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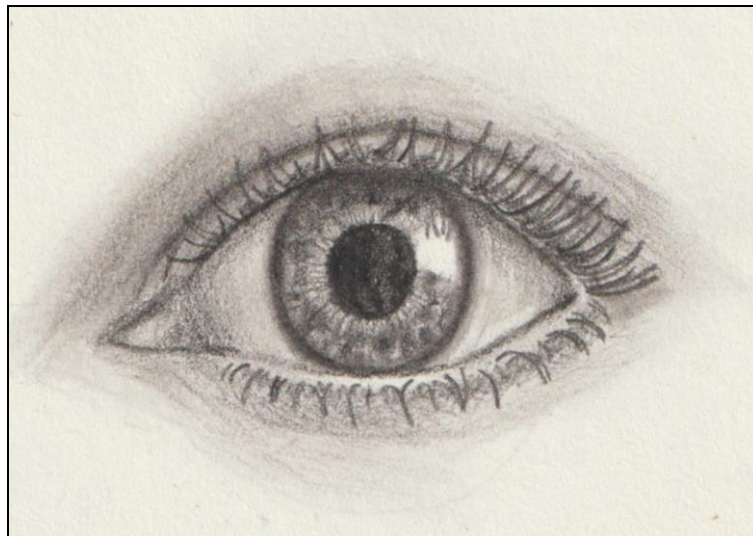
# DISTRIBUTION OF INTRAOCULAR PRESSURE IN A SWEDISH POPULATION

**The Tierp Glaucoma Survey**

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**Title: Distribution of Intraocular Pressure in a Swedish Population**

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## Populärvetenskaplig sammanfattning

### Bakgrund

Glaukom (grön starr) är en fortskridande ögonsjukdom, som kännetecknas av skador i synnervshuvudet och bortfall i synfältet. Globalt är glaukom en ledande orsak till bestående blindhet, och det uppskattas att sjukdomsördan kommer att öka i framtiden. Än idag är reglering av ögontrycket det enda sättet vi kan hindra och påverka sjukdomsförloppet, vilket har lett till ett stort intresse för att dels förstå hur fördelningen av ögontrycket ser ut, dels hitta vilka faktorer som reglerar ögontrycket.

### Syfte

Det huvudsakliga syftet med den här studien är att beskriva hur fördelningen av ögontrycket såg ut hos de personer mellan 65–74 år som deltog i The Tierp Glaucoma Survey. Dessutom vill vi undersöka vilka sjukdomstillstånd och egenskaper hos en individ som hade samband med ett förhöjt ögontryck. Denna studie är den första av sitt slag i Sverige i en befolkning med hög förekomst av pseudoexfoliationer (utfällning av äggviteämnen i främre ögonsegmentet).

### Metod

The Tierp Glaucoma Survey var en befolkningsbaserad undersökning som genomfördes i Tierps kommun i mellersta Sverige, mellan 1984–1986. Dess huvudsakliga syfte var att uppskatta hur stor andel av befolkningen som drabbas av glaukom i åldersgruppen 65–74 år. Den slutliga studiebefolkningen innefattade 733 individer, som fick genomgå en ögonundersökning och svara på frågor angående deras hälsotillstånd. Hos personer i åldern 65–69 år avgjorde slumpen vilket öga som skulle genomgå tryckmätning först. För att kunna dra slutsatser från urvalet, gjordes olika statistiska analyser.

### Resultat

Medelögontrycket i de ögon som hade högst ögontryck var 16,9 mm Hg. Det fanns små skillnader mellan män och kvinnor. I statistiska analyser hittades ett starkt samband mellan förhöjt ögontryck och öppenvinkelglaukom (en typ av grön starr) eller pseudoexfoliationer. Ett samband kunde också fastställas mellan förhöjt ögontryck och diabetes mellitus. Det hittades inget statistiskt säkerställt samband mellan förhöjt ögontryck och ålder, kön eller rökning. Medelögontrycket var högre i det öga som mättes först.

**Slutsatser**

Fördelningen av ögontrycket i den här studien liknar mycket de som tidigare har redovisats i studier med samma åldersspann hos befolkningar av europeiskt ursprung. Ett starkt samband kunde fastställas mellan förhöjt ögontryck och obehandlat öppenvinkelglaukom eller pseudoexfoliationer. Trycket var högre i det öga som mättes först jämfört med det andra ögat.

**Abstract****Purpose**

To study the distribution of intraocular pressure (IOP) in participants 65–74 years of age participating in the Tierp Glaucoma Survey and to estimate predictors of IOP  $\geq 20$  mmHg.

**Methods**

A population-based survey was carried out in Tierp, Sweden between 1984–1986. The study population consisted of 733 individuals aged 65–74 years. The distribution of IOP was illustrated with descriptive statistics. Predictors for IOP  $\geq 20$  mmHg were analysed with stratified analysis and logistic regression models. Covariation of the mean IOP in right and left eyes was assessed with repeated measures analysis of variance.

**Results**

The mean pressure in the eye with the highest IOP was 16.9 mm Hg (95% confidence interval [CI] 16.7–17.2) and the median IOP was 17 mm Hg (interquartile range 15–19 mm Hg). The difference between women and men was small. A strong correlation was found between IOP  $\geq 20$  mm Hg and open-angle glaucoma (odds ratio [OR] 9.11; 95% CI 3.75–22.1) or pseudoexfoliation (OR 2.55; CI 1.59–4.09). An association with diabetes (OR 1.74; 95% CI 1.00–3.03) was recognised. No significant association was found with age, sex, or smoking. The mean pressure was higher in the eye randomly selected to be measured first.

**Conclusions**

The distribution of IOP in this study was close to the values presented in the Framingham and Beaver Dam studies. An IOP  $\geq 20$  mm Hg correlated strongly with untreated open-angle glaucoma and pseudoexfoliation. The pressure in the first measured eye was higher compared with the second eye.

## Background

### Intraocular pressure

In the anterior part of the eye, aqueous humour is produced by the ciliary body, which together with the iris and the choroid forms the uveal layer of the eye. Aqueous humour consists of proteins, cells, and other macromolecules. The inflow of this clear ultrafiltrate happens through the ciliary body to the posterior chamber of the eye. Aqueous humour continues to the anterior chamber and leaves it either through the trabecular meshwork or the uveoscleral route. Aqueous humour is essential for the maintenance and regulation of intraocular pressure (IOP) (Goel *et al.*, 2010). Other functions of aqueous humour include supplying nutrients and oxygen to the anterior parts of the eye, as well as the removal of waste and inflammatory products (*Adler's Physiology of the Eye - 11th Edition*).

When IOP is at a suitable level, it maintains the shape of the eyeball together with the vitreous body. An increased IOP can cause damage to the optical nerve and retinal ganglion cells (Kim and Park, 2019). Intraocular pressure can be calculated by using the Goldmann equation

$$IOP = (F/C) + P$$

where F is aqueous flow rate, C is aqueous outflow and P is the episcleral venous pressure. A change in one of these variables will affect the IOP (Machiele, Motlagh and Patel, 2022).

### Intraocular pressure and glaucoma

Globally, glaucoma is the leading cause of irreversible loss of sight, and it is estimated that in 2040, the number of people suffering from glaucoma will be 111.8 million. The burden of glaucoma is unequally distributed, as the highest rates of open-angle glaucoma (OAG) are found in Africa (4.20%: 95% CI, 2.08-7.35) and angle-closure glaucoma (ACG) in Asia (1.09%; 95% CI, 0.43-2.32) (Tham *et al.*, 2014).

In glaucoma, the retinal ganglion cells degenerate in a progressive manner, leading to so called “cupping” of the optic nerve head and formation of scotomas in the visual field (Nickells *et al.*, 2012). When taking into account the physiology of the eye, glaucoma can be divided into two different types: OAG, in which the drainage angle between the cornea and the iris is open, and ACG, in which the drainage angle between cornea and iris is blocked (Jonas *et al.*, 2017). In adults, OAG is often asymptomatic and in several studies of Western derived populations, around 50% of the participants were first diagnosed during the study (Ekström, 1996; Mitchell *et al.*, 1996; Wensor *et al.*, 1998; Topouzis *et al.*, 2007).

Glaucoma can also be caused by other conditions affecting the eye, such as uveitis or trauma. This type of glaucoma is called secondary glaucoma (Jonas *et al.*, 2017). Although glaucoma is often thought as a disease of the elderly population, it can also affect infants in form of congenital glaucoma. To ensure these children a life with good vision, early detection is essential. The prevalence of congenital glaucoma is dependent on consanguinity and thus varies globally (Ko, Papadopoulos and Khaw, 2015).

Intraocular pressure is the only known modifiable factor to prevent and affect the course of glaucoma, and all the existing interventions for glaucoma aim to lower IOP (Weinreb, Aung and Medeiros, 2014). The relationship between IOP and glaucoma is to this day still not fully understood, but there are several theories that have tried to explain it. The biomechanical theory attributes the relationship between IOP and glaucoma to mechanical processes that damage the optic nerve head (Stowell *et al.*, 2017). The vascular theory, in turn, suggests that increased IOP disturbs the blood supply of the optic nerve head, which leads to ischemia and cell death in the tissue (Flammer *et al.*, 2002).

The relationship between IOP and glaucoma is further complicated by the fact that glaucoma is not always associated with increased IOP. This type of glaucoma is referred to as normal tension glaucoma. Similar to OAG and ACG, the exact mechanism behind this condition is not yet fully understood, even though several theories exist (Killer and Pircher, 2018). Nevertheless, topical ocular hypotensive medication has been shown to be effective both to prevent and delay the onset of OAG in patients with increased IOP. The medication has also been reported to effectively hinder the progression of OAG both in patients with and without increased IOP at baseline (Heijl *et al.*, 2002; Kass *et al.*, 2002).

### **Factors associated with increased intraocular pressure**

Several studies have investigated factors affecting IOP. So far the different factors evaluated have been found to account for only about 6–10% of the variation in IOP (R. Hiller, Sperduto and Krueger, 1982; Leske and Podgor, 1983; Klein, Klein and Linton, 1992). The division between heritability and environmental factors affecting IOP have in twin-studies been approximately 60 and 40 percent, respectively (Pärssinen *et al.*, 2007; Carbonaro *et al.*, 2008).

The presence of OAG has consistently been shown to be correlated with increased IOP (Sommer *et al.*, 1991; Klein, Klein and Linton, 1992; Mitchell *et al.*, 1996; Wensor *et al.*, 1998; Ramakrishnan *et al.*, 2003; Vijaya *et al.*, 2005; Topouzis *et al.*, 2007). Correlation between increased IOP and family history of glaucoma has also been examined, although no significant correlation could be found (Memarzadeh *et al.*, 2008). However, in a another study based on the

same population with Latino background, IOP variation was seen to be an independent risk factor for OAG (Jiang *et al.*, 2018).

One of the factors most strongly correlated with IOP is elevated blood pressure. This has been confirmed in numerous studies (Bengtsson, 1972; Klein, Klein and Linton, 1992; Foster *et al.*, 2003, 2011; Wu *et al.*, 2006; Kawase *et al.*, 2008; Memarzadeh *et al.*, 2008; Tomoyose *et al.*, 2010; Jonas *et al.*, 2011; Zhou *et al.*, 2012; Chan *et al.*, 2016; Wang, Tao and Yao, 2019) with few studies contradicting the hypothesis (Vijaya *et al.*, 2005). The relationship between IOP and blood pressure (especially systolic blood pressure) has been suggested to be explained by the increased filtration of aqueous humour to the posterior chamber due to the increased perfusion pressure in the ciliary arteries (Bulpitt, Hodes and Everitt, 1975).

The presence of diabetes, reported history of diabetes and self-reported diabetes have been identified as positive correlates for a higher IOP in several studies (Klein, Klein and Linton, 1992; Tielsch *et al.*, 1995; Kawase *et al.*, 2008; Memarzadeh *et al.*, 2008; Tomoyose *et al.*, 2010; Zhou *et al.*, 2012). In the nine-year follow up of the population of the Barbados Eye Studies, a bigger change in IOP was reported in individuals with a history of diabetes (Wu *et al.*, 2006). However, in the Central India Eye and Medical Study, no association between increased IOP and diabetes was found (Jonas *et al.*, 2011). None of the studies found in the literature search showed a significant association between cardiovascular disease and IOP (Leske and Podgor, 1983; Klein, Klein and Linton, 1992; Weih *et al.*, 2001; Memarzadeh *et al.*, 2008).

Another commonly examined risk factor is age, and many studies have shown an increase in IOP with age (Hollows and Graham, 1966; Klein, Klein and Linton, 1992; Leske *et al.*, 1994; Bonomi *et al.*, 1998; Memarzadeh *et al.*, 2008), whereas others have reported a decrease in IOP with age (mainly in Japanese populations) (Kawase *et al.*, 2008; Tomoyose *et al.*, 2010) or no significant effect (Bengtsson, 1972; Leibowitz *et al.*, 1980; Mitchell *et al.*, 1996; Wensor *et al.*, 1998; Wu *et al.*, 2006; Foster *et al.*, 2011; Jonas *et al.*, 2011; Wang *et al.*, 2011; Zhou *et al.*, 2012). These differences in findings have been speculated to depend on factors such as ethnicity, cardiovascular risk variables and selective mortality in the oldest age groups. Both in the Blue Mountains Eye Study and the Beaver Dam Eye Study, adjusting for potential confounders in a multivariate analysis made IOP no longer significantly associated with age (Klein, Klein and Linton, 1992; Rochtchina, Mitchell and Wang, 2002).

The correlation between the sex of the participants and their IOP has also varied between studies. Several of them have presented minimal difference, no difference or no statistically significant difference between women and men (Leibowitz *et al.*, 1980; Klein, Klein and Linton, 1992; Mitchell *et al.*, 1996; Foster *et al.*, 2003; Vijaya *et al.*, 2005; Kawase *et al.*, 2008;

Tomoyose *et al.*, 2010; Jonas *et al.*, 2011), whereas some of them have shown a higher IOP in women compared to men (Hollows and Graham, 1966; Bengtsson, 1972; Memarzadeh *et al.*, 2008; Zhou *et al.*, 2012) and vice versa (Bonomi *et al.*, 1998; Wu *et al.*, 2006; Chan *et al.*, 2016). The authors of the nine-year follow up study done on the population of the Barbados Eye Studies suggested that the correlation between male sex and long-term IOP changes could be explained by the higher likelihood of glaucoma in men than in women (Wu *et al.*, 2006), whereas the higher IOP in women in The Los Angeles Latino Eye Study was suggested to depend on a female tendency for increased IOP with age, higher levels of obesity and hypertension and longer life expectancy (Memarzadeh *et al.*, 2008). Of note, none of the above-mentioned studies have argued that the findings necessarily have a clinical significance, despite of the statistical significance found.

In smokers, current smoking has been identified to be related to IOP in at least two studies (Wu and Leske, 1997; Lee *et al.*, 2003), but many others have contradicted these findings both in current smokers and those with a history of smoking (Klein, Klein and Linton, 1992; Weih *et al.*, 2001; Foster *et al.*, 2003, 2011; Kawase *et al.*, 2008; Jonas *et al.*, 2011).

In patients with pseudoexfoliation (PEX), fibrillar extracellular material is produced and progressively accumulated in ocular tissue. The process is age-related and can cause OAG and cataract (Ritch and Schlötzer-Schrehardt, 2001). In addition to its ocular effects, PEX has also been suggested to increase the risk for cardiovascular and cerebrovascular morbidity (Schlötzer-Schrehardt and Naumann, 2006). The genetic background of PEX lies in single-nucleotide polymorphisms in exon 1 of the gene LOXL1. Elastin fibres that play an important role in PEX are modified by the product of the LOXL1 gene (Thorleifsson *et al.*, 2007). In the Reykjavik Eye Study, a statistically significantly higher IOP was reported in eyes affected by PEX compared to the contralateral unaffected eye (Arnarsson *et al.*, 2009). Findings pointing in the same direction have been reported in other studies with varying designs (Rita Hiller, Sperduto and Krueger, 1982; Klemetti, 1988; Davanger, Ringvold and Blika, 1991; Kozobolis *et al.*, 1997; Åström and Lindén, 2007). The Blue Mountains Eye Study found a higher IOP in eyes with PEX compared to eyes without, but couldn't show a statistic significance for the finding (Mitchell, Wang and Hourihan, 1999).

In addition to factors discussed above, seasonal variations, pulse rate, alcohol use and different socioeconomic factors have been evaluated in order to determine the factors associated with IOP (Klein, Klein and Linton, 1992; Yip *et al.*, 2007; Chan *et al.*, 2016).



### Previous studies on intraocular pressure

Several population-based studies have investigated the distribution of IOP amongst different ethnicities. One of the earliest studies based on a European population, conducted in Ferndale in Wales, presented a mean IOP ( $\pm$ standard deviation, SD) measured with applanation tonometry to be  $15.9 \pm 3.04$  mm Hg and  $16.6 \pm 2.97$  mm Hg for men and women, respectively (Hollows and Graham, 1966). In the Framingham Eye Study, the reported mean IOP was 16.5 mm Hg and in the Beaver Dam Eye Study, the mean IOP was  $15.3 \pm 3.4$  mm Hg for men and  $15.5 \pm 3.3$  mm Hg for women. The Framingham Eye Study found the mode IOP to lie between 16–18 mm Hg for both men and women, whereas the Beaver Dam Eye Study found the mode to lie between 16–18 mm Hg for women and 13–15 mm Hg for men (Leibowitz *et al.*, 1980; Klein, Klein and Linton, 1992). The distribution of IOP in these studies amongst persons aged 65–74 is presented in **Table 1**.

Similar results have been demonstrated in the Blue Mountains Eye Study (Mitchell *et al.*, 1996), the Egna-Neumarkt study (Bonomi *et al.*, 1998), the Melbourne Visual Impairment Project (Wensor *et al.*, 1998), the Thessaloniki Eye Study (Topouzis *et al.*, 2007) and the EPIC-Norfolk Eye Study (Foster *et al.*, 2011). In these studies, the populations examined have been mainly or completely of European descent.

The distribution of IOP has also been studied in non-European-derived and mixed populations. These studies have presented lower, equal, and higher IOP values compared to the white European-derived populations. In the studies examining populations of African descent, the mean IOP has tended to be similar or somewhat higher compared to the white populations. Examples include the Baltimore Eye Survey with the mean IOP of 16 mm Hg (Sommer *et al.*, 1991) and the Barbados Eye Study with the mean IOP of 17 mm Hg (Leske *et al.*, 1994). For Latinos in the Los Angeles Latino Eye Study, the mean IOP was 14.4 mm Hg (Jiang *et al.*, 2018).

In the studies performed on Indian populations, the mean IOP has generally been around 14 mm Hg, as shown in the Central India Eye and Medical study, the Aravind Comprehensive Eye Survey and a study conducted in Rural South India (Ramakrishnan *et al.*, 2003; Vijaya *et al.*, 2005; Jonas *et al.*, 2011). In Chinese and Japanese populations, the mean IOP has varied around 15 mm Hg. The studies that have investigated these populations include the Tanjong Pagar Study, the Tajimi Study, the Kumejima Study, the Liwan Eye Study and the Handan Eye Study (Foster *et al.*, 2003; Kawase *et al.*, 2008; Tomoyose *et al.*, 2010; Wang *et al.*, 2011; Zhou *et al.*, 2012).

A longitudinal study done in Skellefteå, northern Sweden, demonstrated a mean IOP of 15.3 mm Hg and 16.3 mm Hg for men and women, respectively at baseline when the subjects were 66

years old. Seven years later in 1988, the approximately same cohort presented similar results among the participants, now 73 years old (Åström, Stenlund and Lindén, 2014).

To the best of our knowledge, only two studies with a similar design to ours have been done with the aim to observe the distribution of IOP in Sweden. The first one, a population-based study conducted in Dalby, southern Sweden, presented the mean IOP of the right eye to be 15.4 mm Hg for the age group 60–69 years and 15.9 mm Hg for the age group 70–79 years (Bengtsson, 1972). A later study focusing on findings associated with glaucomatous visual field defects presented a more dispersed and higher IOP in eyes with enlarged cups compared to those with non-enlarged cups. The distribution of IOP in this study was slightly skewed to the right, and the mean IOP for the eyes without manifest glaucoma was 15.5 mm Hg in 55–69-year-olds (Bengtsson, 1980).

When taking into consideration the results presented above, the distribution of IOP in a cross-sectional population-based setting is not yet adequately studied in Sweden. In addition, to the best of our knowledge, the current study is the first one to investigate the distribution of IOP in a population with a high prevalence of PEX (16%) in Sweden.

**Table 1.** Percent distribution of intraocular pressure in right eyes in individuals aged 65–74 years in the Framingham Eye Study and the Beaver Dam Eye Study by sex.

Study	Sex	IOP (mm Hg)						Mean
		<13	13–15	16–18	19–21	22–24	≥25	
Framingham <sup>1</sup>	Females	10.5	25.4	35.8	19.7	5.0	3.6	17.0 <sup>3</sup>
	Males	13.4	25.3	34.3	17.4	4.7	4.9	16.7 <sup>3</sup>
Beaver Dam <sup>2</sup>	Females	13.8	30.9	36.4	13.4	4.2	1.2	16.0
	Males	18.3	34.0	31.2	10.9	5.1	0.6	15.5

IOP = Intraocular pressure.

<sup>1</sup> Leibowitz et al. 1980.

<sup>2</sup> Klein BEK et al. 1992; the age groups 65–69 years and 70–74 years are combined.

<sup>3</sup> The mean relates to both eyes.

## **Aims**

The aim of this study is to determine the distribution of IOP in subjects 65–74 years of age participating in the Tierp Glaucoma Survey. In addition, the study aspires to establish or negate the possible correlations between IOP and a number of potentially associated factors.

## **Materials and Methods**

### **Population**

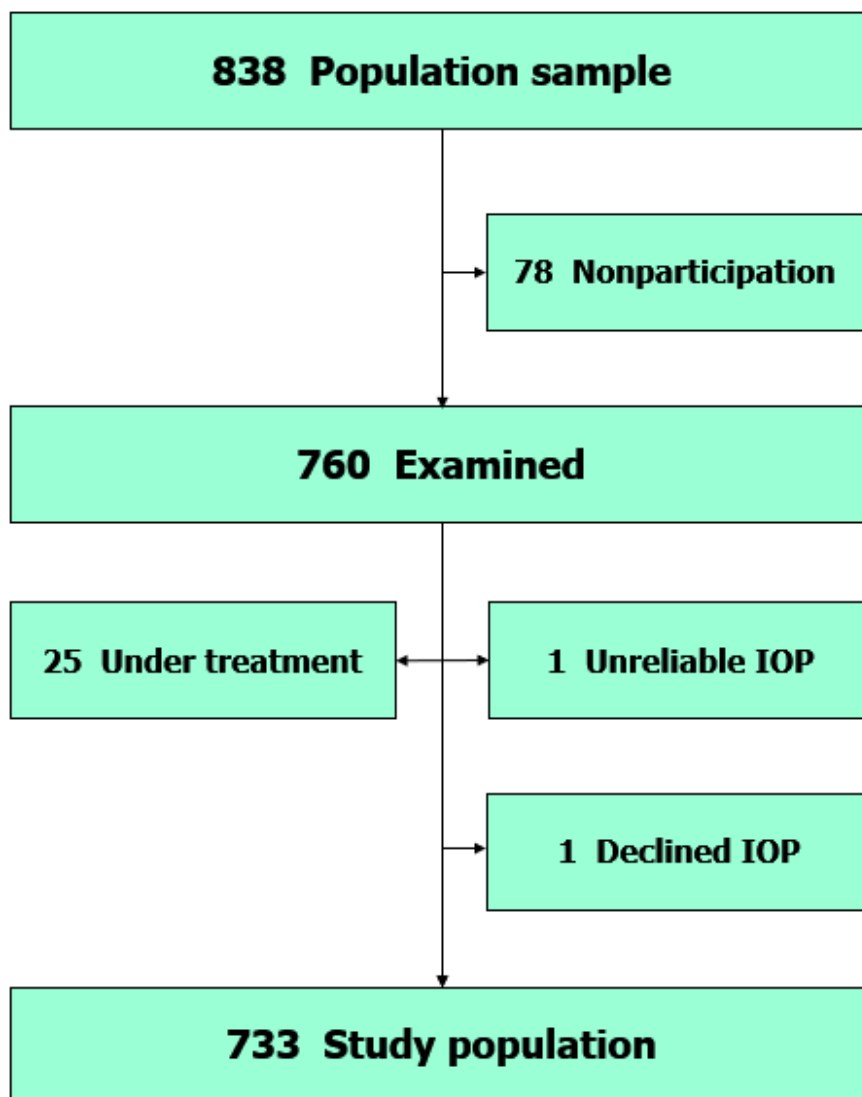
This is a cross-sectional, population-based study on the distribution of IOP in the population of Tierp, south central Sweden. The original goal of the Tierp Glaucoma Survey was to record the prevalence of OAG in the age group 65–74 years in the municipality of Tierp. In the beginning of the study in 1984, Tierp had 20 078 inhabitants, of which 2 377 were in the age group 65 to 74 years, according to official Swedish Statistics for the year in question.

The Department of Social Medicine, at the Uppsala University, provided two lists: one with eligible residents born between 1910 and 1914 and another with the subjects born between 1916 and 1920. For practical reasons, the sample size was limited to about one-third of the target population. As a method of systematic sampling, in both lists, the residents' dates of birth were to be divisible by three. These two lists were based on the population register and included names, addresses and personal code numbers. The lists in question were updated twice. The eligible residents were invited by letter to participate.

The screening examinations took place from March 1984 to March 1986 and were thus completed in approximately 2 years. In the first phase in 1984–1985, participants born in 1910 to 1914 were invited. The appointments were scheduled so that the participants had already had their birthdays to guarantee that all of them were 70–74 years of age at the time of the appointment. Ten residents who died in 1984 were excluded from the study and three residents who moved to Tierp were examined in 1985. The final group of participants in the age group 70–74 years comprised 399 individuals registered in Tierp on December 31, 1984.

In the next phase between 1985 and 1986, a total of 449 residents born in 1916–1920 were invited. Those invited were 65–69 years of age in 1985. In this age group, thirteen residents died or moved out of the area and three persons moved to Tierp. This resulted in the 65–69-year age group comprising 439 persons registered in Tierp on December 31, 1985. In total, 838 individuals aged between 65–74 years were involved in the study, of which 760 (90.7%) were examined.

To determine a sample suitable to answer how IOP is distributed in the general population, further exclusions were made. Twenty-five participants were treated for glaucoma and were thus excluded. In one individual, the measurement of IOP was unreliable despite several attempts. One woman declined IOP measurement. Both participants were excluded, which results in the study population of 733 persons. A flow chart showing how the study population was derived is presented in **Figure 1**.



**Figure 1.** Flow chart showing how the study population of 733 individuals was derived. IOP = intraocular pressure.

### Screening examinations

The eligible residents were examined at the Eye Clinic in Tierp, where a detailed ophthalmological examination was carried out. All the examinations were performed by the same ophthalmologist, except for IOP measurement and automated perimetry, where the measurements were taken by an assistant. Before any eye examination was made, the participants were interviewed regarding their medical history, eye symptoms, family history of glaucoma, current medication, and use of eye health care services.

First, a drop of Fluress (oxybuprocain chloride 4 mg/ml, fluorescein sodium 2,5 mg/ml) was instilled in both eyes. The IOP was then taken by using a Goldmann applanation tonometer mounted on a Haag-Streit slitlamp. In participants who were 65–69 years old, the eye measured first was randomly selected, whereas in those who were 70 years or older, the right eye was always measured first. The tonometer was set to 10 mm Hg before measurement, and after the measurement, the value was read first after the assistant had removed the tonometer away from the eye. In a situation where the readings from both eyes differed by more than 2 mm Hg, a control pressure was taken to minimise the effect of non-perfect patient cooperation, as described by Bengtsson (Bengtsson, 1972). When this event occurred, the control measurement was defined as the IOP for that person.

The visual fields of each participant were examined with the Competer 350 computerised automatic perimeter (Bara Elektronik AB, Lund, Sweden). The sensitivity of 68 locations in the central 20 degrees were measured using a supraliminal threshold-related test logic (Anderson, Drance and Grune & Stratton, 1985). The tests that were regarded as abnormal or unreliable were repeated. If the blind spot could not be identified, and the check light for the blind spot was seen in more than one-third of all exposures, the test was deemed as unreliable.

Next, both eyes were dilated with one drop of Mydriacyl (tropicamide 5mg/ml) and, if needed to achieve a pupil diameter of 3 mm or more, one drop of Neosynephrine (phenylephrine 100 mg/ml). The subjects' anterior eye segments were examined with the slit-lamp and any potential abnormalities and PEX were documented.

The Goldmann one-mirror contact lens was used to examine the optic discs. In order to make a drawing of the discs, a modified version of the scheme recommended by Shaffer was used (Shaffer *et al.*, 1975). The drawings were made based more on shape than colour. The cup diameter was determined from the point where the disc surface made its first definite transition posteriorly, and the margin of the disc was defined as the inner margin of the scleral ring. Further, the optic discs were graded into three categories: 1. non-glaucomatous discs, 2. glaucomatous

discs, not excavated to the disc margin and 3. glaucomatous discs, excavated to the disc margin at any part of the circumference.

To characterise the optic nerve heads with glaucoma, the criterion by Spaeth (Heilmann and Richardson, 1978) was used. The following four findings were considered to be clinical signs of optic nerve damage: marked asymmetry of the optic cup between the two eyes, excavation to the disc margin, localised notching, and pallor of the neutral rim.

Lastly, the width and pigmentation of the anterior chamber angle were graded by using the Scheie's classification (Scheie, 1957). Gonioscopy was done with the Goldmann one-mirror lens. Any potential abnormalities, PEX and vessels were documented.

### **Definitions**

In this study, chronic simple glaucoma and capsular glaucoma were classified as OAG. For a diagnose of definite OAG, a reproducible visual field defect on the Competer, not explainable by other factors, was required.

A participant was regarded to have diabetes mellitus if one of the following conditions was fulfilled: i) an ongoing treatment for diabetes mellitus; ii) a diagnosis of diabetes mellitus acquired from the medical records; iii) a diagnosis of diabetes mellitus added to the medical records within the two coming years from the baseline examination.

Information about ischemic heart disease (IHD) was collected from medical records. All diagnoses compatible with IHD under the last ten years were noted. Diagnoses made up to two years after the population survey were also registered. The following conditions were included in the term IHD: angina pectoris, myocardial infarction, and other types of ischemic heart disease. Self-declared angina pectoris and the use of treatment for angina pectoris were also accepted as IHD.

Ongoing medication for hypertension at the time of the survey or within two years from the baseline examination was recorded. Medical records were used to retrieve additional information when needed. Information about smoking was acquired from participants themselves, medical records, or their relatives. Participants' status as a current (those who were smoking at the baseline examination), or ex-smoker was also noted.

For a diagnosis of PEX, the anterior part of the lens and the edge of the pupil were observed, when dilated to at least 3 mm in width. For a cataract diagnosis, opacities of the lens were recorded with the pupil dilated to at least 3 mm in width. Persons with previous cataract surgery were also defined as having cataract. In the current study, the first stage of lens opacities, referred

to as ‘early senile changes’ in the Framingham Study, was not included in the definition of definite cataract.

### **Statistics**

The pressure distribution is presented in a table and a figure. Repeated measures analysis of variance was done to explore the covariation in IOP between right and left eye depending on which eye was measured first. Odds ratios for increased IOP, defined as a pressure  $\geq 20$  mm Hg in either eye, were estimated using 2 x 2 tables. Control for age and sex was performed according to Mantel–Haenszel. To simultaneously assess several predictors affecting the risk for increased IOP, multiple logistic analyses were employed with an IOP  $\geq 20$  mm Hg as the dependent variable.

### **Ethical Consideration**

The Human Subjects Committee at the Faculty of Medicine, University of Uppsala approved the study on May 11<sup>th</sup>, 1983. Informed consent was obtained from all participants. The tenets of the Declaration of Helsinki were respected.

## **Results**

### **Participation in the Tierp Glaucoma survey**

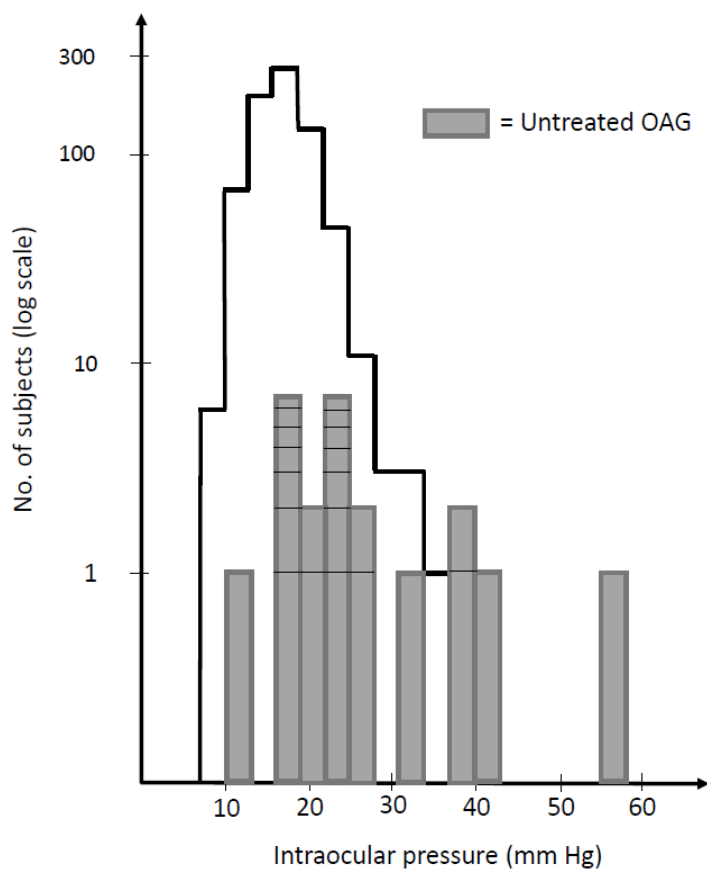
The participation of the survey population, divided by age and sex is presented in **Table 2**. A total of 838 persons participated in the study, of which 429 (51.2 %) were females and 409 (48.8%) males. The participation rate was highest in females aged 65–69 years (93.3 %) and lowest in males aged 70–74 years (87.1%). Overall, a higher participation rate was seen both in females and males in the age group 65–69 years compared to the age group 70–74 years.

### **Distribution of intraocular pressure**

The distribution of the highest untreated pressure in either eye is presented in **Figure 2**. The distribution was slightly skewed to the right, making the pressure non-normally distributed. In the eyes with untreated OAG, the dispersion of IOP was greater compared to those without the condition. The mean pressure in the eye with the highest IOP was 16.9 mm Hg (95% CI 16.7–17.2) and the median pressure 17 mm Hg with an interquartile range of 15–19 mm Hg.

**Table 2.** Participation in the Tierp Glaucoma Survey by age and sex.

	Females ( <i>n</i> = 429)		Males ( <i>n</i> = 409)		
	Examined		Examined		
Age	Yes (%)	No (%)	Yes (%)	No (%)	(%)
65–69 years	209 (93.3)	15 (6.7)	195 (90.7)	20 (9.3)	
70–74 years	187 (91.2)	18 (8.8)	169 (87.1)	25 (12.9)	
65–74 years	396 (92.3)	33 (7.7)	364 (89.0)	45 (11.0)	

**Figure 2.** Distribution of the highest pressure in either eye in the study population of 733 participants in the Tierp glaucoma survey. Twenty-seven individuals are excluded.



The percent distribution in right eyes and the mean IOP in the population is presented in **Table 3**. The mean IOP was 16.5 mm Hg for those aged 65–69, 16.0 mm Hg for those aged 70–74 and 16.3 mm Hg in total. Females had a higher mean IOP in all three groups compared to males. The mode IOP lied between 16–18 mm Hg in all but two groups, which were males aged 70–74 years and males aged 65–74 years. The mode IOP in these two groups lied between 13–15 mm Hg.

**Table 3.** Percent distribution of intraocular pressure in right eyes in 731 participants in the Tierp Glaucoma Survey by age and sex. <sup>1</sup>

Age (Years)	Sex	No.	IOP (mm Hg)						Mean
			<13	13–15	16–18	19–21	22–24	≥25	
65–69	F	202	9.4	29.2	34.7	21.8	3.0	2.0	16.6
65–69	M	187	12.3	32.6	33.2	12.8	6.4	2.7	16.4
65–69	Total	389	10.8	30.8	33.9	17.5	4.6	2.3	16.5
70–74	F	178	17.4	26.4	37.6	9.0	5.6	3.9	16.3
70–74	M	164	16.5	37.8	27.4	12.8	4.3	1.2	15.7
70–74	Total	342	17.0	31.9	32.7	10.8	5.0	2.6	16.0
65–74	F	380	13.2	27.9	36.1	15.8	4.2	2.9	16.5
65–74	M	351	14.2	35.0	30.5	12.8	5.4	2.0	16.1
65–74	Total	731	13.7	31.3	33.4	14.4	4.8	2.5	16.3

IOP = Intraocular pressure; F = females; M = males.

<sup>1</sup> Twenty-nine individuals are excluded from the analyses. The right eye was missing in two subjects.

**Table 4** Mean intraocular pressure in right and left eye in 389 participants 65–69 years of age in the Tierp Glaucoma Survey by the first measured eye. <sup>1</sup>

Eye	Right eye measured first		Left eye measured first	
	No.	IOP (95 % CI)	No.	IOP (95 % CI)
Right eye	200	16.7 (16.1–17.3)	189	16.3 (15.8–16.8)
Left eye	200	16.2 (15.7–16.7)	189	16.5 (16.0–17.0)

IOP = Intraocular pressure (mm Hg); CI = confidence interval.

<sup>1</sup> Fifteen individuals treated for glaucoma are excluded from the analyses.

### Covariation of intraocular pressure in right and left eyes

There were small differences between the mean IOP of the right and left eye. The mean IOP was higher in the right eye with one exception, namely when the pressure was measured first in the left eye (**Table 4**). The mean pressure was higher in the eye measured first. Analysis of variance revealed a significant interaction between measuring the right eye first and the left eye second, resulting in a greater pressure difference than expected.

### Factors associated with increased intraocular pressure

In the stratified analysis, after adjusting for age and gender according to Mantel–Haenszel, no statistically significant effect on the likelihood of having an IOP  $\geq 20$  mmHg was seen regarding age, male sex, hypertension or IHD. However, a strong correlation between OAG (OR 8.97) or PEX (OR 2.40) and an IOP  $\geq 20$  mmHg was seen. Diabetes mellitus (OR 1.83) was also correlated with IOP  $\geq 20$  mmHg. The results are presented in **Table 5**.

In the ultimate logistic regression model, the outcome variable used was IOP  $\geq 20$  mmHg in either eye and the predictors used were age  $\geq 70$  years, male sex, OAG, PEX, smoking status and diabetes mellitus. To acquire a stable model with enough participants for each predictor, IHD, hypertension and cataract were excluded. The results were in accordance with the results from the stratified analysis and are presented in **Table 6**. Intraocular pressure  $\geq 20$  mmHg was strongly

**Table 5.** Odds ratios for intraocular pressure  $\geq 20$  mm Hg in either eye in 733 participants in the Tierp Glaucoma Survey, adjusted for age and gender. <sup>1</sup>

Characteristics		No. of cases		
		( <i>n</i> = 129)	OR <sub>M-H</sub>	95% CI
Age $\geq 70$ years <sup>2</sup>	No	76	1.00	
	Yes	53	0.75	0.51–1.10
Male sex <sup>3</sup>	No	72	1.00	
	Yes	57	0.83	0.57–1.22
Open-angle glaucoma, either eye <sup>2</sup>	No	114	1.00	
	Yes	15	8.97	3.84–20.93
Pseudoexfoliation, either eye	No	93	1.00	
	Yes	36	2.40	1.53–3.76
Cataract, either eye	No	90	1.00	
	Yes	39	1.04	0.68–1.59
Smoking status	Never smoked	78	1.00	
	Past smoker	28	1.61	0.93–2.78
	Current smoker	23	1.43	0.82–2.49
Diabetes	No	106	1.00	
	Yes	23	1.83	1.08–3.09
Hypertension, treated	No	90	1.00	
	Yes	39	1.16	0.76–1.77
Ischaemic heart disease	No	107	1.00	
	Yes	22	1.32	0.79–2.22

CI = confidence interval; OR<sub>M-H</sub> = Mantel-Haenszel adjusted odds ratio

<sup>1</sup> Twenty-seven individuals are excluded from the analyses; <sup>2</sup> Adjusted for sex; <sup>3</sup> Adjusted for age

correlated with OAG (OR 9.11) and PEX (OR 2.55). Diabetes mellitus was also correlated to IOP (OR 1.74), though only when smoking status was included in the model. No significant association between IOP  $\geq 20$  mmHg and age  $\geq 70$  years, male sex or smoking status was seen.

**Table 6.** Logistic regression model assessing predictors for intraocular pressure  $\geq 20$  mmHg in either eye in 733 participants in the Tierp Glaucoma Survey. <sup>1</sup>

Covariate		No. of cases	
		( <i>n</i> = 129)	OR (95% CI)
Age $\geq 70$ years	No	76	1.00
	Yes	53	0.72 (0.48–1.08)
Male sex	No	72	1.00
	Yes	57	0.65 (0.41–1.02)
Open-angle glaucoma, either eye	No	114	1.00
	Yes	15	9.11 (3.75–22.1)
Pseudoexfoliation, either eye	No	93	1.00
	Yes	36	2.55 (1.59–4.09)
Smoking status	Never smoked	78	1.00
	Past smoker	28	1.61 (0.92–2.82)
	Current smoker	23	1.57 (0.88–2.78)
Diabetes	No	106	1.00
	Yes	23	1.74 (1.00–3.03)

OR = odds ratio; CI = confidence interval.

<sup>1</sup> Twenty-seven individuals are excluded from the analyses.

## Discussion

### Rate of participation

The population in this study was of white European origin, and therefore comparisons to studies of similar populations in community-based settings are appropriate. It is, however, important to keep in mind when making these comparisons that the age span chosen for the present study was narrower than in some other studies.

The overall participation rate in the study was 90.7%, which is in the upper range among other studies done on the subject (Sommer *et al.*, 1991; Klein, Klein and Linton, 1992; Topouzis *et al.*, 2007; Tomoyose *et al.*, 2010; Wang *et al.*, 2011). The participation rates among women and men were nearly equal, and there weren't any big differences between the age groups. The slightly lower participation rate for men in the older age group is in accordance with other studies.

### Distribution of intraocular pressure

The mean IOP in the eyes with the highest pressures in the current study was 16.9 mm Hg and the median IOP 17 mm Hg. The IOP was nearly normally distributed.

The percent distribution of IOP in right eyes showed a mean IOP of 16.3 mm Hg for the whole population. The difference between women and men were small. The distribution in the present study compares well to the ones presented in the Framingham Eye Study and the Beaver Dam Eye Study, as can be seen in Tables 1 and 3 (Leibowitz *et al.*, 1980; Klein, Klein and Linton, 1992). Considering that in the population of the Tierp Glaucoma Survey, PEX is a much more common finding than in the two studies mentioned above, one could expect a higher mean IOP. In comparison to the study on IOP distribution in Dalby, Sweden, the mean IOP in the current study is very much alike that of the age group 70–79 years old and somewhat higher compared to the age group 60–69 years old (Bengtsson, 1972).

As expected, the mean IOP in right eyes was higher than in studies of Asian populations, where comparable age groups were examined (Vijaya *et al.*, 2005; Yip *et al.*, 2007; Wang *et al.*, 2011; Zhou *et al.*, 2012). This was also true when the results were compared with a study of a Latino population (Memarzadeh *et al.*, 2008). The mean IOP in the present study was lower compared to the mean IOP of the African-derived population presented in the Barbados Eye Study (Wu and Leske, 1997).

### **Factors associated with increased intraocular pressure**

In the current study, the multivariate regression analysis showed that increased IOP (IOP  $\geq$ 20 mm Hg) was significantly correlated with OAG and PEX. This is in line with results from previous studies (Rita Hiller, Sperduto and Krueger, 1982; Klemetti, 1988; Davanger, Ringvold and Blika, 1991; Sommer *et al.*, 1991; Klein, Klein and Linton, 1992; Kozobolis *et al.*, 1997; Wensor *et al.*, 1998; Mitchell, Wang and Hourihan, 1999; Ramakrishnan *et al.*, 2003; Vijaya *et al.*, 2005; Topouzis *et al.*, 2007; Åström and Lindén, 2007; Arnarsson *et al.*, 2009). A weaker, but still significant, association was shown between increased IOP and diabetes mellitus. No significant association could be established between IOP  $\geq$ 20 mm Hg and age  $\geq$ 70 years, male sex, or smoking status. The results from the stratified analysis were supportive of these findings. In addition, no significant association existed between IOP  $\geq$ 20 mm Hg and cataract, treated hypertension or IHD in the stratified analysis.

In the present study, there was a tendency for a lower IOP in participants 70 years or older. A similar pattern has mainly been seen in studies of Japanese populations (Kawase *et al.*, 2008; Tomoyose *et al.*, 2010), although it has also appeared in other populations of different ethnic backgrounds (Wang *et al.*, 2011). A positive correlation between age and increased IOP has been observed in previous studies of European-derived populations (Hollows and Graham, 1966; Bonomi *et al.*, 1998). The previously found association could potentially be explained by confounding factors since when such factors were adjusted for, the multivariate analysis in both the Blue Mountains Eye Study and the Beaver Dam Eye Study could not find any association (Klein, Klein and Linton, 1992; Rochtchina, Mitchell and Wang, 2002). One explanation for the tendency found in the current study could be selective mortality in persons with a higher IOP because of other conditions, such as diabetes mellitus. It has also been suggested that a reduction of aqueous flow in the aging population could lead to lower IOP with age (Toris *et al.*, 1999). In the Kumejima Eye study, the authors speculated that there might be structural changes in the aging eye that would have an IOP-decreasing effect (Tomoyose *et al.*, 2010). Of note, another study on a Swedish population in Dalby, found no association between age and increased IOP (Bengtsson, 1972). This leaves room to speculate on possible genetic, ethnic, or environmental differences between populations that could explain the findings.

The association between increased IOP and blood pressure (mainly systolic) has been established in several studies (Bengtsson, 1972; Klein, Klein and Linton, 1992; Foster *et al.*, 2003, 2011; Wu *et al.*, 2006; Kawase *et al.*, 2008; Memarzadeh *et al.*, 2008; Tomoyose *et al.*, 2010; Jonas *et al.*, 2011; Zhou *et al.*, 2012; Chan *et al.*, 2016). In the current study, a tendency for an association between increased IOP and treated hypertension was found in the stratified analysis.

Unfortunately, no blood pressure measurements were obtained. Therefore, it is not possible to draw certain conclusions about the association between hypertension and IOP  $\geq 20$  mm Hg. It could, however, be speculated that the tendency would be stronger if hypertension had been ascertained by an actual measurement of the blood pressure and not by presence of ongoing antihypertensive treatment, as this would have excluded those that were normotensive as a result of the treatment.

The lack of association between cataract and IOP  $\geq 20$  mm Hg should be interpreted with the inclusion criteria in mind. Participants who previously had received a cataract operation were also included in the group with cataract. It is possible that cataract surgery in some way had affected the pressure. In the current study, 11 participants had been operated for cataract, six in one eye and five in both eyes. In those who had had cataract surgery done in only one eye, three persons had a lower and three persons had a higher IOP in the operated eye.

The correlation between increased IOP and diabetes mellitus has previously been speculated to depend on an osmotic gradient induced by diabetes, which would in turn force more fluid into the intraocular space and increase IOP (Dielemans *et al.*, 1996). Alternative explanations presented include autonomic dysfunction (Clark and Mapstone, 1985), genetic factors (Clark and Mapstone, 1986), and increased fibronectin syntheses and accumulation in the trabecular meshwork (Sato and Roy, 2002). It has even been suggested that the higher IOP seen in patients with diabetes mellitus could depend on a thicker central cornea causing a *falsely* high IOP measurement (Ozdamar *et al.*, 2010).

In the current study, a tendency for positive correlation between smoking and increased IOP could be seen in those who had a history of smoking or were current smokers. This is in accordance with the results presented in the Barbados Eye Study and in the Blue Mountains Eye Study (Wu and Leske, 1997; Lee *et al.*, 2003), although no statistical significance was obtained in the present study. Mechanisms behind the association have been suggested to include nicotine, which, when administered, changes blood flow in the ophthalmic artery (Rojanapongpun and Drance, 1993). Cigarette smoking has also been suggested to lead to vasoconstriction and increased pressure in episcleral veins, which in turn would lead to inhibition of aqueous outflow (Mehra, Roy and Khare, 1976).

### **Covariation of intraocular pressure in right and left eyes**

The mean IOP in the eye measured first was higher than in the second eye in the present study. Furthermore, there was an indication of interaction between the right eye measured first and the left eye measured second. In the Kumejima study, where the right eye was always measured first,

the pressures in the right eyes were statistically significantly higher than the pressures in left eyes (Tomoyose *et al.*, 2010). Similar results have also been reported in non-population-based settings in eyes with OAG (Yaoeda *et al.*, 2018). There are also several previous reports on linear decrease in IOP with successive measurements (Krakau and Wilke, 1971; Motolko *et al.*, 1982; Gaton *et al.*, 2010).

This phenomenon could depend on various factors. As psychological stress (and even Valsalva manoeuvre) can potentially increase IOP (Kaluza and Maurer, 1997; Brody *et al.*, 1999; Abe *et al.*, 2020), one explanation could possibly be an initial stress reaction in subjects caused by the examination. It is, however, unclear if the time between the two IOP measurements would be enough to normalise this effect and thus lead to a lower IOP measured in the second eye. Other possible explanations could be ocular squeezing (Pekmezci *et al.*, 2011) or even evaporation of the tear film (Grant and English, 1963). It has also been suggested that there may be a reflex mechanism, which would affect the formation of aqueous humour in the second eye, when the first eye is applanated (Stocker, 1958). Although these findings are interesting, they do not have any apparent clinical significance.

### **Strengths and weaknesses**

The obvious strengths of the study include the population-based approach and a high participation rate. The population invited was chosen by random sampling and it can be argued that the sample population is representative for the age groups in question. The population in the present study is also well-defined and the study process described in detail, which makes it comparable to previous and future studies conducted in this field. Open-angle glaucoma was only diagnosed if there was a reproducible defect in the visual field. The findings from the multivariate regression and stratified analysis point in the same direction, which indicates that the ultimate model used was stable and robust.

The weaknesses of this study include a relatively low number of participants, a narrow age gap, and ethnically homogenous population, as compared to the current Swedish population. There is a need for caution when making generalisations for Swedes as a whole, as the results may not be applicable to parts of the population with more diverse ethnic backgrounds. The small size of the study population can contribute to the lack of statistical significance in regard to tendencies found between some variables and increased IOP as well as weaken the reliability of the associations that were found. There is always a risk for misclassification when a diagnosis is based on self-reports, which were used as inclusion criteria for smokers and partly for those with diabetes mellitus, IHD and treated hypertension.



A factor that could be interpreted as both a strength and a limitation, is that only one individual ophthalmologist performed the examinations, as opposed to a group of experts. On one hand, this reduces the possibility of variation between examiners and promotes consistency between diagnoses and observations made. On the other hand, if there was an observation bias, it would be difficult for the study not to be affected by it.

## Conclusions

In this population-based study on subjects 65–74 years of age conducted in south-central Sweden, the distribution of IOP was close to that of the Framingham and Beaver Dam studies. An IOP  $\geq 20$  mm Hg was strongly positively correlated to untreated OAG and PEX both in multiple logistic regression analysis and stratified analysis. The pressure in the first measured eye was higher than in the second eye.

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