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Recreational and residential sun exposure and risk of endometriosis: a prospective cohort study

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STUDY QUESTION: Is recreational and residential sun exposure associated with risk of endometriosis?

SUMMARY ANSWER: Tanning bed use in early adulthood, sunscreen use and history of sunburns were associated with a greater risk of endometriosis; however, higher residential UV exposure was associated with a lower endometriosis risk.

WHAT IS KNOWN ALREADY: Previous research has reported an association between endometriosis and skin cancer, with evidence of shared risk factors between the two diseases. We investigated the potential associations between ultraviolet radiation and endometriosis risk.

STUDY DESIGN, SIZE, DURATION: The Nurses' Health Study II is a prospective cohort of 116 429 female US nurses aged 25–42 years at enrolment in 1989. Participants completed self-administered biennial questionnaires through June 2015.

PARTICIPANTS/MATERIALS, SETTINGS, METHODS: We investigated self-reported measures of recreational sun-exposure and geocoded residential UV exposure in childhood and adulthood in relation to risk of laparoscopically confirmed endometriosis among premenopausal white women. We used Cox proportional hazards models to calculate hazard ratios (HRs) and 95% CIs.

MAIN RESULTS AND THE ROLE OF CHANCE: During follow-up, 4791 incident cases of laparoscopically confirmed endometriosis were reported among 1 252 248 person-years. Tanning bed use during high school/college (≥6 times per year vs. never use: HR = 1.19, 95% CI = 1.01–1.40; P_{trend} = 0.04) and at ages 25–35 (HR = 1.24, 95% CI = 1.12–1.39; $P_{trend} \leq 0.0001$), number of sunburns during adolescence (P_{trend} = 0.03) and percentage of time using sunscreen in adulthood (P_{trend} = 0.002) were positively associated with risk of endometriosis. In contrast, residential UV level at birth (highest vs. lowest quintile: HR = 0.81, 95% CI = 0.72–0.92; P_{trend} = 0.0001), at age 15 (HR = 0.79, 95% CI = 0.70–0.88; $P_{trend} \leq 0.0001$) and at age 30 (HR = 0.90, 95% CI = 0.82–0.99; P_{trend} = 0.21) were associated with a decreased risk of endometriosis.

LIMITATIONS, REASONS FOR CAUTION: Self-reported endometriosis diagnosis may be prone to misclassification; however, we restricted our definition to laparoscopically confirmed endometriosis, which has been shown to have high validity compared to medical records.

†Denotes equal contribution as last author.

WIDER IMPLICATIONS OF THE FINDINGS: Our results suggest that tanning bed use in early adulthood increases endometriosis risk, potentially through a harmful effect of ultraviolet A wavelengths, and that residential UV exposure reduces risk, possibly via optimal vitamin D synthesis. These findings should be investigated further to enhance our understanding of endometriosis aetiology.

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Key words: endometriosis / epidemiology / sunburn / sun exposure / tanning beds / ultraviolet radiation

Introduction

Endometriosis is a common gynaecologic disease that is estimated to burden 10% of women of reproductive age, affecting nearly 190 million women worldwide (Zondervan *et al.*, 2020). The disease occurs when endometrial-like tissue is implanted and grows in ectopic locations (Zondervan *et al.*, 2018), which adversely impacts quality of life as women with endometriosis may experience infertility, severe dysmenorrhea, acyclic pelvic pain and/or pain during intercourse, urination or defecation (Nnoaham *et al.*, 2011). Despite the significant impact from endometriosis on quality of life and healthcare costs (Simoens *et al.*, 2011), there is limited understanding of disease aetiology (Shafrir *et al.*, 2018). In particular, very little is known about modifiable risk factors that could prevent endometriosis development.

Prior research into the long-term health consequences of endometriosis has suggested that women with endometriosis are at greater risk of cutaneous melanoma (Kvaskoff *et al.*, 2015; Farland *et al.*, 2017), the most lethal form of skin cancer. The relationship between endometriosis and non-melanoma skin cancer has yielded inconsistent findings (Wyshak *et al.*, 1989; Brinton *et al.*, 1997; Farland *et al.*, 2017). While the exact mechanisms underlying the association between endometriosis and melanoma are not known, several studies have found a greater risk of endometriosis in women with a sun-sensitive phenotype, including a poor tanning ability (Kvaskoff *et al.*, 2009; Somigliana *et al.*, 2010; Kvaskoff *et al.*, 2014), red hair (Woodworth *et al.*, 1995; Wyshak and Frisch, 2000; Missmer *et al.*, 2006), fair eyes (Somigliana *et al.*, 2010; Vercellini *et al.*, 2014), freckling (Kvaskoff *et al.*, 2009; Somigliana *et al.*, 2010) and/or a high naevus propensity (Frisch *et al.*, 1992; Hornstein *et al.*, 1997; Kvaskoff *et al.*, 2009; Somigliana *et al.*, 2010; Kvaskoff *et al.*, 2014). These associations may reflect a common genetic background between endometriosis and melanoma, or an underlying association between sun exposure and risk of endometriosis. One prior case-control study explored a potential association between sun exposure and endometriosis and found that cases with endometriosis were more likely to report a 'frequently/always burning' skin reaction to first sun exposure, but no association between endometriosis and history of sunburn or UV lamp use; however, the study could only evaluate crude, cross-sectional measures of recreational sun exposure and lacked statistical power, involving 98 patients and 94 hospital controls (Somigliana *et al.*, 2010). Additional research is needed to deepen our understanding of endometriosis aetiology. In the present analysis, we sought to investigate self-reported recreational sun exposure and geospatial measures of residential UV exposure in relation to endometriosis risk in a large prospective cohort.

Materials and methods

Study population and data collection

The Nurses' Health Study II (NHSII) is a prospective cohort study of 116 429 registered female US nurses (Bao *et al.*, 2016). At enrolment in 1989, participants resided in 1 of 14 US states and were aged 25–42 years. Participants have continued to complete biennial questionnaires about their health, medical history and exposures to known or potential risk factors for several chronic diseases. Cumulative response rates of the NHSII participants have been consistently $\geq$90% throughout follow-up. This research received ethical approval from the Institutional Review Boards of Brigham and Women's Hospital and the Harvard T.H. Chan School of Public Health.

For the present study, women were followed from September 1989 to June 2015 in the NHSII cohort. Of the 116 429 women enrolled in the cohort, we excluded participants reporting prevalent endometriosis diagnosis before baseline (n = 5413). We also restricted our analytic sample to women who were premenopausal and had intact uteri, since the incident occurrence of endometriosis is rare after menopause or hysterectomy. Women who reported a previous diagnosis of cancer (including non-melanoma skin cancer) were also excluded, and, given the exposure of interest, we restricted the analyses to white women. Our final sample, after application of exclusion criteria, included 95 080 women.

Endometriosis diagnosis

In 1993, participants were first asked if they had ever had physician-diagnosed endometriosis. If they replied positively, they were asked to report the date of diagnosis and whether it had been confirmed by laparoscopy, the gold-standard for endometriosis diagnosis (Abdalla and Rizk, 1998). These questions were asked again on each subsequent questionnaire cycle. Self-reported endometriosis was validated among a subgroup of NHSII participants (n = 184). For women whose medical records were available, a diagnosis of endometriosis was confirmed in 96% of women reporting laparoscopically confirmed endometriosis, but in only 54% of women without laparoscopic confirmation (Missmer *et al.*, 2004b). Therefore, due to the potential for misclassification of self-reported endometriosis without

laparoscopic confirmation, we restricted our endometriosis definition to laparoscopically confirmed endometriosis for our primary analysis and censored women with a self-reported diagnosis to the date of reported endometriosis diagnosis.

Assessment of exposures

Self-reported tanning bed use

In 2005, information was collected on the frequency of tanning bed usage during high school/college, and between ages 25 and 35 years (none, 1–2 times per year, 3–5 times per year, 6–11 times per year, 12–23 times per year or ≥24 times per year). For this analysis, the three highest categories were collapsed. To assess the potential additive effect of tanning bed use over both periods, we combined exposures at high school/college and at ages 25–35 years (none, <2 times per year ever, ≥3 times per year in high school/college only, ≥3 times per year at ages 25–35 years only, ≥3 times per year over both periods).

Recreational sun exposure

At baseline in 1989, women reported their number of severe blistering sunburns between ages 15 and 20 years (none, 1–2, 3–4, 5–9 or ≥10). The 1993 questionnaire collected data on time spent outdoors in a swimsuit (<once per week, once per week, twice per week, several times per week or daily) and frequency of sunscreen use when outside or at the beach (not in sun, 0%, 25%, 50%, 75% or 100%), both as a teenager and over the summer preceding the women's response to the questionnaire.

Residential UV exposure

Participants' residential address histories were updated every 2 years and geocoded to the street or ZIP Code level and spatially joined to a high spatiotemporal resolution erythemal UV exposure model (VoPham *et al.*, 2016) in a geographic information system (GIS) using ArcMap 10.5.1 (Esri, Redlands, CA). Erythemal UV incorporates information on both ultraviolet A (UVA) and ultraviolet B (UVB) wavelengths. Erythemal UV weights these wavelengths based on their relative effectiveness to induce erythema on white skin (McKinlay and Diffey, 1987; NASA, 2017). Therefore, shorter UVB wavelengths are weighted more heavily in the calculation of erythemal UV. In brief, the UV model was developed by applying area-to-point residual kriging to downscale NASA erythemal UV satellite remote sensing images from the Total Ozone Mapping Spectrometer (TOMS) and Ozone Monitoring Instrument (OMI) satellite sensors (VoPham *et al.*, 2016). Information on established predictors of UV including aerosol optical depth, cloud cover, elevation, ozone and latitude is also incorporated into the model (Kerr and Fioletov, 2008; VoPham *et al.*, 2016). Within the contiguous USA, the model predicts average July noon time erythemal UV irradiance (mW/m^2), with a spatial resolution of 1 km^2 and an annual temporal resolution that varied over time for each year from 1980 to 2015. Model cross-validation demonstrated high predictive performance and relative improvements in absolute error and root mean square error (VoPham *et al.*, 2016, 2019). For each participant, UV exposure during adulthood was calculated as a time-varying cumulative average.

To estimate ambient UV exposure in early life, we linked the self-reported state of residence at birth, age 15 and age 30 with the UV exposure model using GIS (VoPham *et al.*, 2019). The UV model was aggregated to the state level, where UV raster cell centroids intersecting a given state were averaged to calculate a mean state UV exposure value. For California residents, participants reported living in Northern or Southern California; UV exposure was estimated using established boundaries (Weinberg and Kallerman, 2017). For participants who were born, age 15 or age 30 years on or before 1980, we used the UV model estimates from 1980 (earliest available year). For participants who were born, age 15 or age 30 years after 1980, we used the UV model in the subsequent years. Cumulative average of residential UV in adulthood was calculated from averaging UV exposure across all the preceding questionnaires. All UV variables were categorized into quintiles. Latitude of state of birth, at age 15 and at age 30 based on residential address was also used to estimate residential UV exposure. Latitude was dichotomized at 40 degrees, which is an approximate mid-point in the USA.

Assessment of covariates

Weight at age 18 years and current height were reported at baseline, and these measures were used to calculate BMI (kg/m^2) at age 18. Age at menarche was collected in 1989, and current menstrual cycle length and pattern were assessed in 1993. History of parity (defined as the total number of pregnancies lasting 6 months or more) was collected at baseline and updated biennially. A history of oral contraceptive (OC) use since age 13 was recorded at baseline, and information about subsequent use was updated biennially. Women who had used OCs for 2 months or longer were classified as ever users. A detailed cigarette smoking history was obtained at baseline and updated with each biennial questionnaire, allowing for adjustment for smoking status. Data on tendency to sunburn in childhood and self-reported mole count on legs were collected on the baseline questionnaire in 1989. Information on natural hair colour at age 18 years was collected in the 1991 follow-up questionnaire. Predicted 25-hydroxyvitamin D (25(OH)D) score was derived based on known determinants of circulating 25(OH)D, including age, race, UVB radiation flux at residence, dietary and supplementary vitamin D intakes, BMI, physical activity, alcohol intake, post-menopausal hormone use (women only) and season of blood draw, in three nationwide cohorts: the Nurses' Health Study, Nurses' Health Study II and the Health Professionals Follow-up Study (Bertrand *et al.*, 2012). In 2001, participants were asked to report their annual income and self-perceived social, economic and educational standing related to other people in their community on a ladder with 10 rungs, using a validated and often used sociologic construct (Adler *et al.*, 2000). Given the distribution of responses, we categorized self-reported social standing in the community by combining people on the top three rungs as 'high standing', women on the fourth rung as having 'medium standing', and women in the fifth or higher rung as having 'low standing'. In addition, we added adjustment for household income, categorized as <$75 000, 75 000 to <100 000 or ≥100 000.

Statistical analysis

Person-months at risk were calculated from entry into the cohort until death or cancer diagnosis (other than non-melanoma skin cancer), laparoscopically confirmed endometriosis diagnosis, hysterectomy, menopause, or June 2015. We used time-varying Cox proportional

hazards regression models that considered age in months and calendar time as the time scale to estimate multivariable hazard ratios (HRs) and calculate 95% CIs (Model 1). Multivariable models additionally adjusted for BMI at age 18 years, age at menarche, menstrual cycle length, menstrual cycle pattern, parity, OC use, smoking status, childhood reaction to sun exposure, number of moles on leg, natural hair colour, annual income in 2001, self-perceived social, economic and education standing compared to other people in your community, predicted vitamin D score (Bertrand et al., 2012), cumulative average UV (tanning bed use and recreational sun exposure models only) and tanning bed use in high school/college and at ages 25–35 (UV models only). Tests for linear trend in ordinal categorical exposures were calculated by creating an ordinal variable in which the median value or midpoint of each category was assigned to all participants in that group.

Two additional *a priori* sensitivity analyses were conducted: (i) to address the potential diagnostic delay between endometriosis symptom onset and surgical diagnosis (Missmer et al., 2004a; Nnoaham et al., 2011), the date of endometriosis diagnosis was pre-dated by 4, 6 and 8 years; and (ii) to address diagnostic bias, we expanded our endometriosis definition to include reported endometriosis diagnoses with and without laparoscopic confirmation.

Results

A total of 95 080 women contributed 1 252 248 person-years to these analyses, with 4791 incident cases of laparoscopically confirmed endometriosis reported during follow-up. Women who more frequently used tanning beds during high school/college or between ages 25 and 35 were more likely at cohort baseline to be younger, to have short menstrual cycles (<26 days) at age 18, to be nulliparous, and to have ever used OCs (Table I).

Tanning bed use

We found positive linear associations between frequency of tanning bed use in adolescence and early adulthood and risk of endometriosis (high school/college (P_{trend} = 0.04); at ages 25–35 years (P_{trend} < 0.0001); high school/college and ages 25–35 combined (P_{trend} = 0.0001)) (Table II). In multivariable-adjusted models, use of tanning beds six or more times per year between ages 25 and 35 years was associated with a 24% greater risk of endometriosis diagnosis (95% CI = 1.12–1.39). When combining tanning bed exposure over both high school/college and ages 25–35 (i.e. ~ages 15–35 years), the greatest risk for endometriosis was among those who used tanning beds 3 or more times per year during both time periods (HR = 1.30, 95% CI = 1.09–1.54).

Recreational sun exposure

A history of five or more sunburns at ages 15–20 years was associated with a greater risk of endometriosis (HR = 1.12, 95% CI = 1.01–1.24; P_{trend} = 0.03) (Table III). Frequency of sunscreen use as a teenager was not associated with endometriosis risk (P_{trend} = 0.96). However, frequency of sunscreen use when the majority of the cohort was aged in their 30s (i.e. in the summer preceding completion of the 1993 questionnaire) was associated with a significantly higher risk of endometriosis (P_{trend} = 0.002).

Residential sun exposure

Women living in states in the highest quintile of UV exposure at birth, compared with the lowest, had a lower risk of endometriosis (HR = 0.81, 95% CI = 0.72–0.92; P_{trend} = 0.0001) (Table IV). Similarly, an inverse association with endometriosis was observed for UV exposure at ages 15 (HR = 0.79, 95% CI = 0.70–0.88; $P_{trend} \leq 0.0001$) and 30 years (HR = 0.90, 95% CI = 0.82–0.99; P_{trend} = 0.21). A high cumulative average UV exposure during adulthood was also associated with a lower risk of endometriosis (HR = 0.86, 95% CI = 0.78–0.95), although the test for linear trend did not meet the threshold for statistical significance (P_{trend} = 0.15). We found no association between latitude in state of birth, or state of residence at ages 15 or 30 and risk of endometriosis. Results did not meaningfully change in sensitivity analyses where endometriosis diagnosis was pre-dated by 4, 6, 8 years, or where the endometriosis exposure definition was expanded to include all women with self-reported physician-diagnosed endometriosis.

Discussion

In this cohort of premenopausal white women, we observed that recreational sun exposure was associated with a greater risk of endometriosis while residential UV exposures were associated with lower risk of endometriosis. Specifically, factors reflecting intense recreational UV exposure (frequency of tanning bed use in high school/college and early adulthood, use of sunscreen during adulthood and number of sunburns at ages 15–20 years) were associated with a ~20% higher risk of laparoscopically confirmed endometriosis, however, those reflecting higher levels of residential UV exposure (UV in state of residence (mW/m^2) at birth, at age 15, at age 30 and cumulative average) were associated with a ~10–20% lower risk of endometriosis.

This study is the first, to our knowledge, to prospectively investigate the relation between recreational sun exposure, residential sun exposure and risk of endometriosis. While these findings need further replication, there is strong biologic plausibility that supports these associations. Recreational versus residential sun exposure may influence endometriosis risk through different potential pathophysiologic mechanisms of association. Indeed, UV is comprised of both UVA (315–400 nm) and UVB (280–315 nm) wavelengths. Our study found that increased use of tanning beds in adolescence and early adulthood was associated with greater risk of endometriosis. Tanning bed use represents intermittent, but high-intensity, exposure that is associated with DNA damage, apoptosis, inflammation and risk for melanoma (Moller et al., 2002; Narbutt et al., 2009; Muthusamy and Piva, 2010). Moreover, since the 1990s, forms of tanning bed UV lamps in the USA emit predominately UVA wavelengths (>95%) that have been associated with an increased risk of cell damage and weakened immune function (Ullrich et al., 1999; Moyal and Fourtanier, 2002) leading to well-documented greater risk of skin cancers (Levine et al., 2005).

Inflammation (Mu et al., 2017) and immune-system dysfunction have been associated with risk of endometriosis (Zondervan et al., 2018) and research has suggested that endometriosis is associated with

Table I Age-standardized characteristics of participants in the Nurses' Health Study II population at cohort baseline, in 1989, by reported frequency of tanning bed use.

	During high school/college				Tanning bed use between ages 25 and 35			
	None (n = 61 923)	1–2 times/year (n = 2956)	3–5 times/year (n = 1477)	>6 times/year (n = 2048)	None (n = 54853)	1–2 times/year (n = 5463)	3–5 times/year (n = 2900)	>6 times/year (n = 5193)
Age (years)[a,b]	34.95 (4.54)	32.94 (4.88)	32.44 (4.96)	31.76 (4.81)	35.17 (4.53)	33.33 (4.60)	32.80 (4.53)	32.33 (4.46)
Age at menarche								
<11, %	24	21	22	23	24	23	21	24
12–13, %	58	59	59	57	58	58	59	57
14+, %	18	20	19	20	18	19	19	19
Menstrual cycle length at ages 18–22								
<25 days, %	10	10	13	12	10	12	14	14
26–31 days, %	66	67	66	67	66	68	66	67
32–39 days, %	16	16	15	13	16	13	14	12
40+ days, %	8	7	6	8	8	7	7	7
Parous, %	71	66	63	63	72	64	62	65
Current oral contraceptive use %	13	15	16	18	12	16	18	19
History of infertility, %	16	15	16	16	16	16	16	15
BMI at age 18[a], kg/m^2	21.27 (3.26)	21.02 (3.02)	20.93 (2.84)	20.96 (3.25)	21.27 (3.24)	21.00 (3.11)	21.18 (3.29)	21.18 (3.39)
Current BMI[a], kg/m^2	23.91 (4.90)	23.36 (4.62)	23.33 (4.39)	23.36 (4.36)	23.96 (4.95)	23.29 (4.35)	23.51 (4.48)	23.48 (4.56)
Natural hair colour								
Black, %	1	1	1	1	1	1	1	1
Dark brown, %	39	37	39	37	39	37	37	36
Light brown, %	40	41	37	41	39	40	40	42
Blonde, %	16	18	18	18	16	17	19	18
Red, %	4	3	4	3	4	3	3	3
Moles on leg								
None, %	49	47	46	44	50	48	48	46
1–2 moles, %	19	19	20	19	19	18	19	20
3–4 moles, %	10	10	11	11	10	11	11	11
5–9 moles, %	7	7	8	7	7	7	8	7
10+ moles, %	15	17	16	19	15	16	15	17
Current smoker, %	12	13	14	14	11	14	15	18
Predicted vitamin D score[a,c]	31.25 (3.46)	31.69 (3.41)	31.91 (3.35)	31.91 (3.29)	31.20 (3.46)	31.81 (3.32)	31.94 (3.36)	31.71 (3.38)
Annual income								
<$75 000, %	43	40	39	39	43	40	42	44
$75 000 to $99 999, %	21	22	21	23	22	20	21	22
>$100 000, %	35	38	40	38	35	40	37	35

(continued)

Table I Continued

	During high school/college				Tanning bed use between ages 25 and 35			
	None (n = 61 923)	1–2 times/year (n = 2956)	3–5 times/year (n = 1477)	>6 times/year (n = 2048)	None (n = 54853)	1–2 times/year (n = 5463)	3–5 times/year (n = 2900)	>6 times/year (n = 5193)
Subjective social status								
High, %	39	41	38	40	39	39	40	38
Medium, %	23	23	26	22	23	23	22	22
Low, %	38	36	36	38	38	38	38	40

Values of polytomous variables may not sum to 100% due to rounding.
[a]Mean (SD).
[b]Value is not age adjusted.
[c]From 1991 questionnaire.

subsequent risk of autoimmune conditions (Harris *et al.*, 2016a,b; Shigesi *et al.*, 2019).

Conversely, our measure of residential UV reflects chronic UV exposure and more heavily weights the shorter, UVB wavelengths. UVB catalyses cutaneous vitamin D production. Thus, the inverse association observed with residential UV exposure and endometriosis may implicate a protective vitamin D pathway. Vitamin D has been shown to suppress pro-inflammatory processes and regulate immune function (Arnson *et al.*, 2007; Zemel and Sun, 2008). Within the NHSII cohort, higher dietary vitamin D consumption was inversely associated with risk of endometriosis (Harris *et al.*, 2013). While diet contributes to circulating vitamin D levels, the majority of circulating vitamin D is derived from UV exposure. Thus, the reported protective effect of residential sun exposure and endometriosis risk may be influenced by vitamin D production.

We found that ≥5 sunburns as a teenager were associated with a 12% greater risk of endometriosis and there was a linear trend between number of sunburns as a teenager and endometriosis risk (P_{trend} = 0.03). Prior research has shown an association between a sun-sensitive phenotype and risk of endometriosis, with women with light hair colour, poor tanning ability and high naevus propensity at greater risk of endometriosis (Kvaskoff *et al.*, 2010; Somigliana *et al.*, 2010; Kvaskoff *et al.*, 2014), which could act as a potential confounders in the association between UV exposure and endometriosis risk. Given the known association with the sun-sensitivity phenotype and risk of endometriosis, however, our multivariable analyses were *a priori* adjusted for childhood skin's reaction to sun exposure, number of moles on leg and natural hair colour, and the results remained statistically significant.

We found that women who reported using sunscreen all of the time during summer in adulthood had nearly a 10% greater risk of endometriosis compared with women who reported never using sunscreen. This positive association may be explained through at least three mechanisms. First, sunscreen use has been associated with intention to suntan, and thus paradoxically with higher levels of intense recreational sun exposure (Autier, 2009). Second, environmental chemicals within sunscreens have endocrine-disrupting properties (Krause *et al.*, 2012) and prior research has suggested that higher urinary concentrations of endocrine disruptors, like benzophenone-type UV filters, which are chemically active in sunscreen, are associated with risk of endometriosis (Kunisue *et al.*, 2012). Third, those regularly applying sunscreen are more likely to have a sun-sensitivity phenotype, which is also positively associated with endometriosis risk and may not have been fully accounted for with the covariates available in our analysis.

Only one prior case-control study of 98 women with surgically confirmed endometriosis and 94 control women undergoing surgery for other benign gynaecological conditions in Italy has investigated proxies of recreational sun exposure in relation to endometriosis risk (Somigliana *et al.*, 2010). Participants were interviewed by two trained physicians and asked about self-reported recreational sun exposure. They found that women with endometriosis were more likely to report their skin's reaction to first sun exposure as 'frequently/always burning' compared with women without endometriosis (odds ratio (OR) = 2.19, 95% CI = 1.12–4.28). This sun-

Table II Hazard ratios [HR] and 95% CI for endometriosis risk by frequency of tanning bed use, Nurses' Health Study II cohort questionnaire cycles 1989–2015 (n = 95 080).

Tanning bed use	Cases	Person-years	Age-adjusted HR[1] (95% CI)	Multivariable-adjusted HR[2] (95% CI)
During high school (HS)/college				
None	3257	876 553	1.00 (Reference)	1.00 (Reference)
1–2 times/year	171	44 890	0.98 (0.84–1.15)	0.96 (0.82–1.12)
3–5 times/year	104	22 708	1.19 (0.98–1.45)	1.13 (0.93–1.38)
≥6 times/year	156	31 547	1.26 (1.07–1.48)	1.19 (1.01–1.40)
P_{trend}			0.003	0.04
At ages 25–35 years				
None	2750	773 472	1.00 (Reference)	1.00 (Reference)
1–2 times/year	336	82 201	1.11 (0.99–1.24)	1.02 (0.91–1.14)
3–5 times/year	205	43 101	1.26 (1.09–1.45)	1.13 (0.98–1.31)
≥6 times/year	397	77 122	1.37 (1.23–1.52)	1.24 (1.12–1.39)
P_{trend}			<0.0001	<0.0001
Combined HS/college and at ages 25–35				
None	2559	722 280	1.00 (Reference)	1.00 (Reference)
<2 times a year ever	405	104 351	1.06 (0.95–1.17)	0.99 (0.89–1.10)
≥3 times a year in *HS/college only*	118	27 935	1.17 (0.97–1.41)	1.10 (0.91–1.32)
≥3 times a year at *ages 25–35 years only*	454	93 048	1.30 (1.18–1.44)	1.17 (1.06–1.30)
≥3 times a year *both in HS/college and at 25–35 years*	142	26 093	1.43 (1.20–1.70)	1.30 (1.09–1.54)
P_{trend}			<0.0001	0.0001

[1]Adjusted for current age (continuous months) and calendar time (2-year questionnaire period).
[2]Additionally adjusted for BMI at age 18 (<18.5, 18.5–22.4, 22.5–24.9 or ≥25 kg/m^2), age at menarche (≤11, 12–13 or ≥14 years), menstrual cycle length (≤25, 26–31, 32–39 or ≥40 days), current menstrual cycle pattern (regular, usually irregular, always irregular, no menses), parity (nulliparous, or 1, 2, 3 or ≥4 pregnancies lasting ≥6 months), oral contraceptive use (never, past or current use), smoking status (never, past or current smoking), childhood skin's reaction to sun exposure, number of moles on leg, natural hair colour (black, dark brown, light brown, blonde, red), annual income (<75k, 75 to <100k, ≥100k), self-reported social standing in community (high, medium, low), predicted vitamin D score and cumulative average UV.

sensitive phenotype among women with endometriosis supports our findings regarding sunburn, as we found that women who had ≥5 sunburns as a teenager had a 12% greater risk of endometriosis. However, Somigliana *et al.* reported no statistically significant association between endometriosis and experiencing ≥1 sunburn ever (OR = 1.46, 95% CI = 0.80–2.68). It is likely that the heterogeneity among the group of women reporting ≥1 sunburn in their lifetime may attenuate this finding; indeed, we found a linear trend between number of sunburns and endometriosis risk (P_{trend} = 0.03), with no meaningful risk among women who reported 1–2 sunburns (HR = 1.00, 95% CI = 0.93–1.07).

Somigliana *et al.* also found no association between endometriosis and exposure to UV lamps/tanning beds (OR = 0.80, 95% CI = 0.43–1.51). This is in contrast to our finding of a strong association between tanning bed use and increased risk of endometriosis. However, their exposure categorization of 'ever' vs. 'never' UV lamp/tanning bed usage may collapse informative exposure levels, as our study found linear trends between frequency of tanning bed usage and risk of endometriosis (P_{trend} combined high school/college and ages 25–35 = 0.0001). Additionally, there may be underlying cultural differences in tanning bed utilization, which limits generalizability across populations; among the Italian women included in their study, 69% of control women reported ever using UV lamps, whereas in our sample, <10% of women reported ever using tanning beds. Somigliana *et al.* reported an association with other proxy measures of recreational sun exposure. They found an inverse association between endometriosis and regular use of tanning creams (OR = 0.35, 95% CI = 0.15–0.85, for regularly vs. never/rarely), and with ≥21 days per year of sun exposure at the time of study (OR = 0.58, 95% CI = 0.32–1.05). However, other proxies for sun exposure, such as sun exposure during adolescence (OR = 0.89, 95% CI = 0.48–1.66 for ≥28 days/year vs. <28 days/year) and use of suncare creams (OR = 0.77, 95% CI = 0.38–1.57 for never vs. regularly) were not associated with endometriosis risk. There are a number of important differences between the two studies that may influence study results, including differing exposure groups/categorizations, different comparison groups (women undergoing surgery for other benign gynaecological conditions vs. any woman without endometriosis) and prospective vs. cross-sectional ascertainment of exposures.

This is the only prospective investigation into the association between recreational and residential sun exposure and risk of endometriosis. Our endometriosis definition was based on incident self-reported laparoscopic confirmation, which was reported with very high validity, minimizing the potential for misclassification. Since the prevalence of endometriosis is believed to be ~10% in the general population (Shafrir *et al.*, 2018), the inclusion of undiagnosed endometriosis cases

Table III Hazard ratios [HR] and 95% CI for endometriosis risk by sunburns, recreational sun exposure and sunscreen use, Nurses' Health Study II cohort questionnaire cycles 1989–2015 (n = 95 080).

	Cases	Person-years	Age-adjusted HR[1] (95% CI)	Multivariable-adjusted HR[2] (95% CI)
Number of sunburns at ages 15–20				
Never	1565	420 397	1.00 (Reference)	1.00 (Reference)
1–2	1880	501 375	1.00 (0.93–1.07)	1.00 (0.93–1.07)
3–4	835	209 511	1.05 (0.97–1.15)	1.05 (0.96–1.14)
≥5	498	116 777	1.13 (1.02–1.25)	1.12 (1.01–1.24)
P_{trend}			0.02	0.03
Times per week spent outdoors in a swimsuit as a teenager				
<1 per week	471	117 197	1.00 (Reference)	1.00 (Reference)
1 per week	342	96 975	0.87 (0.75–0.99)	0.91 (0.79–1.04)
2 per week	660	170 688	0.94 (0.83–1.06)	1.01 (0.89–1.14)
Several times per week	1972	508 644	0.93 (0.84–1.03)	1.02 (0.92–1.13)
Daily	702	175 342	0.95 (0.84–1.07)	1.05 (0.93–1.18)
P_{trend}			0.73	0.12
Times per week spent outdoors in a swimsuit in the past summer				
<1 per week	2040	499 168	1.00 (Reference)	1.00 (Reference)
1 per week	609	151 936	0.97 (0.88–1.06)	1.05 (0.96–1.15)
2 per week	700	187 426	0.89 (0.82–0.98)	1.00 (0.92–1.09)
Several times per week	682	201 933	0.81 (0.74–0.88)	0.96 (0.88–1.05)
Daily	70	20 532	0.81 (0.64–1.03)	0.99 (0.78–1.26)
P_{trend}			<0.0001	0.47
Percentage of time using sunscreen as a teenager				
Not in sun	61	16 457	0.99 (0.77–1.28)	0.94 (0.72–1.21)
0%	2317	618 073	1.00 (Reference)	1.00 (Reference)
25%	1040	263 151	1.02 (0.94–1.10)	1.02 (0.94–1.10)
50%	459	117 102	1.00 (0.91–1.11)	0.96 (0.87–1.06)
75%	205	47 202	1.12 (0.97–1.29)	1.03 (0.89–1.19)
100%	70	15 045	1.21 (0.95–1.53)	0.99 (0.79–1.26)
P_{trend}			0.11	0.96
Percentage of time using sunscreen in the past summer (<1993)				
Not in sun	242	65 422	1.04 (0.89–1.23)	0.88 (0.74–1.04)
0%	353	98 474	1.00 (Reference)	1.00 (Reference)
25%	493	138 443	0.98 (0.85–1.12)	0.99 (0.86–1.13)
50%	589	160 115	1.02 (0.89–1.16)	1.04 (0.91–1.19)
75%	1088	292 021	1.03 (0.91–1.16)	1.02 (0.90–1.15)
100%	1367	319 629	1.19 (1.06–1.34)	1.10 (0.97–1.24)
P_{trend}			0.0004	0.002

[1]Adjusted for current age (continuous months) and calendar time (2-year questionnaire period).
[2]Additionally adjusted for BMI at age 18 (<18.5, 18.5–22.4, 22.5–24.9 or ≥25 kg/m^2), age at menarche (≤11, 12–13 or ≥14 years), menstrual cycle length (≤25, 26–31, 32–39 or ≥40 days), menstrual cycle pattern (regular, usually irregular, always irregular, no menses), parity (nulliparous, or 1, 2, 3 or ≥4 pregnancies lasting ≥6 months), oral contraceptive use (never, past or current use), and smoking status (never, past or current smoking), childhood skin's reaction to sun exposure (except for number of sunburns at ages 15–20), number of moles on leg, natural hair colour, annual income (<75k, 75 to <100k, ≥100k), self-reported social standing in community (high, medium, low), predicted vitamin D score and cumulative average UV.

Table IV Hazard ratios [HRs] and 95% CI for residential sun UV exposure in relation to endometriosis risk, NHSII cohort questionnaire cycles 1989–2015 (n = 95 080).

	Cases	Person-years	Age-adjusted HR[1] (95% CI)	Multivariable-adjusted HR[2] (95% CI)
UV in state of residence at birth (mW/m^2)[3]				
<169.9	1010	244 193	1.00 (Reference)	1.00 (Reference)
169.9–189.1	1091	268 904	0.99 (0.91–1.08)	1.01 (0.92–1.10)
189.2–195.6	800	209 230	0.86 (0.78–0.94)	0.79 (0.70–0.90)
195.7–217.8	1345	369 190	0.90 (0.83–0.98)	0.93 (0.85–1.01)
≥217.9	392	118 072	0.82 (0.73–0.92)	0.81 (0.72–0.92)
P_{trend}			<0.0001	0.0001
UV in state of residence at age 15 (mW/m^2)[3]				
<168.6	995	243 418	1.00 (Reference)	1.00 (Reference)
168.6–189.1	1118	267 900	1.04 (0.95–1.13)	1.05 (0.96–1.14)
189.2–198.8	790	205 244	0.87 (0.79–0.96)	0.80 (0.70–0.91)
198.9–217.8	1296	355 346	0.91 (0.84–0.99)	0.95 (0.87–1.02)
≥217.9	439	137 680	0.80 (0.71–0.90)	0.79 (0.70–0.88)
P_{trend}			<0.0001	<0.0001
UV in state of residence at age 30 (mW/m^2)[3]				
<166.2	943	251 846	1.00 (Reference)	1.00 (Reference)
166.2–175.7	887	239 366	0.98 (0.89–1.08)	0.97 (0.88–1.06)
175.8–176.8	932	238 626	0.92 (0.84–1.02)	0.85 (0.74–0.96)
176.9–200.8	1039	256 847	1.07 (0.97–1.17)	1.05 (0.95–1.15)
≥200.9	837	222 904	0.99 (0.90–1.09)	0.90 (0.82–0.99)
P_{trend}			0.56	0.21
Cumulative average UV (mW/m^2)[3]				
<166.6	1351	304 655	1.00 (Reference)	1.00 (Reference)
166.6–173.6	823	235 891	0.99 (0.90–1.08)	0.99 (0.91–1.09)
173.7–182.8	844	243 296	0.97 (0.88–1.05)	0.98 (0.90–1.07)
182.9–209.8	990	240 825	1.11 (1.02–1.21)	1.08 (0.99–1.18)
≥209.9	691	203 342	0.95 (0.86–1.04)	0.86 (0.78–0.95)
P_{trend}			0.68	0.15
Latitude in state of birth				
<40 degrees	1713	420 572	1.00 (Reference)	1.00 (Reference)
≥40 degrees	2371	633 501	0.93 (0.87–0.99)	0.97 (0.91–1.03)
Latitude in state of residence at age 15				
<40 degrees	1753	433 995	1.00 (Reference)	1.00 (Reference)
≥40 degrees	2352	631 084	0.93 (0.88–0.99)	0.98 (0.92–1.04)
Latitude in state of residence at age 30				
<40 degrees	1933	484 229	1.00 (Reference)	1.00 (Reference)
≥40 degrees	2009	540 860	0.93 (0.88–1.00)	1.00 (0.94–1.07)

[1]Adjusted for current age (continuous months) and calendar time (2-year questionnaire period).
[2]Additionally adjusted for body mass index at age 18 (<18.5, 18.5–22.4, 22.5–24.9 or ≥25 kg/m^2), age at menarche (≤11, 12–13 or ≥14 years), menstrual cycle length (≤25, 26–31, 32–39 or ≥40 days), menstrual cycle pattern (regular, usually irregular, always irregular, no menses), parity (nulliparous, or 1, 2, 3 or ≥4 pregnancies lasting ≥6 months), oral contraceptive use (never, past or current use), smoking status (never, past or current smoking), childhood skin's reaction to sun exposure, number of moles on leg, natural hair colour, annual income (<$75k, 75 to <100k, ≥100k), self-reported social standing in community (high, medium, low), tanning bed use combined HS/college and at ages 25–35 (none, <2 times a year, ≥3 times a year in high school and college only, ≥3 times a year at ages 25–35 only, ≥3 times a year in HS/college at 25–35 years) and predicted vitamin D.
[3]Milliwatts/metre$^{2.}$

in the comparison group would have a limited effect among the large truly non-case women in this cohort (~80 000) (Zondervan *et al.*, 2002). Moreover, having a small proportion of undiagnosed cases of endometriosis misclassified within the large true non-case in the comparison group would attenuate any effects. While this misclassification still may bias our estimates, the bias is likely non-differential with respect to residential and recreational UV exposure and would most likely attenuate our findings. Residential UV was calculated based on

geographical residence as a proxy for individual UV exposure, thus we may non-differentially misclassify individual-level exposures leading to an attenuation of our findings. Our measures of recreational sun exposure were collected in 1989, 1993 and 2005 when participants were asked to recall their exposure during prior times—including adolescence. This lack of prospective data collection for some exposures is a limitation of these data, because some participants would have been diagnosed with endometriosis prior to self-reporting their recreational sun exposure status in 2005. However, prior research using these measures has shown a robust association with the risk of skin cancer (Cho *et al.*, 2005; Zhang *et al.*, 2012; Walls *et al.*, 2013), suggesting strong face validity of these measures. Additionally, while there is the possibility of differential recall, there had not been publications prior to 2005 suggesting a relationship between sun exposure and endometriosis and therefore we would most likely expect any potential misclassification of recreational sun exposure to be similar for women with and without endometriosis (non-differential misclassification), thus resulting in an observed underestimation of the true associations. In our final analytic models, we adjusted for variables that may be associated with both our exposures and risk of endometriosis, including information on reproductive and demographic characteristics, phenotypic traits and socioeconomic/behavioural traits. As with all studies of self-reported data, there may be residual unmeasured confounding factors, however, all known risk factors for endometriosis have been accounted for (Shafrir *et al.*, 2018) and thus, we hypothesize that any residual confounding would most likely be minimal.

Our population, the NHSII, is not a random sample of US women; therefore, findings may not be generalizable to all women. Specifically, our analysis was restricted to white women and therefore the results regarding this relationship with sun, tanning bed and UV exposures may not be extrapolated to women of other race/ethnicities. Additionally, women were between the ages of 25–42 at enrolment in 1989, thus, they may not be representative of more recent practices related to recreational sun exposure or clinical diagnosis for endometriosis. Given that prior research utilizing this cohort has found replicable relations for our measures of sun exposure (Cho *et al.*, 2005; Zhang *et al.*, 2012; Walls *et al.*, 2013), and endometriosis (Missmer *et al.*, 2004a,b), it is unlikely, that the biologic associations observed in this cohort will differ from women in general (Chavarro *et al.*, 2016; Ley *et al.*, 2016). The high level of education in the NHSII and expertise in medicine are distinct advantages that aid our ability to collect valid, high-quality information and reduce possible confounding by socioeconomic factors.

In sum, we found that factors associated with higher recreational sun exposure were associated with a higher risk of endometriosis, while factors associated with higher residential UV exposure levels were inversely associated with this risk. In order to better understand these findings and their specific mechanisms, these results must be replicated and future research on the biologic effect of UV wavelengths and dose-specific exposure on eutopic endometrium and endometriotic lesions are needed. Beyond skin cancer risk, our research may provide additional incentives to avoid sunburn and tanning beds, particularly during adolescence or young adulthood. These findings are novel and need to be confirmed in other populations. If replicated, these results will add to the knowledge providing evidence that tanning beds and sunburns should be avoided—not only to avoid skin cancers, but also endometriosis.

Data availability

Further information including the procedures to obtain and access data from the Nurses' Health Studies and Health Professionals Follow-up Study is described at https://www.nurseshealthstudy.org/researchers (contact email: nhsaccess@channing.harvard.edu) and https://sites.sph.harvard.edu/hpfs/for-collaborators/

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Authors' roles

M.K., S.A.M. and L.V.F. conceived, designed and supervised the study. M.K., L.V.F. and W.J.D. performed the statistical analysis. L.V.F., W.J.D., H.R.H., J.H., E.C., T.V., M.K. and S.A.M. drafted and critically reviewed the manuscript and approved the final version.

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Conflict of interest

The authors have nothing to disclose.

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