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Open-Angle Glaucoma and Mortality

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Abbreviations

OAG – Open Angle Glaucoma

IOP – Intra Ocular Pressure

ACG – Angle Closure Glaucoma

SMR – Standardized Mortality Ratio

HR – Hazard Ratio

Abstract

Purpose

To evaluate whether patients with Open-angle Glaucoma (OAG) has increased all-cause mortality compared to patients without OAG.

Methods

Standardized mortality ratio (SMR) was calculated for patients with and without OAG in a population based cohort study comprised of patients from a population survey expanded with patient data gathered from glaucoma journals. A total of 1763 people (age 65-74 at baseline examination) were included. The mortality ratio was standardized for age and sex. In addition, Cox proportional hazards model was used to calculate a Hazard Ratio for OAG and covariates that could affect the result. All covariates were adjusted for each other.

Results

SMR calculations adjusted for age and sex showed a SMR of 0.99 (95% CI, 0.87-1.14) between OAG and non-OAG patients. Cox proportional hazard model gave a Hazard Ratio of 1.04 (95% CI, 0.91-1.19) between the two groups.

Conclusion

There is no association between OAG and all-cause mortality.

Populärvetenskaplig sammanfattning

Bakgrund

Glaukom är en grupp ögonsjukdomar som är den näst vanligaste orsaken till irreversibel blindhet globalt. Sjukdomen är kronisk och progressiv. Den orsakas av förlust av nervfiber i synnerven vilket ger minskat synfält och i förlängningen, blindhet. Förlusten av nervfibrer beror ofta på ökat tryck i ögat, men inte alltid. Det uppskattas att över 60 miljoner människor har någon form av glaukom och av dessa är ca 8.4 miljoner blinda till följd av sjukdomen. Antalet fall av glaukom ökar ständigt. År 2020 är det uppskattat att 79.6 miljoner människor kommer att ha glaukom varav 74% kommer att vara öppenvinkelglaukom.

Flera studier har utförts för att utreda sambandet mellan öppenvinkelglaukom och mortalitet. Resultaten av dessa studier har dock inte varit konklusiva. Somliga studier har visat att det föreligger en ökad mortalitet hos patienter med öppenvinkelglaukom jämfört med patienter utan glaukom, medan andra har påvisat att mortaliteten är lika mellan grupperna. Eftersom sjukdomen blir allt vanligare är det av intresse att utreda om det finns någon association mellan öppenvinkelglaukom och dödlighet, för att ta ställning om utökad screening, tidigare behandling eller liknande åtgärder.

Syfte

Syftet med denna studie var att utreda huruvida patienter med öppenvinkelglaukom har ökad dödlighet jämfört med patienter utan öppenvinkelglaukom.

Material och metod

Studien är en kohortstudie som baserades på en befolkningsundersökning med uppföljande ögonundersökning på ögonmottagningen i Tierp. Undersökningen pågick från 1984 till 1986 och patientdata från denna utgjorde ungefär halva studiematerialet. Kohorten expanderades med data insamlad från glaukomjournaler som hade upprättats efter ögonundersökningar på samma klinik mellan 1978 och 2007. Alla patienter var mellan 65 och 74 år gamla vid första undersökningstillfället. Efter exklusion återstod 1763 patienter.

Standardiserad relativ risk för mortalitet beräknades mellan patienter med och utan öppenvinkelglaukom. Detta justerades för ålder och kön. Vidare beräknades en hazard ratio mellan

grupperna genom Cox proportionell regressions analys, där resultatet justerades för flertalet riskfaktorer.

Resultat

Vid första undersökningen hade 314 patienter definitivt öppenvinkelglaukom. Vid slutpunkten för studien hade 1500 patienter gått bort varav 261 med öppenvinkelglaukom. Den relativa risken för död justerat för ålder och kön var 0.99 mellan öppenvinkelglaukomgruppen och gruppen utan. Hazard ration som justerades för flertalet riskfaktorer var 1.04 men saknade signifikans.

Slutsats

Studien visar att patienter med öppenvinkelglaukom inte har ökad dödlighet jämfört med patienter utan öppenvinkelglaukom.

Background

Epidemiology

Glaucoma is a group of eye diseases which is second most common cause of blindness world-wide and the most common cause of irreversible blindness.¹ It is estimated that over 60 million people currently suffer from glaucoma of whom 8.4 million are blind as a cause of the disease.² Age is an established risk factor for glaucoma³, and since life expectancy in general is increasing, glaucoma is becoming more and more common.⁴ By 2020 it is estimated that 79.6 million people will have some type of glaucoma, most of which will have Open-Angle Glaucoma (OAG).⁵ Open angle glaucoma is the most common type of Glaucoma in people with African or European ancestry, in Asian populations Angle-closure glaucoma (ACG) is more common.⁶

Etiology

As with many diseases the pathogenesis of OAG is yet to be fully understood. Traditionally glaucoma has been attributed to elevated intra-ocular pressure (IOP) caused by decrease in outflow and/or increase in aqueous fluid production. The aqueous humour is secreted from the ciliary epithelium and fills both chambers of the eye. It functions as a medium of transport for nutrients in the eye, contains immunoglobulins which protects the eye from pathogens and keeps the IOP up to expand the eye and give it a spherical shape. It is drained through the posterior chamber into the anterior chamber, and exits the eye through two different paths. First of which is Schlemm's canal through the trabecular meshwork. The second path for the aqueous to exit is through the uveoscleral meshwork. (Figure 1 and 2.)

Even though increased IOP generally leads to damages of the optic nerve head it does not explain all the pathogenesis in OAG. The definition of open-angle glaucoma is progressive loss of axons in the optic nerve. In some cases, patients with glaucoma experience vision field loss without increase in IOP and others have increased IOP but do not develop any symptoms of glaucoma. The individual sensitivity of the optic nerve to increased IOP is thought to be dependent on differences in the characteristics of the optic nerve. Low cerebrospinal fluid pressure around the nerve can offer an explanation why people who have a IOP within normal range can develop glaucoma.^{7,8} Other metabolic differences such as circulatory deficiency and oxidative stress is also thought to cause Glaucoma.⁹

Types of glaucoma

Glaucoma is a group of eye diseases, which are categorized according to the angle of the anterior chamber of the eye (OAG/ACG) and etiology (primary or secondary glaucoma). OAG is a chronic disease with a slow rate of progression where the first symptom may be peripheral vision field loss. The classic progression of OAG is peripheral vision loss followed by, if untreated, central vision loss and by extension blindness. On the other side of the spectrum is ACG which most often is an acute condition where the anterior chamber angle is narrowed or fully closed which in turn can lead to a drastic increase in IOP followed by damages to the optic nerve. This can lead to complete irreversible blindness within hours to days. Secondary glaucoma is characterized by increased IOP due to eye diseases such as neovascularization after retinal thrombosis or trauma.

Risk Factors for glaucoma

There are several established risk factors for glaucoma. In the Nordic countries increased IOP and pseudoexfoliation are closely associated with OAG.¹⁰ The incidence of OAG is closely related to age. The prevalence of OAG in American adults under the age of 55 is less than 1 percent, whilst at age 80 or over the prevalence is over 7%.¹¹

The progression of OAG is also highly dependent on race. Glaucoma is most common in people of African descent.¹¹ The progression of glaucoma differs between ethnicities as well. For instance, blindness caused by glaucoma was 6.6 more common in black population compared to Caucasian population when adjusted for age. Even the onset of blindness is on average 10 years earlier in black populations compared to Caucasian.¹²

Heredity plays an important the risk of developing OAG. The relative risk of developing OAG is as much as 3.7 times greater in patients with an affected sibling, and 2.2 times greater with an affected parent. Even though heredity has been shown to affect incidence of OAG the patterns of which OAG is inherited are complex. Likely, several genes are responsible for the disease.¹³

Systemic chronic diseases such as hypertension and diabetes has been suggested as risk factors for glaucoma. The relative risk of OAG in patients with hypertension compared to patients without hypertension was 1.16 in a recent meta-analysis.¹⁴ Patients with diabetes has been proposed to have an increased risk of developing OAG.¹⁵

Clinical Presentation of OAG

First signs of glaucoma are usually found in passing upon thorough examination of the eye. Patients with OAG experience few or no symptoms before onset of visual field loss. An increase in IOP or initial damage the optic nerve does not present itself with other symptoms apart from the visual field loss. OAG is a slowly progressing disease, and the time it takes for patients to completely lose vision is very long.¹⁶ Even extensive visual field loss can go unnoticed by the patient for a long time.

The screening process for glaucoma lacks a golden standard when it comes to criteria for inclusion in screening programs as well as choice of screening method. Tonometry (measurement of IOP) is the method that is most used today but has its flaws since not all OAG patients have increased IOP.

Diagnosis

Glaucoma is best defined as damage on the optic nerve with progressive visual field loss. Therefore, diagnosis is usually decided upon examination of the visual field in combination with examination of the fundus where the physician can see typical structural changes of the optic nerve. Nerve damage can be observed as cupping and thinning of the optic disc and notching and thinning of the nerve disc rim. For the diagnosis of open-angle glaucoma the angle of the anterior chamber must be open. Furthermore, to establish a diagnosis of OAG secondary causes must be ruled out.

For the diagnosis, there are several methods available. To establish damage to the optic nerve, the most commonly examination method used is biomicroscopy of the fundus. Unfortunately, this examination is not sufficient for a diagnosis on its own since sensitivity is generally too low.¹⁷ As an alternative to fundoscopy is a modern method called Optical coherence tomography(OCT) which is an imaging technique that creates three-dimensional images with the use of light and optical scattering. OCT lets physicians visualize damages on the axons of the optical nerve and there is also the possibility of seeing microvascular abnormalities of the retina, both of which are important in glaucoma diagnosis. One study showed that OCT and similar methods are equal to but not better than conventional optic disc stereographs examined by a physician, however, OCT is less user dependent.¹⁸

When it comes to testing of the visual field the method of choice usually is automated perimetry. Compared to manual Goldmann perimetry automated test methods are much more accurate, especially when it comes to detecting arcuate scotomas which are typical for glaucoma.¹⁹ Automatic visual testing can in some instances be troublesome because it requires cooperation from the patient. Confrontation testing can be preferred in cases where the patient cannot fully cooperate such as in cases of dementia, mental illness or diseases of that sort.

Treatment

The main objective whilst treating glaucoma is to lower IOP and thereby hindering progression of the disease. It has been shown that patients treated with IOP-lowering medicine has a lower risk of having progressive visual field loss as well as less optic disc deterioration compared to placebo and non-treated patients.²⁰

Elevated IOP is used as an indication of when to initiate IOP lowering therapy, however, there is no real consensus on a threshold IOP value for initiating treatment.²¹ It is up to the individual physician to judge when treatment should start. There are some reasonable queues for initiating treatment such as:

- Elevated IOP before any symptoms or damage of the optic nerve. Early treatment can delay or even prevent onset of OAG²²
- Optic nerve damage without increase in IOP
- Visual field loss or
- Other condition that causes faster progression of vision field loss.²³

There are three main types of treatments available for decreasing IOP: pharmacological, laser therapy, or conventional surgery.

Pharmacological

The main principle of pharmacological glaucoma therapy is to decrease IOP by either decreasing aqueous production or increasing aqueous flow from the eye. This is achieved by administration of one or more medicines with different mechanisms of action. The most common medications for treating a high IOP are prostaglandins and Beta-blockers, other alternatives are adrenergic agonists, carbonic anhydrase inhibitors and cholinergic agonists amongst others.

First line pharmacological treatment for OAG are prostaglandins, which are usually administered topically. They reduce IOP by increasing uveoscleral outflow and has been shown to have better effect on IOP than B-blockers.²⁴

Since the introduction of prostaglandins beta blockers has been demoted to a 2nd line drug.^{25,26} Beta-blockers has been shown to decrease IOP compared to placebo albeit with marginal effect.²⁷ Side effects of this treatment is mainly systemic; including bradycardia, heart block and airway problems.²⁸

Adrenergic agonists have similar level of effect on IOP as beta blockers. The main difference is that there are more ocular side effects. In patients with a normal IOP glaucoma adrenergic agonists might be preferred to prostaglandins and beta blockers. A study showed that patients treated with brimonidine had less progression of visual field loss that patients treated with timolol when IOP was <22 mmHg. However, there was a much higher drop-out rate among patients treated with brimonidine due to ocular side effects.²⁹

Laser therapy

Laser therapy lowers IOP by increasing aqueous outflow through the trabecular meshwork. It has shown effect on IOP both as a first line treatment and in patients who have full medical therapy.³⁰ There are two types of laser treatment of the trabecular meshwork: argon laser trabeculoplasty (ALT) and selective laser trabeculoplasty (SLT) the most modern and commonly used method is SLT. In SLT, small areas of the trabecular meshwork are burned with laser which leads to opening canal for drainage of aqueous fluid.

Surgery

The final methods for lowering IOP is through surgery. The aim is to create alternative routes for the aqueous fluid to escape the eye. This is achieved through either trabeculectomy where a small fistula is made in the sclera so the aqueous humour can drain to a small reservoir, a “bleb”.

The second alternative is viscocanalostomy where the aim is to increase outflow through the trabecular meshwork(TM) and into Schlemm’s canal(SC). This is achieved by placement of an ophthalmic viscoelastic device through SC. This keeps SC open as well as widening TM.

Morbidity in patients with OAG

OAG is, as expected for a disease which causes vision loss and blindness, associated with decreased quality-of-life. Glaucoma patients have increase in number of visits to eye clinics and number of surgeries performed. Few patients develop complete blindness but it is common for glaucoma patients to lose eligibility to drive or getting a partial sight certification.³¹ Visual impairment is also cause for depression³² and need for extra support in daily activities.

Glaucoma and mortality

There have been several studies investigating if there is a correlation between OAG and mortality. Studies have not been conclusive across the board. Some studies have suggested that there is an increased mortality in OAG patients compared to patients without OAG, while some studies have shown that the mortality is similar between the two groups.^{33,34} A 2009 meta-analysis which included 9 cohort studies showed that there was no increase in mortality in patients with OAG.³⁵ Furthermore some studies have demonstrated increased cardiovascular mortality in people with OAG.³⁶ The same study showed an increased relative risk for cardiovascular mortality in patients who were treated with topical timolols.

Since it has been suggested that there is a higher risk of developing OAG in patients with diabetes and hypertension, and increased cardiovascular mortality in patients with OAG. By extension, there could be a link between OAG and mortality.

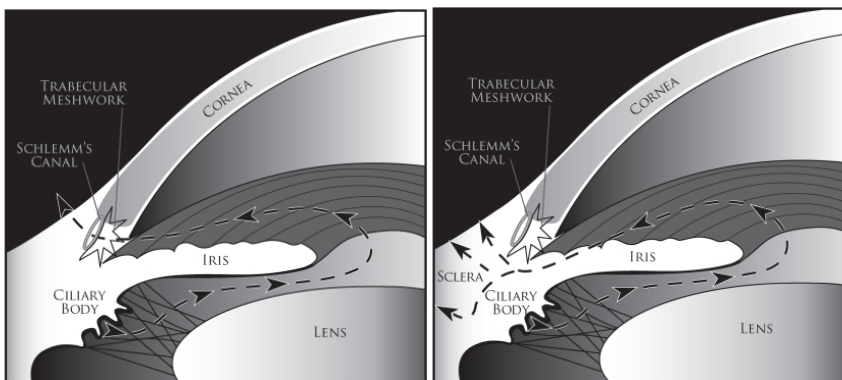


Figure 1. and 2. Diagrams illustrating aqueous humour outflow. (Goel et. Al, 2010)³⁷

Material and method

The study is a cohort study based on data collected from a population survey assessing the prevalence of OAG through screening at the eye-clinic in Tierp municipality between 1984 and 1986. Derived from the target population, 757 people between ages 65 and 74 were examined. One person was added to the population survey after examination in 1993 at age 73 and was included in the cohort.

Examinations included gathering of medical records as well as an on-site interview which included medical history, current medications, previous eye-disorders, current eye-symptoms, and heredity for glaucoma. The physical examination of the eye included automated visual field testing (Comper 350 automated perimeter), tonometry (IOP measurement), slit-lamp biomicroscopy, examination of the optic disc and gonioscopy.

In addition to the population survey data was gathered from glaucoma records in Tierp municipality, which were prepared after examinations at the eye-clinic between 1978 and 2007. The patients who was examined and put in glaucoma records had been seeking medical attention for eye-problems of any kind. Of these patients 1153 were selected to be included in this study. The journals contained information on date of examination, IOP, visual field examination, glaucoma diagnosis and medical treatment.

Definite open-angle glaucoma was defined as visual field loss that is characteristic for glaucomatous damage that could not be a result from other diseases in the eye or optic nerve. The vision field loss was reproducible in automated perimetry or manual Goldmann perimetry. If the visual field was unable to be assessed due to the glaucoma reaching its end-state, it was assessed as advanced OAG. The visual acuity in these cases were only good enough to see fingers held up at two meters or less. Diagnosis of glaucoma was established independently of the IOP of the patient.

Observational start date for the cohort was the time of baseline examination of each individual. The study end-points were death of any cause or end of the study on 15th of august 2017.

Information on baseline characteristics was collected from medical records and study protocols (population survey). The parameters were noted at the time of examination. Potential risk factors included in this study were as follows:

- Age at baseline

- Gender
- Smoking
- Diabetes Mellitus (E10-E14)
- Blood pressure-lowering treatment
- Ischemic heart disease (I20-I25)
- Diseases of arteries (I70-I72)
- Obstructive lung disease (J42-J45)
- Participation in the population survey
- Pseudoexfoliation
- Cancer of any kind at or before examination
- Obesity
- A history of cerebrovascular lesion (CVL, or stroke)

Ethics

The cohort study has an ethics-approval from a previous study, registration number: 2012/428. All patients in the cohort had agreed to participation in concurrence with examination, consent was given verbally or in writing. Patients who declined participation was excluded from the study.

Composition of the cohort

In total 1910 patients were examined during the entirety of the cohort. The population survey included 757 patients and the glaucoma records included 1153 patients.

Patients with ACG were excluded from this study since OAG was the target for examination. In addition, patients with secondary glaucoma were excluded. This amounted to 65 patients in total. Due to incomplete data, 12 patients were excluded. Incomplete data included patients who had moved abroad before study end-point, patients who had missing information in their records such as missing personal identity number or missing information on risk factor. Fourteen patients declined participation in the study and were therefore excluded. In this study, an observation period of at least two years was required for a diagnosis of definite OAG. For this reason, 56 patients who had a follow-up shorter than two years were excluded.

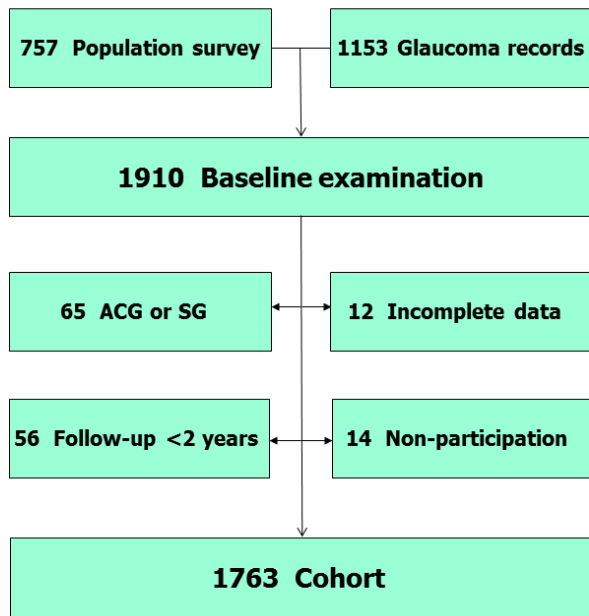


Figure 1. Flow chart showing how the cohort was derived. AGS = angle closure glaucoma. SG = secondary glaucoma.

Statistical analysis

The cohort data was analyzed in several steps. To assess if there was a difference between the mortality of OAG and non-OAG patients standardized mortality ratio (SMR) was calculated. The SMR was calculated by dividing the total number of cases of death by the total time under risk in exposed and unexposed individuals. This gave an incidence of death per year from baseline examination. The ratio was then calculated by dividing the incidence in the OAG group with the incidence in the non-OAG group. This analysis is a simple yet effective way to display the difference in mortality during the observation of the cohort. To get a more accurate result the SMR was standardized for age (under 70 years of age) and gender.

Furthermore, the SMR for potential risk factors were calculated within the OAG and non-OAG groups. (figure 2, results) Individuals without the risk factor was considered as baseline expected mortality (expressed as SMR of 1).

Cox proportional hazard models were used to calculate hazard ratios. The result was expressed as a hazard ratio for mortality where the absence of the risk factor was regarded as baseline hazard. Risk factors (covariates) that were proportional (not time dependent) were OAG, age, birthyear after 1925, smoking, diabetes, blood pressure-lowering treatment, diseases of the arteries.

The time dependent risk factors were male gender and ischemic heart disease (IHD), which had a decreasing impact on mortality further from the baseline examination. The time-dependent risk factors were adjusted for as they changed over time (Figure 3, results).

Results

Of the 1910 who were selected for baseline examination, 1763 people were remaining after exclusion according to the chart above. Glaucoma was found in 411 people at the time of examination or at follow up within 2 years. Out of these, 314 people had definitive OAG. At the end of the study 1500 deaths were reported out of whom 261 had OAG.

There were more female participants (1007) than male (756) which gave a ratio of about 1 male per 1.332 female. As expected men had a shorter life expectancy than women (SMR = 1.29; 95% CI, 1.15-1.44)

The cohort was divided into 2 age groups based on age at time of baseline examination (figure 1). The first group contained people of 65-69 years of age and the second contained people of 70-74 years of age at baseline examination. People in the 65-69 age group lived longer than the second group with a mean follow up time (time from examination until death or cut-off date) of 16.6, compared to a mean follow up time of 13.0 for the second group. People aged ≥ 70 years had a 1.45-fold increased risk for mortality compared to patients < 70 years of age. There was a slight overrepresentation in the 65-69 group which consisted of 949 people, compared to 814 people in the 70-74 group.

When comparing the SMR of specific risk factors of the OAG and non-OAG groups where the SMR of both groups were statistically significant there were 4 risk factors that were associated with a higher SMR in the OAG group compared to the non-OAG group. The risk factors age, diabetes mellitus, ischemic heart disease and diseases of arteries all had greater SMR values in the OAG

group with a CI not overlapping 1 in either of the groups. However, these had overlapping confidence intervals.

The SMR when comparing OAG to non-OAG when standardized for age and sex was 0.99 (95% CI, 0.87-1.14) which showed no increase in all-cause mortality in the definitive OAG group compared to the non-OAG group.

When adjusted for fixed and time-dependent covariates the hazard ratio for OAG patients compared to non-OAG patients was 1.04 (95% CI, 0.91-1.19) which shows that OAG is not related to increase in all-cause mortality in the studied population. The results showed narrow confidence intervals when comparing the mortality of OAG to non-OAG patients which strengthens the reliability of our results.

Table 1. Characteristics of the cohort, by age and gender.

Age group	No. of people (<i>n</i> = 1,763)		Person-years (<i>n</i> = 26,334)	
	Female (%)	Male (%)	Female (%)	Male (%)
65–69 years	552 (55)	397 (53)	9,773 (60)	6,000 (59)
70–74 years	455 (45)	359 (47)	6,439 (40)	4,122 (41)
65–74 years	1,007 (100)	756 (100)	16,212 (100)	10,122 (100)

Mean follow-up time: 14.9 years (standard deviation: 6.9 years)

Table 2. Associations of potential risk factors and death, by presence of open-angle glaucoma, adjusted for age and gender.

Baseline characteristics	OAG (<i>n</i> = 314)		Non OAG (<i>n</i> = 1,449)	
	No. of Deaths	SMR (95% CI)	No. of Deaths	SMR (95% CI)
Age ≥70 years	No	119 1.00	639 1.00	
	Yes	142 1.51 (1.19–1.94)	600 1.45 (1.29–1.61)	
Male gender	No	123 1.00	713 1.00	
	Yes	138 1.17 (0.92–1.49)	526 1.29 (1.15–1.44)	
Current smoking	No	221 1.00	1,037 1.00	
	Yes	40 1.18 (0.84–1.66)	202 1.31 (1.12–1.53)	
Diabetes mellitus (E10–E14)	No	224 1.00	1,046 1.00	
	Yes	37 1.65 (1.16–2.35)	193 1.40 (1.20–1.64)	
Blood pressure-lowering treatment	No	149 1.00	777 1.00	
	Yes	112 1.19 (0.92–1.53)	462 1.19 (1.05–1.33)	
Ischemic heart disease (I20–I25)	No	204 1.00	1,019 1.00	
	Yes	57 1.38 (1.02–1.86)	220 1.27 (1.10–1.47)	
Diseases of arteries (I70–I72)	No	245 1.00	1,184 1.00	
	Yes	16 1.89 (1.13–3.16)	55 1.44 (1.10–1.89)	
Obstructive lung disease (J42–J45)	No	240 1.00	1,141 1.00	
	Yes	21 1.29 (0.83–2.03)	98 1.28 (1.04–1.57)	

OAG = open-angle glaucoma; SMR = standardized mortality ratio; CI = confidence interval.

International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) codes are given in parentheses.

Table 3. Cox regression model using fixed and time-dependent covariates as predictors of survival in a cohort of 1,763 people.

Covariate		No. of Deaths	HR	(95% CI)
<i>Fixed</i>				
Open-angle glaucoma	No	1,239	1.00	
	Yes	261	1.04	(0.91 – 1.19)
Age at baseline (per year)		1,500	1.13	(1.11 – 1.15)
Male gender	No	836	1.00	
	Yes	664	1.83	(1.44 – 2.34)
Year of birth \geq 1925	No	1261	1.00	
	Yes	239	0.73	(0.63 – 0.85)
Current smoking	No	1,258	1.00	
	Yes	242	1.77	(1.53 – 2.05)
Diabetes (E10–E14)	No	1,270	1.00	
	Yes	230	2.31	(2.00 – 2.68)
Blood pressure-lowering treatment	No	926	1.00	
	Yes	574	1.28	(1.15 – 1.43)
Ischaemic heart disease (I20–I25)	No	1,223	1.00	
	Yes	277	2.04	(1.50 – 2.76)
Diseases of arteries (I70–I72)	No	1,429	1.00	
	Yes	71	1.63	(1.28 – 2.09)
<i>Time-dependant</i>				
Male gender *	No	836	1.00	
	Yes	664	0.98	(0.97 – 1.00)
Ischaemic heart disease (I20–I25) *	No	1,223	1.00	
	Yes	277	0.97	(0.95 – 0.99)

HR = hazard ratio; CI = confidence interval. ICD-10-codes are given in parentheses.

* Per year of follow-up.

Discussion

In concurrence with the much larger 2009 meta-analysis Akbari et al.³⁵ as well as Grødum et al.³⁴, Rotterdam³⁸ and Beaver Dam³⁹ investigating the mortality in patients with OAG, we observed that there was no significant increase in mortality of OAG patients compared to non-OAG patients in the population that this cohort was comprised of. The result is in disagreement with Egge and Zahl⁴⁰, and L Xu et al.³³ The SMR showed a close to 1:1 relative risk ratio between the two groups when adjusted for age and sex. Even when adjusted for different covariates through Cox regression analysis there was no significant increase in Hazard Ratio.

Since there are indications that there is an increase in cardiovascular mortality in patients with OAG compared to the population in general, one could expect to also see a total increase in mortality in the OAG group. Additionally, there has been studies that show an increased risk for developing OAG in patients with diabetes and hypertonia. Both these diseases are closely associated with shorter life expectancy. Therefore, one would expect that by extension OAG would be associated with an increase in mortality as well. Both diabetes and hypertonia were shown to be associated with an increase in mortality in this study, however, this was not reflected in the final mortality rates of the OAG group. There could be many reasons why this is not the case. For instance a significant increase in all-cause mortality can be concealed because OAG only causes a marginal increase in cardiovascular mortality.³⁶ The studies conducted which has shown increase in cardiovascular mortality also discussed that the cause of the mortality increase is due to timolol treatment, there was no follow up of medical treatment in this cohort and the data could not be adjusted for that. Regarding the prevalence of diabetes and hypertonia in patients with OAG, there can be a detection bias present which overestimates the prevalence of those diseases in OAG patients. Furthermore, OAG patients could have closer contact with healthcare and therefore receive better treatment for their risk factors than the average population, which would mask a true increase in mortality.

The common theme among studies investigating the mortality of OAG have one problem in common, namely that the OAG group usually is small compared to the entirety of the cohort. This has made a lot of studies to lack power when trying to disprove or prove the connection between OAG and mortality. However, the present study has a good statistical power with narrow confidence intervals.

Studies that have been unable to disprove the 0 hypothesis have still had HRs or SMRs over >1 .^{34,35} The confidence interval of the Akbari et. al meta-analysis was barely overlapping 1. One can then imagine, given a large enough study group, that OAG could be associated with mortality. However, the question remains, whether it is efficient to investigate a potential mortality increase if it is not clearly reproducible in a conventional observational study.

Strengths and limitations

There are many strengths in this study. All patients included in the study were examined at the same clinic, by the same physician and were selected from the same area, which provided a good inter-rater reliability. Subjects selected had a narrow age span at baseline examination. The total population of the study was large which gave a good basis for a statistically reliable result. The follow up time was equal to or greater than the average follow up time of the largest cohorts examining mortality in OAG. (14.9 compared to 4.5-16 years, Akbari et al. meta-analysis)

There are however some limitations of this study which mainly comes from the expansion of the cohort. Patients examined at the clinic at some point were also included in the population in addition to the population survey. One could make many arguments why this can skew the results in one way or another. The most obvious way this could affect the results is that there could be a selection bias present in the glaucoma journal group in the sense that people who visit the eye clinic for other reasons than this study could have more underlying health problems than the average person. One could also argue that there might be a selection bias in the opposite direction in the sense that people who visit the eye-clinic have a better perception of their health and are therefore healthier than patients in the population study. However, adjustment for participation in the population survey had no impact on the result.

Another possible source for errors was also due to the groups being examined in different time spans. One group was examined between 1984 and 1986 while the other group was examined between 1974 and 2007. Materials, methods, routine of the examiner could very well differ during such an extended period. Where one would expect a lesser difference in the 2 years of the population study.

There could also be a report bias in the group participating in the survey since it was a partly self-reported study. Risk factors such as previous diseases and smoking could have been underreported

in this group, especially when compared to the glaucoma journal group where these questions were addressed by a physician at the time of examination.

In conclusion, this study did not find any association between OAG and all-cause mortality.

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