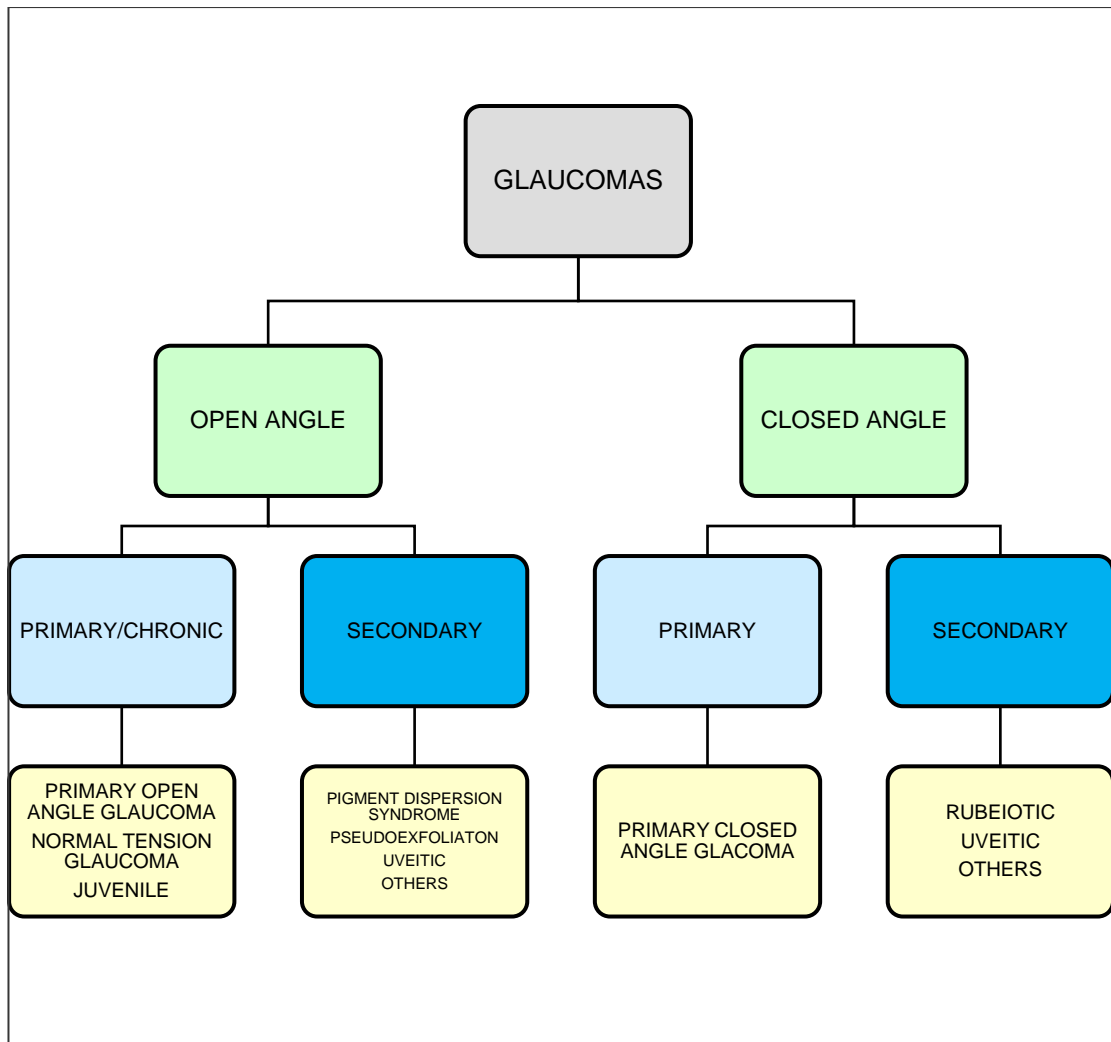


FIGURE 1.6-2 Classifications for open and closed angle glaucoma

1.7 PRIMARY OPEN ANGLE GLAUCOMA

There is a lack of consistency in epidemiology research concerning a precise definition of POAG and criteria for its diagnosis (Kroese & Burton 2003; Bathija et al. 1998). This thesis will use the term POAG but consider literature which has used the terms chronic open angle glaucoma (COAG) and open angle glaucoma (OAG). The literature reviewed in this thesis will aim to use research which defines its criteria for POAG and COAG and if using the term OAG will have excluded any cases with secondary causes.

1.7.1 PRE-PERIMETRIC GLAUCOMA

The term 'pre-perimetric glaucoma' (PPG) has been used to describe glaucomatous eyes that have glaucomatous optic nerve changes and/ or nerve fibre layer defect, yet have a no visual field defect caused by glaucoma. (Sawada et al. 2017).

1.7.2 NORMAL TENSION GLAUCOMA

Normal tension glaucoma (NTG) and (POAG) differ in IOP measurements. In NTG, IOP is consistently at or below 21.0mmHg yet as with POAG, the anterior chamber is open and there are glaucomatous optic nerve changes and a visual field defect (Shields 2008).

1.7.3 OCULAR HYPERTENSION

Ocular hypertension (OHT) is defined as consistently elevated intraocular pressure (IOP) (greater than 21.0mmHg in one or both eyes in the absence of clinical evidence of optic nerve damage, visual field defect or other pathology that could explain high IOP (College of Optometrists 2016).

1.7.4 CLINICAL DIAGNOSIS

Allocco et al. (2017) have suggested a critical pathway for the diagnosis and treatment of POAG. This pathway is useful for understanding how ocular hypertension, normal tension or open angle glaucoma may be diagnosed. The pathway has been adapted to reflect current NICE guidelines (2017) of referral for glaucoma suspects at 24.0mmHg and shown in Figure 1.7-1.

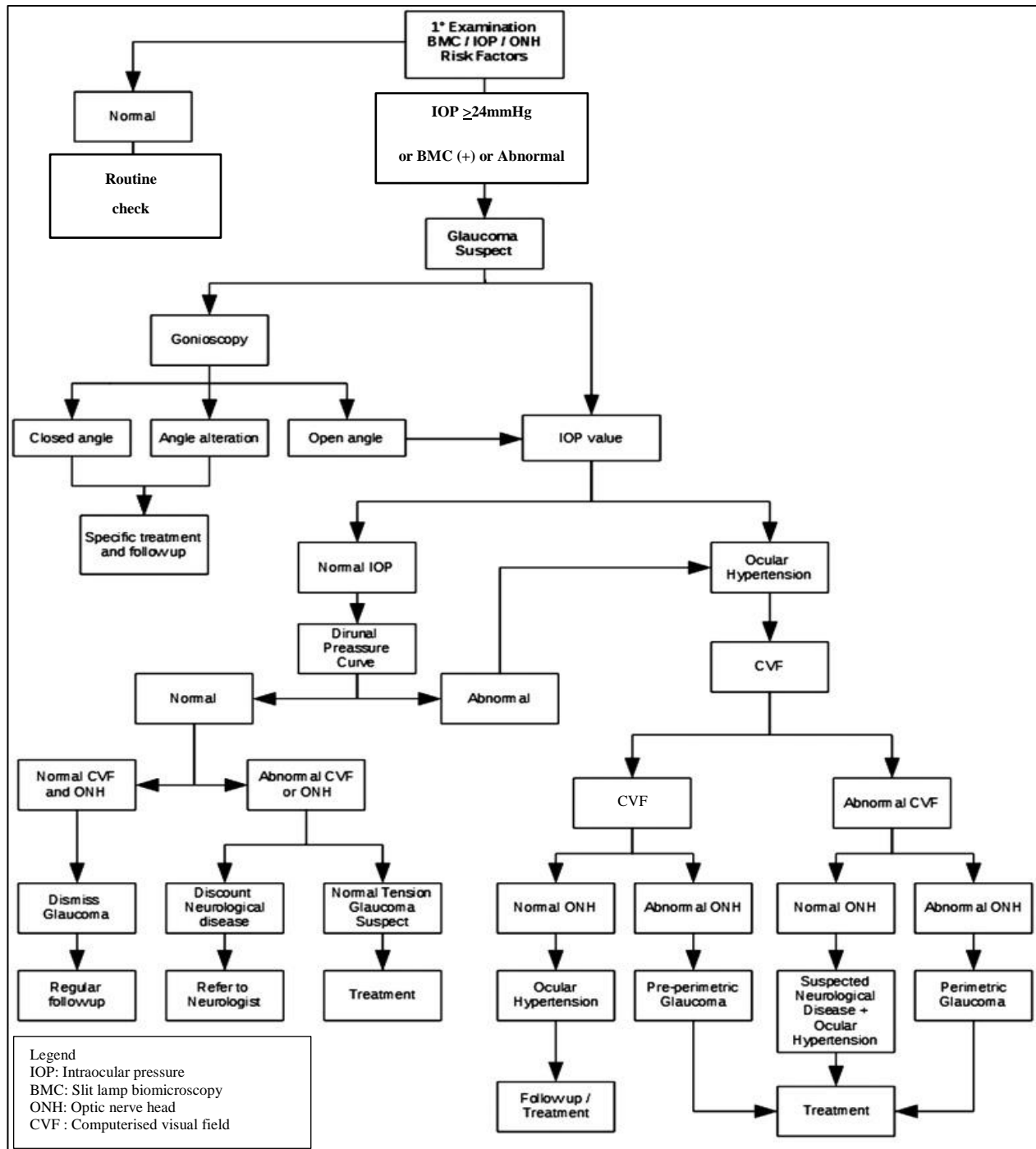


FIGURE 1.7-1 Critical pathway for glaucoma diagnosis. (Adapted from Alloco et al. 2017)

1.8 EPIDEMIOLOGY

Glaucoma was reported to be one of the top three causes of blindness in 2015 (Flaxman et al. 2017). Quigley and Broman (2006) estimated that by 2020, 11.1 million people will be bilaterally blind from primary glaucoma. A systematic review affirms that Black populations

have the highest POAG prevalence from early middle life; (Friedman et al. 2004; Rudnicka et al. 2006). Age-specific increase in POAG prevalence is highest among White populations and Hispanic populations, followed by Asians and is lowered in Black populations (Kapetanakis et al. 2016). Although most people in the UK with a diagnosis of POAG do not go blind (Crabb 2015), 1 in 20 treated people in the UK have a real lifetime risk of serious visual impairment (Saunders et al. 2014; Goh et al. 2011).

1.8.1 PREVALENCE

The prevalence of glaucoma can be defined as the proportion of people in a specified population who have the condition in a defined period (Rudnicka & Owen 2007). Tham et al (2014) predict that by 2040, there will be an increase of 75% in the number of people with glaucoma worldwide (aged 40 years to 80 years) The most current UK population study was set in Norfolk where the prevalence of glaucoma from all causes in those aged 48-92 year was 4.2% (95% CI 3.8 - 4.6) (Chan et al. 2016). Specifically, for POAG, the prevalence found was 3.7% (95% CI 3.3 - 4.0). This echoed findings from the meta-analysis by Tham et al. (2014), in which the prevalence of glaucoma (POAG and PACG) for Europeans aged 40-80years was 2.93% (95% CI 1.85 - 4.40) and the prevalence of primary open angle glaucoma was 2.51% (95% CI 1.54 - 3.89). In another meta-analysis, published in 2006, the pooled prevalence of POAG in White people was 2.1% (95% CI 1.6 - 2.7) (Rudnicka et al. 2006).

The Beaver Dam study considered the prevalence of OAG in the United States (Klein et al.1992). With no significant effect of gender, the overall prevalence of definite open-angle glaucoma was reported to be 2.1%.; the prevalence increased with age from 0.9% in people 43 to 54 years of age to 4.7% in people 75 years of age or older (Klein et al. 1992). The studies mentioned highlight that glaucoma is a condition prevalent in an older population; however, research has not considered what age the earliest changes begin to occur.

The Blue Mountains Eye study found a prevalence of 3.0% (95% CI 2.5 -3.6) of OAG with also an exponential rise in prevalence with increasing age (Mitchell et al. 1996). Ocular

hypertension was present in 3.7% (95% CI 3.1–4.3) of the population but with no significant age-related increase in prevalence. The age range was described as under 60 years to 80 years and over. There was no difference found between genders in the prevalence of ocular hypertension.

1.8.2 RACE

Prevalence increases proportionately with age for each racial group. Estimated prevalence in those older than 70 years of age was 6% in White populations, 16% in Black populations, and 3% in Asian populations (Rudnicka et al. 2006). Black populations had the highest POAG prevalence at all ages but the increase in prevalence with age for POAG is steeper for White populations; increases with age in Black and Asian populations are similar (Rudnicka et al. 2006; Cedrone et al. 2008). Friedman et al. (2004a) also reported that those in Black populations had almost three times the age-adjusted prevalence of glaucoma than those in White populations.

1.8.3 INCIDENCE

The incidence of glaucoma can be defined as the number of new cases occurring in a defined population over a specified period (Rudnicka & Owen 2007). Between 2008 and 2012, glaucoma/OHT prescriptions increased by approximately 3000 per 100,000 in England for patients aged above 40 years (Heng et al. 2016). This variation was reported to be due to age, western African diaspora ethnicity and male gender (Heng et al. 2016).

1.9 RISK FACTORS OF PRIMARY OPEN ANGLE GLAUCOMA

A “risk factor” describes features that may be causal in disease, as they are statistically associated with the disease, and were present before its occurrence, and could conceivably have played an “essential role” along with other factors in incident disease (Boland & Quigley 2007). Boland and Quigley (2007) categorise risk factors of POAG into individual characteristics such as age, gender, race and family history. Raised IOP, increased diurnal IOP variation, myopia and increased disc diameter are listed under ocular anatomy and physiology. Systemic conditions include thyroid conditions, sleep apnoea and migraine. Cortico-steroids also increase risk of POAG.

1.10 PATHOPHYSIOLOGY OF PRIMARY OPEN ANGLE GLAUCOMA

The pathogenesis of glaucoma is not fully understood, but it is recognised that the level of intraocular pressure is related to retinal ganglion cell death (Weinreb et al. 2014). In 1990, Hernandez et al. described alterations in the extracellular matrix of glaucomatous human optic nerve heads, including the deposition of collagen IV and other molecules within the laminar pores. A similar deposition of collagen was noted in monkey eyes with experimental IOP elevation suggesting that IOP plays a causative role in producing the optic neuropathy of human glaucoma (Morrison et al. 1990; Burgoyne & Morrison 2001). Section 1.2.4 discussed the balance between secretion and drainage of AH that determines the intraocular pressure. In patients with OHT and OAG, there is much research to suggest that increased resistance to aqueous outflow through the trabecular meshwork may result in an impaired flow, but the underlying link remains unclear (Alvarado et al. 1984; Wang et al. 2017; Carreon et al. 2017). POAG patients have been shown to have structural differences in Schlemm’s canal diameter and trabecular meshwork than normal patients; this also being negatively correlated with

intraocular pressure (Yan et al. 2016). It is not known if there are congenital differences in intraocular pressure for those who develop glaucoma or if it has a process of change which is different from normal eyes from an early age.

Intraocular pressure may cause mechanical stress and strain on the posterior structures of the eye; the lamina cribrosa is proposed to be the initial site of injury (Voorhees et al. 2017). The sclera is perforated at the lamina where the optic nerve fibres (retinal ganglion cell axons) exit the eye (Weinreb et al. 2014). Stress and strain to the lamina cribrosa is thought to result in compression, deformation, and remodelling leading to consequential mechanical axonal damage and disruption of axonal transport (Fechtner & Weinreb 1994; Burgoyne et al. 2005). Axonal transport damage interrupts delivery of essential trophic factors to retinal ganglion cells from their brainstem target (relay neurons of the lateral geniculate nucleus) (Weinreb et al. 2014). The time between IOP change being manifest to optic nerve alteration is not known. There is little information on glaucomatous eyes many years before diagnosis. Therefore, it is not known if slightly higher than average IOP over many years may cause constant mechanical stress on the optic nerve, thereby causing alterations.

The blood flow of the optic nerve head is tightly controlled so that it can efficiently meet the demands of the retina, including the retinal ganglion cells (Chan et al. 2017). Studies have found that there may be narrowing of retinal vessel diameters in glaucoma (Mitchell et al. 2005). The reasons for this has been proposed to be thinning of the RNFL (Kim et al. 2014). However, it has also been demonstrated that narrowing of retinal vessels may be a risk factor for development of POAG (Kawasaki et al. 2013).

The biomechanical properties of the cornea may provide information regarding the development of glaucoma as they reflect how the eye responds to physical stress. Corneal hysteresis is a term used to describe measurement of the viscoelastic damping of the cornea. It is estimated by analysing corneal responses to deformation induced by an air pulse (Medeiros et al. 2013). This response of the cornea has been suggested to replicate how the optic nerve may also behave under certain stressors (Murphy et al. 2017). The response of the

cornea to deformation may reflect the behaviour of the extracellular matrix, which may also reflect the composition of the lamina cribrosa and sclera and therefore be more affected by IOP damage (Medeiros et al. 2013).

Normal tension ranges can also lead to glaucomatous optic neuropathy. In such patients, there are thoughts that there may be an abnormally low cerebrospinal fluid pressure in the optic nerve subarachnoid space resulting in a large pressure gradient across the lamina (Ren et al. 2011). Other thoughts for the pathogenesis of glaucoma are impaired microcirculation, altered immunity, excitotoxicity, and oxidative stress (Weinreb et al. 2014).

1.11 GENETIC RISK FACTORS OF PRIMARY OPEN ANGLE GLAUCOMA

There have been genes identified to have a role in POAG (Allingham et al. 2009; van Koolwijk et al. 2013; Weinreb et al. 2014). These are myocilin, optineurin and TANK-binding kinase 1 (Monemi et al. 2005; Rezaie et al. 2002; Stone et al. 1997; Fingert 2011; Liu & Allingham 2017). The genes listed are said to account for 5 to 10% of POAG cases in the general population (Kwon et al. 2009; Alward et al. 2003; Fingert et al. 1999; Hauser et al. 2006; Hewitt et al. 2006). Genetic effects have also been shown to account for a significant proportion of the variance in IOP, with heritability estimates ranging from 0.29 to 0.67 (Carbonaro et al. 2008; Chang et al. 2009; Klein et al. 2004; Zheng et al. 2009).

Disease-associated mutations of myocilin generally occur in the juvenile or early adult form of POAG, usually characterised by very high levels of intraocular pressure (Weinreb et al. 2014). In populations of adults with POAG, the prevalence of myocilin mutations varies from 3 to 5% (Kwon et al. 2009; Weinreb et al. 2014). Carriers of disease-associated mutations develop the glaucoma phenotype in approximately 90% of cases (Kwon et al. 2009; Weinreb et al. 2014). Although the mechanism of myocilin-related glaucoma is not fully known (Kwon

et al. 2009), it is said that mutations alter the myocilin protein in a way that disrupts normal regulation of intraocular pressure (Weinreb et al. 2014).

In contrast to individuals with the myocilin gene, those with the optineurin gene have normal levels of intraocular pressure (Rezaie et al. 2002). There is evidence suggesting that optineurin may have a neuroprotective role by reducing the susceptibility of retinal ganglion cells to apoptotic stimuli (Weinreb et al. 2014).

The genetic basis of POAG and IOP has been considered through genetic studies. These studies are beyond the remit of this thesis but suffice to say that as POAG is a complex disease, gene-finding studies give an ambiguous conclusion (van Koolwijk et al. 2013 Normative values of IOP have been reviewed in Section 1.3. However, we do not know if average IOP is different to those that have a family history of glaucoma.

This chapter has covered the structure of the eye and these sections have aided in an understanding of glaucoma and its classification. The diagnosis of glaucoma in the UK will now be reviewed through current NICE guidelines with an overview of treatments. Following this, the assessments used for glaucoma screening and case-finding will be reviewed.

1.12 DIAGNOSTIC CRITERIA FOR PRIMARY OPEN ANGLE GLAUCOMA

Current NICE guidelines (NICE 2017), advise that health professionals involved in case-finding or diagnoses of POAG should be able to perform and interpret the following:

- central visual field assessment using standard automated perimetry (full threshold or supra-threshold) (repeated on different occasions)
- optic nerve assessment and fundus examination using stereoscopic slit lamp biomicroscopy (with pupil dilatation if necessary), and optical coherence tomography (OCT) or optic nerve head image if available

- intraocular pressure measurement using Goldmann-type applanation tonometry (repeated on different occasions)
- peripheral anterior chamber configuration and depth assessments using gonioscopy or, if not available or the patient prefers, the van Herick test or OCT.

Referral for further investigation and diagnosis of COAG and related conditions (after considering repeat measures) is made if:

- there is optic nerve head damage on stereoscopic slit lamp biomicroscopy **or**
- there is a visual field defect consistent with glaucoma **or**
- IOP is 24.0mmHg or more using Goldmann-type applanation tonometry.

The World Glaucoma Association (Weinreb 2016) have issued a preliminary report of the diagnosis of POAG

Consensus statements taken from this report conclude that:

- Clinical diagnosis of glaucoma is predicated on the detection of thinning of the retinal nerve fibre layer (RNFL), narrowing of the neuro-retinal rim, and deformation of the optic nerve head (ONH) (cupping).
- Detecting progressive glaucomatous RNFL thinning and neuro-retinal rim narrowing are the best currently available good standards for glaucoma diagnosis. However, it is important to differentiate between age-related ONH change and disease-related damage.
- The diagnosis of glaucoma does not require the detection of visual field defects with perimetry although perimetry is indispensable for documentation and monitoring of functional decline in glaucoma.
- Assessment of the colour and the configuration (size and shape) of the neuro-retinal rim is important to differentiate glaucomatous from non-glaucomatous optic neuropathies.

- Optic nerve head (ONH) biomechanics, which are the physical manifestations of the IOP force distribution in the tissues, are important to glaucoma pathophysiology. Studies in patients and animal models of glaucoma have linked elevated IOP exposure and/or glaucoma to morphological changes in the lamina cribrosa and peripapillary sclera, and these changes are associated with axonal loss and/or visual field damage.

1.13 TREATMENT STRATEGIES

Lowering intraocular pressure is the only modifiable treatment for glaucoma. Treatment is recommended in patients who are deemed at risk of progression of POAG within their lifetime (NICE 2017). Suggested reduction of IOP is approximately 30% for preservation of retinal ganglion cells and visual function (van der Valk et al. 2005; Garway-Heath et al. 2015; Karaskiewicz et al. 2017). This is achieved in the main through pharmacology treatments. The progressive nature of the pathology of POAG, offers an opportunity for therapeutic intervention (Pascale et al. 2012). Table 1.13-1 presents the groups of drug therapies that are used for lowering IOP.

NICE recommends that treatment for OHT, suspect and COAG with a generic prostaglandin analogue. OHT and suspect COAG patients are offered beta-blocker and carbonic anhydrase inhibitor therapies if the initial line of treatment is unsuccessful. COAG patients are also offered a surgical treatment intervention prior to a different course of therapy (NICE 2017).

A systematic review and meta-analysis (Li et al. 2016) found that all active first-line drugs were effective compared with placebo and that prostaglandins were more efficacious in lowering IOP at three months than beta-blockers, alpha-agonists, or carbonic anhydrase. Bimatoprost, latanoprost, and travoprost were among the most efficacious drugs. Li et al (2016) also reported that most trials did not measure or report visual field or other patient-centred outcomes, such as visual function and blindness.

Selective laser trabeculoplasty (SLT) is a technique used to target pigmented trabecular meshwork cells with a laser (Latina & Park 1995). It is used as an alternative or in combination with medication and has been reported to have successful results in reducing IOP (Li et al. 2015). As there are cost, compliance and adverse reactions involved with regular medication use, laser therapy has suggestion of improving quality of life (De Keyser et al. 2017).

TABLE 1.13-1 Drug treatments for intraocular pressure reduction (Adapted from European Glaucoma Society 2017)

CLASS	COMPOUND	MODE OF ACTION	IOP REDUCTION
Prostaglandin analogues	Latanoprost Tafluprost Travoprost	Increase in uveo-scleral outflow	25-35%
Prostamide	Bimatoprost Bimatoprost	Increase in uveo-scleral outflow	25-35%
Beta-receptor antagonists. Non-selective	Timolol Levobunolol Metipranolol Carteolol Befunolol	Decreases aqueous humour production	20-25 %
Beta-receptor antagonists. selective	Betaxolol	Decreases aqueous humour production	±20%
Carbonic anhydrase inhibitors - topical	Brinzolamide Dorzolamide	Decreases aqueous humour production	20%
Carbonic anhydrase inhibitors - selective	Acetazolamide Methazolamide Dichlorphenamide	Decreases aqueous humour production	30-40%
Alpha-2 Selective Adrenergic Agonists	Brimonidine Apraclonidine	Decreases aqueous humour production and increases uveo-scleral outflow	25-35%

1.14 CLINICAL ASSESSMENTS FOR GLAUCOMA

1.14.1 ANTERIOR CHAMBER ASSESSMENTS

1.14.1.1 GONIOSCOPY

Gonioscopy is a technique used to visualise the structures of the iridocorneal angle and observe any outflow obstruction (Scheie 1957). Gonioscopy is used readily as a tool in

glaucoma diagnosis as the anterior chamber can be examined but anterior segment imaging is also being used (Chansangpetch et al. 2018).

The normal adult iridocorneal angle consists of five anatomical landmarks, from anterior to posterior. These are: Schwalbe's line, anterior (nonpigmented) trabecular meshwork, trabecular meshwork, posterior (pigmented) trabecular meshwork, scleral spur and ciliary body band (Sundaram et al. 2016).

Direct visualisation of the angle by changing the corneal refractive surface with a viewing lens (Koeppé's lens) is a technique that is primarily used in the operating room as the patient is supine. Most commonly in a clinical setting, indirect visualisation is used and is accomplished using a mirrored lens and a slit lamp biomicroscope (Sundaram et al. 2016).

1.14.1.2 LIMBAL ANTERIOR CHAMBER DEPTH

Whilst gonioscopy remains the gold standard for evaluating the anterior chamber angle, it can also be evaluated using the van Herick method (or limbal anterior chamber depth – LACD) (Saeedi et al. 2014; Dabasia et al. 2013). Van Herick described how LACD can be estimated at the slit lamp by directing a slit beam at the temporal limbus with the light source offset at 60 degrees from the axis of the microscope and comparing the depth of the anterior chamber to the thickness of the cornea (Van Herick et al. 1969) (Figure 1.14-1).

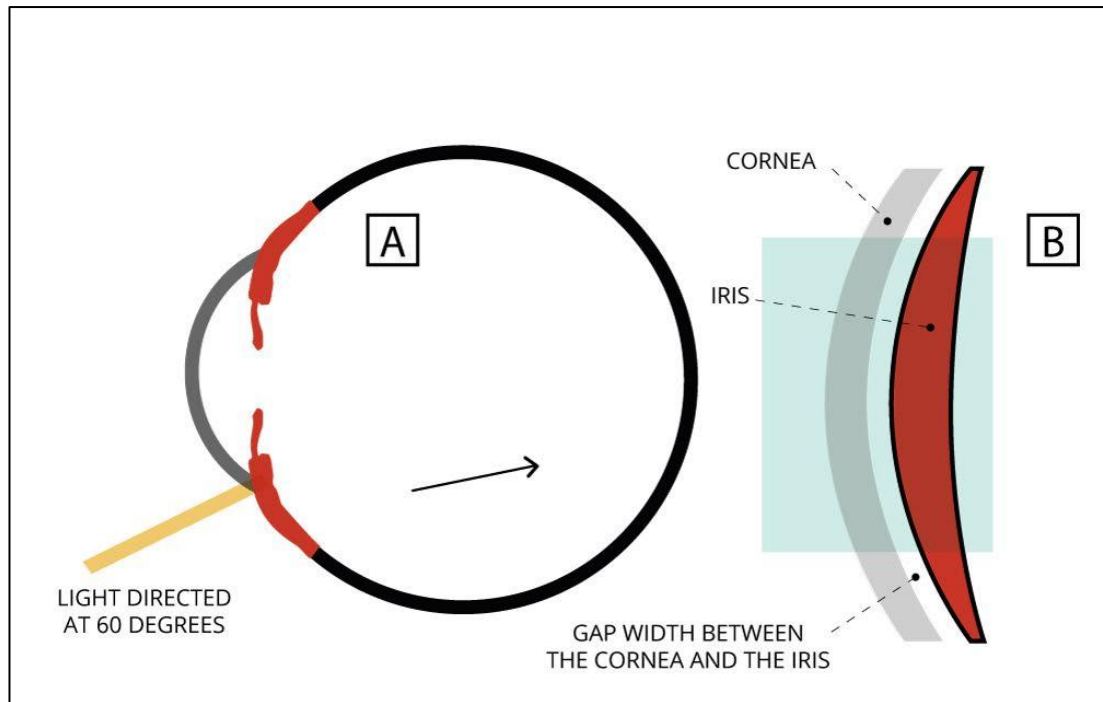


FIGURE 1.14-1 Schematic diagram illustrating practitioner’s view during van Herick assessment. Diagram A presents a light directed at 60 degrees. Diagram B shows the cornea and iris. The depth of the gap in between these structures is compared to the width of the cornea.

1.14.2 INTRAOCULAR PRESSURE ASSESSMENT

In a clinical setting, measurement of intraocular pressure is achieved with a technique called tonometry. Tonometry has been used in eyecare practice since 1885 with first assessment being through indentation of the eye (Maklakoff 1885; Schiotz 1905). Applanation tonometry was first introduced in 1955 (Goldmann & Schmidt, 1957). Goldmann and Schmidt (1957) reported that in a “normal” eye, applanation tonometry with a diameter of flattened cornea between 3.0mm and 3.5mm would result in measurement of undisturbed intraocular pressure. At these diameters meniscus forces due to the tear film are vitiated by forces due to thickness and elasticity of the cornea (Stuckey 2004). This principle is based on the Imbert-Fick principle. The Imbert-Fick law postulates that for an ideal thin walled, dry sphere, the pressure within the sphere (P) is equal to the force needed to flatten its surface (F), divided by the applanation area (A), that is $P=F/A$ (Garcia-Feijoo et al. 2015). Goldmann tonometry is accepted as the standard instrument and all current tonometers are calibrated against it (Stuckey 2004).

The Goldmann tonometer is used as an accessory to a slit lamp biomicroscope, although there is a portable handheld version called the Perkins tonometer. (An anaesthetic and fluorescein stain are instilled in the tear film before a bi-prism probe is rested on the centre of the cornea (Figure 1.14-3). The tonometer is adjusted to obtain a view of a horizontal “S” shape which is achieved when 3.06mm of the central cornea has been applanated. The Perkins tonometer yields IOP measurements that are closely comparable with Goldmann applanation tonometry (Arora et al. 2014). Portable electronic applanation is also available and recognised under names such as Tono-pen.

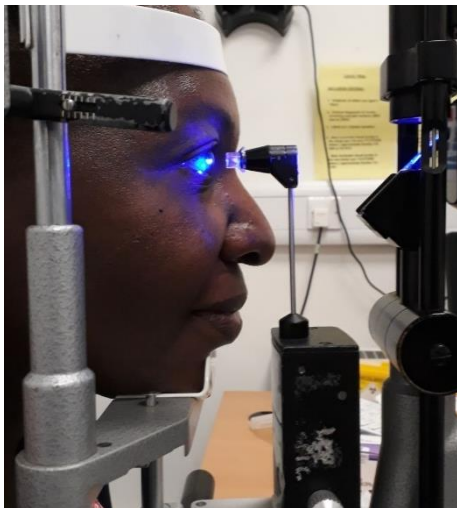


FIGURE 1.14-2 Photograph to demonstrate Goldmann applanation tonometry.

Non-contact tonometry uses air as the applanation force. At the point of flattening 3.06mm diameter of the cornea, a weak laser beam generated from the side, is reflected into a sensor located on the other side of the eye. The force at the moment of applanation is recorded and the value displayed in millimetres of mercury (Stamper 2011). Non-contact tonometry is often used for screening purposes as it does not use anaesthetic or a stain. The measurement achieved by non-contact tonometry gives a snapshot of IOP (Stamper 2011). Non-contact tonometers are table mounted or handheld.

Rebound tonometry has two co-axial coils which are used first to propel a lightweight magnetized probe toward the cornea and then to detect its deceleration when it bounces back off the cornea (Garcia-Feijoo et al. 2015). Among all variables linked to the probe's movement, the inverse of the deceleration velocity correlates best with IOP (Martinez-de-la-Casa et al. 2005). Rebound tonometry does not require topical anaesthesia or a stain. Icare products are the only instrument to date that use rebound tonometry and variability has been shown in its accuracy. (Chalkidou et al. 2016). However, the benefits are that is a handheld portable device that can be used in adults and children of all ages.

Other types of tonometry that are known are the dynamic contour tonometry (DCT) and Ocular Response Analyser (ORA). These are not routinely used in community optometric practice and will not be covered in this thesis. Two devices used to monitor 24-hour IOP and not in optometry practice will also not be reviewed. These are the Triggerfish Contact Lens Sensor and the Implandata EyeMate.

1.14.3 REVIEW OF TONOMETRY TECHNIQUES

Accurate intraocular pressure (IOP) measurement has an important role in diagnosis and follow-up of patients with glaucoma (Kouchaki et al. 2017). A meta-analysis review of the agreement of tonometers with Goldmann tonometry showed that non-contact tonometry showed the least amount of variability with Goldmann; this included handheld non-contact instruments. Results showed that approximately two-thirds of measurements from non-contact tonometers were within 2.0mmHg of Goldmann tonometry measurements (Cook et al. 2012). This also implies that on average one third of intraocular pressure measurements are not reliable, by the 2.0mmHg criterion. Using data from the Blue Mountains Eye Study, Turner et al. (2013) showed that 34% of individuals with ocular hypertension (OHT) would be missed using a tonometer that underestimated IOP by 1.0mmHg and approximately 3% of the population would be falsely diagnosed if screening tests occur using a tonometer that over-read by 1.0mmHg. Cook et al. (2012) also reported that reliability between tonometers was

substantial but variability between repeat measurements was non-negligible. Thus, suggesting that consistent use of the same tonometer during clinical follow-up is arguably almost as important as the choice of tonometer (Cook et al. 2012).

NICE (2017) reviewed the accuracy of tonometers for diagnostic test accuracy and reassessment. They reported that *“when assessing the evidence from a diagnosis and reassessment perspective, all the evidence was of low to very low quality based largely on the uncertainty around the sensitivity estimates, all of which failed to reach the pre-specified threshold for consideration of a non-contact test used in the diagnosis and reassessment context”*. NICE (2017) recommend the use of Goldmann applanation tonometry for suspect glaucoma cases.

Efforts to achieve accuracy for intraocular pressure measurement are paramount for correct diagnosis but accuracy is also important for self-monitoring of intraocular pressure which may become a regular regime for patients who are suspect or diagnosed with glaucoma.

1.14.4 PACHYMETRY

Central corneal thickness is measured using a technique called pachymetry. Pachymetry methods use slit-lamp based devices, optical/laser based pachymetry, ultrasound or optical coherence topography methods.

Goldmann tonometry is effective for an average corneal thickness of 520 μ m measured by pachymetry (Iester et al. 2009). Central corneal thickness has been shown to vary between races; Caucasian, Chinese, Hispanic and Filipino eyes have comparable CCT values compared to a Black population in which they are significantly thinner (Aghaian et al. 2004). Central corneal thickness has shown to be associated in glaucoma progression in patients with higher baseline IOP compared to those with lower baseline IOP (European Glaucoma Prevention Study et al. 2007).

Goldmann tonometry measurements are often corrected for CCT and published formulae are available, however conversion is not recommended (Ehlers et al. 1975; Doughty and Zaman

2000). Available formulae to correct IOP measurements have not demonstrated an improvement for the accuracy of prediction models for development of glaucoma (Brandt et al. 2012; Medeiros & Weinreb 2012). Non-contact tonometers also give corrected IOP values. Rebound tonometry measurements have been shown to be overestimated in eyes with thicker corneas and underestimated in eyes with thin corneas (Brusini et al. 2006).

1.14.5 ASSESSMENT OF THE OPTIC NERVE

Glaucoma is an optic neuropathy and it is therefore paramount that the optic nerve is assessed. To characterise optic nerve damage, optometrists are practiced at assessing the cup-to-disc ratio and neuro-retinal rim (Varma et al. 1992a). Both parameters are dependent on the size of the optic nerve. An increase in optic nerve head cupping is a sign of loss of neuro-retinal rim tissue, and perhaps the most specific sign of glaucomatous optic neuropathy (Anderson 1983). A glaucomatous optic nerve head is shown in Figure 1.14-4. More recently, the disc damage likelihood scale (DDLS) has been devised for assessment of the optic nerve (Spaeth et al. 2002). This is a technique which is based on the neuro-retinal rim width for a given disc diameter (Henderer 2006).

Optometrists regularly examine the optic nerve using a direct ophthalmoscope or indirect ophthalmoscopy. Fundus biomicroscopy is preferred to direct ophthalmoscopy because assessment of size of the cup-to-disc ratio (CDR) is more accurate under stereoscopic conditions (Mwanza et al. 2017; Varma et al. 1992b; Watkins et al. 2003). However, comparison of serial stereoscopic optic disc photographs are considered the gold standard for assessing glaucoma progression (Mwanza et al. 2017; Kass et al. 2002; Leske et al. 1999; Medeiros & Weinreb 2009; Nicolela et al. 2003).

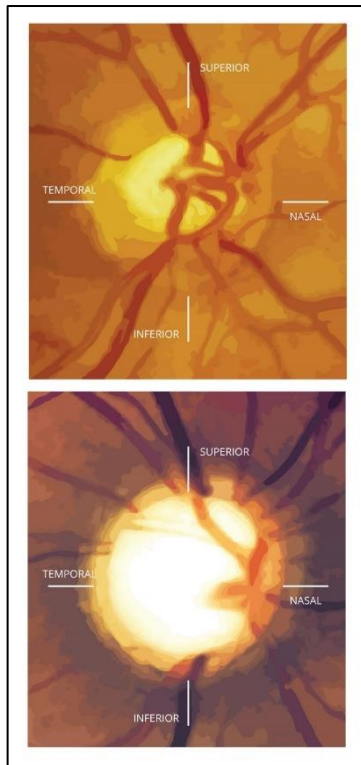


FIGURE 1.14-3 Pictorial image of a normal optic nerve head (top image) and a glaucomatous optic nerve head. in the top image, the neuroretinal rim has a normal shape in that its widest part is the inferior region, followed by the superior region and the nasal region, followed by the temporal region (ISNT). in the lower picture, the glaucomatous optic nerve has a neuroretinal rim which is thinner and the optic cup is larger and the cup is deeper.

1.14.6 ASSESSMENT OF THE RETINAL NERVE FIBRE LAYER

There is a topographical relationship between the location of glaucomatous visual field loss and RNFL damage in glaucoma eyes (Hoffmann et al. 2006). The thickness of RNFL also been shown to be different between ocular hypertensive, glaucomatous and normal eyes (Bowd et al. 2001; Hammel et al. 2017; Miki et al. 2014; Weinreb et al. 1995). The RNFL can be assessed with slit-lamp biomicroscopy, fundus photography or imaging modalities (Blumenthal & Weinreb 2001).

1.14.7 IMAGING

Technology has allowed for development of imaging that can quantify the structure of the retina and optic nerve. Automated imaging technologies are readily used in adjunction to an ophthalmologists/optometrists' assessment (Banister 2016). Clinical biomicroscopic examinations of the optic nerve yield a true view and may reveal glaucomatous features that

are not visible with computer-generated images but similarly the imaging techniques now give clinicians information not visible on direct observation. Examples of imaging instruments are: Confocal scanning laser ophthalmoscopy, which is commercially available as Heidelberg retina tomograph (HRT); it includes two classification algorithms (the Moorfields regression analysis (MRA) (Wollstein et al. 1998) and the glaucoma probability score (GPS) (Coops et al. 2006). Scanning laser polarimetry (Glaucoma Diagnostics (GDx) (Garas et al. 2012) or spectral-domain optical coherence tomography (OCT) (Sehi & Iverson 2013) techniques are used readily to assess the retinal nerve fibre layer.

1.15 ASSESSING THE VISUAL FIELD

Perimetry is the term used for measurement of a person's field of vision. Many perimeters record visual light sensitivity in terms of the decibel (dB), which is a unit to quantify retinal light sensitivity (Rudnicka & Edgar 2007). Perimetry evaluates the retina and the neural pathways responsible for relaying information from the retinal to the higher centres of the brain (Henson 2000). Examination strategies can broadly be divided into kinetic and static. Static tests can be divided into threshold and suprathreshold (Henson 2000).

1.15.1 KINETIC EXAMINATION STRATEGIES

For kinetic examinations, the examiner selects a stimulus of a given size and intensity and moves it from outside the visual field towards its centre, noting the position at which it first becomes visible (Henson 2000). This is repeated along a series of different meridians and the points at which the stimulus first became visible are then joined together by a line which is called an isopter (Henson 2000). A depression or loss within the visual field (scotoma) is detected by continuing to move the stimulus towards the centre of the visual field after it has first been detected (Henson 2000). The whole process can be repeated with stimuli of differing size and/or intensity, to build up a map of the patient's visual field (Henson 2000). Kinetic

perimetry is normally conducted with a bowl perimeter or tangent screen, such as the Goldmann bowl perimetry and the Bjerrum tangent screen (Henson 2000).

1.15.2 STATIC EXAMINATION STRATEGIES

Automated perimetry has been the clinical standard of care since the mid-1980s (Heijl et al. 2012). Suprathreshold tests are when stimuli are presented at an intensity that is calculated to be slightly higher than the patient's threshold and it is recorded whether the stimuli are seen (Henson 2003). The suprathreshold examination strategy has largely been developed as a screening/case finding procedure for conditions such as glaucoma (Henson 2000). The threshold strategy is technique in which the stimulus threshold is estimated at a series of different locations (Henson 2000). Automated perimetry may use a static target (standard automated perimetry) or a technique called frequency doubling technique (FDT). FDT is based on the frequency-doubling illusion which occurs when a sinusoidal grating at a low spatial frequency, flickers at a high temporal frequency (Jung et al. 2017).

1.16 SUMMARY

This section has provided information on the classification of glaucoma and its epidemiology. Pathogenesis, screening and treatment measures have also been reviewed with focus on POAG, NTG and OHT. There is ambiguity in knowledge of the pathogenesis of glaucoma. Age related changes occur in IOP but it is not known if there are people who always have slightly higher IOP than the average and therefore more at risk of optic nerve change. Normative values of average intraocular pressure in younger adults are not known, nor is it known if those with a family history have higher average measurements. It is also not known how many years prior to glaucoma diagnosis, that IOP and the optic nerve begin to change. The literature reviewed thus far reports that there are people who may be more at risk of POAG but is unable to provide information how early changes are detectable in those who are at risk. Chapter 1 has been an introductory review of literature to form a rationale for a formal

literature review on the risk factors of POAG. The literature review will be the basis for the aims and objectives of this thesis.

2. LITERATURE REVIEW

2.1 AIMS OF LITERATURE REVIEW

The introductory chapter has provided an overview of the eye and the structures involved in glaucoma. The aims for this literature review are to investigate the risk factors for primary open angle glaucoma. The literature will be critically appraised using the Critical Appraisal Tools by CASP (2017).

2.2 LITERATURE SEARCH

The literature searches for this thesis were conducted from November 2012 to November 2017 using PubMed, Cochrane Library and Google-scholar databases. Ophthalmology and optometry text books were used for background reading. Publications written in English were reviewed from 1967. Alerts were set using the terms open angle glaucoma, pathogenesis and intraocular pressure for Google and Mendeley. The “related citations” option in PubMed was also used to capture additional articles. The search strategy used the following terms:

- Open angle glaucoma and risk factors
- Open angle glaucoma and intraocular pressure
- Ocular hypertension and intraocular pressure
- Intraocular pressure and normal
- Open angle glaucoma and family history
- Open angle glaucoma and pathogenesis
- Open angle glaucoma and visual field
- Open angle glaucoma and optic nerve
- NICE Guideline and glaucoma

2.3 RESULTS OF THE LITERATURE SEARCH

Pubmed and googlescholar presented approximately 4000 research papers on glaucoma and risk factors. These were screened and refined to approximately 650 papers. The literature was screened by the suitability of the title and abstract. Key epidemiological studies, NICE guidelines and the European Glaucoma Society were also used to search for papers. Studies that were based in the Far East were not included as there is an indication that the prevalence of glaucoma is different in Asia as compared to Europe and the Americas (Chan et al. 2015).

2.4 RISK FACTORS FOR PRIMARY OPEN ANGLE GLAUCOMA

Literature has shown that the key risk factors associated with POAG are age, gender, race, family history, myopia, IOP, corneal biomechanics and systemic factors. These will each be reviewed in turn.

2.4.1 AGE

Observation studies and randomised controlled trials give evidence for the contribution of increasing age in the incidence and prevalence of glaucoma (Leske et al. 1995; Ekström 2012; Gordon et al. 2002; Le et al. 2003; Mukesh et al. 2002; Miglior et al. 2007).

Three population studies have shown an increase in incidence of POAG with age. A five-year study based in Australia reported that there was an incremental change in incidence of OAG from 0.2% at the ages of 40-49 years to 5.4% at ages 80 and over (Le et al. 2003; Mukesh et al. 2002). This study did not report any specific race differences in the participants. A specific definition for OAG was also not given and therefore it is assumed that open angle glaucoma due to secondary causes (e.g. pigment dispersion syndrome or pseudo exfoliation) may have been included in this study (Figure 1.6-2). Similar results were reported by the Rotterdam

Study (Dielemans et al. 1994). This was a five-year prospective cohort study investigating the prevalence of POAG. Increasing age changed prevalence from 0.2% at the ages of 55-59 years to 3.3% at ages 85-80 years. A longer, 20-year population study based in Sweden (Ekstrom 2012) used diagnostic criteria published by Foster (2002) and distinguished POAG and secondary OAG in their analyses. However, the increase risks in OAG with age were reported collectively for both groups. It was reported that participants from 70 years and older experienced a 1.21-3.22 (95% CI) increased risk compared with those under the age of 70 years (Ekstrom 2012). The Barbados Eye Study (Leske et al. 1995) was a population based study for pre-dominantly Black participants between the ages of 40 and 84 years. The study found that 7% of the group had OAG and this group were of an older age; the mean age of the group without OAG was 57.8 ± 11.8 years and the mean of the OAG group was 69.2 ± 10.4 years.

A randomised control trial was conducted by the European Glaucoma Prediction Study (EGPS) (Miglior et al. 2007). Participants with IOP greater than 22.0mmHg in one eye were placed on a double-masked placebo trial to research conversion to OAG. The EGPS study also found that age was “significantly predictive” for the development of OAG. Interestingly, considering current NICE guidelines, referral for consideration of treatment would be considered only if IOP was 24.0mmHg or greater if the optic nerve and visual fields were healthy.

A meta-analysis of 46 observational studies (Rudnicka et al. 2006) reported that although black populations had the highest OAG prevalence at all ages, the increase in prevalence of OAG with age was highest in White populations.

Changes at the trabecular meshwork and retina are two of the suggested reasons why the risk of glaucoma may increase with age.

2.4.1.1 *TRABECULAR MESHWORK*

Morphologic studies have shown that trabecular meshwork dysfunction may result in an increase in intraocular pressure and thereby increase the risk of glaucoma (Chhunchha et al. 2017). The reasons for these changes may be that a natural decrease of the cellularity of the trabecular meshwork with age results in a decrease in outflow (Alvarado et al. 1980; Grierson & Howes 1987) or pathological alterations (Gabelt & Kaufman 2005).

2.4.1.2 *RETINA*

Ageing shows an accumulative change in the structure of the retinal layers. People of increasing age show a loss in retinal vessel density and thinning of the retinal nerve fibre layer and ganglion cell and inner plexiform layer (Wei et al. 2017; Hammel et al. 2017). In contrast to the reduction in the inner retinal layers, thickening of the outer plexiform layer and photoreceptor layer have been reported (Wei et al. 2017) with increasing age. The rate of change in the retinal layers has been reported to be faster in glaucoma subjects (Hammel et al. 2017).

2.4.2 GENDER

Literature on the risk of POAG being different for males and females showed varying results. The Beaver Dam Eye Study (Klein et al. 1992) was a population study that did not find a gender difference with the prevalence of OAG. Rudnicka et al. (2006) reported from their meta-analysis that OAG is more common in men than in women across all racial groups but included only two studies in their analysis for this. Kapetanakis et al. (2016) and Chan et al. (2016) reviewed POAG cases and both reported that age-adjusted prevalence of POAG is higher in males compared with females and that this remains consistent across all ethnic groups.

2.4.3 RACE

A population based prevalence study of POAG in Baltimore, estimated the prevalence to be up to five times higher in the Black race as compared to White (Tielsch 1991). Kapetanakis et al. (2016) summarised in their systematic review that Black populations have a higher prevalence of POAG from early middle life. An evidence-based review of population studies reported that being of Black race is not an independent risk factor but the Black race have thinner corneas, greater cup-to-disc ratios and higher IOP; it is these factors that may increase the risk of POAG (Friedman et al. 2004).

A recent case-control study conducted with a South African population, reported that participants with a higher proportion of genetic African ancestry had a thinner CCT and African ancestry also had a higher IOP in POAG participants (Bonnemaijer et al. 2017). But the study also found that as the proportion of ancestry got stronger, the difference in CCT between POAG and controls lessened. The authors reported that knowing the strength of the racial link is important (Bonnemaijer et al. 2017). This study had defined inclusion criteria and POAG diagnostic criteria.

The prevalence of POAG with race changes with age. Age-specific increase in POAG are higher amongst White and Hispanic populations in later life, followed by Asians and lowest in the Black population (Rudnicka et al. 2006; Kapetanakis et al. 2016).

2.4.4 FAMILY HISTORY OF PRIMARY OPEN GLAUCOMA

This section will review the risk of POAG with a positive family history. Hereditary forms of glaucoma can arise from environmental, gene-environment, and also gene-gene interactions (Doucette et al. 2015). Inheritance can also be as a Mendelian trait; this has been discussed in section 1.11. Kass and Becker (1978) reported a correlation between family history and glaucoma; based on their observations, researchers suggested that the most effective method of glaucoma detection was to check family members (Samples 2010). Prevalence studies have shown the association between POAG and a positive family history.

Rosenthal and Perkins (1985) conducted a 10 to 12 year follow up of 101 participants with a family history of POAG. Confirmed POAG had developed in 3% of the group, while an additional 6% were diagnosed as suspect POAG.

The Baltimore Eye Survey (Tielsch et al. 1991) was a cluster sample survey of 5000 participants (2500 White participants and 2500 Black participants). The ages of the participants subjects were 40 years and greater. POAG was diagnosed by optic nerve and visual field assessment but IOP was not included as part of the diagnostic criteria (Sommer 1996). The age-adjusted association between POAG and family history was shown to be stronger when the affected relative was a sibling (OR 3.7 95% CI 2.1-6.5), rather than a parent (OR 2.2 95% CI 1.1-4.4) or child (OR 1.1 95% CI 0.3-4.9) (Tielsch et al. 1994). These results suggest that a polygenic or multifactorial influence contributes to the expression of POAG (Lichter 1994). The Baltimore Eye Survey may have included secondary glaucoma cases within its sample. This study is based on a single observation whereas a clinical diagnosis basis a diagnosis on structural change of the optic nerve and/or functional change of the visual field.

The absolute and relative risk of primary open glaucoma of first degree relatives was assessed through a population-based study in Rotterdam (Wolfs et al. 1998). The minimum age of the glaucoma cohort was 44 years. The results were for lifetime risk of elevated pressure in those participants with a family history of glaucoma was reported to be 6.3 (95% CI 2.1-19.2). Lifetime risk of enlarged CDR was 3.8 (95% CI 2.3-6.1). The study concluded that the lifetime risk of glaucoma at 80 years was 22.0% for relatives of participants with glaucoma compared to 2.3% of the controls (OR 9.2 95% CI 1.2-7.3). (Wolfs et al. 1998). An enlarged cup to disc ratio was the earliest feature of change reported in those with a family history of glaucoma (Wolfs et al. 1998).

A case-control study carried out to compare the differences between POAG participants and controls in Caucasians over the age of 40 years, found that a family history of glaucoma in first degree relatives had an OR of 7.67 (95% CI 3.25-18.1) (Charliat et al. 1994). The risk

factors were determined by means of a questionnaire and therefore may not have been accurate or confirmed.

The Glaucoma Inheritance Study based in Tasmania (Green et al. 2007) was ethnically homogenous. POAG was found in 60% of the participants who had a family member: 38.6% had a first-degree relative affected, 6.5% had a second-degree relative affected, 6.1% had a third-degree relative affected, and 8.4% had a fourth-degree relative affected (Green et al. 2007). The odds ratio for having a participant with POAG to have a positive family history was stated to be and 4.1 (95% CI 3.2–5.2) (Green et al. 2007). A similarly designed study was the Nottingham Family Glaucoma Screening Study (Sung et al. 2006). This study found the prevalence of OAG (POAG, NTG and OHT) to be 11.8% in siblings (Sung et al. 2006). These results are similar for those found for siblings in the Rotterdam Study and the Baltimore Eye Survey.

A positive family history of POAG is not a simple risk factor (Boland & Quigley 2007). More often, cases of POAG are a combined effect of genetics and environmental risk factors (Fingert 2011). This section has reviewed the population studies for the prevalence of POAG in family members and will discuss the difference in optic nerve and intraocular pressure in family members under each individual section.

2.4.5 REFRACTIVE ERROR

A systematic review on the risk factors of glaucoma that can be assessed in a routine eye examination presented that myopia is associated with POAG (Hollands et al. 2013). Moderate myopia was defined as 3 to 6 dioptres, high myopia was defined as 6 to 8 dioptres, and pathologic myopia is defined as greater than 8 dioptres (Hollands et al. 2013). This review considered minimal studies but found four studies that reported that at a threshold of 3.0 diopters the prevalence of glaucoma was 6.0% (OR 2:1 95% CI 1.3-3.4). Hollands et al. (2013) also reported that compared to other all other risk factors of glaucoma, one study had reported high myopia to have the strongest odds ratio (OR 5.7 95% CI 3.1-11). Findings from a meta-

analysis also reported myopia to double the risk of OAG in comparison to individuals without: pooled OR were 2.46 (95% CI 1.9-3.2) for high myopia (greater than 3 dioptres) and 1.77 (95% CI 1.4-2.2) for low myopia (up to 3 dioptres) (Marcus et al. 2011). The standard deviations in the latter meta-analysis were narrowly spread compared to a wide range of risks; (Poostchi et al. 2012) report that this variation in the risk of glaucoma in individuals may reflect true differences between study populations. Poostchi et al. (2012) performed a regression analysis of the cross-sectional studies selected by Marcus et al. (2011) and found a 50% increase in risk between those with low and high myopia (OR 1.5 95% CI 1.0-2.3).

A large Swedish population study with participants aged between 57 years and 79 years reported that glaucoma was more prevalent in myopic eyes with lower IOP (Grodum et al. 2001). Interestingly, the inclusion criteria included localised narrowing of the optic disc rim, vertically elongated cupping, localised RNFL defects and IOP over 25.0mmHg. This study was also based on undiagnosed glaucoma from a direct assessment rather than detection of change.

The susceptibility of POAG in people with myopia has also been reported in other population studies such as the Blue Mountains Eye Study (Mitchell et al 1999) and the Barbados Eye Study (Wu et al 1999). However, the OHTS (Gordon et al. 2002) did not find myopia to be a baseline predictive factor for POAG development.

2.4.6 INTRAOCULAR PRESSURE

Increased intraocular pressure was previously considered to be a diagnostic feature of POAG, but this is now best described as a modifiable risk factor (Sommer 1989). It is the only risk factor that is modifiable with medication or surgery (Morrison et al. 1998). With current NICE guidelines (NICE 2017), IOP at 24.0mmHg is the level required for referral for assessment if there is no other pathological change.

Literature readily shows that the level of IOP is a risk factor for POAG incidence, prevalence and progression (Boland & Quigley 2007). The literature on IOP will be considered in three

parts: the risk of POAG with higher baseline IOP; the progression of POAG with treated IOP and lastly IOP asymmetry and diurnal variation.

2.4.6.1 RISK OF PRIMARY OPEN ANGLE GLAUCOMA AND INTRAOCULAR PRESSURE

The Rotterdam study showed that a higher level of baseline IOP led to a higher risk of incident OAG in a pre-dominantly white population over the age of 55 years (de Voogd et al. 2005). The Ocular Hypertension Study (OHTS) was a multicentre-randomised control trial on the use of IOP lowering drops for the prevention of POAG (Gordon et al. 2002). The number of participants that developed glaucoma had increased with higher IOP levels. The results showed that 17% of the control group that progressed to develop POAG had a mean IOP of 22.2mmHg; 12% had a mean IOP of 24.9mmHg and 36% had an IOP of 27.9mmHg; all these participants were reported to have a central corneal thickness of 555µm or less.

2.4.6.2 GLAUCOMA PROGRESSION AND INTRAOCULAR PRESSURE

The progression of open angle glaucomas (including secondary causes) have been investigated through four multi-centred randomised clinical trials (Coleman & Miglior 2008). These trials are the Collaborative Normal Tension Glaucoma Study (CNTGS 1998), the Advanced Glaucoma Intervention Study (AGIS) (Gaasterland et al. 2000), the Early Manifest Glaucoma Trial (EMGT) (Leske et al. 1999) and the Collaborative Initial Glaucoma Treatment Study (CIGITS) (Musch et al. 1999). All participants on these trials had OAG. Coleman and Miglior (2008) suggest that these studies report predictive factors rather than prognostic factors as factors associated with endpoints or outcomes were not eliminated. These trials were conducted prior to 2008 when glaucoma specialists held a symposium to discuss glaucoma endpoints and outcomes (Weinreb & Kaufman 2009). Endpoint and outcome measures should be considered with optic nerve parameters and/or visual field indices (Coleman & Miglior

2008). These endpoints are objective and do not reflect the impact of the changes on quality of life (Hartmann & Rhee 2006; Vandebroek et al. 2011).

The CIGITS (Musch et al. 1999) had a participant group of newly diagnosed glaucoma patients. Most of these participants had POAG. Visual field change was monitored in two groups; one group treated with medication and a second through surgery. Each group had an initial IOP of approximately 27.0mmHg which was reduced to 14.0 to 18.0mmHg. Over a period of five years, little change had been noted on visual field outcome (Musch et al. 1999). The CIGITS lowered IOP by 50 % and report that as there was a substantial reduction, it may take longer to show any functional change (Musch et al. 1999). It has also been a suggestion that a 30% reduction in IOP can also be effective in decreasing the rate of visual field loss (Anderson 2003; Heijl et al 2002). The Early Manifest Glaucoma Treatment Study (EMGTS) lowered IOP by an average of 25% in a sample that contained participants with baseline pressures of up to 29.0mmHg. The EMGTS demonstrated that IOP-lowering treatment significantly delayed disease progression in patients with normal tension glaucoma and in those with higher IOP (Heijl 2002).

A major outcome for the AGIS was the stability or progression of visual fields as related to IOP control after the initial intervention (AGIS Investigators. 2000; Nouri-Mahdavi et al. 2004). The participants who had an IOP of less than 18.0mmHg for all visits over the first six years were least likely to show worsening. A lower mean IOP during the 18 months after the initial intervention also predicted a better functional outcome (AGIS Investigators. 2000; Nouri-Mahdavi et al. 2004).

Caprioli (2007) stated that the benefits of IOP reduction have been considered using prospective, randomised, long-term studies, a comparison of medical versus surgical and treatment versus no treatment. These study designs have shown that the progression of glaucoma is reduced with robust IOP reduction (Caprioli 2007).

This review will now follow on to discuss the risks of IOP asymmetry and fluctuation.

2.4.6.3 *INTRAOCULAR PRESSURE ASSYMETRY AND FLUCTUATION*

IOP measurements can fluctuate. This fluctuation may also be asymmetric. The term “short-term IOP fluctuation” can indicate what occurs over hours or days and “long-term IOP fluctuation” to indicate what occurs over months to years (Caprioli 2007). Caprioli (2007) states that “IOP investigation is best suited to standard deviation as it is less affected by outliers and takes the number of measurements into account”. Asymmetry between eyes with IOP measurements in normal tension glaucoma has been shown to lead to greater optic nerve head damage; the eye with the higher IOP has the greater damage (Collaborative Normal-Tension Glaucoma Study Group 1998).

The Advanced Glaucoma Intervention Study (Nouri-Mahdavi et al. 2004) used stability or progression of visual fields as an outcome to measure predictive measures for OAG. The study used single method long term evaluation and point-wise regression analysis. It was suggested that the most consistent predictors for visual field progression were older age and inter-visit IOP fluctuation. The odds for visual field progression increased by approximately 30% for each 1.0mmHg increase in IOP fluctuation and 5-year increment in age (Nouri-Mahdavi et al. 2004). Lee et al (2007) conducted a retrospective analysis of data from 150 subjects over the age of 18 years with POAG, NTG, OHT and glaucoma suspects. Their records were investigated for a variation between intraocular pressure and glaucoma progression over a period of 12 years (minimum 5 years). This study showed through multivariate analysis, that with each 1.0mmHg increase in standard deviation of IOP, glaucoma progression was 4.2 times more likely (Lee et al. 2007). The results of that analysis supported the AGIS data (Gaasterland et al. 2000) with suggestion that IOP variation between visits was a significant predictor of disease progression.

2.4.7 CORNEAL THICKNESS

Corneal thickness has also been implicated as an independent risk factor for the development of glaucoma (Sng et al. 2016). The OHTS demonstrated that thinner central corneal thickness

(CCT) may be an important predictive factor for the development of POAG in both univariate and multivariate models (Gordon et al. 2002). In participants who had ocular hypertension that went on to develop POAG, mean CCT was reported to be $553\mu\text{m} \pm 38.8\mu\text{m}$ compared to $573.4\mu\text{m} \pm 37.8\mu\text{m}$ to the control group that did not have OHT. It was discussed in Section 2.4.3, that literature has reported a higher prevalence of POAG in the Black population. The OHTS supported the evidence by Friedman et al. (2004) in reporting that the Black participants in the study had thinner CCT and larger baseline vertical CDR from baseline and that when multivariate analyses adjusted for these factors race was no longer a statistically significant predictor (Gordon et al. 2002).

CCT has not only been implicated as a risk factor for development of visual field loss among patients diagnosed with OHT but it has also been suggested that it may constitute as a risk factor for progression of visual field loss amongst patients with pre-perimetric glaucoma (Medeiros et al. 2003).

Corneal hysteresis was described in Section 1.2.1. The risk factor of a lower corneal hysteresis measurement and an increased risk of glaucoma progression have been inconclusive. Studies have shown that there is a difference in corneal hysteresis and POAG but it is not known if this is due to ageing or if the association is a cause or an effect (Medeiros et al. 2013; Congdon et al. 2006; Moraes et al. 2012; Khawaja et al. 2014).

2.4.8 OPTIC NERVE HEAD

Section 1.10 has reviewed that common features of glaucoma are loss of retinal ganglion cells, thinning of the retinal nerve fibre layer, and cupping of the optic disc (Jonas et al. 2017). Structural changes to these features are used to detect and monitor progression of glaucoma (Seth et al. 2017).

The European Glaucoma Prevention Study (EGPS Group et al. 2007), reported that larger vertical CDR and larger vertical CDR asymmetry, were statistically significant predictive factors for development of OAG over a 5-year period. These results were determined from a

double-masked trial from OHT participants. The Visual Impairment Project (Le et al. 2003) assessed potential risk factors for the development of OAG in Australia for subjects aged forty years and over. A CDR greater than 0.7 was associated with a greater risk of development of possible OAG. However, the study methodology implies that only those with a CDR of 0.7 or greater were assessed at baseline and 5-year follow for detection of change.

The EPGS also presented results that showed that RNFL changes with OCT assessment were more predictive of changes using a risk calculator than other techniques such as the GDx or HRT (Colombo et al. 2016) (Section 1.14.6). Differences at the RNFL have also been suggested in normal subjects with a first degree relative of POAG when compared to those without a family history. RNFL thinning was detected in normal looking discs on comparison of forty subjects with the family history (Karti et al. 2017). This study would require longer follow up to understand whether the changes were an early indicator of glaucoma (Karti et al. 2017).

Optic disc diameter was found to be a risk factor for POAG in two population studies involving both European-derived (Healey & Mitchell 1999) and African-derived persons (Quigley et al 1999). The Blue Mountains study, involved over 3000 subjects and compared optic disc size in the eyes of those classified as normal to those with open-angle glaucoma, ocular hypertension, or pseudo-exfoliation syndrome (Healey et al 1997). The mean optic disc diameter in glaucomatous eyes was significantly larger than in normal eyes (Healey et al 1997). It was also reported with this study that there was linear relationship between vertical CDR and vertical disc diameter (Crowston et al. 2004)

Ageing changes of the optic nerve have been reported. The Beaver Dam Study concluded from a 5 and 15 year follow up study of normal eyes, that an incremental change in vertical cup-to-disc ratio were associated with an increase in IOP (Klein et al. 1997; Klein et al. 2006). The risk factor of this change being pathological for the optic nerve has been investigated through alterations at the lamina cribrosa. In vivo imaging, albeit in an animal study, showed pressure variations from baseline normal levels caused changes of neural tissues (Tran et al. 2017).

Biomechanical models of the eye have hypothesised that IOP-related stress is dependent on the individual and pathophysiologic levels could cause changes in cell synthesis and tissue microarchitecture. This would result in mechanical failure of the structures of the optic nerve and retinal ganglion cell death (Bellezza et al. 2000; Rebolleda et al. 2017).

2.4.9 SYSTEMIC CONDITIONS AND POAG

Systemic factors have been shown to be associated with the prevalence of POAG but they are not independent risk factors. The Blue Mountains study considered the prevalence of POAG in a population of Australians aged from 49 years to 96 years and suggested that there is an association with diabetes. POAG and OHT prevalence was increased in participants with diabetes when compared to those without (Mitchell et al. 1996). Also for those participants receiving glaucoma treatment, IOP was reported to be consistently higher in those with diabetes (Mitchell et al. 1996). These results have been contradicted by other population studies (Tielsch et al. 1991). However, a recent meta-analysis concluded from a review of thirteen studies that there is a strong association between diabetes and intraocular pressure (Zhou et al. 2014). A similar meta-analysis considering blood pressure and POAG suggested that hypertension was associated with increased IOP but only a possibility in the development of glaucoma (Zhao et al. 2014). These meta-analyses have included studies from all countries whereas this review has concentrated on studies in Europe, Americas and Australia.

The UK Biobank considered the associations of systematic factors with Goldmann-correlated IOP and corneal compensated IOP in a British cohort (Chan et al. 2016). The study reported that diabetes was related to corneal biomechanical properties and systolic blood pressure with a higher IOP (Chan et al. 2016).

Vascular factors have been implicated as risk factors in glaucoma. Examples of these are ocular blood flow, ocular perfusion pressure and retinal calibre changes (Mitchell et al. 2005; Tielsch et al. 1995; Chen et al. 2016; Flammer et al. 2002). The literature on ocular blood flow

is varied as studies have investigated it using different techniques and at different stages of glaucoma (Flammer et al. 2002).

2.5 SUMMARY OF LITERATURE REVIEW

This literature review has discussed the risk factors implicated in POAG. The incidence and prevalence of POAG increase with age. With advancing age, intraocular pressure has also been shown to increase together with increases in vertical cup to disc ratio and thinning of the RNFL. The literature also reports that there is an age specific increase in POAG with the Caucasian race but a higher prevalence in the Black population from early middle life. The male race has a higher prevalence. Myopia is also a risk factor for glaucoma. A family history of glaucoma is strong risk factor of POAG with the odds ratio decreasing from first to fourth degree relative. The literature reviewed has also shown that the research on the risk factors of POAG has largely been based on population studies or treatment studies. All the studies have been on a population age of 40 years and above.

The designation “glaucoma” is reserved for people with damage to the optic nerve (Jampel 2017). POAG changes are not rapid in progression and the processes underlying the subtleties of change in glaucoma have begun to be investigated; one example the use of biomechanics (Rebolleda et al. 2017). These types of studies are beginning to highlight that not enough is known about how these changes are happening and when and why certain individuals are susceptible to changes. However, the literature in this review present studies that have considered what is changing and who is at risk.

A prevalence of 3% to 4% of POAG has been reported in a population aged 48 years or more (Mitchell et al. 1996; Leske et al. 1994). Yet, the literature does not clearly provide information on the glaucomatous changes in adults younger than the age of 40 years. Appreciating that glaucomatous changes are gradual, could there be early detectable changes in those people that are susceptible to glaucoma with known risk factors? The earliest detectable changes are important for screening for the presence of glaucoma in the community

or in a primary eye care setting is increasing. The rationale for early detection is that vision loss from glaucoma can be reduced by treatment to lower IOP and that glaucoma is largely asymptomatic until there is noticeable damage to the optic nerve (Jampel 2017).

This thesis highlights that research is needed to understand the process of glaucoma in those at risk in the years preceding glaucomatous change. This aims for the research for this thesis will be presented in Chapter 3.

3. HYPOTHESES AND THESIS AIMS

3.1 OVERVIEW

The literature review discusses the importance of early detection of primary open angle glaucoma (Chapter 2). There is strong evidence that the risk of developing glaucoma is raised with a positive family history. There are also other factors that place groups of people at risk; examples being those with myopia, male gender and Black race. There is an importance to research the groups of people who are at risk of glaucoma as we do not have knowledge on how these groups present at an earlier age. The questions that have been raised from the literature review are:

- Are people at risk of glaucoma, anatomically predisposed? The increased risk of glaucoma changes with an increased vertical cup to disc ratio have been reviewed. Is it possible that people are born with this difference?
- Does vertical cup to disc ratio change before the start of glaucoma changes or does it change after due to progression of the condition?
- Is intraocular pressure slightly higher for those at risk of glaucoma but still within a normal range prior to glaucoma changes? Could slightly higher IOP cause an increased burden, increasing the risk of glaucomatous changes?
- If intraocular pressure is not slightly higher for those at risk throughout life, could there be an earlier detection point for when it starts to increase? Is it possible that intraocular pressure could be measured higher than average up to ten years, six years or three years before glaucomatous changes?

3.2 THESIS AIMS

The introduction and literature review have raised several questions, answers to which would aid an understanding of the process of glaucomatous change. The aims of this thesis are to investigate glaucomatous change through investigating:

1. People at risk of primary open angle glaucoma due to a family history; and/or
2. People who have primary open angle glaucoma and investigating how they differed from control populations many years before they developed changes.

Knowledge of the risk factors of glaucoma and its progression has been collected from population studies or clinical trials that have on average a follow up period of five to eight years (Broman et al. 2008). Studies have found that baseline IOP, a larger baseline vertical CDR and older age at baseline are all factors which are more likely to cause visual field deterioration over the next eight to nine years (Lee et al. 2014; Leske et al. 2008; Lichter et al. 2001; Gordon et al. 2007). However, the baseline values for glaucoma studies are often set above an IOP of 21.0mmHg and a vertical CDR is 0.7 as confirmed glaucoma participants are being sampled. It would not be ethical to monitor a confirmed glaucoma participant in a prospective study without suitable treatment. This may be why there is gap in the literature on the changes that have occurred with IOP and vertical CDR prior to these factors being termed baseline. To consider changes prospectively in patients who have a risk of developing glaucoma as a longitudinal study would be difficult to bring to fruition due to the sample size that would be required and time scale. However, retrospective analyses of data have successfully been used in past glaucoma studies (Rossetti et al. 2010; Oliver et al. 2002; Kobelt-Nguyen et al. 1998). With consideration of this, and with supervisory discussion and input, the investigations for this thesis were planned through two retrospective studies.

The aims of this thesis are to consider the differences in people with confirmed glaucoma and/or people who at risk of glaucoma due to a family history. This will be done by investigating if patients that have got confirmed glaucoma changes (requiring treatment) had

normal intraocular pressure and optic nerve, ten years prior to diagnosis. If differences against a control group are found, then this raises the possibility of monitoring earlier and screening earlier for changes for earlier intervention. The aims of this thesis are not to answer these questions but to initially ask if there are there detectable differences up to ten years prior to diagnosis.

3.3 AIMS AND OUTCOME MEASURES.

The aims of the research reported in this thesis are to investigate whether there are differences in intraocular pressure or optic disc cupping in young populations who do not have glaucoma; that either have the risk factor of family history of glaucoma or in later years go on to develop glaucoma.

3.3.1 AIM FOR STUDY 1

3.3.1.1 PRIMARY AIM FOR STUDY 1

The primary aim for Study 1 is to investigate intraocular pressure values in patients with a family history of glaucoma and those without a family history of glaucoma.

3.3.1.2 PRIMARY OUTCOME MEASURE FOR STUDY 1

The primary outcome measure for Study 1 is to establish whether intraocular pressure values in patients with a family history of glaucoma is significantly higher than in patients without a family history of glaucoma.

3.3.1.3 SECONDARY AIM FOR STUDY 1

The secondary aim for Study 1 is to compare optic nerve cup to disc ratio measurements in patients with a family history of glaucoma to those without.

3.3.1.4 SECONDARY OUTCOME MEASURE FOR STUDY 1

The secondary outcome measure for Study 1 is to establish whether the optic nerve cup to disc ratio measurements in patients with a family history of glaucoma is significantly larger than in patients without a family history of glaucoma.

3.3.2 AIM FOR STUDY 2

The aim of Study 2 is to investigate if the risk factors for primary open angle glaucoma are present many years before glaucoma develops.

3.3.2.1 PRIMARY AIM FOR STUDY 2

The primary aim for Study 2 is to investigate intraocular pressure values in patients with primary open glaucoma, ten years prior to their diagnosis.

3.3.2.2 PRIMARY OUTCOME MEASURE FOR STUDY 2

The primary outcome measure for Study 2 is to establish whether intraocular pressure values in patients with primary open angle glaucoma are significantly higher ten years prior to diagnosis when compared to a pair-matched control group.

3.3.2.3 SECONDARY AIM FOR STUDY 2

The secondary aim of Study 2 is to investigate optic nerve cup to disc ratio measurements in patients with primary open glaucoma, ten years prior to their diagnosis.

3.3.2.4 SECONDARY OUTCOME MEASURE FOR STUDY 2

The secondary outcome measure for Study 2 is to establish whether the optic nerve cup to disc ratio measurements in patients with primary open angle glaucoma is significantly larger ten years prior to diagnosis when compared to a pair-matched control group.

4. STUDY 1 DESIGN AND METHODS

4.1 STUDY 1 OBJECTIVES

The objectives for Study 1 are:

- To retrospectively collate intraocular pressure readings from anonymised records from participants aged between 18 years and 40 years.
- To create a frequency distribution curve for intraocular pressure measurements for participants between 18 years and 40 years.
- To compare intraocular pressure readings from those participants that reported a family history of glaucoma with those that did not.
- To compare the recorded vertical optic nerve head cup to disc ratio in participants that had a family history with those that did not.

4.2 STUDY 1 DESIGN

Study 1 is an exploratory study for risk factors of primary open angle glaucoma in two groups of adults aged between 18 years and 40 years. From the two groups, one is to have a family history of glaucoma and the other shall not. To conduct this research a cross-sectional study was designed. Cross-sectional studies are like a snapshot, measuring both exposure and outcome at one-time point (Grimes & Schulz 2002). The advantage of cross-sectional studies are that participants are not deliberately exposed, treated, or not treated and hence there may be fewer ethical difficulties. This type of study can also be relatively inexpensive (Mann 2003). A sample size calculation was not conducted as there are no previous studies that have provided adequate information for determining an appropriate effect size.

4.3 ETHICAL APPROVAL

Ethical approval was requested and granted from three separate committees; the Faculty Research Ethics Panel of Anglia Ruskin University, London South Bank University and the

Institute of Optometry. The process for ethical approval took approximately 12 months. The chair of London South Bank University ethics committee stated that ‘the sharing of data and open access to data is an evolving research and ethical area’ and the application for this study was thoroughly considered in view of data protection and anonymisation prior to being given approval. The study did not apply for NHS ethical approval and did not use any NHS patient data. The study adhered to the tenets of the Declaration of Helsinki. The ethics application, information sheet, consent form and approvals letter are shown in Appendices 1 to 6 (Sections 12 to 17).

4.3.1 INCLUSION AND EXCLUSION CRITERIA

To aid recruitment and obtain an expansive sample of cases, this study attempted to have broad inclusion criteria. The inclusion criteria required that the anonymised records included the required variables listed in Section 4.4. Important exclusion criteria were; refractive surgery, corneal pathology, pigment dispersion syndrome, pseudo-exfoliation and glaucoma.

4.3.2 PATIENT INFORMATION SHEET AND CONSENT

The Information Commissioner’s Office (ICO) guidelines (ICO 2017) for procedures for data anonymization were studied and complied with. The anonymised data used in this study were not “processed in such a way that substantial damage or substantial distress was likely to be, caused to any data subject” (ICO 2017). The ICO (2017) advise that patient consent is not needed for anonymised data or pseudonymised data to be extracted for research. This was confirmed by email correspondence. However, each participating optometric practice had written policies on display advising their patients that anonymised data from their clinical records may be used for audits and research purposes. The ethics committees were informed that Anglia Ruskin University Data Protection Register entry listed research as one of the purposes for which data are held. The University Eye Clinic also had a policy in place that required each patient to read and sign a consent document if they agreed for their data to be

used for research purposes. Every record at the University Eye Clinic had a letter of consent associated with it; with consent being reconfirmed at each eye examination. The author also created a participant information and consent form which were written and approved by the ethics committees (Appendices 2 & 3). This was to safeguard ethical practice in the event of the possibility that records needed to be used prior to the date of the policies being in place.

4.4 DATA COLLECTION

The study was designed to collect retrospective data from participants who were under 40 years of age at the time of their eye examination. The data were selected as forming two groups: those with a family history of glaucoma and those with no family history of glaucoma. The University Eye Clinic at Anglia Ruskin University and a community optometric practice in Bedfordshire were the two sites chosen for data collection. The investigator was employed at both practices.

Each eligible anonymised clinical record was used to extract the following data:

1. Sex – coded as male or female.
2. Age - recorded numerically in years as age at time of examination. Only the year of birth was known as all identifiable data had been anonymised.
3. Vision/visual acuity - converted to LogMAR. Recorded numerically for right and left eye.
4. Refractive error – converted to spherical equivalent refraction. Recorded numerically for right and left eye.
5. Family history of glaucoma – coded as yes or no and, if yes, by which family member and by which type of glaucoma (if known).
6. Intraocular pressure measurement- recorded in mmHg. Recorded numerically for right and left eye.
7. Optic nerve head assessment – Vertical cup to disc ratio. Recorded numerically for right and left eye.
8. Visual field assessment. Recorded numerically for right and left eye. Coded to yes or no if an assessment was made. Details of the assessment were summarised as full or defective.

4.5 DATA ANONYMISATION

Study 1 employed a two-stage process for data anonymisation. The researchers involved were the investigator and one of the doctorate supervisors. Both researchers were members of the clinical team who routinely have access in their work to clinical records and who are aware of the need to maintain patient confidentiality and to follow the guidelines on confidentiality of the General Optical Council (General Optical Council 2016).

In the first stage of data collection, the investigator searched the clinical database for eligible records. The University Eye Clinic and the community practice each used an electronic patient database. The support services for the database companies were asked to produce a database of all cases seen between the ages of 18 years to 40 years over a 2-year time-period. They were also asked to create a separate list of cases between the ages of 18 years to 40 years if the database listed them to have a family history of glaucoma. Clinic records were then reviewed and anonymised data were extracted if the patient was between the age of 18 years and under 40 years and an IOP measurement had been taken. Weekly clinic lists were also reviewed and all records under the age of 40 years were assessed for suitability. The anonymised data (Section 4.3) were extracted and recorded onto a spreadsheet. Photographs were not extracted. The data extracted did not include any personal identifying information such as name, address and date of birth. At this stage, each anonymised dataset was identified by the clinic reference number. Once the spreadsheet was complete, the investigator passed this to the assigned doctorate supervisor. The supervisor randomly assigned a unique research number to each dataset and deleted the clinic reference number and randomly re-ordered the data in the spreadsheet. For example, the dataset that was in row 3 might now be in row 250. This second level anonymised spreadsheet was then passed to the investigator for analysis. It included 265 rows of data of the type illustrated in Table 4.5-1. It was implausible that the researcher would know from which patient each dataset originated.

TABLE 4.5-1 Example of the table used for data extraction for Study 1.

CODE	SEX	AGE	RVA	LVA	R SER	L SER	RIOPAV	INSTRUM	LIOPAV	INSTRUM	ONHVR	ONHLV	FHX	VF
0		34	0.0	0.1	0.75	0.75	12	NCT	14	NCT	0.2	0.2	N	N
0		21	0.0	0.2	-3	-3	14	NCT	16	NCT	0.3	0.1	N	Y
1		21	0.1	0.0	0.01	0.01	13	NCT	13	NCT	0.2	0.2	Y	Y

4.6 LIMITATIONS

Prior to the ethics committee application, the initial thoughts for this study were that it could be conducted at several community optometry practices as the data were to be extracted anonymously. London South Bank University Ethics Committee advised that data could only be extracted from case records with consent, and records could not be searched in a practice in which the investigator was not employed as they held identifiable details. The investigator was employed at both centres that were used for data collection. Although both centres were busy with patient flow, it is not currently commonplace practise to routinely measure IOP in patients under the age of 40 years. An assumption was made that the University Eye Clinic would hold a large percentage of patients who were young adults and that IOP would more likely be measured for teaching of clinical skills. However, it is necessary for a teaching clinic to advise when to make appropriate clinical decisions for clinical assessments. The optometry practice in Bedfordshire demographically had an older patient base, although measurement of IOP on all adult patients above the age of 18 years was routinely performed. Challenges were faced in finding records of participants between the ages of 18 years and 40 years in whom IOP had been measured and in finding participants who had a positive family history of glaucoma. These may have been the result of the study being restricted to two study sites and the demographics of the population at each site. Participants between the ages of 18 to 40 years may not have first generation family members with glaucoma as the incidence is lower in younger ages. Therefore, data were also collected from cases that had a family history of glaucoma via second-generation family members. It has been suggested that epidemiology studies that include only first-degree relatives may underestimate the familial/genetic nature of glaucoma (Green et al. 2007). The current study had the advantage of collecting

retrospective data from a “real world” situation, but it is also a recognised limitation of retrospective studies that they generate a lot of “missed data” (Anthonisen 2009).

4.7 SUMMARY

This chapter has detailed the study design and methodology for Study 1. The next chapter will review the data collected and show their results after analyses.

5. STUDY 1 RESULTS

5.1 STUDY 1 OVERVIEW

This chapter presents the descriptive results and statistical analysis for Study 1. Results were conducted on intraocular pressure (IOP) values and vertical cup to disc ratio (CDR) assessments.

5.2 DESCRIPTIVE STATISTICS

Intraocular pressure measurements were documented from 272 cases. Approximately 5000 records were reviewed from both sites. The summary data collected from these records are presented in Table 5.2-1.

The number of the anonymised case records that did not report a family history of glaucoma were 169. This group has been named 'F0'. There were 41 anonymised case records reported with a first-degree relative who had a family history of glaucoma. This group has been named 'F1'. A second degree relative second-degree relative (grandparent or uncle/aunt) was recorded in 62 of the records. This group has been named 'F2'. Records that had documented both a first-degree relative as well as other relatives were recorded only in the first-degree relative category. The confidence intervals of the means were calculated at 95% and an effect size index was calculated using Cohen's D formula (Sections 5.4.1.1& 5.5.1.1).

From the 272 data entries for IOP, 95 were measured with non-contact tonometry (NCT), 138 with Rebound (Icare) tonometry (RBT) and 1 with Perkins applanation tonometry. On 38 records, the technique used to measure the IOP was not recorded. RBT was used on 55.0% of the patients without a family history compared to 44.9% with. NCT was used on 67.3% of the patients with a family history compared to 32.7% without a family history. Applanation tonometry was used to measure IOP on one case of a participant with a family history of glaucoma.

TABLE 5.2-1 Summary of descriptive statistics for Study 1. 'F1' is family history of glaucoma with first degree relative. 'F2' is family history of glaucoma with second- degree relative. 'F0' is negative family history. all ages are in years. 'R' is right eye, 'L' is left eye, 'VA' is visual acuity, SER is spherical equivalent refraction, IOP is intraocular pressure, CDR is cup-disc ratio. 'S.D.' is standard deviation, IQR is interquartile range and 'Min' and 'Max', minimum and maximum results respectively.

GENDER	NUMBER	FAMILY HISTORY	AGE				VA (R)				SER (R)				IOP (R)				ONH (R)			
			Mean	S.D.	Min	Max	Mean	S.D.	Min	Max	Mean	S.D.	Min	Max	Mean	S.D.	Min	Max	Median	IQR	Min	Max
Male	110	F1, n = 17	33.1	6.6	20	40	-0.1	0.6	-0.1	0.1	-1.7	2.8	2.1	-6.8	16.3	2.5	12.0	20.0	0.4	0.3	0.1	0.7
		F2, n = 31	29.4	7.6	19	40	-0.1	0.1	-0.2	0.1	-1.5	2.4	1.6	-7.6	15.5	3.2	10.0	21.0	0.4	0.2	0.0	0.6
		F0, n = 62	27.1	6.8	18	40	-0.1	0.1	-0.2	0.2	-1.3	2.3	4.3	-7.9	14.6	2.8	9.0	21.0	0.3	0.2	0.1	0.7
Female	162	F1, n = 24	33.1	7.2	18	40	-0.2	0.2	-0.2	1.0	-1.0	2.4	3.9	-7.0	14.6	3.7	7.0	22.0	0.2	0.1	0.0	0.5
		F2, n = 31	30.8	6.8	19	39	-0.1	0.9	-0.2	0.2	-1.5	2.3	1.5	-8.8	14.2	3.5	9.0	22.0	0.4	0.3	0.1	0.8
		F0, n = 107	27.6	7.4	18	40	-0.1	0.1	-0.2	0.5	-1.4	3.0	5.0	-17.9	14.7	3.1	8.0	22.0	0.3	0.2	0.0	0.8

GENDER	NUMBER	FAMILY HISTORY	AGE				VA (L)				SER (L)				IOP (L)				ONH (L)			
			Mean	S.D.	Min	Max	Mean	S.D.	Min	Max	Mean	S.D.	Min	Max	Mean	S.D.	Min	Max	Median	IQR	Min	Max
Male	110	F1, n = 17	33.1	6.6	20	40	-0.1	0.1	-0.2	0.3	-1.7	2.8	2.3	-6.4	16.0	3.1	11.0	21.0	0.3	0.2	0.0	0.5
		F2, n = 31	29.4	7.6	19	40	-0.1	0.1	-0.2	0.2	-1.4	2.8	4.5	-8.8	14.8	3.6	9.0	24.0	0.3	0.2	0.1	0.7
		F0, n = 62	27.1	6.8	18	40	-0.1	0.8	-0.2	0.3	-1.3	2.5	4.4	-9.6	14.2	2.6	8.0	20.0	0.3	0.3	0.1	0.7
Female	162	F1, n = 24	33.1	7.2	18	40	-0.1	0.1	-0.2	0.6	-0.8	2.5	4.0	-8.3	14.4	3.4	8.0	22.0	0.2	0.2	0.1	0.7
		F2, n = 31	30.8	6.8	19	39	-0.1	0.1	-0.2	0.1	-1.1	2.6	4.5	-9.0	13.7	3.8	8.0	23.0	0.3	0.3	0.1	0.7
		F0, n = 107	27.6	7.4	18	40	-0.1	0.1	-0.2	0.4	-1.2	2.9	4.8	-18.4	14.3	3.2	6.0	21.0	0.3	0.3	0.1	0.8

5.3 FREQUENCY DISTRIBUTION CHARTS FOR INTRAOCULAR PRESSURE

Four frequency distribution graphs below show the distribution of IOP measurements for right and left eyes; firstly, for the group of cases which did not have a family history and secondly for the complete group of cases with a family history (includes those with a first degree relative and those without a first degree relative but with a second-degree relative). These frequency distribution graphs were created with the aid of a statistical package (SPSS). Data have been tabulated using Microsoft Excel. A frequency distribution chart gives a simple graphical way of depicting a complete set of observations (Altman 1991) and can provide evidence of parametric distribution of data by inspection. This was also confirmed with a Shapiro-Wilk test for normality using SPSS. The values obtained for the Shapiro-Wilk test for each eye have been added under each figure.

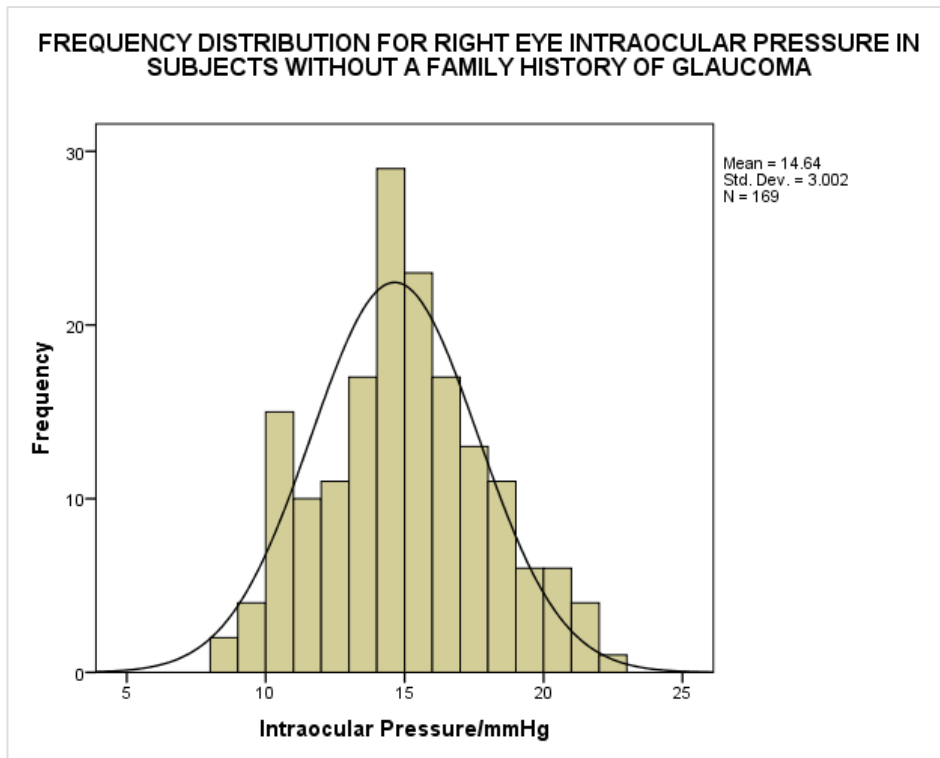


FIGURE 5.3-1 Frequency distribution for right eye intraocular pressure in subjects without a family history of glaucoma. Shapiro-Wilk test: $p = 0.155$.

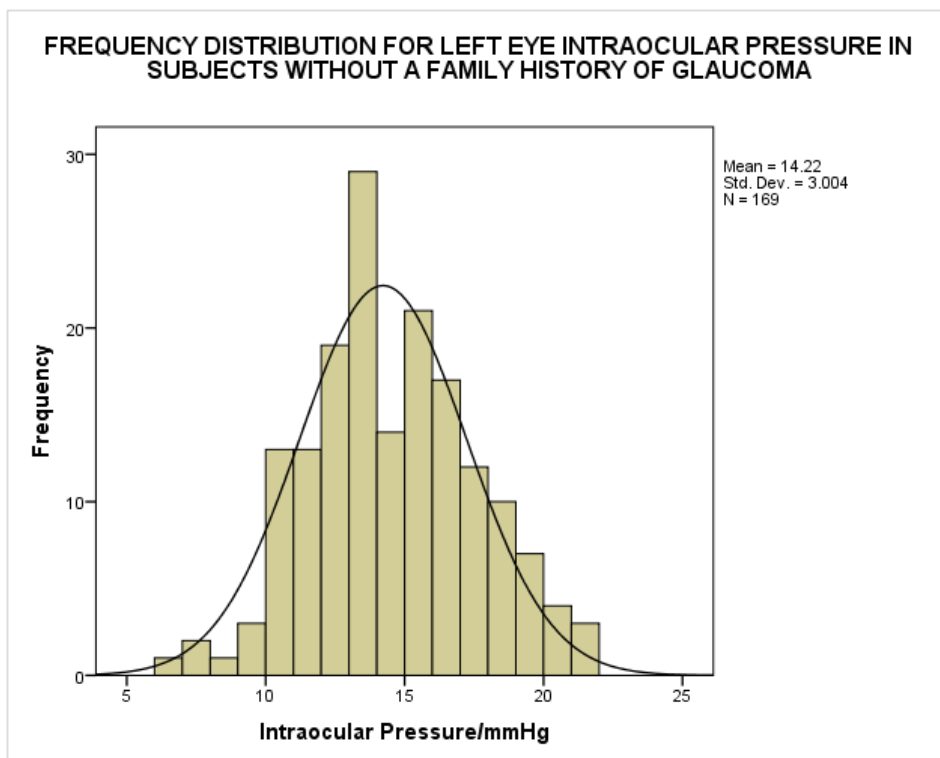


FIGURE 5.3-2 Frequency distribution for left eye intraocular pressure in subjects without a family history of glaucoma. Shapiro-Wilk test: $p = 0.272$

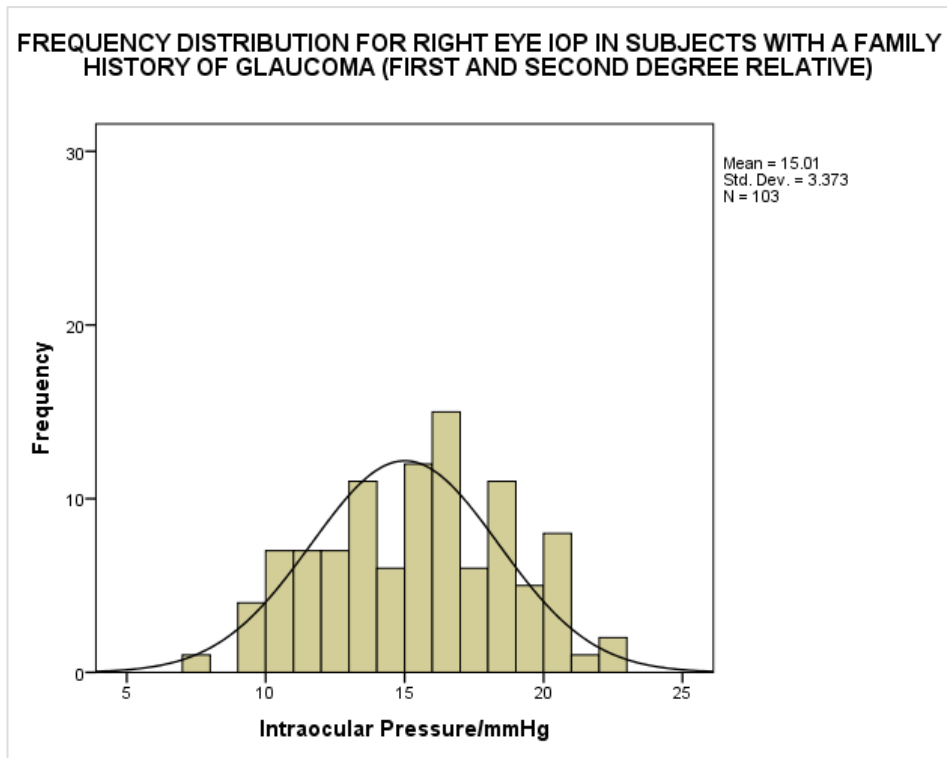


FIGURE 5.3-3 Frequency distribution for right eye intraocular pressure in subjects with a family history of glaucoma (F1 and F2). Shapiro-Wilk test: $p = 0.100$

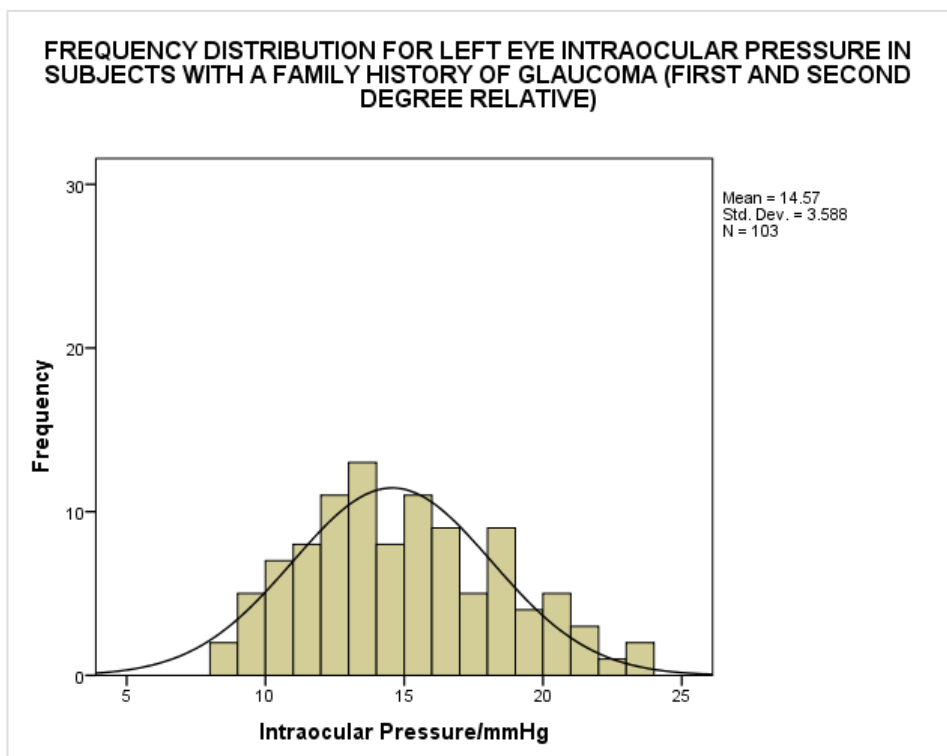


FIGURE 5.3-4 Frequency distribution for left eye intraocular pressure in subjects with a family history of glaucoma (F1 and F2). Shapiro-Wilk test: $p = 0.058$

5.4 STATISTICAL ANALYSIS FOR INTRAOCULAR PRESSURE.

Frequency distribution graphs and the Shapiro-Wilk test demonstrated that the IOP measurements collected for this study were normally distributed. Parametric statistical analyses were therefore justified and an independent samples t-test was used. There were 169 cases in the group that did not have a family history of glaucoma (group F0). The mean IOP for this group was 14.6 mmHg (95% CI 14.2 - 15.1mmHg) for the right eye and 14.2mmHg (95% CI 13.8 - 14.7mmHg) for the left eye.

The total number of cases with a family history of glaucoma was 103 (groups F1 + F2). The mean IOP for all the cases with a family history of glaucoma (groups F1 + F2) were 15.0 mmHg (95% CI 14.4 - 15.7mmHg) for the right eye and 14.6mmHg for the left eye (95% CI 13.9 - 15.3mmHg). These data were further subdivided and for the 41 cases in the group that had only reported a first-degree relative with glaucoma (group F1) the mean IOP was 15.5 mmHg for the right eye (95% CI 14.5-16.4mmHg) and 15.2mmHg (95% CI 14.2-16.2mmHg) for the left eye.

An independent samples t-test was conducted to compare the mean intraocular pressure between groups F0 and F1, and for groups F0 and F1+F2. The descriptive and comparative statistics for these measurements are shown in Table.5.4-1.

Table 5.4-1 Descriptive and comparative statistics for intraocular pressure measurements. ‘F1’ is family history of glaucoma with first degree relative. ‘F2’ is family history of glaucoma with a second-degree relative. ‘N’ is total number. IOP values in mmHg. ‘S.D’ is standard deviation and CI is confidence interval. R is right eye and L is left eye. The ‘p’ values shown in row F1* are calculated with comparing this group with F0 only

GROUP/VARIABLE	N	IOP (R)				IOP (L)			
		Mean	S.D.	CI (95%)	p	Mean	S.D.	CI (95%)	p
F0	169	14.6	3.0	14.2-15.1	-	14.2	3.0	13.8-14.7	-
F1	41	15.5	3.2	14.5-16.4	0.224*	15.2	3.2	14.2-16.2	0.097*
F1 & F2	103	15.0	3.4	14.4-15.7	0.300	14.6	3.6	13.9-15.3	0.4

The intraocular pressure measurements in the group without a family history (group F0) compared to those with a family history of a first degree relative (group F1) did not show a significant statistical difference between means (RIOP; $t(208) = -1.3, p=0.224$; LIOP; $t(208) = -1.7, p=0.097$).

The intraocular pressure measurements in the group without a family history (group F0) compared to those with a family history of a first degree relative and second degree relative (groups F1 and F2) also did not show a statistically significant difference between means (RIOP; $t(270) = -1.0, p=0.353$; (LIOP; $t(270) = -0.88, p=0.398$).

5.4.1.1 EFFECT SIZE

An online statistical calculator was used to confirm the effect size of each group (F0, F1 and F2). (Effect size calculator for Cohen's d: <https://www.cem.org/effect-size-calculator> 2017).

EQUATION 2 COHEN'S D EQUATION FOR STUDY 1 INTRAOCULAR PRESSURE

$$\text{Cohen's } d = (M_2 - M_1) / SD_{\text{pooled}}$$

The values using the above equation for the right eye are shown below:

Comparing F0 effect to F1 = $M = \text{Mean value}$. M_2 is 15.5 (F1), M_1 is the 14.6 (F0) and SD_{pooled} is 3.0. Cohen's D = 0.3

Comparing F) to F1 + F2 = $M = \text{Mean value}$. M_2 is 15.0 (F1 & F2), M_1 is the 14.6 (F0) and SD_{pooled} is 3.2. Cohen's D = 0.13

The values obtained for Cohen's d for the groups compared were all below 0.3 which indicates that the size of the effect is small.

5.5 OPTIC NERVE HEAD/CUP TO DISC RATIO

The secondary aims for this study also included an analysis of the vertical cup to disc ratio measurements between the group of cases that had a family history of glaucoma and those that did not. For this analysis, the group of cases with the family history of glaucoma included both first and second-degree relatives (groups F1 and F2). A statistical package (SPSS) was used to confirm if the data for the CDR had a normal distribution. Both the Kolmogorov-Smirnov and Shapiro-Wilk tests were statistically significant ($p < 0.05$). This confirms that the data collected were not normally distributed and non-parametric testing should be used.

The data collected for optic nerve/cup to disc ratios have been presented using box plots. The medians for each group were 0.3 at the 50th percentile,

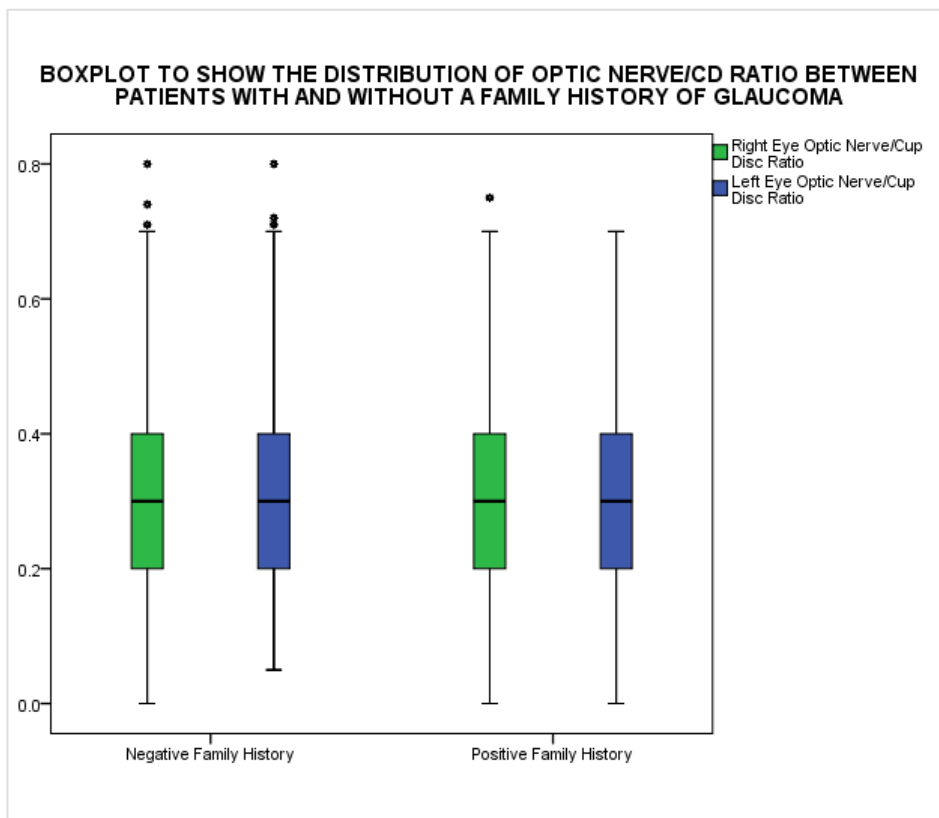


FIGURE 5.5-1 Box plot to present the range of cup to disc ratio measurements in a group of cases with a family history of glaucoma and a group of cases with a negative family history of glaucoma. The Y axis presents the cup to disc ratio values. The median is marked by the horizontal line inside each box. The top and bottom ends of the box represent the interquartile range. The whiskers (lines outside of the box) represent the lower and upper quartiles. The dots above the top whiskers present the outliers and the uppermost measurements.

5.5.1 STATISTICAL ANALYSIS FOR OPTIC NERVE/CUP TO DISC RATIO IN GROUPS WITH A FAMILY HISTORY (FIRST DEGREE AND SECOND-DEGREE RELATIVE) AND NO FAMILY HISTORY.

A Mann-Whitney U test indicated that the optic nerve/cup disc ratio for the group with a family history of glaucoma was not significantly different from that in the group without a family history of glaucoma. The median value in each group was 0.3 (50th percentile) and did not show a statistically significant difference between the two groups (Mann-Whitney U= RE (8618.0) LE (8584.0) (Z = R -.14: L -.19), p R = 0.890 L 0.848).

Table 5.5-1 Descriptive and comparative statistics for optic nerve head/cup to disc ratio measurements. ‘F1’ is family history of glaucoma with first degree relative. ‘F2’ is family history of glaucoma with second- degree relative. ‘n’ is total number. R is right eye. L is left eye. The ‘p’ values shown in row F1* are calculated with comparing this group with F0 only.

GROUP/VARIABLE	N (L)	ONH/CDR (R)		ONH/CDR (L)	
		<i>Median</i>	<i>p</i>	<i>Median</i>	<i>p</i>
F0	169	0.30	-	0.30	-
F1 & F2	103	0.30	0.890	0.30	0.848

5.5.1.1 EFFECT SIZE

SPSS was used to calculate the effect size using the results from the Mann Whitney U test. The effect size η was calculated using the equation listed in Equation 3, where Z is the value given of the calculated Z test from SPSS and N is total number of all cases. The effect size between the two groups of family history and no family history were each 0.0001, showing no effect.

EQUATION 3 EFFECT SIZE CALCULATION FOR STUDY 1 OPTIC NERVE CUP TO DISC RATIO

$$\eta^2 = \frac{Z^2}{N-1} \text{ where } N = 271 \text{ and } Z = -0.138 \text{ (REONH) and } -0.192 \text{ (LEONH)}$$

5.6 SUMMARY OF RESULTS FOR STUDY 1

This chapter has presented a summary of the data collected for intraocular pressure and the optic nerve/cup to disc ratio measurements for a group of cases which had a family history of glaucoma and a group which did not. The aims and objectives presented for this study were achieved. A total of 272 cases were reviewed with an age range of 18 years to 40 years. The mean values of the intraocular pressure and the median values of the cup to disc ratio between the two groups were not statistically significantly different. These results will be discussed in the Chapter 6.

6. DISCUSSION FOR STUDY 1

6.1 OVERVIEW OF DISCUSSION

This chapter will briefly review the results for Study 1, relate them to the literature, and discuss their implications.

6.2 REVIEW OF RESULTS

Study 1 collected data from 272 anonymised cases (Table 5.2-1). Group F0 (n=169) did not have a family history of glaucoma. Group F1 (n=41) had a first degree relative with glaucoma and Group F2 (n=62) had a second-degree relative with glaucoma. The age range of all the cases were between 18 years and 40 years.

The intraocular pressure values were normally distributed and parametric testing was conducted. The mean intraocular pressure values in the right eye for group F0 was 14.6 mmHg (SD 3.0) and for the left eye 14.2 mmHg (SD 3.0). The combined mean IOP for groups F1 and F2 was 15.0mmHg (SD 3.4) for the right eye and 14.6mmHg (SD 3.6) for the left eye.

Statistical analysis was used to compare the mean intraocular pressure values in groups F0 and F1. The second analysis was carried out to compare the means of the group F0 and the combined group of F1 and F2 together. An independent samples t-test showed that the means were not significantly different for either comparison. The 95% confidence intervals were calculated and an effect size index calculation performed using Cohen's D equation. This revealed only a small effect for the comparisons between each group with a family history of glaucoma (F1; n=41 and F1 & F2; n=103) and the groups with no reported family history of glaucoma (F0 n=169) (Section 5.4.1.1).

The data collected for vertical cup to disc ratios were not normally distributed for group F0 or for the combined group (F1 & F2); therefore, non-parametric testing was used. For each group, the median vertical CDR value was 0.3. An effect size calculation revealed a very small effect size in groups F1 and F2 together (Section 5.5.1.1).

6.3 COMPARISON TO CURRENT LITERATURE FOR STUDY 1

To aid recruitment and obtain a broad sample of cases, Study 1 attempted to have broad inclusion criteria; exclusion criteria included corneal pathology, pigment dispersion syndrome and pseudo-exfoliation. As far as could be ascertained, all cases with corneal pathology were excluded; however, it has not always been routine practice for optometrists to use slit lamp examination for assessment of the anterior eye. Optometry practice has had an evolving role in eyecare delivery over the last two decades (Harris 2014; Harper et al. 2016). Optometrists are encouraged to discuss evidence and research in practice (Bullock et al. 2014; Harris 2014), develop clinical skills and work in conjunction with general practitioners and ophthalmologists (Harris 2014). The role of optometrists working within the hospital eye service is also changing and glaucoma has a leading extended role service provided by optometrists (Harper et al. 2016).

The initial research proposal for this study indicated that the race of the participants was also to be collected if available. It was soon apparent that these data were not being collected by the practices involved in the study. Anglia Ruskin University reported their student demographic to be 62% White, 11% Black, 11% Asian and less than 5% for Chinese, Arab and other ethnicities combined (ARU 2016). Central Bedfordshire census data reported its demographics as: White British 89.7% and Non-White British as 10.3% (Bedfordshire Council 2016).

Many of the participants in this study had a myopic refractive error. This may not be representative of the general population as people with refractive errors are most likely to consult optometrists. One of the reasons for this may be that a university eye clinic was used to collect data; a greater prevalence of myopia than would be expected in a general population was also found in first year undergraduate students at another UK university (Logan et al. 2005).

6.3.1 COMPARISON TO CURRENT LITERATURE: INTRAOCULAR PRESSURE

The literature reviewed in Chapter 2 has shown that larger epidemiological studies on POAG have all concentrated on participants over the age of 40 years. It was necessary to consider the literature on intraocular pressure for younger adults for this discussion. A search was conducted using the terms “normal intraocular pressure” and “adult” on PubMed. The search was specified for studies on humans aged between 18 years and 40 years and for studies written in English from years 1967 to 2017. The result was approximately 400 papers. The literature search did not find any studies designed exclusively for measuring the normal range of IOP in young adults. Thus, all abstracts were considered to see which may have measured IOP in adults of age 18 year to 40 years. The intraocular pressures presented in Table 6.3-1 are from papers that have measured intraocular pressure in normal eyes for other research reasons. The studies were European, Australian and American studies which presented IOP in eyes without ocular pathology. Asian studies were not included as changes with intraocular pressure with age are reported to be different (Nomura et al. 2002) and the pathogenesis of glaucoma may have a different process as optic neuropathy has been reported at lower levels of IOP than in Europeans (Shiose et al. 1991).

TABLE 6.3-1 Summary of clinical studies to show intraocular pressure measurements in young adults.

STUDY	COUNTRY	AGE	SUMMARY
Hacopian et al. 2017	US	33.8 years +/- 12.8 years	Tonopen XL Males 13.89 +/- 2.58 mmHg Females 13.02 +/- 2.61 mmHg
Najmanova et al. 2016	Czech	19-25 years	Non-contact tonometry Baseline 15.0 mmHg pre-exercise
Huang & Rosenfield 2015	US	23-28 years	Handheld Tonopen 14 healthy subjects. IOP pre-exercise 14.6 mmHg
Parissinen et al., 2012	Finland	29.2 to 37.4 years Mean 34.5 year +/- 1.57 years	Goldmann Applanation Tonometry (Myopic Rx) Males 16.23 +/- 2.83 mmHg Females 16.39 +/- 2.8 mmHg
Read & Collins 2011	Australia	Mean age 25 +/- 4 years	Goldmann Applanation Tonometry 50% had a myopic prescription 16.52 +/- 2.21 years
Loewen et al 2010	US	Age range 19.6 to 24.7 years	Non-Contact Tonometry Hyperopia. 9 subjects IOP average diurnal sitting 15.3 +/- 1.2 mmHg Emmetropia 21.5 +/- 1.9. 32 subjects IOP average diurnal sitting 16.2 +/- 1.8 mmHg Myopia 21.8 +/- 1.8 34 subjects IOP average diurnal supine 17.6 +/- 2.1 mmHg
Leydolt et al 2008	Austria	Age range 19-29 years	Perkins Applanation Tonometry Mean IOP 14.0 mmHg Range 11-17 mmHg
Morgan et al. 2008	Australia	Mean age 22.7 years SD 15.9	Goldmann Applanation Tonometry Mean IOP at baseline 14.9 S.D. 3.9 mmHg Exclusion criteria not clear – could have included participants with corneal issues
Gonzalez et al 2006	Portugal	Mean age 22.3 (2.94) 18–30	Age differences in central and peripheral intraocular pressure using a rebound tonometer (Icare) Central IOP measure used Mean 15.3 (S.D. 2.9) Range 8 to 23.
Theelan et al (2004)	Netherlands	Mean age 21 Range 19 – 25	Study on neck tie – results chosen of those with neck tie open at slit lamp as most close to normal practice Tonopen Mean IOP readings were 16.9 mmHg (S.D. 2.3).

Epidemiological studies (Section 1.2) have shown mean IOP to be approximately 16.0mmHg with a standard deviation of 3.0 (Colton & Ederer 1980; European Glaucoma Society 2017). More recent research from a UK bio data bank, states that the mean IOP in a Caucasian population (mean age of 57 years) to be 15.7mmHg (Chan et al. 2016). The IOP measured for this study ranged between 13.7mmHg and 16.3mmHg. These reflect the values presented within Table 6.3-1.

There was no statistically significant difference in mean intraocular pressure between the two groups for this study: family history of glaucoma and no family history. When the comparison was limited to between those with no family history of glaucoma and those with a first-degree relative with glaucoma then the difference in mean intraocular pressure was again not statistically different between groups. The age range studied may have been too low to identify sufficient cases with a first degree relative with glaucoma. It should also be considered that optometrists may not document family history of glaucoma if beyond first degree relative. It is often the case that patients are not aware of the details of family conditions. It has been shown that in diagnosed glaucoma patients, 50% can be unaware of a positive family history (McNaught et al. 2000). Furthermore, if patients are aware of a positive history, optometrists do not confirm diagnoses with family members; it is also possible that family members may consider ocular hypertension to be the same as glaucoma (Gordon et al. 2007). Patients with a diagnosis of ocular hypertension have intraocular pressures at 24.0mmHg or higher but normal optic nerve and visual fields. Ocular hypertension can be treated with pressure lowering drops to prevent conversion to POAG (NICE 2017).

Wolfs et al. (1998) demonstrated that siblings of glaucoma patients had significantly higher intraocular pressures and cup-disc ratios than siblings of controls (OR 14.7 95% CI 1.7-130.0). The age range of the cases in the current study would make it unlikely that a case would have a sibling with POAG, NTG or OHT unless this were a sibling with congenital or juvenile glaucoma (Marx-Gross et al. 2017). It was also reported that the lifetime risk of elevated IOP in first degree relatives of patients with glaucoma compared with relatives of controls had a

risk ratio of 6.3 (Wolfs et al.1998). A large familial study of POAG showed that within 59.5% of patients with primary open angle glaucoma, 38.6% had a first- degree relative, 6.5% had a second-degree relative, 6.1% had a third-degree relative and 8.4% had a fourth-degree relative (Green et al. 2007). This study highlights the importance of history taking in optometric practice and gathering information on family history. The reasons for this are that the odds ratio of a person with POAG having a positive family history have been shown to be 4.1 (95% CI 3.2–5.2) (Green et al. 2007).

The techniques used to measure intraocular pressure in this study were almost exclusively either non-contact tonometry (NCT) or rebound (RB) tonometry. 35% had IOP measured with NCT, 51% had IOP measured with RB, less than 1% had applanation tonometry and 14% did not have the measurement technique recorded. An assumption was made for the current study that the calibration of the instrument was accurate at time of IOP measurement. Optometry students may not be practiced with tonometry and may repeat measurements; conversely qualified optometrists may rely on single IOP measurements rather than an advised average. It is possible also that with all subjects (possibly more if a student is conducting the examination) a higher IOP was measured in the first eye as subjects are more likely to squeeze their eyes in apprehension leading to an artefactual rise in IOP (Dabasia et al. 2016).

A systematic review showed that as compared to Goldmann applanation tonometry, the proportion of NCT and handheld applanation tonometers to measure within 2.0mmHg of Goldmann measurements are about 60% (Cook et al. 2012). A study of IOP measurements with RB in children with glaucoma concluded that “normal” IOP readings are likely to be accurate with RB but higher readings can be overestimated (Dahlmann-Noor et al. 2013). IOP in children has been said to reach adult levels from the age of 12 years (Bresson-Dumont. 2009). A more recent study which compared rebound tonometry with applanation tonometry in children found that the IOP amongst 214 eyes with an age range of 7 years to 17 years (mean 12.0 years) resulted in a mean IOP of 17.5mmHg with RB and 16.2mmHg with GAT

(Grigorian et al. 2012). The study by Grigorian et al. (2012) supports previous studies which reported that RB can measure higher than GAT in children (Dahlman-Noor. 2013).

Although the mean IOPs were not statistically significant between groups in this study, the mean values are higher in the group with a family history than without. The right eye values for the groups were F0=14.6mmHg, F1 & F2=15.0mmHg and F1=15.5mmHg. The intraocular pressure values for the left eye show symmetry with the right eye: F0=14.2mmHg, F1 & F2=14.6mmHg and F1=15.2mmHg. In particular, the intraocular pressure was approximately 1.0mmHg higher in the group with a first-degree family history compared to those with no family history. Intraocular pressure asymmetry has been shown to be a risk factor for having POAG (OR 2.14) (Williams et al. 2013). The cases presented in Study 1 did not show asymmetry even though the range of asymmetry has been said to be more represented with NCT than GAT (Vernon & Jones 1991).

6.3.2 COMPARISON TO CURRENT LITERATURE: OPTIC NERVE/CUP TO DISC RATIO

One of the main clinical indicators for differentiation between normal and glaucomatous optic nerve heads is an increase in vertical CDR over time (Jonas et al. 1999; Mwanza et al. 2017) and therefore it is paramount that accurate baseline clinical assessments are recorded. However, the data collected and analysed for optic nerve/cup to disc ratio in Study 1 were obtained in busy primary care clinics in patients of ages where glaucoma prevalence is very low. Therefore, it is likely that the measurements were not recorded with the same attention to detail as would occur in, for example, a hospital glaucoma clinic. The median values for the vertical CDR in each group (with and without a family history of glaucoma) were identical and there was no statistically significant difference between medians. Vertical CDRs have been observed to be 0.34 ± 0.25 measured in 419 optic nerve heads in normal subjects with fundus photography (Jonas et al. 1988). Consideration of change in CDR over an 11 year

follow up study of optic nerve topography in healthy volunteers reported the median for CDR to be 0.3 both at baseline and after 11 years (See et al. 2009).

The vertical CDR measurement is important to measure as a larger vertical CDR has been shown to be a risk factor of open angle glaucoma (OR 1.34 95% CI 1.14-1.58) (Miglior et al. 2007). The records assessed in the current study did not indicate consistently whether the optic disc was viewed with direct or indirect methods. Direct and monocular examination of the optic nerve has long been known to be a sub-optimal method for viewing or describing optic nerve features as they are not accurate enough to detect small changes (Odberg & Riise 1985). Estimation of the optic nerve using cup to disc parameters is a complex process and subjective assessment can differ between clinicians (Tielsch et al. 1988). However, Harper & Reeves (2000) reported optic nerve assessment with direct ophthalmoscopy can achieve comparable sensitivities and specificities compared with stereophotographic assessment. Although the cup to disc ratio has historically been an indicator in glaucoma (Armaly 1967; Armaly & Sayegh. 1969), a more recent recommendation is to observe the neuroretinal rim (Hoskins et al. 1975; Bengtsson 1976). The current study has isolated one assessment of the optic nerve but “it is the ‘global’ view of the disc (including the inter-eye comparison) which is used in discriminating normal and glaucomatous discs, rather than individual features in isolation” (Harper & Reeves 2000). For future studies, we are now further aided by fundus imaging to make an objective assessment of a complete optic nerve.

6.4 STRENGTHS AND LIMITATIONS

6.4.1 STRENGTHS

This study has assessed intraocular pressure measurements in 272 cases of normal eyes in adults aged 18 years to 40 years. A review of the literature showed that, to date, this topic has not been investigated in isolation. The data were sourced from two established and reputable

optometric practices and there has been consistency in the tonometers used for intraocular pressure measurement at each study site.

6.4.2 LIMITATIONS

This study was unable to collect a large sample of data which may have been due to demographics, the age of the subjects being too young for them to have family who have developed glaucoma, and deficiencies in the details of family history documented on history taking.

The data collected for optic nerve assessment show consistency for the median values obtained when compared with published research. However, the CDR observations for this study were not confirmed using fundus photography or other imaging sources; although there would have been verification of student observations from the University Eye Clinic from qualified optometrists.

6.5 CONCLUSIONS

Study 1 has presented intraocular pressure and optic nerve/cup to disc ratios for two groups of cases; a group with a family history of glaucoma and a second group without. The study found that the differences in mean intraocular pressure measurements were not statistically significant different. The optic nerve vertical CDR measurements presented identical median values in each group with no statistically significantly differences between groups.

These results have initiated a gap in knowledge about intraocular pressure in younger adults. Optometrist make a clinical decision as to when to measure intraocular pressure and this may be worth more consideration if a young adult has strong risk factors such as family history, and other risks such as myopia and large vertical cup to disc ratio. Patients at the age of 18 years may not yet have family who have developed glaucoma at that age; measurements only on those who are known at risk may miss a large spectrum of cases. The mean intraocular pressure values for the group with a family history, particularly those with a first-degree

relative family history, were higher albeit not statistically significant. The standard deviation of the mean IOP measurements were also higher in the family history groups which has been suggested to provide more information for IOP fluctuation than isolated measurements (Caprioli & Coleman 2008; Caprioli 2007). Further research would be beneficial with a larger sample. This study would also provide further information as a prospective study with potential of other measurements such as CCT and OCT.

The following chapter will present the second study for this thesis. There is knowledge still to be investigated about intraocular pressure as Study 1 has leaves a question mark as to whether a difference would have been significant with a larger sample size. There have been challenges faced obtaining intraocular pressure results in young adults. For this reason, Study 2 will approach investigating possible early signs of glaucoma in a more direct way. Study 2 will conduct a retrospective study of historical clinical records in people who subsequently went on to develop glaucoma.

7. STUDY 2 DESIGN AND METHODS

7.1 STUDY 2 OBJECTIVES

The objectives for Study 2 are to:

- retrospectively collate intraocular pressure readings from anonymised records of patients who subsequently developed primary open angle glaucoma and matched control.
- retrospectively collate vertical optic nerve head cup to disc ratio from anonymised records of patients who subsequently developed primary open angle glaucoma and their matched controls.
- statistically analyse the mean intraocular pressure measurements between two groups of cases: the group who subsequently develop glaucoma (pre-diagnosed glaucoma) and their case-matched controls.
- statistically analyse the vertical optic nerve cup to disc ratio between two groups of cases: the group who subsequently develop glaucoma (pre-diagnosed glaucoma) and their case-matched controls.

7.2 STUDY 2 DESIGN

Study 2 is an exploratory study for risk factors of primary open angle glaucoma in adults up to ten years prior to diagnosis. A review of clinical assessments from an outcome group of primary open angle glaucoma (POAG) normal tension glaucoma (NTG), pre-perimetric glaucoma (PPG) suspect glaucoma and ocular hypertension (OHT) cases over a period of ten years preceding diagnosis were compared against group-matched case controls. Data collection was conducted by matching an outcome case with a control case. The outcome group were labelled the PG group (pre-diagnosed glaucoma) and the matched case controls were called the CC group (case-control). Although there was individual matching of

individuals (on a paired basis), the purpose of this was to ensure that there were two groups that were approximately matched in mean age, gender and refractive error. Case control studies are often the design of first choice for observational research and aetiological studies, showing advantages in speed and efficiency (Knoll et al. 2008; Rosendaal 2001). Controls were chosen using a technique called density sampling. Density sampling involves using controls that are sampled concurrently with each case; each time a new glaucoma case was selected, a control was selected from the population at that point in time (Knoll et al. 2008). A sample size calculation was not conducted as there are no previous studies that would provide adequate information for determining an appropriate effect size.

7.3 ETHICS APPLICATION

Ethical approval was requested and granted by the NHS, London South Bank University and the Institute of Optometry. The study adhered to the tenets of the Declaration of Helsinki. The process of NHS approval spanned a 12-month period. The application for this study was discussed at length with the research optometry lead and with the support officer at the Research Management and Governance office at Cambridge and Peterborough Clinical Commissioning Group (CCG) prior to submission. NHS approval was achieved through proportionate review from NHS Grampian in April 2015 (Appendices 7 to 15). Following NHS approval, a Research and Development application was made to the local CCG. Following their approval, an ethics application was made to London South Bank University and the Institute of Optometry and approved in May 2015. Individual applications were then made to eight different CCGs for a National Institute of Health Research passport (NIHR 2015). This process needed a degree of perseverance and patience as each CCG group had a separate process and not every CCG had a research and governance officer. The research passport consists of a letter of access for research and a letter of assurance from the regional Research Management and Governance office. These letters were given as confirmation that the regional CCG gives approval for this research to be conducted in that area. The letter of

assurance and access were supplied to the community optometry practice in that region. (Sections 24 & 25). An annual NHS research review report was submitted in April 2016 and April 2017.

7.4 INCLUSION AND EXCLUSION CRITERIA

The inclusion and exclusion criteria that were used for selecting case records are listed below.

These are referred to in Section 7.5.

Table 7.4-1 Study 1 Inclusion criteria

INCLUSION CRITERIA	
GROUP: PRE-DIAGNOSED GLAUCOMA (PG)	GROUP: CASE-MATCHED CONTROLS (CC)
Diagnosis of POAG, NTG, OH, Pre-perimetric or suspect glaucoma and receiving glaucoma medication prescribed by an ophthalmologist. Patients who have had surgical intervention to lower IOP are not eligible.	No diagnosis of POAG and no suspicion of any variant of glaucoma or ocular hypertension. Patients who have had surgical intervention to lower IOP are not eligible.
The patient will have been seen at the same practice for a minimum of 10 years prior to diagnosis of POAG. If there are breaks in clinical records these should be no more than 4 years.	The patient will have been seen at the same practice for a minimum of 10 years. If there are breaks in clinical records these should be no more than 4 years.
May or may not have a family history of glaucoma (if so, the type and relation will be documented).	No recorded family history of glaucoma.
Intraocular pressure readings available for 10 years prior to glaucoma diagnosis.	Intraocular pressure readings available for all 10 years.
Visual field tests at least twice within the 10- year history prior to IOP treatment.	Visual field tests at least twice within the 10-year history.

Table 7.4-2 Study 1 Exclusion Criteria

GROUP: PRE-DIAGNOSED GLAUCOMA (PD)
Other pathology likely to affect the visual field. Examples: Toxoplasmosis, optic nerve head drusen, retinal detachment, congenital visual field defect, photocoagulation for diabetes, angle closure glaucoma, strokes or other lesions affecting the visual pathway, secondary glaucomas, wet AMD if affects the visual field. Exclude any patients who have had refractive surgery or other corneal surgery.

7.5 DATA COLLECTION

This study involved the collection of anonymised retrospective clinical data from cases of POAG, NTG, PPG, suspect glaucoma, OHT and matched controls from optometric practices. The optometry practices were identified in London and the East of England. Only those practices that were known to the investigators to be established over 15 years were approached; this was to ensure that they would hold case records for longer than a 10-year period.

Identified optometric practices were approached and the study design was discussed and supported with written information. If the practice felt they could participate, written information and a practice consent form was completed (Sections 20&21). To maintain anonymity and ease of data extraction, recruitment was limited to optometric practices that could print or photocopy patient records after anonymising all identifying information. A total of 15 optometric practices were identified and 8 CCGs were contacted. Introductory conversations by telephone were also made to give information on the study. This was often with the practice manager so then follow up meetings were made with the practice manager and the lead optometrist. From the 15 practices, 4 did not return email or telephone contact. There were 3 of the practices who were visited twice to discuss the study and give support for finding cases but they were unable to commit. Even though these 7 practices did not take part, a prior application was made to their CCG so the study could be discussed with them. Recruitment was made of 6 practices; 4 practices were able to provide data for this

study. The minimum number of emails and telephone calls prior to collection of data were between 10 and 30 per practice.

For each of the 6 practices that consented to the study, regular contact was made. An initial email was sent to each practice with introduction of the study. A spreadsheet was created for the practices with the exclusion and inclusion criteria so the team could keep a record of any suitable cases. The communication with the practices was ongoing. It was found that the best way of ensuring significant numbers of records was to make regular contact by telephone calls and emails to encourage them to continue to seek records and to offer support. For the 4 practices that could provide data, regular weekly contact was kept up over the course of 18 months.

Optometric practices were keen to help but often records were not available for 10 years preceding diagnosis. The main reason for this included not having cases that spanned 10 years prior to diagnosis. This was due to the case records not preceding 10 years to diagnosis but also due to practices having had a transition to electronic clinical records and papers records being archived. There were also cases that were excluded even though they had records spanning 10 years for patients seen prior to the age of 40, intraocular pressure measurements were not always recorded.

The optometry practices used their databases to select cases of subjects being treated for POAG, NTG, PPG or OH glaucoma. The record was reviewed to check if that case had historical records tracking 10 years for that case prior to diagnosis. Specific eligibility criteria are listed in section 7.4-1 and 7.4-2. Cases were excluded if there was any suspicion that changes in IOP and or/ optic nerve or visual fields were caused by any reason other than from POAG, NTG, PPG or OH. A control case was matched to the outcome case by gender, age and spherical equivalent refraction (SER) (within +/-2 dioptres). Each case record was photocopied and all identifiable data were anonymised with a black permanent marker. These records were then passed on to one of the doctorate supervisors to check anonymisation before being given to the investigator for data extraction.

It took approximately 18 months for collection of data. During this time, the investigator was working in any way possible to encourage and assist the practices. Suggestions were given for sourcing cases from the electronic database. A spreadsheet log with matching criteria was also devised for the practices to help log any identifiable patients. Each consented practice was asked to provide a minimum of 6 cases for the pre-diagnosis group (POAG, NTG, PPG, OH) and a further 6 cases as controls.

The optometric practices searched case records for subjects that had been attending the practice for eye examinations for 10 years prior to their glaucoma diagnosis and start of treatment. Practices also checked historical records for patients as they were booked in. Any suitable records were photocopied for one eye examination following diagnosis and all examinations for 10 years prior to diagnosis. The case records, together with any evidence of confirmed diagnosis for the glaucoma patient and visual field plots and fundus images were photocopied and anonymised of any identifiable data. The supervisor reviewed the record for anonymization and passed it on to the investigator. If the record met the selection criteria, the data listed above were extracted and the investigator asked the practice to find a control record with matching gender, race (if known) age and refractive error. The same system was used for double checking anonymisation before the control record was given to the investigator. The photocopies of anonymised records were destroyed as soon as the data were extracted onto the spreadsheet.

7.5.1 DATA EXTRACTION

The data for each anonymised record preceding confirmation of glaucoma diagnosis was extracted. To ensure that all data was accurately being collected prior to diagnosis, the practices were asked to photocopy the record for one entry from beginning treatment. Any correspondence from the hospital was also requested to be photocopied. The data collected was in order of, gender month and year of birth, age at eye examination, details of family history of glaucoma, visual acuity, refractive error, intraocular pressure, tonometer details,

vertical cup to disc ratio, visual field records and extra information. Each of these details were recorded for each eye. An Excel data sheet was used to record this data. The inputted data were regularly checked for inaccuracies.

7.5.2 DATA CLEANING

This study was dependent on 10 years retrospective clinical data for 182 cases. The study involved the collection of many records and it was essential that the collected data were scrutinised and inspected for errors. It was also important to interpret clinical notations correctly for each practice. The process of reviewing anonymised paper records was an ongoing and time-consuming task but necessary to ensure that all clinical data were transferred correctly. Every column had to be checked for errors and cross checked with the paper records. Any uncertain clinical notations were checked with the practice and if there was any uncertainty, the data were not recorded. No interpretation was made on the case records and every case was treated with complete neutrality.

7.5.3 DATA ANALYSES

The statistical package SPSS was used for the statistical analyses of the results and figures. The tables were created using Excel. Analyses were data from the eye which was either diagnosed first; if both eyes were diagnosed at the same time, a decision was made from the notes as to which eye was the more affected. This determination was from either a higher pressure, greater change in CDR over time or larger CDR or visual field change. If the records indicated that one eye was weaker due to poorer development at childhood (amblyopia) than the non-amblyopic eye was chosen. This criterion allowed a decision to be made on every case. The same eye was chosen for the control case.

The statistical analyses performed on the data included initial statistical testing for normative distribution for intraocular pressure measurements and optic nerve head cup to disc ratio assessments. T-test analyses were performed on the variables used to match the groups.

Correlation and one-tailed parametric t-tests were used for analyses of the intraocular pressure measurements collected. Correlation and non-parametric Mann Whitney U tests were used for analyses for optic nerve head/cup to disc ratio assessments. Visual field data were tabulated but not statistically analysed.

8. STUDY 2 RESULTS

8.1 OVERVIEW OF DATA

For each section in this chapter, the data for the pre-glaucoma (PG) group cases will be presented first, followed by the case matched controls (CC).

The results for Study 2 are based on a total of 182 anonymous case records supplied from four community optometric clinics (92 PG cases and 90 CC cases) (Table 8.1-1). Initially, 184 records were collected but with further screening, 2 cases were excluded as they were cases of a secondary form of open angle glaucoma. For each record, data were extracted over a 10-year period for the right and left eye, resulting in a minimum of 4 visit entries and a maximum of 11 visit entries (average 5) for each PG case and a minimum of 3 and maximum of 11 (average 4) visit entries for each control case. Once data collection had been completed, the cases were reviewed and one eye per PG case was selected as specified in Section 7.5.1. Analyses were conducted on data from the eye which was either diagnosed first; if both eyes were diagnosed at the same time, a decision was made from the notes as to which eye was the more affected.

Table 8.1-1 Number and category of cases obtained from each optometric practice.

GROUP	Practice 1	Practice 2	Practice2	Practice 4	Total
Controls	41	13	16	20	90
Primary Open Angle Glaucoma	24	11	17	20	72
Normal Tension Glaucoma	4	5	2	2	13
Ocular Hypertension	2	0	0	1	3
Glaucoma Suspect	2	0	2	0	4
Total Records	73	29	37	43	182

8.2 DESCRIPTIVE DATA

The anonymised case records for this study were collected in order of a PG case first; following which a CC case was matched individually for gender, age and refractive error (Tables 8.2-1 & 8.2-2). Data were extracted from the records over a retrospective span of 10 years detailing the variables listed in Section 7.4. The inclusion criteria for the study were that the subjects were seen at regular intervals at the practice over a 10-year period (with no more than four years of gaps between intervals). The earliest recorded year for a case record was 1982 and the latest was 2016.

TABLE 8.2-1 Descriptive data for gender and chosen eye

GROUP	MALE	FEMALE	RIGHT EYE	LEFT EYE
Pre-Diagnosis	63.3%	36.7%	57.1%	42.9%
Case-matched Control	65.7%	34.3%	56.9%	43.1%

Table 8.2-2 Descriptive statistics for all Pre-Diagnosis and Case-Matched Control Cases.

Central measure was mean and Measure of spread was standard deviation for all variables except ONH. The ONH measurements were not normally distributed and therefore their central measure was median and spread was interquartile range. Age in years, SER (spherical equivalent refraction, Visual Acuity as LogMAR, Intraocular Pressure in mmHg and Optic Nerve/Cup to Disc Ratio. Min=Minimum. Max=Maximum.

VARIABLE	GROUP	CENTRAL MEASURE	MEASURE OF SPREAD	MIN	MAX
Age/Years	Pre-Diagnosis	64.9	10.4	30.0	88.0
	Case-matched	65.1	10.6	30.0	88.0
SER	Pre-Diagnosis	-0.8	3.5	-12.8	7.8
	Case-matched	-0.8	3.3	-11.1	12.0
Visual Acuity	Pre-Diagnosis	0.1	0.1	-0.2	1.0
	Case-matched	0.1	0.1	-0.2	0.6
IOP	Pre-Diagnosis	18.9	4.5	9.0	36.0
	Case-matched	14.9	3.2	7.0	25.0
ONH	Pre-Diagnosis	0.5	0.3	0.1	1.0
	Case-matched	0.3	0.2	0.0	0.9

8.2.1 PRE-GLAUCOMA GROUP

Table 8.1-1 presents the number of cases collected for the subtypes of glaucoma. The records were extracted from the visit preceding the start of treatment for the PG case and where possible this was confirmed from the case notes and a correspondence letter from an ophthalmologist (anonymised) (Table 8.2-3). This visit was taken as the baseline visit. Records were then extracted 10 years prior to this. The total number of PG cases were 92. The majority of cases had POAG (n=72), followed by NTG (n=13). A small number of cases were collected for both glaucoma suspect patients on treatment (n=4) and OHT on treatment (n=3) (Table 8.1-1). The number of cases referred for glaucoma assessment by the community optometrist and discharged and re-referred were documented. Details were also compiled for the number of years that cases were monitored by the ophthalmologist before a confirmed diagnosis and treatment was started. Cataract surgery had been performed on 6 of the PG cases during over the 10- year duration (Table 8.2-3).

Table 8.2-1 show that 63.3% of the PG Group were male and 36.7% were female. 57.1% of the data were for the right eye and 42.9% for the left eye. The PG Group had a minimum age of 30 years and a maximum age of 88 years. The mean age was 65 years and the standard deviation was 10.4 years. The mean spherical refraction equivalent for the relevant eye were -0.8 DS and the range was -12.8 DS to +7.8 DS. The mean visual acuity for the relevant eye were log Mar 0.1 and the range was -0.2 to 1.00 (Table 8.2-2). The mean number of days over which the clinical records spanned for the PG group were 3918 (10.7 years).

8.2.2 CASE-MATCHED CONTROL GROUP

There were 90 cases of matched controls. These matched the PG group for gender, age and spherical equivalent refraction (Table 8.2-4). Unpaired T-test analysis was used to confirm that there was not a significance difference in means between the matched groups, thereby verifying that the groups were matched. Every effort was made to match each PG case to a CC case at the same practice; 9 controls could not be matched from the same practice and

these were matched by request from one of the other recruited practices. There were 2 of the control cases included in the study which had been referred to the Hospital Eye Service for raised intraocular pressure and optic nerve head assessment but were discharged. Cataract surgery has been performed on 12 of the cases in the CC group (Table 8.2-3).

Table 8.2-2 shows that 56.9% of the data for the CC group were for the right eye and 43.1% for the left eye. The group had a minimum age of 30 years and a maximum age of 88 years. The mean age was 65 years and the standard deviation was 10.6 years. 66.4 % of the group were male and 33.6% were female. The mean spherical refraction equivalent for the relevant eye was -1.0 DS and the range was -11.1 to +12.0 DS. The mean visual acuity for the relevant eye was LogMAR 0.1. The mean number of days over which the clinical records spanned for the CC group were 3894 (10.7 years).

TABLE 8.2-3 Information extracted from case records

Case	Cataract Surgery	Case notes on Referrals	Monitored by ophthalmologist	Consultant Letter			
				P1	P2	P3	P4
Controls	12	Referred for raised IOP. Discharged with increased corneal thickness. Referred for optic nerve appearance. Discharged with diagnosis of physiological cupping.		0	0	0	0
Primary Open Angle Glaucoma	4	Referred 2009 for OAG. Discharged. Re-referred 2011.	5 cases for 2 years. 5 cases for 3 years. 2 cases for 4 years. 2 cases for 5 years. 1 case for 9 years.	11	1	3	13
Normal Tension Glaucoma	1	Discharged twice (2001 & 2007). Re-referred again in 2012. Referred 2006 for OAG. Discharged. Re-referred 2008	2 cases for 2 years. 1 case for 3 years.	4	1	0	2
Ocular Hypertensive on Treatment	1	Referred in 1988 - monitored and discharged. Re-referred in 2008.	1 case for 2 years.	2	0	0	0
Glaucoma Suspect on Treatment	0		1 case for 5 years. 1 case for 6 years	2	0	0	0

TABLE 8.2-4 Descriptive and comparative statistics. "SER" is spherical equivalent data. "S.D." is standard deviation. "p" values calculated from unpaired t-test.

Group/Variable	CONTROL		PRE-DIAGNOSIS		
	<i>Mean</i>	<i>S.D.</i>	<i>Mean</i>	<i>S.D.</i>	<i>p</i>
Age	65.1	10.6	64.9	10.4	0.7
Visual Acuity	0.1	0.1	0.1	0.1	0.6
SER	-1.0	3.5	-0.8	3.3	0.2

8.3 ANALYSIS

The historical data were collected to analyse three specific variables: intraocular pressure, optic nerve head and visual fields. These variables may change with the progression of glaucoma. The results collected for each of these variables will be considered in turn.

8.3.1 INTRAOCULAR PRESSURE

The equipment used to measure intraocular pressure was tabulated from the last observed measurement for each case per group (Table 8.3-1). For each group, the most common method for measuring intraocular pressure was non-contact tonometry, followed by rebound tonometry (Icare), and lastly by Goldmann applanation tonometry.

TABLE 8.3-1 Methods of tonometry used at the last observed measurement per group. All values shown as percentage.

EQUIPMENT	PRE-DIAGNOSIS	CASE-MATCHED CONTROL
Pulsair Non-Contact Tonometry	42.2	48.5
ICare Rebound	30.1	38.7
Perkins Applanation Tonometry	9.6	7.5
Desktop Non-Contact Tonometry	7.3	0
A O Reichart Non-Contact Tonometry	7.2	4.3
Goldmann Applanation Tonometry	3.6	1.1

8.3.2 PRE-DIAGNOSIS GROUP

The frequency distribution charts show that the data for intraocular pressure for the PG group closely approximated a normal distribution. (Figure 8.3-1). The intraocular pressure for the PG group had a minimum measurement of 9.0mmHg and a maximum of 36.0mmHg. The mean intraocular pressure was 18.9 mmHg with a standard deviation of 4.4

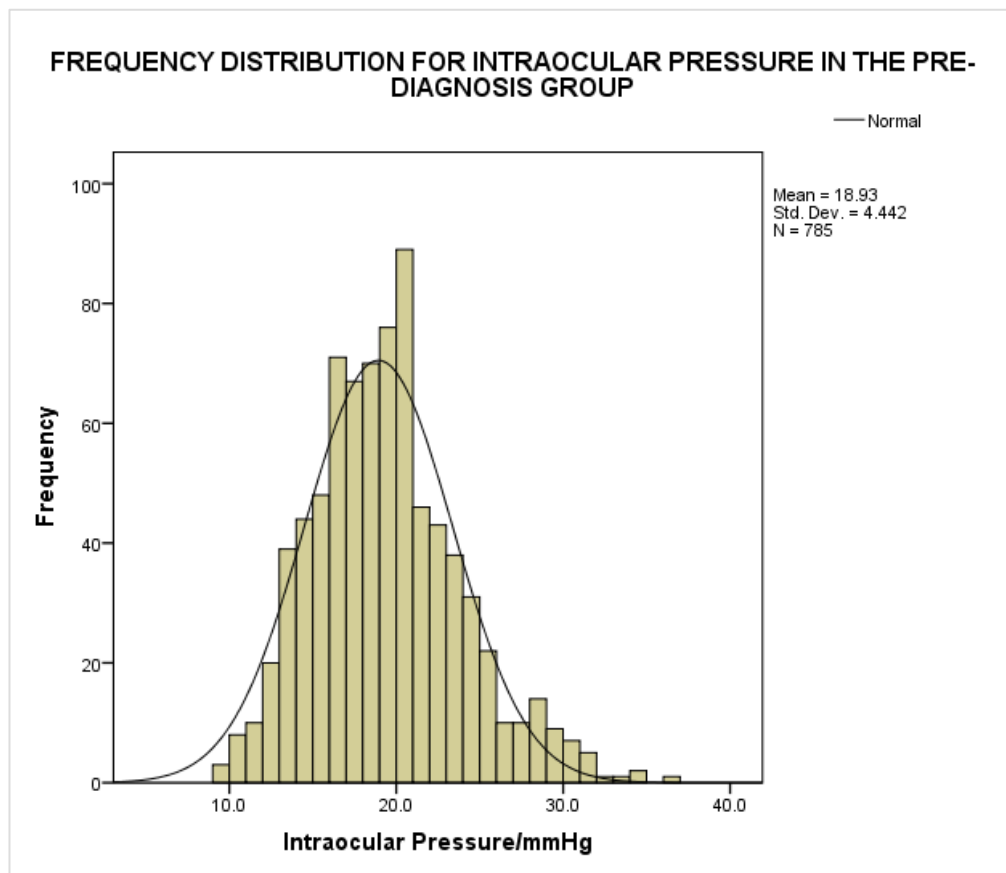


FIGURE 8.3-1 Frequency distribution for intraocular pressure in the Pre-Diagnosis Group.

8.4 CASE-MATCHED CONTROL GROUP

The frequency distribution chart show that the data for intraocular pressure were of a normal distribution (Figure 8.4-1). The intraocular pressure for the CC group had a minimum measurement of 7.0mmHg and a maximum of 25.0mmHg. The mean intraocular pressure was 14.8mmHg with a standard deviation of 3.3.

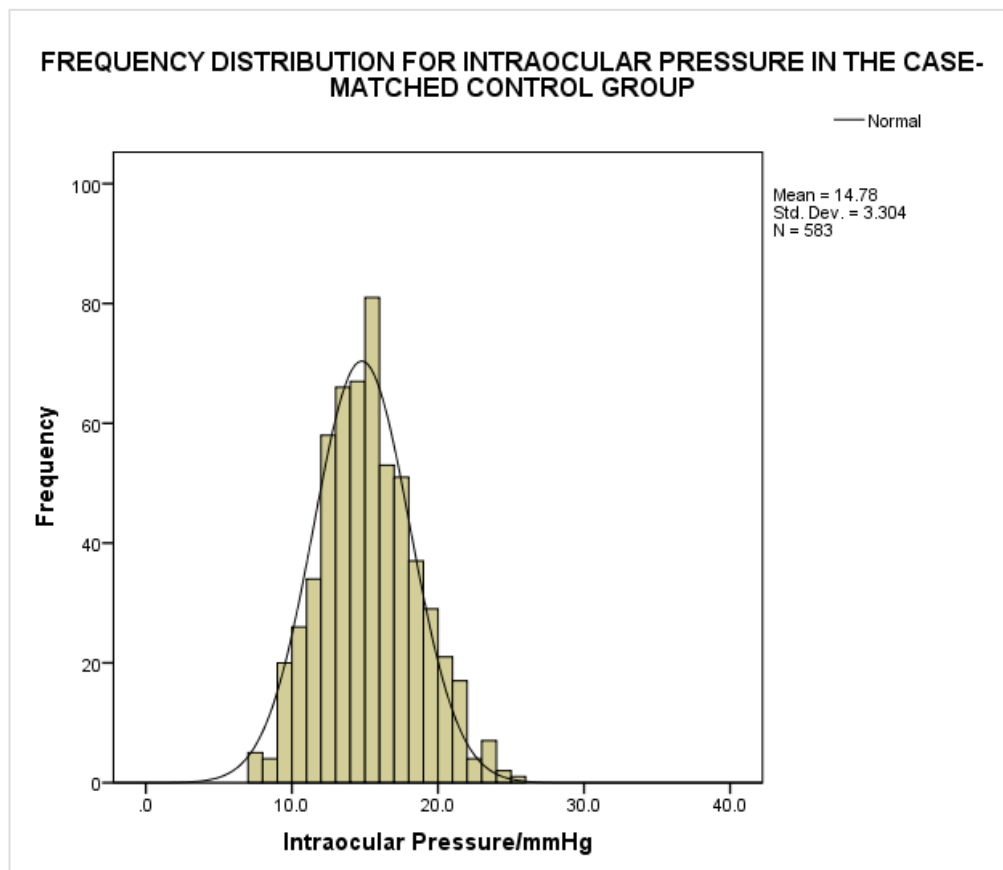


FIGURE 8.4-1 Frequency distribution for intraocular pressure in the Case-Matched Control group.

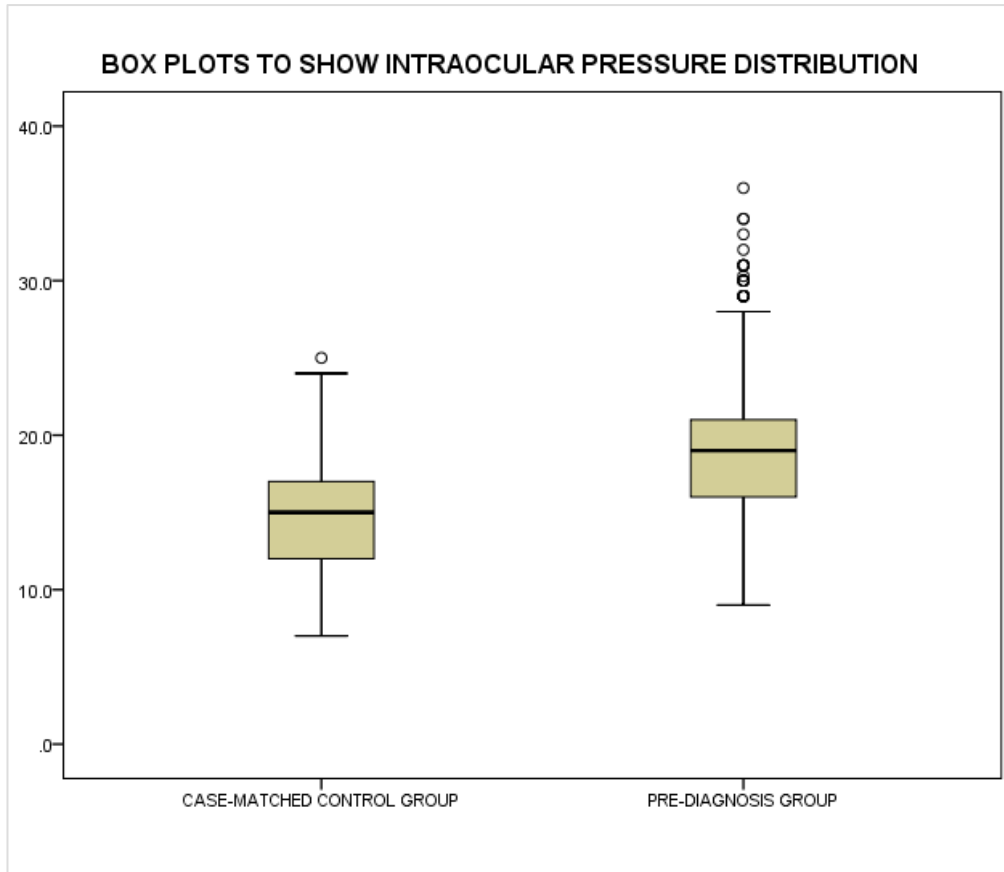


FIGURE 8.4-2 Box plots to present intraocular pressure distribution in the Pre-Diagnosis Group and Case-Matched Control Group. The Y axis presents the intraocular pressure values in mmHg. The mean is marked by the horizontal line inside each box. The lower whiskers (lines outside of the box) represent the lowest measurements. The stars above the top whiskers present the outliers and the highest measurements.

8.4.1 CORRELATION FOR INTRAOCULAR PRESSURE

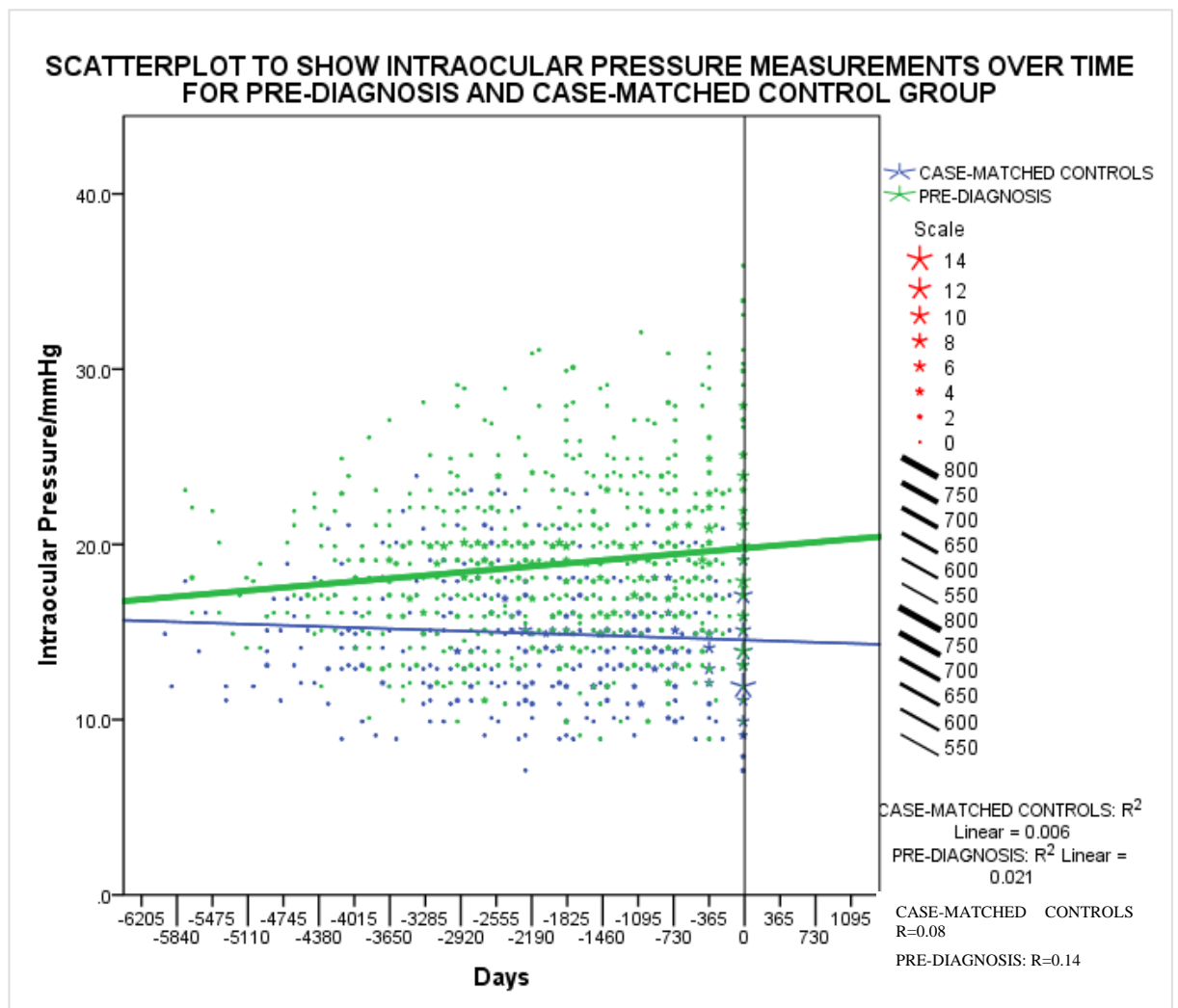


FIGURE 8.4-3 Scatterplot to show correlation of intraocular pressure over time in days in groups Pre-Diagnosis Glaucoma and Case-Matched Controls.

A scatterplot and correlation was presented to observe the relationship and change in IOP over time between the PG group and the CC group. The first correlation was conducted for the CC group. The results of the correlation indicated that time explained 0.66% of the variance in intraocular pressure for the CC group ($R^2 = 0.0066$), $F(1,563)$, $p=0.74$). An R value was also calculated using an online tool for the CC group and found to be 0.08. The second correlation was conducted for the PG group. The results of this correlation indicated that time explained 2.1% of the variance in intraocular pressure for the PG group ($R^2 = 0.021$), $F(1,765)$, $p<0.001$). The R value for the PG group was 0.14.

8.4.2 COMPARISON OF INTRAOCULAR PRESSURE BETWEEN THE PRE- GLAUCOMA GROUP AND THE CASE-MATCHED CONTROL GROUP: 5 YEARS AND 10 YEARS BEFORE DIAGNOSIS.

Parametric t-test analysis was used to consider the difference in IOP at specific time intervals. T-tests were used to determine whether IOP differed between the 2 groups at 5 years and 10 years prior to diagnosis. The data were restricted to a single measurement at or over years 5 and under years 6 for both the PG group and the CC group. The same procedure was carried out for each group for a single data point at year 8 or above and below year 11. All the entries were filtered for years equal to or greater than 5 years and no more than 6. The entries were screened and if there were 2 entries per case, the case which was closest in time to 5 years was kept; for example, if the same case had case records for year 5 and year 5.9, then year 5 was selected. The same process was used for cases between 8 and 10 years but on this occasion the cases closest to 10 years were selected.

The data for 5 years are presented in Tables 8.4-1 and 8.4-2. The data for 10 years are presented in Tables 8.4-3 and 8.4-4 There were more cases for whom data entry points were available at 10 years than at 5 years.

TABLE 8.4-1 Descriptive statistics for Pre-Diagnosis Glaucoma and Case-Matched Cases selected at 5 year assessment. “SER” is spherical equivalent refraction. “IOP” is intraocular pressure in mmHg “ONH” is optic nerve head cup to disc ratio. “S.D.” is standard deviation. “Min” in minimum and “Max” is maximum. The *values under ONH are median (below mean) and mode (below min).

VARIABLE	GROUP	NUMBER	MEAN	S.D.	MIN	MAX
Age/Years	Pre-Diagnosis	58	65.8	9.0	41.0	82.0
	Case-matched Control	46	65.8	9.4	38.0	80.0
SER	Pre-Diagnosis	56	-1.0	3.4	-9.5	7.3
	Case-matched Control	46	-0.4	3.3	-10.6	4.4
Visual Acuity	Pre-Diagnosis	57	0.1	0.1	-0.1	0.5
	Case-matched Control	46	0.0	0.1	-0.1	0.5
IOP	Pre-Diagnosis	56	19.2	4.1	13.0	31.0
	Case-matched Control	45	14.8	3.2	9.0	21.0
ONH	Pre-Diagnosis	48	0.4*	0.2	0.4*	
	Case-matched Control	38	0.3*	0.2	0.2*	

TABLE 8.4-2 Descriptive and comparative statistics for Pre-Diagnosis Glaucoma and Case-Matched Cases selected at 5 year assessment. “IOP” is intraocular pressure in mmHg. “SER” is spherical equivalent data. “S.D.” is standard deviation, “CI” is confidence intervals, “p” values calculated from unpaired t-test.

Group	Number	Mean years prior to Diagnosis	Mean Age	Mean IOP	S.D IOP	CI (95%)	t-test
Pre-Diagnosis	56	5.4	65.8	19.2	3.1	18.1-20.3	
Case-Matched	45	5.4	65.8	14.8	4.1	13.9-15.7	<i>P</i> <0.00000001

TABLE 8.4-3 Descriptive statistics for pre-glaucoma group and case matched control cases selected at 10 year assessment. “SER” is spherical equivalent refraction. “IOP” is intraocular pressure in mmHg. “ONH” is optic nerve head cup to disc ratio. “S.D.” is standard deviation. “Min” in minimum and “Max” is maximum.

VARIABLE	GROUP	NUMBER	MEAN	S.D.	MIN	MAX
Age/Years	Pre-Diagnosis	82	59.5	10.1	36.0	78.0
	Case-matched Control	55	58.2	9.5	36.0	76.0
SER/DS	Pre-Diagnosis	81	-1.3	3.6	-11.9	7.0
	Case-matched Control	55	1.1	3.6	-11.0	5.3
Visual Acuity	Pre-Diagnosis	82	0.0	0.1	0.0	1.0
	Case-matched Control	54	0.0	0.1	0.0	0.0
IOP	Pre-Diagnosis	82	18.2	4.1	10.0	29.0
	Case-matched Control	50	15.1	3.3	9.0	24.0
ONH	Pre-Diagnosis	64	0.5*	0.2	0.3*	
	Case-matched Control	37	0.3*	0.2	0.3*	

TABLE 8.4-4 Descriptive and comparative statistics for Pre-Glaucoma Group and Case Matched Control Cases selected at 10 year assessment. “SER” is spherical equivalent data. “IOP” is intraocular pressure in mmHg “S.D.” is standard deviation, “CI” is confidence intervals, “p” values calculated from unpaired t-test.

Group	Number	Mean years prior to Diagnosis	Mean Age	Mean IOP	S.D IOP	CI (95%)	t-test
Pre-Diagnosis	82	9.6	59.5	18.2	4.1	17.3-19.1	
Case-Matched	55	9.8	58.2	15.1	3.3	14.1-16.1	<i>P</i> <0.000008

8.4.2.1 COMPARISON OF INTRAOCULAR PRESSURE BETWEEN THE PRE-GLAUCOMA GROUP AND THE CASE-MATCHED CONTROL GROUP: 5 YEARS AND 10 YEARS BEFORE DIAGNOSIS (EXCLUDING CATARACT CASES)

The cases selected to determine whether IOP differed between the two groups at five years and ten years prior in Section 8.42 were screened for cases that had cataract surgery performed. These cases were removed and parametric T-test analyses were repeated (Tables 8.4-3 & 8.4-4).

TABLE 8.4-5 Descriptive and comparative statistics for Pre-Glaucoma and Case Matched Control Cases who had not had cataract surgery. Cases selected at 5 year assessment. "IOP" is intraocular pressure in mmHg "SER" is spherical equivalent data. "S.D." is standard deviation. "p" values calculated from unpaired t-test.

GROUP	NUMBER	MEAN YEARS PRIOR TO DIAGNOSIS	MEAN AGE	MEAN IOP	SD IOP	T-TEST
Pre-Diagnosis	55	5.4	65.8	19.2	4.1	-
Case-matched	38	5.4	65.8	14.3	3.0	P<0.05

TABLE 8.4-6 Descriptive and comparative statistics for Pre-Glaucoma and Case Matched Control Cases who had not had cataract surgery. Cases selected at 10 year assessment. "IOP" is intraocular pressure in mmHg "SER" is spherical equivalent data. "S.D." is standard deviation. "p" values calculated from unpaired t-test.

GROUP	NUMBER	MEAN YEARS PRIOR TO DIAGNOSIS	MEAN AGE	MEAN IOP	SD IOP	T-TEST
Pre-Diagnosis	82	9.6	59.5	18.2	4.1	-
Case-matched	47	9.8	58.2	15.0	3.4	P<0.05

8.4.3 SECONDARY ANALYSIS FAMILY HISTORY OF GLAUCOMA

Secondary analysis was conducted to look for differences in intraocular pressure at 5 years prior to diagnosis in all PG cases who had a direct family member (PGFHG) with glaucoma compared to those in the PG group without a family history (PGnFHG) of the condition. A correlation was calculated to observe the relationship and change in IOP over the last 5 years between these two subgroups from the PG cases. The results of the correlation indicated that time explained 0.8% of the variance in intraocular pressure for the PGnFHG group ($R^2 = 0.008$). The second correlation was conducted for the PGFHG group. The results of this correlation indicated that time explained 0.7% of the variance in intraocular pressure for the PGFHG group ($R^2 = 0.007$)

8.4.3.1 SECONDARY ANALYSIS 5-6 YEARS

A t-test was conducted to compare mean IOP measurements in the PGFHG with PGnFHG at the time point 5 years. The mean intraocular pressure was not significantly different in the patients who had a family history of glaucoma and those that did not 5 years prior to diagnosis ($p=0.80$) (Table 8.4-5).

TABLE 8.4-7 Descriptive and comparative statistics for mean IOP in “PGFHG” (Pre-Diagnosis Group with a family history of glaucoma).and “PGFnHG” (Pre-Diagnosis Group without a family history of glaucoma) at 5 years prior to diagnosis. “IOP” is intraocular pressure in mmHg. “N” is number. “S.D” is standard deviation. “p” values calculated from unpaired t-test.

GROUP/VARIABLE	NUMBER	IOP		
		Mean	S.D.	p
PGFHG	27	20.2	4.9	-
PGFnFHG	29	18.3	3.0	0.8

8.4.3.2 SECONDARY ANALYSIS 8-11 YEARS

A t-test was conducted to compare IOP in the group of patients that had a family history of glaucoma and those that did not, specifically in the Group of patients that went on to develop glaucoma 10 years later. A t-test was conducted to compare IOP in the Group of patients that had a family history of glaucoma and those that did not, specifically in the Group of patients that went on to develop glaucoma 10 years later. The mean intraocular pressure was significantly different in the patients who had a family history of glaucoma and those that did not five years prior to diagnosis (p=0.04) (Table 8.4-6).

TABLE 8.4-8 Descriptive and comparative statistics for mean IOP in “PGFHG” (Pre-Diagnosis Group with a family history of glaucoma).and “PGFnHG” (Pre-Diagnosis Group without a family history of glaucoma) at 10 years prior to diagnosis. “IOP” is intraocular pressure in mmHg. “N” is number. “S.D” is standard deviation. “p” values calculated from unpaired t-test

GROUP/VARIABLE	NUMBER	IOP		
		Mean	S.D.	p
PGFHG	33	19.3	4.2	-
PGFnFHG	49	17.4	3.8	0.04

8.5 OPTIC NERVE HEAD

Vertical CDR measurements were recorded from the PG Group and the CC Group. The details for these are described below. Frequency distribution and box plots were charted for each group (Figures 8-5 to 8-5.3). The frequency distribution charts confirm that the distribution for CDR in the PG group and the CC group were not of a normal distribution and therefore

non-parametric testing would be required. The Levene statistic was significant for the test of homogeneity ($p < 0.05$)

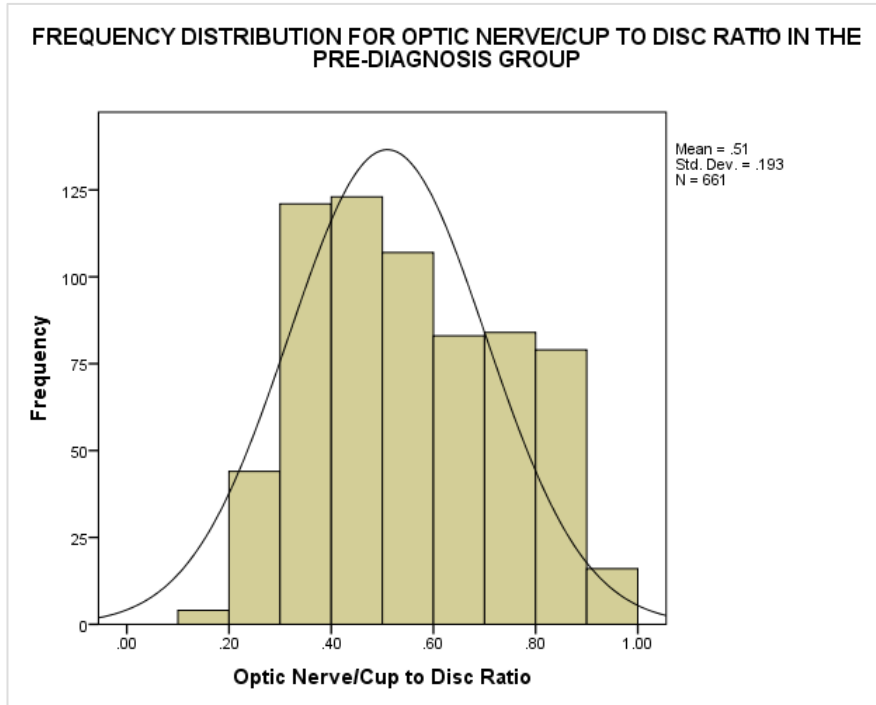


FIGURE 8-5 Frequency distribution for optic nerve/cup to disc ratio in the Pre-Diagnosis group.

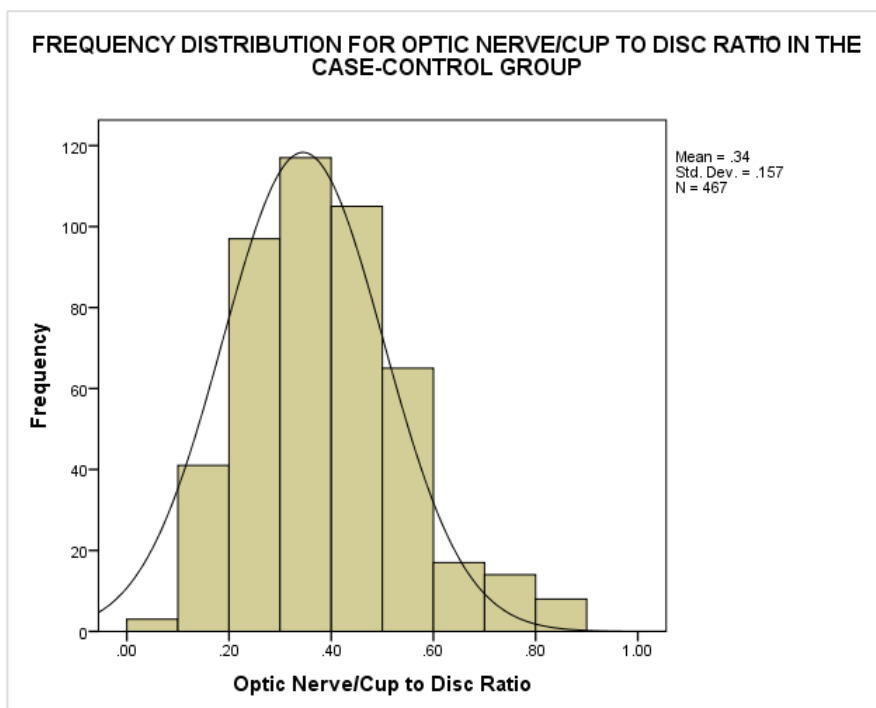


FIGURE 8.5-1 Frequency distribution for optic nerve/cup to disc ratio in the Case-Matched Control group.

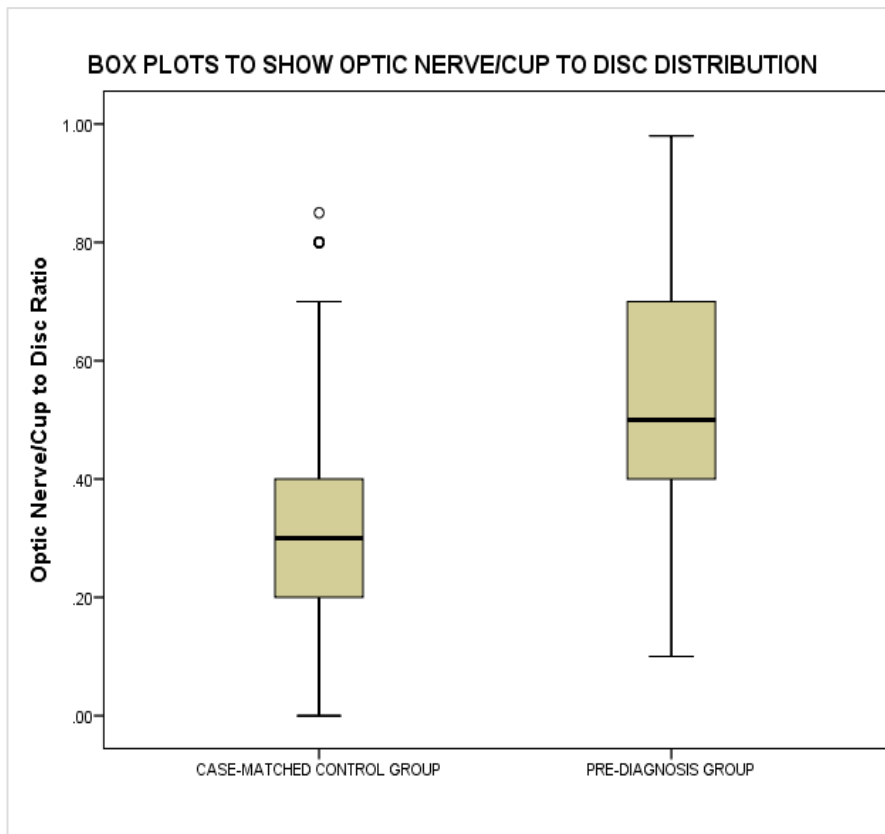


FIGURE 8.5-2 Box plots to present optic nerve/cup to disc distribution in the Pre-Diagnosis group and Case-Matched Control group. The Y axis presents cup to disc ratios. The mode by the horizontal line inside each box. The lower whiskers (lines outside of the box) represent the lowest measurements. The stars above the top whiskers present the outliers and the highest measurements.

8.6 CORRELATION FOR OPTIC NERVE CUP TO DISC RATIO AND TIME.

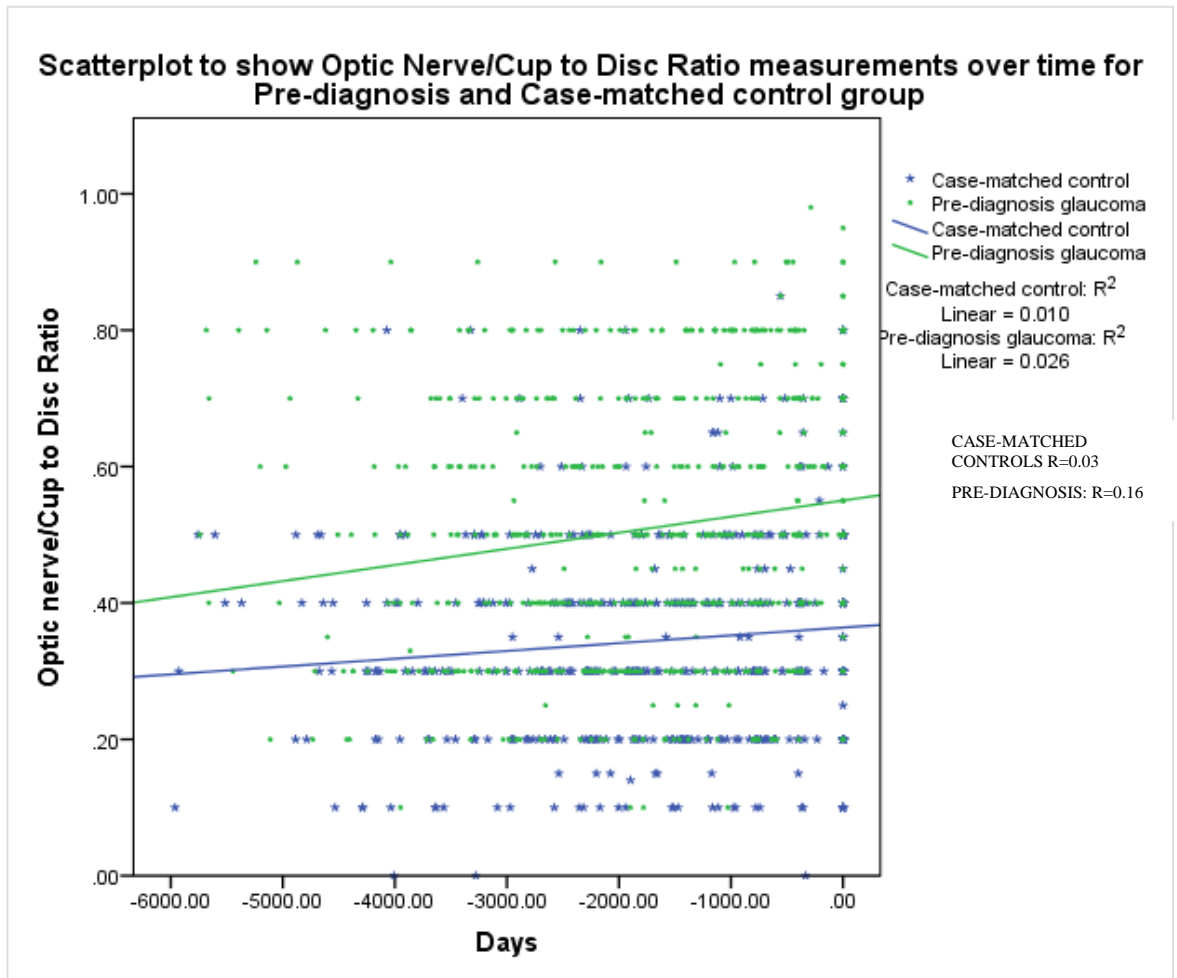


FIGURE 8.5-3 Scatterplot to show the correlation of optic nerve/cup to disc ratio over time in days

A correlation was calculated to observe the relationship and change in cup to disc ratio over time between the PG group and the CC group. The correlation was conducted for the CC group. The results of the correlation indicated that time explained 1.0% of the variance in cup to disc ratio for the CC group ($R^2 = 0.001$). The correlation was conducted for the PG group. The results of this correlation indicated that time explained 2.6% of the variance in intraocular pressure for the PG group ($R^2 = 0.026$).

8.6.1 ANALYSIS CUP TO DISC RATIO

Optic nerve cup to disc ratios were tabulated for the first data entry for CDR for each case for groups PG and CC (Table 8.6-1) and tabulated for each data entry over 10 years.

A non-parametric test was used to test for significance as the data were heteroscedastic (the standard deviation was greater in the PG group) (Spencer et al. 2017). The Levene statistic was significant for the test of homogeneity ($p < 0.05$). The median optic nerve cup to disc ratio was significantly greater in the group PG (median 0.5 ± 0.2) group CC (0.3 ± 0.2) as per the Mann Whitney U test ($p < 0.05$).

TABLE 8.6-1 Descriptive and comparative statistics. “ONH/CDR” is optic nerve head/cup to disc ratio. “N” is number of data entries. “S.D” is standard deviation, “CI” is confidence intervals, “p” values calculated from Mann Whitney U test.

GROUP/VARIABLE	NUMBER	ONH/CDR			
		Median	S.D.	CI 95%	p
Pre-Diagnosis	661	0.5	0.2	0.3-0.4	-
Case-matched	467	0.3	0.2	0.5-0.5	<0.05
Visit 1 Pre-Diagnosis	57	0.4	0.2	0.2	
Visit 1 Case-matched	66	0.4	0.2	0.2	

8.6.2 ANALYSIS CUP TO DISC RATIO AT 5-6 YEARS

The Mann Whitney U test was also used to determine whether the CD ratio in each Group significantly differed at five years prior to diagnosis. The cases were chosen with the same method as for the intraocular pressure analysis described in Section 8.4.2. The data were restricted for a single measurement at or over years 5 and 0 months and under years 6 and 0 months for both the PG group and the CC group. The descriptive data is presented at 5 years in Table 8.6-2. Five years before diagnosis the median CDR was statistically greater (Mann Whitney U test, $p < 0.05$) in group PG (median 0.4 ± 0.2) than group CC (median 0.3 ± 0.2).

TABLE 8.6-2 Descriptive and comparative statistics. Cup to disc ratio 5-6 years “ONH/CDR” is optic nerve head/cup to disc ratio. “N” is number of data entries. “S.D.” is standard deviation, “CI” is confidence intervals, “p” values calculated from Mann Whitney U Test.

GROUP/VARIABLE	NUMBER	ONH/CDR			
		Median	S.D.	CI 95%	p
Pre-Diagnosis	48	0.4	0.2	0.4-0.5	
Case-matched Control	38	0.3	0.2	0.3-0.4	<0.05

8.6.3 ANALYSIS CUP TO DISC RATIO 8-11 YEARS

The Mann Whitney U test was used to determine whether the CD ratio was different at ten years prior to diagnosis. The data were restricted for a single measurement at or over years 8 and 0 months and under years 11 and 0 months for both the PD group and the CC group. The descriptive data are shown in Table 8.6-3. Ten years before diagnosis the median CDR was statistically significantly greater (Mann Whitney U test, $p < 0.05$) in group PG (median 0.5 ± 0.2) than group CC (median 0.3 ± 0.2).

TABLE 8.6-3 Descriptive and comparative statistics. Cup to disc ratio 8-11 years “ONH/CDR” is optic nerve head/cup to disc ratio. “N” is number of data entries. “S.D” is standard deviation. “p” values calculated from Mann Whitney U test.

GROUP/VARIABLE	NUMBER	ONH/CDR			
		<i>Median</i>	<i>S.D.</i>	<i>CI 95%</i>	<i>p</i>
Pre-Diagnosis	64	0.5	0.2	0.4-0.5	
Case-matched Control	37	0.3	0.2	0.3-0.4	<0.05

8.7 VISUAL FIELDS

The outcome of every visual field test was recorded from each case between the glaucoma and control Group. The outcomes for each subgroup with the PG group and the CC group are shown in Table 8.7-1. The visual field instruments used were documented for each case although the data were not tabulated.

8.7.1 PRE-DIAGNOSIS GROUP

A full visual field was recorded in 58.9% of the PG group. 29.4% of the patients had no record of a visual field test. Approximately 9% of the clinical records had notes for the visual field plot to be reviewed; a suspicious visual field recorded was recorded in 2.3%. There was 1 case that had notes for visual fields to be repeated and 1 case that was having visual fields conducted at the hospital eye service. Figure 8.8-1 presents a pie-chart with the details of the visual field plot outcomes for the PG cases at their last visit prior to glaucoma diagnosis.

8.7.2 CASE-MATCHED CONTROL GROUP

64.4% had a full visual field recorded. 29.2% of the patients had no record of a visual field test. 6.4% had notes to review the visual field plot (Table 8.7-1) presents a pie-chart with the details of the visual field plot outcomes for the CC group cases at their last visit.

TABLE 8.7-1 Outcome of visual field assessments for all cases. Values in percentage.

Description	Pre-Diagnosis Group %age	Case-matched Control Group %age
Full visual field	58.9	64.4
Suspect	2.3	0
Review visual field	9.3	6.4
Visual fields at hospital	0.1	0
No record of assessment	29.4	29.2

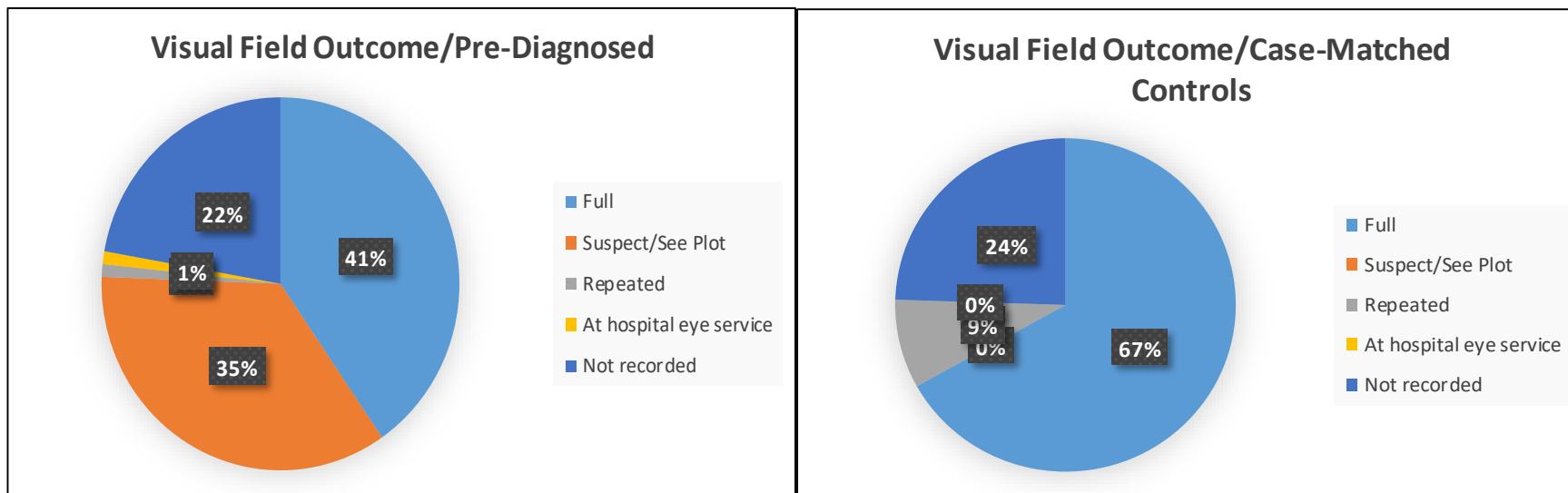


FIGURE 8.7-1 pie chart to show visual field plots Pre Diagnosis Group: at last visit prior to diagnosis

Figure 8.7-2 Pie chart to show visual field plots case-measured control at last visit prior to diagnosis

TABLE 8.7-2. Visual field outcomes calculated from last visit prior to diagnosis

Visual field outcome from last visit prior to diagnosis	Pre-Diagnosis Group	Case-matched control group
Full	40.0	66.9
Suspect/See Plot	35.2	0
Repeated	1.1	8.6
At hospital eye service	1.1	0
Not recorded	22.2	24.5

8.8 SUMMARY OF RESULTS FOR STUDY 2

This chapter has presented a summary of the data collected for intraocular pressure, optic nerve/cup to disc ratio measurements and visual field outcomes for two groups of cases (groups PG and CC). A total of 182 cases were reviewed. Both groups data were observed over a period of ten years. Statistical analyses were conducted using correlation and a comparison on mean and median values. The results for intraocular pressure measurements demonstrated that mean values for the PG group were statistically significantly greater at five years and up to ten years prior to diagnosis when compared to the CC group. Similarly, median optic nerve cup to disc ratio values were statistically significantly greater at five and ten years prior to diagnoses in the PG group. Visual field outcomes were tabulated to review the outcomes for all the cases and for the last visit prior to confirmed diagnosis. These results will be discussed in Chapter 9.

9. DISCUSSION FOR STUDY 2

9.1 OVERVIEW FOR DISCUSSION

This chapter will review and discuss the results for the ten years clinical data found for a group of subjects that were subsequently diagnosed with glaucoma (Chapter 8). The discussion will review the results on intraocular pressure followed by a discussion on the optic nerve head/cup to disc ratio findings and the visual fields data. A summary will be provided at the end of the chapter followed by a general discussions and conclusions chapter.

9.2 REVIEW OF RESULTS FOR STUDY 2

9.2.1 STUDY DESIGN

Study 2 involved individual matching of case records (on a paired basis). This type of study design is beneficial for efficiency by forcing the case and control samples to have similar distributions across confounding variables (Rose & Laan 2009). The limitations to the recruitment of the cohorts for this study are selection bias and misclassification. Selection bias can occur if the controls differ in an unknown way from the pool of controls (Keogh & Cox 2014). In this study, attempts were made to collect each paired glaucoma and control case from the same practice to control for some demographic biases. This approach was mostly successful, with only four control cases needed to be matched from other practices. The matched cases being registered at the same optometry practice does not confirm that the cases are demographically from the same area. It is not unknown for subjects to travel out of their area to see a recommended optometrist.

The data for Study 2, as in Study 1, were real world data and collected in routine community optometry practices. The clinical measurements were not measured or recorded for research purposes. The four practices that were used all had established practitioners who had achieved further optometry training. This had an advantage for extraction of data as there was some consistency with records and familiarity. There is also a control of measurement error in two

ways; repeatability of the same observer and between observers (Coggon et al. 2003). All the community practices used had more than one optometrist and therefore it is likely that over the time span that the case records were used, there would have been on occasions different optometrists assessing the participant, albeit the same practice.

Almost two thirds of the PG group were male. This supports the results reported in the literature review (Section 2.4.2) for males to have a higher prevalence of POAG. Tham et al. (2014) also reported in a global prevalence report that men were more likely to have POAG than women (OR 1.36).

9.3 INTRAOCULAR PRESSURE

9.3.1 TONOMETRY

The equipment used to measure intraocular pressure was tabulated from the last observed measurement for the PG group and CC group. The results showed that the type of each instrument was similar in each group (Table 8.3-1). The most popular method of measuring IOP was with the Pulsair non-contact tonometry; followed by the Icare rebound instrument. Contact tonometry was used in 13.2% of the PG cases and in 8.6% of CC. Although contact tonometry is the current recommended guideline for IOP measurement before referral for OAG (NICE 2017), the cases have ranged in date from 1983 to 2016. The span of years for the last observed measurement was from 1995 to 2016. These results agree with a national survey of diagnostic tests reported by UK community optometrists for the detection of OAG which reported non-contact tonometry methods to be the most popular (78%) and contact applanation being used 16% of the time (Myint et al. 2011).

Consideration should be made to the time-span in which the intraocular pressure measurements were taken. The data have been collected over a span of 33 years. Tonometry equipment has developed and refined over that time so consideration is given that the more recent measurements may be more accurate.

9.3.1.1 SUMMARY OF RESULTS FOR INTRAOCULAR PRESSURE IN THE PRE-GLAUCOMA GROUP AND IN THE CASE-MATCHED CONTROL GROUP

The minimum IOP measurement in the PG group was 9.0mmHg and the maximum was 36.0mmHg. The mean IOP was 18.9 mmHg with a standard deviation of 4.4. The minimum IOP measurement in the CC group was 7.0mmHg and the maximum was 25.0mmHg. The mean IOP was 14.9mmHg with a standard deviation of 3.3. The correlation results from group PG indicated that time explained 2.1% of the change in IOP as opposed to the CC group indication of 0.66%. The difference in intraocular pressure at specific time points was also considered between the groups PG and CC. At 5 years before diagnosis, the mean IOP was statistically significantly greater (unpaired t-test, $p < 0.00000001$) in the PG Group (mean 19.2 ± 4.1) than the CC Group (mean 14.8 ± 3.1). At 10 years before diagnosis, the mean IOP was statistically significantly greater (unpaired t-test, $p < 0.000008$) in the PG Group (mean 18.2 ± 4.1) than the CC Group (mean 15.1 ± 3.3).

Intraocular pressure was compared between the cases who had a family history of glaucoma (PGFHG) and those who did not have a family history of glaucoma (PGnFHG) at two-time intervals. At five years before diagnosis the mean IOP was not statistically different (unpaired t-test, $p = 0.8$) in the group PGFHG (mean 20.2 ± 4.9) than group PGnFHG (mean 18.3 ± 3.0). At 10 years before diagnosis the mean IOP was statistically significantly different (unpaired t-test, $p = 0.044$) in the group PGFHG (mean 19.3 ± 4.2) than group PGnFHG (mean 17.4 ± 3.8).

9.3.2 COMPARISON OF INTRAOCULAR PRESSURE RESULTS TO LITERATURE

This study was reliant on the retrospective data and therefore there was little control on the quality of the data being extracted. The information that was controlled for was which eye was used for data analyses. Analyses were data from the eye which was either diagnosed first; if both eyes were diagnosed at the same time, a decision was made from the notes as to which

eye was the more affected (Section 7.5.3). The same eye was chosen for the control case. Research supports the view that the eye chosen for the case control could be either right or left, as symmetrical variation has been shown in IOP in untreated healthy individuals between ages 18 years to 74 years (Liu et al. 2005). The order of IOP measurement has been shown to be important. IOP measured in the first eye, whether the right or the left, is on average higher than the IOP measured in the fellow eye (Pekmezci et al. 2011; Chan et al. 2016). Optometrists are taught to measure and record investigations of the eye from right to left. However, as Study 2 reported 56.9% measurements for the right eye and 43.1% for the left, this may have counteracted this difference. Recommendations from a predictive model for POAG in OHT patients evaluated using the “worse” eye or the means of right and left eyes and concluded that the latter is the more robust to measurement variability and error (The OHT Study Group and EGP Study Group. 2007). This study used the “worse” eye; taking the mean of the two eyes would not have been appropriate as often treatment can be initiated in both eyes to prevent progression in the worse eye is affected.

Study 2 did not have a cut off for IOP measurements and the range extends to 36.0mmHg for group PG. This value was recorded for a participant at the time they were referred and diagnosed with POAG. Group CC had a maximum IOP value of 25.0mmHg. This entry was an isolated reading for the control case with all other measurements being below 21.0mmHg. The percentage of IOP entries that were recorded above 21.0mmHg were 29.7% for group PG and 5.1% for group CC. NICE guidelines recommend that all repeatable intraocular pressures over 21.0mmHg measured by applanation tonometry in people aged 18 years and over, should be assessed by a suitably trained healthcare professional (NICE 2017). In this study, relatively few of the PG cases were referred for IOP over 21.0mmHg; although this group did have a higher percentage of IOP measurements recorded by applanation tonometry than the group CC. The optometrists at each practice were monitoring these cases over many years and it is possible that PG cases had glaucomatous changes before referral was considered necessary. These results show that the optometrists who were monitoring these cases were vigilant in

assessing whether risk factors were changing into confirmed glaucomatous changes. This is evident through the extra visits and visual field assessments that the PG cases had. Literature supports that elevated intraocular pressure is a strong risk factor for glaucoma, but there are substantial numbers of people with elevated intraocular pressure who do not develop glaucoma even during lengthy follow-up (Weinreb & Khaw 2004; NICE 2017). Formal screening of glaucoma is not conducted in the UK and there is evidence that many cases of glaucoma may be undetected (Lawrenson 2012); Study 2 has suggested that optometrists may be informally screening all the time as is evident with the monitoring of the cases seen in this study. The 4 community clinics recruited were only asked to provide data on the confirmed glaucoma cases; there would therefore be many cases that they monitor just as closely who do not develop glaucoma. Table 8-2.3 gives evidence on the close monitoring of cases as there were cases that were re-referred to the hospital eye service but also several cases that were monitored by the hospital eye service. False referrals have been historically documented to occur to the hospital eye service (Salmon et al. 2007) but Study 2 has delivered information on the accuracy of optometry referrals. One of the commonest reasons why a patient was assessed as normal from referral was due to assessment of the optic disc (Salmon et al. 2007) but as imaging is regularly used in day to day optometry practice now, this may have improved.

The mean intraocular pressure for the group PG was 18.9mmHg (S.D.4.4) (Chapter 8 & Section 9.22). Although the frequency distribution chart for the PG cases closely approximated a normal distribution, there is a slight skew towards higher IOP measurements (Figure 8.3-1). This pattern of IOP has also been suggested in the Bedford Glaucoma Survey (Bankes et al. 1968; Harper & Reeves 1995) but these were single point IOP measurements as opposed to ten-year variation of IOP change. The normal distribution chart for group CC showed a steady rise in IOP to 15.0mmHg then a sharper fall (mean 14.9mmHg) (Figure 8.4-1). The percentage difference between the mean IOP for group PG and group CC was 27.5%.

The UK Glaucoma Treatment Study (Garway-Heath et al. 2015) recruited newly diagnosed participants with open angle glaucoma for a randomised control trial to investigate preservation of the visual field with an intraocular-pressure-lowering drug. Interestingly the participants recruited to this study had mean IOP of 19.6mmHg (S.D.4.6) and 20.1mmHg (S.D.4.8). These intraocular pressure measurements and standard deviations are comparable for the mean IOP and standard deviation for group PG ($18.9 \pm \text{S.D.}4.5$). The initial reduction from baseline IOP for the treatment group for the UK Glaucoma Treatment Study was 5.0 mmHg (26%). This 5.0% difference is in line with the percentage difference between the mean IOP values between the PG and CC group. Hong et al (2007) conducted a nine-year retrospective study to associate long-term IOP fluctuation and visual field change. They found that standard deviation was more important even if IOP was less than 18.0mmHg. Caprioli (2007) also suggests that “standard deviation is a more robust measure, less affected by outliers, and takes the number of measurements into account”.

There has been suggestion from the literature that IOP variability between visits may be more important than mean IOP (Singh & Sit 2011). Long-term IOP fluctuation (IOP peak minus IOP trough measured in a stated time-period) may have been represented from the correlation. Isolating the IOP measurements at specific time periods, may have indicated the IOP peak (Sultan et al. 2009).

There have been many studies showing that a reduction in IOP is in many cases an effective intervention at controlling the progression of POAG. The Early Manifest Glaucoma Trial (Heijl et al. 2002) demonstrated that progression of OAG may be controlled with a 25% reduction in IOP in patients with newly diagnosed OAG. This level of reduction has also been shown to be beneficial in patients with ocular hypertension. The Ocular Hypertension Treatment Study (OHTS) showed that a 20% reduction from baseline by topical medical therapy may delay or prevent the onset of POAG over the course of five years in individuals with elevated IOP (Kass et al. 2002). The implications of the results for this study when considered with the results of these and other studies are that they may be evidence to start

treatment earlier before structural and functional change becomes manifest. There are implications of starting treatment prematurely as glaucoma influences a patient's quality of life (Quaranta et al. 2016), as there are implications of long term treatment, hospital visits and the anxiety of diagnosis or even mis-diagnoses; but this also must be balanced with the importance of timely glaucoma diagnosis for preserving vision (Quaranta et al. 2016; European Glaucoma Society 2017).

The scatterplot (Figure 8.4-3) showed that there were differences in IOP over time between the two groups of PG and CC cases. The chart shows the distribution of IOP measurements for PG cases to be concentrated at higher IOP measures than CC cases.

Inspection of the scatterplot shows that IOP for the case-control group stayed constant and appeared to plateau, if not lower after 10 years. The EPIC-Norfolk Eye Study (Foster et al. 2011) and the UK Biobank Study (Chan et al. 2017) also found the same trend among women, however Study 2 had more male cases than female. Oestrogen use has been implicated with IOP and retinal ganglion cell protection, thereby reducing the risks of POAG (Newman-Casey et al. 2014). The relationship between age and IOP has not shown clear consistent relationships (Klein et al. 1992; Wu & Leske. 1997; Tomoyose et al. 2010; Wong et al. 2009). Consideration has been given to the fact that 12 of the cases from group CC had undergone cataract surgery compared to 6 of group PG. Cataract surgery has been demonstrated to reduce IOP in glaucoma as well as normal subjects (Shingleton et al. 2006). For this reason, the analyses were repeated at the 5-year interval and 10-year interval with all the cases who had had cataract surgery removed and the mean IOP difference remained to be statistically significantly different. (Section 8.4.2.1).

The scatterplot also reveals that the trend over time in intraocular pressure for group PG shows long term change (Sit 2014). Intraocular pressure has a greater increase over time in the cases who go on to develop glaucoma. Downs (2015) aptly reports that the vulnerability of IOP may be underestimated if mean IOP is presented with snapshot measurements. Subtle changes in intraocular pressure, although keeping under 24.0mmHg (NICE 2017), may still be

contributory to optic nerve head alterations (Jiang et al. 2017). There are very few studies to date which have reviewed longitudinal change in IOP. One study that has done this is the Barbados Eye Study (Wu et al. 2006). This study reported on intraocular pressure change over 9 years in non-glaucomatous African subjects. Over the 9 years, the mean IOP change was 0.4mmHg (S.D. 4.0). The Barbados Eye Study also showed that over 9 years, from the participants who had an IOP of 21.0mmHg or less at baseline, 6.5% had an elevation of IOP after 9 years; 3.8% had subsequent IOP-lowering treatment and 2.7% developed OAG.

The mean IOP for group PG was 18.2mmHg at 8-11 years prior to diagnosis; and 19.1mmHg at 5-6 year prior to diagnosis. In contrast, group CC had an IOP of 15.1mmHg at 8-11 years and 14.8mmHg at 5-6 years. These mean IOP differences between each group are statistically significantly different ($p < 0.000008$). These results indicate that glaucomatous changes may be initiated much earlier than we have anticipated and corroborate with the results with Study 1 that isolated intraocular pressure readings may provide very little information on their own but the pattern of change is important.

9.3.3 SECONDARY ANALYSIS OF FAMILY HISTORY AT 5 AND 10 YEARS

Mean intraocular pressure in the cases who had a family history of glaucoma were found to be significantly higher to those that did not within group PG at 8-11 years prior to diagnosis but not at 5-6 years. Interestingly, there were fewer data points for these sub groups at 5-6 years compared to 8-11 years. There may have been fewer if at this point the participants were beginning to be referred for second opinions to the hospital eye service. The reasons why a statistical difference in mean IOP was found at 8-11 years but not at 5-6 years are unclear. The results show that the mean IOP differences are unchanged between the two groups although both are higher. However, the standard deviation has decreased at 5-6 years from 3.8 to 3.0 in the group without a family history.

9.4 OPTIC NERVE HEAD ASSESSMENT/CUP TO DISC RATIO

9.4.1 SUMMARY OF RESULTS FOR OPTIC NERVE HEAD/CUP TO DISC RATIO

The values for the whole data set showed the median value for group PG to be 0.5. Comparatively, these values were 0.3 for the median for group CC. The median CDR values for the first visit for each case were 0.3 in each group. Having substantially more entries for the whole data set may account for the change in median. However, a decrease in median for the control group may be accounted for by increasing accuracy if measurement techniques changed over the 10 years of the participants eye examinations. The Blue Mountains study found that in non-glaucomatous eyes, mean CDR increased 0.001 for every year of age and increased by 0.004 for each 1.0 mmHg increase in IOP (Healey et al. 1997). Thus, group CC would be expected to show little to no change, even accounting for age related axonal loss (Harwerth et al. 2008).

9.4.1.1 SUMMARY OF STATISTICAL ANALYSIS FOR THE PRE-DIAGNOSIS GROUP AND THE CASE-CONTROL GROUP FOR OPTIC NERVE HEAD/CUP TO DISC RATIO

Statistical analysis with Mann Whitney U test showed that the median cup to disc ratio measured in group PG compared to the cases for group CC was significantly larger ($p < 0.05$). The difference in cup to disc ratio at specific time points was also considered between groups PG and CC. The data were restricted to a single measurement at or over 5 years 0 months and under 6 years and 0 months for each group. The same was done for each group for a single data point at year 8 years and 0 months and under 11 years and 0 months.

Five years before diagnosis the median CDR was significantly greater (Mann Whitney U test, $p < 0.05$) in group PG (median 0.4 ± 0.2) than group CC (median 0.3 ± 0.2).

Ten years before diagnosis the median CDR was statistically significantly greater (Mann Whitney U test, $p < 0.05$) in group PG (median 0.5 ± 0.2) than group CC (median 0.3 ± 0.2).

9.4.2 OPTIC NERVE/CUP TO DISC RATIO: COMPARISON TO CURRENT LITERATURE

The results presented for median CDR values, when considered alongside the mean IOP values, concur with the Beaver Dam Eye Study (Klein et al. 1992). The Beaver Dam Eye Study found that amongst normal tension and open angle glaucoma subjects, vertical CD ratio was 0.5 with a mean IOP of 17.6mmHg. The values reported for the non-glaucoma group were CD ratio of 0.4 and mean IOP of 15.2mmHg. (Klein et al. 1992). The observations were made with a slit lamp microscope and accessory lens and photographs were taken. This is relevant as when screening for glaucoma, clinicians will readily use this procedure to screen and monitor for glaucoma changes (NICE 2017). Community optometry has evolved with not only its partnership with ophthalmology but also with the techniques used for assessments. Over the span of 15 years, optometry has progressed to having slit-lamp biomicroscopy as standard practice and many practices will use supplementary imaging with retinal photography or optical coherence topography. Historically, ophthalmologists used to have a higher interobserver agreement in estimating CDR for glaucomatous nerve damage when compared to optometrists (Abrams et al. 1994) but this may have changed positively (Roberts et al. 2015) as many optometrists are now part of glaucoma enhances schemes and monitoring services (Baker et al. 2016).

The results show that the optic nerve assessment by CDR appear different in the PG group than the CC group. Observation of the frequency distribution charts present more data entries spread across a median of 0.3 to 0.9 whereas the CC group are concentrated between 0.3 and 0.5. The correlation (Figure 8.5-3) does present a change over time. Thought has been given as to whether some cases may have had pathological changes and early glaucoma was not

being detected. However, these results suggest that the practitioners were monitoring subtle changes over the time and would therefore be less likely to miss pathology. This is supported also by observing the results of the CC group also had an increase in CDR over time, albeit it small. The median values of CDR from the first visit of each group suggest that the groups did not have distinct difference ten years prior to glaucoma diagnosis. Systemic risk factors of glaucoma should be considered as they may have some effect on the optic nerve. Evidence has been shown to suggest that localised ischemia affecting the papillomacular bundle of the neuronal tissue may cause thinning at the Bruchs membrane and result in associated VF loss (Park et al. 2011; Taniguchi et al. 2017). There are associations with these changes to be more likely in people with vascular dysregulation in conditions such as Raynaud's syndrome (Park et al. 2011). Hypothetically there may be anatomical differences in the optic nerve cup of patients that could account for an added risk of mechanical or vascular possibly with or without an increase in IOP. Structural differences in the anatomy of the optic nerve such as the Bruch membrane have been indicated as new structural biomarkers associated with glaucoma (Taniguchi et al. 2017). Glaucoma research is advancing through consideration neuroprotection of the optic nerve and with analysis of the nerve with advancements of OCT. These techniques will broaden the scope of being able to detect early precursors of glaucoma (Sena & Lindsley 2013; Daneshvar & Nouri-Mahdavi 2017).

Vertical cup to disc ratio has been recommended for observation of the optic nerve head (Garway-Heath et al.,1998) but being a retrospective study, the method of observation or accuracy was largely assumed. The structure of the optic nerve head and its examination have been reviewed in Section 1.14.5. Clinicians rely on descriptive data for the optic nerve as well as objective measurements. Descriptions such as the "ISNT" rule, optic disc size or cup position were not tabulated. The reasons for this are that there were different practitioners at the practices over the time span that the data were collected and the notes were recorded in various ways and not suitable for extraction and analyses. These details are also largely subjective (Tatham et al. 2015). The records also spanned several years and there were some records where descriptive words were used such as "normal" or WNL (within normal limits).

Comparison of CDR asymmetry was not used for this study as the details for the most affected eye were extracted; the most affected eye which would be suggestive of the one with the most acquired damage. Cup to disc ratio is a basis for further follow up for glaucoma suspects or those with risk factors but it is not used for screening purposes (Qiu et al. 2017).

The mean refractive error for groups PG and CC was approximately -1.00DS; each group having a small amount of myopia. A systematic review and meta-analysis showed that glaucoma studies have described low myopia from -3.00DS and emmetropia up to -1.50DS (Marcus et al. 2011). With vertical CDR being shown to be 0.3 in normal eyes (Jonas et al. 1988), the alteration over time for the PG cases are more likely due to a pathological alteration as opposed to any difficulties or abnormalities due to a myopia-related optic nerve (Chang & Singh 2013).

9.5 VISUAL FIELD ASSESSMENT

9.5.1 SUMMARY OF DESCRIPTIVE DATA FOR VISUAL FIELD ASSESSMENT.

Descriptive data were tabulated from the visual field results from each case for groups PG and CC. Table 8.7-1 presents the outcomes for visual field plots for each data entry. Table 8.7-2 shows the outcomes tabulated for each group only from the last visit.

For the PG group, less than 50 % had a full visual field recorded prior to diagnosis but as these records were not accessible it is unknown if they were glaucomatous. This could also not be determined for the fields that were recorded as “see plot” or “defect”. A small percentage of cases were being monitored at the hospital. In contrast, group CC had 66.9% with a full visual field recorded. A quarter of cases in each group did not have a record of a visual field.

9.5.1.1 VISUAL FIELD ANALYSIS: COMPARISON TO CURRENT LITERATURE

Visual field plots are often stored on the hard drive of the perimeter and it could be that there were plots that were asked to be reviewed by screening staff for anomalies such as false

positive results or lack of fixation. A quarter of cases for both groups did not have a visual field plot recorded. This may be as there were visual fields conducted but not recorded on the case record; or that a clinical decision was made not to perform perimetry for other reasons.

Functional changes for glaucoma are thought to become evident once glaucoma has become manifest, yet there are no longitudinal studies comparing the value of assessing structural and functional progress at different states of glaucoma (Öhnell et al. 2017). The research described in this thesis was considering the subtleties in glaucoma changes which occur prior to diagnosis and therefore prior to visual field loss. Ideally, to meet the inclusion criteria, it was expected that there would have been record of every case to have had 2 visual field assessments over the 10 years.

9.6 STRENGTHS AND LIMITATIONS

Study 2 presented a novel approach for considering the status of glaucoma patients 10 years prior to diagnosis. Using real clinical data has also shown the huge resource available in “real world” optometric data. The scope of this is expanding with many optometrists using advanced imaging such as OCT and routinely doing visual fields. Study 2 has also been successful in achieving a large sample size. With the support of four community optometrists, robust retrospective data were collected. As there was more than one practice, a broader and more representative sample of cases were collected than if one practice alone had been used. A challenge was finding practices that had had been observing patients over a considerable length of time. A great advantage to the data was that it spanned 33 years but a limitation that many records were hand-written which can require cautious examination. Although the cases were closely matched by group, the number of data entries per case differed and for this reason there was a difference in entry points for each group. Missing data is a limitation of retrospective data. Study 2 has benefits of using real data but also limitations that this research is relying on historical data of community clinical practices staffed by clinicians and not researchers. This means that we have variability in the use of equipment, limited visual field

data, and possibly optic nerve assessments made without dilation. Having awareness that some of these assessments were not made, there is the potential limitation that some of the PG group had glaucoma several years before diagnosis. Study 2 included data of patients who were being monitored by an ophthalmologist but not on treatment and this highlights the difficulty between a suspicion of glaucoma and confirmed glaucoma. This is discussed further in Chapter 10.

9.7 CONCLUSIONS

Study 2 has presented data which shows that both IOP and optic nerve cup to disc ratio increase in value over a ten-year period in patients who subsequently progress to develop POAG. IOP is the only modifiable risk factor for glaucoma, yet its role in the development and progression of glaucoma are not well understood (Downs 2015). This discussion has presented mean IOP results in pre-diagnosed cases which are comparable to mean IOP data from recognised prevalence studies and randomised controlled trials, indicating further that changes in IOP increase the risk of glaucomatous optic nerve change. The reduction of intraocular pressure therapeutically, has been shown to slow the rate of glaucomatous change (Musch 1999; Anderson 2003). This study indicates that the mean IOP was higher over time in those that subsequently develop glaucoma, therefore there may be implications for starting treatment earlier for patients who have higher risks of glaucoma. Mean IOP measurements were also noted to be statistically higher in those that had a family history of glaucoma at ten years prior to diagnosis. The mean age recorded from all the cases was 65 years. The mean age observed for the specific cases at 10 years prior to diagnosis group PG was approximately 60 years. These specific cases had a minimum age of 36 years and a maximum age of 78 years. Although it may not be usual to observe POAG in patients under 40 years, there is stronger suspicion that changes may be happening a lot earlier than expected. It may be these cases that are most instructive concerning the pattern of change. The increase in IOP over a ten-year duration for the PG cases corroborated with an increase in optic nerve CDR. The results of

Study 2 suggest that although visual field testing was being conducted, the details of these were difficult to interpret and this may be worth consideration if notes should be reviewed by other health professionals. Approximately 30% of the PG cases had a mean IOP over 21.0mmHg. Current NICE guidelines advise that referral for investigation of POAG is to be made if IOP is measured at 24.0mmHg. The results from this study imply that optometrists should be monitoring closely the change of IOP over time and provide “results of all examinations and tests with referral” as advised by NICE (2017).

10. GENERAL DISCUSSION AND CONCLUSIONS

10.1 GENERAL DISCUSSION

This thesis describes two retrospective studies to investigate the risk factors of primary open glaucoma. Each study has reviewed measurements of intraocular pressure and cup to disc ratio assessments.

Study 1 has reviewed intraocular pressure measurements in young adults aged between 18 years and 40 years. As a known risk factor for glaucoma is family history, intraocular pressure measurements were collected between two groups; a group with a family history of glaucoma and a group without. Although firm conclusions cannot be drawn because the findings were not significant, the fact that there was a mean difference requires further investigation with larger sample sizes. The optic nerve cup to disc ratio measurements between each group did not show an observed difference.

Study 2 collected retrospective data from case records of patients that subsequently went on to develop primary open angle glaucoma or be treated for ocular hypertension, pre-perimetric, normal tension or suspect glaucoma. The cases were approximately matched by age, gender and refractive error with a control case. The results demonstrated that there is a difference in correlation over time in the intraocular pressure measurements of patients that develop glaucoma. Mean intraocular pressure in the cases that subsequently went on to develop glaucoma compared to case-matched controls were shown to be significantly higher at 5-years and 10-year time points before diagnosis. Comparison of mean intraocular pressure for two subgroups (family history and no family history) amongst the cases that developed glaucoma were also significantly higher at 10 years prior to diagnosis. Optic nerve analysis for cup to disc ratio measurements also showed a correlation over time with the pre-diagnosed glaucoma group showing to have an increasing CD ratio when compared to case controls. The Mann Whitney U test showed that the median cup to disc ratios were significantly higher at 5 and

10-year time points. Information taken from case records for visual field plots presented that there were more recorded field plots prior to diagnosis but also highlighted that visual fields are not always being recorded and a minimum requirement or guideline may be needed with additional funding to upgrade the NHS sight test to include visual fields.

Both Study 1 and 2 have provided supporting evidence that the pathogenesis of primary open angle glaucoma has many challenges as it is multifactorial. This agrees with the literature reviewed in Chapter 2. Rossetti et al. (p. 56) states that *“the growing evidence about the wide variability in disease progression and outcomes between patients means that it is essential to study the risk factors that influence this variability. More knowledge in this field will help the clinician to identify the patients who require more care and might need a more aggressive treatment to achieve a better outcome”* Spaeth (1993 p.63) was quoted in Section 1.5: *“the most important characteristic of the glaucomatous process is change in the appearance of the disc from its former state”*. The results from Study 1 and 2 have provided early evidence that the glaucomatous process may also be a change in the normal pattern of intraocular pressure. Patients’ often ask what “normal” intraocular pressure is and as optometrists we may answer what the normal range is for a given population (Colton & Ederer 1980). Optometrists are also aware that the risk of glaucoma increases with age as does intraocular pressure and thus standard practice can be to observe intraocular pressure after the age of 40 years. Yet few studies have investigated intraocular pressure measures in those with risk factors before the age of 40. Both Study 1 and 2 should be discussed with the issue of sampling. Study 1 used only one data entry point per case; Study 2 used one data entry point per visit. This may not represent the normal IOP for that given patient. In view of the increased diurnal variation in glaucoma, the odds of a low reading truly indicating normality (true negative) is also not that high (false negative). Study 1 and 2 each used purposeful sampling which has been described to be informationally representative (Sandelowski 2000). Study 1 and 2 reveal that even although IOP may be within the normal range, in those at risk of glaucoma or who subsequently develop glaucoma the IOP may be higher than that in a control group; and this could be

causing subtle changes in structure. Whether these changes are a pre-cursor of glaucoma or might be related to subtle functional deficits that are not clinically detectable by community optometrists requires further research.

The introductory chapter has reviewed the vascular and mechanical theories of glaucomatous change (Chapter 1). There are theories that suggest that an increase in IOP may cause compression of capillaries leading to impaired blood flow to the optic nerve head (vascular) or that an increase in intraocular pressure may alter the integrity of the lamina cribrosa (mechanical). The importance of developing knowledge of the precursors for glaucoma by the earliest detection come from acknowledging that the physical manifestations optometrists detect in practice may be at the end of a chain of events that can follow from an increase in IOP. Histological data shows that even at an early stage, the burden of increased IOP can cause changes in the lamina cribrosa in addition to loss of capillary vessels and axonal and glial cells (Evangelho et al. 2017). It is also worth briefly mentioning that animal studies have shown, sustained effects of raised intraocular pressure. Artificially raising IOP in a rat by injection at one week showed that fine processes of optic nerve astrocytes are damaged but with no damage to axons. However, despite lowering IOP to normal levels, at four weeks there was damage to all the astrocytes and the majority of axons (Dai et al. 2012). These examples of changes give further concern that Study 2 demonstrated a significant difference in mean IOP at ten years preceding diagnosis. It may be that knowledge of the earliest point of change in intraocular pressure or retinal structure may also be the earliest point of intervention if target IOP can be individualised (Rossetti et al. 2015).

Technology is a supporting asset and the use of optical coherence tomography is rapidly changing the detail of information optometrists can collect at examinations. All this does suggest, that optometrists continue to keep accurate records and all information is relayed to ophthalmologists on referral. The case records that were reviewed in this study show the benefits of long term case records and the pattern that can be seen together with building up a relationship with a patient. Current NICE guidelines recommend that referral is necessary for

a measured intraocular pressure of 24.0mmHg with no other pathological changes. Considering the results of this thesis, the responsibility lies even more with optometrists to be monitoring for early detectable changes to prevent structural and functional optic nerve change. This will also aid in patients understanding of glaucoma and relaying this to family members. As with all things, learning takes time and these studies suggest that time is needed to learn and observe how an individual patients' eyes may change. There is an informal risk analysis happening at each examination. The records from this study suggest optometrists do this all the time by annotating notes with words such as “suspect” or “monitor”.

10.2 STRENGTHS AND LIMITATIONS

This thesis brings with its results a lot of information about optometry practice. Study 1 showed that retrospective intraocular pressures measurements were difficult to collect in young adults. And Study 2 had difficulties too in sourcing data from cases of patients that had remained at the same practice for several years. The retail element of optometry brings with it competition and this means that patients do not stay registered at a single practice; this brings a challenge of being able to record observations over time and monitor change. In the wider scheme of public health, both optometry and patient education is needed about the regularity of eye examinations and if risk factors of glaucoma are present, the importance of monitoring change. It is interesting to consider whether full eye examination reports should be given to patients rather than optical prescription details alone. The results from this thesis also support the notion that optic nerve change occurs slowly over time in those that subsequently develop glaucoma. Optometrists are recognised as partners in eye health care by ophthalmologists and patients are best served by the two professions working together; certainly, prevention is better than cure for the growing older population together with the financial constraints of health care.

10.3 RECOMMENDATIONS FOR FURTHER RESEARCH

Further analyses of the data obtained in Study 2 could include requesting full visual field details from the practices, although this would be of limited use as only some of the practices routinely test visual fields on every adult. Further statistically analyses of the change in standard deviation over time would also provide interesting knowledge as to how intraocular changed in the PG and CC group. Analyses of data with further categorising of the cases for myopia would also be interesting.

Future work arising from this thesis are recommendations to repeat Study 1 as a retrospective or prospective study. It may be possible to repeat Study 1 using non-independent optometric practices that have a protocol to routinely screen all adults. If these data are electronically available then it would be a way of access to gather extensive data on the proviso that there was a policy that the data could be used and no data protection acts were being breached. Study 1 would also be suitable to be conducted as a prospective study. It would be interesting to repeat Study 2 and to obtain OCT and full visual plots. A possible variation of this study could be to work with a hospital eye service and gather information on baseline visits prior to treatment and request previous data from community optometrists. These suggestions may not be feasible for the same obstacles that Study 2 encountered. Study 2 would be difficult to conduct as a prospective study due to an unknown longevity of conversion to POAG. But if further detail from a repeat retrospective study, than it would also be of interest to consider colour vision and contrast sensitivity and any perceived visual changes as these have been reported to be affected prior to development of localised nerve fibre bundle defects (Airaksinen & Drance 1985; Viswanathan et al. 1999).

More generally, the research in this thesis has demonstrated the potential for research using optometric clinical records. The present research is not the first to use such an approach (Pointer 2001; Pointer 2011), and it needs to be noted that an optometric population is not the same as the general population (Pointer 2000). With improvements in standards of care of community optometry (e.g., many optometrists now have a higher qualification in glaucoma),

the quality of data in the clinical records of many practitioners is likely to have improved since the period surveyed in this research. The use of sophisticated imaging technologies (e.g., OCT, wide field scans) and hospital eye service standard visual field equipment in many practices further increases the potential for research of the type described in this thesis. With over 22 million eye examinations carried out each year by community optometrists (Optical Confederation, 2015), there would appear to be a real potential for an “optometric biobank” approach to furthering the understanding of many ocular conditions.

10.4 CONCLUSIONS

This thesis has achieved its aims to retrospectively investigate the differences in intraocular pressure and optic nerve cup to disc ratio in a group of cases that had a family history; together with analyses of how these measurements changed over a ten-year period in a group of participants that subsequently developed glaucoma. By “connecting the dots looking back”, this thesis has provided results demonstrating statistically significant differences in mean intraocular pressure measurements and optic nerve cup to disc ratios up to ten years prior to a diagnosis of glaucoma. The results indicate that there is further investigation needed to understand the subtleties of changes in the years leading up to a diagnosis of glaucoma and confirms the importance of monitoring change in the groups of people that have risk factors of primary open angle glaucoma. Further research would be needed to show if early intervention to lower intraocular pressure would be beneficial. This thesis has supported and provided evidence on the profusion of information accessible from clinical optometric records. The vital role that community optometrists hold in guarding the borders between pre-glaucoma and glaucoma have also been brought to light.

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12. APPENDIX 1 - STUDY 1 ETHICS APPLICATION

CONFIDENTIAL

Anglia Ruskin University: Ethics Application Form

PLEASE COMPLETE THE FORM IN WORD PROCESSING FORMAT. HANDWRITTEN APPLICATIONS WILL NOT BE ACCEPTED.

Name	SHARIFA HIRANI
Faculty	SCIENCE AND TECHNOLOGY
Title of Proposed Research	A RETROSPECTIVE REVIEW OF ANONYMISED CLINICAL RECORDS TO INVESTIGATE THE RISK FACTORS FOR PRIMARY OPEN ANGLE GLAUCOMA (POAG) IN PEOPLE WITH AND WITHOUT A FAMILY HISTORY OF POAG.
Address	UNIVERSITY EYE CLINIC, ANGLIA RUSKIN UNIVERSITY, EAST ROAD, CAMBRIDGE, CB1 1PT
E-mail address	Sharifa.hirani@anglia.ac.uk
Type of Researcher (please tick)	Undergraduate student Postgraduate student: <input type="checkbox"/> Masters <input type="checkbox"/> Doctorate <input checked="" type="checkbox"/> Other please state..... <input checked="" type="checkbox"/> Member of staff (registered for professional doctorate at London South Bank University)
Supervisor/Project Director	Dr Peter Allen Director of Clinics, Anglia Ruskin University. peter.allen@anglia.ac.uk Academic supervisors: Professor Bruce Evans, Institute of Optometry & London South Bank University. bjwe@bruce-evans.co.uk Professor David Edgar, City University. d.f.edgar@city.ac.uk Professor Pam Eakin, London South Bank University. eakinpa@lsbu.ac.uk
Collaborators	
Expected date of commencement	November 2013
Approximate duration	3 MONTHS
Externally funded	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

The University offers indemnity insurance to researchers who have obtained formal written ethics approval for their research. For details see page 25 of "Ethics Committee Procedures for the Conduct of Research".

1. Briefly describe the rationale for and state the value of the research you wish to undertake.
<p>Primary open angle glaucoma (POAG) is an eye disease in which the optic nerve becomes damaged (Pache and Flammer 2006). This leads to characteristic changes to the optic nerve head and the retina and a loss of visual field. Elevated intraocular pressure is one of the major risk factors for developing primary open angle glaucoma (Pache and Flammer 2006).</p> <p>Despite much research over many years, the pathogenesis of primary open angle glaucoma is not fully understood (Pache and Flammer 2006). Substantial research has been conducted on the risk factors that can be related to the disease (Boland and Quigley 2007) and these are summarised below.</p>

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1. Age: both incidence and prevalence of POAG are said to increase linearly with age (Quigley & Vitale 1997) and POAG is often described as a disease affecting people over the age of 40 years.
2. Genetics/family history: the relative risk of POAG is more than ten times higher if a first degree relative is diagnosed with the condition (Wolfs et al 1998).
3. Race: it has been consistently found that persons who are of African-Caribbean descent are more likely to have POAG than all other ethnicities (Boland & Quigley 2007).
4. Gender: POAG is 1.4 times more likely to affect males (Rudnicka et al 2006).
5. Myopia: doubles the risk of POAG (Marcus et al 2011)
6. Intraocular pressure: the only modifiable risk factor for POAG (Johnson et al 1998)
7. Increased optic disc diameter (Healey & Mitchell 2000).

A literature review (Hirani et al 2012) indicates that in POAG intraocular pressure plays a key role as a risk factor, diagnostic sign, and measure of the effectiveness of treatment. Intraocular pressure is generally measured in the over 40s when the risk of glaucomatous visual field loss becomes significant. But very little is known about this particular risk factor in the younger population. We hypothesise that intraocular pressure may be higher in people predisposed to POAG for many years before they reach an age when glaucoma may become manifest. This idea has led to the development of a research question which asks "are there pre-clinical signs for POAG?"

2. Suitability/qualifications of researchers to undertake the research.

The student investigator (Sharifa Hirani) is in the fifth year of the Doctorate of Optometry programme run by the Allied Health Sciences department at London South Bank University.

Sharifa Hirani completed her first undergraduate degree in nursing in 1996 followed by an MSc in Neuroscience in 2000. Sharifa studied optometry at Anglia Ruskin University, qualifying in 2005 and has supervised third year optometry students at Anglia Ruskin University Eye Clinic since December 2005. In addition to her work at Anglia Ruskin University, Sharifa is employed as an optometrist at a private practice.

One of the supervisors, Dr Peter Allen, is an experienced optometrist and the Clinic Director of the Anglia Ruskin University Eye Clinic. Two of the co-supervisors are experienced optometrists and professors of optometry.

3. What are the aims of the research?

The proposed research aims to investigate whether people with a family history of glaucoma but who are too young to develop glaucoma may have early clinical signs suggestive of an increased risk of glaucoma.

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4. Briefly describe the overall design of the project

The proposed study is a retrospective review of anonymised historical clinical data relating to tests used to screen for POAG. The clinical data that will be reviewed will be data relating to the seven risk factors discussed above. Data will be collected from the records of two groups of patients all aged under 40 years: those with a family history of POAG, and those without a family history of POAG.

5. Briefly describe the methods of data collection and analysis

Sample size calculation

A sample size calculation was carried out which indicates a total sample of 256 anonymised records, comprising 128 anonymised records from patients with a family history of glaucoma and 128 anonymised records from patients without a family history of glaucoma.

Data anonymisation

The Anglia Ruskin University Data Protection Register entry lists Research as one of the Purposes for which data is held, so its use for this purpose is clearly permitted. There will be two stages to the data anonymisation to ensure that the anonymisation process (described below) is watertight. The two people involved in this will be Sharifa Hirani (who is employed in the University Eye Clinic) and Dr Peter Allen (Director of the Eye Clinic). Both these individuals are members of the clinical team who routinely have access in their work to the University Eye Clinic records and who are aware of the need to maintain patient confidentiality and to follow the guidelines on confidentiality of the College of Optometrists and of the General Optical Council.

The data anonymisation will be carried out according to the recommendations of the Information Commissioner Officer's Code of Conduct on Anonymisation (ICO, 2012). As an additional precaution, there will be two stages to the data anonymisation. We feel that this is advisable because Sharifa Hirani will have two roles: first as a member of the clinical team to search the clinical data and anonymise the data and second as a member of the research team to analyse the data. The purpose of the second stage of the data anonymisation is to ensure that it is not possible for Sharifa Hirani to recollect any personal details when viewing the anonymised data.

In the first stage of data anonymisation, Sharifa Hirani will search the clinical database for relevant records and, if consent is given (see below), extract the relevant data (see Appendix) from the clinical records by typing this into a spreadsheet **without extracting any personal identifying data such as name, address and date of birth**. At this stage, each anonymised dataset will be identified by the clinic reference number.

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Once the spreadsheet is complete, Sharifa Hirani will pass this to Dr Allen. Dr Allen will randomly assign a unique research number to each dataset and will delete the clinic reference number and randomly re-order the data in the spreadsheet. For example, the dataset that was in row 3 might now be in row 250. This 2nd level anonymised spreadsheet will then be passed to Sharifa Hirani to remove from the clinic for analysis. This will include 256 rows of data of the type illustrated in the Appendix and it is implausible (see Section 22) that Sharifa Hirani, as the researcher, will know from which patient each dataset originated.

Data that will be extracted

The following anonymised data will be extracted from the clinical records:

1. Gender – coded as male or female.
2. Age - recorded numerically as age at time of examination.
3. Race – coded by Caucasian, African, or Asian.
4. Vision/visual acuity.
5. Refractive error – recorded for right and left eyes in dioptre sphere and dioptre cylinder.
6. Family history of glaucoma – coded as yes or no and if yes by which family member and by which type of glaucoma if known.
7. Intraocular pressure - recorded numerically in mmHg.
8. Optic nerve head assessment - recorded numerically as right and left eye cup to disc ratio measurement.
9. Visual field screening results if available.

Examples of the type of data that will be extracted are included in the Appendix. There is nothing in these data (individually or combined) that would make it possible to identify a patient. No photographs will be extracted.

Specifics of data extraction

1. The clinic database will be used to search for eligible records.
2. The search will generate a list of records that, in the clinic database, will each have a unique patient record number. These patients will be contacted by mail and invited to participate. Only patients who return signed consent forms (see below) will be included in the research.
3. For the consenting patients, each patient record will be accessed and viewed only by the person (Sharifa Hirani) carrying out the anonymisation.
4. The 1st stage anonymised data collected from the records of these consenting patients will be entered into an Excel datasheet together with the clinic reference number. When complete, this spreadsheet will be passed to Dr Allen who will apply a unique research number to each dataset and delete the clinic reference number. The datasheet will not have any patient identifiable markers. Dr Allen will randomly reorder the rows so that, for example, the dataset in row 2 may become the dataset in row 250.
5. Dr Allen will pass the 2nd stage anonymised spreadsheet of reordered data from anonymised participants to Sharifa Hirani who will remove this from the clinic for data analysis. This spreadsheet will be stored on 2

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devices: a laptop which has a locked password and on a hard-drive for back up purposes. Both the laptop and hard-drive will be encrypted. The hard-drive will be kept in a locked filing cabinet. The data will not be accessible from a smart phone. The laptop will be registered with a PC theft tracker called PREY.

In summary, no personal details (names, addresses, dates of birth) or any other data that could identify the patient will be included in the data extracted from the clinic.

Data analysis

The anonymised data will be analysed with SPSS using intraocular pressure as a continuous variable.

The data will be considered by either treating family history as a binary variable (i.e. either a patient has a family history of glaucoma or not) and/or as continuous variable. If the binary variable approach is used, variables would be compared: for example intraocular pressure in people with a family history of glaucoma could be compared with those without a family history.

Another option in consideration for analysis of the data would be to treat family history as a continuous variable and use a scoring system to reflect the strength of the family history (based on the number of relatives with glaucoma and the genetic lineage involved). This would allow a group comparison approach to be used and also opens up the possibility of using measures of association. The decision on the type(s) of analysis to be carried out will be taken once the anonymised data have been inspected to determine the level of detail with which the family history has been coded.

APPENDIX: DATA COLLECTION TABLE (with illustrative fabricated data for 4 hypothetical datasets)

Res. No.	Gender (M/F)	Age at test/ Years	Race (C/A/I)	R VA	L VA	Rx R	Rx L	IOP R	IOP L	ONH R	ONH L	VF	FHx Y/N/ FM/ Type
1	M	35	C	6/5	6/6	+0.50	+0.25	16	17	0.5	0.4	OK	No
2	F	30	A	6/4	6/5	Plano	Plano	18	19	0.4	0.3	OK	Y, M
3	M	26	I	6/5	6/6	-0.50	-0.75	19	15	0.6	0.5	OK	No

Key

1. Res. No. = Research Number
2. M = Male
3. F = Female
4. C = Caucasian
5. A = African
6. I = Indian
7. RVA = Right Visual Acuity
8. LVA = Left Visual Acuity
9. Rx = Optical prescription
10. R = Right
11. L = Left
12. IOP = Intraocular pressure
13. ONH = Optic nerve head

To be used in conjunction with the Anglia Ruskin University publication: University Research Ethics Committee (UREC) Policy and Code of Practice for the Conduct of Research with Human Participants

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14. VF = Visual field
15. FHx = family history
16. FM = family member

References

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http://www.ico.org.uk/for_organisations/data_protection/topic_guides/~media/documents/library/Data_Protection/Practical_application/anonymisation_code_summary.ashx
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6. Describe the participants: give the age range, gender and any particular characteristics pertinent to the research project. *For experimental studies state the inclusion and exclusion criteria*

The research involves collecting anonymised historical data from clinical records for two age groups. Group one will have been aged 20-30 years at the time of the eye examination and group two will be aged from 31-40 years. A minimum of 64 anonymised records within each group (128 in total) from consenting patients who have a family history of POAG is needed. For comparison purposes, data will also be collected from the anonymised records of a control group consisting of another 128 consenting patients who do not have a family history of POAG. For each anonymised record with a family history of POAG, data will be collected for an age-matched person who does not have a family history of POAG. Where possible, we will also try to match approximately the subject pairs for refractive error.

Exclusion criteria for this retrospective review will be data from those diagnosed with glaucoma, ocular
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hypertension, or whose records indicate that they were considered by an ophthalmologist to be at risk of glaucoma. Patients with learning disabilities (who might not understand consent) will not be invited to participate (this is likely to apply to very few, if any, of the potential participants).

7. If your participants are under 18, please attach a copy of your clearance letter from the Criminal Records Bureau (if UK) or equivalent non-UK clearance, or, if not, explain below:

N/A

8. How will the participants be selected and recruited?

The research is a retrospective review of anonymised data extracted from University Eye Clinic historical records. Consent will be sought from eligible patients for their anonymised data to be extracted for the research.

9. How many participants will be involved? For experimental studies, specify how the sample size was determined. In clinical trials, a Power calculation *must* be included.

The research involves collecting anonymised data from historical University Eye Clinic records from two age groups. A sample size calculation has been carried out using a standard formula (Jones et al 2003) to detect a mean difference between the two groups of 1.5mmHg. The standard deviation used in the formula (3.0) was based on previous studies of optometric populations (Pointer, 1997, 2000). For a two-tailed analysis this gives a sample size of 64 in each sub-group, which with 2 age-groups each divided into 2 disease conditions (glaucoma and no glaucoma) gives a total sample size of 256.

References

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

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10. What procedures will be carried out on the participants (if applicable)?

Not applicable.

11. What potential risks to the participants do you foresee?

Clinical data will be viewed in the process of anonymisation and this raises Data Protection issues. However, the data will only be viewed by a clinician who already regularly views historical clinical data in this clinic (e.g., when teaching students) and the Information Commissioner's Office Code of Conduct on Data Anonymisation states "There is clear legal authority for the view that where an organisation converts personal data into an anonymised form and discloses it, this will not amount to a disclosure of personal data". Nonetheless, there is a potential risk if the Data Protection Act Code of Conduct for Data Anonymisation is not correctly followed and this is why the two stage anonymisation process described in section 5 will be followed.

12. How do you propose to ameliorate/deal with potential risks to participants?

Ethical issues have been carefully considered for this study. The study does not involve direct patient testing but anonymised data will be extracted from historical clinical records for consenting patients. These

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CONFIDENTIAL

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original clinical records contain identifiable details such as name, address and date of birth and therefore the Information Commissioners Office Code of Practice on Anonymisation (2012) will be followed. Specifically, the extracted data will be anonymised by the removal of all identifiable markers such as name, address and date of birth, as detailed above.

13. What potential risks to the interests of the researchers do you foresee?

There are no foreseeable risks to the researchers.

14. How will you ameliorate/deal with potential risks to the interests of researchers?

N/A

15. Has a risk assessment been completed? (Yes/No) (Please be aware that the risk assessment must be kept on file and updated annually). Details of the risk assessment procedure can be found at <http://rmd.anglia.ac.uk/form.asp?id=17§ionid=19>

Yes

16. How will you brief and debrief participants? (Attach copy of information to be given to participants).

The proposed research is a retrospective review of anonymised data extracted from historical clinical records. Participants will not be seen as part of this research. The researchers will contact each patient whose record is eligible for data collection. Each of these patients will be written to by postal letter. The letter will give information about the study and will give the patient the opportunity to ask the researchers by phone or email any questions about the study. The letter will include a consent form and stamp addressed envelope for the patients to return if they are happy for their data to be included in the study. The consent form will advise that, if consent is given, anonymised data will be taken from the clinical records and that consent to take part in the study is voluntary. The patient is free to withdraw at any time, without giving reason. If a patient decides to withdraw consent, any anonymised data that has already been anonymised and removed from the clinic will be analysed, unless the patient asks for the data to be removed from the study in which case this request will be followed and those data deleted. The letter and consent form are attached in Appendix 1 and 2. Patients who do not reply will not be included in the study and their data will not be extracted.

NHS ethical approval is not needed for this study as there will be no historical data collected from NHS patient records.

17. Will informed consent be sought from participants?	Yes (Please attach a copy of the consent form)	
	Yes	<input checked="" type="checkbox"/>

If no, please explain below:

18. If there are doubts about participants' abilities to give informed consent, what steps have you taken to ensure that they are willing to participate?

Patients with learning disabilities (who might not understand consent) will not be invited to participate (this is likely to apply to very few, if any, of the potential participants).

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19. If participants are under 18 years of age please describe how you will seek informed consent
Not applicable.

20. How will consent be recorded?
Signed paper consent forms will be used and the completed consent forms will be stored securely by Dr Peter Allen.

21. Will participants be informed of the right to withdraw without penalty?	Yes <input checked="" type="checkbox"/>
	No

<i>If no, please detail the reasons for this:</i>
Not applicable; please see response to items 16 and 17 above.

22. How do you propose to ensure participants' confidentiality and anonymity?
<p>The anonymised data collected will be entered into a password protected Excel datasheet. The data sheet will not include personal identifiers. The Information Commissioner's Office Code of Conduct on Data Anonymisation (2012) gives (p.51) examples of personal identifiers as name, address, date of birth and lists data masking (extracting data without these identifiers) as a legitimate method of anonymisation. The Code of Conduct on Anonymisation states (p.16): "The DPA is not framed in terms of the possibility of an individual being identified. Its definition of personal data is based on the identification or likely identification of an individual. This means that, although it may not be possible to determine with absolute certainty that no individual will ever be identified as a result of the disclosure of anonymised data, this does not mean that personal data has been disclosed."</p> <p>The Code of Conduct recommends that proposed data anonymisation is checked by carrying out a "motivated intruder test". We have done this and are confident that even if a motivated intruder gained access to our anonymised data (which will be password protected), then they would still not be able to identify an individual from the data we will hold.</p>

23. Please describe which of the following will be involved in your arrangements for storing data:
<input type="checkbox"/> Manual files (e.g. paper documents or X-rays) <input checked="" type="checkbox"/> Home or other personal computer <input type="checkbox"/> University computer <input type="checkbox"/> Private company or work-based computer <input type="checkbox"/> Laptop computer - WORK <input type="checkbox"/> Other (please define)
Please explain, for each of the above, the arrangements you will make for the security of the data (please note that any data stored on computer must have password protection as a minimum requirement):
The information that will be stored on the researcher's computer will contain no personal identifiable data and therefore is not considered to be data under the Data Protection Act. Nonetheless, the computer will be password protected.

24. Will payments be made to participants?	Yes <input type="checkbox"/>
	No <input checked="" type="checkbox"/>

<i>If yes, please specify:</i>

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25. Modification of Proposal

Not applicable

26. (EXTERNALLY-FUNDED PROJECTS ONLY) Has the funding body been informed of and agreed to abide by Anglia Ruskin University's Ethics Procedures and standards? N/A	Yes	<input type="checkbox"/>
	No	<input type="checkbox"/>

If no, please explain below:

27. (EXTERNALLY-FUNDED PROJECTS ONLY) Has the funder placed any restrictions on a) the conduct of the research b) publication of results? N/A	Yes	<input type="checkbox"/>
	No	<input type="checkbox"/>

If yes, please detail below:

28. Are there any further points you wish to make in justification of the proposed research?

No

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Anglia Ruskin University: Ethics Application Form

UREC REGISTER

UREC publishes a list of approved projects on the University intranet, which is searchable by all staff and students of the University. The entry for each project comprises the following data:

- project title
- funding body (if appropriate)
- duration of project
- date and expiry of ethics approval
- name of researcher

Inclusion on this list is a condition of ethics approval, unless the Committee is informed of compelling reasons for an exemption. If you wish to request that your information is withheld, please tick the box below and state the reasons for your request.

I **do not** wish my project details to be included on the UREC list for the following reasons:

Please indicate that you are enclosing with this form the following completed documents:

- Participant consent form Participant Information Sheet
- Summary of the research

Signed _____ Date _____

Statement of Supervisor's / Project Director's support*

I support this application:



Signed

Date 23.9.13

Title Dr Peter Allen

***applications not countersigned by a supervisor/project director will not be accepted; please note that this applies equally to members of staff who are also students**

To be used in conjunction with the Anglia Ruskin University publication: University Research Ethics Committee (UREC) Policy and Code of Practice for the Conduct of Research with Human Participants

13. APPENDIX 2 - STUDY 1 INFORMATION SHEET



Anglia Ruskin
University

Cambridge Chelmsford Peterborough

Cambridge Campus
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Cambridge
CB1 1PT

T: 0845 271 3333
Int: +44 (0)1223 363271
www.anglia.ac.uk

Dear

I am an optometrist and clinic supervisor at the Eye Clinic at Anglia Ruskin University. I am studying for a doctorate and working alongside Dr Peter Allen (University Eye Clinic Director and Principal Lecturer). We are studying the risk factors which are known to be associated with open angle glaucoma.

Open angle glaucoma is an eye condition which results in peripheral vision loss as the optic nerve changes. The reason why the optic nerve changes is unclear. My doctorate study is looking into the risk factors of open angle glaucoma with an aim to give a better understanding of the condition. To do this, I will be collecting data from eye examinations already conducted at the University Eye clinic for people who do not have glaucoma. Your clinical record would be useful for my study. The data I hope to extract from your clinic record will be unidentifiable and none of your personal information will be transferred.

With your agreement, I would like to take the following information from your clinical record:

1. Your gender.
2. The age you were at the time of your eye examination. I will only record your age and I will not record your date of birth.
3. Your race.
4. If you have a family history of open angle glaucoma.
5. Your spectacle prescription.
6. Your level of sight (visual acuity).
7. A description of your optic nerve.
8. The measurement of each of your eye pressures.
9. If a visual field test was carried out, I will record the results of this.

I will not be extracting any information which could be used to identify you.

I would be very grateful if I could use your clinic record to extract data for my study. If you are happy for me to do this please could I ask you to read and complete the consent form and return to me in the stamp addressed envelope enclosed by 30 November 2013. I am happy for you to contact me on telephone number 07909 968786 or email me at sharifa.hirani@anglia.ac.uk, if you have any questions about the study.

Yours faithfully

Miss Sharifa Hirani

MCOptom MSc BSc

14. APPENDIX 3 - STUDY 1 CONSENT FORM



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CONSENT FORM

Full title of Project:

AN INVESTIGATION OF PRIMARY OPEN ANGLE GLAUCOMA AND THE RISK FACTORS OF INTRAOCULAR PRESSURE AND OPTIC NERVE CUP TO DISC RATIO IN PEOPLE WHO ARE UNDER THE AGE OF FORTY YEARS AND WHO HAVE A FAMILY HISTORY OF PRIMARY OPEN ANGLE GLAUCOMA.

Name, position and contact address of Researcher:

MISS SHARIFA HIRANI. OPTOMETRIST

ANGLIA RUSKIN UNIVERISTY EYE CLINIC. EAST ROAD. CAMBRIDGE CB1 1PT

Please initial box

I confirm that I have read and understand the information letter for the above study.

I understand that anonymised data will be taken from my clinical records and that I cannot be identified from the any of the extracted information. I understand that my consent to take part in the study is voluntary and that I am free to withdraw at any time, without giving reason. I understand that if I withdraw after some anonymised data have been removed from the clinic then no further data will be collected. I understand that any data that have already been anonymised and removed from the clinic will be analysed, unless I ask for the data to be removed from the study in which case this request will be followed and that data deleted.

I agree to take part in the above study.

Name of Participant

Date

Signature

15. APPENDIX 4 - STUDY 1 ANGLIA RUSKIN UNIVERSITY RESEARCH ETHICS APPROVAL



Anglia Ruskin
University

Cambridge Chelmsford Peterborough

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23rd September 2013

Dear Peter

Project Number: FST/FREP/12/337

Project Title: *A retrospective review of anonymised clinical records to investigate the risk factors for primary open angle glaucoma (POAG) in people with and without a family history of POAG.*

Principal Investigator: Dr Peter Allen

Thank you for supplying revisions to your application for ethical approval, as requested by the Faculty Research Ethics Panel (FREP) following its meeting on 23rd July 2013.

I am pleased to inform you that your application has been approved by the Chair of the Faculty Research Ethics Panel under the terms of Anglia Ruskin University's *Policy and Code of Practice for the Conduct of Research with Human Participants*. Approval is for a period of three years from 23rd September 2013.

It is your responsibility to ensure that you comply with *Anglia Ruskin University's Policy and Code of Practice for Research with Human Participants*, and specifically:

- The Participant Information Sheet and Participant Consent Form should be on Anglia Ruskin University headed paper.
- For online surveys it is recommended that the researcher turns off the IP logging software to ensure secure communication between the survey taker and server.
- The procedure for submitting substantial amendments to the committee, should there be any changes to your research. You cannot implement these changes until you have received approval from FREP for them.
- The procedure for reporting adverse events and incidents.
- The Data Protection Act (1998) and any other legislation relevant to your research. You must also ensure that you are aware of any emerging legislation relating to your research and make any changes to your study (which you will need to obtain ethical approval for) to comply with this.
- Obtaining any further ethical approval required from the organisation or country (if not carrying out research in the UK) where you will be carrying the research out. Please ensure that you send the FREP Secretary copies of this documentation.
- Any laws of the country where you are carrying the research out (if these conflict with any aspects of the ethical approval given, please notify FREP prior to starting the research).

-
- Any professional codes of conduct relating to research or research or requirements from your funding body (please note that for externally funded research, a project risk assessment must have been carried out prior to starting the research). • Notifying the FREP Secretary when your study has ended.

Information about the above can be obtained on our website at:

<http://web.anglia.ac.uk/anet/rdcs/ethics/index.ohtml/> and or
<http://www.anglia.ac.uk/ruskin/en/home/faculties/fst/research0/ethics.html>

Please also note that your research may be subject to random monitoring by the Committee.

Please be advised that, if your research has not been completed within three years, you will need to apply to our Faculty Research Ethics Panel for an extension of ethics approval prior to the date your approval expires. The procedure for this can also be found on the above website.

Should you have any queries, please do not hesitate to contact me. I would like to wish you the best of luck with your research.

Yours sincerely,



Sue Short

Secretary to the Faculty Research Ethics Panel (FREP)

Faculty of Science and Technology

MAR325

Tel: 01245 683927 or 0845 196 3927

Email: EST-Ethics@anglia.ac.uk

16. APPENDIX 5 - STUDY 1 LONDON SOUTH BANK UNIVERSITY RESEARCH ETHICS APPROVAL

**London South Bank
University**

Direct line: 020-7815 6025
E-mail: mitchen5@lsbu.ac.uk
Ref: UREC 1523

Sharifa Hirani
University of Hertfordshire
2 F412 College Lane
College Lane
Hatfield
AL10 9AB

Tuesday 9 June 2015

Dear Sharifa

RE: A retrospective review of anonymised clinical records to investigate whether risk factors for primary open angle glaucoma are present many years before glaucoma develops.

Thank you for submitting this proposal and for your response to the reviewers' comments.

I am pleased to inform you that Full Chair's Approval has been given by Vice Chair on behalf of the University Research Ethics Committee.

I wish you every success with your research.

Yours sincerely,



Nicola Mitchell
Secretary, LSBU Research Ethics Committee

cc:

Prof Shushma Patel, Chair, LSBU Research Ethics Committee

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17. APPENDIX 6 - STUDY 1 ANGLIA RUSKIN
UNIVERSITY RESEARCH ETHICS AMENDMENT



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Dr Peter Allen
Department of Vision and Hearing Sciences
Anglia Ruskin University
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CB1 1PT

6th May 2014

Dear Peter

Project Number: FST/FREP/12/337
Project Title: A retrospective review of anonymised clinical records to investigate the risk factors for primary open angle glaucoma (POAG) in people with and without a family history of POAG.

Principal Investigator: Dr Peter Allen

The Chair of Faculty Research Ethics Panel (FREP), acting on behalf of the Committee, has agreed to grant ethical approval for the amendments you requested, which are listed below. Under the terms of Anglia Ruskin University's *Policy and Code of Practice for the Conduct of Research with Human Participants*, approval is from 2nd May 2014.

Amendments

- The participant group will include anonymised clinical data from consenting private patients at an independent optometry practice that Miss Sharifa Hiranl (co-researcher) works at in Dunstable.

Should you have any queries, please do not hesitate to contact me.

Yours sincerely,

Sue Short

Secretary to the Faculty Research Ethics Panel (FREP)
Faculty of Science and Technology
Tel: 01245 683927 or 0845 196 3927
Email: FST-Ethics@anglia.ac.uk



18. APPENDIX 7 - STUDY 2 NHS REC (PROPORTIONATE REVIEW) FORM

NHS REC Form

Reference:
15/NS/0032

IRAS Version 4.0.0

Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please complete the questions in order. If you change the response to a question, please select 'Save' and review all the questions as your change may have affected subsequent questions.

Please enter a short title for this project (maximum 70 characters)
REVIEW OF ANONYMISED CLINICAL RECORDS TO STUDY OPEN ANGLE GLAUCOMA.

1. Is your project research?

Yes No

2. Select one category from the list below:

- Clinical trial of an investigational medicinal product
- Clinical investigation or other study of a medical device
- Combined trial of an investigational medicinal product and an investigational medical device
- Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice
- Basic science study involving procedures with human participants
- Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology
- Study involving qualitative methods only
- Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)
- Study limited to working with data (specific project only)
- Research tissue bank
- Research database

If your work does not fit any of these categories, select the option below:

Other study

2a. Please answer the following question(s):

a) Will you be processing identifiable data at any stage of the research (including in the identification of participants)? Yes No

3. In which countries of the UK will the research sites be located? (Tick all that apply)

- England
- Scotland
- Wales
- Northern Ireland

3a. In which country of the UK will the lead NHS R&D office be located:

England

Date: 25/03/2015

1

170742/7695211/894

- Scotland
 Wales
 Northern Ireland
 This study does not involve the NHS

4. Which review bodies are you applying to?

- NHS/HSC Research and Development offices
 Social Care Research Ethics Committee
 Research Ethics Committee
 Confidentiality Advisory Group (CAG)
 National Offender Management Service (NOMS) (Prisons & Probation)

For NHS/HSC R&D offices, the CI must create Site-Specific Information Forms for each site, in addition to the study-wide forms, and transfer them to the PIs or local collaborators.

5. Will any research sites in this study be NHS organisations?

- Yes No

5a. Are all the research costs and infrastructure costs for this study provided by an NIHR Biomedical Research Centre, NIHR Biomedical Research Unit, NIHR Collaboration for Leadership in Health Research and Care (CLAHRC) or NIHR Research Centre for Patient Safety & Service Quality in all study sites?

- Yes No

If yes, NHS permission for your study will be processed through the NIHR Coordinated System for gaining NHS Permission (NIHR CSP).

5b. Do you wish to make an application for the study to be considered for NIHR Clinical Research Network (CRN) support and inclusion in the NIHR Clinical Research Network (CRN) Portfolio? Please see information button for further details.

- Yes No

If yes, NHS permission for your study will be processed through the NIHR Coordinated System for gaining NHS Permission (NIHR CSP) and you must complete a NIHR Clinical Research Network (CRN) Portfolio Application Form immediately after completing this project filter and before completing and submitting other applications.

6. Do you plan to include any participants who are children?

- Yes No

7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?

- Yes No

Answer Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the Confidentiality Advisory Group to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.

8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?

- Yes No

9. Is the study or any part of it being undertaken as an educational project?

Yes No

Please describe briefly the involvement of the student(s):
The student is conducting this research towards a Doctorate of Optometry.

9a. Is the project being undertaken in part fulfilment of a PhD or other doctorate?

Yes No

10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?

Yes No

11. Will identifiable patient data be accessed outside the care team without prior consent at any stage of the project (including identification of potential participants)?

Yes No

Integrated Research Application System
Application Form for Study limited to working with data (specific project only)



The Chief Investigator should complete this form. Guidance on the questions is available wherever you see this symbol displayed. We recommend reading the guidance first. The complete guidance and a glossary are available by selecting [Help](#).

Please define any terms or acronyms that might not be familiar to lay reviewers of the application.

Short title and version number: (maximum 70 characters - this will be inserted as header on all forms)
 REVIEW OF ANONYMISED CLINICAL RECORDS TO STUDY OPEN ANGLE GLAUCOMA.

Please complete these details after you have booked the REC application for review.

REC Name:
 North of Scotland Research Ethics Committee 1

REC Reference Number:
 15/NS/0032

Submission date:
 25/03/2015

PART A: Core study information

1. ADMINISTRATIVE DETAILS

A1. Full title of the research:

A retrospective review of anonymised clinical records to investigate whether risk factors for primary open angle glaucoma are present many years before glaucoma develops.

A2-1. Educational projects

Name and contact details of student(s):

Student 1

	Title	Forename/Initials	Surname
	Miss	Sharifa	Hirani
Address	University of Hertfordshire		
	2 F412 College Lane		
	College Lane, Hatfield.		
Post Code	AL10 9AB		
E-mail	sharifa@gmail.com		
Telephone	07909968786		
Fax			

Give details of the educational course or degree for which this research is being undertaken:

Name and level of course/ degree:
Doctorate of Optometry

Name of educational establishment:
London South Bank University and Institute of Optometry.

Name and contact details of academic supervisor(s):

Academic supervisor 1

	Title	Forename/Initials	Surname
	Professor	Bruce	Evans
Address	Institute of Optometry 56-62 Newington Causeway London		
Post Code	SE1 6DS		
E-mail	bjwe@bruce-evans.co.uk		
Telephone	02072349641		
Fax			

Academic supervisor 2

	Title	Forename/Initials	Surname
	Professor	David	Edgar
Address	City University Northampton Square London		
Post Code	EC1V 0HB		
E-mail	d.f.edgar@city.ac.uk		
Telephone	0207 0404322		
Fax			

Academic supervisor 3

	Title	Forename/Initials	Surname
	Professor	Peter	Allen
Address	Anglia Ruskin University Coslett Building, Room 201 East Road, Cambridge		
Post Code	CB1 1PT		
E-mail	peter.allen@anglia.ac.uk		
Telephone	0845 196 2687		
Fax			

Please state which academic supervisor(s) has responsibility for which student(s):
Please click "Save now" before completing this table. This will ensure that all of the student and academic supervisor details are shown correctly.

Student(s)	Academic supervisor(s)
Student 1 Miss Sharifa Hirani	<input checked="" type="checkbox"/> Professor Bruce Evans

- Professor David Edgar
- Professor Peter Allen

A copy of a current CV for the student and the academic supervisor (maximum 2 pages of A4) must be submitted with the application.

A2-2. Who will act as Chief Investigator for this study?

- Student
- Academic supervisor
- Other

A3-1. Chief Investigator:

	Title	Forename/Initials	Surname
		Miss Sharifa	Hirani
Post	Senior Lecturer		
Qualifications	BSc Hons Nursing BSc Optometry MSc Neuroscience		
Employer	University of Hertfordshire		
Work Address	2 F412 College Lane Hatfield Herts		
Post Code	AL10 9AB		
Work E-mail	s.hirani3@herts.ac.uk		
* Personal E-mail	sharifa@gmail.com		
Work Telephone	01707285206		
* Personal Telephone/Mobile	07909968786		
Fax			

** This information is optional. It will not be placed in the public domain or disclosed to any other third party without prior consent.*

A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application.

A4. Who is the contact on behalf of the sponsor for all correspondence relating to applications for this project?

This contact will receive copies of all correspondence from REC and R&D reviewers that is sent to the CI.

	Title	Forename/Initials	Surname
		Professor Nicola	Crichton
Address	London South Bank University School of Health and Social Care 103 Borough Road, London		
Post Code	SE1 0AA		
E-mail	crichtnj@lsbu.ac.uk		
Telephone	02078156742		
Fax			

A5-1. Research reference numbers. *Please give any relevant references for your study:*

Applicant's/organisation's own reference number, e.g. R & D (if available): N/A

Sponsor's/protocol number:

Protocol Version:

Protocol Date:

Funder's reference number:

Project website:

Additional reference number(s):

Ref.Number	Description	Reference Number
------------	-------------	------------------

Registration of research studies is encouraged wherever possible. You may be able to register your study through your NHS organisation or a register run by a medical research charity, or publish your protocol through an open access publisher. If you have registered your study please give details in the "Additional reference number(s)" section.

A5-2. Is this application linked to a previous study or another current application?

Yes No

Please give brief details and reference numbers.

2. OVERVIEW OF THE RESEARCH

To provide all the information required by review bodies and research information systems, we ask a number of specific questions. This section invites you to give an overview using language comprehensible to lay reviewers and members of the public. Please read the guidance notes for advice on this section.

A6-1. Summary of the study. *Please provide a brief summary of the research (maximum 300 words) using language easily understood by lay reviewers and members of the public. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, this summary will be published on the website of the National Research Ethics Service following the ethical review.*

This study aims to investigate primary open angle glaucoma by comparing anonymised historical data of patients who subsequently develop primary open angle glaucoma compared to controls.

Volunteer community optometry practices will be consented to collate and provide anonymised clinical records for patients at least 10 years prior to the date of diagnosis of glaucoma. The same community optometry practices will be asked to collate and provide anonymised clinical records for a control group. This control group will be individually matched for, in addition to optometric practice, age, race, gender, and approximate refractive error with the glaucoma group but will not have received a diagnosis of glaucoma or have a family history of glaucoma.

The objectives for the study are:

1. To compare intraocular pressure 10 years before glaucoma diagnosis with a control group.
2. To investigate any differences of the optic nerve head 10 years before diagnosis of glaucoma patients with the control group.
3. To investigate any associations between the other risk factors of primary open angle glaucoma 10 years before diagnosis with glaucoma with a control group.

A6-2. Summary of main issues. *Please summarise the main ethical, legal, or management issues arising from your study and say how you have addressed them.*

Not all studies raise significant issues. Some studies may have straightforward ethical or other issues that can be identified and managed routinely. Others may present significant issues requiring further consideration by a REC, R&D office or other review body (as appropriate to the issue). Studies that present a minimal risk to participants may raise complex organisational or legal issues. You should try to consider all the types of issues that the different reviewers may need to consider.

This study is doctoral research and will investigate intraocular pressure, optic nerve appearance and other associated risk factors of primary open angle glaucoma. The study specifically aims to investigate these risk factors over a ten year period prior to diagnosis in patients who have subsequently been diagnosed with glaucoma and compare these findings to matched controls. The purpose of this study is to investigate if primary open glaucoma has earlier detectable changes in those patients who subsequently develop glaucoma.

I am the student and chief investigator of the study. Myself and my doctorate supervisors have listed community optometry practices that may hold long standing clinical records for patients. Approximately twenty practices have been identified. The study will seek agreement from approximately ten practices, who are able to provide anonymised clinical records for approximately six patients who they have seen for at least ten years prior to their diagnosis of primary open angle glaucoma. I will gain consent from each optometry practice's local R & D office prior to the study commencing and also secure an assurance letter to collect anonymised data from Cambridgeshire R & D. There will be no financial agreement with each practice.

This study will research primary open angle glaucoma by collecting anonymised data from clinical records. Data protection and collection of anonymised data is guided from the Information Commissioners Office (ICO). I have had email correspondence with the ICO and received written confirmation that individual patient consent will NOT be needed as the study has been robustly designed for the practices to anonymise the records, with a double check, before data extraction.

The double check will be achieved by the practice staff selecting and photocopying (or printing if computerised) relevant records and then using a marker pen to redact personal data (e.g., name, contact details, only extracting month and year of birth). The redacted photocopies will then be inspected by one of the supervisors who will carry out any further necessary redaction to ensure complete anonymisation. After this double check the redacted photocopies will then be collected by myself and the relevant data entered into a spreadsheet.

A6-3. Proportionate review of REC application *The initial project filter has identified that your study may be suitable for proportionate review by a REC sub-committee. Please consult the current guidance notes from NRES and indicate whether you wish to apply through the proportionate review service or, taking into account your answer to A6-2, you consider there are ethical issues that require consideration at a full REC meeting.*

Yes - proportionate review No - review by full REC meeting

Further comments (optional):

I have had regular email and one to one meetings with Emily Ikele from R & D department in Cambridge and it has been confirmed the study is eligible for proportionate review.

Note: This question only applies to the REC application.

3. PURPOSE AND DESIGN OF THE RESEARCH

A7. Select the appropriate methodology description for this research. Please tick all that apply:

- Case series/ case note review
- Case control
- Cohort observation
- Controlled trial without randomisation
- Cross-sectional study
- Database analysis
- Epidemiology
- Feasibility/ pilot study
- Laboratory study

- Metanalysis
- Qualitative research
- Questionnaire, interview or observation study
- Randomised controlled trial
- Other (please specify)

A10. What is the principal research question/objective? *Please put this in language comprehensible to a lay person.*

The principle research question is whether, 10 years before glaucoma diagnosis, the intraocular pressure of patients who subsequently develop glaucoma was higher than that of matched controls who did not go on to develop glaucoma.

A11. What are the secondary research questions/objectives if applicable? *Please put this in language comprehensible to a lay person.*

There are two secondary research questions:

1. Are there optic nerve head differences in patients 10 years before glaucoma diagnosis compared to matched controls who do not go on to develop glaucoma?
2. Are there any other associations of risk factors (e.g., visual fields) 10 years before glaucoma diagnosis.

A12. What is the scientific justification for the research? *Please put this in language comprehensible to a lay person.*

Primary open angle glaucoma (POAG) is a chronic condition where optic nerve changes lead to a loss of visual field. The reasons why POAG occurs are not fully understood. However, substantial research has been conducted on the risk factors for the disease. The risk factors that have been associated with POAG are: age, genetics, race, gender, myopia, intraocular pressure and increased optic nerve head disc diameter. The only risk factor that can be modified is intraocular pressure.

Most new cases of glaucoma are referred to the Hospital Eye Service by community optometrists. Typically, the hospital eye clinic diagnoses glaucoma at or soon after they first see the glaucoma suspect. Sometimes, the hospital follows cases for a period before diagnosing glaucoma, but this is typically for less than five years. Very little is known about whether people who go on to develop glaucoma have the risk factors for glaucoma more than five years before diagnosis. This information is sometimes available in community optometry practices. A consideration of these factors has led to the development of a research question that asks:

"Are there pre-clinical signs for primary open angle glaucoma that are present more than 5 years before the diagnosis of glaucoma?"

A13. Please summarise your design and methodology. *It should be clear exactly what will happen to the research participant, how many times and in what order. Please complete this section in language comprehensible to the lay person. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.*

The research design investigates quantitative variables and therefore uses quantitative methods. The research design is a retrospective cohort study. It can be characterised as observational research as historical data will be analysed with explorations of associations between variables.

The established process for checking the anonymisation of data extracted from the optometry practices is:

1. Optometry practice sources clinical record of patient using inclusion and exclusion criteria
2. Clinical record is photocopied (or, if computerised, printed)
3. Name and contact details are blocked out from photocopied or printed clinical record. The day part of the date of birth will be redacted, just leaving the month and year
4. Sharifa Hirani will collect all records once sourced from the practice and deliver to an assigned doctorate supervisor.
5. Doctorate supervisor will check each record for anonymity and make further redactions if needed.
6. Sharifa Hirani will collect the clinical records once they have been double checked and extract the required fields of data.

The fields of data that will be extracted are:

1. Gender
2. Month and year of birth
3. Race if known
4. Right visual acuity
5. Left visual acuity
6. Right eye refractive error
7. Left eye refractive error
8. Right intraocular pressure measurement. Instrument used & time of day
9. Left intraocular pressure measurement
10. Right optic nerve head description
11. Left optic nerve head description
12. Visual field result. Instrument and test used.
13. Optic nerve head photograph
14. Details of family history of glaucoma
15. Details of diagnosis of glaucoma

4. RISKS AND ETHICAL ISSUES

RESEARCH PARTICIPANTS

A17-1. Please list the principal inclusion criteria (list the most important, max 5000 characters).

Anonymised data will be collected from two categories of patients. The first inclusion criterion (diagnosis) will divide the two groups into those with a diagnosis of POAG to those without such a diagnosis. The inclusion criteria thereafter will be the same for each group.

1. For glaucoma group, diagnosis of POAG from a consultant ophthalmologist. These patients may or may not have a family history of glaucoma.
2. OR for control group no Diagnosis of POAG and no suspicion of any variant of glaucoma or ocular hypertension. These patients may not have a family history of glaucoma.
3. The patient will have been seen at the same practice for a minimum of 10 years prior to diagnosis of POAG. If there are breaks in continuity of care (e.g., periods where there are no routine eye examinations) these should be no more than 4 years.
4. Intraocular pressure readings available for 10 years prior to last record.
5. Visual field tests at least twice within the 10 year history.

A17-2. Please list the principal exclusion criteria (list the most important, max 5000 characters).

Exclude any patients who have pathology likely to affect the visual field

Examples:

Toxoplasmosis, optic nerve head drusen, retinal detachment, congenital visual field defect, photocoagulation for diabetes, closed angle glaucoma, strokes or other lesions affecting the visual pathway, secondary glaucomas, wet AMD if affects the visual field.

Exclude any patients who have had refractive surgery.

RECRUITMENT AND INFORMED CONSENT

In this section we ask you to describe the recruitment procedures for the study. Please give separate details for different study groups where appropriate.

A27-1. How will potential participants, records or samples be identified? Who will carry this out and what resources will be used? For example, identification may involve a disease register, computerised search of GP records, or review of medical records. Indicate whether this will be done by the direct healthcare team or by researchers acting under arrangements with the responsible care organisation(s).

Community optometry practices that have been identified to potentially provide anonymised clinical records are known practices to myself and my doctorate supervisors. The practices will only be approached once approval has been granted from all ethics applications required for the study. It will be made clear to the practices that their participation in the research is completely voluntary.

A27-2. Will the identification of potential participants involve reviewing or screening the identifiable personal information of patients, service users or any other person?

Yes No

Please give details below:

A28. Will any participants be recruited by publicity through posters, leaflets, adverts or websites?

Yes No

A29. How and by whom will potential participants first be approached?

The community optometric practices will be approached by the Chief Investigator or her supervisors.

A30-1. Will you obtain informed consent from or on behalf of research participants?

Yes No

If you will be obtaining consent from adult participants, please give details of who will take consent and how it will be done, with details of any steps to provide information (a written information sheet, videos, or interactive material). Arrangements for adults unable to consent for themselves should be described separately in Part B Section 6, and for children in Part B Section 7.

If you plan to seek informed consent from vulnerable groups, say how you will ensure that consent is voluntary and fully informed.

Agreement to take part in the study will be obtained from the optometric practices taking part in the study. Each optometric practice will be provided with a written information sheet.

If you are not obtaining consent, please explain why not.

Please enclose a copy of the information sheet(s) and consent form(s).

A30-2. Will you record informed consent (or advice from consultees) in writing?

Yes No

A31. How long will you allow potential participants to decide whether or not to take part?

I will contact and meet with each optometric practice. Two weeks will be allowed for each practice to decide whether they would like to take part.

A33-1. What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs?(e.g. translation, use of interpreters)

The written information leaflets and consent forms for participating practices are written in English as the practice principals will all be fluent English speakers. Verbal explanations can be provided and time will be spent with each practice to explain the study.

A35. What steps would you take if a participant, who has given informed consent, loses capacity to consent during the study? *Tick one option only.*

- The participant and all identifiable data or tissue collected would be withdrawn from the study. Data or tissue which is not identifiable to the research team may be retained.
- The participant would be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant.
- The participant would continue to be included in the study.
- Not applicable – informed consent will not be sought from any participants in this research.
- Not applicable – it is not practicable for the research team to monitor capacity and continued capacity will be assumed.

Further details:

CONFIDENTIALITY

In this section, personal data means any data relating to a participant who could potentially be identified. It includes pseudonymised data capable of being linked to a participant through a unique code number.

Storage and use of personal data during the study

A36. Will you be undertaking any of the following activities at any stage (including in the identification of potential participants)? *(Tick as appropriate)*

- Access to medical records by those outside the direct healthcare team
- Electronic transfer by magnetic or optical media, email or computer networks
- Sharing of personal data with other organisations
- Export of personal data outside the EEA
- Use of personal addresses, postcodes, faxes, emails or telephone numbers
- Publication of direct quotations from respondents
- Publication of data that might allow identification of individuals
- Use of audio/visual recording devices
- Storage of personal data on any of the following:
- Manual files including X-rays
 - NHS computers
 - Home or other personal computers
 - University computers
 - Private company computers
 - Laptop computers

Further details:

There will be NO storage of identifiable personal data.

A38. How will you ensure the confidentiality of personal data? Please provide a general statement of the policy and procedures for ensuring confidentiality, e.g. anonymisation or pseudonymisation of data.

This study has used the guidance of the Information Commissioner's Office for anonymisation of all data to be used in the study. There will be NO extraction of identifiable personal data.

A40. Who will have access to participants' personal data during the study? Where access is by individuals outside the direct care team, please justify and say whether consent will be sought.

There will be no access to participant's personal data during the study.

Storage and use of data after the end of the study

A43. How long will personal data be stored or accessed after the study has ended?

- Less than 3 months
 3 – 6 months
 6 – 12 months
 12 months – 3 years
 Over 3 years

INCENTIVES AND PAYMENTS

A46. Will research participants receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in this research?

- Yes No

A47. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research?

- Yes No

A48. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?

- Yes No

NOTIFICATION OF OTHER PROFESSIONALS

PUBLICATION AND DISSEMINATION

A50. Will the research be registered on a public database?

- Yes No

Please give details, or justify if not registering the research.

The research is not a clinical trial but is solely a review of retrospective anonymised data.

Registration of research studies is encouraged wherever possible. You may be able to register your study through your NHS organisation or a register run by a medical research charity, or publish your protocol through an open access publisher. If you are aware of a suitable register or other method of publication, please give details. If not, you may indicate that no suitable register exists. Please ensure that you have entered registry reference number(s) in question A5-1.

A51. How do you intend to report and disseminate the results of the study? Tick as appropriate:

- Peer reviewed scientific journals
 Internal report
 Conference presentation
 Publication on website
 Other publication
 Submission to regulatory authorities
 Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators
 No plans to report or disseminate the results
 Other (please specify)
 Doctorate thesis

A53. Will you inform participants of the results?

Yes No

Please give details of how you will inform participants or justify if not doing so.
 The optometric practices involved in the study will be advised of the outcome of the research.

5. Scientific and Statistical Review

A54. How has the scientific quality of the research been assessed? Tick as appropriate:

- Independent external review
 Review within a company
 Review within a multi-centre research group
 Review within the Chief Investigator's institution or host organisation
 Review within the research team
 Review by educational supervisor
 Other

Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:
 In addition to regular meetings with the supervisory team I participate in the doctoral support group at London South Bank University. This is multi-disciplinary group that meets once a month and I have presented my research plans and received useful feedback.

For all studies except non-doctoral student research, please enclose a copy of any available scientific critique reports, together with any related correspondence.

For non-doctoral student research, please enclose a copy of the assessment from your educational supervisor/ institution.

A56. How have the statistical aspects of the research been reviewed? Tick as appropriate:

- Review by independent statistician commissioned by funder or sponsor
 Other review by independent statistician

- Review by company statistician
 Review by a statistician within the Chief Investigator's institution
 Review by a statistician within the research team or multi-centre group
 Review by educational supervisor
 Other review by individual with relevant statistical expertise
 No review necessary as only frequencies and associations will be assessed – details of statistical input not required

In all cases please give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.

	Title	Forename/Initials	Surname
	Professor	Bruce	Evans
Department			
Institution	Insitute of Optometry		
Work Address	56-62 Newington Causeway London		
Post Code	SE1 6DS		
Telephone	02072349641		
Fax			
Mobile			
E-mail	bjwe@bruce-evans.co.uk		

Please enclose a copy of any available comments or reports from a statistician.

A57. What is the primary outcome measure for the study?

The primary outcome measure for the study is:
Intraocular pressure in the ten years preceding a diagnosis of primary open angle glaucoma compared to that in a matched control

A58. What are the secondary outcome measures? (if any)

Visual field and optic disc cupping in the ten years preceding a diagnosis of primary open angle glaucoma compared to that in a matched control.

A59. What is the sample size for the research? How many participants/samples/data records do you plan to study in total? If there is more than one group, please give further details below.

Total UK sample size: 110
Total international sample size (including UK): 110
Total in European Economic Area:

Further details:

A60. How was the sample size decided upon? If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.

A sample size calculation was conducted using the methods of Armitage and Berry (1987). The calculation set type 2 errors at 90 per cent and found the result to be 55 anonymised pairs of records (i.e., 110 in total).

A61. Will participants be allocated to groups at random?

Date: 25/03/2015

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170742/769521/1/894

Yes No

A62. Please describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.

The data collected for this retrospective anonymised study will be analysed statistically concentrating on comparisons between the glaucoma and control groups. Data will be analysed with Excel and SPSS. Although each dataset in the glaucoma group will be individually matched with a dataset in the control group this matching is designed solely to reduce potential confounding variables. It is not implied that this matching will enable matched pairs statistical analyses and indeed it is envisaged that this will not be appropriate. The statistical analysis that will be most appropriate will be to compare the two groups using normal unpaired t-tests, unpaired ANOVA, or non-parametric equivalents of these tests as appropriate.

6. MANAGEMENT OF THE RESEARCH

A63. Other key investigators/collaborators. Please include all grant co-applicants, protocol co-authors and other key members of the Chief Investigator's team, including non-doctoral student researchers.

Title Forename/Initials Surname
Post
Qualifications
Employer
Work Address
Post Code
Telephone
Fax
Mobile
Work Email

A64. Details of research sponsor(s)

A64-1. Sponsor

Lead Sponsor	
Status:	Commercial status: Non-Commercial
<input type="radio"/> NHS or HSC care organisation	
<input checked="" type="radio"/> Academic	
<input type="radio"/> Pharmaceutical industry	
<input type="radio"/> Medical device industry	
<input type="radio"/> Local Authority	
<input type="radio"/> Other social care provider (including voluntary sector or private organisation)	
<input type="radio"/> Other	
<i>If Other, please specify:</i>	

Contact person

Name of organisation London South Bank Univeristy
 Given name Nicola
 Family name Crichton
 Address 103 Borough Road
 Town/city London
 Post code SE1 0AA
 Country UNITED KINGDOM
 Telephone 02078156742
 Fax
 E-mail crichtnj@lsbu.ac.uk

Is the sponsor based outside the UK?

Yes No

Under the Research Governance Framework for Health and Social Care, a sponsor outside the UK must appoint a legal representative established in the UK. Please consult the guidance notes.

A65. Has external funding for the research been secured?

- Funding secured from one or more funders
 External funding application to one or more funders in progress
 No application for external funding will be made

What type of research project is this?

- Standalone project
 Project that is part of a programme grant
 Project that is part of a Centre grant
 Project that is part of a fellowship/ personal award/ research training award
 Other

Other – please state:

Project that is part of professional doctorate award.

A67. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another country?

Yes No

Please provide a copy of the unfavourable opinion letter(s). You should explain in your answer to question A6-2 how the reasons for the unfavourable opinion have been addressed in this application.

A68-1. Give details of the lead NHS R&D contact for this research:

Title Forename/Initials Surname
 Miss Emily Ikele
 Organisation Research Management & Governance, NHS Cambridgeshire and Peterborough CCG

Date: 25/03/2015

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Address	Lockton House Cambridge
Post Code	CB2 8FH
Work Email	emily.ikelle@nhs.net
Telephone	01223725467
Fax	
Mobile	

Details can be obtained from the NHS R&D Forum website: <http://www.rdforum.nhs.uk>

A69-1. How long do you expect the study to last in the UK?

Planned start date: 02/04/2015
 Planned end date: 01/10/2015
 Total duration:
 Years: 0 Months: 6 Days: 0

A71-2. Where will the research take place? (Tick as appropriate)

- England
 Scotland
 Wales
 Northern Ireland
 Other countries in European Economic Area

Total UK sites in study 20

Does this trial involve countries outside the EU?

- Yes No

A72. What host organisations (NHS or other) in the UK will be responsible for the research sites? Please indicate the type of organisation by ticking the box and give approximate numbers of planned research sites:

- NHS organisations in England 20
 NHS organisations in Wales
 NHS organisations in Scotland
 HSC organisations in Northern Ireland
 GP practices in England
 GP practices in Wales
 GP practices in Scotland
 GP practices in Northern Ireland
 Social care organisations
 Phase 1 trial units
 Prison establishments
 Probation areas
 Independent hospitals
 Educational establishments
 Independent research units
 Other (give details)

Total UK sites in study:	20
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A76. Insurance/ indemnity to meet potential legal liabilities

Note: In this question to NHS indemnity schemes include equivalent schemes provided by Health and Social Care (HSC) in Northern Ireland

A76-1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research? Please tick box(es) as applicable.

Note: Where a NHS organisation has agreed to act as sponsor or co-sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, please describe the arrangements and provide evidence.

- NHS indemnity scheme will apply (NHS sponsors only)
 Other insurance or indemnity arrangements will apply (give details below)

This study will use anonymised historical data. There is no contact with participants and no participant testing or interventions. Although we can think of no potential for harm the research is nonetheless indemnified under London South Bank University insurance cover.

Please enclose a copy of relevant documents.

A76-2. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research? Please tick box(es) as applicable.

Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), please describe the arrangements and provide evidence.

- NHS indemnity scheme will apply (protocol authors with NHS contracts only)
 Other insurance or indemnity arrangements will apply (give details below)

This study will use anonymised historical data. There is no contact with participants and no participant testing or interventions. Although we can think of no potential for harm the research is nonetheless indemnified under London South Bank University insurance cover.

Please enclose a copy of relevant documents.

A76-3. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research?

Note: Where the participants are NHS patients, indemnity is provided through the NHS schemes or through professional indemnity. Indicate if this applies to the whole study (there is no need to provide documentary evidence). Where non-NHS sites are to be included in the research, including private practices, please describe the arrangements which will be made at these sites and provide evidence.

- NHS indemnity scheme or professional indemnity will apply (participants recruited at NHS sites only)
 Research includes non-NHS sites (give details of insurance/ indemnity arrangements for these sites below)

This study will use anonymised historical data. There is no contact with participants and no participant testing or interventions. Although we can think of no potential for harm the research is nonetheless indemnified under London South Bank University insurance cover.

Please enclose a copy of relevant documents.

PART C: Overview of research sites

Please enter details of the host organisations (Local Authority, NHS or other) in the UK that will be responsible for the research sites. For NHS sites, the host organisation is the Trust or Health Board. Where the research site is a primary care site, e.g. GP practice, please insert the host organisation (PCT or Health Board) in the Institution row and insert the research site (e.g. GP practice) in the Department row.

Research site	Investigator/ Collaborator/ Contact
Institution name East and North Herts PCT	Title
Department name	First name/ Initials
Street address Charter House, Parkway	Surname
Town/city Welwyn Garden City	
Post Code AL8 6JL	
Institution name NHS Basildon & Brentwood CCG	Title
Department name Phoenix House	First name/ Initials
Street address Christopher Martin Road	Surname
Town/city Basilton	
Post Code SS14 3HG	
Institution name Barnet CCG	Title
Department name North London Business Park	First name/ Initials
Street address Oakleigh Road South	Surname
Town/city New Southgate	
Post Code N11 1NP	
Institution name Cambridge and Peterborough CCG	Title
Department name Lockton House	First name/ Initials
Street address Clarendon Road	Surname
Town/city Cambridge	
Post Code CB2 8FH	
Institution name NHS Central London Clinical Commissioning Group	Title
Department name Ferguson House	First name/ Initials
Street address 15 Marylebone Road	Surname
Town/city London	
Post Code NW1 5JD	
Institution name West Leicestershire CCG	Title
Department name	First name/ Initials
Street address 56 Wood Gate	Surname
Town/city Loughborough	
Post Code LE11 2TZ	

Institution name	NHS Nene Clinical Commissioning Group	Title
Department name	Francis Crick House	First name/ Initials
Street address	Summerhouse Road Moulton Park	Surname
Town/city	Northampton	
Post Code	NN3 6BF	
Institution name	NHS Stockport Clinical Commissioning Group	Title
Department name	Floor 7 Regent House	First name/ Initials
Street address	Heaton Lane	Surname
Town/city	Stockport, Cheshire	
Post Code	SK4 1BS	
Institution name	Southampton City Clinical Commissioning Group	Title
Department name	Trust Headquarters	First name/ Initials
Street address	Oakley Road	Surname
Town/city	Southampton	
Post Code	SO16 4GX	
Institution name	Ipswich and East Suffolk CCG	Title
Department name	Rushbrook House	First name/ Initials
Street address	Paper Mill Lane, Bramford	Surname
Town/city	Ipswich	
Post Code	IP8 4DE	
Institution name	NHS North East Essex Colchester Primary Care Centr	Title
Department name		First name/ Initials
Street address		Surname
Town/city		
Post Code		
Institution name	NHS Brent CCG	Title
Department name		First name/ Initials
Street address		Surname
Town/city		
Post Code		

PART D: Declarations**D1. Declaration by Chief Investigator**

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.
2. I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.
3. If the research is approved I undertake to adhere to the study protocol, the terms of the full application as approved and any conditions set out by review bodies in giving approval.
4. I undertake to notify review bodies of substantial amendments to the protocol or the terms of the approved application, and to seek a favourable opinion from the main REC before implementing the amendment.
5. I undertake to submit annual progress reports setting out the progress of the research, as required by review bodies.
6. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer. I understand that I am not permitted to disclose identifiable data to third parties unless the disclosure has the consent of the data subject or, in the case of patient data in England and Wales, the disclosure is covered by the terms of an approval under Section 251 of the NHS Act 2006.
7. I understand that research records/data may be subject to inspection by review bodies for audit purposes if required.
8. I understand that any personal data in this application will be held by review bodies and their operational managers and that this will be managed according to the principles established in the Data Protection Act 1998.
9. I understand that the information contained in this application, any supporting documentation and all correspondence with review bodies or their operational managers relating to the application:
 - Will be held by the REC (where applicable) until at least 3 years after the end of the study; and by NHS R&D offices (where the research requires NHS management permission) in accordance with the NHS Code of Practice on Records Management.
 - May be disclosed to the operational managers of review bodies, or the appointing authority for the REC (where applicable), in order to check that the application has been processed correctly or to investigate any complaint.
 - May be seen by auditors appointed to undertake accreditation of RECs (where applicable).
 - Will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.
 - May be sent by email to REC members.
10. I understand that information relating to this research, including the contact details on this application, may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 1998.
11. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named below. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

Contact point for publication*(Not applicable for R&D Forms)*

NRES would like to include a contact point with the published summary of the study for those wishing to seek further information. We would be grateful if you would indicate one of the contact points below.

- Chief Investigator
 Sponsor

- Study co-ordinator
- Student
- Other – please give details
- None

Access to application for training purposes (Not applicable for R&D Forms)

Optional – please tick as appropriate:

- I would be content for members of other RECs to have access to the information in the application in confidence for training purposes. All personal identifiers and references to sponsors, funders and research units would be removed.

This section was signed electronically by Miss Sharifa Hirani on 24/03/2015 14:43.

Job Title/Post: Senior Lecturer/Chief Investigator
Organisation: University of Hertfordshire
Email: sharifa@gmail.com

D2. Declaration by the sponsor's representative

If there is more than one sponsor, this declaration should be signed on behalf of the co-sponsors by a representative of the lead sponsor named at A64-1.

I confirm that:

1. This research proposal has been discussed with the Chief Investigator and agreement in principle to sponsor the research is in place.
2. An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.
3. Any necessary indemnity or insurance arrangements, as described in question A76, will be in place before this research starts. Insurance or indemnity policies will be renewed for the duration of the study where necessary.
4. Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.
5. Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.
6. The duties of sponsors set out in the Research Governance Framework for Health and Social Care will be undertaken in relation to this research.
7. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named in this application. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.
8. Specifically, for submissions to the Research Ethics Committees (RECs) I declare that any and all clinical trials approved by the HRA since 30th September 2013 (as defined on IRAS categories as clinical trials of medicines, devices, combination of medicines and devices or other clinical trials) have been registered on a publically accessible register in compliance with the HRA registration requirements for the UK, or that any deferral granted by the HRA still applies.

Signature:

Print Name:

Post:

Organisation:

Date: (dd/mm/yyyy)

D3. Declaration for student projects by academic supervisor(s)

1. I have read and approved both the research proposal and this application. I am satisfied that the scientific content of the research is satisfactory for an educational qualification at this level.
2. I undertake to fulfil the responsibilities of the supervisor for this study as set out in the Research Governance Framework for Health and Social Care.
3. I take responsibility for ensuring that this study is conducted in accordance with the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research, in conjunction with clinical supervisors as appropriate.
4. I take responsibility for ensuring that the applicant is up to date and complies with the requirements of the law and relevant guidelines relating to security and confidentiality of patient and other personal data, in conjunction with clinical supervisors as appropriate.

Academic supervisor 1

This section was signed electronically by Professor Peter Allen on 24/03/2015 18:17.

Job Title/Post:

Organisation:

Email:

Academic supervisor 2

This section was signed electronically by Professor David Edgar on 24/03/2015 21:44.

Job Title/Post: Emeritus Professor

Organisation: City University London

Email: d.f.edgar@city.ac.uk

Academic supervisor 3

This section was signed electronically by Bruce Evans on 24/03/2015 17:56.

Job Title/Post: Director of Research

Organisation: Institute of Optometry

Email: bjwe@bruce-evans.co.uk

19. APPENDIX 8 - STUDY 2 LONDON SOUTH BANK

UNIVERSITY SPONSORSHIP AND INDEMNITY LETTER

**London South Bank
University**

School of Health and Social Care
103 Borough Road
London SE1 0AA
T: 020 7815 7815
F: 020 7815 8099
www.lsbu.ac.uk

Professor Nicola Crichton
Pro Dean Research, School of
Health & Social Care
T: 020 7815 6742
F: 020 7815 8490
Email: crichtnj@lsbu.ac.uk

18 March 2015

Dear Sir

Title of study: *Review of anonymised clinical records to study
open angle glaucoma.*

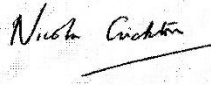
Name of student: *Sharifa Hirani*

LONDON SOUTH BANK UNIVERSITY is willing to take on the role of sponsor in relation to this research project, to be carried out by Sharifa Hirani who is currently a student studying for a Professional Doctorate in Optometry. The research study is part of that award. The academic supervisor for the project is Professor Bruce Evans.

I confirm that indemnity will be in place covering this project the details of the cover are in the attached statement of insurance cover.

All correspondence for the sponsor should be marked for the attention of Professor Nicola Crichton.

Yours sincerely,



Professor Nicola Crichton
Pro Dean Research

20. APPENDIX 9 - STUDY 2 INFORMATION SHEET

London South Bank University

Information Sheet for Community Optometric Practices

Name of Researcher: **Miss Sharifa Hirani**

Study title: **A retrospective review of anonymised clinical records to investigate whether risk factors for glaucoma are present many years before glaucoma develops.**

INVITATION

I am an optometrist and am studying for my professional doctorate in optometry through London South Bank University and the Institute of Optometry. My doctorate supervisors are: Professor Bruce Evans, Professor David Edgar and Professor Peter Allen.

I am inviting community optometric practices to assist me with my research study. The study aims to review anonymised clinical records of patients who have a diagnosis of Primary Open Angle Glaucoma (POAG). I would like to review records of POAG patients subsequent to them being diagnosed, against a control group; I require each optometric practice that assist me with my study to provide a minimum of six such records.

Before you make your decision, I would like to give you background to my study, as it is important for you to understand why the study is being done and what it will involve. Please take the time to read the following information carefully.

BACKGROUND TO THE STUDY

POAG is a chronic condition with characteristic optic nerve change and a loss of visual field. The pathology of POAG is not fully understood; but substantial research has been conducted on the risk factors for the disease. The risk factors that have been associated with POAG are: age, genetics, race, gender, myopia, intraocular pressure and increased optic nerve head disc diameter. The only risk factor, which can be controlled, is intraocular pressure. There is very little known about this particular risk factor in those under the age of forty years. This has led to the development of a research question that asks:

"Are there pre-clinical signs for POAG that are present more than 5 years before the diagnosis of glaucoma?"

V2 14/03/15

Sharifa Hirani

Information Sheet

A retrospective review of anonymised clinical records to investigate whether risk factors for glaucoma are present many years before glaucoma develops.

WHAT WILL THE STUDY INVOLVE?

You have been asked to take part in the study, as your community optometric practice has clinical records for patients with a diagnosis of POAG. We want to collate data from patients who have been attending your practice for at least ten years prior to a diagnosis of POAG. We would also need data for a control group. The control group will need to be individually matched for age, race, gender, and approximate refractive error with the group of patients who have POAG but will not have received a diagnosis of glaucoma or have a family history of glaucoma.

I am approaching a minimum of ten practices to secure 55 anonymised records.

The anonymised data collected from your practice will help:

1. To compare intraocular pressure 10 years before glaucoma diagnosis in a group who have POAG with a control group.
2. To investigate any differences in cup to disc ratio of the optic nerve head 10 years before diagnosis with glaucoma in a POAG group compared to a control group.
3. To investigate any associations between the other risk factors for POAG 10 years before diagnosis with glaucoma in the POAG group compared with the control group.

V2 14/03/15
Information Sheet

Sharifa Hirani

A retrospective review of anonymised clinical records to investigate whether risk factors for glaucoma are present many years before glaucoma develops.

WHAT DOES THE STUDY INVOLVE?

If you would like to take part in the study, we will ask you to find clinical records of patients who have been seen at the practice for ten years prior to a diagnosis of POAG. We would then ask that you find an age and refraction-matched control for this patient. Below is a table that gives details of specific details of what you would look for with each clinical record in each group

Group 1 POAG	Group 2 Controls.
Diagnosis of POAG from an ophthalmologist.	No Diagnosis of POAG and no suspicion of any variant of glaucoma or ocular hypertension.
The patient will have been seen at the same practice for a minimum of 10 years prior to diagnosis of POAG. There are no breaks of more than 4 years during which the patient has not attended.	The patient will have been seen at the same practice for a minimum of 10 years. There are no breaks of more than 4 years during which the patient has not attended.
Can have a family history of glaucoma (if so, this will be documented).	No known family history of glaucoma
Exclude other pathology likely to affect the visual field Examples: Toxoplasmosis, optic nerve head drusen, retinal detachment, congenital visual field defect, photocoagulation for diabetes, closed angle glaucoma, strokes or other lesions affecting the visual pathway, secondary glaucomas, wet AMD if affects the visual field.	Exclude pathology likely to affect the visual field Examples: Toxoplasmosis, optic nerve head drusen, retinal detachment, congenital visual field defect, photocoagulation for diabetes, closed angle glaucoma, strokes or other lesions affecting the visual pathway, secondary glaucomas, wet AMD if affects the visual field.
Exclude any patients who have had refractive surgery.	Exclude any patients who have had refractive surgery.
These records will be selected first and then controls selected to individually match each member of the POAG group.	For each POAG record, a control record will be selected that meets the selection criteria and matches the POAG record for: Age \pm 5y, Refractive error (SER) \pm 2D,

V2 14/03/15

Sharifa Hirani

Information Sheet

A retrospective review of anonymised clinical records to investigate whether risk factors for glaucoma are present many years before glaucoma develops.

	Gender and Race where possible
Intraocular pressure readings available for 10 years prior to glaucoma diagnosis.	Intraocular pressure readings available for all examinations carried out during the 10 years.
Visual field tests at least twice within the 10 year history prior to POAG diagnosis.	Visual field tests at least twice within the 10-year history.

You will be required to photocopy or print out each clinical record and **block out with a marker pen any detail, which would identify the patient (name, day of the month of their date of birth, and address)**. The responsibility for removing all identifiable patient information will lie with you. Once all patient information has been redacted from the photocopied records, I will collect them in a sealed envelope and deliver them by hand to my doctorate supervisors.

Patient identifiable information includes:

- Patient name, address, full post code, date of birth;
- Pictures, photographs, videos, audio-tapes or other images of patients;
- NHS number and local patient identifiable codes;
- Anything else that may be used to identify a patient directly or indirectly. For example, rare diseases, drug treatments or statistical analyses which have very small numbers within a small population may allow individuals to be identified.

ADDITIONAL INFORMATION

The Information Governance Lead/Caldicott Lead for your practice will take responsibility for signing the practice consent form for this study. The responsibility for removing all identifiable patient information will lie with the consenting practice.

You are able to withdraw from the study at any time without giving a reason. Any anonymised data that I may have received from you would be used but no further anonymised data would be collected. Copies of records will be disposed of securely.

There is no financial incentive to taking part in the study but your input will help answer the research questions.

I have gained ethics approval from NRES Committees—North of Scotland, London South Bank University and The Institute of Optometry.

WHAT TO DO NOW?

V2 14/03/15

Information Sheet

Sharifa Hirani

A retrospective review of anonymised clinical records to investigate whether risk factors for glaucoma are present many years before glaucoma develops.

If you need any further information, please do not hesitate to contact me. If you are happy to take part in the study, I will arrange to see you to complete the consent form. My contact details are:

Miss Sharifa Hirani

Email: sharifa@gmail.com

Telephone number: 07909 968786

If there is a problem, please contact Professor Bruce Evans

Email: bjwe@bruce-evans.co.uk

V2 14/03/15

Information Sheet

Sharifa Hirani

A retrospective review of anonymised clinical records to investigate whether risk factors for glaucoma are present many years before glaucoma develops.

21. APPENDIX 10 - STUDY 2 CONSENT FORM

London South Bank University

CONSENT FORM

Title of Project: **A retrospective review of anonymised clinical records to investigate whether risk factors for glaucoma are present many years before glaucoma develops.**

Name of Researcher: **Miss Sharifa Hirani**

Please initial box

1. I confirm that I have read the Information Sheet dated..... (Version 2) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

2. I understand that participation from the practice is voluntary and that we can withdraw at any time without giving any reason and without legal rights being affected.

3. I agree to take part in the above study.

Name

Date

Signature

(Information Governance/Caldecott Lead)

Address of Practice

Name of Person

Date

Signature

taking consent

Version 2 14/03/15

Consent form for Study:

A retrospective review of anonymised clinical records to investigate whether risk factors for glaucoma are present many years before glaucoma develops.

22. APPENDIX 11 - STUDY 2 NHS REC (PROPORTIONATE REVIEW) APPROVAL

NRES Committees - North of Scotland

Summerfield House
2 Eday Road
Aberdeen
AB15 6RE

Telephone: 01224 558458
Facsimile: 01224 558609
Email: nosres@nhs.net



1 April 2015

Miss Sharifa Hirani
University of Hertfordshire
2 F412 College Lane
College Lane
HATFIELD
AL10 9AB

Dear Miss Hirani

Study title: A retrospective review of anonymised clinical records to investigate whether risk factors for primary open angle glaucoma are present many years before glaucoma develops.
REC reference: 15/NS/0032
IRAS project ID: 170742

The Proportionate Review Sub-Committee of the NRES Committees - North of Scotland (1) reviewed the above application by correspondence.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager Mrs Carol Irvine, nosres@nhs.net. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Ethical opinion

On behalf of the Committee, the Proportionate Review Sub-Committee gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

- 1 Please confirm who will consent on behalf of the practice.

Participant Information Sheet

- 2 Please insert a sentence to make it clear to participants that the burden of identification is on the practice.
- 3 Under the heading 'What does the study involve?', please amend the Information Sheet regarding the collection of data sheets.
- 4 Under the heading 'Additional Information?', please insert 'NRES Committees – North of Scotland (1)'.

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which can be made available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at <http://www.rdforum.nhs.uk>.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from NRES. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:

<http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/>

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at <http://www.hra.nhs.uk/hra-training/>

With the Committee's best wishes for the success of this project.

15/NS/0032	Please quote this number on all correspondence
-------------------	---

Yours sincerely



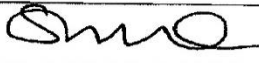
Professor Helen Galley
Chair

Enclosures: List of names and professions of members who took part in the review "After ethical review – guidance for researchers" SL-AR2

23. APPENDIX 12- STUDY 2 RESEARCH PASSPORT APPLICATION

Research Passport Application Form – Version 3 01/09/2012

Please refer to the guidance notes before completing the form.

Section 1 - Details of Researcher To be completed by Researcher				
1.	Surname: Hirani	Prof <input type="checkbox"/> Dr <input type="checkbox"/> Mr <input type="checkbox"/> Mrs <input type="checkbox"/>		
	Forename(s): Sharifa	Miss x Ms <input type="checkbox"/> Other <input type="checkbox"/>		
Home Address: 35 Waterford Green, Welwyn Garden City				
Work Tel: 01707 285206 Mobile: 07909968786 Email: sharifa@gmail.com				
2.	Date of birth: 12/10/1974	Gender: Male <input type="checkbox"/> Female <input checked="" type="checkbox"/>		
	Ethnicity: British	National Insurance number: JA 91 5666C		
3.	Professional registration details, if applicable (Doctors undertaking any form of medical practice should confirm they have a licence to practise). N/A <input type="checkbox"/> General Optical Council. Registration Number 01-21961			
4.	Employer: or place of study: London South Bank University			
	Work Address/Place of Study: 103 Borough Road, London SE1 0AA			
	Post or status held: Doctorate of Optometry Student/Allied Health Professionals Programme			
Section 2 - Details of Research To be completed by Researcher				
5.	What type of Research Passport do you need? Project-specific <input checked="" type="checkbox"/> Multi-project <input type="checkbox"/>			
	<i>If you will be conducting one project only please complete the details below. If you anticipate that you will be undertaking more than one project at any one time, please give details in the Appendix.</i>			
	Project Title: REVIEW OF ANONYMISED CLINICAL RECORDS TO STUDY OPEN ANGLE GLAUCOMA.			
	Project Start Date: 05/05/2015 End Date: 01/10/2015			
	Proposed start and end-date of 3-year Research Passport: Start Date: 05/05/2015 End Date: 01/10/2015			
	NHS organisation(s):	Dept(s):	Proposed research activities:	Manager in NHS organisation:
	Optometry community Cambridgeshire practices East North Herts.		accessing anonymised patient data. " "	Practice manager Practice Manager
Section 3 - Declaration by Researcher To be completed by Researcher				
6.	Have you ever been refused an honorary research contract?		Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>	
	Have you ever had an honorary research contract revoked?		Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>	
	If yes to either question, please give details:			
I consent to the information provided as part of this Research Passport and attached documents being used, recorded and stored by authorised staff of the NHS organisations where I will be conducting research.				
Signed: 		Date: 29/04/2015		
When Sections 1-3 have been completed, the researcher should forward the form to the appropriate person to complete Section 4.				

Section 4 - Suitability of Researcher <i>To be completed by researcher's substantive employer, e.g. line manager, or academic supervisor</i>										
7.a	Will this person's research activity mean that they may be undertaking regulated activity with children and/or adults as defined in the Safeguarding Vulnerable Groups Act 2006, as amended (in particular by the Protection of Freedoms Act 2012)? (please use the Research Passport algorithm to make this judgement)	Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>								
7.b	I am satisfied that the above named individual is suitably trained and experienced to undertake the duties associated with the research activities outlined in this Research Passport form.									
	Signed: <i>Bruce Evans</i>	Date: 29/04/2015								
	Name: Bruce Evans	Job Title: Director of Research, Institute of Optometry Visiting Professor, London South Bank University								
	Department and Organisation: Research Department, Institute of Optometry									
	Address: 56-62 Newington Causeway London, SE1 6DS									
	Tel No: 020 7407 4184	Email: bjwe@bruce-evans.co.uk								
	Managerial responsibility for the applicant: Academic Supervisor									
<i>When Section 4 has been completed, the researcher should forward the form to the appropriate person to complete Section 5.</i>										
Section 5 - Pre-engagement checks <i>To be completed by the HR department of the researcher's substantive employer or registry at place of study</i>										
8.	Does the above named individual's research involve Regulated Activity with children and/or adults as defined in the Safeguarding Vulnerable Groups Act 2006, as amended (in particular by the Protection of Freedoms Act 2012)?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No								
	If yes to the above, has the above named individual been checked against ISA barred lists for adults and/or children, as appropriate and have you received confirmation via the criminal record disclosure that the person is not barred from working with adults and/or children? (NB individuals who are barred from working with adults or children must not undertake a regulated activity in the NHS with the vulnerable group from which they are barred, and you must not submit a Research Passport form in such cases).	Checked against: ISA Adults List? Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input checked="" type="checkbox"/> ISA Children's List? Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input checked="" type="checkbox"/>								
	Can you confirm that a clear criminal record disclosure has been obtained for the above-named individual, with no subsequent reports from the individual of changes to this record? NB for Regulated Activity this must be an enhanced level criminal record check. For non-regulated activity, ensure the criminal record check is at the mandated level.	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input checked="" type="checkbox"/>								
	If yes, please provide details of the clear disclosure:									
	Date of disclosure:	Type of disclosure:								
	Disclosure No.:	Organisation that requested disclosure:								
9.	Have the pre-engagement checks described below been carried out with regard to the above-named individual and is confirmation of the necessary checks, including any required satisfactory documentary evidence, available in the employing organisation's/place of study's records?									
	<input checked="" type="checkbox"/> Employment/student screening: <table border="1"> <tr> <td><input type="checkbox"/> ID with photograph</td> <td>Yes x No <input type="checkbox"/></td> </tr> <tr> <td><input type="checkbox"/> two references</td> <td>Yes x No <input type="checkbox"/></td> </tr> <tr> <td><input type="checkbox"/> verification of permission to work/study in the UK</td> <td>Yes x No <input type="checkbox"/></td> </tr> <tr> <td><input type="checkbox"/> exploration of any gaps in employment</td> <td>Yes x No <input type="checkbox"/></td> </tr> </table>		<input type="checkbox"/> ID with photograph	Yes x No <input type="checkbox"/>	<input type="checkbox"/> two references	Yes x No <input type="checkbox"/>	<input type="checkbox"/> verification of permission to work/study in the UK	Yes x No <input type="checkbox"/>	<input type="checkbox"/> exploration of any gaps in employment	Yes x No <input type="checkbox"/>
<input type="checkbox"/> ID with photograph	Yes x No <input type="checkbox"/>									
<input type="checkbox"/> two references	Yes x No <input type="checkbox"/>									
<input type="checkbox"/> verification of permission to work/study in the UK	Yes x No <input type="checkbox"/>									
<input type="checkbox"/> exploration of any gaps in employment	Yes x No <input type="checkbox"/>									
	<input checked="" type="checkbox"/> Evidence of current professional registration	Yes x No <input type="checkbox"/> N/A <input type="checkbox"/>								
	<input checked="" type="checkbox"/> Evidence of qualifications	Yes x No <input type="checkbox"/>								
	<input checked="" type="checkbox"/> Occupational health screening / clearance	Yes x No <input type="checkbox"/>								
	Is the named individual on a fixed term contract or is the contract end imminent? Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>									
	Please indicate current contract end-date	Date: 29 th April 2015								
	Signed: <i>K Hanson</i>									

Name: Lindsey Ranson	Job Title: Lecturer
Organisation: University of Hertfordshire	Department: Postgraduate Medicine
Address:	
Tel No:	Email:
<i>Please return the form to the researcher.</i>	

Section 6 - Instructions to applicants	
<i>To be completed by Researcher</i>	
<i>Please indicate which of the following documents are attached to this Research Passport:</i>	
Current curriculum vitae, including details of qualifications, training and professional registration (please use the template C.V. at http://www.rdforum.nhs.uk/docs/template_cv.doc)	Yes x No <input type="checkbox"/>
Researcher's copy of criminal record disclosure. NB where research involves regulated activity with children and/or adults as defined in the Safeguarding Vulnerable Groups Act 2006, as amended (in particular by the Protection of Freedoms Act 2012), the disclosure must include confirmation of a check against the appropriate ISA barred list(s).	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input checked="" type="checkbox"/>
Evidence of occupational health screening / clearance	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input checked="" type="checkbox"/>
Appendix – List of projects and amendments	Appendix numbers: N/A <input type="checkbox"/>

Please send the completed form and original documents to the Lead R&D office. The completed form and original documents will be returned to you. This package of documents will be used to validate your completed Research Passport form. You may then, and where relevant, provide the Research Passport to other NHS organisations.

You must inform all NHS organisations that have received this Research Passport of any changes to the information supplied above. Failure to do so may result in withdrawal of your honorary research contract or letter of access. As part of the quality control procedures for the Research Passport, random checks on the accuracy of the information held on this Research Passport may be made.

Section 7			
This section should be completed by HR in the Lead NHS organisation, only if additional checks are undertaken			
The following additional checks have been completed:			
Having confirmed that the necessary additional pre-engagement checks have been completed, I am satisfied that the above named researcher is suitable to carry out the duties associated with their research activity outlined in this Research Passport.			
Signed:		Date:	
Name:		Job Title:	
Organisation:		Department:	
Email:			
Section 8 - For Office Use Only			
<i>This section should be completed by the NHS R&D office that received the initial application. The NHS R&D office must countersign and date retained photocopies of the documents. The grey section must be completed before the form is returned to the applicant.</i>			
CV reviewed?	Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>	Training?	Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>
Evidence of qualifications?	Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>	Appendix pages reviewed?	Numbers: /
Professional registration details reviewed?	Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A <input type="checkbox"/>	Occupational health clearance reviewed?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input checked="" type="checkbox"/>
Criminal record disclosure reviewed?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input checked="" type="checkbox"/>	Date of disclosure:	/
		Disclosure No:	/
For regulated activity as defined in the Safeguarding Vulnerable Groups Act 2006, as amended (in particular by the Protection of Freedoms Act 2012), did the criminal record disclosure confirm a satisfactory check against the appropriate ISA barred list(s)			Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input checked="" type="checkbox"/>
Enter Electronic Staff Record Number (if issued): /			
Confirmation of valid Research Passport:			
Project specific <input checked="" type="checkbox"/> Three-year <input type="checkbox"/> Other End date <input type="checkbox"/> Date:			
Signed:	V Shaw		Date: 28/4/15
Name:	V SHAW		
NHS Organisation Name and contact details			
NHS Cambridgeshire & Peterborough CCG Tel 01223 725466			
Date Honorary Research Contract/letter of access issued (delete as appropriate)			April 2015

If required, this section should be added to the Research Passport Form and completed by each NHS R&D office receiving the valid Research Passport. The original Research Passport form and documents should be returned to the applicant.

Has the Research Passport been validated by a Lead NHS organisation and is this validation acceptable to this NHS organisation? Yes <input type="checkbox"/> No <input type="checkbox"/>			
CV reviewed?	Yes <input type="checkbox"/> No <input type="checkbox"/>	Training?	Yes <input type="checkbox"/> No <input type="checkbox"/>
Evidence of qualifications?	Yes <input type="checkbox"/> No <input type="checkbox"/>	Appendix pages reviewed?	Numbers:
Professional Registration details reviewed?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>	Occupational health clearance reviewed?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>
Criminal record disclosure reviewed?	Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>	Date of disclosure: Disclosure No:	
For regulated activity as defined in the Safeguarding Vulnerable Groups Act 2006, as amended by the Protection of Freedoms Act 2012, did the criminal record disclosure confirm a satisfactory check against the appropriate ISA barred list(s)			Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>
Checked Electronic Staff Record: Yes <input type="checkbox"/> No <input type="checkbox"/> N/A <input type="checkbox"/>			
Signed:			Date:
Name:			
NHS organisation name and contact details:			
Date honorary research contract/letter of access issued (<i>delete as appropriate</i>)			

Passport Appendix. List of projects and amendments

Appendix Number:

If you are applying for a three-year Research Passport, please use this section to enter details of projects and activities that will be covered by this Research Passport. Once you have a validated Research Passport, you may add details of subsequent projects during the three years that this Research Passport is valid.

If you are applying for a project-specific Research Passport, but need to add further sites to the project, please enter the details below.

Whenever you add further details, the full Research Passport and accompanying documents must be submitted to the relevant NHS organisations.

Title:		Start Date:	End Date:
NHS organisation(s):	Dept(s):	Proposed research activities:	Manager in NHS organisation:

Amendments to the Research Passport

Please state what these are, e.g. they might be a change in name or employment details, or a change in research activities.

Please check with the NHS organisation where you are undertaking your research if you are unsure whether you will need to submit new evidence of pre-engagement checks on a new Research Passport form, which will need to be validated by the NHS organisation(s) hosting your research.

Date	Old Details	New Details	Office use only NHS R&D contact details and signature

To add more projects please copy this page or download further blank pages. Each appendix page should be numbered.

*For office use only:
A photocopy of the appendix should be retained whenever any amendments or additions to the appendix are made.*

24. APPENDIX 13 - STUDY 2 RESEARCH GOVERNANCE

LETTER OF ASSURANCE



Cambridgeshire and Peterborough
Clinical Commissioning Group

Ref: L01445

Miss Sharifa Hirani
University of Hertfordshire
College Lane
Hatfield
AL10 9AB

Hosted by NHS Cambridgeshire and Peterborough CCG
RMG office,
Lockton house, Clarendon Road,
Cambridge
CB2 8FH
Tel: 01223 725466
Fax: 01223 725401
E-mail: v.shaw@nhs.net
www.camstrad.nhs.uk

29th April 2015

Dear Miss Hirani

Re: L01445 A retrospective review of anonymised clinical records to investigate whether risk factors for primary open angle glaucoma are present many years before glaucoma develops

REC Number: 15/NS/0032

Chief Investigator: Miss Sharifa Hirani

Sponsor: South Bank University

Primary care Localities / Practices: Optometry practices in Cambs, Bedfordshire, East & North Herts and North East Essex

Thank you for submitting your application for the above study, your application has been reviewed by the Research Management Governance team based in Cambridge. We provide assurance to primary care providers¹ in CRN Eastern that research proposals meet nationally agreed research governance criteria to assist primary care providers in deciding whether to take part in a research study.

This assurance letter confirms that the Research Management Team has reviewed your submission in accordance with Department of Health Research Governance Framework for Health and Social Care for the above practices/localities and that your submission has satisfied the governance criteria

Please note that a copy of this letter together with governance checks must be provided to Primary Care Providers. This letter does not place any obligations on them to participate in this study. You must obtain confirmation from each provider of their willingness to take part in the study.

Community optometry practices responsibilities:

Community optometry practices will be consented to collate and provide anonymised clinical records for patients at least 10 years prior to the date of diagnosis of glaucoma. The optometry practices will collate and provide anonymised clinical records for a control group. This control group will be

¹ Primary care providers include GP practices, Pharmacists, Dentist and Opticians

L01445

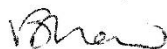
individually matched for, in addition to optometric practice, age, race, gender, and approximate refractive error with the glaucoma group but will not have received a diagnosis of glaucoma or have a family history of glaucoma.

General conditions follow:

- The project must follow the agreed protocol and be conducted in accordance with practice policies and procedures in relation to data protection, health and safety and information governance standards.
- Please let us know of any deviations from the protocol or protocol breaches including any urgent safety measures taken in order to protect research participants against any immediate hazard to their health or safety.
- Please ensure that any amendments are submitted to the research ethics committee and the Research Management Team for review as appropriate.
- Members of the research team must where instructed, have appropriate substantive or honorary research contracts or letters of access for research access in Primary care prior to commencing work on the study. Additional researchers joining the study must also hold a suitable contract or letter of access.
- You are required to notify us, the sponsor and the chief investigator of any serious adverse events relevant to the conduct of research and of all incidents or complaints occurring during the research within CRN Eastern.
- You are also required to notify us of the study conclusion and/or termination of the study.
- Primary care providers are expected to follow guidance issued by their relevant professional bodies in relation to research².

May I take this opportunity to wish you well with your research and we look forward to hearing the outcomes for the study. Please note, the reference number for this study is **L01445** and this should be quoted on all correspondence.

Yours sincerely



Vivienne Shaw
Research Governance Manager


cc: Professor Nicola Crichton
Professor Bruce Evans
Professor David Edgar
Professor Peter Allen

² E.g GMC Guidance on research - http://www.gmc-uk.org/guidance/ethical_guidance/research.asp

L01445

25. APPENDIX 14 - STUDY 2 RESEARCH GOVERNANCE

LETTER OF ACCESS

 Cambridgeshire and Peterborough Clinical Commissioning Group	
35 Waterford Green Welwyn Garden City Hertfordshire AL7 2LE	Hosted by NHS Cambridgeshire and Peterborough CCG Lockton house, Clarendon Road, Cambridge CB2 8FH Tel: 01223 725466 Fax: 01223 725401 E-mail: v.shaw@nhs.net www.camstrad.nhs.uk
RMG office, Hosted by NHS Cambridgeshire and Peterborough CCG Lockton house, Clarendon Road, Cambridge CB2 8FH Tel: 01223 725466 Fax: 01223 725401 E-mail: v.shaw@nhs.net www.camstrad.nhs.uk	
29 th April 2015	

Dear Sharifa Hirani,

Letter of access for research: Project-specific (L01145)- LCS12 VS Nexplanon

This letter confirms that the necessary pre-engagement checks have been undertaken in line with the 'Research in the NHS: HR Good Practice resource Pack'. Please provide this letter as evidence to **participating Optometry Community practices in Cambridgeshire, East North Herts and North East Essex** that these checks have been carried out in order for them to grant access to their site for research purposes.

This letter sets out the terms & conditions for access to primary care sites. Access is conditional upon the research study receiving, in writing, a letter of assurance from Cambridgeshire and East North Herts Research Office and **where NHS permission has been granted for this research by individual practices**. Please note that you cannot start the research until the Principal Investigator for the research project has received the letter of assurance and permission from each participating practice to conduct the project. In line with the 'Research in the NHS: HR Good Practice resource Pack', access rights will end on **31st December 2015** unless terminated earlier in accordance with the clauses below.

The information supplied about your role in research has been reviewed and you do not require an honorary research contract at Optometry Community practices in Cambridgeshire and East North Herts. We are satisfied that such pre-engagement checks as we consider necessary have been carried out.

You are considered to be a legal visitor to Optometry Community practices in Cambridgeshire and East North Herts who have given permission for the study. You are not entitled to any form of payment or access to other benefits provided by these practices to employees and this letter does not give rise to any other relationship between you and these practices, in particular that of an employee.

While undertaking research through Optometry Community practices in Cambridgeshire and East North Herts, you will remain accountable to your employer, **London South Bank University**, but you are required to follow the reasonable instructions of **the practice manager of each participating practice** or those given on her/his behalf in relation to the terms of this right of access.

Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by the Optometry Community practice or the Cambridgeshire and East North Herts Research Office in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

You must act in accordance with participating practices policies and procedures, which are available to you upon request, and the Research Governance Framework.

You are required to co-operate with each participating practice in discharging its duties under the Health and Safety at Work etc Act 1974 and other health and safety legislation and to take reasonable care for the health and safety of yourself and others while on practice premises. You must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of any other contract holder and you must act appropriately, responsibly and professionally at all times.

If you have a physical or mental health condition or disability which may affect your research role and which might require special adjustments to your role, if you have not already done so, you must notify your employer and each participating practice (please inform your nominated manager as named above) prior to commencing your research role at the practice.

You are required to ensure that all information regarding patients or staff remains secure and *strictly confidential* at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice (<http://www.dh.gov.uk/assetRoot/04/06/92/54/04069254.pdf>) and the Data Protection Act 1998. Furthermore you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.

You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on the premises you wear your ID badge at all times, or are able to prove your identity if challenged. Please note that participating practices accept no responsibility for damage to or loss of personal property.

We may terminate your right to attend at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we reasonably consider to amount to serious misconduct or to be disruptive and/or prejudicial to the interests and/or business of participating practices or if you are convicted of any criminal offence. You must not undertake regulated activity if you are barred from such work. If you are barred from working with adults or children this letter of access is immediately terminated. Your employer will immediately withdraw you from undertaking this or any other regulated activity and you **MUST** stop undertaking any regulated activity immediately.

Your substantive employer is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you.

Practices will not indemnify you against any liability incurred as a result of any breach of confidentiality or breach of the Data Protection Act 1998. Any breach of the Data

26. APPENDIX 15 - STUDY 2 LONDON SOUTH BANK UNIVERSITY RESEARCH ETHICS APPROVAL

**London South Bank
University**

Direct line: 020-7815 6025
E-mail: mitchen5@lsbu.ac.uk
Ref: UREC 1523

Sharifa Hirani
University of Hertfordshire
2 F412 College Lane
College Lane
Hatfield
AL10 9AB

Tuesday 9 June 2015

Dear Sharifa

RE: A retrospective review of anonymised clinical records to investigate whether risk factors for primary open angle glaucoma are present many years before glaucoma develops.

Thank you for submitting this proposal and for your response to the reviewers' comments.

I am pleased to inform you that Full Chair's Approval has been given by Vice Chair on behalf of the University Research Ethics Committee.

I wish you every success with your research.

Yours sincerely,



Nicola Mitchell
Secretary, LSBU Research Ethics Committee

cc:

Prof Shushma Patel, Chair, LSBU Research Ethics Committee

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