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Demographic and Geographic Features of Exfoliation Glaucoma in Two United States-based Prospective Cohorts

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Abstract

Purpose—To prospectively examine the association between demographic and geographic factors in relation to exfoliation glaucoma or exfoliation glaucoma suspect (EG/EGS).

Design—Prospective cohort study.

Participants—We included 78,955 women in the Nurses' Health Study and 41,191 men in the Health Professionals Follow-up Study.

Methods—Female and male health professionals were prospectively followed during the periods 1980–2008 and 1986–2008, respectively. Eligible participants were 40+ years old, did not have EG/EGS at baseline and reported receiving eye examinations during follow-up. Information regarding demographic features, lifetime geographic residence and potential confounders was collected. During follow-up, 348 EG/EGS cases were confirmed with medical record review. We estimated the relative risk of EG/EGS in each cohort separately and pooled the results with meta-analysis.

Main outcome measures—Multivariable rate ratios (MVRR) of EG/EGS and their 95% confidence intervals (95% CI).

Results—EG/EGS was strongly age-related with subjects ≥ 75 years old at 46.22-fold (95% CI, 22.77 – 93.80) increased risk compared to those between aged 40–55 years. While men were 68% less likely to develop EG/EGS than women (MVRR = 0.32; 95% CI, 0.23 – 0.46), no predisposition to EG/EGS by ancestry, particularly Scandinavian ancestry, emerged. Compared to a lifetime of living in the Northern tier of the continental US, lifetime residence in the middle

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geographical tier (MVRR = 0.53; 95% CI, 0.40 – 0.71) and in the southern geographical tier (MVRR = 0.25; 95% CI, 0.09 – 0.71) was associated with markedly reduced risks of EG/EGS.

Conclusions—In this mainly Caucasian cohort from the United States (US), increasing age and female gender were significant risk factors for EG/EGS; however, Scandinavian heritage was not. Living in the middle or southern regions of the US relative to living in the northern region was associated with a reduced risk of EG/EGS.

INTRODUCTION

In exfoliation syndrome (ES), extracellular deposits are distributed in a characteristic pattern in the anterior segment of the eye. In ES, an open-angle glaucoma typically associated with marked elevation of intraocular pressure (IOP) occurs commonly,[1] but premature cataract[2] and retinal venous occlusive disease also occur.[3–6] Furthermore, the surgical management of cataract in ES is often accompanied by intraoperative zonulolysis[7–9] and early postoperative capsular opacification.[10] Considerable advances in understanding ES have been made since Lindberg's original description of this condition in 1917,[11] including Eagle's disordered extracellular matrix metabolism hypothesis[12] and the discovery of an association with common variants in the lysyl oxidase-like 1 (LOXL1) gene;[13] yet, many questions remain regarding the etiology of this disorder.

Although many studies from around the world have reported on the burden of disease, some aspects of the basic descriptive epidemiology, which may help to shed light on the etiology, are inconsistent. For example, while it is established that this is a strongly age-related condition, the data are inconsistent regarding the relation with gender. In addition, while the condition is hyperendemic in Northern European countries,[14–16] there is no definitive study demonstrating that Scandinavian heritage is a risk factor. Interestingly, in Iceland, where the prevalence is ~20% among people older than 60 years and where the association with *LOXL1* was discovered, approximately 98% of cases and 80% of controls had disease-associated *LOXL1* gene variants,[13] and similar percentages were observed in cases and controls in Australia where the disease prevalence is only ~1%.[17, 18] These data suggest that there is a complex interplay between genetic and environmental factors in the etiology.

The hyperendemicity in Northern Europe is part of a general trend of increasing prevalence with increasing latitude, which has been observed throughout Europe, the Middle East and Asia[14, 19–22] (although there are some exceptions, for example, in Chinese populations where the condition is extremely uncommon[23]). For instance, in Andhra Pradesh, India (latitude: 12°North), the prevalence ranges between 3–6%,[24] while it is 11% in Greece (39°N)[19] and 23% in Sweden (62°N).[15] Within the continental United States (US), an association with latitude was also observed: Stein et al.[25] used the i3 InVision Data Mart database and confirmed that current residence in the southern tier of the continental US was associated with a reduced risk. However, what is not yet known is how lifetime residential history from birth and not just the most recent residence may be associated.

We used data from 78,955 women in the Nurses' Health Study and 41,191 men in the Health Professionals Follow-up Study residing throughout the continental United States (US) who were prospectively followed for 20+ years and provided lifetime residence information as well as other lifestyle and health information to examine the descriptive epidemiology of exfoliation glaucoma or exfoliation glaucoma suspect (EG/EGS).

METHODS

Description of the cohort at risk for exfoliation glaucoma

The Nurses' Health Study (NHS) is an ongoing population-based cohort of registered female nurses. The NHS was established in 1976 when 121,700 US women were invited to complete a questionnaire regarding lifestyle, health behavior and chronic diseases. The Health Professionals Follow-Up Study (HPFS) is an ongoing cohort created in 1986 when 51,529 male health professionals (dentists, veterinarians, pharmacists, optometrists, osteopaths and podiatrists) completed a similar health survey. The participants in both cohorts have been followed biennially with mailed questionnaires that have updated health and lifestyle information. The study period was 1980 – 2008 in the women and 1986 – 2008 in the men. The Human Research Committee of the Brigham & Women's Hospital approved this study; this study adhered to the tenets of the Declaration of Helsinki.

Participants were excluded from the study at baseline (defined as 1980 in NHS and 1986 in HPFS) for the following reasons: 1) 23,239 women in NHS who did not respond to the initial 1980 semiquantitative food frequency questionnaire (SFFQ) as the relation between diet and glaucoma was a major objective of this study 2) 5,994 women and 1,596 men with inadequate dietary information on the SFFQ (for women adequate dietary information consisted of > 50 of 61 items completed yielding 500–3500 kcal/day, while > 61 out of 131 items completed with a total caloric intake range of 800–4200 kcal/day was regarded as adequate for men), 3) 3,624 women and 1,927 men who reported cancers excluding nonmelanoma skin cancer prior to a glaucoma diagnosis (because a cancer diagnosis could profoundly affect lifestyle), 4) 868 women and 1,032 men who self-reported a diagnosis of glaucoma or glaucoma suspect at baseline, 5) 739 women and 1,085 men lost to follow-up immediately after baseline, 6) 5804 women and 3,374 men who never reported an eye exam during follow-up and 7) 173 women and 672 with a history of cataract extraction in either eye at baseline (because exfoliation material is difficult to detect in the pseudophakic or aphakic state). After these exclusions, 81,259 women and 41,843 men remained. At each two-year period, we applied additional exclusions for participants who were under age 40 (because incidence rises in middle age) and who did not report having had an eye exam in the two years at risk. For example, in the first two-year risk period 36,500 women and 12,809 men (17,256 women and 233 men who were < 40 years old and 19,244 women and 12,576 men who did not report an eye exam) were excluded, leaving 44,759 women and 29,034 men eligible in the first two-year risk period. At later periods, the 36,500 women and 12,809 men could contribute person-time of observation, if they reached 40 years of age and reported receiving eye exams. Hence, by 2008, a total of 78,955 women and 41,191 men contributed person-time. Follow-up rates through 2008 were high (> 85% of the total possible person-time). Participants contributed person-time until confirmed EG/EGS, a self-report of glaucoma, death, loss to follow-up, a diagnosis of cancer other than nonmelanoma skin cancer, a self-report of cataract extraction or the end of the study (2008), and then they were censored.

Case identification and confirmation

In all biennial questionnaires from 1986, participants were asked if they had physician-diagnosed glaucoma. Among participants who gave a positive response to this question, we obtained their permission to retrieve their medical information. The diagnosing eye care provider of record was sent a request to complete a glaucoma questionnaire, which asked about the presence of exfoliation material or other secondary causes for elevated IOP, maximum IOP, optic nerve features, status of the filtration apparatus and to send all available visual field (VF) reports. In lieu of completing the questionnaire, eye care providers could send the complete medical records and all VF reports related to the

glaucoma diagnosis. A glaucoma specialist (LRP) evaluated the questionnaire/medical record information as well as the VF data in a standardized manner for confirmation and classification.

We analyzed cases of either exfoliation glaucoma or exfoliation glaucoma suspect (EG/EGS). Specifically, exfoliation glaucoma was defined as the presence of exfoliation material in combination with 2 or more reliable tests showing reproducible VF loss consistent with glaucoma, and exfoliation glaucoma suspect was defined as the presence of exfoliation material in combination with 1) a history of IOP > 21 mm Hg or 2) cup-disc ratio (CDR) ≥ 0.6 or the inter-eye difference in CDR≥ 0.2 or 3) only 1 reliable test showing VF loss consistent with glaucoma. Those with a presence of exfoliation material only without any VF loss or elevation in IOP or abnormal cup-disc ratios (as defined above) were not considered as cases of EG/EGS.

During the study period, 7,495 women and 3,242 men reported that they had been diagnosed with glaucoma. Among the subset of 5,022 women and the 1,848 men in whom we were able to receive a response from the diagnosing eye care provider, we observed the following breakdown: EG/EGS (8% women; 5% men), exfoliation material only without any glaucomatous signs (0.4% women; 0.3% of men), primary open-angle glaucoma with VF loss (40% women; 48% men), only elevated IOP or optic disc cupping without secondary causes of IOP elevation (31% women; 29% men) and other types of glaucomas or glaucoma suspect (21% women; 17% men). For the analysis, we included 288 women and 60 men who met the standardized case definition of incident EG/EGS.

Ascertainment of Determinants

In 1992 in the NHS and in 1986 in the HPFS we asked about major ancestry (Caucasian, African American, Asian or Native American); for Caucasians, we asked about Southern European heritage, Scandinavian heritage or other Caucasian heritage. Hispanic ethnicity was only asked in the NHS in 1992. Eye color was only asked in the HPFS in 1988.

We also asked about lifetime residence; in 1992 in both cohorts, we ascertained the US state of residence at birth, at age 15, at age 25 (HPFS)/30 (NHS) and from 1976 in the NHS and 1986 in the HPFS, most recent residence information was available. In the main analysis, we examined the risk of EG/EGS in relation to the most recent residence. Based on the methods used in a study of latitude and multiple sclerosis in our cohorts[26], we divided the continental US into northern, middle and southern tiers; states that are north of the 41–42 degrees latitude north were categorized in the northern tier (AK, CT, ID, ME, MA, MI, MN, MT, NE, NH, NY, ND, OR, RI, SD, VT, WA, WI, WY), the states south of the 37 degrees latitude north were categorized in the southern tier (AL, AZ, AR, FL, GA, HI, LA, MS, NM, NC, OK, PR, SC, TN, TX and southern California from Los Angeles to its southern border) and the remainder of states between 37–40 degrees latitude north (CO, DE, DC, IL, IN, IA, KS, KY, MD, MO, NV, NJ, OH, PA, UT, VA, WV including the remainder of California north of Los Angeles) were categorized in the middle tier. To examine the associations with the lifetime residence, we did similar categorizations of the residence at birth, age 15 and age 25/30. We examined the independent associations with the residence at each of these life periods (birth, age 15, age 25/30 and most recent). In addition, we constructed a cumulative updated lifetime history, where we took into account all the available information on residence as of each 2-year period at risk. We categorized the person-time into 5 categories: a) consistent residence from birth to the current time in the northern tier, b) consistent residence from birth to the current time in the middle tier, c) consistent residence from birth to the current time in the southern tier, d) residence from birth to the current time restricted to only the northern or middle tiers and e) residence from birth to the current time restricted

to only the middle or southern tiers. This variable represented the lifetime cumulative averaged residential history.

For covariates, we also collected information from the biennial questionnaires on family history of glaucoma (the type of glaucoma was not specified; positive family history was defined as a self-report of any glaucoma in biologic parents, siblings or children) and updated information on the presence of cataract or age-related macular degeneration, history of cataract extraction, body mass index (BMI), systemic hypertension, high cholesterol, diabetes mellitus (DM) and history of myocardial infarction.

Statistical Analysis

For statistical analyses, we first calculated cohort-specific incidence rates of EG/EGS by dividing the incident cases by the person-years accrued for each exposure category of interest. We adjusted for age using six categories (40–54y, 55–60y, 60–64y, 65–69y, 70–74y, 75+y) and calculated Mantel-Haenszel age-adjusted incidence rate ratios (RR) and their 95% confidence intervals (CIs).

We first analyzed the data from each cohort separately in multivariable analyses and performed tests for heterogeneity of the cohort specific results to check for appropriateness of pooling the results. For multivariable analyses, we controlled for potential EG/EGS risk factors by including them simultaneously in Cox proportional hazards analysis stratified by age in months and the specific 2-year period at risk.[27] Parameters included as covariates were family history of glaucoma, BMI, self-reported hypertension, DM, high cholesterol and myocardial infarction. Then, we pooled the results using meta-analytic methods incorporating random effects.[28] To determine the association with gender, we pooled the actual data from the individual cohorts and used Cox proportional hazards models, controlling for the same covariates as the main analyses. $P<0.05$ was considered statistically significant.

RESULTS

We identified 288 incident EG/EGS cases in the NHS and 60 incident EG/EGS cases in the HPFS during the study period. The total accrued person-time was 1,761,676 person-years (1,289,264 in the NHS and 472,412 in the HPFS). Of the 78,955 women and 41,191 men who ever contributed person-time, 5,482 (7.0%) women and 4,591 (11.2%) men reported Scandinavian ancestry, 12,967 (16.4%) women and 9,484 (23.0%) men reported Southern European ancestry, 58,662 (74.3%) women and 25,248 (61.3%) men reported other Caucasian ancestry, 1,119 (1.4%) women and 357 (0.9%) men reported African ancestry, 568 (0.7%) women and 671 (1.6%) men reported Asian ancestry and 157 (0.2%) women and 840 (2.0%) men reported Native American or Hawaiian ancestry. Hispanic/non-Hispanic ethnicity was only assessed in the NHS (n=656; 0.8% of women).

The mean age at diagnosis of EG/EGS was 68.1 ± 6.6 years in women and 70.8 ± 6.9 years in men (Table 1); female cases were much more likely to be diagnosed before age 65 years compared with men. The maximum IOP at diagnosis averaged 27.8 ± 6.3 mm Hg in women and 29.2 ± 7.6 mm Hg in men. There was a strong unilateral presentation of EG/EGS, where in 59% of the women and 63% of the men were affected in just one eye, although the right and left eyes were similarly affected. In about 41% of all EG/EGS cases, at least one abnormal VF in the eye(s) with exfoliation material was documented. Among all cases, 90% of women and 92% of men had elevated IOP; 55% of women and 60% of men had abnormal optic discs or glaucomatous VF loss in the affected eye. Family history of glaucoma, history of cataract and high cholesterol were more common in female cases than in male cases, whereas diabetes was less common in female cases than in male cases (Table 1).

In the women, the percentage of the total person time from the northern, middle and southern tiers were 36%, 48% and 16%, respectively, while in men, the percentages were 32%, 39% and 29%, respectively. Most characteristics such as Scandinavian ancestry were evenly distributed across geographic tiers. More men with northern tier residence reported Southern European ancestry. Residence at birth, age 15 and age 25/30 were strongly associated with current residence, especially for the northern and middle tiers, indicating more migration to southern tiers in later life. Any differences in the distribution of variables that might confound the relation between geographic tier and EG/EGS were adjusted for in multivariable analysis.

Multivariable analysis indicates that EG/EGS is a strongly age-related condition (Table 2). Compared to those aged 40–55y, the risk of EG/EGS in those 75 years of age or older was 46.22-fold in pooled analysis (95% CI, 22.77 – 93.80). A family history of any glaucoma was associated with a doubling of risk of EG/EGS (MVRR = 2.29; 95% CI, 1.39 – 3.78). Men were 68% less likely to develop EG/EGS than women (MVRR = 0.32; 95% CI, 0.23 – 0.46). Among the covariates we adjusted for in multivariable analyses, vascular conditions such as DM, hypertension, history of myocardial infarction and hypertension were not significantly associated with EG/EGS risk (data not shown). Increasing BMI appeared to be inversely associated with EG/EGS risk, with significant associations for the BMI 26 to 28 kg/m^2 category compared to BMI <22 kg/m^2 (MVRR = 0.55; 95% CI, 0.37 – 0.83).

People of Scandinavian (MVRR = 0.75; 95% CI, 0.48 – 1.17) and Southern European ancestry (MVRR = 0.98; 95% CI, 0.56 – 1.72) were not at increased risk of EG/EGS compared to the reference group of mostly other Caucasians, African-Americans, Asian-Americans and Americans of other racial heritage (Table 2).

Among men in whom eye color information was available, compared to those with blue or light eye color, having medium eye color (MVRR = 0.87; 95% CI, 0.43 – 1.74) or dark eye color (MVRR = 0.84; 95% CI, 0.42 – 1.68) was not associated with EG/EGS (Table 2).

Participants who reported current residence in the middle (MVRR = 0.59; 95% CI, 0.47 – 0.75) and southern tier (MVRR = 0.51; 95% CI, 0.37 – 0.69) had markedly reduced risks of EG/EGS compared to participants currently living in the northern tier (Table 2).

We also evaluated whether there may be associations with the longitude of current residence that were independent of latitude. We observed that longitude (in 3 categories: east coast to −84°, −84° to −104°, −105° to west coast) was indeed independently associated: compared with residence in the east, residence in the middle and western US was associated with lower risk (MVRR = 0.56; 95% CI, 0.36 – 0.88 and MVRR = 0.49; 95% CI, 0.32 – 0.76, respectively). However, the association with longitude was not observed in the northern tier but was most evident in the middle and southern tiers, which was in contrast to the association with latitude, which was apparent in all the longitude categories.

Similar strong significant inverse associations with living in the middle and southern tiers in relation to EG/EGS were observed when we evaluated multivariable models substituting current residence with residence at birth, residence at age 15 or residence at age 25/30 (data not shown). Because current residence was strongly correlated with residence at other life periods, and there may be different associations between residence and EG/EGS depending on the life period, we examined multivariable models for current residence that also simultaneously controlled for residence at birth, age 15 and age 25/30 (Table 2). Indeed, the association with current residence in the southern tier remained significantly inverse, but it was attenuated (MVRR = 0.67; 95% CI, 0.45 – 0.98) as was the association with residence in the middle tier, which was no longer significant (MVRR = 0.76; 95% CI, 0.53 – 1.10). Interestingly, in this model, residence at birth and age 25/30 were not independently

associated with risk of EG/EGS, but residence at age 15 at either the middle or southern tier was strongly, significantly and independently associated with EG/EGS risk (middle tier: MVRR = 0.55; 95% CI, 0.32 – 0.94; southern tier: MVRR = 0.40; 95% CI, 0.16 – 0.99).

When we examined the long-term cumulative life residential history from birth to the current residence, compared to those who consistently lived only in the northern tier, those who consistently lived in the middle tier had a 47% reduced risk of EG/EGS (MVRR = 0.53; 95% CI, 0.40 – 0.71) and those who consistently lived in the southern tier had a 75% reduced risk of EG/EGS (MVRR = 0.25; 95% CI, 0.09 – 0.71) (Table 2).

DISCUSSION

In this large prospective study of 20+ years in two US-based cohorts, we have confirmed established associations with age and family history and EG/EGS as well as provided new data on associations with gender, eye color and ancestry. Importantly, we observed that those with a lifetime residential history of living in the middle tier and the southern tier of the US was associated with 47% and 75% reduced risks, respectively, compared to living in the northern tier and that across the life span, residence at age 15 was the most strongly associated with risk, followed by current residence.

Age and gender

We observed strong relations between older age and increased risk, a finding consistent with most epidemiological investigations, including two prospective studies.[29, 30] Prevalence studies have shown widely varying relations with gender, but our finding of increased risks in females was consistent with findings from two prior incident studies.[29, 30] It is unclear whether gender specific differences between ocular factors such as axial length differences or environmental factors related to lifestyle account for why female gender is a risk factor in this multivariable analysis.[31]

Family history

We observed that a positive family history of glaucoma was associated with over a doubling of risk. Although we could not confirm the self-reports of glaucoma in family members, and the positive association could represent a form of detection bias (where those with the disease are more aware of the family history of glaucoma), these data add to the general literature supporting a contribution of genetic causes.[13]

Ethnicity

Most prior studies have been performed in ethnically homogeneous populations and very few found any ethnic differences in the occurrence.[32, 33] Given the high prevalence (exceeding 10%) in surveys from Scandinavian countries,[34, 35] this condition has long been considered a “Scandinavian disease”.[36] However, in our US-based study, which consisted of mainly Caucasian participants with heterogeneous European heritage, neither Scandinavian descent nor Southern European ancestry was associated with risk compared with the large reference group of mainly other Caucasians. This indicates that there may also be strong environmental factors that may increase the risk among populations in Scandinavian countries.

Overall, we lacked adequate power to determine whether incidence rates differed by minority groups. Prior studies have found that this condition is uncommon in African Americans,[37] although it is more common in African people dwelling in South Africa.[38, 39] While there were 1,476 African-Americans in this study (1% of the study participants who contributed 19,081 person-years of observation), we found only one case in this group;

similarly, although we had 656 Hispanics among the women, we found only one case in this group. While it is rare in Chinese,[23] it does occur commonly in Asians from Japan[40] and India.[24, 41, 42] We had 1,239 Asian-American participants (1% of the study participants who contributed 16,329 person-years of observation) in this study, and we could not identify a single case in this group.

Iris color

Based on the data in men, even after controlling for ethnicity and other factors, iris color was not a risk factor. The literature has been inconsistent on this relationship. For example, while Arnarsson et al.[43] found that having more pigmented irises (e.g., brown irises versus light blue irises) was associated with increased prevalence, they did not find an association with incidence in their follow-up study,[44] which was consistent with our null findings in men. One limitation of this study was that we were unable to examine this relationship in women as it was not asked in the NHS. Another limitation is that information on iris color was based on self-report leading to misclassification and bias towards the null.

Geographic area of residence

In analyses that account for age, gender, ethnicity and other factors, current residence in the middle or southern tier of the US was associated with a markedly reduced risk. This finding is consistent with the results of Stein et al. who also reported a reduced risk among those with most recent residence in the southern tier of the continental US relative to the middle tier.[25] Additionally, two point prevalence studies in the southern US[37, 45] reported prevalence estimates that were similar to those seen in studies from southern Asia.[22, 46] Although studies of US populations like ours could only examine differences in the frequency in a region that spans only 15 degrees of latitude, our results were consistent with the broader worldwide trend (with few exceptions[23, 33]) of higher prevalence throughout Europe and Asia as a function of increasing latitude.[22, 47–49] In a study that involved samples from 11 countries, Forsius et al. observed that while the prevalence generally increased markedly after age 50, there appeared to be about a 10 year delay in the presentation in tropical areas.[33]

The unique contribution of this study was the availability of lifetime residential history from birth, age 15, age 25/30 and current residential history, which was updated every 2 years from 1976 in the NHS and from 1986 in the HPFS. Consistently living in the middle and southern tiers were associated with 47–75% reductions in the risk, pointing to the possibility that major environmental or climatic factors may be important in the etiology. Interestingly, in analyses that examined the independent associations with residence at various time periods in life (birth, age 15, age 25 and current residence), living in the middle or southern tier at age 15 was the most strongly inversely associated with risk, followed by current residence. It is likely that in adolescence and after retirement (the mean age of the accrued person-time in our study was 60+ years), the amount of time spent outdoors is the greatest, and thus these periods may be critical times when exposure to relevant environmental or climatic factors is maximal. It also indicates that exposures in early life may be important for EG/EGS, which is a condition that typically manifests after age 60. While one could speculate that given the insidiousness of ES, which produces no symptoms, there may be issues of detection that may vary by geographic region, but this possibility seems very unlikely to explain all of the associations with geographic tier.

The geographic differential in the prevalence has been frequently observed and has often been attributed to ethnic differences in the predisposition. However, Stein et al. examined the association with US geographic tier only among non-Caucasians and found results that were materially similar to those reported here (in our study non-Caucasians only contributed

~1% of the total person time to this study, so a similar analysis is not possible).[25] This provided strong evidence that the associations with geographic tier may be driven more by environmental differences than ethnic differences or differences in ascertainment.

It has been established that *LOXL1* variants, which are attractive functional candidates for altering extracellular matrix metabolism, are associated with risk. Our data raises the possibility that important environmental factors may impact the anterior segment physiology and interact with causative genetic variants to exacerbate dysregulated extracellular matrix turnover. Stein et al.[25] suggested that lower ambient temperature, lower elevation and more solar exposure may be factors that impact the anterior ocular segment physiology to increase the risk. In support of this, we observed associations with longitude where residence in western states that have higher temperature and higher elevation was associated with lower risk, particularly in the southern states. More studies are needed to identify the specific environmental risk factors (e.g., climatic or other factors).

One limitation of this study is that the confirmation of the outcome was based upon an initial self-report of glaucoma confirmed with review of medical record/questionnaire information. Also, because we could not conduct direct repeated eye exams in these large cohorts, our method of case ascertainment had low sensitivity, particularly given that the presence of exfoliation material or exfoliation glaucoma can be easily missed. However, the purpose of our study was not to provide estimates of absolute incidence rates, which are better accomplished with population-based studies using direct standardized eye exams; rather, the aim of our study was to study *relative* rate ratios across people of varying exposures. Methodologically, it has been established that even with low sensitivity for detecting the outcome, incidence rate *ratios* can still be validly estimated provided that the case definition is highly specific and the ascertainment method is not related to exposure.[3] We believe that our case ascertainment was highly specific as we chose a definition with a high specificity for ES: all cases had evidence of exfoliation material, with consequences that were severe enough to be associated with reproducible glaucomatous visual field loss (which has the greatest public health impact) or a glaucomatous sign that might indicate the need for treatment. Differences in ascertainment method by gender or geographic tier are possible but unlikely to explain all of the results. With regards to detection bias by geographic tier, in a study of Louisiana residents where direct eye exams were conducted, a low prevalence of exfoliation syndrome among glaucoma patients was confirmed, which indicated that even where detection bias was minimized, a generally lower frequency in the south was observed. [37] Furthermore, if ES/EGS is thought of as a “Scandinavian disease”, then doctors might diagnose it more often in those with Scandinavian ancestry. However, Scandinavian ancestry was not a risk factor for EG/EGS in this study. Thus, given the specificity of the association with geographic tier and other variables, that are consistent with prior studies, we believe that detection bias, though possible, is unlikely to explain all of our results. Also, while we had updated information on our participants’ residential information after the beginning of the studies, there might have been migration between birth, age 15, age 25/30 and 1976/1986 that we were not able to capture; however, this missing information would likely have led to a bias towards the null from random misclassification of residential history. Finally, the generalizability of the results might be limited, because our participants were mostly European-derived Caucasians; therefore, studies in other ethnic groups are needed.

Overall, our study has several strengths. It included over 120,000 participants followed prospectively over 20+ years, thus the exposure information (such as geographic tier) and covariate information was not susceptible to recall bias as may occur in case-control studies. Our analyses were adjusted for many key covariates including age, ancestry, family history of glaucoma and numerous vascular conditions. We applied standardized protocols and

definitions in case confirmation, and in support of the validity of our case definition, the cases exhibited ocular characteristics known to be consistent with this condition including high IOP, later age of onset (68 years in women and 71 years in men), and a strong unilaterality in presentation[50] compared to POAG (64 years and 67 years).[31] Finally, we had unique data on the residential histories at various life periods in our participants, allowing us to evaluate whether there was a critical time period when geographical tier was related to risk as well as the associations with cumulative lifetime residential history.

In conclusion, in this US-based predominantly Caucasian population from two prospective cohort studies, we confirmed established associations with age and family history, observed that Scandinavian ancestry was not related to the risk of EG/EGS and provided strong evidence for male gender and living in the middle or southern tier being associated with reduced risks. These results suggest that in addition to genetic factors, environmental factors may contribute to the etiology. The elucidation of these environmental factors could have a major impact in reducing the related ocular morbidity.

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Table 1

Descriptive factors of exfoliation glaucoma cases in Nurses' Health Study (n=288) and Health Professionals' Follow-up Study (n=60) [a]

	Women		Men	
Characteristic	***Mean (SD)***	***N***	***Mean (SD)***	***N***
Age at Diagnosis	68.1 (6.6)	288	70.8 (6.9)	60
Intraocular pressure (mmHg)	27.8 (6.3)	282	29.2 (7.6)	60
Cup: disc ratio	0.5 (0.2)	240	0.6 (0.2)	44
Body mass index (kg/m^2)	25.7 (4.9)	284	23.0 (7.5)	60
	N (%)		*N (%)*	
Diagnosis before age 65	94 (32.6)		10 (16.7)	
Eyes with exfoliation material				
Right eye only	80 (27.8)		18 (30.0)	
Left eye only	90 (31.2)		20 (33.3)	
Both eyes	118 (41.0)		22 (36.7)	
Glaucomatous features [b]				
ES + Elevated IOP + ≥2 VF	45 (15.6)		10 (16.7)	
ES + Normal IOP + ≥2 VF	7 (2.4)		2 (3.3)	
ES + Elevated IOP + 1 VF	44 (15.3)		9 (15.0)	
ES + Normal IOP + 1 VF	7 (2.4)		0 (0.0)	
ES + Elevated IOP + Abnormal disc only	41 (14.3)		12 (20.0)	
ES + Normal IOP + Abnormal disc only	14 (4.9)		3 (5.0)	
ES + Elevated IOP only	130 (45.1)		24 (40.0)	
Family history of glaucoma	76 (27.6)		11 (20.0)	
Cataract	50 (17.4)		7 (11.7)	
Macular degeneration	14 (4.9)		3 (5.0)	
Diabetes mellitus	8 (2.8)		3 (5.0)	
Hypertension	121 (42.0)		24 (40.0)	
High cholesterol	157 (54.5)		23 (38.3)	
Myocardial infarction	12 (4.2)		3 (5.0)	
African-American	1 (0.3)		0 (0.0)	
Asian-American/Other race	0 (0.0)		0 (0.0)	

[a] SD: Standard Deviation; N: Number of people; ES: Exfoliation Syndrome; IOP: Intraocular Pressure; VF: visual fields showing loss consistent with glaucoma.

[b] Elevated IOP was defined as untreated IOP > 21 mm Hg in the eye affected with ES; Normal IOP was defined as untreated IOP ≤ 21 mmHg in the eye affected with ES. Abnormal disc only was defined as cup-disc ratio ≥ 0.60 or cup-disc ratio in eye affected with ES is ≥ 0.20 than that in the other eye with a lack of documentation of abnormal visual field loss.

Table 2

Age-adjusted and multivariable adjusted rate ratios for various risk factors for exfoliation glaucoma

Demographic and Personal Characteristics		%	RR, multivariable[a] (95% CI)
Age	**40–55 years**	33.0	**1.00 (reference)**
	55–60 years	18.9	4.33 (2.19, 8.56)
	60–65 years	18.6	10.43 (5.50, 19.78)
	65–70 years	14.6	19.88 (10.41, 37.96)
	70–75 years	9.2	33.54 (17.23, 65.29)
	75+ years	5.6	46.22 (22.77, 93.80)
Family History of Glaucoma	**No history**	87.0	**1.00 (reference)**
	History	13.0	2.29 (1.39, 3.78)
Race	**Other**[b]	73.2	**1.00 (reference)**
	Southern European	18.5	0.98 (0.56, 1.72)
	Scandinavian	8.3	0.75 (0.48, 1.17)
Eye color[c]	**Blue/light**	34.3	**1.00 (reference)**
	Hazel/green/medium	31.6	0.87 (0.43, 1.74)
	Brown/dark	34.1	0.84 (0.42, 1.68)
Gender	**Female**	73.2	**1.00 (reference)**
	Male	26.8	0.32 (0.23, 0.46)
Residence			
I) Latitude tier of current residence[d]	**Northern**	35.3	**1.00 (reference)**
	Middle	45.2	0.59 (0.47, 0.75)
	Southern	19.4	0.51 (0.37, 0.69)
II) Latitude tier of residence at birth[e]	**Northern tier**	41.1	**1.00 (reference)**
	Middle tier	49.0	1.19 (0.73, 1.94)
	Southern tier	9.9	1.16 (0.49, 2.71)
at age 15[e]	**Northern tier**	40.5	**1.00 (reference)**
	Middle tier	48.9	0.55 (0.32, 0.94)
	Southern tier	10.6	0.40 (0.16, 0.99)
at age 25[e]	**Northern tier**	37.6	**1.00 (reference)**
	Middle tier	47.9	1.02 (0.67,1.54)
	Southern tier	14.5	1.00 (0.60, 1.68)
at current residence[e]	**Northern tier**	35.3	**1.00 (reference)**
	Middle tier	45.2	0.76 (0.53, 1.10)
	Southern tier	19.4	0.67 (0.45, 0.98)
III) Latitude tier of cumulative life residential history[f]	**Northern tier only**	30.7	**1.00 (reference)**

Demographic and Personal Characteristics		%	RR, multivariable[a] (95% CI)
	Northern or Middle	14.3	0.81 (0.53, 1.24)
	Middle tier only	38.6	0.53 (0.40, 0.71)
	Middle or Southern	9.7	0.47 (0.28, 0.77)
	Southern tier only	6.6	0.25 (0.09, 0.71)

[a] RR: Rate Ratio; 95% CI: 95% Confidence Interval. Multivariable rate ratios were derived from models with age, race, geographical tier, family history of glaucoma, high cholesterol, hypertension, diabetes, body mass index and history of myocardial infarction.

[b] This category includes other Caucasian-Americans, African-Americans, Asian-Americans and other races

[c] Eye color was only available for HPFS; n/a = not available; this result was from models adjusting for the same covariates as in footnote[1].

[d] See footnote[1] in Table 2 for definition of geographic tier.

[e] Multivariable rate ratios are adjusted for age, race, geographical tier, family history of glaucoma, hypertension, high cholesterol, diabetes, history of myocardial infarction, residence at birth, residence at age 15, residence at age 25 and current residence. See footnote[1] in Table 2 for definition of latitude tier.

[f] Multivariable rate ratios are adjusted for age, race, geographical tier, family history of glaucoma, hypertension, high cholesterol, diabetes, history of myocardial infarction. Cumulative life residential history was determined among those with complete information residence at birth, at age 15, at age 25/30, at 1976 for NHS or 1986 for HPFS and all intervening questionnaires including the most recent residence. For Northern tier only/Middle tier only/Southern tier only categories, all of the available residence information from birth to the period at risk were consistently in the same tier; Northern or Middle refers to residence from birth to the current residence that migrated only between the Northern and Middle tiers; Middle or Southern refers to residence from birth to the current residence that migrated only between the Middle and Southern tier