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Association between Diabetes and Exfoliation Syndrome

A Systematic Review and Meta-Analysis of Observational Studies

Megan Yu, BS,[1,2] Hannah H. Hwang, BS,[3] Janey L. Wiggs, MD, PhD,[4] Louis R. Pasquale, MD,[5] Jae H. Kang, ScD[1]

Topic: This systematic review and meta-analysis summarizes the existing evidence for the association of diabetes mellitus (DM) and exfoliation syndrome (XFS).

Clinical Relevance: Understanding and quantifying these associations may aid clinical guidelines or treatment strategies and shed light on disease pathogenesis. The role of DM in determining XFS risk may also be of interest from an individual or public health perspective.

Methods: The study protocol was preregistered on the International Prospective Register of Systematic Reviews with registration number CRD42023429771. We systematically searched PubMed and Embase from inception to June 15, 2023. Screening and full-text review were conducted by 2 independent reviewers. All observational studies reporting an age-adjusted odds ratio (OR) and 95% confidence interval (CI) for the association between DM and XFS among adults were included. Quantitative synthesis involved a random-effects meta-analysis using the DerSimonian-Laird method to generate a pooled OR. Risk of bias was evaluated using the Newcastle-Ottawa Scale.

Results: Fourteen studies (9 cross-sectional and 5 case-control) comprising 47 853 participants were included in the systematic review and meta-analysis. Random-effects meta-analysis indicated no overall association between DM and XFS (OR 0.94; 95% CI, 0.73−1.21; $I^2 = 68.5\%$). However, subgroup analysis revealed a significant inverse association among individuals $\geq$ 65 years (OR 0.71; 95% CI, 0.54−0.93) versus individuals $<$ 65 years (OR 1.22; 95% CI, 0.80−1.87; $P_{effect\ modification} = 0.04$). The relation between DM and XFS was also inverse in case-control studies (OR 0.75; 95% CI, 0.58−0.97) but was nonsignificant in cross-sectional studies (OR 1.17; 95% CI, 0.83−1.66; $P_{effect\ modification} = 0.04$). Overall risk of bias was low, with tests for publication bias showing $P \geq 0.06$.

Conclusion: This meta-analysis suggests no association between DM and XFS overall, with possible inverse associations of DM with XFS in older populations. However, given the substantial heterogeneity and borderline significance for publication bias, these findings should be interpreted with caution. Our results give insight into the unique etiology and clinical relevance of XFS while proposing the need for larger longitudinal and genetic biomarker studies.

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Exfoliation syndrome (XFS) is a systemic, age-related disorder characterized by the deposition of fibrillin material in the anterior chamber and other parts of the body.[1] Clinically, XFS is important as an established risk factor for secondary open-angle glaucoma, specifically exfoliation glaucoma (XFG), characterized by higher intraocular pressure (IOP) and faster progression relative to the more common primary open-angle glaucoma (POAG).[2–5] It is also associated with instability of the lens zonules during cataract surgery, increasing the risk of intraoperative and postoperative complications.[6,7] The prevalence of XFS varies from 0.2% to 30% depending on the study population examined and the detection method applied.[8–17] The etiology of XFS is poorly understood, although it likely involves an interaction between environmental and genetic factors, with older age and family history of glaucoma associated with the development of XFS.[8,10] Exfoliation syndrome is strongly associated with certain single nucleotide polymorphisms of the lysyl oxidase-like 1 gene involved in elastic fiber formation.[9]

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Prior studies have attempted to link XFS and systemic vascular diseases.[18,19] One major cardiovascular risk factor is diabetes mellitus (DM). Diabetes mellitus is a common disease worldwide, with prevalence and incidence increasing in most populations.[20] However, the relationship between DM and XFS is controversial, as prior studies have demonstrated conflicting results with proposed mechanisms for both positive and inverse associations.[21,22] Suggested biological mechanisms that link the 2 conditions may involve underlying vascular changes, oxidative stress, or IOP fluctuations. Altered systemic vasoregulation and decreased peripheral blood flow seen in DM is also a feature of XFS.[23,24] Reduced ocular blood flow and trabecular outflow in DM may disrupt exfoliation material clearance mechanisms, potentially contributing to XFS. The increased oxidative stress and reactive oxygen species observed in DM have also been hypothesized to play a role in XFS pathogenesis, as inadequate antioxidant enzyme response has been reported in XFS patients.[18,25] High IOP fluctuation may also link DM and XFS; high IOP fluctuation is associated with neuroinflammation and neurodegeneration and is observed in both DM and XFS.[26,27] In contrast, a proposed hypothesis for the lower frequency of XFS with DM is the increased amount of advanced glycation end products observed in DM due to hyperglycemia, resulting in the abnormal glycation of basement membrane components that may reduce the deposition of exfoliation material.[28,29]

If there is strong support for an inverse relationship between DM and XFS, it will provide insights into the abnormal accumulation of elastin fibers, extracellular matrix, and proteoglycans in XFS. If there is a potential adverse association between DM and XFS, there are available lifestyle modifications and treatments that can assist in the prevention and management of DM to potentially influence the subsequent risk of XFS. To our knowledge, there are no meta-analyses or systematic reviews evaluating the relationship between DM and the risk of XFS. Given the inconclusive relationship between DM and XFS, as well as the increasing prevalence and incidence of DM,[30] which may be a risk factor for the development and progression of XFS, our objective thus was to conduct a comprehensive systematic review and meta-analysis of observational studies to summarize the association between DM and risk of XFS in the adult population.

Methods

The present study evaluates the association between DM and XFS in adults through a systematic review and meta-analysis of observational studies. This work was conducted following the Declaration of Helsinki, Meta-analysis of Observational Studies in Epidemiology, and Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines for reporting (Appendix A and Appendix B, available at https://www.ophthalmologyscience.org/).[31,32] An *a priori* protocol for the review was preregistered and can be accessed on the International Prospective Register of Systematic Reviews with registration number CRD42023429771.[33] Because the study did not directly involve human subjects, it was exempt from Institutional Review Board approval. Informed consent was not obtained nor required because no individual-level patient information was used in this meta-analysis of published studies.

Eligibility Criteria for Considering Studies for This Review

The population of interest was adults $\geq$ 18 years of age. Diabetes mellitus was measured by self-report, confirmed diagnosis, fasting blood glucose test of $\geq$ 126 mg/dL, hemoglobin A1C test of $\geq$ 6.5%, or glucose tolerance test of $\geq$ 200 mg/dL. The primary outcome was any type of XFS, namely "pseudoexfoliation," XFS alone, and/or XFG; studies defined XFS by self-report, confirmed diagnosis, masked assessment, or record linkage. Given that many studies do not differentiate between pseudoexfoliation, XFS, or XFG, this expanded definition was appropriate to capture all types of XFS cases. No specific control group or comparator was considered. As our preliminary search found no randomized controlled trials, we considered studies of all observational study designs (cohort, case-control, cross-sectional, etc.) reporting adjusted odds ratios (ORs; with adjustment for age at a minimum) and 95% confidence intervals (CIs). We rationalized that these criteria would ensure that the studies included in the review were of high quality.

Search Methods for Identifying Studies

One author (M.Y.) conducted the systematic search on PubMed and Embase to identify studies published from inception to June 15, 2023 on DM and XFS. The search strategy used controlled vocabulary terms (MeSH and Emtree) and field tags to narrow the search (Appendix C, available at https://www.ophthalmologyscience.org/). Hand searching (M.Y.) and citation searching on reference lists of included studies (H.H.) were also performed to identify additional studies.

Study Selection

The search strategy was used to retrieve titles and abstracts for initial screening. Two authors (M.Y. and H.H.) independently screened records for inclusion based on relevance to DM and/or XFS and were blinded to each other's decisions. After title/abstract screening, selected articles proceeded to full text review to assess eligibility. Inclusion criteria for the systematic review and meta-analysis included the following: (1) study population $\geq$ 18 years of age, (2) measured DM as an exposure, (3) measured pseudoexfoliation, XFS, and/or XFG as an outcome, and (4) reported an age-adjusted OR and 95% CI. We excluded studies if they (1) were unpublished studies, nonresearch articles, conference abstracts, animal studies, reviews, meta-analyses, editorials, letters, case reports, or case series, (2) had no accessible full text, (3) were published in a non-English language, (4) included an adolescent population ($<$ 18 years), (5) did not measure DM or XFS, (6) focused on POAG, or (7) did not specify the type of glaucoma. Articles were judged by the same 2 reviewers (M.Y. and H.H.) for inclusion and whether they contained information on the association between DM and XFS. Any disagreements were resolved through discussion if necessary. Covidence was used for all steps in the screening and study selection process, including managing identified records and eligibility status.[34]

Data Collection and Risk of Bias Assessment

Data were extracted and recorded on a standardized data collection sheet shared among coauthors. We first piloted the data extraction form for a single study and ran through the data extraction as a group to identify variables that needed to be added or were unnecessary. After deciding on a final standardized template, 1 reviewer independently extracted the data from the articles, and a

Table 1. Key Characteristics of the 14 Included Studies in a Meta-Analysis of the Association of Diabetes and Exfoliation Syndrome

Author	Publication Year	Study Location	Study Design	Study Population	Mean Age, years (SD if Reported)	Exposure (DM) Assessment	Outcome (XFS) Assessment
Arnarsson et al	2010	Iceland	CS	Random sample of citizens in the Icelandic national population census aged ≥ 50 years enrolled in the Reykjavik Eye Study	XFS: 72.3 (8.9) Control: 62.6 (8.7)	Questionnaire	XFS on dilated SLE
Atum et al	2022	Turkey	CS	Patients of Sakarya University Training and Research Hospital, Ophthalmology, and Cardiology Clinics between Jan and Dec 2019	XFS: 68.6 (8.4) Control: 67.3 (7.4)	Not reported	XFS on dilated SLE
Fujiwara et al	2022	Japan	CS	Japanese community dwellers ≥ 40 years and enrolled in the Hisayama Study from 2017 to 2018	64.6 (13.9)	Glucose tolerance test or antidiabetic medication	XFS/XFG on dilated SLE
Hashemi et al	2016	Iran	CS	Iranians aged 45–69 years enrolled in Shahroud Eye Cohort Study 2014	55.7 (6.2)	Blood test or antidiabetic medication	XFS on SLE
Kılıç et al	2014	Turkey	CC	Indigenous Central Anatolian patients > 45 years who visited Sivas Province Numune Hospital Ophthalmology Clinic between May 2013 and Oct 2013	XFS: 71.8 (9.2) Control: 58.7 (9.6)	Standard query	XFS on dilated SLE
Mansour et al	2021	Lebanon	CS	Patients in data registry of a single center/single surgeon between Jan 2010 and Apr 2020 after having undergone bilateral cataract extraction	XFS: 78.4 (9.0) Control: 71.0 (10.3)	Data registry	XFS on dilated SLE
Miyazaki et al	2005	Japan	CS	Residents of Hisayama aged ≥ 50 years in 1998 (as part of the Hisayama Study) who underwent eye examination	XFS: 71.0 (7.0) Control: 65.0 (9.0)	Blood test or medical history	XFS on dilated SLE
Pasquale et al	2014	United States and Israel	CC	Patients ≥ 60 years in the US (Mass Eye and Ear) and Israel (Goldschleger Eye Institute) from Nov 2, 2010 to Dec 20, 2012	US XFS: 75.2 (7.6) US Control: 69.7 (7.3) Israel XFS: 74.4 (7.0) Israel Control: 71.6 (7.0)	Medical record review	XFS/XFG on dilated SLE
Spečkauskas et al	2012	Lithuania	CC	Patients aged 45–72 years randomly drawn from population register of Kaunas as part of Health, Alcohol, and Psychosocial Factors in Eastern Europe Study	Not reported	Standard query or blood test	XFS on dilated SLE
Tarkkanen et al	2008	Finland	CS	Population-based registry survey of consecutive patients whom the Social Insurance Institution of Finland had granted free medication for glaucoma (POAG or XFG) according to national criteria between Jun 2004-Dec 2005	XFS: 73.0 Control: 69.0	Population registry or repeated blood test	XFS/XFG on SLE
Vardhan et al	2017	India	CS	South Indian patients > 40 years enrolled in Aravind Pseudoexfoliation Study who required cataract surgery at 1 of 4 Aravind Eye Hospitals in Tamil Nadu from Dec 2, 2010 to Mar 26, 2012	XFS: 64.8 (6.8) Control: 59.9 (7.3)	Blood test or antidiabetic medication	XFS on dilated SLE

(*Continued*)

Table 1. (Continued.)

Author	Publication Year	Study Location	Study Design	Study Population	Mean Age, years (SD if Reported)	Exposure (DM) Assessment	Outcome (XFS) Assessment
Viso et al	2010	Spain	CS	Age-stratified random sample of subjects ≥ 40 years drawn from National Health Registry in O Salnés as part of the Salnés Eye Study from May 2005 to Mar 2006	63.4 (14.5)	Interview with questionnaire and medical history	XFS on dilated SLE
Wood et al	2011	United States	CC	Outpatients seen in VA Boston Healthcare System eye clinics between Jan 2003 and Dec 2007	XFS: 79.7 (7.5) Control: 79.8 (7.5)	ICD codes, antidiabetic medication, or PCP clinical notes	XFS on dilated SLE or XFS/XFG ICD code
Zehavi-Dorin et al	2021	Israel	CC	Maccabi Health Services members between Jan 2003 and Apr 2016	XFS: 78.3 (8.94) Control: 76.2 (8.54)	ICD codes	XFS ICD or CPT code from ≥ 2 exams

CC = case-control; CPT = Current Procedural Terminology; CS = cross-sectional; DM = diabetes mellitus; ICD = International Classification of Diseases; PCP = primary care physician; POAG = primary open-angle glaucoma; SD = standard deviation; SLE = slit lamp examination; US = United States; VA = Veterans Affairs; XFG = exfoliation glaucoma; XFS = exfoliation syndrome.

second reviewed the data to validate the extraction. Disagreements were resolved through discussion. If there was unreported data that was crucial to the analysis, we contacted authors for additional details, such as the adjusted covariates and CIs.

The following items were extracted from each study: identification number assigned by Covidence, title, authors, digital object identifier, publication year, study origin (country), largest ethnic group (ethnicity), study design, study population description, exclusion criteria, assessment and definition of DM exposure, assessment and definition of XFS outcome, mean age, male:female ratio, mean or median body mass index (BMI), number with hypertension by XFS case status, total sample size, sample size by XFS case status, number of diabetics by XFS case status, adjusted OR from the most fully adjusted model, standard error, 95% CI, *P* value, adjusted covariates, and main findings.

The Newcastle-Ottawa Scale (NOS) for case-control studies and adapted NOS for cross-sectional studies from Herzog et al was used to assess risk of bias in 3 domains: selection, comparability, and exposure.[35–37] Individual quality assessment was conducted at the study level by evaluating the design, sample size, data collection methods, and statistical analyses in each study. Confounding factors were also evaluated, including age and sex. One independent investigator (H.H.) performed the assessment, followed by a second investigator (J.H.K.). Any discrepancies were resolved through discussion. Cross-sectional studies were evaluated as follows: very good, 9 to 10; good, 7 to 8; satisfactory, 5 to 6; unsatisfactory, 0 to 4. Case-control studies were evaluated as follows: very good, 8 to 9; good, 7; satisfactory, 5 to 6; unsatisfactory, 0 to 4. For all assessments, we rated the studies as very good, good, satisfactory, or unsatisfactory. A study with ≥ 7 stars was considered high-quality.[37–39] The results of the quality assessment were used in the context of interpreting our results and to further select studies for quantitative synthesis and grade the strength and internal validity of each study's findings. The lowest-rated studies (satisfactory and unsatisfactory) were excluded in a post hoc sensitivity analysis and the results were interpreted with caution.

Data Synthesis and Analysis

The primary summary measure was a pooled OR comparing the odds of XFS among individuals with and without DM. Because XFS is relatively uncommon, the OR can be interpreted as a risk ratio.[40] Descriptive statistics were calculated based on the characteristics of each study (Table 1). Odds ratios from individual studies were combined in an inverse-variance weighted, random-effects meta-analysis model using the DerSimonian-Laird method to generate a pooled summary measure for the association between DM and XFS.[41] A prediction interval was calculated to determine the range of predicted effects in an individual new study. To evaluate heterogeneity, an I^2 statistic and 95% CI were calculated to determine the percentage of total variability that was due to heterogeneity between studies.[42] We used thresholds suggested by the Cochrane Collaboration: 0% to 40% (might not be important), 30% to 60% (may represent moderate heterogeneity), 50% to 90% (may represent substantial heterogeneity), and 75% to 100% (considerable heterogeneity).[43] Cochran Q test was conducted to determine the significance of the heterogeneity. Statistical analyses were performed in Stata version 17.0 (StataCorp LLC) using the meta program,[44] and 2-tailed comparisons were made with a statistically significant threshold of $P < 0.05$ for all analyses.

To explore potential sources of heterogeneity, meta-regression and subgroup analyses were conducted. Potential effect modification was assessed using DerSimonian-Laird estimation in meta-regression analysis to determine whether the pooled OR varied by continuous covariates including age, sex (male:female ratio), and average latitude. For age, we used the mean age in the study population or calculated a weighted average using the sample size in each group if the provided age was stratified across groups. For latitude, we took the average latitude of the study country.[45] This allowed us to determine whether the magnitude of effect was a function of these covariates and whether the variables were important predictors or effect modifiers of the association between DM and XFS.

We categorized studies based on their study population characteristics to conduct subgroup analyses by mean age (< 65 vs. ≥ 65 years), study design (cross-sectional vs. case-control), study region (Europe, Asia, Middle East, North America), ethnicity (European, Central and South Asian, East Asian, Western Asian and North African), mean or median BMI (< 25 vs. ≥ 25 kg/m^2), and proportion of hypertensive individuals in the study population (< 50% vs. ≥ 50%). We expected some differences as females

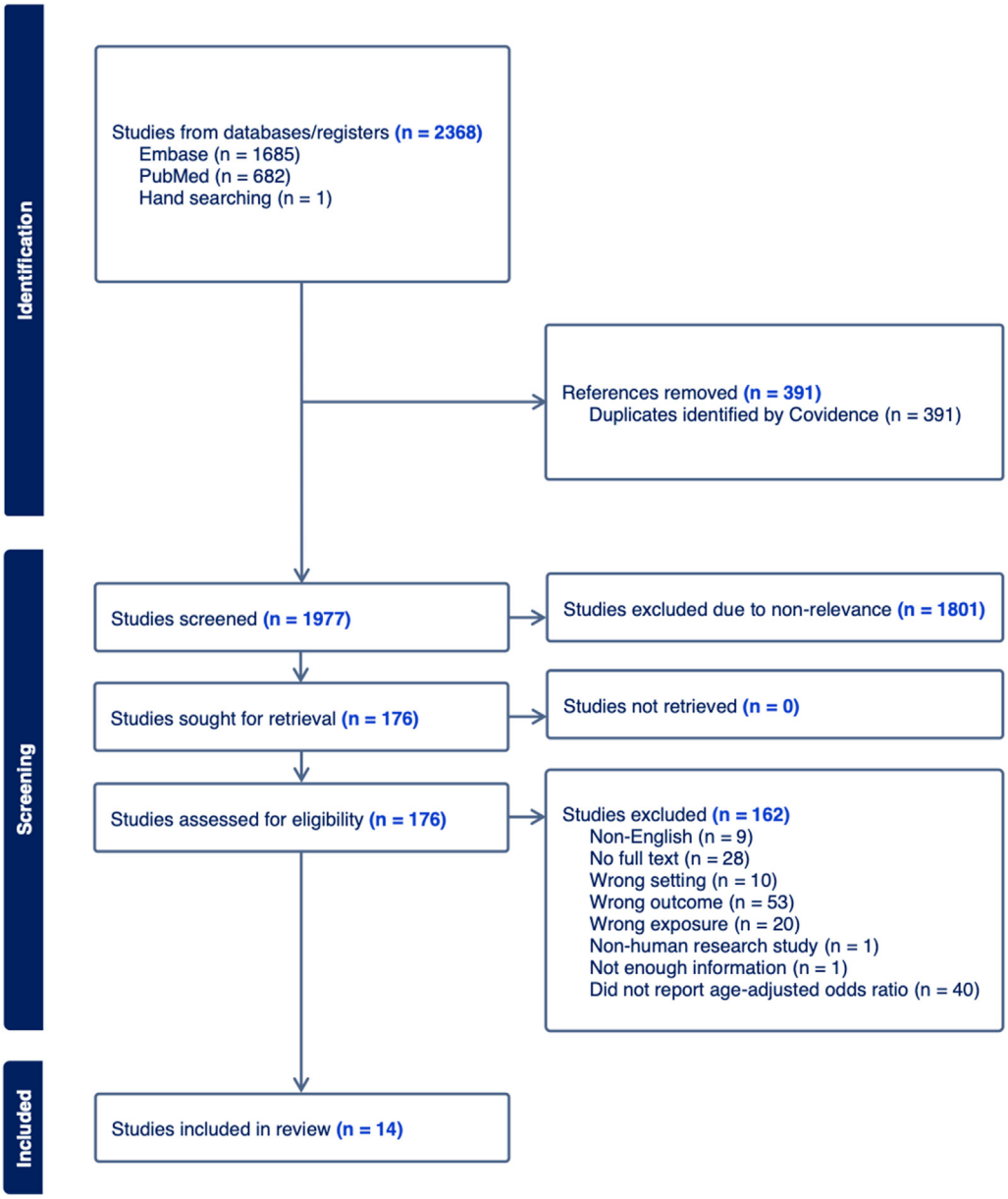

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart summarizing the screening and study selection process.

tend to have a higher prevalence of visual impairment compared to males, and age is positively associated with glaucoma and BMI is a risk factor for DM.[46–48] Studies have shown that latitude and hypertension may be risk factors for XFS.[49,50] We tested for effect modification using Cochran Q test of group differences and evaluated the statistical significance of the *P* value.[51,52] We did not adjust for multiple testing for the various subgroup analyses as these analyses were hypothesis-generating; therefore, subgroup analyses should be interpreted with caution.

Additional prespecified analyses were also performed. As part of a sensitivity analysis, we conducted a leave-one-out meta-analysis using a DerSimonian-Laird random-effects model by seeing how the pooled estimate changed when a specific study was omitted. We also conducted other sensitivity analyses to assess the robustness of our findings, such as omitting studies of lower quality and studies with small sample sizes. Cumulative meta-analysis was conducted to determine whether there were time trends and to see when any significant effects first became significantly apparent (if time-cumulative) or when the pooled estimate became more stabilized.

To assess publication bias, we plotted a funnel plot using inverse-variance weights and inspected for asymmetry across the pooled OR. The traditional Egger test[53] and Begg test[54] for small-study effects were performed to statistically assess evidence for publication bias. Selective reporting was evaluated by examining outliers on the funnel plot and further assessing the study design and completeness of outcome data within studies. Finally, a post hoc nonparametric trim-and-fill analysis of publication bias was

Table 3. Individual Findings of Included Studies in the Meta-Analysis of the Association between Diabetes and Exfoliation Syndrome

Author	Control Group	Total Number of Participants (Sample Size per Group)	OR	95% CI	*P* Value	Adjustment (Covariates or Matched Variables)
Arnarsson et al	No XFS	1045 (108 XFS, 937 non-cases)	1.95	0.82–4.63	> 0.05	Age, gender, smoking
Atum et al	No XFS. Patients admitted to ophthalmology clinic for mild cataract or presbyopia; same clinic and matched for age and sex	161 (55 XFS, 106 non-cases)	1.62	0.24–10.84	0.62	Age[†], sex[†], CAVI, ankle-brachial index, IOP, BMI, HTN, dyslipidemia, smoking, CAD
Fujiwara et al	No XFS	3405 (36 XFS, 3369 non-cases)*	1.93	0.92–4.05	0.08	Age, sex
Hashemi et al	No XFS	4554 (21 XFS, 4533 non-cases)	0.89	0.35–2.31	0.82	Age, sex, smoking, dyslipidemia, HTN
Kılıç et al	No XFS	2103 (212 XFS, 1891 control)	0.71	0.47–1.05	0.09	Age
Mansour et al	No XFS on dilated exams before cataract surgery	110 (49 XFS, 61 non-cases)	0.90	0.43–1.98	0.4	Age, gender, HTN, CAD
Miyazaki et al	No XFS	1464 (50 XFS, 1414 non-cases)	0.57	0.20–1.62	> 0.05	Age
Pasquale et al	No XFS (if pseudophakic, no XFS on ≥ 1 dilated exam before cataract surgery); could have forms of glaucoma other than XFG	363 (118 US XFS, 67 Israel XFS, 106 US control, 72 Israel control)	US: 0.22 Israel: 1.87	US: 0.08–0.59 Israel: 0.72–4.86	US: 0.003 Israel: 0.20	Age, sex, iris color, HTN, family history of glaucoma, lifetime average number of hours spent outside per week, weighted lifetime average latitude of residence
Spečkauskas et al	No XFS	1065 (152 XFS, 913 control)	1.10	0.50–2.40	0.90	Age[‡], sex[‡]
Tarkkanen et al	POAG	499 (155 XFS, 344 non-cases)	0.42	0.18–0.99	0.047	Age, gender
Vardhan et al	No XFS on dilated exams before cataract surgery	1406 (930 XFS, 476 non-cases)	1.37	0.94–2.00	0.10	Age, sex
Viso et al	No XFS	619 (55 XFS, 564 non-cases)	1.98	0.91–4.32	0.08	Age, sex, rose bengal staining, glaucoma, cataract surgery
Wood et al	No XFS but allowed to have glaucoma; same clinic and matched for age	656 (328 XFS, 328 control)	0.81	0.57–1.14	> 0.05	Age[†], sex, BMI, race, glaucoma status

Table 3. (Continued.)

Author	Control Group	Total Number of Participants (Sample Size per Group)	OR	95% CI	P Value	Adjustment (Covariates or Matched Variables)
Zehavi-Dorin et al	No XFS on exams within 12 months and without prior cataract surgery; matched on age, sex, ancestry	30 403 (16 338 XFS, 14 015 control)	0.7	0.67−0.74	≤ 0.05	Age†, sex†, country of birth†

BMI = body mass index; CAD = coronary artery disease; CAVI = cardio-ankle vascular index; CI = confidence interval; HTN = hypertension; IOP = intraocular pressure; OR = odds ratio; POAG = primary open-angle glaucoma; US = United States; XFG = exfoliation glaucoma; XFS = exfoliation syndrome.
*Calculated from prevalence.
†Matching factor.
‡Used poststratification weights.

conducted using a linear estimator and DerSimonian-Laird random-effects model to impute studies.

Results

Study Selection

The search strategy was used to retrieve 2368 records (682 from PubMed, 1685 from Embase, and 1 from hand searching). After excluding 391 duplicates identified by Covidence, a total of 1977 titles and abstracts were screened for study relevance, with 1801 studies deemed irrelevant. We conducted a full-text review of the 176 remaining studies to assess eligibility, and 162 were excluded based on several reasons: non-English, no full text, wrong setting (i.e., clinical profile of a hospital), wrong outcome (i.e., focus on a different subtype such as POAG), wrong exposure (i.e., not looking at DM as an exposure), nonhuman research studies, not including enough information, or not reporting an age-adjusted OR (Fig 1). Overall inter-rater reliability was high for both title and abstract screening ($\kappa = 0.70$) and full-text review ($\kappa = 0.85$). A total of 14 studies were included in the meta-analysis and systematic review. Notably, 1 study yielded 2 separate effect estimates due to including 2 distinct populations, the United States and Israel, but is referred to as a single study.[55] Funding and conflict of interest statements of included studies can be found in Appendix D (available at https://www.ophthalmologyscience.org/).

Study Characteristics

Table 1 and Table S2 (available at https://www.ophthalmologyscience.org/) summarize the individual characteristics of the 14 observational studies[18,50,55–66] that met eligibility criteria. The studies were published between 2005 and 2022 and took place in various countries worldwide. Sample size ranged from 110 to 30 403 participants, resulting in a total sample size of 47 853 participants. In terms of study design, 9 were cross-sectional studies[18,50,56–62] and 5 were case-control studies[55,63–66]; there were no cohort studies. A majority of studies[18,50,55–64,66] had more females than males (male:female ratio < 1), which was expected due to the higher prevalence of glaucoma in older women.[46] Most used a comparator group consisting of those without XFS, with the exception of 1 study that compared XFS cases to those with POAG.[18] Seven studies[18,50,55,60,61,65,66] included study populations with weighted mean age of ≥ 65 years and 4 studies[50,64–66] included participants with mean or median BMI ≥ 25 kg/m^2. Diabetes mellitus was assessed through a variety of methods including questionnaires, registries, medical history, blood tests, and medical diagnosis codes. No study distinguished between type 1 versus type 2 DM. Given that type 2 DM is more common, it is highly likely that most cases of DM were type 2.[67] Exfoliation syndrome was primarily assessed by slit lamp examination or medical diagnosis codes such as the International Classification of Diseases.

Results of Individual Studies

Table 3 highlights each study's findings on the association between DM and XFS. Of the included studies, 3 of them[18,55,66] reported a statistically significant inverse association between DM and XFS, while 1 study[60] reported a marginally significant positive association, and the rest reported no association.[50,56–61,63–65] All studies controlled for age, which is an important risk factor for both DM and XFS. Eleven studies[18,50,55–60,62,65,66] additionally adjusted for sex or gender.

Synthesis of Results

Using a random-effects meta-analysis model, the pooled OR for the association between DM and XFS across the 14 studies was 0.94 (95% CI, 0.73−1.21; $P = 0.63$; Fig 2). One

study yielded 2 different effect estimates due to the inclusion of results that were significantly heterogeneous across the 2 populations from the United States and Israel.[55] The prediction interval estimating the range of the effect estimate for a new individual study was 0.43 to 2.07. There was substantial heterogeneity (I^2 = 68.5%; 95% CI, 46%−82%; $P < 0.001$).

Additional Analysis

We explored potential sources of heterogeneity through subgroup analyses based on mean age (< 65 vs. ≥ 65 years), study design (case-control vs. cross-sectional), study region (Europe, Asia, Middle East, North America), ethnicity (European, Central and South Asian, East Asian, Western Asian and North African), mean or median BMI (< 25 vs. ≥ 25 kg/m^2), and proportion of the population with hypertension (< 50% vs. ≥ 50%). Twelve studies reported the mean age of the overall population or stratified by XFS and control.[18,50,55,57–63,65,66] In studies with a mean age of ≥ 65 years, there was a significant inverse association between DM and XFS, with an OR of 0.71 (95% CI, 0.54−0.93; $P = 0.01$). On the other hand, for those < 65 years of age, the OR was 1.22 (95% CI, 0.80−1.87; $P = 0.35$). The test for subgroup differences suggested that there was statistically significant evidence of heterogeneity, suggesting that age modifies the association between DM and XFS ($P_{effect\ modification} = 0.04$; Fig 3). Subgroup analysis of all 14 studies by study design revealed that the estimate from case-control studies showed a statistically significant inverse association between DM and XFS (OR 0.75; 95% CI, 0.58−0.97; $P = 0.03$), while that from cross-sectional studies was nonsignificant (OR 1.17; 95% CI, 0.83−1.66; $P = 0.38$). There was a significant subgroup difference by study design as shown in Fig S4 ($P_{effect\ modification} = 0.04$; available at https://www.ophthalmologyscience.org/). In terms of study region, the estimate from the Middle East region showed a significant inverse association (OR 0.73; 95% CI, 0.63−0.84; $P < 0.001$), while that from all other regions were not significant ($P > 0.05$). The test for subgroup differences indicated that there was marginally significant evidence of effect modification; however, the analysis may not be able to detect these differences due to the uneven distribution of studies per region ($P_{effect\ modification} = 0.09$; Fig S5, available at https://www.ophthalmologyscience.org/). With regards to ethnicity, the results were similar to the subgroup analysis by study region with only the Western Asian and North African ethnic group showing a significant inverse association (OR 0.73; 95% CI, 0.63−0.84; $P < 0.001$). There was significant evidence of effect modification by ethnicity, likely due to the single Central and South Asian study[57] as shown in Fig S6 ($P_{effect\ modification} = 0.02$; available at https://www.ophthalmologyscience.org/). Six studies reported mean or median BMI.[50,58,61,64–66] Among the overweight or obese population (BMI ≥ 25 kg/m^2), there was a significant inverse association between DM and XFS (OR 0.70; 95% CI, 0.67−0.74; $P < 0.001$), while among populations of normal weight, DM showed no association with XFS ($P = 0.86$). There was insignificant evidence of heterogeneity by BMI ($P_{effect\ modification} = 0.45$; Fig S7, available at https://www.ophthalmologyscience.org/). Twelve studies[18,50,55,57–64,66] reported the proportion of people with hypertension, but there was no significant association in subgroups defined by a lower ($P = 0.98$) or higher

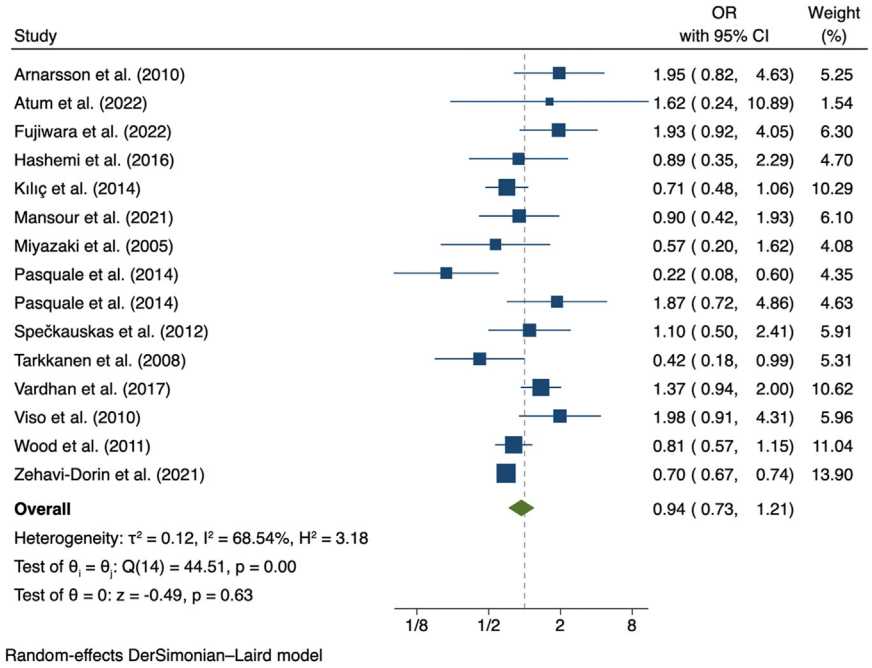

Figure 2. Forest plot from a random-effects meta-analysis of the association between diabetes and exfoliation syndrome. Confidence intervals (CIs) in this figure slightly differ from those presented in Table 3 due to rounding. OR = odds ratio.

Table 4. Sensitivity Analyses

Description (Number of Studies Included)	OR	95% CI
Exclude studies that allowed the control group to have other types of glaucoma such as POAG (i.e., exclude Pasquale, Tarkannen, Wood) (11)	1.07	(0.79−1.44)
Exclude studies of satisfactory or unsatisfactory quality with < 7 NOS score (i.e., exclude Atum, Kılıç, Pasquale) (11)	1.00	(0.75−1.34)
Include only studies that adjusted for at least age and sex/gender (i.e., exclude Kılıç, Miyazaki, Spečkauskas) (11)	0.99	(0.73−1.36)
Include only studies with medically confirmed diabetes assessment and exclude self-reported (i.e., exclude Arnarsson, Atum, Kılıç, Spečkauskas, Viso) (9)	0.85	(0.63, 1.15)
Exclude Wood study due to predominantly male population (13)	0.96	(0.72−1.28)
Pool Pasquale study into one (14)	0.96	(0.75, 1.22)
Exclude small studies (Atum, Mansour) (12)	0.94	(0.72, 1.22)

CI = confidence interval; NOS = Newcastle-Ottawa Scale; OR = odds ratio; POAG = primary open-angle glaucoma.

($P = 0.45$) proportion with hypertension and no evidence of effect modification ($P_{effect\ modification} = 0.53$; Fig S8, available at https://www.ophthalmologyscience.org/).

We also conducted meta-regression analysis with continuous variables including sex (male:female ratio), age (weighted average), and average latitude to evaluate potential effect modification. However, none of these appeared to modify the association between DM and XFS ($P_{effect\ modification} \geq 0.26$).

For sensitivity analyses, we assessed the robustness of the pooled OR by evaluating how the estimate changed when a single study was omitted in a leave-one-out meta-analysis. We found that no study had a major influence on the pooled OR due to the significant overlap in the 95% CIs. The pooled estimate did not change significantly after omitting 1 study at a time (Fig S9, available at https://www.ophthalmologyscience.org/). Cumulative meta-analysis showed apparent time trends with earlier studies reporting much more extreme effect estimates, but ultimately stabilizing near the null after 2010 (Fig S10, available at https://www.ophthalmologyscience.org/). Effect estimates from various sensitivity analyses did not substantially alter from the original pooled OR (range of 0.85−1.07), but the loss of study numbers and participants resulted in lower precision and slightly wider CIs (Table 4).

Risk of Bias Across Studies

Visual inspection of the funnel plot identified slight asymmetry with more studies appearing to the right of the pooled OR, suggesting possible evidence of publication bias (Figure 11). The Egger test and Begg test of whether there were small-study effects were not significant ($P = 0.06$ and $P = 0.55$, respectively); however, because Egger's test had borderline significance, findings should be interpreted with caution. Trim-and-fill analysis resulted in the imputation of 2 studies on the left of the pooled OR. The updated estimate based on 15 observed and 2 imputed studies became further from the null and showed a stronger, but not yet significant, inverse association (OR 0.85; 95% CI, 0.67−1.09; Figure S12, available at https://www.ophthalmologyscience.org/).

Risk of Bias Within Studies

For the assessment of study quality using the adapted NOS for cross-sectional studies, the average score was 8.3 (range of 6−10), with a maximum of 10 points (Table 5). For case-control studies, the NOS criteria does not include the important consideration of whether a case-control study evaluated the etiologically relevant exposure of interest (i.e., prediagnostic exposure status); none of the case-control studies clarified that DM status came before XFS diagnosis was assessed. Nevertheless, 3 out of 5 case-control studies scored ≥ 7 points on the NOS, and the average score for case-control studies was 6.6 (range of 5−8), with a maximum of 9 points (Table 5). Selection of participants was identified as a domain of concern, with most studies showing risk of bias and only 2 cross-sectional studies and 1 case-control study determined to achieve the full subscore. All cross-sectional studies and case-control studies were adjusted for age as a confounding factor. However, most studies had few covariates such as hypertension or family history of glaucoma that were adjusted for. All cross-sectional studies were determined to have full subscores for adequate assessment of the outcome and appropriate statistical tests. However, out of all case-control studies, only 1 was determined to have full subscores for adequacy of ascertainment of exposure, with the majority of studies failing to describe response rates between groups. Although these risks varied among the included studies, assessment of study quality was not used as a weighting tool or exclusion criterion for the final meta-analysis. A post hoc sensitivity analysis excluding studies scoring < 7 did not materially change the overall effect estimate.[37−39]

Discussion

Summary of Evidence

This study provides a systematic review of the current evidence for the association of DM with XFS. In the current literature, the relationship between DM and XFS is controversial, with prior studies demonstrating conflicting results.[21,22] Although some studies provided quantitative estimates for these associations, few were designed

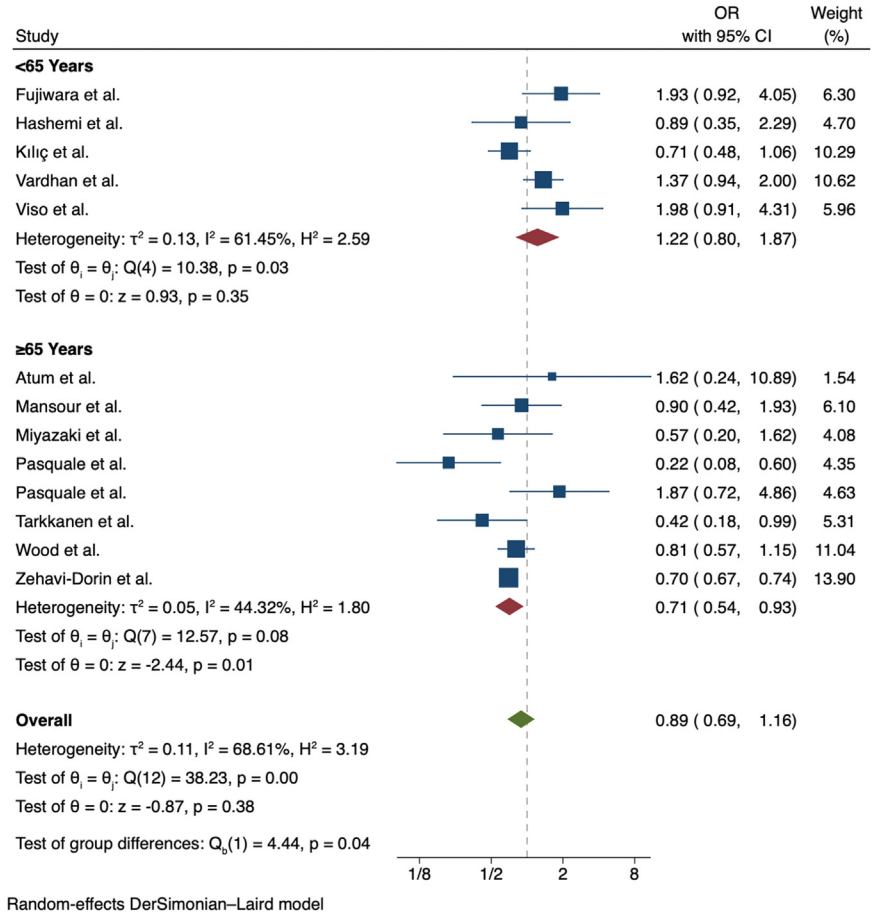

Figure 3. Subgroup analysis by mean age comparing < 65 years and ≥ 65 years. Confidence intervals (CIs) in this figure slightly differ from those presented in Table 3 due to rounding. OR = odds ratio.

specifically to investigate these relationships. There is considerable controversy in the current literature, and most results are limited without further interrogation or sensitivity analyses. In this meta-analysis and systematic review of 14 observational studies, overall, we observed no association between DM and XFS. However, we observed a suggestive effect modification by older mean age of the study population ($P_{effect\ modification} = 0.04$). On subgroup analysis, among studies of populations with a mean age ≥ 65 years, who are at highest risk of XFS, there was a significant inverse association between DM and XFS (OR 0.71; 95% CI, 0.54−0.93). Given the substantial heterogeneity and marginally significant publication bias across the included studies, this meta-analysis should not in itself be considered strong evidence for a null association, but rather as an effort to synthesize a widely heterogeneous evidence base that is best considered alongside a qualitative appraisal of the evidence.

A suggestive but notable inverse association between DM and XFS was observed in a subgroup analysis that was restricted to studies that included older populations (mean age ≥ 65 years). Exfoliation syndrome in younger populations is relatively uncommon, and evidence suggests that the etiology of early-onset XFS may frequently involve ocular trauma or surgery;[68,69] however, for the much more common late-onset XFS occurring at ages ≥ 65 years, the etiology of XFS may involve age-related processes that reflect the interaction of genetic and environmental factors. Our results support the hypothesis that a lower frequency of XFS may have been observed in older individuals with DM due to the long-standing hyperglycemic state in DM that can result in greater levels of advanced glycation end products. Greater advanced glycation end products may result in abnormal glycation of key macromolecules[70] or basement membrane components in individuals with DM, which in turn may slow the formation of exfoliation material.[28,29] Interestingly, one transmission electron microscopy study of anterior lens epithelial cells in a small sample of XFS patients found that the XFS in those with DM presented with less intense modifications on the lens and a better-conserved epithelium compared with the XFS in those without DM.[71] This underscores the importance of continuing the efforts to elucidate the disease mechanism of XFS and the etiology of abnormal accumulation of fibrillin material. Searching for a potential association between XFS and other systemic diseases may provide important new insight into the potential treatment and management of XFS. These findings provide a basis for future research to confirm these findings with larger-scale, longitudinal epidemiological data and correlation with objective markers of DM disease severity and progression such as hemoglobin A1C.

Table 5. Quality Assessment of Included Studies (Newcastle-Ottawa Scale for Case-Control Studies and Adapted Newcastle-Ottawa Scale for Cross-Sectional Studies)

Cross-Sectional

	Selection (max 5 stars†)					*Comparability (max 2 stars)*		*Outcome (max 3 stars)*				
Study	*Representativeness of Sample*	*Sample Size*	*Non-Respondents*	*Ascertainment of Exposure*	*Subtotal*	*Based on Design and Analysis*	*Subtotal*	*Assessment of Outcome*	*Statistical Test*	*Subtotal*	*Total Score (max 10)*	*Evaluation*
Arnarsson et al	*	*	*		3	**	2	**	*	3	8	Good
Atum et al		*			1	**	2	**	*	3	6	Satisfactory
Fujiwara et al	*	*		**	4	**	2	**	*	3	9	Very Good
Hashemi et al	*	*	*	**	5	**	2	**	*	3	10	Very Good
Mansour et al		*		*	2	**	2	**	*	3	7	Good
Miyazaki et al	*	*	*	**	5	**	2	**	*	3	10	Very Good
Tarkkanen et al	*	*		*	3	**	2	**	*	3	8	Good
Vardhan et al	*	*		*	3	**	2	**	*	3	8	Good
Viso et al	*	*	*	*	4	**	2	**	*	3	9	Very Good

Case-Control

	Selection (max 1 star per question)					*Comparability (max 2 stars)*		*Exposure (max 1 star per question)*					
Study	*Adequacy of Case Definition*	*Representativeness of Cases*	*Selection of Controls*	*Definition of Controls*	*Subtotal*	*Based on Design and Analysis*	*Subtotal*	*Ascertainment of Exposure*	*Same Method of Ascertainment*	*Non-Response Rate*	*Subtotal*	*Total Score (max 9)*	*Evaluation*
Kılıç et al	*	*		*	3	*	1		*		1	5	Satisfactory
Pasquale et al	*			*	2	**	2	*	*		2	6	Satisfactory
Spečkauskas et al	*	*	*	*	4	**	2	*	*		2	8	Very Good
Wood et al		*		*	2	**	2	*	*	*	3	7	Good
Zehavi-Dorin et al		*	*	*	3	**	2	*	*		2	7	Good

†Number of asterisks corresponds to number of stars given.

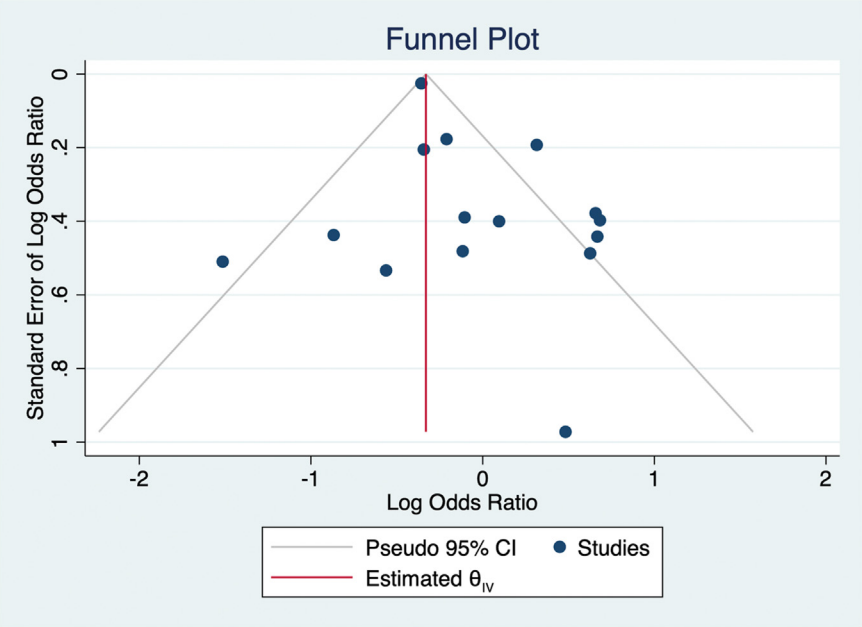

Figure 11. Overall funnel plot of studies included in the meta-analysis of diabetes and exfoliation syndrome. CI = confidence interval; IV = inverse-variance.

Strengths and Limitations

One major strength of this study was that it addresses the lack of systematic reviews and meta-analyses evaluating the association with DM, a chronic disease that is projected to surge in prevalence.[72] We employed a comprehensive search strategy involving controlled vocabulary terms (MeSH and Emtree) and all possible synonyms related to DM and XFS to yield complete retrieval of identified research studies (Appendix C, available at https://www.ophthalmologyscience.org/). Screening and study selection involved 2 independent reviewers at every step to ensure that each study was considered fairly. In addition to the primary quantitative synthesis, we investigated the association more thoroughly through subgroup analyses and meta-regression to examine the sources of heterogeneity, as well as sensitivity analyses to ensure our findings were robust.

However, evidence was limited to cross-sectional and case-control studies with no prospective cohort studies; such observational studies come with inherent weaknesses and risks of bias. There may be potential for unmeasured or residual confounding, detection bias, selection bias, and reverse causality, particularly for cross-sectional study designs. For example, studies may be biased (1) toward an adverse association, as those with DM may undergo more rigorous or frequent eye exams, increasing the likelihood of detecting XFS or (2) toward an inverse association, as older populations, especially those with DM, may be more likely to undergo cataract surgery, and clinicians may not see the exfoliation material as readily on synthetic lenses. For the latter, this may be less of an issue as most studies excluded participants with any prior cataract surgery, and for pseudophakic and aphakic individuals, studies used either exam information before the surgery or excluded people with missing data if the exam information was unavailable. While there was significant heterogeneity by ethnicity, these results could still be confounded by geographic region/latitude. Similarly, within each geographic region, residual confounding by race/ethnicity may still exist. Therefore, our subgroup analyses by race/ethnicity or region should be interpreted with caution. The present study may be susceptible to these biases in the pooled analysis despite the studies' attempts to minimize them. Our quality assessment using the NOS showed that most included studies scored $\geq$ 7 points and highlighted the selection of participants as a particular domain of concern, while controlling for confounding factors and assessment of outcome were considered as relative strengths. While the NOS is one of the most widely used, validated scales to assess the risk of bias in observational studies because of its ease of use and adaptability, there is no consensus on the most ideal quality assessment tool to use and no standard cutoffs have been established to distinguish high- versus low-quality studies.[73,74] In this study, we used an adapted version to assess cross-sectional studies, which has not been previously validated, and a commonly used threshold of 7 stars to be considered a high-quality study.[36–39]

Another limitation was that the included studies may have been subject to exposure misclassification. Measurements and definitions for DM were quite variable and included self-reported questionnaires, laboratory-confirmed tests, International Classification of Diseases codes, and chart review. For those that involved questionnaires or interviews, participants may be prone to recall or social desirability bias. In addition, studies have not evaluated various aspects of DM history, such as age of onset, duration, severity, control of DM, or treatment by insulin or oral hypoglycemic agents. Among the 5 studies that used antidiabetic medication as one of the criteria to assess

DM,[57–59,62,65] none reported separate ORs by type of DM control but rather used DM as a binary outcome. Future studies should evaluate whether the association may differ by type of DM control, severity, or duration. A more significant limitation of the included studies in terms of DM assessment was that none of the included studies clarified that the data collected on DM status was from the period prior to XFS diagnosis; hence, by the potential inclusion of DM diagnosed after a XFS diagnosis, the ability to make temporal inferences may be weakened, and the studies may have been biased towards the null given this exposure misclassification. However, it is unlikely that XFS predates DM as the typical age of onset for DM is much younger than the typical age of onset for XFS.[10,75] In contrast, a strength of the included studies was that the majority used standardized eye exams for the ascertainment of XFS. Outcome ascertainment for XFS was relatively standardized and comparable, with most studies using slit lamp examinations with similar definitions or medically confirmed cases by International Classification of Diseases codes. Due to only 2 studies[18,58] making the distinction between XFS and XFG, we were not able to evaluate the difference in relations between DM and XFS versus DM and XFG.[76]

A limitation at the review level is the potential for publication bias. Visual inspection of the funnel plot showed slight asymmetry with more studies reporting a positive association, and Egger test was barely above the significance threshold despite the fact that Egger and Begg tests of small-study effects tend to be underpowered, especially with a relatively uncommon outcome like XFS. We hypothesize that this bias may have arisen because, except for 2 studies,[64,65] the included studies were not specifically conducted to evaluate the association between DM and XFS, but rather, DM was included as one of many factors evaluated in relation to XFS occurrence. Most ORs were derived from studies that reported multiple other factors that were significantly associated with XFS, which may have increased the likelihood of biases where only significant associations were reported.

Conclusions

While the meta-analysis observed no overall significant association between DM and XFS, we observed a suggestive inverse association between DM and XFS in studies that included populations $\geq$ 65 years of age. These findings should be interpreted with caution due to the substantial heterogeneity and marginally significant publication bias across the studies. Future research should consider more large-scale prospective cohort studies that incorporate gene-environment interactions as well as studies that rely less on self-report of DM and more objective, standardized definitions (e.g., hemoglobin A1C, fasting glucose).[77–79] While we found that latitude of studies did not modify the pooled association between DM and XFS, there also may be other environmental factors and gene-environment interactions that should be considered. As populations age globally, it is important to gain insight into the etiology and pathogenesis of XFS to inform clinical decision-making and lead to novel interventions and treatment strategies.

Footnotes and Disclosures

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[1] Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts.
[2] Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts.
[3] Department of Ophthalmology, Weill Cornell Medicine, New York, New York.
[4] Department of Ophthalmology, Massachusetts Eye and Ear, Harvard Medical School, Boston, Massachusetts.
[5] Department of Ophthalmology, Icahn School of Medicine at Mount Sinai, New York, New York.

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Because the study did not directly involve human subjects, it was exempt from institutional review board approval. Informed consent was not obtained nor required because no individual-level patient information was used in this meta-analysis of published studies. This work was conducted following the Declaration of Helsinki, Meta-analysis of Observational Studies in Epidemiology (MOOSE), and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines for reporting (Appendix A and Appendix B, available at https://www.ophthalmologyscience.org/).

No animal subjects were included in this study.

Author Contributions:

Conception and design: Yu, Kang

Analysis and interpretation: Yu, Hwang, Wiggs, Pasquale, Kang

Data collection: Yu, Hwang, Kang

Obtaining funding: Wiggs, Kang (NIH R01EY020928)

Manuscript writing: Yu, Hwang, Wiggs, Kang

Abbreviations and Acronyms:
BMI = body mass index; **CI** = confidence interval; **DM** = diabetes mellitus; **IOP** = intraocular pressure; **NOS** = Newcastle-Ottawa Scale; **OR** = odds ratio; **POAG** = primary open-angle glaucoma; **XFG** = exfoliation glaucoma; **XFS** = exfoliation syndrome.

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Correspondence:
Jae Hee Kang, ScD, Brigham and Women's Hospital, 181 Longwood Ave, Boston, MA 02115. E-mail: nhjhk@channing.harvard.edu.

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