Long-term follow-up of pseudoexfoliation, intraocular pressure and glaucoma
Epidemiological studies in northern Sweden

Siv Åström
To my parents
ABSTRACT

Purpose
An age-cohort was studied with long-term follow-up. The population was born in 1915, living in the municipality of Skellefteå in 1981. The purpose was to investigate the prevalence and incidence of pseudoexfoliation (PEX), its influence on intraocular pressure (IOP) and development of open-angle glaucoma (OAG). Another purpose was to estimate the value of screening for glaucoma by comparing the screened group within the cohort with the remaining unscreened group.

Methods
In 1981, 339 (40%) of the 856 individuals in the cohort underwent an eye examination. This screened group was re-examined at seven-year intervals until 2002. At each visit the presence of PEX was registered, IOP was measured and the presence of glaucoma was assessed. After the 21-year follow-up period, glaucoma cases were also searched for in the medical records of the remaining unscreened individuals in the cohort. Proportions of glaucoma were compared between the two groups.

Results
The prevalence of PEX was 23% (95% confidence interval (CI): 20-26%) at the age of 66 and increased to 61% (CI: 50-71%) at the age of 87. The annual incidence of PEX was 1.8% (CI: 1.3-2.4%). The prevalence of OAG increased from 2.1% (CI: 0.8-4.3%) at the age of 66 years to 25% (CI: 16-35%) at 87 years. The overall annual incidence of OAG was 0.9% (CI: 0.6-1.3%) and for OAG with PEX 2.1% (CI: 1.2-3.3%). PEX increased the risk of developing glaucoma at least four-fold. The incidence of diagnosed OAG in women was higher in the screened group than in the unscreened group (incidence rate ratio (IRR)=1.94, p=0.035). A corresponding difference could not be verified for men (p=0.58). The mean, age-dependent, increase in IOP during the 21-year observation period was 0.05 mmHg/year.
**Conclusion**

The prevalence of PEX in this study population was the highest reported, and it increased with age. The presence of PEX increased the risk of developing OAG four times. In this study a higher proportion of OAG was revealed by screening among women but not among men. The age-related IOP increase was clinically insignificant.

**Key words**

Pseudoexfoliation, glaucoma, intraocular pressure, age cohort, screening, long-term follow-up
Långtidsuppföljning av pseudoexfoliationer, ögontryck och glaukom - Epidemiologiska studier in norra Sverige


Avhandlingen är en sammanläggning av fyra delarbeten och ramberättelse.

Målen med studien

Det övergripande målet var en epidemiologisk studie av PEX, ögontryck och öppenvinkelglaukom, OAG, i en åldersgrupp i norra Sverige för att få kunskap om hur en befolkning med hög andel PEX skall tas om hand. Ytterligare ett mål var att få insikt om screening för PEX och OAG är ändamålsenligt och meningsfullt såväl mänskligt som samhällsekonomiskt.

De mer specifika målen var

- att klarrätta förekomsten och utveckling av PEX och OAG över tiden.
- att utvärdera PEX som riskfaktor för utveckling av glaukom.
- att undersöka hur PEX och grästarroperation påverkar ögontryck.
- att undersöka skillnaderna i upptäckten av OAG mellan den återkommande undersökta, screenade, gruppen och resten av åldersgruppen.
Glaukom


PEX


Undersökningen


Resultat

Förekomsten av PEX i ett eller båda ögonen var 23% vid 66 års ålder och ökade till 61% vid 87 års ålder. Antalet nya fall var 1,8 per hundra personer per år. Ögontrycket var i medeltal högre i ögon med PEX. Ögontrycket ökade 0,05 mmHg per år i genomsnitt. Förekomst av PEX medförde fyra gånger större tryckökning och ökade risken för att utveckla glaukom åtminstone 4 gånger jämfört med risken för icke-PEX ögon. Förekomsten av OAG var 2,1% vid 66 år och 25% vid 87 års ålder. Det tidigaste fallet av OAG hade diagnostiserats hos en 52-årig man. Den årliga tillkomsten av nya OAG fall var i hela åldersgruppen 0,9%, 0,5% hos personer som inte hade PEX och 2,1% hos personer med PEX.
Jämförelse visade att dubbelt så många nya OAG fall upptäcktes under uppföljningstiden bland kvinnor i den undersökta delen av åldersgruppen som i den icke undersökta. Jämförelse mellan männen i de två grupperna visade ingen skillnad.

**Diskussion**

PEX är mycket vanlig förekommande hos befolkningen i Skellefteå, men eftersom det inte finns någon tillgänglig behandling av PEX, bör man inte söka efter dessa fall. PEX förhöjer ögontrycket och ökar därmed risken för att utveckla OAG. Det är därför motiverat att uppmuntra till ögontryckkontroller efter 50 års ålder. Tryckkontroll kan ske hos optiker. Jämförelse mellan denna studie och andra publikationer visar att ögontryck över 25 mmHg kan vara en lämplig nivå för vidare undersökning av ögonläkare. Denna studie har inte omfattat hur OAG påverkar synfunktionen och livskvalitéen. Detta bör studeras innan slutsatser om vinster med screening kan dras.

**Slutsatser**

Denna studie har visat den högsta förekomst av PEX som publicerats över hela världen. Förekomsten av PEX ökade med stigande ålder. PEX ökade risken för att utveckla OAG åtminstone fyra gånger. Genom regelbundna undersökningar upptäcktes dubbelt så många nya OAG fall hos kvinnor men inte bland män.

**Nyckelord**

öppenvinkelglaukom, pseudoexfoliation, långtidsuppföljning, ögontryck, screening
LIST OF PUBLICATIONS

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals.


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III. Intraocular pressure changes over 21 years. A longitudinal age-cohort study in northern Sweden. Åström S, Stenlund H, Lindén C.

   Submitted

IV. Open-angle glaucoma in screened versus unscreened subjects. A long-term age-cohort study. Åström S, Stenlund H, Lindén C.

   Submitted
ABBREVIATIONS

ACG  Angle-Closure Glaucoma
CI   95% Confidence Interval
IOP  IntraOcular Pressure
NTG  Normal-Tension Glaucoma
OAG  Open-Angle Glaucoma
PEX  Pseudoexfoliation
SD   Standard Deviation
WHO  World Health Organization
INTRODUCTION

This study started in 1981 when I was working at the Department of Ophthalmology in Skellefteå Hospital. At that time we were following a substantial number of patients that incidentally had been observed to have pseudoexfoliation (PEX) on the anterior lens surface. We knew that there were many persons who had PEX in the population. The prevalence and incidence had never been estimated. It was also known that PEX was a risk factor for open-angle glaucoma (OAG), while the magnitude of the risk was unknown. For this reason we decided to perform this study. At that time there was a local ethics committee at the Skellefteå Hospital. Approval of the study was granted by this committee.

Glaucoma

Glaucoma is a disease characterized by degeneration of the optic nerve leading to defects in the visual field. It is the second most common cause of blindness in the world. WHO estimates that in 2010 glaucoma accounted for 8% of all blindness in the world (1).

There are different types of glaucoma, and OAG is the most common in the western countries. Angle-closure glaucoma (ACG) is the most common type among Chinese people (2). The aetiology of glaucoma is not completely understood.

The initial symptoms of OAG are discrete, and the lack of striking symptoms leads to a delayed diagnosis of the disease. For early detection, visual field examination or assessment of the optic nerve head is essential. It is estimated that more than half of the individuals with the disease are unaware of it (3-8), and that proportion is even greater in developing countries (2). Glaucoma was previously thought to be a disease of high intraocular pressure (IOP). Many studies done by screening with visual field assessment have revealed visual field defects typical for glaucoma with normal IOP (3-5, 7-11) and these are called normal-tension glaucoma (NTG). Still, high IOP is the main risk factor for developing glaucoma (12).

OAG is a disease that primarily affects elderly people. The prevalence of OAG increases with age (13, 14). Offspring of glaucoma-affected people have an increased risk (15), even though the heritabilities of OAG and increased IOP are not completely understood (16).
**Pseudoexfoliation**

PEX is produced and accumulates in the anterior segment of the eye. By microscopy it can easily be detected on the anterior surface on the lens after dilatation of the pupil. It has a central disc of grey material that corresponds to the size of the pupil, there is a surrounding free zone where the pupil moves, and more peripherally there is a spotty aggregation.

PEX on the anterior surface of the lens.

PEX is built up as an elastic fibril system of complex glycoprotein structure (17). It is produced by different intraocular cells including ciliary epithelium, vascular endothelial cells, and different cell types of the iris, trabecular endothelium, and lens epithelium.

PEX is a major risk factor for developing glaucoma. The glaucomatous effect of PEX has been shown to be mediated through elevated IOP (18). The accumulation of PEX material in the trabecular meshwork is probably the mechanism for increasing IOP. The correlation between PEX and increased IOP has been shown in many studies. (19-23). Eyes with OAG and PEX are regarded as a special type of primary glaucoma in this study and in most other Scandinavian studies. However, in other parts of the world, OAG with PEX is sometimes regarded as a secondary glaucoma.

Eyes affected by PEX have an increased risk of developing cataract, the zonula threads become weaker with time, which increases the risk at cataract surgery, the iris is atrophic, and the pupil is more difficult to dilate (24).

PEX is an age-related disorder, and the prevalence increases with age (20, 22).
Epidemiology

Glaucoma is a worldwide disease. Reported prevalences over the world vary depending on glaucoma definition, age and ethnicity (2, 25-27). Roughly 2% of the world’s population over age 40 suffer from glaucoma. OAG is the most common type in Western countries and Africa (2). In black populations the prevalence of OAG is higher, and the onset of the disease is earlier in life (2, 7).

PEX was previously thought to affect mainly people in the Nordic countries. It is easily overlooked when the pupil is not dilated. Increasing interest by ophthalmologists since the 1970s has resulting in many prevalence studies that have shown that PEX is distributed worldwide. Reported prevalences of PEX vary depending on age and ethnicity. Results, including sex distribution, from a number of population-based studies are shown in Table 1. All studies confirm an increased prevalence with age and variation in sex distribution (19-21, 28-34).

Table 1. Prevalences of PEX in population-based studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number</th>
<th>Age</th>
<th>PEX prevalence %</th>
<th>PEX prevalence female %</th>
<th>PEX prevalence men %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ekström Sweden</td>
<td>760</td>
<td>65-74</td>
<td>17.9</td>
<td>22.0</td>
<td>13.5</td>
</tr>
<tr>
<td>Ringvold Norway</td>
<td>1887</td>
<td>&gt;64</td>
<td>16.9</td>
<td>18.7</td>
<td>14.6</td>
</tr>
<tr>
<td>Kozobolis Greece</td>
<td>777</td>
<td>&gt;40</td>
<td>16.0</td>
<td>12.6</td>
<td>21.3</td>
</tr>
<tr>
<td>Nouri-Mahdavi Iran</td>
<td>405</td>
<td>&gt;50</td>
<td>13.1</td>
<td>8.1</td>
<td>18.4</td>
</tr>
<tr>
<td>Summonen Saudi Arabia</td>
<td>376</td>
<td>&gt;56</td>
<td>9.3</td>
<td>9.2</td>
<td>10.0</td>
</tr>
<tr>
<td>Krishnadas India</td>
<td>5150</td>
<td>&gt;40</td>
<td>6.0</td>
<td>4.6</td>
<td>7.9</td>
</tr>
<tr>
<td>Abdul-Rahman Burma</td>
<td>2076</td>
<td>&gt;40</td>
<td>3.4</td>
<td>No sex difference</td>
<td>No sex difference</td>
</tr>
<tr>
<td>Miyazaki Japan</td>
<td>1464</td>
<td>&gt;59</td>
<td>3.4</td>
<td>3.5</td>
<td>3.2</td>
</tr>
<tr>
<td>Mitchell Australia</td>
<td>3654</td>
<td>49-97</td>
<td>2.3</td>
<td>2.6</td>
<td>1.8</td>
</tr>
<tr>
<td>Hiller USA</td>
<td>1906</td>
<td>52-85</td>
<td>1.8</td>
<td>2.4</td>
<td>1.0</td>
</tr>
</tbody>
</table>
PEX varies with ethnicity. A higher prevalence is found among indigenous Australians than Caucasian Australians (35). PEX seems to be rare in Chinese populations (36, 37). The prevalence differs among tribes in Nepal, but the living circumstances related to the height over sea level do not seem to have any influence on the prevalence (38). A study from India shows a significantly higher prevalence of PEX among outdoor workers (39). Studies from USA indicate that the prevalence of PEX may be associated with temperature and sun exposure (40).
AIMS OF THE THESIS

The general objective of this thesis was to study the epidemiology of PEX, IOP and OAG in an age cohort in northern Sweden and to acquire knowledge about how to handle a population affected by PEX. An additional aim was to investigate the effect of screening. More specifically, the aims were:

- To assess the prevalence and incidence of PEX and OAG,
- To evaluate PEX as a risk factor for OAG and to estimate the risk of developing OAG over time,
- To study how the IOP changes with increasing age and to estimate the change if PEX is present or cataract surgery is performed,
- To investigate differences in OAG development between the screened and the unscreened parts of the age cohort, and
- To investigate the effect of screening and to evaluate if screening for PEX and/or OAG should be performed.
METHODS

Study design

This was a cohort study on PEX and OAG with two groups, one selected group, which was followed, and another group which was retrospectively analysed. The cohort is an age cohort that includes the whole population born in 1915 living in the municipality of Skellefteå in 1981.

Forty percent of the age cohort were randomly selected and examined in 1981. Suspected glaucoma cases were followed and the remaining individuals were further examined in 1988, 1995 and 2002. This group is called the screened group.

To evaluate the total number of persons in the cohort treated for OAG, medical records were sought in the archives at Skellefteå Hospital, where medical records are archived indefinitely. No subject born in 1915 was treated by the only private ophthalmologist in the region. Medical records for the whole cohort were analysed after 2002. Comparison of OAG development was done between the screened group and the rest of the cohort, called the unscreened group. Year for cataract surgery was also registered for the screened and the unscreened groups.

Study area

Skellefteå is situated about 250 kilometers south of the Polar circle. The winter is long and cold with snow half of the year, and the summer is short. In 1981 there were 74,275 inhabitants in the municipality of Skellefteå in the county of Västerbotten in the north of Sweden. Most of the inhabitants lived in the central town and the rest in small villages within 50 kilometers. The ophthalmic health care was provided by one hospital clinic and one private ophthalmologist. In the late nineties there was also another private ophthalmologist for a few years.

Study population and screening methodology

People born in 1915 were selected for the study because they were assumed to be old enough to have developed PEX in a significant proportion. They were recently retired and would have time to participate in the study. 856 residents were born in 1915 according to the official records from the Swedish Census Bureau. They were all numbered and 389 (45%) were selected by a random table. Twenty-nine of those persons had visited the
eye-clinic during the last 12 months and full medical information was obtained from their medical records. Written information about the study and an invitation to an ophthalmic examination was sent to each of the remaining 360 persons. 310 persons accepted the invitation so the screened group included 339 persons. After the initial examination participants diagnosed as having glaucoma or increased risk for developing glaucoma were taken care of according to normal clinical praxis by ophthalmologists at Skellefteå hospital. At follow-up visits in 1988, 1995 and 2002 those alive were invited to re-examination unless we found medical records containing information from the same year.

**Eye examination**

The first and last examinations were performed by the same observer (S.Å.). The second and third examinations were performed by three different persons.

**Intraocular pressure:** Throughout the study the IOP was measured with a Goldmann applanation tonometer mounted on a Haag-Streit slitlamp. IOP was measured once in each eye. The same assistant performed all tonometry measurements during the first and second examinations. Two other assistants performed the tonometry during the third and fourth examinations.

**Pupil dilatation:** Pupil dilatation was done with one drop of tropicamide and phenylephrine. To evaluate the efficacy of this dilatation the pupil size was measured in the eyes of the first forty-two individuals at the initial examination. 93% and 99% of the eyes with and without PEX, respectively, got a pupil width >5 mm, which was found to be enough for detection of PEX.

**Anterior segment evaluation:** After pupil dilatation the presence of PEX was investigated by detailed slit lamp assessment. PEX was identified as a grey layer on the anterior surface of the lens capsule. For individuals where information was obtained from medical records, PEX were considered to be present if positively mentioned. After cataract surgery PEX is difficult to identify. Therefore, eyes without PEX before cataract surgery were considered to be PEX free during the rest of the study.

**Optic disc evaluation:** In 1981 binocular assessment of the optic disc was done using a Goldmann lens after dilatation of the pupil. From 1988 and onwards a 90-D lens was used. The disc was graded as glaucomatous or suspected glaucomatous if one or more of the following criteria were present: 1) totally excavated optic disc, 2) excavated to the disc margin, 3) cup-disc
asymmetry of 0.2 or more between the eyes, 4) vertical excavation ratio greater than horizontal, or 5) optic disc haemorrhage.

**Visual field testing:** In all eyes where the optic disc was graded as glaucomatous or suspected glaucomatous or where the IOP exceeded 22 mmHg a visual field test was performed in 1981. The screening program in the Competer 350 computerised automatic perimeter (Bara Elektronik AB, Lund, Sweden) was used. A supplementary manual perimetry was performed if needed. At follow-up visits and for some of the cases taken care of between the screening visits Competer threshold program, Ring perimetry and Goldman perimetry were used. At the highest ages there were difficulties in obtaining reliable visual field measurements, and visual field testing sometimes had to be omitted.

**Glaucoma diagnosis:** In 1981 the diagnosis of glaucoma was based on the presence of a visual field defect consistent with glaucoma and not explainable on other grounds. For definition of visual field defects we used the criteria suggested by Heijl (41). At the re-examinations in 1988, 1995 and 2002 the study criteria for visual field defects for OAG diagnosis were not always fulfilled. Instead, at least two of the following three criteria had to be fulfilled for an OAG diagnosis at follow-up: 1) IOP of >30 mmHg at the time of diagnosis or an IOP elevation of >10 mmHg from base line, 2) glaucomatous excavation of the optic disc, or 3) visual field defect consistent with glaucoma. Normal-tension glaucoma (NTG) was defined as no more than one registered pressure reading >21 mmHg and none >24 mmHg at the time of diagnosis. Ocular hypertension was defined as IOP >23 mmHg but not fulfilling the remaining OAG criteria.

Cases with OAG and suspected OAG during follow-up were taken care of according to clinical praxis by ophthalmologists at Skellefteå hospital between the study visits. Due to a great propensity to start treatment on the second eye if OAG was present in the first eye, it was difficult to unambiguously identify bilateral glaucoma cases fulfilling our glaucoma criteria. Therefore, bilateral OAGs were not extensively investigated.

The same criteria for OAG were used for the unscreened group as for the screened group except for the IOP elevation of >10 mmHg from base line, since there was no baseline measurement in the unscreened group. This means that the diagnosis was based on at least two of following criteria: 1) IOP of >30 mmHg at the time of diagnosis, 2) glaucomatous excavation of the optic disc, or 3) visual field defect consistent with glaucoma. NTG and PEX glaucoma were classified as OAG.

In the comparison study between the screened and unscreened groups, the year for starting treatment was used as the year for diagnosis for both the screened and the unscreened group of the cohort. This was done due to the
difficulties in determining the exact date for diagnosis of OAG. Even if the criteria for OAG were not fulfilled when treatment was started, they were fulfilled at a later time. As a consequence the years for OAG diagnosis in the screened group in paper IV differed from the years used in paper II. In paper II the dates of diagnosis were estimated to be in the middle of the screening intervals.

Statistical methods

**Paper I**

The ratio between the number of subjects with PEX in at least one eye and the number of screened individuals was used to calculate the prevalence of PEX. The 95% confidence intervals (CIs) were adjusted with finite population factor. To test differences in proportion, the $\chi^2$-test was used, and the paired t-test was used to test differences in IOP between eyes within individuals.

**Paper II**

The prevalences of OAG and PEX at each age were calculated as the ratio between the number of subjects with OAG or PEX in at least one eye and the number of individuals in the cohort at that age. The 95% CIs of the prevalences were estimated using the large-sample form of CI for a proportion.

The incidences of OAG and PEX were calculated for each period of follow-up at age 66–73, 73–80 and 80–87 years based on those free of OAG and free of PEX, respectively, at the start of each follow-up period. Since the exact date of OAG or PEX occurrence was unknown it was assumed that it occurred after three and a half years, i.e. in the middle of the age interval. Deaths were treated as censored observations contributing with time from start of follow-up to death in the calculation of person times. The Fisher CIs for incidences of OAG and PEX were also calculated.

The chi square test was used to compare prevalences. Prevalences for different age intervals were compared using chi square test for trend. Pairs of incidences were compared with the mid-P test. To compensate for multiple tests Bonferroni adjustment of p-values was used.
**Paper III**

IOP data from each individual were summarized using means and standard deviations (SDs). The impact of sex, eye (right or left), PEX, cataract extraction and time on IOP was analysed using a linear mixed model. The benefit of the mixed model is that it handles correlated data.

**Paper IV**

The proportions of men and women in the screened and the unscreened groups were compared using the chi-square test. The Kaplan-Meier method was used to analyse length of life and occurrence of new cases of OAG in both groups. Comparison between the two groups was done using the Log Rank-test. Glaucoma cases diagnosed before the investigation in 1981 were excluded.

In all papers a p-value <0.05 was considered statistically significant. IBM SPSS v 20 was used for all calculations.
RESULTS

The cohort

The number of persons in the cohort during the study period is illustrated in Fig 1.

Fig 1. Flow chart for the age cohort born in 1915, living in the municipality of Skellefteå in 1981.
**Screened group**

Seven patients were found to have OAG at the first examination in 1981 giving a prevalence of 2.1% (CI: 0.9-3.2%). Six of these had OAG with PEX, and three of these six cases were previously known of which one was bilateral. One case with bilateral NTG with severe visual field defects was found. Baseline flow chart for the screened group is shown in Fig 2.

![Flow chart for the screened group at the first examination in 1981.](image)

**PEX in the screened group**

The overall prevalence of PEX increased with age (p<0.001) from 23% (CI: 20-26%) at age 66 to 61% (CI: 50-71%) at age 87 years in the screened group. The prevalence was higher in women at age 66 (p=0.002) and at age 87 (p=0.02). PEX was bilateral in one third of the persons with PEX at age 66 and in more than 50% of the persons at age 87 years.

The annual incidence of PEX was counted for each seven-year period. The annual incidence for the total follow-up period was 1.81% (CI: 1.35-2.39) with no significant difference between the sexes (women 2.05% CI: 1.41-2.91%, men 1.50% CI: 0.89-2.37%). In Table 2 the annual incidence of PEX with respect to age intervals and sex in the screened group is shown.
Table 2. Annual incidence of PEX with respect to age intervals and sex in the screened group.

<table>
<thead>
<tr>
<th>Age interval</th>
<th>Female</th>
<th>Male</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Person years</td>
<td>Incidence (%)</td>
<td>CI</td>
</tr>
<tr>
<td>67 to 73</td>
<td>16 799</td>
<td>2.00 1.14-3.25</td>
<td>10 1477</td>
</tr>
<tr>
<td>73 to 80</td>
<td>6 482</td>
<td>1.25 0.45-2.71</td>
<td>7 838</td>
</tr>
<tr>
<td>80 to 87</td>
<td>10 278</td>
<td>3.60 1.72-6.62</td>
<td>1 164</td>
</tr>
</tbody>
</table>

IOP in the screened group

One hundred and twenty-nine persons (38%) in the screened group were alive when the study ended in 2002. Fifty persons had received glaucoma treatment and were excluded from the IOP calculations after treatment had started. The IOP from age 66 to 87 years increased by 0.05 mmHg/year (p<0.001) provided no cataract surgery had been performed. The increase was largest during the first seven years of observation (0.05 mmHg/year). During the last interval from 80 to 87 years the IOP declined (-0.02 mmHg/year).

Cataract extraction was performed in seventy persons. For 14 individuals there were no IOP registrations after cataract surgery, and twenty-one were treated for glaucoma before surgery. Excluding these, the calculation of IOP after cataract surgery, was based on 91 registrations in 35 individuals. No change in IOP over time was found if persons who had had cataract surgery were included in the model. Cataract surgery reduced the IOP by 2.13 mmHg (p<0.001) and PEX increased the IOP by 2.05 mmHg (p<0.001). The yearly IOP increase in PEX eyes was four times greater than in non-PEX eyes: 0.12 (p=0.001) vs. 0.03 (p=0.002) mmHg, respectively. The mean IOP in women was 1.22 mmHg higher than in men (p=0.001).

In the IOP calculations in 1981 (paper I), three previously known OAG patients and one patient treated for ocular hypertension were excluded. The mean IOP was higher in eyes with PEX (17.3 mmHg, SD 4.5 mmHg) than in eyes without PEX (15.7 mmHg, SD 3.7 mmHg; p<0.001). In individuals with unilateral PEX, the mean IOP in the eye with PEX was higher than the non-PEX eye (p<0.001). Comparing mean IOP in non-PEX eyes in individuals
with unilateral PEX, with the IOP in individuals without PEX, there was no significant difference. In the measurements of IOP in the longitudinal study (paper III), together with the four cases mentioned above (three with OAG and one with ocular hypertension), another two individuals with treatment for ocular hypertension and two patients with secondary glaucoma were excluded. In the cross sectional study from 1981 (paper I) these four were not excluded. Recalculation of the values from 1981, after excluding these four treated cases, made a small but non-significant change in the different mean IOP values.

**OAG in the screened group**

There were 39 persons with OAG in the screened group diagnosed before the study ended in 2002. Thirty-two cases were detected after the first examination. Thirteen of these had OAG without PEX. Fifteen had PEX at the first screening and later developed OAG. Four of the new 32 cases had neither OAG nor PEX at the first screening. Two of these were found to have both OAG and PEX at the next screening in 1988. The other two had developed both PEX and OAG at the second screening in 1995. These four cases were classified as OAG without PEX in paper II. The prevalence of OAG increased with age (p<0.001) from 2.1% at age 66 to 24.5% at age 87. The overall incidence of OAG for the whole study period was 0.9% (CI: 0.6-1.3%). For OAG without PEX it was 0.5% (CI: 0.2-0.9%) and with PEX 2.1% (CI: 1.2-3.3%). PEX was found to increase the risk for glaucoma four-fold as shown in Table 3. If the four new OAG cases, which were classified as OAG without PEX in paper II, instead were classified as OAG with PEX, the results were somewhat changed. Of the new OAG cases, 72% had PEX. The overall annual incidence for OAG without PEX would be 0.3% (CI: 0.2-0.6%) and the incidence for OAG with PEX would be 2.4% (CI: 1.6-3.5%). PEX increased the risk for OAG seven-fold (Table 4). If the four cases were excluded, then PEX increased the risk for OAG six-fold.
Table 3. Annual incidence of OAG with and without PEX with respect to sex in the screened group as presented in paper II. Nine female OAG cases were classified as OAG without PEX.

<table>
<thead>
<tr>
<th></th>
<th>Age 66 to 87</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No PEX</td>
<td>PEX</td>
<td></td>
</tr>
<tr>
<td>Female OAG</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Person years</td>
<td>9</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Incidence (%)</td>
<td>1459.5</td>
<td>622.5</td>
<td></td>
</tr>
<tr>
<td>RR</td>
<td>0.62</td>
<td>2.41</td>
<td></td>
</tr>
<tr>
<td>CI</td>
<td>1</td>
<td>3.91</td>
<td>1.75-8.74</td>
</tr>
<tr>
<td>Male OAG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Person years</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Incidence (%)</td>
<td>1182</td>
<td>299</td>
<td></td>
</tr>
<tr>
<td>RR</td>
<td>0.34</td>
<td>1.34</td>
<td></td>
</tr>
<tr>
<td>CI</td>
<td>1</td>
<td>3.95</td>
<td>1.08-14.42</td>
</tr>
<tr>
<td>Total OAG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Person years</td>
<td>2641.5</td>
<td>921.5</td>
<td></td>
</tr>
<tr>
<td>Incidence (%)</td>
<td>0.49</td>
<td>2.06</td>
<td></td>
</tr>
<tr>
<td>RR</td>
<td>1</td>
<td>4.19</td>
<td></td>
</tr>
<tr>
<td>CI</td>
<td></td>
<td>2.10-8.37</td>
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</table>

Fifty persons developed PEX after the first screening in 1981. As mentioned previously, four of these developed OAG and PEX during the period prior to the next screening. There was only one OAG case without PEX who developed PEX several years after glaucoma diagnosis. That case was classified as OAG without PEX.

Table 4. Annual incidence of OAG with and without PEX with respect to sex in the screened group. Four out of nine female cases, classified as OAG without PEX in paper II, have been reclassified as OAG with PEX in this table.

<table>
<thead>
<tr>
<th></th>
<th>Age 66 to 87</th>
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<tbody>
<tr>
<td></td>
<td>No PEX</td>
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<td>Female OAG</td>
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<td>Person years</td>
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<td>Incidence (%)</td>
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</tr>
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</tr>
<tr>
<td>Male OAG</td>
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</tr>
<tr>
<td>Person years</td>
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<td>4</td>
<td></td>
</tr>
<tr>
<td>Incidence (%)</td>
<td>1182</td>
<td>299</td>
<td></td>
</tr>
<tr>
<td>RR</td>
<td>0.34</td>
<td>1.34</td>
<td></td>
</tr>
<tr>
<td>CI</td>
<td></td>
<td>1.08-14.42</td>
<td></td>
</tr>
<tr>
<td>Total OAG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Person years</td>
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<tr>
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Comparison of OAG between the screened and the unscreened group

The total number of OAG cases was 79 with 39 in the screened group and 40 in the unscreened group. Thirty-three OAG cases in the screened group and 31 in the unscreened group were diagnosed during the screening periods between 1981 and 2002. In the comparison study (paper IV), the year for start of treatment was used as the year for diagnosis. This means that the number of new OAG cases in the screened group differed from the number in the incidence/prevalence study (paper II). There were three persons in the screened group who were treated for OAG without fulfilling our criteria for OAG at the first screening. These three were classified as not having OAG in paper I. Later these three cases developed visual field defects and were reclassified as OAG cases. Since we used year for start of treatment as year
for OAG diagnosis in paper IV these three cases were classified as known OAG in 1981 in paper IV. Thus, six out of 39 in the screened group and nine out of 40 cases in the unscreened group were treated before the investigation started in 1981. All these 15 cases, who had sought eye care due to visual symptoms prior to the start of the study and had PEX, had IOP over 25 mmHg at start of treatment, and the youngest was 52 years old. The four OAG cases in the screened group, diagnosed at the first screening in 1981, were included in the comparison of new cases between the groups.

Comparison of new OAG cases between the two groups showed a trend towards a higher incidence in the screened group, but this trend was not statistically significant (p=0.053). Separate analyses for women and men showed more new cases of OAG in women in the screened group than women in the unscreened group (Fig. 2a) (p=0.035). There was no difference between men in the two groups (Fig. 2b) (p=0.58).

![Fig 2a. Comparison of new OAG cases in women between the screened group and the unscreened group (p=0.035).](image1)

![Fig 2b. Comparison of new OAG cases in men between the screened group and the unscreened group (p=0.58).](image2)
There were 3 persons with NTG in the screened group and none in the unscreened group. Fifteen patients, eleven in the screened group and four in the unscreened group, were treated for glaucoma without fulfilling our stated criteria for glaucoma during the follow-up time. They all had ocular hypertension with two exceptions. In the screened group all but one had PEX. They were classified as not having glaucoma. Two persons in the screened group and two in the unscreened group had other forms of glaucoma before the study started and were excluded from the comparison.

**Mortality**

There was no difference in mortality between the screened and the unscreened groups (p=0.149). The mortality was higher for men in both groups (p<0.001). There was no difference in mortality within sexes between the two groups (p=0.733 men, p=0.350 women). There was no difference in mortality between individuals with and without PEX in the screened group.
DISCUSSION

The cohort

It is important to emphasize that this study was conducted in an age-cohort. The subjects were born during the First World War. We did not record their places of birth, but the infrastructure in Northern Sweden was bad during their youth, moving long distances was difficult, and therefore people seldom moved far from their place of birth. Their migration during their lifetime was not investigated, but after retirement very few of them left Skellefteå permanently. There are no reasons to believe that this age cohort differs in any important ways from the rest of the population in Skellefteå, at least the part born in the first part of the 1900s. However, many things have changed since this age cohort was born, and conclusions about the population in Skellefteå today should be drawn with caution.

OAG

The prevalence of OAG increased from 2.1% at age 66 to 24.5% at age 87 years in this study. Differences in disease definition influenced the calculated prevalence. There is currently no worldwide general consensus on the definition of OAG (42). Visual field defects are generally required as a part of the defining criteria (43). However, in the USA a visual field defect is no longer required as a part of an OAG definition (44). Methods for finding incident glaucoma cases have been evaluated in several investigations (45). In the 1981 screening we used the criteria for glaucomatous optic neuropathy commonly used at that time: cup/disc asymmetry of 0.2 or more, vertical excavation greater than horizontal as suggested by Weisman (46), optic disc haemorrhages and obvious damage such as total excavated disc or excavation to the disc margin. The same criteria were used at follow-up visits. Other criteria for assessment of optic nerve head damage have later been evaluated and suggested (47, 48), but these were not used in our study. A screening test for a low prevalence disease such as OAG must be highly specific. In a meta-analysis the specificity for ophthalmoscopy and tonometry proved to be 94% (45). This means that by screening with ophthalmoscopy and tonometry false positive cases would be rare in our study. On the other hand, the sensitivity for ophthalmoscopy and tonometry ranged from 11% to 100% (45), making the risk of false negative cases a reality in our study.

An underestimation of NTG would lead to an overestimation of the risk ratio for OAG with PEX cases with high IOP. Only three cases (7.2%) of NTG were diagnosed, which is far fewer than in cross-sectional studies where the
Discussion

screening is based on visual field tests (3, 7, 9, 49). In the Tierp survey, where the prevalences of OAG (5.3%) and PEX (17.2%) are high between 65 and 74 years, NTG cases account for 18% of all glaucoma cases (5). In Skåne in the south of Sweden, where the prevalence of OAG is 0.93% between 56 and 70 years of age (3), and 1.5% between 57 and 76 years (50) and PEX seems to be rare, the NTG prevalence is more than 50% (9). Apart from the suspicion of false negative cases of NTG in our survey, an additional explanation for the low prevalence of NTG might be that PEX transforms a number of possible NTG to high-pressure OAG with PEX.

**OAG incidence**

The annual incidence of OAG (0.9%) in our screened group was higher than those reported in studies with a predominantly white population (51, 52) but correspond fairly well with reports from high-risk populations (11, 49).

Thirty-two new cases of OAG were found during follow-up. Categorization of the four individuals with both OAG and PEX diagnosed at the same event was not possible, since we did not know what came first, PEX or OAG. From a statistical point of view these individuals should have been excluded. However, they still had glaucoma with visual field defects. By including these four cases as OAG with PEX gives an overall annual incidence of 2.4% for OAG with PEX (Table IV). Classifying glaucoma cases that have PEX and OAG at the time for glaucoma diagnosis as OAG with PEX, is part of our standard clinical practice. The new incidence calculation shows that PEX increases the risk for OAG seven-fold as compared with four-fold in the previous calculation.

Four out of seven OAG cases were not previously known at the first screening event in 1981. Even though the number is small it corroborates other studies where more than fifty per cent of glaucoma cases are undiagnosed (3-8). In the long-term comparison of incidence of OAG between the two groups in the cohort there were about twice as many new OAG cases among women in the screened group than among women in the un-screened group. When the incidence of OAG between women and men was compared in the screened group or in the unscreened group there was no significant difference. The higher incidence in women in the screened group was expected. The lack of difference among men is more difficult to explain. The absolute number of men was small, but there was not even a tendency towards a higher incidence among the screened men. Men were car-drivers to a higher extent in the population born in 1915 (53) and hunting is mainly a male activity (54), which might have made men more aware of the necessity to have good vision, and therefore men were more prone to ask for eye examinations.

Fifteen persons, 11 in the screened group and four in the unscreened group, were treated for glaucoma without fulfilling our criteria for OAG. Topical
medication for lowering IOP in ocular hypertension has been shown to delay the development of optic disc and visual field damage (55). PEX is the only factor related to the increase of IOP in early glaucoma cases (56). Lowering IOP in glaucoma patients decreases the risk for progression of visual field defects (57). Perhaps some of the cases with ocular hypertension and PEX in our study would have been included in the OAG group if not treated with IOP-lowering medication.

PEX

To our knowledge, this study has revealed the highest prevalence of PEX in a population described in the literature. The regional distribution of PEX in Sweden varies. In Skåne, which is in the south of Sweden, the prevalence seems to be low (3), while in the middle of Sweden it is higher (17.2% in the age group 65-74 years) (32). The regional tendency is similar in Finland with a higher prevalence in northern Finland (58-60). The higher prevalence in the north of the Scandinavian countries might lead to speculations about environmental influences on PEX development.

Although the aetiology of PEX remains largely unknown, several possible mechanisms have been discussed. Hereditary factors have been in the focus of interest. Genetic studies have managed to identify single-nucleotide polymorphism in the LOXL1 gene on chromosome 15 associated with PEX and OAG with PEX (61). This haplotype is very common in Sweden and Iceland (61). Similar allelic architecture is found among the Caucasian population in Australia, but the lifetime incidence of PEX is nine-fold lower (62). The sex distribution of PEX varies (Table 1). Racial differences are reported from Nepal (38) and Australia (35). In a compilation on PEX publications it is suggested that current data support the hypothesis that genetic predisposition and environmental factors such as ultraviolet (UV) radiation or infectious agents cause PEX production (63). However, the UV light from the sun is generally not considered to be a problem in this northern part of the world, and any unusual sources of UV exposure in this population is unlikely. Historically the communities of northern Sweden were isolated for long periods due to lack of infrastructure such as railroads, etc. A hereditary factor seems likely, but some unknown environmental factor might also contribute to the high prevalence of PEX in the present study.

The incidence of PEX was 1.81% per year during the 21-year period. There was no significant difference in incidence between females and males. This incidence estimation is unique, and there are no other prospective studies with which to compare.
IOP

The mean IOP was significantly higher in eyes with PEX than without PEX. This is in accordance with other studies (19, 21, 23, 29, 64-66). Cataract surgery lowered the IOP, which confirms the results in other reports (67-71). The IOP increased significantly over time if the cataract-extracted eyes were excluded. If cataract-extracted eyes were included the increase was non-significant. Other longitudinal studies present different results with a yearly mean IOP change that ranges between -0.12 and 0.051 mmHg (10, 69, 72-75). In the black Barbados population with a high prevalence of OAG (13) the yearly increase is 0.044 mmHg in the 40-84 year age range of African origin (75), which is slightly lower than our mean rate of 0.05 mmHg/year. The frequency of cataract surgery or prevalence of PEX is not stated in that report.

In individuals with unilateral PEX, the mean IOP in the PEX eye was significantly higher than the mean IOP in the other eye. The mean IOP in the non-affected eye in individuals with unilateral PEX was not significantly higher than the IOP in cases without PEX. It has been shown that the glaucomatous effect of PEX is mediated though elevation of IOP and not by PEX per se (18). The mechanism for PEX to increase the IOP is probably by occluding the trabecular meshwork. The amount of chamber angle pigmentation is more pronounced in OAG with PEX than in non-glaucomatous eyes with PEX (76). Still, there are some eyes that have PEX for a long time without elevation of IOP. Among indigenous Australians, where the prevalence of PEX is also high (12.7% over age 60), PEX it is not associated with ocular hypertension or glaucoma but with corneal keratopathy (35). It seems reasonable to think that other factors besides PEX are necessary for the IOP increase in PEX eyes. One patient at age 58 years was found to have unilateral OAG with PEX and the IOP was 60 mmHg. She developed PEX, but never OAG, later in life in the other eye. She reported that she read thrillers late at night and had no complaints about her vision one month before she died at age 91 years.

The explanation for the difference in the mean IOP in 1981 between the two different estimations in 1981 (papers I and III), is explained by the fact that four persons with IOP-lowering treatment were included in paper I but not in paper III. Recalculation of the mean IOP after excluding those four individuals, did not change the statistical significance of the difference between IOP values in PEX and non-PEX eyes.

Screening

PEX is a sign that does not fulfill the demands for screening (77); it is not a serious health problem per se, there is no available proven treatment, and
even though PEX leads to an increased risk for OAG and acceptable screening methods are available, it should not be screened for.

General population screening for OAG is not cost-effective, but targeted screening of high-risk groups may be (45). This conclusion is based on a Cochrane systematic review and an economic model, which is highly sensitive to parameters with considerable uncertainty such as societal and health service costs for visual impairment. For screening for OAG, the prevalence of OAG should be 3-4% at the age 40 (45). In the present study the prevalence was only 2.1% at 66 years of age in the screened group. This strongly suggests that a screening procedure would not be cost-effective by the criteria used in the Cochrane report. However, the conclusions of the Cochrane report were drawn from several studies on treatment effects in subjects with a low frequency of PEX glaucoma. More than one out of four persons over 65 years of age in Skellefteå has PEX, and therefore they have about a five-fold increased risk for OAG. The progression rate for PEX glaucoma is twice as fast as non-PEX glaucoma in untreated cases, and OAG with PEX is generally considered to have a worse prognosis with a faster course of the disease than non-PEX glaucoma (78). Furthermore, in a clinical material, in treated cases with OAG, the presence of PEX is not associated with a faster progression of visual field defects (62). Thus, there are arguments for OAG screening in a population with a high prevalence of PEX.

The risk for visual disability during a person’s lifetime is greater when the disease debuts at a lower age (79). Fifteen persons in our cohort were diagnosed with OAG before 1981 and have the greatest risk of serious glaucoma damage due to a longer expected life with the disease. These cases, which were diagnosed prior to age 66, all had IOP over 25 mmHg in the glaucomatous eye when the treatment was started, and the youngest was only 52 years old. To find those cases with greatest risk, the screening should start at the age of 50 years, which is in concordance with the suggestion in the Cochrane report (45). The yearly IOP increase in PEX eyes (0.12 mmHg) is four-fold greater than in non-PEX eyes. The annual incidence of OAG with PEX before the survey started is unknown, but from the age 66 years it was 2.4% per year in eyes with PEX. Therefore, the optimal screening interval has yet to be established, but a ten-year interval seems to be too long.

By screening with IOP and optic nerve assessments, the specificity is high (45), but cases with NTG might be missed (5, 9). In our population very few NTG cases were found. However, it is also unlikely that many persons with NTG that gave considerable visual disability would have stayed undetected during follow up. The low prevalence of NTG would not make screening with visual field testing cost-effective. In addition, delay of treatment of OAG with early visual field defects, does not seem to influence vision-targeted quality of life (80, 81). According to the Cochrane report, a test with automated
classification, followed by assessment for test positives, is the most cost-effective. IOP screening would be such a test and could be done by opticians. There was a general consensus in the professional groups in the Cochrane report to include an IOP level of 26 mmHg as cut off (45). Putting a cut off at 26 mmHg would have detected most of the OAG cases in our cohort. However, high-pressure OAG with PEX progresses faster, and persons with IOP in the upper span of normality are at risk and should be encouraged to repeat the IOP measurements. An upper age-limit for this screening is uncertain. It is estimated that in untreated cases of OAG, progression to blindness in at least one eye occurs after approximately 23 years (45). We do not know the impact of undiagnosed glaucoma on visual disability and on quality of life in the elderly population. The visual disability due to OAG and the inconvenience of screening and follow-ups for the participants should be further investigated.
CONCLUSIONS

- This long-term study showed that the prevalence of pseudoexfoliation (PEX) syndrome in northern Sweden was the highest that has ever been reported. Every fourth individual in the studied population, an age cohort born in 1915 and living in Skellefteå in 1981, was affected at age 66 years. The prevalence increased with age and reached 61% at age 87 years. The incidence was estimated to be 1.81% per year.

- The incidence of open-angle glaucoma (OAG) was high in this population, and PEX glaucoma was the most common type of OAG. The prevalence of OAG increased with age and was very high among the 87-year-olds.

- The annual increase of IOP was four times higher in PEX eyes than in non-PEX eyes. The IOP rose slowly with increasing age in the interval of 66 to 80 years. The increase was minute and was completely blunted by cataract surgery, which lowered the IOP, while age and PEX increased the IOP.

- In this population, with a high prevalence of PEX, OAG was diagnosed twice as often among screened women than among unscreened. No similar effect was detected in men.

- Screening for PEX revealed a great number of PEX cases with at least a four-fold increased risk for developing OAG. Screening for OAG detected a substantial number of previously unknown glaucoma cases. No unambiguous conclusion about the value of screening for OAG could be drawn from these study results. This is because the health service costs, the impact of undiagnosed glaucoma on visual function and quality of life in the elderly, and the societal costs for visual impairment have not been adequately evaluated.
ACKNOWLEDGEMENTS

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Thanks to the women and men born in 1915 and living in Skellefteå in 1981-2002 for their invaluable contributions to this study.

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REFERENCES


