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Primary Open-Angle Glaucoma & Exfoliative Glaucoma

Survival, Comorbidity and Genetics

Thesis for the degree doctor medicinae

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1. Resymé (Summary in Norwegian)

Glaukom er en kronisk nevrodegenerativ sykdom som rammer nervus opticus, og er en av de vanligste årsakene til synstap i verden. Primært åpenvinklet glaukom (POAG) og eksfoliasjonsglaukom (XFG) er de hyppigst forekommende glaukomtyper i Norge. Eksfoliasjonsmateriale hos pasienter med XFG/eksfoliasjonssyndrom (XFS) har vært funnet på flere lokalisasjoner utenfor øyet, og dette ledet fram til hypotesene om at XFS kan være et ledd i en systemsykdom og at dødeligheten i denne pasientgruppen kunne være høyere. Flere tidligere studier har konkludert med at glaukompasienter har høyere mortalitet enn gjennomsnittsbefolkningen. Vi undersøkte retrospektivt om det var forskjeller mellom POAG og XFG med hensyn til overlevelse, dødsårsaker og assosiasjoner med andre sykdommer hos 1147 pasienter innlagt for glaukom mellom 1961 og 1970. Det ble ikke observert forskjeller mellom de to diagnosegruppene når det gjaldt overlevelse. Akutt cerebrovaskulær sykdom og kronisk cerebral sykdom som senil demens, cerebral atrofi og kronisk cerebral iskemi, var hyppigere assosiert med XFG enn POAG. Bruk av acetazolamid peroralt medførte økt risiko for kroniske cerebrale sykdommer og redusert overlevelse. Både OAG og XFG forekommer hyppigere hos pasienter med Alzheimers sykdom (AD). Vi undersøkte om subgrupper av APOE- og CHRNA4-genotypen som har vært assosiert med AD, hadde påvirkning på nervefiberlagstykkelse på papillen, intraokulært trykk (IOP), forekomst av eksfoliasjonssyndrom (XFS), katarakt og aldersrelatert makuladegenerasjon (AMD) hos 88 friske deltakere. Vi fant ingen sammenheng mellom APOE- og CHRNA4-genotyper og nervefiberlagtykkelse på papillen. IOP var lavere hos APOE2-bærerne enn hos ikke-APOE2-bærerne. XFS var mindre hyppig hos CC-bærerne av CHRNA4-genotypen enn hos TT- og TC-bærerne. Vi fant ingen sammenheng mellom APOE-genotype og forekomst av AMD. APOE3-bærerne hadde tykkere makula og bedre visus enn ikke-APOE3-bærerne. APOE4-bærerne hadde lavere risiko for å utvikle katarakt enn ikke-APOE4-bærerne.

2. Acknowledgements

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3. Papers included in the thesis

The thesis is based on the following publications, which are referred to by their Roman numerals:

I. Ritland JS, Egge K, Lydersen S, Juul R, Semb SO.
Comparison of survival of exfoliative glaucoma patients and primary open-angle glaucoma patients: impact of acetazolamide use.
Acta Ophthalmol Scand 2004; **82**: 397-400.

II. Ritland JS, Egge K, Lydersen S, Juul R, Semb SO.
Exfoliative glaucoma and primary open-angle glaucoma: associations with death causes and comorbidity.
Acta Ophthalmol Scand 2004; **82**: 401-404.

III. Ritland JS, Utheim TP, Utheim ØA, Espeseth T, Lydersen S, Semb SO, Rootwelt H, Elsås T.
Effects of APOE- and CHRNA4-genotypes on the retinal nerve fibre layer thickness at the optic disc, and on the risk of developing exfoliation syndrome.
Acta Ophthalmol Scand 2007; **85**: 257-261.

IV. Utheim ØA, Ritland JS, Utheim TP, Espeseth T, Lydersen S, Semb SO, Rootwelt H, Elsås T.
Apolipoprotein E-genotype and risk of development of cataract and age-related macular degeneration.
Acta Ophthalmol Scand, accepted for publication Aug 2007

4. Introduction

Glaucoma is one of the leading causes of vision loss in the world, particularly among the elderly (Leske 1983; Quigley 1996). The disease is characterized by retinal ganglion cell death, axon loss, and an excavated appearance to the optic nerve head, and progressive visual field loss (Quigley & Green 1979). Although elevation of intraocular pressure (IOP) is recognized as a major risk factor for optic damage in glaucoma (Anderson 1989), multiple factors other than IOP, including genetic factors (Friedman & Walter 1999), are likely to have a role in the pathogenesis of glaucomatous optic neuropathy.

Survival

Primary open-angle glaucoma (POAG) and exfoliative glaucoma (XFG) are the most frequent types of glaucoma in the Norwegian population (Ringvold et al. 1991). Previous studies have shown reduced survival rates for patients with open-angle glaucoma (Belloc 1963; Thorburn & Lindholm 1983; Hiller et al. 1999; Lee et al. 2003). XFG and exfoliation syndrome (XFS) were earlier considered to be a condition of purely ophthalmological interest. However, similar deposits of exfoliation material have been found in a large number of extraocular locations such as visceral organs and skin (Ringvold 1972, 1973; Layden & Schaffer 1974; Harnisch 1977; Eagle et al. 1979; Streeten et al 1990, 1992; Sugino 1990; Schlötzer-Schrehardt et al. 1991, 1992).These findings have led to the hypothesis that XFS/XFG is part of a generalized disorder, and suggested that this group of patients might have increased mortality rate.

Comorbidity

Recently, increasing attention has been paid to the associations between POAG, XFG and XFS with some other diseases. Waldmann et al. (1996) found glaucoma, especially normal tension glaucoma, to be significantly associated with silent myocardial ischaemia. A high frequency of XFS has been observed in eyes with positive iris transluminance in patients who had been diagnosed with a transient ischaemic attack (Repo et al. 1995). Mitchell et al. (1997) found XFS to be significantly associated with a history of angina pectoris or hypertension or a combined history of angina pectoris, acute myocardial infarction or stroke. Studies have shown that patients with Alzheimer's disease (AD) have a higher occurrence rate of glaucoma (Bayer et al. 2002; Tamura et al. 2006) and XFS (Hagadus et al. 1989; Linnér et al. 2001). Lower prevalence of diabetes mellitus in patients with XFS (Shingleton et al. 2003) and patients with XFG requiring surgery (Konstas et al. 1998) have also been demonstrated.

Genetics

Glaucoma is a neurodegenerative disease with a polygenic aetiology (Libby et al. 2005). McKinnon (2003) suggested the hypothesis of retinal ganglion cell death involving chronic amyloid-β neurotoxicity, mimicking AD at the molecular level, and questioned whether glaucoma may be an ocular form of AD. Inheritance of the ε4 allele of the gene encoding Apolipoprotein E (APOE), has been associated with AD (Corder et al. 1993). The APOE4 allele may be a common risk factor for neurodegenerative diseases, and may be associated with increased loss of ganglion cells in the retina. Previous studies comparing APOE-genotypes of glaucoma patients with controls have so far shown both positive (Vickers et al. 2002; Jünemann et al. 2004; Mabuchi et al. 2005) and negative associations (Ressiniotis et al. 2004; Lake et al. 2004).

APOE may promote the aggregation of amyloidogenic proteins into β-pleated sheet conformation that is typical of all amyloid deposits, and is directly involved in the amyloid deposition and fibril formation (Strittmatter et al. 1993; Castano et al. 1995). Therefore, it has been suggested that APOE-genotype may influence the risk for developing XFS, since the exfoliation material is an amyloid or at least an amyloid-like structure (Ringvold & Husby 1973; Davanger & Pedersen 1975; Dark et al. 1977; Meretoja & Tarkkanen 1977; Streeten et al. 1986). Yilmaz and co-workers (2005) found the APOE2 allele to be significantly associated with the development of XFS, whereas the APOE3 allele was found to be protective.

There is evidence for nicotinic cholinergic neurotransmission in the human retina (Hutchins & Hollyfield 1985), and recently nicotinic receptor subunit genes (CHRNA4 and CHRNB2) have been associated with AD (Kawamata & Shimohama 2002; Cook et al. 2004). APOE may influence the synthesis of acetylcholine (ACh) (Poirier 2000), the metabolism in cholinergic neurons (Dubelaar et al. 2004), the availability of ACh in the synapse (Cohen et al. 2003), and the affinity of cholinergic receptors (Klein & Yakel 2004), and therefore, it has been suggested that nicotinic receptor genes and APOE-genotype may have joint effects.

APOE-genotypes and other eye diseases

APOE-genotype may also have an impact on risk of development of other eye diseases among the elderly, such as cataract and age-related macular degeneration (AMD). Cataract and Alzheimer's disease (AD) are both degenerative disorders where pathological protein aggregates plays an important role in the pathogenesis. It has been suggested that cataract and Alzheimer's disease share the same aetiological mechanisms. Beta-amyloid (Abeta) deposited in the brain is a hallmark of Alzheimer's disease (Benjamin et al. 1994), and Abeta is also found to be present in the lens of people with Alzheimer's disease, causing equatorial, supranuclear cataract (Goldstein et al. 2003). Zetterberg and coworkers (2005) investigated

APOE alleles in 502 patients with senile cataract and a control group of 187 persons without finding any significant differences for any of the alleles.

Several recent studies of APOE genotypes in patients with AMD compared to control groups found the APOE4-genotype to have a protective effect against AMD, while the APOE2-genotype may increase the risk (Schmidt et al 2002; Baird et al. 2004). However, in a large population based cross sectional study with participants from the Atherosclerosis Risk in Communities study, no association was found (Wong et al. 2006).

5. Aims of the studies

We wanted to compare the survival of patients hospitalized with either XFG or POAG, retrospectively, and to study the impacts of gender and acetazolamide use on survival.

We also decided to look for differences between XFG and POAG patients in terms of acute cerebrovascular disease, heart disease and cancer diagnosed as the main cause of death, and to study if there was difference in comorbidity registered as acute cerebrovascular diseases, cardiovascular diseases, heart failure, cancer, senile dementia and cerebral atrophy/ chronic cerebrovascular ischaemia.

We also wanted to study the impacts of acetazolamide on comorbidity.

We wanted to evaluate the effects of APOE- and CHRNA4 (cholinergic receptor, nicotinic, alpha polypeptide 4)-genotypes on RNFL thickness at the optic disc, IOP, and on the risk of developing XFS.

Furthermore, we wished to study if there is an association between APOE- genotype and cataract or AMD.

6. Material and methods

The data of *paper I* and *II* includes patients with XFG or POAG finally hospitalized at the Eye Department, The National Hospital, Oslo, between 1961 and 1970. Patients with the additional diagnosis of diabetes mellitus were excluded. Of a total of 1320 patients registered, the central population register by the Norwegian Government Computer Centre gave information about lifetimes of 1147 individuals on a follow-up to 1 April 1994. Among them, 20 women and 15 men were still alive. It was not possible to identify the remaining 173 individuals separately. We found main death cause and additional diagnoses for all the dead individuals in the Norwegian Causes of Death Register. The study included 718 patients (438 males/280 females) with a XFG and 429 patients (234 males/ 195 females) with a POAG.
At the time of hospitalization the patients were routinely examined after dilatation of the pupil, and the diagnosis of XFG was made when finding pseudoexfoliation material on the anterior lens surface or dots at the pupillary border.
We also categorized the patients according to the use of peroral acetazolamide. An acetazolamide user was defined as a patient who had used the medicine for at least 2 years and/or had left the hospital last time with a prescription for acetazolamide. There were 492 patients defined as acetazolamide users, while 655 were defined as non-users. The data were analysed using a Cox proportional hazard model (Cox 1972). Possible non-linear effects of age and time covariates, possible interactions, and possible confounding effects, were checked and included in the model when present.

The study population for *paper II* was identical to the one described above for *paper I*. We categorized the patients in subgroups according to diagnoses registered as main causes of death and comorbidity. Patients with acute cerebrovascular disease were registered with diagnoses

as cerebral thrombosis/embolism, cerebral haemorrhage or subarachnoidal haemorrhage. Diagnoses as acute myocardial infarction, angina pectoris and cardiovascular atherosclerosis were categorized as an ischaemic cardiovascular disease. Chronic cerebral diseases like cerebral atrophy and chronic cerebrovascular ischaemia were put in a unite group. Binary logistic regression was carried out with glaucoma type, acetazolamide use, gender, and age at death or last follow-up as possible explanatory variables. Separate analyses were carried out with the following endpoints: 1. Main death cause – *cerebrovascular disease, cardiac disease and cancer*. 2. Comorbidity – *acute cerebrovascular disease, senile dementia, cerebral atrophy/ chronic cerebral ischaemia, senile dementia or cerebral atrophy/ chronic cerebral ischaemia, cancer, ischaemic cardiovascular disease and heart failure*.
Backwards likelihood ratio variable selection was performed, with p-entry = 0.05 and p-remove = 0.10. Possible interactions were checked for variables in the models. Possible deviations from linear effect of age on odds ratio were checked by categorising age in quartiles. Effects were given as estimates and 95% confidence intervals.

The study population for *paper III* and *IV* was a sample of 96 healthy middle-aged and older adults (50-75 years), participating in a study concerning cognitive ageing and genotyped for APOE and CHRNA4, who volunteered to enter the study. The study population was designed with 50 % APOE4-carriers and 50 % non-APOE4-carriers. The non-APOE4-carriers were frequency-matched for age and gender to the APOE4-carriers. 88 participants (25 males/ 63 females, mean age 65.5 years) showed up for the examination. The carriers/ non-carriers ratio for the APOE-genotypes was; APOE2: 20/ 68, APOE3: 71/ 17 and APOE4: 43/ 45. The CHRNA4 genotypes had the following distribution; TT=29, TC=43 and CC=16. All participants underwent an eye examination including slit lamp examination, fundus photography as well as measurements of visual acuity, refraction, intraocular pressure (IOP),

and the retinal nerve fibre layer (NFL) thickness at the optic disc by optical coherence tomography. The average retinal NFL thickness at the optic disc (360 degrees) was measured, as well as the retinal NFL thickness in the superior, nasal, inferior and temporal quadrants. In case of possible glaucoma, another eye examination which included visual field testing by Humphrey autoperimeter and pachymetry was later performed. XFS was diagnosed during the slit-lamp examination after pupils were dilated by pharmacological agents. The physicians participating in the study were blinded for APOE- and CHRNA4-genotypes.

The two-by-two tables were analyzed by the Fisher-Boschloo unconditional full multinomial test as recommended in small samples to avoid overly conservative results (Mehrotra et al 2003). Two sample t-tests were used for comparing means of scale variables. All tests were two-sided, and p-values less than 0.05 were considered significant.

The study population for *paper IV* was identical to the one described above for *paper III*. Fundus photography was also performed. The photos were analyzed and graded for macular pathology, such as drusen, hyperpigmentation, hypopigmentation, geographic atrophy, and neovascular AMD by the Reading Centre, Moorfields Eye Hospital, London. Macular thickness was measured by optical coherence tomography. Lens opacities were classified as nuclear, cortical, posterior subcapsular, or mixed forms of cataract. Intraocular lenses (IOL) due to previous cataract surgery were registered. Cataracts were classified only from a morphologic point of view, irrespective of visual acuity. The physicians were blinded for APOE-genotypes. The statistical methods for *paper IV* were identical with those used in *paper III*.

7. Summary of results

Paper I

The relative survival of the different subgroups of patients were analysed using the Cox proportional hazard model, based on survival time in years after diagnosis of glaucoma. We found no statistical significant differences of survival between XFG and POAG (p=0.85). Separate analyses for men and women confirmed these results. As expected, female gender as well as younger age at the time of diagnosis, was associated with longer survival. The use of acetazolamide had no statistical significant influence on survival until year of birth was included in the analyses. More recent birth date, or equivalently, more recent date of glaucoma diagnosis, was highly significantly associated with a reduction in survival. When year of birth was included in the analyses, the use of acetazolamide was associated with reduced survival (n=492, p=0.02).

Paper II

None of the explanatory variables were significantly associated with acute cerebrovascular disease as main cause of death. POAG versus XFG tended towards significance (p = 0.073, odds ratio 0.73, c.i. 0.52 to 1.03). Only age and gender were associated with cardiovascular disease as main cause of death; and only age was associated with death caused by cancer. The resulting logistic regression models for comorbidity analyses disclosed some interesting significant differences between the patients with XFG and POAG. Patients with a XFG more often had senile dementia (n=51, p=0.044) and senile dementia and/or cerebral atrophy/ chronic cerebral ischaemia (n=81, p=0.011) than patients with a POAG. Patients with XFG had a higher probability of having an acute cerebrovascular disease than patients with POAG (n=228, p=0.028). We also found that the use of acetazolamide was positively associated with

cerebral atrophy/ chronic cerebral ischaemia (p = 0.050) and with senile dementia and/or cerebral atrophy/ chronic cerebral ischaemia (p = 0.029). Increasing age turned out to be a significant explanatory variable in all the subgroups. Males were more likely than females to get an ischaemic cardiovascular disease (n=263, p=0.003), while females more often suffered from an acute cerebrovascular disease (n=228, p=0.052). In all the other subgroups gender was not a significant explanatory variable.

Paper III

No effect of the APOE- and CHRNA4-genotypes on the 360° RNFL thickness or on the four quadrants at the optic discs were revealed. The average RNFL thickness of the two eyes in the temporal quadrant showed a trend towards being thinner in the group of APOE4-carriers that were also CHRNA4-TT-carriers (mean 37.4 μm) than in the non-APOE4/ CHRNA4-TT-carriers (mean 40.8 μm) (p=0.055, CI: -0.76 to 6.80). However, the mean values of the RNFL thickness at the optic disc (360°) was non-significantly higher (104.6 μm) in the group of APOE4/ CHRNA4-TT-carriers than in the non-APOE4/ CHRNA4-TT-carriers (102.0 μm), as well as for the other three quadrants at the optic disc. There was no difference in refraction between any of the subgroups in the study.

The average IOP of the two eyes of the participants had a mean value of 14.44 mmHg (range 9-23 mmHg), while the maximum IOP for each person had a mean value of 15.15 mmHg (range 9-27 mmHg). We observed that the mean of the average IOP in the two eyes of the non-APOE2-carriers (14.82 mmHg) was significantly higher than in the eyes of the APOE2-carriers (13.18 mmHg) (p=0.014, CI: 0.34 to 2.94). We found no other associations between the other APOE- and CHRNA4-alleles and IOP.

Exfoliation syndrome was present in one or both eyes in 15 participants. The presence of pseudoexfoliation was less likely in the CC-carriers of CHRNA4 than the TT- and TC-carriers (p=0.049). APOE-genotype did not show significant association with XFS.

Paper IV

There was no significant age difference between the APOE4 carriers (mean age 65.1 years) and the non-APOE4 carriers (mean age 65.9 years). Among the participants, 32 were diagnosed with cataract or had been through cataract surgery in one or both eyes, while 56 showed no signs of cataract. We found that the APOE4-carriers were less likely to have cataract than the non-APOE4-carriers (p=0.039). The number of participants in the subgroups were; nuclear (3), cortical (15), posterior subcapsular cataract (16) and IOL (6). No significant associations were found between APOE-genotypes and subgroups of cataract. The participants diagnosed with cataract were older (mean 69.7 years) than those without (mean 63.1 years) (p<0.001, CI: -9.30 to -3.82).

Analyses of the fundus photographies of the macular region showed evidence of soft drusen in one or both eyes in 25 of 86 participants. However, only two persons had soft drusen with a size ≥ 125 µm. Hyperpigmentation was seen in 62 of 86 participants, while 33 out of 86 had areas of hypopigmentation. None of the participants showed evidence of geographic atrophy or neovascular AMD. No significant association between genotype and morphologic changes in the macular region of the retina was discovered. However, the APOE3-carriers had significantly higher average macular thickness (216.1µm) of the two eyes than the non-APOE3-carriers (201.2µm) (p=0.012, CI: 3.42 to 26.38), and the APOE3-carriers also had a significantly better visual acuity (0.95) than the non-APOE3-carriers (0.87) (p=0.041, CI: 0.003 to 0.153).

6. Discussion

Ad I: Some previous studies have shown reduced survival rate for patients with open-angle glaucoma (Belloc 1963; Thorburn & Lindblom 1983; Egge & Zahl 1999; Hiller et al. 1999; Lee et al. 2003), while some other studies could not verify this (Bengtsson 1984; Borger et al. 2003; Grødum et al. 2004; Knudtson et al. 2006; Lee et al. 2006). The studies based on older materials from the 1960s (Egge & Zahl 1999), 1970s (Hiller et al. 1999) and the 1980s (Thorburn & Lindblom 1983) show a tendency towards poorer survival among the glaucoma patients, while most of the studies based on more recent materials show no increased mortality among the glaucoma patients (Borger et al. 2003; Grødum et al. 2004; Knudtson et al. 2006; Lee et al. 2006). The diagnostic criteria and the glaucoma therapy have been through several changes during the last decades. Therefore, the study populations are presumably different in the older materials than in the more recent ones. The reasons why the studies based on older materials show a tendency towards reduced survival may be due to more severe glaucoma in the study groups, adverse effects of the therapy used at that time, or perhaps because longer follow-up increases the possibility of detecting a significant difference.

Knudtson and coworkers (2006) demonstrated that visual impairment was associated with poorer survival and not explained by traditional risk factors for mortality. Accordingly, the divergence in study results could be related to the degree of visual impairment in the study sample. Whether the reduced survival rate for patients with open-angle glaucoma found in some of the studies is not caused by the glaucoma, but rather by the visual impairment, is yet not to be answered. However, Lee and coworkers (2006) have found an increased cardiovascular mortality in persons with previously diagnosed glaucoma.

It has been suggested that exfoliation syndrome or exfoliative glaucoma is part of a systemic process (Streeten et al. 1992) that may lead to increased mortality. To date no clear-cut association with a systemic disease has been shown. Recent studies showed no association between ocular XFS (Ringvold et al. 1997) or XFG (Grødum et al. 2004) and total, cardiovascular, and cerebrovascular mortality (Shrum et al. 2000).

In the same study sample as we have studied, Egge & Zahl (1999) found an indication of increased mortality for glaucoma patients when the disease had lasted for some time. A comparative study of survival between patients with POAG and XFG (Paper I), have to our knowledge, not previously been performed. We found no statistical significant differences of survival between XFG and POAG.

In the initial analyses, acetazolamide use had no significant impact on survival. When year of diagnosis was included in the analyses, acetazolamide use was significantly associated with reduced survival ($p=0.02$). If this was due to changes in cerebral blood flow when using acetazolamide that have been shown (Dahl et al. 1995; Shiogai et al. 2003), well known side effects such as metabolic acidosis and disturbances of the electrolyte balance, other unknown side-effects after long-term use of acetazolamide, or somehow related to that the glaucomas were more refractive to therapy, remains unknown. Literature studies and Medline search have not shown other reports of associations of acetazolamide use and reduced survival. There were no general guidelines at the National Hospital in the 1960s, whether the patients should undergo surgery or acetazolamide treatment when topical medication failed to control the disease. The patients were evaluated at an individual basis and several physicians were involved. A weakness of this study is that we were unable to find out whether the decision to treat with acetazolamide was based on considerations that patients were too frail to undergo surgery.

Surprisingly, more recent diagnosis of glaucoma or more recent birth date were highly significantly associated with increased mortality. The reason for this finding remains unclear. The distribution of ophthalmologists and the reference practice to the National Hospital did presumably not change much during the study period. The use of peroral acetazolamide seems to play a role, but this tendency could also be related to topical medical therapy for glaucoma, or maybe to drug-interaction of β-blockers, α_2-agonists or miotic agents due to polypharmacy which became more common in elderly people in later years (Frishman et al. 2001). Lee and co-workers (2006) have suggested a higher cardiovascular mortality in patients using topical timolol.

Ad II: The use of acetazolamide was positively associated with cerebral atrophy/chronic cerebral ischaemia (n=30, p = 0.050) and/or senile dementia (n=81, p = 0.029). However, it remains unclear whether acetazolamide use contributed to the development of senile dementia, or if this group of patients used more acetazolamide because they were more refractive to antiglaucomatous therapy (Bayer & Ferrari 2002) or not suited for surgery. Interestingly, in this study, we found that patients with a XFG were more likely to have senile dementia (n=51, p = 0.044), and/or chronic cerebrovascular ischaemia or cerebral atrophy (n=81, p=0.011). The reason why some persons with XFS develop XFG, and some not, remains unknown (Ritch et al. 2003). We have only studied patients with exfoliation syndrome who have developed glaucoma. Whether one could find the same associations for XFS that we have found for XFG, is at present an unanswered question.

Konstas et al. (1998) found a lower prevalence of diabetes in patients with XFG requiring surgery than those with POAG. Shingleton et al. (2003) confirmed this finding by reporting a significantly greater prevalence of diabetes and hypertension in the non-exfoliation group than in the exfoliation group. We chose to exclude patients with diabetes mellitus, and this may have contributed to a small overrepresentation of XFG in our study.

A problem for retrospective studies like these is that some diagnoses may be missing, and the accuracy of the diagnoses may vary because some of the diseases have been diagnosed clinically without the use of modern paraclinically diagnostic techniques like ultrasound, MRI- and CT-scanning. Therefore, the percentages are probably lower than the true numbers of associated diagnoses and should not be read as absolute values. We presume, however, that if some co-diagnoses are missing or may not be accurate, these errors should be equally distributed in the subgroups we have studied. We are aware of the limitations of a retrospective study like this. Our results need to be followed up with further prospective studies before any definitive conclusion can be made of possible associations between XFG and chronic cerebral diseases and acute cerebrovascular disease.

Ad III: In the studies investigating associations between APOE-genotypes and eye diseases such as glaucoma, AMD and cataract, our study design differed from the previous ones by examining a group of healthy volunteers where the selection was based on APOE genotype. By doing this, some of the bias associated with the case-control study design that had been used in the previous studies, were presumably avoided.

Thinning of the RNFL at the optic disc may be the first sign of an optic neuropathy, and measurements of the RNFL thickness was chosen as a parameter to see if there were differences in the groups concerning loss of neural tissue. As far as we know, a study measuring RNFL thickness in subgroups of the APOE- and CHRNA4-genes has not been performed before. We found no significant difference of the RNFL thickness at the optic disc in the different genotype carriers of the APOE- and CHRNA4-genes, and thereby no evidence for increased loss of ganglion cells as an effect of these genes. The RNFL thickness in the temporal quadrant of the optic disc showed a trend towards being thinner in the group of APOE4-carriers that also were CHRNA4-TT-carriers ($p=0.055$). However, the mean values

of the RNFL thickness at the optic disc (360°) was non-significantly higher (104.6 μm) in the group of APOE4/ CHRNA4-TT-carriers than in the non-APOE4/ CHRNA4-TT-carriers (102.0 μm), as well as for the three other quadrants at the optic disc. Therefore, we cannot interpret this trend as a sign of increased neurodegeneration in the APOE4/ CHRNA4-TT subgroup.

We found that the mean IOP in of the non-APOE2-carriers (14.8 mmHg) was significantly higher than the IOP of the APOE2-carriers (13.2 mmHg) ($p=0.014$), suggesting that the APOE2-genotype may have a lowering effect on the IOP. However, the retinal NFL thickness measurements showed no difference between these two groups, and both values are clearly within normal range, so the clinical relevance of this association remains uncertain. Our observation differs from a study of Jünemann and co-workers (2004) showing significantly higher IOP among the APOE2-carriers. However, the IOP-values in our study were not adjusted for corneal thickness. Mabuchi and co-workers (2005) have reported significantly lower IOP among the APOE4-carriers than among the non-APOE4-carriers.

We studied the effect of genotype of APOE and of CHRNA4, a candidate gene for association with AD (Kawamata & Shimohama 2002; Cook et al. 2004), on the development of XFS. The presence of exfoliation was less likely in the CC-carriers of CHRNA4 than the TT- and TC-carriers ($p=0.049$). However, Thorleifsson and co-workers (2007) recently identified two nonsynonymous single-nucleotide polymorphisms in exon 1 of the gene LOXL1. The study showed that the homozygous for the highest-risk haplotype had an increased risk of suffering from XFG of more than 100 times that of individuals carrying only low-risk haplotypes. The product of LOXL1 catalyzes the formation of elastin fibers. Therefore, it seems more likely that the exfoliation material is caused by disturbances in the elastin formation, rather than being an amyloid structure.

Ad IV: A study designed with healthy individuals genotyped for APOE to investigate a possible association between cataract and APOE polymorphism has, to our knowledge, not previously been performed. In our study, we found a weak negative correlation between APOE4 and cataract. This differs from the results of a case-control study where no such association was found (Zetterberg et al. 2004).

Our study shows no significant association between morphologic changes in the macula and APOE genotype. The fact that population based cross sectional studies have failed to show an association between AMD risk and APOE genotype (Wong et al. 2006), in spite of animal models and studies on AMD patients demonstrating such a correlation, raises the issue whether the APOE genotype plays a role only if not another unknown factor is present at the same time. Further studies investigating APOE polymorphisms along with other variables in AMD patients are warranted to find possible factors contributing to the APOE4 genotype to give a protective effect in only certain populations.

In our study, the APOE3-carriers had a significantly higher average macular thickness than the non-APOE3-carriers. Optical coherence tomography also demonstrated that the higher average macular thickness was not due to macular oedema in either of the participants. Hence, the higher macular thickness possibly explains why the APOE3-carriers also demonstrated a significantly better visual acuity than the non-APOE3-carriers. Consequently, APOE3 may act as a protective factor against loss of nerve fibres in the macular region.

7. Conclusions

-There were no statistical significant differences in survival between the patients with XFG and POAG.

-Female gender as well as younger age at the time of diagnosis were significantly associated with longer survival.

-Patients with more recent birth date showed a shorter relative survival than the patients with an earlier birth date, and when this was included in the analyses, the use of acetazolamide was associated with reduced survival.

-XFG and POAG showed no significant differences in rates of death caused by acute cerebrovascular diseases, cardiac diseases and cancer.

-Chronic cerebral diseases as senile dementia, cerebral atrophy and chronic cerebral ischemia were more common in patients with XFG than with POAG, and in the group of acetazolamide users.

-Patients with XFG had a higher probability of getting an acute cerebrovascular disease than patients with POAG.

-No significant difference of the RNFL thickness at the optic disc in the different genotype carriers of the APOE- and CHRNA4-genes was found, and thereby no evidence for increased loss of ganglion cells in the retina as an effect of these genes.

-The APOE2-carriers had significantly lower IOP than the non-APOE2-carriers.

-The CC-carriers of the CHRNA4-gene in our study population were less likely to develop XFS.

-There was no association between AMD and APOE polymorphism.

-A weak negative association between APOE4 and cataract was disclosed.

-APOE3-carriers demonstrated a significantly higher average macular thickness and a better visual acuity than the non-APOE3-carriers.

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92. Nina-Beate Liabakk: DEVELOPMENT OF IMMUNOASSAYS FOR TNF AND ITS SOLUBLE RECEPTORS.
93. Sverre Helge Torp: *erb*B ONCOGENES IN HUMAN GLIOMAS AND MENINGIOMAS.
94. Olav M. Linaker: MENTAL RETARDATION AND PSYCHIATRY. Past and present.
95. Per Oscar Feet: INCREASED ANTIDEPRESSANT AND ANTIPANIC EFFECT IN COMBINED TREATMENT WITH DIXYRAZINE AND TRICYCLIC ANTIDEPRESSANTS.
96. Stein Olav Samstad: CROSS SECTIONAL FLOW VELOCITY PROFILES FROM TWO-DIMENSIONAL DOPPLER ULTRASOUND: Studies on early mitral blood flow.
97. Bjørn Backe: STUDIES IN ANTENATAL CARE.
98. Gerd Inger Ringdal: QUALITY OF LIFE IN CANCER PATIENTS.
99. Torvid Kiserud: THE DUCTUS VENOSUS IN THE HUMAN FETUS.
100. Hans E. Fjøsne: HORMONAL REGULATION OF PROSTATIC METABOLISM.
101. Eylert Brodtkorb: CLINICAL ASPECTS OF EPILEPSY IN THE MENTALLY RETARDED.
102. Roar Juul: PEPTIDERGIC MECHANISMS IN HUMAN SUBARACHNOID HEMORRHAGE.
103. Unni Syversen: CHROMOGRANIN A. Phsysiological and Clinical Role.

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104. Odd Gunnar Brakstad: THERMOSTABLE NUCLEASE AND THE *nuc* GENE IN THE DIAGNOSIS OF *Staphylococcus aureus* INFECTIONS.
105. Terje Engan: NUCLEAR MAGNETIC RESONANCE (NMR) SPECTROSCOPY OF PLASMA IN MALIGNANT DISEASE.
106. Kirsten Rasmussen: VIOLENCE IN THE MENTALLY DISORDERED.
107. Finn Egil Skjeldestad: INDUCED ABORTION: Timetrends and Determinants.
108. Roar Stenseth: THORACIC EPIDURAL ANALGESIA IN AORTOCORONARY BYPASS SURGERY.
109. Arild Faxvaag: STUDIES OF IMMUNE CELL FUNCTION *in mice infected with* MURINE RETROVIRUS.

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110. Svend Aakhus: NONINVASIVE COMPUTERIZED ASSESSMENT OF LEFT VENTRICULAR FUNCTION AND SYSTEMIC ARTERIAL PROPERTIES. Methodology and some clinical applications.

111. Klaus-Dieter Bolz: INTRAVASCULAR ULTRASONOGRAPHY.
112. Petter Aadahl: CARDIOVASCULAR EFFECTS OF THORACIC AORTIC CROSS-CLAMPING.
113. Sigurd Steinshamn: CYTOKINE MEDIATORS DURING GRANULOCYTOPENIC INFECTIONS.
114. Hans Stifoss-Hanssen: SEEKING MEANING OR HAPPINESS?
115. Anne Kvikstad: LIFE CHANGE EVENTS AND MARITAL STATUS IN RELATION TO RISK AND PROGNOSIS OF CANSER.
116. Torbjørn Grøntvedt: TREATMENT OF ACUTE AND CHRONIC ANTERIOR CRUCIATE LIGAMENT INJURIES. A clinical and biomechanical study.
117. Sigrid Hørven Wigers: CLINICAL STUDIES OF FIBROMYALGIA WITH FOCUS ON ETIOLOGY, TREATMENT AND OUTCOME.
118. Jan Schjøtt: MYOCARDIAL PROTECTION: Functional and Metabolic Characteristics of Two Endogenous Protective Principles.
119. Marit Martinussen: STUDIES OF INTESTINAL BLOOD FLOW AND ITS RELATION TO TRANSITIONAL CIRCULATORY ADAPATION IN NEWBORN INFANTS.
120. Tomm B. Müller: MAGNETIC RESONANCE IMAGING IN FOCAL CEREBRAL ISCHEMIA.
121. Rune Haaverstad: OEDEMA FORMATION OF THE LOWER EXTREMITIES.
122. Magne Børset: THE ROLE OF CYTOKINES IN MULTIPLE MYELOMA, WITH SPECIAL REFERENCE TO HEPATOCYTE GROWTH FACTOR.
123. Geir Smedslund: A THEORETICAL AND EMPIRICAL INVESTIGATION OF SMOKING, STRESS AND DISEASE: RESULTS FROM A POPULATION SURVEY.

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124. Torstein Vik: GROWTH, MORBIDITY, AND PSYCHOMOTOR DEVELOPMENT IN INFANTS WHO WERE GROWTH RETARDED *IN UTERO*.
125. Siri Forsmo: ASPECTS AND CONSEQUENCES OF OPPORTUNISTIC SCREENING FOR CERVICAL CANCER. Results based on data from three Norwegian counties.
126. Jon S. Skranes: CEREBRAL MRI AND NEURODEVELOPMENTAL OUTCOME IN VERY LOW BIRTH WEIGHT (VLBW) CHILDREN. A follow-up study of a geographically based year cohort of VLBW children at ages one and six years.
127. Knut Bjørnstad: COMPUTERIZED ECHOCARDIOGRAPHY FOR EVALUTION OF CORONARY ARTERY DISEASE.
128. Grethe Elisabeth Borchgrevink: DIAGNOSIS AND TREATMENT OF WHIPLASH/NECK SPRAIN INJURIES CAUSED BY CAR ACCIDENTS.
129. Tor Elsås: NEUROPEPTIDES AND NITRIC OXIDE SYNTHASE IN OCULAR AUTONOMIC AND SENSORY NERVES.
130. Rolf W. Gråwe: EPIDEMIOLOGICAL AND NEUROPSYCHOLOGICAL PERSPECTIVES ON SCHIZOPHRENIA.
131. Tonje Strømholm: CEREBRAL HAEMODYNAMICS DURING THORACIC AORTIC CROSSCLAMPING. An experimental study in pigs.

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132. Martinus Bråten: STUDIES ON SOME PROBLEMS REALTED TO INTRAMEDULLARY NAILING OF FEMORAL FRACTURES.
133. Ståle Nordgård: PROLIFERATIVE ACTIVITY AND DNA CONTENT AS PROGNOSTIC INDICATORS IN ADENOID CYSTIC CARCINOMA OF THE HEAD AND NECK.
134. Egil Lien: SOLUBLE RECEPTORS FOR **TNF** AND **LPS**: RELEASE PATTERN AND POSSIBLE SIGNIFICANCE IN DISEASE.
135. Marit Bjørgaas: HYPOGLYCAEMIA IN CHILDREN WITH DIABETES MELLITUS
136. Frank Skorpen: GENETIC AND FUNCTIONAL ANALYSES OF DNA REPAIR IN HUMAN CELLS.
137. Juan A. Pareja: SUNCT SYNDROME. ON THE CLINICAL PICTURE. ITS DISTINCTION FROM OTHER, SIMILAR HEADACHES.
138. Anders Angelsen: NEUROENDOCRINE CELLS IN HUMAN PROSTATIC CARCINOMAS AND THE PROSTATIC COMPLEX OF RAT, GUINEA PIG, CAT AND DOG.
139. Fabio Antonaci: CHRONIC PAROXYSMAL HEMICRANIA AND HEMICRANIA CONTINUA: TWO DIFFERENT ENTITIES?
140. Sven M. Carlsen: ENDOCRINE AND METABOLIC EFFECTS OF METFORMIN WITH SPECIAL EMPHASIS ON CARDIOVASCULAR RISK FACTORES.

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141. Terje A. Murberg: DEPRESSIVE SYMPTOMS AND COPING AMONG PATIENTS WITH CONGESTIVE HEART FAILURE.

142. Harm-Gerd Karl Blaas: THE EMBRYONIC EXAMINATION. Ultrasound studies on the development of the human embryo.
143. Noèmi Becser Andersen:THE CEPHALIC SENSORY NERVES IN UNILATERAL HEADACHES. Anatomical background and neurophysiological evaluation.
144. Eli-Janne Fiskerstrand: LASER TREATMENT OF PORT WINE STAINS. A study of the efficacy and limitations of the pulsed dye laser. Clinical and morfological analyses aimed at improving the therapeutic outcome.
145. Bård Kulseng: A STUDY OF ALGINATE CAPSULE PROPERTIES AND CYTOKINES IN RELATION TO INSULIN DEPENDENT DIABETES MELLITUS.
146. Terje Haug: STRUCTURE AND REGULATION OF THE HUMAN UNG GENE ENCODING URACIL-DNA GLYCOSYLASE.
147. Heidi Brurok: MANGANESE AND THE HEART. A Magic Metal with Diagnostic and Therapeutic Possibilites.
148. Agnes Kathrine Lie: DIAGNOSIS AND PREVALENCE OF HUMAN PAPILLOMAVIRUS INFECTION IN CERVICAL INTRAEPITELIAL NEOPLASIA. Relationship to Cell Cycle Regulatory Proteins and HLA DQBI Genes.
149. Ronald Mårvik: PHARMACOLOGICAL, PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL STUDIES ON ISOLATED STOMACS.
150. Ketil Jarl Holen: THE ROLE OF ULTRASONOGRAPHY IN THE DIAGNOSIS AND TREATMENT OF HIP DYSPLASIA IN NEWBORNS.
151. Irene Hetlevik: THE ROLE OF CLINICAL GUIDELINES IN CARDIOVASCULAR RISK INTERVENTION IN GENERAL PRACTICE.
152. Katarina Tunòn: ULTRASOUND AND PREDICTION OF GESTATIONAL AGE.
153. Johannes Soma: INTERACTION BETWEEN THE LEFT VENTRICLE AND THE SYSTEMIC ARTERIES.
154. Arild Aamodt: DEVELOPMENT AND PRE-CLINICAL EVALUATION OF A CUSTOM-MADE FEMORAL STEM.
155. Agnar Tegnander: DIAGNOSIS AND FOLLOW-UP OF CHILDREN WITH SUSPECTED OR KNOWN HIP DYSPLASIA.
156. Bent Indredavik: STROKE UNIT TREATMENT: SHORT AND LONG-TERM EFFECTS
157. Jolanta Vanagaite Vingen: PHOTOPHOBIA AND PHONOPHOBIA IN PRIMARY HEADACHES

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158. Ola Dalsegg Sæther: PATHOPHYSIOLOGY DURING PROXIMAL AORTIC CROSS-CLAMPING CLINICAL AND EXPERIMENTAL STUDIES
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160. Christina Vogt Isaksen: PRENATAL ULTRASOUND AND POSTMORTEM FINDINGS – A TEN YEAR CORRELATIVE STUDY OF FETUSES AND INFANTS WITH DEVELOPMENTAL ANOMALIES.
161. Holger Seidel: HIGH-DOSE METHOTREXATE THERAPY IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA: DOSE, CONCENTRATION, AND EFFECT CONSIDERATIONS.
162. Stein Hallan: IMPLEMENTATION OF MODERN MEDICAL DECISION ANALYSIS INTO CLINICAL DIAGNOSIS AND TREATMENT.
163. Malcolm Sue-Chu: INVASIVE AND NON-INVASIVE STUDIES IN CROSS-COUNTRY SKIERS WITH ASTHMA-LIKE SYMPTOMS.
164. Ole-Lars Brekke: EFFECTS OF ANTIOXIDANTS AND FATTY ACIDS ON TUMOR NECROSIS FACTOR-INDUCED CYTOTOXICITY.
165. Jan Lundbom: AORTOCORONARY BYPASS SURGERY: CLINICAL ASPECTS, COST CONSIDERATIONS AND WORKING ABILITY.
166. John-Anker Zwart: LUMBAR NERVE ROOT COMPRESSION, BIOCHEMICAL AND NEUROPHYSIOLOGICAL ASPECTS.
167. Geir Falck: HYPEROSMOLALITY AND THE HEART.
168. Eirik Skogvoll: CARDIAC ARREST Incidence, Intervention and Outcome.
169. Dalius Bansevicius: SHOULDER-NECK REGION IN CERTAIN HEADACHES AND CHRONIC PAIN SYNDROMES.
170. Bettina Kinge: REFRACTIVE ERRORS AND BIOMETRIC CHANGES AMONG UNIVERSITY STUDENTS IN NORWAY.
171. Gunnar Qvigstad: CONSEQUENCES OF HYPERGASTRINEMIA IN MAN
172. Hanne Ellekjær: EPIDEMIOLOGICAL STUDIES OF STROKE IN A NORWEGIAN POPULATION. INCIDENCE, RISK FACTORS AND PROGNOSIS
173. Hilde Grimstad: VIOLENCE AGAINST WOMEN AND PREGNANCY OUTCOME.

174. Astrid Hjelde: SURFACE TENSION AND COMPLEMENT ACTIVATION: Factors influencing bubble formation and bubble effects after decompression.
175. Kjell A. Kvistad: MR IN BREAST CANCER – A CLINICAL STUDY.
176. Ivar Rossvoll: ELECTIVE ORTHOPAEDIC SURGERY IN A DEFINED POPULATION. Studies on demand, waiting time for treatment and incapacity for work.
177. Carina Seidel: PROGNOSTIC VALUE AND BIOLOGICAL EFFECTS OF HEPATOCYTE GROWTH FACTOR AND SYNDECAN-1 IN MULTIPLE MYELOMA.

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178. Alexander Wahba: THE INFLUENCE OF CARDIOPULMONARY BYPASS ON PLATELET FUNCTION AND BLOOD COAGULATION – DETERMINANTS AND CLINICAL CONSEQUENSES
179. Marcus Schmitt-Egenolf: THE RELEVANCE OF THE MAJOR hISTOCOMPATIBILITY COMPLEX FOR THE GENETICS OF PSORIASIS
180. Odrun Arna Gederaas: BIOLOGICAL MECHANISMS INVOLVED IN 5-AMINOLEVULINIC ACID BASED PHOTODYNAMIC THERAPY
181. Pål Richard Romundstad: CANCER INCIDENCE AMONG NORWEGIAN ALUMINIUM WORKERS
182. Henrik Hjorth-Hansen: NOVEL CYTOKINES IN GROWTH CONTROL AND BONE DISEASE OF MULTIPLE MYELOMA
183. Gunnar Morken: SEASONAL VARIATION OF HUMAN MOOD AND BEHAVIOUR
184. Bjørn Olav Haugen: MEASUREMENT OF CARDIAC OUTPUT AND STUDIES OF VELOCITY PROFILES IN AORTIC AND MITRAL FLOW USING TWO- AND THREE-DIMENSIONAL COLOUR FLOW IMAGING
185. Geir Bråthen: THE CLASSIFICATION AND CLINICAL DIAGNOSIS OF ALCOHOL-RELATED SEIZURES
186. Knut Ivar Aasarød: RENAL INVOLVEMENT IN INFLAMMATORY RHEUMATIC DISEASE. A Study of Renal Disease in Wegener's Granulomatosis and in Primary Sjögren's Syndrome
187. Trude Helen Flo: RESEPTORS INVOLVED IN CELL ACTIVATION BY DEFINED URONIC ACID POLYMERS AND BACTERIAL COMPONENTS
188. Bodil Kavli: HUMAN URACIL-DNA GLYCOSYLASES FROM THE UNG GENE: STRUCTRUAL BASIS FOR SUBSTRATE SPECIFICITY AND REPAIR
189. Liv Thommesen: MOLECULAR MECHANISMS INVOLVED IN TNF- AND GASTRIN-MEDIATED GENE REGULATION
190. Turid Lingaas Holmen: SMOKING AND HEALTH IN ADOLESCENCE; THE NORD-TRØNDELAG HEALTH STUDY, 1995-97
191. Øyvind Hjertner: MULTIPLE MYELOMA: INTERACTIONS BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MICROENVIRONMENT
192. Asbjørn Støylen: STRAIN RATE IMAGING OF THE LEFT VENTRICLE BY ULTRASOUND. FEASIBILITY, CLINICAL VALIDATION AND PHYSIOLOGICAL ASPECTS
193. Kristian Midthjell: DIABETES IN ADULTS IN NORD-TRØNDELAG. PUBLIC HEALTH ASPECTS OF DIABETES MELLITUS IN A LARGE, NON-SELECTED NORWEGIAN POPULATION.
194. Guanglin Cui: FUNCTIONAL ASPECTS OF THE ECL CELL IN RODENTS
195. Ulrik Wisløff: CARDIAC EFFECTS OF AEROBIC ENDURANCE TRAINING: HYPERTROPHY, CONTRACTILITY AND CALCUIM HANDLING IN NORMAL AND FAILING HEART
196. Øyvind Halaas: MECHANISMS OF IMMUNOMODULATION AND CELL-MEDIATED CYTOTOXICITY INDUCED BY BACTERIAL PRODUCTS
197. Tore Amundsen: PERFUSION MR IMAGING IN THE DIAGNOSIS OF PULMONARY EMBOLISM
198. Nanna Kurtze: THE SIGNIFICANCE OF ANXIETY AND DEPRESSION IN FATIQUE AND PATTERNS OF PAIN AMONG INDIVIDUALS DIAGNOSED WITH FIBROMYALGIA: RELATIONS WITH QUALITY OF LIFE, FUNCTIONAL DISABILITY, LIFESTYLE, EMPLOYMENT STATUS, CO-MORBIDITY AND GENDER
199. Tom Ivar Lund Nilsen: PROSPECTIVE STUDIES OF CANCER RISK IN NORD-TRØNDELAG: THE HUNT STUDY. Associations with anthropometric, socioeconomic, and lifestyle risk factors
200. Asta Kristine Håberg: A NEW APPROACH TO THE STUDY OF MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT USING MAGNETIC RESONANCE TECHNIQUES

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201. Knut Jørgen Arntzen: PREGNANCY AND CYTOKINES
202. Henrik Døllner: INFLAMMATORY MEDIATORS IN PERINATAL INFECTIONS

203. Asta Bye: LOW FAT, LOW LACTOSE DIET USED AS PROPHYLACTIC TREATMENT OF ACUTE INTESTINAL REACTIONS DURING PELVIC RADIOTHERAPY. A PROSPECTIVE RANDOMISED STUDY.
204. Sylvester Moyo: STUDIES ON STREPTOCOCCUS AGALACTIAE (GROUP B STREPTOCOCCUS) SURFACE-ANCHORED MARKERS WITH EMPHASIS ON STRAINS AND HUMAN SERA FROM ZIMBABWE.
205. Knut Hagen: HEAD-HUNT: THE EPIDEMIOLOGY OF HEADACHE IN NORD-TRØNDELAG
206. Li Lixin: ON THE REGULATION AND ROLE OF UNCOUPLING PROTEIN-2 IN INSULIN PRODUCING ß-CELLS
207. Anne Hildur Henriksen: SYMPTOMS OF ALLERGY AND ASTHMA VERSUS MARKERS OF LOWER AIRWAY INFLAMMATION AMONG ADOLESCENTS
208. Egil Andreas Fors: NON-MALIGNANT PAIN IN RELATION TO PSYCHOLOGICAL AND ENVIRONTENTAL FACTORS. EXPERIENTAL AND CLINICAL STUDES OF PAIN WITH FOCUS ON FIBROMYALGIA
209. Pål Klepstad: MORPHINE FOR CANCER PAIN
210. Ingunn Bakke: MECHANISMS AND CONSEQUENCES OF PEROXISOME PROLIFERATOR-INDUCED HYPERFUNCTION OF THE RAT GASTRIN PRODUCING CELL
211. Ingrid Susann Gribbestad: MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY OF BREAST CANCER
212. Rønnaug Astri Ødegård: PREECLAMPSIA – MATERNAL RISK FACTORS AND FETAL GROWTH
213. Johan Haux: STUDIES ON CYTOTOXICITY INDUCED BY HUMAN NATURAL KILLER CELLS AND DIGITOXIN
214. Turid Suzanne Berg-Nielsen: PARENTING PRACTICES AND MENTALLY DISORDERED ADOLESCENTS
215. Astrid Rydning: BLOOD FLOW AS A PROTECTIVE FACTOR FOR THE STOMACH MUCOSA. AN EXPERIMENTAL STUDY ON THE ROLE OF MAST CELLS AND SENSORY AFFERENT NEURONS

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216. Jan Pål Loennechen: HEART FAILURE AFTER MYOCARDIAL INFARCTION. Regional Differences, Myocyte Function, Gene Expression, and Response to Cariporide, Losartan, and Exercise Training.
217. Elisabeth Qvigstad: EFFECTS OF FATTY ACIDS AND OVER-STIMULATION ON INSULIN SECRETION IN MAN
218. Arne Åsberg: EPIDEMIOLOGICAL STUDIES IN HEREDITARY HEMOCHROMATOSIS: PREVALENCE, MORBIDITY AND BENEFIT OF SCREENING.
219. Johan Fredrik Skomsvoll: REPRODUCTIVE OUTCOME IN WOMEN WITH RHEUMATIC DISEASE. A population registry based study of the effects of inflammatory rheumatic disease and connective tissue disease on reproductive outcome in Norwegian women in 1967-1995.
220. Siv Mørkved: URINARY INCONTINENCE DURING PREGNANCY AND AFTER DELIVERY: EFFECT OF PELVIC FLOOR MUSCLE TRAINING IN PREVENTION AND TREATMENT
221. Marit S. Jordhøy: THE IMPACT OF COMPREHENSIVE PALLIATIVE CARE
222. Tom Christian Martinsen: HYPERGASTRINEMIA AND HYPOACIDITY IN RODENTS – CAUSES AND CONSEQUENCES
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224. Haytham Eloqayli: METABOLIC CHANGES IN THE BRAIN CAUSED BY EPILEPTIC SEIZURES
225. Torunn Bruland: STUDIES OF EARLY RETROVIRUS-HOST INTERACTIONS – VIRAL DETERMINANTS FOR PATHOGENESIS AND THE INFLUENCE OF SEX ON THE SUSCEPTIBILITY TO FRIEND MURINE LEUKAEMIA VIRUS INFECTION
226. Torstein Hole: DOPPLER ECHOCARDIOGRAPHIC EVALUATION OF LEFT VENTRICULAR FUNCTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION
227. Vibeke Nossum: THE EFFECT OF VASCULAR BUBBLES ON ENDOTHELIAL FUNCTION
228. Sigurd Fasting: ROUTINE BASED RECORDING OF ADVERSE EVENTS DURING ANAESTHESIA – APPLICATION IN QUALITY IMPROVEMENT AND SAFETY
229. Solfrid Romundstad: EPIDEMIOLOGICAL STUDIES OF MICROALBUMINURIA. THE NORD-TRØNDELAG HEALTH STUDY 1995-97 (HUNT 2)
230. Geir Torheim: PROCESSING OF DYNAMIC DATA SETS IN MAGNETIC RESONANCE IMAGING

231. Catrine Ahlén: SKIN INFECTIONS IN OCCUPATIONAL SATURATION DIVERS IN THE NORTH SEA AND THE IMPACT OF THE ENVIRONMENT
232. Arnulf Langhammer: RESPIRATORY SYMPTOMS, LUNG FUNCTION AND BONE MINERAL DENSITY IN A COMPREHENSIVE POPULATION SURVEY. THE NORD-TRØNDELAG HEALTH STUDY 1995-97. THE BRONCHIAL OBSTRUCTION IN NORD-TRØNDELAG STUDY
233. Einar Kjelsås: EATING DISORDERS AND PHYSICAL ACTIVITY IN NON-CLINICAL SAMPLES
234. Arne Wibe: RECTAL CANCER TREATMENT IN NORWAY – STANDARDISATION OF SURGERY AND QUALITY ASSURANCE

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235. Eivind Witsø: BONE GRAFT AS AN ANTIBIOTIC CARRIER
236. Anne Mari Sund: DEVELOPMENT OF DEPRESSIVE SYMPTOMS IN EARLY ADOLESCENCE
237. Hallvard Lærum: EVALUATION OF ELECTRONIC MEDICAL RECORDS – A CLINICAL TASK PERSPECTIVE
238. Gustav Mikkelsen: ACCESSIBILITY OF INFORMATION IN ELECTRONIC PATIENT RECORDS; AN EVALUATION OF THE ROLE OF DATA QUALITY
239. Steinar Krokstad: SOCIOECONOMIC INEQUALITIES IN HEALTH AND DISABILITY. SOCIAL EPIDEMIOLOGY IN THE NORD-TRØNDELAG HEALTH STUDY (HUNT), NORWAY
240. Arne Kristian Myhre: NORMAL VARIATION IN ANOGENITAL ANATOMY AND MICROBIOLOGY IN NON-ABUSED PRESCHOOL CHILDREN
241. Ingunn Dybedal: NEGATIVE REGULATORS OF HEMATOPOIETEC STEM AND PROGENITOR CELLS
242. Beate Sitter: TISSUE CHARACTERIZATION BY HIGH RESOLUTION MAGIC ANGLE SPINNING MR SPECTROSCOPY
243. Per Arne Aas: MACROMOLECULAR MAINTENANCE IN HUMAN CELLS – REPAIR OF URACIL IN DNA AND METHYLATIONS IN DNA AND RNA
244. Anna Bofin: FINE NEEDLE ASPIRATION CYTOLOGY IN THE PRIMARY INVESTIGATION OF BREAST TUMOURS AND IN THE DETERMINATION OF TREATMENT STRATEGIES
245. Jim Aage Nøttestad: DEINSTITUTIONALIZATION AND MENTAL HEALTH CHANGES AMONG PEOPLE WITH MENTAL RETARDATION
246. Reidar Fossmark: GASTRIC CANCER IN JAPANESE COTTON RATS
247. Wibeke Nordhøy: MANGANESE AND THE HEART, INTRACELLULAR MR RELAXATION AND WATER EXCHANGE ACROSS THE CARDIAC CELL MEMBRANE

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248. Sturla Molden: QUANTITATIVE ANALYSES OF SINGLE UNITS RECORDED FROM THE HIPPOCAMPUS AND ENTORHINAL CORTEX OF BEHAVING RATS
249. Wenche Brenne Drøyvold: EPIDEMIOLOGICAL STUDIES ON WEIGHT CHANGE AND HEALTH IN A LARGE POPULATION. THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
250. Ragnhild Støen: ENDOTHELIUM-DEPENDENT VASODILATION IN THE FEMORAL ARTERY OF DEVELOPING PIGLETS
251. Aslak Steinsbekk: HOMEOPATHY IN THE PREVENTION OF UPPER RESPIRATORY TRACT INFECTIONS IN CHILDREN
252. Hill-Aina Steffenach: MEMORY IN HIPPOCAMPAL AND CORTICO-HIPPOCAMPAL CIRCUITS
253. Eystein Stordal: ASPECTS OF THE EPIDEMIOLOGY OF DEPRESSIONS BASED ON SELF-RATING IN A LARGE GENERAL HEALTH STUDY (THE HUNT-2 STUDY)
254. Viggo Pettersen: FROM MUSCLES TO SINGING: THE ACTIVITY OF ACCESSORY BREATHING MUSCLES AND THORAX MOVEMENT IN CLASSICAL SINGING
255. Marianne Fyhn: SPATIAL MAPS IN THE HIPPOCAMPUS AND ENTORHINAL CORTEX
256. Robert Valderhaug: OBSESSIVE-COMPULSIVE DISORDER AMONG CHILDREN AND ADOLESCENTS: CHARACTERISTICS AND PSYCHOLOGICAL MANAGEMENT OF PATIENTS IN OUTPATIENT PSYCHIATRIC CLINICS
257. Erik Skaaheim Haug: INFRARENAL ABDOMINAL AORTIC ANEURYSMS – COMORBIDITY AND RESULTS FOLLOWING OPEN SURGERY
258. Daniel Kondziella: GLIAL-NEURONAL INTERACTIONS IN EXPERIMENTAL BRAIN DISORDERS
259. Vegard Heimly Brun: ROUTES TO SPATIAL MEMORY IN HIPPOCAMPAL PLACE CELLS

260. Kenneth McMillan: PHYSIOLOGICAL ASSESSMENT AND TRAINING OF ENDURANCE AND STRENGTH IN PROFESSIONAL YOUTH SOCCER PLAYERS
261. Marit Sæbø Indredavik: MENTAL HEALTH AND CEREBRAL MAGNETIC RESONANCE IMAGING IN ADOLESCENTS WITH LOW BIRTH WEIGHT
262. Ole Johan Kemi: ON THE CELLULAR BASIS OF AEROBIC FITNESS, INTENSITY-DEPENDENCE AND TIME-COURSE OF CARDIOMYOCYTE AND ENDOTHELIAL ADAPTATIONS TO EXERCISE TRAINING
263. Eszter Vanky: POLYCYSTIC OVARY SYNDROME – METFORMIN TREATMENT IN PREGNANCY
264. Hild Fjærtoft: EXTENDED STROKE UNIT SERVICE AND EARLY SUPPORTED DISCHARGE. SHORT AND LONG-TERM EFFECTS
265. Grete Dyb: POSTTRAUMATIC STRESS REACTIONS IN CHILDREN AND ADOLESCENTS
266. Vidar Fykse: SOMATOSTATIN AND THE STOMACH
267. Kirsti Berg: OXIDATIVE STRESS AND THE ISCHEMIC HEART: A STUDY IN PATIENTS UNDERGOING CORONARY REVASCULARIZATION
268. Björn Inge Gustafsson: THE SEROTONIN PRODUCING ENTEROCHROMAFFIN CELL, AND EFFECTS OF HYPERSEROTONINEMIA ON HEART AND BONE

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269. Torstein Baade Rø: EFFECTS OF BONE MORPHOGENETIC PROTEINS, HEPATOCYTE GROWTH FACTOR AND INTERLEUKIN-21 IN MULTIPLE MYELOMA
270. May-Britt Tessem: METABOLIC EFFECTS OF ULTRAVIOLET RADIATION ON THE ANTERIOR PART OF THE EYE
271. Anne-Sofie Helvik: COPING AND EVERYDAY LIFE IN A POPULATION OF ADULTS WITH HEARING IMPAIRMENT
272. Therese Standal: MULTIPLE MYELOMA: THE INTERPLAY BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MARROW MICROENVIRONMENT
273. Ingvild Saltvedt: TREATMENT OF ACUTELY SICK, FRAIL ELDERLY PATIENTS IN A GERIATRIC EVALUATION AND MANAGEMENT UNIT – RESULTS FROM A PROSPECTIVE RANDOMISED TRIAL
274. Birger Henning Endreseth: STRATEGIES IN RECTAL CANCER TREATMENT – FOCUS ON EARLY RECTAL CANCER AND THE INFLUENCE OF AGE ON PROGNOSIS
275. Anne Mari Aukan Rokstad: ALGINATE CAPSULES AS BIOREACTORS FOR CELL THERAPY
276. Mansour Akbari: HUMAN BASE EXCISION REPAIR FOR PRESERVATION OF GENOMIC STABILITY
277. Stein Sundstrøm: IMPROVING TREATMENT IN PATIENTS WITH LUNG CANCER – RESULTS FROM TWO MULITCENTRE RANDOMISED STUDIES
278. Hilde Pleym: BLEEDING AFTER CORONARY ARTERY BYPASS SURGERY - STUDIES ON HEMOSTATIC MECHANISMS, PROPHYLACTIC DRUG TREATMENT AND EFFECTS OF AUTOTRANSFUSION
279. Line Merethe Oldervoll: PHYSICAL ACTIVITY AND EXERCISE INTERVENTIONS IN CANCER PATIENTS
280. Boye Welde: THE SIGNIFICANCE OF ENDURANCE TRAINING, RESISTANCE TRAINING AND MOTIVATIONAL STYLES IN ATHLETIC PERFORMANCE AMONG ELITE JUNIOR CROSS-COUNTRY SKIERS
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