EXTENDED REPORT

Exposure to ultraviolet-B and risk of developing rheumatoid arthritis among women in the Nurses' Health Study

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ABSTRACT

Objective To examine the association between ultraviolet-B (UV-B) light exposure and rheumatoid arthritis (RA) risk among women in two large prospective cohort studies, the Nurses' Health Study (NHS) and the Nurses' Health Study II (NHSII).

Methods A total of 106 368 women from NHS, aged 30–55 years in 1976, and 115 561 women from NHSII, aged 25–42 in 1989, were included in the analysis. We identified women with incident RA from the start of each cohort until 2008 (NHS) and 2009 (NHSII). Cumulative average UV-B flux, a composite measure of ambient UV exposure based on latitude, altitude and cloud cover, was estimated according to state of residence and categorised as low, medium or high. Estimates of UV-B at birth and age 15 years were also examined. We used multivariable-adjusted Cox proportional hazards models to estimate HR and 95% CI.

Results 1314 incident RA cases were identified in total. Among NHS participants, higher cumulative average UV-B exposure was associated with decreased RA risk; those in the highest versus lowest category had a 21% decreased RA risk (HR (95% CI); 0.79 (0.66 to 0.94)). UV-B was not associated with RA risk among younger women in NHSII (1.12 (0.87 to 1.44)). Results were similar for UV-B at birth and at age 15.

Conclusions These results suggest that ambient UV-B exposure is associated with a lower RA risk in NHS, but not NHSII. Differences in sun-protective behaviours (eg, greater use of sun block in younger generations) may explain the disparate results.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic inflammatory disease associated with both genetic and environmental factors. Previous studies have shown that people living in the northeast USA have a higher risk of RA,[1 2] which may be due to lower ultraviolet (UV) light exposure. In experimental studies, UV radiation acts as an immunosuppressant by up-regulating Th2 cells and down-regulating Th1 cells,[3–5] inducing interleukin-10 production, an anti-inflammatory cytokine, as well as the production of T-regulatory cells.[6–10] UV-B (from 290 to 315 nm) exposure causes both sunburn and skin damage and stimulates cutaneous synthesis of vitamin D and could thus decrease risk of RA through increasing vitamin D, which has known immunomodulating effects.[11–14] UV-B may depress disease activity in patients with RA, but strong epidemiologic evidence of its role before RA onset is lacking.[15–17] Either through vitamin D production or through pathways independent of vitamin D, UV-B has the potential to be a modifiable risk factor for RA. To date, no study of prospectively measured UV exposure and risk of RA has been conducted.

UV-B flux is a composite measure of mean UV-B radiation level based on latitude, altitude and cloud cover,[18] and represents ambient exposure better than geographic region. UV-B flux has been shown to be associated with risk of skin cancer,[19] suggesting that it is a good proxy for sun exposure. In this study, our objective was to examine the association between cumulative average UV-B flux based on residential location, and risk of RA among women followed in two large prospective cohort studies, the Nurses' Health Study (NHS) and the Nurses' Health Study II (NHSII).

METHODS

Study population

The NHS is a prospective cohort of 121 700 female nurses aged 30–55 years living in 11 states in the USA in 1976. The NHSII is a similar cohort started in 1989 of 116 430 female nurses aged 25–42 years living in 14 US states. The NHS and NHSII participants completed questionnaires at baseline and every 2 years regarding diseases, lifestyle and health practices and food frequency questionnaires were completed approximately every 4 years. All participants provided informed consent.

Women with prevalent RA at start of follow-up were excluded. Follow-up began at the start of each cohort and ended at death, RA diagnosis, loss to follow-up or end of analytic follow-up (NHS: 2008, NHSII: 2009). Over the course of follow-up, the participants moved to all 50 states as well as to Puerto Rico and Washington DC. A total of 106 368 women contributed 2 898 433 person-years in NHS, and 115 561 women contributed 2 042 274 person-years in NHSII.

UV-B exposure

We used UV-B flux data from the Robertson–Berger meter network across the US, which

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collected measurements from 1974 to 1985.[20 21] UV-B flux, a composite measure of mean UV-B radiation level based on latitude, altitude and cloud cover, measured in Robertson–Berger units$\times 10^{-4}$ (R-B) was estimated according to the method adapted from Scotto and Fears[18 22] and has been shown to be stable over time.[23] A count of 440 R-B units over one half hour is sufficient to produce slight redness in untanned Caucasian skin.[21] Each state was assigned one UV-B value (except California, which was split based on zip code into Northern and Southern California) using the average of annual UV-B from the 11-year collection period (1974–1985). UV-B for each study participant was estimated based on state of residence and updated every 2 years. UV-B estimates ranged from 93 (eg, Alaska and Oregon) to 196 R-B (eg, Hawaii and Arizona). Values were not directly estimated for some states, therefore, values from nearby states were imputed (see online supplementary text for details). Residential locations were available for 1976 and 1986–2006 for NHS, and 1989–2007 for NHSII. In NHS, if the woman lived in the same state in 1976 as in 1986, we assumed that she lived in the same state for the intervening years. If the state of residence in 1976 and 1986 was different, we assumed that in 1978–1980 she lived in the state listed in 1976, and in 1982–1984 she lived in the state listed in 1986. The vast majority (89%) of NHS participants did not move between 1976 and 1986. We calculated the cumulative average UV-B flux for each participant to represent long-term exposure throughout follow-up; RA incidence between each 2-year questionnaire cycle was related to the cumulative average of UV-B calculated from all the preceding questionnaires (see online supplementary text). Cumulative average UV-B was categorised into approximate tertiles: low (≤109 R-B), medium (>109 to ≤117 R-B) and high (>117 R-B). We also estimated UV-B for each participant at birth and at age 15 based on the state of residence at those times, which was reported on the 1992 NHS and 1993 NHSII questionnaires. Therefore, we restricted analyses of UV-B at birth and age 15 to those participants who were still eligible and responded to those questionnaires (67% of NHS and 78% of NHSII).

Identification of RA

In NHS from 1976 to 1982, participants self-reported a diagnosis of RA or other connective tissue diseases (CTD) in a write-in section of the questionnaire. Starting in 1982, participants were asked specifically whether they had been diagnosed with RA by a physician. All nurse participants who self-reported any CTD were sent the CTD Screening Questionnaire (CSQ) for symptoms.[24] If positive for symptoms, a detailed medical record review for American College of Rheumatology (ACR) classification criteria for RA[25] was performed. Subjects with 4 of 7 of the ACR criteria documented in the medical record were considered to have confirmed RA. Participants were excluded if they had RA at the start of the cohort, if they denied the diagnosis of RA after self-report, denied permission for medical record review, or the CSQ was negative. In NHSII, case ascertainment was conducted using the same procedure as in NHS (self-report by questionnaire, CSQ to determine if positive for symptoms, then medical record review) starting at the beginning of follow-up (1989).

Covariate information

Information on potential confounders was collected from biennial questionnaires and, when appropriate, covariate values were updated every 2 years and treated as time-varying. On the basis of past findings in these cohorts,[26 27] the following variables were included as covariates: pack-years smoking (product of years smoking and packs of cigarettes/day), parity, breast feeding (did not breast feed, breastfed <1 year, breastfed ≥1 year), postmenopausal status (pre-, peri- or postmenopausal) and postmenopausal hormone use (never, past, current user). Other variables were also examined as potential confounders: race (Caucasian, African–American, other), physical activity (metabolic equivalent-hours/week, in quintiles), alcohol consumption (0, <5, 5–<9, 9–<15, ≥15 grams/day), husband's education (<high school, high school, college, >college education), census-tract median income (based on census-tract data, in quintiles), body mass index (BMI), vitamin D intake (energy-adjusted, from both supplements and diet), and mean number of rheumatologists per zip code (in tertiles; 1989–2008 from data provided by ACR to account for access to rheumatology specialists as a potential explanation of regional variation in RA diagnosis rates). Vitamin D and BMI did not appreciably affect HR estimates, and therefore, were not included in final models.

We considered several variables as effect modifiers. Because people with lighter skin or those who do not use sunscreen are more able to absorb UV-B and may benefit more from exposure, we examined effect modification by Fitzpatrick skin type[28] (skin reaction to sun and ability to burn; from 1992 NHS questionnaire only) and sunscreen use (NHS 1980 and NHSII 1993 questionnaires). In NHS, participants were asked in 1980 if they regularly spent time outdoors during the summer, and if so, if they usually wore sunscreen. In NHSII, sunscreen use as a teenager was assessed in 1993, and categorised as used sunscreen <50% or ≥50% of the time. In addition, we examined effect modification by vitamin D intake and supplement use (≥400 IUD vs <400 IUD) because those with a diet rich in vitamin D may not benefit as much from UV-B exposure. Lastly, we examined the heterogeneity of effect by physical activity and BMI; those with a higher BMI and/or lower physical activity level may not spend as much time outdoors, decreasing the effect of UV-B.

Statistical analysis

We used Cox proportional hazards models stratified by 2-year questionnaire period and age in months as the time scale to estimate HRs and 95% CIs. Our final multivariable models included age, parity, breast feeding, pack-years smoking, race, postmenopausal status, postmenopausal hormone use, alcohol intake, physical activity, husband's education, US census-tract median income, and mean number of rheumatologists per zip code. Indicators for missing covariate data were used.

We performed several sensitivity analyses. We examined UV-B exposure with a 6-year lag to evaluate if HRs were biased by reverse causation (early RA symptoms causing a change in residential location and therefore UV-B exposure). We also restricted the study population to Caucasians because UV-B absorption is higher in Caucasians. To determine whether the association varies by age, we stratified results by age during follow-up (<52 and ≥52 years old). We explored whether there was a threshold effect by estimating the HR for UV-B ≥164 R-B. We restricted to those with ≥400 IU vitamin D/day to determine if the effect of UV exposure was mitigated by higher vitamin D intake. Lastly, because UV-B measurements may be more accurate for the cohort assembled closer in time to R-B measurement collection (NHS) and less accurate for the later cohort (NHSII), we restricted analysis to those who were 10–20 years old in 1974–1985. We calculated the 20-year cumulative hazard for a 40-year-old Caucasian non-smoker in each cohort to estimate the 20-year absolute risk for the average study participant.

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Table 1 Baseline age-adjusted characteristics of NHS and NHSII study participants according to category of UV-B*

	NHS in 1976 (n=106368)			NHSII in 1989 (n=115561)		
	Low UV-B (n=41 305)	Medium UV-B (n=43 227)	High UV-B (n=21 836)	Low UV-B (n=35 808)	Medium UV-B (n=31 755)	High UV-B (n=47 998)
Age in years, mean (SD)	42.4 (7.2)	42.2 (7.3)	44.1 (7.0)	34.5 (4.7)	35.1 (4.6)	34.9 (4.6)
Caucasian (%)	94	95	92	93	96	90
BMI, mean (SD) (kg/m^2)	23.7 (4.1)	23.8 (4.2)	23.4 (4.0)	24.1 (5.0)	24.4 (5.2)	23.9 (5.0)
Never smoker (%)	40	45	47	60	66	68
Pack-years, mean (SD)†	11.2 (14.8)	9.7 (14.1)	10.0 (15.1)	4.6 (7.8)	3.8 (7.1)	3.5 (7.0)
Physical activity, mean (SD), MET-hours/week	14.4 (22.1)	13.6 (19.7)	14.8 (21.5)	26.0 (38.2)	23.8 (35.3)	24.8 (36.9)
Vitamin D intake ≥400IU/day‡ (%)	28	28	31	40	36	38
Nulliparous, %	7	7	9	31	27	32
Total breast feeding ≥12 months§ (%)	14	14	15	21	22	20
Premenopausal (%)	74	73	66	98	97	96
Alcohol, mean (SD) (grams/day)	6.9 (10.5)	5.4 (9.7)	7.8 (12.1)	3.3 (6.0)	2.7 (5.5)	3.3 (6.5)
Husband's education >college (%)	16	13	18	24	21	23
Median income <US$42000 (%)	11	17	20	11	18	20

All variables (except age) are standardised to the age distribution of the population in 1976 (NHS) and 1989 (NHSII). Means with SD or percentages are shown.
*Low: ≤109 Robertson–Berger units×10^{-4} (R-B), medium: >109 to ≤117 R-B, high: >117 R-B.
†Among ever-smokers only.
‡Vitamin D intake from diet and supplements adjusted for energy intake in international units (IU) per day.
§Among parous women only.
BMI, body mass index; MET, metabolic equivalent; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; UV-B, ultraviolet-B.

Additive effect modification was assessed by calculating a relative excess risk due to interaction using the reference group with the most decreased risk.[29] Multiplicative effect modification was assessed using the likelihood ratio test comparing a model with the interaction terms for joint exposure categories with a main-effects-only model. For all statistical tests, we considered p values <0.05 to be significant. SAS V.9.3 was used for all analyses.

RESULTS

A total of 221 929 women were included from NHS and NHSII (table 1). Women in the highest category of UV-B had a lower median income and were more likely to have ever smoked. We confirmed 1314 incident RA cases (NHS: 933, NHSII: 381). Because NHSII was a younger cohort at the start, women with RA in NHSII were younger at diagnosis than those in NHS (mean age at diagnosis 47.0 years in NHSII vs 58.7 in NHS, table 2).

Among women in NHS, higher cumulative average UV-B exposure was associated with a significant decrease in RA risk. In multivariable-adjusted models, those in the highest category had a 21% decreased risk of RA (HR 0.79 (95% CI 0.66 to 0.94)) compared with the lowest (p trend 0.005; table 3). The equivalent HR in NHSII was 1.12 (95% CI 0.87 to 1.44), p trend 0.37. The 20-year absolute risk in NHS for the highest UV-B category was 0.7% (95% CI 0.6 to 0.9) and 1.2% (95% CI 0.9 to 1.5) for the lowest category (risk difference 0.5% (95% CI 0.2 to 0.8)). In NHSII, the 20-year absolute risk was 0.5% (95% CI 0.4 to 0.7) for the highest category and 0.5% (95% CI 0.3 to 0.7) for the lowest (risk difference 0% (95% CI −0.2 to 0.2)). Results with a 6-year lag in exposure were similar to main analyses (highest category compared with lowest: NHS HR 0.81 (95% CI 0.66 to 0.98), NHSII HR 1.16 (95%CI 0.87 to 1.53)). Analyses restricted to Caucasians were similar (highest compared with lowest: NHS HR 0.78 (95% CI 0.65 to 0.94), NHSII HR 1.11 (95% CI 0.86 to 1.44)) as were results of analyses of UV-B at birth and at age 15 (table 4). The highest category at birth compared with the lowest was 0.77 (95% CI 0.62 to 0.97) in NHS and 0.91 (95% CI 0.69 to 1.20) in NHSII. There was no significant heterogeneity in effects by BMI, physical activity, vitamin D, skin type or sunscreen use (p interaction >0.10).

We did not find that there was a greater effect for the highest UV-B exposure (UV-B ≥164 R-B); results were similar to those in main analyses (≥164 UV-B vs ≤109 NHS HR 0.78 (0.63 to 0.97) and NHSII HR 1.17 (0.84 to 1.64)). We found that estimates were similar to main analyses when restricted to those with ≥400 IU vitamin D/day (NHS HR 0.74 (0.55 to 1.01), NHSII HR 0.95 (0.60 to 1.48) comparing highest to lowest UV-B). Stratifying results by age during follow-up, the HR for women aged ≥52 during follow-up in NHSII was similar to the HR observed for women in NHS; HR comparing highest UV-B category to lowest in NHSII was 0.79 (95% CI 0.47 to 1.33) (table 5). In analyses of UV-B flux exposure at age 15 in a restricted NHSII study population (those 10–20 years old in 1974–1985), the HR was 0.90 (0.60 to 1.36) comparing highest UV-B with lowest.

Table 2 Characteristics of the RA cases at diagnosis in NHS and NHSII

	NHS (n=933)	NHSII (n=381)
Age at diagnosis, mean (SD)	58.7 (9.7)	47.0 (7.1)
Seropositive* (%)	59.0	61.2
X-ray changes (%)	29.7	26.8
Diagnosed by ACR member (%)	85.4	89.8
Symmetric arthritis (%)	96.4	96.1
Nodules (%)	13.4	12.3

*Rheumatoid factor positive and/or anticyclic citrullinated peptide antibody-positive.
ACR, American College of Rheumatology; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; RA, rheumatoid arthritis.

DISCUSSION

An inverse association between cumulative UV-B exposure and incident RA was found in NHS, but there was no evidence of an association among the younger NHSII cohort. The observed inverse association in NHS is consistent with the results of previous studies of geographic region and RA risk.[1 2] Indeed, in

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Table 3 HR of incident rheumatoid arthritis, according to cumulative average UV-B exposure in NHS and NHSII

	Cumulative average UV-B*			
	Low	Medium	High	p Trend
NHS				
Median UV-B	104	113	164	
RA cases/person-years	374/1 038 261	340/1 120 965	219/739 207	
Age-adjusted HR (95% CI)	1.0 (ref)	0.84 (0.73 to 0.98)	0.79 (0.67 to 0.93)	0.004
Multivariable-adjusted HR† (95% CI)	1.0 (ref)	0.84 (0.73 to 0.98)	0.79 (0.66 to 0.94)	0.005
NHSII				
Median UV-B	104	113	145	
RA cases/person-years	101/600 134	108/558 559	172/883 582	
Age-adjusted HR (95% CI)	1.0 (ref)	1.10 (0.84 to 1.45)	1.12 (0.87 to 1.43)	0.39
Multivariable-adjusted HR† (95% CI)	1.0 (ref)	1.04 (0.79 to 1.37)	1.12 (0.87 to 1.44)	0.37

*Low: ≤109 Robertson–Berger units$\times 10^{-4}$ (R-B), medium: >109 to ≤117 R-B, high: >117 R-B.
†Adjusted for age, pack-years smoking, parity, breast feeding, physical activity, alcohol consumption, race, husband's education, census-tract median income, postmenopausal status and hormone use, mean number of rheumatologists per zip code.
HR, hazard ratio; RA, rheumatoid arthritis; UV-B, ultraviolet-B.

our past study in NHS, we found that women who lived in the northeast USA had a 45% increased risk of RA compared with women who lived in the west. By contrast, the current study used UV-B by state to quantify exposure instead of geographic region and data on residence from baseline throughout follow-up captured a more long-term exposure. The estimated 20-year absolute risk difference comparing high UV-B with low was 0.5% for the average study participant in NHS. Adjustment for area-level confounders, such as number of rheumatologists per zip code and area-level socioeconomic status minimised bias due to regional differences in diagnosis of RA and access to care. Inclusion of these variables, however, did not change estimates significantly.

Our results are consistent with epidemiologic studies of other autoimmune diseases, such as type 1 diabetes, inflammatory bowel disease and multiple sclerosis, which have found an increased disease risk associated with higher latitudes.[30–35] A past ecologic study of RA prevalence rates in Australia reported no statistically significant association between UV radiation and RA, but not adjusting for individual-level confounders and use of self-reported prevalent RA may have biased results due to unmeasured confounders, misclassification of disease and/or reverse causation.[36] Our results support the hypothesis that UV radiation decreases risk of RA, which may be through several different pathways. UV radiation is the primary source of vitamin D, which regulates the growth and differentiation

Table 4 HR of incident rheumatoid arthritis according to UV-B exposure at birth and at age 15 in NHS and NHSII

	UV-B* at Birth			
	Low	Medium	High	p Trend
NHS				
Median UV-B	104	113	145	
RA cases/person-years	373/907 481	326/968 621	104/328 171	
Age-adjusted HR (95% CI)	1.0 (ref)	0.82 (0.70 to 0.95)	0.76 (0.61 to 0.95)	0.003
Multivariable-adjusted HR† (95% CI)	1.0 (ref)	0.82 (0.70 to 0.95)	0.77 (0.62 to 0.97)	0.005
NHSII				
Median UV-B	104	113	144	
RA cases/person-years	111/561 772	114/567 584	97/520 394	
Age-adjusted HR (95% CI)	1.0 (ref)	1.00 (0.77 to 1.30)	0.95 (0.72 to 1.25)	0.72
Multivariable-adjusted HR† (95% CI)	1.0 (ref)	0.95 (0.73 to 1.24)	0.91 (0.69 to 1.20)	0.48
	UV-B* at Age 15			
	Low	Medium	High	p Trend
NHS				
Median UV-B	104	113	154	
RA cases/person-years	379/147 027	320/168 257	107/54 650	
Age-adjusted HR (95% CI)	1.0 (ref)	0.74 (0.64 to 0.86)	0.79 (0.63 to 0.98)	0.001
Multivariable-adjusted HR† (95% CI)	1.0 (ref)	0.76 (0.65 to 0.89)	0.84 (0.67 to 1.05)	0.009
NHSII				
Median UV-B	104	113	145	
RA cases/person-years	101/559 317	120/561 961	105/548 576	
Age-adjusted HR (95% CI)	1.0 (ref)	1.16 (0.89 to 1.52)	1.07 (0.81 to 1.40)	0.65
Multivariable-adjusted HR† (95% CI)	1.0 (ref)	1.11 (0.85 to 1.46)	1.04 (0.78 to 1.37)	0.82

*Low: ≤109 Robertson–Berger units$\times 10^{-4}$ (R-B), medium: >109 to ≤117 R-B, high: >117 R-B.
†Adjusted for age, pack-years smoking, parity, breast feeding, physical activity, alcohol consumption, race, husband's education, census-tract median income, postmenopausal status and hormone use, mean number of rheumatologists per zip code.
HR, hazard ratio; RA, rheumatoid arthritis; UV-B, ultraviolet-B.

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Table 5 HR of incident rheumatoid arthritis according to cumulative average UV-B exposure in NHS and NHS II stratified by age

	Cumulative average UV-B*			
	Low	Medium	High	p Trend
NHS				
<52 years old				
RA cases/person-years	125/407 699	109/438 475	44/211 690	
Multivariable-adjusted HR† (95% CI)	1.0 (ref)	0.80 (0.62 to 1.04)	0.67 (0.47 to 0.95)	0.01
≥52 years old				
RA cases/person-years	249/630 562	231/682 490	175/527 517	
Multivariable-adjusted HR† (95% CI)	1.0 (ref)	0.87 (0.72 to 1.04)	0.85 (0.69 to 1.04)	0.08
NHS II				
<52 years old				
RA cases/person-years	74/532 449	88/488 495	139/768 973	
Multivariable-adjusted HR† (95% CI)	1.0 (ref)	1.17 (0.85 to 1.61)	1.24 (0.93 to 1.65)	0.15
≥52 years old				
RA cases/person-years	27/67 686	20/70 063	33/114 608	
Multivariable-adjusted HR† (95% CI)	1.0 (ref)	0.67 (0.37 to 1.21)	0.79 (0.47 to 1.33)	0.43

*Low: ≤109 Robertson–Berger units$\times 10^{-4}$ (R-B), medium: >109 to ≤117 R-B, high: >117 R-B.
†Adjusted for age, pack-years smoking, parity, breast feeding, physical activity, alcohol consumption, race, husband's education, census-tract median income, postmenopausal status and hormone use, mean number of rheumatologists per zip code.
UV-B, ultraviolet-B.
HR, hazard ratio; RA, rheumatoid arthritis; UV-B, ultraviolet-B.

of cells involved in regulating the immune system, and acts as an immunosuppressive agent once metabolised to 1α,25 $(OH)_2D_3$, a steroid hormone.[37–42] UV light, independent of vitamin D synthesis, has also been shown to have properties that could depress autoimmunity through up-regulating production of Th2 cells and T-regulatory cells.[43–45]

It is unclear whether the relevant window for UV-B exposure related to RA risk is at birth, in adolescence or throughout adulthood. Many study participants did not move during childhood; 89.4% of women in NHS and 83.1% of NHSII lived in the same state at birth and at age 15. The majority of the participants also resided in the same state at age 15 as they did at age 30 (NHS: 78.3%, NHSII: 73.4%). Therefore, it is difficult to determine whether the effect we observed is due to exposure during childhood or during adulthood.

As we do not have individual-level data on time spent outdoors, travel to sunny destinations, and sunscreen use throughout follow-up, our exposure estimates may not accurately capture actual exposure to sunlight. However, in our cohort, UV-B flux has been shown to be associated with non-melanoma skin cancer risk (A Qureshi, personal communication), and therefore, is a reasonable proxy for sun exposure. Our use of state-level measurement of UV-B exposure may introduce non-differential measurement error due to variations of altitude and cloud cover within each state that likely biases the findings toward the null. Although these measurements were shown to be stable over time,[23] analyses showing stability only included data from meters through 1991. The results of this study pertain to mainly Caucasian women, limiting its generalisability to other populations.

We did not find that the effect of UV-B was the same in NHS as in NHSII, and there are several possible explanations for this difference. Analyses examining a threshold effect, or restricting the cohorts to similar levels of vitamin D intake, resulted in similarly null HR estimates in NHSII as main analyses. UV-B measurements may be less accurate for the cohort assembled after R-B measurement collection (NHSII), but restricting NHSII analyses to those participants 10–20 years old from 1974 to 1985, and using data from residence at age 15, the results remained null for NHSII. UV-B exposure may decrease risk of older-onset RA but not younger-onset RA (mean age at onset 59 years in NHS and 47 years in NHSII). When stratified by age, the effects in the two cohorts were similar for women aged ≥52, although the estimate for NHSII was based on small numbers.

The difference between the cohorts could also be due to a difference in sun-protective behaviours; the later birth cohort of NHSII participants (born between 1946 and 1964) were more likely aware of the dangers of sun exposure and, perhaps, had more sun-protective behaviour making residential UV-B not as good a proxy for actual sun exposure in NHSII. According to the National Health Interview survey, even over a short period of time (1992–2008), sun protection behaviours increased in the USA.[46] Evidence of a cohort difference is also suggested by an analysis that found that UV-B flux at the time of blood draw (NHS: 1989–1990, NHSII: 1996–1999) using the same R-B meter data used in our study was a significant predictor of plasma vitamin D levels among participants in NHS ($p<0.001$), but not in NHSII ($p=0.67$).[47] We cannot rule out that another unmeasured behavioural or environmental factor differed by cohort (we had 80% power to detect a decreased risk by the effect modifiers examined of 15–35% in NHS and 30–40% in NHSII) or that a very modest association was not detected due to lower statistical power in NHSII.

Despite its limitations, our study has many strengths. The use of UV-B flux exposure over many years is an improvement over geographic region and allowed us to better quantify exposure and to examine the effect of long-term UV-B exposure, which is more biologically relevant than from just one point in time. UV-B, according to prospectively assessed residential location, avoids recall error bias. If the pathway through which UV-B affects RA risk is indeed through vitamin D synthesis, UV-B exposure may be a better measurement of vitamin D than using food frequency questionnaires or a one-time serum measurement because sunlight is the body's primary source of vitamin D. Using the rich questionnaire data provided by the participants of NHS and NHSII over several decades of follow-up, we were able to adjust for many confounding factors and explore several possible effect modifiers.

In conclusion, our study adds to the growing evidence that exposure to UV-B light is associated with decreased risk of RA.

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The mechanisms are not yet understood, but could be mediated by cutaneous production of vitamin D and attenuated by use of sunscreen or sun avoidant behaviour. Future studies are necessary to identify dose effects and the relevant time window of UV-B exposure during life that is associated with decreased risk.

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