Aspects of screening for open-angle glaucoma

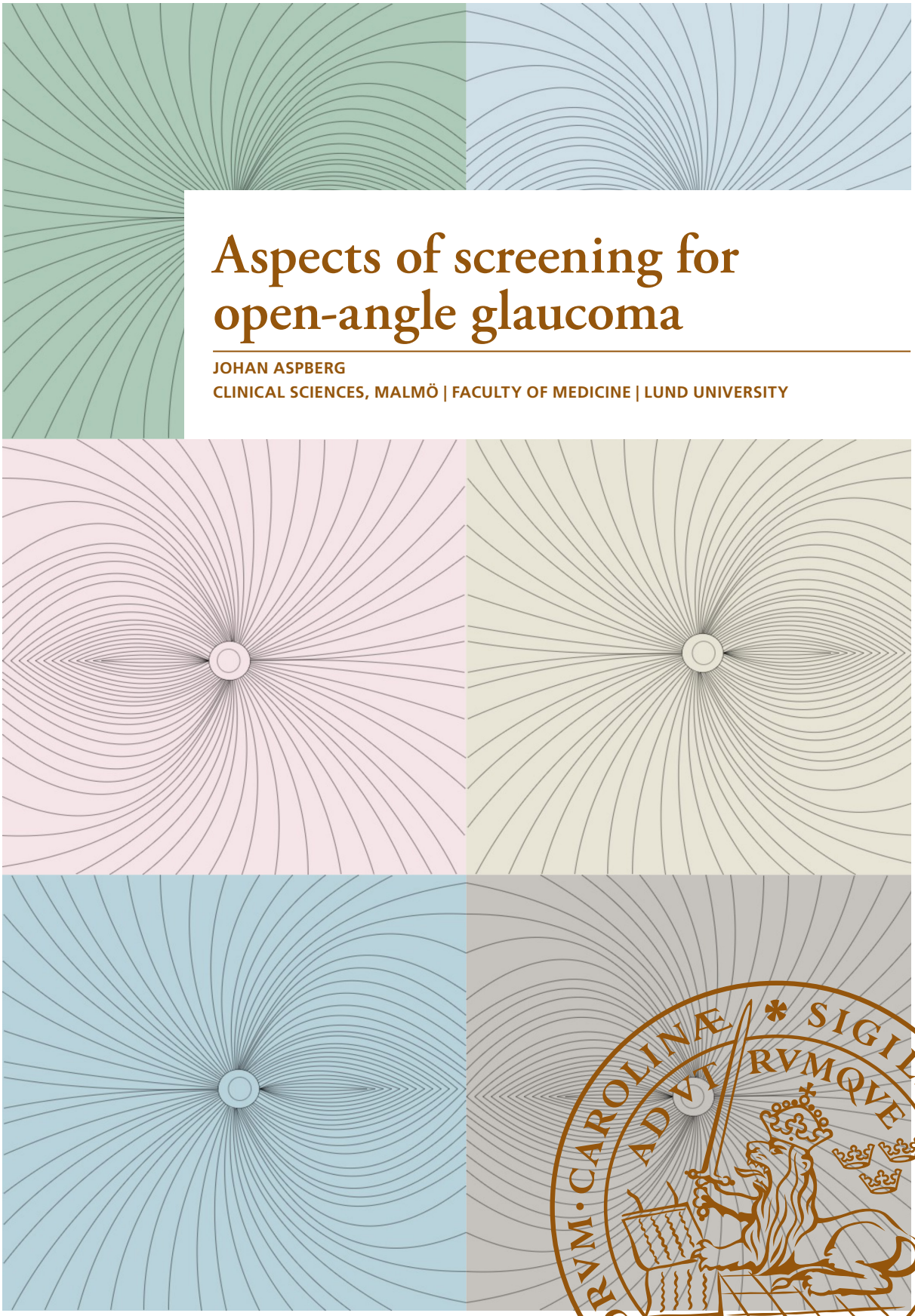
Aspberg, Johan

2022

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

Aspects of screening for open-angle glaucoma

JOHAN ASPBERG
CLINICAL SCIENCES, MALMÖ | FACULTY OF MEDICINE | LUND UNIVERSITY



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

LUND UNIVERSITY

FACULTY OF MEDICINE

Department of Clinical Sciences, Malmö

Lund University, Faculty of Medicine
Doctoral Dissertation Series 2022:176
ISBN 978-91-8021-338-7
ISSN 1652-8220

Aspects of screening for open-angle glaucoma

Aspects of screening for open-angle glaucoma

Johan Aspberg

LUND
UNIVERSITY

DOCTORAL DISSERTATION

by due permission of the Faculty of Medicine at Lund University, Sweden.

To be publicly defended on December 15, 2022 at 08.30 in Jubileumsaulan lecture hall, Jan Waldenströms gata 1, Skåne University Hospital, Malmö

Faculty opponent
Professor Eija Vesti, Åbo University

Organization: LUND UNIVERSITY

Document name: Doctoral dissertation **Date of issue** 2022-11-24

Author(s): Johan Aspberg **Sponsoring organization:-**

Title and subtitle: Aspects of screening for open-angle glaucoma.

Abstract: Glaucoma is the leading cause of irreversible blindness in the world. Open-angle glaucoma is the most common form of glaucoma with a prevalence of 2% in white populations from the age of 40. The prevalence is very low at 40, but increases exponentially with age. Approximately 50% of glaucoma cases are undiagnosed in developed countries. In initial to moderate stages of the disease symptoms are few, and a diagnosis at late stages of the disease, the major risk factor for blindness, is relatively common, suggesting that screening could reduce the prevalence of blindness from glaucoma.

Aims:

In paper I, we investigate how the influence of various criteria for vision impairment affect the assessment of low vision and blindness from glaucoma. In paper II and III we evaluate a large screening for open-angle glaucoma conducted in the 1990s, with almost 33,000 participants aged 57-77 years. We measured its effect on blindness from glaucoma, and estimated the preclinical detectable phase (PCDP) for open-angle glaucoma, i.e. the average time from which glaucoma can be detected by screening, to its clinical diagnosis. In paper IV we present results from a glaucoma screening of people aged 77-89 in Malmö in 2020. Paper V compares the amount of baseline visual field damage in patients diagnosed from 2013 to 2017, to patients diagnosed at the large screening in the 1990s.

Results:

Paper I: Prevalence of glaucoma blindness will be seriously flawed if one excludes visual field status in the assessment; 65% of the patients by the World Health Organization (WHO), and 54% by the United States (US) criteria were blind by visual field constriction, and not by visual acuity. Thirty percent more patients in our population were classified as blind by the US than by the WHO definition. Paper II: We present the first study of the real-life long-term effects of screening on rates of glaucoma blindness with a follow-up of over 20 years. Our results suggested that bilateral low vision and blindness caused by glaucoma may be reduced by approximately 50% by population screening. Paper III: The mean PCDP was estimated by two different methods, one simple and one more complex, to 10.7 (95% CI: 8.7-13.0) years, and 10.1 (8.9-11.2) years, respectively. The results suggested that repeated screening could be done with an interval of at least 5 years. Paper IV: The prevalence of glaucoma was high in individuals between 77-89 years old, but the glaucoma cases detected at the screening had low risk for developing severe glaucoma during their expected lifetime, since the great majority had early stages of disease and normal levels of IOP. Paper V: The median visual field damage at presentation in clinically diagnosed patients had improved the last 20 years, but the relative number of patients, almost 20%, with severe visual field loss in at least one eye was still high, considered that severe damage at presentation is the most important risk factor for development of glaucoma blindness.

Conclusions:

Various critera on vision impairment had a large effect on estimates of the prevalence of glaucoma blindness. Omitting visual field status from the assessment seriously underestimated glaucoma blindness. Population screening for glaucoma reduced the number of blind by 50% in the screened part of the population. The PCDP for glaucoma was long enough for repeated screening with at least 5 year intervals. Screening in the oldest age groups did not seem to be worthwhile, since the cases detected had low risk for developing blindness during their remaining lifetime. Glaucoma cases detected today had less visual field loss than in the 1990s, but a considerable proportion still had severe vision loss in at least one eye, with high risk of developing bilateral blindness.

Key words: Open-angle glaucoma, screening, preclinical detectable phase, vision impairment, blindness

Classification system and/or index terms (if any) Supplementary bibliographical information

Language English **ISSN and key title**: 1652-8220

ISBN: 978-91-8021-338-7

Recipient's notes **Number of pages**:54

Price Security classification

Signature Date 2022-11-09

Aspects of screening for open-angle glaucoma

Johan Aspberg

LUND
UNIVERSITY

Cover art by Johan Aspberg

‘

Faculty of Medicine

Department of Clinical Sciences, Malmö

ISBN 978-91-8021-338-7

ISSN 1652-8220

Printed in Sweden by Media-Tryck, Lund University

Lund 2022

To my wife and children

Table of Contents

Abstract

Glaucoma is the leading cause of irreversible blindness in the world. Open-angle glaucoma is the most common form of glaucoma with a prevalence of 2% in white populations from the age of 40. The prevalence is very low at 40, but increases exponentially with age. Approximately 50% of glaucoma cases are undiagnosed in developed countries. In initial to moderate stages of the disease symptoms are few, and a diagnosis at late stages of the disease, the major risk factor for blindness, is relatively common, suggesting that screening could reduce the prevalence of blindness from glaucoma.

Aims:

In paper I, we investigate how the influence of various criteria for vision impairment affect the assessment of low vision and blindness from glaucoma. In paper II and III we evaluate a large screening for open-angle glaucoma conducted in the 1990s, with almost 33,000 participants aged 57-77 years. We measured its effect on blindness from glaucoma, and estimated the preclinical detectable phase (PCDP) for open-angle glaucoma, i.e. the average time from which glaucoma can be detected by screening, to its clinical diagnosis. In paper IV we present results from a glaucoma screening of people aged 77-89 in Malmö in 2020. Paper V compares the amount of baseline visual field damage in patients diagnosed from 2013 to 2017, to patients diagnosed at the large screening in the 1990s.

Results:

Paper I: Prevalence of glaucoma blindness will be seriously flawed if one excludes visual field status in the assessment; 65% of the patients by the World Health Organization (WHO), and 54% by the United States (US) criteria were blind by visual field constriction, and not by visual acuity. Thirty percent more patients in our population were classified as blind by the US than by the WHO definition. Paper II: We present the first study of the real-life long-term effects of screening on rates of glaucoma blindness with a follow-up of over 20 years. Our results suggested that bilateral low vision and blindness caused by glaucoma may be reduced by approximately 50% by population screening. Paper III: The mean PCDP was estimated by two different methods, one simple and one more complex, to 10.7 (95% CI: 8.7-13.0) years, and 10.1 (8.9-11.2) years, respectively. The results suggested that repeated screening could be done with an interval of at least 5 years. Paper IV: The prevalence of glaucoma was high in individuals between 77-89 years old, but the glaucoma cases detected at the screening had low risk for developing severe glaucoma during their expected lifetime, since the great majority had early stages of disease and normal levels of IOP. Paper V: The median visual field damage at presentation in clinically diagnosed patients had improved the last 20 years, but the relative number of patients, almost 20%, with severe visual field loss in at least

one eye was still high, considered that severe damage at presentation is the most important risk factor for development of glaucoma blindness.

Conclusions:

Various critera on vision impairment had a large effect on estimates of the prevalence of glaucoma blindness. Omitting visual field status from the assessment seriously underestimated glaucoma blindness. Population screening for glaucoma reduced the number of blind by 50% in the screened part of the population. The PCDP for glaucoma was long enough for repeated screening with at least 5 year intervals. Screening in the oldest age groups did not seem to be worthwhile, since the cases detected had low risk for developing blindness during their remaining lifetime. Glaucoma cases detected today had less visual field loss than in the 1990s, but a considerable proportion still had severe vision loss in at least one eye, with high risk of developing bilateral blindness.

Populärvetenskaplig sammanfattning

Glaukom är den främsta orsaken till obotbar blindhet. Öppenvinkelglaukom är den vanligaste typen av glaukom och förekommer hos ca. 2% av Sveriges befolkning över 40 år. Nästan ingen har sjukdomen vid 40 års ålder, men därefter ökar andelen drabbade exponentiellt, och vid 75 års ålder har ca. 5 % i Malmö sjukdomen. Vid glaukom skadas synnervens nervfibertrådar, vilket ger upphov till bortfall i synfältet. Kopplingen mellan näthinnan och hjärnans synbark bryts i dessa områden, och inga synintryck registreras. Området försvinner från synen och fylls i av intryck från närliggande områden. Man lägger vanligtvis inte märke till bortfallen förrän de blivit stora, och sjukdomen upptäcks därför ofta sent i förloppet. Ett område i synfältet som är borta även hos friska personer kallas blinda fläcken. Det är det område i näthinnan där synnervstrådarna samlas ihop till synnerven och lämnar ögat, och där finns ingen näthinna. Man kan själv hitta blinda fläcken för att få en uppfattning om hur lömska synfältsdefekterna vid glaukom är, ett flertal beskrivningar finns att tillgå vid en enkel sökning på internet En upptäckt av sjukdomen i sent stadium är den största riskfaktorn för blindhet i båda ögonen, och detta har gjort att många förespråkat screening för glaukom för att upptäcka fallen i tidigare stadium, för att med tidigare insatt behandling kunna minska andelen blinda i befolkningen.

Ett förhöjt intraokulärt tryck (IOP), är en riskfaktor både för utveckling av glaukom och försämring av sjukdomen. Ett flertal studier har visat att det lönar sig att sänka IOP för att minska risken för utveckling eller försämring av glaukom, oavsett om trycket före behandling är högt eller lågt. Diagnosen öppenvinkelglaukom sätts oberoende av IOP och kräver att man har synfältsdefekter. Oftast har man då också en tydlig påverkan av synnerven i motsvarande område där synfältsdefekterna finns. Synfältstest görs nuförtiden främst med automatisk datorstyrd statisk perimetri. Det är ett test där ljusglimtar visas i synfältet i förutbestämda punkter, i det paracentrala synfältet ut till 24-30 grader runtom centrum. Nivån på glimtarnas ljusstyrka varieras och det går därmed att kartlägga områden med nedsatt känslighet för ljus. Man testar alltså funktionen i synfältet och man kan även mäta förändringar över tid som tyder på försämring. I ögon med synfältsskador kan försämring av funktionen hittas tidigare med synfältsundersökning än med bedömning av synnervens utseende, och synfältsundersökning är därför standardtestet vid långtidsuppföljning av glaukom.

Behandling av glaukom sker med ögontryckssänkande droppar, laserbehandling eller kirurgi. Man börjar oftast med droppar, kompletterar med laserbehandling, och kirurgi brukar användas mer sparsamt. Syftet med behandlingen är att sänka IOP till en nivå där synfältet antingen upphör att bli sämre, eller där försämringstakten är tillräckligt långsam för att bevara en god synfunktion livet ut. En acceptabel försämringstakt varierar mellan patienter, och beror bl.a. på hur många år patienten beräknas ha kvar att leva, och på skadornas storlek vid diagnos. Hos exempelvis en

ung patient med mycket synfältsskador vid diagnosen bör försämringstakten vara mycket låg, medan hos en mycket gammal patient med små skador kan en högre försämringstakt tolereras.

I Malmö utfördes på 1990-talet en stor screeningundersökning för öppenvinkelglaukom med syfte att hitta tidigare oupptäckta personer med glaukom som kunde ingå i en behandlingsstudie, Early Manifest Glaucoma Study. I två studier i denna avhandling har vi tagit fram journaldata från alla glaukompatienter som gått på Ögonkliniken i Malmö mellan 1987 och 2017. Utifrån dessa data har vi sedan analyserat om screeningen på 1990-talet givit en lägre förekomst av synhandikapp och blindhet pga glaukom i Malmö (Paper II), och dessutom beräknat den s.k. prekliniska sjukdomsdurationen (PCDP) för öppenvinkelglaukom, en viktig del av naturalförloppet för sjukdomen (Paper III). PCDP kan bl.a. ge en uppfattning om med vilka intervall screening kan utföras.

Vi har mätt betydelsen av att använda synfältsstatus vid utvärdering för blindhet i glaukom och jämfört WHOs kriterier med de mindre strikta amerikanska (US) kriterierna (Paper I). Medelåldern och andelen äldre i befolkningen ökar i Sverige, vilket betyder att antalet glaukompatienter, och därmed antalet blinda, kommer att öka. Vi har utfört en screeningundersökning för glaukom hos äldre, 77-89 år, i Malmö för att bestämma glaukomförekomsten och sjukdomsgraden vid diagnosen (Paper IV). Denna ger oss information om hur vi ska planera glaukomvården framöver, och om screening hos denna åldersgrupp skulle kunna minska glaukomblindheten i Malmö.

Vi har undersökt status vid diagnosen för patienter diagnosticerade mellan 2013-2017 och jämfört med de som fick diagnosen vid tiden för screeningen på 1990-talet (Paper V). De senaste tio åren har allt fler optiker börjat mäta ögontrycket på sina kunder som rutin, vilket kan ha gjort att glaukompatienter hittas i tidigare stadium idag. Vi tror också att kunskapen hos befolkningen om glaukom har ökat sedan 1990-talet, vilket också kan leda till tidigare upptäckt.

Resultat:

Paper I visar att man missade 65% av de blinda enligt WHO:s kriterier, och 54% enligt amerikanska kriterier, vid utvärdering av glaukomblindhet om man bortser från synfältsstatus, dvs. de som är blinda enligt kriterierna för synfältsinskränkning. Trettio procent fler räknades som blinda med de amerikanska jämfört med WHO:s kriterier, när man inkluderade synfältsstatus.

Paper II: Den första studien som redovisar resultat gällande effekten på glaukomblindhet av populationsscreening. Vi kunde påvisa en reduktion av glaukomblindhet med 50% i den screenade delen av befolkningen.

Paper III: Den första beräkningen av den prekliniska sjukdomsdurationen (PCDP) för glaukom. Medellängden av PCDP beräknades till ca. 10 år med 2 olika metoder. Om upprepad screening skulle införas kan man göra den med relativt långa intervall, t.ex. 5 år.

Paper IV: Screeningen hos äldre visade en hög förekomst av glaukom, 6,6% vid 77-79 år, 11,4% vid 80-84 år, och 11,2% vid 85-89 års ålder. Även om förekomsten var hög, så var andelen patienter med normala ögontryck 91%, och majoriteten hade tidigt glaukom vid diagnosen. Detta innebär att det troligen inte skulle löna sig att screena i dessa åldrar, eftersom risken för att utveckla blindhet hos dessa patienter är låg.

Paper V: Synfältsskadorna vid diagnosen har förbättrats avsevärt åren som gått efter screeningen på 1990-talet, men cirka 20% hade ändock allvarliga skador i minst ett öga, vilket ökar risken för framtida blindhet betydligt.

Slutsatser:

Vi har publicerat den första utvärderingen av populationsscreening för öppenvinkelglaukom och kunde visa efter mer än 20 års uppföljning att blindhet pga glaukom minskade med 50% i den screenade delen av befolkningen. Vi är också först med att publicera resultat för den prekliniska sjukdomsdurationen för glaukom, som beräknades med 2 olika metoder till ca. 10 år. Slutsatsen vi dragit av detta är att upprepad screening för glaukom kan göras med relativt långa intervall, t.ex. 5 år. Prevalensen av glaukomblindhet påverkas i stor omfattning av vilka kriterier för blindhet som används. En utvärdering bör innefatta synfältsstatus, inte enbart synskärpa, annars missar man en stor andel fall, som enbart uppfyller synfältskriterierna för blindhet. Vår screening för öppenvinkelglaukom hos äldre i Malmö 2020 visade en hög prevalens på ca. 11% vid 85 år ålder, dock hade de nyupptäckta patienterna mestadels normala ögontryck och lindriga skador vid diagnosen, vilket betyder låg risk att utveckla blindhet p.g.a. glaukom. Screening i dessa åldrar torde därmed inte vara aktuell. Hos nyupptäckta individer med glaukom 2013-2017 i Malmö var skadenivån avsevärt bättre än på 90-talet, men en alltför stor andel av patienterna, 20%, har fortfarande allvarliga skador i minst ett öga vid upptäckt, och har således en hög risk att utveckla blindhet.

List of Papers

Paper I

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

Paper II

Aspberg J, Heijl A, Bengtsson B. (2021) Screening for open-angle glaucoma and its effect on blindness. American journal of ophthalmology, 228:106-116. doi: 10.1016/j.ajo.2021.03.030.

Paper III

Aspberg J, Heijl A, Bengtsson B. Estimating the length of the preclinical detectable phase for open-angle glaucoma. JAMA Ophthalmology, accepted for publication October 9, 2022.

Paper IV

Aspberg, J, Oskarsdottir, SE, Heijl, A, Bengtsson B. Prevalence of open-angle glaucoma in the elderly - Interim analysis of a screening investigation. Manuscript.

Paper V

Bengtsson B, Villalba C, Peters D, Aspberg J. A comparison of disease severity in glaucoma patients identified by screening in the 1990s and in standard clinical care in the 2010s in Sweden. Manuscript.

Abbreviations

dB	Decibel
EMGT	Early Manifest Glaucoma Trial
HFA	Humphrey Field Analyzer
IOP	Intraocular pressure
MD	Mean Deviation
ODH	Optic disc hemorrhage
PCDP	Preclinical detectable phase
US	United States
VA	Visual acuity
VF	Visual field/ fields
WHO	World Health Organization

Introduction

Glaucoma is a chronic optic neuropathy, causing progressive loss of the ganglion cells of the retina and their axons, which transfer visual information from the retina to the brain. The damage is often easy to observe with ophthalmoscopy of the area where the axons from around the retina collectively leave the eye, the optic disc. Here, the optic nerve begins, and in glaucoma one can typically see a thinning of the nerve bundles. Often, the thinning is focal, and therefore easier to spot than a more generalised thinning. At advanced stages of glaucoma, the optic disc has a large excavation with little or no nerve fiber tissue left at the rim, figure 1.

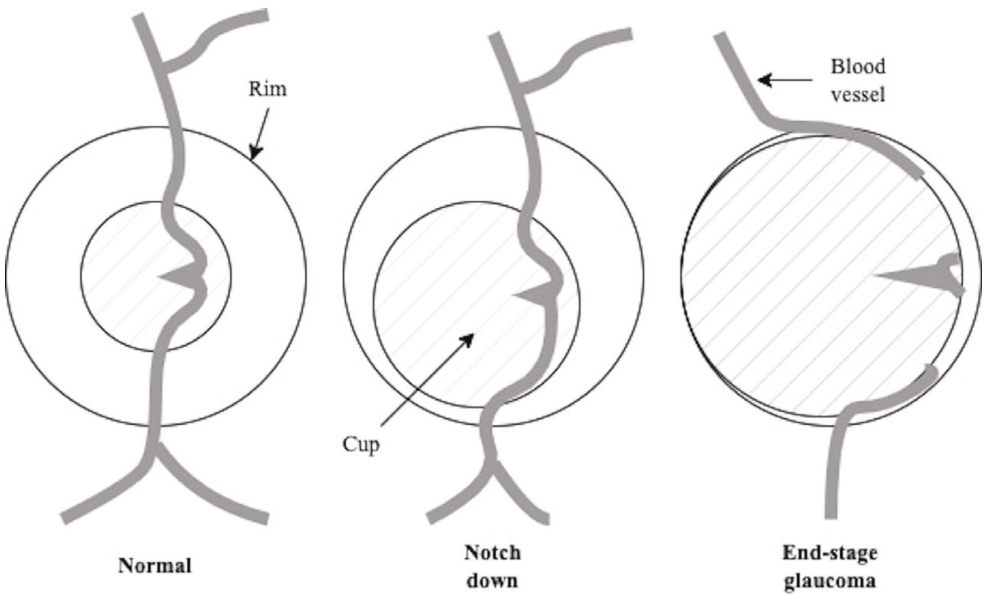


Figure 1.
Optic disc appearance in glaucoma.

In primary open-angle glaucoma, no secondary causes are present to explain the disease process. The chamber angle is open, letting the aqueous humor leave the eye through the major outflow channel of the eye, the trabecular meshwork. This dissertation only deals with open-angle glaucoma, called glaucoma from now on.

The aqueous humor is a clear fluid that fills out the anterior part of the eye, and provides nutrients to the iris, lens and cornea. The intraocular pressure (IOP) is a product of the balance between the production of aqueous humor in the ciliary body, and elimination, mainly through the trabecular meshwork, figure 2.

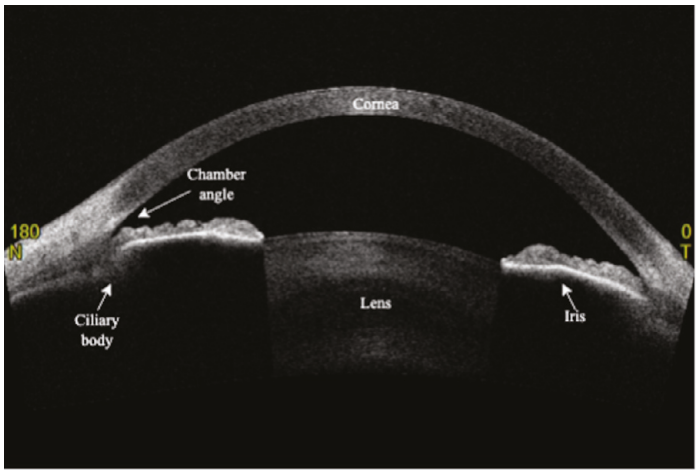


Figure 2
The anterior part of the left eye of the author, imaged by Optical Coherence Tomography.

The IOP level is not included in the definition of glaucoma. The definition of a raised IOP is based on the upper limit of the 95% confidence interval of the observed mean IOP with a Gaussian distribution, from a population-based study using the Schiötz tonometer (Leydhecker et al. 1958). Some interpreted these findings as evidence to merit a division of glaucoma patients into those with normal IOP, called "normal-tension" glaucoma, and those with elevated IOP, "high-tension" glaucoma, even suggesting different mechanisms of causation. An elevated IOP was equivalent to glaucoma for many clinicians, and to lower the IOP below 21 mmHg was for many an informal standard for a good treatment effect of IOP-lowering drops or surgery (Wilson 1997). From several population studies (Hollows & Graham 1966, Kahn & Milton 1980, Bengtsson 1981, Tielsch et al. 1991, Mitchell et al. 1996, Wensor et al. 1998), we now know that the IOP level does not define glaucoma, as about 50% of glaucoma patients have pressures lower than 21 mmHg, and consequently the IOP of many persons with glaucoma overlap with the IOP of persons without glaucoma. We also know that the IOP is not normally distributed but positively skewed towards higher pressures (Armaly 1965, Hollows & Graham 1966, Bankes et al. 1968, Colton & Ederer 1980), and that lowering the IOP also slows disease progression even at low or normal initial IOP levels (Collaborative Normal-Tension Glaucoma Study Group (CNGTS) 1998, Heijl et al. 2002, Garway-Heath et al. 2015). Today, IOP is considered most appropriate to be reported as a continuous variable.

The diagnosis of glaucoma is confirmed by the presence of visual field defects, most commonly by automated perimetry, e.g. with the Humphrey field analyzer (HFA). These visual field changes should be consistent with glaucoma and not explained by other disease, e.g. neurological or retinal disorders. Most glaucoma patients do not notice the visual field defects before diagnosis; the defects in glaucoma are so called negative scotomas. Visual information in these areas is not available to the brain, and nothing is shown in the area afflicted, just like in the physiological blind spot. The blind spot is the area where the optic nerve exits the eye, and no retina is present here. The brain fills in the blind area with information from nearby areas (Safran & Landis 1999), figure 3, and because of the lack of symptoms, many glaucoma patients are diagnosed at late stages of the disease,.

Figure 3. Visual field defect appearance in glaucoma.
To the left is how the situation appears to a person with a normal visual field; to the right how it appears for a person with glaucoma and field defects to the right.

Glaucoma is treated by lowering the IOP, which slows the progression of visual field defects (CNGTS group 1998, Heijl et al. 2002, Garway-Heath et al. 2015). Treatment is usually started with IOP-lowering eye drops, often complemented with laser trabeculoplasty. In Sweden, surgery to lower the pressure is mainly done in the cases where IOP cannot be lowered enough by drops or laser treatment. Today, we have moved towards personalised treatment of glaucoma. Variations of the progression rate between individuals are large, and the IOP level and other risk factors only account for a part of this variability. To get reliable measures of the progression rate of the individual, after initiation of treatment, five to six visual field exams are needed the first 2-3 years. Thereafter, evaluation of the rate is done, and

extra treatment initiated if needed. If the progression rate and IOP are stable, intervals between visits may be extended. The aim of treatment is to keep the progression rate at a rate low enough to ensure vision at a level that will not compromise the quality of life (QOL) of the patient (EGS Terminology & guidelines 2020). A study on patients participating in the EMGT showed that QOL starts to diminish at a Mean Deviation (MD) of the visual field of <-18 decibel (dB) in both eyes (Peters et al. 2015) Other studies (Hirooka et al. 2016, Jones et al. 2017) have suggested that a measurable effect on vision related QoL starts when approximately less than 50% of a full visual field remains, which corresponds to MD values between -18 dB to -14 dB depending on patient age. An important risk factor for developing blindness is late stage glaucoma at the diagnosis (Oliver et al. 2002, Chen et al. 2003, Chang et al. 2005, Forsman et al. 2007, Kooner et al. 2008, Peters et al. 2014). Therefore, screening for glaucoma, and finding the patients at an earlier stage of glaucoma, has been a recurring topic of discussion.

Epidemiology of glaucoma

Prevalence

Open-angle glaucoma is the most common form of glaucoma. The disease is age-related, with clear differences in prevalence depending on race or ethnicity, figure 4. In predominantly white populations the prevalence is about 2% in people ≥40 years of age (Kapetanakis et al. 2016). At 40 years, the prevalence is low but increases exponentially with age; in Malmö, Sweden, the prevalence is 5% at the age of 75 (own unpublished data). One of the papers in this dissertation presents results of the prevalence in the oldest part of the population in Malmö; in the 80-84 years group the prevalence was high, about 11%. With a high prevalence at older age, and an expected increase in longevity (www.scb.se), the number of glaucoma patients, and consequently the number of blind from glaucoma, will increase in the future.

Incidence

The incidence of open-angle glaucoma is less known than the prevalence. To estimate incidence in a population, one has to measure the prevalence in a population and then perform a follow-up estimate a few years later in the same individuals that were measured at the first occasion. The studies published (Bengtsson 1981, Mukesh et al. 2002, De Voogd et al. 2005, Hitzl et al. 2006, Leske et al. 2007, Czudowska et al. 2010, Cedrone et al. 2012, Varma et al. 2012, Kawasaki et al. 2013, Pan et al. 2017, Founti et al. 2021), have methodological

differences among them, e.g. in the definition of glaucoma, time intervals measured and mean age of the population, which complicates comparisons. There are, however, methods of indirectly estimating the incidence from prevalence in irreversible non-fatal disease (Leske et al. 1981).

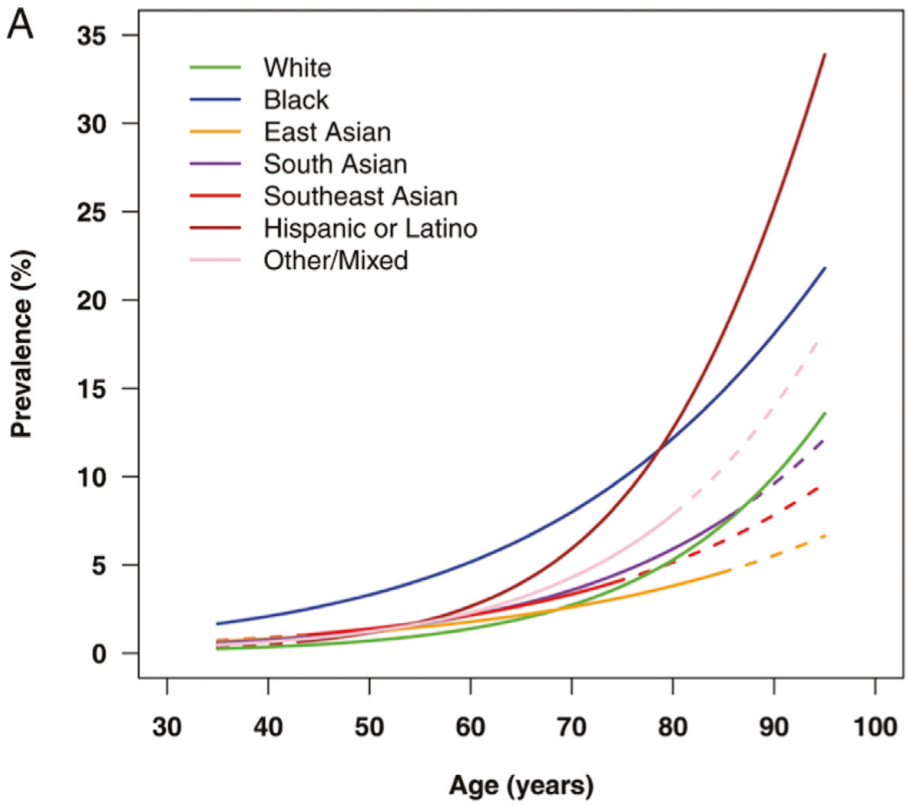


Figure 4
Prevalence of open-angle glaucoma by age and ethniticity. From Kapetanakis et al. 2016.

Risk factors for developing glaucoma

Several population-based longitudinal studies have shown that IOP is a risk factor for developing glaucoma, with a 10-18% risk increase/mmHg higher IOP than the population average at baseline, and that older age at baseline increased the risk by 4-6%/year (Gordon et al. 2002, Le et al. 2003, Bengtsson & Heijl 2005, de Voogd et al. 2006, Müskens et al. 2007, Miglior et al. 2007, Leske et al. 2008). Myopia of any degree has been found to double the risk for glaucoma, in Malmö (Grødum et al. 2001), and in a meta-analysis of several studies (Ha et al. 2022), which also found

an increased risk for developing glaucoma of 20% per myopic diopter increase. Heredity is an important risk factor for glaucoma. Studies have reported an increased risk of 2 to 9 times for first-degree relatives to glaucoma patients (Tielsch et al. 1994, Wolfs et al. 1998, Nemesure et al. 2001, Mitchell et al. 2002, Green et al. 2007). Pseudoexfoliations, a fibrillopathy common in Scandinavia and often seen as flakes on the anterior lens capsule, increases the risk of glaucoma 2-5 times (Mitchell et al. 1999, Grødum et al. 2005, Åström et al. 2007, Topouzis et al. 2011, Ekström 2012). Optic disc haemorrhages (ODH), small splinter-like bleedings appearing at the rim of the optic nerve head, increase the risk of developing glaucoma by a factor of 2.0-3.7 (Budenz et al. 2006, Miglior et al. 2007). Race is sometimes regarded as a risk factor, see the chapter on prevalence above and figure 4.

Risk factors for progression and blindness

Baseline predictive factors

The presence of ODH increases the risk for progression in glaucoma by a factor of 2.1-3.6 (Rasker et al. 1997, Ishida et al. 2000, Drance et al. 2001, Leske et al. 2007, De Moraes et al. 2011, Founti et al. 2020). In the EMGT, an increased risk was seen for an untreated IOP ≥21 mmHg: 1.7; MD ≤-4.0: 1.55; presence of exfoliation syndrome: 2.31; systolic blood pressure ≤125 mmHg: 1.42 (Leske et al. 2007). Older age was a predictive factor in three studies: ≥68 years: 1.43, in the EMGT (Leske et al. 2007); per 5 years older: 1.28, in the Advanced Glaucoma Intervention Study (AGIS 2000); per year older: 1.04, in the Collaborative Initial Glaucoma Treatment Study (Lichter et al. 2001). In the United Kingdom Glaucoma Treatment Study (UKGTS), a risk increase was seen for higher mean IOP by 1.07/mmHg; bilateral disease: 1.59; and smoking seemed to have a protective effect, 0.59.

Post-baseline predictive factors

Higher mean IOP at follow-up (mean IOP at all follow-up visits): 1.13/mmHg; ODH: risk increase of 1.02 / % of visits with ODH (Leske et al. 2007).

Risk factors for developing blindness

At baseline: Disease stage: 1.8 per worse stage (in the better eye), untreated IOP level: 1.08/mmHg higher (Peters et al. 2014); ≥22 mmHg: 1.54 (Kooner et al. 2008); Risk reduction: 0.83 per dB better MD (Chen 2003). Other: Age at death 1.09/year (Peters et al. 2014).

Other studies that have reported on risk factors for progression or blindness include: Oliver et al. 2002, Forsman et al. 2007, Chang et al. 2005, Fukuchi et al. 2013.

Vision impairment

Glaucoma, all forms included, is the most common cause of irreversible blindness globally (Resnikoff 2004, Flaxman 2017). In Sweden and the other Nordic countries, glaucoma patients have a lifetime risk of bilateral blindness from glaucoma of about 15%. (Forsman 2007, Peters 2013). Evaluation of vision impairment is based on visual acuity (VA) alone for most eye diseases. Glaucoma is one of the diseases, together with onchocerciasis, where visual field (VF) constriction is included in the criteria for impairment. There are two dominating definitions of vision impairment in the ophthalmic literature: the criteria defined by the World Health Organisation (WHO) and by the United States (US) (table 1). These definitions are different in the cut-off for both VA and VF constriction, e.g. for blindness. This has made comparisons of the prevalence of impairment in populations from different countries and regions complicated.

In paper I and II, we had to estimate the number of impaired glaucoma patients from VF constriction, mainly from HFA printouts. We created a method to calculate the remaining VF by modifying an earlier method by the US Social Security Agency (Social Security Ruling, SSR 07-01p). In short, one plots a so called pseudoisopter between "seeing" (≥10dB) and "blind" points (<10dB) on the HFA dB printout, and then measure the remaining VF around the fixation point, figure 5.

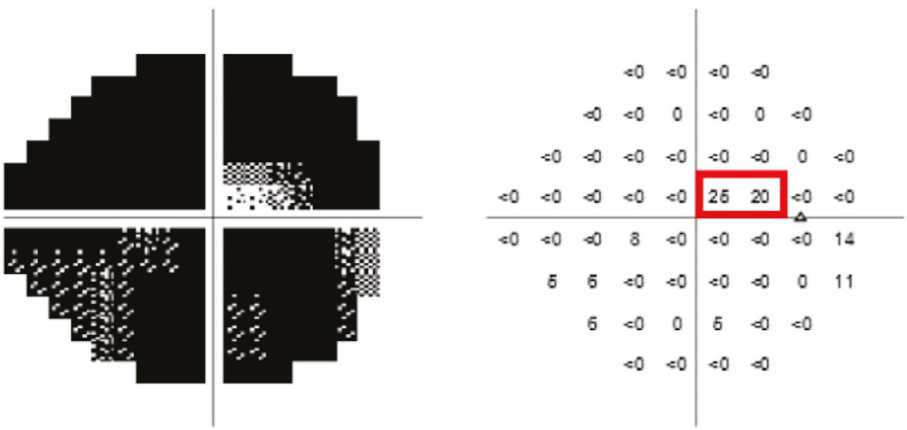


Figure 5. How to measure the extent of the remaining visual field.
The pseudoisopter is the red line, and only adjacent points ≥10 dB around fixation are marked. The distance between points is 6°, and from a point to the pseudoisopter is 3°. This visual field is constricted to 12° within fixation.

There are other methods of measuring the severity of glaucoma from VF which are less time-consuming. The US Social Security Agency has used a cut-off of a MD of ≤-22 to use in disability determinations (Social Security Ruling, SSR 07-01p), a definition which we also included for comparison in paper I. Different glaucoma

staging systems have been proposed over the years, we used one of these (Mills et al. 2006), in a modified form in paper IV.

Table 1: Criteria for vision impairment
World Health Organization

Category	Visual acuity in the better eye	
	Worse than:	*Equal to or better than:*
1 Mild vision impairment	0.5 (20/40)	0.3 (20/70)
2 Moderate vision impairment[a]	0.3 (20/70)	0.1 (20/200)
3 Severe vision impairment[a]	0.1 (20/200)	0.05 (20/400)
4-6 Blindness	0.05 (20/400)	
Category	Remaining central visual field (better eye)	
	Less than:	*Equal to or more than:*
3 Severe vision impairment[a]	20°	10°
4-6 Blindness	10°	

[a] Called low vision in this study

United States criteria

Category	**Visual acuity in the better eye**	
	Equal to or less than:	*Better than:*
1 Visual acuity loss	0.5 (20/40)	0.1 (20/200)
2 Blindness	0.1 (20/200)	-
Category	Remaining central visual field in the better eye	
	Less than:	*Equal to or more than:*
2 Blindness	20°	-

Screening

The purpose of screening is to detect disease at earlier stages than it would be diagnosed under normal circumstances, e.g. by symptoms, or sometimes by chance. Earlier detection and appropriate treatment may then lead to a reduction of the morbidity/mortality from the disease. In Sweden, there has been screening programs for breast cancer and cervical cancer for many years (https://www.socialstyrelsen.se/kunskapsstod-och-regler/regler-och-riktlinjer/nationella-screeningprogram/).

Before starting a screening program, the potential benefits of screening must be compared to the harms it may cause. X-ray or endoscopic examinations, for example, are not risk free screening tests, neither is the surgery or medical treatment of cancer. Some of the cases detected at screening would not be detected during the person´s remaining lifetime, so called overdiagnosis (Morrison 1992), causing undue anxiety in the patient, and sometimes unnecessary treatment. Indiscriminate screening or case-finding without a clear strategy may consume resources improperly, and not lead to a reduction of the mortality/morbidity from the disease, the foremost goal of screening (Anonymous 1985). Thus, population screening should not be started without careful risk and cost-effectiveness analysis and clear evidence of a benefit of screening.

In 1968, WHO published a paper that proposed ten principles to help decide if a disease was "screenable" (Wilson & Jungner 1968), table 2.

Table 2. Wilson and Jungner's principles of screening

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a "once and for all" project.

The World Glaucoma Association (Weinreb et al. 2008) has concluded that open-angle glaucoma fulfilled all these principles except for cost-effectiveness. Several reports have evaluated glaucoma screening (Hatt et al. 2006, Ervin et al. 2012, UK National Screening Committee 2019, Chou et al. 2022,), but did not recommend it, mostly due to the lack of evidence of a positive effect on glaucoma blindness. The cost-effectiveness of glaucoma screening has been the subject of many reports (Gottlieb et al. 1983, Boivin et al. 1996, Tuck & Crick 1997, Burr et al. 2007, Vaahtoranta-Lehtonen et al. 2007, Burr et al. 2014, John & Parikh 2017, Tang et al. 2019), however, the results were predictions made with models based on prevalence data and a presumed effect of glaucoma treatment.

Paper II is the first report of real-life long-term effects of population screening on rates of glaucoma blindness, an evaluation made 20 years after a large screening in Malmö with 33,000 participants. It is a retrospective observational study of a closed cohort, i.e. no new individuals moving in to Malmö were added to the cohort after the screening invitation. The best design for a study of the effect of screening would be a randomised controlled trial (RCT), randomising individuals to a study group or a control group and thereby minimising the risk of bias. The screening in Malmö, though, had been conducted to find undiagnosed glaucoma patients for possible inclusion in a treatment study, the Early Manifest Glaucoma Trial (EMGT) (Leske et al. 1999), and no control group was created at the time of the screening. In these cases, one would need to create a control group, from e.g. historical cases, or an unscreened population in another area. In our study, the control group was created from persons in Malmö belonging to age cohorts older and younger than the cohorts invited to the screening, with corrections for age, figure 6.

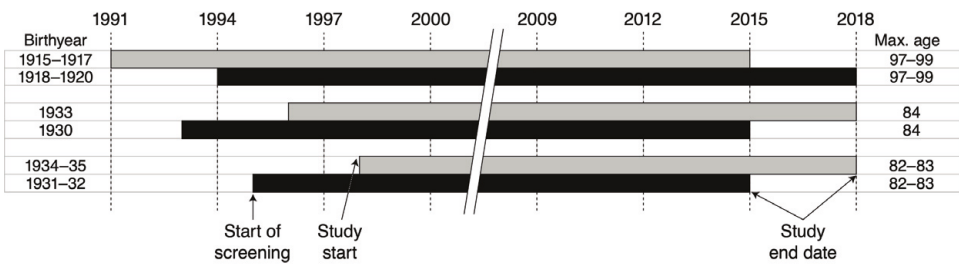


Figure 6. Creation of the uninvited comparison group and corresponding non-responders.
Patients from the unscreened comparison group (gray bars) were assigned the same day and month for the study start as the non- responders (black bars), but the year was adjusted to match for the age of the non-responder subjects. Similarly, the year for study end was adjusted to obtain the same follow-up time period for both groups. From Aspberg et al. 2021.

Thereby, we could compare the effect of screening on blindness in the screened, non-responders to the screening (persons invited who did not participate) and control group, and eventually correct the results for selection bias (Cuzick et al. 1997, Duffy et al. 2002). This form of bias is created when there is a difference in

characteristics of the persons in the exposed group compared to the not exposed, in this case screened and non-responders (both invited to the screening). For example, if the non-responders in a cancer screening happen to have more fast-growing, malignant tumours than in the screened group, and the groups were compared, one could see a positive effect of screening on mortality, even if there was no real effect, as the screened individuals had a better prognosis at baseline.

Another form of bias associated with screening is length bias. Slow-developing cases with a long duration, often less malignant than cases developing fast, are more likely to be detected at screening, and therefore a comparison of survival with clinically detected cases may be biased. Overdiagnosis is an extreme form of length bias, when screening detects cases that would never be detected during a person´s remaining lifetime (Morrison, 1992).

If survival time is compared between screen-detected cases and clinically detected cases, the screen-detected cases will always get a survival benefit in years corresponding to the lead time, the period of time that the diagnosis is advanced by screening. One may correct for this lead time bias, as well as length bias (Duffy et al. 2008), but a more appropriate method to use for evaluating the effect of screening is to compare the proportion having reached an end-point (e.g. death, or here blindness) between groups, counting only cases detected at the time for the screening and onward.

Evaluation of the effect of a screening on mortality/morbidity from a disease, the main outcome, is often not possible until many years have passed after the screening. There are, however, ways of measuring an effect earlier. In a screening program, e.g. for breast cancer, screening is repeated every few years, and a control group is not available, as the whole population of a certain age is invited. A positive effect of screening would then be suggested by a reduction of the percentage of late stage tumors in subsequent screening rounds. Cancers detected between 2 rounds are called interval cancers, and consist of cases missed at the previous screening, i.e. false negatives, and cancers newly developed after the screening. The incidence of interval cases would ideally be low following a screening round in a program with high sensitivity, i.e. low false negative rate. Sensitivity is the probability of a test to be positive in cases who have the disease in question, and specificity is the probability of the test to be negative in the persons who do not have the disease. Interval cases can be expressed as a proportion of the underlying (expected) incidence in the population, and may thus be compared between populations that have different incidence of the disease. If screening is stopped, the incidence of the disease will return to its expected levels without screening, see figure 1b in paper III. For a screening with 100% sensitivity, the distribution of this recovering incidence correlates to the distribution of the preclinical detectable period (PCDP) (Etzioni & Self 1995). Thus, interval cases are indicators of both the sensitivity of the screening programme and the length of the PCDP.

The PCDP, also called sojourn time, is an important component of the natural history of a disease, essential for planning and early evaluation of screening (Morrison, 1992). It is the period of time from which a disease can be detected by a screening test to the time of its clinical diagnosis, figure 7. If the PCDP is short, the disease develops fast, and the interval between screening rounds needs to be correspondingly short, and vice versa. Lead time is the amount of time gained by the earlier detection by screening.

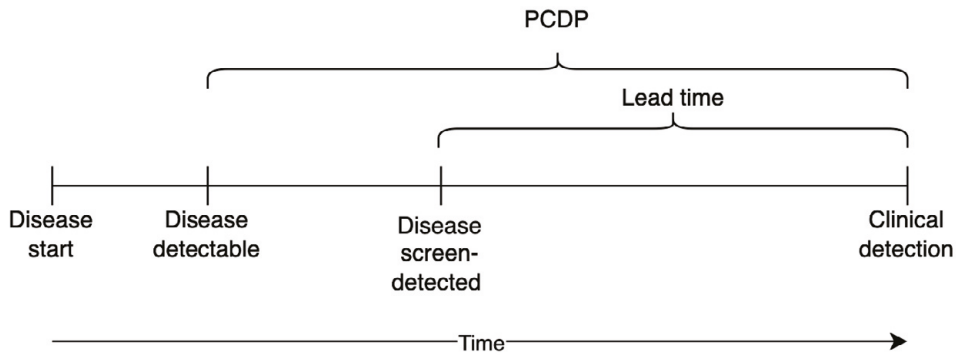


Figure 7.
The preclinical detectable phase (PCDP) is the period of time from which the disease is possible to detect by screening, to the time of clinical diagnosis. Lead time is the amount of time gained by earlier detection by screening.

The length of the mean PCDP can be estimated by several methods (Geurts et al. 2022), and in Study III we decided to use two of them: 1. Division of the prevalence of screen-detected disease with the expected incidence without screening, with a fixed 100% sensitivity of the screening. This corresponds to the number of years it would take to accrue the cases detected at the screening, in an unscreened population; 2. A Bayesian Markov chain Monte Carlo (MCMC) simulation, which simultaneously derives both the mean PCDP and sensitivity of the screening.

When screening for glaucoma, several tests are often combined, e.g. measurement of the IOP by Goldmann tonometry, and fundus photography of the optic nerve. There are many different methods to choose from, and for more information see Mowatt et al. 2008. If sensitivity for a test increases, specificity decreases, and vice versa, and one has to find a balance between the two that suits the disease screened for. Generally, in population screening, one wants a high specificity of the test/tests, to avoid too many false positives, i.e. people who do not have the disease in question, that require follow-up examinations and cause unnecessary anxiety. Sensitivity of the test should be at a level where one minimises the number of missed cases.

Aims

Study I

To investigate how estimates of vision impairment from glaucoma are influenced by different criteria of impairment, and the effect of omitting visual field status.

Study II

To evaluate the effect of population screening on low vision and blindness from open-angle glaucoma.

Study III

To estimate the preclinical detectable phase for open-angle glaucoma, i.e. the average time from which glaucoma can be detected by screening, to its clinical diagnosis.

Study IV

To estimate the prevalence and stage of open-angle glaucoma in individuals 77-89 years old in Malmö.

Study V

To compare visual field damage at diagnosis between open-angle glaucoma patients screened in the 1990s, and clinical patients diagnosed 20 years later in Malmö.

Methods

Ethics

All studies included in the thesis adhered to the Declaration of Helsinki and were approved by the Swedish Ethical Review Authority.

Glaucoma screening in Malmö

A major screening examination for open-angle glaucoma was conducted in Malmö from 1992 to 1997. All individuals living in Malmö born from 1918 to 1932, and women born from 1933 to 1939, were invited to participate. The screening was mainly initiated to find previously undiagnosed glaucoma patients for inclusion in a treatment study, the Early Manifest Glaucoma Trial (EMGT) (Leske et al. 1999). A total of 32918 persons participated, and 9579 were non-responders to screening, i.e. chose not to participate. Patients who had visited the Eye department at Malmö university hospital within a year from their screening date were not invited to the screening (n=4117).

The screening procedure included: a health questionnaire regarding medical and family history and current medications, refraction, visual acuity, a fundus photograph of the optic nerve head, and IOP measured by Goldmann tonometry; also, eyes with IOP >20 mmHg had their pupils dilated and were examined for the presence of pseudoexfoliations.

Persons fulfilling one or more of the following were invited to post-screening examinations: IOP >25 mm Hg in at least one eye; 2) findings in the fundus photographs: a glaucomatous optic disc - suspected or evident, retinal nerve fiber defects, or an optic disc haemorrhage; 3) presence of exfoliation syndrome; or 4) ≥1 first-degree relative with manifest glaucoma.

One or two post-screening examinations were performed to confirm or reject a glaucoma diagnosis. A full eye examination was done, including a HFA 24-2 visual field test.

In the EMGT, as well as in the studies of this thesis, the diagnosis of glaucoma were based on criteria as follows: a Humphrey Full Threshold 24-2 or 30-2 visual field test with a Glaucoma Hemifield Test (GHT) result "outside normal limits" or "borderline". For "borderline" cases there had to be obvious glaucomatous changes of the optic disc which corresponded to the field defect. The results had to be present in two consecutive tests and the same GHT sectors had to be abnormal in both tests. A later study has estimated the specificity of the criteria to be 97% (Öhnell et al. 2019). The major screening examination was not intended as a population screening with the purpose to evaluate the effect of glaucoma screening on blindness and no control group was created at the screening.

Study I

A retrospective study of 914 open-angle glaucoma patients visiting the Department of Ophthalmology at Malmö University Hospital between 1 June 2004 and 31 May 2006. We identified how many of the patients that fulfilled the 2 major criteria for bilateral vision impairment, the US and WHO criteria (table 1) and also applied a visual field criterion used by the US Social security agency (US-SSA) for determining eligibility for benefits. The latter is based on an MD value of the visual field of ≤-22 dB.

Vision impairment for most eye disorders is based on VA alone, usually with best correction (glasses). For glaucoma there is also a second criterion, visual field constriction, and a person can be considered impaired by VA or visual field constriction, or both.

We also identified how many of our patients that were impaired if we did not take the visual field status into consideration. Glaucoma patients considered blind by visual field constriction often has preserved VA, because of a visual field remnant centrally.

Study II

We did a retrospective review of all patients with a diagnosis of primary open-angle glaucoma or pseudoexfoliation glaucoma who had visited the Department of Ophthalmology at Malmö University Hospital between Jan 1 1987, and Dec 31 2017. The patients fulfilling the diagnostic criteria for glaucoma were then assessed for the presence of bilateral vision impairment, which includes blindness, according to the WHO criteria. We compared the rates of bilateral vision impairment due to glaucoma in 3 groups: 1. The participants of the screening. 2. The non-responders

to screening, i.e. persons that chose not to participate. 3. A control group consisting of persons not invited to screening, older and younger than the persons invited to the screening. The proportions of potential confounders were compared between the three groups. Cumulative incidence of vision impairment for each group, and risk ratios between groups were calculated. Selection bias was corrected by creating a group of potential screening participants from group 3, figure 8.

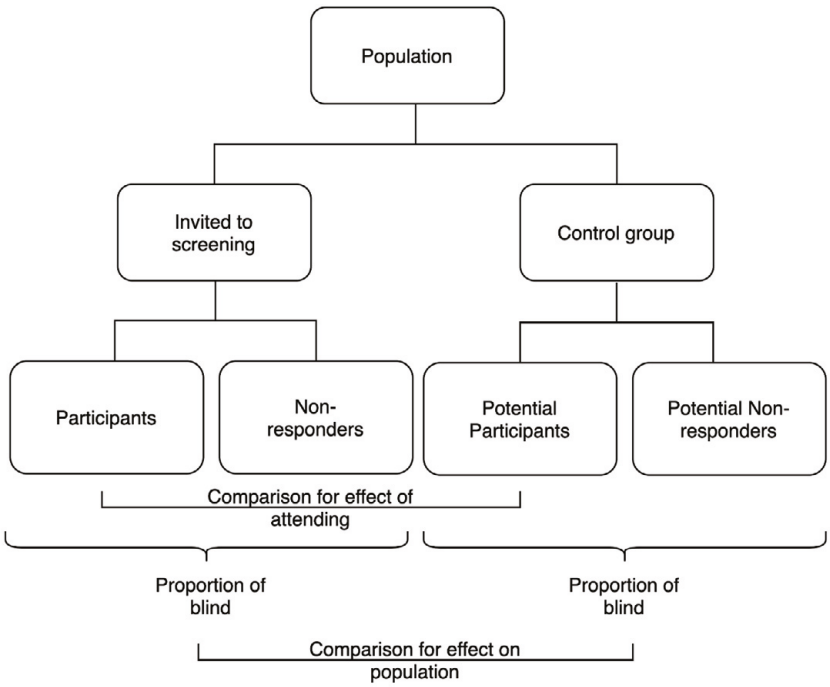


Figure 8. Correction for selection bias
A group of potential participants, people who would participate in a screening study if asked, can be created from a control group to correct for selection bias. The proportion of non-responders and blind non-responders is considered the same in the invited and the control group. The corresponding numbers in the potential participants group are calculated by subtracting the number of cases of the potential non-responders from the total of the control group . Adapted from Aspberg et al. 2021.

Study III

Retrospective review of the same study population as in study I. The mean preclinical detectable phase (PCDP) is the period from when a disease can be detected by a screening test to the time of clinical diagnosis, a component of the natural history of a disease, important for planning and early evaluation of screening programs. It was estimated by two different methods: 1. The prevalence of undetected (preclinical) glaucoma diagnosed at the screening was divided by the

incidence of clinically detected glaucoma. 2. A Markov chain Monte Carlo algorithm (MCMC), which simultaneously derives both the mean PCDP and sensitivity of the screening.

We calculated the prevalence of glaucoma detected at the screening, the expected clinical incidence, and the clinical incidence of glaucoma yearly after the screening, in the screened part of the population. The patients were divided into 2 groups, see figure 2 in paper III:

1. Patients living in Malmö who were diagnosed from the time of screening to December 31, 2017, and belonged to the screen-invited birth cohorts, born 1918-39. From this group, the prevalence at the screening and the clinical incidence after the screening could be calculated.

2. Patients who belonged to the screen-invited birth cohorts living in Malmö who were diagnosed clinically from January 1, 1987 up to their respective screening dates, and secondly, patients from age groups not invited to the screening born 1915-17 who were living in Malmö at the time of clinical diagnosis from January 1,1987 to December 31, 2008. From this group we could calculate the underlying clinical incidence of glaucoma at different ages in Malmö.

Study IV

In Sweden, the prevalence and severity of undetected glaucoma in the oldest part of the population has not been estimated. The average life expectancy, and the proportion of elderly in the population is increasing. Prevalence of open-angle glaucoma increases dramatically with age, and we expect to see an increase of the number of glaucoma patients and, consequently, the number of people blind from glaucoma. To understand at what ages glaucoma screening is most effective, and to properly allocate resources for glaucoma care with an ageing population, we performed a screening examination for glaucoma in persons aged from 77-89 years in Malmö. Due to the COVID-19 pandemic, we had to discontinue the screening prematurely, when just over half of the planned number of individuals had been examined. This is an interim report based on the data collected so far.

We extracted the number of individuals aged from 77 to 89 years and living in Malmö from the Swedish population register, and did a random and age-stratified sampling to select 1,199 of 16,311 eligible persons, who then received an invitation to participate in the screening. Patients already diagnosed with glaucoma at our department were excluded from participation. We asked the participants about previous and present eye disease and the use of any eye drops. Visual acuity and refraction were measured with an automatic refractor, manual refraction was performed if the acuity was less than 0.1. The intraocular pressure (IOP) was

measured with an Icare ic200 rebound technique tonometer. Perimetry was performed with the C-20-1 program of the Frequency Doubling Technique (FDT) perimeter. A photograph of the optic nerve head (ONH) was taken through an undilated pupil with a Visuscout 100 Mobile Retina.

A person was screen-positive, if at least one of the following criteria was present in at least one eye:

1. IOP ≥25 mmHg
2. At missed stimulus on the FDT C-20-1, repeated in a second test at the same or an adjacent test location.
3. Suspected glaucoma seen on the fundus photograph.

Screen-positives were invited to a post-screening visit, where a full ocular examination was made. Visual acuity and intraocular pressure (IOP) was measured, and gonioscopy and a dilated examination of the fundus were performed. The presence of pseudoexfoliation syndrome was registered. All subjects were tested with the SITA Standard 24-2 program of the Humphrey Field Analyzer.

The test results were analysed in three different age groups: 77-79, 80-84, and 85-89 years old. We calculated the proportion of glaucoma cases in each age group separately for the newly detected patients, and patients with a prior glaucoma diagnosis alive at the time of the screening. The total prevalence in each age group was calculated, by adding the screen-detected cases to the cases of those diagnosed prior to the screening, and dividing with the total population. Disease severity was presented as the median of the Mean Deviation of the visual field in the worse eye, median IOP, the proportion of bilateral glaucoma and pseudoexfoliation syndrome.

Study V

In a previous study from our research group (Grødum et al. 2002), VF damage at the time for diagnosis for 402 patients identified by the large screening in Malmö in the 1990s, was compared to the VF damage at the time of the screening for 354 patients of the same age diagnosed in routine clinical practice before the screening. The latter group had much worse VF damage.

In the current study, VF damage at the time for diagnosis was compared between the same patients diagnosed in the 1990s, and patients of the same ages, i.e., between 57 and 77 years, that we call clinical patients, diagnosed at our department 20 years later, from 2013 to 2017. The perimetric Mean Deviation (MD) value was compared between the two groups of patients.

Results

Study I

By the WHO criteria, forty patients (4.4%) were bilaterally blind from glaucoma, and fifty-two (5.7%) were blind by the the US criterion. When we assessed only visual acuity, 14 (1.5%) patients were blind by the WHO criteria and 24 (2.6%) by the US definition, table 3. The US SSA disability criterion was fulfilled in eighty-five (9.3%) patients, among whom, 52 were impaired also by the WHO definition. Of the patients impaired by the WHO criteria, none had MD values better than -22 dB.

Table 3. Influence of visual field status on the number of patients blind/ visually impaired from glaucoma.

	Visual fields + VA No. (% of all patients)	VA alone No. (%)
WHO – blindness	40 (4,3%)	14 (1,5%)
WHO – vision impairment	58 (6,3%)	37 (4,0%)
US - blindness	52 (5,6%)	24 (2,6%)

VA, Visual acuity

Study II

The screened population had a cumulative incidence of blindness of 0.17% compared to 0.32% among the potential participants; for low vision the numbers were 0.25% versus 0.53%, respectively. The risk ratio (95% confidence interval) between the screened and potential participants was 0.52 (0.32-0.84) for blindness and 0.46 (0.31-0.68) for low vision. The proportions of potential confounders in the comparison group and those in the non-responders did not differ.

Study III

Mean length of the PCDP of the whole study population by the P/I method was 10.7 (95% CI: 8.7-13.0) years, and by the MCMC method 10.1 (8.9-11.2) years. Patients 55-59 and 60-64 years old at the screening had a slightly longer PCDP with the P/I

method. The sensitivity of the screening was 94% (95% CI; 93-96), estimated by the MCMC method.

Study IV

The participation rate of the screening was 27%. Twenty-three (7.4%) cases were detected at the screening. The total prevalence of glaucoma, new and known glaucoma, in the ages 77-79, 80-84 and 85-89 years was (95% confidence interval (CI)): 6.6% (6.0-7.3), 11.4% (10.7-12.2), and 11.2% (10.3-12.1), respectively. The screen-detected patients had mostly early glaucoma, and almost all patients (91%) had intraocular pressures (IOP) within normal statistical limits.

Study V

From 2013 to 2017, 281 patients were diagnosed with manifest glaucoma. In the patients with bilateral glaucoma, the median MD in the better eye was -5.1 dB in the clinical patients and -6.5 dB in the screened patients, p=0.28, and in the worse eye -13.0 dB and -11.5 dB, p=0.67, respectively. In patients with unilateral glaucoma the median MD was -6.0 dB and -6.9 dB, p=0.29, in clinical and screened patients respectively. Severe visual field loss, defined as MD <–20 dB in the worse eye, was more common in the clinical patients, 18.5%, than in the screened patients, 12.7%.

Conclusions

Study I

Numbers of the prevalence of glaucoma blindness will be seriously flawed if one excludes visual field status in the assessment; 2/3 of the blind by visual fields only by the WHO criteria, and about 50% by the US criteria, are missed. Thirty percent more patients in our population were classified as blind by the US than by the WHO definition, and 60% more were identified as visually impaired by the US SSA criterion than by the WHO definition. The assessment of visual field status is vital to determine vision impairment caused by glaucoma.

Study II

Our results suggest that bilateral low vision and blindness caused by glaucoma may be reduced by approximately 50% by population screening. Our results need to be confirmed by other studies before any recommendations about general population screening can be made.

Study III

Both methods of analysis showed a similar mean PCDP, approximately 10 years. A mean PCDP of 10 years would allow for screening with reasonably long intervals, e.g., 5 years.

Study IV

The prevalence of glaucoma was high in all age groups, and comparable to that of other Nordic countries, figure 9. The majority of the screen-detected cases had early stages of disease and normal levels of IOP and therefore have a low risk of developing severe glaucoma during their remaining lifetime.

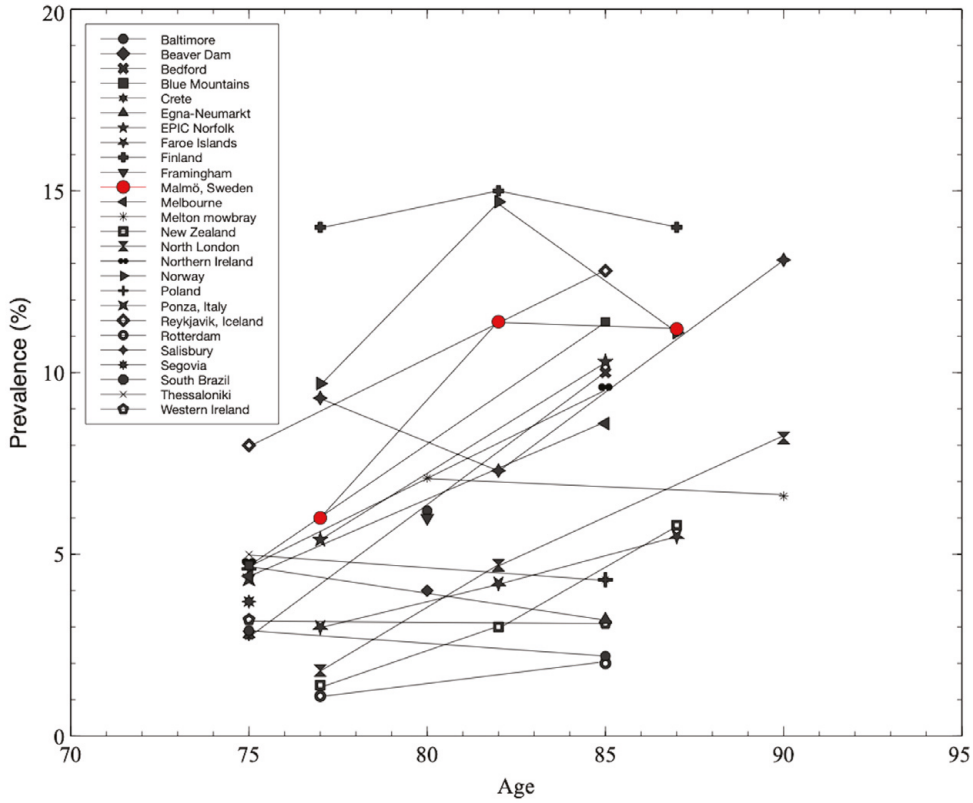


Figure 9.
Prevalence of open-angle glaucoma in white populations. For studies where there are no upper bound to an age group, e.g. 80+, 5 years have been added to the lower bound.

Study V

The median visual field damage at presentation in clinically diagnosed patients has improved tremendously since the 1990s, but a large proportion of the patients diagnosed 2013-2017, almost 20%, had severe visual field loss in at least one eye, and have a high risk of developing glaucoma blindness.

Discussion and future outlook

In this thesis, we have presented the first evaluation of a population screening for open-angle glaucoma, which showed a 50% reduction on the cumulative rate of blindness in the screened part of the population. A large randomised screening trial would be able to confirm our results, but the wait for results on the effect on blindness would be long. One can hope that other large glaucoma screening projects, e.g. the incidence studies mentioned above, will evaluate the effect on blindness in their populations retrospectively. The large screening in Malmö in the 1990s was most probably not cost-effective. There are, however, ways that screening could be made more cost-effective. A fast and inexpensive single screening test for glaucoma is one alternative, concentrating the screening effort on groups with higher risk of developing blindness another. Computer-assisted analysis of optic disc photographs and OCT scans is being researched, and will probably be available in the near future (Thompson et al. 2020, Mayro et al. 2020). Currently there are a few ongoing screening projects targeting high-risk groups in the US (Hark et al. 2017, Zhou et al. 2017), which will be interesting to follow. Genetic research on glaucoma is a rapidly evolving field of research (Choquet et al. 2020), and in the future perhaps a single blood sample could decide who is at risk for developing glaucoma, or even offer guidance on the risk of blindness in glaucoma patients.

We modified an earlier method by the US Social Security Agency (Social Security Ruling, SSR 07-01p) to create a method to calculate the the constriction of visual fields, which was a requisite to evaluate the effect of the screening. During this work, we noticed that many of the patients who were considered blind by visual field constriction had a VA that was better than cut-off for blindness, some even had 20/20 (1.0) vision. In paper I we reported that almost 2/3 of the blind patients by the WHO criteria and 50% of those by the US criteria would have been missed if the visual field status had not been considered in the evaluation of blindness. Many reports on blindness have used only VA for estimates on glaucoma blindness, and in paper I we suggested that a correction factor of 2.2 for the US, and 2.9 for the WHO criteria, could be used to get an estimate of the prevalence of glaucoma blindness, with visual field status included.

We investigated if there is a basis for glaucoma screening in Sweden today, in both paper IV and V. In the former we show that although the prevalence is very high among the oldest people in Malmö, the risk for the screen-detected cases of developing bilateral blindness during their remaining lifetime is low, and screening

at these ages would not be wortwhile. Also, screening persons that have reached high age is not always straight-forward work (Wensor, Friedman et al. 2006). The attendance rate will be low due to general health issues of the elderly, especially if one, as in our study, do not have the possibility to do home visits, e.g. to examine nursing home residents. In our screening study, the attendance rate would have been higher if the COVID-19 epidemic had not stopped the study, as we had many more invited persons booked for examination. Some of the participants also have difficulties contributing to parts of the examinations, and many have other eye disease, e.g. cataract or macular degeneration, which lead to extra visits, e.g. when fundus photography is not possible, or due to a low VA not previously known.

In paper V we reported that patients diagnosed in our clinic between 2013 and 2017 had much less visual field damage compared to patients detected clinically at the time for the large screening in the 1990s. The damage level in the recently diagnosed was almost the same as in the screen-detected cases in the 1990s. This improvement is probably an effect of increased case-finding by opticians/optometrists, an increased awareness of the disease in society together with the recruitment of glaucoma patients to the study Glaucoma Intensive Treatment Study, where many newly detected cases were referred to our clinic that otherwise would have been treated in private care. The last 10 years, the proportion of glaucoma patients in Malmö followed in private practice has been higher than before. From our finds, one could draw the conclusion that screening no longer would be necessary because of the improvement in severity at diagnosis, but still a considerate part of the patients, 20%, had severe damage in at least one eye, which increases the risk of bilateral blindness. Case-finding by opticians/optometrists probably leads to detection of a larger proportion of the glaucoma patients in the population today than in the 1990s, but we do not know which of the cases detected earlier today that would benefit by it. In future research we will try to estimate the amount of overdiagnosis at the 1990s screening, i.e. cases detected by screening that would never be detected during their remaining lifetime.

We have reported the mean length of the PCDP, the first estimation for glaucoma of this important component of the natural history of a disease. The duration was long, about 10 years, which is good, as a shorter duration would mean more fast-growing disease, and repeated screening would need to be done with shorter intervals. Other screening studies should be able to present results on the PCDP with the prevalence/incidence method without too much effort.

In short, our work has shown that prevention of blindness from glaucoma is possible. Even if population screening will not be an alternative, the future outlook for targeted screening is bright, with cost-reducing methods probably soon available.

Acknowledgements

I wish to express my sincere gratitude to:

Professor Anders Heijl

Thank you for hiring me and giving me the privilege to work on the unique material of the screening for the EMGT, and for your patience over the years. Your vast knowledge, experience, and guidance have been essential for the completion of the thesis.

Professor Boel Bengtsson

Thank you for taking me under your wings after Anders retired. You have always had time for questions, or just a chat, and your enthusiasm and sense of humour is a great source of inspiration. Your energy and creativeness with a constant bubbling of thoughts and ideas, paired with a meticulous scentific mind, will never cease to amaze me. You really are one of a kind.

Jesper Hougaard & Dorothea Peters

My roommates and companions for many years now. Thanks for the many laughs and being such good friends.

Sigridur Oskarsdottir

My co-worker on the screening of elderly, for excellent co-operation.

Dimitrios Bizios

For the many interesting and always amusing discussions.

Catarina Villalba

For all support and help with the screening of the elderly, and GITS.

Johnny Ring

For the help with computers, old perimeters, and everything else.

Birgitta Celinder, Arkivcentrum Syd

For the help with copying and delivering archived patient records. I could not have done this thesis without it.

I also want to thank all my colleagues and friends at the Eye Department at Skåne University Hospital for creating such a great workplace.

References

Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration.The AGIS Investigators. (2000). Am J Ophthalmol, 130(4), 429-440. doi:10.1016/s0002-9394(00)00538-9

Anonymous. (1985). Cancer of the cervix: death by incompetence. Lancet, 2(8455), 603-604.

Armaly, M. F. (1965). On the Distribution of Applanation Pressure. I. Statistical Features and the Effect of Age, Sex, and Family History of Glaucoma. Arch Ophthalmol, 73, 11-18. doi:10.1001/archopht.1965.00970030013005

Aspberg, J., Heijl, A., & Bengtsson, B. (2021). Screening for Open-Angle Glaucoma and Its Effect on Blindness. Am J Ophthalmol, 228, 106-116. doi:10.1016/j.ajo.2021.03.030

Bankes, J. L., Perkins, E. S., Tsolakis, S., & Wright, J. E. (1968). Bedford glaucoma survey. Br Med J, 1(5595), 791-796.

Bengtsson, B.O. (1981). The prevalence of glaucoma. Br J Ophthalmol, 65(1), 46-49

Bengtsson, B.O. (1989). Incidence of manifest glaucoma. Br J Ophthalmol, 73(7), 483-487.

Bengtsson, B., & Heijl, A. (2005). A long-term prospective study of risk factors for glaucomatous visual field loss in patients with ocular hypertension. J Glaucoma, 14(2), 135-138.

Boivin, J. F., McGregor, M., & Archer, C. (1996). Cost effectiveness of screening for primary open angle glaucoma. J Med Screen, 3(3), 154-163. doi:10.1177/096914139600300309

Budenz, D. L., Anderson, D. R., Feuer, W. J., Beiser, J. A., Schiffman, J., Parrish, R. K., 2nd, Piltz-Seymour, J. R., Gordon, M. O., & Kass, M. A. (2006). Detection and prognostic significance of optic disc hemorrhages during the Ocular Hypertension Treatment Study. Ophthalmology, 113(12), 2137-2143. doi:10.1016/j.ophtha.2006.06.022

Burr, J. M., Mowatt, G., Hernandez, R., Siddiqui, M. A., Cook, J., Lourenco, T., Ramsay, C., Vale, L., Fraser, C., Azuara-Blanco, A., Deeks, J., Cairns, J., Wormald, R., McPherson, S., Rabindranath, K., & Grant, A. (2007). The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation. Health Technol Assess, 11(41), iii-iv, ix-x, 1-190.

Burr, J., Hernandez, R., Ramsay, C., Prior, M., Campbell, S., Azuara-Blanco, A., Campbell, M., Francis, J., & Vale, L. (2014). Is it worthwhile to conduct a randomized controlled trial of glaucoma screening in the United Kingdom? J Health Serv Res Policy, 19(1), 42-51. doi:10.1177/1355819613499748

Cedrone, C., Mancino, R., Ricci, F., Cerulli, A., Culasso, F., & Nucci, C. (2012). The 12-year incidence of glaucoma and glaucoma-related visual field loss in Italy: the Ponza eye study. J Glaucoma, 21(1), 1-6. doi:10.1097/IJG.0b013e3182027796

Chang, L. C., Teng, M. C., Chang, H. W., Lai, I. C., Lin, P. W., & Tsai, J. C. (2005). The probability of blindness in patients treated for glaucoma. Chang Gung Med J, 28(7), 492-497.

Chen, P. P. (2003). Blindness in patients with treated open-angle glaucoma. Ophthalmology, 110(4), 726-733. doi:10.1016/s0161-6420(02)01974-7

Choquet, H., Wiggs, J. L., & Khawaja, A. P. (2020). Clinical implications of recent advances in primary open-angle glaucoma genetics. Eye (Lond), 34(1), 29-39. doi:10.1038/s41433-019-0632-7

Chou, R., Selph, S., Blazina, I., Bougatsos, C., Jungbauer, R., Fu, R., Grusing, S., Jonas, D. E., & Tehrani, S. (2022). Screening for Glaucoma in Adults: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA, 327(20), 1998-2012. doi:10.1001/jama.2022.6290

Collaborative Normal-Tension Glaucoma Study Group (1998). The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. Am J Ophthalmol, 126(4), 498-505.

Colton, T., & Ederer, F. (1980). The distribution of intraocular pressures in the general population. Surv Ophthalmol, 25(3), 123-129. doi:10.1016/0039-6257(80)90086-7

Cuzick, J., Edwards, R., & Segnan, N. (1997). Adjusting for non-compliance and contamination in randomized clinical trials. Stat Med, 16(9), 1017-1029.

Czudowska, M. A., Ramdas, W. D., Wolfs, R. C., Hofman, A., De Jong, P. T., Vingerling, J. R., & Jansonius, N. M. (2010). Incidence of glaucomatous visual field loss: a ten-year follow-up from the Rotterdam Study. Ophthalmology, 117(9), 1705-1712. doi:10.1016/j.ophtha.2010.01.034

De Moraes, C. G., Juthani, V. J., Liebmann, J. M., Teng, C. C., Tello, C., Susanna, R., Jr., & Ritch, R. (2011). Risk factors for visual field progression in treated glaucoma. Arch Ophthalmol, 129(5), 562-568. doi:10.1001/archophthalmol.2011.72

de Voogd, S., Ikram, M. K., Wolfs, R. C., Jansonius, N. M., Hofman, A., & de Jong, P. T. (2005). Incidence of open-angle glaucoma in a general elderly population: the Rotterdam Study. Ophthalmology, 112(9), 1487-1493. doi:10.1016/j.ophtha.2005.04.018

Doshi, V., Ying-Lai, M., Azen, S. P., Varma, R., & Los Angeles Latino Eye Study, G. (2008). Sociodemographic, family history, and lifestyle risk factors for open-angle glaucoma and ocular hypertension. The Los Angeles Latino Eye Study. Ophthalmology, 115(4), 639-647 e632. doi:10.1016/j.ophtha.2007.05.032

Drance, S., Anderson, D. R., Schulzer, M., & Collaborative Normal-Tension Glaucoma Study Group (2001). Risk factors for progression of visual field abnormalities in normal-tension glaucoma. Am J Ophthalmol, 131(6), 699-708.

Duffy, S. W., Cuzick, J., Tabar, L., Vitak, B., Hsiu-Hsi Chen, T., Yen, M.-F., & Smith, R. A. (2002). Correcting for non-compliance bias in case–control studies to evaluate cancer screening programmes. J. Royal Statistical Society, 51(2), 235-243.

Duffy, S. W., Nagtegaal, I. D., Wallis, M., Cafferty, F. H., Houssami, N., Warwick, J., Allgood, P. C., Kearins, O., Tappenden, N., O'Sullivan, E., & Lawrence, G. (2008). Correcting for lead time and length bias in estimating the effect of screen detection on cancer survival. Am J Epidemiol, 168(1), 98-104. doi:10.1093/aje/kwn120

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

Ekstrom, C. (2012). Risk factors for incident open-angle glaucoma: a population-based 20-year follow-up study. Acta Ophthalmol, 90(4), 316-321. doi:10.1111/j.1755-3768.2010.01943.x

Ervin, A. M., Boland, M. V., Myrowitz, E. H., Prince, J., Hawkins, B., Vollenweider, D., Ward, D., Suarez-Cuervo, C., & Robinson, K. A. (2012). Screening for Glaucoma: Comparative Effectiveness. Agency for Healthcare Research and Quality (US). Rockville (MD).

Etzioni, R., & Self, S. G. (1995). On the catch-up time method for analyzing cancer screening trials. Biometrics, 51(1), 31-43.

Flaxman, S. R., Bourne, R. R. A., Resnikoff, S., Ackland, P., Braithwaite, T., Cicinelli, M. V., Das, A., Jonas, J. B., Keeffe, J., Kempen, J. H., Leasher, J., Limburg, H., Naidoo, K., Pesudovs, K., Silvester, A., Stevens, G. A., Tahhan, N., Wong, T. Y., Taylor, H. R., & Vision Loss Expert Group of the Global Burden of Disease Study. (2017). Global causes of blindness and distance vision impairment 1990-2020: a systematic review and meta-analysis. Lancet Glob Health, 5(12), e1221-e1234. doi:10.1016/S2214-109X(17)30393-5

Forsman, E., Kivela, T., & Vesti, E. (2007). Lifetime visual disability in open-angle glaucoma and ocular hypertension. J Glaucoma, 16(3), 313-319. doi:10.1097/IJG.0b013e318033500f

Founti, P., Bunce, C., Khawaja, A. P., Dore, C. J., Mohamed-Noriega, J., Garway-Heath, D. F., & United Kingdom Glaucoma Treatment Study, G. (2020). Risk Factors for Visual Field Deterioration in the United Kingdom Glaucoma Treatment Study. Ophthalmology, 127(12), 1642-1651. doi:10.1016/j.ophtha.2020.06.009

Founti, P., Coleman, A. L., Wilson, M. R., Yu, F., Harris, A., Pappas, T., Anastasopoulos, E., Koskosas, A., Salonikiou, A., Keskini, C., Malamas, A., Kilintzis, V., Raptou, A., Tzoanou, G., & Topouzis, F. (2021). Twelve-Year Incidence of Open-angle Glaucoma: The Thessaloniki Eye Study. J Glaucoma, 30(9), 851-858. doi:10.1097/ijg.0000000000001899

Friedman, D. S., Jampel, H. D., Munoz, B., & West, S. K. (2006). The prevalence of open-angle glaucoma among blacks and whites 73 years and older - The Salisbury Eye Evaluation glaucoma study. Arch Ophthalmol, 124(11), 1625-1630. doi:DOI 10.1001/archopht.124.11.1625

Fukuchi, T., Yoshino, T., Sawada, H., Seki, M., Togano, T., Tanaka, T., Ueda, J., & Abe, H. (2013). The relationship between the mean deviation slope and follow-up intraocular pressure in open-angle glaucoma patients. J Glaucoma, 22(9), 689-697. doi:10.1097/IJG.0b013e318264b779

Garway-Heath, D. F., Crabb, D. P., Bunce, C., Lascaratos, G., Amalfitano, F., Anand, N., Azuara-Blanco, A., Bourne, R. R., Broadway, D. C., Cunliffe, I. A., Diamond, J. P., Fraser, S. G., Ho, T. A., Martin, K. R., McNaught, A. I., Negi, A., Patel, K., Russell, R. A., Shah, A., Spry, P. G., Suzuki, K., White, E. T., Wormald, R. P., Xing, W., & Zeyen, T. G. (2015). Latanoprost for open-angle glaucoma (UKGTS): a randomised, multicentre, placebo-controlled trial. Lancet, 385(9975), 1295-1304. doi:10.1016/S0140-6736(14)62111-5

Geurts, S. M. E., Aarts, A., Verbeek, A. L. M., Chen, T. H. H., Broeders, M. J. M., & Duffy, S. W. (2022). Quantifying the duration of the preclinical detectable phase in cancer screening: a systematic review. Epidemiol Health, 44, e2022008. doi:10.4178/epih.e2022008

Gordon, M. O., Beiser, J. A., Brandt, J. D., Heuer, D. K., Higginbotham, E. J., Johnson, C. A., Keltner, J. L., Miller, J. P., Parrish, R. K., 2nd, Wilson, M. R., & Kass, M. A. (2002). The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. Arch Ophthalmol, 120(6), 714-720.

Gottlieb, L. K., Schwartz, B., & Pauker, S. G. (1983). Glaucoma screening. A cost-effectiveness analysis. Surv Ophthalmol, 28(3), 206-226.

Green, C. M., Kearns, L. S., Wu, J., Barbour, J. M., Wilkinson, R. M., Ring, M. A., Craig, J. E., Wong, T. L., Hewitt, A. W., & Mackey, D. A. (2007). How significant is a family history of glaucoma? Experience from the Glaucoma Inheritance Study in Tasmania. Clin Exp Ophthalmol, 35(9), 793-799. doi:10.1111/j.1442-9071.2007.01612.x

Grødum, K., Heijl, A., & Bengtsson, B. (2001). Refractive error and glaucoma. Acta Ophthalmol Scand, 79(6), 560-566.

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(6), 627-631.

Grødum, K., Heijl, A., & Bengtsson, B. (2005). Risk of glaucoma in ocular hypertension with and without pseudoexfoliation. Ophthalmology, 112(3), 386-390. doi:10.1016/j.ophtha.2004.09.024

Ha, A., Kim, C. Y., Shim, S. R., Chang, I. B., & Kim, Y. K. (2022). Degree of Myopia and Glaucoma Risk: A Dose-Response Meta-analysis. Am J Ophthalmol, 236, 107-119. doi:10.1016/j.ajo.2021.10.007

Hark, L. A., Katz, L. J., Myers, J. S., Waisbourd, M., Johnson, D., Pizzi, L. T., Leiby, B. E., Fudemberg, S. J., Mantravadi, A. V., Henderer, J. D., Zhan, T., Molineaux, J., Doyle, V., Divers, M., Burns, C., Murchison, A. P., Reber, S., Resende, A., Bui, T. D. V., Lee, J., Crews, J. E., Saaddine, J. B., Lee, P. P., Pasquale, L. R., & Haller, J. A. (2017). Philadelphia Telemedicine Glaucoma Detection and Follow-up Study: Methods and Screening Results. Am J Ophthalmol, 181, 114-124. doi:10.1016/j.ajo.2017.06.024

Hatt, S., Wormald, R., & Burr, J. (2006). Screening for prevention of optic nerve damage due to chronic open angle glaucoma. Cochrane Database Syst Rev(4), CD006129. doi:10.1002/14651858.CD006129.pub2

Heijl, A., Leske, M. C., Bengtsson, B., Hyman, L., Bengtsson, B., Hussein, M., & Early Manifest Glaucoma Trial, G. (2002). Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. Arch Ophthalmol, 120(10), 1268-1279.

Hirooka, K., Sato, S., Nitta, E., & Tsujikawa, A. (2016). The Relationship Between Vision-related Quality of Life and Visual Function in Glaucoma Patients. J Glaucoma, 25(6), 505-509. doi:10.1097/IJG.0000000000000372

Hitzl, W., Stollinger, M., Grabner, G., Reitsamer, H. A., & Hornykewycz, K. (2006). [The Salzburg-Moorfields Collaborative Glaucoma Study: first results of the prevalence and 5-year incidences in this prospective, population-based longitudinal study]. Klin Monbl Augenheilkd, 223(12), 970-973. doi:10.1055/s-2006-927102

Hollows, F. C., & Graham, P. A. (1966). Intra-ocular pressure, glaucoma, and glaucoma suspects in a defined population. Br J Ophthalmol, 50(10), 570-586.

Ishida, K., Yamamoto, T., Sugiyama, K., & Kitazawa, Y. (2000). Disk hemorrhage is a significantly negative prognostic factor in normal-tension glaucoma. Am J Ophthalmol, 129(6), 707-714. doi:https://doi.org/10.1016/S0002-9394(00)00441-4

John, D., & Parikh, R. (2017). Cost-effectiveness and cost utility of community screening for glaucoma in urban India. Public Health, 148, 37-48. doi:10.1016/j.puhe.2017.02.016

Jones, L., Bryan, S. R., & Crabb, D. P. (2017). Gradually Then Suddenly? Decline in Vision-Related Quality of Life as Glaucoma Worsens. J Ophthalmol, 2017, 1621640. doi:10.1155/2017/1621640

Kahn, H. A., & Milton, R. C. (1980). Revised Framingham eye study prevalence of glaucoma and diabetic retinopathy. Am J Epidemiol, 111(6), 769-776.

Kapetanakis, V. V., Chan, M. P., Foster, P. J., Cook, D. G., Owen, C. G., & Rudnicka, A. R. (2016). Global variations and time trends in the prevalence of primary open angle glaucoma (POAG): a systematic review and meta-analysis. Br J Ophthalmol, 100(1), 86-93. doi:10.1136/bjophthalmol-2015-307223

Kawasaki, R., Wang, J. J., Rochtchina, E., Lee, A. J., Wong, T. Y., & Mitchell, P. (2013). Retinal vessel caliber is associated with the 10-year incidence of glaucoma: the Blue Mountains Eye Study. Ophthalmology, 120(1), 84-90. doi:10.1016/j.ophtha.2012.07.007

Kooner, K. S., AlBdoor, M., Cho, B. J., & Adams-Huet, B. (2008). Risk factors for progression to blindness in high tension primary open angle glaucoma: Comparison of blind and nonblind subjects. Clin Ophthalmol, 2(4), 757-762. doi:10.2147/opth.s3139

Le, A., Mukesh, B. N., McCarty, C. A., & Taylor, H. R. (2003). Risk factors associated with the incidence of open-angle glaucoma: the visual impairment project. Invest Ophthalmol Vis Sci, 44(9), 3783-3789.

Leske, M. C., Ederer, F., & Podgor, M. (1981). Estimating incidence from age-specific prevalence in glaucoma. Am J Epidemiol, 113(5), 606-613.

Leske, M. C., Heijl, A., Hyman, L., & Bengtsson, B. (1999). Early Manifest Glaucoma Trial: design and baseline data. Ophthalmology, 106(11), 2144-2153.

Leske, M. C., Heijl, A., Hussein, M., Bengtsson, B., Hyman, L., Komaroff, E., & Early Manifest Glaucoma Trial Group. (2003). Factors for glaucoma progression and the effect of treatment: the early manifest glaucoma trial. Arch Ophthalmol, 121(1), 48-56.

Leske, M. C., Wu, S. Y., Honkanen, R., Nemesure, B., Schachat, A., Hyman, L., Hennis, A., & Barbados Eye Studies Group. (2007). Nine-year incidence of open-angle glaucoma in the Barbados Eye Studies. Ophthalmology, 114(6), 1058-1064. doi:10.1016/j.ophtha.2006.08.051

Leske, M. C., Wu, S. Y., Hennis, A., Honkanen, R., Nemesure, B., & Barbados Eye Studies Group (2008). Risk factors for incident open-angle glaucoma: the Barbados Eye Studies. Ophthalmology, 115(1), 85-93. doi:10.1016/j.ophtha.2007.03.017

Leydhecker, W., Akiyama, K., & Neumann, H. G. (1958). Der intraokulare Druck gesunder Menschlicher Augen. Klin Monatsbl Augenheilkd, 133(5), 662-670.

Lichter, P. R., Musch, D. C., Gillespie, B. W., Guire, K. E., Janz, N. K., Wren, P. A., Mills, R. P., & Collaborative Initial Glaucoma Treatment Study Group (2001). Interim clinical outcomes in the Collaborative Initial Glaucoma Treatment Study comparing initial treatment randomized to medications or surgery. Ophthalmology, 108(11), 1943-1953.

Mayro, E. L., Wang, M., Elze, T., & Pasquale, L. R. (2020). The impact of artificial intelligence in the diagnosis and management of glaucoma. Eye (Lond), 34(1), 1-11. doi:10.1038/s41433-019-0577-x

Miglior, S., Pfeiffer, N., Torri, V., Zeyen, T., Cunha-Vaz, J., & Adamsons, I. (2007). Predictive factors for open-angle glaucoma among patients with ocular hypertension in the European Glaucoma Prevention Study. Ophthalmology, 114(1), 3-9. doi:10.1016/j.ophtha.2006.05.075

Miglior, S., Torri, V., Zeyen, T., Pfeiffer, N., Vaz, J. C., Adamsons, I., & European Glaucoma Prevention Study Group. (2007). Intercurrent factors associated with the development of open-angle glaucoma in the European glaucoma prevention study. Am J Ophthalmol, 144(2), 266-275. doi:10.1016/j.ajo.2007.04.040

Mills, R. P., Budenz, D. L., Lee, P. P., Noecker, R. J., Walt, J. G., Siegartel, L. R., Evans, S. J., & Doyle, J. J. (2006). Categorizing the stage of glaucoma from pre-diagnosis to end-stage disease. Am J Ophthalmol, 141(1), 24-30. doi:10.1016/j.ajo.2005.07.044

Mitchell, P., Smith, W., Attebo, K., & Healey, P. R. (1996). Prevalence of open-angle glaucoma in Australia. The Blue Mountains Eye Study. Ophthalmology, 103(10), 1661-1669.

Mitchell, P., Wang, J. J., & Hourihan, F. (1999). The relationship between glaucoma and pseudoexfoliation: the Blue Mountains Eye Study. Arch Ophthalmol, 117(10), 1319-1324.

Mitchell, P., Rochtchina, E., Lee, A. J., & Wang, J. J. (2002). Bias in self-reported family history and relationship to glaucoma: The Blue Mountains Eye Study. Ophthalmic Epidemiol, 9(5), 333-345. doi:10.1076/opep.9.5.333.10335

Morrison, A. S. (1982). The effects of early treatment, lead time and length bias on the mortality experienced by cases detected by screening. Int J Epidemiol, 11(3), 261-267. doi:10.1093/ije/11.3.261

Morrison, A. S. (1992). Screening in chronic disease (2nd ed.). New York: Oxford University Press.

Mukesh, B. N., McCarty, C. A., Rait, J. L., & Taylor, H. R. (2002). Five-year incidence of open-angle glaucoma: the visual impairment project. Ophthalmology, 109(6), 1047-1051.

Müskens, R. P., de Voogd, S., Wolfs, R. C., Witteman, J. C., Hofman, A., de Jong, P. T., Stricker, B. H., & Jansonius, N. M. (2007). Systemic antihypertensive medication and incident open-angle glaucoma. Ophthalmology, 114(12), 2221-2226. doi:10.1016/j.ophtha.2007.03.047

Nemesure, B., He, Q., Mendell, N., Wu, S. Y., Hejtmancik, J. F., Hennis, A., Leske, M. C., & Barbados Family Study Group. (2001). Inheritance of open-angle glaucoma in the Barbados family study. Am J Med Genet, 103(1), 36-43. doi:10.1002/ajmg.1498

Oliver, J. E., Hattenhauer, M. G., Herman, D., Hodge, D. O., Kennedy, R., Fang-Yen, M., & Johnson, D. H. (2002). Blindness and glaucoma: a comparison of patients progressing to blindness from glaucoma with patients maintaining vision. Am J Ophthalmol, 133(6), 764-772. doi:10.1016/s0002-9394(02)01403-4

Pan, C. W., Yang, W. Y., Hu, D. N., Xu, J. G., Niu, Z. Q., Yuan, Y. S., Yu, M. B., & Zhong, H. (2017). Longitudinal Cohort Study on the Incidence of Primary Open-Angle Glaucoma in Bai Chinese. Am J Ophthalmol, 176, 127-133. doi:10.1016/j.ajo.2017.01.008

Peters, D., Bengtsson, B., & Heijl, A. (2013). Lifetime risk of blindness in open-angle glaucoma. Am J Ophthalmol, 156(4), 724-730. doi:10.1016/j.ajo.2013.05.027

Peters, D., Bengtsson, B., & Heijl, A. (2014). Factors associated with lifetime risk of open-angle glaucoma blindness. Acta Ophthalmol, 92(5), 421-425. doi:10.1111/aos.12203

Peters, D., Heijl, A., Brenner, L., & Bengtsson, B. (2015). Visual impairment and vision-related quality of life in the Early Manifest Glaucoma Trial after 20 years of follow-up. Acta Ophthalmol, 93(8), 745-752. doi:10.1111/aos.12839

Rasker, M. T., van den Enden, A., Bakker, D., & Hoyng, P. F. (1997). Deterioration of visual fields in patients with glaucoma with and without optic disc hemorrhages. Arch Ophthalmol, 115(10), 1257-1262. doi:10.1001/archopht.1997.01100160427006

Resnikoff, S., Pascolini, D., Etya'ale, D., Kocur, I., Pararajasegaram, R., Pokharel, G. P., & Mariotti, S. P. (2004). Global data on visual impairment in the year 2002. Bull World Health Organ, 82(11), 844-851. doi:/S0042-96862004001100009

Safran, A. B., & Landis, T. (1999). From cortical plasticity to unawareness of visual field defects. J Neuroophthalmol, 19(2), 84-88.

Tang, J., Liang, Y., O'Neill, C., Kee, F., Jiang, J., & Congdon, N. (2019). Cost-effectiveness and cost-utility of population-based glaucoma screening in China: a decision-analytic Markov model. Lancet Glob Health, 7(7), e968-e978. doi:10.1016/S2214-109X(19)30201-3

Thompson, A. C., Jammal, A. A., & Medeiros, F. A. (2020). A Review of Deep Learning for Screening, Diagnosis, and Detection of Glaucoma Progression. Transl Vis Sci Technol, 9(2), 42. doi:10.1167/tvst.9.2.42

Tielsch, J. M., Sommer, A., Katz, J., Royall, R. M., Quigley, H. A., & Javitt, J. (1991). Racial variations in the prevalence of primary open-angle glaucoma. The Baltimore Eye Survey. JAMA, 266(3), 369-374.

Tielsch, J. M., Katz, J., Sommer, A., Quigley, H. A., & Javitt, J. C. (1994). Family history and risk of primary open angle glaucoma. The Baltimore Eye Survey. Arch Ophthalmol, 112(1), 69-73. doi:10.1001/archopht.1994.01090130079022

Topouzis, F., Wilson, M. R., Harris, A., Founti, P., Yu, F., Anastasopoulos, E., Pappas, T., Koskosas, A., Salonikiou, A., & Coleman, A. L. (2011). Risk factors for primary open-angle glaucoma and pseudoexfoliative glaucoma in the Thessaloniki eye study. Am J Ophthalmol, 152(2), 219-228 e211. doi:10.1016/j.ajo.2011.01.032

Tuck, M. W., & Crick, R. P. (1997). The cost-effectiveness of various modes of screening for primary open angle glaucoma. Ophthalmic Epidemiol, 4(1), 3-17.

UK National Screening Committee. Screening for Glaucoma: External review against programme appraisal criteria for the UK National Screening Committee. 2019. https://legacyscreening.phe.org.uk/glaucoma.

US Social Security Ruling, SSR 07-01p; Titles II and XVI: Evaluating Visual Field Loss Using Automated Static Threshold Perimetry. Available at: https://www.ssa.gov/disability/professionals/bluebook/2.00-SpecialSensesandSpeech-Adult.htm; & http://www.ssa.gov/OP_Home/rulings/di/01/SSR2007-01-di-01.html.

Vaahtoranta-Lehtonen, H., Tuulonen, A., Aronen, P., Sintonen, H., Suoranta, L., Kovanen, N., Linna, M., Laara, E., & Malmivaara, A. (2007). Cost effectiveness and cost utility of an organized screening programme for glaucoma. Acta Ophthalmol Scand, 85(5), 508-518. doi:10.1111/j.1600-0420.2007.00947.x

Varma, R., Wang, D., Wu, C., Francis, B. A., Nguyen, B. B., Chopra, V., Memarzadeh, F., Torres, M., Azen, S. P., & Los Angeles Latino Eye Study Group. (2012). Four-year incidence of open-angle glaucoma and ocular hypertension: the Los Angeles Latino Eye Study. Am J Ophthalmol, 154(2), 315-325 e311. doi:10.1016/j.ajo.2012.02.014

Weinreb RH, Healey PR, Topouzis F, eds. (2008). Glaucoma Screening. WGA Consensus Series; No. 5. Amsterdam, The Netherlands: Kugler Publications.

Wensor, M. D., McCarty, C. A., Stanislavsky, Y. L., Livingston, P. M., & Taylor, H. R. (1998). The prevalence of glaucoma in the Melbourne Visual Impairment Project. Ophthalmology, 105(4), 733-739. doi:10.1016/S0161-6420(98)94031-3

Wilson, J. M. G., & Jungner, G. (1968). Principles and practice of screening for disease. Geneva,: World Health Organization.

Wilson, M. R. (1997). The myth of "21". J Glaucoma, 6(2), 75-77.

Wolfs, R. C., Klaver, C. C., Ramrattan, R. S., van Duijn, C. M., Hofman, A., & de Jong, P. T. (1998). Genetic risk of primary open-angle glaucoma. Population-based familial aggregation study. Arch Ophthalmol, 116(12), 1640-1645. doi:10.1001/archopht.116.12.1640

Zhao, D., Guallar, E., Gajwani, P., Swenor, B., Crews, J., Saaddine, J., Mudie, L., Varadaraj, V., Friedman, D. S., & Screening to Prevent Glaucoma Study Group. (2017). Optimizing Glaucoma Screening in High-Risk Population: Design and 1-Year Findings of the Screening to Prevent (SToP) Glaucoma Study. Am J Ophthalmol, 180, 18-28. doi:10.1016/j.ajo.2017.05.017

Åström, S., Stenlund, H., & Lindén, C. (2007). Incidence and prevalence of pseudoexfoliations and open-angle glaucoma in northern Sweden: II. Results after 21 years of follow-up. Acta Ophthalmol Scand, 85(8), 832-837. doi:10.1111/j.1600-0420.2007.00980.x

Öhnell, H., Bengtsson, B., & Heijl, A. (2019). Making a Correct Diagnosis of Glaucoma: Data From the EMGT. J Glaucoma, 28(10), 859-864. doi:10.1097/IJG.0000000000001342

Paper I

Heijl et al. BMC Ophthalmology 2011, 11:31
http://www.biomedcentral.com/1471-2415/11/31

BMC Ophthalmology

RESEARCH ARTICLE Open Access

The effect of different criteria on the number of patients blind from open-angle glaucoma

Anders Heijl*, Johan Aspberg and Boel Bengtsson

Abstract

Background: The prevalence of blindness and visual impairment from glaucoma is influenced by the criteria used to define these entities, which differ between countries and regions, as well as among published reports. The objective of the present study was to ascertain the extent to which different criteria of blindness and visual impairment influence estimates of the number of patients classified as blind or visually impaired by glaucoma in a clinic-based population.

Methods: We conducted a retrospective chart review of 914 patients with open-angle glaucoma to compare numbers of patients identified as visually impaired with and without considering visual field status. We also compared proportions classified using World Health Organisation (WHO) and United States (US) blindness criteria, and applying a new US Social Security Administration (SSA) disability criterion: perimetric mean deviation (MD) ≤ -22 dB.

Results: Forty patients (4.4%) were bilaterally blind from glaucoma by the WHO criteria. Fifty-two (5.7%) were blind by the the US criterion. Assessing only visual acuity, 14 (1.5%) patients were blind by the WHO criteria and 24 (2.6%) by the US definition. Eighty-five (9.3%) met the US SSA disability criterion. Among those, 52 were impaired also by the WHO definition. No patients impaired according to the WHO criteria had MD values better than -22 dB.

Conclusions: Excluding visual field status will seriously underestimate the prevalence of glaucoma blindness. In our patient population, 30% more patients were classified as blind by the US than by the WHO definition. Also, 60% more were identified as visually impaired by the US SSA criterion than by the WHO criteria. Visual field assessment is vital to determine visual impairment caused by glaucoma.

Background

Open-angle glaucoma is the second most common cause of blindness globally [1]. It is important that we have knowledge about the prevalence of visual impairment caused by glaucoma in order to enable correct allocation of resources for glaucoma care, and also to allow evaluation of the effects of treatment and potential benefits of population screening.

Evaluation of the prevalence of blindness and visual impairment from glaucoma is influenced by the criteria used to define these entities, which differ between countries and regions. The definition of visual impairment stipulated by the World Health Organisation (WHO) can be considered the current gold standard in this context. However, many countries use their own criteria for blindness. An example of this is the definition used in the United States here designated the US criteria, which is also widely accepted and used in other countries. The number of people identified as blind from glaucoma should be higher when using the US definition than with the WHO definition, since the latter includes stricter criteria for blindness both by visual acuity (VA) and visual field loss.

In some cases, the prevalence of visual impairment (blindness and low vision) in glaucoma is studied and reported based on VA alone, i.e., not including visual field status [2-21]. It seems obvious that this approach will yield falsely low estimates of the prevalence, because visual impairment will not be recognised in patients who have end-stage glaucomatous visual field loss with preserved central VA.

The US Social Security Administration (SSA) recently endorsed use of a new criterion for disability determinations, the perimetric mean deviation (MD). This ruling [22] states that an MD of -22 dB on a 30-2 Humphrey threshold visual field corresponds approximately to a

* Correspondence: anders.heijl@med.lu.se
Department of Clinical Sciences in Malmö, Ophthalmology, Lund University, Malmö, Sweden

constriction of the visual field to less than 20° of fixation, and recommends an MD of ≤ -22 dB as a visual field criterion to define disability.

The objective of the present study was to ascertain the extent to which different criteria of blindness and visual impairment influence estimates of the number of patients classified as blind or visually impaired by glaucoma. Our primary aim was to investigate how omitting visual field status from criteria affects the rate of visual impairment. We also wanted to compare the number of patients identified as blind from glaucoma by the US and the WHO glaucoma blindness definitions, respectively, and to estimate the number classified as disabled by the US SSA visual field criterion compared to the WHO criteria.

Methods

Patients

We performed a retrospective chart review of patients diagnosed with open-angle glaucoma who visited the Department of Ophthalmology at Malmö University Hospital between 1 June 2004 and 31 May 2006. The great majority of these patients had reproducible visual field defects defined as a Glaucoma Hemifield Test "outside normal limits" on a SITA Standard test performed on a Humphrey Field Analyzer (HFA; Carl Zeiss Meditec Inc., Dublin, CA, USA), compatible with glaucoma, and not explained by other ocular or neurological disorders.

We selected patients born on days 1-15 of each month and used a study period of 2 years so that we would not miss those who made only infrequent visits to the Malmö Department of Ophthalmology. Glaucoma patients not treated primarily at this department (e.g., those referred for cataract surgery, laser treatment, or a second opinion) were not eligible, because our records on such cases contained insufficient data for reliable classifications.

For each patient, we recorded VA, perimetric findings in both eyes (as MD values of SITA Standard 30-2 tests in the great majority of cases, but also by Goldmann kinetic perimetry in a few), age, and presence/absence of visual impairment determined by the various criteria studied. Patients who met the WHO blindness criterion for VA and lacked visual field data were assigned an MD value of -30 dB.

The study was approved by the Regional Ethics Board in Lund, Sweden, and the tenets of the Declaration of Helsinki were followed.

Comparisons of criteria

The term visual impairment includes both low vision and blindness. Here, bilateral visual impairment was based on best-corrected VA and/or visual field status in the best eye, and hence a person with one blind eye and low vision in the other was considered to have low vision.

Each patient was evaluated for the presence of visual impairment using these different criteria:

1. Low vision and blindness according to the WHO criteria
2. Blindness according to the US criteria
3. Impairment according to the perimetric MD value criterion suggested by the US SSA [22] (Table 1)
4. Low vision and blindness based on VA alone, thus omitting visual field data

Visual field status is not included in the US criterion, defining low vision as VA < 0.5. Therefore, we chose not to register patients classified as having low vision according to this criterion.

We calculated the diameter of the remaining visual field as recommended by the SSA [23]. Pseudoisopters were drawn on the HFA numerical threshold dB printouts, midway between test point locations with threshold sensitivity values of 10 dB or better, and points with sensitivity less than 10 dB (Figure 1).

The causes of visual loss were determined for all patients with visual impairment. For each impaired eye, the disease that initially contributed to visual loss was noted as the leading cause. However, if the time for impairment could not be established, the disease that was deemed to contribute most to the impairment was registered as the main cause. Visual field data were available in most cases in which glaucoma was deemed to be the main cause. Such data were lacking in some cases, such as for elderly patients with end-stage glaucoma who could not participate in visual field testing, or when VA was so low that visual field testing had been abandoned. Classification in those cases was based solely on VA.

We used both the WHO criteria and the US criterion (blindness only) to determine the number of bilaterally blind/visually impaired patients, and we calculated the effect of omitting visual field status from the definition of visual impairment. We also investigated the difference in the numbers of patients defined as blind by the WHO and US criteria. The numbers of patients classified as impaired with WHO criteria and the US SSA visual field criterion were compared.

Statistical analyses

We applied descriptive statistics to compare the US and WHO criteria regarding the number of patients identified as blind and visually impaired, and the number of patients with and without using visual field data. The number classified as blind and visually impaired will always be larger when visual field criteria are applied than when they are omitted, because all patients who are blind according to VA criteria alone are also blind when field data are included. Similarly, all patients who are

Table 1 Visual impairment criteria*

	WHO	US	US SSA
Low vision	VA < 0.3 (20/70) and/or a constriction of the central visual field to < 20°	VA < 0.5 (20/40).	MD ≤ -22 dB in both eyes.
Blindness	VA < 0.05 (20/400) and/or a constriction of the central visual field to < 10°	VA ≤ 0.1 (6/60) and/or a constriction of the central visual field to < 20°	

*Visual impairment = low vision + blindness.

VA, visual acuity; MD, mean deviation; dB, decibel.

identified as blind according to the WHO criteria are also blind according to the less stricter US criteria. Analyses of numbers of blind according to WHO and US criteria and with and without taking visual fields into account were, therefore, purely descriptive, and no analyses for significances were performed.

Results

A total of 914 eligible patients were evaluated. Their mean age was 79 years (range 30-100 years). Nearly all the patients were Caucasians.

Table 2 presents the total numbers of patients identified as blind or visually impaired by the WHO and US criteria with and without taking visual field status into account. The number of blind patients was 30% higher according to the US criteria than the WHO criteria. Using the WHO criteria, the number of patients classified as blind was 40 when visual field was included but only 14 when visual field status was omitted, which represents a 65% reduction (Figure 2). Similarly, the WHO criteria identified visual impairment in only 37 patients when visual field status was ignored as compared to 58 patients when field status was included, a 36% reduction. Using the US criterion, the number of blind patients was only 24 when visual fields were omitted compared to 52 when field status was included, a reduction of 54%.

Eighty-five patients (9.3%) met the SSA criterion of bilateral visual impairment caused by glaucoma in both eyes with measured or assigned MD values ≤ -22 dB. Among those, 52 were visually impaired also by the WHO definition. No patients who were impaired according to the WHO criteria had MD values better than -22 dB.

Fifty-four patients had visual fields tested in one eye only, and 36 had no field tests at all. In 54 (60%) of those cases, the reason tests were not performed was that the patients already had very low VA and totally cupped discs at the initial visit, and in 28 cases it was because the patients' visual impairment was due to a cause other than glaucoma. For nine patients, perimetric results were not available for the study period or had been obtained only by testing on the Competer perimeter. Three patients were considered unable to do undergo perimetric testing.

Discussion

The most important finding of the current study is that a very large proportion of the visually impaired glaucoma patients were not identified as being visually impaired when only VA criteria were used to define such low vision.

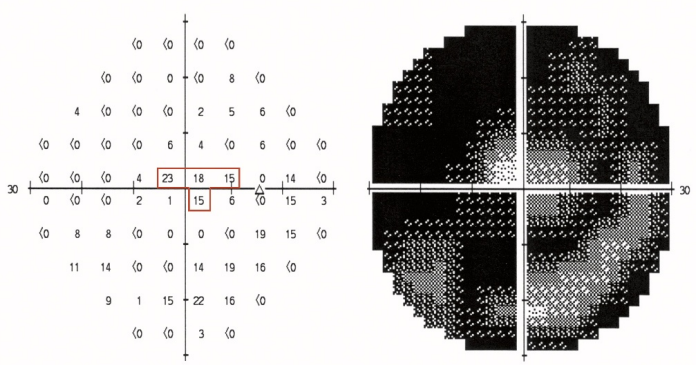


Figure 1 Calculation of the diameter of the remaining visual field. The central visual field is indicated by the pseudoisopter (red line). The distance is 6° between each test point location and 3° between test points and the pseudoisopter. The pseudoisopter is used to calculate the widest diameter of the remaining central visual field. This field is constricted to 18° around the point of fixation.

Table 2 Influence of visual field status on the number of patients classified as blind/visually impaired from glaucoma

	Visual fields + VA* No. (% of all patients)	VA alone No. (%)
WHO - blindness	40 (4.4%)	14 (1.5%)
WHO - visual impairment	58 (6.3%)	37 (4.0%)
US - blindness	52 (5.7%)	24 (2.6%)

* VA, visual acuity.

This can be compared with an investigation performed by Hattenhauer et al [24], in which the risk of bilateral blindness was calculated for patients 20 years after a glaucoma diagnosis had been made using the US definition of blindness. Those authors found that the risk was 9% based on both visual field status and VA together but was 5% when based on VA alone, which is similar to our results. The visual field data in the study by Hattenhauer and colleagues came mainly from kinetic Goldmann perimetry. The Baltimore Eye Survey [25] using similar visual field testing, on the other hand suggested that the number of patients classified as having bilateral blindness would increase by at most 25% when combining visual field data and VA compared to if evaluation were based on VA alone. The visual field criteria for blindness and for visual impairment are quite restrictive. In glaucoma the remaining visual field is seldom circular, and many eyes are not classified as blind despite very small remaining field areas. A narrow segment of the field with test points with sensitivity values of 10 dB or better, that extends outside 10° from fixation may be enough for an eye not to fulfill any of the two blindness criteria (Figure 3). It is, therefore, obvious that impairment caused by glaucomatous field loss requires loss of a very considerable proportion of normal function and has large consequences if bilateral, and that field loss is a very important part of the visual burden caused by glaucoma.

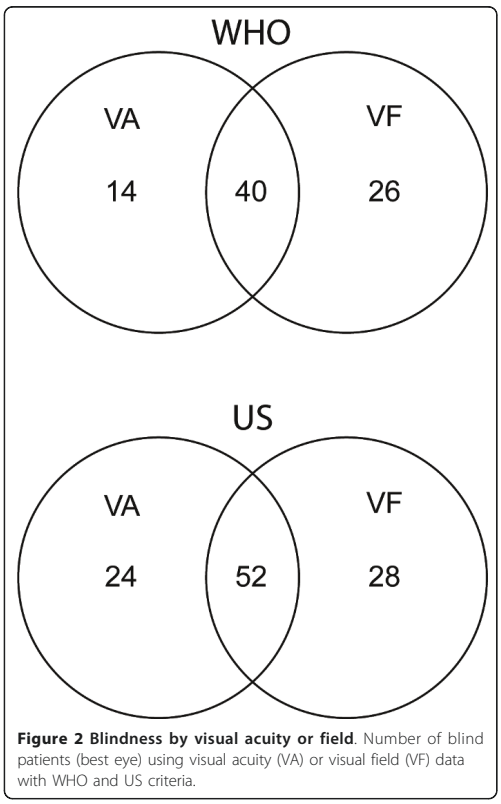


Figure 2 Blindness by visual acuity or field. Number of blind patients (best eye) using visual acuity (VA) or visual field (VF) data with WHO and US criteria.

Our results indicate that it is very likely that glaucoma impairment and blindness have been considerably underestimated in papers reporting rates of blindness determined using VA data, but omitting visual field status [3,4,15,18]. Furthermore, glaucoma must have been substantially underestimated as a cause of blindness in numerous population studies which have relied solely on VA [2,5-14,16,17,19-21]. Relying on visual acuity alone results in under-estimation of impairment caused by other disease, e.g., in onchocerciasis [26].

The number of patients classified as blind from glaucoma differs between investigations using the US criteria and those applying the WHO criteria. To our knowledge only two studies including visual field status has used both the WHO and the US definition to evaluate glaucoma blindness [27,28]. However, very few patients in the cited investigations were blind from glaucoma, and thus the results of that evaluation do not allow any conclusions to be drawn about the difference in the numbers of blind identified using these two approaches.

We found it interesting to study results obtained using the US SSA criteria for visual impairment. To our knowledge no other investigators have published visual impairment data based on MD values. It would no doubt be easier to use this MD-based criterion in surveys comparing visual impairment than performing actual measurements of visual field constriction, and that would also facilitate comparison of observations made in different studies.

This study had several strengths. Automated HFA perimetry is standard practice in our clinical setting, and other types of perimetry are rarely used. Ophthalmic practice in Sweden is somewhat unusual in that glaucoma care is delivered predominantly by the public health services. Our hospital provides primary glaucoma care for approximately three quarters of all patients with this disease in the catchment area. The current study was

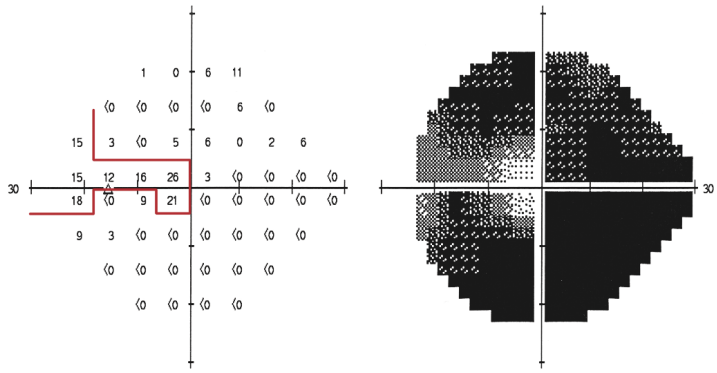


Figure 3 Example of the classification of a visual field. This field does not fulfill WHO or US blindness criteria, despite very advanced field loss (MD: -27.19).

cross-sectional in design and included a rather large number of visually impaired patients. Therefore, our results should be reasonably representative of clinic-based populations. One may speculate on whether the proportions of individuals classified as blind from glaucoma using visual acuity alone or taking both visual acuity and fields into account are the same in clinic-based cohorts and in the population. If so the true prevalences of glaucoma blindness could be more than twice as large as those reported from many countries, and a "correction/multiplication factor" of 2.2 (US) or 2.9 (WHO) could be used to help provide at least a rough estimate of the total number of blind glaucoma patients in areas where such blindness has been estimated using visual acuity alone. Similar multiplication factors have been used by WHO to estimate low vision in areas where only blindness and not low vision have been assessed [29]. Reduced visual acuity seems to influence measurable reduction of quality of life earlier than field loss, and measurable utility may not be affected until end stage visual field status in the better eye [30,31]. It is, therefore, even possible that the proportion of undiagnosed individuals with glaucoma in the population who are blind according to visual field criteria, but not because of poor visual acuity, are even more common in the population than in clinic-based cohorts.

A relative weakness of our investigation is that it was retrospective, and therefore some data were incomplete or missing. However, missing data constitute a problem in prospective studies as well. Visual field testing can also pose a problem in very old patients or in elderly with very low vision, who might have to be followed without such testing during their last few years of life. Also, considering prospective studies, some institutionalised patients are lost to follow-up, and some continue to come for examinations but no subjective measurements of visual function can be performed. The great majority of our patients were subjected to regular follow-up that included visual field testing, and there was little occurrence of incomplete or missing data.

Conclusions

In conclusion, we found that the number of patients with bilateral blindness from glaucoma was greatly underestimated when the evaluation was based solely on VA testing. The number of bilaterally blind was considerably higher when using the US definition of blindness compared to the WHO definition. The number of impaired patients was 60% higher by the US SSA impairment criterion than by the WHO criteria. Visual field testing is very important to achieve correct assessment of visual impairment caused by glaucoma.

Acknowledgements

Financial support

This study was supported by the Swedish Research Council K2005-74X-10426-13A, the Järnhardt Foundation, the Foundation for Visually Impaired in Former Malmöhus Län, and Crown Princess Margareta's Foundation for Visually Impaired.

Authors' contributions

AH initiated the study, participated in the analysis and interpretation of data, has revised the manuscript, checked and approved the initial and revised manuscripts throughout the process. JA collected and analysed the data, drafted the first manuscript versions in collaboration with AH, and checked and approved the initial and revised manuscripts throughout the process. BB has participated in the study design, and in the analysis and interpretation of data, has revised the manuscripts, checked and approved the final manuscripts.

Competing interests

The authors declare that they have no competing interests.

Received: 13 June 2011 Accepted: 10 November 2011
Published: 10 November 2011

References

1. Resnikoff S, Pascolini D, Etya'ale D, Kocur I, Pararajasegaram R, Pokharel GP, Mariotti SP: **Global data on visual impairment in the year 2002.** *Bull World Health Organ* 2004, **82**:844-51.
2. Araujo Filho A, Salomao SR, Berezovsky A, Cinoto RW, Morales PH, Santos FR, Belfort R Jr: **Prevalence of visual impairment, blindness, ocular disorders and cataract surgery outcomes in low-income elderly from a metropolitan region of Sao Paulo-Brazil.** *Arq Bras Oftalmol* 2008, **71**:246-53.
3. Blomdahl S, Calissendorff BM, Tengroth B, Wallin O: **Blindness in glaucoma patients.** *Acta Ophthalmol Scand* 1997, **75**:589-91.
4. Casson RJ, Newland HS, Muecke J, McGovern S, Abraham L, Shein WK, Selva D, Aung T: **Prevalence of glaucoma in rural Myanmar: the Meiktila Eye Study.** *Br J Ophthalmol* 2007, **91**:710-4.
5. Dineen BP, Bourne RR, Ali SM, Huq DM, Johnson GJ: **Prevalence and causes of blindness and visual impairment in Bangladeshi adults: results of the National Blindness and Low Vision Survey of Bangladesh.** *Br J Ophthalmol* 2003, **87**:820-8.
6. Edussuriya K, Sennanayake S, Senaratne T, Marshall D, Sullivan T, Selva D, Casson RJ: **The prevalence and causes of visual impairment in central Sri Lanka the Kandy Eye study.** *Ophthalmology* 2009, **116**:52-6.
7. Hirvela H, Laatikainen L: **Visual acuity in a population aged 70 years or older; prevalence and causes of visual impairment.** *Acta Ophthalmol Scand* 1995, **73**:99-104.
8. Hsu WM, Cheng CY, Liu JH, Tsai SY, Chou P: **Prevalence and causes of visual impairment in an elderly Chinese population in Taiwan: the Shihpai Eye Study.** *Ophthalmology* 2004, **111**:62-9.
9. Kortlang C, Koster JC, Coulibaly S, Dubbeldam RP: **Prevalence of blindness and visual impairment in the region of Segou, Mali. A baseline survey for a primary eye care programme.** *Trop Med Int Health* 1996, **1**:314-9.
10. Liang YB, Friedman DS, Wong TY, Zhan SY, Sun LP, Wang JJ, Duan XR, Yang XH, Wang FH, Zhou Q, Wang NL: **Prevalence and causes of low vision and blindness in a rural chinese adult population: the Handan Eye Study.** *Ophthalmology* 2008, **115**:1965-72.
11. Mansour AM, Kassak K, Chaya M, Hourani T, Sibai A, Alameddine MN: **National survey of blindness and low vision in Lebanon.** *Br J Ophthalmol* 1997, **81**:905-6.
12. Murthy GV, Gupta S, Ellwein LB, Munoz SR, Bachani D, Dada VK: **A population-based eye survey of older adults in a rural district of Rajasthan: I. Central vision impairment, blindness, and cataract surgery.** *Ophthalmology* 2001, **108**:679-85.
13. Murthy GV, Gupta SK, Bachani D, Jose R, John N: **Current estimates of blindness in India.** *Br J Ophthalmol* 2005, **89**:257-60.
14. Nirmalan PK, Thulasiraj RD, Maneksha V, Rahmathullah R, Ramakrishnan R, Padmavathi A, Munoz SR, Ellwein LB: **A population based eye survey of older adults in Tirunelveli district of south India: blindness, cataract surgery, and visual outcomes.** *Br J Ophthalmol* 2002, **86**:505-12.
15. Rahman MM, Rahman N, Foster PJ, Haque Z, Zaman AU, Dineen B, Johnson GJ: **The prevalence of glaucoma in Bangladesh: a population based survey in Dhaka division.** *Br J Ophthalmol* 2004, **88**:1493-7.
16. Rutzen AR, Ellish NJ, Schwab L, Graham PJ, Pizzarello LD, Hemady RK, Maldonado MJ: **Blindness and eye disease in Cambodia.** *Ophthalmic Epidemiol* 2007, **14**:360-6.
17. Shahriari HA, Izadi S, Rouhani MR, Ghasemzadeh F, Maleki AR: **Prevalence and causes of visual impairment and blindness in Sistan-va-Baluchestan Province, Iran: Zahedan Eye Study.** *Br J Ophthalmol* 2007, **91**:579-84.
18. 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.
19. Vassileva P, Gieser SC, Vitale S, Cholakova T, Katz J, West S: **Blindness and visual impairment in western Bulgaria.** *Ophthalmic Epidemiol* 1996, **3**:143-9.
20. Wilson MR, Mansour M, Ross-Degnan D, Moukouri E, Fobi G, Alemayehu W, Martone JF, Casey R, Bazargan M: **Prevalence and causes of low vision and blindness in the Extreme North Province of Cameroon, West Africa.** *Ophthalmic Epidemiol* 1996, **3**:23-33.
21. Wong TY, Chong EW, Wong WL, Rosman M, Aung T, Loo JL, Shen S, Loon SC, Tan DT, Tai ES, Saw SM: **Prevalence and causes of low vision and blindness in an urban malay population: the Singapore Malay Eye Study.** *Arch Ophthalmol* 2008, **126**:1091-9.
22. **Disability Evaluation Under Social Security (Blue Book-August 2010) 2.00 Special senses and speech - Adult.** [http://www.ssa.gov/disability/professionals/bluebook/2.00-SpecialSensesandSpeech-Adult.htm#203].
23. **Social Security Ruling, SSR 07-01p; Titles II and XVI: Evaluating Visual Field Loss Using Automated Static Threshold Perimetry.** [http://www.ssa.gov/disability/professionals/bluebook/2.00-SpecialSensesandSpeech-Adult.htm#203], http://www.ssa.gov/OP_Home/rulings/di/01/SSR2007-01-di-01.html.
24. Hattenhauer MG, Johnson DH, Ing HH, Herman DC, Hodge DO, Yawn BP, Butterfield LC, Gray DT: **The probability of blindness from open-angle glaucoma.** *Ophthalmology* 1998, **105**:2099-104.
25. Quigley HA: **Proportion of those with open-angle glaucoma who become blind.** *Ophthalmology* 1999, **106**:2039-41.
26. Murdoch IE, Jones BR, Cousens S, Liman I, Babalola OE, Dauda J, Abiose A: **Visual field constriction as a cause of blindness or visual impairment.** *Bull World Health Organ* 1997, **75**:141-6.
27. Buch H, Vinding T, La Cour M, Nielsen NV: **The prevalence and causes of bilateral and unilateral blindness in an elderly urban Danish population. The Copenhagen City Eye Study.** *Acta Ophthalmol Scand* 2001, **79**:441-9.
28. Gunnlaugsdottir E, Arnarsson A, Jonasson F: **Prevalence and causes of visual impairment and blindness in Icelanders aged 50 years and older: the Reykjavik Eye Study.** *Acta Ophthalmol* 2008, **86**:778-85.
29. Thylefors B, Negrel AD, Pararajasegaram R, Dadzie KY: **Global data on blindness.** *Bull World Health Organ* 1995, **73**:115-21.
30. Hyman LG, Komaroff E, Heijl A, Bengtsson B, Leske MC: **Early Manifest Glaucoma Trial Group: Treatment and vision-related quality of life in the early manifest glaucoma trial.** *Ophthalmology* 2005, **112**:1505-1513.
31. van Gestel A, Webers CAB, Beckers HJM, van Dongen MCJM, Severens JL, Hendrikse F, Schouten JSAG: **The relationship between visual field loss in glaucoma and health-related quality-of-life.** *Eye* 2010, **24**:1759-69.

Pre-publication history

The pre-publication history for this paper can be accessed here:
http://www.biomedcentral.com/1471-2415/11/31/prepub

doi:10.1186/1471-2415-11-31
Cite this article as: Heijl *et al.*: The effect of different criteria on the number of patients blind from open-angle glaucoma. *BMC Ophthalmology* 2011 **11**:31.

Paper II

ORIGINAL ARTICLE

Screening for Open-Angle Glaucoma and Its Effect on Blindness

JOHAN ASPBERG, ANDERS HEIJL, AND BOEL BENGTSSON

• PURPOSE: **To evaluate the effect of population screening on low vision and blindness from open-angle glaucoma.**

• DESIGN: **Retrospective cohort study.**

• METHODS: **A large population-based screening for glaucoma was conducted in Malmö, Sweden, from 1992 to 1997. A total of 42,497 subjects were invited, of which 32,918 were screened, and 9,579 were non-responders (ie, did not participate). The records of glaucoma patients who had visited the Department of Ophthalmology at Malmö University Hospital from January 1, 1987, to December 31, 2017, were reviewed. Patients diagnosed at or after the screening were assessed for moderate or severe vision impairment, here called low vision, or blindness by the World Health Organization definition. Selection bias was corrected by creating a group of potential screening participants from a comparison group of clinical patients. Main outcome measures were the risk ratios of the cumulative incidence for bilateral low vision or blindness caused by glaucoma in screened patients compared with the potential participants.**

• RESULTS: **The cumulative incidence of blindness was 0.17% in the screened population versus 0.32% among the potential participants; and for low vision 0.25% versus 0.53%. The risk ratio (95% confidence interval) between the two was 0.52 (0.32-0.84) for blindness and 0.46 (0.31-0.68) for low vision. There were no differences between the proportions of potential confounders in the comparison group and those in the non-responders.**

• CONCLUSIONS: **The results suggest that population screening may reduce bilateral low vision and blindness caused by glaucoma by approximately 50%.**

Accepted for publication March 18, 2021.

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

Inquiries to: Johan Aspberg, Department of Clinical Sciences in Malmö, Ophthalmology, Lund University, SE- 20502 Malmö, Sweden.; e-mail: johan.aspberg@med.lu.se

Glaucoma is one of the leading causes of irreversible blindness worldwide.[1,2] Late presentation is the major risk factor for developing blindness from open-angle glaucoma,[3-8] which suggests that screening for the disease (ie, earlier detection with subsequent treatment) may reduce the prevalence of glaucoma-induced blindness. In developed countries, approximately 50% of glaucoma cases are undiagnosed.[9] Most of the criteria for a screenable disease are fulfilled by open-angle glaucoma, with the exception of the cost-effectiveness.[10,11] Several reports have been published regarding the potential benefit of population screening in reducing the risk of impairment due to glaucoma,[12-19] but the results of those investigations represent predictions made using models based on prevalence data and presumed effects of glaucoma treatment. No study has yet reported real-life long-term effects of screening on rates of glaucoma blindness.

In the 1990s, the largest screening ever performed for open-angle glaucoma was conducted, which included 44,243 subjects, of whom 32,918 lived in Malmö. Twenty years later, that screening offered a unique opportunity to investigate the effect of screening on impairment from glaucoma, the intent of the present study.

METHODS

The population screening for open-angle glaucoma was conducted from 1992-1997 in the cities of Malmö and Helsingborg, Sweden, with populations at that time of 250,000 and 135,000 citizens, respectively. The purpose was to recruit subjects with previously undetected glaucoma for possible inclusion in the Early Manifest Glaucoma Trial (EMGT).[20] In Malmö, all residents born between 1918 and 1932 and all women born between 1933 and 1939 were invited to the screening, excluding any individuals who had visited the Department of Ophthalmology at Malmö University Hospital during the year prior to screening.

The screening procedure and study design have been described previously in detail.[20-22] In short, the screening included measurement of intraocular pressure (IOP), refraction, visual acuity (VA), fundus photography, and questions regarding medical and family history and current medica-

0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2021.03.030

tions. Monoscopic fundus color photographs were obtained through dilated pupils using the non-mydriatic TRC-NW3 fundus camera (Tokyo Optical Company, Tokyo, Japan) and Kodachrome 64 slide film (Kodak, Rochester, New York, USA). The picture angle was 50 degrees with the optic disc in the center of the image. All images were inspected at 10-fold magnification and searched for signs of glaucomatous disc or retinal nerve fiber layer damage by 1 glaucoma expert with considerable experience in glaucoma screening.[23] Individuals who screened positive for at least 1 of the following criteria returned for additional examinations: 1) IOP >25 mm Hg in at least 1 eye; 2) suspected or evident glaucomatous changes in the optic disc, retinal nerve fiber defects, or optic disc hemorrhages visible in fundus photographs; 3) exfoliation syndrome; or 4) manifest glaucoma in at least 1 first-degree relative.

The post-screening examinations included repeated perimetry using the Humphrey Field Analyzer (Carl Zeiss Meditec, Dublin, California, USA) Full Threshold program, measurement of IOP using Goldmann applanation tonometry, dilated slit-lamp examination, and ophthalmoscopy.

Patients included in the EMGT were 50-79 years old and had newly diagnosed, previously untreated chronic primary open-angle glaucoma (POAG) or exfoliation glaucoma (PEXG), confirmed by 2 consecutive Humphrey Full Threshold tests with glaucomatous field defects. Defects found in the 2 field tests had to affect the same sector of the Glaucoma Hemifield Test and be classified as "outside normal limits," or if "borderline," with obvious localized glaucomatous changes of the optic disc in an area corresponding to the field defect.[20]

Subjects with POAG or PEXG who fulfilled the other criteria for inclusion in the EMGT were asked to participate in the trial. Screened individuals with suspected or manifest glaucoma who did not fulfill the inclusion criteria or who refused to participate in the trial were recommended and offered treatment and follow-up care at the Department of Ophthalmology at Malmö University Hospital or with an ophthalmologist in private practice of their own choice.

• **SUBJECTS:** The main population of this study consisted of subjects of the screen-invited birth cohorts, men and women born between 1918 and 1932, and women born between 1933 and 1939 who were living in the city of Malmö from 1992-1997 and had been diagnosed with POAG or PEXG, either at or after the screening or study start. Patients with secondary or angle-closure glaucoma were not eligible for the current study and neither were patients with POAG or PEXG diagnosed before the screening or study start. With few exceptions, glaucoma could be defined by criteria equivalent to those in the EMGT (ie, 2 consecutive Humphrey field analyzer threshold visual field test results with glaucomatous defects that had to affect the same sector of the field). The Glaucoma Hemifield Test had to be "outside normal limits," or if "borderline," with obvious localized glaucomatous changes of the optic disc corresponding to the field defect.[20]

The present study compared the frequency of bilateral impairment from glaucoma among 3 groups. The "screened" group included those who attended the screening. The second group, the "non-responders to screening," included those who had been invited to the screening but chose not to attend. The third group consisted of subjects who were a few years older or younger than the invited screening cohorts, designated the "uninvited comparison group," which included men and women born between 1915 and 1917 and men born between 1933 and 1935. Subjects in this third group were not invited to the screening and would reveal what the proportion of impaired subjects would be without screening.[24,25] In the selection of patients into the uninvited comparison group, we tried to mimic the selection process used for the screened and non-responders as closely as possible. Inclusion and exclusion criteria were the same, and only the study start and end dates were adjusted. An overview of the selection process of the patients eligible for the present study is shown in Figure 1.

The study start date for the screened glaucoma patients was defined as each patient's individual screening date. Each screened age cohort had been examined consecutively according to date of birth. Non-responders to screening were assigned a study start date which was the same as the screening date for screened subjects having the same birthdate. This strategy resulted in almost identical start and follow-up times. The study end for both groups was December 31, 2017. For the uninvited comparison group, the start and end of the study period were adjusted to match age and follow-up time to those of the non-responders, who kept their original study start date. In the nonresponder age cohorts born between 1930 and 1932, the study end was shortened by 3 years to match ages and follow-up times of the respective uninvited age cohorts (Figure 2).

• **ETHICS:** The EMGT (US National Institutes of Health Clinical Trials.gov identifier NCT00000132; registered Sept 23, 1999) and the screening were approved by the Ethics Committee at Lund University, Sweden, in 1992, and approval was also given to the current study in 2006, with extensions most recently approved in 2019. Advertisements were published in local newspapers to allow glaucoma patients who had visited the department not to be included in the study. The EMGT was also approved by the Committee on Research Involving Human Subjects at the State University of New York at Stony Brook, USA. All studies followed the tenets of the Declaration of Helsinki.

• **DATA COLLECTION:** Data were collected from medical records on visits to the Department of Ophthalmology at Malmö University Hospital from January 1, 1987, up to December 31, 2017, and were reviewed to ascertain the date of diagnosis. The start date for review was set a few years

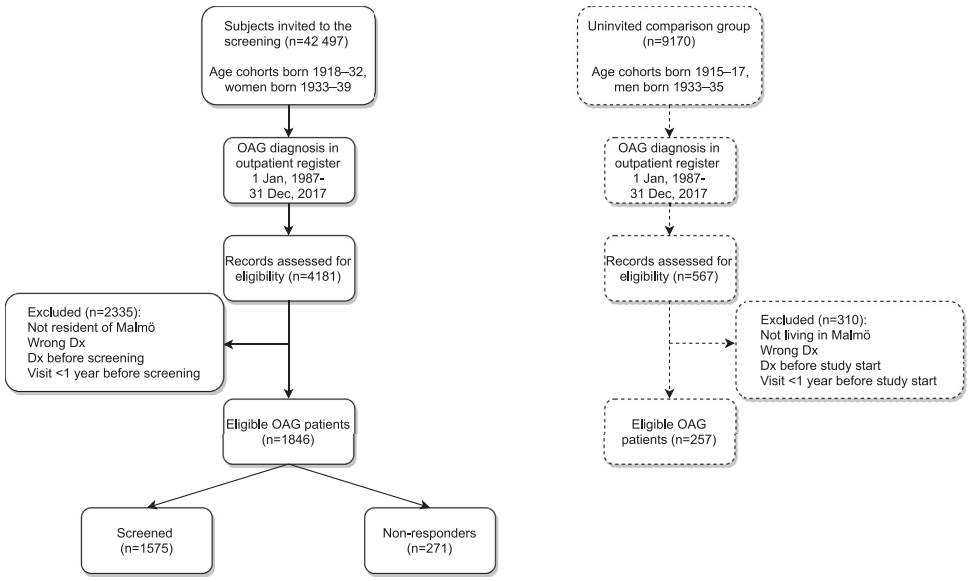


FIGURE 1. Flowchart of selection of data from patient records. Screened subjects and subjects not responding to the screening invitation are shown to the left, the uninvited comparison group is shown on the right. Dx = diagnosis; OAG = open-angle glaucoma.

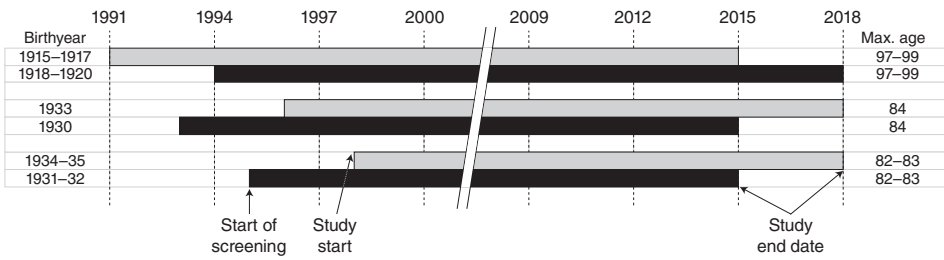


FIGURE 2. Creation of the uninvited comparison group and corresponding non-responders.
Patients from the unscreened comparison group (gray bars) were assigned the same day and month for the study start as the non-responders (black bars), but the year was adjusted to match for the age of the non-responder subjects. Similarly, the year for study end was adjusted to obtain the same follow-up time period for both groups.

before the screening was initiated to ensure that only previously undiagnosed subjects were included in the current investigation.

Data for the size of the population of screen-invited cohorts were retrieved from screening records and protocols in paper format. The uninvited comparison group population was not part of the screening, and therefore, the mid-year number of subjects in this population was obtained from the Swedish Central Bureau of Statistics (http://www.scb.se) and adjusted for the proportion of individuals in the screening population who were not invited to the screening.

Ages for all glaucoma patients were recorded at the start and at the end of the study. In addition, sex, date of diagnosis, date of death or loss to follow-up, VA, and the amount of visual field loss, which was noted as mean deviation (MD) for each eye at the last visit, were recorded.[26] The presence of exfoliative material in either eye on the anterior lens capsule or pupillary margin was also noted. In the cases with

TABLE 1. World Health Organization criteria for vision impairment

Category	Visual acuity in the better eye	
	Worse than:	Equal to or better than:
1 Mild vision impairment	0.5 (20/40)	0.3 (20/70)
2 Moderate vision impairment[a]	0.3 (20/70)	0.1 (20/200)
3 Severe vision impairment[a]	0.1 (20/200)	0.05 (20/400)
4-6 Blindness	0.05 (20/400)	
Category	**Remaining central visual field in the better eye**	
	Less than:	Equal to or more than:
3 Severe vision impairment[a]	20°	10°
4-6 Blindness	10°	-

[a]Called low vision in this study.

unilateral exfoliation syndrome, the patient was considered to be affected.

Furthermore, for each patient, the final data obtained before study end were assessed for possible impairment in either eye, as well as its cause and date of occurrence. The term vision impairment, defined according to World Health Organization (WHO) criteria (Table 1), includes reversible causes of decreased vision (eg, uncorrected refractive errors). This study recorded best-corrected visual acuity and therefore used the terms low vision, corresponding to moderate and severe vision impairment of the WHO criteria, and blindness. Numbers of low vision in this report include blindness.

Bilateral low-vision was reported, based on best-corrected visual acuity and/or visual field status in the best eye. Thus, a subject with 1 blind eye and low vision in the other eye was considered to have low vision. Each eye was counted as having low vision/blindness when VA got below the threshold for low vision or blindness (ie, <20/70 or <20/400, respectively) and did not improve on subsequent visits. The same was done for visual field data, with total extent of the central field of <20 degrees but ≥10 degrees, defined as low vision, and central field extent <10 degrees defined as blindness. A temporal aspect was applied: the disease that first caused low vision or blindness was registered as the main cause for that eye. If 2 or more diseases contributed to the visual loss in 1 eye, and the date of visual loss was not known, the disease that was judged to contribute most extensively to the impairment was registered as the main cause.

The constriction of visual fields was determined by a previously described approach.[27,28] Briefly, the diameter of the remaining visual field was calculated by drawing pseudoisopters on the numerical threshold decibel (dB) map on Statpac[26] single-field analysis printouts from the Humphrey perimeter, midway between test point locations with threshold sensitivity values of 10 dB or better and points with sensitivity less than 10 dB.

In 96% of patients in this study, low vision and blindness from glaucoma were determined based on both visual field data and VA. However, in the 4% of patients in whom visual field data were lacking, the classification was based solely on VA.

The main risk factors for rapid progression and/or glaucoma blindness were recorded from the non-responders and the uninvited comparison group (ie, presence of exfoliation syndrome; age at death; and at study start: bilateral glaucoma; level of visual field loss by mean deviation; and untreated IOP level).[3,29] The untreated IOP was noted as the mean of the measurements recorded within 3 months before either the date of diagnosis or the starting date of IOP-reducing treatment, the latter for patients who were treated before receiving a diagnosis of glaucoma.

To determine whether care practice had differed among groups, data were analyzed from a random sample of 100 patients from each of the 3 groups. The number of visits per patient within 3 years after diagnosis or referral to our department was registered, in addition to the number of patients who had been treated with laser trabeculoplasty or other glaucoma surgical procedures.

• **ANALYSIS:** Bilateral low vision and blindness due to glaucoma were the main outcome variables. Patients were considered to have been lost to follow-up if they moved to other parts of Sweden or out of the country, and as a result, their ophthalmological data were not available to this study.

Subjects who attend a screening sometimes have a different risk of developing the disease endpoint than non-responders to screening.[30,31] The self-selection bias that may occur when comparing the outcome of screening attenders to non-responders can be corrected by the method of Duffy and associates,[32] in which a noninvited compar-

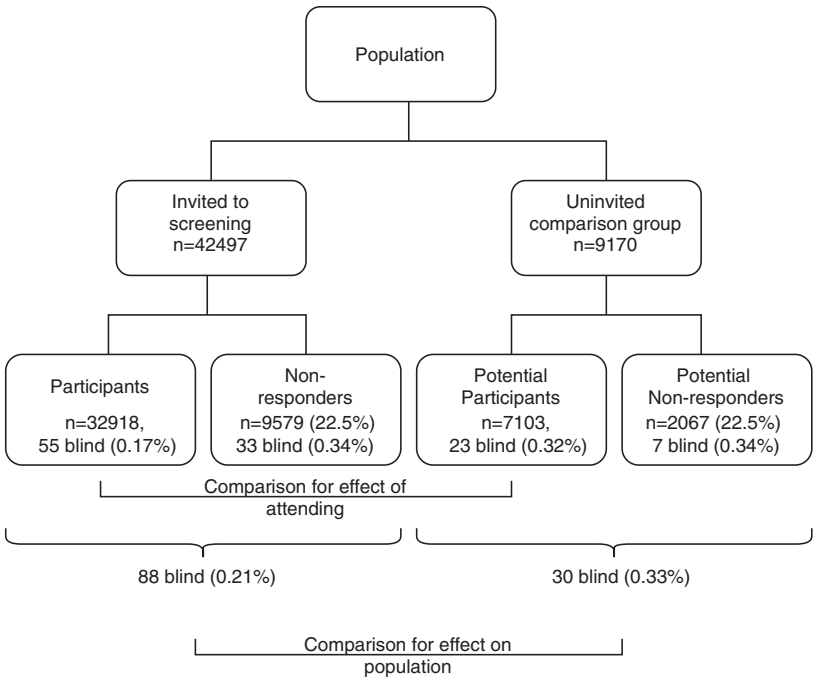


FIGURE 3. Correction for selection bias. The figure illustrates how the effect of the screening is calculated both for screening participants and for the population.[33,34] It is assumed that the proportion of non-responders would be the same in the uninvited comparison group as in the screening-invited subjects.[32] The number of potential non-responders and the number of blind in this group were derived from the proportions among the non-responders.

ison group was included. This correction is based on the assumption that the population of the uninvited comparison group would have the same proportions of screening attenders and non-responders as in the screen-invited population (Figure 3).[33,34] The number of subjects and persons with low vision or blindness from glaucoma was calculated in both the potential non-responders and the potential participants in the uninvited comparison group. Results were rounded to the nearest integer.

Means of normally distributed continuous variables between groups were compared by Student́s *t*-test. The nonparametric Mann-Whitney *U* test was performed for comparisons when appropriate. Associations between categorical variables were assessed using the χ^2 test or by the *z*-test in case of 2 independent population proportions. The follow-up time was defined as the number of years from a patient's study start date to the study end date. The reverse Kaplan-Meier method was used to calculate median follow-up time, where events and censoring are reversed.[35] Thus, the events of death or bilateral blindness from any cause were treated as censored, and censored patients (ie, those lost to follow-up and those alive at study end) were treated as events. Distributions of follow-up time were compared between groups by using the log rank test. Rates and risk ratios for the cumulative incidence of low vision and blindness were calculated. Sample size and power calculations were not made for this study, because no samples were taken. The screening invited full age cohorts, and the study included all glaucoma patients visiting the authors' department from the time of screening/study start to study end. The Statistical Package for the Social Sciences version 24.0 software (IBM, Armonk, New York, USA) was used. Risk ratios with confidence intervals (CI) were calculated using OpenEpi version 3.0.1 software (updated April 6, 2013, accessed October 25, 2019; OpenEpi, Minneapolis, Minnesota, USA).

RESULTS

A total of 32,918 subjects born between 1918 and 1939 were screened; 9,579 individuals refused the screening invitation; and 4,117 subjects were not invited to the screening,

TABLE 2. Descriptives of screened glaucoma patients (n=1575) and glaucoma patients who were invited to but did not attend the screening (non-responders) (n=271)

	Screened	Non-responders	Number of patients in analysis (screened/non-responders)
Mean age at screening, years (95% CI)	67.5 (67.3–67.7)	68.0 (67.4–68.5)	1575/271
Cumulative incidence of glaucoma, rate in % (95% CI)	4.8% (4.6-5.0)	2.8% (2.5-3.2)	1575 of 32918/ 271 of 9579
Male sex (patients born 1918–1932) (95% CI)	37.8% (0.35–0.40)	30.9% (0.25–0.37)	514 of 1360/ 76 of 246
Follow-up time, years (median + 95% CI)	22.6 (22.5–22.8)	22.8 (22.2–23.4)	1571/271
Age at death, years (mean + 95% CI)	85.3 (85.0–85.7)	85.8 (84.9–86.7)	990/187
Exfoliation glaucoma (95% CI)	50.0% (0.48–0.53)	56.5% (0.50–0.62)	1575/271
MD, dB in worse eye at study end (median + IQR)	−17.3 (17.0)	−25.4 (15.0)	1498/242[a]
MD, dB in best eye at study end (median + IQR)	−7.0 (9.8)	−9.0 (13.3)	1498/242[a]

MD=mean deviation. CI=confidence interval. POAG=primary open-angle glaucoma. IQR=interquartile range. dB=decibel.
[a] Data missing for part of the patients.

because they had visited the Department of Ophthalmology during the year prior to screening. Thus, the screening had an attendance rate of 77.5%. Most attendees were of European origin.

Among all individuals invited to the screening, 1,846 patients were identified who had diagnoses of POAG or PEXG at the screening or during the follow-up period; 1,575 patients were screened, and 271 were non-responders to screening. The diagnosis was set at or within 6 months of the screening in 427, and at more than 6 months after the screening in 1,148 of the screened patients. Of the latter patients, 155 received diagnoses of ocular hypertension or suspected glaucoma at the screening and were subsequently followed by regular checkups at the authors' department or an ophthalmologist in private practice. A flowchart of the selection of patients eligible for the present study is presented in Figure 1.

The mean age of all screen-invited glaucoma patients (ie, screened and non-responders) at the time of the screening was 67.6 years; 67.5 years for the screened, and 68.0 years for non-responders. Maximum follow-up time for each age cohort ranged from 22-25 years, and the median follow-up time for all invited patients was 23 years. Among the invited patients, 51% had PEXG, and 49% had POAG. The proportion of PEXG between screened and non-responders differed somewhat: 50% (95% CI: 0.48-0.53) and 56.5% (95% CI: 0.50-0.62), respectively ($P = 0.048$, z-score). Characteristics of the screened and non-responder patients are presented in Table 2.

The diagnosis of glaucoma was based on the intended eligibility criteria: reproducible visual field defects and corresponding optic disc damage in 1,680 (91%) of the patients. In 93 patients (5%), only 1 visual field was available, but corresponding optic disc damage was present. Visual field test results were missing for 73 patients (4%), in whom the diagnosis was based on optic disc appearance alone on photographs or in a written description. Of these patients, 3/4 had been screened, and 1/4 were non-responders. Approximately half of them (ie, 2% of all included) were patients referred to the authors' department from ophthalmologists in private practice for cataract surgery or laser trabeculoplasty, in whom no visual field tests had been performed before the patients returned to the referring doctor. Poor vision, physical restrictions, or mental illness were other reasons for not testing the visual field. Data for VA were missing for only 7 patients, 5 screened and 2 non-responders.

A total of 23 patients, not including deceased, were lost to follow-up. At the end of the study, 36% of the glaucoma patients were alive. Median time from the last visual field to study end date was 1 year for both screened and non-responders; median time from the last VA test to study end was 0 years for both groups.

Characteristics of the glaucoma patients in the non-responder and uninvited comparison groups are presented in Table 3. No statistically significant differences were found between the groups regarding risk factors for rapid progression of glaucoma and/or glaucoma blindness (ie, the presence of exfoliation syndrome; age at death, and at study start: bilateral glaucoma; level of visual field loss by mean deviation; and untreated IOP level). The cumulative incidence of glaucoma was similar in both groups.

TABLE 3. Descriptives of the uninvited comparison group patients (n=257) and the corresponding group of non-responder patients (invited to but did not attend the screening) (n=68), including risk factors for glaucoma blindness and/or rapid progression

	Uninvited comparison group	Non-responders	Number of patients in analysis (non-responders/ uninvited comparison group)
Patient and eye characteristics			
Mean age at diagnosis, years (95% CI)	79.3 (78.5–80.1)	79.2 (77.7–80.6)	68/257
Cumulative incidence of glaucoma (95% CI)	2.80% (2.48–3.16)	2.84% (2.23–3.61)	68 of 2392/257 of 9170
Male sex (patients from older age cohorts) (95% CI)	31.5% (0.25-0.39)	30.0% (0.19-0.44)	15 of 50/57 of 181
Follow-up time, years (median + 95% CI)	21.3 (19.5–23.1)	23.3 (19.7–26.9)	68/257
MD in best eye at study end (dB) (median + IQR)	–9.28 (17.4)	–9.68 (14.9)	60/233[a]
MD in worse eye at study end (dB) (median + IQR)	–24.9 (14.5)	–25.3 (15.2)	60/229[a]
Risk factors for fast progression and/or blindness			
Exfoliation glaucoma (95% CI)	49.4% (0.43–0.56)	50.0% (0.38–0.62)	68/257
Mean age at death, years (95% CI)	89.5 (88.7–90.3)	88.7 (86.9–90.5)	55/181
Bilateral glaucoma at diagnosis (95% CI)	34.6% (0.29–0.41)	36.7% (0.25–0.50)	60/243[a]
Max. IOP, at diagnosis (mmHg) (median + IQR)	30.0 (10.5)	31.0 (14.0)	58/233[a]
Min. IOP at diagnosis (mmHg) (median + IQR)	22.0 (9.0)	24.0 (10.0)	57/233[a]
MD in best eye at diagnosis (dB) (median + IQR)	–4.72 (8.65)	–5.41 (11.0)	58/205[a]
MD, in worse eye at diagnosis (dB) (median + IQR)	–17.2 (15.8)	–16.8 (19.9)	58/206[a]

MD=mean deviation. CI=confidence interval. IOP=intraocular pressure. IQR=interquartile range. dB=decibel.
[a]Data missing for part of the patients.

TABLE 4. Comparison of cumulative incidence of bilateral blindness and low vision from glaucoma in the uninvited comparison group and non-responders to screening.

	Number of subjects at study start	Blind in both eyes, rate in %, (n)	Low vision or blind in best eye, rate in %, (n)[a]
Uninvited comparison group	9170	0.33 (30)	0.51 (47)
Non-responders	2392	0.29 (7)	0.42 (10)
Risk ratio Uninvited/ Non-responders (95% CI)		1.12 (0.49-2.54)	1.23 (0.62-2.42)

CI=confidence interval.
[a]Numbers on blindness are included in the low vision category.

The risk ratio of the cumulative incidence of bilateral low vision or blindness caused by glaucoma differed somewhat between the groups but not significantly (Table 4).

There were no statistically significant differences among the screened, the nonresponder, and the uninvited groups regarding care practice; the median number of visits and percentages of patients who had been treated with laser trabeculoplasty or surgery were similar in all 3 groups (Table 5).

The cumulative incidence of bilateral low vision and blindness caused by glaucoma was significantly lower in the screened population than in the potential participants: 0.17% of the screened were blind versus 0.32% of the potential participants. The proportions of low vision, blindness included, were 0.25% versus 0.53%, respectively (Figure 3). The risk ratios between the two were 0.52 (95% CI: 0.32-0.84) for blindness and 0.46 (95% CI: 0.31-0.68) for low vision. The risk ratios, calculated according to the method of Duffy and associates were equal to our calculations: 0.52 and 0.46, respectively (Table 6).[32]

TABLE 5. Comparison of care practice between the patients of the screened, the non-responders to screening, and uninvited comparison groups.

	Screened, n=100	Non-responders, n=100	Uninvited, n=100
Number of visits during the first 3 years			
Median	7	7	6
Mean	8.12	8.78	7.25
Number of laser trabeculoplasties			
0	62	62	66
1	24	18	23
2	10	15	8
≥3	4	5	3
Number of surgical procedures*			
0	95	90	95
1	3	7	5
2	2	0	0
≥3	0	3	0

*trabeculectomies, shunts, or cyclodiode laser treatments

TABLE 6. Cumulative incidences of bilateral blindness and low vision from glaucoma in the screened population, the non-responders to screening and the potential participants population.

	Number of subjects at study start	Blind in both eyes, (n)	Low vision or blind in best eye, (n)[a]
Screened	32 918	0.17% (55)	0.25% (81)
Non-responders	9579	0.34% (33)	0.44% (42)
Potential participants	7103	0.32% (23)	0.53% (38)
Risk ratio			
Screened/ Potential		0.52	0.46
participants		(0.32–0.84)	(0.31–0.68)
(95% CI)		p=0.01	p=0.000

CI=confidence interval.
[a]Numbers on blindness are included in the low vision category.

DISCUSSION

This is the first study to present real-life long-term results regarding the impact of population screening on glaucoma-induced low vision or blindness. Our findings suggest that the screening and subsequent treatment had a protective effect. The risk ratios over a follow-up time of more than 20 years revealed that approximately half as many subjects in the screened group developed low vision or blindness caused by glaucoma compared to subjects in the potential participants group. These findings are not surprising, considering that glaucoma is detected at earlier stages by screening than by diagnosis in routine clinical practice[21] and that the amount of visual field loss at the time of diagnosis is the most important risk factor for developing blindness from glaucoma.[3-8]

The main strengths of the current study are the large numbers of subjects included in the screened group (n = 32,918) and the non-responders to screening (n = 9,579) and the length of follow-up. Also, only 1.2% of the patients in this study were lost to follow-up. Another advantage of this investigation is that approximately 75% of the patients with the diagnosis of glaucoma in the city of Malmö are followed at our hospital. Our department serves as the primary and tertiary glaucoma center for residents of Malmö and as the tertiary glaucoma center for a large part of southern Sweden, and we receive all referrals for glaucoma surgery and most referrals for laser trabeculoplasty or a second opinion from private practitioners in Malmö.

Patients with severe glaucoma managed in private care in Malmö have most likely visited our department on some occasion. In an earlier study of lifetime risk of glaucoma blindness in Malmö,[36] only approximately 3% of the 592 glaucoma patients who were included had not visited the

authors' department. Accordingly, we believe that the few glaucoma patients with low vision or blindness who might not have visited this department could not have seriously biased the results of the study.

The most important limitation of the current study is the lack of randomization of subjects. Therefore, we investigated whether confounders were present in the 3 major groups compared: the screened, the non-responders, and the uninvited. The last group had a cumulative incidence of glaucoma similar to that of the non-responders, which indicates that this is the expected rate without screening. Risk factors for rapid progression/blindness did not differ significantly between these 2 groups. Median follow-up time did not differ significantly between screened and non-responders. No statistically significant differences were found among the 3 groups regarding care practice. Overall, the comparisons regarding potential confounders suggest that there were no important differences that needed to be corrected for in the analysis of the main outcome measures.

A comparison between the outcomes of the screened and those of the non-responder group would be susceptible to selection bias, as non-responders to a screening examination may have a higher or a lower risk of developing the outcome of interest compared to the general population. Selection bias may result in a flawed estimation of the true effect of screening.[30,31] Therefore, correction was made for selection bias (Figure 3) in the calculation of risk ratios for the main outcome.

We have shown that the uninvited comparison group was similar to the corresponding age groups of the non-responders regarding potential confounders and the cumulative incidence of glaucoma. However, the cumulative incidence of blindness was lower, 0.29%, in those non-responders who were compared with the uninvited comparison group (Table 4) than in all non-responders, 0.34% (Table 6). For the non-responders born between 1921 and 1929 who were not included in the comparison with the uninvited group, the proportion of blindness was 0.36%. If it is assumed that this higher proportion of blindness in all non-responders would be the same in a fictive uninvited comparison group of the corresponding ages and population size, the corrected proportion of blindness in the latter would be 0.39%, and result in a risk ratio of blindness of 0.42 in screened subjects compared to potential participants (ie, a larger effect of screening). We chose not to make such a correction due to the uncertainties generated by the small numbers of blind subjects in the non-responder group who are compared with the uninvited group. Instead, a more conservative estimate was presented based on the uncorrected blindness rate of 0.33% in the uninvited comparison group and the blindness rate of 0.34% of all the non-responders (Figure 3).

Other sources of bias that may occur in screening studies, such as lead time, length time, and overdiagnosis bias, are not relevant to the present study. The main outcome is presented as the risk ratio of low vision and blindness from glaucoma, not by survival analysis. The study start of the different compared groups is based on the screening dates of the screened, which gives the same follow-up time for all patients of the same age at study start, and patients with a diagnosis date before study start were not included.[24,25]

This is a retrospective investigation, an approach that has known limitations. Missing data and loss to follow-up are aspects of all observational studies, especially those assessing an elderly population in which other illnesses and age-related frailties affect follow-up and the ability of the subjects to manage examinations. However, only 1.2% of the patients in this study were lost to follow-up. Lack of visual field data can lead to an underestimation of low vision or blindness caused by glaucoma but was missing for only 4% of patients.[28]

If any cases of glaucoma-induced low vision or blindness among the patients without visual field data were not accounted for, the number of such subjects would have been small and probably would not have had a substantial impact on the main results.

The authors of 3 major reviews[37-39] were unable to identify a single randomized controlled trial or observational study of screening for open-angle glaucoma and its effect on low vision or blindness caused by this disease, and we have not found any more recent reports on this subject. Therefore, we cannot compare our results with the findings of earlier studies.

Most screened subjects were white Europeans, and a considerable proportion of the glaucoma patients had exfoliation glaucoma, which makes direct comparisons with other regions or by race difficult.

Our results suggest that population screening may lead to reductions in glaucoma-induced low vision or blindness of approximately 50%. This potential is, of course, valid only if glaucoma patients detected at screening are offered treatment and follow-up and are managed according to generally accepted principles.

A possible limitation to observational studies, as the current study, is that one cannot be certain that all confounding factors have been identified and controlled for. The reductions in low vision and blindness are large, however, and would probably not change much even if these unknown confounding factors were identified and corrected. A randomized controlled trial of glaucoma screening could provide even more conclusive evidence, but that would take many years. In the shorter term, follow-up evaluation of subjects who have been enrolled in earlier population studies may provide quick and independent confirmation or refutation of our results.

We hope that these findings will encourage further research of screening for glaucoma, which may reduce the effect of glaucoma on patients' quality of life, especially as longevity increases over time. Ideally, a screening test

for glaucoma would be quick, simple, and affordable without compromising the most important property of a screening method, high specificity, which reduces the emotional harm caused by false positive findings. With recent progress in computer-assisted analysis of optic disc photographs and OCT scans, tests of this kind might be available in the near future.[40]

The cost-effectiveness of population screening depends on the prevalence of the disease in question. Therefore, it may not be cost-effective to screen for glaucoma in younger age groups in whom prevalence is low, but it may be worthwhile in older age groups or in groups with higher prevalence (eg, in people of African descent or in those with a family history of glaucoma).[15,16]

Opportunistic screening by optometrists may result in earlier detection of glaucoma but also in an increased burden on ophthalmologists because of larger numbers of referred patients. Clear-cut guidelines of suitable screening methods, what ages to screen, and criteria for referral to ophthalmologists and re-screening intervals are desirable.

In conclusion, we have made the first long-term evaluation of the effectiveness of real-life glaucoma screening using follow-up data from the largest screening for open-angle glaucoma conducted so far. The results suggest that low vision or blindness in the screened population was reduced by half. Confirmatory studies will be necessary before making any recommendations about general population screening. However, it may be correct to consider opportunistic screening of older subjects if performed by trained personnel using methods with high specificity.

TOC

This study evaluated the effect on blindness of a large population screening for open-angle glaucoma. The screening was conducted in the 1990s in Malmö, Sweden, with approximately 33,000 participants. The results suggest that population screening may reduce blindness in those screened by approximately 50%.

ACKNOWLEDGMENTS: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

FUNDING/SUPPORT: Publication of this article was supported by Swedish Research Council grants K98-27X and K2002-74X-10426-10A; US National Eye Institute grants U10EY10260 and U10EY10261; regional agreements between Lund University and Skåne Regional Council (ALF); and grants from the Herman Järnhardt Foundation, the Foundation for Visually Impaired in Former Malmöhus County, the Margit and Kjell Stoltz Foundation, and the Ingrid Nordmark Foundation. The National Eye Institute participated in the design of the Early Manifest Glaucoma Trial. Other funding organizations had no role in the design or conduct of the current study. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication. All authors attest that they meet the current ICMJE criteria for authorship.

FINANCIAL DISCLOSURES: Anders Heijl is a consultant for Carl Zeiss Meditec and Allergan. Boel Bengtsson is a consultant for Carl Zeiss Meditec. Johan Aspberg has reported he has nothing to disclose.

REFERENCES

1. Flaxman SR, Bourne RRA, Resnikoff S, et al. Global causes of blindness and distance vision impairment 1990-2020: a systematic review and meta-analysis. *Lancet Glob Health*. 2017;5(12):e1221–e1234.
2. Resnikoff S, Pascolini D, Etya'ale D, et al. Global data on visual impairment in the year 2002. *Bull World Health Organ*. 2004;82(11):844–851.
3. Peters D, Bengtsson B, Heijl A. Factors associated with lifetime risk of open-angle glaucoma blindness. *Acta Ophthalmol*. 2014;92(5):421–425.
4. Ang GS, Eke T. Lifetime visual prognosis for patients with primary open-angle glaucoma. *Eye*. 2007;21(5):604–608.
5. 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.
6. Goh YW, Ang GS, Azuara-Blanco A. Lifetime visual prognosis of patients with glaucoma. *Clin Exp Ophthalmol*. 2011;39(8):766–770.
7. Forsman E, Kivela T, Vesti E. Lifetime visual disability in open-angle glaucoma and ocular hypertension. *J Glaucoma*. 2007;16(3):313–319.
8. Saunders LJ, Russell RA, Kirwan JF, McNaught AI, Crabb DP. Examining visual field loss in patients in glaucoma clinics during their predicted remaining lifetime. *Invest Ophthalmol Vis Sci*. 2014;55(1):102–109.
9. Quigley HA. Glaucoma. *Lancet*. 2011;377(9774):1367–1377.
10. Wilson JMG, Jungner G. *Principles and practice of screening for disease*. Geneva: World Health Organization; 1968. Available at: *https://apps.who.int/iris/bitstream/handle/10665/37650/WHO_PHP_34.pdf?sequence=17*.
11. Weinreb RH, Healey PR, Topouzis F, eds. *Glaucoma Screening. WGA Consensus Series; No*. 5. Amsterdam, The Netherlands: Kugler Publications; 2008. Available at *https://www.kuglerpublications.com/index.php?p=269&page=publication*.
12. Gottlieb LK, Schwartz B, Pauker SG. Glaucoma screening. A cost-effectiveness analysis. *Surv Ophthalmol*. 1983;28(3):206–226.
13. Boivin JF, McGregor M, Archer C. Cost effectiveness of screening for primary open angle glaucoma. *J Med Screen*. 1996;3(3):154–163.
14. Tuck MW, Crick RP. The cost-effectiveness of various modes of screening for primary open angle glaucoma. *Ophthalmic Epidemiology*. 1997;4(1):3–17.
15. Burr JM, Mowatt G, Hernandez R, et al. The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation. *Health Technol Assess*. 2007;11(41):1–190 iii–iv, ix–x.

16. Vaahtoranta-Lehtonen H, Tuulonen A, Aronen P, et al. Cost effectiveness and cost utility of an organized screening programme for glaucoma. *Acta Ophthalmol Scand*. 2007;85(5):508–518.
17. Burr J, Hernandez R, Ramsay C, et al. Is it worthwhile to conduct a randomized controlled trial of glaucoma screening in the United Kingdom? *J Health Serv Res Policy*. 2014;19(1):42–51.
18. John D, Parikh R. Cost-effectiveness and cost utility of community screening for glaucoma in urban India. *Public Health*. 2017;148:37–48.
19. Tang J, Liang Y, O'Neill C, Kee F, Jiang J, Congdon N. Cost–effectiveness and cost-utility of population-based glaucoma screening in China: a decision-analytic Markov model. *Lancet Glob Health*. 2019;7(7):e968–e978.
20. Leske MC, Heijl A, Hyman L, et al. Early Manifest Glaucoma Trial: design and baseline data. *Ophthalmology*. 1999;106(11):2144–2153.
21. Grodum K, Heijl A, Bengtsson B. A comparison of glaucoma patients identified through mass screening and in routine clinical practice. *Acta Ophthalmol Scand*. 2002;80(6):627–631.
22. Grodum K, Heijl A, Bengtsson B. Refractive error and glaucoma. *Acta Ophthalmologica Scandinavica*. 2001;79(6):560–566.
23. Bengtsson Bo. Aspects of the epidemiology of chronic glaucoma [thesis]. *Acta Ophthalmologica Supplementum*. 1981;146 Scriptor.
24. Morrison AS. *Screening in Chronic Disease*. 2nd edition. New York: Oxford University Press; 1992.
25. Sankila R, Démaret E, Hakama M, Lynge E, Schouten L, Parkin DM, eds. *Evaluation and monitoring of screening programmes*. Brussels-Luxembourg: European Commission; 2001 Available at: *https://core.ac.uk/download/pdf/10596485.pdf*.
26. Heijl A, Lindgren G, Olsson J. A package for the statistical analysis of visual fields. In: Greve EL, Heijl A, eds. *Seventh International Visual Field Symposium, Amsterdam, September 1986*. Dordrecht: Springer; Netherlands; 1987:153–168.
27. Social Security Ruling, SSR 07-01p; Titles II and XVI: Evaluating Visual Field Loss Using Automated Static Threshold Perimetry. Available at: https://www.ssa.gov/disability/professionals/bluebook/2.00-SpecialSensesandSpeech-Adult.htm; & http://www.ssa.gov/OP_Home/rulings/di/01/SSR2007-01-di-01.html.
28. 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.
29. Coleman AL, Miglior S. Risk factors for glaucoma onset and progression. *Surv Ophthalmol*. 2008;53(Suppl 1):S3–10.
30. Gordis L. Epidemiology. Fifth edition. Philadelphia, PA: Elsevier/Saunders; 2014.
31. Rothman KJ, Greenland S, Lash TL. *Modern epidemiology*. 3rd edition. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2008.
32. Duffy SW, Cuzick J, Tabar L, et al. Correcting for non-compliance bias in case–control studies to evaluate cancer screening programmes. *J Royal Statistical Society*. 2002;51(2):235–243.
33. Cuzick J, Edwards R, Segnan N. Adjusting for non-compliance and contamination in randomized clinical trials. *Stat Med*. 1997;16(9):1017–1029.
34. Sommer A, Zeger SL. On estimating efficacy from clinical trials. *Stat Med*. 1991;10(1):45–52.
35. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Control Clin Trials*. 1996;17(4):343–346.
36. Peters D, Bengtsson B, Heijl A. Lifetime risk of blindness in open-angle glaucoma. *Am J Ophthalmol*. 2013;156(4):724–730.
37. Hatt S, Wormald R, Burr J. Screening for prevention of optic nerve damage due to chronic open angle glaucoma. *Cochrane Database Syst Rev*. 2006(4).
38. Ervin AM, Boland MV, Myrowitz EH, et al. *Screening for Glaucoma: Comparative Effectiveness. Rockville (MD)*. Agency for Healthcare Research and Quality (US); April 2012.
39. Moyer VA. Screening for glaucoma: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med*. 2013;159(7):484–489.
40. Thompson AC, Jammal AA, Medeiros FA. A review of deep learning for screening, diagnosis, and detection of glaucoma progression. *Transl Vis Sci Technol*. 2020;9(2):42.