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Relation between time spent outdoors and exfoliation glaucoma or exfoliation glaucoma suspect

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Abstract

Purpose—To evaluate the relation between time spent outdoors at various life periods and risk of exfoliation glaucoma or exfoliation glaucoma suspect.

Design—Retrospective cohort study in the United States.

Methods—Participants (49,033 women in the Nurses Health Study and 20,066 men in the Health Professionals Follow-up Study) were 60+ years old, free of glaucoma and cataract, reported eye exams and completed questions about time spent outdoors in direct sunlight at mid-day at 3 life periods: high school to age 24 years, age 25-35 years, and age 36-59 years (asked in 2006 in women and 2008 in men). Participants were followed biennially with mailed questionnaires from 1980 (women) / 1986 (men) to 2010. Incident cases (223 women and 38 men) were confirmed with medical records. Cohort-specific multivariable-adjusted rate ratios from Cox proportional hazards models were estimated and pooled with meta-analysis.

Results—Although no association was observed with greater time spent outdoors in the ages of 25-35 or ages 36-59 years, the pooled multivariable-adjusted rate ratios for ≥11 hours per week spent outdoors in high school to age 24 years compared with ≤5 hours per week was 2.00 (95% confidence interval=1.30, 3.08; p for linear trend=0.001). In women, this association was stronger in those who resided in the southern geographic tier in young adulthood (p for interaction = 0.07).

Conclusions—Greater time spent outdoors in young adulthood was associated with risk of exfoliation glaucoma or exfoliation glaucoma suspect, supporting an etiologic role of early exposures to climatic factors.

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INTRODUCTION

Exfoliation syndrome can lead to serious ocular disease, such as secondary glaucoma[1] and retinal vein occlusion.[2-5] It can also lead to premature cataract[6] and is frequently associated with cataract surgery complications.[7-10] The underlying pathologic mechanisms of exfoliation syndrome that lead to the characteristic extracellular deposits in the anterior segment of the eye is believed to involve disordered extracellular matrix metabolism;[11] this is bolstered by the established link with common variants in the gene *LOXL1* that codes for lysyl oxidase-like 1 enzyme,[12] which catalyzes the first step in the formation of crosslinks in collagens and elastin. However, *LOXL1* gene variants occur in roughly 80% of controls, indicating that many unanswered questions remain regarding the etiology of exfoliation syndrome.

One clue that may shed light on the etiology of exfoliation syndrome is the striking trend of the disease being more common with greater distance from the equator, which has been observed throughout Europe, the Middle East, Asia and North America.[13-19] For example, in the cohorts of the Nurses Health Study and Health Professionals Follow-up Study from the United States, compared to northern tier residence (≥42° north), southern tier residence (<37° north), p articularly in adolescence, was associated with a 75% reduced risk of exfoliation glaucoma or exfoliation glaucoma suspect.[18] In addition, Stein et al.[19] confirmed that in the United States, current residence in the southern tier was associated with the lowest risk of exfoliation syndrome; in this study, several climatic factors were explored to elucidate the latitude gradient – of these, colder temperatures in the summer and winter months as well as greater number of sunny days per year were identified as independent predictors of increased risk of exfoliation syndrome. These data might suggest that greater time spent outdoors would increase the risk. Indeed, one study from Andhra Pradesh, India, found that working in occupations involving outdoor activities[20] was associated with ES,[21] and this was confirmed in other studies from the subcontinent.[22,23] However, only one study has evaluated current time spent outdoors in a general population and did not identify it as risk factor for exfoliation syndrome.[24] Thus, the data is limited, and time spent outdoors at different life stages has been little explored.

We used data from two cohorts of 49,033 women and 20,066 men aged 60 or more years living in the United States who were followed for at least 20 years for this analysis. They provided information on residence and time spent outdoors at 3 life periods (high school to age 24 years, age 25-35 years, and age 36-59 years) as well as other lifestyle and health information so we could examine the relation between time spent outdoors and risk of exfoliation glaucoma or exfoliation glaucoma suspect.

METHODS

Description of the cohort at risk for exfoliation glaucoma or exfoliation glaucoma suspect

This was a retrospective cohort study using data from two health professional cohorts. The Nurses Health Study is an ongoing cohort study initiated in 1976 when 121,700 female registered nurses completed a health questionnaire; the aim was to evaluate the long-term health effects of oral contraceptives.[25, 26] Established in 1986, the Health Professionals

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Follow-up Study is an ongoing cohort of 51,529 male health professionals (dentists, veterinarians, pharmacists, optometrists, osteopaths and podiatrists); participants completed a similar questionnaire for the evaluation of the health effects of nutritional factors.[27] Participants from both cohorts have been followed biennially with mailed questionnaires that allowed for updating health and lifestyle information. The study period was 1980 – 2010 for women and 1986 – 2010 for men. The study and data accrual were carried out with prospective approval from the Institutional Review Boards of the Brigham & Women's Hospital and Harvard School of Public Health and are in accordance with Health Insurance Portability and Accountability Act regulations.

Participants were excluded from analysis at baseline (defined as 1980 for women and 1986 for men) for the following reasons: 1) 23,239 women who did not respond to the initial 1980 semiquantitative food frequency questionnaire (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 food questionnaire (for women, adequate dietary information consisted of >50 of 61 items completed, yielding 500-3500 kilocalories per day, while for men, >61 out of 131 items completed with a total caloric intake range of 800-4200 kilocalories per day was regarded as adequate), 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) 846 women and 1,034 men who self-reported a diagnosis of glaucoma or glaucoma suspect at baseline, 5) 739 women and 984 men lost to follow-up shortly after baseline, 6) 5,659 women and 3,281 men who never reported an eye exam during follow-up and 7) 91 women and 169 with a history of cataract extraction in either eye at baseline (because exfoliation material is difficult to detect in the pseudophakic or aphakic state) and 8) 24,945 women and 19,982 men with missing information on time spent outdoors at various life periods, which were asked about in the 2006 and 2008 questionnaires, respectively. At each two-year risk period, we applied additional exclusions for participants who were under age 60 years and who did not report having had an eye exam in the two years at risk; we only included participants in a given 2-year risk period if they were at least 60 years of age or reported an eye exam. By 2010, a total of 49,033 women and 20,006 men contributed person-time. Follow-up rates through 2010 were high (> 85% of the total possible person-time). Participants contributed person-time until the date of confirmation as cases of exfoliation glaucoma or exfoliation glaucoma suspect, a self-report of glaucoma, a self-report of cataract extraction, a diagnosis of cancer other than nonmelanoma skin cancer, loss to follow-up, death, or the end of the study (2010), and then they were censored.

Case identification and confirmation

In all biennial questionnaires from 1986 in both cohorts, we included a question on physician-diagnosed glaucoma. For participants who self-reported such a diagnosis, we sought permission to obtain their medical information from all eye care providers. We then asked the diagnosing eye care provider of record to send all available visual field reports and to fill out a glaucoma questionnaire, which asked about the presence of exfoliation material or other secondary causes for elevated intraocular pressure, maximum untreated intraocular pressure, optic nerve features, and status of the filtration apparatus. Alternatively, eye care providers could provide copies of the complete medical records and all visual field reports related to the glaucoma diagnosis. For confirmation and classification, a glaucoma specialist (Dr. Louis R. Pasquale) evaluated the questionnaire or medical record information as well as the visual field data in a standardized manner. We included in the analysis only those cases classified as having either exfoliation glaucoma or exfoliation glaucoma suspect. Specifically, exfoliation glaucoma was considered to be present if documentation showed exfoliation material with ≥2 reliable visual field tests showing reproducible visual field loss consistent with glaucoma, and exfoliation glaucoma suspect was considered to be present if documentation showed exfoliation material plus one of the following three glaucomatous signs in the same affected eye(s): 1) a history of intraocular pressure >21 mm Hg or 2) cup-to-disc ratio >0.7 or the inter-eye difference in cup-to-disc ratio ≥0.2 or 3) only one reliable visual field test showing glaucomatous visual field loss. Those found to have exfoliation material only without any visual field loss, intraocular pressure elevation or abnormal cup-to-disc ratios in the affected eye(s) were not considered as cases and were censored from the analysis as of diagnosis date. During the study period, 8,032 women and 3,316 men reported that they had been diagnosed with glaucoma. Among the subset of 5,185 women and the 1,909 men in whom we were able to receive a confirmatory response from the diagnosing eye care provider, we observed the following breakdown: exfoliation glaucoma or exfoliation glaucoma suspect (368 women (7%); 85 men (4%)), primary open-angle glaucoma with visual field loss (2,148 women (42%); 929 men (49%)), only elevated intraocular pressure or optic disc cupping without secondary causes of intraocular pressure elevation (1,514 women (29%); 560 men (29%)) and other types of glaucomas or glaucoma suspect (1,155 women (22%); 335 men (18%)). For the analysis, we included 223 women and 38 men who met the standardized case definition of incident exfoliation glaucoma or exfoliation glaucoma suspect as well as other eligibility criteria.

Ascertainment of time spent outdoors

In 2006 in the Nurses Health Study and in 2008 in the Health Professionals Follow-up Study, participants were asked about the average time (≤1, 2-5, 6-10, ≥11 hours per week) spent outdoors in direct sunlight at the mid-day (10 am to 3 pm) for work or recreation purposes at 3 life periods: high school to age 24 years, age 25-35 years and age 36-59 years. In 1992 in both cohorts, we also asked about lifetime residence; we ascertained the state of residence at birth, at age 15, at age 25 (Health Professionals Follow-up Study) or 30 (Nurses Health Study), and we had updated current residence from 1976 in women and from 1986 in men. For other covariates, we also collected information from the biennial questionnaires on age, family history of glaucoma (any glaucoma in biologic parents or siblings), ancestry (Scandinavian Caucasian, southern European Caucasian, other Caucasian, other races) and updated information on history of cancer diagnosis, cataract diagnosis, cataract extraction, body mass index, systemic hypertension, high cholesterol, diabetes mellitus and history of myocardial infarction and pack years of cigarette smoking. Dietary intake of caffeine, alcohol and folate were assessed every 2 to 4 years from 1980 in the Nurses Health Study and 1986 in the Health Professionals Follow-up Study.

Statistical Analysis

First, we analyzed the data from each cohort separately in multivariable analyses and performed tests for heterogeneity to check whether pooling the results was appropriate. We used univariate and multivariable Cox proportional hazards analysis stratified by age in months and the specific 2-year period at risk to estimate relative risks and 95% confidence intervals.[28] In multivariable analyses, we controlled for potential exfoliation glaucoma risk factors by including them simultaneously as covariates. Covariates included were ancestry, family history of glaucoma, body mass index, self-reported hypertension, diabetes mellitus, high cholesterol, myocardial infarction, pack-years of cigarette smoking, caffeine, alcohol intake, folate intake, total caloric intake, geographical tier of residence at age 15, at age 25 (Health Professionals Follow-up Study) or 30 (Nurses Health Study) years, residence at 1976 in the Nurses Health Study and 1986 in the Health Professionals Follow-up Study) and current residence. We pooled the results using meta-analytic methods incorporating random effects.[29] We conducted tests for linear trend by including the midpoint values within each intake category of hours spent outdoors per week. $P<0.05$ was considered statistically significant. To investigate effect modification by family history of glaucoma and lifetime residential history,[18] we examined categories that represent cross-classifications between time spent outdoors and these potential effect modifiers in relation to risk of exfoliation glaucoma or exfoliation glaucoma suspect. We tested for effect modifications by testing interaction terms in models. SAS (v9.3, SAS Institute Inc., Cary, NC, USA) was used for all analyses.

RESULTS

We identified 223 women and 38 men with incident exfoliation glaucoma or exfoliation glaucoma suspect from 1980 to 2010 in the Nurses Health Study and 1986 to 2010 in the Health Professionals Follow-up Study, respectively. The total accrued person-time was 664,259 person-years (491,841 person-years from 49,033 women and 172,418 person-years from 20,006 men).

In the women and in the men, age and various age-adjusted characteristics that may be risk factors for exfoliation glaucoma were overall similar between the extremes of time spent outdoors (Table 1); compared to those with 1-5 hours per week spent outdoors, those with ≥11 hours per week spent outdoors at all life periods had higher caloric intakes. In general, participants who spent ≥11 hours per week outdoors in high school to age 24 years spent less time outdoors at later ages (Table 1 and Table 2), but those who spent ≥11 hours per week outdoors at any life period were also more likely to spend ≥11 hours per week outdoors at other life periods.

In univariate analyses, in women, compared to 1-5 hours per week spent outdoors, ≥11 hours per week spent outdoors in high school to age 24 years, at age 25-35 years and at age 36-59 years was adversely associated with exfoliation glaucoma or exfoliation glaucoma suspect status. In men, compared to 1-5 hours per week spent outdoors, ≥11 hours per week spent outdoors only in high school to age 24 years was associated with higher risk of exfoliation glaucoma or exfoliation glaucoma suspect status (Table 2). In multivariable analyses where the time spent outdoors at the three life periods were simultaneously adjusted for in the same model to allow for evaluating the independent associations for time spent outdoors at each life period, in both women and men, it was only greater time spent outdoors in high school to age 24 years that was adversely associated with exfoliation glaucoma or exfoliation glaucoma suspect status (Table 2). Compared to spending 1-5 hours per week outdoors, the pooled relative risk for spending 6-10 hours per week was 1.37 (95% confidence interval=0.99, 1.89), and the pooled relative risk for spending ≥11 hours per week was 2.00 (95% confidence interval=1.30, 3.08; pooled p for linear trend=0.001). The independent associations with greater time spent outdoors in ages 25-35 years and in ages 36-59 years were not significant (pooled p for linear trend of 0.67 and 0.11, respectively).

We explored whether the association with greater time spent outdoors in high school to age 24 years differed by robust risk factors for exfoliation glaucoma such as latitude of residence at age 15 or family history of glaucoma; these interactions were evaluated among women where we had greater power for statistical testing (Table 3). We observed that while the interactions were not statistically significant (p for interaction was 0.07 for residence and was 0.17 for family history), there were suggestive trends where greater time spent outdoors in high school to age 24 years was more strongly associated with exfoliation glaucoma or exfoliation glaucoma suspect status in subgroups at overall lower risk of exfoliation glaucoma, such as in those without a family history than in those with a family history of glaucoma and in those who lived closer to the equator (<42° north) than those who lived further away (≥42° north). The contrast of relative risks between ≥11 hours per week and 1-5 hours per week categories were 2.36 (95% confidence interval=1.21, 4.60) versus 1.00 in the <42° north stratum, which was stronger than the corresponding contrast of 4.08 (95% confidence interval=2.03, 8.22) versus 2.35 (95% confidence interval=1.41, 3.90) in the ≥42° north stratum.

DISCUSSION

In this large study involving two United States-based cohorts of participants aged 60 or more years, greater time spent outdoors from high school to age 24 was independently associated with a greater risk of exfoliation glaucoma or exfoliation glaucoma suspect status, supporting an etiologic role of early exposures to outdoor climatic factors on exfoliation glaucoma risk. No independent associations were observed for greater time spent outdoors in the ages of 25-35 years or ages 36-59 years. While suggestive interactions were observed with residence and family history, these findings may be due to chance and should be interpreted with caution.

Greater time spent outdoors represents an indicator of greater exposure to various climatic factors. Several lines of evidence point to the importance of climatic factors in exfoliation syndrome etiology. Multiple studies show that the prevalence of exfoliation syndrome is higher in non-equatorial regions than in equatorial regions.[13-19, 30] While many climatic factors may differ between these regions, two factors may be important for exfoliation syndrome:[19] colder temperature and greater ocular ultraviolet light exposures. Colder temperatures may facilitate the nucleation reactions that lead to the formation of extracellular deposits in exfoliation syndrome, especially in the anterior chamber and lens that are exposed to ambient temperature; however, these are likely to be more downstream influences.[19] Greater ultraviolet exposure has long been suspected to play a role in exfoliation syndrome, given the high exfoliation syndrome prevalences in populations with high sun exposure, including Australian Aborigines[31] and Navajo Indians[32] and the strong associations between exfoliation syndrome and climatic droplet keratopathy,[33] a condition associated with ultraviolet light exposure.[34] *In vitro* studies of human Tenon's capsule fibroblasts provide some support to ultraviolet light in exfoliation syndrome etiology: ultraviolet light exposure has been found to upregulate the expression of *LOXL1* and major elastic fiber proteins found in the exfoliation extracellular deposits and to lead to the formation of elastic microfibrillar aggregates resembling these deposits in the extracellular space.[35] While overall ultraviolet radiation to the body's skin and ambient ultraviolet radiation is greatest near equatorial regions, experimental studies have shown that ultraviolet exposure to the eye is actually greatest in non-equatorial latitudes,[36] especially close to the polar regions where ultraviolet intensity may be greatest.[37, 38] In addition to the indirect ocular ultraviolet exposure from scattered ultraviolet rays found in all latitudes, non-equatorial regions allow for significantly more direct entry of ultraviolet rays to the eye than equatorial regions due to the sun's rays coming in at a lower angle in the sky throughout the day (~ 40° angle). In addition, non-equatorial regions allow for more of the indirect reflected ocular ultraviolet exposure as they are more likely to have snow, which can reflect up to 80% of the sun's rays,[39] further increasing the intensity of ocular ultraviolet exposure in those living in such regions. Although the association with exposure to climatic factors throughout the lifetime may be important, we observed that the association with exfoliation glaucoma or exfoliation glaucoma suspect status was most strongly adverse for the amount of time spent outdoors during mid-day in high school to age 24 years in contrast to the associations with time spent outdoors at other ages. This may be due to the fact that for most participants, time spent outdoors was maximal in this life period than at later periods. Also, at younger ages, pupils are larger, lenses are thinner and clearer, and so the anterior chamber at early ages may be more vulnerable to ultraviolet damage,[40, 41] and this damage could manifest at a later age.[42]

Few previous studies have evaluated time spent outdoors in relation to exfoliation glaucoma. One measure of time spent outdoors is type of occupation;[20] one study from Andhra Pradesh, India, found that working in occupations involving outdoor activities was associated with exfoliation syndrome,[21] and this was confirmed in other studies from the subcontinent.[22,23] Only one other study has evaluated time spent outdoors and did not observe that it predicted incidence of exfoliation syndrome after various follow-up periods;[24, 43] however, it is possible that the null association was because only current time spent outdoors was assessed and not the time spent outdoors at various life periods. Thus, further studies of time spent outdoors at all life periods are warranted.

We observed trends of stronger associations with time spent outdoors during mid-day in those without a family history and in those who resided <42° north at age 15 years. These trends may have been due to chance and should be interpreted with caution. One could speculate that the possible weaker association with time spent outdoors during mid-day (10 am to 3 pm) in high school to age 24 in those who resided in the northern states (≥42° north) at age 15 compared to those who resided in lower states may be because new risk factors may be easier to detect in populations with lower risk of disease than in those with higher risk such as those residing in higher latitudes. Alternatively, it may be because in the northern states, for most of the year except the winter, the greatest direct ocular ultraviolet exposure is actually from 8 to 10 am in the morning and from 2-4 pm when the sun's rays come in at a low angle (~ 40° angle) than during mid-day, and our questions did not capture time spent outdoors at those other times.[36]

This study had other limitations. One limitation is that we could not conduct direct repeated eye exams in these large cohorts, and thus, our case ascertainment method had low sensitivity, and we likely missed many true cases, especially as exfoliation syndrome is difficult to detect and diagnose. In addition, our method was susceptible to differing detection rates of exfoliation syndrome or exfoliation glaucoma depending on eye care providers. However, because our intent was to estimate the relative rate ratios across exposure categories, and our case ascertainment method had high specificity, the proportion who were under-ascertained due to participant or eye care provider characteristics was likely not related to the exposure; thus, methodologically, the estimates will be valid.[44] Another limitation was that the assessment of time spent outdoors at various life stages relied on self-report, which is susceptible to inaccuracies in recalling distant past events compared to objective measures of outdoor exposure. The resulting measurement errors, which are not differential with respect to the case status, would likely produce null findings and may explain some of the null associations we observed with time spent outdoors in the later life stages. Also, the questions on exposure to time spent outdoors at various life stages occurred in 2006 for women and 2008 for men, which was towards the end of the follow-up period such that for most exfoliation glaucoma or exfoliation glaucoma suspect cases, the exposure was assessed after their disease. While this was a retrospective cohort study with some potential for recall bias (where those with a potentially blinding disease are more likely to recall greater time spent outdoors), the fact that associations were specific to exposures at young adulthood rather than showing systematic positive associations with greater exposure at all life periods makes it unlikely that such bias may explain all of the association with exposures at young adulthood. In addition, bias may arise from differential follow-up with respect to exposure and case status; however, follow-up differed minimally by time spent outdoors, making this possibility unlikely. Also, the crude measure of overall time spent outdoors did not allow us to evaluate associations with patterns of time spent outdoors, which may show seasonal and geographic variability. Finally, this study was on mostly healthy European-derived Caucasians in the United States; the associations with time spent outdoors, particularly in adolescence, may differ by latitude and population as the hypothesized climatic factors and susceptibility to them may vary by geographic region and population characteristics.

Overall, this study's strengths included the large sample size (over 65,000 participants) and updated information on many important covariates including age, ancestry, family history of glaucoma and various medical conditions and lifestyle factors as well as the exposure information in combination with residential histories at various life periods, allowing us to evaluate whether there was a critical time period for when greater time spent outdoors may be important for exfoliation glaucoma or exfoliation glaucoma suspect risk. If confirmed by other studies, this may offer a strategy to reduce the incidence of exfoliation glaucoma by the modification of exposure to the outdoors at young ages.

In conclusion, in this study from the United States of a predominantly Caucasian population of adults over age 60 years, greater time spent outdoors in young adulthood was associated with a greater risk of exfoliation glaucoma or exfoliation glaucoma suspect status supporting an etiologic role of early exposures to outdoor climatic factors on exfoliation glaucoma risk.

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Biography

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Table 1

Age and age-adjusted characteristics of the person-time accumulated over the follow-up period in women (491,841 person-years from 1980 to 2010) and in men (172,418 person-years from 1986 to 2010) for extreme categories of time spent outdoors (hours per week) at three life periods: high school to age 24 years, ages 25-35 years and ages 36-59 years

	Time outdoors – high school-age 24 years		Time outdoors – age 25-35 years		Time outdoors – age 36-59 years	
WOMEN	**1-5 hours per week**	**≥11 hours per week**	**1-5 hours per week**	**≥11 hours per week**	**1-5 hours per week**	**≥11 hours per week**
Mean age (years) [Standard Deviation]	67[6]	67[5]	67[6]	66[5]	67[5]	67[5]
Total folate (micrograms/day) [Standard Deviation]	462[180]	471[181]	461[179]	469[177]	463[178]	464[179]
Total caloric intake (kilocalories per day) [Standard Deviation]	1683[406]	1770[419]	1679[404]	1778[418]	1686[404]	1777[419]
Alcohol intake (grams per day) [Standard Deviation]	6[9]	6[9]	6[8]	7[9]	6[8]	7[10]
Caffeine intake (grans per day) [Standard Deviation]	281[181]	284[179]	281[182]	286[181]	281[181]	285[181]
Residence in the northern tier[a] in high school (%)	43	42	42	44	42	44
Residence in the northern tier[a] at age 25-35 years (%)	41	41	40	42	40	43
Residence in the northern tier[a] in 1976 (%)	40	40	39	41	39	42
Scandinavian ancestry (%)	7	8	7	8	7	7
Family history of glaucoma (%)	13	13	13	14	13	13
Self-reported diabetes diagnosis (%)	7	8	7	8	7	7
Self-reported hypertension diagnosis (%)	49	50	49	50	50	48
Self-reported high cholesterol diagnosis (%)	60	61	60	61	61	60
Self-reported myocardial infarction (%)	3	3	3	3	3	3
≥30 pack-years of cigarette smoking (%)	17	18	17	17	17	18
Body mass index (kilograms per meter^2) ≥30 (%)	19	22	20	21	20	19
Mean number of eye exams reported (of 11) [Standard Deviation]	7[3]	8[3]	7[3]	8[3]	7[3]	8[3]
≥11 hours per week outdoors in high school to age 24 years (%)	0	100	2	58	4	51
≥11 hours per week outdoors at age 25-35 years (%)	3	53	0	100	1	77
≥11 hours per week outdoors at age 36-59 years (%)	3	36	1	60	0	100
MEN						
Mean age (years) [Standard Deviation]	68[6]	67[6]	68[6]	67[6]	68[6]	67[6]

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	Time outdoors – high school-age 24 years		Time outdoors – age 25-35 years		Time outdoors – age 36-59 years	
WOMEN	**1-5 hours per week**	**≥11 hours per week**	**1-5 hours per week**	**≥11 hours per week**	**1-5 hours per week**	**≥11 hours per week**
Total folate (micrograms per day) [Standard Deviation]	597[254]	581[226]	598[248]	573[227]	597[247]	569[226]
Total caloric intake (kilocalories/day) [Standard Deviation]	1908[510]	2046[519]	1914[506]	2062[526]	1924[510]	2069[530]
Alcohol intake (grams per day) [Standard Deviation]	11[13]	12[13]	11[13]	12[13]	10[13]	13[13]
Caffeine intake (grams per day) [Standard Deviation]	220[203]	223[194]	222[202]	228[196]	221[201]	232[197]
Residence in the northern tier[a] in high school (%)	40	37	39	37	38	38
Residence in the northern tier[a] at age 25-35 years (%)	33	31	32	31	31	32
Residence in the northern tier[a] in 1986 (%)	33	34	32	34	32	35
Scandinavian ancestry (%)	8	13	9	13	10	14
Family history of glaucoma (%)	11	12	12	12	11	12
Self-reported diabetes diagnosis (%)	8	7	8	7	8	7
Self-reported hypertension diagnosis (%)	43	41	42	42	42	42
Self-reported high cholesterol diagnosis (%)	52	54	53	54	52	54
Self-reported myocardial infarction (%)	8	7	7	7	8	7
≥30 pack-years of cigarette smoking (%)	17	16	15	17	15	17
Body mass index (kilograms per meter^2) ≥30 (%)	10	12	10	13	11	12
Mean number of eye exams reported (of 11) [Standard Deviation]	7[3]	7[3]	7[3]	7[3]	7[3]	7[3]
≥11 hours per week outdoors in high school to age 24 years (%)	0	100	14	89	19	85
≥11 hours per week outdoors at age 25-35 years (%)	3	58	0	100	3	87
≥11 hours per week outdoors at age 36-59 years (%)	5	48	2	75	0	100

[a] Residence in states north of the 41-42 degrees latitude north (AK, CT, ID, ME, MA, MI, MN, MT, NE, NH, NY, ND, OR, RI, SD, VT, WA, WI, WY)

Table 2

Time spent outdoors at three life periods (determined in 2006 in women and 2008 in men)[a] in relation to the risks of exfoliation glaucoma or exfoliation glaucoma suspect _in women (1980-2010) and in men (1986-2010)

			Time spent outdoors (hours per week)			
Time spent outdoors [a]			**1-5**	**6-10**	**≥11**	**P for linear trend**
High School to Age 24 years	Women	%	63	24	13	
		Cases	123	62	38	
		Person-time	307,741	120,055	64,045	
		Age-adjusted Rate Ratio (95% Confidence Interval)	1.00 (reference)	1.42 (1.04, 1.93)	1.71 (1.18, 2.47)	0.002
		Multivariable Rate Ratio (95% Confidence Interval)[b]	1.00 (reference)	1.42 (1.01, 1.99)	1.96 (1.23, 3.12)	0.004
	Men	%	28	24	48	
		Cases	10	9	19	
		Person-time	48,611	41,179	82,628	
		Age-adjusted Rate Ratio (95% Confidence Interval)	1.00 (reference)	0.76 (0.29, 2.04)	1.16 (0.53, 2.52)	0.32
		Multivariable Rate Ratio (95% Confidence Interval)[b]	1.00 (reference)	0.96 (0.32, 2.89)	2.31 (0.74, 7.19)	0.09
	Pooled	Multivariable Rate Ratio (95% Confidence Interval)[b, c]	1.00 (reference)	1.37 (0.99, 1.89)	2.00 (1.30, 3.08)	0.001
Age 25-35 years	Women	%	60	28	12	
		Cases	124	72	27	
		Person-time	295,162	137,968	58,711	
		Age-adjusted Rate Ratio (95% Confidence Interval)	1.00 (reference)	1.39 (1.03, 1.86)	1.28 (0.84, 1.95)	0.05
		Multivariable Rate Ratio (95% Confidence Interval)[b]	1.00 (reference)	1.28 (0.87, 1.87)	1.05 (0.54, 2.04)	0.54
	Men	%	40	29	31	
		Cases	16	8	14	
		Person-time	67,979	50,575	53,865	
		Age-adjusted Rate Ratio (95% Confidence Interval)	1.00 (reference)	0.61 (0.25, 1.45)	0.98 (0.46, 2.11)	0.80
		Multivariable Rate Ratio (95% Confidence Interval)[b]	1.00 (reference)	0.65 (0.20, 2.10)	0.70 (0.12, 4.03)	0.88

Time spent outdoors [a]			Time spent outdoors (hours per week) 1-5	6-10	≥11	P for linear trend
	Pooled	Multivariable Rate Ratio (95% Confidence Interval)[b, c]	1.00 (reference)	1.15 (0.72, 1.85)	1.00 (0.54, 1.86)	0.67
Age 36-59 years	Women	%	67	24	9	
		Cases	145	58	20	
		Person-time	326,620	119,522	45,699	
		Age-adjusted Rate Ratio (95% Confidence Interval)	1.00 (reference)	1.14 (0.84, 1.56)	1.08 (0.67, 1.72)	0.44
		Multivariable Rate Ratio (95% Confidence Interval)[b]	1.00 (reference)	0.84 (0.57, 1.24)	0.69 (0.36, 1.35)	0.18
	Men	%	44	29	27	
		Cases	19	7	12	
		Person-time	75,579	50,427	46,412	
		Age-adjusted Rate Ratio (95% Confidence Interval)	1.00 (reference)	0.45 (0.18, 1.14)	0.97 (0.45, 2.05)	0.85
		Multivariable Rate Ratio (95% Confidence Interval)[b]	1.00 (reference)	0.35 (0.10, 1.17)	0.68 (0.13, 3.49)	0.39
	Pooled	Multivariable Rate Ratio (95% Confidence Interval)[b, c]	1.00 (reference)	0.66 (0.30, 1.44)	0.69 (0.37, 1.28)	0.11

[a] Average hours per week spent outdoors in direct sunlight at mid-day for work or recreation purposes (questions were asked in 2006 in women and 2008 in men)

[b] All multivariable analyses were stratified by age in months and period at risk, and they were adjusted for the following variables: ancestry (Scandinavian Caucasian, southern European Caucasian, other Caucasian, other races), family history of glaucoma, self-reported history of high cholesterol, hypertension, diabetes, myocardial infarction, body mass index (22-23, 24-25, 26-27, 28-29, 30+ kilograms per meter^2), cumulatively averaged total energy intake (kilocalories per day), alcohol intake (grams per day), caffeine intake (milligrams per day), folate intake (micrograms per day), pack-years of cigarette smoking (1-9, 10-19, 20-29, 30+ pack-years), residence in states north of the 41-42 degrees latitude north (AK, CT, ID, ME, MA, MI, MN, MT, NE, NH, NY, ND, OR, RI, SD, VT, WA, WI, WY); residence in the states south of the 37 degrees latitude north (AL, AZ, AR, C2, FL, GA, HI, LA, MS, NM, NC, OK, PR, SC, TN, TX and southern California from Los Angeles to its southern border) and residence in 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, at age 15, age 25 (men) / 30 (women), residence in 1976 in women and 1986 in men, and current residence. The time spent outdoors for the three life stages were simultaneously adjusted for in models.

[c] Pooled results were calculated using Dersimonian and Laird methods with random effects; p-values for heterogeneity between cohorts for all results were > 0.05.

Table 3

Multivariable relative risks (95% confidence intervals)[a] for time spent outdoors from high school to age 24 years by residence at age 15 years and family history in relation to the risks of exfoliation glaucoma or exfoliation glaucoma suspect in women only (1980-2010)

	Time spent outdoors (hours per week)			
By residence at age 15years	**1-5**	**6-10**	**≥11**	**P for interaction**
<42° north (middle or southern tier)[b]	1.00 (reference)	2.11 (1.28, 3.47)	2.36 (1.21, 4.60)	
≥ ***42°north (northern tier)***[b]	2.35 (1.41, 3.90)	2.48 (1.36, 4.53)	4.08 (2.03, 8.22)	0.07
By family history of glaucoma				
Without family history	1.00 (reference)	1.63 (1.11, 2.38)	2.21 (1.33, 3.67)	
With family history	3.20 (2.17, 4.73)	3.04 (1.62, 5.73)	4.61 (2.07, 10.29)	0.17

[a]Multivariable analyses were adjusted for the same covariates as listed in b footnote of Table 2.

[b]States in each geographic tier of the United States are listed in footnote b of Table 2.