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Ultraviolet radiation exposure and risk of herpes zoster in three prospective cohort studies

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Abstract

Objective: To examine the association between ultraviolet radiation (UVR) exposure and risk of herpes zoster (HZ) in three prospective cohorts.

Patients and Methods: We included 205,756 participants from the Health Professionals Follow-up Study (HPFS; 1986–2008), Nurses' Health Study (NHS; 1996–2012), and Nurses' Health Study II (NHS II; 1991–2013). Ambient UVR exposure was based on updated geocoded address histories linked with a high-resolution spatiotemporal UV model. Incident HZ cases were identified by self-reported clinician diagnosis. Sunburn history, medical, lifestyle and dietary factors were assessed via biennial questionnaires. Multivariable Cox proportional hazards models were used.

Results: A total of 24,201 cases of HZ occurred during 3,626,131 person-years. Ambient UVR exposure was associated with a higher risk of HZ in men (multivariable-adjusted hazard ratio [MVHR] comparing highest vs. lowest quintiles: 1.14; 95% CI: 1.02, 1.29; *P*-trend=.03 in HPFS), but not in women (MVHR 0.99; 95% CI: 0.93, 1.05 in NHS and MVHR 0.96; 95% CI: 0.90, 1.03 in NHS II). Higher lifetime number of severe sunburns was associated with a higher risk of HZ in all cohorts (MVHR for ≥10 sunburns vs. none: 1.08; 95% CI: 0.96, 1.20; *P*-trend=.02 in HPFS;

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MVHR 1.14; 95% CI: 1.05, 1.22; *P*-trend=.01 in NHS; and MVHR 1.13; 95% CI: 1.00, 1.28; *P*-trend<.001 in NHS II).

Conclusion: Ambient UVR was associated with a higher risk of HZ in men but not women. A history of severe sunburn was associated with a modest increased risk of HZ in men and women, possibly due to immunosuppression from overexposure to the sun.

Introduction

Herpes zoster (HZ), also known as shingles, causes a painful, blistering rash, and results from the reactivation of the latent varicella-zoster virus (VZV).[1, 2] One of the serious complications is postherpetic neuralgia (PHN), as pain may persist for several months to years. The major risk factors for HZ are age and immunocompromising conditions that result in impaired cell-mediated immunity.[2, 3] Other reported risk factors include family history of shingles, autoimmune diseases, depression, asthma, diabetes mellitus, and chronic obstructive pulmonary disease.[4–6] However, HZ can occur unpredictably and the precipitant is often unknown. The age-specific incidence of HZ has increased over time across the world.[7–12] In the U.S., the incidence rate of HZ rose from 0.76 to 3.15 per 1000 person-years between 1945–49 and 2005–07.[11] Although the reasons remain unknown, environmental factors may play a role.

One plausible risk factor for HZ is exposure to ultraviolet radiation (UVR) from sunlight, because it may suppress cell-mediated immune response.[13, 14] Several observations support this hypothesis. The risk of HZ is higher in the summer than other seasons, possibly due to high UVR exposure.[9, 10, 14] Ecological studies from Taiwan and Australia suggested that high UV index correlates with the incidence of HZ over time.[10, 15] Additionally, a study of transplant recipients reported that high UVR was associated with an increased risk of reactivation of VZV and herpes simplex virus (HSV).[16] It is noteworthy that VZV belongs to the same member of the *herpesviridae* family as HSV, which has been shown to reactivate from its latent state from UVR.[13, 17] Black individuals have almost a 50% lower risk of developing HZ than white individuals.[5, 7] This may plausibly be due to the increased skin melanin content providing photoprotection against UVR exposure. UVR exposure is a major risk factor for skin cancer and accumulating evidence suggests that UVR causes local and systemic immunosuppression, a potential underlying mechanism for the development of skin cancer.[18] To our knowledge, no prior longitudinal study has examined the association of UVR with the risk of HZ.

The objective of our study was to examine the association between ambient UVR exposure and the incidence of HZ in three prospective cohorts involving more than 205,000 participants: Health Professionals Follow-up Study, Nurses' Health Study, and Nurses' Health Study II. We also examined the relation of skin reaction to prolonged sun exposure during childhood/adolescence, lifetime number of severe sunburns, and natural hair color and risk of HZ.

Methods

Study population

The Health Professionals Follow-up Study (HPFS) began in 1986 and enrolled 51,529 male health professionals aged 40 to 75 years. The Nurses' Health Study (NHS) was established in 1976 and enrolled 121,700 female registered nurses aged 30 to 55 years. The Nurses' Health Study II (NHS II) began in 1989 and enrolled 116,430 female registered nurses aged 25 to 42 years. In all three ongoing cohort studies, participants are followed via biennial questionnaires on medical and lifestyle information. The follow-up has exceeded 90% of eligible person-time in all three studies. Three large, long-term prospective cohort studies provided an opportunity to investigate the association between UVR exposure and incidence of HZ in men and women.

The current study was conducted during 22 years of follow-up in HPFS (1986–2008), 16 years of follow-up in NHS (1996–2012), and 22 years of follow-up in NHS II (1991–2013). We restricted the study to white men and women because the majority of participants were white and the association between UVR and the risk of HZ may differ by race. We excluded participants with a history of HZ at baseline. After exclusion, 29,123 men from the HPFS, 81,143 women from the NHS, and 95,490 women from the NHS II were included in the current study. This study was approved by the Institutional Review Board of Brigham and Women's Hospital.

Exposure assessment

UV exposure was estimated using a high spatiotemporal resolution model that predicts average July noon-time erythemal UV irradiance in units of mW/m^2. Erythemal UV incorporates UV-A and UV-B wavelengths to calculate a measure describing the relative effectiveness of UV to induce erythema on Caucasian skin. The UV exposure model was created by applying area-to-point residual kriging to downscale National Aeronautics and Space Administration (NASA) erythemal UV satellite remote sensing images and incorporates information on known predictors of UV including aerosol optical depth, cloud cover, and ozone.[19] The spatial resolution of the model is 1 km^2. Model cross-validation demonstrated high predictive performance, showing positive percent relative improvements in mean absolute error (0.6–31.5%) and root mean square error (3.6–29.4%) in UV exposure prediction compared to using NASA satellite images only. The annual erythemal UVR exposure was based on updated address histories and treated as a time-varying variable during follow-up. The mailing address of each participant was updated every 2 years. Thus, the recent UVR exposure was based on the most recent residential address, which was up to 2 years old. At the time of enrollment, HPFS participants were from all 50 states. NHS participants resided in 11 states and NHS II participants resided in 14 states; participants have since dispersed across the county.

Participants were queried on skin reaction to prolonged sun exposure during childhood or adolescence. HPFS participants were asked about skin reaction in the following categories: tan without burning, burn then tan, or painfully burn then peel. NHS and NHS II participants were asked about skin reaction to prolonged sun exposure in the following categories:

practically none, some redness only, burn, painful burn, or painful burn with blisters. The number of lifetime severe/blistering sunburns (none, 1–4, 5–9, ≥10) and natural hair color (red or blonde, light brown, dark brown, black) were also queried. Information regarding history of sunburn was assessed in 1992 in the HPFS, in 1982 in the NHS, and in 1989 in the NHS II.

Outcome assessment

The outcome of interest was a self-reported clinician diagnosis of HZ. Participants were queried about clinician diagnosed "shingles" and the year of diagnosis on the questionnaires in 2004, 2006 and 2008 in HPFS, in 2000, 2004, 2008, and 2012 in NHS, and in 2001, 2005, and 2013 in NHS II. To confirm the validity of self-report diagnosis, we mailed a supplementary questionnaire to 99 women in NHS II asking for permission to obtain medical records relating to the diagnosis of HZ. The records received were reviewed by a physician investigator (GCC) and the diagnosis of HZ was confirmed in 97%, demonstrating that self-reported diagnosis of HZ is highly reliable.

Assessment of covariates

We considered a number of demographic, medical, diet and lifestyle factors that could be potential confounding factors in our analyses. Based on the prior studies of HZ, we considered age and the following comorbidities: cancer, rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, chronic kidney disease, diabetes mellitus, asthma, chronic obstructive pulmonary disease, and depression.[4, 5] Though limited, prior studies suggested that diet, cholesterol level, smoking, sleep duration, and weight may be associated with risk of HZ.[20–22] These factors and other relevant factors that may affect immune status were considered in the multivariable model. Use of corticosteroids, use of analgesics (ibuprofen, acetaminophen, and aspirin), and elevated cholesterol were included. For lifestyle factors, we considered smoking status, body mass index (BMI), waist circumference, physical activity, sleep duration, and the alternate Mediterranean diet (AMED) score, which is a measure of adherence to the Mediterranean diet pattern.[23, 24] The AMED includes 9 components: vegetables, fruits, nuts, whole grains, legumes, fish, red or processed meats, alcohol consumption, and monounsaturated fatty acid–saturated fatty acid ratio. Additionally, parity, oral contraceptive use, and hormone therapy were considered among women in NHS and NHS II.

Statistical analysis

Ambient UVR exposure was categorized into quintiles. Participants contributed person-time from the date of completion of the baseline questionnaire (1986 in the HPFS, 1996 in the NHS, and 1991 in the NHS II) until the first diagnosis of shingles, death, loss to follow up, or the end of follow up. Multivariable Cox proportional hazards models, stratified by age and calendar year (2-year cycles) as the underlying time scale, were used to examine the association between UVR and risk of HZ. Proportional hazards assumption was evaluated by entering interaction term between UVR exposure and follow-up time; no violations of the assumption were found. *P*-values for trend were based on the median values for ordered categorical variables. We also performed a competing risk analysis. The cause-specific

hazards were modeled to account for death being a competing risk to shingles. We obtained similar results when competing risk was accounted for.

We conducted subgroup analyses by age group (<65 years vs. ≥65 years for HPFS and NHS and <50 years vs. ≥50 years for NHS II) to examine whether the association between UVR and risk of HZ differed by age group. We also evaluated interaction between ambient UVR exposure and skin reaction to prolonged sunlight by including the interaction terms in the models. Because UVR exposure affects the risk of skin cancer, we conducted a sensitivity analysis in which participants were censored when they were diagnosed with melanoma, squamous cell carcinoma, or basal cell carcinoma. Statistical significance was based on a 2-sided $P < .05$. All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

Among 205,756 participants, mean age was 52 years in HPFS, 62 years in NHS, and 36 years in NHS II at baseline. Baseline characteristics of participants according to ambient UVR exposure status are presented in Table 1 (Supplemental Tables 1–3). In all three cohorts, the characteristics of participants, including age, physical activity, and comorbidities, were similar across the quintiles of UVR exposure groups. Among men, 2,977 incident cases of HZ occurred during 551,364 person-years of follow-up. Among women, 11,314 incident cases of HZ occurred during 1,106,517 person-years of follow-up in the NHS and 9,910 incident cases of HZ occurred during 1,968,250 person-years of follow-up in the NHS II.

Higher ambient UVR exposure was associated with a higher risk of HZ in men but not women (Table 2). In men, the multivariable-adjusted hazard ratio (MVHR) for the highest quintile compared with the lowest quintile of updated ambient UVR exposure was 1.14 (95% CI: 1.02, 1.29; P for trend = .03). In women, the MVHR was 0.99 (95% CI: 0.93, 1.05) in NHS and 0.96 (95% CI: 0.90, 1.03) in NHS II. The age-adjusted and multivariable-adjusted HRs were similar in all three cohorts (Supplemental Table 4). We obtained similar results when we examined the association between the baseline ambient UVR exposure and risk of HZ.

Skin reaction to prolonged sunlight during childhood/adolescence was associated with a higher risk of HZ in men (MVHR for severe burn vs. none = 1.20; 95% CI: 1.08, 1.33; P for trend <.001) and women in NHS II (MVHR = 1.12; 95% CI: 1.02, 1.22; P for trend = .002), but not in NHS (MVHR = 1.01; 95% CI: 0.92, 1.12; P for trend = .71) (Table 3). Higher number of severe or blistering sunburns was associated with an increased risk of HZ in men (MVHR for ≥10 sunburns vs. none = 1.08; 95% CI: 0.96, 1.20; P for trend = .02), and in women (NHS: MVHR = 1.14; 95% CI: 1.05, 1.22; P for trend = .01 and NHS II: MVHR = 1.13; 95% CI: 1.00, 1.28; P for trend <.001). No association between natural hair color and risk of HZ was observed in any of the cohorts.

We also examined the associations stratified by age category in each cohort and overall observed similar findings across age groups (P-values for interaction > .05). However, for

NHS II, skin reaction during childhood/adolescence was associated with a higher risk of HZ for women <50 years of age (MVHR for painful burn with blisters vs. none = 1.18; 95% CI: 1.05, 1.33) but not women ≥50 years of age (MVHR = 1.04; 95% CI: 0.91, 1.18; *P* for interaction = .02). We did not observe any significant interaction between ambient UVR exposure and skin reaction to prolonged sunlight in all three cohorts (*P*-values for interaction > .05). In sensitivity analysis censoring patients diagnosed with skin cancer, results were similar to the main findings (Supplemental Table 5).

Discussion

We examined the association between UVR exposure and risk of HZ in three large cohorts of men and women. Recent ambient UVR exposure was associated with a higher risk of HZ among men in HPFS but not among women in NHS and NHS II. In addition, skin reaction to prolonged sunlight was associated with a higher risk of HZ in men in HPFS and younger women in NHS II. Higher lifetime number of severe/blistering sunburns was associated with an increased risk of HZ in all three cohorts.

This is the first report of the longitudinal association of UVR exposure and risk of HZ. Seasonal variation in the incidence of HZ has been reported, peaking in the summer.[9, 10, 14] Ecological studies also suggest that higher UV index correlates with the incidence of HZ.[10, 15] One possible mechanism for the increased risk of HZ is UV-induced immunosuppression. UV exposure causes local immunosuppression but also initiates a cascade of events that lead to systemic immunosuppression.[13, 18] UV absorption in the skin causes DNA damage and isomerization of *trans*-to *cis*-urocanic acid, which is a mediator of immunosuppression.[25] UV exposure impairs function of antigen-presenting cells and releases a wide range of immune mediators such as prostaglandin-E_2, IL-4, TNF-α, in the draining lymph node, which leads to a shift from Th1 towards Th2 response.[26] UV exposure also leads to secretion of immunoregulatory cytokines such as IL-10, which results in up-regulation of T regulatory cells and suppression of T cell-mediated immunity.[27] Robust VZV-specific T cell-mediated immunity is essential to limit the propagation of the VZV virus when the latent VZV reactivates.

We found that greater susceptibility to sunburn during childhood/adolescence was associated with a higher risk of HZ in men in HPFS and younger women in NHS II. Sunburn is common, especially among young adults.[28] Higher lifetime number of severe/blistering sunburns was associated with an increased risk of HZ later in life in all three cohorts. Susceptibility to sunburn may be a marker of increased sensitivity to harmful effects of UVR, including immunosuppression. Alternatively, severe sunburns during early life may have long-term immunomodulating effects, which may suppress the immune response to VZV reactivation later in life. It is difficult from our study to determine whether the increased risk of HZ was largely due to the acute effects or long-term effects of UV-induced immunosuppression. Our findings support the importance of protection from intense UVR exposure to potentially reduce risk of HZ, particularly in people prone to sunburn.

Higher ambient UVR exposure was previously demonstrated to increase the risk of skin cancer.[29, 30] Our hypothesis was based on the assumption that UVR may trigger acute

effects on the risk of HZ. Thus, we used updated geocoded address histories to examine the recent ambient UVR exposure. Ambient erythemal UVR was based on the high-resolution spatiotemporal UV exposure model that accounted for ozone, aerosol optical depth, cloud cover, latitude, and other predictors of UV. Although an objective measure, ambient UVR does not account for the individual amount of time spent outdoors, proportion of exposed skin, or exposure during holiday travel. It is unclear why the association of ambient UVR with risk of HZ was observed in men but not women. The observed difference may be due to biological or behavioral differences. Prior studies found that men were more susceptible to UV-induced immunosuppression and had lower threshold to induce immunosuppression than women.[31, 32] It may also be due to sex difference in the use of sunscreen or other sun protection.

Our findings have important public health implications and provide additional support for promoting preventive measures to protect against the risks from sun exposure. Our study also sheds light on the importance of studying the long-term impact of environmental factors on infectious diseases and public health, as UVR exposure may affect the human's host response to viral infections.

Major strengths of our study include the prospective cohort study design, large number of participants, updated exposure measurements, and a long follow-up period of almost 20 years. Moreover, an evaluation of three independent cohort studies allowed us to evaluate the consistency and robustness of our findings. Although cases of HZ were based on self-reported clinician diagnosis, our validation study demonstrated high reliability. The validity of HZ obtained by self-report may not be as high in the general population;[33] however, self-reported cases of HZ are likely valid in our study consisting of healthcare professionals. We adjusted for potential confounding factors including age, comorbidities, physical activities, diet, smoking, and other lifestyle factors. Our study also has limitations. The ambient UVR exposure and a history of sunburn may be subject to measurement error. Personal time spent outdoors and use of sun protection were not evaluated. Such misclassification of exposure may have attenuated our findings. Better understanding of the amount and time course of UVR exposure would be important in future research. We did not have information on HZ vaccination; however, the uptake of zoster vaccine has been low. National vaccine coverage was 24% in 2013 among adults >60 years of age.[34] Most of the study period occurred before the vaccine became available in 2006. Most participants from NHS II were younger than recommended age of vaccination. Thus, vaccine uptake is unlikely to have affected our findings. Additionally, this was an observational study and findings may have been affected by unmeasured confounding factors. Our analyses were restricted to white individuals; therefore, our findings may not be generalizable to other races.

Conclusion

Ambient UVR exposure was associated with a higher risk of HZ in men in HPFS but not women in NHS and NHS II. Higher lifetime number of severe sunburns was associated with a modest increased risk of HZ in all three cohorts. Our findings highlight the importance of future research on long-term immunomodulating effects from overexposure to UVR.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

UVR	ultraviolet radiation
HZ	herpes zoster
VZV	varicella-zoster virus
HPFS	Health Professionals Follow-up Study
NHS	Nurses' Health Study
NHS II	Nurses' Health Study II
HR	hazard ratio
MVHR	multivariable-adjusted hazard ratio
CI	confidence interval

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Table 1.

Baseline characteristics of study participants according to quintile of ambient ultraviolet radiation exposure in Health Professionals Follow-up Study (1986), Nurses' Health Study (1996), and Nurses' Health Study II (1991)

	HPFS			NHS			NHS II		
	Q1	**Q3**	**Q5**	**Q1**	**Q3**	**Q5**	**Q1**	**Q3**	**Q5**
Participants, n	5380	5486	5117	15632	15692	14696	18644	19548	17327
Ambient UVR, mW/m^2, median (IQR)	164 (162–167)	183 (181–186)	237 (228–245)	165 (163–168)	185 (182–188)	248 (221–261)	162 (159–166)	177 (176–179)	221 (212–242)
Age, years, mean (SD)	52.3 (8.9)	51.5 (8.5)	52.0 (9.0)	61.3 (7.0)	61.4 (7.0)	63.3 (7.0)	35.7 (4.8)	36.1 (4.6)	36.6 (4.6)
Body mass index, kg/m^2, mean (SD)	25.0 (4.5)	25.0 (4.5)	24.7 (4.7)	26.9 (5.3)	26.6 (5.2)	26.1 (5.2)	24.6 (5.3)	24.8 (5.5)	24.1 (5.0)
Physical activity, METs/week, mean (SD)	21.8 (28.6)	20.4 (26.8)	22.6 (27.4)	17.2 (21.3)	18.1 (21.9)	18.1 (22.5)	21.5 (28.5)	20.0 (25.9)	21.7 (28.0)
AMED diet score, mean (SD)	4.4 (1.9)	4.3 (1.9)	4.5 (1.9)	4.3 (1.9)	4.4 (1.9)	4.6 (1.9)	3.9 (1.9)	3.8 (1.8)	4.3 (1.9)
Current smoking, %	6.9	7.5	5.8	12.1	12.1	11.1	13.5	12.6	9.5
Asthma, %	5.9	5.7	7.6	7.9	8.4	10.3	6.2	6.0	7.2
Cancer, %	2.3	2.3	2.6	10.9	11.4	13.1	0.5	0.6	0.7
Rheumatoid arthritis, %	1.8	1.8	2.0	8.8	8.7	8.1	0.8	0.8	0.7
Inflammatory bowel disease, %	1.0	0.9	0.8	2.0	1.8	2.0	1.0	1.0	0.9
Chronic obstructive pulmonary disease, %	0.4	0.6	0.7	4.7	5.5	5.5	0.6	0.7	0.7
Corticosteroid use, %	0.5	0.6	0.5	1.8	2.0	2.1	1.4	1.4	1.3
History of diabetes mellitus, %	1.7	1.7	1.5	7.0	6.8	6.2	0.8	0.8	0.8
Depression, %	1.1	1.2	1.0	5.5	5.6	6.3	7.8	7.9	9.4
Skin reaction to the sun, painful/ blistering sunburn, %	23.4	25.7	27.6	13.5	13.6	15.7	24.3	22.6	26.1
Number of lifetime severe sunburns, %									
None	9.3	8.1	6.4	11.5	10.9	8.7	33.2	36.5	28.1
1 – 4	41.4	36.5	34.1	31.3	31.3	27.7	56.4	54.7	58.5
5 – 9	17.3	20.0	19.9	22.6	22.0	21.8	7.6	6.6	9.2
≥10	32.1	35.3	39.5	34.6	35.8	41.8	2.5	2.0	3.9
Natural hair color, dark brown or black, %	57.2	51.4	50.3	46.0	46.0	43.5	41.3	40.8	36.5

Participants in the lowest (Q1), middle (Q3), and highest quintiles (Q5) of UVR exposure are shown.

Abbreviations: UVR, ultraviolet radiation; HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study; NHS II, Nurses' Health Study II; METs, metabolic equivalent task hours; AMED, alternate Mediterranean diet score (range 0 to 9, with higher score indicating a healthier diet); Q, quintile.

Table 2.

Ambient ultraviolet radiation exposure and incidence of herpes zoster in three prospective cohorts

	HPFS			NHS			NHS II		
	Cases	**Person-years**	**Multivariable adjusted HR (95% CI)**	**Cases**	**Person-years**	**Multivariable adjusted HR (95% CI)**	**Cases**	**Person-years**	**Multivariable adjusted HR (95% CI)**
Ambient UVR									
Quintile 1	541	110,729	Reference	2277	222,019	Reference	1964	402,358	Reference
Quintile 2	606	111,760	1.09 (0.97, 1.23)	2237	221,006	0.99 (0.93, 1.05)	2087	404,443	1.05 (0.99, 1.12)
Quintile 3	598	112,670	1.09 (0.97, 1.22)	2325	226,402	1.01 (0.95, 1.07)	2027	402,495	1.03 (0.95, 1.09)
Quintile 4	611	109,433	1.13 (1.01, 1.27)	2279	225,281	0.99 (0.93, 1.05)	2025	395,342	1.04 (0.98, 1.11)
Quintile 5	621	106,772	1.14 (1.02, 1.29)	2196	211,809	0.99 (0.93, 1.05)	1807	363,612	0.96 (0.90, 1.03)
***p* for trend**			.03			.83			.04

Adjusted for age, cancer, rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, chronic kidney disease, diabetes mellitus, asthma, chronic obstructive pulmonary diseases, depression, use of corticosteroids, smoking, BMI, waist circumference, physical activity, alternate Mediterranean diet score, sleep, analgesics (ibuprofen, acetaminophen, and aspirin), and elevated cholesterol. Additionally, parity, oral contraceptives, and hormone therapy were adjusted in the multivariable model among women in NHS and NHS II.

Abbreviations: UVR, ultraviolet radiation; HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study; NHS II, Nurses' Health Study II; HR, hazard ratio; CI, confidence interval.

Table 3.

Skin reaction to prolonged sunlight, lifetime number of severe sunburns, hair color, and risk of herpes zoster in three prospective cohorts

	HPFS			NHS			NHS II		
	Cases	Person-years	Multivariable adjusted HR (95% CI)	Cases	Person-years	Multivariable adjusted HR (95% CI)	Cases	Person-years	Multivariable adjusted HR (95% CI)
Skin reaction									
None	734	146,928	Reference	1865	179,722	Reference	1380	280,424	Reference
Some redness	-	-	-	4298	408,761	1.01 (0.95, 1.06)	3515	728,883	1.01 (0.95, 1.07)
Burn	1225	229,951	1.06 (0.96, 1.16)	2129	206,560	0.99 (0.93, 1.05)	2385	479,310	1.03 (0.96, 1.10)
Painful burn	-	-	-	915	88,624	0.98 (0.91, 1.06)	1781	332,969	1.07 (1.00, 1.15)
Burn with blisters	780	127,314	1.20 (1.08, 1.33)	494	45,780	1.01 (0.92, 1.12)	833	143,129	1.12 (1.02, 1.22)
***p* for trend**			<.001			.71			.002
Lifetime number of severe sunburns									
None	414	78,228	Reference	907	98,279	Reference	3078	648,360	Reference
1–4	501	98,640	0.96 (0.84, 1.10)	2888	275,822	1.11 (1.03, 1.20)	5673	1,115,062	1.07 (1.02, 1.12)
5–9	481	92,546	0.97 (0.85, 1.11)	2171	206,871	1.12 (1.04, 1.21)	836	147,400	1.15 (1.06, 1.24)
≥10	1355	237,549	1.08 (0.96, 1.20)	3726	347,302	1.14 (1.05, 1.22)	285	50,822	1.13 (1.00, 1.28)
***p* for trend**			.02			.01			<.001
Natural hair color									
Red or blonde	384	64,928	1.03 (0.91, 1.16)	1552	144,622	1.04 (0.98, 1.10)	1824	362,268	0.99 (0.93, 1.04)
Light brown	903	161,436	Reference	3695	360,981	Reference	3675	703,153	Reference
Dark brown	1106	205,699	0.95 (0.87, 1.04)	4174	396,858	1.03 (0.99, 1.08)	3489	677,263	0.98 (0.94, 1.03)
Black	229	43,203	0.88 (0.76, 1.02)	283	26,414	1.05 (0.93, 1.18)	129	23,970	1.01 (0.85, 1.20)
***p* for trend**			.19			.68			.82

Adjusted for age, cancer, rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, chronic kidney disease, diabetes mellitus, asthma, chronic obstructive pulmonary diseases, depression, use of corticosteroids, smoking status, BMI, waist circumference, physical activity, alternate Mediterranean diet score, sleep, analgesics (ibuprofen, acetaminophen, and aspirin), and elevated cholesterol. Additionally, parity, oral contraceptives, and hormone therapy were adjusted in the multivariable model among women in NHS and NHS II.

Numbers of cases and person-years may not add up to totals because of missing data on skin reaction, lifetime number of severe sunburns, and hair color.

Abbreviations: HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study; NHS II, Nurses' Health Study II; HR, hazard ratio; CI, confidence interval.