Assessing Risks of Glaucoma

Oskarsdottir, Sigridur

2022

Document Version:
Publisher's PDF, also known as Version of record

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SIGRÍÐUR ERLA ÓSKARSDÓTTIR
DEPT. OF CLINICAL SCIENCES, MALMÖ | FACULTY OF MEDICINE | LUND UNIVERSITY

About the author

SIGRÍÐUR ERLA ÓSKARSDÓTTIR received her medical degree from the University of Iceland and is currently an ophthalmologist at the Department of Ophthalmology at Skåne University Hospital. This thesis consists of four different works exploring the prevalence and severity of undetected glaucoma in different age groups, the proportion of undetected glaucoma in different IOP- and age groups and the lifetime risk of glaucoma visual impairment in patients followed-up for raised intraocular pressure. The presented work may be used when evaluating the need for improved case-finding or the healthcare needs of patients at risk of developing glaucoma.

Printed by Media-Tryck, Lund 2022 NORDIC SWAN ECOLABEL 3041 0903

LUND UNIVERSITY

FACULTY OF MEDICINE

Ophthalmology
Department of Clinical Sciences in Malmö

Lund University, Faculty of Medicine
Doctoral Dissertation Series 2022:26
ISBN 978-91-8021-187-1
ISSN 1652-8220

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Sigríður Erla Óskarsdóttir

LUND
UNIVERSITY

DOCTORAL DISSERTATION

by due permission of the Faculty of Medicine, Lund University, Sweden.
To be defended at Agardhsalen, Jan Waldenströms gata 35, Malmö,
March 11, 2022, at 1 pm.

Faculty opponent

Docent Mika Harju
University of Helsinki

Organization
LUND UNIVERSITY
Department of Clinical Sciences in Malmö, Ophthalmology, Skåne University Hospital, Sweden

Author(s) Sigridur Erla Oskarsdottir

Document name
DOCTORAL DISSERTATION

Date of issue
11. march 2022

Sponsoring organization

Title and subtitle
ASSESSING RISKS OF GLAUCOMA

Abstract
Glaucoma is a potentially blinding disease where the affected individual often first notices symptoms when the disease has reached a late stage. If glaucoma is detected early, visual impairment can be minimized. There are many factors that affect a patient´s risk of developing glaucoma or visual impairment due to glaucoma. In the four studies of this thesis, the main focus was to evaluate such factors, mainly age, intraocular pressure and severity at detection, to provide more information if pathways for improved detection are to be formulated in the future.

The objectives of Study I and IV were to report the prevalence and severity of undetected glaucoma in different age groups when detected at screening. Study I was based on data originally collected in a large population screening for individuals 57-77 years old performed in the 90´s. In Study IV we screened 322 elderly individuals 77-89 years old for glaucoma in 2019-2021. We found that the prevalence of undetected glaucoma increased with age but disease severity was similar in age groups 60-77 years and milder in subjects 57-59 years and 77-89 years.

Using the large screening material from the 90´s with about 33.000 individuals we created a regression model for the prediction of undetected glaucoma, calculating the combined effect of age and intraocular pressure (Study II). Glaucoma increased exponentially with age and even more so with intraocular pressure.

Study III aimed to find the lifetime risk of glaucoma visual impairment in individuals followed-up for raised intraocular pressure. We found that only 9% of subjects developed bilateral visual impairment and 3% bilateral blindness resulting from glaucoma.

The results are of value when estimating the need for improved glaucoma detection and when considering the management of patients with raised intraocular pressure.

Key words Glaucoma, prevalence, severity, intraocular pressure, prediction model, lifetime risk

Classification system and/or index terms (if any)

Supplementary bibliographical information | **Language** English

ISSN and key title
1652-8220

ISBN
978-91-8021-187-1

Recipient's notes

Number of pages
68

Price

Security classification

Signature  Date 2022-01-27

Assessing Risks of Glaucoma

Sigríður Erla Óskarsdóttir

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Coverphoto by Sigríður Erla Óskarsdóttir

Profile photo on back cover by Ljósmyndir Rutar og Silju

Faculty of Medicine
Department of Clinical Sciences in Malmö

ISBN 978-91-8021-187-1
ISSN 1652-8220

Printed in Sweden by Media-Tryck, Lund University
Lund 2022

Palli var einn í heiminum

(Jens Sigsgaard's children´s book "Palle alene i verden" 1942)

og þá var bankað

Table of Contents

Précis

I met my supervisor and co-supervisor after applying for a residency at the Ophthalmology department in Malmö in 2010. We met for the job interview and talked about the research position available. Accepting this position would require me to start a life-changing journey, not only figuratively speaking, but also quite literally. I was positive about the opportunity and a few months later I had packed my belongings to start a new chapter in my life in another country. Doing research was new to me and every so often challenging. I had a lot to learn but the projects were interesting and I was grateful for the opportunities the position implied. I still had doubts that glaucoma was the subfield I wanted to specialize in and work with in the future as an ophthalmologist. It took a few years before I realized that the interest in glaucoma had gradually and discreetly sneaked up on me and given me tunnel-vision for the field, before I even noticed it.

Abstract

Glaucoma is a potentially blinding disease where the affected individual often first notices symptoms when the disease has reached a late stage. If glaucoma is detected early e.g., at screening, the risk for visual impairment can be reduced. There are many factors that affect a patient´s risk of developing glaucoma or visual impairment due to glaucoma. In the four studies of this thesis, the general aim was to evaluate such factors, focussing mainly on age, intraocular pressure and severity at detection, to provide more information on the need for improved case detection.

The objectives of Study I and IV were to report the prevalence and severity of undetected glaucoma in different age groups when detected at screening. Study I was based on data originally collected in a large population screening for individuals 57-77 years old performed in 1992-1997. In Study IV, 322 elderly subjects 77-89 years old were screened for glaucoma in 2019-2021. We found that the prevalence of undetected glaucoma increased with age but disease severity was similar at 60-77 years of age with about 30% of glaucomatous eyes with advanced disease or worse, but mostly early in elderly patients 77-89 years old.

Using the large screening material from 1992-1997 that included 32,918 subjects, we created a regression model for the prediction of undetected glaucoma based on the combined effect of age and intraocular pressure (Study II). Glaucoma increased exponentially with age and intraocular pressure.

Study III aimed to find the lifetime risk of glaucoma visual impairment in individuals followed-up for raised intraocular pressure since the 1980s. We found that only 9% of subjects developed bilateral visual impairment and 3% bilateral blindness resulting from glaucoma.

The results are of value when estimating the need for improved glaucoma detection and when considering the management of patients with raised intraocular pressure.

List of papers

Published papers

Study I. Heijl A, Bengtsson B, Oskarsdottir SE. Prevalence and severity of undetected manifest glaucoma: results from the Early Manifest Glaucoma Trial Screening. *Ophthalmology.* 2013 Aug; 120(8):1541-5.

Study II. Oskarsdottir S, Heijl A, Bengtsson B. Predicting undetected glaucoma according to age and IOP: A prediction model developed from a primarily European derived population. *Acta Ophthalmol.* 2019 Jun; 97(4):422-426.

Study III. Oskarsdottir S, Heijl A, Midlöv P, Bengtsson B. Lifetime risk of visual impairment resulting from glaucoma in patients initially followed-up for elevated intraocular pressure. *Ophthalmology Glaucoma*. Available online Oct 2019.

Manuscript

Study IV. Oskarsdottir S, Aspberg J, Heijl A, Midlöv P, Bengtsson B. Prevalence and severity of open-angle glaucoma detected at screening in the elderly; Interim analysis of a glaucoma screening study. Manuscript 2021.

The papers are referred to in the text as Studies I-IV and the published papers are reproduced with permission of the copyright holders.

Abbreviations

ALT	Argon laser trabeculoplasty
AMD	Age-related Macular Degeneration
dB	decibel
EMGT	Early Manifest Glaucoma Trial
FDT	Frequency Doubling Technology
GSS	Glaucoma Staging System
HFA	Humphrey Field Analyzer
IOP	Intraocular pressure
MD	Mean Deviation
mmHg	Millimeter mercury
NNT	Number needed to treat
OH	Ocular hypertension
ONH	Optic nerve head
PEX	Pseudoexfoliation syndrome
POAG	Primary open-angle glaucoma
PPV	Positive predictive value
PS	Post-screening
RNFL	Retinal Nerve Fibre Layer
SITA	Swedish Interactive Threshold Algorithm
SLT	Selective laser trabeculoplasty
VA	Visual acuity
VF	Visual field
WHO	World Health Organization

Introduction

Glaucoma - the condition

Glaucoma was first documented by the Ancient Greeks, who described a condition with blindness in one or both eyes and a pupil with the colour of the sea occurring mostly in elderly individuals (Tsatsos & Broadway 2007).

The condition causes permanent and progressive visual field loss by injury to the optic nerve head (ONH) (Quigley et al. 1981), with characteristic cupping of the optic disc (Müller 1872), Fig. 1 a) and b), and thinning of the retinal nerve fibre layer (RNFL) (Airaksinen et al. 1981; Airaksinen & Heijl 1983). Primary glaucoma is classified as open angle or closed angle glaucoma, distinguished by the anatomy of the anterior segment of the eye, Fig. 1 c) and d). Primary open-angle glaucoma (POAG) is the most common form of glaucoma and is defined by anatomically normal anterior chamber angle structures in the absence of other causes. A relatively recent updated global report estimated that POAG accounted for about 84% of primary glaucoma cases (Tham et al. 2014).

Although the cause of glaucoma is still unknown (Quigley 2011; Jonas et al. 2017), several risk factors have been identified that increase the risk of developing glaucoma, such as age, raised intraocular pressure (IOP), origin and heredity (Leske 2007).

The functional loss in patients´ visual fields commonly begins in the periphery and causes a negative scotoma that often goes undetected by the patient initially (Ramachandran & Gregory 1991). A well-known example of a negative scotoma that goes undetected unless tested is the physiologic blind spot corresponding to the location of the optic nerve head (Brudenell Carter 1872), Fig. 2. The disease therefore often remains asymptomatic in early stages and as a result patients often present late (Grødum et al. 2002; Boodhna & Crabb 2015; Liang et al. 2018), which increases the risk of an adverse outcome (Grant & Burke 1982; Wilson et al. 1982; Oliver et al. 2002; Chen 2003; Forsman et al. 2007; Kooner et al. 2008; Lee et al. 2014; Peters et al. 2014; Saunders et al. 2014).

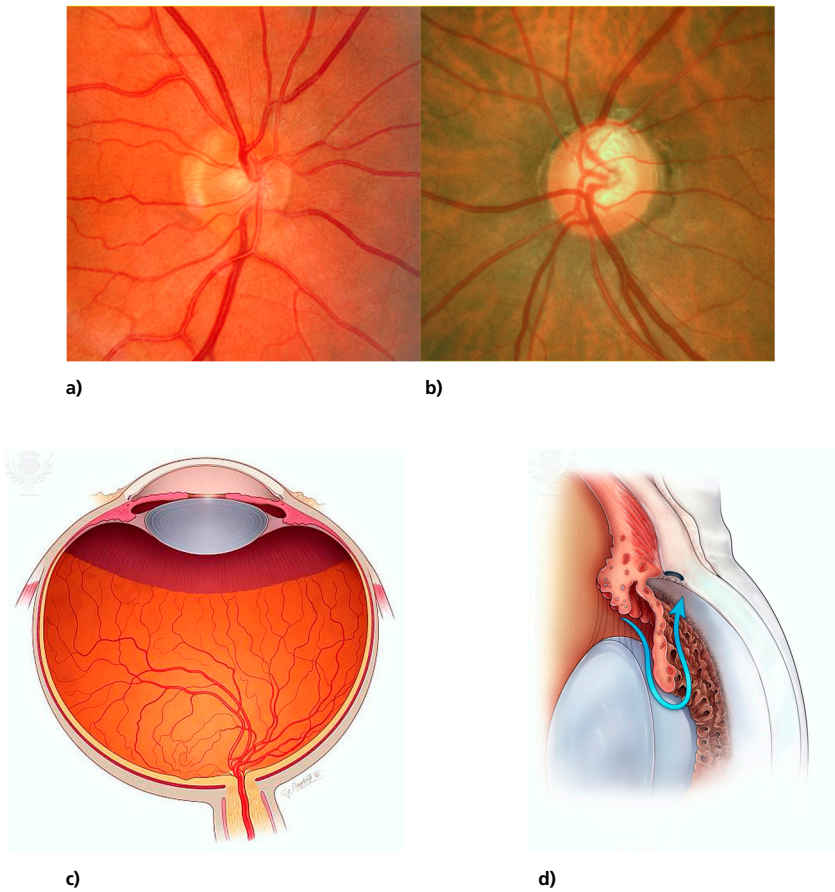
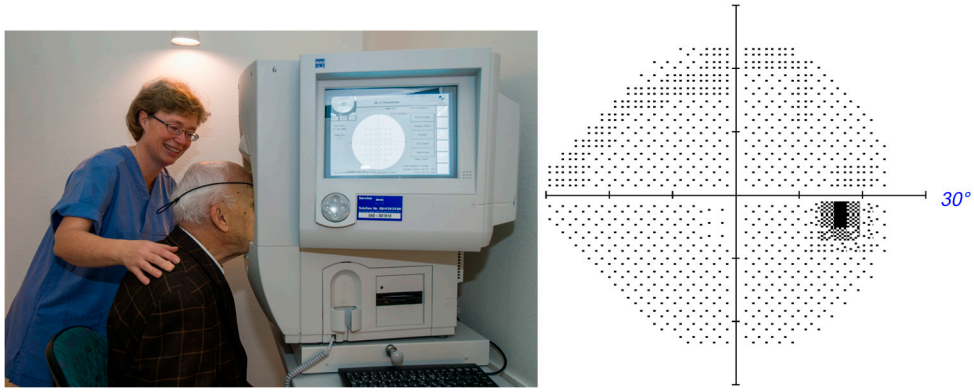


Figure 1
a) Healthy optic nerve head.*Illustration by courtesy of Johnny Ring.* b) Structural glaucomatous changes at the optic nerve head. *Illustration by courtesy of Johnny Ring.* c) Transverse section of the eye showing where the optic nerve exits the eye. *Illustration by courtesy of Britannica Image Quest.* d) Anterior segment of the eye showing the anterior chamber angle and production of aqueous humor. *Illustration by courtesy of Britannica Image Quest.*

The size, depth and locations of the scotomas can be detected by performing a visual field test (Heijl et al. 2012). Campimetry was first introduced in the mid-19th century by Graefe (1856), with a primitive version using a flat surface. By the end of the 19th century, Bjerrum (1889) had identified the characteristic arc-shaped scotoma resulting from glaucoma. Manual static perimetry evolved during the 20th century (Sloan 1939; Goldmann 1945; Harms 1960), but it wasn´t until automated perimetry was developed (Fankhauser et al. 1972; Heijl & Krakau 1975; Heijl 1985) that static perimetry started to gain popularity in the latter half of the 20th century. Today, automated static perimetry testing is considered crucial in glaucoma care (EGS 2020), for example using the Humphrey Field Analyzer (HFA) (Carl Zeiss Meditec, Dublin, California), Fig. 2.



a) b)

Figure 2
a) Patient perimetry being performed. *Illustration by courtesy of Johnny Ring.* b) Humphrey Field Analyzer visual field test results, greyscale, right eye. Normal results where the blind spot can be visualized.

The progression of glaucoma can be slowed by lowering the intraocular pressure (IOP) (Leske et al. 2003; Garway-Heath et al. 2015). It is therefore important to detect the disease early in order to reduce the risk of visual impairment. Continuous use of pressure-lowering eye drops is the most common treatment method for glaucoma, but the IOP can also be lowered by surgery (Cairns 1968) or by applying laser treatment to the trabecular meshwork; selective laser trabeculoplasty (SLT) (Latina et al. 1998) or argon laser trabeculoplasty (ALT) (Wise & Witter 1979). Regular follow-ups are needed in order to evaluate IOP level and progression of the disease, and for adjustment of treatment to the individual patient´s needs (Gardiner & Crabb 2002; Jansonius 2007; Chauhan et al. 2008; Nouri-Mahdavi et al. 2011; Crabb & Garway-Heath 2012).

Prevalence

The overall prevalence of primary open-angle glaucoma worldwide has been estimated to be 3.05% in persons 40-80 years old (Tham et al. 2014).

Several epidemiological studies have shown that at least 50% of glaucoma is undetected (Hollows & Graham 1966; Kahn et al. 1977; Bengtsson 1981; Tielsch et al. 1991; Mitchell et al. 1996; Wensor et al. 1998), and Africa and Asia show higher proportions of undetected disease compared to Europe (Soh et al. 2021).

Previous studies have found that prevalence differs depending on geographic regions and ethnicity (Leske 2007; Tham et al. 2014), and prevalence has been reported to be higher in persons of African ancestry (Mason et al. 1989; Tielsch et al. 1991; Leske et

al. 1994; Ashaye et al. 2013; Budenz et al. 2013; Kyari et al. 2015) and Hispanics (Varma et al. 2004; Gupta et al. 2016), compared to European ancestry (Hollows & Graham 1966; Bankes et al. 1968; Kahn et al. 1977; Bengtsson 1981; Tielsch et al. 1991; Coffey et al. 1993; Dielemans et al. 1994; Mitchell et al. 1996; Wensor et al. 1998; Jonasson et al. 2003; Friedman et al. 2006; Topouzis et al. 2007; Chan et al. 2017), and Asian ancestry (Foster et al. 2000; Bourne et al. 2003; Liang et al. 2011; Song et al. 2011; Narayanaswamy et al. 2013; Li et al. 2014; Baskaran et al. 2015; Pan et al. 2016).

It is well known that the prevalence of glaucoma increases with age, and has been reported to be 6% at age 70 and older in people of European ancestry (Rudnicka et al. 2006).

Several studies have reported the prevalence in elderly individuals 75 years or older in European-derived populations (Bankes et al. 1968; Kahn et al. 1977; Tielsch et al. 1991; Coffey et al. 1993; Dielemans et al. 1994; Hirvelä et al. 1994; Mitchell et al. 1996; Wensor et al. 1998; Jonasson et al. 2003; Friedman et al. 2006; Topouzis et al. 2007; Chan et al. 2017; Keel et al. 2019; Bikbov et al. 2020). Most studies that have reported the prevalence for individuals 80 years and older have screened relatively few subjects in that age category, often including about 400 participants or fewer (Bankes et al. 1968; Kahn et al. 1977; Tielsch et al. 1991; Coffey et al. 1993; Dielemans et al. 1994; Hirvelä et al. 1994; Mitchell et al. 1996; Wensor et al. 1998; Jonasson et al. 2003; Friedman et al. 2006; Topouzis et al. 2007). The EPIC-Norfolk Eye study is the largest so far, with about 800 subjects 80 years and older screened (Chan et al. 2017). The prevalence is reported to be about 8%-13% in the larger studies, whereof about 34-50% were undetected prior to the study screening (Tielsch et al. 1991; Mitchell et al. 1996; Wensor et al. 1998; Friedman et al. 2006; Topouzis et al. 2007; Chan et al. 2017).

Severity

Glaucoma is one of the most common causes of irreversible blindness worldwide (Bourne et al. 2013; WHO 2021). The proportion of people who are blind due to glaucoma has increased in recent decades and is now the cause of 6.6% of world blindness, or 1 in 15 blind persons (Bourne et al. 2016). Globally, the proportion of individuals older than 65 years is projected to rise from 9% in 2019 to 16% in 2050, according to estimates by the United Nations (UN 2019). The absolute number of patients with glaucoma is predicted to increase in the future (Tham et al. 2014) due to growing populations and a higher proportion of elderly individuals.

Despite regular follow-ups and treatment, a high proportion of patients become blind in at least one eye during their lifetime, 42% (Peters et al. 2013), and 12-16% have been reported to develop bilateral blindness (Forsman et al. 2007; Peters et al. 2013).

Evaluating the severity of glaucoma is important in order to evaluate the burden of disease as the condition worsens. The severity can be measured by using glaucoma staging systems (GSS). Different staging systems have been introduced that allow for retrospective grading of disease based on visual field test printouts, with minimal physician interpretation (Aulhorn & Karmeyer 1977; Hodapp et al. 1993; Mills et al. 2006; Brusini & Johnson 2007; Ng et al. 2012), e.g., the Bascom Palmer (Hodapp-Parrish-Andersson) staging system or the GSS presented by Mills et al. in 2006. The systems allow for quantification of progression of the disease, comparison of direct and indirect costs, reporting in scientific studies, evaluation of cost-effectiveness of treatment, and also the patient´s health-related quality of life at different stages of the disease (Varma et al. 2011).

Previously published studies have found that having advanced glaucoma at detection is an important risk factor for blindness due to glaucoma (Grant & Burke 1982; Oliver et al. 2002; Chen 2003; Forsman et al. 2007; Kooner et al. 2008; Peters et al. 2014).

Glaucoma can be detected at earlier stages by screening (Grødum et al. 2002; Liang et al. 2018). A recent study has also shown that visual impairment can be reduced by 50% by screening (Aspberg et al. 2021) and screening for glaucoma has often been a topic of discussion.

Glaucoma fulfills many of the criteria presented by Wilson and Jungner (1968) that should to be met in order for population screening to be recommended (Mowatt et al. 2008). In Sweden, these criteria have since been modified for adaptation to the Swedish healthcare system (Socialstyrelsen 2019). Although glaucoma is suitable for screening in many ways e.g., glaucoma is an important public health problem and treatment for the condition is available that has been proven to reduce the consequences of the disease, population screening is not cost effective and population screening programs for glaucoma have not been recommended to date (Burr et al. 2007). If screening of some sort becomes relevant in the future, or if pathways for improved case detection are constructed, it is important to recognize what groups should be invited. Estimation of prevalence and severity of undetected glaucoma is important for the formulation of adequate health policies in the future.

Raised intraocular pressure: a risk factor for glaucoma

Raised intraocular pressure has been linked with glaucoma long before standardized tonometry methods were introduced in the 20th century (Schiøtz 1905; Goldmann 1954) by noting hard eyes on palpation (Mackenzie 1830). In 1958, Leydhecker et al. published the results of a large screening presenting the IOP distribution in a population, after which eyes with IOP above 20.5 mmHg were considered to have glaucoma. The mean IOP in the study was 15.5 mmHg and, assuming a Gaussian distribution, this statistical upper limit of normal IOP was presented. Later, epidemiological studies found that about half of all patients with glaucoma had IOPs within the statistical normal limit (Hollows & Graham 1966; Bengtsson 1981).

Having an IOP above the statistical normal limit of 21 mmHg without any signs of glaucoma is referred to as ocular hypertension (OH) and the condition is considerably more common than glaucoma, with a prevalence of about 5-10% of individuals 40 years and older in primarily European-derived populations (Leske 2007).

Raised intraocular pressure is a strong risk factor for glaucoma (Gordon et al. 2002) and the only modifiable one (Leske 2007). Pseudoexfoliation syndrome (Lindberg 1917) in combination with raised IOP increases the risk of developing glaucoma (Brooks & Gillies 1988; Ekström 1993; Grødum et al. 2005). IOP-lowering treatment lowers the incidence of glaucoma in OH, and the hazard ratio for medication in a large randomized clinical trial comparing treatment vs. close observation, called the Ocular hypertension treatment study (OHTS), was 0.4 after 5-years of follow-up, where the number needed to treat (NNT) to prevent progression to glaucoma was 1 in 20 (Gordon & Kass 2018). Still, even without treatment a large proportion of OH patients do not develop glaucoma (Linnér 1976; Lundberg et al. 1987; Gordon et al. 2002; Forsman et al. 2007).

Since ocular hypertension is common and resources in healthcare are limited, many questions remain to be answered about the management of these individuals. There is no absolute consensus about how these patients should be followed-up or when to treat (Tuulonen 2016). Knowing the lifetime risk of visual impairment in patients followed-up for raised intraocular pressure would add information to consider when contemplating the care for these patients. The question has been addressed by long-term follow-up in prior reports, but only one study that included 40 patients (Forsman et al. 2007) with OH has evaluated the lifetime risk of visual impairment resulting from glaucoma, and more information is needed.

a) b)

Figure 3
Intraocular pressure measured with a) Goldmann applanation tonometry. Fluorescein dye and topical anaesthetics are placed in the patients eye before applying a flattening force to the cornea using a split-image prism. *Illustration by courtesy of Johnny Ring*. b) Icare rebound technology that measures the speed of deceleration of a rod probe after it hits the corneal surface.

Currently, there is no formal strategy for early detection of glaucoma in Sweden and detection is instead opportunistic.

Glaucoma can be detected by chance in an individual who receives eye care for another eye condition, in the acute phase or during regular follow-ups e.g., patients with diabetes who are regularly followed-up for diabetic retinopathy with fundus photographs. Unfortunately, patients with IOPs within normal limits are often overlooked in clinical practice (Grødum et al. 2002).

Opticians in Sweden, of whom 20% are optometrists, perform the majority of primary eye examinations in Sweden (Optikerförbundet 2021). Individuals who visit an optician for a prescription of glasses are often offered an IOP measurement as a part of their eye examination, or sometimes even a visual field test or imaging of the ONH. If the IOP is above 21 mmHg, opticians are recommended to refer the customer to an ophthalmologist (Skjöld et al. 2019). Studies have shown an increase in glaucoma referrals (Shah & Murdoch 2011; Ratnarajan et al. 2013; Nilsson & Peters 2021), and that a large proportion of referrals for suspect glaucoma were due to IOP >21 mmHg as the only referral criterion (Tuck & Crick 1991; Ratnarajan et al. 2013; Landgren & Peters 2021). IOP alone is insufficient as a screening method (Mowatt et al. 2008) and false positive referrals to ophthalmology clinics may cause resource overuse (Bowling et al. 2005; Salmon et al. 2007; Ratnarajan et al. 2013). Furthermore, exposing healthy individuals to unnecessary examination may cause distress for the individual (Davey et al. 2013). Improvements in the referral process might reasonably be sought.

A report from 2013 revealed that glaucoma healthcare was about 25% of eye health outpatient visits in Sweden (Lindén et al. 2013). Glaucoma-related referrals represent

20% of all referrals to ophthalmology departments (Davey et al. 2011). With an ageing population, the current diagnostic and management services in clinics providing glaucoma care could become overloaded with large volumes of healthy individuals undergoing medical examinations, with subsequent risk of increased burden to glaucoma clinics and delay in follow-up of patients with manifest glaucoma.

We had access to data from a large population-based screening for glaucoma performed in the 1990s where 32,918 individuals were screened. This provided us with an opportunity to estimate the combined effect of age and IOP on undetected glaucoma in a screened population. We developed a prediction model that may be valuable when criteria for referral to an ophthalmologist due to raised IOP are created or revised.

Aims

Study-specific aims

Study I

To report the prevalence and severity of undetected glaucoma at screening in a large population study performed in the 1990s, where 32,918 individuals 57-77 years old were screened in Malmö, Sweden.

Study II

To model prediction of undetected glaucoma for the combined effect of age and IOP by using the results from a large screening study performed in Malmö in the 1990s.

Study III

To report the lifetime risk of glaucoma visual impairment in individuals with raised intraocular pressure and at least one more risk factor for glaucoma, who were regularly followed-up since the 1980s.

Study IV

To report the prevalence and severity of undetected glaucoma in 322 elderly individuals aged 77-89 years old, who were screened for glaucoma in 2019-2021 in Malmö, Sweden.

Methods

Ethics

The studies in this thesis adhere to the Declaration of Helsinki and have been approved by the Swedish Ethical Review Authority.

Study I

Study design and study population

Study I was based on a large population screening performed in the 1990s in order to recruit patients with newly detected glaucoma for a randomized controlled treatment trial, called the Early Manifest Glaucoma Trial (EMGT). The screening was performed in Malmö during the years 1992-1997. Inhabitants of Malmö aged 57-77 years were invited, excluding those with a prior glaucoma diagnosis at the Ophthalmology department of Malmö General Hospital (now Skåne University Hospital), and those who had visited the Ophthalmology department within a year prior to the screening. Only women were invited in the age interval of 57-59 years. A total of 32,918 individuals attended the screening (77.5% of the invited population). A total of 255 patients participated in the EMGT, but additional glaucoma patients were detected at the screening who did not fulfill inclusion criteria for the EMGT e.g., due to IOP exceeding the inclusion criteria or severe disease (Leske et al. 1999). For the purpose of Study I, data was retrospectively collected for all patients with glaucoma detected by the screening.

Screening procedure

At the screening, all subjects answered a short health questionnaire. Dilated fundus photographs of the ONH were obtained, and IOP was measured using Goldmann applanation tonometry, Fig. 3 a). If one or more of the following findings were present; suspect optic discs, IOP more than 25 mmHg, or heredity of glaucoma in siblings,

subjects were invited for 1-2 post-screening visits to establish or reject a glaucoma diagnosis. At the post-screening visits a full ocular examination, including visual field testing with HFA 24-2, was performed.

Criteria for a glaucoma diagnosis

A glaucoma diagnosis was made if a subject had repeatable visual field defects that were compatible with glaucoma that could not be explained by other causes, Fig. 4. If only one visual field was available, then the combination of a visual field defect compatible with glaucoma and corresponding ONH disc rim thinning was needed to make the diagnosis. A diagnosis could also be made if no visual fields were available e.g., due to blindness or inability to perform the test, if the ONH had obvious glaucoma damage or end-stage disease, Fig. 5.

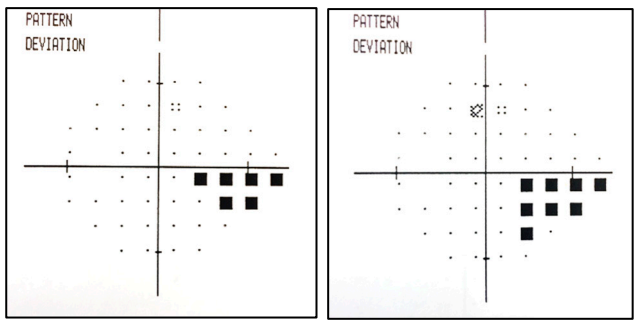


Figure 4
Repeatable visual field defects compatable with glaucoma on the pattern deviation map of the Humphrey visual field analyzer. Inferior nasal defects in the left eye.

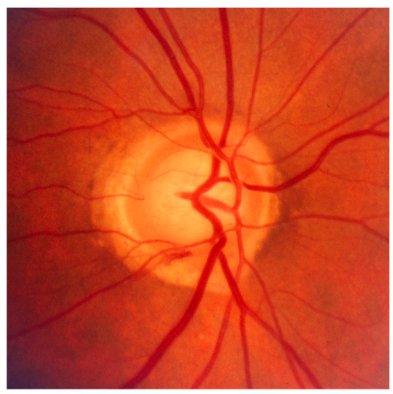


Figure 5
Structural changes of the optic nerve head consistent with glaucoma. *Illustration by courtesy of Johnny Ring.*

Prevalence

The prevalence of undetected glaucoma was reported for 5 predetermined age groups using an existing database created during the screening.

Severity

A modified version of a glaucoma staging system introduced by Mills et al. (2006) was chosen to evaluate glaucoma severity at detection. In this version, the perimetric Mean Deviation value (MD) was used to categorize patients´ visual field test results in 5 different glaucoma stages, Table 1. The MD value is the overall depression of a patient´s visual field compared with normal age-matched values in all test locations of the total deviation numerical plot, Fig. 6. The more negative a value is, the more deviation from normal and more advanced field loss. The MD value can be affected by other diseases, such as cataract.

We collected patients´ first visual field tests and medical records from the time of diagnosis to analyse the severity of disease at detection for each glaucomatous eye and categorized according to the stages presented in Table 1. Eyes that were already blind due to glaucoma, i.e., that fulfilled the World Health Organization (WHO) criteria for blindness (WHO 2007), Table 2, were categorized as glaucoma stage 5. For the purpose of this thesis, for further simplification glaucoma stages 3-5 were categorized together, with closer resemblance to the Bascom-Palmer glaucoma staging system (Hodapp et al. 1993).

Table 1.
Glaucoma staging

Glaucoma Stage	Mean Deviation (MD) value	Severity of glaucoma
1	Better than -6.00 dB	Early
2	-6.01 to -12.00 dB	Moderate
3	-12.01 to -20.00 dB	Advanced
4	Worse than -20.01 dB	Severe
5	Blind*	Blind*

*Fulfills blindness criteria according to the WHO definitions, see Table 2.

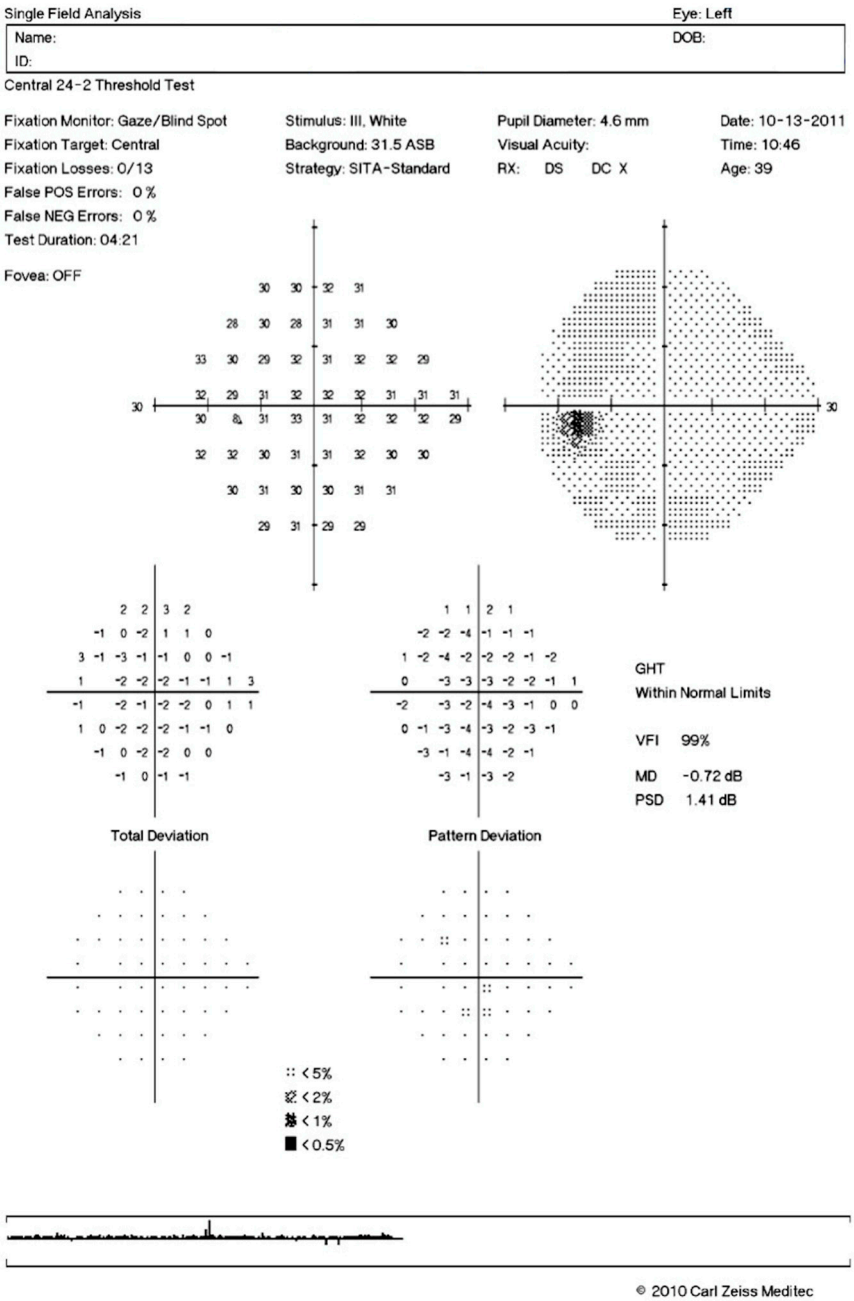


Figure 6
Visual field printout from a STATPAC single field analysis SITA standard 24-2. Normal test results. *Illustration by courtesy of Johnny Ring.*

Study II

Study design and study population

Study II is based on the same large population screening as Study I. All screened subjects who had IOP measurements in at least one eye and that did not have a prior glaucoma diagnosis were included.

Criteria for a glaucoma diagnosis

A diagnosis of glaucoma was made according to the same criteria as in Study I.

Prediction model

The intraocular pressures for all screened subjects were analysed to find the proportion of glaucoma at different IOP values in different age groups. The IOP at screening in the eye with the higher IOP was used for analysis. Proportions were reported in 5 mmHg intervals between 10-34 mmHg, and values <10 mmHg and ≥35 mmHg were grouped together. The same age groups were used as in Study I.

Multiple regression analysis was performed, including residual analysis. The coefficients from the regression analysis were used to model prediction of undetected glaucoma using age, IOP, and the interaction between the two.

Study III

Study design and study population

Study III is based on the life-long follow-up of subjects enrolled in the Malmö High Risk Ocular Hypertension Treatment Study in the 1980s (Heijl & Bengtsson 2000). The original study was a double blind randomized clinical trial comparing the effects of placebo vs. 0.5% timolol in 90 subjects, and the study ended in 1995. Subjects with raised intraocular pressure and no signs of glaucoma were included. Additionally, all subjects had to have at least one more risk factor for glaucoma. The risk factors considered were pseudoexfoliation syndrome, heredity, IOP ≥27mmHg, or a suspect optic disc. The subjects were followed-up for up to 10 years for the purpose of the

original study. For the purpose of Study III, medical records were retrospectively collected until December 2017, or up to 33 years later. At the time of the data collection, 77 subjects were deceased and the lifetime risk of visual impairment due to glaucoma could be analysed.

Criteria for a glaucoma diagnosis

A diagnosis of glaucoma was made according to the same criteria as in Study I and II.

Cumulative incidence of glaucoma visual impairment

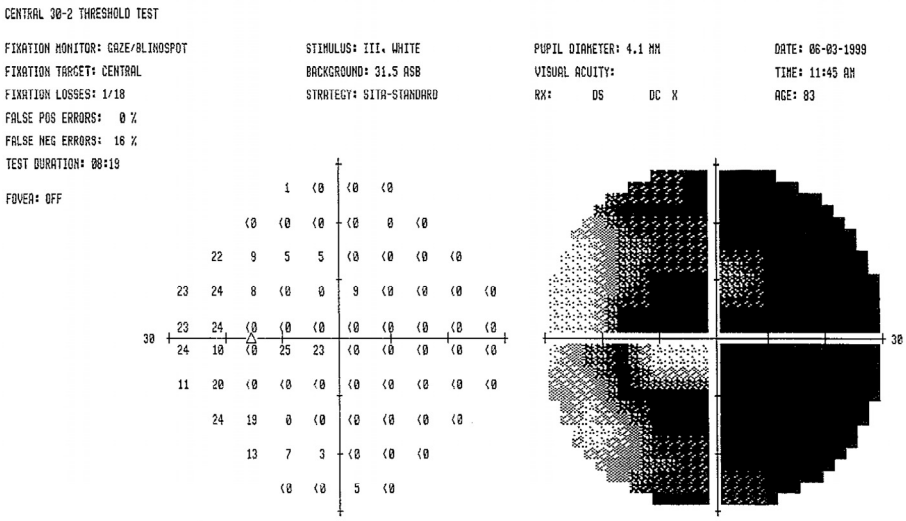
The World Health Organization criteria (WHO 2007) were used to determine if a subject developed visual impairment (low vision and blindness), Table 2. Visual impairment was therefore evaluated for the subjects´ results from both visual acuity testing and visual field analysis to avoid underestimation (Heijl et al. 2011). The cause of visual impairment was evaluated using the medical records. The date when subjects developed low vision or blindness was registered for each eye and the cause was evaluated separately for each eye and for each event.

Table 2.
The World Health Organization (WHO) criteria for visual impairment

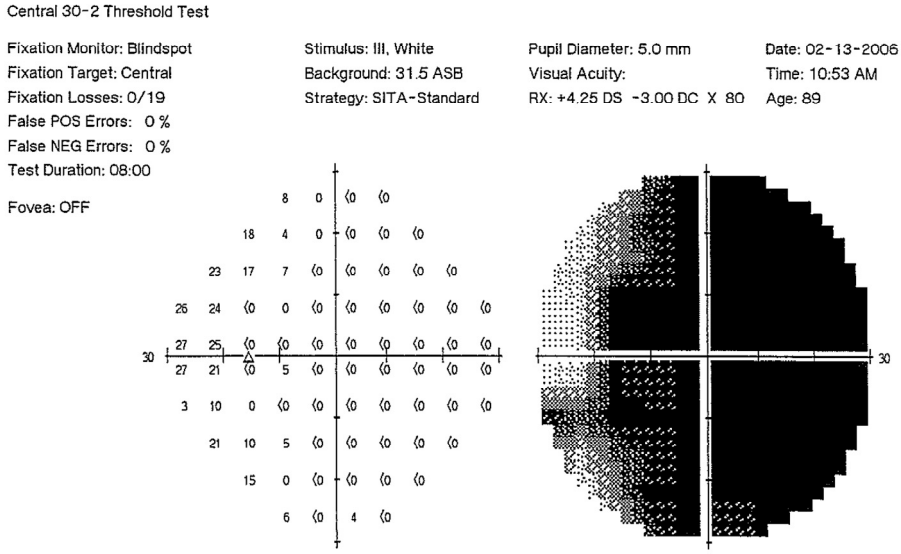
Visual impairment:	Low vision	Blindness
Visual acuity	Permanently reduced to between <0.3 and 0.05	Permanently reduced to <0.05
Central visual field	Constricted to <20° and ≥10°	Constricted to <10°

A pseudoisopter was used to estimate the degrees of visual field constriction. A pseudoisopter differentiates the seeing area of the visual field test results from the non-seeing area. The American Social Security Administration (ASSA) have outlined recommendations on how to measure the pseudoisopter (ASSA 2007). A line was drawn midway between seen points, that is points with a threshold value of 10 dB or more, and points not seen (<10 dB). The widest diameter could be calculated since points are 6° apart. The pseudoisopter had to include the point of fixation, Fig. 7.

The cumulative incidence of glaucoma visual impairment, glaucoma blindness and for glaucoma diagnosis was calculated with a method considering competing risks, in this instance death or bilateral blindness resulting from conditions other than glaucoma (Gray 1988; Kim 2007).



a)



b)

Figure 7
Visual field test results showing a patient´s glaucoma progressing from a) low vision at age 83, with a maximum pseudoisopter of (3°+6°+3°=) 12°, to b) blindness at age 89. The pseudoisopter is not measureable around the point of fixation.

Study IV

Study design and study population

Study IV was a cross-sectional study where a population screening of elderly individuals living in Malmö was performed. A total of 16,311 residents of Malmö aged 77-89 years were eligible for participation. Patients with a glaucoma diagnosis at the Ophthalmology department at Skåne University Hospital were excluded. After randomization, a total of 1,199 individuals were invited to the screening, which 322 attended (27%).

Screening procedure

At the screening, IOP was measured using an Icare ic200 rebound technique tonometer (Icare Finland Oy, Finland), Fig. 3 b). Photographs of the ONH were obtained, visual acuity was measured using an auto-refractor and a screening visual field test was performed with the FDT perimeter, Fig. 8 a) and b). Subjects were also asked about previous eye diagnoses and if they were administering eye drops, specifically intraocular pressure-lowering eye drops. The screening was considered positive if at least one criterion of the following was met: IOP >25 mmHg; a suspect optic disc; missed stimulus in one or more test locations on FDT (repeated results), Fig. 9.

Frequency doubling technique perimeter (FDT)

The FDT perimeter uses frequency doubling technique based on a flicker illusion that creates an image that appears double in its spatial frequency. Vertical bars (grey/black and white) appear on the perimeter screen, Fig. 8 b). These bars flicker in 17 different locations to detect damage.

a) b)

Figure 8
a) An FDT perimeter. *Illustration by courtesy of Johnny Ring.* b) A patient´s view when performing a FDT test showing the fixation object centrally and vertical flickering lines inferiorly in one of 17 test locations. *Illustration by courtesy of Johnny Ring.*

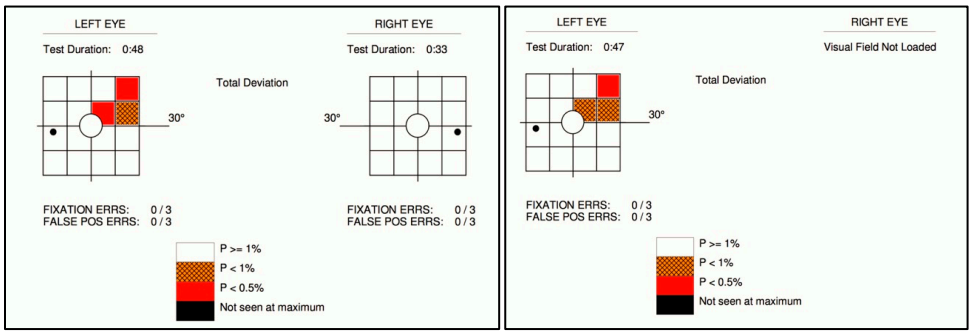


Figure 9
Printouts for FDT at screening for a patient who was found to have glaucoma in their left eye at post-screening. The patient had positive results with a visual field defect in one or more test locations that was repeatable in the same subfield or adjacent subfield, on tests fulfilling reliability criteria.

Criteria for a glaucoma diagnosis

Subjects with positive screening criteria were offered post-screening visits, where a full ophthalmic examination and visual field test using the SITA Full threshold program of the HFA were performed. A diagnosis of glaucoma was made according to the same criteria as in Study I, II and III. Results were reported for patients with POAG.

Prevalence

The prevalence of undetected glaucoma was reported for 2 different age groups; a younger age group inluding subjects 77-82 years old, and an older age group of subjects aged 83-89 years. In this thesis, the results from Study I and IV are shown together and therefore 3 different age groups were included; 77-79 years, 80-84 years and 85-89 years. As in Study I, patients with a known glaucoma diagnosis prior to the screening were excluded.

Severity

Severity was analysed in the same manner as in Study I, Table 1. In this thesis, results are shown for glaucoma stage 3-5 together.

Results

Study I and IV

Prevalence

Study I and IV reported the prevalence of undetected glaucoma found at screening in subjects aged 57-77 years and 77-89 years, respectively. In this thesis, the prevalence is reported for each age group from the two studies combined, from age 57 to 89 years, Table 1. A total of 406 patients were found to have glaucoma in Study I, which included subjects aged 57-77 years (1.2%), and 23 were diagnosed with glaucoma in Study IV (7.4%) at age 77-89 years. The prevalence increased with age from 0.55% in the youngest age group to 8.4% in the 80-84 years age group, and then decreased to 5% in the oldest age group. The prevalence of undetected glaucoma was therefore 1.29% in subjects aged 57-89 years.

The participation rate was 77.5% in Study I and 27% in Study IV. The glaucoma diagnosis was confirmed on visual field defects in 95% of glaucomatous eyes in Study I, and in all eyes in Study IV.

Table 3.
Number of screened subjects and glaucoma prevalence (newly detected) in different age groups.

Age cohorts (years)	57-59	60-64	65-69	70-74	75-79	80-84	85-89	Total
No. of screened subjects	2,704	8,779	11,226	7,423	2,807	221	80	33,240
No. of diagnosed patients	15	64	145	106	77	18	4	429
Prevalence %*	0.55	0.73	1.30	1.43	2.8	8.4	5	1.29

* Patients with previously diagnosed glaucoma were excluded; a total of 93 patients in the studies combined.

Severity

In Study I and IV, the severity of undetected glaucoma was reported at screening for the different age groups. In this thesis, glaucoma stages were further simplified with a closer resemblance to the Bascom-Palmer glaucoma staging system, with 3 glaucoma stages reported, see Methods. Early disease (MD value better than -6 dB) was the most

common glaucoma stage in both studies. The severity was similar in age groups between 60-77 years-old. In elderly patients, most glaucomatous eyes had early disease, Fig. 10.

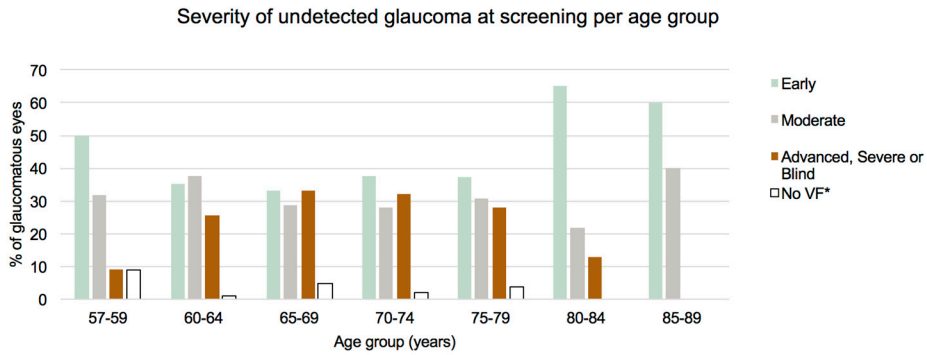


Figure 10
The proportion of glaucomatous eyes in each glaucoma stage per age group.
*No visual field (VF) available for glaucoma staging

In Study I and IV, we reported the number of patients with undetected glaucoma who fulfilled the WHO criteria for blindness due to glaucoma on detection at screening. Such cases were found in all age groups in Study I. No such case was found in the oldest 2 age categories (Study IV).

The number of eyes in each age group in each glaucoma stage is shown in Table 4. Nineteen glaucomatous eyes could not be categorized to a glaucoma stage in Study I, and these are shown as white columns in Fig. 10. These patients could not perform visual field tests e.g., due to underlying disease such as Parkinson´s disease, or visual field testing had been missed, or were totally unreliable (2 patients).

Table 4.
The severity of newly detected glaucomatous eyes at screening in different age groups.

	Severity/Age (years)	57-59	60-64	65-69	70-74	75-79	80-84	85-89	Total
Study I	**Early**	11	29	62	55	39	-	-	196
	Moderate	7	31	54	41	34	-	-	167
	Advanced or worse	2	21	62	47	31	-	-	163
	No VF*	2	1	9	3	4	-	-	19
	Total	22	82	187	146	108	-		545
Study IV	**Early**	-	-	-	-	2	15	3	20
	Moderate	-	-	-	-	0	5	2	7
	Advanced or worse	-	-	-	-	0	3	0	3
	No VF*	-	-	-	-	0	0	0	0
	Total	-	-	-	-	2	23	5	30
Study I + IV	**Early**	11	29	62	55	41	15	4	216
	Moderate	7	31	54	41	34	5	3	174
	Advanced or worse	2	21	62	47	31	3	7	166
	No VF*	2	1	9	3	4	0	0	19
	Total	22	82	187	146	108	23	14	575

*No visual field (VF) available for glaucoma staging.

PEX in undetected glaucoma

Pseudoexfoliations were found in 90 glaucomatous eyes (17%) in Study I, and in 7 glaucomatous eyes (23%) in Study IV. The proportions of glaucomatous eyes with pseudoexfoliations in both studies are shown in Table 5 for each age group and IOP interval.

Table 5
Proportion (%) of glaucomatous eyes with pseudoexfoliations at different IOP intervals and age groups.

IOP mmHg/Years	57-59	60-64	65-69	70-74	75-79	80-84	85-89	Total
<10	0	0	0	0	0	100	0	0
10-14	0	9	11	8	8	31	0	13
15-19	0	0	3	7	16	20	0	6
20-24	0	10	13	6	18	33	0	12
25-29	0	33	21	20	25	0	0	23
30-34	0	50	40	25	63	0	0	39
35 or more	0	80	60	54	100	0	0	61
Total	0	15	17	14	23	30	0	17

Study II

Prediction model

The large material of 32,918 screened individuals provided an opportunity to report the proportion of undetected glaucoma according age and IOP combined.

One eye per patient was used for analysis and the eye with the higher IOP of the two was used. A total of 32,509 subjects were included for analysis, after excluding 83 patients with a glaucoma diagnosis prior to screening and 326 subjects with no IOP measurements.

In Table 6, the proportion of undetected glaucoma in each age group and at each IOP interval is shown. Glaucoma was uncommon at IOP levels up to 25 mmHg, but rose steeply at IOP 25 mmHg or above. The proportion of undetected glaucoma increased exponentially with both older age and higher IOP.

A majority of patients with glaucoma were found to have IOPs within normal limits, 57%. Still, only 0.8% of screened subjects were found to have glaucoma if the IOP was 21 mmHg or less. The proportion of screened subjects with glaucoma at IOP above 21 mmHg was 7.5% (175 patients of 2,342 screened), but was 2.4% at IOP 22-24 mmHg and 18.3% at IOP 25 mmHg or above. A large number of screened subjects had IOP above the statistical upper normal limit of 21 mmHg without a glaucoma diagnosis; 2,167 subjects, 6.7% of all included subjects.

Results from Study IV:

For the purpose of this thesis, proportions of undetected glaucoma at different IOP and age intervals from Study IV were analysed in the same manner as in Study II, but were not used for calculations of the prediction model.

Ten patients were excluded from analysis due to prior glaucoma diagnosis, as well as one subject who refused IOP measurement and 12 subjects who were administering IOP-lowering eye drops prior to the study, whereof one had newly detected glaucoma. A total of 299 subjects remained for analysis.

Higher proportions of glaucoma were found at lower IOPs than in Study II, Table 6.

Table 6
The proportion of undetected glaucoma according to IOP at diagnosis for each age group. The number of glaucoma patients/screened individuals in each cell are shown to the right.

IOP mmHg/Years	57-59	60-64	65-69	70-74	75-79	80-84	85-89	Total
<10	0% 0/12	0% 0/22	0% 0/47	0% 0/49	0% 0/13	0% 0/6	0% 0/2	0% 0/151
10-14	0% 1/746	1% 6/2,415	0% 4/3,343	0% 3/2,082	1% 6/855	9% 8/87	5% 2/36	0% 30/9,564
15-19	1% 9/1,515	1% 23/4,740	1% 46/5,812	1% 42/3,979	2% 33/1407	6% 6/89	7% 2/24	1% 161/17,566
20-24	1% 2/368	1% 19/1,341	2% 39/1,610	5% 26/1,049	5% 19/421	8% 2/23	0% 0/8	2% 107/4,820
25-29	6% 1/18	7% 8/116	14% 29/211	11% 14/127	16% 8/49	0% 0/2	0% 0/1	11% 60/524
30-34	0% 0/0	18% 3/17	21% 8/39	28% 10/36	32% 6/19	50% 1/2	0% 0/0	25% 28/113
35 or more	100% 2/2	42% 5/12	63% 19/30	63% 12/19	57% 4/7	0% 0/0	0% 0/0	60% 42/70
Total	1% 15/2,661	1% 64/8,663	1% 145/11,092	1% 107/7,341	3% 76/2,771	8% 17/209	6% 4/71	1% 428/32,808

*One eye per patient; the eye with the higher IOP was used.

A prediction model for undetected glaucoma was created and IOP had a greater impact on the presence of undetected glaucoma than age, although both increased the risk of glaucoma, Equation 1. The model fit well to the data with a coefficient of determination (R^2) of 0.97.

Equation 1.

$$ln(proportion\ glaucoma) = -9.96 + 0.54\ \text{age group} + 1.34\ \text{IOP group} - 0.07\ (age\ group \times IOP\ group)$$

Study III

Cumulative incidence of glaucoma visual impairment

Seventy-seven of the 90 subjects originally included in the Malmö High Risk Ocular Hypertension Treatment Study in the 1980s were deceased at the time of data collection in 2017. The maximum follow-up time was 33 years. Only 4 subjects were considered lost to follow-up.

Seven subjects became bilaterally visually impaired due to glaucoma, two of whom developed bilateral blindness resulting from glaucoma (3% of subjects).

The cumulative incidence of visual impairment and blindness in at least one eye due to glaucoma is shown in Table 7. The cumulative incidence is shown for every 5th year from inclusion in the original prospective study. The cumulative incidence for visual impairment in at least one eye due to glaucoma was 0.22 after 30 years, and 0.17 for blindness.

Patients who developed glaucoma visual impairment in both eyes developed visual impairment in their better eye at a mean age of 83.7 years (standard deviation 6.1 years).

Table 7.
Cumulative incidence (in %) of glaucoma visual impairment or blindness (at least one eye) in subjects initially followed-up for raised intraocular pressure and at least one more risk factor for glaucoma. The number of subjects at risk is shown to the right. The cumulative incidence is corrected for competing risks.

Years from inclusion in the Malmö High Risk Ocular Hypertension Treatment Study	Visual impairment (%)	At risk	Blindness	At risk
0	0%	77	0%	77
5	0%	71	0%	71
10	1%	60	1%	60
15	10%	47	3%	52
20	17%	28	5%	37
25	22%	13	12%	22
30	22%	4	17%	7

A total of 62% of subjects developed glaucoma, and 4% of these patients developed bilateral blindness due to the disease. Twenty patients developed visual impairment in at least one eye due to reasons other than glaucoma, most often due to age-related macular degeneration, Fig. 11.

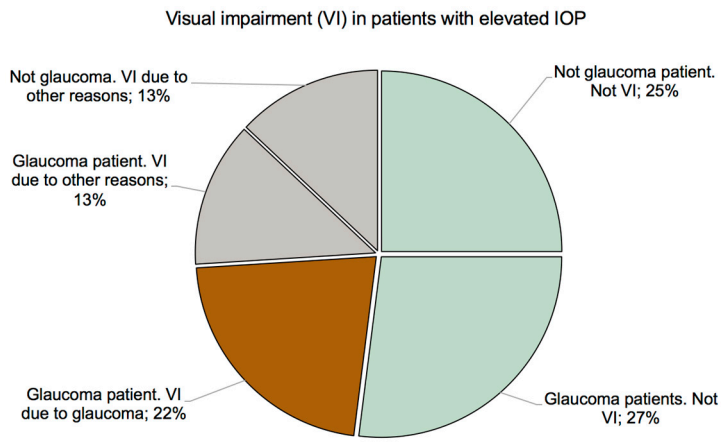


Figure 11
Proportions of subjects with visual impairment due to glaucoma or other reasons than glaucoma at their last visit to an ophthalmology department. VI = Visual Impairment

The baseline risk factors evaluated in this study did not significantly increase the risk of developing visual impairment resulting from glaucoma.

There was no significant difference in the lifetime risk of glaucoma visual impairment between subjects randomized to 0.5% timolol and those who received placebo for up to 10 years in the original prospective study.

Discussion and conclusions

Study I and IV:

With ageing populations, the burden of glaucoma for healthcare is projected to increase in the future (Tham et al. 2014). It is important to detect glaucoma early in order to reduce the likelihood of patients developing visual impairment due to the condition (Grant & Burke 1982; Oliver et al. 2002; Chen 2003; Forsman et al. 2007; Kooner et al. 2008; Peters et al. 2014). Estimation of prevalence and severity of undetected glaucoma is important for the formulation of adequate health policies in the future.

We therefore performed two studies evaluating these factors in different age groups of individuals aged 57-89 years in Malmö, Sweden.

In Study I, a large screening material of 32,918 subjects who had been screened for glaucoma in the 1990s was available for further analysis. This screening is still one of the largest population screenings for glaucoma performed to date. In Study IV, 322 elderly individuals were screened in 2019-2021. We planned to screen about 600 subjects aged 77-89 years who were not already diagnosed with glaucoma. The screening had to be paused due to the coronavirus pandemic. Scheduled screening appointments were cancelled (n=101), which in part contributed to a lower attendance rate. There is still some uncertainty regarding when the study can resume and the remaining 300 subjects can be screened, but preliminary plans are for the fall of 2022.

Prevalence

The prevalence of undetected glaucoma increased with age from 0.55% in the age category of 57-59 years-old, to 7.4% in individuals 77-89 years-old, with a combined prevalence of 1.29%.

Our results were similar to findings in previously published studies, when assuming that about half of all glaucoma cases were undetected, and where the prevalence has been reported to be 2.51% in individuals aged 40-80 years among Europeans (Tham et al. 2014).

The prevalence in elderly individuals, 80 years and older, has been shown to be about 8% to 13% in European derived populations, whereof 34-50% were undetected (Tielsch et al. 1991; Mitchell et al. 1996; Wensor et al. 1998; Friedman et al. 2006; Topouzis et al. 2007; Chan et al. 2017). Assuming that about half of all patients were still undetected in Sweden at the time of the screening in Study IV, it would suggest a higher prevalence in this study compared to earlier screening studies in this age category.

Severity

The severity of newly detected glaucoma was similar in patients aged 60-77 years with about one third of glaucomatous eyes with early disease, one third with moderate disease and one third with advanced, severe or end-stage disease. In elderly patients aged 77-89 years, a great majority had early or moderate disease (90%).

Analysis of visual field loss at presentation is important for the development of appropriate public health pathways and interventions.

At the time of publication of Study I there was a clear need for more information on the analysis of VF loss in glaucoma patients detected at screening using glaucoma staging. Blindness was commonly reported in population screening studies, but reports including some variant of severity staging were sparse. Severity was reported in some studies by analysis of visual acuity (Coffey et al. 1993; Dielemans et al. 1994; Ramakrishnan et al. 2003; Wang et al. 2010), or by descriptions of different patterns of defects (Kahn et al. 1977; Lee et al. 2003), and the studies reported severity for undetected and previously detected glaucoma combined. The Andra Pradesh Eye Disease Study (India) provided results from a stepwise glaucoma staging based on visual field test results in combination with optic-disc criteria (Dandona et al. 2000). They also reported that 52% of patients had advanced field damage in at least one eye at detection, based on optic-disc and visual field criteria combined (<-12dB). The Blue Mountains Eye Study reported the proportion of patients with advanced disease classified as MD <-12 dB in the worse eye for patients with a prior glaucoma diagnosis and newly detected patients combined (Lee et al. 2003).

More recent studies have reported glaucoma stages at detection. Boodhna and Crabb (2015) reported that about 1 in 3 newly detected glaucoma patients had advanced (MD -12 dB or worse) disease in the worse eye at presentation at four eye clinics in England. Chua et al. (2015) reported the prevalence and severity of undetected glaucoma in a population study in Singapore. Severity was reported for the same 5 glaucoma stages as used in Study I and Study IV. About 13% of undiagnosed cases had primary angle-closure glaucoma, but the remaining had open angles. They reported results for the

worse eye and found that glaucoma severity increased with age. A large screening study conducted in China, where about 27,000 subjects were screened (Liang et al. 2018), presented severity at detection using the same staging as we used in Study I and Study IV, and advanced disease or worse (worse eye) was found in about 1/3 of patients detected by the screening. Jones et al. (2020) reported results after retrospective VF extraction of electronic medical records from a medical center in Tanzania. Severity was reported for early, moderate and severe disease. A total of 58% of patients with glaucoma presented with advanced glaucoma in their worst eye.

The two glaucoma screenings evaluated in this thesis (Study I and Study IV) were performed about 25 years apart and different age categories were screened in the two studies. Boodhna and Crabb reported results in 2015 from a study where visual field records were analysed over a 13 years period in England. Glaucoma was found to be diagnosed at earlier stages with fewer individuals having advanced disease at detection (Boodhna & Crabb 2015). A more recent report from England found that 14% of patients (worst eye) had developed advanced visual field defects (MD -12dB or worse) at their first hospital visit in England (Jones et al. 2020), which was lower than reported in the study by Boodhna and Crabb a few years earlier. Another ongoing study with unpublished results within our research group suggests that glaucoma is detected earlier now than in previous decades (Bengtsson, unpublished). In Study IV, we found almost only early glaucoma with low IOPs. This could be a further indication of a trend that glaucoma may be diagnosed earlier than at the time the screening for Study I was performed. Other factors may contribute to the difference in severity at detection reported in I and Study IV, however, as discussed in Manuscript IV.

Given our results from Study I and IV, current case finding pathways for glaucoma are likely sufficient in elderly individuals, aged 77-89 years, since subjects with undetected glaucoma most often had unilateral, early disease and normal tension glaucoma and therefore a low risk for blindness developing given the residual life expectancy. If population screening is started, or case finding strategies enhanced in the future, our results indicate that current pathways for case-detection in elderly individuals may be sufficient.

Study II:

Opticians in Sweden are recommended to refer individuals with IOP above the statistical normal limit of 21 mmHg to glaucoma clinics for evaluation of glaucoma (Skjöld et al. 2019). Ocular hypertension is common in the population (Leske 2007) and this may cause an overload on glaucoma healthcare with subsequent risk for delay in regular follow-up of glaucoma patients with manifest glaucoma. It is important for

glaucoma patients to receive regular follow-up for early detection of progression (Gardiner & Crabb 2002; Jansonius 2007; Chauhan et al. 2008; Nouri-Mahdavi et al. 2011; Crabb & Garway-Heath 2012).

The aim of Study II was to create a prediction model to describe the combined effect of age and IOP on undetected glaucoma. The model could be informative when pathways for glaucoma referral are updated in order to increase the positive predictive value (PPV) of referrals from opticians.

Prediction model

We found an exponential increase in the observed proportions of undetected glaucoma with higher age and higher IOP. Many previous studies have reported an increased prevalence of glaucoma with age and higher IOP (Hollows & Graham 1966; Bankes et al. 1968; Kahn et al. 1977; Bengtsson 1981; Sommer et al. 1991; Dielemans et al. 1994; Mitchell et al. 1996; Wensor et al. 1998; Chan et al. 2017).

We created a predictive model to describe the combined effect of age and IOP on the presence of undetected glaucoma and we found that the model had good correlation to the data (R^2= 0.97). The predicted rate of undetected glaucoma was low if IOP was lower than 25 mmHg. The rate rose rapidly with higher IOP, up to 81% for the group with IOP >35 mmHg and age range 75-77 years. However, most glaucoma patients had normal tension glaucoma (57%) and it should not be forgotten that the sensitivity for IOP as a screening tool is low (Mowatt et al. 2008). Here, the sensitivity was 32% if IOP 25 mmHg was used as a cut-off point.

With an increasingly aging population and a subsequent rise in predicted number of patients with glaucoma who need regular follow-ups, pathways in glaucoma healthcare will likely need to be reappraised and modified.

Recent studies have found that higher IOP limits for IOP-only referrals could reduce the number of referrals without detecting fewer glaucoma cases (Founti et al. 2018; Landgren & Peters 2021; Nilsson & Peters 2021). In the study by Founti et al., in 2018, they found that by raising the referral criterion of the IOP level to an IOP of 27 mmHg would reduce the number of referrals by 44% without missing glaucoma cases. In the Swedish study, by Landgren and Peters (2021), 77% of referrals to the glaucoma section of the Ophthalmology of Skåne University hospital due to raised IOP were due to raised IOP as the only referral criterion. Nilsson and Peters (2021) reported that by applying an age limit of 45 years or more and an IOP of 25 mmHg or more, referrals due to raised IOP would be reduced by 27% without missing glaucoma cases.

The model may be useful when first line eye care providers, such as opticians or general practitioners, consider referral to an ophthalmology clinic. Using the model, this could probably reduce the number of referrals to ophthalmology clinics by reducing false positive referrals.

Study III:

There is no absolute consensus in how patients with ocular hypertension should be followed-up or treated (Tuulonen 2016). As mentioned earlier, OH is a relatively common condition and with an increased burden of glaucoma to society, resources need to be spent effectively. A large proportion of patients with ocular hypertension do not develop glaucoma in long-term follow-up studies (Linnér 1976; Lundberg et al. 1987; Gordon et al. 2002; Forsman et al. 2007). Knowing the lifetime risk of patients with raised IOP of visual impairment resulting from glaucoma is of interest when assessing the healthcare needs for these patients. Only one study, which included 40 subjects with OH, has previously reported results on this matter (Forsman et al. 2007). We were able to retrospectively assess the lifetime risk of visual impairment and blindness for 77 patients who had been followed-up for raised intraocular pressure since the 1980s.

Cumulative incidence of glaucoma visual impairment

Only a small proportion of the included subjects developed bilateral visual impairment due to glaucoma during their lifetime (9%), and only 3% of subjects developed glaucoma blindness in both eyes. We also reported the cumulative incidence correcting for competing risks, see Methods and Results in Study III.

The proportion of glaucoma patients developing visual impairment was low compared to previous studies. Other studies have shown that about 12-16% of glaucoma patients develop bilateral blindness during their lifetime (Forsman et al. 2007; Peters et al. 2013). All subjects had at least one additional risk factor and were considered to have high risk of developing glaucoma. One of the additional risk factors considered was having a suspect disc, which today would give suspicion of pre-perimetric glaucoma (Gordon et al. 2002).

Despite the subjects´ high risk of developing glaucoma, only a small proportion developed glaucoma blindness during their lifetime. This may in part be explained by the fact that the patients in the current study were followed-up regularly, since large

visual field defects at detection are a strong risk factor for glaucoma blindness. The patients received early treatment and half of the patients were randomized to treatment with IOP-lowering drops as a part of the original prospective study for up to 10 years, or received IOP-lowering treatment after the prospective study during follow-up.

The long follow-up time of 33 years was a strength of the study. The power of the study was however low, with only 77 subjects available for analysis, whereof 4 were lost to follow-up.

Conclusions

Study-specific conclusions

Study I

The prevalence of undetected glaucoma increased with age, from 0.55% in the age category 57-59 years, to 2.73% in the oldest age category of 75-77 years, with a total prevalence of 1.23%.

The severity of newly detected glaucoma was similar in patients aged 60-77 years, with about one third of glaucomatous eyes with early disease, one third with moderate disease and one third with advanced, severe or end-stage disease.

Study II

A prediction model for undetected glaucoma was created based on the combined effect of age and IOP and the interaction between the two. The proportion of undetected glaucoma increased markedly at IOP 25 mmHg or above.

Study III

The lifetime risk of bilateral visual impairment due to glaucoma in subjects initially followed-up for elevated IOP and at least one additional risk factor for glaucoma, was 9%, and 3% (2 of 77 patients) of subjects developed bilateral blindness resulting from glaucoma.

Study IV

The prevalence of undetected glaucoma was 7.4% in patients aged 77-89 years. A great majority of patients had early or moderate disease and only 8% of eyes had advanced disease, with no eyes having severe disease or end-stage disease.

Future outlook

Due to the projected growth of the number of patients with glaucoma and the substantial risk for visual impairment from the disease, pathways for detection and management of glaucoma need to be effective to enable the healthcare system to manage the increased burden resulting from the disease.

Future studies could investigate ways to increase the PPV of referral from first line eye healthcare professionals. The safety and cost-effectiveness of higher demands on referrals would simultaneously need to be assessed.

Today, there is a considerable risk for glaucoma patients´ regular follow-up appointments to be delayed, with an increased risk for late detection of progression of the disease. The costs will likely need to be reduced and strategies evolved in order to reduce negative consequences of changes in glaucoma care. Prioritizing patients with higher risk of developing glaucoma visual impairment may be needed.

My research plans for the near future include screening the remaining 300 subjects of Study IV, and analysing the results. Furthermore, it would be interesting to follow-up the patients who were found to have glaucoma at the screening and evaluate the lifetime risk of visual impairment due to glaucoma for this group. If only a small proportion of patients are found to develop visual impairment or blindness due to glaucoma, it would suggest that further case finding e.g., if population screening is started, then individuals in those age categories would probably not need to be invited.

The prediction model in Study II remains to be validated using an independent population in order to determine the applicability of the model.

Summary in Swedish

Glaukom (grön starr) är en av de vanligaste orsakerna till irreversibel blindhet i världen. Sjukdomen påverkar synnerven i ögat och orsakar inskränkt synfält, som oftast börjar i periferin. I tidigt stadie märker den drabbade individen inte av sjukdomen och därför upptäcks sjukdomen ofta först när individen förlorat en stor del av sitt synfält. I länder med utvecklad sjukvård som Sverige, har sjukdomen visat sig vara oupptäckt i inte mindre än hälften av fallen.

Orsaken till sjukdomen är okänd, men flertalet riskfaktorer har identifierats, där förhöjt ögontryck är en av de mest betydande. Sjukdomen är ovanlig före 50 års ålder, men tillkomsten ökar med ålder och har rapporterats till ca 6% i individer >70 år med europeisk härkomst. Prevalensen varierar ganska mycket beroende på populationens etnicitet och är högre bland annat i individer med afrikanskt eller latin-amerikanskt ursprung.

Behandling av sjukdomen kan bromsa sjukdomsprogressen och tidig upptäckt är därför viktig för att minska utveckling av synhandikapp. Sjukdomen kan upptäckas tidigare med screening, och förekomsten av synsvaghet och blindhet har nyligen rapporterats kunna minska med 50% efter screening av populationen.

Screening av glaukom för allmänheten är ej rekommenderad i nuläget och metoder för att diagnosticera glaukom är resurskrävande. För att diagnostisera glaukom behövs undersökning av synnerven, med en ögonläkarbedömning av synnervshuvudet och dessutom krävs tester som mäter funktionen i synfältet, så kallad synfältsundersökning.

Ögontrycket är en stark riskfaktor för utveckling av glaukom men trots det utvecklar en stor andel individer som har högt ögontryck inte glaukom. Hälften av alla individer med glaukom har normala ögontryck och ögontrycket är således inte en del av diagnostiken men är viktig för uppföljning av sjukdomen och för att bedöma effekten av behandling.

Första arbetet i denna avhandling syftade till att finna hur många individer hade oupptäckt glaukom och synfältsdefekternas omfattning från 57-77 års ålder vid en populationsscreening av 32.918 individer som utfördes i Malmö på 1990 talet. Det fjärde arbetet hade samma syfte, fast i äldre individer, d.v.s. att genom screening

kartlägga prevalensen av glaukom samt synfältsdefekternas omfattning i tidigare oupptäckt glaukom hos individer i Malmö som var 77-89 år där 322 individer screenades. Vi fann att prevalensen för oupptäckt glaukom ökade från 0,55% i den yngsta åldersgruppen 57-59 år, till 7,4% i den äldsta åldersgruppen 77-89 år (Tabell 3). När omfattningen av synfältsskadorna undersöktes såg vi att i åldrarna 60-77 år hade ungefär en tredjedel av glaukomögon tidig sjukdom, en tredjedel måttlig sjukdom och en tredjedel hade redan utvecklat allvarlig sjukdom (Fig. 10). Hos både yngre och äldre individer var sjukdomen oftare tidig och mer sällan hade de utvecklat allvarlig sjukdom.

Betydelsen av bedömning av prevalens och synfältsdefekternas omfattning är av intresse för bedömning av sannolikhet för utveckling av synsvaghet och blindhet orsakad av glaukom. Exempelvis är det sannolikt att mycket få av de äldre deltagarna skulle hinna utveckla blindhet i båda ögon p.g.a. glaukom under sin livstid eftersom att trots hög prevalens så var sjukdomen oftast mild.

Det andra delarbetet syftade till skapa en prediktionsmodell för beräkning av förekomst av oupptäckt glaukom baserat på ålder och ögontryck kombinerat, där samma screeningmaterial som i det första delarbetet användes. Proportionen av oupptäckt glaukom utifrån ålder och tryck kombinerat visade att oupptäckt glaukom ökade kraftigt vid ögontryck 25 mmHg i åldrarna 60-77 år. Prediktion av glaukom baserat på enkelt uppmätta faktorer som dessa kan underlätta bedömningar hos t.ex. optiker, när en remiss till ögonläkare övervägs.

Det tredje arbetet syftade till att finna livstidsrisken för synsvaghet och blindhet till följd av glaukom hos individer med förhöjt ögontryck som inkluderades till en longitudinell studie på 1980-talet och följdes efter studieslut på Ögonkliniken i Malmö. Alla deltagare hade högt ögontryck i minst ett öga och ytterligare en eller flera riskfaktorer för utveckling av glaukom. Vid uppföljning 33 år senare hade 77 av 90 deltagare avlidit. Två av dessa 77 individer hade utvecklat blindhet p.g.a. glaukom i båda ögon. Ungefär 60% utvecklade glaukom. En låg andel av dessa glaukompatienter utvecklade blindhet i båda ögon trots att de bedöms ha hög risk för utveckling av glaukom med tanke på riskfaktorerna. Andelen var lägre än vad tidigare studier visar, som visar att runt 12-16% av glaukompatienter utvecklar blindhet i båda ögon under sin livstid. Skillnaden beror sannolikt på att patienterna fick sin diagnos tidigt och därmed tidigt insatt behandling, men studien hade relativt få deltagare. Få långtidsstudier har publicerats som bedömt risk för synsvaghet och blindhet hos patienter med enbart högt ögontryck. Denna kunskap är av intresse för att bedöma sjukvårdsbehovet för denna grupp av patienter.

Summary in Icelandic

Augnsjúkdómurinn gláka er ein algengasta orsök varanlegrar blindu hjá fólki á heimsvísu (WHO). Sjúkdómurinn veldur því að sjónsviðið skerðist. Skerðingin byrjar oftast yst í sjónsviðinu en þegar sjúkdómurinn versnar eykst sjónsviðsskerðingin. Sjúkdómurinn er oftast einkennalaus í byrjun og því er algengt að hann uppgötvist fyrst þegar talsverður hluti af sjónsviðinu er horfinn. Rannsóknir, sem hafa skimað einkennalausa einstaklinga fyrir gláku, hafa sýnt að einungis um helmingur einstaklinga sem reynast vera með gláku verða þess varir.

Sjónsviðsskerðingin sem verður af völdum gláku er óafturkræf og er því mikilvægt að uppgötva sjúkdóminn snemma og helst áður en einstaklingurinn er farinn að finna fyrir einkennum. Meðferðin við gláku felur í sér að lækka augnþrýstinginn, oftast með þrýstingslækkandi augndropum. Einnig er hægt að lækka augnþrýsting með öðrum leiðum en augndropum, þ.e. með lasermeðferð eða skurðaðgerð.

Sömu meðferð er beitt óháð því hvort augnþrýstingurinn hafi verið hár eða lágur í upphafi. Hár augnþrýstingur er skilgreindur sem >21 mmHg (millimetrar kvikasilfurs). Hækkaður augnþrýstingur er vel þekktur sem sterkur áhættuþáttur fyrir gláku. Aðrir þekktir áhættuþættir eru m.a. aldur, kynþáttur og ættarsaga.

Hægt er að greina sjúkdóminn með skoðun hjá augnlækni þar sem læknirinn skoðar sjóntaugina þar sem hún kemur inn í augað. Útlit sjóntaugarinnar inni í auganu breytist þegar einstaklingur fær gláku (sjá Mynd 1). Með sjónsviðsprófi er einnig hægt að mæla sjónsviðstapið sem verður vegna gláku og þegar hvort tveggja er til staðar þá er hægt að setja greininguna.

Í Rannsókn 1 och 4 (Study I og Study IV) var leitast við að finna algengi ógreindrar gláku hjá einstaklingum á aldursbilinu 57- 89 ára og skoðað hversu langt sjúkdómurinn var genginn þegar þeir greindust við skimun. Fyrsta rannsóknin byggði á skimun sem var framkvæmd á tíunda áratug síðustu aldar og þá voru alls 32.918 einstaklingar skimaðir fyrir gláku í Malmö (Málmey) í suðurhluta Svíþjóðar. Niðurstöður sjónsviðsrannsókna þeirra einstaklinga sem fengu glákugreiningu við skimunina var safnað og þau skoðuð, til að finna alvarleika sjúkdómsins við greiningu. Einstaklingar í þessari skimun voru á aldrinum 57-77 ára. Í Rannsókn 4 voru sömu spurningar lagðar fyrir eldri einstaklinga 77-89 ára og alls 322 einstaklingar tóku þátt. Niðurstöður

þessara tveggja rannsókna sýndu aukið algengi með auknum aldri, frá 0,55% í yngsta aldurshópnum 57-59 ára upp í 7,4% í eldri aldurshópnum 77-89 ára (sjá Töflu 3). Þegar alvarleiki sjúkdómsins var skoðaður var alvarleiki svipaður hjá einstaklingum á aldursbilinu 60-77 ára (sjá Mynd 10). Hjá einstaklingum á aldursbilinu 60-77 ára var um þriðjungur af glákuaugum með vægan sjúkdóm, um þriðjungur hafði meðalalvarlegan sjúkdóm og þriðjungur hafði þegar þróast út í að vera með alvarlegan sjúkdóm. Hærra hlutfall einstaklinga var með vægari sjúkdóm við greiningu í eldri einstaklingum 77-89 ára.

Í rannsókninni okkar voru eldri einstaklingar með hátt algengi af ógreindri gláku, en hins vegar var sjúkdómurinn vægur í nær öllum tilfellum. Þar af leiðandi má teljast ólíklegt að þessir einstaklingar munu þróa með sér blindu vegna gláku á lífsleiðinni.

Í Rannsókn 2 (Study II) var augnþrýstingurinn í glákuaugum þeirra einstaklinga sem greindust við sömu skimun og í Rannsókn 1 skoðaður, sjá Töflu nr. 5. Algengi ógreindrar gláku jókst við aukinn augnþrýsting og aukinn aldur, en þetta var þekkt áður sbr. áhættuþættina sem nefndir voru hér ofar í textanum. Við sáum að algengi gláku varð allhátt fyrst við augnþrýsting 25 mmHg á aldursbilinu 60-77 ára. Við bjuggum til formúlu sem lýsir líkum einstaklinga á að hafa ógreinda gláku þegar tekið er tillit til bæði aldurs og augnþrýstings. Mögulega er hægt að hafa formúluna til hliðsjónar þegar metið er hvort senda eigi einstakling til augnlæknis í skoðun, til dæmis ef augnþrýstingurinn er mældur hjá sjóntæknifræðingi við gleraugnamælingu.

Í þriðju rannsókninni (Study III) er athyglinni beint að einstaklingum með háan augnþrýsting sem áhættuþátt. Þrýstingur 21 mmHg er tölfræðileg mörk hás augnþrýstings en margir með háan augnþrýsting sem fylgt er eftir þróa aldrei með sér gláku. Tilgangur Rannsóknar 3 var að athuga hversu margir af þeim sem hafa þennan áhættuþátt þrói með sér blindu eða sjónskerðingu af völdum gláku á lífsleiðinni. Slíkar niðurstöður gætu reynst gagnlegar við þróun leiðbeininga um hvernig skipuleggja eigi meðhöndlun og eftirfylgd einstaklinga með þennan áhættuþátt. Við höfðum aðgang að eldri rannsóknargögnum frá níunda áratug síðustu aldar, þar sem framkvæmd var rannsókn á hópi einstaklinga með háan augnþrýsting sem fylgt var eftir í 10 ár. Allir þátttakendur höfðu háan augnþrýsting í a.m.k. öðru auganu, en allir höfðu einnig a.m.k. einn auka áhættuþátt fyrir gláku. Þegar Rannsókn 3 hófst höfðu 77 einstaklingar látist og við gátum þess vegna fundið lífstíðarniðurstöður fyrir þennan hóp. Við skoðuðum hversu margir höfðu orðið blindir eða sjónskertir vegna gláku við síðustu skoðun hjá augnlækni fyrir andlát.

Niðurstöðurnar sýndu að einungis 2 af 77 urðu blindir af völdum gláku í báðum augum, þrátt fyrir mikla áhættu á gláku. Um 60% þróuðu hins vegar með sér gláku í öðru eða báðum augum (sjá Mynd 11). Einungis 4% af þeim sjúklingum sem greindust

með gláku urðu blindir í báðum augum, sem er lægra hlutfall en aðrar rannsóknir hafa sýnt fram á. Aðrar rannsóknir hafa sýnt fram á að u.þ.b. 12-16% glákusjúklinga verða blindir á báðum augum þrátt fyrir meðferð. Skýringin gæti verið að sjúklingarnir í okkar rannsókn fundust snemma í ferlinu og meðferð var sett inn snemma, áður en einstaklingarnir þróuðu með sér allvarlegan sjúkdóm.

Acknowledgements

I moved to Sweden and began my research education in the year 2010. I have many people to thank who have given me invaluable support over the (many) years. I would especially like to acknowledge the following:

Boel Bengtson, my main supervisor. I am grateful to you for accepting being my supervisor many years ago. I admire your ambition and I feel privileged that I have had the opportunity to learn from world-renowned scientists. I will carry with me all the valuable advice, the striving for high quality research, and all the laughs along the way.

Anders Heijl, my co-supervisor. Thank you for hiring me and giving me the opportunity to explore the world of research. I have appreciated your honest and helpful reviews on my work through the years. I feel fortunate that I got to work on the impressive screening material from the EMGT screening as a part of my thesis.

Patrik Midlöv, my co-supervisor. Thank you for your insights from another perspective and your valuable advice when planning, gathering data and writing the manuscripts.

Catarina Villalba and Johnny Ring: Thank you for all your help with the execution of Study IV. We would not have made it in time without you!

Johan Aspberg, my colleage and co-author of Study IV: I highly appreciate our great co-operation when planning and executing Study IV and I would also like to thank you for the excellent co-operation in Pokemon raids. Keep calm and carry on.

Head of Department: **Lena Rung, Kristina Johansson and Sten Kjellström** I am grateful that research is highly prioritized at our department and that your positive attitude towards research has remained unchanged even at tough times during the pandemic.

HannaMaria Öhnell, my colleage and friend: So increadibly driven and a force of nature when it comes to research. Thank you for bringing me along to the "all you can eat" shrimp buffet at Översten restaurant when I was completely new and alone in Malmö. I am thankful for all the unforgettable moments through the years. Helsinki,

Florence, Umeå and of course Malmö would not have been the same without you as my friend.

Elín Gunnlaugsdóttir, Rannveig Linda Þórisdóttir, Johanna Sundgren: Oh, happy days at work! The everyday fun we have, our Tuesday lunches and sparkling afterworks. Looking forward to many more to come!

My colleages at the Ophthalmology department SUS Malmö and Lund. I especially want to thank the glaucoma research group for your advice through the years.

All individuals who are prepared to participate in scientific research and contribute to science for the benefit of future generations.

My friends Halla, Erna Karen, Inga Sjöfn, Hrafnhildur, Ágústa, Helga, Ragna og Ólöf. I am grateful for finding you and for becoming your friend in college. I am blessed to have friends who accept me for who I am and to know our friendship will last a lifetime.

My in-laws Gullvi and Göran, and Malin and Filip. Thank you for welcoming me to your wonderful family with open arms. I am proud to be a part of the "family of chefs" (kockafamiljen).

My family: Bryndís, Óskar, Magga, Guðrún and Guðjón.

I remember us sitting in the car, the whole family, somewhere in middle Sweden, surrounded by only trees as far as the eye could see and suddenly my father Óskar bursts out: "Look! Monkeys, lions and polar bears!"

You are all my rolemodels in life. Thank you for all your support, always. You are the most wonderful, amazing, fun, supportive and inspirational people I know.

My sons **Oskar** and **Harald:**

You are my joy and what gives me energy, your hugs and laughter. You make me live in the moment, to be present and focus on the important things in life. I couldn't love you more.

My beloved **Jakob**.

Thank you for going out after work that evening in October 2011, so that we could meet for the first time. Thank you for all your support, for tolerating my sense of humour and for being a little bit crazy, like me. I love you.

References

Airaksinen PJ & A Heijl (1983): Visual field and retinal nerve fibre layer in early glaucoma after optic disc haemorrhage. Acta Ophthalmol (Copenh) **61**: 186-194.

Airaksinen PJ, E Mustonen & HI Alanko (1981): Optic disc haemorrhages precede retinal nerve fibre layer defects in ocular hypertension. Acta Ophthalmol (Copenh) **59**: 627-641.

Ashaye A, O Ashaolu, O Komolafe, BG Ajayi, O Olawoye, B Olusanya & C Adeoti (2013): Prevalence and types of glaucoma among an indigenous African population in southwestern Nigeria. Invest Ophthalmol Vis Sci **54**: 7410-7416.

Aspberg J, A Heijl & B Bengtsson (2021): Screening for Open-Angle Glaucoma and Its Effect on Blindness. Am J Ophthalmol **228**: 106-116.

ASSA (2007): American Social Security Administration. Social Security Ruling 07-01p: Titles II and XVI: Evaluating Visual Field Loss Using Automated Static Threshold Perimetry. Federal Register Vol. 72, No 146. p 41796. (Visited 2021-12-28). URL: https://www.ssa.gov/OP_Home/rulings/di/01/SSR2007-01-di-01.html.

Aulhorn E & H Karmeyer (1977): Frequency distribution in early glaucomatous visual field defects. . *Doc Ophthalmol Proc Ser*: 75-83.

Bankes JL, ES Perkins, S Tsolakis & JE Wright (1968): Bedford glaucoma survey. Br Med J **1**: 791-796.

Baskaran M, RC Foo, CY Cheng, AK Narayanaswamy, YF Zheng, R Wu, SM Saw, PJ Foster, TY Wong & T Aung (2015): The Prevalence and Types of Glaucoma in an Urban Chinese Population: The Singapore Chinese Eye Study. JAMA Ophthalmol **133**: 874-880.

Bengtsson B (1981): The prevalence of glaucoma. Br J Ophthalmol **65**: 46-49.

Bikbov MM, TR Gilmanshin, RM Zainullin, GM Kazakbaeva, II Arslangareeva, S Panda-Jonas, RI Khikmatullin, SK Aminev, IF Nuriev, AF Zaynetdinov, YV Uzianbaeva, NA Nikitin, SR Mukhamadieva, DF Yakupova, EM Rakhimova, IA Rusakova, NI Bolshakova, KR Safiullina & JB Jonas (2020): Prevalence and associated factors of glaucoma in the Russian Ural Eye and Medical Study. Sci Rep **10**: 20307.

Bjerrum J (1889): Om en Tilföjelse til den sädvanlige Synsfeltsundersögelse samt om Synsfeltet ved Glavkom. Nord Ophthalmol Tidskrift: 141-185.

Boodhna T & DP Crabb (2015): Disease severity in newly diagnosed glaucoma patients with visual field loss: trends from more than a decade of data. Ophthalmic Physiol Opt **35**: 225-230.

Bourne RR, GA Stevens, RA White, JL Smith, SR Flaxman, H Price, JB Jonas, J Keeffe, J Leasher, K Naidoo, K Pesudovs, S Resnikoff, HR Taylor & VLE Group (2013): Causes of vision loss worldwide, 1990-2010: a systematic analysis. Lancet Glob Health **1**: e339-349.

Bourne RR, P Sukudom, PJ Foster, V Tantisevi, S Jitapunkul, PS Lee, GJ Johnson & P Rojanapongpun (2003): Prevalence of glaucoma in Thailand: a population based survey in Rom Klao District, Bangkok. Br J Ophthalmol **87**: 1069-1074.

Bourne RR, HR Taylor, SR Flaxman, J Keeffe, J Leasher, K Naidoo, K Pesudovs, RA White, TY Wong, S Resnikoff, JB Jonas & VLEGotGBoD Study (2016): Number of People Blind or Visually Impaired by Glaucoma Worldwide and in World Regions 1990 - 2010: A Meta-Analysis. PLoS One **11**: e0162229.

Bowling B, SD Chen & JF Salmon (2005): Outcomes of referrals by community optometrists to a hospital glaucoma service. Br J Ophthalmol **89**: 1102-1104.

Brooks AM & WE Gillies (1988): The presentation and prognosis of glaucoma in pseudoexfoliation of the lens capsule. Ophthalmology **95**: 271-276.

Brudenell Carter R (1872): Description of an improved demonstrating ophthalmoscope, and of a perimeter. In: Power H (ed.) Fourth Ophthalmological Congress. King´s College, London. Savill, Edwards and co: 69-75.

Brusini P & CA Johnson (2007): Staging functional damage in glaucoma: review of different classification methods. Surv Ophthalmol **52**: 156-179.

Budenz DL, K Barton, J Whiteside-de Vos, J Schiffman, J Bandi, W Nolan, L Herndon, H Kim, G Hay-Smith, JM Tielsch & TESS Group (2013): Prevalence of glaucoma in an urban West African population: the Tema Eye Survey. JAMA Ophthalmol **131**: 651-658.

Burr JM, G Mowatt, R Hernández, MA Siddiqui, J Cook, T Lourenco, C Ramsay, L Vale, C Fraser, A Azuara-Blanco, J Deeks, J Cairns, R Wormald, S McPherson, K Rabindranath & A Grant (2007): The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation. Health Technol Assess **11**: iii-iv, ix-x, 1-190.

Cairns JE (1968): Trabeculectomy. Preliminary report of a new method. Am J Ophthalmol **66**: 673-679.

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

Chauhan BC, FS Mikelberg, AG Balaszi, RP LeBlanc, MR Lesk, GE Trope & CGS Group (2008): Canadian Glaucoma Study: 2. risk factors for the progression of open-angle glaucoma. Arch Ophthalmol **126**: 1030-1036.

Chen PP (2003): Blindness in patients with treated open-angle glaucoma. Ophthalmology **110**: 726-733.

Chua J, M Baskaran, PG Ong, Y Zheng, TY Wong, T Aung & CY Cheng (2015): Prevalence, Risk Factors, and Visual Features of Undiagnosed Glaucoma: The Singapore Epidemiology of Eye Diseases Study. JAMA Ophthalmol **133**: 938-946.

Coffey M, A Reidy, R Wormald, WX Xian, L Wright & P Courtney (1993): Prevalence of glaucoma in the west of Ireland. Br J Ophthalmol **77**: 17-21.

Crabb DP & DF Garway-Heath (2012): Intervals between visual field tests when monitoring the glaucomatous patient: wait-and-see approach. Invest Ophthalmol Vis Sci **53**: 2770-2776.

Dandona L, R Dandona, M Srinivas, P Mandal, RK John, CA McCarty & GN Rao (2000): Open-angle glaucoma in an urban population in southern India: the Andhra Pradesh eye disease study. Ophthalmology **107**: 1702-1709.

Davey CJ, C Green & DB Elliott (2011): Assessment of referrals to the hospital eye service by optometrists and GPs in Bradford and Airedale. Ophthalmic Physiol Opt **31**: 23-28.

Davey CJ, C Harley & DB Elliott (2013): Levels of state and trait anxiety in patients referred to ophthalmology by primary care clinicians: a cross sectional study. PLoS One **8**: e65708.

Dielemans I, JR Vingerling, RC Wolfs, A Hofman, DE Grobbee & PT de Jong (1994): The prevalence of primary open-angle glaucoma in a population-based study in The Netherlands. The Rotterdam Study. Ophthalmology **101**: 1851-1855.

EGS (2020): European Glaucoma Society. Terminology and guidelines for glaucoma 5th ed. Savona, Italy. PubliComm.

Ekström C (1993): Elevated intraocular pressure and pseudoexfoliation of the lens capsule as risk factors for chronic open-angle glaucoma. A population-based five-year follow-up study. Acta Ophthalmol (Copenh) **71**: 189-195.

Fankhauser F, P Koch & A Roulier (1972): On automation of perimetry. Albrecht Von Graefes Arch Klin Exp Ophthalmol **184**: 126-150.

Forsman E, T Kivela & E Vesti (2007): Lifetime visual disability in open-angle glaucoma and ocular hypertension. J Glaucoma **16**: 313-319.

Foster PJ, FT Oen, D Machin, TP Ng, JG Devereux, GJ Johnson, PT Khaw & SK Seah (2000): The prevalence of glaucoma in Chinese residents of Singapore: a cross-sectional population survey of the Tanjong Pagar district. Arch Ophthalmol **118**: 1105-1111.

Founti P, F Topouzis, G Holló, B Cvenkel, M Iester, AB Haidich, P Kóthy, A Kiana, D Kolokotroni & AC Viswanathan (2018): Prospective study of glaucoma referrals across Europe: are we using resources wisely? Br J Ophthalmol **102**: 329-337.

Friedman DS, HD Jampel, B Muñoz & SK West (2006): The prevalence of open-angle glaucoma among blacks and whites 73 years and older: the Salisbury Eye Evaluation Glaucoma Study. Arch Ophthalmol **124**: 1625-1630.

Gardiner SK & DP Crabb (2002): Frequency of testing for detecting visual field progression. Br J Ophthalmol **86**: 560-564.

Garway-Heath DF, DP Crabb, C Bunce, G Lascaratos, F Amalfitano, N Anand, A Azuara-Blanco, RR Bourne, DC Broadway, IA Cunliffe, JP Diamond, SG Fraser, TA Ho, KR Martin, AI McNaught, A Negi, K Patel, RA Russell, A Shah, PG Spry, K Suzuki, ET White, RP Wormald, W Xing & TG Zeyen (2015): Latanoprost for open-angle glaucoma (UKGTS): a randomised, multicentre, placebo-controlled trial. Lancet **385**: 1295-1304.

Goldmann H (1945): Ein selbstregistrierendes Projektionskugelperimeter. Ophthalmologica: 72-79.

Goldmann H (1954): [A new applanation tonometer]. Bull Mem Soc Fr Ophtalmol **67**: 474-477; discussion, 477-478.

Gordon MO, JA Beiser, JD Brandt, DK Heuer, EJ Higginbotham, CA Johnson, JL Keltner, JP Miller, RK Parrish, 2nd, MR Wilson & MA Kass (2002): The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. Arch Ophthalmol **120**: 714-720; discussion 829-730.

Gordon MO & MA Kass (2018): What We Have Learned From the Ocular Hypertension Treatment Study. Am J Ophthalmol **189**: xxiv-xxvii.

Grant WM & JF Burke, Jr. (1982): Why do some people go blind from glaucoma? Ophthalmology **89**: 991-998.

Gray RJ (1988): A Class of K-Sample Tests for Comparing the Cumulative Incidence of a Competing Risk. The Annals of Statistics. Institute of Mathematical Statistics: 1141-1154.

Grødum K, A Heijl & B Bengtsson (2002): A comparison of glaucoma patients identified through mass screening and in routine clinical practice. Acta Ophthalmol Scand **80**: 627-631.

Grødum K, A Heijl & B Bengtsson (2005): Risk of glaucoma in ocular hypertension with and without pseudoexfoliation. Ophthalmology **112**: 386-390.

Gupta P, D Zhao, E Guallar, F Ko, MV Boland & DS Friedman (2016): Prevalence of Glaucoma in the United States: The 2005-2008 National Health and Nutrition Examination Survey. Invest Ophthalmol Vis Sci **57**: 2905–2913.

Harms H (1960): Die Bedeutung einer einheitlichen Prüfweise aller Sehfunktionen. München. Bericht über die 63. Zusammenkunft der Deutschen Ophthalmologischen Gesellschaft in Berlin vom 25.-29. September 1960: 535-543.

Heijl A (1985): The Humphrey Field Analyzer: Concepts and Clinical Results. In: Greve E.L., Leydhecker W., Raitta C. (eds) Second European Glaucoma Symposium, Helsinki, May 1984. Documenta Ophthalmologica Proceedings Series, Springer, Dordrecht.

Heijl A, J Aspberg & B Bengtsson (2011): The effect of different criteria on the number of patients blind from open-angle glaucoma. BMC Ophthalmol **11**: 31.

Heijl A & B Bengtsson (2000): Long-term effects of timolol therapy in ocular hypertension: a double-masked, randomised trial. Graefes Arch Clin Exp Ophthalmol **238**: 877-883.

Heijl A & CE Krakau (1975): An automatic perimeter for glaucoma visual field screening and control. Construction and clinical cases. Albrecht Von Graefes Arch Klin Exp Ophthalmol **197**: 13-23.

Heijl A, VM Patella & B Bengtsson (2012): The Field Analyzer Primer: Effective Perimetry. Dublin, California, USA. Carl Zeiss Meditec, Inc.

Hirvelä H, A Tuulonen & L Laatikainen (1994): Intraocular pressure and prevalence of glaucoma in elderly people in Finland: a population-based study. Int Ophthalmol **18**: 299-307.

Hodapp E, R Parrish & D Anderson (1993): Clinical decisions in glaucoma, 52-61 ed. St. Louis, MO: CV Mosby.

Hollows FC & PA Graham (1966): Intra-ocular pressure, glaucoma, and glaucoma suspects in a defined population. Br J Ophthalmol **50**: 570-586.

Jansonius NM (2007): Progression detection in glaucoma can be made more efficient by using a variable interval between successive visual field tests. Graefes Arch Clin Exp Ophthalmol **245**: 1647-1651.

Jonas JB, T Aung, RR Bourne, AM Bron, R Ritch & S Panda-Jonas (2017): Glaucoma. Lancet **390**: 2183-2193.

Jonasson F, KF Damji, A Arnarsson, T Sverrisson, L Wang, H Sasaki & K Sasaki (2003): Prevalence of open-angle glaucoma in Iceland: Reykjavik Eye Study. Eye (Lond) **17**: 747-753.

Jones PR, H Philippin, WU Makupa, MJ Burton & DP Crabb (2020): Severity of Visual Field Loss at First Presentation to Glaucoma Clinics in England and Tanzania. Ophthalmic Epidemiol **27**: 10-18.

Kahn HA, HM Leibowitz, JP Ganley, MM Kini, T Colton, RS Nickerson & TR Dawber (1977): The Framingham Eye Study. I. Outline and major prevalence findings. Am J Epidemiol **106**: 17-32.

Keel S, J Xie, J Foreman, PY Lee, M Alwan, ET Fahy, P van Wijngaarden, JC Fan Gaskin, GS Ang, JG Crowston, HR Taylor & M Dirani (2019): Prevalence of glaucoma in the Australian National Eye Health Survey. Br J Ophthalmol **103**: 191-195.

Kim HT (2007): Cumulative incidence in competing risks data and competing risks regression analysis. Clin Cancer Res **13**: 559-565.

Kooner KS, M AlBdoor, BJ Cho & B Adams-Huet (2008): Risk factors for progression to blindness in high tension primary open angle glaucoma: Comparison of blind and nonblind subjects. Clin Ophthalmol **2**: 757-762.

Kyari F, G Entekume, M Rabiu, P Spry, R Wormald, W Nolan, GV Murthy, CE Gilbert & NNBaVIS Group (2015): A Population-based survey of the prevalence and types of glaucoma in Nigeria: results from the Nigeria National Blindness and Visual Impairment Survey. BMC Ophthalmol **15**: 176.

Landgren K & D Peters (2021): A prospective study on effectiveness of elevated intraocular pressure as a criterion for glaucoma referrals by optometric practitioners in Sweden. Acta Ophthalmol **99**: e1098-e1105.

Latina MA, SA Sibayan, DH Shin, RJ Noecker & G Marcellino (1998): Q-switched 532-nm Nd:YAG laser trabeculoplasty (selective laser trabeculoplasty): a multicenter, pilot, clinical study. Ophthalmology **105**: 2082-2088; discussion 2089-2090.

Lee AJ, JJ Wang, E Rochtchina, P Healey, EM Chia & P Mitchell (2003): Patterns of glaucomatous visual field defects in an older population: the Blue Mountains Eye Study. Clin Exp Ophthalmol **31**: 331-335.

Lee JM, J Caprioli, K Nouri-Mahdavi, AA Afifi, E Morales, M Ramanathan, F Yu & AL Coleman (2014): Baseline prognostic factors predict rapid visual field deterioration in glaucoma. Invest Ophthalmol Vis Sci **55**: 2228-2236.

Leske MC (2007): Open-angle glaucoma -- an epidemiologic overview. Ophthalmic Epidemiol **14**: 166-172.

Leske MC, AM Connell, AP Schachat & L Hyman (1994): The Barbados Eye Study. Prevalence of open angle glaucoma. Arch Ophthalmol **112**: 821-829.

Leske MC, A Heijl, M Hussein, B Bengtsson, L Hyman, E Komaroff & EMGT Group (2003): Factors for glaucoma progression and the effect of treatment: the early manifest glaucoma trial. Arch Ophthalmol **121**: 48-56.

Leske MC, A Heijl, L Hyman & B Bengtsson (1999): Early Manifest Glaucoma Trial: design and baseline data. Ophthalmology **106**: 2144-2153.

Leydhecker W, K Akiyama & H Neumann (1958): Intraocular pressure in normal human eyes. Klin Monbl Augenheilkd Augenarztl Fortbild: 662-670.

Li H, YY Zhang, SC Liu, XG He, CJ Li, CH Li, G Li, J Xu, YF Wu & SF Song (2014): Prevalence of open-angle glaucoma in southwestern China: the Yongchuan Glaucoma study. J Huazhong Univ Sci Technolog Med Sci **34**: 137-141.

Liang Y, J Jiang, W Ou, X Peng, R Sun, X Xu, J Yang, C Hu, C Ye, N Congdon & F Lu (2018): Effect of Community Screening on the Demographic Makeup and Clinical Severity of Glaucoma Patients Receiving Care in Urban China. Am J Ophthalmol **195**: 1-7.

Liang YB, DS Friedman, Q Zhou, X Yang, LP Sun, LX Guo, QS Tao, DS Chang, NL Wang & HES Group (2011): Prevalence of primary open angle glaucoma in a rural adult Chinese population: the Handan eye study. Invest Ophthalmol Vis Sci **52**: 8250-8257.

Lindberg J (1917): Clinical investigations on depigmentation of the pupillary border and translucency of the iris in cases of senile cataract and in normal eyes in elderly persons. Thesis. Helsinki. (English translation, 1989). Copenhagen. Acta Ophthalmol Suppl: 1-96.

Lindén C, B Bengtsson, A Alm, B Calissendorff, I Eckerlund & A Heijl (2013): Glaucoma management in Sweden -- results from a nationwide survey. Acta Ophthalmol **91**: 20-24.

Linnér E (1976): Ocular hypertension. I. The clinical course during ten years without therapy. Aqueous humour dynamics. Acta Ophthalmol (Copenh) **54**: 707-720.

Lundberg L, K Wettrell & E Linnér (1987): Ocular hypertension. A prospective twenty-year follow-up study. Acta Ophthalmol (Copenh) **65**: 705-708.

Mackenzie W (1830): A practical treatise on diseases of the eye. London: Longman, Rees, Orme, Brown and Green: 892.

Mason RP, O Kosoko, MR Wilson, JF Martone, CL Cowan, JC Gear & D Ross-Degnan (1989): National survey of the prevalence and risk factors of glaucoma in St. Lucia, West Indies. Part I. Prevalence findings. Ophthalmology **96**: 1363-1368.

Mills RP, DL Budenz, PP Lee, RJ Noecker, JG Walt, LR Siegartel, SJ Evans & JJ Doyle (2006): Categorizing the stage of glaucoma from pre-diagnosis to end-stage disease. Am J Ophthalmol **141**: 24-30.

Mitchell P, W Smith, K Attebo & PR Healey (1996): Prevalence of open-angle glaucoma in Australia. The Blue Mountains Eye Study. Ophthalmology **103**: 1661-1669.

Mowatt G, JM Burr, JA Cook, MA Siddiqui, C Ramsay, C Fraser, A Azuara-Blanco & JJ Deeks (2008): Screening tests for detecting open-angle glaucoma: systematic review and meta-analysis. Invest Ophthalmol Vis Sci **49**: 5373-5385.

Müller H (1872): Heinrich Müller's gesammelte und hinterlassene Schriften zur Anatomie und Physiologie des Auges; VII. Glaukom und Excavation des Sehnerven. Leipzig. Verlag von Wilhelm Engelmann.

Narayanaswamy A, M Baskaran, Y Zheng, R Lavanya, R Wu, WL Wong, SM Saw, CY Cheng, TY Wong & T Aung (2013): The prevalence and types of glaucoma in an urban Indian population: the Singapore Indian Eye Study. Invest Ophthalmol Vis Sci **54**: 4621-4627.

Ng M, PA Sample, JP Pascual, LM Zangwill, CA Girkin, JM Liebmann, RN Weinreb & L Racette (2012): Comparison of visual field severity classification systems for glaucoma. J Glaucoma **21**: 551-561.

Nilsson AG & D Peters (2021): Effectiveness of Elevated Intraocular Pressure as a Criterion for Glaucoma Referral After 6 Years of Follow-Up. Clin Ophthalmol **15**: 3041-3049.

Nouri-Mahdavi K, N Nassiri, A Giangiacomo & J Caprioli (2011): Detection of visual field progression in glaucoma with standard achromatic perimetry: a review and practical implications. Graefes Arch Clin Exp Ophthalmol **249**: 1593-1616.

Oliver JE, MG Hattenhauer, D Herman, DO Hodge, R Kennedy, M Fang-Yen & DH Johnson (2002): Blindness and glaucoma: a comparison of patients progressing to blindness from glaucoma with patients maintaining vision. Am J Ophthalmol **133**: 764-772.

Optikerförbundet (2021): Optikerförbundets riktlinjer. (Visited 2021-12-02). URL: https://optikerforbundet.se/optikerforbundets-riktlinjer/.

Pan CW, CH Zhao, MB Yu, Q Cun, Q Chen, W Shen, J Li, JG Xu, Y Yuan & H Zhong (2016): Prevalence, types and awareness of glaucoma in a multi-ethnic population in rural China: the Yunnan Minority Eye Study. Ophthalmic Physiol Opt **36**: 664-670.

Peters D, B Bengtsson & A Heijl (2013): Lifetime risk of blindness in open-angle glaucoma. Am J Ophthalmol **156**: 724-730.

Peters D, B Bengtsson & A Heijl (2014): Factors associated with lifetime risk of open-angle glaucoma blindness. Acta Ophthalmol **92**: 421-425.

Quigley HA (2011): Glaucoma. Lancet **377**: 1367-1377.

Quigley HA, EM Addicks, WR Green & AE Maumenee (1981): Optic nerve damage in human glaucoma. II. The site of injury and susceptibility to damage. Arch Ophthalmol **99**: 635-649.

Ramachandran VS & RL Gregory (1991): Perceptual filling in of artificially induced scotomas in human vision. Nature **350**: 699-702.

Ramakrishnan R, PK Nirmalan, R Krishnadas, RD Thulasiraj, JM Tielsch, J Katz, DS Friedman & AL Robin (2003): Glaucoma in a rural population of southern India: the Aravind comprehensive eye survey. Ophthalmology **110**: 1484-1490.

Ratnarajan G, W Newsom, SA Vernon, C Fenerty, D Henson, F Spencer, Y Wang, R Harper, A McNaught, L Collins, M Parker, J Lawrenson, R Hudson, PT Khaw, R Wormald, D Garway-Heath & R Bourne (2013): The effectiveness of schemes that refine referrals between primary and secondary care--the UK experience with glaucoma referrals: the Health Innovation & Education Cluster (HIEC) Glaucoma Pathways Project. BMJ Open **3**.

Rudnicka AR, S Mt-Isa, CG Owen, DG Cook & D Ashby (2006): Variations in primary open-angle glaucoma prevalence by age, gender, and race: a Bayesian meta-analysis. Invest Ophthalmol Vis Sci **47**: 4254-4261.

Salmon NJ, HP Terry, AD Farmery & JF Salmon (2007): An analysis of patients discharged from a hospital-based glaucoma case-finding clinic over a 3-year period. Ophthalmic Physiol Opt **27**: 399-403.

Saunders LJ, RA Russell, JF Kirwan, AI McNaught & DP Crabb (2014): Examining visual field loss in patients in glaucoma clinics during their predicted remaining lifetime. Invest Ophthalmol Vis Sci **55**: 102-109.

Schiøtz H (1905): Et nyt tonometer, tonometri. Norsk Mag Lægevidensk: 597-622.

Shah S & IE Murdoch (2011): NICE - impact on glaucoma case detection. Ophthalmic Physiol Opt **31**: 339-342.

Sigsgaard J (1942): Palle alene i verden. Copenhagen. Gyldendal.

Skjöld G, R Sidestam & M Ayala (2019): Riktlinjer vid undersökningar utförda av optometrister och optiker i Sverige: Hantering av patienter med ökad risk för glaukom. (Visited 2021-12-03). URL: https://optikerforbundet.se/wp-content/uploads/2021/01/Hantering-av-patienter-med-o%CC%88kad-risk-fo%CC%88r-glaukom_20210128.pdf. Optikerförbundet.

Sloan LL (1939): Instruments and technics for the clinical testing of light sense III. An apparatus for studying regional differences in light sense. Arch Ophthalmol: 233-251.

Socialstyrelsen (2019): Nationella screeningprogram. Modell för bedömning, införande och uppföljning. (Visited 2021-12-02). URL: https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/nationella-screeningprogram/2019-4-12.pdf. Socialstyrelsen.

Soh Z, M Yu, BK Betzler, S Majithia, S Thakur, YC Tham, TY Wong, T Aung, DS Friedman & CY Cheng (2021): The Global Extent of Undetected Glaucoma in Adults: A Systematic Review and Meta-analysis. Ophthalmology **128**: 1393-1404.

Sommer A, JM Tielsch, J Katz, HA Quigley, JD Gottsch, J Javitt & K Singh (1991): Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans. The Baltimore Eye Survey. Arch Ophthalmol **109**: 1090-1095.

Song W, L Shan, F Cheng, P Fan, L Zhang, W Qu, Q Zhang & H Yuan (2011): Prevalence of glaucoma in a rural northern china adult population: a population-based survey in kailu county, inner mongolia. Ophthalmology **118**: 1982-1988.

Tham YC, X Li, TY Wong, HA Quigley, T Aung & CY Cheng (2014): Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. Ophthalmology **121**: 2081-2090.

Tielsch JM, A Sommer, J Katz, RM Royall, HA Quigley & J Javitt (1991): Racial variations in the prevalence of primary open-angle glaucoma. The Baltimore Eye Survey. JAMA **266**: 369-374.

Topouzis F, MR Wilson, A Harris, E Anastasopoulos, F Yu, L Mavroudis, T Pappas, A Koskosas & AL Coleman (2007): Prevalence of open-angle glaucoma in Greece: the Thessaloniki Eye Study. Am J Ophthalmol **144**: 511-519.

Tsatsos M & D Broadway (2007): Controversies in the history of glaucoma: is it all a load of old Greek? Br J Ophthalmol **91**: 1561-1562.

Tuck MW & RP Crick (1991): Efficiency of referral for suspected glaucoma. BMJ **302**: 998-1000.

Tuulonen A (2016): Treatment of ocular hypertension: is it cost effective? Curr Opin Ophthalmol **27**: 89-93.

UN (2019): United Nations. Global Issues Aging. (Visited 2021-12-03). URL: https://www.un.org/en/global-issues/ageing.

Varma R, PP Lee, I Goldberg & S Kotak (2011): An assessment of the health and economic burdens of glaucoma. Am J Ophthalmol **152**: 515-522.

Varma R, M Ying-Lai, BA Francis, BB Nguyen, J Deneen, MR Wilson & SP Azen (2004): Prevalence of open-angle glaucoma and ocular hypertension in Latinos: the Los Angeles Latino Eye Study. Ophthalmology **111**: 1439-1448.

von Graefe A (1856): Ueber die Untersuchung des Gesichtsfeldes bei amblyopischen Affectionen. Albrecht Von Graefes Arch Ophthalmol: 258-298.

Wang YX, L Xu, H Yang & JB Jonas (2010): Prevalence of glaucoma in North China: the Beijing Eye Study. Am J Ophthalmol **150**: 917-924.

Wensor MD, CA McCarty, YL Stanislavsky, PM Livingston & HR Taylor (1998): The prevalence of glaucoma in the Melbourne Visual Impairment Project. Ophthalmology **105**: 733-739.

WHO (2007): World Health Organization. Vision 2020. The right to sight. Global initiative for the elimination of avoidable blindness. Action plan. (Visited 2021-12-05). URL: https://www.who.int/blindness/Vision2020_report.pdf.

WHO (2021): World Health Organization. Blindness and vision impairment. (Visited 2021-12-04). URL: https://www.who.int/news-room/fact-sheets/detail/blindness-and-visual-impairment.

Wilson J & Y Jungner (1968): Principles and practice of mass screening for disease. Bol Of Sanit Panam (Engl): 281-393.

Wilson R, AM Walker, DK Dueker & RP Crick (1982): Risk factors for rate of progression of glaucomatous visual field loss: a computer-based analysis. Arch Ophthalmol **100**: 737-741.

Wise JB & SL Witter (1979): Argon laser therapy for open-angle glaucoma. A pilot study. Arch Ophthalmol **97**: 319-322.

Paper I

Prevalence and Severity of Undetected Manifest Glaucoma

Results from the Early Manifest Glaucoma Trial Screening

Anders Heijl, MD, PhD,[1] *Boel Bengtsson, PhD,*[1] *Sigridur Erla Oskarsdottir, MD*[1]

Purpose: To estimate the prevalence and severity of undetected glaucoma in the population.

Design: Cross-sectional study.

Participants: A total of 32 918 subjects aged 55 to 79 years from Malmö, Sweden, who were screened between 1992 and 1997. All subjects in the screened age groups living in the catchment area, and for whom there were no recent records at the Malmö University Hospital Ophthalmology department, were invited. The main purpose of the screening was to recruit subjects for the Early Manifest Glaucoma Trial.

Methods: We registered the age, sex, and amount of visual field loss in subjects with previously undiagnosed glaucoma identified at the screening. The disease was categorized into 5 stages based on perimetric mean deviation values.

Main Outcome Measures: Prevalence of undetected glaucoma at various disease stages in different age groups expressed as percentages.

Results: Among the screened subjects, who were 77.5% of all invited subjects, a total of 406 subjects (1.23%) were identified with previously undetected glaucoma. Prevalence increased with age, from 0.55% at 55 to 59 years to 2.73% at 75 to 79 years. Unilateral disease accounted for 66% of all cases. Extent of visual field loss was similar in all age groups from 60 years and more. Most eyes had early (35%) or moderate (31%) glaucomatous visual field defects, but 134 subjects (33%) had advanced visual field loss in at least 1 eye. No subject was blind in both eyes, but 3.4% of the newly diagnosed patients were unilaterally blind because of glaucoma.

Conclusions: Prevalence of undetected glaucoma increased with age, whereas disease severity did not increase in subjects older than 60 years of age. One third of subjects with previously undetected glaucoma had advanced or later-stage disease in at least 1 eye. Unilaterally blind subjects were present in all age groups.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references.
Ophthalmology 2013;120:1541-1545 © 2013 by the American Academy of Ophthalmology.

Population-based studies have shown that in developed countries, approximately half of all persons with manifest glaucoma are unaware of their disease.[1–6] Because of its asymptomatic initial phases, glaucoma is often detected late, when patients have extensive and irreversible damage, or by chance.[7] Early detection and subsequent management are important to prevent visual impairment, and population screening for glaucoma has been discussed. However, there are many important considerations when determining whether some form of screening is worthwhile[8]; these include the age-specific prevalence and severity of undetected disease.

The aim of this article was to determine the prevalence of undetected glaucoma in different age groups and the magnitude of visual field loss of the subjects identified with previously undetected glaucoma.

Materials and Methods

A population-based screening of 32 918 residents of Malmö was performed during 1991 to 1997 to identify subjects with previously undetected glaucoma for recruitment to the Early Manifest Glaucoma Trial (EMGT)[9] (National Institutes of Health clinical trials.gov identifier NCT00000132; registered September 23, 1999).

Residents of Malmö, Sweden, were invited to a free eye health examination at the Department of Ophthalmology of Malmö University Hospital. All men aged 60 to 79 years and women aged 55 to 79 years were invited to the screening with the exception of those who had visited the Department of Ophthalmology at Malmö University Hospital within the previous year. Screened subjects found to have been diagnosed with glaucoma before the screening were removed from the analysis. The EMGT and screening were approved by the ethics committee of the University of Lund.

The screening examination has been described in detail elsewhere.[7,9] Briefly, we measured visual acuity and refractive error, and intraocular pressure (IOP) was measured using Goldmann tonometry. Monoscopic fundus color photographs were obtained after dilation using Topcon nonmydriatic TRC-NW3 fundus cameras (Topcon, Inc., Tokyo, Japan) and Kodachrome 64 ASA film (Kodak, Rochester, NY). All subjects completed a questionnaire about their ophthalmic history and listed all current medications.

Positive screening criteria were IOP >25 mmHg and suspect glaucomatous optic nerve head (e.g., localized narrowing of the

ISSN 0161-6420/13/$ - see front matter
http://dx.doi.org/10.1016/j.ophtha.2013.01.043

rim or vertically extended cupping, optic disc hemorrhages, or retinal nerve fiber layer defects) as assessed by at least 1 glaucoma specialist on a fundus photograph. Another positive screening criterion was a first-degree relative with glaucoma. Subjects who screened positively were invited to a postscreening examination.

Postscreening examinations were intended to establish or reject a diagnosis of glaucoma and ascertain whether the patient met the inclusion criteria of the EMGT. A complete ophthalmic history was obtained, and a standard ophthalmic examination was performed, including visual acuity, tonometry, and fundus examination. Visual field testing with the 24-2 Full-Threshold program of the Humphrey Field Analyzer (Carl Zeiss Meditec, Dublin, CA) was also performed in both eyes.

A glaucoma diagnosis was made when subjects fulfilled one of the following criteria:

1. Repeatable visual field defects compatible with glaucoma and not explained by other causes.
2. In subjects for whom only 1 visual field test was available, visual field defects compatible with glaucoma and corresponding structural damage of the optic nerve head or retinal nerve fiber layer were required.
3. In subjects in whom no visual field tests were available, obvious glaucoma damage at the optic nerve head was sufficient.

Humphrey Full-Threshold visual fields had been obtained at the postscreening visit in 91.7% of the newly diagnosed glaucoma eyes and in 0.7% already at the screening. In another 3.5% of the eyes, visual fields had been obtained within 1 year from the screening examination. In 4% of glaucomatous eyes, no visual fields had been obtained or the first fields had been obtained more than 1 year after the screening. Such late fields were not used. Reliability indices of visual field tests were not considered. Thus, no visual fields were excluded unless they were obviously erratic (e.g., a cloverleaf field[10]; compare with the "Results" section).

The magnitude of visual field damage was defined by the mean deviation value from the first visual field test. We used a simplified version of the Glaucoma Staging System described by Mills et al[11] in 2006 to categorize glaucomatous eyes into 5 glaucoma stages (1–5) (Table 1).

Blindness was defined according to World Health Organization (WHO) criteria[12]: visual acuity less than 3/60 with best possible correction or constriction of the central visual field to less than 10° in its widest diameter.

Results were calculated for 5-year age groups, from 55 to 60 years and up to 75 to 79 years. Only women were screened in the youngest age group (55 to 60 years).

Results

Of 46 614 citizens in the age group of interest, 4117 were not invited because they had visited the Department of Ophthalmology of Malmö University Hospital within 1 year before the time of the screening. Thus, 42 497 citizens were invited. A total of 32 918 subjects (77.5%), 21 218 women and 11 700 men, attended the screening program. Our department delivers approximately 75% of all primary glaucoma care in the catchment area.

Table 1. Perimetric Glaucoma Staging

Glaucoma Stage	Mean Deviation	Severity of Disease
1	>−6.00 dB	Early
2	−6.01 to −12.00 dB	Moderate
3	−12.01 to −20.00 dB	Advanced
4	≤−20.01 dB	Severe
5	Not applicable	End-stage/blind

A total of 545 eyes of 406 subjects, who were previously unaware of their condition, were diagnosed with glaucoma. In 86% of eyes, the diagnosis was based on the presence of repeatable visual field loss compatible with glaucoma; in 9% of eyes, the diagnosis was based on visual field loss compatible with glaucoma at a single field test plus corresponding optic nerve changes; and in 5% of eyes (29 eyes in 24 patients), the diagnosis was based on disc appearance only because useful visual fields were not available. Reasons for missing fields were inability to undergo perimetry (e.g., blindness) (n=10), lost to follow-up (n=8), or perimetry had not been performed for unknown reasons (n=3). There were also 3 patients with grossly artifactual visual fields that could not be used (e.g., fields with cloverleaf patterns).[10]

The total prevalence of undetected glaucoma in the screened population was 1.23% (Table 2). Prevalence increased with increasing age and was approximately 5 times higher in the oldest age group than in the youngest age group. Sex distribution of undetected glaucoma was equal between men and women, after correcting for the fact that more women than men were screened.

Most of the glaucoma eyes in each age cohort had early disease (stage 1). The extent of field loss was similar in all age groups from 60 to 64 years and older (Fig 1), whereas early-stage glaucoma was more frequent in the youngest group aged 55 to 59 years. The mean age of patients in each glaucoma stage was similar, between 69 and 70 years.

A total of 267 patients (66%) had unilateral disease. The proportion of patients with bilateral disease increased with age in age groups greater than 60 years, ranging from 28% in ages 60 to 64 years to 42% in the oldest age group.

The distribution of glaucoma severity in the affected eye in patients with unilateral disease was of similar magnitude to that of the better eye in patients with bilateral disease. Thirty-seven percent of patients with bilateral disease were at the same glaucoma stage in both eyes.

No subjects were bilaterally blind, but 14 (3.4%) were blind in 1 eye because of glaucoma (Table 3). Seven eyes were blind according to the WHO visual field criterion. Another 7 eyes were blind according to the WHO visual acuity criterion, but no visual fields were available in these eyes. Half of the patients with a blind eye had unilateral glaucoma.

Discussion

The primary aim of this study was to assess age-specific prevalences and severity of visual field loss in previously undetected glaucoma. The total prevalence of undetected glaucoma in the surveyed population was 1.23% and increased with increasing age. These findings are consistent with previously published findings if we consider that undetected glaucoma often represents approximately 50% of all glaucoma cases in a population.[1–6] Disease severity was similar in all age groups, except for more frequent early-stage glaucoma among the youngest (aged 55–59 years). The sample size is probably large enough to motivate the latter negative statement, that disease severity does not increase substantially with age, because the power of detecting a worsening corresponding to 1 stage in the staging system by Mills et al[11] (=6 dB) in the 75- to 79-year-old group compared with the 60- to 64-year-old

Table 2. Number of Screened Subjects and Glaucoma Prevalences in Different Age Groups

Age Cohorts (yrs)	Women			Men			Total	Prevalence Change between Each Age Group*	
	No. Screened	*No. Diagnosed*	*Prevalence (%)*	*No. Screened*	*No. Diagnosed*	*Prevalence (%)*		*Prevalence Increase*	*%*
55–59	2704	15	0.55	0	0	N/A	0.55	N/A	N/A
60–64	6391	49	0.77	2388	15	0.63	0.73	0.18	33
65–69	6266	84	1.34	4960	61	1.23	1.29	0.56	77
70–74	4208	57	1.35	3215	49	1.52	1.43	0.14	11
75–79	1649	49	2.97	1137	27	2.37	2.73	1.3	91
Total	21 218	254	1.2	11 700	152	1.3	1.23	N/A	N/A

N/A = not available.
*The unit of measure is percentage (of all subjects screened).

group was 99%. The power to detect a worsening of 3 dB was 83%. One third of newly diagnosed subjects had advanced, severe, or end-stage disease, a seemingly high proportion of subjects with serious visual field loss being unaware of their disease.

With knowledge of typical rates of progression in untreated glaucoma,[13] we can conclude that the average undiagnosed subject must have had detectable disease present for several or many years. The difference in levels of glaucoma damage in patients detected at this screening and in routine clinical practice is large,[7] with an average mean deviation of −8.0 dB in the worse eye in patients who were detected at the screening versus −16.2 dB in clinically diagnosed patients in the same age groups in Malmö. This indicates that in the average patient detected at the screening, a number of years would have passed before a clinical diagnosis would have been made.

One strength of this study is that it is based on a large population-based screening of 32 918 subjects. This made it possible to estimate prevalences of undetected glaucoma and amount of visual field damage for different age groups. No other population survey to date has examined as many subjects. The second largest study was performed in Japan and included 8126 screened subjects.[14] Other major population studies typically screened approximately 3000 to 6000 individuals[2,15–25,28] or less.[6,26,27] Another study strength is that the majority of patients with newly detected glaucoma underwent visual field testing with a commonly used standard test.

One limitation of the study is that patients were only invited to a postscreening visit including a full ophthalmic examination and visual field testing if they screened positive according to our criteria. It is likely that a number of patients with glaucoma who had normal or almost normal IOPs and

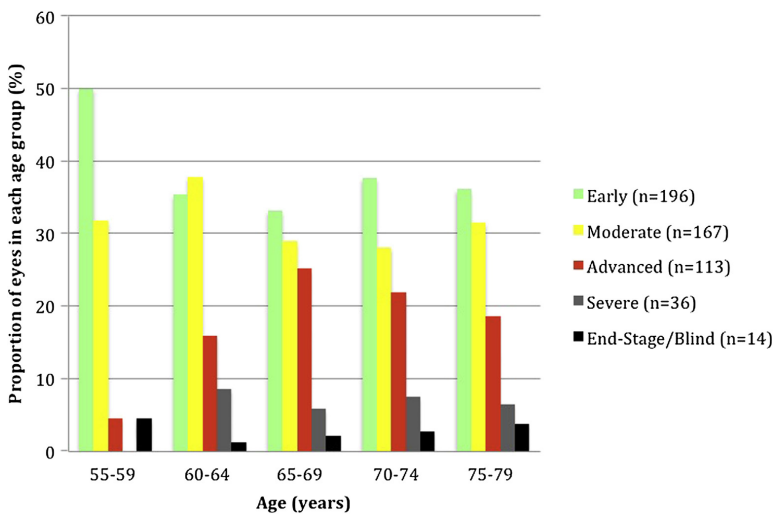


Figure 1. Stages of glaucomatous visual field loss in eyes with newly detected disease. The severity of field loss was similarly distributed from age 60 years and more, with 30% to 40% at the early stage and more than ≥25% at advanced, severe, or end stages.

Table 3. Unilateral Blindness (Number of Subjects and Prevalence) in Different Age Groups

Age Group (yrs)	Subjects with Glaucoma, n	Unilaterally Blind Subjects, n (%)	Prevalence (%)
55–59	15	1 (7)	0.04
60–64	64	1 (2)	0.01
65–69	145	4 (3)	0.04
70–74	106	4 (4)	0.05
75–79	76	4 (5)	0.14
All	406	14 (3.4)	0.04

small optic nerve heads may have been missed. Thus, in the population-based Visual Impairment Project in Melbourne, 6 of 26 patients with previously undetected definite glaucoma had visual field defects but normal IOP values and cup-to-disc ratios <0.7.[18] Therefore, our estimates of undetected manifest glaucoma with field loss in the population are minimum estimates and somewhat lower than the true rates. However, it is reassuring that in the Malmö screening few patients who underwent visual field testing because they screened positive (e.g., because of elevated IOP) had normal optic discs (unpublished data).

Another limitation is that the population screened in this study was mainly Caucasian. Therefore, our results cannot be used to draw conclusions about the prevalence and magnitude of undetected glaucoma in other racial groups. Whether our results can be generalized to other Caucasian populations depends, among other things, on the availability of eye care to the populations. The number of ophthalmologists in Sweden is similar to that of many other countries: approximately 1 ophthalmologist per 12 000 inhabitants. There are relatively few optometrists in Sweden, but a large number of opticians. Many opticians routinely measure IOP in older customers and refer those with elevated pressure. One reason to believe that the current results may be representative for many Western countries is that we know this screening approximately doubled the number of subjects with known glaucoma in the population in the screened age groups. Thus, 354 clinically diagnosed patients of the same age cohorts as those screened were followed at the Department of Ophthalmology at Malmö University Hospital compared with 402 patients detected in the screening.[7] The majority of patients with glaucoma in the catchment area were followed at the university Department of Ophthalmology, but a smaller proportion was seen in a few private practices. Thus, the proportion of patients with undetected glaucoma in Malmö was similar to that reported in other Western countries where population studies have been performed.[1,6,20,27,28]

The screening was conducted between 1992 and 1997. This might raise concerns of whether the results are still valid today. There have been no major changes in glaucoma practice or case finding, and the number of eye care professionals in the catchment area is still similar. Therefore, we believe that the results would have been similar if the population-based screening had been conducted during the past year.

In conclusion, the prevalence of undetected glaucoma increased with age, whereas disease severity did not, in subjects aged more than 60 to 65 years. One third of patients with undetected glaucoma had advanced disease. Unilaterally blind subjects were found even in the youngest age group. Knowledge of age-specific prevalence and disease severity is important for health service decisions. It is clear that these type of data will be useful in assessing the value of population-based screening for glaucoma.[29]

References

1. Tielsch JM, Sommer A, Katz J, et al. Racial variations in the prevalence of primary open angle variations in the prevalence of primary open angle glaucoma: the Baltimore Eye Survey. JAMA 1991;266:369–74.
2. Leske MC, Connell AM, Schachat AP, Hyman LBarbados Eye Study Group. The Barbados Eye Study: prevalence of open angle glaucoma. Arch Ophthalmol 1994;112:821–9.
3. Rudnicka AR, Mt-Isa S, Owen CG, et al. Variations in primary open-angle glaucoma prevalence by age, gender and race: a Bayesian meta-analysis. Invest Ophthalmol Vis Sci 2006;47:4254–61.
4. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. Br J Ophthalmol 2006;90:262–7.
5. Leske MC. Open-angle glaucoma—an epidemiologic overview. Ophthalmic Epidemiol 2007;14:166–72.
6. Topouzis F, Coleman AL, Harris A, et al. Factors associated with undiagnosed open-angle glaucoma: the Thessaloniki Eye Study. Am J Ophthalmol 2008;145:327–35.
7. Grødum K, Heijl A, Bengtsson B. A comparison of glaucoma patients identified through mass screening and in routine clinical practice. Acta Ophthalmol Scand 2002;80:627–31.
8. Wilson JM, Jungner G. Principles and Practice of Screening for Disease. Geneva: WHO; 1968:26–27. Available at: http://whqlibdoc.who.int/php/WHO_PHP_34.pdf. Accessed November 22, 2012.
9. Leske MC, Heijl A, Hyman L, Bengtsson B, Early Manifest Glaucoma Trial Group. Early Manifest Glaucoma Trial: design and baseline data. Ophthalmology 1999;106:2144–53.
10. Cioffi GA, ed. Basic and Clinical Science Course 2010-2011, Section 10 Glaucoma. San Francisco, CA: American Academy of Ophthalmology; 2011:74.
11. Mills RP, Budenz DL, Lee PP, et al. Categorizing the stage of glaucoma from pre-diagnosis to end-stage disease. Am J Ophthalmol 2006;141:24–30.
12. World Health Organization ICD 10 definition H 54.4 och H54.9. Recommendations of the WHO Consultation on "Development of Standards for Characterization of Vision Loss and Visual Functioning" September 2003. Available at: http://apps.who.int/classifications/icd10/browse/2010/en#/H53-H54. Accessed January 14, 2013.
13. Heijl A, Bengtsson B, Hyman K, Leske MC, Early Manifest Glaucoma Trial Group. Natural history of open-angle glaucoma. Ophthalmology 2009;116:2271–6.
14. Shiose Y, Kitazawa Y, Tsukahara S, et al. Epidemiology of glaucoma in Japan—a nationwide glaucoma survey. Jpn J Ophthalmol 1991;35:133–55.
15. Hollows FS, Graham PA. Intraocular pressure, glaucoma, and glaucoma suspects in a defined population. Br J Ophthalmol 1966;50:570–86.
16. Bankes JL, Perkins ES, Tsolakis S, Wright JE. Bedford glaucoma survey. Br Med J 1968;1:791–6.
17. Klein BE, Klein R, Sponsel WE, et al. Prevalence of glaucoma: the Beaver Dam Eye Study. Ophthalmology 1992;99:1499–504.

18. Wensor MD, McCarty CA, Stanislavsky YL, et al. The prevalence of glaucoma in the Melbourne Visual Impairment Project. Ophthalmology 1998;105:733–9.
19. Bonomi L, Marchini G, Marraffa M, et al. Prevalence of glaucoma and intraocular pressure distribution in a defined population: the Egna-Neumarkt Study. Ophthalmology 1998;105:209–15.
20. Mitchell P, Smith W, Attebo K, Healey PR. Prevalence of open-angle glaucoma in Australia: the Blue Mountains Eye Study. Ophthalmology 1996;103:1661–9.
21. Quigley HA, West SK, Rodrigues J, et al. The prevalence of glaucoma in a population-based study of Hispanic subjects: Proyecto VER. Arch Ophthalmol 2001;119:1819–26.
22. Ramakrishnan R, Nirmalan PK, Krishnadas R, et al. Glaucoma in a rural population of southern India: the Aravind Comprehensive Eye Survey. Ophthalmology 2003;110:1484–90.
23. Varma R, Ying-Lai M, Francis BA, et al, Los Angeles Latino Eye Study Group. Prevalence of open-angle glaucoma and ocular hypertension in Latinos: the Los Angeles Latino Eye Study. Ophthalmology 2004;111:1439–48.
24. Wang YX, Xu L, Yang H, Jonas JB. Prevalence of glaucoma in North China: the Beijing Eye Study. Am J Ophthalmol 2010;150:917–24.
25. Wong EY, Keeffe JE, Rait JL, et al. Detection of undiagnosed glaucoma by eye health professionals. Ophthalmology 2004;111:1508–14.
26. Bengtsson B. The prevalence of glaucoma. Br J Ophthalmol 1981;65:46–9.
27. Coffey M, Reidy A, Wormald R, et al. Prevalence of glaucoma in the west of Ireland. Br J Ophthalmol 1993;77:17–21.
28. Dielemans I, Vingerling JR, Wolfs RC, et al. The prevalence of primary open-angle glaucoma in a population-based study in The Netherlands: the Rotterdam Study. Ophthalmology 1994;101:1851–5.
29. Wilson R, Leske C, Lee P, et al. Screening for open-angle glaucoma: where are we now and where to from here? Report from the Global AIGS Committee on screening for open angle glaucoma. Intl Glauc Rev 2006;7-3: 350–4.

Footnotes and Financial Disclosures

Originally received: August 8, 2012.
Final revision: January 15, 2013.
Accepted: January 17, 2013.
Available online: April 28, 2013. Manuscript no. 2012-1212.

[1] Lund University, Department of Clinical Sciences Malmö, Ophthalmology, Skåne University Hospital, Malmö, Sweden.

Financial Disclosure(s):
The author(s) have made the following disclosure(s): A.H. is a consultant of Carl Zeiss Meditec, Allergan, and Alcon, and has received research grants and patent royalties from Carl Zeiss Meditec. B.B. is a consultant of Carl Zeiss Meditec. No conflicting relationships exist for S.E.O.

Funding:
Swedish Research Council Grant K2011-63X-10426-19-3, National Eye Institute (Bethesda, MD) Grant NU10EY10260, The Herman Järnhardt Foundation, the Foundation for Visually Impaired in Former Malmöhus County, and Crown Princess Margareta's Foundation. The National Eye Institute participated in the design of the study. Other sponsors or funding organizations had no role in the design or conduct of this research.

Correspondence:
Anders Heijl, MD, PhD, Department of Clinical Sciences in Malmö, Ophthalmology, Lund University, Skåne University Hospital, SE-20502 Malmö, Sweden. E-mail: anders.heijl@med.lu.se.

Paper II

Acta Ophthalmologica

Acta Ophthalmologica 2019

Predicting undetected glaucoma according to age and IOP: a prediction model developed from a primarily European-derived population

Sigridur E. Oskarsdottir Anders Heijl and Boel Bengtsson

Department of Clinical Sciences, Ophthalmology, Lund University, Malmö, Sweden

ABSTRACT.

Purpose: **To model prediction of undetected glaucoma in a predominantly white population, based on intraocular pressure (IOP) and subject age.**

Methods: **In 1992–1997, a population screening for glaucoma was performed at Malmö University Hospital where individuals between 55–79 years of age (n = 46 614) living in Malmö, were invited to a free eye health examination. Recently examined patients were not invited (n = 4117). IOP and age were recorded for all screened subjects. Subjects who screened positive were further examined to establish or reject a glaucoma diagnosis. We performed multiple regression analysis of the combined effect of age and IOP on the likelihood of undetected glaucoma.**

Results: **In all, 32 918 subjects attended the screening (77.5% of invited), 22 218 women and 11 700 men, while 9579 refrained from participation. Glaucoma was diagnosed in 406 subjects. The proportion of subjects with glaucoma increased exponentially with increasing IOP and older age. Still, the majority of subjects with glaucoma (57%) had ≤IOP 21 mmHg. The predicted rate of undetected glaucoma was low, <5%, for subjects with IOP <25 mmHg, but rose rapidly with higher IOP, reaching 81% in the group with IOP >35 mmHg and age 75–79 years. The model fit well to the data (R^2 = 0.97).**

Conclusion: **We created a model estimating the combined effect of IOP and age on the likelihood of undetected glaucoma. The model may facilitate case-finding in European-derived populations. Despite the important impact of IOP on the risk of glaucoma, a large proportion of subjects with undetected glaucoma had IOP ≤ 21 mmHg.**

Key words: age – glaucoma – IOP – prediction – screening – undetected

Acta Ophthalmol. 2019: 97: 422–426

doi: 10.1111/aos.13941

Introduction

Several risk factors for glaucoma have been identified (Leske 2007), and higher intraocular pressure (IOP) and older age are frequently reported in this context (Hollows & Graham 1966; Bankes et al. 1968; Kahn et al. 1977; Bengtsson 1981; Sommer et al. 1991; Klein et al. 1992; Dielemans et al. 1994; Mitchell et al. 1996; Wensor et al. 1998; Gordon et al. 2002; Iwase et al. 2004; Quigley & Broman 2006; Nemesure et al. 2007; Heijl et al. 2013). Half of all glaucoma cases in developed countries are undetected (Rudnicka et al. 2006), and population screening would seem to be ideal for detecting glaucoma, due to its relatively high prevalence, severity of disease and asymptomatic initial stage. However, population screening for glaucoma is not generally recommended, because available methods are time-consuming and expensive, and not sufficiently specific. Nevertheless, it may be cost effective to screen high-risk groups (Mowatt et al. 2008), and there is a need for improved case detection (Quigley 2011).

Community optometrists/opticians represent a valuable resource for the detection of glaucoma. Indeed, conducting opportunistic glaucoma case-finding during regular optician visits can help reach a large proportion of the population at risk of developing glaucoma (Stoutenbeek & Jansonius 2006).

Many opticians already screen their customers for elevated IOP, as recommended by, for example, AAOs Preferred Practice Pattern for POAG Suspects (Prum et al. 2016). Individuals with elevated intraocular pressure (IOP) are recommended to have a comprehensive medical eye evaluation.

A very sizeable data set is needed to calculate the combined effect of more than one factor on the likelihood of glaucoma. We have access to data from a large population screening of 32 918 subjects that can be used to estimate the combined effect of age and IOP on the likelihood of undetected glaucoma and to develop a diagnostic prediction model for risk assessment that may improve case detection and provide a valuable tool for recommendations of referrals to ophthalmologists. Accordingly, we conducted the present study to develop such a model.

Materials and Methods

Source of data

A population screening was performed at Malmö University Hospital in Sweden between October 1992 and January 1997 to identify individuals with undiagnosed manifest glaucoma

for possible inclusion in a randomized controlled treatment study, the Early Manifest Glaucoma Trial (EMGT) (Leske et al. 1999). The screening was approved by the Ethics Committee of the University of Lund.

Participants

A free eye health examination was offered to all female residents in Malmö aged 55–79 years and all male residents aged 60–79 years. Those who had recently been examined at the department of Ophthalmology in Malmö, and individuals already having a glaucoma diagnosis, were not invited to the screening ($n = 4117$). Individuals with a glaucoma diagnosis who had received the diagnosis elsewhere and came to the screening were excluded from the analysis. Subjects with IOP missing in both eyes, for example, if they declined tonometry, were excluded.

Outcome

Subjects who fulfilled any of the following criteria were invited to one or two post-screening visits: intraocular pressure >25 mmHg with Goldmann applanation tonometry and/or suspected glaucomatous optic disc changes (vertically elongated cupping of the disc, localized narrowing of the optic disc rim, nerve fibre layer defect, optic disc haemorrhages) in the photographs, and/or those who had a self-reported family history of glaucoma in siblings. The post-screening examinations were intended to establish or reject the diagnosis of glaucoma and eligibility for the EMGT. At these visits, a full eye examination was performed including standard automated perimetry (SAP) with the 24-2 Full Threshold program of the Humphrey Field Analyzer (Carl Zeiss Meditec, Dublin, CA, USA).

The glaucoma diagnosis was based on the presence of repeatable visual field defects compatible with glaucoma and not explained by other causes. In subjects with only one visual field test, corresponding defects in the optic nerve head (as evaluated by at least one glaucoma specialist) and/or in the retinal nerve fibre layer (RNFL) were required. If no visual field was available (e.g., due to physical disability or blindness), or if the visual field was erratic (e.g., a clover-leaf field), obvious glaucomatous damage in the optic nerve head and/or RNFL was required.

Predictors

At the screening examination, IOP was measured and fundus colour photographs were obtained. In the present study, the predictors used were as follows: Screening IOP divided into 5-mmHg intervals ranging from 10 to 34 mmHg. We used the IOP of the eye with the higher IOP of the two for analysis, and subjects were categorized into two groups, glaucoma in at least one eye versus no glaucoma. Eyes with IOP values <10 and ≥35 mmHg were assigned to two separate groups. The other predictor was subject age categorized in age groups at 5-year intervals, from 55 to 79 years. The proportions of newly detected subjects with glaucoma were calculated for each combination of the seven IOP groups and the five age groups.

Populations size and missing data

A total of 42 497 individuals within the target age intervals, with the exception of individuals who had visited the department within one year prior to the screening, were invited to the screening. Those not attending the screening, 9579 individuals or 22.5% of all invited, were not considered in the current analysis, no imputation method was applied. The mean age of those not attending was 66.7 years (SD 5.6 years) and for those attending 67.1 years (SD 5.6 years).

Statistical analysis

A multivariate regression analysis was performed in order to model the association between age and IOP and the interaction between age and IOP on one hand, and the proportion of previously undetected glaucoma on the other. Both age and IOP showed exponential relationships to the proportion of newly detected glaucomatous subjects. To obtain a linear relationship, a logarithmic (ln) transformation was performed on the dependent variable: proportion of glaucomatous subjects at different levels of IOP and age. To facilitate conversion of data back to the original scale, cells with no glaucoma were regarded as missing values rather than adding an arbitrary constant to the data. A multiple linear regression including residual analysis was performed:

$$\ln(\text{proportion glaucoma}) = a + b_1\text{age} + b_2\text{IOP} + b_3(\text{IOP} * \text{age}) + e$$

The coefficients from the regression analysis were used to model the combined effect of age and IOP level on the predicted proportion of glaucomatous subjects for each combination of age and IOP groups.

Results

Participants

The flow of participants is shown in Fig. 1. In all, 77.5% of the 42 497 individuals who were invited attended the screening, resulting in 32 918 screened subjects. Recently examined individuals, a total of 4117 individuals, were not invited. Eighty-three subjects with a prior diagnosis of glaucoma unknown to us were screened, but excluded from the current analysis. We identified 545 undiagnosed glaucomatous eyes in 406 subjects, and 231 (57%) had an IOP value ≤21 mmHg in the eye with the higher IOP. In 86% of the newly detected glaucomatous eyes, the diagnosis was based on repeatable visual field defects compatible with glaucoma and not explained by other causes; considering the remaining 14%, the diagnosis was based on a single field with corresponding optic disc changes in 9% and on optic disc appearance alone in 5%.

A total of 32 509 subjects were evaluated. Intraocular pressure (IOP) measurements were missing for 726 eyes (1.1% of all eyes) in 400 subjects, but none of those eyes were glaucomatous. In 326 subjects, the IOP for both eyes was missing and thus not used in the model development. In 74 subjects, the IOP for one eye was missing. The most common explanation for a missing IOP measurement was that the subject declined tonometry. The largest group of screened subjects, 34%, were between 65 to 69 years of age followed by the group between 60 to 64 years of age. The distribution of age of screened subjects can be seen in Table 1. A large majority (30 261 subjects) of the screened subjects had IOP within statistically normal limits in the eye with higher IOP.

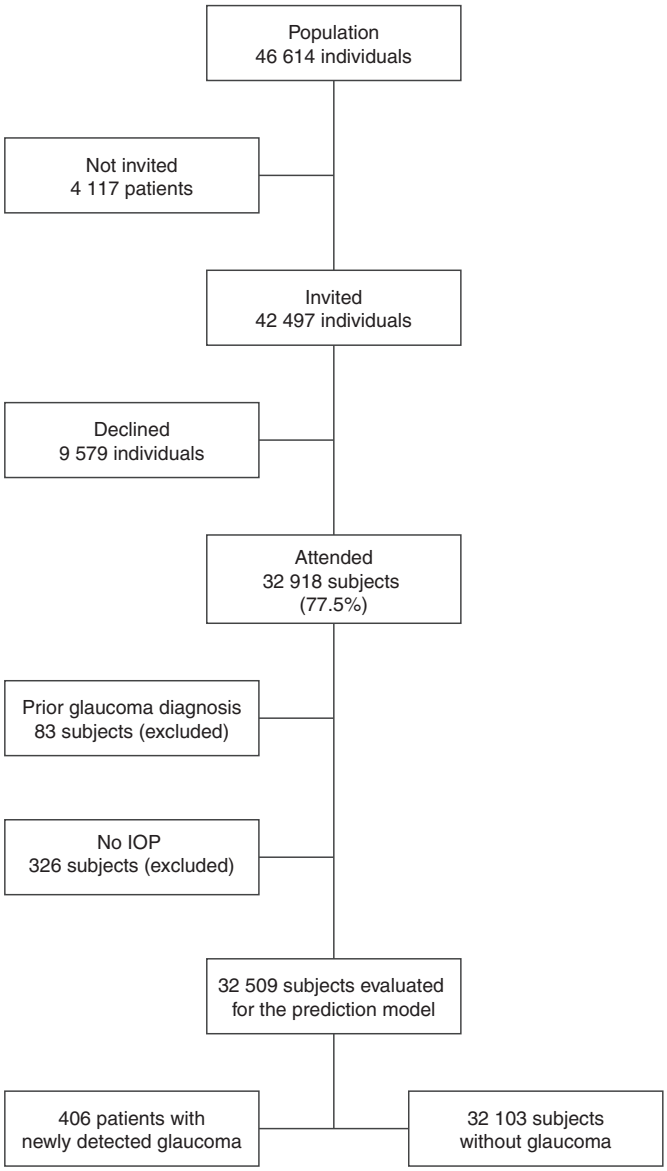


Fig. 1. Flow chart of screened subjects.

Model development

The observed proportions of subjects with newly detected glaucoma in at least one eye and the number of glaucomatous subjects versus screened subjects in each age and IOP group are shown in Table 1. No subjects with glaucoma were detected at IOP levels <10 mmHg in the eye with the higher pressure and only 19 subjects with glaucoma had IOP in the interval between 10 to 14 mmHg. Although the majority of subjects with glaucoma detected by the screening had pressures of 21 mmHg or less (231 subjects, 57%), this resulted in a proportion of glaucoma of 0.8% of all screened subjects at ages 55–79 years with IOP 21 mmHg or less. Forty-six subjects with glaucoma had IOP 22–24 mmHg, resulting in a proportion of glaucoma of 2.4% of all screened subjects with IOP 22–24 mmHg, considering all age groups. Proportions of glaucoma were thus small up to the 25 mmHg level. The proportion increased slightly with age up to the 25 mmHg level. Higher proportion (18.3%) was seen if IOP was ≥25 mmHg. The proportion increased with age and was high (i.e., ≥20%) at IOP levels ≥30 mmHg in subjects aged ≥65 years.

Model specifications

The likelihood of undiagnosed glaucoma increased exponentially with both age and IOP level, and the combined effect of age and IOP was highly significant ($p = 0.000$). The effect of IOP alone was greater than that of age alone, although the effects of both factors were highly significant ($p = 0.000$). Table 2 presents the proportions predicted when using the following formula:

$$\begin{aligned}\ln(\text{prop. glaucoma}) &= -9.96 + 0.54\text{age group} \\ &\quad + 1.34\text{IOP group} - 0.07(\text{age} * \text{IOP})\end{aligned}$$

Model performance

The regression model fit well to the data, with a coefficient of determination (R^2) of 0.97. The residuals were normally distributed and were randomly dispersed around the horizontal zero line. The 95% confidence interval was ± 0.30 for the age coefficient, ± 0.21 for the IOP coefficient, and ± 0.06 for the interaction between the two.

Discussion

We were able to study the combined effect of IOP and age on the likelihood of undetected glaucoma, because we had access to data from a large-scale population screening of almost 33 000 subjects. Although 57% of all subjects with previously undetected glaucoma had an IOP of ≤21 mmHg in the eye with the higher IOP, the influence of IOP was considerably greater than that of age. Relatively few screened subjects had pressures above 24 mmHg (2.2%),

Table 1. Observed proportions (%) of subjects with glaucoma detected at population screening in each age and IOP group. The number of subjects with glaucoma/number of screened subjects is shown to the right. Relatively few subjects were screened in the youngest and the oldest group compared to the other three groups.

Age (years) IOP (mmHg)	55-59	60-64	65-69	70-74	75-79	Total
<10	0% 0/12	0% 0/22	0% 0/47	0% 0/49	0% 0/13	0/143
10-14	0% 1/746	1% 6/2,415	0% 4/3,343	0% 3/2,082	1% 5/844	19/9,430
15-19	1% 9/1,515	1% 23/4,740	1% 46/5,812	1% 42/3,979	2% 33/1,402	153/17,448
20-24	1% 2/368	1% 19/1,341	2% 39/1,610	5% 26/1,049	5% 19/418	105/4,786
25-29	6% 1/18	7% 8/116	14% 29/211	11% 14/127	16% 8/49	60/521
30-34	0% 0/0	18% 3/17	21% 8/39	28% 10/36	32% 6/19	27/111
≥35	100% 2/2	42% 5/12	63% 19/30	63% 12/19	57% 4/7	42/70
Total	15/2,661	64/8,663	145/11,092	107/7,341	75/2,752	406/32,509

Table 2. Predicted proportions of undetected glaucoma at different levels of age and IOP in the population.

Age (years) IOP (mmHg)	55-59	60-64	65-69	70-74	75-79
<10	0%	0%	0%	0%	0%
10-14	0%	0%	0%	0%	1%
15-19	0%	1%	1%	1%	1%
20-24	1%	2%	2%	3%	4%
25-29	5%	6%	7%	9%	11%
30-34	17%	20%	23%	26%	30%
≥35	61%	66%	71 %	76 %	81 %

but the proportion of glaucomatous eyes with pressure above 24 mmHg was markedly higher than in those with lower IOP values.

A weakness of the current investigation is that some of the proportions presented here may be lower than the true numbers. All subjects with IOP >25 mmHg underwent visual field testing, but eyes with IOP ≤25 mmHg screened negative unless disc or RNFL findings were suspicious or if subjects had a positive family history of glaucoma. The reason for using 25 mmHg was that the original purpose of the screening was to identify previously undetected subjects with glaucoma to be included in EMGT. Thus, glaucomatous eyes with small optic discs may have been missed, since glaucoma eyes with small discs often appear healthy (Heijl & Molder 1993). Another reason that suggests that the number of subjects with glaucoma and IOP ≤ 21 mmHg is underestimated in the current study due to the screening criteria is that Springelkamp et al. (2017) showed that one out of four newly detected glaucoma cases had discs within normal limits according to the (strict) ISGEO criteria and the mean IOP of those cases was 16.3 mmHg. Another study showed higher proportions of normal-tension glaucoma detected when screened with visual fields and optic disc evaluation for all subjects (Stoutenbeek et al. 2008).

Interpretation

Predicted proportions of undetected glaucoma were relatively small in subjects with IOP levels up to 25 mmHg but increased slightly with age. Markedly higher proportions of ≥17% were noted at IOP levels ≥30 mmHg. At IOP levels of ≥35 mmHg, the predicted proportions of glaucoma ranged from 61% in the youngest age group to 81% in the oldest age group, although the number of subjects with those IOPs was small, representing only 0.2% of all screened subjects.

The strengths of this study are the large size of the screened population and the fact that the diagnosis was confirmed with visual field tests in most eyes (95%). Due to the considerable size of the material, the denominator was relatively large in most cells: 51% of the cells (18/35) included ≥100 subjects, and 31% (11/35) comprised ≥1000 screened subjects, Table 1.

Many studies have shown increasing rates of glaucoma at higher IOP values (Sommer et al. 1991; Mitchell et al. 1996; Iwase et al. 2004) or older age (Bengtsson 1981; Dielemans et al. 1994; Leske et al. 1994; Wensor et al. 1998; Quigley & Broman 2006). We have presented a model that shows the combined effect of age and IOP and the interaction of age and IOP on the presence of undetected glaucoma in the community.

Implications

Considering possible general applicability of our results, it can be noted that the proportion of undetected glaucoma in the Malmö screening was very similar to rates previously reported in other developed countries (Kahn et al. 1977; Sommer et al. 1991; Coffey et al. 1993; Dielemans et al. 1994; Mitchell et al. 1996; Wensor et al. 1998).

Ocular hypertension is a well-known risk factor for glaucoma (Gordon et al. 2002) and as recommended by the Preferred Practice Pattern for POAG Suspects of the AAO, eye care providers should measure IOP in all individuals over 40 years of age (Prum et al. 2016). False-positive test results lead to a reduction in the predictive power of positive testing and increase the number of patients that require hospital care and thus add to both the workload at outpatient departments and the costs of

Table 3. Number needed to screen to detect one new case of glaucoma in each age/IOP group using the prediction model.

Age (years) IOP (mmHg)	55–59	60–64	65–69	70–74	75–79
<10	3334	2000	1429	834	527
10–14	1000	625	435	286	189
15–19	271	193	137	98	70
20–24	76	58	44	34	26
25–29	21	18	14	12	10
30–34	6	6	5	4	4
35 or more	2	2	2	2	2

health care. Since the prevalence of glaucoma increases with age and people are living longer, the burden of disease to society are increasing. The model could reduce the number of individuals referred to an ophthalmologist when referral is based solely on age and IOP, although there is still a considerable rate of false positives using the model, even at higher IOP values. Table 3 shows the number needed to screen to detect one new case of glaucoma in each age-IOP group. We can see an inverted exponential relationship, with more subjects needed to be screened to detect one subject with glaucoma with lower IOP and younger age.

As previously mentioned, although very small proportions of subjects with IOP ≤21 mmHg had glaucoma, they represented 57% of all subjects found to have glaucoma in the screening. The explanation could be, or at least in part be, that individuals with undetected glaucoma and high IOP are more likely to be discovered in routine clinical practice or being referred to an ophthalmologist from an optician than individuals with IOP within the statistically normal limits (Grødum et al. 2002). It has been shown that individuals with undetected glaucoma and ≤IOP 21 mmHg are often overlooked in routine clinical practice (Grødum et al. 2002). Another reason could be that the natural course of the disease is slower on a group level when the IOP is ≤21 mmHg, than with high untreated IOP (Heijl et al. 2009), and more time could pass before symptoms develop that make the patient seek ophthalmologic care.

The specificity of the model would be 99% when using a cutoff at 25 mmHg for referral. However, the sensitivity would be low, only 32%.

Here, we have presented a model for the prediction of undiagnosed glaucoma based on the combined effect of IOP and age and the interaction between the two factors. By knowing the subjects age and measuring the IOP the model can be used to calculate the probability of the subject to have undetected glaucoma. Our results may prove useful when updating guidelines for referrals to ophthalmologists from primary eye care professionals i.e., opticians, optometrists or general practitioners.

References

Bankes JL, Perkins ES, Tsolakis S & Wright JE (1968): Bedford glaucoma survey. BMJ **1**: 791–796.

Bengtsson B (1981): The prevalence of glaucoma. British J Ophthalmol **65**: 46–49.

Coffey M, Reidy A, Wormald R, Xian WX, Wright L & Courtney P (1993): Prevalence of glaucoma in the west of Ireland. British J Ophthalmol **77**: 17–21.

Dielemans I, Vingerling JR, Wolfs RC, Hofman A, Grobbee DE & de Jong PT (1994): The prevalence of primary open-angle glaucoma in a population-based study in The Netherlands. The Rotterdam Study. Ophthalmology **101**: 1851–1855.

Gordon MO, Beiser JA, Brandt JD et al. (2002): The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. Arch Ophthalmol (Chicago, IL: 1960) **120**: 714–720; discussion 829-730.

Grødum K, Heijl A & Bengtsson B (2002): A comparison of glaucoma patients identified through mass screening and in routine clinical practice. Acta Ophthalmol Scand **80**: 627–631.

Heijl A & Molder H (1993): Optic disc diameter influences the ability to detect glaucomatous disc damage. Acta Ophthalmol **71**: 122–129.

Heijl A, Bengtsson B, Hyman L, Leske MC & EMGT Group (2009): Natural history of open-angle glaucoma. Ophthalmology **116**: 2271–2276.

Heijl A, Bengtsson B & Oskarsdottir SE (2013): Prevalence and severity of undetected manifest glaucoma: results from the early manifest glaucoma trial screening. Ophthalmology **120**: 1541–1545.

Hollows FC & Graham PA (1966): Intra-ocular pressure, glaucoma, and glaucoma suspects in a defined population. British J Ophthalmol **50**: 570–586.

Iwase A, Suzuki Y, Araie M et al. (2004): The prevalence of primary open-angle glaucoma in Japanese: the Tajimi Study. Ophthalmology **111**: 1641–1648.

Kahn HA, Leibowitz HM, Ganley JP, Kini MM, Colton T, Nickerson RS & Dawber TR (1977): The Framingham Eye Study. I. Outline and major prevalence findings. Am J Epidemiol **106**: 17–32.

Klein BE, Klein R, Sponsel WE, Franke T, Cantor LB, Martone J & Menage MJ (1992): Prevalence of glaucoma. The Beaver Dam Eye Study. Ophthalmology **99**: 1499–1504.

Leske MC (2007): Open-angle glaucoma – an epidemiologic overview. Ophthalmic Epidemiol **14**: 166–172.

Leske MC, Connell AM, Schachat AP & Hyman L (1994): The Barbados Eye Study. Prevalence of open angle glaucoma. Arch Ophthalmol (Chicago, IL: 1960) **112**: 821–829.

Leske MC, Heijl A, Hyman L & Bengtsson B (1999): Early manifest glaucoma trial: design and baseline data. Ophthalmology **106**: 2144–2153.

Mitchell P, Smith W, Attebo K & Healey PR (1996): Prevalence of open-angle glaucoma in Australia. The Blue Mountains Eye Study. Ophthalmology **103**: 1661–1669.

Mowatt G, Burr JM, Cook JA, Siddiqui MA, Ramsay C, Fraser C, Azuara-Blanco A & Deeks JJ (2008): Screening tests for detecting open-angle glaucoma: systematic review and meta-analysis. Invest Ophthalmol Vis Sci **49**: 5373–5385.

Nemesure B, Honkanen R, Hennis A, Wu SY & Leske MC (2007): Incident open-angle glaucoma and intraocular pressure. Ophthalmology **114**: 1810–1815.

Prum BE Jr, Lim MC, Mansberger SL et al. (2016): Primary open-angle glaucoma suspect preferred practice Pattern® Guidelines. Ophthalmology **123**: 112–151.

Quigley HA (2011): Glaucoma. Lancet (London, England) **377**: 1367–1377.

Quigley HA & Broman AT (2006): The number of people with glaucoma worldwide in 2010 and 2020. British J Ophthalmol **90**: 262–267.

Rudnicka AR, Mt-Isa S, Owen CG, Cook DG & Ashby D (2006): Variations in primary open-angle glaucoma prevalence by age, gender, and race: a Bayesian meta-analysis. Invest Ophthalmol Vis Sci **47**: 4254–4261.

Sommer A, Tielsch JM, Katz J, Quigley HA, Gottsch JD, Javitt J & Singh K (1991): Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans. The Baltimore Eye Survey. Arch Ophthalmol (Chicago, IL: 1960) **109**: 1090–1095.

Springelkamp H, Wolfs RC, Ramdas WD, Hofman A, Vingerling JR, Klaver CC & Jansonius NM (2017): Incidence of glaucomatous visual field loss after two decades of follow-up: the Rotterdam Study. Eur J Epidemiol **32**: 691–699.

Stoutenbeek R & Jansonius NM (2006): Glaucoma screening during regular optician visits: can the population at risk of developing glaucoma be reached? Br J Ophthalmol **90**: 1242–1244.

Stoutenbeek R, de Voogd S, Wolfs RC, Hofman A, de Jong PT & Jansonius NM (2008): The additional yield of a periodic screening programme for open-angle glaucoma: a population-based comparison of incident glaucoma cases detected in regular ophthalmic care with cases detected during screening. Br J Ophthalmol **92**: 1222–1226.

Wensor MD, McCarty CA, Stanislavsky YL, Livingston PM & Taylor HR (1998): The prevalence of glaucoma in the Melbourne Visual Impairment Project. Ophthalmology **105**: 733–739.

Received on April 4th, 2018.
Accepted on September 14th, 2018.

Correspondence:
Sigridur E. Oskarsdottir, MD
Jan Waldenströms gata 24
SE 205 02 Malmö
Sweden
Tel: + 46 40 33 27 18
Email: sigridur.oskarsdottir@med.lu.se

Contributorship: All authors contributed according to the ICMJE Recommendations. Sigridur Oskarsdottir: Analysis of the data, manuscript writing. Anders Heijl: Data gathering and design of the screening, assisted in manuscript writing. Boel Bengtsson: Statistical analysis, assisted in manuscript writing. Anders Heijl serves as a consultant for Zeiss and Allergan and has received speaker honoraria from Allergan and Santen. Boel Bengtsson is a consultant to Zeiss. No conflicting relationships exist for Sigridur Oskarsdottir. This study was supported by grants from the following: the Swedish Research Council (grant K2011-63X-10426-19-3), the National Eye Institute, Bethesda, Maryland (grant no U10EY10260), the Herman Järnhardt Foundation, the Foundation for Visually Impaired in Former Malmöhus County, and Crown Princess Margareta's Foundation. The National Eye Institute participated in the design of the study. Other sponsors or funding organizations had no role in the design or performance of this research.

Paper III

AMERICAN ACADEMY OF OPHTHALMOLOGY®

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Lifetime Risk of Visual Impairment Resulting from Glaucoma in Patients Initially Followed up for Elevated Intraocular Pressure

Sigridur E. Oskarsdottir, MD,[1] *Anders Heijl, MD, PhD,*[1] *Patrik Midlöv, MD, PhD,*[2] *Boel Bengtsson, PhD*[1]

Purpose: To report the lifetime risk of visual impairment resulting from glaucoma in patients originally followed up in a 10-year prospective randomized study initiated in 1981 to assess patients with elevated intraocular pressure (IOP).

Design: Retrospective patient chart review.

Participants: Data on deceased patients who initially were followed up prospectively in the randomized controlled study and thereafter were followed up in ordinary clinical practice were collected until the end of 2017. Inclusion in the original study required an untreated IOP of 22 mmHg or more and 1 or more risk factors for glaucoma.

Methods: Visual impairment, low vision, and blindness were defined according to the World Health Organization criteria. All eyes that became visually impaired were registered, including the date and cause of the impairment; the cumulative incidence of visual impairment corrected for competing risks was calculated; and the Kaplan-Meier method was used to analyze the importance of risk factors present at baseline for 1 eye per patient.

Main Outcome Measures: The proportion of patients who became bilaterally visually impaired because of glaucoma, the cumulative incidence of glaucoma-related visual impairment in at least 1 eye, and potential baseline risk factors for visual impairment caused by glaucoma.

Results: Seventy-seven of 90 patients (86%) included in the initial randomized study were deceased at the end of 2017. Four patients were lost to follow-up during the clinical follow-up. Of the 77 patients, 7 (9%) became bilaterally visually impaired and 2 of those 7 became bilaterally blind because of glaucoma. The cumulative incidence of glaucoma-induced visual impairment in at least 1 eye increased from 0.00 after 5 years to 0.22 (95% confidence interval [CI], −0.01 to 0.67) after 30 years. The cumulative incidence of glaucoma blindness in at least 1 eye increased from 0.00 after 5 years to 0.17 (95% CI, 0.10−0.54) after 30 years. No specific risk factor significantly increased the risk of visual impairment caused by glaucoma.

Conclusions: Although the investigated patients showed elevated IOP and at least 1 additional glaucoma risk factor (i.e., they were high-risk patients), only a relatively small proportion of the patients with glaucoma demonstrated visual impairment. *Ophthalmology Glaucoma 2019;■:1−6 © 2019 by the American Academy of Ophthalmology*

Elevated intraocular pressure (IOP) is a well-established risk factor for glaucoma.[1−6] Ocular hypertension is a relatively common condition that affects approximately 3% to 10% of persons 40 years of age and older in primarily European-derived populations.[7−11] Individuals with elevated IOP usually are monitored regularly for glaucoma and often receive treatment to prevent damage caused by this condition. Many questions remain about the management of these individuals, and the risk of visual impairment developing may be one of the most important aspects in this context. Other studies have assessed this issue through long-term follow-up[12,13] or by creating models to calculate the risk.[14,15] However, the lifelong risk of visual impairment has been analyzed in only 1 investigation, which included 40 patients with ocular hypertension.[16]

We have access to longitudinal data on patients originally included in the Malmö High-Risk Ocular Hypertension Study in Sweden,[17] which was a prospective randomized controlled investigation comparing the effects of timolol and placebo treatment on development of glaucoma in 90 patients with elevated IOP and at least 1 additional risk factor. These patients were recruited to the original study between 1981 and 1987 and initially were followed up prospectively for up to 10 years. The study ended in 1995, and thereafter most patients continued their medical check-ups at our facility in Sweden (called Malmö General Hospital in 1995 and presently called Skåne University Hospital, Malmö). Most of the patients (n = 77) have died, and hence the lifetime risk of visual impairment can be studied in those individuals. In the current assessment, our aim was to determine the lifetime risk of visual impairment

https://doi.org/10.1016/j.ogla.2019.09.002
ISSN 2589-4196/19

caused by glaucoma in patients with elevated IOP and at least 1 additional risk factor for glaucoma.

Methods

Patients and Data Collection

The prospective Malmö High-Risk Ocular Hypertension Study was approved in 1981 by the ethics committee of the Medical Faculty of Lund University, and all patients gave informed consent to participate. The current retrospective follow-up investigation of the poststudy clinical follow-up charts of these patients was approved by the Regional Ethical Review Board in Lund, Sweden. Both studies were performed according to the tenets of the Declaration of Helsinki.

To be included in the prospective study, patients were to have had the following: untreated IOP in 1 or both eyes in the range of 22 to 34 mmHg measured by Goldmann applanation tonometry, no visual field defects on Competer computerized threshold perimetry (Bara Elektronik, Lund, Sweden),[18] and at least 1 additional risk factor for glaucoma. These 5 risk factors were considered: (1) self-reported positive family history of glaucoma in first-degree relatives, (2) exfoliation syndrome or pigment dispersion syndrome, (3) diabetes, (4) IOP of 27 mmHg or more, and (5) a suspect optic disc. Features that classified a disc as suspect were disc hemorrhage, the presence of a localized complete or incomplete notch, a cup-to-disc ratio of 0.6 or more, asymmetry of the cup-to-disc ratio of 0.2 or more between the 2 eyes, or a vertical cup-to-disc ratio that exceeded the horizontal cup-to-disc ratio by 0.2 or more.

The original Malmö study was a double-masked randomized trial performed to investigate the effect of IOP-lowering eye drops on the risk of glaucoma developing. The patients were randomized to 0.5% timolol or placebo eye drops and were followed up every 3 months with diurnal office hour tension curves for up to 10 years. The following were performed at each visit: visual acuity with Snellen decimal value, IOP with Goldmann applanation tonometry, Competer computerized static threshold perimetry, disc photography, and ocular examination by a glaucoma specialist (A.H.). Patients who demonstrated glaucomatous visual field defects or other ocular conditions that prevented further participation in the prospective study (e.g., neurologic visual field defects) were withdrawn from that investigation but continued to be followed up at the department.

After completion of the prospective study, or after withdrawal from that investigation, patients were followed up according to clinical routine using 30-2 full-threshold and later Swedish international threshold algorithm standard visual field testing on a Humphrey Field Analyzer (Carl Zeiss Meditec, Dublin, CA) and were treated or left untreated according to standard clinical care. Characteristics and results of the prospective study have been published previously.[17,19]

For the present investigation, we reviewed the deceased patients' charts and all visits from the protocol applied in the prospective study. We collected data on visual acuity, visual fields, and IOP for both eyes in all patients. For each eye, we recorded the date of visual impairment and the date of a glaucoma diagnosis. The primary reason for visual impairment was assessed using the patients' records in combination with visual field charts.

Criteria for Visual Impairment

The World Health Organization criteria were used to define visual impairment (low vision and blindness) for each eye. Thus, eyes were considered visually impaired when visual acuity was permanently reduced to less than 0.3 or the central visual field was constricted to less than 20° and were regarded as blind when visual acuity was reduced permanently to less than 0.05 or the central visual field was constricted to less than 10°. Criteria for low vision thus were visual acuity in the interval of less than 0.3 to 0.05, central visual field constricted to between less than 20° and 10°, or both. A pseudoisopter[20] was used to estimate the degrees of remaining visual fields according to instructions from the American Social Security Administration[21] (2007; accessed September 20, 2018).

Criteria for Glaucoma

A glaucoma diagnosis was made if the patient showed repeatable visual field defects in 2 or more consecutive fields that were consistent with glaucoma and were not explained by other causes. The date of glaucoma diagnosis was set as the time when the first of the consecutive visual fields showing glaucomatous defects was observed. If only one visual field chart showing glaucomatous defects was available (e.g., because of some other serious disease, death, or loss to follow-up), it was required that the optic disc with abnormal findings at the corresponding location be described in the patient's records. If no visual field charts were available, an obviously glaucomatous optic disc had to be described in the patient's records.

Statistical Analysis

The cumulative incidence of visual impairment resulting from glaucoma in at least 1 eye was calculated. We corrected for competing risks,[22] which comprised death without visual impairment and visual impairment caused by other factors in both eyes. Patients with visual impairment resulting from other causes in only 1 eye could still be at risk of glaucoma-induced visual impairment developing in the other eye.

Risk factors at baseline were assessed by Kaplan-Meier survival analysis and were tested for significance using the log-rank method. For the risk analysis, we included 1 eye per patient, and only eyes that fulfilled the baseline criteria for inclusion in the prospective study were included. For patients with a visual impairment event caused by glaucoma in at least 1 eye, the first eye to exhibit this event was included in the risk factor analysis. If a patient became visually impaired because of causes other than glaucoma, the second eye to reach that outcome was included. In patients who did not become visually impaired in either eye and whose two eyes fulfilled the inclusion criteria, the right eye was included in the analysis. In patients who demonstrated visual impairment, the time variable was calculated in years from inclusion in the original study to the event of visual impairment, or if no visual impairment occurred, then to the patient's date of death.

Results

Of the 90 patients who participated in the initial prospective study, 77 were deceased in December 2017 when data used in the present assessment were collected. The 13 patients who were still alive at that time were not included in our analysis. We had access to data on time of death for all patients compiled by the Swedish Tax Agency.

Among the 77 deceased patients included in the present analysis, the age at inclusion ranged from 34 to 79 years (median, 66 years). Forty-three women and 34 men were included. Both eyes of 61 patients (79%) were included in the original prospective study.

The mean IOP for the 137 study eyes at baseline was 26.3 mmHg (range, 22–34 mmHg), and the mean IOP for all 154 eyes at baseline was 25.5 mmHg. The final visit occurred within 3 years of death for 69 patients (90%). Four patients who had not reached a study outcome had 3 years or more between the last visit to an ophthalmology department and death and were considered lost to follow-up. For all patients, the mean follow-up time was 17.6 years, ranging from 0.5 to 33 years, and the mean age at death was 83.5 years.

Visual Impairment Caused by Glaucoma

Seven patients (9%) became bilaterally visually impaired because of glaucoma, and 2 of those 7 became blind (Table 1). The patients who became bilaterally visually impaired because of glaucoma reached that stage in the better eye at a mean age of 83.7 years (standard deviation [SD], 6.1 years); the youngest of these patients was 72 years of age, and the oldest was 91 years of age. In both of the patients with bilateral blindness, the blindness arose in their better eye at the age of 87 years, and glaucoma had been diagnosed 20 and 23 years earlier, respectively. One of these 2 patients died 1 year and the other patient 4 years after blindness developed in the better eye. Thirteen patients (17%) became blind in at least 1 eye because of glaucoma.

Cumulative Incidence of Visual Impairment Resulting from Glaucoma

The cumulative incidence of visual impairment or blindness in at least 1 eye because of glaucoma are shown with correction for competing risks in Figures 1 and 2, respectively. The cumulative incidence of glaucoma-related visual impairment in at least 1 eye was 0.00 (95% confidence interval [CI], 0.00–0.05) at 5 years, increased to 0.10 (95% CI, 0.04–0.22) at 15 years, and reached 0.22 after 30 years (95% CI, −0.01 to 0.67). The cumulative incidence of glaucoma blindness in at least 1 eye was 0.00 (95% CI, 0.00–0.05) at 5 years, increased to 0.03 (95% CI, 0.01–0.13) at 15 years, and reached 0.17 (95% CI, 0.1–0.54) at 30 years. The median age at which visual impairment resulting from glaucoma developed in a patient's first eye was 81 years; the youngest patient was 64 years of age and the oldest was 91 years of age.

Baseline Risk Factors

All participants demonstrated elevated IOP in one or both eyes and at least 1 additional risk factor. The distribution of the additional risk factors is shown in Table 2. Most patients (52%) demonstrated

Table 1. Number and Proportion of Patients with Visual Impairment, Low Vision, and Blindness Resulting from Glaucoma at Final Visit to an Ophthalmology Department before Death

Condition at Last Visit	No. of Patients	Patients with Glaucoma (%; n = 48)	All Patients (%; n = 77)
Bilateral blindness	2	4	3
Unilateral blindness	6	13	8
Low vision in 1 eye, blind in the other	5	10	6
Bilateral low vision	0	0	0
Unilateral low vision	4	8	5
Total	17	35	22

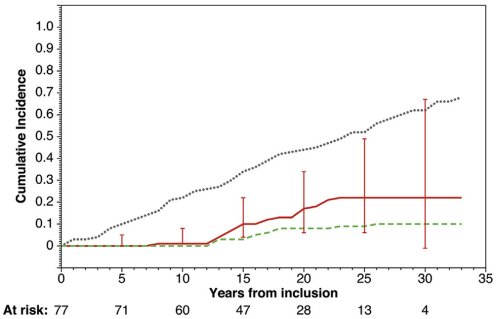

Figure 1. Graph showing the cumulative incidence of visual impairment caused by glaucoma in at least 1 eye (n = 17; red) and 95% confidence intervals at every 5 years of follow-up. Competing risks are visual impairment in both eyes resulting from causes other than glaucoma (n = 8; green) and death (n = 52; grey). The confidence interval increased with time because fewer patients were at risk. The 30-year cumulative incidence of glaucoma visual impairment in at least 1 eye was 0.22.

1 additional risk factor, 24 patients (32%) demonstrated 2 additional risk factors, and the remaining 13 patients (16%) demonstrated 3 additional risk factors. No additional risk factor proved to be statistically significant.

Timolol versus Placebo

Of all the participants included in the current evaluation, half (38 patients) had been randomized to timolol 0.5% eye drops and the other half (39 patients) to placebo eye drops in the initial prospective study. After the prospective study ended, patients were treated according to standard clinical care, which meant increased treatment with progression of disease, using topical agents, laser therapy (argon laser trabeculoplasty or selective laser trabeculoplasty), or incisional surgery. A total of 13 patients did not receive any IOP-lowering treatment during the entire study period, none of whom demonstrated glaucoma. Twenty-six received topical IOP-lowering agents in at least 1 eye at some

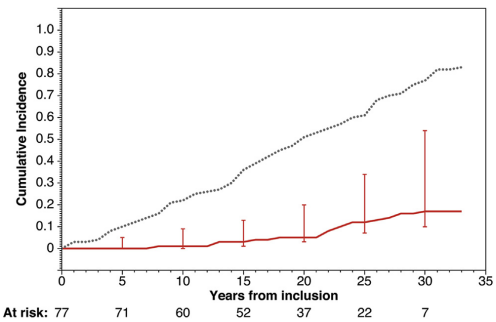

Figure 2. Graph showing the cumulative incidence of blindness in at least 1 eye caused by glaucoma (n = 13; red) and confidence intervals at every 5 years of follow-up. Competing risks are death (n = 63) and bilateral blindness resulting from other reasons (n = 1; grey). The 30-year cumulative incidence of glaucoma blindness in at least 1 eye was 0.17.

Table 2. Risk Factors for Visual Impairment Resulting from Glaucoma

Risk Factor	At Baseline	No. of Patients (Timolol/Placebo)	Mean Survival (Years to Event)	95% Confidence Interval	Log-Rank Test for Significance
Exfoliation syndrome	Yes	22 (16/6)	22.8	17.5–28.2	0.070
	No	55 (22/33)	26.0	23.9–28.1	
Suspect optic disc	Yes	12 (7/5)	19.0	14.3–23.7	0.195
	No	65 (31/34)	26.7	24.3–29.1	
IOP ≥27 mmHg	Yes	35 (19/16)	22.9	19.6–26.1	0.063
	No	42 (19/23)	28.2	25.5–30.8	
Self-reported 1° heredity	Yes	28 (11/17)	26.4	23.0–29.8	0.900
	No	49 (27/22)	24.8	22.1–27.6	
Treatment in study	Timolol	38	22.4	19.6–25.1	0.184
	Placebo	39	27.7	24.9–30.5	

IOP = intraocular pressure.
Diabetes and pigment dispersion syndrome are not shown because of the small number of patients with those risk factors.

point, of whom 12 did not have glaucoma. A total of 31 patients received topical IOP-lowering agents and 1 or more laser treatments in one or both eyes, of whom 4 did not have glaucoma. Six glaucoma patients underwent incisional surgery and 1 glaucoma patient was treated with laser therapy only. Randomization to timolol at baseline did not have a protective effect. The mean age of the patients at the time the first eye became visually impaired because of glaucoma was 82.3 years (SD, 7.9 years; minimum, 64 years; maximum, 91 years) in the timolol group and 80.7 years (SD, 5.5 years; minimum, 71 years; maximum, 88 years) in the placebo group. There was no difference in age at death between the 2 groups, with a mean of 83.3 years (SD, 8.3 years) in both. The number of eyes with fewer than 2 additional risk factors was 20 in the timolol group compared with 26 eyes in the placebo group, and 2 or more additional risk factors were noted for 18 eyes in the timolol group compared with 13 eyes in the placebo group.

Incidence of Manifest Glaucoma

A total of 48 patients (62%) had received a glaucoma diagnosis before or at the final visit before death. Glaucoma was diagnosed at a mean age of 73.5 years of age (SD, 6.9 years); the youngest patient was 56 years of age and the oldest was 90 years of age. The mean duration of diagnosed glaucoma was 11.9 years (range, 1–25 years; SD, 6.2 years). The cumulative incidence of glaucoma in at least 1 eye increased from 0.19 (95% CI, 0.14–0.33) after 5 years to 0.55 after 15 years (95% CI, 0.35–0.69) and reached 0.62 (95% CI, 0.15–0.81) after 30 years (Fig 3).

In 70 eyes (89%), the diagnosis was confirmed by repeatable visual field defects consistent with glaucoma and not explained by other causes. In 4 eyes (5%), the diagnosis was based on the presence of a visual field defect at the last visual field chart together with a glaucomatous optic disc corresponding to the field defect. In 5 eyes (6%), the diagnosis was based on the presence of a clearly glaucomatous optic disc according to the patient records, in the absence of visual field test results from that specific time point or later.

Visual Impairment Resulting from Causes Other than Glaucoma

Twenty patients (26%) demonstrated visual impairment in at least 1 eye as a result of causes other than glaucoma. The most common cause of impairment was age-related macular degeneration (8 patients). Other causes were cataract (5 patients), retinal vascular occlusion (4 patients), diabetic retinopathy (1 patient), and unclear (2 patients). One patient became blind in both eyes because of age-related macular degeneration.

Discussion

We have described the lifetime risk of visual impairment (i.e., low vision and blindness) in 77 patients who were included in the Malmö High-Risk Ocular Hypertension Study more than 30 years ago. In all, 9% of the patients demonstrated bilateral visual impairment resulting from glaucoma, and 2 of those patients (representing 3% of all patients) became bilaterally blind. The cumulative incidence of visual impairment caused by glaucoma in at least 1 eye was 0.22 after 30 years.

The strengths of our study include the long follow-up time of up to 33 years and the fact that the final visit occurred within 3 years of the date of death for 90% of the patients. A weakness is the relatively low number of patients, which affected the statistical power of our analysis. In the 1980s, when the prospective study was initiated,

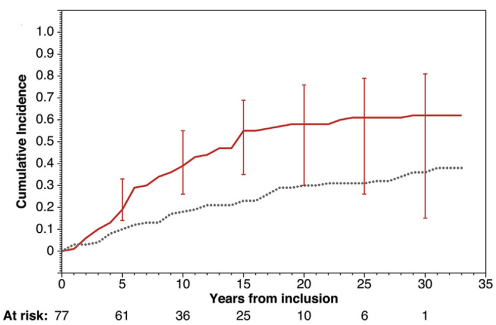

Figure 3. Graph showing the cumulative incidence of glaucoma in at least 1 eye (n = 48; red), 95% confidence intervals at every 5 years of follow-up, and of death without glaucoma (n = 29; grey). The 30-year cumulative incidence of glaucoma in at least 1 eye was 0.62.

statistical power was seldom considered in medical research,[23–25] and thus our original study also had low statistical power. This may explain why well-known risk factors for faster progression, such as higher IOP,[26–28] did not show significant effects on glaucoma-related visual impairment. Another limitation of the study is that 9 patients had known ocular hypertension before their enrollment to the Malmö High-Risk Ocular Hypertension Study, which likely overpredicts the lifetime risk of visual impairment.

Some of the patients included in the Malmö High-Risk Ocular Hypertension Study, and hence also in the current investigation, today would be considered to have preperimetric glaucoma. At the time the Malmö High-Risk Ocular Hypertension Study was initiated, it was common to disregard the status of the optic disc and the retinal nerve fiber layer when making a diagnosis of ocular hypertension; that is, this diagnosis often simply meant that the IOP was elevated, but the visual field was normal.

Early treatment of ocular hypertension had no apparent positive effect on later development of visual impairment resulting from glaucoma, although the group with such treatment showed a significant and sustained IOP reduction compared with the placebo group.[29] It is well known that IOP-lowering eye drops reduce both the incidence of glaucoma in ocular hypertensive patients[4] and the progression of glaucoma.[30–32] We speculate that the reason that the present study did not show a better outcome in patients receiving early timolol eye drops as compared with those given placebo was that the severity of risk factors differed between the 2 groups. More eyes in the timolol group showed a suspect optic disc and exfoliation syndrome at baseline, and the total number of risk factors also was higher in this group. High attrition in the prospective part of the study and treatment after the prospective study ended also may have contributed. Only 13 of the 29 patients who did not demonstrate glaucoma did not receive any treatment at any time during the entire follow-up period. Also, patients lost to follow-up create a level of uncertainty. These factors should be kept in mind when considering the generalizability of our results to the wider ocular hypertension population.

The lifetime risk of glaucoma blindness developing was considerably lower in the present study compared with results noted in earlier studies. In short, 4% (2/48) of the current glaucoma patients became bilaterally blind, which can be compared with 15% in the study of lifetime risk of blindness in open-angle glaucoma reported in 2013 by Peters et al[33] and 12% in an assessment conducted by Forsman et al.[16] This difference is apparent even though all our patients showed elevated IOP and more than half of the glaucoma patients (58%) showed 2 to 3 additional risk factors. However, the present patients were followed up regularly with perimetry and IOP measurements, which led to early detection of the disease. Advanced visual field loss at the time that glaucoma is diagnosed is the most important risk factor for glaucoma-induced blindness developing,[16,28,34–39] and therefore it is not surprising that fewer glaucoma patients in our study demonstrated visual impairment than in the investigations mentioned above.

To conclude, we have presented the lifetime risk of visual impairment resulting from glaucoma in patients with high IOP and at least 1 additional risk factor for glaucoma. A large percentage of these high-risk patients demonstrated manifest glaucoma, but only 4% of the patients with glaucoma demonstrated bilateral blindness caused by the disease during their lifetimes.

References

1. Shiose Y, Kitazawa Y, Tsukahara S, et al. Epidemiology of glaucoma in Japan—a nationwide glaucoma survey. *Jpn J Ophthalmol*. 1991;35(2):133–155.
2. Mitchell P, Smith W, Attebo K, Healey PR. Prevalence of open-angle glaucoma in Australia. The Blue Mountains Eye Study. *Ophthalmology*. 1996;103(10):1661–1669.
3. Gordon MO, Beiser JA, Brandt JD, et al. The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. *Arch Ophthalmol*. 2002;120(6):714–720. discussion 829–830.
4. Varma R, Ying-Lai M, Francis BA, et al. Prevalence of open-angle glaucoma and ocular hypertension in Latinos: the Los Angeles Latino Eye Study. *Ophthalmology*. 2004;111(8):1439–1448.
5. Leske MC. Open-angle glaucoma—an epidemiologic overview. *Ophthalmic Epidemiol*. 2007;14(4):166–172.
6. Sommer A, Tielsch JM, Katz J, et al. Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans. The Baltimore Eye Survey. *Arch Ophthalmol*. 1991;109(8):1090–1095.
7. Hollows FC, Graham PA. Intra-ocular pressure, glaucoma, and glaucoma suspects in a defined population. *Br J Ophthalmol*. 1966;50(10):570–586.
8. Kahn HA, Leibowitz HM, Ganley JP, et al. The Framingham Eye Study. I. Outline and major prevalence findings. *Am J Epidemiol*. 1977;106(1):17–32.
9. Coffey M, Reidy A, Wormald R, et al. Prevalence of glaucoma in the west of Ireland. *Br J Ophthalmol*. 1993;77(1):17–21.
10. Rochtchina E, Mitchell P. Projected number of Australians with glaucoma in 2000 and 2030. *Clin Exp Ophthalmol*. 2000;28(3):146–148.
11. Chan MPY, Broadway DC, Khawaja AP, et al. Glaucoma and intraocular pressure in EPIC-Norfolk Eye Study: cross sectional study. *BMJ*. 2017;358:1–7. j3889.
12. Hattenhauer MG, Johnson DH, Ing HH, et al. The probability of blindness from open-angle glaucoma. *Ophthalmology*. 1998;105(11):2099–2104.
13. Wilson MR, Kosoko O, Cowan Jr CL, et al. Progression of visual field loss in untreated glaucoma patients and glaucoma suspects in St. Lucia, West Indies. *Am J Ophthalmol*. 2002;134(3):399–405.
14. Weinreb RN, Friedman DS, Fechtner RD, et al. Risk assessment in the management of patients with ocular hypertension. *Am J Ophthalmol*. 2004;138(3):458–467.
15. van Gestel A, Webers CA, Beckers HJ, et al. Ocular hypertension and the risk of blindness. *J Glaucoma*. 2015;24(1):9–11.
16. Forsman E, Kivela T, Vesti E. Lifetime visual disability in open-angle glaucoma and ocular hypertension. *J Glaucoma*. 2007;16(3):313–319.
17. Heijl A, Bengtsson B. Long-term effects of timolol therapy in ocular hypertension: a double-masked, randomised trial. *Graefes Arch Clin Exp Ophthalmol*. 2000;238(11):877–883.

18. Heijl A, Krakau CE. An automatic perimeter for glaucoma visual field screening and control. Construction and clinical cases. *Graefes Arch Klin Exp Ophthalmol*. 1975;197(1):13–23.
19. Bengtsson B, Heijl A. A long-term prospective study of risk factors for glaucomatous visual field loss in patients with ocular hypertension. *J Glaucoma*. 2005;14(2):135–138.
20. Heijl A, Aspberg J, Bengtsson B. The effect of different criteria on the number of patients blind from open-angle glaucoma. *BMC Ophthalmol*. 2011;11:31.
21. Social Security Administration. Social Security Ruling SSR 07-01p Titles II and XVI: Evaluating Visual Field Loss Using Automated Static Threshold Perimetry. Available at: http://policy.ssa.gov/poms.nsf/lnx/0424535005; 2007. Accessed 20/09/18.
22. Kim HT. Cumulative incidence in competing risks data and competing risks regression analysis. *Clin Cancer Res*. 2007;13(2 Pt 1):559–565.
23. Kass MA, Gordon MO, Hoff MR, et al. Topical timolol administration reduces the incidence of glaucomatous damage in ocular hypertensive individuals. A randomized, double-masked, long-term clinical trial. *Arch Ophthalmol*. 1989;107(11):1590–1598.
24. Epstein DL, Krug Jr JH, Hertzmark E, et al. A long-term clinical trial of timolol therapy versus no treatment in the management of glaucoma suspects. *Ophthalmology*. 1989;96(10):1460–1467.
25. Schulzer M, Drance SM, Douglas GR. A comparison of treated and untreated glaucoma suspects. *Ophthalmology*. 1991;98(3):301–307.
26. Leske MC, Heijl A, Hyman L, et al. Predictors of long-term progression in the early manifest glaucoma trial. *Ophthalmology*. 2007;114(11):1965–1972.
27. Ernest PJ, Schouten JS, Beckers HJ, et al. An evidence-based review of prognostic factors for glaucomatous visual field progression. *Ophthalmology*. 2013;120(3):512–519.
28. Peters D, Bengtsson B, Heijl A. Factors associated with lifetime risk of open-angle glaucoma blindness. *Acta Ophthalmol*. 2014;92(5):421–425.
29. Bengtsson B, Heijl A. Lack of long-term drift in timolol's effectiveness in patients with ocular hypertension. *Invest Ophthalmol Vis Sci*. 2001;42(12):2839–2842.
30. Heijl A, Leske MC, Bengtsson B, et al. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. *Arch Ophthalmol*. 2002;120(10):1268–1279.
31. Garway-Heath DF, Crabb DP, Bunce C, et al. Latanoprost for open-angle glaucoma (UKGTS): a randomised, multicentre, placebo-controlled trial. *Lancet*. 2015;385(9975):1295–1304.
32. The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. Collaborative Normal-Tension Glaucoma Study Group. *Am J Ophthalmol*. 1998;126(4):498–505.
33. Peters D, Bengtsson B, Heijl A. Lifetime risk of blindness in open-angle glaucoma. *Am J Ophthalmol*. 2013;156(4):724–730.
34. Grant WM, Burke Jr JF. Why do some people go blind from glaucoma? *Ophthalmology*. 1982;89(9):991–998.
35. Oliver JE, Hattenhauer MG, Herman D, et al. Blindness and glaucoma: a comparison of patients progressing to blindness from glaucoma with patients maintaining vision. *Am J Ophthalmol*. 2002;133(6):764–772.
36. Chen PP. Blindness in patients with treated open-angle glaucoma. *Ophthalmology*. 2003;110(4):726–733.
37. Kooner KS, AlBdoor M, Cho BJ, Adams-Huet B. Risk factors for progression to blindness in high tension primary open angle glaucoma: comparison of blind and nonblind subjects. *Clin Ophthalmol*. 2008;2(4):757–762.
38. Ernest PJ, Busch MJ, Webers CA, et al. Prevalence of end-of-life visual impairment in patients followed for glaucoma. *Acta Ophthalmol*. 2013;91(8):738–743.
39. Saunders LJ, Russell RA, Kirwan JF, et al. Examining visual field loss in patients in glaucoma clinics during their predicted remaining lifetime. *Invest Ophthalmol Vis Sci*. 2014;55(1):102–109.

Footnotes and Financial Disclosures

Originally received: June 3, 2019.
Final revision: September 11, 2019.
Accepted: September 24, 2019.
Available online: ■■■. Manuscript no. 2019-115.

[1] Department of Clinical Sciences Malmö, Department of Ophthalmology, Lund University, Malmö, Sweden.

[2] Department of Clinical Sciences Malmö, Center for Primary Health Care Research, Lund University, Malmö, Sweden.

Presented in part at: Swedish Glaucoma Society Annual Meeting, October 2018, Umeå, Sweden.

Financial Disclosure(s):
The author(s) have made the following disclosure(s): A.H.: Consultant – Carl Zeiss Meditec, Allergan; Financial support – Zeiss, Allergan.

B.B.: Consultant – Carl Zeiss Meditec; Royalties – Zeiss.

Supported by Lund University, Malmö, Sweden; Skåne County Council (ALF); the Herman Järnhardt Foundation, the Margit and Kjell Stoltz Foundation; and the Ingrid Nordmark Foundation.

HUMAN SUBJECTS: Human subjects were included in this study. The human ethics committees at Lund University and the Regional Ethical Review Board in Lund, Sweden approved the study. All research adhered to the tenets of the Declaration of Helsinki. All participants provided informed consent.

No animal subjects were included in this study.

Author Contributions:

Conception and design: Oskarsdottir, Heijl, Midlöv, Bengtsson

Analysis and interpretation: Oskarsdottir, Heijl, Midlöv, Bengtsson

Data collection: Oskarsdottir, Heijl, Bengtsson

Obtained funding: Heijl, Bengtsson

Overall responsibility: Oskarsdottir, Heijl, Midlöv, Bengtsson

Abbreviations and Acronyms:
CI = confidence interval; **IOP** = intraocular pressure; **n** = number of individuals; **SD** = standard deviation.

Correspondence:
Sigridur E. Oskarsdottir, MD, Department of Ophthalmology, Skåne University Hospital, Jan Waldenströms gata 24, SE 205 02 Malmö, Sweden. E-mail: sigridur.oskarsdottir@med.lu.se.

Paper IV