Geographic and Climatic Factors Associated With Exfoliation Syndrome

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Objective: To identify geographic and climatic risk factors associated with exfoliation syndrome (ES).

Methods: A retrospective study of 626,901 eye care recipients, dating from 2001 to 2007 from 47 US states in a managed care network. Incident ES cases-patients (N = 3367) were identified by using billing codes. We assessed the risk of ES by geographic latitude tier in the continental United States and assigned state-level climatic data (eg, ambient temperature, elevation, and sun exposure) according to patients’ residential location. The hazard of ES was calculated by using multivariable-adjusted Cox proportional hazards regression models.

Results: Compared with middle-tier residence, northern-tier residence (above 42°N) was associated with an increased hazard of ES (adjusted hazard ratio [HR], 2.14; 95% confidence interval [CI], 1.94-2.35). Southern-tier (below 37°N) was associated with a reduced hazard of ES (HR, 0.83; 95% CI, 0.75-0.93). Excluding whites did not change these associations. After adjustment for joint environmental effects, for every 1° increase in July high temperature, the hazard of ES decreased by 9% (HR, 0.91; 95% CI, 0.89-0.93); for every 1° increase in January low temperature, the hazard decreased 3% (0.97; 0.96-0.98). For each additional sunny day annually, the hazard increased by 1.5% (HR, 1.02; 95% CI, 1.01-1.02) in locations with average levels of other climatic factors.

Conclusion: Ambient temperature and sun exposure may be important environmental triggers of ES.

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EXFOLIATION SYNDROME (ES) is an extracellular deposit disorder that causes significant ocular morbidity. It is the most common cause of secondary open-angle glaucoma. Elevated intraocular pressure commonly results because exfoliation material and uveal pigment lodge in the ocular outflow pathway, although glaucoma associated with ES is clearly multifactorial. In addition, ES is cataractogenic, and cataract surgery in affected eyes can be fraught with complications, due largely to inherent zonular instability. In ES, gray-white deposits are readily visible in the ocular anterior segment using minimal magnification. These aggregates consist of macromolecules mostly involved in basement membrane biosynthesis, although markers of complement activation, oxidative stress, ischemia, and inflammation are also found. In contrast to the ocular deposits in ES, electron microscopy is typically needed to demonstrate exfoliation material in visceral organs, which are more insulated from environmental effects, such as ambient temperature, compared with the eye.

In a landmark genome-wide association study, common variants in the gene LOXL1 (coding for lysyl oxidaselike 1) were associated with ES in participants in Iceland and Sweden, where ES is hyperendemic. Subsequent gene association studies confirmed these findings in persons with ES throughout the world. In the aggregate, these studies indicate that although LOXL1 risk genotypes are present in 92% or more of patients with ES, they are also seen in 74% or more of control participants, suggesting that other genetic or environmental factors contribute to ES.

The prevalence of ES varies worldwide from 0% to greater than 20%. Although some notable exceptions exist, point estimates of ES prevalence tend to increase with latitude in the Northern hemi-
sphere, from 1% in Sri Lanka (7°N) to greater than 20% in Sweden (64°N).33 We analyzed a fully annotated health care claims database with beneficiaries residing throughout the continental United States, a region spanning 15° of latitude, to investigate latitude as a risk factor for ES. Furthermore, we assessed whether selected climatic variables are associated with ES.

The University of Michigan institutional review board found this study, with its de-identified database, to be exempt from institutional review board review.

DATA SOURCE

The i3 InVision Data Mart database (Ingenix, Eden Prairie, Minnesota) contains detailed, fully de-identified records of all beneficiaries in a large US managed care network. We used data for all beneficiaries in this database receiving any eye care between January 1, 2001, and December 31, 2007. This subset comprised patients with at least 1 International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM),16 code for an eye-related diagnosis (360-379.9); Current Procedural Terminology17 code for an eye-related visit or a diagnostic or therapeutic procedure (65091-68899 or 92002-92499); or another ICD-9-CM or Current Procedural Terminology code assigned by an ophthalmologist or optometrist during their time in the plan. For this patient subset, we had all medical claims (inpatient, outpatient, and skilled nursing facility) for any medical conditions and detailed sociodemographic information. This data source has been used previously to identify risk factors associated with other medical conditions.38,39

STUDY SAMPLE AND CASE IDENTIFICATION

Because ES is strongly age associated, we identified all individuals 60 years and older who were in the database for 1 or more consecutive years and had at least 1 visit to an eye care provider. Individuals in the plan for fewer than 365 days or with noncontinuous plan enrollment were excluded (Figure 1). Since continental US geographic region (ie, northern, middle, and southern tiers) was the exposure of interest, California residents were excluded because that state spans the southern and middle tiers (approximately 9° of latitude) and we did not know patients’ specific location in their state of residence. Because the numbers of Hawaiians and Alaskans were insufficient for subgroup analysis, persons from these states were also excluded. Beneficiaries with an ICD-9-CM billing code of 365.32 (pseudoxfoliation glaucoma) or 366.11 (pseudoxfoliation of the lens capsule) were classified as having ES.

STATISTICAL ANALYSIS

Analyses were performed using a commercially available software program (SAS, version 9.2; SAS Institute, Inc, Cary, North Carolina). Patient characteristics were summarized by using means (SDs) for continuous variables and frequencies and percentages for categorical variables. For all the analyses, P < .05 was considered statistically significant.

Cox proportional hazards regression models were developed to compare the hazards of ES by the variables of interest, with adjustment for sociodemographic variables, ocular conditions, and systemic diseases.40 For the analyses, we used the first year of beneficiary enrollment in the plan as a look-back period. To capture incident ES cases, case identification commenced after 1 year of medical plan enrollment. Patients receiving an ES diagnosis in their first year of enrollment were considered prevalent cases and were excluded. Patients were observed until development of the event (ES) or censoring (ie, on leaving the plan or December 31, 2007, the study end date). Patient age at event or censoring was determined. By using age as the time axis and region of residence as the key predictor of interest, the Cox proportional hazards regression model was left truncated at the age of index (1 year after medical plan entry). Models were adjusted for sex, race, education, diabetes mellitus, hypertension, hyperlipidemia, obesity, myocardial infarction, peripheral vascular disease, systemic hypotension, skin cancer (surrogate for long-term sun exposure), migraine headaches, sleep apnea, cataract, pseudophakia/aphakia, diabetic retinopathy, age-related macular degeneration, and Charlson comorbidity index score (an overall health measure)41 (eTable; http://www.archophthalmol.com).

By Region

Using information in the database on beneficiaries’ state of residence at enrollment, we categorized patients according to residence in a northern-tier (above latitude 42°N), middle-tier, or southern-tier (below 37°N) state (Figure 2).42

By State

Multivariable-adjusted Cox proportional hazards regression models were used to estimate the hazard of ES for each US state of residence. Missouri was designated as the reference state because this middle-tier state has relatively uniform altitude and is close to the geographic center of the continental United States. For each other state, patients’ hazard of developing ES relative to patients in Missouri was estimated.

By Climatic Factor

We calculated the state-specific incidence of ES as the number of new cases in the state divided by the number of person-years at risk in which enrollees were under ophthalmic care. Poisson regression was used to model the ES incidence rate for
all states using the number of incident cases per state as the dependent variable and the cumulative person-years at risk as the offset. For each state, we assessed the possible association between ES incidence and the following variables, using National Climatic Data Center data: mean annual rainfall and snowfall (in inches), mean annual numbers of sunny days and days with precipitation, mean high temperature in July, mean low temperature in January, UV index, mean elevation (in feet) above sea level, and mean latitude and longitude.

Tests to check for multicollinearity were performed, and factors highly correlated with others were removed from the models. Only factors significant at $P < .05$ by backward selection procedures were retained. Next, based on the coefficients estimated by the Cox proportional hazards regression model, including the significant factors, we calculated the multivariable hazards of developing ES for residents of each US state relative to Missourians.

## RESULTS

Of 626,901 patients who met the inclusion criteria, 3367 (0.54%) had at least 1 ES diagnosis. Of the 3367 patients with ES, 2194 (65.2%) had ICD-9-CM code 366.11 (ES), 894 (26.6%) had ICD-9-CM code 365.52 (exfoliation glaucoma), and 279 (8.3%) had both codes documented. The mean (SD) patient age was higher in those with ES than in other types of ophthalmic patients (71.7 [6.8] vs 68.1 [6.8] years; $P < .001$). A greater proportion of patients with ES were women (66.4%) than men and were non-Hispanic white (91.8%) rather than another race ($P < .001$). The age-adjusted proportion of patients with cataract, pseudophakia/aphakia, macular degeneration, branch or central retinal vein occlusion, and hearing loss was higher in patients with ES than in the others ($P < .001$ for each comparison) (Table 1). These associations between ES and age, lens status, retinal vein occlusive disease, and sensorineural hearing loss, are consistent with the findings of previous studies in which patients were identified by using standardized ophthalmic or histopathologic examination.

### ES HAZARD BY US REGION

Residence in the northern geographic tier was associated with a 114% increased hazard of ES (adjusted hazard ratio [HR], 2.14; 95% confidence interval [CI], 1.94-2.35) and in the southern tier a 17% decreased hazard (0.83; 0.75-0.93) compared with residence in the middle tier. To determine whether the observed regional differences are attributable to a disproportionate number of whites living in the northern tier, we performed a secondary analysis excluding white patients. The increased hazard in northern-tier residents remained significant (adjusted HR, 3.27; 95% CI, 2.17-4.92); however, the hazard of ES in nonwhite beneficiaries did not differ between residents of southern-tier vs middle-tier states (1.31; 0.87-1.97).

### ES HAZARD BY STATE

Residents of 25 of the 46 states had elevated hazards of ES relative to Missourians (Table 2). North Dakotans (adjusted HR, 7.77; 95% CI, 3.86-15.62) and Minnesotans (5.62; 4.34-7.29) had the highest hazards of ES. Most states in which patients’ likelihood of ES was considerably el-

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**Figure 2.** Distribution of US states into tiers based on latitude.
Little is known about whether geographic factors are independently associated with the development of ES. In

### Table 1. Characteristics of Beneficiaries With and Without ES

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ES</th>
<th>No ES</th>
<th>Total</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>White</td>
<td>2521 (91.8)</td>
<td>431 857 (88.7)</td>
<td>434 378 (88.7)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>75 (2.7)</td>
<td>23 296 (4.8)</td>
<td>23 371 (4.8)</td>
<td></td>
</tr>
<tr>
<td>Latino</td>
<td>94 (3.4)</td>
<td>19 896 (4.1)</td>
<td>1 9990 (4.1)</td>
<td></td>
</tr>
<tr>
<td>Asian American</td>
<td>38 (1.4)</td>
<td>82 866 (1.7)</td>
<td>8324 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>17 (0.6)</td>
<td>3529 (0.7)</td>
<td>3546 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Female</td>
<td>2234 (66.3)</td>
<td>338 382 (54.3)</td>
<td>340 616 (54.3)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1133 (33.7)</td>
<td>285 058 (45.7)</td>
<td>286 191 (45.7)</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>&lt; High school</td>
<td>23 (0.8)</td>
<td>6910 (1.3)</td>
<td>6933 (1.3)</td>
<td></td>
</tr>
<tr>
<td>High school diploma</td>
<td>950 (31.6)</td>
<td>196 483 (38.1)</td>
<td>197 433 (38.0)</td>
<td></td>
</tr>
<tr>
<td>Some college</td>
<td>1219 (40.6)</td>
<td>201 407 (39.0)</td>
<td>202 626 (39.0)</td>
<td></td>
</tr>
<tr>
<td>College diploma</td>
<td>804 (26.8)</td>
<td>110 351 (21.4)</td>
<td>1 111 155 (21.4)</td>
<td></td>
</tr>
<tr>
<td>&gt; College</td>
<td>9 (0.3)</td>
<td>1000 (0.2)</td>
<td>1009 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>2656 (76.2)</td>
<td>456 195 (73.8)</td>
<td>458 851 (73.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>2475 (74.7)</td>
<td>450 835 (72.3)</td>
<td>453 310 (72.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Obesity</td>
<td>227 (7.6)</td>
<td>45 655 (7.9)</td>
<td>45 882 (7.3)</td>
<td>.17</td>
</tr>
<tr>
<td>Cataract</td>
<td>2710 (78.8)</td>
<td>358 984 (67.7)</td>
<td>361 694 (67.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pseudophakia/aphakia</td>
<td>1025 (21.1)</td>
<td>100 869 (19.9)</td>
<td>101 894 (19.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Macular degeneration</td>
<td>703 (13.7)</td>
<td>77 227 (10.5)</td>
<td>77 930 (12.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>259 (5.7)</td>
<td>32 830 (5.4)</td>
<td>33 089 (5.3)</td>
<td>&lt;.007</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>178 (5.9)</td>
<td>38 203 (6.0)</td>
<td>38 381 (6.0)</td>
<td>.86</td>
</tr>
<tr>
<td>Migraine</td>
<td>136 (4.6)</td>
<td>21 281 (3.2)</td>
<td>21 417 (3.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>883 (25.8)</td>
<td>185 523 (29.8)</td>
<td>186 406 (29.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>307 (7.4)</td>
<td>50 004 (7.7)</td>
<td>50 311 (7.7)</td>
<td>.55</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>770 (17.9)</td>
<td>107 088 (16.2)</td>
<td>107 858 (17.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Skin cancer, any type</td>
<td>547 (13.7)</td>
<td>78 036 (12.1)</td>
<td>78 583 (12.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diabetic retinopathy</td>
<td>237 (7.1)</td>
<td>47 552 (7.6)</td>
<td>47 789 (7.6)</td>
<td>.30</td>
</tr>
<tr>
<td>BRVO/BRVO</td>
<td>90 (2.1)</td>
<td>17 471 (2.9)</td>
<td>17 561 (2.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>616 (16.1)</td>
<td>71 168 (11.2)</td>
<td>71 784 (11.5)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; ES, exfoliation syndrome.

a The ES, No ES, and Total columns list the actual number of individuals in the analysis with these conditions. The percentages of ES and No ES are adjusted for age. The P values compare the age-adjusted percentages between these 2 groups.

Evolved were in the upper Midwest (Iowa, Minnesota, Montana, Nebraska, North Dakota, and Wisconsin) and, to a lesser extent, New England (Connecticut, Maine, and Massachusetts). Patients’ hazard of ES was elevated (>1.00) in 13 of the 18 northern-tier states (72%) compared with 5 of the 13 southern-tier states (38%) (Arizona, Florida, New Mexico, North Carolina, and Oklahoma).

### ES HAZARD BY CLIMATIC FACTOR

Poisson regression analysis revealed that 4 variables were associated with increased ES incidence: an increase in the annual number of sunny days (P = .001), decreased mean high July temperature (P < .001), decreased mean January low temperature (P < .001), and lower elevation above sea level (P = .004) (Table 3).

Additional regression models assessed whether joint environmental effects were present, and 2 interactions were found: a positive interaction between sunny days and January low temperature and a negative interaction between sunny days and elevation above sea level (P < .001 for both). After adjustment for the 2 interactions and other potential confounders, every 1° increase in July average temperature decreased the hazard of ES by 9% (adjusted HR, 0.91; 95% CI, 0.89-0.93). Every 1-day increase in sunny days increased the likelihood of ES (adjusted HR, 1.02; 95% CI, 1.01-1.02) at medium altitude (1053 ft) and medium average January temperature (23.5°F) (Table 4). This association was attenuated by higher altitude (P interaction < .001) and lower mean January temperature (P interaction < .001) (Table 4). Whereas every 1° increase in mean January low temperature decreased the hazard of ES by 2% (adjusted HR, 0.98; 95% CI, 0.97-0.98), the association was enhanced in locales with fewer sunny days (P interaction < .001) (Table 5). A 100-ft rise in altitude increased the hazard of ES by 2% (adjusted HR, 1.02; 95% CI, 1.01-1.03) in locales with the fewest sunny days (164 days) but not in those with the most sunny days (P interaction < .001) (Table 5). These findings did not materially change whether we adjusted for all skin cancers or all skin cancers except melanoma, which, unlike other skin cancers, is not necessarily related to long-term sun exposure (results not shown).

**Comment**

Little is known about whether geographic factors are independently associated with the development of ES. In
this sample, individuals in northern states had considerably higher hazards of ES relative to those in middle and southern states, and persons living in upper Midwestern states had substantially higher hazards of ES relative to Missourians. These models demonstrate that greater sunshine exposure and lower ambient temperatures in summer and winter increase the likelihood of ES. The
Lanka (latitude, 7°N), South India (12°N), Pakistan (30°N), Greece (39°N), and Sweden (62°N) are 1.1%, 3.8%, 6.5%, 11.9%, and 23%, respectively. In 2 clinic-based US studies, which might overestimate the burden of ES because of referral bias, the prevalences were low: 3% in adults 60 years or older in North Carolina (latitude, 35°N) and 1.4% in Louisiana (30°N). In the present study, crude prevalences of ES in various US states were considerably lower than previously reported estimates for Europe and Asia. Mississippi (latitude, 32°N) had the lowest crude prevalence (0.23%), whereas Minnesota (45°N) had the highest (2.84%) (data not shown). The lower prevalences in the present study have many possible explanations. Nevertheless, in this study, where patients' residences spanned a latitude range of 15°, living in the northern continental US tier was associated with an increased hazard for ES; residing in North Dakota was associated with the highest risk of ES relative to living in Missouri. The association with latitude was the same in white and nonwhite beneficiaries, suggesting that a trend toward genetically predisposed Northern Europeans populating northern-tier states does not explain these findings. Colder temperatures in summer and winter months increased the hazard of ES. Many of the highest reported ES prevalences are from countries with cold mean temperatures. For example, ES prevalences in Icelanders, Finns, and Lapps are greater than 20%. One explanation may be that the extracellular deposits of ES represent a nucleation reaction that is prone to develop at lower temperatures. Although the temperature in the vascular iris may be close to the core body temperature, the temperatures in the avascular ocular segments, such as the anterior chamber and lens, may be susceptible to ambient temperatures. One notable exception to the cold-precipitation hypothesis was a study in which the ES prevalence in Inuits in Alaska, Canada, and Greenland was 0%. Perhaps in Inuits a thicker iris and more abundant periorbital fat help to keep ocular temperatures high enough to prevent extracellular deposit formation. Alternatively, the finding could be related to cultural practices—style of dress or housing design—that may modulate climate impact.

The hazard of ES increased in states with more sunny days, and sunshine exposure seems to modify the associations with winter temperature and elevation. Studies have reported strong associations between ES and climatic droplet keratopathy, a condition associated with UV light exposure. Furthermore, high ES prevalences have been found in populations with considerable sun exposure, including Australian Aborigines (latitude, 27°S) and Navajo Indians (37°N). The cornea transmits UV rays and UV radiation may add to the impaired elastogenesis caused by abnormal LOXL1 function, although further research is needed to confirm this.

The association between elevation and ES was modified by sunshine exposure. In locales with relatively few sunny days, higher altitude was associated with an increased risk of ES, whereas the opposite was true for locales with more sunshine. The reason for this finding is not entirely clear and may be confounded by other variables. To date, little is known about the potential effect of altitude on ES prevalence. At 6%, the prevalence of ES was relatively high in 50 Navajo Indians, aged 60 years or older, living on an Arizona reservation at a latitude of 36°N and an altitude of 1500 m. These data suggest that high altitude may contribute to ES; more studies with detailed estimation of exposure to altitude are needed to better understand its impact.

In a study of 350 Aborigines living in different regions of Australia, ES was associated with lower latitudes (north of the 29th parallel south) and greater levels of total global radiation exposure. Temperature, relative humidity, evaporation rate, rainfall, sunlight, and UV radiation exposure were not statistically significant. Direct comparisons between that study and this one are difficult because of differences in climatic factors between Australia and the United States, the sociodemographic characteristics of the samples, and the covariates included for adjustment in the analyses. We did not have information on total radiation levels for each US state to incorporate this factor into the analyses.

Using a large administrative database to investigate the environmental variables associated with ES has several benefits. The large number of ES cases provided ample power to study the relationship between geographic factors and ES. In addition, this sample is geographically and sociodemographically diverse. Clinic- or hospital-based studies are affected by selective referral of severe cases to ophthalmic centers, but this sample was not limited to referral cases or patients seen by specialists or at academic medical centers.

The present study also has several limitations. First, misclassification of ES likely existed in the database; however, these cases had known comorbid conditions, demographic features, and ocular characteristics consistent with ES. Second, we cannot rule out the possibility that differential detection of ES in northern-vs southern-tier states explains the results, although this seems unlikely. For example, residence in North Dakota, a state with no academic ophthalmology centers, was associated with the highest ES risk relative to Missouri, which has several such centers. Yet, we still cannot rule out detection bias, whereby northern eye care providers are more prone to detect ES than are practitioners in the other tiers. Third, the claims database contained no zip code–level information on beneficiaries. Therefore, the average levels of each environmental factor for a given state used for these analyses may not precisely reflect individuals' actual exposure. We minimized such misclassification by excluding residents of California, a state that spans 9° of latitude. Fourth, we knew neither how long beneficiaries lived in their state nor whether they generally spend most or all months of the year living there. For example, the increased hazard of ES associated with Floridian residence may reflect recent migration from a northern state, but such migratory trends would have driven the tier-related results to the null. Furthermore, considerable ancillary evidence indicates that sunshine is implicated in ES. Fifth, we cannot capture the extent to which individuals residing in a given US state are exposed to the environmental conditions characteristic of that state. Some enrollees spend significant time outdoors because of their occupation or hobbies, whereas others may have limited exposure to environmental conditions. This eco-
logic bias may affect the present findings. Sixth, all the participants were US residents with health insurance; these findings may be nongeneralizable to other populations and regions. In conclusion, these data suggest that climatic factors may contribute to ES. More work exploring the relation between individual-level environmental exposures (with adjustment for lifestyle choices that might modify the ocular impact of climatic factors) and ES is needed. Discovery of environmental factors linked to ES could lead to primary prevention measures for this condition.

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Online-Only Material: The eTable is available at: www.archophthalmol.com.


