ÁRSÆLL MÁR ARNARSSON

Epidemiology of Exfoliation Syndrome in the Reykjavik Eye Study

UNIVERSITY OF ICELAND

Faculty of Medicine

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Supervisor: Professor Friðbert Jónasson, M.D.

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This thesis is dedicated to the
loving memory of my friend
Vignir Þórsson (1967-2002)

ÁGRIP

Inngangur: Flögnunarheilkenni (XFS) er veigamikill áhættuþáttur gláku. Það einkennist af uppsöfnun á formlausum bandvefsþráðum í forhólfi augans. Líklegt er að sú hækkun á augnþrýstingi (IOP) sem fylgir gjarnan XFS, sé tilkomin vegna þess að flögur efnisins stífli síuvef (trabecular meshwork) og auki þannig viðnám við útflæði augnvökvans. Flögnunargláka hefur hraðan sjúkdómsgang, svarar illa lyfjameðferð og hefur verri horfur en önnur form gláku. Gríðarlega munur er milli niðurstaðna rannsókna á algengi heilkennisins, sem hefur hvatt til frekari athugunar á hugsanlegum mun milli kynþátta og áhrifum umhverfisþátta. XFS hefur einnig verið spyrt við ýmsar annarskonar breytingar í augum svo sem; breytingar í þykkt hornhimnu (CCT), bognari hornhimnu (CC) og skýmyndanir í kjarna augasteins. Sumar rannsóknir hafa fundið tengsl milli XFS og kerfissjúkdóma; þá aðallega hjarta- og æðasjúkdóma. Áhrif útfjólublás ljóss (UV) hafa einnig verið rannsökuð sem hugsanlegur orsakavaldur, ásamt öðrum þáttum.

Aðferðir og efniviður: Reykjavíkuraugnrannsóknin (RES) er framsæ rannsókn sem byggð er á slembiúrtak í Þjóðskrá. Upphafsskoðunin var gerð haustið 1996, þegar 1.045 einstaklingar eldri en 50 ára tóku þátt. Af þeim mættu 846 (88,2% eftirlifenda) í eftirfylgni fimm árum síðar. Allir þátttakendur fóru í gegnum staðlaða augnskoðun og svöruðu yfirgripsmiklum spurningalista um heilsufar og lífsstíl.

Niðurstöður: Í algengisrannsókninni greindist XFS hjá 10,7% þátttakenda og frekar hjá konum og þeim sem eldri voru. Fimm árum síðar greindist heilkennið í 5,2% til viðbótar. Sterk tengsl milli XFS og IOP voru greinileg. Engin munur var hinsvegar merkjanlegur á byggingu forhólfs augans. Marktækt meira tap á taugavef hjá þeim sem höfðu XFS kom skýrt í ljós í mælingum á hlutfalli milli sjóntaugarbolla og sjóntaugaróss (optic disk).

Ályktanir: XFS er algengt meðal íslendinga, meira meðal kvenna og þeirra sem eldri eru. Greiningarviðmiðin sem stuðst er við eru áreiðanleg yfir tíma. Við finnum líka breytingar í áhættu sem benda til þess að andoxun gegni hlutverki í framgangi heilkennisins.

Lykilorð: Flögnunarheilkenni – Gláka – Algengi – Nýgengi - Áhætta

ABSTRACT

Introduction: Exfoliation syndrome (XFS) is a major risk factor for glaucoma. It is characterized by a pathological accumulation of polymorphic fibrillar-material in the anterior segment of the eye. It is likely that the increase in intraocular pressure (IOP) seen in XFS patients, is at least in part due to flakes of material clogging up the trabecular meshwork, and thereby increasing the resistance to outflow and increasing IOP. XFS glaucoma progresses more rapidly, is more resistant to medical treatment, and has worse prognosis than other glaucomas. The prevalence of XFS has been found to vary greatly between different studies, raising the possibility of both racial and/or environmental modulators. XFS has also been linked to other changes in ophthalmological structures such as; changes in central corneal thickness (CCT), steeper corneal curvature (CC), and nuclear lens opacifications. Some studies have found XFS to be associated with systemic diseases, mostly cardiovascular and cerebrovascular. Exposure to ultra-violet (UV) light has also been investigated as a possible culprit, along with several other plausible factors. The aim of the present study was to determine the prevalence and 5-year incidence of XFS, to establish possible risk factors and/or concomitant symptoms, and finally to investigate the relationship between XFS and glaucomatous changes.

Materials and Methods: The Reykjavík Eye Study (RES) is a prospective study based on a random sample from the Icelandic national population sample. The baseline examination was done in the autumn of 1996, when 1,045 persons older than 50 years participated. Of these, 846 (88.2% of survivors) participated in a follow-up 5 years later. All participants went through a standard examination protocol, and answered a comprehensive questionnaire on health and life-style.

Results: In the prevalence study, XFS was found in 10.7% of subjects, more frequently in females and older persons. Five years later a further 5.2% of those that participated in the follow-up study, and had no signs of XFS at baseline, were diagnosed having XFS. We found a strong correlation between IOP and XFS. No difference was found in the anterior segment parameters measured, but there was a significant loss of neural tissue in the XFS as demonstrated by measurements of cup/disk ratio.

Conclusions: We find XFS to be frequent among Icelanders, increasing with age and more in females. Our diagnostic criteria are reliable over time. We have also identified possible risk factors that point to a role of antioxidants in the development of XFS. We find changes in corneal curvature and thickness more related to age than XFS.

Key words: Exfoliation syndrome – Glaucoma – Prevalence – Incidence - Risk

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ABBREVIATIONS

95% CI	95% confidence intervals
ARM	Age-related Maculopathy
CC	Corneal Curvature
CCT	Central Corneal Thickness
C/D	Cup to Disk ratio
GON	Glaucomatous Optic Neuropathy
GS	Glaucoma Suspects
GVFD	Glaucomatous Visual Field Defect
IOP	Intraocular pressure
LOXL 1 gene	Lysyl Oxidase-Like 1 Gene
mmHg	Pressure Measured in Millimeters Mercury
n.s.	Not Significant
OAG	Open-angle glaucoma
OR	Odds ratio
PEX	Pseudoexfoliation syndrome/Exfoliation syndrome
RES	Reykjavík Eye Study
SD	Standard Deviation
UV	Ultra Violet
VA	Visual Acuity
VCDR	Vertical Cup to Disk Ratio
XFS	Exfoliation syndrome/Pseudoexfoliation syndrome

LIST OF PAPERS

This thesis is based on the following papers which are referred to in the text by Roman numeral.

I. Pseudoexfoliation in the Reykjavik Eye Study: Prevalence and Related Ophthalmological Variables.

Ársæll Arnarsson, Karim Damji, Þórður Sverrisson, Hiroshi Sasaki, Friðbert Jónasson.

Acta Ophthalmologica 2007; 85: 822-827.

II. Pseudoexfoliation in the Reykjavik Eye Study: 5-year Incidence and Changes in Related Ophthalmological Variables.

Ársæll Arnarsson, Karim Damji, Hiroshi Sasaki, Þórður Sverrisson, Friðbert Jónasson

American Journal of Ophthalmology 2009; Forthcoming

III. Corneal Curvature and Central Corneal Thickness in Pseudoexfoliation: The Reykjavik Eye Study.

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IV. Prevalence of Open-angle Glaucoma in Iceland: Reykjavik Eye Study.

Friðbert Jónasson, Karim Damji, Ársæll Arnarsson, Þórður Sverrisson, Lan Wang, Hiroshi Sasaki, Kazayuki Sasaki, Reykjavik Eye Study Group.

Eye 2003; 17(6): 747-753.

V. Exfoliation Syndrome in the Reykjavik Eye Study: Risk factors for Baseline Prevalence and 5-Year Incidence.

Ársæll Arnarsson, Friðbert Jónasson, Karim Damji, María Soffía Gottfreðsdóttir, Þórður Sverrisson, Hiroshi Sasaki.

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VI. Risk Factors for Nuclear Lens Opacifications: The Reykjavik Eye Study.

Ársæll Arnarsson, Friðbert Jónasson, Hiroshi Sasaki, Masaji Ono, Vésteinn Jónsson, Masami Kojima, Nobuyo Katoh, Kazayuki Sasaki, The Reykjavik Eye Study Group.

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VII. Risk Factors for 5-Year Incidence of Age-Related Macular Degeneration - Reykjavik Eye Study.

Arnarsson Á, Sverrisson T, Stefánsson E, Sigurðsson H, Sasaki H, Sasaki K, Jónasson F.

American Journal of Ophthalmology 2006; 142(3):419-428.

INTRODUCTION

Relevance of exfoliation syndrome

Exfoliation syndrome (XFS), also called Pseudoexfoliation (PEX), is a degenerative age-related condition characterized by a pathological accumulation of polymorphic fibrillar-material in the anterior segment of the eye (Schlötzer-Schrehardt & Naumann, 2006). It was first described by a Finnish ophthalmologist, Lindberg, in his doctoral thesis in 1917 (English translation 1989). The patient does usually not notice any symptoms, and the diagnosis requires a thorough ophthalmological examination, including dilatation in many cases. The XFS material appears to be produced by various intraocular cells such as the preequatorial lens epithelium, nonpigmented ciliary epithelium, trabecular epithelium, corneal endothelium, vascular endothelial cells, and virtually all cell types of the iris. Most importantly, XFS has been identified as a major risk factor for open-angle glaucoma (OAG), an association first described by Vogt in 1925 (*see* Naumann et al., 1998). XFS glaucoma is classified as secondary open-angle glaucoma (Naumann et al., 1998), and is characterized with rapid progression, more resistance to medical treatment and worse prognosis than primary open-angle glaucoma (Jonasson, 2007; Leske et al., 2003; Schlötzer-Schrehardt & Naumann, 2006). Elevated intraocular pressure (IOP), with or without glaucomatous changes, has been reported in about a quarter of eyes with XFS, which is 6 to 10 times more frequent than in normal eyes.

Pathology

The intraocular pressure elevation seen in XFS is likely caused by XFS material detaching from the cells that produce it and then floating in the anterior segment until it attaches itself in the trabecular meshwork, thereby creating an increased resistance to outflow of aqueous humour (Schlötzer-Schrehardt & Naumann, 2006). However, some studies have indicated that the effects of XFS on ocular pathology may be more

complicated than merely through pressure increase caused by decreased outflow. In a 3-year prospective study, Puska and associates (1999) found for example, that in normotensive patients with unilateral XFS and equal IOP throughout the study, changes in the optic disk were found only in the eye with XFS. This would suggest a presence of a deteriorating factor other than IOP. Apart from the occluding effects on the trabecular meshwork, XFS has also been linked with vasculopathy both intra- and extraocular (Ritch & Schlotzer-Schrehardt, 2001).

Even so, the relationship between glaucomatous damage and IOP seems stronger in XFS glaucoma than in other OAG patients. Correlation can be found between diurnal IOP fluctuations and nerve fiber layer thickness (Gumus et al., 2005), as well as between time of diagnosis and mean visual field defect (Teus et al., 1998), in patients with XFS glaucoma but not in OAG patients. Similarly studies have shown greater clinical benefit from IOP lowering for XFS glaucoma patients than others (Bergea et al., 1999).

XFS has also been linked to a number of other ocular pathologies such as zonular and lens capsule weakness, poor pupillary dilatation, blood aqueous barrier breakdown, corneal endothelial decompensation, and retinal vein occlusion. These concomitant signs cause the increased risk of ocular surgical complications frequently seen in these patients (Scorolli et al., 1998; Schlötzer-Schrehardt & Naumann, 2006). XFS has furthermore been associated with increased lens opacification (Aravind et al., 2003) and Jonas & Papastathopoulus (1997) found the optic disk in eyes with XFS to be slightly smaller than in eyes without XFS.

There is much interest currently in studying the cornea of glaucoma patients, and investigating whether either its thickness or the curvature may play a role (Behki et al., 2007). This interest has also extended to XFS. Recent reports suggest that the central cornea in XFS patients might be thinner than in normal subjects (Inoue et al., 2003) although other reports refute this (Ventura et al., 2001). Our previous studies (Eysteinsson et al., 2002) have found corneal curvature (CC) to be independent of age and intraocular pressure (IOP), but significantly steeper in females. Central corneal curvature (CCT) on the other hand was found to be independent of age and gender, but positively related to IOP. In a recently published paper, Hepsen et al. (2007) reported significantly steeper CC in eyes with XFS in patients of Turkish ethnicity. The authors also found central corneal thickness (CCT) to be significantly thinner in

normotensive XFS eyes, but significantly thicker in glaucomatous XFS eyes, when compared with normal eyes.

Epidemiology

In all reports the prevalence of XFS has been shown to increase with age. The influence of sex has been shown to vary much more. Some studies have shown XFS to be significantly more prevalent in women than in men (Åstrom et al., 2007; Ekström, 1987; Hiller et al., 1982), while other studies show no gender difference (Arvind et al., 2003; Jeng et al., 2007; McCarty & Taylor, 2000; Miyazaki et al., 2005; Stefaniotou et al., 1990), and some find the condition to be more prevalent in males (Kozobolis et al., 1997; Nouri-Mahdavi et al., 1999; Taylor, 1979; Yalaz et al., 1992).

Considerable emphasis has been placed on the effect of geography in XFS research over several decades, specifically whether race or certain environmental factors might play a role in the pathogenesis of the disease. The prevalence of XFS is higher in specific geographical areas, varying substantially even within the same country (Colin et al., 1988). Until the 1960's it was thought that XFS was more or less a "Scandinavian" disease, due to reports of very high prevalence (Orzalesi et al., 1993). The geographical clustering and ethnic influence of XFS have not been fully elaborated or explained, and may indeed in some instances be due to methodological differences. Some sampling methods call for cautious extrapolations of results, and it may not be straightforward to compare results from samples taken randomly from a population to a sample of patients from a general ophthalmology or a specialized glaucoma clinic. For one, the ever important age- and sex-distribution in a sample that is not randomized or population-based may come into play. Diagnostic criteria also differ significantly between studies and may be missing in some research papers altogether. In retrospective studies especially, the lack of a specific protocol is almost always an issue. The use of mydriatics, or more importantly, the lack thereof, can also have profound effects on the results. Even so, it seems plausible that XFS is more prevalent in some areas than others. Pioneering studies by Forsius (1988) in which the same researcher using the same methodology and diagnostic criteria examined the

whole sample, revealed great variation in prevalence. This author found no signs of XFS in 96 Eskimoes from Greenland, USA and Canada, whereas he found a prevalence of 21% in Finns over 60 year of age. Contrary to Forsius, Aasved (1969) examined prevalence of XFS in old people's homes in Norway, Germany and UK and found them no different. These seemingly conflicting results perhaps suggest that although there probably is a racial difference in prevalence of XFS, it may in some studies be due to purely methodological differences. Therefore a more unified approach by the researchers is called for.

Extremely low prevalence has been found in several populations. Recollecting that no signs of XFS were found among Eskimoes, it is interesting to note that low prevalence of 3.4% in persons 50 years and older has also been found in Japan (Miyazaki et al., 2005). Other Japanese studies have reported even lower prevelance, such as 1.2% in persons older than 80 years (Yamamoto et al., 2005). A study of Chinese cataract-patients 60 years and older revealed a prevalence of 0.4% (Young et al., 2004).

In Australia (McCarty & Taylor, 2000; Mitchell, 1999) and USA (Cashwell & Shields, 1988; Hiller et al., 1982) the prevalence in samples roughly 50 years and older has been found to be around 2-3%. An exception is 38% in the American Navajo Indians (Faulkner, 1971). Thomas et al. (2005) reported 6.3% prevalence in persons 60 years of age or older living in India, which is similar to the 8.5% that Arvind et al. (2003) found in their study, but lower than the 14.5% in a study by Krishnadas et al. (2003). Low prevalence of XFS has also been reported for Peru and the Himalayas (Forsius, 1988).

The Nordic countries, with the exception of Denmark, have consistently reported higher prevalence of XFS than most others. Icelanders and Finns have been found to have clinically detectable prevalence of 20 – 25% in persons 60 years and older (Forsius, 1979; Krause, 1973, 1988; Sveinsson, 1974). In samples of 65 years and older from both Norway (Ringvold et al., 1988) and Sweden (Ekström, 1987), XFS was found in 16.9% and 17.9% of the samples, respectively. A Swedish study spanning 21 years showed the prevalence of XFS to be 23% in 66 year old persons, increasing to 61% at the time that the sample reached the age of 87 (Astrom et al., 2007). High prevalence of XFS has also been consistently reported in Greek and

Turkish populations (Kozobolis et al., 1997; Stefaniotou et al., 1990; Yalaz et al., 1992).

The small number of diagnosed cases in Denmark raises the question of clinical under-diagnosis, but a recent histopathological study of Danish and Finnish eyes with absolute glaucoma and uveal melanoma supported what had repeatedly been seen clinically (Alyahya et al., 2005), namely that in both conditions, XFS was around ten times more likely to be found in the Finnish eyes.

In accordance with the varying reports of prevalence of XFS in general, there is a remarkable variance in the reported number of XFS cases in glaucoma patients. Luntz (1972) found this prevalence to be 1% among white OAG patients but 20% among blacks in South-Africa. All of these studies, including those with low overall prevalence of XFS (Cashwell & Shields, 1988), report a much higher prevalence of XFS amongst glaucoma patients. A study by Jeng et al. (2007) found 16% of XFS patients to have glaucoma at the time of diagnosis, and subsequently that the 15-year risk of XFS conversion to XFS glaucoma to be about 60%. In the study by Astrom et al. (2007), 59% of glaucoma cases also had XFS at the age of 87 years. Conversion of ocular hypertensives with XFS to glaucoma has been found to be more common than conversion of ocular hypertensives without XFS (Grödum et al., 2005).

Association with systemic conditions

Although the only documented pathological effect is on the eyes, studies by Streeten et al. (1990, 1992) suggest that XFS is not exclusively an ocular condition but rather a systemic one. XFS material has been identified in various tissues of the body, primarily in connective tissue portion of visceral organs, and may be an indicator of impaired cellular protection mechanisms (Schlötzer-Schrehardt & Naumann, 2006). The presence of abnormal elastin fibers in the heart, lungs, liver, kidneys, gallbladder and meninges of XFS patients, has prompted studies of potential systemic co-morbidities (Schlötzer-Schrehardt and Naumann, 2006). Most of these studies have suggested cardiovascular and cerebrovascular involvement (Repo et al., 1993, 1995; Schumacher et al., 2001; Bojic et al., 2005; Linner et al., 2001; Viscontai et al., 2006). Arterial hypertension as well as ischaemic heart disease has been found to be more

frequent among XFS patients (Mitchell et al., 1997; Miyazaki et al., 2005), and Ritland et al. (2004) found the frequency of cerebrovascular disease to be higher among patients with XFS glaucoma than in other glaucoma patients. Reduced ocular and cerebral blood flow has been reported by several authors (Akarsu & Unal, 2005; Harju & Vesti, 2001; Repo et al., 1995; Yüksel et al., 2006). However, the association between XFS and systemic diseases has not been uniformly found in all studies. Jonas & Gründler (1998) did not find arterial hypertension more commonly in XFS patients and similarly Tarkkanen et al. (2008) using the Finnish national registry, found no difference in the frequency of arterial hypertension or ischaemic heart disease in patients with non-XFS glaucoma or XFS glaucoma. However, both studies reported lower frequency of diabetes mellitus in XFS patients, although it reached statistical significance only in the latter. In a small Icelandic sample, no association between XFS and cardiovascular disease, cerebrovascular disease, systemic hypertension, or diabetes mellitus was found (Allingham et al., 2001). Finally, it is important to note that the overall mortality rates have not been found higher in XFS patients (Ringvold et al., 1997; Ritland et al., 2004; Shrum et al., 2004).

Etiology

The search for the etiology of XFS has been directed both towards genetic and environmental factors. Since this is an age-related disease many researchers have chosen to focus mainly on the latter (Forsius, 1988), but given the variations in prevalence in different ethnic groups a possible genetic cause has been favoured by others.

Taylor (1979) found a high prevalence of XFS among aborigines in Australia. His results pointed to a possible correlation with exposure to ultraviolet (UV) light. Many of his cases also had climatic keratopathy, a condition that is also linked to UV exposure. That was later affirmed in a study by Resnikoff et al. (1991). Pointing to the contrary is the fact that in some areas with high UV radiation, like among the Inuit of Greenland and Peruvian mountain Indians, the prevalence of XFS has been found extremely low (Forsius, 1988).

In a study by Altintaş et al., (2005) an elevated plasma homocysteine level was found in persons with both XFS and XFS glaucoma, but not in patients with open-angle glaucoma (OAG) or control subjects. The authors linked these results with reports of increased vascular disease risk among XFS patients, pointing to hyperhomocysteinemia as a common culprit.
Previous studies from several countries including Iceland (Allingham et al., 2001; Aasved, 1975; Damji et al., 1998; Gottfredsdottir et al., 1999) suggested a genetic component in exfoliation syndrome. Using our present cohort, Thorleifsson et al. (2007) were the first to identify two risk variants in the lysyl oxidase-like 1 (LOXL 1) gene to be strongly associated with exfoliative glaucoma. The LOXL 1 is one of the enzymes essential for the formation and maintainance of elastin fibers (Jonasson, 2007).

Aims

The Reykjavik Eye Study is a population-based prospective cohort study that has been studying age-related eye diseases since 1996. Among its topics are exfoliation syndrome (Arnarsson et al., 2007; Thorleifsson et al., 2007), glaucoma (Jonasson et al., 2003), risk factors for nuclear lens opacifications (Arnarsson et al., 2002), and corneal curvature and thickness (Eysteinsson et al., 2002). The aim of the present study was to shed light upon the epidemiological aspects of exfoliation syndrome. Specifically, to determine the prevalence and 5-year incidence of the disease in this population, to establish possible risk factors and/or concomitant symptoms, and finally to investigate the relationship between XFS and glaucomatous changes. A clearer understanding of the epidemiology of XFS is of great value in early diagnosis and subsequent management of glaucoma, and could hopefully lead to better management of surgical complications and perhaps in identifying persons with higher risk of various systemic diseases. Finally, prevention of the condition is of course the ultimate goal. Specific goals of each paper (I-VII) were:

I. To determine the prevalence of Exfoliation Syndrome in a random sample of Icelanders 50 years and older. To examine differences in related ophthalmological variables between XFS cases and normal subjects.

II. To examine the 5-year incidence of definite and possible XFS in a random population sample, and to monitor changes in related ophthalmological variables. Incidence studies of exfoliation syndrome are few, especially those drawing from a random population sample. The study also gives us the opportunity to determine the reliability of XFS diagnosis over 5 years.

III. To assess the possible role of structural differences in the anterior segment has been of interest recently. We addressed possible structural difference in the cornea of those with XFS.

IV. To establish the age- and sex-specific prevalence of chronic open-angle glaucoma, subsuming pseudoexfoliation in a random sample of Icelanders 50 years and older.

V. To investigate possible risk factors for developing XFS. This study attempts to identify risk factors for both baseline prevalence and 5-year incidence of XFS.

VI. To study whether a relationship exists between XFS and nuclear lens opacification.

VII. To look at the correlation between XFS and age-related maculopathy (ARM).

MATERIAL AND METHODS

Participants

The Reykjavik Eye Study (RES) is a prospective study of age-related eye diseases based on a random sample from the Icelandic national population census. The baseline examination was done in September to October 1996, using a sample including 6.4% of the citizens of Reykjavik who were 50 years or older at that time. Of those 1700 randomly sampled, 65 had died and 256 could not be located at their addresses indicated in the population census, apparently since they had moved without yet informing the census bureau. 1379 persons could be contacted and were eligible. Of these, 1045 elected to participate, 461 males and 584 females, yielding a response rate of 75.8%. All were Caucasians. Those unwilling to participate all answered a short questionnaire over the phone, among other things giving their reasons for non-participation.

Of the 1045 individuals, 846 (88.2% of survivors) participated in the follow-up examination and interviews in September and October 2001.

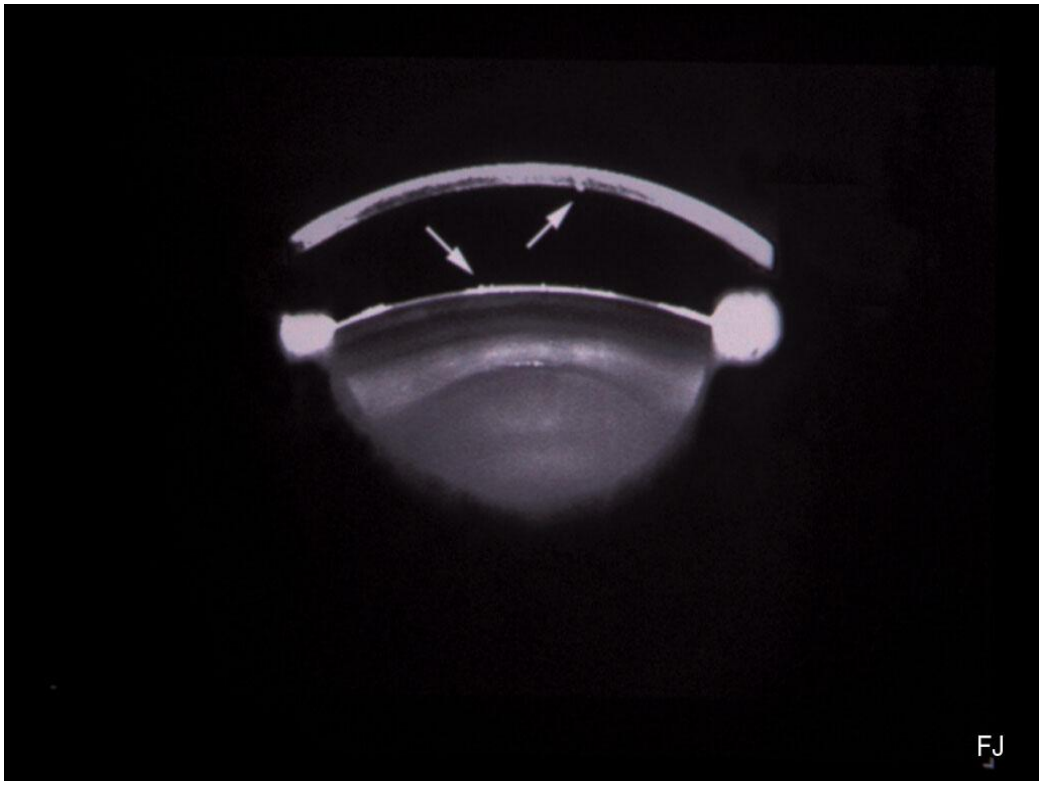
Procedure

The participants were examined at the University Eye Department in Reykjavik. Appropriate ethical approvals were obtained from the Data Protection Commission and the National Bioethics Committee following the guidelines of the Helsinki declaration. Written informed consent was obtained from all participants after the study had been explained to them.

All participants went through a standard examination protocol including keratorefractometry (ARK 900; Nidek Co Ltd, Gamagori, Japan), air puff tonometry (NT 2000; Nidek), noncontact specular microscopy and photography (Noncon ROBO, Konan, Japan), axial length and central corneal thickness measurements (Echoscan US800, Nidek), and visual acuity measurements. For central corneal thickness measurements we used Scheimpflug slit images of the anterior eye segment

using the Nidek EAS 1000 automated eye analysis system (Eysteinsson et al. 2002). The Scheimpflug photography of the anterior segment was also used for measurements of the anterior chamber depth and lens thickness, as well as grading the type and severity of the lens opacification using the Japanese lens grading system and a conversion to LOCS II (Sasaki et al. 2000). Additionally, Scheimpflug photographs can reveal XFS flakes as demonstrated in figure 1.

Figure 1: Scheimpflug photograph showing XFS flake in the corneal endothelium (arrow), a central shield and a peripheral band



The pupils were maximally dilated with Tropicamide 1% and Phenylephrine 10%, and a slit lamp biomicroscopy of the fundi using 78D lens was performed. One simultaneous color stereo fundus photograph for each eye (30°) was taken centred on the optic disk (Nidek 3 Dx/NM). Horizontal and vertical disk diameter (mm) was determined in a masked manner by a glaucoma specialist following the Beaver Dam Eye Study protocol (Klein et al., 1987; Klein et al., 1992). This was done by using a plastic template with circles of increasing size. The circles are superimposed over the disks and cups measuring the largest cup/disk ratio within 20º of the horizontal and

vertical midline. We also did measurements in millimetres using the Nidek 3D Station (Eysteinsson et al., 2005). Images of unsatisfactory quality were disregarded.

A subgroup of 85 participants was recalled at approximately 3 and 12 months after the baseline examination, for a full threshold visual field assessment (Octopus G1X) and gonioscopy (Goldman single-mirror lens).

For the purpose of diagnosing maculopathy, two simultaneous color stereo fundus photographs (30°) were taken, one centered on the fovea and the other on the optic disk (3Dx/NM; Nidek). We used Ektachrome Professional Plus film (EPP 5005, Kodak, Rochester, New York, USA). The 35-mm slides were framed and analyzed with a pocket stereoscope with a x2.8 lenses (Cartographic Engineering Ltd, Hampshire, England, United Kingdom). We used the international classification and grading system for ARM and AMD (Bird et al., 1995) which is based on the Wisconsin system by Klein and associates (1991). The grading was carried out at the Moorfields Eye Hospital Reading Centre in London. The grading of photographs was done by the same two graders for both baseline and incidence data. The graders were masked with regards to identity, age, and clinical history of the subjects. A standard Wisconsin grid for ARM classification was used (Klein et al., 1991). The present study includes only those lesions present within the grid.

The diagnosis of lens opacification and grading of this followed the Japanese cooperative cataract epidemiology study group system (Sasaki et al.
1994). The diagnosis of type and grading for data analysis, was done using Scheimpflug photography, slit- and retroillumination images.

Grading of early ARM included presence of soft, indistinct, or reticular drusen and pigmentary abnormalities ≥63 μm in diameter within the grid. Late AMD was divided into geographic atrophy, defined as a discrete area of retinal depigmentation characterized by sharp edges >175 μm in diameter with visible choroidal vessels and exudative AMD, including serous or hemorrhagic detachment of the pigment epithelium or sensory retina, presence of subretinal or subpigment epithelium hemorrhage, or subretinal fibrous scar.

Furthermore, all participants were required to answer a comprehensive questionnaire regarding lifestyle, food consumption, health, disease, previous surgery and medication. The items of this questionnaire were the following:

1. Aging indices: Age, Age at menopause, Senile pigment spots.

2. Gender, Marital status, Education.

3. Body Mass Index (BMI) based on self-reported height and weight, categorized into three groups: a) <22 kg/m2, b) 22–30 kg/m2, and c) >30 kg/m^2.

4. Smoking status (current smoker, former, or never), type of tobacco, and lifetime exposure (pack-years).

5. Alcohol-consumption status (current user, former, never), amount used (once a month or more often, less than once a month, never), and type of alcoholic beverages consumed (wine, beer or spirits).

6. Outdoor exposure: Daytime hours spend outside/weekdays only, wear of spectacles, sunglasses or hats. Occupation. Terrain (with respect to reflection) when outside.

7. Self-reported history of diseases and use of medication. Diabetes mellitus, arterial hypertension, coronary heart disease, arteriosclerosis, chronic bronchitis, asthma, rheumatism, thyroid disease, osteoporosis, atopy and gout.

8. Skin type: a) always sunburn, never tan, b) always sunburn, sometimes tan, c) sometimes sunburn, always tan.

9. History of eye diseases (confirmed on examination): myopia, hyperopia, glaucoma, uveitis, cataract and cataract surgery, macular degeneration.

10. The participants were asked about frequency of food intake for three different periods in their lives: a) in their 20’s–30’s, b) in their 40’s–50’s, and c) presently (at baseline in 1996), 4 to 7 times/week, 2 to 3 times/week, 1 to 2 times/2 weeks, less than once monthly. The food items inquired about were the following:

a. Green or yellow vegetables
b. Dietary fiber rich vegetables: tomatoes, cucumbers and red peppers
c. Beans, legumes, soy products
d. Fresh fish
e. Meat and meat products
f. Liver and liver products
g. Eggs and egg dishes
h. Herring
i. Seaweeds

j. Fresh fruits

k. Milk

l. Yogurt, sour milk, curdle

m. Plant oil

n. Tea

o. Cod liver oil

p. Sweeteners

Diagnostic criteria for XFS

After dilation of the pupil, a slit-lamp examination was performed looking specifically for XFS. To be classified as having *definite* XFS, participants had to have a partial or complete central shield on the anterior lens capsule and/or a peripheral band (Allingham et al. 2001) in at least one eye, as seen in figure 2. We also identified participants having *possible* XFS as being those with either suspected XFS flakes on anterior segment structure or precapsular haze/frosting on the central lens capsule in at least one eye.

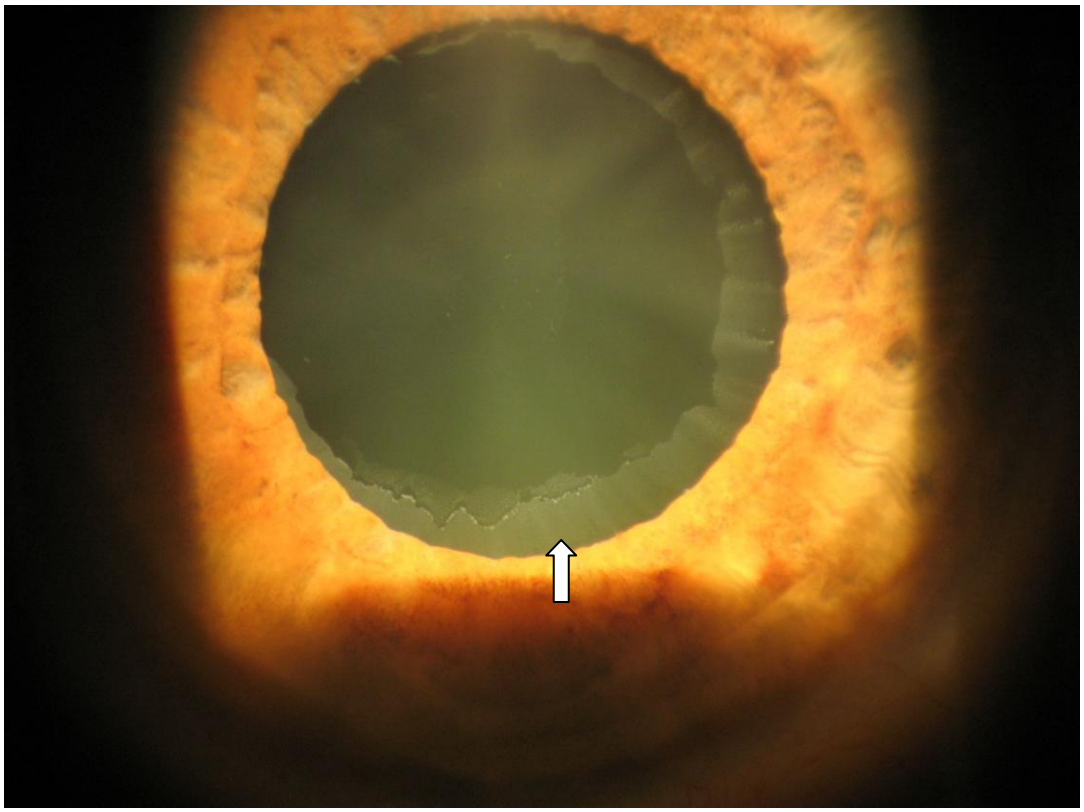
Five year incidence of definite XFS was defined as the appearance of a lesion in either eye at follow-up that was absent in both eyes at baseline, and no distinction is made to eyes having no or possible XFS.

Diagnostic criteria for open-angle glaucoma

In keeping with Wolfs et al. (2000) and Foster et al. (2002) for the diagnosis of glaucoma in cross-sectional prevalence studies, we used the optic nerve head of those not with glaucoma to establish the 97.5^{th} and the 99.5^{th} percentile. Selection of vertical cup/disk ratio (VCDR) >0.7 and 0.8 was based on these 97.5^{th} and 99.5^{th} percentiles, respectively. Also included are cup/disk ratio (C/D) asymmetry of the 97.5^{th} percentile (>0.2) and 99.5^{th} percentiles ($\geq$ 0.3), as well as focal glaucomatous disk changes. The 97.5^{th} percentiles are used for patients with glaucoma where glaucomatous visual field defects are also established and the stricter structural definition of 99.5^{th} percentiles (category 2) is used for those where visual field loss

has not been shown possibly due to poor performance of the participants or he/she was too frail to do a visual field test.

Figure 2: A photograph of the anterior segment clearly showing a peripheral band



The diagnostic criterion for open-angle glaucoma was modified from Foster et al 2002, and included either of the following categories:

1. Category 1 diagnosis includes both structural and functional evidence. Two out of the following three are present with a glaucomatous visual field (GVFD):
    a. Vertical cup/disk ratio ≥97.5th percentile (>0.7)
    b. Focal glaucomatous disk change, such as disk haemorrhage, notch of the neuroretinal rim, marked sloping of rim tissue or narrowest remaining rim of 0.1 disk diameter or less
    c. Cup/disk asymmetry between eyes ≥ 97.5th percentile (>0.2)
2. Category 2 diagnosis includes structural evidence only while the visual field loss remains unproven. Two out of the following three are present:
    a. Vertical cup/disk ratio ≥99.5th percentile (>0.8)

b. Focal glaucomatous disk change, such as disk haemorrhage, notch of the neuroretinal rim, marked sloping of rim tissue or narrowest remaining rim of 0.1 disk diameter or less
c. Cup/disk asymmetry between eyes ≥ 99.5th percentile (>0.3)

Diagnostic criteria for open-angle glaucoma suspects

A diagnostic criterion for open-angle glaucoma suspects includes one of the following signs:

1. IOP ≥ 23 mmHg
2. IOP ≥ 23 mmHg with one of the three following criteria for glaucomatous optic neuropathy (GON):
    a. Vertical cup/disk ratio ≥99.5th percentile (>0.8)
    b. Focal glaucomatous disk change, such as disk haemorrhage, notch of the neuroretinal rim, marked sloping of rim tissue or narrowest remaining rim of 0.1 disk diameter or less
    c. Cup/disk asymmetry between eyes ≥ 99.5th percentile (>0.3)
3. IOP ≥ 23 mmHg with GVFD
4. GVFD
5. Any one of the three criterions for GON listed in 2 above

Criteria for GVFD included the following:

1. Asymmetry across the horizontal midline (in early/moderate cases)
2. Located in the mid-periphery (in early/moderate cases)
3. Clustering in neighbouring test points
4. Not explained by any other disease
5. Considered a valid representation of the subject's functional status (based on performance indices such as false-positive rate)

Exclusion criteria

Exclusion criteria for XFS were history of previous glass blowing, previous trauma, or intra-ocular surgery. All eyes with pseudophakia at baseline or at the follow-up

examination 5 years later were excluded from the incidence analysis. All persons with either eye pseudophakic were excluded from analysis of incidence in either eye. Since XFS is an age-related disease, this will surely cause underestimation of incidence. For incidence analysis, we additionally exclude those eyes that already were found to have definite XFS at baseline. Cases of regression are dealt with separately.

Data handling and statistical methods

We used SPSS (version 13.0 and 15.0, SPSS Inc, Chicago, Illinois, USA) for statistical analysis, which included descriptive statistics, t-tests, chi-square, ANOVA with Bonferroni post-hoc tests, Kolmogorov-Smirnov normality test, linear regression, binary and multinominal logistic regression. Odds ratios (OR) and 95% confidence intervals (CI) were calculated first by a univariate logistic model, and then all variables that showed some trend toward significant association were analyzed further by the multivariate logistic model. In all multivariate calculations, we controlled for the effects of age, gender, smoking, and possible XFS.
All risk analysis for XFS was done using worse/affected eye diagnosis. All risk analysis was performed for persons with both definite and possible XFS, but the latter failed to reveal any significant associations. In the multivariate analysis however, we did always control for possible XFS.

RESULTS

A summary of the main results of the thesis is provided below. Detailed results are presented in the series of papers I-V, which are in the appendix I.
Table 1 shows the number, age and sex of the participants that attended first the prevalence examination in 1996, and then the 5-year incidence examination in 2001.

Table 1: Number of participants by age and sex, at baseline and follow-up

Prevalence examination in 1996			
Age (years)	Males	Females	Combined
50-59	167	195	362
60-69	144	210	354
70-79	116	135	251
80+	34	44	78
Total	461	584	1045
5 year incidence examination in 1996			
Age (years)	Males	Females	Combined
50-59	142	161	303
60-69	125	178	303
70-79	94	110	204
80+	16	20	36
Total	377	460	846

Prevalence of exfoliation syndrome

In the prevalence study of XFS (paper I), signs of exfoliation was found in either eye of 108 subjects (10.7%). We found greater rates of prevalence with increasing age: 2.5% of people aged 50–59 years had XFS; whereas 40.6% of those aged ≥80 years were affected. The difference between all 10-year age groups was significant ($p < 0.05$). Women were more frequently diagnosed with XFS in at least one eye (12.3% versus 8.7% of men), a difference that remained highly statistically significant ($p <$

0.001) after controlling for the effect of age. Table 2 shows the prevalence of XFS in details.

Table 2: Prevalence of exfoliation syndrome in at least one eye, by age and sex, including 95% confidence intervals

Age (years)	At risk (n)	XFS % (95% CI)
Females		
50–59	193	3.6 (1.0–6.3)
60–69	207	9.2 (5.2–13.1)
70–79	125	21.6 (14.3–28.9)
≥ 80	36	44.4 (27.4–61.5)
Total	561	12.3 (9.6–15.0)
Males		
50–59	166	1.2 (0.0–2.9)
60–69	144	8.3 (3.8–12.9)
70–79	112	13.4 (7.0–19.8)
≥ 80	28	35.7 (16.8–54.6)
Total	450	8.7 (6.1–11.3)
Males and females combined		
50–59	359	2.5 (0.9–4.1)
60–69	351	8.8 (5.8–11.8)
70–79	237	17.7 (12.8–22.6)
≥ 80	64	40.6 (28.3–53.0)
Total	1011	10.7 (8.8–12.6)

Analysis of the data for right eyes only (Table 3) showed similar trends for both age and sex. The results for left eyes are not shown, but were similar.

We found unilateral XFS in 62 persons (in 33 right eyes and 29 left eyes) and bilateral XFS in 35 persons. The mean ages of people with uni- and bilateral XFS were 72.0 years and 71.0 years, respectively. Men constituted 35% of cases with unilateral XFS, and 40% of cases with bilateral XFS. This gender difference between uni- and

bilateral XFS was not statistically significant. Additionally, 11 persons had unilateral XFS and pseudophakia in the other eye.

Table 3: Prevalence of exfoliation syndrome by age, sex and right eye, including 95% confidence intervals

Age (years)	At risk (n)	XFS % (95% CI)
Females		
50–59	194	2.6 (0.3–4.8)
60–69	207	7.7 (4.1–11.4)
70–79	123	16.3 (9.6–22.9)
≥ 80	32	28.1 (11.7–44.6)
Total	584	8.7 (6.3–10.8)
Males		
50–59	166	1.2 (0.0–2.9)
60–69	144	4.2 (0.9–7.5)
70–79	112	7.1 (2.3–12.0)
≥ 80	26	26.9 (8.7–45.2)
Total	462	5.0 (3.0–7.0)
Males and females combined		
50–59	360	1.9 (0.5–3.4)
60–69	351	6.3 (3.7–8.8)
70–79	235	11.9 (7.7–16.1)
≥ 80	58	27.6 (15.7–39.4)
Total	1004	7.3 (5.7–8.9)

5-year Incidence

The 5 year changes in right eyes based on XFS status at baseline (1996) are demonstrated in table 4 from paper II. A total of 1004 right eyes could be examined

with regards to XFS in 1996. Vast majority, or 68%, of those right eyes that did not have XFS in 1996 remained the same 5 years later, whereas 11% were deemed to have progressed to possible XFS and 2% had progressed to definite XFS. Of the right eyes that were diagnosed as having possible XFS in 1996, 27% could not be examined again in 2001, due to non-participation including death or pseudophakia. 47% of the right eyes diagnosed with possible XFS in 1996, were not found to have signs of XFS in 2001. Thus two-third of cases found to have possible XFS in 1996 were not identified in a double-blinded manner 5 years later by the same examiners. 21% continued to be diagnosed as possible XFS and 5% progressed to definite XFS. There is no significant difference in the likelihood of having possible or definite XFS in 2001, based on whether the eye had either no sign of XFS or possible XFS in 1996 ($p = 0.930$). All right eyes with possible XFS in 1996 were considered to be at risk for definite XFS in 2001.

Table 4: Five year changes in diagnosis of XFS in right eyes with respect to status at baseline (percentage and number)

	1996			
2001		**No XFS**	**Possible XFS**	**Definite XFS**
	No XFS	68% (N=538)	47% (N=67)	5% (N=4)
	Possible XFS	11% (N=85)	21% (N=30)	8% (N=6)
	XFS	2% (N=19)	5% (N=7)	51% (N=37)
	No lens	2% (N=17)	1% (N=2)	8% (N=6)
	Missing	16% (N=129)	26% (N=37)	27% (N=20)
	Total	100% (N=788)	100% (N=143)	100% (N=73)

Four right eyes out of 47 examined and diagnosed as having XFS in 1996, were found to have no XFS in 2001. Six right eyes that were diagnosed as having XFS in 1996 were found to be pseudophakic in 2001, and six diagnosed as definite in 1996 were considered possible in 2001. Majority of right eyes diagnosed as XFS in 1996 remained unchanged 5 years later, but it is also worth noting that the number of right

eyes with XFS in 1996 that have undergone lens surgery five years later, is proportionally higher than in the other two groups ($p = 0.001$).

41 persons that were diagnosed as having unilateral XFS in 1996 could be examined for bilateral changes in 2001. Of these, no XFS was found in 4 persons (10%), 26 were still unilateral (63%), and 11 had progressed to bilateral XFS (27%). No significant difference was found in gender or mean age of these three groups.

All cases counted as "No lens" or "Missing" in table 4, were excluded from our incidence analysis. Not surprisingly, the persons that already had XFS in 1996, have the highest percentage of "no lens" or "missing", 5 years later.

Table 5 shows the 5-year incidence of XFS in at least one eye, in percentages with 95% confidence intervals. Only persons that had both eyes diagnosed with possible and/or no XFS in 1996 and could be examined again in 2001, were considered to be at risk. We excluded all persons that did not attend the 2001 examination, as well as all those that had pseudophakia in either eye in the 1996 or 2001 examination. Additionally, 96 phakic persons that had already been diagnosed with XFS in 1996 in either eye were excluded from this analysis.

Of those persons at risk, 5.2% were diagnosed as having XFS in either eye after 5 years where none had been detected before. Females outnumbered males, 6.7% versus 3.4% respectively. Incidence was more frequent among older participants, although the high percentage in the age-group of 80 years and older at baseline, can also be attributed to pseudophakia and low-participation rate in the oldest age-group. In total we found that 37 persons had XFS in either eye in 2001 where none had been found 5 years earlier. Four of them developed bilateral XFS, 12 had developed unilateral XFS accompanied by possible XFS in the contra-lateral eye, whereas 21 persons had unilateral XFS with no sign of XFS in the other eye.

Table 5: Five year incidence of exfoliation syndrome (XFS) in at least one eye, by age at baseline and sex

5YEAR INCIDENCE OF XFS IN EITHER EYE				
	At risk	**Afflicted**	**Percentage**	**95% CI**
Females				
50-59	158	7	4.4%	1.2-7.7
60-69	151	10	6.6%	2.6-10.6
70-79	72	8	11.1%	3.7-18.5
80+	7	1	14.3%	0.0-49.2
Total	388	26	6.7%	4.2-9.2
Males				
50-59	140	4	2.9%	0.1-5.7
60-69	112	4	3.6%	0.1-7.1
70-79	67	1	1.5%	0.0-4.5
80+	5	2	40.0%	0.0-100.0
Total	324	11	3.4%	1.4-5.4
Combined sexes				
50-59	298	11	3.7%	1.5-5.8
60-69	263	14	5.3%	2.6-8.1
70-79	139	9	6.5%	2.3-10.6
80+	12	3	25.0%	0.0-53.7
Total	712	37	5.2%	3.6-6.8

Table 6 shows the 5-year incidence of XFS in right eyes in percentages with 95% confidence intervals. Right eyes with possible or no XFS in 1996 and that were examined again in 2001 were considered to be at risk. All right eyes that had been diagnosed with XFS in 1996 were excluded from this analysis. Also excluded were pseudo- or aphakic right eyes in either the 1996 or 2001 examination.

Table 6: Five year incidence of exfoliation syndrome (XFS) in right eyes, by age at baseline and sex

	At risk	Afflicted	Percentage	95% CI
Females				
50-59	162	3	1.9%	0.0-4.0
60-69	156	9	5.8%	2.1-9.5
70-79	82	5	6.1%	0.8-11.4
80+	9	1	11.1%	0.0-36.7
Total	409	18	4.4%	2.4-6.4
Males				
50-59	140	3	2.1%	0.0-4.6
60-69	119	1	0.8%	0.0-2.5
70-79	72	3	4.2%	0.0-8.9
80+	5	1	20.0%	0.0-75.5
Total	336	8	2.4%	0.7-4.0
Combined sexes				
50-59	302	6	2.0%	0.4-3.6
60-69	275	10	3.6%	1.4-5.9
70-79	154	8	5.2%	1.7-8.7
80+	14	2	14.3%	0.0-35.3
Total	745	26	3.5%	2.2-4.8

XFS was found in 3.5% of all right eyes, 4.4% in females and 2.4% in males. Right eyes in older individuals were more likely to develop XFS during the five years, although the high percentage in the oldest group is also associated with few eyes available for examination due to pseudophakia.

The incidence of XFS was found to be twofold higher in females compared with males (OR = 2.04; 95% CI 0.99 – 4.20; p = 0.05), after we had controlled for the effects of age. Increasing age was also significantly linked to the incidence of XFS with the risk increasing by an average of 5% between the 10-year age-groups (95% CI 1.01 – 1.09; p = 0.022).

Exfoliation syndrome and intraocular pressure

As table 7 shows, we found at baseline (paper I), significantly higher ($p < 0.05$) IOP of right eyes with XFS (16.1 mmHg), compared with right eyes with no signs of XFS (15.4 mmHg). These results were verified in a model controlling for the effects of age. We also found women to have significantly higher IOP than men, 15.8 mmHg versus 15.1 mmHg respectively ($p < 0.005$). Given that women have both a higher frequency of XFS and higher overall IOP, possible confounding effects had to be taken into account. Controlling for the effects of age and sex in a regression model did not affect the significance of the association between IOP and XFS. We also found IOP > 21 mmHg in 5.5% of right eyes with XFS and 3.5% of right eyes without XFS at baseline. The difference was not significant (Table 7). Sixty eyes with unilateral XFS had reliable IOP measurements in both eyes. Mean IOP in eyes with XFS was 16.0 mmHg, but 14.9 mmHg in the contralateral unaffected eye ($p < 0.001$).
We also studied the changes that occur in IOP over a 5 year period in paper II. Table 8 shows these changes in three groups of right eyes: The first group already had XFS in 1996, the second group had no XFS at baseline but had XFS in 2001, and in the third group are those that had no XFS at baseline or after five years. In the total sample, we did not see significant changes in intra-ocular pressure (IOP) over the five years. Of the 832 right eyes that were measured on baseline and again five years later, we found the mean IOP to be 15.5 mmHg on both occasions. However, comparing those that did not have 5-year incident XFS to those that did (table 8), we find that the latter group shows a statistically significant increase in IOP ($p=0.007$), also after controlling for the effects of age and gender. In right eyes developing XFS during the five years there is an increase in IOP by 1.64 mmHg, while the other two groups show no change.
In paper II, we also examined IOP in persons diagnosed with unilateral XFS in 1996 and again in 2001. The mean 5-year change in all eyes afflicted with XFS was +0.8 mmHg, but +1.4 mmHg if those eyes that had ocular antihypertensive treatment were excluded. In the contra-lateral eyes the 5-year change was +0.4 mmHg, but the difference is not statistically significant. However, it is important to keep in mind that at baseline the XFS afflicted eyes have higher IOP than the contra-lateral unafflicted eye, 15.1 and 14.2 mmHg respectively. This means that eyes afflicted with XFS have

statistically significantly higher IOP than the contra-lateral eyes in 2001, 16.4 versus 14.6 mmHg respectively (p = 0.03).

Table 7: Various ophthalmic parameters in right eyes with or without exfoliation syndrome including standard deviation (SD), at baseline

	XFS	No XFS	Significance Univariate	Significance Multivariate Model*
IOP mmHg - Mean (SD)	16.1 (3.6)	15.4 (3.2)	P<0.05	P<0.05
IOP > 21 mmHg - % of eyes	5.5%	3.5%	n.s.	n.s.
Nuclear cataract - % of eyes	39.7%	16.1%	P<0.001	n.s.
Corneal thickness - Mean (SD)	533µ (32)	527µ (40)	n.s.	n.s.
Anterior chamber depth - Mean (SD)	2.61 (0.35)	2.80 (0.37)	P<0.05	n.s.
Lens thickness - Mean (SD)	4.39 (0.41)	4.26 (0.33)	P<0.05	n.s.
Disk diam vert - Mean (SD)	1.61 (0.15)	1.57 (0.16)	n.s.	n.s.
Disk Area - Mean (SD)	1.93 (0.32)	1.82 (0.37)	n.s.	n.s.
Cup-disk ratio - Mean (SD)	0.72 (0.10)	0.68 (0.10)	n.s.	n.s.

* Adjusted for age and sex

Exfoliation syndrome and anterior segment structures

As seen in table 7, we found no significant difference at baseline in CCT, anterior chamber depth or lens thickness, between those that had XFS and those without any signs, after adjusting for the effects of age, sex, and other possible confounders (paper I). This point was elaborated upon in paper III, where we looked at average CCT in patients identified with XFS-glaucoma and measured it as 0.541, compared with 0.532 in eyes that had XFS but no glaucoma. The difference is not statistically significant (p = 0.597). In paper III we also looked specifically at the relationship between XFS and corneal curvature (CC). Data on both XFS and CC were available in 821 participants. Of the 90 eyes that had XFS we found the average CC to be 7.667. This was not significantly different (p = 0.489) from the 731 eyes that had no signs of XFS, where the average CC was found to be 7.707.

At baseline (paper I), we report that 39.7% of right eyes with XFS also had nuclear lens opacifications, as did 28.0% of those without XFS (Table 7). This difference was highly significant until the effects of age were controlled for, when p = 0.872.

Table 8: Five year change in IOP and C/D ratio in right eyes with different XFS status (mean and standard deviation)

		XFS at baseline in 1996	**Incidence of XFS in 2001**	**No XFS in 2001**
IOP	**1996**	16.1 (3.6)	15.3 (3.1)	15.5 (3.2)
	2001	16.2 (4.9)	17.0 (4.2)	15.5 (3.2)
	Change	0.0 (4.16)	1.6 (3.6)*	0.0 (2.3)
CD Ratio Vert	**1996**	0.42 (0.24)	0.45 (0.20)	0.45 (0.21)
	2001	0.51 (0.25)	0.49 (0.20)	0.49 (0.21)
	Change	0.09 (0.16) †	0.04 (0.09)	0.04 (0.10) †

Significance is calculated between columns

*p<0.05

†p<0.01

Exfoliation syndrome, the optic disk and glaucoma

In paper IV we examine the relationship between XFS and glaucoma. Table 9 shows the age- and sex- specific prevalence of open-angle glaucoma (OAG) in the Reykjavík Eye Study (RES). A total of 42 persons were diagnosed with OAG; 17 according to the category 1 criteria, which was explained in length in the Materials and Methods chapter and includes 2/3 disk criteria and glaucomatous visual field defect. Seven out of the 17 also had XFS. Twenty-five were diagnosed on criteria for category 2, i.e. without visual fields or without visual field defect. No participant was classified according to category 3, since none had VA<3/60 related to OAG.

Additionally, 123 persons were diagnosed as glaucoma suspects (GS), according to the criteria outlined in the Materials and Methods chapter. Two had IOP ≥ 23 mmHg and 1/3 disk criteria, 13 had IOP ≥ 23 mmHg only and 95 had disk criteria only. Forty-three people had a history of OAG and had reiceived pressure-lowering treatment, some possibly for ocular hypertension. Seventeen of the 43 with a history of glaucoma were identified among the 42 persons diagnosed with glaucoma, all according to the category 1 criteria. Further 16 were considered GSs, and 10 participants remained unidentified by our criteria and may have been treated for ocular hypertension. Of the 42 people diagnosed with glaucoma in our study, 13 were considered to have normal tension glaucoma (31%) having IOP < 21 mmHg without pressure-lowering treatment.

On review of stereo optic nerve photographs, 10 females and two males had optic disk haemorrhage in one eye, and were thus classified as OAG suspects. None of these patients had other disk or visual field features to suggest definitive OAG classification.

Of the 42 persons diagnosed with glaucoma at baseline, 13 (31.0%) had definite XFS as well, and a further seven (16.7%) were suspected of having XFS. Of the 123 glaucoma suspects, 23 persons (18.4%) were found to have definite XFS, while in the group (861 persons) that did not show signs of glaucoma, 8.4% had XFS.

Table 7 demonstrates no difference in mean values and standard deviations for vertical disk diameter, disk area and VCDR in right eyes with XFS and no XFS at baseline (paper I). When we analysed the number of persons with and without XFS and with or without glaucoma, we found that 9.3% (95% CI 3.7–14.8) of subjects with XFS had glaucoma, as did 2.5% (95% CI 1.4–3.7) of those without XFS.

Table 8 is taken from paper II, and shows the changes in cup/disk ratio over a five year period. CD ratio increases for all participants, similarly for those that have no sign of XFS and the 5-year incidence cases, but significantly more for those participants that already had XFS at baseline. We found 20 persons that had developed glaucoma during the five year period of the study. In three cases XFS could not be assessed. Three of these patients already had XFS at baseline, and in two cases the XFS developed concomitantly with the glaucoma over the five year period.

Table 9: Age- and sex specific prevalence (%) of OAG and 95% CI

Age (years)	Males	Females	Combined
50-59	1.2 (0.0-2.9)	0	0.6 (0.0-1.3)
60-69	2.8 (0.1-5.5)	2.9 (0.6-5.1)	2.8 (1.1-4.6)
70-79	8.6 (3.4-13.8)	7.4 (2.9-11.9)	8.0 (4.6-11.3)
80+	17.6 (4.1-31.1)	9.1 (0.2-17.9)	12.8 (5.5-21.2)
Total	4.8 (2.8-6.7)	3.4 (1.9-4.9)	4.0 (2.8-5.2)

Risk factors for having exfoliation syndrome at baseline

In paper V we looked at the persons having XFS at baseline, and compared them to those that did not have XFS at that time, in terms of various possible risk factors related to health and life-style. All the items in the questionnaire listed in the Material and Methods section, were tested for possible risk association. Age is a dominant risk factor for XFS, a factor already described in papers I-IV, as well as in all other similar studies. In our sample the average age at baseline of persons with definite XFS is 72.3 years, with possible XFS it was 67.0 years, and for those with no sign of XFS it was 62.6 years. This difference was highly significant between all groups by ANOVA ($p < 0.001$). The likelihood of having definite XFS in either eye was dramatically increased for each year people got older after the age of 50 years (OR=8.49; 95%CI 8.31 – 8.8.77, $p<0.001$).

Pupil colour is a significant risk factor for having definite XFS in our sample. We find that compared with light blue/gray iris colour (OR=1.00) both persons with brown irides (OR=2.53; 95% CI 1.24-5.15, $p<0.05$) and mixed iris colour (OR=1.87; 95% CI 1.10-3.17, $p<0.05$) have raised risk in a multivariate model.

Compared with persons that never used alcohol (OR=1.00), those that used alcohol in moderation (once weekly) were less likely to have definite XFS (OR=0.47; 95% CI 0.28-0.78, $p<0.01$). More frequent users did not have a significantly different risk than never-users (OR=0.72; 95% CI 0.27-1.92) in a multivariate model controlling for the effects of age, sex, and smoking.

Table 10 also shows that more frequent consumption of dietary fiber rich vegetables reduces the likelihood of having definite XFS. Even after controlling for the effects of age, gender, smoking and possible XFS, we see that those individuals consuming dietary fiber rich vegetables 1-2 times/2 weeks earlier in their lives, are significantly less likely to have XFS compared with those who consume them less than once a month. Even more frequent consumption lowers the risk albeit non-significantly. Similarly we see that people eating green or yellow vegetables more frequently in their 20's and 30's are less likely to have definite XFS, even in a multivariate model. More frequent fruit consumption also shows a favourable trend in the univariate analysis, and remains significant in one instance in the multivariate model, that is, participants that consumed fruits 1-2 times/2 weeks are significantly less likely to have XFS than those that consumed fruits less than monthly.

Table 10: The Association between Consumption of Vegetables and Fruits, and the Risk of Having XFS in Univariate and Multivariate Analysis

Mean intake	In their 20´s and 40's OR (95% CI)	In their 40's and 60´s OR (95% CI)	Baseline OR (95% CI)
	Dietary fiber rich vegetables - Univariate Analysis		
Less than monthly	1.00	1.00	1.00
1-2 times/2 weeks	0.33 ()†	0.36 (0.19-0.68)†	0.61 (0.31-1.21)
2-3 times/week	0.36 ()†	0.41 (0.23-0.73)†	0.47 (0.24-0.91)*
4-7 times/week	0.35 ()*	0.21 (0.10-0.49)†	0.44 (0.22-0.87)*
	Dietary fiber rich vegetables - Multivariate Analysis		
Less than monthly	1.00	1.00	1.00
1-2 times/2 weeks	0.52 (0.28-0.97)*	0.46 (0.23-0.92)*	0.68 (0.32-1.41)
2-3 times/week	0.87 (0.43-1.76)	0.75 (0.38-1.44)	0.73 (0.36-1.51)
4-7 times/week	0.68 (0.22-2.07)	0.45 (0.18-1.14)	0.62 (0.30-1.30)
	Green or yellow vegetables - Univariate Analysis		
Less than monthly	1.00	1.00	1.00
1-2 times/2 weeks	0.36 (0.20-0.66)†	0.96 (0.42-2.18)	0.54 (0.26-1.12)
2-3 times/week	0.40 (0.21-0.74)†	0.77 (0.33-1.76)	0.68 (0.34-1.35)

4-7 times/week	0.58 (0.24-1.40)	0.88 (0.33-2.38)	0.81 (0.37-1.76)
	Green or yellow vegetables - Multivariate Analysis		
Less than monthly	1.00	1.00	1.00
1-2 times/2 weeks	0.42 (0.22-0.81)†	1.07 (0.44-2.60)	0.68 (0.31-1.48)
2-3 times/week	0.44 (0.23-0.87)*	0.76 (0.31-1.88)	0.74 (0.35-1.56)
4-7 times/week	0.60 (0.23-1.54)	0.82 (0.28-2.41)	0.82 (0.35-1.91)
	Fruits - Univariate Analysis		
Less than monthly	1.00	1.00	1.00
1-2 times/2 weeks	0.32 (0.18-0.57)†	0.65 (0.30-1.37)	0.88 (0.35-2.17)
2-3 times/week	0.30 (0.16-0.56)†	0.43 (0.20-0.92)*	0.65 (0.28-1.55)
4-7 times/week	0.45 (0.18-0.57)*	0.45 (0.21-0.98)*	1.07 (0.48-2.42)
	Fruits - Multivariate Analysis		
Less than monthly	1.00	1.00	1.00
1-2 times/2 weeks	0.47 (0.26-0.88)*	0.70 (0.31-1.59)	1.17 (0.44-3.10)
2-3 times/week	0.63 (0.31-1.26)	0.59 (0.26-1.34)	0.69 (0.27-1.73)
4-7 times/week	0.90 (0.43-1.90)	0.73 (0.31-1.70)	1.02 (0.43-2.44)

Multivariate analysis included age, gender and smoking

*$p<0.05$

†$p<0.01$

Being married was shown to be protective for definite XFS in a univariate analysis. However, controlling for the effect of age eliminated this association. The same pattern was seen in individuals considering themselves "very healthy", and persons reporting the most frequent consumption of vegetable oil. The loss of significance when we control for the effects of age for these three variables (i.e. marital status, self-reported health and vegetable oil consumption) simply illustrates that younger persons are less likely to have definite XFS, more likely to be married, to use vegetable oil and to enjoy better health than older persons.

We also examined the association between various self-reported diseases and the risk of having definite XFS. The only diseases that showed any association with having definite XFS were diabetes, arterial hypertension, a combination of all cardiovascular-related diseases and asthma. In a multivariate model only asthma retained its significance (OR=1.91; 95% CI 1.00-3.62, $p<0.05$).

In papers VI and VII, we examined the correlation between XFS and nuclear lens opacification and age-related maculopathy. The association between these three conditions was not found to be significant, although they are of course all age-related.

Risk factors for getting exfoliation syndrome over five years

In paper V we also looked at the persons that got XFS during the five year period following the baseline examination, and compared them to those that did not. Excluded from this analysis were of course all persons that had already been diagnosed with XFS at baseline. The comparison included various possible risk factors related to health and life-style, which were recorded in the baseline examination. All the items in the questionnaire listed in the Materials and Method chapter, were tested for possible risk association.

When examing the risk of five year incidence of XFS, we divided the participants up in 10- year age-groups, and found that on average there was a 5% increase in risk of developing definite XFS for every decade people were older than 50 (OR = 1.05; 95% CI 1.01-1.09, p=0.022).

Males were found to be significantly less likely to have a five year incident XFS than females, although only marginally when the effects of age had been controlled for (OR = 0.49; 95% CI 0.24 – 1.01, p = 0.05).

We did not see an increase in 5-year incident XFS relating to cataract-diagnosis at baseline. There was no effect of smoking. Persons with rheumatoid arthritis, gout and asthma had twofold more incidences of XFS, but this difference was not statistically significant. Iris-colour, self-reported health, marital status, did not affect 5-year incidence. More frequent fish-consumption was correlated with increase risk of 5-year incidence of XFS. However, this association vanished when we controlled for the effects of age, revealing the common theme in our data, that fish consumption is higher among older Icelandic persons than among younger. The only food-item we found significantly correlated with XFS-incidence, was that people that consumed fruits 4-7 times per week in their 20’s to 40’s were significantly less likely to have 5-year incidence of XFS than those that consumed fresh fruits seldom or never (OR = 0.20, 95% CI 0.04 – 0.91, p =0.04).

DISCUSSION AND CONCLUSION

The main findings in this thesis are that the prevalence and 5-year incidence of exfoliation syndrome in a random sample of Icelanders 50 years and older, has been established. We have also compared XFS cases to normal subjects on various parameters, both at baseline and over the 5 year period. That way we have examined the association of XFS with anterior segment structures, optic disk changes, intra-ocular pressure, glaucoma and other features, but also looked at possible risk factors that might influence the likelihood of developing the disease.
In general, the strengths of this study are the random population sample, the relatively high prevalence of XFS in this population and the inclusion of both cross sectional and longitudinal data. Limitations may include relatively low number of total participants resulting in limited statistical power, high proportion of pseudophakes in the oldest age-group lowering the detection rate of XFS and that the information on systemic disease is self reported. XFS may be somewhat underrepresented in the Reykjavik Eye Study, since this is a random sample with a fixed examination location and without the opportunity to examine immobile persons, who theoretically could be more commonly afflicted with diseases. However, in a study by Krause et al. (1988), two subsamples of institutionalized older individuals were found to have similar prevalence of XFS as non-institutionalized aged matched individuals.

Prevalence

Interestingly, exfoliative material was rarely found on the iris or corneal endothelium unless also found on the anterior lens capsule. XFS is found in either eye of 11% of those examined in RES and the prevalence increases significantly with increasing age. The same trend appears when examining right eyes only. There was a higher prevalence of women with XFS as compared with men both when considering at least one eye affected only as well as right eyes only. This preponderance of women is found in spite of the fact that women in the Reykjavik Eye Study, had pseudophakia more commonly than men, 12% versus 5% in those 70 – 79 years old and 33% versus 27% in persons 80 years and older and eyes with XFS may have increased risk of lens

surgery (Sasaki et al. 2000). This is important since our definition of exfoliation syndrome includes those only with central shield and/or peripheral band on the anterior lens capsule and which has been removed to a great extent in pseuodophakics and those individuals are therefore excluded by definition. Studies have revealed varying gender difference. Some have reported a higher prevalence for women (Hiller et al. 1982, Ekstrom 1987; Mitchell et al. 1999), others have found no gender difference (Summanen & Tönjum 1988), and others still have found greater prevalence in men (McCarty & Taylor 2000). It is of importance to accurately determine, through sampling and/or calculation, the effects of age and gender on variables linked to XFS. Age in our study profoundly increases the prevalence of XFS, but also affects a plethora of other ophthalmological variables, and is thus an important confounder to consider. Similarly, since we find females to be more likely to have XFS, it is important to look into the confounding effects of gender. The most obvious issue is that females have on average smaller eyes and shallower anterior chamber than males (Eysteinsson et al. 2005). Since we find XFS more commonly in women than in men, failing to control for gender difference in anterior chamber depth may therefore wrongly lead to the conclusion that eyes with XFS have shallower anterior chamber than eyes without XFS.

Our prevalence numbers are similar to those reported by Sveinsson in Iceland (Sveinsson 1974), Krause and coworkers in Finland (1988) and higher than reported in the Framingham Eye Study (Hiller et al. 1982) and The Blue Mountain Eye Study in Australia (Mitchell et al. 1999).

Table 11 shows the results of our prevalence study in relations to other similar studies. Although the prevalence varies greatly, it is difficult to discern a clear geographical trend. Perhaps we can conclude that persons of East Asian origin have a low prevalence of XFS, while the opposite is true of Nordic countries, as well as populations in the eastern Mediterreanian. Our results are similar to those seen in Finland, Greece, and Turkey, especially the study by Yalaz et al. (1992).

Again it is of utmost importance when reviewing table 11, to bear in mind the difference between many of these studies in their diagnostic criteria, the use of mydriatics, sampling-methods and age-distribution within those crude strata. Such tables can thus only serve as a crude reference.

Table 11: Prevalence of Exfoliation Syndrome found in various studies

Region	50-69 years	>70 years	Author
Eskimoes	0.0%	0.0%	Forsius (1988)
Toulon, France		3.6%	Colin et al. (1985)
Denmark		4.8%	Bockhaus & Lorentzen (1966)
Hisayama, Japan	2.2%	5.9%	Miyazaki et al. (2005)
India	4.5%	11.9%	Aravind et al. (2003)
Peru	0.8%	14.3%	Forsius (1988)
India	8.2%	20.1%	Krishnadas et al. (2003)
Brest, France		20.6%	Colin et al. (1985)
Turkey	4.6%	22.9%	Yalaz et al. (1992)
Iceland	5.6%	22.6%	Arnarsson et al. (2007)
Åland	12.7%	24.6%	Forsius (1988)
N-Finland	10.0%	25.3%	Forsius (1988)
Epirus, Greece	15.6%	29.7%	Stefaniotou et al. (1990)
Iceland	11.0%	31.5%	Forsius (1988)
Lapps	14.8%	35.3%	Forsius (1988)
Crete, Greece	7.2%	39.1%	Kozobolis et al. (1997)

In the current study we report prevalence and incidence both in terms of right eyes (randomly selected from the two), and by afflicted persons. However, all available studies indicate that XFS is basically a bilateral syndrome although the clinical presentation is often unilateral (Hammer et al., 2001; Kivela et al., 1997).
Using the present cohort, Thorleifsson et al. (2007) in Iceland were the first to identify two genetic risk variants in the first exon of lysyl oxidase like 1 (LOXL1) gene to be strongly associated with exfoliation syndrome and exfoliative glaucoma. This discovery may explain to some extent the geographical/ethnic differences in prevalence of clinically detectable XFS, although further studies will be required.

Five-year incidence

Prospective, randomly-sampled incidence studies of XFS are very few. Not surprisingly, we find the incidence of XFS to increase with age, and the condition seems to be more common in females. These are similar results as those of Karger et al., (2003) in Minnisota, although the total incidence rate in that study was considerably lower than in the current study. The results for the age-group 80 years and older at baseline are unfortunately not very informative. These individuals are 85 years and older at the time of the second examination and very few are still phakic at that age.

Although adding to the limited information in incidence of XFS is in itself a worthy goal, the study also gives us a wellcomed opportunity to monitor the quality of our diagnostic criteria over a longer term. Our results confirm that the diagnosis of definite XFS holds well over five years. In a double-blind manner, definite XFS was found again in 79% of those that could be examined after the five years. Contrarily, the diagnosis of possible XFS does not seem reliable in our hands. 64% of those diagnosed with possible XFS at baseline show no sign of the condition five years later. This was confirmed in our genetic study where the LOXL1 gene variants were similarly commonly found in the group with possible XFS as in those without XFS, whereas it is found in almost all of those diagnosed with definite XFS (Thorleifsson et al., 2007). This information was however not included in that article.

This highlights the importance of an accurate diagnosis of XFS, which should be based on the available scientific facts. Before such a common diagnosis is established, all results observing geographical difference in prevalence, and in fact all study results relating to XFS, will be subject to justifiable reservations.

Differences in anterior segment and lens

We find no difference in CCT in eyes with or without XFS. This is in concordance with the results of Hepsen *et al.* (2007). However, when they subdivided the XFS eyes into normotensive and glaucomatous, they found the former to be thinner and the

latter to be thicker than normal eyes. We are not able to replicate this result in the current study. Hepsen *et al.* (2007) also report steeper CC in XFS eyes than in normal eyes, and again we are not finding the same results in our sample.

The difference between the current study and Hepsen *et al.* (2007) can be explained by several hypotheses. Firstly the difference could be due to selection biases. The sampling-methods have pro's and con's. Our random population-based sample minimizes selection-biases of patients and controls, but limits the number of glaucoma-cases. The reverse is true of the method used by Hepsen *et al.* (2007), but the sampling might be confounded by the usage of preoperative cataract-patients as controls. Secondly there could be a difference in the diagnostic criteria. It is likely that some of the XFS eyes identified in the Turkish material would have been described as "possible XFS" by our criterion and thus excluded from the analysis. It is also noteworthy that the diagnosis of glaucoma is based on clinical evaluation in the Turkish study but on an epidemiological protocol in our case. Thirdly there could be racial differences, in which case only further studies will illuminate the true causes. All these issues have been very important in XFS-studies for a long time.

Some studies (f.x. Aravind et al., 2003) have shown relationship between nuclear opacifications and XFS. In the current study, as well as in previous publications (Arnarsson et al., 2002), we are not able to replicate these results. Of course both XFS and nuclear opacifications are age-related, but we do not find them otherwise related. Similarly to the result of the present study, McCarty & Taylor (2000) found no significant effect on the risk of XFS from cataract. We are however unable to solve this issue conclusively since in those older than 80 years a considerable number of cataracts has been removed together with a proportion of the anterior lens capsule thus possibly affecting the assessment of a relationship.

Examining the anterior chamber variables, we found that differences in lens thickness and anterior chamber depth could be attributed to age and gender but not XFS (Eysteinsson et al., 2005). Like Ventura et al (2001) we found no difference in central corneal thickness between participants with or without XFS, which is contrary to studies by Bechmann et al (2000), Inoue et al (2003), and Aghaian et al (2004), who all found XFS patients to have thinner corneas than those without XFS. The discrepancy may be due to difference in sampling and examination, since the above mentioned studies are mostly based on glaucoma clinic patients while we are

examining a random population-based sample with relatively few glaucoma cases. It is also possible that this difference is attributable to different distribution of age in the sample, or ultimately different races.
Smaller optic disks have been reported in eyes with XFS (Jonas & Papastathopoulos 1997). In a previous publication, we have reported significantly larger optic disks in glaucoma patients compared with normal eyes (Wang et al. 2003). However, we were unable to confirm association of XFS and disk morphology in the present study.

Association between XFS, IOP, optic disk changes and glaucoma

Eyes with XFS were found to have higher IOP than normal eyes in our sample. We also find that in persons with unilateral XFS, the IOP is significantly higher in the afflicted eye. Our results may also indicate that the increase in IOP that usually accompanies XFS develops in the same period as the XFS changes become visible. The increase in cup/disk ratio seem to accelerate after the XFS changes have established and not before.
We find the minimum prevalence of OAG in our study to be 4.0%. A recent study using retrospective material from the west coast of Iceland (Jóhannesson et al., 2005), found very similar prevalence of glaucoma as in the Reykjavik Eye Study. The prevalence in Tierp Glaucoma Survey in Sweden of definite OAG in people 65–74 years of age, 5.3% (Ekström & Alm, 2008), which again is very similar to the current study. The variation in the prevalence of XFS is further exaggerated when looking at the percentage of XFS in OAG patients in various studies. But then again so is the difficulty in comparing different studies. In these instances we need to have comparable diagnostic criteria for both diseases; XFS and glaucoma. The issue of sampling also becomes even more important since a majority of studies base their assumptions on clinical material, and quite a few on pre-operative glaucoma patients. It is not farfetched to imagine that these might be the most difficult glaucoma cases and that XFS could be over-represented, since eyes with XFS glaucoma do not respond well to medical treatment and thus would be more likely to require glaucoma surgery. Finland and Norway have consistently reported high numbers of XFS in OAG patients in their studies through the years. The numbers in Finland have varied

from around 40-70%. In Norway the lowest reported percentages have been around 30% and the highest around 90%. In other countries, such as England, France, Germany and USA, the percentage rarely exceeds 20% (Forsius, 1988). We find that 9.3% of persons with XFS have glaucoma and 2.5% of persons with no XFS. In the Blue Mountains Eye Study (Mitchell et al. 1999) a strong relationship was found between glaucoma and XFS with glaucomatous damage present in 14% of eyes with XFS compared with 2% of eyes without XFS. However, the total prevalence of XFS in Blue Mountains Eye Study is 2.3%, while in our sample with comparable sampling methods, age and sex distribution, the prevalence of XFS is 10.7%. Their number of participants and number of glaucoma patients is however much higher than ours, while we have more participants with XFS than they do.
The 5 year incidence of exfoliation glaucoma is much higher than was seen in the Minnisota-study (Karger et al., 2003), but since only five cases represent our material, modest interpretation of this difference is called for.

Risk factors for XFS

We can identify three risk factors that hold both for the prevalence risk at baseline and also for the 5 year incidence risk. These factors are; age, sex, and fruit consumption. Additional factors can be identified for prevalence risk but not for 5 year incidence risk.
We find more pigmented irises to be associated with increased risk for having XFS at baseline. In Israel Meyer et al. (1984) found persons with brown irides more susceptible to XFS that those with lighter iris colour. Forsius (1988) did however, not find association between iris colour and XFS in Lapps or Finns, suggesting that this association is more complex. McCarty & Taylor (2000) did not see any significant effect of iris colour on the risk of XFS. This complexity of the heredity of iris colour has been confirmed in a recent study, partially using the present data set (Sulem et al., 2007).
More frequent consumption of dietary fiber rich vegetables is associated with a lowered risk of having definite XFS at baseline, and the same applies to eating green or yellow vegetables more frequently in their 20's and 30's. Coupled with the

observed effect of increased fruit consumption on both prevalence and 5-year incidence risk, these results may be suggestive of dietary antioxidative effect being protective for XFS and may call for a prospective study similar to the Age-related Eye Disease Study (AREDS 2001) to evaluate this hypothesis. Moderate users of alcohol (once weekly) are less likely to have definite XFS at baseline, again pointing to the possible influence of antioxidants. A study by Koliakos et al. (2008) suggests that in persons with XFS, the oxidative stress (perhaps originated through radiation, environmental chemicals or atmospheric oxygen) is counterbalanced in the aqueous humour by antioxidants, but that this equilibrium is disrupted with the further development of XFS glaucoma whereby oxidants levels increase.

The only systemic disease associated with XFS at baseline in the present study is bronchial asthma, which again may be associated with oxidative stress. Mitchell et al. (1997) found angina, hypertension, and combined vascular events (angina, acute myocardial infarction, and stroke) to be significantly associated with XFS in an Australian population and Miyazaki et al., (2005) in Japan found XFS to be associated with hypertension, hyperlipideamia and diabetes. We can only confirm the findings of risk of arterial hypertension and diabetes in a univariate analysis but not in models controlling for the effects of age. McCarty & Taylor (2000) found no significant association between of XFS and hypertension, gout, arthritis, or diabetes.

We do not find smoking to be a significant risk factor for XFS. This is in line with studies of McCarty & Taylor (2000).

Taylor (1980) identified exposure to ultraviolet light as a risk factor for XFS in Austrialian aborigines and Thomas et al. (2005) confirmed this finding in an Indian population. We could not confirm these findings in the current study, and similarly Forsius (1988) found the prevalence of XFS to be extremely low in both Greenland and Peru, locations with high UV exposure. Furthermore, McCarty & Taylor (2000) found no association between UV exposure and XFS.

Strengths and limitations

The use of a population-based, randomized sample is clearly the most important strength of the Reykjavík Eye study. But the use of a specific diagnostic protocol and

the fact that all patients were examined by the same ophthalmologists in both the 1996 and 2001 study in a blinded fashion is also very important.

The use of non-probability sampling in some epidemiological studies of XFS is the greatest hindrance for comparison between studies, and carries the greatest risk of spurious findings. The present study examines individuals with XFS that are found in a large randomized sample, and not in samples taken from general ophthalmological or glaucoma clinics. Randomized population-based studies such as ours are an improvement although not without limitations. Low participation among those 80 years and older is a common problem in studies, including the present study, using standardized examination protocol and equipment so that participants can not be examined at home but have to travel to the centre of investigation.

It is also important to be aware of the criteria used for definite and possible XFS in the present study, and that persons that only have possible XFS are omitted from risk analysis. This is done since stability of probable XFS over time was found to be poor when examined in a blinded manner which is in an agreement with examination of the genetic risk of these same cases (Thorleifsson et al., 2007). Our definition for XFS, adopted from Allingham et al (2001), may seem somewhat strict compared to some studies (Thomas et al. 2005). It is also of particular importance to note that the definition of glaucoma has changed considerably in recent years. Older studies usually include intraocular pressure and in some instances glaucoma medication as the only glaucoma criteria. Thus, a direct comparison is not always helpful.

Medical interventions also need to be considered. In the present study, XFS may be underestimated to some extent due to strict exclusion criteria relating to those that have had lens surgery. However, no person 50 – 59 years old and only 1% of those 60 – 69 years old had pseudophakia.

It is important to distinguish between possible risk factors for prevalence and incidence, particularly in a study were the participants are older. The prevalent risk is determined by lifetime exposure. However, it is quite possible that some more potent risk factors have already exerted their effects and and are thus not detected by 5-year incidence risk analysis. Incidence risk analysis on the other hand, is important because it allows us to predict the progress of the condition and in some cases may even be used to give the patient evidence-based advice on how to counteract this progress.

There are several very important considerations regarding risk factor analysis. In our studies we do many calculations, and by doing so risk that some of them might be wrongly stated as statistically significant merely on the basis the law of probability, that is to say, that the share volume of calculations done in such analysis raises the possibility of fallacious results. A falsely significant relationship could be expected to come out of 5% of calculations. Equally important is that even though our sample exceeds 1.000 participants, it would be premature to ignore all possible correlations between XFS and health- and lifestyle factors, although some of them do not show significant effect in our studies. Some such associations would require the use of a far bigger sample to be successfully elicited, and the current study simply does not possess enough statistical power.

In summary, we find exfoliation syndrome frequently amongst Icelanders, increasingly with increasing age, and more commonly in women. Our diagnostic criterion seems to be reliable over time. We have also identified possible risk factors which might point to an association with oxidation. Importantly our studies highlight the issues of random samples and controlling for the effects of age.

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PAPER I

Ársæll Arnarsson, Karim Damji, Þórður Sverrisson, Hiroshi Sasaki, Friðbert Jónasson. Pseudoexfoliation in the Reykjavik Eye Study: Prevalence and Related Ophthalmological Variables. Acta Ophthalmologica 2007; 85: 822-827.

PAPER II

Ársæll Arnarsson, Karim Damji, Hiroshi Sasaki, Þórður Sverrisson, Friðbert Jónasson Pseudoexfoliation in the Reykjavik Eye Study: 5-year Incidence and Changes in Related Ophthalmological Variables. American Journal of Ophthalmology 2009; Forthcoming

PAPER III

Ársæll Arnarsson, Friðbert Jónasson, Karim Damji. Corneal Curvature and Central Corneal Thickness in Pseudoexfoliation: The Reykjavik Eye Study. Canadian Journal of Ophthalmology 2008; 43(4): 484-485.

PAPER IV

Friðbert Jónasson, Karim Damji, Ársæll Arnarsson, Þórður Sverrisson, Lan Wang, Hiroshi Sasaki, Kazayuki Sasaki, Reykjavik Eye Study Group. Prevalence of Open-angle Glaucoma in Iceland: Reykjavik Eye Study. Eye 2003; 17(6): 747-753.

PAPER V

Ársæll Arnarsson, Friðbert Jónasson, Karim Damji, María Soffía Gottfreðsdóttir, Þórður Sverrisson, Hiroshi Sasaki. Exfoliation Syndrome in the Reykjavik Eye Study: Risk factors for Baseline Prevalence and 5-Year Incidence. Submitted for publication

Exfoliation syndrome in the Reykjavik Eye Study: Risk factors for Baseline Prevalence and 5-Year Incidence

Arsaell Arnarsson MSc[1,2] , Fridbert Jonasson MD[1,3], Karim F. Damji MD[4] Maria S. Gottfredsdottir MD[3], Thordur Sverrisson MD[3], Hiroshi Sasaki MD[5].

1. Department of Ophthalmology, Faculty of Medicine, University of Iceland, Reykjavik, Iceland

2. Neuroscience Research, University of Akureyri, Akureyri, Iceland

3. Department of Ophthalmology, Landspitalinn, 101 Reykjavik, Iceland

4. Department of Ophthalmology, University of Alberta, Edmonton, Alberta, Canada

5. Department of Ophthalmology, Kanazawa Medical University, Uchinada, Japan

Corresponding author:

Fridbert Jonasson MD

Professor of Ophthalmology

University of Iceland

Landspitali-Haskolasjukrahus

101 Reykjavik

Iceland.

e-mail: fridbert@landspitali.is

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Abstract.

Purpose: To examine the age- and gender- specific prevalent and 5-year incident risk of developing exfoliation syndrome (XFS).

Methods and Participants: A population-based random sample of citizens 50 years and older, 1045 persons had baseline examination in 1996; 846 of the 958 survivors (88.2%) had a follow-up examination in 2001.

Following maximum dilatation of pupils diagnosis of exfoliation was established on slit lamp examination. An extensive questionnaire was administered at baseline and follow-up examination. Prevalent and incident risk was then calculated using a multivariate model.

Results: Prevalent risk: Comparing those consuming the following items less than once a month (=1.00) with those consuming the same food items 1-2 times every two weeks from age 20-40 the following were found to lower risk: dietary fibre rich vegetables odds ratio (OR) 0.52 (95% CI 0.28-0.97) $p<0.05$; green/yellow vegetables OR 0.42 (95% CI 0.22-0.81) $p<0.01$, fruits, OR 0.47 (95% CI 0.26-0.88) $p<0.05$ and moderate alcohol consumption OR 0.47 (95%CI 0.28-0.78) $p<0.01$. Increased iris pigmentation increased the risk of XFS, OR 2.53 (95%CI 1.24-5.15) $p<0.05$.

Conclusion: Food items that are possibly surrogates for antioxidative effect may decrease the risk of XFS and increased iris pigmentation may increase the risk.

Exfoliation Syndrome (XFS) also called pseudoexfoliation presents as a pathological accumulation of polymorphic fibrillar material in the anterior chamber of the eye. It is thought to be an elastic microfibrillopathy related to oxidative stress.[1] Studies by Streeten et al [2,3] suggest that XFS may be a systemic condition and exfoliative material has been identified in various tissues of the body and associated among others with cardiovascular and cerebrovascular co-morbidities .[4-10]

The prevalence of XFS is higher among older individuals and in some specific geographical areas.[11] Using the present cohort, we were the first to identify two polymorphisms in the first exon of lysyl oxidase like 1 (LOXL1) gene to be strongly associated with exfoliation syndrome and exfoliative glaucoma (XFG).[12] This discovery and subsequent replications explain to some extent the geographical/ethnic differences in prevalence of clinically detectable XFS.

Ocular manifestations associated with XFS include glaucoma, cataract, zonular and lens capsule weakness, poor pupillary dilatation, blood aqueous barrier breakdown, corneal endothelial decompensation, and retinal vein occlusion. [1] Elevated intraocular pressure (IOP), with or without glaucomatous changes, has been reported in about a quarter of eyes with XFS, which is 6 to 10 times more frequent than in normal eyes and and XFG eyes have been found to have a worse prognosis and a more aggressive course than primary open angle glaucoma.[13]

Numerous studies have been published describing XFS as a risk factor for glaucoma. Studies examining other risks than age and gender of developing XFS have been few. The present study attempts to identify risk factors for both baseline prevalence and 5-year incidence of XFS in the discovery cohort of the association of LOXL1 polymorphisms and XFS.

Material and Methods

The Reykjavik Eye Study (RES) is a prospective study of age-related eye diseases based on a random sample from the Icelandic national population census. The baseline examination was done in September to October 1996, using a sample including 6.4% of the citizens of Reykjavik who were 50 years or older at that time. 1045 elected to participate, 461 males and 584 females, a response rate of 75.8%. All were Caucasians. Appropriate ethical approvals were obtained from the Data Protection Commission and the National Bioethics Committee following the guidelines of the Helsinki declaration.

Of the 1045 individuals, 846 (88.2% of survivors) participated in the follow-up examination in 2001. More detailed description can be found in previous publications of the Reykjavik Eye Study.[14-17]

All participants went through a standard examination protocol. [14-17] The pupils were maximally dilated with Tropicamide 1% and Phenylephrine 10%, and a slit lamp biomicroscopy performed looking specifically for XFS. Two simultaneous colour stereo fundus photographs (30°) were taken, one centred on the fovea and the other on the optic disk (3Dx/NM; Nidek). Exclusion criteria for XFS were history of previous glass blowing, previous trauma, or intra-ocular surgery.

The definition of XFS includes complete or partial peripheral band and/or central shield of exfoliative material on the anterior lens capsule. These changes were frequently accompanied by grayish-white deposits elsewhere in the anterior chamber and iris atrophy. If however even incomplete peripheral band or central shield were not present the individuals with the last characteristics were classified as XFS suspects. For the present analysis only XFS is considered. All calculations were however also performed for XFS suspects but these last failed to reveal any

significant associations. In the multivariate analysis however, we did always control for possible XFS. Incidence of XFS is defined as the appearance of a lesion in either eye at follow-up that was absent in both eyes at baseline, and no distinction is made to eyes having no or possible XFS.

Furthermore, all participants were required to answer a comprehensive questionnaire regarding lifestyle, food consumption, health, disease, previous surgery and medication. For the food items, participants were asked to indicate their estimated average frequency of consumption from their age 20-40 years, 40-60 years, and at present if this differed from age-group 40-60 years.[18]

We used SPSS (version 13.0, 2004, SPSS Inc, Chicago, Illinois, USA) for statistical analysis. Odds ratios (OR) and 95% confidence intervals (CI) were calculated first by a univariate logistic model, and then all variables that showed some trend toward significant association were analyzed further by the multivariate logistic model. In all multivariate calculations, we controlled for the effects of age, gender, smoking and possible XFS.

All analysis were done using at least one eye affected diagnosis.

Results

Prevalence risk

Table 1 shows all the items from the questionnaire that were tested without any association being revealed.

Table 1: Items in Questionnaire found to have no association with Definite XFS in univariate or multivariate analysis.

1. Age at menopause, number of births, age at first birth

2. Frequency of intake of following food items for three different periods in the lives; i) in their 20's - 40's, ii) in their 40's - 60's, and iii) presently (at baseline in 1996). Frequency was categorized in 4-7 times/week, 2-3 times/week, 1-2 times/2 weeks, less than once monthly.

a. Fresh fish

b. Liver and liver products

c. Beans, legumes, soy products

d. Herring

e. Seaweeds

f. Milk

g. Yogurt, sour milk, curdle

h. Tea

i. Sweeteners

j. Cod liver oil

k. Meat and meat products

l. Eggs

3. Smoking status (current smoker, former, never), type of tobacco, and life-time exposure (pack-years)

4. Self-reported diseases including: Coronary heart disease, atherosclerosis, chronic bronchitis, rheumatism, thyroid disease, osteoporosis, atopy, and gout.

5. Body mass index

6. Outdoor exposure: Daytime hours spent outside/weekdays only, wear of spectacles, sunglasses or hats

7. Skin type: a) always sunburn, never tan, b) always sunburn, sometimes tan, c) sometimes sunburn, always tan

As we and others have reported earlier [14], age is a dominant risk factor for XFS. In our sample the average age at baseline of persons with XFS is 72.3 (SD ±8.9) years, with possible XFS it was 67.0 (SD ±9.8) years, and for those with no sign of XFS it was 62.6 (SD ±8.7) years. This difference was highly significant between all groups ($p < 0.001$). The likelihood of having XFS in either eye was dramatically increased for each year people got older after the age of 50 years (OR=8.49; 95%CI 8.31 – 8.77, $p<0.001$).

As seen in table 2, being married was shown to be protective for XFS in a univariate analysis. However, controlling for the effect of age eliminated this association.

Table 2: Effect of Maritial Status on the Risk of Having Definite XFS

	Divorced/Widowed OR	Single OR (95% CI)	Married OR (95% CI)
Univariate	1.00	0.87 (0.43-1.78)	0.59 (0.36-0.95)*
Age-adjusted	1.00	0.97 (0.45-2.08)	1.04 (0.62-1.75)

* $p<0.05$

The same pattern can be seen in table 3 where individuals considering themselves "very healthy" have less risk of XFS than those reporting worse health namely the loss of significance when we control for the effects of age, marital status and self-reported health. Combined, these two examples illustrate that younger persons are less likely to have XFS, more likely to be married and to enjoy better health than older persons.

Table 3: Self-reported Health and the Risk of Having Definite XFS

	Disabled OR	Healthy OR (95% CI)	Very Healthy OR (95% CI)
Univariate	1.00	0.63 (0.37-1.08)	0.30 (0.14-0.65)*
Age-adjusted	1.00	0.89 (0.50-1.58)	0.56 (0.25-1.27)

* $p<0.05$

Iris colour is a significant risk factor for having XFS in our sample. We find that compared with light blue/gray iris colour (OR=1.00) both persons with brown irises (OR=2.53; 95% CI 1.24-5.15, $p<0.05$) and mixed iris colour (OR=1.87; 95% CI 1.10-3.17, $p<0.05$) have raised risk in a multivariate model.

Compared with persons that never used alcohol (OR=1.00), those that used alcohol in moderation (once weekly) were less likely to have XFS (OR=0.47; 95% CI 0.28-0.78, $p<0.01$). More frequent users did not have a significantly different risk than never-users (OR=0.72; 95% CI 0.27-1.92) in a multivariate model controlling for the effects of age, sex, and smoking.

Table 4 lists up the food consumption variables that showed relations to having XFS.

Table 4: Association Between Consumption of Vegetable Oil, Vegetables and Fruits, and the Risk of Having XFS in Univariate and Multivariate Analysis

Mean intake	In their 20´s and 40's OR (95% CI)	In their 40's and 60´s OR (95% CI)	Baseline OR (95% CI)
	Vegatable Oil - Univariate Analysis		
Less than monthly	1.00	1.00	1.00
1-2 times/2 weeks	0.17 (0.04-0.71)*	0.34 (0.16-0.72)*	0.61 (0.33-1.13)

2-3 times/week	0.32 (0.10-1.05)	0.22 (0.10-0.49)†	0.58 (0.35-0.98)*
4-7 times/week	-	-	-
	Vegetable Oil - Multivariate Analysis		
Less than monthly	1.00	1.00	1.00
1-2 times/2 weeks	0.41 (0.21-2.49)	0.58 (0.20-1.13)	0.98 (0.51-1.89)
2-3 times/week	0.72 (0.10-1.79)	0.48 (0.26-1.30)	0.86 (0.49-1.52)
4-7 times/week	-	-	-
	Dietary fiber rich vegetables - Univariate Analysis		
Less than monthly	1.00	1.00	1.00
1-2 times/2 weeks	0.33 ()†	0.36 (0.19-0.68)†	0.61 (0.31-1.21)
2-3 times/week	0.36 ()†	0.41 (0.23-0.73)†	0.47 (0.24-0.91)*
4-7 times/week	0.35 ()*	0.21 (0.10-0.49)†	0.44 (0.22-0.87)*
	Dietary fiber rich vegetables - Multivariate Analysis		
Less than monthly	1.00	1.00	1.00
1-2 times/2 weeks	0.52 (0.28-0.97)*	0.46 (0.23-0.92)*	0.68 (0.32-1.41)
2-3 times/week	0.87 (0.43-1.76)	0.75 (0.38-1.44)	0.73 (0.36-1.51)
4-7 times/week	0.68 (0.22-2.07)	0.45 (0.18-1.14)	0.62 (0.30-1.30)
	Green or yellow vegetables - Univariate Analysis		
Less than monthly	1.00	1.00	1.00
1-2 times/2 weeks	0.36 (0.20-0.66)†	0.96 (0.42-2.18)	0.54 (0.26-1.12)
2-3 times/week	0.40 (0.21-0.74)†	0.77 (0.33-1.76)	0.68 (0.34-1.35)
4-7 times/week	0.58 (0.24-1.40)	0.88 (0.33-2.38)	0.81 (0.37-1.76)
	Green or yellow vegetables - Multivariate Analysis		

Less than monthly	1.00	1.00	1.00
1-2 times/2 weeks	0.42 (0.22-0.81)†	1.07 (0.44-2.60)	0.68 (0.31-1.48)
2-3 times/week	0.44 (0.23-0.87)*	0.76 (0.31-1.88)	0.74 (0.35-1.56)
4-7 times/week	0.60 (0.23-1.54)	0.82 (0.28-2.41)	0.82 (0.35-1.91)
	Fruits - Univariate Analysis		
Less than monthly	1.00	1.00	1.00
1-2 times/2 weeks	0.32 (0.18-0.57)†	0.65 (0.30-1.37)	0.88 (0.35-2.17)
2-3 times/week	0.30 (0.16-0.56)†	0.43 (0.20-0.92)*	0.65 (0.28-1.55)
4-7 times/week	0.45 (0.18-0.57)*	0.45 (0.21-0.98)*	1.07 (0.48-2.42)
	Fruits - Multivariate Analysis		
Less than monthly	1.00	1.00	1.00
1-2 times/2 weeks	0.47 (0.26-0.88)*	0.70 (0.31-1.59)	1.17 (0.44-3.10)
2-3 times/week	0.63 (0.31-1.26)	0.59 (0.26-1.34)	0.69 (0.27-1.73)
4-7 times/week	0.90 (0.43-1.90)	0.73 (0.31-1.70)	1.02 (0.43-2.44)

Multivariate analysis included age, gender and smoking

*$p<0.05$

†$p<0.01$

More frequent consumption of vegetable oil seems to be protective against having XFS but only in a univariate analysis and not after adjusting for the effects of age, sex and smoking.

Even after controlling for the effects of age, gender, smoking and possible XFS. Individuals consuming dietary fiber rich vegetables 1-2 times 2 weekly, earlier in their lives, are significantly less likely to have XFS compared with those who consume them less than once a month in a multivariate model (table 4). Even more frequent consumption lowers the risk further, albeit non-significantly. Similarly, people eating green or yellow vegetables more frequently in their 20's - 40's are less likely to have XFS, also in a multivariate model. In the multivariate model, participants that consumed fruits 1-2 times 2 weekly are significantly less likely to have XFS than those that consumed fruits less than monthly (table 4).

Persons taking vitamins regularly had a raised frequency of XFS compared with those who never took vitamins (OR=2.07; 95% CI 1.29-3.33, p<0.01) in a univariate model, but not after adjusting for the effects of age, sex and smoking (OR=1.54; 95% CI 0.3-2.55).

Table 5 shows the association between various self-reported diseases and the risk of having XFS.

Table 5: Association between Diseases and the Risk of Having Definite XFS in Univariate and Multivariate Analysis

	Univariate Analysis OR (95% CI)	Multivariate Analysis OR (95% CI)
Diabetes	2.77 (1.25-6.12)*	1.95 (0.82-4.63)
Arterial Hypertension	1.97 (1.31-2.98)†	1.19 (0.76-1.86)
Asthma	2.01 (1.11-3.64)*	1.91 (1.00-3.62)*
Combined CVD	1.80 (1.21-2.70)†	1.02 (0.66-1.59)

Multivariate analysis included age, gender and smoking

*p<0.05

†p<0.01

The only systemic diseases that showed association with having XFS were diabetes, arterial hypertension, a combination of all cardiovascular-related diseases and asthma. In a multivariate model only asthma holds significance.

Five year incidence risk

When examining the risk of five year incidence of XFS, we divided the participants up in 10- year age-groups, and found that on average there was a 5% increase in risk of developing XFS for every decade people were older than 50 (OR = 1.05; 95% CI 1.01-1.09, p=0.022).

Males were found to be significantly less likely to have a five year incident XFS than females, although only marginally when the effects of age had been controlled for (OR = 0.49; 95% CI 0.24 – 1.01, p = 0.05).

We did not find an increase in 5-year incident XFS relating to cataract-diagnosis at baseline. Smoking,. iris-colour, self-reported health and marital status did not affect 5-year incidence. More frequent fish-consumption was correlated with increased risk of 5-year incidence of XFS in an univariate model and not when we controlled for the effects of age, confirming that fish consumption is higher among older Icelanders than younger ones. The only food-item we found significantly correlated with XFS-incidence, was that people that consumed fruits 4-7 times per week in their 20's to 40's were significantly less likely to have 5-year incidence of XFS than those that consumed fresh fruits seldom or never (OR = 0.20, 95% CI 0.04 – 0.91, p =0.04).

Persons with rheumatoid arthritis, gout and asthma had twofold incidence of XFS, but this difference was not statistically significant.

Discussion

The strength of this study may be the random population sample, the high prevalence of XFS in this population and including both cross sectional and longitudinal data. Limitations of our study may include relatively low total number of participants even though the percentage of those with XFS is high, and that the information on systemic disease, food intake and skin type are self reported.

XFS increases with increasing age and is more commonly found in females than in males in both the prevalent and the incident part of the study. Not surprisingly, the incidence of possible XFS varies much more with regard to both sex and age confirming that the diagnosis is uncertain.

We find more pigmented irises to be associated with increased risk for XFS. The literature has been conflicting on this issue. [19] Taylor identified exposure to ultraviolet light as a risk factor for XFS in Austrialian aborigines [20] and Thomas et al confirmed this finding in an Indian population .[21] We could not confirm this findings and Forsius found the prevalence of XFS to be extremely low in both Greenland and Peru [19], locations with high UV exposure.

Mitchell et al found angina, hypertension, and combined vascular events to be significantly associated with XFS in an Australian population [5] and Miyazaki et al in Japan found XFS to be associated with hypertension, hyperlipidamiae and diabetes.[22] We can only confirm the findings of risk of arterial hypertension and diabetes in an univariate analysis but not in a multivariate models. Our findings are however, in an

agreement with recent findings of Tarkkanen et al. who in a large study, were unable to establish association with systemic vascular disease.[23]

Consuming some vegetables and fruits 1-2 times 2 weekly lowers the risk as compared to those that consume these items less than monthly. Further increase does however not reach statistical significance in a multivariate model. The reason for this may be that the number of persons consuming dietary fiber-rich vegetables and/or fruits more than 2 times every 2 weeks, is relatively low in Iceland, thus significant effect of further increased consumption of these food products is only seen in those persons with a 2 weekly consumption of x 1-2 because they are most numerous.

Fewer variables are seen affecting incidence risk than prevalence risk. There may be two plausible explanations for this. One is that the variables that exert lifetime risk, such as iris colour, have already had their say in altering the baseline risk. The second, and perhaps the more important reason for many variables, is that in our incidence risk analysis there are naturally much fewer cases than in the prevalence risk analysis.

In summary: In a multivariate model, we did find increased iris pigmentation to increase the prevalent risk of XFS. Frequent intake in their tventies - forties of dietary fiber rich vegetables, green or yellow vegetables and fruits did however seem to reduce the risk of XFS when compared to less frequent intake, using a multivariate model. The same is true for moderate intake of alcohol as compared with never and more frequent intake of alcohol. Vegetables, fruit and alcohol may be markers for antioxidative effect. One systemic disease namely bronchial asthma was found to be associated with increased prevalent risk of XFS which again may be associated with oxidative stress.

Regarding 5-year incident risk for XFS females were again found to be more frequently affected than males and frequent consumption of fruit in the 20´s and 40´s

was found to lower the risk of developing XFS. This study calls for further studies for clarification of risk factors and may call for a prospective study similar to the Age-related Eye Disease Study study to evaluate the hypothesis that antioxidants may be protective against XFS. [24]

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PAPER VII

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