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Faculty of Health and Social Sciences
–

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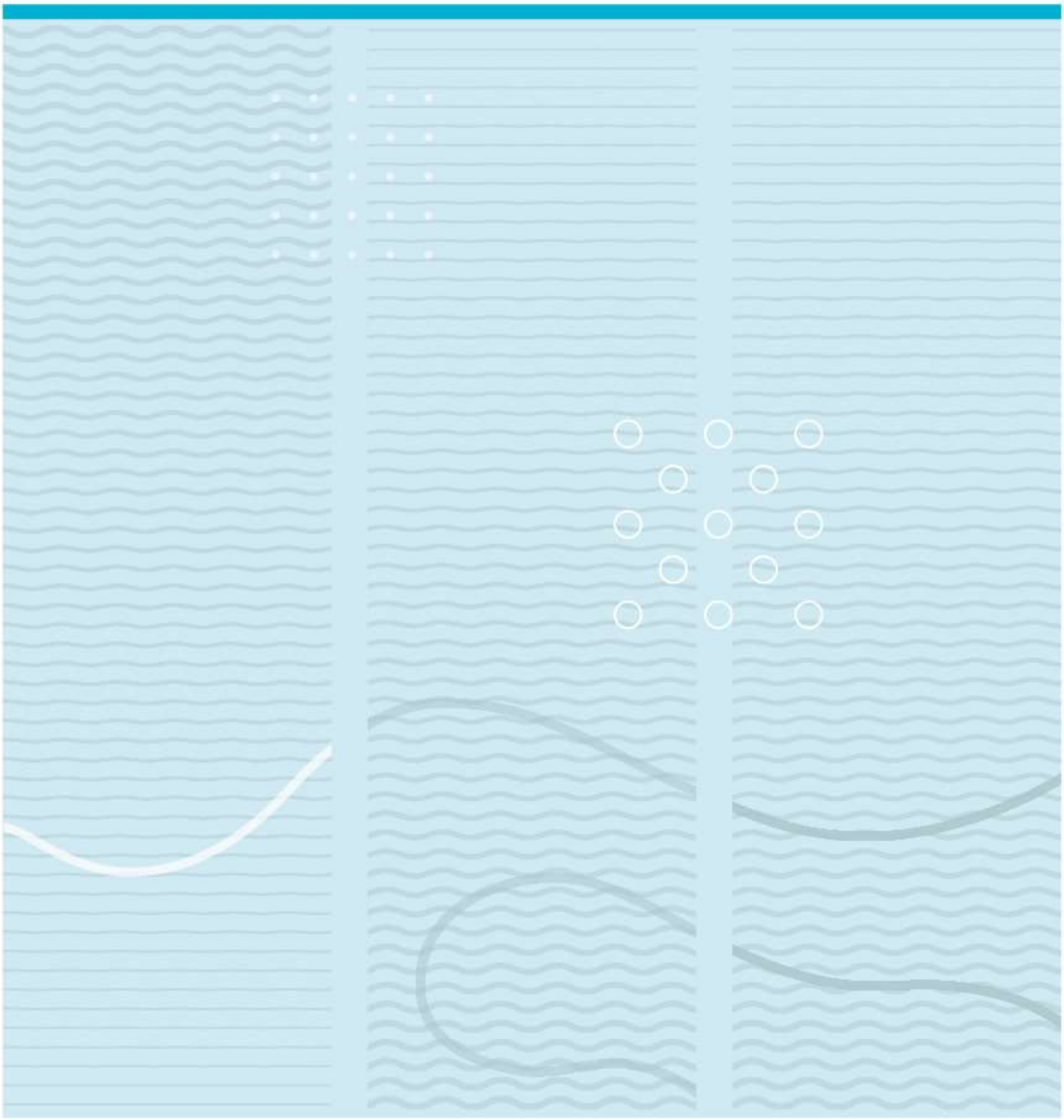
Occurrence of exfoliation syndrome in an optometric practice in Norway

Occurrence of ocular exfoliation syndrome and its correlation with ocular findings associated with glaucomatous optic neuropathy in persons aged 40 and over in an optometric practice in Norway



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This thesis is worth 30 study points

Abstract

Purpose

The primary aim of this study was to investigate the occurrence and distribution of suspected exfoliation syndrome (XFS) in persons aged 40 and older who attended an optometric practice in Norway for a routine optometric examination. Secondary objective was to investigate if there was an association between confirmed XFS and findings associated with glaucoma.

Methods

This is a cross sectional study where the study population were all Norwegian women and men over the age of 40 years who underwent a voluntary optometric examination at the practice Krogh Optikk Majorstuen between January 2022 and February 2022. Patients was recruited consecutively. There were two parts of this study. 1: Screening for findings of XFS during a standard optometric examination by means of an extended slit lamp biomicroscope (SLM) examination. 2: Confirmation of XFS in participants with one or more suspect findings of XFS in at least one eye by the means of an extended SLM investigation of the intraocular lens with the use of diagnostic eyedrops (tropicamide 0.5%) at a separate appointment. Statistical analyses were performed on person level (XFS in at least one eye) for the study population, prevalence and frequencies. Correlation analyses between XFS and findings associated with glaucoma was based on the right eye. Descriptive analyses consisted of spread of values (standard deviation, percentages, frequencies), central values (mean, confidence intervals). Inferential statistics consisted of comparisons of means with independent t-test and chi square test. Statistical significance set to $\alpha = 0.05$ two-sided.

Results

91 people participated in this study from age 40-79 years with a mean age of 57 (±10.1 SD) years where 55% were woman. 17 participants had suspect findings of XFS. The prevalence of suspect XFS over the age of 40 years of was found to be 18.7% (n=17/91) and in the age groups; 40-49 years 9.1% (n=2/22), 50-59 years 13.9% (n=5/36), 60-69 years 23.5% (n=4/17) and 70-79 years 37.5% (n=6/16). Nine of these underwent the second investigation to confirm/disconfirm the condition. 7 participants were confirmed with XFS where 6 was identified as bilateral and 1 as unilateral. Correlation analyses found a statistically significant difference (α=0.05, two-sided) in mean (independent t-test) with the measurements of average global parapapillary nerve fibre thickness with a p value of 0.002 between confirmed XFS (mean 71.75µm ±18.39) and no XFS (mean 92.79µm ±9.95). No other correlations were found.

Conclusion

This study shows that XFS is present in optometric practice in Norway. The prevalence found seem to be higher than other studies with similar populations, but because of the small sample size of this study, it is difficult to transfer the results to a bigger population. The increase of prevalence by age supports the understanding that XFS is an age-related condition. Only one finding associated with glaucoma was found to be associated with confirmed XFS, even so, XFS is a known risk for glaucoma, therefore diagnosing XFS should be considered clinically important. The study demonstrates that diagnostic eyedrops is clinically useful in diagnosing XFS. More research is needed to establish the prevalence of XFS in optometric practice in Norway.

Keywords: Prevalence, Exfoliation syndrome, glaucoma, dilating eyedrops

Abstrakt

Formål
Hovedformålet med dette studie var å undersøke forekomsten og fordelingen av mistenkt eksfoliasjons syndrom (XFS) i personer fra 40 år og eldre som besøkte en optometrisk praksis i Norge for en optometrisk rutineundersøkelse. Sekundærformålet var å undersøke om det var en assosiasjon mellom bekreftet XFS og funn relatert til glaukom.

Metoder
Dette var et tverrsnittsstudie med en studiepopulasjon bestående av Norske kvinner og menn over 40 år som tok en frivilling optometrisk undersøkelse hos Krogh Optikk Majorstuen mellom januar 2022 og februar 2022. Pasienter var rekruttert fortløpende. Det var to deler til dette studie: 1. Rutine optometrisk undersøkelse med utvidet spaltelampe mikroskopi (SLM). 2: Bekreftelse av XFS hos pasienter med et eller flere XFS suspekte funn i minst ett øye ved bruk av utvidet SLM undersøkelse av linsen i øyet og diagnostiske øyedråper (Tropikamid 0.5%) utført på en etterkontroll. Statistiske analyser ble utført på personnivå (XFS i minst 1 øye) for studiepopulasjonen, prevalens og frekvens. Korrelasjons analyser mellom XFS og funn relatert til glaukom var basert på høyre øye. Beskrivende analyser besto av spredning av verdier (standard deviasjon, prosent, frekvens), sentrale verdier (gjennomsnitt, konfidens intervall). Inferensielle analyser besto av sammenligninger mellom gjennomsnitt ved bruk av «independent t-test» og «chi square test». Statistisk signifikans var satt til $\alpha = 0.05$ (tosidig).

Resultater
91 personer deltok i studie med et aldersspenn fra 40-79 år og gjennomsnittsalder på 57 (±10.1 SD) år, hvor 55% var kvinner. 17 deltakere hadde suspekte funn for XFS. Prevalensen for suspekt XFS over 40 år kom på 18.7% (n=17/91) og i aldersgruppene; 40-49 år 9.1% (n=2/22), 50-59 år 13.9% (n=5/36), 60-69 år 23.5% (n=4/17) og 70-79 år 37.5% (n=6/16). Ni av disse deltok på del 2 for å bekrefte/avkrefte XFS. Syv deltakere fikk bekreftet XFS hvor 6 var identifisert bilateralt og 1 unilateralt. Korrelasjons analysene fant en statistisk signifikans (α=0.05, tosidig) i gjennomsnitt mellom målene av global parapapillær nervefibertykkelse med en p-verdi på 0.002 mellom bekreftet XFS og de uten XFS. Ingen andre signifikante korrelasjoner ble funnet.

Konklusjon
Dette studie viser at XFS er tilstede i optometrisk praksis i Norge. Prevalensen funnet ser ut til å være høyere enn andre studier med lignende populasjoner, men grunnet dette studies mindre utvalg av deltakere, er det vanskelig å overføre resultatene til en større populasjon. Prevalensen øker med alder, noe som støtter forståelsen av at XFS er en alders relatert tilstand. Det er kun ett funn assosiert med glaukom som det ble funnet en korrelasjon med bekreftet XFS. XFS er forstått en kjent risikofaktor for å utvikle glaukom, derfor bør diagnostisering av XFS vurderes som klinisk viktig. Studie demonstrerer også bruken av diagnostiske øyedråper er klinisk nyttig for å bekrefte XFS. Videre forskning er nødvendig for å finne prevalensen av XFS i optometrisk praksis i Norge.

Nøkkelord: Prevalens, Eksfoliasjons syndrom, glaukom, dilaterende øyedråper

Contents

Foreword

I would like to thank the University of south-Eastern Norway for the opportunity to do this research and Krogh Optikk AS for allowing me to use their facilities, equipment, and time both during and after workhours for this research. A special thank you to my colleagues Kristine Høydal, Theresa K. Nguyen, Benedicte D. Christensen, Krista Pintyi, Jenny Hoemsnes, Marte Roti, Maria Gustavsson and John Sverre S. Nergaard for participating in recruitment and data collection. A special thank you to my supervisor Per O. Lundmark for guidance, help and support during the entire process.

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Oslo, 27.04.2022

Rebekka Bang Hagen

This thesis contains parts of the project protocol that has been presented as the final exam in MRES019 Research methods and project description (Hagen, 2021) at USN (unpublished).

References, tables and figures are presented in accordance with the APA 7th style.

1 Introduction

Exfoliation syndrome (XFS) is a systemic condition, with exfoliative material produced and accumulated in ocular structures (Ritch & Schlötzer-Schrehardt, 2001, p. 265). It is an age-related condition as it is rarely seen in patients younger than 50 years of age (Vesti & Kivelä, 2000, p. 348) and it is noted to be more commonly seen in women than men (Bowling et al., 2016, p. 366). The prevalence is reported to be higher in northern Europeans, especially in Scandinavia (Tekin et al., 2019, p. 453). The prevalence of the condition varies in studies from 6.3% over the age of 60 found by Aasved (1979) to 14.9% found by Pavičić-Astaloš et al. (2016) in the same age group. Common findings of XFS include among other; exfoliative material on the intraocular lens, pigment deposits on the corneal endothelium and transillumination close to the pupillary border (Ritch & Schlötzer-Schrehardt, 2001, pp. 270-274). XFS is clinically diagnosed by the presence of exfoliative material on the intraocular lens with a dilated pupil (Tekin et al., 2019, p. 454). Increased risk of developing cataract and complication during and after cataract surgery are linked with XFS (Shingleton et al., 2009, pp. 1103-1105). Glaucoma is the most known secondary risk of XFS, and is shown to have a faster progression with damage to the optic nerve and irreversible visual field loss when secondary to XFS (Bowling et al., 2016, p. 306). High intraocular pressure in combination with XFS is shown to heighten the risk of glaucoma (Grødum et al., 2005, pp. 386-390).

This study is about an investigation of occurrence of suspect XFS in optometric practice in persons aged 40 and over by looking for suspect findings of XFS in a random selected study sample, as well as using dilating eyedrops to see how many of the suspect XFS are confirmed with XFS. Association between confirmed XFS and various findings associated with glaucoma are also investigated. An overview of the current literature of XFS, its suspect findings and association with glaucoma are first given. The study's methods and results are then presented and discussed in more detail and a conclusion are given at the end.

1.1 Exfoliation syndrome

XFS is a age-related condition with a progressive development of fibrillar material produced and accumulated in ocular structures, mainly seen on the intraocular lens (Ritch & Schlötzer-Schrehardt, 2001, p. 265). Exfoliative material was first described in 1917 by John Lindberg as greyish flakey deposits on the pupillary border and anterior lens which could form a round disc and membrane on the anterior lens capsule (Lindberg, 1917, as cited in Tarkkanen, 2018, pp. 1-2). Exfoliative material was then thought to originate from the intraocular lens itself (Schacknow & Samples, 2010, p. 507) by peeling of the anterior lens capsule (Plateroti et al., 2015, p. 1). Over the years exfoliative material has been reported on other ocular structures like the zonules and ciliary body, and even in pseudophakia eyes, leading to a general understanding that the lens itself has a minor role in the development of exfoliative material (Plateroti et al., 2015, pp. 1-2). Today XFS is recognized as a systemic condition as exfoliative material has been found in other structures such as in connective tissue around internal organs (Schlötzer-Schrehardt et al., 1992, pp. 1752-1765; Streeten et al., 1992, pp. 1757-1762). Association between XFS and various cardiovascular diseases such as hypertension and stroke has been found (Andrikopoulos et al., 2014, pp. 847-854; Hollo, 2018, pp. 72-73). In 2007 an Islandic study identified an association between dysfunctions of the Lysyl Oxidase-Like 1 (LOXL1) gene and the development of exfoliative material (Thorleifsson et al., 2007, pp. 1397-1400). A dysfunction of LOXL1 can cause disturbances with the elastin metabolism and exfoliative material has been linked to disturbances in this mechanism, resulting in the association between XFS and LOXL1 (Schacknow & Samples, 2010, pp. 507-508). A recent study by Pompoco et al. (2021) investigated the correlation between various systemic conditions with dysfunctions in the LOXL1 gene and XFS and found that there is an correlation and that the presence of XFS may help in identifying various systemic conditions with associated gene dysfunction, but further studies are needed (pp. 1-6). Although there is an increase of reported correlation with XFS and various systemic conditions, there is not enough research to conclude that XFS is worsening the correlated condition, nor an increase in mortality by the presence of XFS (Ritch, 2014, p. 1). On the contrary one recent study from 2021 which compared the lifespan of patients with primary open-angle glaucoma without XFS and with XFS, showed that patients with XFS present had a longer lifespan then those without (Slettedal et al., 2021, pp. 1-5). The composition of exfoliative material itself is not known (Ritch & Schlötzer-Schrehardt, 2001, pp. 281-282), but is understood to be an abnormal fibrillar material (Schacknow & Samples, 2010, p. 507) consisting of various proteins (Challa & Johnson, 2018, pp. 29-31). Even though XFS is linked to disturbances in the LOXL1 gene

(Thorleifsson et al., 2007, pp. 1397-1400), the origin of exfoliative material is still not well known, though it is thought to be produced by various ocular structures like the trabecular meshwork, the ciliary body and the iris (Ritch, 2014, pp. 4-5). Environmental risk factors for XFS that have been suggested include UV- exposure, northern altitudes, ambient temperatures, and time spent outdoors (Stein et al., 2011, pp. 1053-1060). XFS is reported in many different ethnicities, but the prevalence is reported to be higher in northern Europeans, especially in Scandinavia (Tekin et al., 2019, p. 453). It is noted to be more commonly seen in women than men (Bowling et al., 2016, p. 366) although it varies in studies. The study by Pavičić-Astaloš et al. (2016) did not find any significant differences in XFS between woman and men whereas the study by Arnarsson et al. (2007) found a higher prevalence of XFS in woman then men.
XFS is associated with age as it is rarely seen in patients under the age of 50, as well as the prevalence gets higher with increased age (Vesti & Kivelä, 2000, p. 348) as can be seen in table 1.

1.1.1 Prevalence

The prevalence of XFS varies widely, even in Nordic and Caucasian populations where the prevalence is reported to be higher than other (Tekin et al., 2019, p. 493). As Konstans and Ringvold (2018) states "*The epidemiology of exfoliation syndrome (XFS) is one of the most controversial subjects in ophthalmic literature*" (p. 4). The reported prevalence is suspected to be largely unclear and difficult to obtain, even though XFS is considered to be a common condition (Konstas & Ringvold, 2018, p. 4). An overview of reported prevalence of XFS in Nordic and Caucasian populations is displayed in table 1. In Norway Aasved (1979) found the prevalence to be 0.9% for patients from 40 years of age and 6.3% after the age of 60 years, whereas Ringvold et al. (1987) found the prevalence to be between 10.2% and 21.0% for patients over the age of 65 years at three different locations in Norway. In Finland Krause et al. (1988) found the prevalence to be 14.2% in the age group 60-69 years and 34.7% over the age of 80 years of age, and in Iceland Arnarsson et al. (2007) found the prevalence in the same age groups to be 10.7% and 40.6% respectively. In Sweden the prevalence is reported to be particularly high in the population of Skellefteå, with 23% at the age of 66 years, 45.6% at the age of 80 years and 60.7% at the age of 87 years (Åström et al., 2007). In Croatia Pavičić-Astaloš et al. (2016) also found the prevalence to be particularly high over the age of 70 years with 80.9% and quite low in the age group 45-49 years with only 0.5%. A more recent study in Russia by Bikbov et al. (2020) found the prevalence to be 0.2% in the age group 40-45 years with a slight increase of prevalence by age, ending at 12% at 80 years of age and older. One

possible explanation for why the reported prevalence varies could be because of the lack of using dilating eyedrops to examine the lens during routine eye examinations. Thus the diagnose of XFS goes undetected, as in one incidence where the XFS diagnosis was missed in 60% of the referred patients to an glaucoma clinic (Crittendon & Shields, 1988, as cited in Ritch & Schlötzer-Schrehardt, 2001, p.267). The prevalence may also vary according to the examiners skill to detect XFS in its early stages (Ritch & Schlötzer-Schrehardt, 2001, p. 267). To better future prevalence studies Konstas and Ringvold (2018) suggest four key points to be considered 1. Always dilate the pupil, as 10-25% of XFS may be missed, 2. Include younger patients under the age of 60 years, as it is reported to be seen in younger age groups, 3. Include XFS suspects, as patients with subtle sign of XFS may be overlooked, 4. The examiner should have a complete clinical knowledge of XFS and its signs, experience and interest in the condition to ensure high diagnostic sensitivity (Konstas & Ringvold, 2018, pp. 6-7).

1.1.1.1 Table 1

Prevalence of XFS in Different Nordic and Caucasian Populations

Author (year) Place, country	Group by age (n sample size)	Prevalence of XFS (Location)
Aasved (1979)	> 40 (n= 8537)	0.9%
Bergen, Norway	40-49 (n= 3091)	0.0%
	50-59 (n=2827)	0.4%
	60-69 (n= 1829)	1.0%
	70-79 (n=476)	4.8%
Ringvold et al. (1987)	65 (n= 671)	10.2% (Hitra)
South-Trøndelag, Norway	65 (n= 681)	21% (Holtålen)
	65 (n= 589)	19.6% (Rennebu)
Krause et al. (1988)	60-69 (n= 239)	14.2%
Oulu, Finland	70-79 (n= 383)	21.9%
	80 (n= 173)	34.7%
Arnarsson et al. (2007)	> 50 (n= 674)	10.7%
Reykjavik, Iceland	50-59 (n= 359)	2.5%
	60-69 (n= 351)	8.8%
	80 (n= 64)	40.6%
Åström et al. (2007)	66 (n=339)	23%
Skellefteå, Sweden	73 (n= 224)	36.6%
	80 (n= 160)	45.6%
	87 (n= 102)	60.7%
Pavičić-Astaloš et al. (2016)	45-49 (n= 705)	0.5%
Koprivnica, northwestern Croatia	50-59 (n= 1370)	3.7%
	60-69 (n= 1287)	14.9%
	>70 (n= 1987)	80.9%
Bikbov et al. (2020)	40 (n= 5451)	4.9%
Bashkortostan, Russia	40-45 (n= 491)	0.2%
	55-50 (n= 900)	2.1%
	60-65 (n= 871)	7.0%

Note. Prevalence of XFS in different Nordic and Caucasian populations. n= number of people.

1.1.2 Diagnostics

Suspect findings of XFS are primarily seen on posterior segments of the eye, including among other; the intraocular lens, iris, pupil and the corneal endothelium (Ritch & Schlötzer-Schrehardt, 2001, pp. 270-274). As such, to investigate the condition an ocular examination with a slit lamp biomicroscope (SLM) is the best tool to use, as with an SLM, several different techniques can be used to optimize the evaluation of different posterior segments of the eye (Elliott, 2014, pp. 210-217). SLM gives the advantage of adjustable magnification and illumination, depth of field and give the possibility to evaluate shape, location, size, and depth of opacities and abnormalities of ocular posterior segments better compared to direct ophthalmoscope, loupes or penlights (Elliott, 2014, pp. 210-214).

Although there are many suspect findings associated with XFS, exfoliative material deposits on the intraocular lens with a dilated pupil is the diagnostic criteria of the condition (Tekin et al., 2019, p. 454). Exfoliative material usually accumulates a classic three zone pattern (Ritch & Schlötzer-Schrehardt, 2001, pp. 270-271) although there is no current literature that indicate that the pattern itself is a diagnostic criterium. This might be due to the fact that exfoliative material may differ in amount and appearance according to the stage of development (Tekin et al., 2019, p. 454), presence of a biological lens or an implant (Park & Kee, 2007, pp. 1815-1817) and because the central zone is not always present (Plateroti et al., 2015, p. 2). To follow is a description of how various suspect findings of XFS may present itself with illustrations.

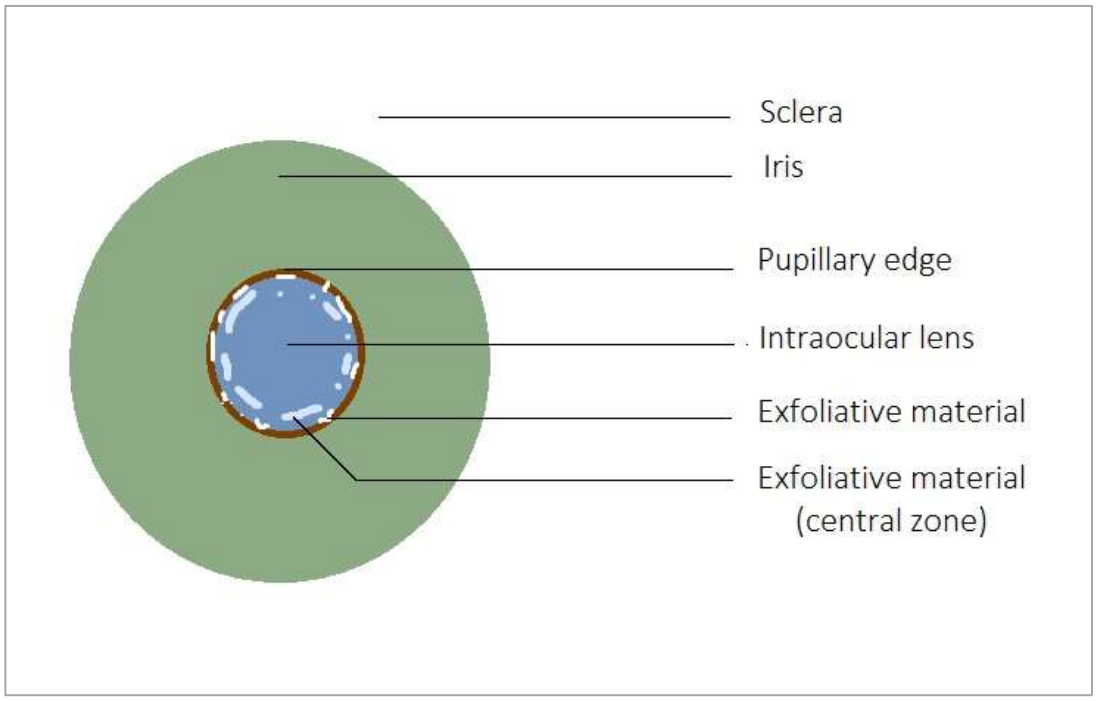
1.1.2.1 Intraocular lens

The primary diagnostic criteria of ocular XFS are exfoliative material on the anterior surface on the intraocular lens (Ritch, 2014, p. 1). When the pupil is undilated exfoliative material can be seen as a central zone with ruffled grey-white deposits on the pupillary margin and/or the central anterior surface of the intraocular lens, in a circular formation (Ritch & Schlötzer-Schrehardt, 2001, pp. 270-276) as seen in figure 1. When the pupil is dilated the exfoliative material deposits can be seen as a characteristic three zone pattern as follows (Figure 2.): a central homogeneous grey-white circle close to the habitual pupillary margin, a peripheral grey-white circle with radial striations and a clear zone separating the two (Ritch & Schlötzer-Schrehardt, 2001, pp. 270-271). The clear zone between the two are caused by the rubbing motion by the iris when the pupil is adjusting in diameter (Ritch, 2014, p. 1). To see all three zones, it is necessary to pharmacologically dilate the pupil (Ritch & Schlötzer-Schrehardt, 2001, pp. 270-271). In early stages the central zone might not

be seen as is reported to be missing in 20% of cases, while the peripheral zone is always present (Plateroti et al., 2015, p. 2). On an intra ocular lens implant, the exfoliative material may be scattered and can be seen on the lens implant, on the posterior lens capsule and even in the vitreous (Ritch & Schlötzer-Schrehardt, 2001, p. 277). Exfoliative material on an intraocular lens implant has been seen deposits in different ways with grey-white radial striations in the periphery of the posterior lens surface, scattered grey-white dot-like deposits the posterior, central lens surface and on the posterior lens capsule (Park & Kee, 2007, pp. 1815-1817).

Figure 1.

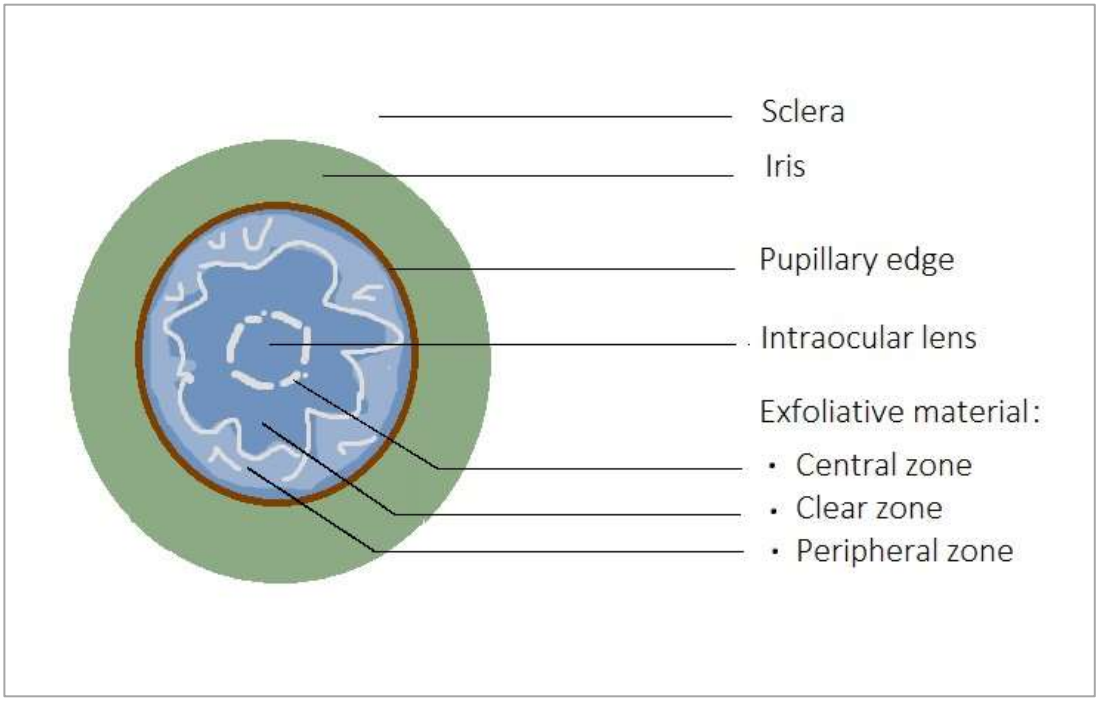
Exfoliative Material Deposits on the Pupillary Margin and Anterior Surface of the Intraocular Lens Without Dilation of the Pupil



Note. Illustration of anterior segments of the eye viewed from the front. Exfoliative material illustrated as white deposits on the pupillary margin and grey-white deposits forming a circular, central zone on the anterior surface of the intraocular lens. With permission of the illustrator Rebekka B. Hagen

Figure 2.

Exfoliative Material Deposits on the Anterior Surface of the Lens in the Classic Three Zones, When the Pupil is Dilated



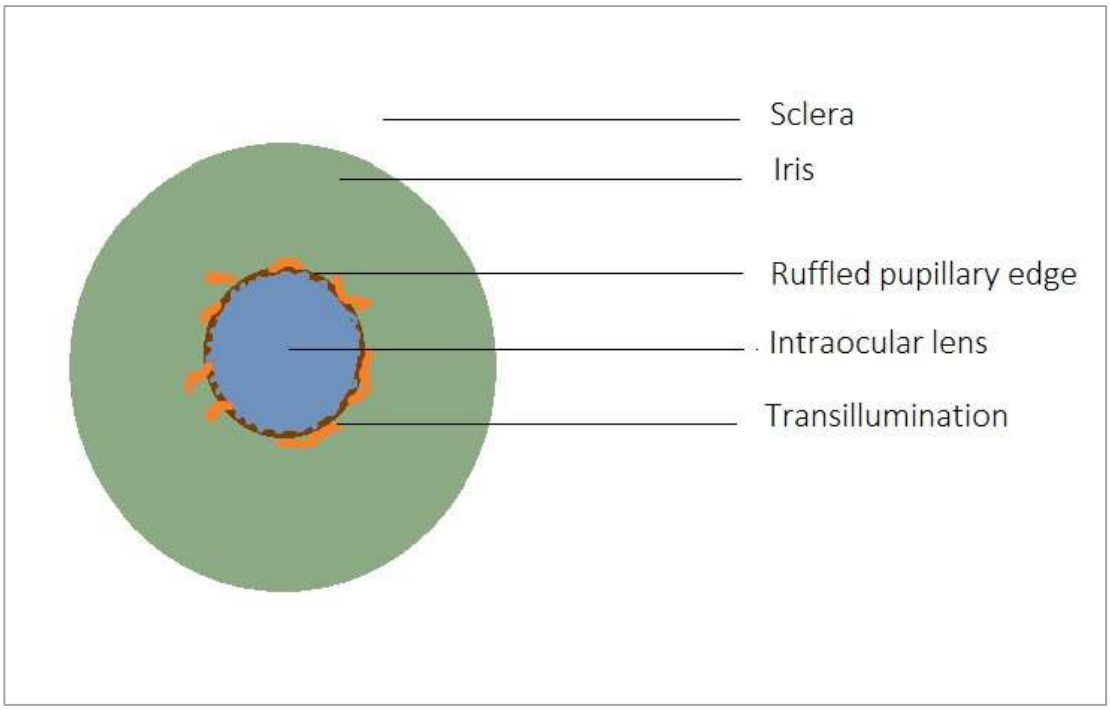
Note. Illustration of anterior segments of the eye viewed from the front. Exfoliative material illustrated as grey-white deposits on the anterior surface of the intraocular lens in the classic three zones, when the pupil is dilated. With permission of the illustrator Rebekka B. Hagen

1.1.2.2 Iris and pupil

Changes to the iris and pupil are recognised as significant related findings of XFS (Ritch & Schlötzer-Schrehardt, 2001, p. 271). The rubbing motion of the iris movement on the exfoliative material on the lens causes rupture to the pigment epithelial in the iris, leading to loss of the pupillary ruff and transillumination close to the pupillary edge (Ritch, 2014, p. 1) as seen in figure 3. In cases where the pigmentation loss is more extensive, more peripheral transillumination can occur with a diffuse appearance (Repo et al., 1990, pp. 1027-1029).

Figure 3.

Ruffled Pupillary Edge and Transillumination Close to the Pupillary Edge



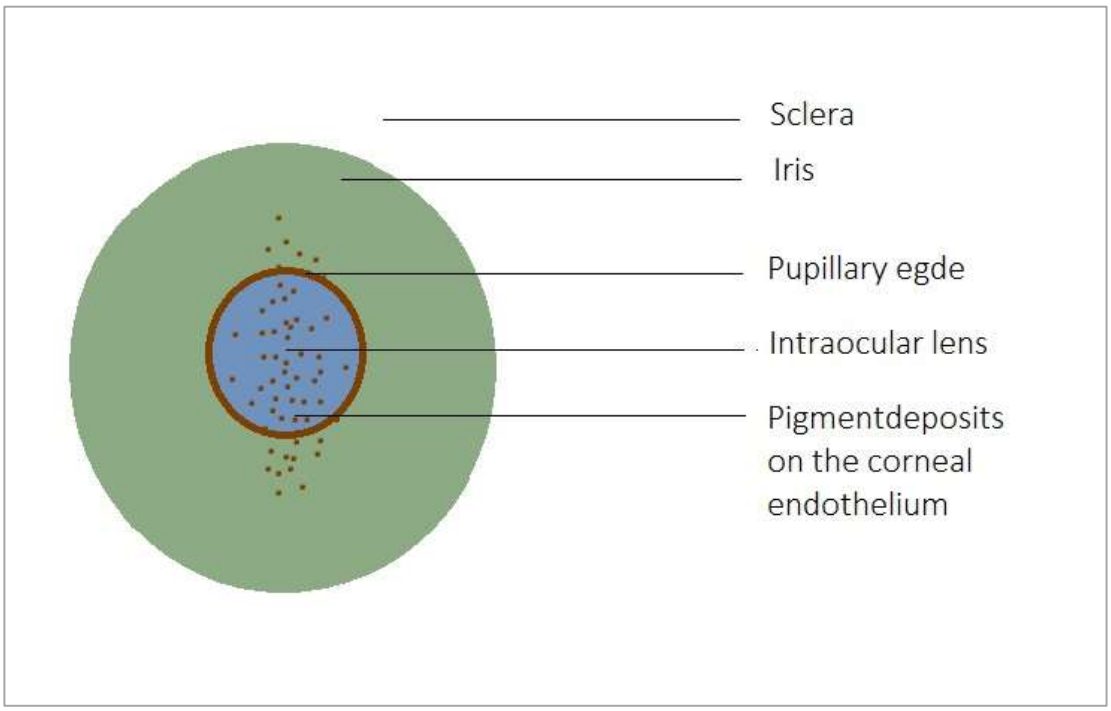
Note. Illustration of anterior segments of the eye viewed from the front. Ruffled pupillary edge illustrated as seen. Transillumination illustrated as orange spots/streaks close to the pupillary edge. With permission of the illustrator Rebekka B. Hagen

1.1.2.3 Cornea

Exfoliative material can be seen on the endothelial layer in the cornea, often misinterpreted as inflammatory precipitates (Plateroti et al., 2015, p. 2). Moore commonly, findings of pigment deposits on the endothelial layer in the cornea can be seen with XFS, usually recognised as scattered, brown spots on the central part of the corneal endothelium (Ritch & Schlötzer-Schrehardt, 2001, p. 274) as seen in figure 4. The pigment deposits can often resemble a "Krukenberg's spindle" more associated with pigment dispersion syndrome, but with a more scattered look (Bowling et al., 2016, pp. 366-367).

Figure 4.

Pigment Deposits on the Corneal Endothelium Resembling a "Krukenberg's Spindle"



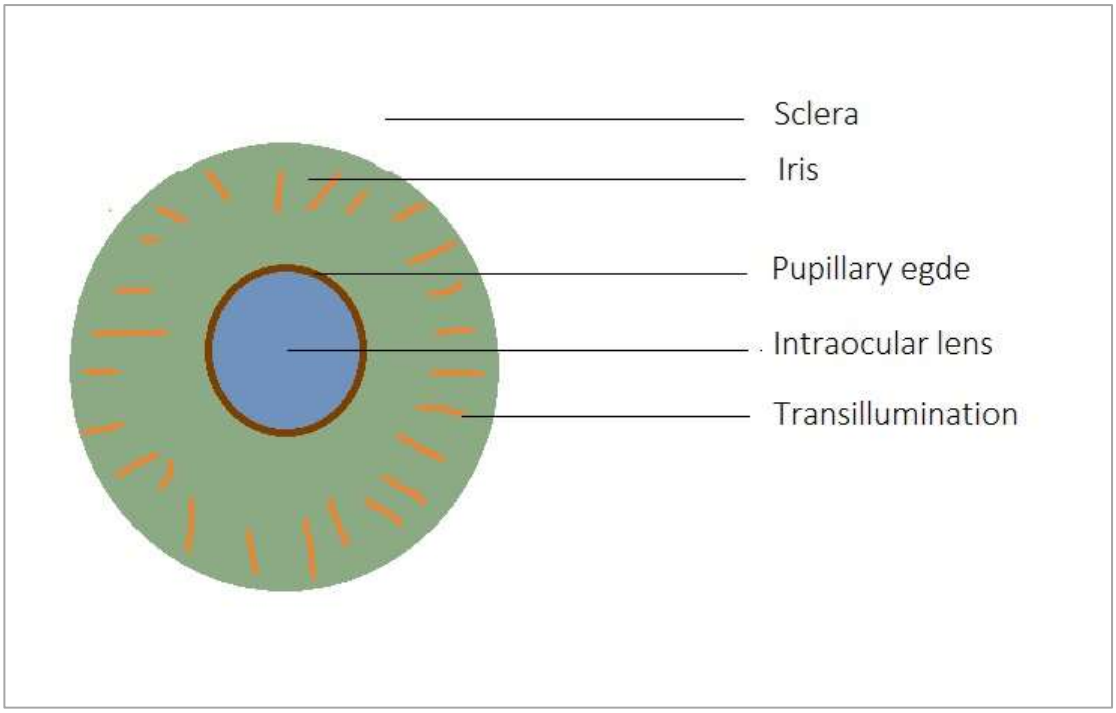
Note. Illustration of anterior segments of the eye viewed from the front. Pigment deposits on the corneal endothelium resembling a "Krukenberg's spindle" is illustrated as brown spots. With permission of the illustrator Rebekka B. Hagen

1.1.3 Differential diagnosis: Pigment dispersion syndrome

A common differential diagnosis to XFS is pigment dispersion syndrome (PDS) as both condition can give findings of pigment deposits on the corneal endothelium, resembling a "Krukenberg's spindle" as mentioned above (Bowling et al., 2016, pp. 366-370). Previously patients were labelled as XFS suspects, when findings was more associated with PDS (Ritch & Schlötzer-Schrehardt, 2001, p. 273). Both XFS and PDS can give a finding of transillumination, but it can be distinguished by the presentation of the finding as follows: The transillumination in XFS appear close to the pupillary edge as mention above (figure 3.), whereas in PDS the transillumination will appear in radial striations on the mid-periphery of the iris (Niyadurupola & Broadway, 2008, p. 869) as seen in figure 5. XFS and PDS are also similar in the way that both conditions give a higher risk of developing glaucoma (Bowling et al., 2016, pp. 366-368).

Figure 5.

Transillumination in the Mid-periphery Caused by PDS



Note. Illustration of anterior segments of the eye viewed from the front. Transillumination in the mid-periphery illustrated as orange streaks. Illustrator: Rebekka B. Hagen

1.2 Ocular complications

XFS is associated with an increased risk of developing cataract (Shingleton et al., 2009, pp. 1104-1105). A population-based follow-up study over 30 years in Sweden found that XFS was the second most common predictor after lens opacities for cataract surgery (Ekström & Botling Taube, 2015, pp. 774-777). Patients with XFS has also shown to be more prone to developing complications after cataract surgery (Shingleton et al., 2009, pp. 1103-1104), with one study showing a risk of complication 5 times higher than those without XFS (Scorolli et al., 1998, pp. 278-280). Complications during surgical removal of cataract is believed to be caused by weak zonule strength and poor dilation of the pupil in XFS (Shingleton et al., 2009, pp. 1104-1105). Postoperative complication for eyes with XFS includes among other; corneal oedema, macular oedema, posterior capsular opacification (Shingleton et al., 2009, p. 1104), capsule rupture, vitreous loss and intraocular lens dislocation (Fontana et al., 2017, pp. 1377-1383). XFS is also associated with having narrow anterior chamber angles, but angle-closure glaucoma is rarely seen in patients with XFS

(Ritch & Schlötzer-Schrehardt, 2001, pp. 274-275). Pavičić-Astaloš et al. (2016) found in their study of people diagnosed with XFS and glaucoma that there were only 1.1% diagnosed with angle-closure glaucoma, compared to primary open glaucoma which was 63.3% (p. 486). One study investigated the effect of dilating eyedrops on eyes with XFS with an open anterior chamber angle and found there was no narrowing of the anterior chamber angle when using dilating eyedrops (Mocan et al., 2013, pp. 51-56). Dilating eyedrops is found to give a less mydriasis of the pupil in patients with XFS than those without (Watson et al., 1995, pp. 341-342). Other ocular association include a higher risk of developing posterior synechiae between the iris and lens, blood-aqueous barrier dysfunction and blood vessel abnormalities in the iris causing ischemia and neovascularization (Ritch & Schlötzer-Schrehardt, 2001, pp. 279-280).

1.3 XFS and glaucoma

John Lindberg who first described XFS in 1917, found that 50% of his patients with XFS also had glaucoma, starting the suspicion that there is an association between XFS and glaucoma early on (Lindberg, 1917, as cited in Tarkkanen, 2018, pp. 1-3) . Glaucoma is an eye disease which can lead to progressive optic nerve damage and corresponding irreversible visual field loss (Bowling et al., 2016, p. 306). Today XFS is considered to be the most common cause of secondary open-angle glaucoma and it is usually then referred to as exfoliative glaucoma (Schacknow & Samples, 2010, p. 507). Other terms used to describe glaucoma secondary to XFS are capsular glaucoma and pseudoexfoliation glaucoma (Vesti & Kivelä, 2000, pp. 346-348). Why XFS can lead to glaucoma is not completely understood, but one strong theory is that exfoliative material and pigment deposits accumulates in the anterior chamber angle, causing an increase in intraocular pressure, resulting in damage to the optic nerve head (Ozaki, 2018, p. 83; Schacknow & Samples, 2010, p. 510). The accumulations of the deposits can disrupt the flow of the aqueous humour through the trabecular meshwork in the anterior chamber angle and cause a rise in intraocular pressure (Ghaffari Sharaf et al., 2020, p. 114). The combination of high intraocular pressure and the presence of exfoliative material is shown to doubles the risk of developing glaucoma (Grødum et al., 2005, pp. 386-390). Patients with XFS without elevated intraocular pressure initially, is also shown to have a higher risk of glaucoma, as it is seen over a period of 10 years, 30% can develop glaucoma (Schacknow & Samples, 2010, p. 510). Glaucoma secondary to XFS has shown to have a greater fluctuation in diurnal curve and often respond less to topical IOP lowering treatments, and as a consequence will often require a more aggressive treatment (Michalik & Kaufman, 2018, p. 87). Unfortunately

glaucoma secondary to XFS is shown to have a faster progression with damage to the optic nerve and wide visual field loss (Schacknow & Samples, 2010, pp. 512-513).

1.4 Findings associated with glaucoma

1.4.1 Elevated intraocular pressure

An association between high intraocular pressure (IOP) and glaucoma has long been known, first described as far back as in 810 C.E., then later confirmed in the late 1900s (Schacknow & Samples, 2010, p. 35). Normal values of IOP can range from 10.5 to 20.5 with a mean of 15.5 measured in millimetre of mercury (mmHg) (Bergmanson, 2015, p. 148). A standard deviation of 2 mmHg is usually accepted in Caucasian populations (Bowling et al., 2016, p. 307). High IOP alone does not mean that a patients has glaucoma, but because IOP lowering treatments do show an effect of slowing down the progression of glaucoma, the causal link is evident (Schacknow & Samples, 2010, p. 35). One study found a risk of progression of glaucoma to increase 11% per 1 mmHg in elevation, indicating a significant correlation between the two (Bengtsson et al., 2007, pp. 205-209).

1.4.2 Thinning of the nerve fiber thickness of the parapapillary retina

Evaluating the retinal nerve fiber layer (RNFL) thickness has been essential for detection of glaucomatous optic neuropathy since 1973 when Hoyt et. al. first descried RNFL atrophy in glaucoma (Hoyt et al., 1973, p. 814; Park & Kim, 2021, p. 14). It is shown that OCT imaging can detect early superior and inferior thinning of the RNFL thickness which correlated with visual field defects caused by glaucoma and in ocular hypertension without visual defects, suggesting a possibility to detect glaucoma before visual defects occur (Rispoli et al., 2021, pp. 160-161). A study from 2014 showed that the rate of parapapillary RNFL atrophy over time measured with OCT where almost twice as fast in glaucomatous eyes who developed visual filed defects compared to those without (Miki et al., 2014, pp. 1350-1358). OCT uses a normative values to determine if the RNFL thickness is within normal or not (Bowling et al., 2016, p. 320). Although OCT is considered a good diagnostic tool for glaucoma, Virgili et al. (2015) review suggest the diagnostic accuracy varies in studies and may be overestimated (pp. 17-18).

1.4.3 Thinning of the neuroretinal rim of the parapapillary retina

A method to evaluate of there is neuroretinal rim thinning is the cup-disk ratio technique introduced by Armaly and Sayegh (1969). The technique consist of comparing the size of the cup to the size disc as follows; the disk is divided into tens, then the size of the cup is compared to the disk size vertically and horizontally (Schacknow & Samples, 2010, p. 172). One study found the cup-disk ratio (C/D) to be approximately 0.44 with a SD of 0.15 in normal eyes and 0.67 with a SD of 0.10 in glaucomatous eyes (Garway-Heath et al., 1998, pp. 1118-1124). The normal cup-disk ratio varies greatly from 0.0 to 0.9 (Jost B. Jonas et al., 1988, pp. 522-530) and varies according to disk size from small to large (Jonas & Budde, 2000, p. 8). However, it is shown that the vertical C/D increases faster than the horizontal C/D in glaucoma (Jonas & Budde, 2000, p. 8) and a C/D of more than 0.6 or a asymmetry of 0.2 between the eyes are often considered suspect of glaucoma (Schacknow & Samples, 2010, p. 173). The ISNT assessment or "rule" is another method to evaluate if there is neuroretinal rim thinning and is based on the expected normal neuroretinal rim width of the optic disk in four quadrants and is considered a valuable clinical method of evaluating the optic disk for suspect glaucoma, although not specific (Bowling et al., 2016, p. 316). It was first described in 1988 when Jonas et al. calculated the rim thickness of normal optic disks and found the thickness decreased in four quadrants as follows: inferior (I), superior (S), nasal (N) and temporal (T), with inferior the thickest and temporal the thinnest (J. B. Jonas et al., 1988). Since glaucoma causes atrophy of the neuroretinal rim, usually in the superior and inferior section first, the ISNT assessment is considered to be a good tool to evaluate if there is glaucomatous atrophy if the neuroretinal rim does not follow the expected order (Schacknow & Samples, 2010, p. 170). Although it should be noted that not all normal or glaucomatous optic disks follow this rule as approximately 25% of glaucomatous eyes do follow the ISNT rule and 20% of normal eyes do not (Harizman et al., 2006, pp. 1579-1583).

The existing literature of the prevalence of XFS is conflicting in Norway, with Aasved (1979) found a prevalence of 1.0% in the age group 60-69 years whereas Ringvold et al. (1987) found a prevalence up to 21.0% at the age of 65 years. The prevalence in optometric practice in Norway is also not known, as to my knowledge, is has not been investigated. The result of this study is expected to give a better understanding of the prevalence of the condition and aid optometrist and other healthcare workers to better detect XFS, as such also provide better follow up of patients with a heighten risk

of glaucoma. The study can also aid in a development of a guideline for detection and handling of patients with XFS in optometric practice in Norway, as there is currently none.

1.5 Research objectives

The primary objective of this study was to investigate the occurrence of suspected XFS in men and women over the age of 40 years, who undergo a routine optometric examination in an optometric practice in Norway.

Primary objective was based on two following questions:

- What is the frequency of suspected XFS?
- What is the distribution of suspected XFS in different age groups, 40-49 years, 50-59 years, 60-69 years and so on?

The secondary objective was to investigate an association between ocular findings associated with glaucomatous optic neuropathy and confirmed XFS.

Secondary objective was based on the following questions and hypothesises:

- Is there an association between average intraocular pressure and confirmed XFS?
  Hypothesis: Average intraocular pressure is higher for those with confirmed XFS compared to those with no XFS
- Is there an association between average global nerve layer thickness of the parapapillary retina and confirmed XFS?
  Hypothesis: Average global nerve layer thickness of the parapapillary retina is thinner for those with confirmed XFS compared with those with no XFS
- Is there an association between average cup- disk ratio of the optic nerve head and confirmed XFS?
  Hypothesis: Average cup-disk ratio is greater for those with confirmed XFS compared with those with no XFS.
- Is there an association between the outcome of ISNT assessment of the optic nerve head and confirmed XFS?
  Hypothesis: There is an association between confirmed XFS and the outcome of ISNT assessment of the optic nerve head compared with those with no XFS.

2 Methods

A cross sectional study design with prospective data collection was chosen and the target population were all Norwegian women and men who undergo optometric examinations. Invited were woman and men over the age of 40 years who voluntary underwent an optometric examination in the optometric practice of Krogh Optikk Majorstuen between January 2022 and February 2022. Excluded were patients with insufficient view of the anterior eye, defined as any kind of corneal opacities that made identification of pigment and exfoliative deposits uncertain. If a patient had a narrow or dangerously narrow anterior chamber angle, they were excluded to participate in the second part of this study (Further detailed under heading recruitment and measurements). Excluded patients were followed up in accordance with the practice routines and if necessary, referred to an appropriate practitioner.

2.1 Recruitment

Patients who had an appointment would be asked to participate by the receptionist in the waiting room both orally and in writing (appendix 1). The receptionist would then wait at least 5 minutes to give the patient enough time to read and consider participation, before following up the invitation and collecting the written consent. The receptionist marked in the appointment book when information was given, and written consent was collected. The patients would then be called inn by the clinician and underwent the test procedures with no dilation of the pupils. Patients with findings that indicated exfoliative syndrome would then be invited to participate in the second part of this study. Hence, recruitment was performed in two steps: a) examination with no dilation of the pupil, and b) dilated examination. Invitation to the second part was first orally by the clinician in the examination room, then orally and in writing (appendix X) by the receptionist in the waiting room. The patients had at several hours to consider participation. At the second appointment the receptionist would collect the written consent in the waiting room. There was no charge for the second appointment. The patient would then be called in by the clinician and underwent the test procedures with dilation of the pupils.

The recruitment period was ordinally set to start September 2021 to February 2022. The study had to be revised, and thus the project had a late start (January 2022). The aim of recruitment was then set to 100 participants with an estimated 20 to 30 participating in part two of this study.

2.2 Measurements

All patients underwent a full routine optometric examination (both eyes) following the clinical guideline given by the Norwegian Association of Optometry (Optikerforbund, n.d.).
Intraocular pressure was measured with non-contact tonometry (Topcon Auto kerato-refracto-tonometer TRK-1P) per eye. Global nerve fiber thickness of the parapapillary retina was measured with optical coherence tomography (Topcon 3D OCT-1 Maestro) per eye. Cup-disk ratio was measured by comparing the vertical extension of the cup to the vertical extension of the disk in fraction per eye with a volk lens (90D double aspheric) and/or fundus photography (Optos panoramic ophthalmoscope p200dtx or Topcon 3D OCT-1 Maestro). ISNT rule was measured by evaluating if the neruoretinal rim width of the optic nerve head decreases in expected order; > Inferior > Superior > Nasal > Temporal or not per eye with a volk lens (90D double aspheric) and/or fundus photography (Optos panoramic ophthalmoscope p200dtx or Topcon 3D OCT-1 Maestro). Posterior segments of the eye were evaluated with a slit lamp biomicroscope (Topcon SL-7F or Topcon SL-D4) (further details given below). Six clinicians were involved in collecting data in the study (including the project manager Rebekka B. Hagen). All clinicians are authorized optometrists who work in the practice. Before the study all clinicians went through a training course with the project manager to ensure that all were informed about the study and that the optometric examination was performed in a standardized manner. They were all provided with a written protocol to follow (appendix Z), and the project manager would routinely ensure that all clinicians were following the protocol given throughout the recruitment period. The examination with the use of diagnostic eyedrops in the second part of this study and all transfer of data were performed by the project manager only (Rebekka B. Hagen). Patients who had given written consent to participate in the first part of this study underwent the auxiliary investigation which included an extended slit lamp biomicroscope examination without the use of diagnostic eyedrops (table 2.) This extended the routine optometric examination by approximately 5 minutes.

2.2.1 Table 2.

Screening for Signs of Ocular Exfoliative Syndrome (Part 1)

Investigated structure	XFS related findings	Slit lamp biomicroscope technique
Posterior surface of the cornea	Pigment deposits on the corneal endothelium	Parallelepiped beam, retro-illumination from the iris and optic section in approximately 45° in 10x-40x magnification
Iris and pupil	Transillumination close to pupillary margin	Retro-illumination from the fundus with 1-2 millimeters [mm] parallelepiped beam in the height of the pupil in 0° placed in the center of the pupil with 10x magnification
Pupillary edge	Exfoliative deposits on the pupillary edge and/or ruffled pupillary edge	Indirect illumination with 1-2 millimeters [mm] parallelepiped beam in approximately 45° with 10x-40x magnification
Anterior surface of the intraocular lens	Exfoliative deposits in the area corresponding to position of the pupil opening	Direct illumination with a parallelepiped beam and optic section in 45° to 15° in 10x-40x magnification
Intraocular lens implant	Exfoliative deposits on the anterior lens and/or exfoliative deposits on the posterior capsule and/or in the vitreous	Direct illumination with a parallelepiped beam and optic section in 45° to 15° in 10x-40x magnification and retro-illumination from the fundus and optic section in 45° in 10x-40x magnification

Note. The table shows the screening of signs of ocular exfoliative syndrome and the techniques used. All techniques are modified from the book “Clinical Procedures in Primary Eye Care” (Elliott, 2014, pp. 210-217) and the article “Exfoliation syndrome” by Ritch and Schlötzer-Schrehardt (2001, pp. 270-278). XFS= exfoliation syndrome. ° = degrees.

Participants with one or more of the findings presented in table 2. on one eye or both eyes were invited to participate in the second part of this study. Before the second invitation the clinician would assess the anterior chamber angle temporally and nasally on both eyes with the Van Hericks technique (0= dangerously narrow, 1=narrow, 2= moderate open, 3= open, 4= wide open) (Rabbetts & Bennett, 2007, p. 316). If the anterior chamber angle was dangerously narrow or narrow (Van Hericks 0 or 1) they would not be invited to the second part of this study. Participants who had findings of XFS in either one or both eyes was registered as XFS suspects.

The second part of this study was performed at a second appointment and lasted approximately 20 minutes. Patients who had given written consent to participate in the second part of this study underwent dilation with the use of 1-2 drops of tropicamide minims 0.5% (Felleskatalogen, 2020) and an extended slit lamp biomicroscope examination of the intraocular lens on both eyes (Table 3.). The intraocular lens was examined after 10-15 minutes after the administration of the diagnostic eyedrops. Exfoliation syndrome was diagnosed when exfoliative material was detected on the anterior surface of the intraocular lens (Figure 2.) in either one or both eyes and was registered as confirmed XFS.

2.2.2 Table 3

Diagnostic Investigation of Ocular Exfoliative Syndrome (Part 2)

Investigated structure	XFS related findings	Slit lamp biomicroscope technique
Anterior surface of the Intraocular lens	Exfoliative deposits in a central and/or peripheral zone on the anterior surface of the lens with/without a clear zone separating the two	Direct illumination with a parallelepiped beam in 45°in 10x-40x magnification
Intraocular lens implant	Exfoliative deposits on the anterior lens and/or exfoliative deposits on the posterior capsule and/or in the vitreous	Direct illumination with a parallelepiped beam in 45° to 15° in 10x to 40x magnification, optic section in 45° in 10x to 40x magnification and retro-illumination from the fundus and optic section in 45 in 10x to 40x magnification

Note. The table show the diagnostic investigation of ocular exfoliative syndrome and the technique used. All techniques are modified from the book "Clinical Procedures in Primary Eye Care" (Elliott, 2014, pp. 210-217) and the article "Exfoliation syndrome" by Ritch and Schlötzer-Schrehardt (2001, pp. 270-278). XFS= exfoliation syndrome. ° = degrees.

2.3 Analyses

All results from the full routine optometric examination, the auxiliary investigation and the second investigation were recorded in the patient's journal. Findings from the auxiliary investigation and the second investigation was recorded in a registration form (Appendix 2). Other results relevant for the study was transferred from the patient's journal and OCT imagine storing system to the same registration form. Name of patients were replaced with a three-digit unique ID numbers. All results were organized in a database (Excel, Microsoft Office) and stored in the secure sky database OneDrive (Office 365) through Microsoft Teams (MS Teams) which the University of South-East Norway (USN) is licensed to use. Only the project manager and principal investigator have access to the OneDrive sky database though MS Teams. Pictures were not transferred from their respected

storing places. Unrealistic values and missing data were flagged and identified by an algorithm in Excel. Results were transferred to a statistical program (IBM SPSS Statistics 28) for analysis. SPSS Statistics 28 are owned by the International Business Machines Corporation (IMB) and USN are licensed to use the program.

Descriptive analysis consisted of spread of values (standard deviations, percentages, frequencies) and central values (mean). Central values also included confidence intervals (95% CI) that was calculated by hand (Dawson & Trapp, 2004, pp. 111-112). Inferential statistics consisted of comparison between groups and correlation by comparing means with independent sample t-tests and chi square test with level of significance set to $\alpha = 0.05$ two-sided. Statistical analyses were performed on person level (XFS in at least one eye) for the study population, prevalence, frequencies and findings associated with XFS. Findings associated with glaucoma was analyzed for the right eye as all the confirmed XFS had the condition on the right eye (7/7), whereas only 6/7 had XFS on the left eye. Details of the specific analysis used are given under results (chapter 3).

2.4 Privacy protection and Ethical considerations

Ethical approval from the Regional Committees for Medical and Health Research Ethics (REC) was obtained 16.12.2021 (Appendix Y) for this study after revision of recruitment process to ensure the patients had enough time to consider participating, and to ensure voluntariness to be dilated with diagnostic eyedrops.

All patients who underwent the second investigation had both their eyes dilated with 1-2 drops of tropicamide minims 0.5% (Felleskatalogen, 2020) to give a short-duration dilation of the pupil for better examination of the intraocular lens. All patients were orally informed about common side effects which include a mild burning sensation when administrated and slight photophobia, and that the pupils would slowly return to normal size after approximately 6-8 hours (Phillips, 1984), before the investigation. They would also receive a written form which contained information regarding tropicamide, side effects and what to do if they experienced any. Serious side effect is very rare, even for high risk patients with a narrow anterior chamber angle the risk of developing an acute angle closure block is less than 1 % (Radcliffe, 2020). Even with the low risk, all patients had their anterior chamber angle evaluated with the Van Hericks technique to ensure administration was safe. Those with a narrow anterior chamber angle equal to 1 or less on the Van Hericks grading (Rabbetts & Bennett, 2007, p. 316) did not have dilation of the pupils performed. The intraocular

pressure was measured on patients who was dilated after administration to ensure there was no significant elevation. A significant elevation of more than 6-8 mmHg would have been followed up in the practice according to the routines or referred to an ophthalmologist the same day if necessary (Optikerforbund, n.d.) To minimize discomfort from light exposure , the slit lamp examination was done in less than 5 minutes, both eyes included.

All patients were informed orally and in writing (Appendix 1 and X) that participation was voluntary and that they could withdraw their consent any time with no consequence or explanation. They were all given opportunity to ask questions and receive answers about the study. If there were any indication for further examination, the patients were offered follow up in the practice or referred to the appropriate practitioner. All participants names were replaced with a unique ID number that deidentified their data collected in this study. The ID number was used on the registration forms and datasets. The list that connects the participants names and ID number was stored safely on an encrypted USB memory stick, distanced from the datasets and registration forms. The list will be stored for five years after the project completion in accordance with rules set by the Regional Committees for Medical and Health research Ethics (REC). After five years (latest December 31, 2027) the list will be deleted.

3 Results

91 people participated in this study from age 40 to 79 years, with a mean age of 57 (±10,1 SD). Out of the 91 participants there were 50 (55%) woman and 41 (45%) men. Demographics of the study sample are displayed in table 4.

3.1 Table 4

Study Sample

Age group	n	Mean age (SD)	n woman (%)	n men (%)
40-49	22	45.18 (2.95)	10 (45.5)	12 (54.5)
50-59	36	54.47 (2.73)	23 (63.9)	13 (36.1)
60-69	17	64.71 (2.82)	10 (58.8)	7 (41.1)
70-79	16	73.25 (2.72)	7 (43.8)	9 (56.3)
Total	91	57.44 (10.11)	50 (54.9)	41 (45.1)

Note. n= number of people. SD= standard deviation. %= percent.

Prevalence of suspect XFS in at least one eye is shown in table 5 and figure 6. The prevalence of suspect XFS over the age of 40 years came to a total of 18.7% and in the age groups it increases from 9.1% in the age group 40-49 years to 37.5% in the age group 70-79 years. There was a total of 17 participants with one or more findings of suspect XFS in at least one eye. Out of those 17 suspect XFS, 9 underwent the second investigation with dilation of both pupils. Frequencies of confirmed XFS out of the suspect XFS in at least one eye is shown in table 6.

3.2 Table 5

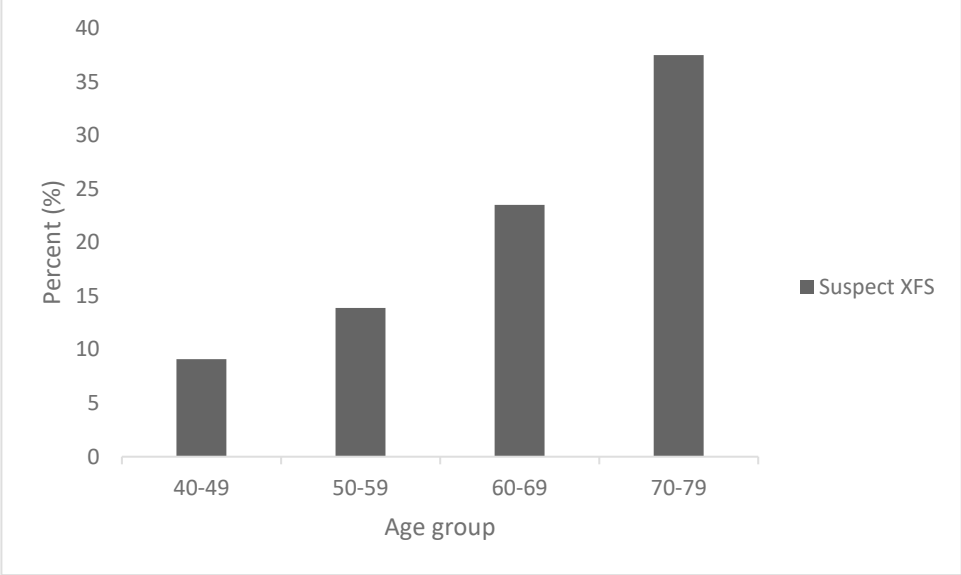
Prevalence of Suspect XFS in Persons Over 40 Years and in Age Groups

Age group	n	n suspect XFS	% (95% CI)
40-49	22	2	9.1 (-2.9 - 21)
50-59	36	5	13.9 (2.6 - 25)
60-69	17	4	23.5 (3.3 - 43)
70-79	16	6	37.5 (13 - 61)
Total	91	17	18.7 (10 - 26)

Note. n= number of people. XFS= exfoliation syndrome. CI= confidence interval. %= percent.

3.1 Figure 6

Prevalence of Suspect XFS



Note. Prevalence of suspect XFS in age groups in percent (%). XFS= exfoliation syndrome.

3.2 Table 6

Frequency of Confirmed XFS in Persons with Suspect XFS Over 40 Years and Over in Age Groups

Age group	n suspect XFS (%)	n confirmed XFS (%)
40-49	2 (100)	0 (0)
50-59	4 (80)	1 (20)
60-69	2 (50)	2 (50)
70-79	2 (33.3)	4 (66.7)
Total	17 (100)	7 (41.2)

Note. Nine of the suspect XFS (n=17) underwent the second investigation with dilation of the pupils, were 7 was confirmed with XFS. n= number of people. XFS= exfoliation syndrome. %= percent.

The association between confirmed XFS and ocular findings in the same eye (right eye) is shown in table 7. and table 8. There was a statistically significant difference (α= 0.05, two sided) in mean (SD) (t-test) between confirmed XFS and no XFS with the global nerve fibre layer thickness of the parapapillary retina (RNFL) (confirmed XFS= 71.75µm ±18.39, no XFS= 92.79µm ±9.95) with a p value of 0.002. The ISNT rule show some differences in percentage with those with confirmed XFS and no XFS. In the no XFS group 20.4% do not follow the rule and in the confirmed XFS 42.9% do

not follow the rule, although the p vale is not significant (p=0.335) based on chi square test (α=0.05, two-sided).

3.3 Table 7

Association Between Confirmed XFS and Intraocular Pressure, Global Nerve Fiber Thickness of the Parapapillary Retina and Cup-disk Ratio on the Right Eye

	Confirmed XFS		No XFS		
	Mean (SD)	n	Mean (SD)	n	p value
IOP [mmHg]	15 (2.82)	7	16.80 (2.16)	54	0.51
RNFL [µm]	71.75 (18.39)	4	92.79 (9.95)	24	0.002
C/D	0.38 (0.09)	7	0.34 (0.12)	54	0.43

Note. Based on results from participants between the age of 50 to 79 years for more accurate comparison, as there is none confirmed XFS from 40-49 years of age in the study population (n=91). IOP= intraocular pressure. RNFL= Global nerve fiber thickness of the parapapillary retina. C/D= cup-disk ratio. n= number of people. XFS= exfoliation syndrome. SD= standard deviation. µm= micrometer. mmHg= millimetre of mercury.

3.4 Table 8

Association Between Confirmed XFS and the ISNT Rule on the Right Eye

	n do not follow	n follow	p value
n no XFS (%)	11 (20.4)	43 (79.6)	0.335
n XFS (%)	3 (42.9)	4 (57.1)	

Note. Based on results from participants between the age of 50 to 79 years for more accurate comparison, as there is none confirmed XFS from 40-49 years of age in the study population (n=91). n= number of people. XFS= exfoliation syndrome. %= percent.

Post hoc analyses of the frequencies of suspect findings of XFS without dilation of the pupils in the suspect XFS and confirmed XFS group is shown in table 9. The most frequent suspect finding in the suspect XFS and confirmed XFS group were ruffled pupillary edge.

3.5 Table 9

Suspect Findings of XFS Without Dilation of the Pupils

	n suspect XFS (%)	n confirmed XFS (%)
Pigment deposits on the corneal endothelium	8 (47.1)	2 (28.6)
Exfoliative deposits on the pupillary edge	6 (35.3)	3 (42.9)
Exfoliative deposits on the intraocular lens	6 (35.3)	3 (42.9)
Ruffled pupillary edge	12 (70.6)	5 (71.4)
Transillumination close to the pupillary margin	7 (41.2)	4 (57.1)

Note. The most recurrent findings in suspect (n=17) and confirmed (n=7) XFS without dilation of the pupils. n= number of people. XFS= exfoliation syndrome. %= percent.

4 Discussion

The primary aim of this study was to investigate the occurrence of suspected XFS in an optometric practice in Norway, all women and men included over the age of 40 years. The aim was based on two questions, what is the frequency of suspected XFS over the age of 40 years and what is the distribution of suspected XFS in different age groups, 40-49 years, 50-59 years and older? Secondary the aim was to investigate an association between confirmed XFS, and various clinical findings associated with glaucoma, with the hypothesis that there is an association.

The results indicate that there is an occurrence of suspect XFS in optometric practice with a prevalence of 18.7% over the age of 40 years of age (Table 5.). The results differ quite significantly compared to Aasved (1979) who found the prevalence of XFS over the age of 40 years to be 0.9% (Table 1.) in Bergen. One suspicion for the difference of results could be the methods in with the results are based on, as in this study the 18.7% is based on suspected XFS, whereas in Aasved (1979) study the prevalence of 0,9% is based on confirmed XFS with the use of dilation eyedrops. (pp. 293-294). Another suspicion of why it differs is that the sample size itself is affecting the accuracy, as in this study the prevalence of suspected XFS of 18.7% is based on 17 people out of 91, whereas Aasved (1979) study had a sample size of 8537 in total (p.293). Although Aasved (1979) study sample also contain a much higher volume of younger people than older with 2303 people in the 40-49 years of age group (with 0 confirmed XFS) and only 184 in age group 70-79 (with 23 confirmed XFS) (p. 293). As XFS is an age-related condition (Ritch & Schlötzer-Schrehardt, 2001, p. 265), this high volume of younger people in the study sample might have skewed the prevalence lower than what truly it was. Compared with this study's distribution of age, which was 22 people and 16 people in the correspond age-groups (Table 4.), this study has a more equally spread-out distribution of age. This might indicate that even though Aasved (1979) had a much bigger sample size, the distribution of XFS though the age groups might be better represented in this study. Now, the calculated confidence interval for the prevalence 18.7% in this study is quite wide with a range from 10 to 26 (Table 5.), which indicate an uncertainty in the accuracy of the result, as the result may differ if the study is repeated. Interestingly Aasved (1979) study is quite similar to this study's result in the way the prevalence of XFS increase by age (p. 293). Aasved (1979) found from 0% in the age group 40-49 years to 4.8% in the age group 70-79 years (p. 293) compared to this study's result of 9.1% to 37.5% in the corresponding age groups (Table 5.). Even with the high confidence intervals and small sample size of this study, this increase by age is similar to all the other studies

displayed in table 1. As for the prevalence of suspect XFS itself, it seems to be quite higher compared to other studies that have investigated the prevalence in the same age groups (Table 1.).

In the age groups 40-49 Aasved (1979) found a prevalence of 0%, Bikbov et al. (2020) found in age group 40-45 a prevalence of 0.2% and Pavičić-Astaloš et al. (2016) found a prevalence of 0.5% in age group 45-49 years which is much lower than 9.1% in the age group of 40-49 years of suspect XFS in this study. Although both Bikbov et al. (2020) and Aasved (1979) used dilating eyedrops to diagnose XFS which could mean suspected XFS participants were excluded. XFS is noted to rarely be seen under the age of 50 years old (Vesti & Kivelä, 2000, p. 348), although the fact that 9.1% where found to be suspects of XFS in this study (Table 5.), brings up the questing if the prevalence in younger age groups is underestimated. Konstas and Ringvold (2018) also suggest that the prevalence of XFS is underestimated overall, and that XFS suspects and younger age groups should be included to better prevalence's studies of XFS (pp. 4-6). The result in the age group 50-59 years also reflects this, as the prevalence of suspected XFS was found to be 13,9% (Table 5.) in this study, whereas Arnarsson et al. (2007) found a prevalence of 2.5%, Aasved (1979) found a prevalence of 0.4% and Bikbov et al. (2020) found a prevalence of 2.1 % in the same age group which is much lower. In the age group 60-69 years Krause et al. (1988) found a prevalence of 14.2% and Pavičić-Astaloš et al. (2016) found a prevalence of 14.9% whereas Aasved (1979) found the prevalence to be only 1.0% and Bikbov et al. (2020) found a prevalence of only 7.0% in the same age group. All of the prevalence in this age group (60-69) varies quite significantly compared to this study result of 23,5% and from each other. The prevalence's of XFS vary quite significantly between studies, even withing the same study population of Bergen, Ringvold et al. (1987) found the prevalence of XFS over the age of 65 years, varied from 10.2% to 21.0% in two different locations.
This variation between studies might be due to different methods such as inclusion/execution criteria, diagnostic criteria of XFS and where the study sample has been collected. Comparing this study's results to Pavičić-Astaloš et al. (2016) study, which are similar by the way both seem to have found somewhat higher prevalence's compared to some others studies (Table 1.) and both included younger patients (patients in their 40's) (p. 484). Pavičić-Astaloš et al. (2016) study is also similar to this study as it does not use dilation eyedrops to confirm XFS, which could mean that XFS suspects were included in their results (p. 484). Now, despite these similarities, Pavičić-Astaloš et al. (2016) study was performed in an ophthalmology department in a hospital (p. 484), whereas this study was performed in an optometric practice, which might give a rather different study sample. The

study sample may be less representable for a bigger population, as there is probably a higher incidence of ocular abnormalities in people visiting a hospital ophthalmology department. Pavičić-Astaloš et al. (2016) differs from this study as they also excluded patients with intraocular lens implants (p. 484). As XFS are related to an increased risk of developing cataract (Shingleton et al., 2009, pp. 1104-1105), this might unintentionally excluded many patients with XFS.

In the oldest age group of this study (70-79 years) the prevalence of suspect XFS of 37.5% is much higher compared to (Aasved, 1979) study who found a prevalence of 4,8% and (Krause et al., 1988) study who found a prevalence of 21,9% in the same age group. Although compared to (Åström et al., 2007) who found a prevalence of 36,6% at the age of 73 years, it is quite similar. This might indicate that even with the low sample size, the results of this study might be somewhat representable and should not be discarded even if it varies quite significantly from other studies as it could contributes to a better understanding of the prevalence of XFS. Even though the sample size is low (n=91) and the results may not reflect the true prevalence because of it, it is still showing an increase by age (Table 5.), meaning the results could contribute to the understanding that XFS is an age-related condition, as it is widely understood to be (Vesti & Kivelä, 2000, p. 348).

So why should it be so important to detect suspect XFS and using dilating eyedrops for confirmation during an ocular examination? What implications do this have for the patient? XFS is associated with having an increased risk of developing cataract, as well as developing complication during and after cataract surgery (Shingleton et al., 2009, pp. 1104-1105). More consequential though, is the heighten risk of developing glaucoma secondary to XFS as the condition is today considered to be most know cause of secondary open-angle glaucoma (Schacknow & Samples, 2010, p. 507). Because of this, when XFS is diagnosed, the practitioner should be more aware of other findings associated with glaucoma. In this study, several measurements were taken to investigate if there is a correlation between confirmed XFS and findings associated with glaucoma for the right eye (Table 7 and 8). As elevated intraocular pressure in combination with XFS is associated with heighten risk of glaucoma (Grødum et al., 2005, pp. 386-390), the hypothesis was that the confirmed XFS group would have a higher intraocular pressure compared to those with no XFS. The results in this study do not show a significant difference in mean between those with no XFS and those with confirmed XFS with a p value of 0.51 (Table 7.). On the contrary the confirmed XFS (mean 15mmHg ±2.82) had a slightly lower intraocular pressure than those with no XFS (mean 16.8mmHg ±2.16). even though

the results somewhat contradict the hypothesis, there is no statistically significant difference and is based on a small sample size (n=54), therefore it is difficult to conclude if the results are representable. Compared to Bikbov et al. (2020) study it differ quite significantly, as they found a strong correlation between heighten intraocular pressure and XFS with a p=0.001 (α= 0.05, two-sided) (pp. 159-161).Thinning of the nerve fibre thickness of the RNFL is also a sign of glaucoma as it can indicate glaucomatous atrophy (Hoyt et al., 1973, p. 814). Measurements of the RNFL measured with optical coherence tomography (OCT) in this study did interestingly show a significant difference in mean (α=0.05, two-sided) between those with no XFS and confirmed XFS with a p= 0.002 (Table 7.). It is the group with confirmed XFS that has the lowest mean of RNFL thickness, with a mean of 71.75µm (±18.39) compared to the RNFL thickness of those without XFS with a mean of 92.97µm (±9.95) (Table 7.). This could indicate that the results are in line with the hypothesis that those with confirmed XFS have a thinner global RNFL thickness that those without. As the significant p value (p=0.002) for the global RNFL measurements are based on very few measurements with only 24 with no XFS and 4 with XFS (Table 7.), it is difficult to say if this is a random or true relationship. The low number of measurements was due to the fact that during the study recruitment period, the OCT broke down which was unfortunate. There seem to be a lack of studies investigating association between global RNFL thickness and confirmed XFS (measured with an OCT), as none of the studies mentioned in Table 1. have investigated this, although Pavičić-Astaloš et al. (2016) do mention the lack of using OCT was a limitation in their study (p. 487). Neuroretinal rim thinning caused by glaucoma can be assessed with the cup-disk (C/D) ratio technique, by comparing the size of the cup to the size of the disk (Armaly & Sayegh, 1969; Schacknow & Samples, 2010, p. 172). It is shown that the vertical C/D ratio increases faster in glaucoma (Jonas & Budde, 2000, p. 8) and that the C/D ratio is usually bigger in glaucoma compared to those without (Garway-Heath et al., 1998, pp. 1118-1124). These facts give the hypothesis that there is an as between a greater C/D ratio and confirmed XFS. There were however not any significant differences in mean between the C/D ratio of those with no XFS (mean 0.34 ±0.12) and confirmed XFS (mean 0.38 ±0.09) in this study, with a p value of 0.43 (Table 7.). Arnarsson et al. (2007) did also not find any significance association between cup-disk ratio and XFS with a p value of 0.60 (p.824). This indicates there is no association between C/D ratio and confirmed XFS. Interestingly though, the results are similar to what Garway-Heath et al. (1998, pp. 1118-1124) found to be the normal C/D ratio in normal eyes (0.44 ±0.15), which can suggest the results are somewhat representable of what a normal C/D ratio is, even with the small sample size. The ISNT

rule is another method to evaluate if there is thinning in the neuroretina rim (Bowling et al., 2016, p. 316), by assessing if the rim thickness follows the expected order in quadrant as follows; Inferior (I), superior (S), nasal (N), and temporal (T), with inferior thickest and temporal thinnest (J. B. Jonas et al., 1988). If the rim thickness does not follow the rule, it is suspect of glaucoma (Schacknow & Samples, 2010, p. 170). The hypothesis of their being an association between the outcome of the ISNT rule and confirmed XFS seems to be supported in the results as 42.9% of the confirmed XFS do not follow the ISNT rule and only 20.4% in the no XFS group do not (Table 8). However, the 42.9% in the XFS group is only based on 3/7 participants which make it difficult to say if this is a representable vale (Table 8). The p-vale of 0.335 also indicate that there is no statistical significance in the difference (Chi-square, α=0.05, two-sided). In literature it is noted that about 20% of normal eyes no not follow the ISNT rule (Harizman et al., 2006, pp. 1579-1583), which suggest that the finding of about 20% in the no XFS group do not follow the ISNT rule substantiates.

Measurements of the global RNFL thickness with an OCT, the cup-disk ratio and the ISNT rule are all measurements taken to assess if there are signs of glaucomatous atrophy on the papillary retina, as mentioned previously. Why were the measurements of the global RNFL thickness the only one that showed a significance difference in mean between those with no XFS and with confirmed XFS? Now, both the cup-disk ratio and ISNT rule are subjective test, as they are evaluated by the practitioners themselves, whereas the measurements of the global RNFL thickness are measured with a machine (OCT), hence an objective test. This might indicate that potential glaucomatous atrophy might have gone undetected or was too small to detect by subjective test but was picked up by the OCT machine. It has been shown in literature that OCT measurements can detect early RNFL thinning, suggesting a possibility of detecting glaucoma before visual defect occur (Rispoli et al., 2021, pp. 160-161). Although Virgili et al. (2015) review suggest the diagnostic accuracy of OCT measurements varies and may be overestimated (pp. 17-18). The data in this study also lacks the information if any of the participants had glaucoma or not, which could have affected the results.

In this study, 9 participants underwent the second investigation with the use of dilation eyedrops, were 7 was confirmed with XFS which was 41.2% out of all the suspect XFS (n=17) (Table 6.). This demonstrates that using dilating eyedrops is clinically useful to diagnose XFS and brings up the question if the prevalence would have been higher if all the 17 suspect XFS had been examined with the use of dilating eyedrops. The lack of using dilating eyedrops for diagnosing XFS, is seen as

hindrance of acquiring the true prevalence of XFS (Konstas & Ringvold, 2018, p. 6) as mentioned in introduction in one incidence 60% of patients with XFS referred to a glaucoma clinic, the XFS diagnosis was missed (Crittendon & Shields, 1988, as cited in Ritch & Schlötzer-Schrehardt, 2001, p.267). There are several suspect findings that should indicate further investigation such as pigment deposits on the corneal endothelium, ruffled pupillary edge and transillumination close to the pupillary edge (Ritch & Schlötzer-Schrehardt, 2001, pp. 270-274). Results of this study show that the most frequent suspect finding of XFS was ruffled pupillary edge with 70.6% in the suspect XFS group and 71.4% in the confirmed XFS group had this before dilation of the pupils (Table 9.). Other frequent findings of suspect XFS in the suspect XFS group was pigment deposits on the corneal endothelium (47.1%) and transillumination close to the pupillary edge (41.2%) (Table 9.). In the confirmed XFS group the second most frequent finding were also transillumination close to the pupillary edge (57.1%) (Table 9.). These results suggest that even if exfoliative deposits cannot be seen, it does not mean is not present, and dilation of the pupils with eyedrops to investigate the intraocular lens should be considered when suspect findings of XFS are detected during ocular examination. As seen in table 9. only 3 out of the 7 confirmed XFS had visible signs of exfoliative material before dilation of the pupils, suggesting that the other 4 might have gone undetected if not dilation of the pupils had been performed. The necessity of using dilating eyedrops to diagnose XFS could be discussed as Aasved (1979) found in his study about only 10% (n= 5/48) the XFS diagnose was missed before they had their pupils dilated with eyedrops (pp. 293-294). Although those results might be bias, as it is a study about the prevalence of XFS, the practitioner might have intentionally looked for XFS, and as a result the ocular examination might have had higher sensitivity to diagnose XFS than usual. Konstas and Ringvold (2018) do however suggest that to better prevalence studies of XFS, the examinator should have an complete knowledge and interest in XFS to ensure high diagnostic sensitivity (pp. 6-7). When it comes to general optometric practice though, it may not be expected that all practitioners have a complete knowledge, interest, or high experience with XFS, therefore the use of dilation eyedrops could be highly useful to diagnose the condition.

In this study, the prevalence is based on the suspect XFS without dilation of pupils, which might be a limitation as the XFS diagnosis were not confirmed. It might also be a limitation when comparing to other studies as all the other studies mention in this thesis used dilating eyedrops to confirm XFS (Arnarsson et al., 2007, p. 823; Bikbov et al., 2020, p. 159; Krause et al., 1988, pp. 120-121; Ringvold

et al., 1987, p. 17; Åström et al., 2007, p. 833; Aasved, 1979, pp. 293-294) apart from Pavičić-Astaloš et al. (2016) study. The low sample size of this study is a another limitation, as even though the results might be similar to some other studies, and it do show that XFS is precent in optometric practice in Norway, is difficult to assess whether the result can represent a bigger population in Norway. As noted under the chapter 2 (methods), the recruitment period was originally set to September 2021 to February 2022 but started January 2022. The late start was a consequence of having to revise the recruitment process to receive ethical approval from REK (Chapter 2., Methods). The main reason for this, was due to the use of dilating eyedrops in this study, and REK wanted the participants to have enough time to evaluate this before giving consent (Appendix Y). Ethical approval was received after the study was revised to give the patients several hours to consider participating further, by having the participant come in for a second appointment given a second information/consent form (Appendix X). This may have weakened the study as it was a cross-sectional study design, the variables should have been collected at one point in time (Wang & Cheng, 2020, p. 65). As this was in the middle of a pandemic (Convid-19), this caused a problem with many of the participants did not want to come in for a second appointment, to limit their time spent outdoor and with other people. This may be the cause of why only 9 out of the 17 suspect XFS came in for the second appointment. From personal experience during the recruitment process, many of the suspect XFS participant did consent to having their eyes dilated with eyedrops but did not want to come back for a second appointment to do this, but wanted it done during the original appointment. This caused an ethical dilemma; as an optometrist I want to give the best care for the patients, which means dilating their pupils if there is indication for this, but according to the approvals given to the study (Appendix Y), I cannot do this without giving the participant several hours to consider this. As a result, those who gave consent for dilation of the pupils during their original appointment but did not want to come back for a second appointment did get their pupils dilated. The results of that were not collected for this study. The patients care trumps the data collection for this study, and as the patients was informed in the first consent and information form (Appendix 1), the patient care would not differ if they chose to participate or not. If I had chosen to not dilate their pupils just because they did not want to come back for a second appointment, it would have violated the first consent form they consented to. Another problem arising from the fact that patients with suspect XFS had to come in for a second appointment was the fact that is caused worry for many of patients as they did not like the fact that they had to wait to get a complete answer if they had XFS or not. This could had been avoided if the dilation of the pupils

had been done at the first appointment. The Covid-19 pandemic also caused another problem during the recruitment period, as several of the optometrist and the receptionists, got the Covid-19 virus, and consequently there was only 1 or 2 out of the 6 optometrists actively participating during almost the whole recruitment period.

Even though the study had several limitations the study had only one exclusion criteria, giving the study a more representable sample, such as not excluding patients with intraocular lens implants. As explained in under methods (Chapter 2.) The selection of participants was not done by the practitioners themselves, but by the receptionist who was not participating in data collection who would ask every patient over 40 years who came in for an optometric examination. This was a strength of the study, as the practitioners could not choose who was invited based on how well the patient would fit in according to the study's objectives. The study was conducted at the optometric practice Krogh Optikk Majorstuen which is a big practice with 8 examination rooms and a variety of optometrist with different specialities, attracting a wide range of people. This was an advantage, as the selection of people visiting the practice could have potentially given a good representable study sample as the practice does not attract one group of people but several. Another strength was that the second investigation with the use of dilation eyedrops was done by the same optometrist, meaning all the confirmed XFS was diagnosed based on the same evaluation method.

To my knowledge, this was the first study to investigate the occurrence of suspect XFS in an optometric practice in Norway. To investigate the prevalence of suspect XFS in an optometric practice could potentially give a more accurate prevalence of the population, as the study sample may be based on a more random selection of people, compared to studies conducted in ophthalmology practices as the study sample collected there may have a higher incidence of ocular abnormalities. The prevalence of suspect XFS in optometric practice should be more investigated as XFS is a known risk for secondary glaucoma (Schacknow & Samples, 2010, p. 507). A better understanding of the condition could lead to better the care and follow up for patients at risk of developing glaucoma in optometric practice. In 2019 Menon economics report estimated that glaucoma is the second most cost for the Norwegian society after uncorrected ametropias (Skogli et al., 2019, pp. 23-24). The same report also found an estimated 75% of people in Norway choose to visit an optometrist to get an ocular examination (Skogli et al., 2019, p. 14). This indicate that the role of the optometrist to detect signs and risk factors of glaucoma should be of high value for the Norwegian society. To better future research the recruitment period should be longer to get a

larger sample size to represent a bigger population. I would recommend future studies to be done between several practises to get a larger sample size and could also give a wider range of people in the study sample. I would also recommend the use of dilating eyedrops, and if possible, during the first investigation. In this study, suspect findings of XFS were found in the age group 40-49 years and an increase of prevalence by age, as such I would recommend including younger patients and investigate the prevalence in different age groups.

5 Conclusion

This study shows that XFS is present in optometric practice in Norway. The prevalence found seem to be higher than other studies with similar populations, but because of the small sample size of this study, it is difficult to transfer the results to a bigger population. The increase of prevalence by age supports the understanding that XFS is an age-related condition. Only one finding associated with glaucoma was found to be associated with confirmed XFS, even so, XFS is a known risk for glaucoma, therefore diagnosing XFS should be considered clinically important. The study demonstrates that diagnostic eyedrops is clinically useful in diagnosing XFS. More research is needed to establish the prevalence of XFS in optometric practice in Norway.

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7 Appendix

7.1 Appendix 1: consent and information form part 1

Universitetet i Sørøst-Norge

Krogh Optikk

VIL DU DELTA I FORSKNINGSPROSJEKTET *FOREKOMST AV EKSFOLIASJONS SYNDROM HOS OPTIKER?* ***DEL 1***

FORMÅLET MED PROSJEKTET OG HVORFOR DU BLIR SPURT

Dette er et spørsmål til deg om å delta i et forskningsprosjekt for å undersøke hvor vanlig en øyetilstand som kalles eksfoliasjonssyndrom er blant de som blir undersøkt hos en optiker. Eksfoliasjonssyndrom er en tilstand knyttet til alder som gir belegg på linsen i øyet. Tilstanden er i seg selv en helt ufarlig tilstand, men kan gi en høyere risiko for utvikling av grønn stær. Grønn stær er en øyesykdom som over tid kan gi skade på synsnerven og det er derfor viktig å avdekke risikofaktorer for dette. Alle kvinner og menn over 40 år som tar en full synsundersøkelse her på Krogh Optikk Majorstuen kan delta. Universitetet i Sørøst-Norge er ansvarlig for prosjektet.

HVA INNEBÆRER PROSJEKTET FOR DEG?

Som deltaker i dette forskningsprosjektet vil du få utført en undersøkelse av linsen i øyet. Undersøkelsen av linsen vil forlenge synsundersøkelsen med 5 minutter.

Ved funn som kan indikere at du har tilstanden vil du få tilbud om å delta i del 2 av dette prosjektet. Del 2 gir en utvidet grundig undersøkelse av linsen i øyet, hvor pupillene dine vil bli utvidet med bruk av øyedråper. Dette for å bekrefte eller avkreftet funnen. Det vil da settes av 20 minutter en annen tid uten ekstra kostnad. Du vil få utvidet informasjon om dette om du får tilbud om å delta i del 2.

I prosjektet vil vi innhente og registrere opplysninger om deg. Opplysningene vil bli hentet fra din journal og fra et registreringsskjema for den grundige linseundersøkelsen og vil bli lagret i en forskningsdatabase hvor ditt navn er erstattet med et tilfeldig ID-nummer. Det vil opprettes en koblingsnøkkel som oppbevares separat fra registreringsskjema. Det vil ikke være mulig å koble opplysninger i registreringsskjema til dine journalopplysninger uten koblingsnøkkelen. Opplysninger som hentes ut fra journal er informasjon om utseende på regnbuehinnen, hornhinnen, linsen og synsnerven fra begge øyne, samt øyetrykket fra begge øyne. Alder og kjønn hentes også ut.

MULIGE FORDELER OG ULEMPER

Det er ingen direkte fordeler eller ulemper forent med deltakelse i prosjektet.

Om det avdekkes mistenkt sykdom vil du følges opp her i praksisen eller henvises videre til lege.

FRIVILLIG DELTAKELSE OG MULIGHET FOR Å TREKKE DITT SAMTYKKE

Det er frivillig å delta i prosjektet. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke. Det vil ikke ha noen negative konsekvenser for deg eller din behandling hos optikeren hvis du ikke vil delta eller senere velger å trekke deg.

Dersom du trekker deg fra prosjektet, kan du kreve å få slettet innsamlede opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner.

Dersom du senere ønsker å trekke deg eller har spørsmål til prosjektet, kan du kontakte Universitetet i Sørøst-Norge ved Per O. Lundmark, eller prosjektmedarbeider Rebekka Bang Hagen (se kontaktinformasjon på side 2).

HVA SKJER MED OPPLYSNINGENE OM DEG?

Opplysningene som registreres om deg skal kun brukes slik som beskrevet i hensikten med prosjektet, og planlegges brukt til 31.12.2022. Eventuelle utvidelser i bruk og oppbevaringstid kan kun skje etter godkjenning fra REK og andre relevante myndigheter. Så lenge du kan identifiseres i datamaterialet så har du rett til innsyn i hvilke opplysninger som er registrert om deg og rett til å få korrigert eventuelle feil i de opplysningene som er registrert. Du har også rett til å få innsyn i sikkerhetstiltakene ved behandling av opplysningene. Du kan klage på behandlingen av dine opplysninger til Datatilsynet og institusjonen sitt personvernombud.

Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger gjennom en navneliste. Det er kun Per Olof Lundmark og Rebekka Bang Hagen som har tilgang til denne listen.

Etter at forskningsprosjektet er ferdig, vil opplysningene om deg bli oppbevart i fem år av kontrollhensyn (31 desember 2027). Da vil navnelisten slettes og øvrige opplysninger slettes.

FORSIKRING

Alle deltakere i prosjektet er dekket av pasientskadeerstatningsordningen.

ØKONOMI

Forskningen er finansiert av Krogh Optikk AS.

Det vil ikke bli gitt kompensasjon eller dekning av utgifter for deltakere.

GODKJENNINGER

Regional komité for medisinsk og helsefaglig forskningsetikk har vurdert prosjektet, og har gitt forhåndsgodkjenning, saksnummer 275866 (16.12.2021).

Etter ny personopplysningslov har behandlingsansvarlig institusjon Universitetet i Sørøst-Norge og prosjektleder Per O. Lundmark et selvstendig ansvar for å sikre at behandlingen av dine opplysninger har et lovlig grunnlag. Dette prosjektet har rettslig grunnlag i EUs personvernforordning artikkel 6 nr. 1a og artikkel 9 nr. 2a og ditt samtykke.

På oppdrag fra Universitetet i Sørøst-Norge har NSD – Norsk senter for forskningsdata AS vurdert at behandlingen av personopplysninger i dette prosjektet er i samsvar med personvernregelverket.

KONTAKTOPPLYSNINGER

Dersom du har spørsmål til prosjektet kan du ta kontakt med prosjektmedarbeider Rebekka Bang Hagen, e-post rebekka_bang@hotmail.com, mobil 47 27 25 86, eller prosjektansvarlig Per O. Lundmark, e-post per.lundmark@usn.no, tel. 31 00 89 37.

Dersom du har spørsmål om personvernet i prosjektet kan du ta kontakt med personvernombudet ved Universitetet i Sørøst-Norge er Paal Are Solberg, e-post paal.a.solberg@usn.no, tlf 35 57 50 53/918 60 041.

JEG SAMTYKKER TIL Å DELTA I PROSJEKTET OG TIL AT MINE PERSONOPPLYSNINGER BRUKES SLIK DET ER BESKREVET

Sted og dato	Deltakers signatur
	Deltakers navn med trykte bokstaver

Jeg bekrefter å ha gitt informasjon om prosjektet

Sted og dato	Signatur
	Optikers stempel

7.2 Appendix X: consent and information form part 2

Universitetet i Sørøst-Norge

Krogh Optikk

VIL DU DELTA I FORSKNINGSPROSJEKTET *FOREKOMST AV EKSFOLIASJONS SYNDROM HOS OPTIKER?* ***DEL 2***

FORMÅLET MED PROSJEKTET OG HVORFOR DU BLIR SPURT

Dette er et spørsmål til deg som har deltatt i den første delen av et forskningsprosjekt som har til formål å undersøke hvor vanlig en øyetilstand som kalles eksfoliasjonssyndrom er blant de som blir undersøkt hos en optiker. Fordi det ble gjort funn som kan indikere at du har tilstanden blir du spurt om å delta i en andre del av prosjektet som har til formål å bekrefte eller avkrefte funnen.

Universitetet i Sørøst-Norge er ansvarlig for prosjektet.

HVA INNEBÆRER PROSJEKTET FOR DEG?

Som deltaker i denne del av forskningsprosjektet vil du få utført en grundig undersøkelse av linsen i øyet. For å kunne gjøre dette må pupillene i øyet utvides med øyedråper (Tropikamid). Den grundige undersøkelsen av linsen vil være opp til 20 minutter og koster deg ikke noe.

I denne del av prosjektet vil vi innhente og registrere opplysninger fra et registreringsskjema for den grundige linseundersøkelsen. Opplysningene og vil bli lagret i en forskningsdatabase hvor ditt navn er erstattet med et anonymt ID-nummer.

MULIGE FORDELER OG ULEMPER

Det er ingen direkte fordeler eller ulemper forent med deltakelse i prosjektet.

Om drypping med øyedråper gjennomføres kan det medføre lett svie ved dryppingen som vil vare et par sekunder. Siden pupillene er utvidet kan man bli kortvarig lyssky etter undersøkelsen og det anbefales å unngå bilkjøring til effekten avtar. Dråpenes utvidende effekt på pupillene vil avta over tid og det kan ta 2-8 timer før dem er tilbake til normal størrelse. Utvidet informasjon om dråpene vil gis muntlig og skriftlig om det er hensiktsmessig å dryppe med øyedråper under synsundersøkelsen.

Om det avdekkes mistenkt sykdom vil du følges opp her i praksisen eller henvises videre til lege.

FRIVILLIG DELTAKELSE OG MULIGHET FOR Å TREKKE DITT SAMTYKKE

Det er frivillig å delta i prosjektet. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke. Det vil ikke ha noen negative konsekvenser for deg eller din behandling hos optikeren hvis du ikke vil delta eller senere velger å trekke deg. Dersom du trekker deg fra prosjektet, kan du kreve å få slettet innsamlede opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner.

Dersom du senere ønsker å trekke deg eller har spørsmål til prosjektet, kan du kontakte Universitetet i Sørøst-Norge ved Per O. Lundmark, eller prosjektmedarbeider Rebekka Bang Hagen (se kontaktinformasjon på side 2).

HVA SKJER MED OPPLYSNINGENE OM DEG?

Opplysningene som registreres om deg skal kun brukes slik som beskrevet i hensikten med prosjektet, og planlegges brukt til 31.12.2022. Eventuelle utvidelser i bruk og oppbevaringstid kan kun skje etter godkjenning fra REK og andre relevante myndigheter. Så lenge du kan identifiseres i datamaterialet så har du rett til innsyn i hvilke opplysninger som er registrert om deg og rett til å få korrigert eventuelle feil i de opplysningene som er registrert. Du har også rett til å få innsyn i sikkerhetstiltakene ved behandling av opplysningene. Du kan klage på behandlingen av dine opplysninger til Datatilsynet og institusjonen sitt personvernombud.

Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger gjennom en navneliste. Det er kun Per Olof Lundmark og Rebekka Bang Hagen som har tilgang til denne listen.

Etter at forskningsprosjektet er ferdig, vil opplysningene om deg bli oppbevart i fem år av kontrollhensyn (31 desember 2027). Da vil navnelisten slettes og øvrige opplysninger slettes.

FORSIKRING

Alle deltakere i prosjektet er dekket av pasientskadeerstatningsordningen.

ØKONOMI

Forskningen er finansiert av Krogh Optikk AS.

Det vil ikke bli gitt kompensasjon eller dekning av utgifter for deltakere.

GODKJENNINGER

Regional komité for medisinsk og helsefaglig forskningsetikk har vurdert prosjektet, og har gitt forhåndsgodkjenning, saksnummer 275866 (16.12.2021).

Etter ny personopplysningslov har behandlingsansvarlig institusjon Universitetet i Sørøst-Norge og prosjektleder Per O. Lundmark et selvstendig ansvar for å sikre at behandlingen av dine opplysninger har et lovlig grunnlag. Dette prosjektet har rettslig grunnlag i EUs personvernforordning artikkel 6 nr. 1a og artikkel 9 nr. 2a og ditt samtykke.

På oppdrag fra Universitetet i Sørøst-Norge har NSD – Norsk senter for forskningsdata AS vurdert at behandlingen av personopplysninger i dette prosjektet er i samsvar med personvernregelverket.

KONTAKTOPPLYSNINGER

Dersom du har spørsmål til prosjektet kan du ta kontakt med prosjektmedarbeider Rebekka Bang Hagen, e-post rebekka_bang@hotmail.com, mobil 47 27 25 86, eller prosjektansvarlig Per O. Lundmark, e-post per.lundmark@usn.no, tel. 31 00 89 37.

Dersom du har spørsmål om personvernet i prosjektet kan du ta kontakt med personvernombudet ved Universitetet i Sørøst-Norge er Paal Are Solberg, e-post paal.a.solberg@usn.no, tlf 35 57 50 53/918 60 041.

JEG SAMTYKKER TIL Å DELTA I PROSJEKTET OG TIL AT MINE PERSONOPPLYSNINGER BRUKES SLIK DET ER BESKREVET

Sted og dato	Deltakers signatur
	Deltakers navn med trykte bokstaver

Jeg bekrefter å ha gitt informasjon om prosjektet

Sted og dato	Signatur
	Optikers stempel

7.3 Appendix 2: registration form

Journalnr: **(FJERNES/KLIPPES BORT OG ERSTATTES MED ID)**

ID:

Alder:	**Kjønn**	1 Kvinne	2 Mann

	OD		**OS**	
C/D (horisontal/vertikal)				
ISNT	1 Følger	0 Følger ikke	1 Følger	0 Følger ikke
Linse	0 Biologisk	1 Implantat	0 Biologisk	1 Implantat
IOT	mmHg		mmHg	
Papille NFL tykkelse (OCT)	µm		µm	

Indikasjon på utvidet SLM med tropikamid ved positiv av 1 eller flere av følgende funn.

	OD		**OS**	
Pigmentavleiring kornea endotel	0 neg	1 pos	0 neg	1 pos
Transilluminasjon nær pupillerand	0 neg	1 pos	0 neg	1 pos
Rufsete pupillerand	0 neg	1 pos	0 neg	1 pos
Eksfoliat nær pupillekant	0 neg	1 pos	0 neg	1 pos
Eksfoliat på linsen	0 neg	1 pos	0 neg	1 pos

SLM kvalitet	0 bra	1 redusert	2 dårlig

Bra ved veldig lett vurdering. Redusert når OK vurdering. Dårlig når vanskelig vurdering.

Eksfoliasjons syndrom

	Neg	Suspekt	Pos
OD	0	1	2
OS	0	1	2

Utvidet SLM ved suspekt eksfoliasjons syndrom med drypping av tropikamid:

Ved Van Hericks 1 eller mindre nasalt og temporal skal ikke drypping utføres:

	OD	OS
Horisontal pupillestørrelse før tropikamind	mm	mm
Horisontal pupillestørrelse etter tropikamid	mm	mm
Van hericks (0-4)	Temp/nas:	Temp/nas:

Kryss av

	OD		OS	
Dryppet med tropikamid	0 neg	1 pos	0 neg	1 pos

7.4 Appendix Z: Written protocol for clinicians

Forskningsprosjekt

- Alle kvinner og menn og 40 år opp oppover som tar en full SU
- De inviteres først av den som sitter i linseresepsjon (samtykke/infoskjema gis)
- De gis 5 min før vi henter dem til SU (det skal noteres inn når de er gitt samtykke/infoskjema på fremsida i heads)
- Den som sitter i resepsjon innhenter samtykkeskjema, men du tar den med slik at du får lagt sammen registreringsskjema sammen med samtykkeskjema (skal legges sammen, frem til jeg gir dem en kodenøkkel og separerer dem).
- Noter på registerings skjema under SU (lettere å gjøre det underveis enn etterpå)
- Ved funn av 1 eller flere tegn til eksfoliasjonssyndrom – spør om de ønsker å delta i del 2 muntlig (drypping) – målet er da å bekrefte/avkrefte XFS
- Skriftlig samtykkeskjema gis av den som sitter i resepsjonen – den får de med seg og de skal ta den med seg på etterkontrollen om de ønsker å delta.
- Den som sitter i resepsjonen, booker etterkontrollen.
- Sjekk kammervinkel FØR dere tilbyr etterkontroll med drypping på de som har indikasjon for det. Hvis for trang vinkel – da kan jeg ikke dryppe og blir for dumt at de kommer for «ingenting». Kunden regnes da som «eksfoliasjons syndrom suspekt».
- EK settes av på tirsdager i min «studiebok» - 20 minutter - jeg må ta alle dryppinger i min studietid. Det er GRATIS for kunden.
- OBS! i samtykkeskjemaene skal dere stemple med deres stempel

- **Full SU inkluderer:**
- IOT
- Fundusvurdering (C/D og ISNT vurdering)
- 3D wide scan med OCT av papille (trenger nervefiberlagtykkelse – skal noteres i registerings skjema)
- SLM vurdering av fremre segment (cornea, linse, iris, Van hericks)
- **EK med drypping hos meg inkluderer:**
- 20 minutter
- Måling av pupillstørrelse før/etter drypping
- Drypping med tropikamid
- SLM vurdering av linser
- Ny IOT mål (frivillig for kunden, ikke en del av studie)

I registreringsskjema skal dere notere journalnummer. Dette så jeg vet hvem det gjelder. Når dataen hentes ut, erstatter jeg denne med en kodenøkkel (klippes bort og makuleres). Registerings skjema og samtykke/info skjema vil da lagres separat fra hverandre.

Det er to blå bokser bak i linseresepsjon:

Samtykke/info skjema legges sammen med registreringsskjema i blå boks i linseresepsjon (pin dem sammen).

- De som er ferdig legges i blå boks nr. 1
- De som settes opp på EK for drypping legges i blå boks nr. 2

Screening of signs of ocular exfoliative syndrome

Anterior segment	Findings	Slit lamp biomicroscope
Posterior segment of the cornea	Pigment deposits on the corneal endothelium	Parallelepiped beam, retro-illumination from the iris and optic section in approximately 45° in 10x-40x magnification
Iris and pupil	Transillumination close to pupillary margin	Retro-illumination from the fundus with 1-2 millimeters [mm] parallelepiped beam in the height of the pupil in 0° placed in the center of the pupil with 10x magnification
Pupillary edge	Exfoliative deposits on the pupillary edge and/or ruffled pupillary edge	Indirect illumination with 1-2 millimeters [mm] parallelepiped beam in approximately 45° with 10x-40x magnification
Anterior surface of the intraocular lens	Exfoliative deposits in the area corresponding to position of the pupil opening	Direct illumination with a parallelepiped beam and optic section in 45° to 15° in 10x-40x magnification
Intraocular lens implant	Exfoliative deposits and/or exfoliative deposits on the posterior capsule and/or in the vitreous	Direct illumination with a parallelepiped beam and optic section in 45° to 15° in 10x-40x magnification and retro-illumination from the fundus and optic section in 45° in 10x-40x magnification

7.5 Appendix Y: REC approval (1-4)

7.5.1 1. Approval with conditions

REK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst B	Hanne Johansen Pekovic	22845501	17.09.2021	275866

Per Olof Lundmark

Prosjektsøknad: Forekomst av okulær eksfoliasjonssyndrom hos optiker
Søknadsnummer: 275866
Forskningsansvarlig institusjon: Universitetet i Sørøst-Norge

Prosjektsøknad godkjennes med vilkår

Søkers beskrivelse

Hovedmålet med prosjektet er å undersøke forekomsten av okulær eksfoliasjonssyndrom hos pasienter over 40 år som tar en synsundersøkelse hos en optiker. Okulær eksfoliasjonssyndrom er en aldersrelatert tilstand karakterisert av en økende utvikling av ekstracellulære fibriller i okulært vev, hovedsakelig sett på linsen i øyet som et hvitaktig belegg. Prevalensen varierer en del i litteraturen, men øker etter fylte 50 år. Tilstanden er forent med en økt risiko for utvikling av grønn stær.
Det sekundære formålet med studiet er å undersøke sammenhengen mellom okulær eksfoliasjonssyndrom og funn i øyet som kan innebære en økt risiko for grønn stær. Informert samtykke vil bli innhentet før undersøkelsen og all informasjon vil bli avidentifisert. I studien vil det bli søkt spor etter okulær eksfoliasjonssyndrom med spaltlampemikroskop. Ved misstanke blir øyedråper brukt for å utvide pupillen slik at tilsanden kan bekrefties eller avkrefties. Funne blir koblet til resultater fra synsundersøkelse som er en del av vurderingen av risikoen for grønn stær, eks øyetrykk og utseendet på synsnerven i øyet. Resultatene fra studie er forventet å gi en bedre forståelse av forekomsten av okulær eksfoliasjonssyndrom hos optikere i Norge og kan hjelpe optikere å bedre oppdage tilstanden og følge opp pasienter med risiko for sekundær grønn stær.

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK sør-øst B) i møtet 18.08.2021. Vurderingen er gjort med hjemmel i helseforskningslovens § 10.

REKs vurdering

Formålet med prosjektet, slik det fremkommer av søknad og protokoll, er å undersøke forekomsten av okulær eksfoliasjonssyndrom, og sammenhengen med funn i øyet som kan innebære økt risiko for grønn stær hos pasienter over 40 år.

REK sør-øst B
Besøksadresse: Gullhaugveien 1-3, 0484 Oslo
Telefon:22 84 55 11 | **E-post**:rek-sorost@medisin.uio.no
Web:https://rekportalen.no

Det skal inkluderes 800 personer over 40 år, som vil bli forespurt deltakelse i prosjektet i forbindelse med en rutineundersøkelse ved Krogh optikk i Oslo. Forespørselen vil bli gitt ved oppmøte, og det skal gis skriftlig informasjon og innhentes skriftlig samtykke.

Ved inklusjon vil deltaker gjennomføre en synsundersøkelse som vanlig. Det skal i tillegg utføres spaltlampevurderingen av okulær eksfoliasjonssyndrom med spaltelampemikroskop. Ved mistanke anvendes det øyedråper for å utvide pupillen slik at tilstanden kan bekreftes eller avkreftes. Forventet ekstra tidsbruk ved deltakelse i prosjektet er 15 minutter.

Det skal innhentes opplysninger fra den generelle øyehelsevurderingen og vurderingen av grønn stær (blant annet øyetrykk, nervefiberlagstykkelse, utseende på synsnerve), samt alder og kjønn.

Komiteen har vurdert prosjektet og mener dette er et nyttig prosjekt som vil gi økt kunnskap om forekomsten av okulær eksfoliasjonssyndrom. Komiteen godkjenner derfor prosjektet på følgende vilkår:

- Rekrutteringsprosedyren må revideres slik at utvalget får nok betenkningstid og forespørselen oppleves som reelt frivillig. Slik prosedyren er lagt opp nå kan deltaker oppleve et press til å delta på grunn av behandlingssituasjonen.
- Informasjonsskrivet må revideres slik at det fremkommer hvor lenge effekten av øyedråpene typisk varer, og avsnitt om oppbevaring må endres slik at det fremkommer at opplysninger anonymiseres 5 år etter prosjektslutt (desember 2027).
- Krogh optikk må legges til som forskningsansvarlig institusjon, da datainnsamlingen skal foregå her.

Revidert protokoll og informasjonsskriv, samt opplysninger om ny forskningsansvarlig institusjon, bes innsendes REK ved å benytte skjema for «Endring og/eller henvendelse» som finnes etter innlogging på http://rekportalen.no.

Alle endringer i dokumenter skal markeres med sporede endringer som viser hva som har blitt endret, lagt til, og/eller slettet, samt med oppdaterte versjonsnumre og dato.

Vedtak

REK har gjort en helhetlig forskningsetisk vurdering av alle prosjektets sider. Prosjektet godkjennes med hjemmel i helseforskningsloven § 10, under forutsetning av at ovennevnte vilkår er oppfylt.

I tillegg til vilkår som fremgår av dette vedtaket, er godkjenningen gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknad og protokoll, og de bestemmelser som følger av helseforskningsloven med forskrifter.

Prosjektet er godkjent frem til sluttdato 31.12.2022.

Komiteens avgjørelse var enstemmig.

Etter prosjektslutt skal opplysningene oppbevares i fem år for dokumentasjonshensyn. Enhver tilgang til prosjektdataene skal da være knyttet til behovet for etterkontroll.

Prosjektdata skal således ikke være tilgjengelig for prosjektet. Prosjektleder og forskningsansvarlig institusjon er ansvarlig for at opplysningene oppbevares indirekte personidentifiserbart i denne perioden, dvs. atskilt i en nøkkel- og en datafil.

Etter disse fem årene skal data slettes eller anonymiseres. Vi gjør oppmerksom på at anonymisering kan være mer omfattende enn å kun slette koblingsnøkkelen, jf. Datatilsynets veileder om anonymiserings-teknikker.

Vi gjør samtidig oppmerksom på at det også må foreligge et behandlingsgrunnlag etter personvernforordningen. Dette må forankres i egen institusjon.

Sluttmelding
Prosjektleder skal sende sluttmelding til REK på eget skjema via REK-portalen senest senest 6 måneder etter sluttdato 31.12.2022, jf. helseforskningsloven § 12. Dersom prosjektet ikke starter opp eller gjennomføres meldes dette også via skjemaet for sluttmelding.

Søknad om endring
Dersom man ønsker å foreta vesentlige endringer i formål, metode, tidsløp eller organisering må prosjektleder sende søknad om endring via portalen på eget skjema til REK, jf. helseforskningsloven § 11.

Klageadgang
Du kan klage på REKs vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes på eget skjema via REK portalen. Klagefristen er tre uker fra du mottar dette brevet. Dersom REK opprettholder vedtaket, sender REK klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag (NEM) for endelig vurdering, jf. forskningsetikkloven § 10 og helseforskningsloven § 10.

Med vennlig hilsen

Ragnhild Emblem
Professor, dr. med.
leder REK sør-øst B

Hanne Johansen Pekovic
Rådgiver, REK sør-øst B

Kopi til:

Universitetet i Sørøst-Norge

7.5.2 2. Approval with conditions

REK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst B	Hanna Johansen Pekovic	22845501	11.11.2021	275866

Per Olof Lundmark

Prosjektsøknad: Forekomst av okulær eksfoliasjonssyndrom hos optiker
Søknadsnummer: 275866
Forskningsansvarlig institusjon: Universitetet i Sørøst-Norge

Prosjektsøknad: Endring godkjennes med vilkår

Søkers beskrivelse

Hovedmålet med prosjektet er å undersøke forekomsten av okulær eksfoliasjonssyndrom hos pasienter over 40 år som tar en synsundersøkelse hos en optiker. Okulær eksfoliasjonssyndrom er en aldersrelatert tilstand karakterisert av en økende utvikling av ekstracellulære fibriller i okulært vev, hovedsakelig sett på linsen i øyet som et hvitaktig belegg. Prevalensen varierer en del i litteraturen, men øker etter fylte 50 år. Tilstanden er forent med en økt risiko for utvikling av grønn stær.
Det sekundære formålet med studiet er å undersøke sammenhengen mellom okulær eksfoliasjonssyndrom og funn i øyet som kan innebære en økt risiko for grønn stær. Informert samtykke vil bli innhentet før undersøkelsen og all informasjon vil bli avidentifisert. I studien vil det bli søkt spor etter okulær eksfoliasjonssyndrom med spaltlampemikroskop. Ved misstanke blir øyedråper brukt for å utvide pupillen slik at tilsanden kan bekreftes eller avkreftes. Funne blir koblet til resultater fra synsundersøkelse som er en del av vurderingen av risikoen for grønn stær, eks øyetrykk og utseendet på synsnerven i øyet. Resultatene fra studie er forventet å gi en bedre forståelse av forekomsten av okulær eksfoliasjonssyndrom hos optikere i Norge og kan hjelpe optikere å bedre oppdage tilstanden og følge opp pasienter med risiko for sekundær grønn stær.

Vi viser til søknad om prosjektendring mottatt 29.10.21 for ovennevnte forskningsprosjekt. Søknaden er behandlet av leder for REK sør-øst B på delegert fullmaktfra komiteen, med hjemmel i forskningsetikkforskriften § 7, første ledd, tredje punktum. Søknaden er vurdert med hjemmel i helseforskningsloven § 11.

REKs vurdering

Prosjektet ble godkjent med vilkår i vedtak datert 17.09.21. Det ble stilt vilkår om at man utformet en ny rekrutteringsprosedyre som sikret deltaker tilstrekkelig betenkningstid og frivillighet, reviderte informasjonsskrivet og meldte Krogh Optik inn som forskningsansvarlig institusjon. Prosjektleder har i endringsmeldingen gitt tilbakemelding på disse vilkårene.

REK sør-øst B
Besøksadresse: Gullhaugveien 1-3, 0484 Oslo
Telefon:22 84 55 11 | **E-post**:rek-sorost@medisin.uio.no
Web:https://rekportalen.no

Rekrutteringsprosedyren er revidert slik at kunder som ankommer Krogh Optik for forhåndsbestilt time til en av åtte klinikere, vil bli gitt muntlig og skriftlig informasjon av resepsjonist. Vedkommende vil ha minst fem minutters betenkningstid i venterommet. Behandler/kliniker vil i oppstart av timen gi utfyllende informasjon om prosjektet og innhente skriftlig samtykke.

Informasjonsskrivet er revidert ved at det er lagt til informasjon om at øyedråpene kan ha en effekt på pupillens størrelse i opptil 2 - 8 timer. Prosjektleder oppgir i endringsmeldingen at den rellee virkningstiden på synet er kortere, rundt 2 timer. Og videre at Tropikamid brukes for rutineundersøkelse av øyet og er derfor del av standard prosedyre i optometrisk praksis.

Krogh Optikk AS er lagt til som samarbeidende institusjon.

Komiteens leder har vurdert tilbakemeldingen. Vilkårene for revidering av informasjonsskriv og innmelding av Krogh Optikk AS som samarbeidende institusjon anses som oppfylt.

Vedrørende rekruttering er REK fortsatt av den vurderingen at den beskrevne rekrutteringsprosedyren vil gi utvalget for kort betekningstid. Siden samtykket skal innhentes av kliniker/behandler i behandlingssituasjon, så er heller ikke kravet om reell frivillighet etter helseforskningslovens § 13 tredje ledd tilstrekkelig oppfylt. Vilkåret for revidert rekrutteringsprosdyre vurderes derfor som ikke oppfylt.

Endringsmeldingen godkjennes på dette grunnlag med vilkår om at det utformes en rekrutteringsprosedyre som vil gi deltakerne tilstrekkelig betenkningstid, og at samtykket innhentes av en person som deltaker ikke kan sies å være i et avhengighetsforhold til.

Revidert rekrutteringsprosedyre og protokoll bes innsendes REK ved å benytte skjema for «Endring og/eller henvendelse» som finnes etter innlogging på http://rekportalen.no.

Vedtak

REK godkjenner med hjemmel i helseforskningsloven § 11 annet ledd at prosjektet videreføres i samsvar med det som fremgår av søknaden om prosjektendring under forutsetning av at ovennevnte vilkår oppfylles og i samsvar med de bestemmelser som følger av helseforskningsloven med forskrifter.

Vi gjør samtidig oppmerksom på at det etter personopplysningsloven av 2018 også må foreligge et behandlingsgrunnlag etter personvernforordningen. Dette må forankres i egen institusjon.

Godkjenningen gjelder til 31.12.2022.

Sluttmelding
Prosjektleder skal sende sluttmelding til REK på eget skjema via REK-portalen senest 6 måneder etter sluttdato 31.12.2022, jf. helseforskningsloven § 12. Dersom prosjektet ikke starter opp eller gjennomføres meldes dette også via skjemaet for sluttmelding.

Søknad om endring
Dersom man ønsker å foreta vesentlige endringer i formål, metode, tidsløp eller

organisering må prosjektleder sende søknad om endring via portalen på eget skjema til REK, jf. helseforskningsloven § 11.

Klageadgang
Du kan klage på REKs vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes på eget skjema via REK portalen. Klagefristen er tre uker fra du mottar dette brevet. Dersom REK opprettholder vedtaket, sender REK klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag (NEM) for endelig vurdering, jf. forskningsetikkloven § 10 og helseforskningsloven § 10.

Med vennlig hilsen

Ragnhild Emblem
Professor, dr. med.
leder REK sør-øst B

Hanne Johansen Pekovic
Rådgiver, REK sør-øst B

Kopi til:

Universitetet i Sørøst-Norge

7.5.3 3. Approval with conditions

REK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst B	Hanne Johansen Pekovic	22845501	09.12.2021	275866

Per Olof Lundmark

Prosjektsøknad: Forekomst av okulær eksfoliasjonssyndrom hos optiker
Søknadsnummer: 275866
Forskningsansvarlig institusjon: Universitetet i Sørøst-Norge

Prosjektsøknad: Endring godkjennes med vilkår

Søkers beskrivelse

Hovedmålet med prosjektet er å undersøke forekomsten av okulær eksfoliasjonssyndrom hos pasienter over 40 år som tar en synsundersøkelse hos en optiker. Okulær eksfoliasjonssyndrom er en aldersrelatert tilstand karakterisert av en økende utvikling av ekstracellulære fibriller i okulært vev, hovedsakelig sett på linsen i øyet som et hvitaktig belegg. Prevalensen varierer en del i litteraturen, men øker etter fylte 50 år. Tilstanden er forent med en økt risiko for utvikling av grønn stær.
Det sekundære formålet med studiet er å undersøke sammenhengen mellom okulær eksfoliasjonssyndrom og funn i øyet som kan innebære en økt risiko for grønn stær. Informert samtykke vil bli innhentet før undersøkelsen og all informasjon vil bli avidentifisert. I studien vil det bli søkt spor etter okulær eksfoliasjonssyndrom med spaltlampemikroskop. Ved misstanke blir øyedråper brukt for å utvide pupillen slik at tilsanden kan bekreftes eller avkreftes. Funne blir koblet til resultater fra synsundersøkelse som er en del av vurderingen av risikoen for grønn stær, eks øyetrykk og utseendet på synsnerven i øyet. Resultatene fra studie er forventet å gi en bedre forståelse av forekomsten av okulær eksfoliasjonssyndrom hos optikere i Norge og kan hjelpe optikere å bedre oppdage tilstanden og følge opp pasienter med risiko for sekundær grønn stær.

Vi viser til søknad om prosjektendring mottatt 25.11.21 for ovennevnte forskningsprosjekt. Søknaden er behandlet av sekretariatet i Regional komité for medisinsk og helsefaglig forskningsetikk (REK) sør-øst B på delegert fullmakt fra komiteen, med hjemmel i forskningsetikkforskriften § 7, første ledd, tredje punktum. Søknaden er vurdert med hjemmel i helseforskningsloven § 11.

REKs vurdering

Endringen er tilbakemelding på vilkår stilt i vedtak 17.09.21 og 11.11.21.

REK har vurdert følgende endringer:

REK sør-øst B
Besøksadresse: Gullhaugveien 1-3, 0484 Oslo
Telefon:22 84 55 11 | **E-post**:rek-sorost@medisin.uio.no
Web:https://rekportalen.no

- Revidert rekrutteringsprosedyre
- Revidert protokoll og informasjonsskriv

Prosjektleder oppgir at man nå ønsker å gjennomføre rekrutteringen av deltakere i to steg:
1) Pasienter rekrutteres til undersøkelse uten drypping med Tropikamid.
2) Pasienter med funn som gir grunn for utvidet undersøkelse blir invitert til å delta i en utvidet undersøkelse hvor de blir dryppet med Tropikamid.

Det er utformet egne informasjonsskriv for de to undersøkelsene, og det skal innhentes to samtykker. Dersom pasienten gir sitt samtykke til delundersøkelse 2, settes den utvidede undersøkelsen opp som en separat avtale uten kostnad.

Sekretariat i REK sør-øst B har vurdert tilbakemeldingen, og oppfatter at løsningen med todelt rekruttering er god, og gir utvalget tiltrekkelig betenkningstid for tilleggsundersøkelsen som medfører drypping av øyet. Dette vilkåret vurderes dermed som oppfylt.

Det bemerkes at det i den reviderte protokollen fortsatt er lagt opp til at det er behandler som skal innehente samtykke, og det vises til merknad i vedtak 11.11.21: "*Siden samtykket skal innhentes av kliniker/behandler i behandlingssituasjon, så er heller ikke kravet om reell frivillighet etter helseforskningslovens § 13 tredje ledd tilstrekkelig oppfylt.*".

Det er fortsatt ikke tatt høyde for at det ikke er behandler som skal innhente samtykke, hverken for delundersøkelse en eller to. Det setter derfor som vilkår for godkjennig at det ikke er behandler som innhenter samtykke.

Videre bør det i informasjonsskriv for delundersøkelse 1 legges til informasjon om at deltaker kan bli invitert til en oppfølgingsundersøkelse (del 2), dersom man gjør funn som gir grunn for utvidet undersøkelse og drypping av øyet. Det settes derfor som vilkår at informasjon om mulig invitasjon til oppfølgingsundersøkelse legges til i informasjonsskriv 1.

REK godkjenner endring av rekrutteringsprosedyre med vilkår om at det ikke er behandler som innhenter samtykke, hverken for delundersøkelse en eller to, og at informasjonsskrivet redigeres i henhold til ovennevnte merknad.

Protokoll revidert for innhenting av samtykke, samt revidert informasjonsskriv, bes innsendes REK ved å benytte skjema for «Endring og/eller henvendelse» som finnes etter innlogging på http://rekportalen.no.

Vedtak

REK godkjenner med hjemmel i helseforskningsloven § 11 annet ledd at prosjektet videreføres i samsvar med det som fremgår av søknaden om prosjektendring under forutsetning av at ovennevnte vilkår oppfylles og i samsvar med de bestemmelser som følger av helseforskningsloven med forskrifter.

Vi gjør samtidig oppmerksom på at det etter personopplysningsloven av 2018 også må foreligge et behandlingsgrunnlag etter personvernforordningen. Dette må forankres i egen institusjon.

Godkjenningen gjelder til 31.12.2022.

Sluttmelding
Prosjektleder skal sende sluttmelding til REK på eget skjema via REK-portalen senest 6 måneder etter sluttdato 31.12.2022, jf. helseforskningsloven § 12. Dersom prosjektet ikke starter opp eller gjennomføres meldes dette også via skjemaet for sluttmelding.

Søknad om endring
Dersom man ønsker å foreta vesentlige endringer i formål, metode, tidsløp eller organisering må prosjektleder sende søknad om endring via portalen på eget skjema til REK, jf. helseforskningsloven § 11.

Klageadgang
Du kan klage på REKs vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes på eget skjema via REK portalen. Klagefristen er tre uker fra du mottar dette brevet. Dersom REK opprettholder vedtaket, sender REK klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag (NEM) for endelig vurdering, jf. forskningsetikkloven § 10 og helseforskningsloven § 10.

Med vennlig hilsen

Jacob C. Hølen
Sekretariatsleder
REK sør-øst

Hanne Johansen Pekovic
Rådgiver, REK sør-øst B

Kopi til:

Universitetet i Sørøst-Norge

7.5.4 4. Approval with all conditions fulfilled

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst B	Hanne Johansen Pekovic	22845501	16.12.2021	275866

Per Olof Lundmark

275866 Forekomst av okulær eksfoliasjonssyndrom hos optiker

Forskningsansvarlig: Universitetet i Sørøst-Norge

Søker: Per Olof Lundmark

REKs svar på generell henvendelse

Hei,

Jeg viser til henvendelse mottatt 12.12.2021 for prosjekt 275866 - Forekomst av okulær eksfoliasjonssyndrom hos optiker.

Informasjonsskrivet og rekrutteringsprosedyren er revidert i henhold til merknader fra REK i vedtak den 09.12.21. Vilkår stilt i vedtaket anses som oppfylt, og prosjektet som formelt godkjent.

Med vennlig hilsen
Hanne Johansen Pekovic
Rådgiver, REK sør-øst B

Vennlig hilsen
Regionale komiteer for medisinsk og helsefaglig forskningsetikk

Denne e-posten er sendt automatisk fra REK og kan ikke besvares

REK sør-øst B
Besøksadresse: Gullhaugveien 1-3, 0484 Oslo
Telefon:22 84 55 11 | **E-post**:rek-sorost@medisin.uio.no
Web:https://rekportalen.no

7.6 Appendix 3: NSD approval

NSD NORSK SENTER FOR FORSKNINGSDATA

Vurdering

Referansenummer

742282

Prosjekttittel

Forekomst av eksfoliasjonssyndrom hos optiker

Behandlingsansvarlig institusjon

Universitetet i Sørøst-Norge / Fakultet for helse- og sosialvitenskap / Institutt for optometri, radiografi og lysdesign

Prosjektansvarlig (vitenskapelig ansatt/veileder eller stipendiat)

Per O. Lundmark , Per.Lundmark@usn.no, tlf: 31008937

Type prosjekt

Studentprosjekt, masterstudium

Kontaktinformasjon, student

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Prosjektperiode

01.09.2021 - 31.12.2022

Vurdering (1)

20.12.2021 - Vurdert

BAKGRUNN
Prosjektet er vurdert og godkjent etter helseforskningsloven § 10 av Regionale komiteer for medisinsk og helsefaglig forskningsetikk (REK) i vedtak av 17.09.2021, deres referanse 275866 (se under Tillatelser).

VURDERING
Det er vår vurdering at behandlingen vil være i samsvar med personvernlovgivningen, så fremt den gjennomføres i tråd med det som er dokumentert i meldeskjemaet den 20.12.2021 med vedlegg, samt i meldingsdialogen mellom innmelder og NSD. Behandlingen kan starte.

TYPE OPPLYSNINGER OG VARIGHET
Prosjektet vil behandle alminnelige personopplysninger, særlige kategorier av personopplysninger om helseforhold frem til 31.12.2022. Etter prosjektslutt skal opplysningene oppbevares i fem år av dokumentasjonshensyn. Enhver tilgang til prosjektdataene skal da være knyttet til behovet for etterkontroll. Prosjektdata skal da ikke være tilgjengelig for prosjektet.

Prosjektleder og forskningsansvarlig institusjon er ansvarlig for at opplysningene oppbevares av-identifisert i denne perioden, dvs. atskilt i en nøkkel- og en datafil. Etter disse fem årene skal data slettes eller

anonymiseres.

LOVLIG GRUNNLAG
Prosjektet vil innhente samtykke fra de registrerte til behandlingen av personopplysninger. Vår vurdering er at prosjektet legger opp til et samtykke i samsvar med kravene i art. 4 nr. 11 og 7, ved at det er en frivillig, spesifikk, informert og utvetydig bekreftelse, som kan dokumenteres, og som den registrerte kan trekke tilbake.

For alminnelige personopplysninger vil lovlig grunnlag for behandlingen være den registrertes samtykke, jf. personvernforordningen art. 6 nr. 1 a.

For særlige kategorier av personopplysninger vil lovlig grunnlag for behandlingen være den registrertes uttrykkelige samtykke, jf. personvernforordningen art. 6 nr. 1 a, jf. personvernforordningen art. 9 nr. 2 a, jf. personopplysningsloven § 10, jf. § 9 (2).

PERSONVERNPRINSIPPER
NSD vurderer at den planlagte behandlingen av personopplysninger vil følge prinsippene i personvernforordningen:

- om lovlighet, rettferdighet og åpenhet (art. 5.1 a), ved at de registrerte får tilfredsstillende informasjon om og samtykker til behandlingen
- formålsbegrensning (art. 5.1 b), ved at personopplysninger samles inn for spesifikke, uttrykkelig angitte og berettigede formål, og ikke viderebehandles til nye uforenlige formål
- dataminimering (art. 5.1 c), ved at det kun behandles opplysninger som er adekvate, relevante og nødvendige for formålet med prosjektet
- lagringsbegrensning (art. 5.1 e), ved at personopplysningene ikke lagres lengre enn nødvendig for å oppfylle formålet.

DE REGISTRERTES RETTIGHETER
NSD vurderer at informasjonen om behandlingen som de registrerte vil motta oppfyller lovens krav til form og innhold, jf. art. 12.1 og art. 13.

Så lenge de registrerte kan identifiseres i datamaterialet vil de ha følgende rettigheter: innsyn (art. 15), retting (art. 16), sletting (art. 17), begrensning (art. 18) og dataportabilitet (art. 20).

Vi minner om at hvis en registrert tar kontakt om sine rettigheter, har behandlingsansvarlig institusjon plikt til å svare innen en måned.

UNNTAK FRA RETTEN TIL SLETTING
I utgangspunktet har alle som registreres i forskningsprosjektet rett til å få slettet opplysninger som er registrert om dem. Etter helseforskningsloven § 16 tredje ledd vil imidlertid adgangen til å kreve sletting av sine helseopplysninger ikke gjelde dersom materialet eller opplysningene er anonymisert, dersom materialet etter bearbeidelse inngår i et annet biologisk produkt, eller dersom opplysningene allerede er inngått i utførte analyser. Regelen henviser til at sletting i slike situasjoner vil være svært vanskelig og/eller ødeleggende for forskningen, og dermed forhindre at formålet med forskningen oppnås.

Etter personvernforordningen art 17 nr. 3 d kan man unnta fra retten til sletting dersom behandlingen er nødvendig for formål knyttet til vitenskapelig eller historisk forskning eller for statistiske formål i samsvar med artikkel 89 nr. 1 i den grad sletting sannsynligvis vil gjøre det umulig eller i alvorlig grad vil hindre at målene med nevnte behandling nås.

NSD vurderer dermed at det kan gjøres unntak fra retten til sletting av helseopplysninger etter helseforskningslovens § 16 tredje ledd og personvernforordningen art 17 nr. 3 d, når materialet er bearbeidet slik at det inngår i et annet biologisk produkt, eller dersom opplysningene allerede er inngått i utførte analyser.

Vi presiserer at helseopplysninger inngår i utførte analyser dersom de er sammenstilt eller koblet med andre opplysninger eller prøvesvar. Vi gjør oppmerksom på at øvrige opplysninger må slettes og det kan ikke

innhentes ytterligere opplysninger fra deltakeren.

FØLG DIN INSTITUSJONS RETNINGSLINJER
NSD legger til grunn at behandlingen oppfyller kravene i personvernforordningen om riktighet (art. 5.1 d), integritet og konfidensialitet (art. 5.1. f) og sikkerhet (art. 32).

For å forsikre dere om at kravene oppfylles, må prosjektansvarlig følge interne retningslinjer/rådføre dere med behandlingsansvarlig institusjon.

MELD VESENTLIGE ENDRINGER
Dersom det skjer vesentlige endringer i behandlingen av personopplysninger, kan det være nødvendig å melde dette til NSD ved å oppdatere meldeskjemaet. Før du melder inn en endring, oppfordrer vi deg til å lese om hvilken type endringer det er nødvendig å melde:
https://www.nsd.no/personvernfjenester/fylle-ut-meldeskjema-for-personopplysninger/melde-endringer-i-meldeskjema
Du må vente på svar fra NSD før endringen gjennomføres.

OPPFØLGING AV PROSJEKTET
NSD vil følge opp underveis (hvert annet år) og ved planlagt avslutning for å avklare om behandlingen av personopplysningene er avsluttet/pågår i tråd med den behandlingen som er dokumentert.

Kontaktperson hos NSD: Jørgen Wincentsen

Lykke til med prosjektet!