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Risk of Age-Related Macular Degeneration in Patients with Exfoliation Syndrome: The Utah Project on Exfoliation Syndrome (UPEXS)

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Abstract: Objective: To investigate any relationships between exfoliation syndrome or exfoliation glaucoma and age-related macular degeneration utilizing the Utah population database. Design: This was a retrospective, case–control cohort study. Subjects, Participants, and/or Controls: We identified 3405 patients diagnosed with exfoliation syndrome (XFS) or exfoliation glaucoma (XFG) during a dilated eye exam within the UHealth system from 1996 to 2021, whose dry or wet age-related macular degeneration (AMD) status was assessed. A population-based control pool of 257,714 UHealth patients with no XFS/XFG diagnosis and a dilated eye exam history from 1996 to 2021 was compiled, with its patients randomly selected and individually matched 3:1 to cases based on sex and age at index diagnosis of their respective case. Methods: A covariate analysis was performed of characteristics and risk factors associated with XFS/XFG, which included race/ethnicity, residence location, partner/marital status, and family history of XFS/XFG, obesity, tobacco use, alcohol use, osteoporosis/vitamin D deficiency, primary/essential hypertension, ocular hypertension, and cataract surgery. Main Outcome Measure: We studied the trends of non-exudative (dry) or exudative (wet) AMD in a large Utah population study of XFS/XFG patients and controls. Results: Of 3396 XFS/XFG patients, as well as 10,179 individually matched 3:1 control patients, 64% were female and the average age of XFS onset was 74.3 yrs. In a univariate model, we observed a very modest increased risk of wet AMD in XFS/XFG patients (odds ratio, OR = 1.14, 95% confidence interval (CI) 0.99–1.32), which did not achieve statistical significance ($p = 0.07$). After adjusting for the main effects of potential confounders, there was no greater presentation of AMD in XFS/XFG patients when compared with controls (dry AMD: OR = 0.94, 95% CI 0.85–1.05, $p = 031$; wet AMD: OR = 0.98, 95% CI 0.83–1.14, $p = 0.76$). In XFS/XFG patients compared to controls, the risk of having cataract surgery was elevated (OR = 2.39, 95% CI 2.18–2.62). However, after accounting for an interaction with AMD, XFS/XFG patients who underwent cataract surgery did not exhibit an increased risk of either dry or wet AMD (dry AMD: OR = 0.91, 95% CI 0.80–1.03; wet AMD: OR = 0.89, 95% CI 0.75–1.07). The risk of AMD in XFS/XFG patients vs. controls showed no association with osteoporosis/vitamin D deficiency for dry (OR 0.78 95% CI 0.66–0.92 $p = 0.004$) or wet AMD (OR = 0.72 95% CI 0.56–0.92 $p = 0.01$), while we found a borderline positive association with both dry and wet AMD if they had osteoporosis/vitamin D deficiency. Conclusion: Using the Utah Population Database, we found that a cataract surgery history significantly impacts the association between AMD and XFS, and that vitamin D deficiency/osteoporosis is a significant confounder of the association. However, no direct association between XFS and AMD was found in this study.

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1. Introduction

Exfoliation syndrome (XFS), a leading cause of blindness worldwide, is an age-related systemic condition characterized by dysregulated deposition of extracellular material (ECM) in both systemic and ocular tissues [1]. Diagnosis of XFS is typically conducted through a dilated slit lamp exam, which involves identifying accumulations of fibrillar ECM or exfoliative material in the anterior segment [2]. XFS can progress quickly to exfoliation glaucoma (XFG), a particularly aggressive form of secondary open-angle glaucoma. This advanced stage is marked by more pronounced cataract development, lens instability (subluxation), and a heightened likelihood of central retinal vein occlusion (CRVO) and other ocular comorbidities [3,4].

The clinical diagnosis of XFS in the anterior segment involves identifying the fibrillar ECM or exfoliative material on the lens capsule, iris, and angle [2]. These abnormalities in the ECM, including elastin, extend beyond the eye, contributing to dysregulated ECM deposition throughout the body [5]. Studies of individuals with XFS reveal a common etiology involving abnormal ECM metabolism and repair mechanisms, which may underlie systemic comorbidities such as coronary artery disease, vascular dysfunction, pelvic organ prolapse, and Alzheimer's-like dementia [4,6–10]. Furthermore, the impact of abnormal elastin may not be limited to the anterior segment, as elastin is also present within the posterior segment. Other studies have shown that XFS can affect the choroidal thickness [11] and retinal vascular density [12], linking changes between the anterior and posterior segments.

The development of XFS can arise from both intrinsic and extrinsic factors. Intrinsic factors include risk alleles in the *lysyl-oxidase-like* gene (*LOXL1*), a crucial enzyme involved in the stabilization and repair of the ECM [13]. A genome-wide association study (GWAS) by Thorleifsson et al. [14] showed that multiple single-nucleotide polymorphisms (SNPs) in a specific region were associated with XFG, explained by two non-synonymous SNPs in the *LOXL1* gene. Subsequent GWASs have identified XFS susceptibility loci other than in *LOXL1* [15]. Elastin plays a critical role within the ECM, and disruptions in its metabolism, repair, and production are associated with the *LOXL1* gene. Studies demonstrate that mice lacking this gene fail to generate normal elastic fibers [16]. Further exploration into elastin irregularities has revealed that modifications in its degradation, whether heightened or altered, can elevate the likelihood of developing emphysema, atherosclerosis, and cancer [17]. Elastin degradation is implicated in chronic obstructive pulmonary disease (COPD) and with XFS [9,18]. Although the direct translation of findings from *LOXL1* knockout mice to human clinical pathology is not straightforward, investigations have effectively guided research to address potential correlations between XFS and associated systemic pathologies involving ECM, collagen, and elastin metabolism [13].

Extrinsic factors believed to contribute to XFS development include epigenetic influences such as UV exposure [19,20] and altitude [21]. These epigenetic factors have the potential to increase reactive oxygen species (ROS) and DNA methylation, potentially impairing the repair processes essential for establishing ECM homeostasis [22]. Oxidative stress, characterized by cell damage from ROS, has been hypothesized to be a contributor to age-related ocular conditions such as XFS and age-related macular degeneration (AMD) [23].

AMD is a chronic retinal macular pathology caused by progressive damage within the macula and eventually affecting central vision. Over time, early nonexudative or 'dry' AMD can progress to late-stage forms of the disease: (1) neovascular ('wet') AMD, characterized by the growth of abnormal vasculature within the macular retina and/or choroid, often resulting in macular scarring and death of retinal pigment epithelium cells (RPEs) [24], and/or (2) geographic atrophy, in which the RPE degenerates within the macula and elsewhere, without an association with new vessel formation. The RPE, choriocapillaris,

Bruch's membrane, and photoreceptor cells are all components of the macula that can be damaged in AMD [25].

In all ECM compartments, the properties and structure of the various components of the ECM, including elastin, are continuously being synthesized and degraded to maintain optimal functioning in a healthy system. When the homeostasis of this process is abnormal, pathologies pertaining to the ECM, such as in Bruch's membrane, can arise [26]. Genetic risk alleles account for a major proportion of AMD in humans, primarily within the complement regulatory gene Complement Factor H and its associated Complement Factor H-like genes and the HTRA1/ARMS2 locus [27–29]. Environmental factors associated with increased ROS, such as smoking and increased UV light exposure, have been linked to AMD risk [30]. DNA and LINE-1 methylation and associations with AMD have recently been reported [31]. Hunter et al. showed significant differences in DNA methylation and mRNA levels when comparing AMD and healthy retinas [32].

Previous studies have shown an association between XFS and the development of AMD, in which an emphasis was placed on the two diseases having similar predisposing factors, epidemiology, and pathogenesis [33,34]. Factors such as genetic predisposition, age, and other risk factors contribute to both these complex and heterogenous diseases. Biochemical factors such as epigenetics, ROS, and ECM abnormities and damage have been discussed extensively in studies pertaining to XFS and AMD. The purpose of this retrospective, case–control cohort study was to characterize the association between XFS and AMD in a large Utah population.

2. Materials and Methods

2.1. Utah Population Database

The Utah Population Database (UPDB) is a unique research repository that contains 63 million integrated data records of more than 11 million individuals. The database includes family relationships from this extensive genealogy, demographics, and health-related information, collated by linking various data sources, including a statewide cancer registry, medical records, vital records, and links to clinical information of patients of the two largest healthcare providers in Utah. The history and content of this unique resource have been described in detail [35]. For this study, we utilized UPDB demographic data, vital records, family relationships, and links to clinical records of 2.35 million patients in the University of Utah Health (UHealth) system of hospitals and clinics, including John Moran Eye Center (JMEC) facilities, from 1996 to 2021. The JMEC provides the majority of eye care for ocular disorders in Utah. This study integrated lifestyle and comorbidities' diagnoses from statewide inpatient and ambulatory facilities (1996–2020) and Utah All Payer Claims (2013–2020) data in the UPDB provided by the Utah Department of Health and Human Services. It also integrated georeferenced Utah residential address histories of study subjects available in the UPDB. Study approvals were obtained from the Institutional Review Boards of the University of Utah (IRB_00081512, approval date 17 July 2015) and from the Resource for Genetic and Epidemiologic Research, which governs the use of UPDB data.

2.2. Exfoliation Syndrome/Exfoliation Glaucoma Case Selection

We identified 3405 patients diagnosed with XFS or XFG during a dilated eye exam within the UHealth system from 1996 to 2021 based on one or more International Classification of Diseases (ICD) diagnostic codes (versions 9 and 10): 365.52, 366.11 (ICD-9); H40.14, H25.89 (ICD-10). In addition, 176 patients without the preceding codes, but with an open-angle glaucoma diagnosis of 365.1 (ICD-9) or H40.10–H40.13, H40.15 (ICD-10), who also had a text string indicating exfoliation (e.g., pseudoexfoliation, PXE, exfoliation, XFG) and an XFS/XFG diagnosis by chart review, were identified. In total, 3581 case patients were assessed for study eligibility. For inclusion, a case had to be aged 50 years or older at index diagnosis and have at least one appropriate matched control. A detailed chart review was performed in a subset of 506 cases, and we found that 19 of 3415 eligible patients (<1%)

did not have a clinical diagnosis of XFS/XFG, meaning they were excluded along with their matched controls. Ultimately, 3396 eligible XFS/XFG patients in Utah were identified for this study (Figure 1).

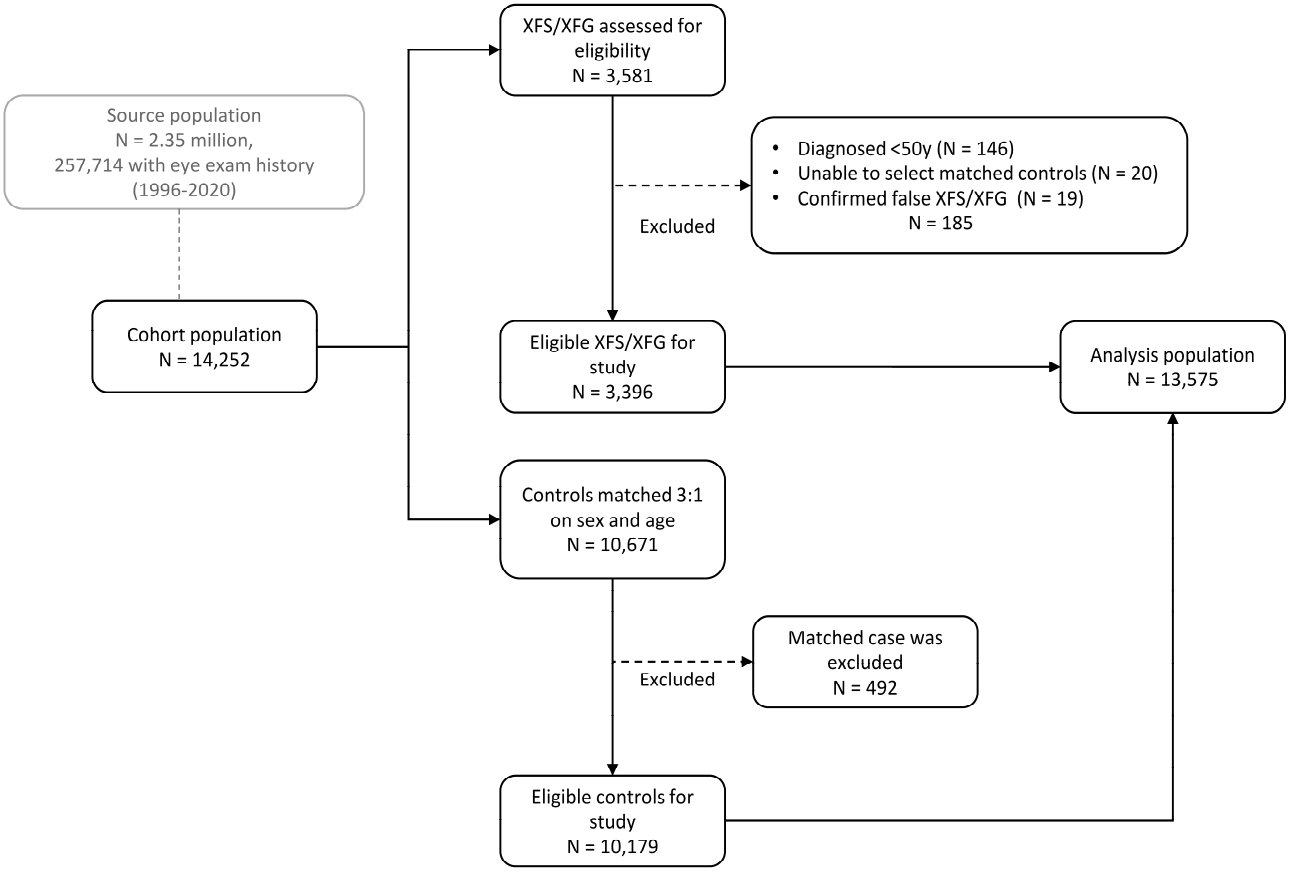

Figure 1. Exfoliation syndrome/exfoliation glaucoma (XFS/XFG) patient and control cohort seletion.

2.3. Control Selection

A population-based control pool of 257,714 UHealth patients with no XFS/XFG diagnosis and a dilated eye exam history from 1996 to 2021 based on Current Procedural Terminology (CPT) codes was available for control selection: eye visit, new patient (92,000, 92,002, 92,004); eye visit, established patient (92,012, 92,014); evaluation and management, new patient (99,201–99,205 and eye care facility code at visit); evaluation and management, established patient (99,211–99,215 and eye care facility code at visit); and patient consultation (99,241–99,245 and eye care facility code at visit). Controls were randomly selected and individually matched 3:1 to cases based on sex and age (within ±2 years) at index diagnosis of their respective case. In addition, controls had to have follow-up in the UPDB of a similar length to that of their respective case. In total, 10,179 controls were selected and individually matched to cases (see Figure 1).

2.4. Age-Related Macular Degeneration

An outcome of age-related macular degeneration (AMD) and the decision on the AMD subtype were based on one or more International Classification of Diseases (ICD) diagnostic codes (versions 9 and 10) in the medical record from 1996 to 2021: unspecified as to dry or wet AMD, 362.50/H35.30 (ICD9/10); nonexudative (dry) AMD, 362.51/H35.31 (ICD9/10); exudative (wet) AMD, 362.52/H35.32 (ICD9/10); and degenerative drusen AMD, 362.57/H35.36 ICD9/10). For wet AMD, a patient had to have at least one occurrence of CPT code 67028 (intravitreal injection, standard treatment for wet AMD) in the medical record in addition to the AMD diagnosis to minimize misclassification of wet AMD. Patients

with a diagnostic code for wet AMD who did not have an injection history were designated as having non-exudative AMD. For association analyses, either an outcome of wet AMD with injection(s) or an outcome of a non-wet form of AMD (dry, drusen, unspecified only with no wet AMD history) was compared with a reference of no AMD history. Wet AMD differs from dry AMD in the underlying etiology and treatment, and given our preliminary data that wet and dry associations with XFS/XFG may differ, we decided a priori to analyze wet and non-wet forms of AMD separately.

2.5. Covariates

Risk factors associated with XFS/XFG in our studies and in those of others included race/ethnicity, place of residence, partner/marital status, family history of XFS/XFG, obesity, tobacco use, alcohol use, osteoporosis/vitamin D deficiency, primary/essential hypertension, ocular hypertension, and cataract surgery. The study population was primarily white and non-Hispanic based on records in the UPDB, which mirrors the Utah population [35]. As the JMEC patient catchment area extends beyond Utah, we adjusted for residence in Utah compared to outside of Utah, as non-ocular medical conditions may have been diagnosed elsewhere. Married/living with a partner vs. living alone has been related to healthcare-seeking behavior that differs by gender [36]. An XFS/XFG family history was determined from UPDB genealogy data linked to diagnoses that did not depend on self-reports. History of obesity, inversely related to XFS/XFG, was based on a body mass index (BMI) of $\geq$30 from driver license height and weight data nearest the time of case diagnosis or from a diagnostic code indicating obesity [37]. Histories of tobacco and alcohol use were determined from ICD9/10 diagnostic codes in the medical record. Tobacco is a reported risk factor for XFS/XFG, and alcohol has also been associated [38]. As we were unable to directly assess UV exposure in all subjects, we used an ICD9/10 diagnosis of osteoporosis or vitamin D deficiency to indicate a low level of UV sunshine exposure. We previously showed that hypertension history modified the association of XFS/XFG in atrial fibrillation and obstructive sleep apnea patients. Previous studies have shown a correlation between ocular hypertension and XFS/XFG, which we observed in the preliminary data, and therefore we examined the history of an ocular hypertension diagnosis. Although the findings are mixed, evidence suggests that cataract surgery may play a role in glaucoma development. One study found that XFS increased IOP, glaucomatous optic neuropathy, and coronary heart disease in an aging cataract population [39]. Meanwhile, another study found that cataract surgery performed via phacoemulsification lowers the IOP in XFS patients more compared to non-XFS patients [40]. We examined the history of cataract surgery based on CPT codes 66982–66984 in the medical record. The codes used to identify XFS/XFG, AMD, and a history of non-ocular and ocular comorbidities are provided in an online Appendix. To account for differences in overall health and the history of chronic conditions, we also examined the Charlson comorbidity index (CCI) available for each subject from their most recent patient visit, grouped as none, mild, moderate, and severe levels of comorbidity [41].

2.6. Statistical Methods

We first examined differences in frequencies of demographic characteristics and reported risk factors in XFS/XFG patients compared to controls using a chi-square test of association for categorical data and a t-test for continuous data. To estimate the risk of dry or wet AMD in XFS/XFG patients compared to controls, we used conditional logistic regression models controlling for sex and age. These included a univariate model of the main effect of an AMD outcome in XFS/XFG when controlling for sex and age, but with no further covariate adjustment, and a multivariate model including the main effect of AMD when simultaneously adjusting for the main effects of covariates previously associated with XFS/XFG patients, as some factors associated with XFS/XFG have also been reported to be associated with AMD (e.g., race, aging, tobacco use) [42]. We stratified the covariate characteristics by the absence or presence of AMD in XFS/XFG patients and controls and

performed an F test of the interaction between the history of AMD, a given covariate, and the XFS/XFG status. Covariates with $p < 0.01$ for the interaction with AMD and XFS/XFG were included in a multivariate logistic regression model with a multiplicative term for interaction.

3. Results

Characteristics of the control and XFS/XFG patient cohorts are shown in Table 1. Of 3396 XFS/XFG patients and 10,179 individually matched for age and sex 3:1 with control patients, 64% were female. The average age of XFS onset was in the seventh decade of life, 74.3 y on average for those 50 years and older. The study cohorts were comprised primarily of white and non-Hispanic individuals, mirroring the 2020 Utah population of adults ≥ 50 y (91% white and non-Hispanic) [43]. Exfoliation patients were more likely to reside outside of Utah than controls, reflecting the JMEC catchment area from neighboring states. XFS/XFG patients had a higher proportion of tobacco and alcohol use disorders, while exhibiting less obesity and osteoporosis or vitamin D deficiency than in controls. Those with XFS/XFG had higher rates of essential hypertension (22.6% vs. 19.4% controls), ocular hypertension (14.2% vs. 4.8%), and cataract surgery histories (72.8% vs. 55.4%), and they had higher Charlson comorbidity scores than controls (mild: 22.2% vs. 19.7%; moderate: 6.6% vs. 6.3%; severe: 5.4% vs. 5.1%).

Table 1. Characteristics of exfoliation syndrome/exfoliation glaucoma and 3:1 control patients.

	Controls		**XFS/XFG**		
Characteristic	N	col%	N	col%	*p*
Total	10,179		3396		
Sex					
Female	6550	64.3	2185	64.3	0.65
Male	3629	35.7	1211	35.7	
Age at case diagnosis					
Mean (±SD)	74.3	0.2	74.3	0.2	0.33
50 to 59 y	774	7.6	259	7.6	0.37
60 to 69 y	2320	22.8	774	22.8	
70 to 79 y	3913	38.4	1305	38.4	
80 y and older	3172	31.2	1058	31.2	
Race/ethnicity					
White, non-Hispanic	9446	92.8	3090	91	0.002
White, Hispanic	398	3.9	170	5	
non-White, any ethnicity	335	3.3	136	4	
Utah resident					
Resides in Utah	10,036	98.6	3062	90.2	<0.0001
Resides outside of Utah	143	1.4	334	9.8	
Marital/partnership status					
Living alone (single, divorced, widowed)	5861	57.6	2224	65.5	<0.0001
Living with a partner	4318	42.4	1172	34.5	
Family history of XFS/XFG					
No first-degree family history	9922	97.5	3244	95.5	<0.0001
Any first-degree relative	257	2.5	152	4.5	
Obesity history (BMI ≥ 30)					
Not obese	7718	75.8	2764	81.4	<0.0001
Obese	2461	24.2	632	18.6	
Tobacco use disorder history					
No	7837	77	2540	74.8	0.009
Yes	2342	23	856	25.2	
Alcohol use disorder history					
No	9733	95.6	3201	94.3	0.001
Yes	446	4.4	195	5.7	

Table 1. *Cont.*

	Controls		XFS/XFG		
Osteoporosis and/or vitamin D deficiency					
No	4927	48.4	1854	54.6	<0.0001
Yes	5252	51.6	1542	45.4	
Essential/primary hypertension history					
No	1973	19.4	766	22.6	<0.0001
Yes	8206	80.6	2630	77.4	
History of ocular hypertension					
No	9694	95.2	2915	85.8	<0.0001
Yes	485	4.8	481	14.2	
History of cataract surgery					
No	4537	44.6	923	27.2	<0.0001
Yes	5642	55.4	2473	72.8	
Charlson comorbidity index (CCI)					
None (CCI = 0)	7020	69	2235	65.8	0.006
Mild (CCI 1–2)	2002	19.7	754	22.2	
Moderate (CCI 3–4)	639	6.3	224	6.6	
Severe (CCI $\geq$ 5)	518	5.1	183	5.4	
Age-related macular degeneration (AMD)					
No history of AMD	7667	75.3	2523	74.3	0.2
History of unspecified, dry or drusen AMD only	1793	17.6	603	17.8	
History of wet AMD requiring injection(s)	719	7.1	270	8	

Abbreviations: XFS/XFG, exfoliation syndrome/glaucoma; BMI, body mass index; AMD, age-related macular degeneration. *p* for chi-square test of association (categorical) or *t*-test (continuous), XFS/XFG patients vs. controls.

As shown in Table 2, a univariate model without covariate adjustment suggested only a slight non-statistically significant increased risk of wet AMD vs. no AMD in XFS/XFG patients compared to controls (OR 1.14 (0.99–1.32, $p = 0.07$)). In the multivariate model, we did not detect greater dry or wet AMD in XFS/XFG patients compared to controls (Table 2). In the multivariate model, covariates independently associated with XFS/XFG with odds ratios of 2.0 or higher (an estimated doubling of risk in XFS/XFG) compared to controls included the following: having a first-degree family history of XFS/XFG in one or more relatives vs. no family history, residing outside of Utah at the time of diagnosis vs. in Utah, a history of ocular hypertension vs. no history, and a history of having cataract surgery vs. none (Table 2). Compared with controls, XFS/XFG patients had a 25% decreased risk of obesity and a 29% decreased risk of an osteoporosis or vitamin D deficiency diagnosis (Table 2).

Based on XFS/XFG patient and control subject characteristics, shown in Table 1 stratified by the absence or presence of AMD, we identified a history of osteoporosis or vitamin D deficiency and a history of cataract surgery as two factors potentially interacting with AMD and XFS/XFG status (p-interaction < 0.01) (see Supplemental Table S1, available online). Table 3a and 3b show the risk of AMD in XFS/XFG in the presence of osteoporosis/vitamin D deficiency and a history of cataract surgery, respectively, with adjustment for other covariates. When stratifying by osteoporosis/vitamin D deficiency status (Table 3a), XFS/XFG patients who had no osteoporosis and were not vitamin D deficient had a decreased risk of both dry and wet AMD, while patients with osteoporosis and/or vitamin D deficiency exhibited a 1.2-fold increased risk of wet AMD (p int < 0.001). When stratifying by cataract surgery status (Table 3b), XFS/XFG patients who had no history of cataract surgery exhibited a 1.3-fold non-statistically significant increased risk of wet AMD ($p = 0.09$), while we did not observe a difference in AMD risk in patients who underwent cataract surgery compared to controls (Table 3b).

Table 2. Risk of age-related macular degeneration in exfoliation syndrome/glaucoma patients vs. controls.

	OR (95% CI)	*p*
Univariate model		
Age-related macular degeneration (AMD)		
No history of AMD	1.00 (ref)	
History of unspecified, dry or drusen AMD only	1.02 (0.92, 1.13)	0.68
History of wet AMD requiring injection(s)	1.14 (0.99, 1.32)	0.07
Multivariate model		
Age-related macular degeneration (AMD)		
No history of AMD	1.00 (ref)	
History of unspecified, dry or drusen AMD only	0.94 (0.85, 1.05)	0.31
History of wet AMD requiring injection(s)	0.98 (0.83, 1.14)	0.76
Race/Ethnicity		
White, non-Hispanic	1.00 (ref)	
White, Hispanic	1.40 (1.15, 1.69)	<0.001
non-White, any ethnicity	1.29 (1.04, 1.60)	0.02
Marital/partnership status		
Living alone (single, divorced, widowed)	1.00 (ref)	
Living with a partner	0.74 (0.68, 0.80)	<0.001
Family history of XFS/XFG		
No first-degree relative history	1.00 (ref)	
Any first-degree relative	2.03 (1.64, 2.52)	<0.001
Utah resident		
Resides in Utah	1.00 (ref)	
Resides outside of Utah	8.51 (7.20, 10.06)	<0.001
Obesity history (BMI $\geq$ 30)		
Not obese	1.00 (ref)	
Obese	0.75 (0.68, 0.83)	<0.001
Tobacco use disorder history		
No	1.00 (ref)	
Yes	1.13 (1.03, 1.25)	0.01
Alcohol use disorder history		
No	1.00 (ref)	
Yes	1.37 (1.14, 1.65)	<0.001
Osteoporosis and/or vitamin D deficiency		
No	1.00 (ref)	
Yes	0.79 (0.72, 0.85)	<0.001
Essential/primary hypertension history		
No	1.00 (ref)	
Yes	0.88 (0.79, 0.98)	0.02
Ocular hypertension history		
No	1.00 (ref)	
Yes	3.32 (2.89, 3.82)	<0.001
Cataract surgery history		
No	1.00 (ref)	
Yes	2.39 (2.18, 2.62)	<0.001
Charlson comorbidity index (CCI)		
None (CCI = 0)	1.00 (ref)	
Mild (CCI 1–2)	1.26 (1.14, 1.40)	<0.001
Moderate (CCI 3–4)	1.23 (1.03, 1.46)	0.02
Severe (CCI $\geq$ 5)	1.23 (1.02, 1.48)	0.03

Abbreviations: OR, odds ratio; CI, confidence interval; XFS/XFG exfoliation syndrome/glaucoma; AMD age-related macular degeneration. *p* for Wald chi-square test.

Table 3. (a) Risk of age-related macular degeneration in exfoliation syndrome/glaucoma vs. control patients by osteoporosis/vitamin D deficiency [1]. (b) Risk of age-related macular degeneration in exfoliation syndrome/glaucoma vs. control patients by history of cataract surgery [1].

	(a)				
	No Osteoporosis or Vitamin D Deficiency		**Osteoporosis or Vitamin D Deficiency**		
	OR (95% CI)	***p***	**OR (95% CI)**	***p***	***p* int**
AMD					
No history of AMD	1.00 (ref)		1.00 (ref)		<0.001
History of unspecified, dry, or drusen AMD only	0.78 (0.66, 0.92)	0.004	1.11 (0.96, 1.29)	0.14	
History of wet AMD requiring injection(s)	0.72 (0.56, 0.92)	0.01	1.23 (1.00, 1.51)	0.05	
	(b)				
	No History of Cataract Surgery		**History of Cataract Surgery**		
	OR (95% CI)	***p***	**OR (95% CI)**	***p***	***p* int**
AMD					
No history of AMD	1.00 (ref)		1.00 (ref)		0.004
History of unspecified, dry, or drusen AMD only	1.02 (0.81, 1.27)	0.88	0.91 (0.80, 1.03)	0.14	
History of wet AMD requiring injection(s)	1.33 (0.96, 1.85)	0.09	0.89 (0.75, 1.07)	0.12	

Abbreviations: OR, odds ratio; CI, confidence interval; int, interaction; XFS/XFG, exfoliation syndrome/glaucoma; AMD, age-related macular degeneration. [1] Interaction models: all odds ratios and *p*-values were adjusted for main effects of AMD, osteoporosis or vitamin D deficiency, history of cataract surgery, Utah residency, race/ethnicity, marital/partnership status, family history of XFS, history of obesity, history of tobacco use, history of alcohol use, hypertension, ocular hypertension, and Charlson comorbidity index (CCI).

4. Discussion

XFS/XFG and wet AMD are debilitating, age-related, heterogenous, and multifactorial diseases that may be related through associations not yet well-described [33]. Zengin et al. [44]. found a slower progression from dry to wet AMD in XFS patients compared to controls. It is not understood how XFS/XFG could be associated with AMD; thus, the goal of this study was to elucidate the association and potential contributing factors by utilizing a large cohort. A proposed shared pathogenesis is of disrupted ECM metabolism and thus a disrupted integrity of basement membranes (i.e., Bruch's membrane) by reactive oxidative stress, DNA methylation, inflammation, and trauma, linking these conditions. Vitamin D was included, using osteoporosis as a surrogate for low vitamin D levels, given a possible association with wet AMD, and XFS/XFG given the positive [45,46] as well as negative [47] associations reported in the literature. However, no direct association was found between XFS and AMD in this study.

Although we did not observe a statistically significant association between an individual's risk of developing XFS and their history of wet or dry AMD with or without cataract surgery, we found in this dataset that the relationship between AMD and XFS differed depending on whether patients had a history of cataract surgery. Individuals without cataract surgery had a positive association with AMD and XFS (OR > 1), while we observed a negative association for individuals with a history of cataract surgery (OR < 1). We did not find a significant association in the stratified models, possibly due to their low power, but when combined, there was a significant difference (OR 2.39, 2.18–2.62, $p < 0.001$). To our knowledge, the association between patients with XFS/XFG and AMD in the setting of cataract surgery has not been assessed in the extant literature, thus making this a novel observation.

It is well-documented and accepted that surgery, a traumatic event, creates oxidative stress or ROS from oxygen metabolism and inflammation [48]. This occurs with cataract surgery as well [49]. Within the crystalline lens, the mitochondria and reduced glutathione

function as antioxidants, thus with cataract removal, during the surgery and with exposure to oxygen, more oxidative species will be present in the eye [50,51]. Oxidative stress can create and increase the likelihood of glaucoma [52], and it can promote the accumulation of advanced glycation end products in glaucomatous tissue [53]. Overall cataract incidence is increased in XFS [54,55], and earlier and more advanced cataract formation is observed [56]. In 2008, Shingleton [57] found that 137 patients with unilateral XFS required more IOP-lowering medications overall and at 3 to 5 years compared to controls, suggesting that these surgical eyes were more prone to developing glaucoma following cataract surgery. This could be due to the inherent increase in post-operative inflammation and trauma with XFS eyes. It is known that eyes with XFS/XFG have a high likelihood of post-surgical inflammation and aqueous barrier breakdown [58]. It has also been recognized that increasing amounts of ROS, due to trauma, inflammation, and or surgery intraocularly, are associated with DNA damage affecting the trabecular meshwork, concordant visual field defects, and increased IOP associated with the development and progression of glaucoma [59–62].

Likewise, ROS play a role in AMD pathology. Some studies have demonstrated no changes in intensity of anti-VEGF treatment or macular architecture following cataract surgery [63], but these studies have lacked large cohorts, totaling only 300+ patients between them [64–66]. Other studies have shown that treatment with antioxidants (zinc and other vitamins) benefits patients with dry AMD. The Age-Related Eye Disease Study (AREDS) showed decreased vision loss and progression in patients with dry AMD and recommended this treatment for patients with mild to severe dry AMD when present in one eye [67].

Factors other than surgical trauma may have played a role in both the development of XFS/XFG and AMD in our cohort, for instance, those influencing the epigenetics. Hanyuda [68] found in 705 XFG/XFG suspects out of 195,408 participants that greater total alcohol consumption (>15 g/day vs. nondrinkers) was associated with XFS/XFG risk. Our findings are in concordance with this, as there was increased XFS/XFG incidence with a history of alcohol use disorder—controls 4.4% vs. 5.7% for XFS/XFG cases (p 0.001). The underlying connection with alcohol is unclear, but hypotheses include increased ROS [69], an altered ECM from dysregulated retinoic acid function, and decreased folate levels from alcohol metabolism potentially disrupting *LOXL1* gene expression [70–72]. Kang et al. [19] also showed that a higher total folate intake was associated with a suggested lower risk of XFS/XFG. Moreover, an alcohol study showed decreased folate bioavailability [73]. Concerning elevated ROS, Arnarsson et al. [38]. found that individuals consuming foods rich in antioxidants more frequently are less likely to develop XFS. A meta-analysis suggested that increased alcohol consumption led to early AMD [74], and a large population study supported a possible causal association between increased alcohol consumption and the risk of geographic atrophy [75]. Also, folate deficiency was associated with increased incident risk of AMD and XFS [76].

Studies have hypothesized that an increased ocular exposure to UV light and an increasing altitude and latitude could be risk factors for XFS/XFG [21,77]. UV light has also been proposed as a risk factor for AMD, although studies have shown that this is not necessarily the case [78]. We found no significant association of either condition with osteoporosis when using vitamin D levels as a proxy marker for UV exposure. We found a decreased wet/dry AMD risk in XFS/XFG patients with no osteoporosis or vitamin D deficiency. This was potentially due to using vitamin D levels as a proxy marker, which could have masked an association that was present.

One study conducted in Greece in 1999 found a significant correlation between XFS and AMD (p = 0.002) [33]. Kozobolis also showed significant direct correlations of XFS and AMD with age and altitude. This study's sample size consisted of 777 patients from the Cretan (Greek) population, which could explain the difference in outcomes compared to other studies, as this sample size was smaller and taken from an isolated population on an island off Greece's mainland. Furthermore, confounding variables in the Greek study

were not taken into consideration, which may also account for the differences in outcomes between studies.

5. Strengths

Strengths of this study are the large population size, the benefit of having knowledge of familial relationships through the unique Utah population database, and the review of the charts for accurate CPT codes and diagnoses. Some might feel research is not productive if an association is not noted, yet it is equally impactful to provide data not supportive of an association. For example, Table 2 shows that XFS/XFG patients with a history of cataract surgery have an increased OR for the risk of AMD (wet and dry), yet Table 3 shows that XFS/XFG patients without cataract surgery do not have an increased risk of dry or wet AMD (not significant). Hence, the hypothesis of increased ROS from surgery (supported by previous studies) fits with Table 2, but is not supported by Table 3 when looking at the breakdown of dry vs. wet AMD.

6. Limitations

Data collection was reliant upon CPT and ICD9/10 codes, which are problematic because these are administrative codes used for billing and may not correctly reflect what is observed clinically. Additionally, we did not collect serum levels of vitamin D, instead using osteoporosis as a surrogate for vitamin D levels. Other systemic factors could have contributed to an osteoporosis diagnosis besides vitamin D levels, which we were unable to identify. It is also important to note that the study population was predominantly non-Hispanic white, mostly with ancestry from northern Europe (UPDB website), and may not be generalizable to other, more diverse populations. As previously mentioned, many patients in the XFS/XFG cohort resided outside of Utah and thus may only have attended one or two visits annually with their Utah ophthalmologist, which may have limited the amount of information gathered on these individuals. Finally, in patients who have advanced to severe wet AMD disease, cataract surgery may be deferred due to limited visual acuity improvement; these patients were likely included in the XFS/XFG and control groups, and underlying variability in this regard between the groups may have existed, which we were unable to assess.

7. Conclusions

Exfoliation syndrome is a complex, multifactorial, age-related systemic disorder with underlying genetic and environmental influences, found to be associated with various clinical comorbidities. Our findings based on data from the Utah Population Database suggest that an association with cataract surgery links AMD and XFS/XFG, perhaps from a shared pathogenesis of oxidative stress, inciting trauma and or DNA methylation. We did not assess the degree to which the rate of progression from dry to wet AMD or from XFS to XFG was impacted by ocular and surgical risk factors, and further studies in other large populations are recommended to delineate this impact.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcto2040012/s1, Table S1: Characteristics of exfoliation syndrome/exfoliation glaucoma patients and controls stratified by age-related macular degeneration history.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of University of Utah (IRB_00081512; 17 July 2015).

Informed Consent Statement: HUMAN SUBJECTS: Human subjects were included in this study. Study approvals were obtained from the Institutional Review Board (IRB) of the University of Utah (IRB_00081512) and from the Resource for Genetic and Epidemiologic Research, which governs research use of UPDB data. This study complies with the Declaration of Helsinki and was performed according to IRB approval. The need to obtain informed patient consent was not required for this noncontact, retrospective data study was waived by the IRB. No animal subjects were included in this study.

Data Availability Statement: Data are available in a public, open access repository. Data are available upon reasonable request.

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Conflicts of Interest: G.S.H. is a shareholder, consultant and co-founder of—and receives research support from—Perceive Biotherapeutics Inc. G.S.H. is an inventor on patents and patent applications owned by the University of Utah and University of Iowa.

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