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Pseudoexfoliation and mortality

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Abstract

Svensson, R. Pseudoexfoliation and mortality.

Purpose: To evaluate the relationship between pseudoexfoliation (PEX) and all-cause mortality.

Methods: A cohort of people aged 65–74 years was formed, using a population based study in the municipality of Tierp, Sweden, in 1984–86 and one of its follow-up studies as a main source. To increase the cohort, people aged 65–74 years were recruited from special glaucoma case records established in Tierp in 1978–2007. In this way, the cohort embraced 1,524 people, representing more than 21,000 person-years at risk. Occurrence of PEX was determined from screening examination protocols and the glaucoma case records, respectively. Death dates were collected from the Swedish census registry. Standardized mortality ratios (SMRs) were calculated and Cox proportional hazards regression analyses, controlling for age, gender, smoking, birth year and participation in the population survey, were performed to assess hazard ratios for all-cause mortality.

Results: Mean follow-up time was 14 years. A total number of 1,280 deaths occurred, out of which 350 occurred in the group exposed to PEX. Calculation of SMR showed no association between PEX and mortality; neither did the Cox proportional hazards regression analyses (hazard ratio 1.02; 95% confidence interval 0.90–1.16).

Conclusion: The results of this study strongly suggest that PEX does not have any effect on all-cause mortality.

Sammanfattning på svenska

Svensson, R. Pseudoexfoliationer och mortalitet.

Syfte: Att undersöka sambandet mellan pseudoexfoliationer (PEX) och mortalitet (oberoende av dödsorsak).

Metod: En kohort med personer i åldrarna 65–74 år skapades med utgångspunkt från en befolkningsundersökning i Tierps kommun 1984–86 samt en av dess uppföljande studier. För att utöka kohorten inkluderades personer i åldern 65–74 år vid det första besöket från ett glaukomregister upprättat i Tierp 1978–2007. På det viset innefattade kohorten totalt 1524 personer som sammanlagt representerade mer än 21000 personår under risk. Förekomsten av PEX bestämdes från screeningprotokollen respektive från glaukomregistret. Dödsdatum erhöles från befolkningsregistret. ”Standardized mortality ratios” (SMR) beräknades och en regressionsanalys enligt Cox genomfördes, där man kontrollerade för ålder, kön, rökning, födelseår och deltagande i befolkningsundersökningen.

Resultat: Uppföljningstiden var i genomsnitt 13.9 år. Antalet dödsfall uppgick till 1280, av vilka 350 inträffade i gruppen med PEX. Varken SMR eller regressionsanalysen enligt Cox (hazardkvot 1.02; 95% konfidensintervall 0.90–1.16) visade något samband mellan PEX och mortalitet.

Slutsatser: Resultaten i studien tyder starkt på att PEX inte påverkar överlevnaden.

Introduction

Pseudoexfoliation

It is possible that pseudoexfoliation (PEX) should not only be viewed as a risk factor for glaucoma, but rather as a systemic disease that affects other parts of the body than just the eye.^{1,2} PEX is an age-related disease characterized by the production and accumulation of fibrillar extracellular material. It is a known risk factor for open angle glaucoma (OAG).²⁻⁶ Accumulation of PEX material can be found in the anterior segment of the eye, in the conjunctiva and in orbital structures.^{1,2} Pseudoexfoliation is diagnosed clinically and requires a slit-lamp examination. The most common clinical findings are small visible white deposits on the anterior lens capsule and the pupillary border.² The exact composition of the exfoliation material is unknown. However, immunohistochemical studies have indicated exfoliation material to consist of glycoproteins/proteoglycans with epitopes of the basement membrane and elastic fiber system, such as elastin, tropoelastin, amyloid P, vitronectin, fibrillin-1, microfibril associated glycoprotein (MAGP-1) and latent TGF- β binding proteins (LTBP-1 and LTBP-2).^{1,2} Other identified components of exfoliation material are laminin, fibronectin, clusterin, fibulin, desmocollin-2, serum amyloid protein, the glucoseaminoglycans syndecan-3, the tissue inhibitor of metalloprotease-3 (TIMP-3), complement factor 1q (C1q) and metalloproteases of the “A Disintegrin and metalloprotease” (ADAM) family.⁷

The current pathological theory identifies growth factors, cellular and oxidative stress, an impaired system for cellular protection and aggregation of misfolded proteins to be important pathogenic factors.¹ Concerning gene expression, tissues with PEX mainly show a different expression of genes related to extracellular matrix metabolism and cellular stress than do normal tissues.⁸ Polymorphisms in lysyl oxidase like 1 (LOXL1) on chromosome 15q24 have been identified as strong genetic risk factors for PEX formation. The gene codes for a protein responsible for synthesis and maintenance of elastic fibers.^{9,10}

The prevalence of PEX varies between studies carried out on different populations and with different methods.² In the Swedish municipality of Tierp, 17% of people aged 65-74 years have PEX.¹¹ Research investigating difference between men and women shows ambiguous results. The prevalence of PEX is higher in hospital based studies than in those based on the general population.² More than 60% of patients with a known diagnosis of OAG in Tierp have PEX.¹²

Open-angle glaucoma and pseudoexfoliation

Glaucoma is a disease of the optic nerve that globally accounts for 2% of all visual impairment and 8% of all blindness.¹³ Open-angle glaucoma is the predominant form of glaucoma. The only treatable risk factor for OAG is increased intraocular pressure (IOP). Other known risk factors are PEX, high age, heredity and myopia.⁵ Studies investigating the possibility of an increased mortality in patients with OAG show ambiguous results.¹⁴⁻²⁰ A comprehensive meta-analysis does not demonstrate any difference in mortality.²¹

Pseudoexfoliation increases IOP^{2,4} and is thought to give a more rapid progression of the disease.²²⁻²⁶ Glaucoma with PEX is more resistant to therapy than glaucoma without PEX.^{23,27} Additionally, PEX predisposes for complications in association with cataract surgery.^{28,29} Research suggests that PEX is associated with cataract formation.³⁰⁻³⁵

Systemic occurrence of pseudoexfoliation

Other than the eye, PEX material has been found in connective tissue and fibrovascular septa in other organs,^{1,2} such as lungs, heart, liver, skin, kidneys, cerebral meninges and gallbladder.^{36,37} It seems to originate from connective tissue fibroblasts, smooth and striated muscle cells and heart muscle cells.¹

In view of the systemic occurrence of PEX, studies have been made to examine a connection between PEX and other diseases than those of the eye. The results are not unambiguous. One study suggests an increased prevalence of angina pectoris, hypertension and the combination of angina pectoris, myocardial infarction or stroke among patients with PEX.³⁸ Others conclude that PEX is associated with coronary artery disease³⁹, aneurysms of the abdominal aorta⁴⁰ and sensorineural hearing loss.⁴¹ Patients with PEX have also been found to have increased levels of homocysteine in plasma, something which in itself constitutes a risk factor for cardiovascular disease.⁴² Another study contradicts a possible association between PEX and systemic diseases, including ischemic heart disease, hypertension and diabetes.⁴³ Other studies have demonstrated an actual decrease in prevalence of diabetes in patients with PEX.^{25,44} One study discovered an association between PEX and senile dementia, cerebral atrophy, chronic cerebral ischemia and the probability of developing an acute cerebrovascular disease. It did however fail to show an increased rate of death caused by cancer, cardiac diseases or acute cardiovascular diseases.⁴⁵ An association between age-related dementia and PEX is supported in another study.⁴⁶ Furthermore, a group of researchers found, with the help of magnetic resonance imaging, that patients with PEX had more white

matter lesions in the brain than did controls.⁴⁷ However, a recent study concludes that PEX is not a predictor of Alzheimer's disease.⁴⁸

In the end, no studies have been able to show an increased mortality in patients with PEX.^{1,49-52} The purpose of this study is to evaluate if PEX has such a harmful effect on health as some previous research might suggest. This will be done by investigating if people with PEX have an increased all-cause mortality.

Materials and Methods

The cohort

In 1984–86, a population based survey on the prevalence of OAG was performed in the municipality of Tierp, Sweden. It had a defined target population of 2,429 people aged 65–74 years. The study involved 838 people, one third of the target population, whom were invited to an eye examination at the Eye clinic in Tierp. Out of these, 760 were examined. One additional person, who did not participate in the study, joined the cohort after being examined in 1993. The screening examination included IOP measurements, visual field testing with the Competer 350 automated perimeter (Bara Elektronik AB, Lund, Sweden), slit-lamp biomicroscopy after dilation of the pupil, binocular assessment of the optic disc and gonioscopy. It also included a personal interview covering medical history, eye symptoms, current medication, previously received eye healthcare and family history of glaucoma. Medical records were also used to obtain information.⁵³ The 761 people involved in the population survey constitute about half of the cohort.

Up until December 2006, a follow-up of the population survey was conducted. Recruitments were made to the follow-up study in order to increase the cohort. Sixty-six people aged 65–74 years were selected, using registers of people having visited either the Eye clinic in Tierp or the eye clinic at Uppsala University Hospital. These participants were offered free eye examinations at the Eye clinic in Tierp. Out of these, 58 people are included in the present cohort, after removing 8 doublets.

To expand the cohort, people from special glaucoma case records, established at the Eye clinic in Tierp, are included in the cohort. The glaucoma case records cover 2,159 patients with glaucoma or suspected glaucoma examined in Tierp between August 1978 and February 2007. People with eye disease discovered in the population survey are not included. The records include information on examination dates, visual acuity, IOP, visual field examinations, PEX, glaucoma diagnoses, medical treatment and eye operations. The first visit at the Eye clinic in Tierp constitutes the baseline examination from which information about PEX is retrieved. Patients who were aged 65–74 years during the calendar year of the first visit in Tierp (788 people) are included in the study.

Thus, the cohort of the present study might include 1607 people. However, out of these, 83 are excluded for various reasons: 5 people were never examined in Tierp; 3 people were not registered in the municipality of Tierp or the adjacent municipality of Älvkarleby; 6 people

were in the wrong age at baseline examination; 44 people had either secondary glaucoma or angle-closure glaucoma; 9 people had undergone bilateral lens extraction at baseline examination; for 6 people it was impossible to obtain all necessary information, and 10 people declined participation in the study. The remaining 1524 constitute the study cohort, whose characteristics are presented in Table 1.

Ethics

All living participants included in the study have given written or oral consent to the usage of their personal data in research purposes. The Regional Ethical Review Board of Uppsala University approved the study.

Collection of data

The presence of PEX is defined as the deposition of characteristic white flakes on the lens capsule and/or on the pupillary border, as can be seen using slit-lamp examination after dilating the pupil with tropicamide. Subjects with PEX in either eye at baseline are defined as exposed to PEX. Information about other factors, such as smoking, diabetes mellitus, blood-pressure lowering treatment (as a marker for hypertension), ischaemic heart disease, chronic obstructive lung disease and IOP, was collected either through interviews, from the glaucoma case record or from ordinary medical records.

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

Age group	No. of people ($n = 1,524$)		Person-years ($n = 21,156$)	
	Female (%)	Male (%)	Female (%)	Male (%)
65–69 years	413 (49)	316 (47)	6,985 (54)	4,520 (54)
70–74 years	434 (51)	361 (53)	5,854 (46)	3,798 (46)
65–74 years	847 (100)	677 (100)	12,838 (100)	8,318 (100)

Mean follow-up time: 13.9 years (standard deviation 7.0).

Follow-up started at baseline examination and ended in August 15, 2013 (censor date). Death dates were obtained from the Swedish census registry.

Statistical methods

To assess whether people exposed to pseudoexfoliation (PEX) have an increased all-cause mortality compared to people unexposed, age- and gender-standardized mortality ratios (SMRs) were estimated. Age groups were defined as people <70 years of age and ≥ 70 years of age, respectively. Ninety-five percent confidence intervals (CIs) for the SMRs were calculated.

Apart from standardized analyses, Cox proportional hazards regression analyses were used to estimate the effect of more than one predictor. The analysis was adjusted to age, gender and smoking. The influence of birth year and participation in the population based study was also tested. Statistica 8.0 (Stat-Soft, Inc., Tulsa, OK, USA) was used for multivariable analyses.

Results

Out of the 1,524 people who comprise the cohort, 440 were exposed to PEX, and 1,084 were unexposed. A total number of 1,280 deaths occurred, out of which 350 occurred in the exposed group. The SMR for exposed versus unexposed subjects amounted to 1.00 (95% CI 0.88–1.13), showing no indication of an increased mortality in the exposed group. The stratified data is illustrated in Table 2.

Table 3 provides SMRs for a number of potential risk factors at baseline. Notable differences in SMRs between the people with and without PEX were detected only for smoking habits and chronic obstructive lung disease. The rest of the baseline characteristics were substantially identical for the two groups, indicating that PEX has no effect on mortality.

Exposure to PEX, together with either current smoking or chronic obstructive lung disease is associated with an increased all-cause mortality. However, the CI is wide as a consequence of low numbers.

Participants born 1918 or later had a lower mortality compared to participants born before 1918, with a SMR of 0.72 (95% CI 0.64–0.82). A standardized analysis showed that the population sample had an increased mortality compared to the part of the cohort selected from the glaucoma case records, with a SMR of 1.20 (95% CI 1.07–1.34).

Table 2. Strata used in the analysis of age- and gender standardized mortality ratios.

		PEX (<i>n</i> = 440)		No PEX (<i>n</i> = 1,084)	
		Deaths	Person-years	Deaths	Person-years
Males	≥ 70 years of age	79	953	236	2,844
	< 70 years of age	51	837	229	3,683
Females	≥ 70 years of age	124	1,971	246	3,883
	< 70 years of age	96	2,094	219	4,891

PEX = pseudoexfoliation.

Table 3. Associations of potential risk factors and death, by presence of pseudoexfoliation.

Baseline characteristics	PEX (<i>n</i> = 440)			No PEX (<i>n</i> = 1,084)		
	Deaths	SMR	(95% CI)	Deaths	SMR	(95% CI)
Age \geq 70 years	203	1.37	(1.11–1.69)	482	1.37	(1.21–1.56)
Male gender	130	1.32	(1.06–1.64)	465	1.35	(1.18–1.53)
Medical history factors						
Current smoking	46	1.53	(1.12–2.11)	161	1.30	(1.09–1.56)
Diabetes mellitus (E10–E14)	56	1.55	(1.16–2.06)	143	1.55	(1.30–1.86)
Blood pressure-lowering treatment	142	1.17	(0.94–1.45)	306	1.16	(1.01–1.34)
Ischaemic heart disease (I20–I25)	75	1.47	(1.14–1.90)	168	1.45	(1.22–1.72)
Obstructive lung disease (J42–J45)	30	1.47	(1.01–2.15)	71	1.12	(0.88–1.43)
Ocular factors, any eye						
IOP \geq 20 mmHg, untreated	220	0.87	(0.70–1.08)	317	0.96	(0.84–1.10)

SMR = standardized mortality ratio; CI = confidence interval; IOP = intraocular pressure;

PEX = pseudoexfoliation.

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

Table 4. Cox model assessing the influence of pseudoexfoliation on mortality.

Covariate	Coef.	Std. error	HR	(95% CI)
PEX	0.020	0.064	1.02	(0.90–1.16)
Age (per year)*	0.121	0.009	1.13	(1.11–1.15)
Male gender	0.411	0.059	1.51	(1.34–1.69)
Current smoking	0.522	0.080	1.69	(1.44–1.97)

Coef. = Coefficient; Std. error = Standard error; HR = hazard ratio;

CI = confidence interval

* Age at baseline, continuous variable

The Cox proportional hazards models included PEX, age, gender, smoking, birth year and participation in the population survey. The results were almost identical to that of the stratified analysis, with no association between PEX and mortality. The ultimate model is presented in Table 4. Adjustments neither for birth year, nor for participation in the population survey had any influence on the estimates (data not shown).

Discussion

In the present study, after a mean follow-up of 14 years, no increased mortality in people exposed to PEX was found. This is in agreement with results from previous studies investigating the association between PEX and all-cause mortality^{1,49-52} and undermines the hypothesis of PEX being a disease with harmful systemic effects on health. Applying a confidence level of 95% and a power of 80%, the study could detect a 19% increased risk. With a hazard ratio of 1.02 and a good statistical power, an association between PEX and mortality is highly unlikely in the examined population.

The strengths of the present study include its long-term follow-up, the sizeable cohort and its community-based design. About half of the cohort is randomly selected. Another advantage is that the study is largely based on objective data. Death dates were obtained from the Swedish census registry and the presence of PEX from either the screening examination protocols or the glaucoma case records. Practically all clinical identification of PEX was made by the same eye doctor. Considering confounding factors, the multivariate analyses were adjusted for age, gender, current smoking, birth year and participation in the population survey. The analyses were not adjusted for the other possible risk factors presented in Table 3 since the standardized analyses showed that they had no effect.

The people recruited from the glaucoma records have themselves sought medical care, unlike the people from the population survey, and it is not unlikely that the two groups have different spectra of other diseases. Moreover, the prevalence of PEX in the glaucoma record group was higher than that in the population sample, 18 and 40%, respectively. The composition of the cohort, being recruited in different ways, should however not be a confounding factor. To enlarge the cohort by adding patients from the glaucoma case records will never bias the result as long as the identification of deaths was independent of the exposure under study, which was the case in the present study. Adjusting for participation in the population survey did not influence the multivariate estimate.

People with earlier birth dates have, both according to the standardized analysis and the multivariate analysis, an increased mortality compared to people born later. This association is not fully understood. Some of the association might result from a gradually increasing life expectancy in Sweden due to enhanced medical care and a healthier way of living. Some of it might be a statistical artefact due to the fact that more people born in early 20th century have died at the end of the study period than people born later. However, adjusting for birth dates did not influence the estimates.

Interestingly, the SMRs presented in Table 3 indicate that current smoking and chronic obstructive lung disease, together with exposure to PEX, is associated with an increased all-cause mortality. The standardized analyses indicating this are based on too small a sample to permit any conclusions, but it is worth noting. Might exposure to PEX, being a disease of elastic components in connective tissue, make people more sensitive to negative effects of smoking? This might make out the challenge of future research projects.

Unfortunately, this study also has some weaknesses. The analyses are based on PEX discovered at baseline and do not consider PEX developed during follow-up. Since the occurrence of PEX is age-related, a gradually increased prevalence is to be expected throughout the follow-up. Individuals who developed PEX later will dilute the unexposed group. It is however uncertain what effect this might have on the estimate.

The data on smoking is rather uncertain. It is obtained through medical records or interviews. Hence, it depends both on the honesty of self-report and on the interviewer asking and documenting the answers. In the present study, current smokers are compared to non-smokers, making no distinction between a person who has previously smoked for 40 years but stopped a month ago and a person who has never smoked. This may dilute the effect of smoking in the analyses.

In the population survey there were 78 non-participants. It is possible that people who were ill, and therefore might have an increased mortality, declined participation in the population survey. However, for the non-participants to affect the results of the present study, they also need to have a prevalence of PEX different from that of the rest of the cohort. It is unlikely that the low number of non-participants has any influence on the estimates.

To sum up, the cohort study in Tierp investigated the association between PEX and mortality over an average follow-up time of 14 years. No association between PEX and all-cause mortality was found.

References

1. Schlötzer-Schrehardt U, Naumann GO. Ocular and systemic pseudoexfoliation syndrome. *Am J Ophthalmol*. May 2006;141(5):921-937.
2. Ritch R, Schlötzer-Schrehardt U. Exfoliation syndrome. *Surv Ophthalmol*. Jan-Feb 2001;45(4):265-315.
3. Ekström C. Elevated intraocular pressure and pseudoexfoliation of the lens capsule as risk factors for chronic open-angle glaucoma. A population-based five-year follow up study. *Acta Ophthalmol (Copenh)*. Apr 1993;71(2):189-195.
4. Ringvold A, Blika S, Elsås T, et al. The middle-Norway eye-screening study. II. Prevalence of simple and capsular glaucoma. *Acta Ophthalmol (Copenh)*. Jun 1991;69(3):273-280.
5. Ekström C. Risk factors for incident open-angle glaucoma: a population-based 20-year follow-up study. *Acta Ophthalmol*. Jun 2012;90(4):316-321.
6. Åström S, Stenlund H, Lindén C. Incidence and prevalence of pseudoexfoliations and open-angle glaucoma in northern Sweden: II. Results after 21 years of follow-up. *Acta Ophthalmol Scand*. Dec 2007;85(8):832-837.
7. Ovodenko B, Rostagno A, Neubert TA, et al. Proteomic analysis of exfoliation deposits. *Invest Ophthalmol Vis Sci*. Apr 2007;48(4):1447-1457.
8. Zenkel M, Pöschl E, von der Mark K, et al. Differential gene expression in pseudoexfoliation syndrome. *Invest Ophthalmol Vis Sci*. Vol 46. United States 2005:3742-3752.
9. Jonasson F. From epidemiology to lysyl oxidase like one (LOXL1) polymorphisms discovery. *Acta Ophthalmol*. Aug 2009;87(5):478-487.
10. Thorleifsson G, Magnusson KP, Sulem P, et al. Common sequence variants in the LOXL1 gene confer susceptibility to exfoliation. *Science*. Sep 7 2007;317(5843):1397-1400.
11. Ekström C, Alm A. Pseudoexfoliation as a risk factor for prevalent open-angle glaucoma. *Acta Ophthalmol*. Nov 2008;86(7):741-746.
12. Ekström C, Haglund B. Chronic open-angle glaucoma and advanced visual field defects in a defined population. *Acta Ophthalmol (Copenh)*. Oct 1991;69(5):574-580.
13. Pascolini D, Mariotti SP. Global estimates of visual impairment: 2010. *Br J Ophthalmol*. May 2012;96(5):614-618.
14. Xu L, Wang YX, Wang J, Jonas JJ. Mortality and ocular diseases: The Beijing Eye Study. *Ophthalmology*. Apr 2009;116(4):732-738.
15. French DD, Margo CE, Harman LE. Ocular pseudoexfoliation and cardiovascular disease: a national cross-section comparison study. *N Am J Med Sci*. Oct 2012;4(10):468-473.
16. Lee DJ, Gómez-Marín O, Lam BL, Zheng DD. Glaucoma and survival: The National Health Interview Survey 1986-1994. *Ophthalmology*. Aug 2003;110(8):1476-1483.
17. Lee AJ, Wang JJ, Kifley A, Mitchell P. Open-angle glaucoma and cardiovascular mortality: The Blue Mountains Eye Study. *Ophthalmology*. Jul 2006;113(7):1069-1076.
18. Wu SY, Nemesure B, Hennis A, Schachat AP, Hyman L, Leske MC. Open-angle glaucoma and mortality: The Barbados Eye Studies. *Arch Ophthalmol*. Mar 2008;126(3):365-370.
19. Knudtson MD, Klein BE, Klein R. Age-related eye disease, visual impairment, and survival: The Beaver Dam Eye Study. *Arch Ophthalmol*. Feb 2006;124(2):243-249.
20. Borger PH, van Leeuwen R, Hulsman CA, et al. Is there a direct association between age-related eye diseases and mortality? The Rotterdam Study. *Ophthalmology*. Jul 2003;110(7):1292-1296.
21. Akbari M, Akbari S, Pasquale LR. The association of primary open-angle glaucoma with mortality: a meta-analysis of observational studies. *Arch Ophthalmol*. Feb 2009;127(2):204-210.
22. Leske MC, Heijl A, Hussein M, Bengtsson B, Hyman L, Komaroff E. Factors for glaucoma progression and the effect of treatment: The Early Manifest Glaucoma Trial. *Arch Ophthalmol*. Vol 121. United States 2003:48-56.

23. Konstas AG, Stewart WC, Stroman GA, Sine CS. Clinical presentation and initial treatment patterns in patients with exfoliation glaucoma versus primary open-angle glaucoma. *Ophthalmic Surg Lasers*. Feb 1997;28(2):111-117.
24. Futa R, Shimizu T, Furuyoshi N, Nishiyama M, Hagihara O. Clinical features of capsular glaucoma in comparison with primary open-angle glaucoma in Japan. *Acta Ophthalmol (Copenh)*. Apr 1992;70(2):214-219.
25. Konstas AG, Tsatsos I, Kardasopoulos A, Bufidis T, Maskaleris G. Preoperative features of patients with exfoliation glaucoma and primary open-angle glaucoma. The AHEPA Study. *Acta Ophthalmol Scand*. Apr 1998;76(2):208-212.
26. Moreno-Montañés J, Alvarez Serna A, Alcolea Paredes A. Pseudoexfoliative glaucoma in patients with open-angle glaucoma in the northwest of Spain. *Acta Ophthalmol (Copenh)*. Dec 1990;68(6):695-699.
27. Brooks AM, Gillies WE. The presentation and prognosis of glaucoma in pseudoexfoliation of the lens capsule. *Ophthalmology*. Feb 1988;95(2):271-276.
28. Naumann GO, Schlötzer-Schrehardt U, Küchle M. Pseudoexfoliation syndrome for the comprehensive ophthalmologist. Intraocular and systemic manifestations. *Ophthalmology*. Vol 105. United States 1998;951-968.
29. Lumme P, Laatikainen L. Exfoliation syndrome and cataract extraction. *Am J Ophthalmol*. Jul 15 1993;116(1):51-55.
30. Hirvelä H, Luukinen H, Laatikainen L. Prevalence and risk factors of lens opacities in the elderly in Finland. A population-based study. *Ophthalmology*. Jan 1995;102(1):108-117.
31. Hietanen J, Kivelä T, Vesti E, Tarkkanen A. Exfoliation syndrome in patients scheduled for cataract surgery. *Acta Ophthalmol (Copenh)*. Aug 1992;70(4):440-446.
32. Madden JG, Crowley MJ. Factors in the exfoliation syndrome. *Br J Ophthalmol*. Jul 1982;66(7):432-437.
33. Puska P, Raitta C. Exfoliation syndrome as a risk factor for optic disc changes in nonglaucomatous eyes. *Graefes Arch Clin Exp Ophthalmol*. 1992;230(6):501-504.
34. Seland JH, Chylack LT, Jr. Cataracts in the exfoliation syndrome (fibrillogluthia epitheliocapsularis). *Trans Ophthalmol Soc U K*. 1982;102 Pt 3:375-379.
35. Kanthan GL, Mitchell P, Burlutsky G, Rochtchina E, Wang JJ. Pseudoexfoliation syndrome and the long-term incidence of cataract and cataract surgery: The Blue Mountains Eye Study. *Am J Ophthalmol*. Jan 2013;155(1):83-88.e81.
36. Schlötzer-Schrehardt UM, Koca MR, Naumann GO, Volkholz H. Pseudoexfoliation syndrome. Ocular manifestation of a systemic disorder? *Arch Ophthalmol*. Dec 1992;110(12):1752-1756.
37. Streeten BW, Li ZY, Wallace RN, Eagle RC, Jr., Keshgegian AA. Pseudoexfoliative fibrillogluthia in visceral organs of a patient with pseudoexfoliation syndrome. *Arch Ophthalmol*. Dec 1992;110(12):1757-1762.
38. Mitchell P, Wang JJ, Smith W. Association of pseudoexfoliation syndrome with increased vascular risk. *Am J Ophthalmol*. Nov 1997;124(5):685-687.
39. Andrikopoulos GK, Mela EK, Georgakopoulos CD, et al. Pseudoexfoliation syndrome prevalence in Greek patients with cataract and its association to glaucoma and coronary artery disease. *Eye (Lond)*. Feb 2009;23(2):442-447.
40. Schumacher S, Schlötzer-Schrehardt U, Martus P, Lang W, Naumann GO. Pseudoexfoliation syndrome and aneurysms of the abdominal aorta. *Lancet*. Vol 357. England 2001;359-360.
41. Cahill M, Early A, Stack S, Blayney AW, Eustace P. Pseudoexfoliation and sensorineural hearing loss. *Eye (Lond)*. May 2002;16(3):261-266.
42. Altıntaş O, Maral H, Yüksel N, Karabaş VL, Dillioğlugil MO, Çağlar Y. Homocysteine and nitric oxide levels in plasma of patients with pseudoexfoliation. *Graefes Arch Clin Exp Ophthalmol*. Jul 2005;243(7):677-683.

43. Špečkauskas M, Tamošiūnas A, Jašinskas V. Association of ocular pseudoexfoliation syndrome with ischaemic heart disease. *Acta Ophthalmol*. Sep 2012;90(6):e470-475.
44. Tarkkanen A, Reunanen A, Kivelä T. Frequency of systemic vascular diseases in patients with primary open-angle glaucoma and exfoliation glaucoma. *Acta Ophthalmol*. Sep 2008;86(6):598-602.
45. Ritland JS, Egge K, Lydersen S, Juul R, Semb SO. Exfoliative glaucoma and primary open-angle glaucoma: associations with death. *Acta Ophthalmol Scand*. Aug 2004;82(4):401-404.
46. Linnér E, Popovic V, Gottfries CG, Jonsson M, Sjögren M, Wallin A. The exfoliation syndrome in cognitive impairment of cerebrovascular or Alzheimer's type. *Acta Ophthalmol Scand*. Vol 79. Denmark2001:283-285.
47. Yüksel N, Anik Y, Altuntaş O, Onur I, Çağlar Y, Demirci A. Magnetic resonance imaging of the brain in patients with pseudoexfoliation. *Ophthalmologica*. 2006;220(2):125-130.
48. Ekström C, Kilander L. Pseudoexfoliation and Alzheimer's disease: a population-based 30-year follow-up study. *Acta Ophthalmol*. Jul 23 2013.
49. Grødum K, Heijl A, Bengtsson B. Glaucoma and mortality. *Graefes Arch Clin Exp Ophthalmol*. May 2004;242(5):397-401.
50. Ringvold A, Blika S, Sandvik L. Pseudo-exfoliation and mortality. *Acta Ophthalmol Scand*. Jun 1997;75(3):255-256.
51. Shrum KR, Hattenhauer MG, Hodge D. Cardiovascular and cerebrovascular mortality associated with ocular pseudoexfoliation. *Am J Ophthalmol*. Jan 2000;129(1):83-86.
52. Ritland JS, Egge K, Lydersen S, Juul R, Semb SO. Comparison of survival of exfoliative glaucoma patients and primary open-angle glaucoma patients: impact of acetazolamide use. *Acta Ophthalmol Scand*. Aug 2004;82(4):397-400.
53. Ekström C. Prevalence of open-angle glaucoma in central Sweden. The Tierp Glaucoma Survey. *Acta Ophthalmol Scand*. Apr 1996;74(2):107-112.