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ORIGINAL ARTICLE

Association between sun exposure habits and disease progression in multiple sclerosis

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Abstract

Background and purpose: Higher latitude has been associated with increased occurrence of multiple sclerosis (MS) and with more severe disease. The aim was to study the impact of sun exposure habits on MS disease progression and health-related quality of life.

Methods: Patients from a population-based case–control study were categorized based on sun exposure habits at diagnosis and were followed up to 15 years post-diagnosis through the Swedish MS registry ($n = 3314$) with regard to changes in Expanded Disability Status Scale (EDSS). Linear mixed models were used to analyse long-term changes, while Cox regression models, with 95% confidence intervals, were used to investigate outcomes, including 24-week confirmed diasability worsening, EDSS3, EDSS4, and physical worsening as measured by the physical component of the Multiple Sclerosis Impact Scale 29.

Results: Compared to average sun exposure (median value), low exposure to sunlight was associated with faster EDSS progression, increased risk of confirmed disability worsening (hazard ratio [HR] 1.48, 95% CI 1.21–1.81), increased risk of reaching EDSS 3 (HR 1.35, 95% CI 1.02–1.79), EDSS 4 (HR 1.47, 95% CI 1.01–2.20) and self-reported physical worsening (HR 1.27, 95% CI 1.00–1.62). Significant trends revealed a lower risk of unfavourable outcomes with increasing sun exposure.

Conclusions: Very low levels of sun exposure are associated with worse disease progression and health-related quality of life in patients with MS.

KEYWORDS
disability worsening, disease activity, Expanded Disability Status Scale, life quality, multiple sclerosis, sun exposure

BACKGROUND

Multiple sclerosis (MS) is a complex inflammatory and neurodegenerative disorder of the central nervous system, and its occurrence is positively associated with increasing latitude [1]. Insufficient sun exposure and vitamin D deficiency have consistently been associated with an increased risk of the disease [2, 3]. Higher latitude has also been associated with more severe disease [4, 5]. However, since sunlight regulates the cutaneous production of vitamin D, it has been difficult to separate the effects of vitamin D from ultraviolet radiation. Several studies have reported associations between low vitamin D levels and unfavourable MS-specific outcomes [6–10], but clinical trials of vitamin D supplementation have been somewhat disappointing [11–13].

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Ultraviolet radiation also affects immune functions through molecular mechanisms that are independent of the immunomodulatory effects of vitamin D [14, 15]. However, previous studies regarding sun exposure and MS progression have given inconclusive results [16–18]. These studies have been based on prevalent cases of MS and information regarding sun exposure has been collected retrospectively and recall bias may thus be a concern.

By following up patients with MS from an incident population-based case–control study, the aim was to study the influence of sun exposure habits on MS disease progression and health-related quality of life.

METHODS

Epidemiological Investigation of Multiple Sclerosis (EIMS) is a Swedish nationwide population-based case–control study. During the study period April 2005 to December 2019, EIMS recruited 3567 newly diagnosed patients with MS from hospital-based neurology units and privately run clinics in Sweden. The response rate amongst cases was 93%. All cases were diagnosed according to the McDonald criteria [19, 20]. All participants provided information on environmental exposures and lifestyle habits at study inclusion by filling out a standardized questionnaire. They were also asked to provide blood samples for genetic and serological analyses. More details on study design and methods are given elsewhere [21]. Of the 3567 patients, 3365 (94%) were followed up with Expanded Disability Status Scale (EDSS) scores in the Swedish MS registry. Those with incomplete information regarding the exposure under investigation were excluded ($n = 51$). The present study thus comprised 3314 patients with MS.

As a complement, patients participating in the study were requested to complete a digitalized follow-up questionnaire in 2021, capturing lifestyle habits from the time of diagnosis. These follow-up questionnaires were completed between May and December 2021. Of the 1823 patients (response rate 66%) who completed the questionnaire, 1733 patients were followed up with EDSS in the Swedish MS registry. The studies were approved by the Regional Ethical Review Board at Karolinska Institute and have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Definition of exposures

The participants assessed their sun exposure habits at the time of inclusion in EIMS, close to diagnosis/baseline. They assessed their sun exposure habits during the 5-year period prior to inclusion, including current exposure. The following questions were answered: (1) how often do you sunbathe if the weather is sunny (never, a few times/month, a few times/week, daily) and (2) how often do you visit a country that is sunnier than Sweden (never, seldom, once a year, more than once a year). Each answer alternative was reported on a 4-point scale, and an index was constructed by adding the numbers together and thus a value between 2 and 8 was acquired where higher numbers indicate higher sun exposure. Sun exposure was categorized into the following groups: 2, 3, 4, 5, 6, 7–8. Both the mean and the median index value was 5 (SD 1.7, range 2–8), and this group was considered the reference category. Only 6% reported a sun exposure of 8 and those with an index value of 7 or 8 were merged into one group.

Measurement of vitamin D

For patients recruited between 2005 and 2009, vitamin D status was measured as levels of 25-hydroxyvitamin D using a chemiluminescent immunoassay from Diasorin (Diasorin AB, Sundbyberg, Sweden) and a LIASON instrument provided by Diasorin AB with equimolar measurement of both 25-hydroxyvitamin D_2 and D_3. Vitamin D status was categorized into <25, 25–49, 50–74, 75–99 or >99 ng/mL, or unknown.

Outcome measures

The Swedish MS registry is used in all neurology units across the country and is integrated in the clinical documentation system. For each patient, data are continuously recorded by physicians and nurses regarding medical treatment, disease activity, physical functioning, as well as mental health and quality of life.

In order to study changes in severity/disability over time, the baseline was defined as the date of the first recorded EDSS. Confirmed disability worsening (CDW) was defined as an increase in the EDSS score with at least 1 point from baseline sustained between two follow-up visits separated in time by no less than 6 months (1.5 points if EDSS at baseline was 0, 0.5 points for baseline EDSS ≥5.5). Time to milestones EDSS 3 and 4 were studied as secondary outcomes and were limited to subgroups of patients with a baseline EDSS of less than 3. Another secondary outcome was physical worsening. An increased score of 7.5 points or more in the physical component of the Multiple Sclerosis Impact Scale 29 (MSIS-29) was defined as physical worsening from the patient's perspective [22].

Statistical analysis

Categorical variables were summarized using frequency and percentage. Continuous variables were summarized using mean and standard deviation (SD) or median and interquartile range as appropriate. The sun exposure index was validated by calculating correlations between sun exposure and vitamin D levels, both treated as continuous variables, using the Pearson correlation coefficient based on the 1220 cases with vitamin D measurements.

Linear mixed effect models were used to determine the association between sun exposure and the annual rate of change in

EDSS scores. The models considered fixed effects by including the sun exposure levels, time, their interactions and the covariates in the models. The nonlinear change in MS progression scores was tested by including a quadratic term of time in the models but was not significant and the linear prediction showed a lower Akaike information criterion indicating better goodness of fit. The estimated trajectories of MS progression scores by sun exposure were constructed by plotting coefficients from the mixed models during the follow-up.

Time to 24-week CDW and the secondary milestones EDSS 3 and 4 end-points as well as physical worsening from the patient's perspective were analysed using multivariable Cox proportional hazard regression. The follow-up time was calculated as the time from baseline until the onset of the events of interest, drop-out, death or end of follow-up, whichever occurred first. The proportional hazard assumption was tested through the Schoenfeld residuals. No violations of proportionality were observed. *p* values for trend were calculated using a variable representing the ordered categories of sun exposure and each outcome variable.

To assess the effect of persistent low or high levels of sun exposure on MS progression scores, the analysis was performed restricted to those who had not changed their sun exposure habits between diagnosis and the time of completing the follow-up questionnaire in 2021. Those who reported no sensitivity to heat at follow-up (47%) were also separately studied. Finally, taking into account the possibility of variations in clinical assessments and practices over the recruitment period, a sensitivity analysis was performed specifically focusing on the subset of participants enrolled during the peak 5-year period (2007–2011). All analyses controlled for age at diagnosis, sex, county ($n = 21$), ancestry (Nordic or non-Nordic), disease phenotype, disease duration, baseline EDSS, disease-modifying therapy, use of sunbeds (never, a few times/year, once/month, once/week) and smoking (current smoker or non-smoker). The influence of treatment was accounted for by calculating the proportion of the duration of follow-up spent on disease-modifying therapy. A model was also performed in which further adjustment for vitamin D status and month of vitamin D sampling was made. The following potential confounding variables were not kept in the final model since they had negligible influence on the results: having another autoimmune disease than MS (yes or no), alcohol consumption at diagnosis (no consumption, low, moderate or high consumption according to cutoffs used by Statistics Sweden [23]), passive smoking (ever or never), a history of mononucleosis (yes, no or unknown), body mass index (underweight, normal weight, overweight or obese according to cutoffs used by the World Health Organization [24]), physical activity (sedentary leisure time, moderate exercise, regular exercise 1–2 times/week and regular exercise 3 or more times/week) and vitamin D supplements at baseline (yes or no). All analyses were conducted in Stata version 17.0 (StataCorp, TX, USA) and Statistical Analysis System (SAS) version 9.4.

RESULTS

In total, 3314 patients with MS were followed for up to 15 years. The mean age at diagnosis of MS was 37.7 years (SD 11.2) and the mean age at inclusion in EIMS was 38.2 years (SD 11.2). Baseline characteristics of cases of the overall sample and by sun exposure habits are presented in Table 1. Those who reported low exposure to sunlight generally had higher EDSS and scored lower on the physical component of the MSIS-29 scale. They had lower levels of vitamin D, higher body mass index and reported less physical activity. Sunbeds were used primarily by individuals who scored high in the sun exposure sources. Alcohol consumption was highest amongst those with high sun exposure (Table 1). The correlation coefficient between self-reported sun exposure habits and baseline vitamin D status was 0.3 ($p < 0.0001$).

Sunbathing and travelling to sunnier countries

Amongst individuals who never travelled to sunnier countries, there was a significant trend showing lower risk of CDW with increasing frequency of sunbathing (hazard ratio [HR] 0.82, 95% confidence interval [CI] 0.73–0.92). Similarly, amongst those who never spent time sunbathing, a significant trend was observed showing lower risk of CDW with increasing frequency of travelling to sunnier countries (HR 0.87, 95% CI 0.76–1.00). When both sunbathing and travelling to sunnier countries were put in the same model, significant trends were observed showing lower risk of CDW with increasing sunbathing (HR 0.89, 95% CI 0.84–0.95) and travel to sunnier countries (HR 0.94, 95% CI 0.89–1.00).

Sun exposure index (ranging between 2 and 8)

At baseline, the two groups with the lowest exposure to sunlight had higher EDSS scores compared to the reference group (Table 2, Figures 1 and S1). During follow-up, the annual increase in EDSS was faster amongst those with the lowest sun exposure ($\beta_{\text{sun index 3} \times \text{time}}$ 0.02, 95% CI 0.00, 0.05), whereas it was slower amongst those with the highest exposure ($\beta_{\text{sun index 9} \times \text{time}}$ −0.2, 95% CI 0.05, −0.00), compared to the reference group (Table 2, Figures 1 and S1).

The lowest exposure to sunlight was significantly associated with an increased risk of CDW (adjusted HR 1.48, 95% CI 1.21–1.81) and increased risk of reaching EDSS 3 (adjusted HR 1.35, 95% CI 1.02–1.79) and EDSS 4 (adjusted HR 1.47, 95% CI 1.01–2.20) compared to the reference group (Table 3; Figure S2). When comparing the annual EDSS increase between the lowest and highest sun exposure groups, the annual EDSS increase was 0.05 (95% CI 0.01–0.08) amongst those with the lowest sun exposure (not in table).

Low sun exposure was also associated with physical worsening as measured by MSIS-29 physical score (HR 1.27, 95% CI 1.00–1.62).

TABLE 1 Baseline characteristics of overall sample and by sun exposure habits at diagnosis.

		Sun exposure						
	Total	2	3	4	5	6	7–8	
N	3314	250	452	808	887	636	281	*p* value
Age at diagnosis, years (SD)	37.7 (11.2)	39.8 (11.6)	38.7 (11.3)	37.0 (10.8)	37.3 (11.0)	37.6 (11.3)	37.8 (11.9)	0.006
Female, *n* (%)	2341 (71)	135 (54)	299 (66)	568 (70)	648 (73)	478 (75)	213 (76)	<0.0001
Nordic origin, *n* (%)	2663 (80)	209 (84)	370 (82)	662 (82)	714 (27)	499 (19)	209 (74)	0.04
Treatment, *n* (%)	3154 (95)	234 (94)	421 (93)	769 (95)	851 (96)	608 (96)	271 (96)	0.17
MS phenotype								
Relapsing onset, *n* (%)	3108 (94)	234 (94)	416 (92)	754 (93)	835 (94)	606 (95)	263 (94)	0.52
Progressive onset, *n* (%)	160 (4.8)	13 (5.2)	28 (6.2)	43 (5.3)	40 (25)	21 (3.3)	15 (5.3)	
Unknown, *n* (%)	46 (1.4)	3 (1.2)	8 (1.8)	11 (1.4)	12 (1.4)	9 (1.4)	3 (1.1)	
Disease duration, years (SD)	2.6 (3.7)	2.9 (4.2)	3.0 (4.0)	2.5 (3.7)	2.4 (3.5)	2.6 (3.6)	2.7 (3.7)	0.29
Baseline EDSS (SD)	1.8 (1.4)	2.3 (1.7)	2.0 (1.5)	1.8 (1.5)	1.6 (1.3)	1.6 (1.3)	1.7 (1.3)	<0.0001
Baseline MSIS-PHYS (SD)	20 (21)	30 (24)	22 (22)	21 (22)	19 (20)	18 (20)	18 (19)	<0.0001
Vitamin D, ng/mL (SD)	62 (27)	45 (19)	53 (25)	60 (25)	65 (28)	68 (28)	71 (24)	<0.0001
Use of sunbeds, *n* (%)	1073 (32)	25 (10)	76 (17)	238 (29)	320 (36)	279 (44)	135 (48)	<0.0001
Physical activity (SD)	2.3 (1.0)	1.9 (0.9)	2.1 (0.9)	2.2 (0.9)	2.4 (1.0)	2.6 (1.0)	2.7 (1.0)	<0.0001
Body mass index, kg/m^2 (SD)	25.1 (5.1)	26.7 (6.1)	26.3 (6.1)	25.4 (5.2)	24.7 (4.4)	24.5 (4.5)	24.1 (3.9)	<0.0001
Current smoking, *n* (%)	732 (22)	75 (30)	98 (22)	175 (22)	195 (22)	135 (21)	54 (19)	0.05
Alcohol (g/week, SD)	43.1 (67.7)	41.1 (1)	42.2 (62.0)	41.1 (63.3)	42.2 (62.0)	46.8 (59.8)	57.4 (91.7)	<0.0001

Note: Self-reported sun exposure, quantified on a scale from 2 to 8, reflects participant responses to questions about sunbathing frequency and travel to sunnier countries. The index values capture a spectrum of sun exposure habits, with higher values indicating more frequent and intense exposure. *p* value for differences between groups.

Abbreviations: EDSS, Expanded Disability Status Scale; MSIS-PHYS, Multiple Sclerosis Impact Scale 29, physical score.

TABLE 2 Coefficients with 95% CIs of the associations between sun exposure levels and MS progression over 15 years using linear mixed effect models.

Sun exposure level	Coefficient (95% CI)
2	0.58 (0.40, 0.76)
3	0.27 (0.13, 0.41)
4	0.14 (0.02, 0.26)
5	Reference
6	−0.02 (−0.15, 0.11)
7–8	0.03 (−0.14, 0.19)
Difference in annual rate of change in EDSS scores, by level of sun exposure	
2 × time	0.02 (−0.00, 0.05)
3 × time	−0.00 (−0.03, 0.02)
4 × time	0.00 (0.01, 0.02)
5 × time	Reference
6 × time	−0.01 (−0.03, 0.01)
7–8 × time	−0.02 (−0.05, 0.00)

Note: Adjusted for age at diagnosis, sex, residential area, ancestry, disease phenotype, disease duration, baseline EDSS, disease-modifying therapy, use of sunbeds and smoking.

Abbreviations: CI, confidence interval; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis.

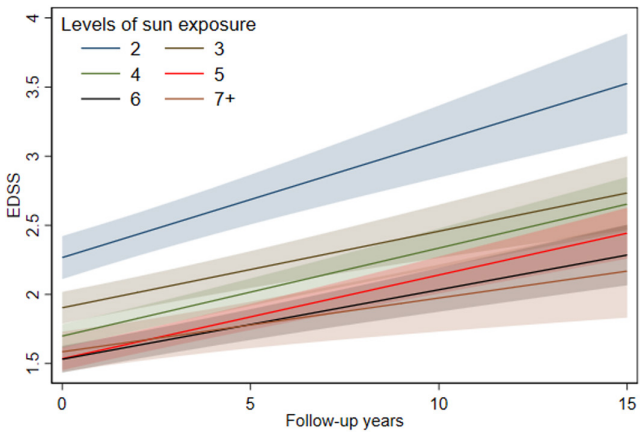

FIGURE 1 Trajectories of EDSS score over a 15-year period post-diagnosis, by sun exposure levels at diagnosis. Self-reported sun exposure, quantified on a scale from 2 to 8, reflects participant responses to questions about sunbathing frequency and travel to sunnier countries. The index values capture a spectrum of sun exposure habits, with higher values indicating more frequent and intense exposure. Adjusted for age at diagnosis, sex, residential area, ancestry, disease phenotype, disease duration, baseline EDSS, disease-modifying therapy, use of sunbeds and smoking.

Significant trends revealed a lower risk of the EDSS-related outcomes with increasing sun exposure (Table 3). Our findings remained similar when patients of non-Nordic ancestry were excluded (not in table).

The associations between low sun exposure and unfavourable outcomes became more pronounced when the analysis was restricted to patients who had not changed their sun exposure following the diagnosis of MS (Table 4; Figure S3). Significant associations were also observed between low sun exposure and increased risk of all outcomes when only patients without heat sensitivity were included at follow-up (not in table). When the analysis was performed based on those recruited during the period 2007–2011, the association between low sun exposure and risk of CDW remained significant (HR 1.43, 95% CI 1.01–2.04), as was the trend showing lower risk of CDW with increasing sun exposure (HR 0.92, 95% CI 0.87–0.97).

DISCUSSION

Low sun exposure was associated with worse disease progression and health-related quality of life in MS. Similar results were observed amongst participants with persistent sun exposure habits during follow-up and amongst those without heat sensitivity at follow-up, indicating that reverse causation is unlikely to be contributing substantially to the association.

The precise role of vitamin D as a possible intermediary link between sun exposure and the risk and progression of MS is not clearly understood. In terms of MS risk, it has been previously reported that low sun exposure appears to act both directly and indirectly, by affecting vitamin D status [3]. Low vitamin D levels have been associated with higher disease activity and faster disease progression in several observational studies [6–10]. However, clinical trials of vitamin D supplementation have not been conclusive [11–13] and there is not yet sufficient evidence to support vitamin D therapy in MS. Immunomodulation resulting directly from sun exposure is therefore gaining increasing attention and several clinical trials with narrowband ultraviolet radiation B phototherapy in patients with clinically isolated syndrome have been conducted and shown promising results [25–27]. Sun exposure induces suppression of cell mediated immunity by activating regulatory B cells, inhibiting effector and memory T cell activation, and leading to the release of numerous secondary immune mediators [28, 29] which may directly or indirectly impact disease progression in MS. A suppressive effect of ultraviolet radiation, independent of vitamin D, has also been confirmed in numerous experimental studies [27, 30, 31].

Sun exposure habits have changed partly due to campaigns aimed at preventing skin cancer. However, serious health consequences due to insufficient sun exposure have become an increasing public health problem [32]. In particular in countries where the levels of ultraviolet radiation are comparatively low, such as in Sweden, insufficient sun exposure may not just result in insufficient vitamin D levels but also negatively impact optimal immune functioning, and in patients with MS negatively impact disease progression. Some exposure to sunlight, whilst adhering to recommendations from public health authorities, may thus offer benefits in MS and should be encouraged if tolerated.

The strengths of our study are the population-based design using incident cases of MS, the high response rate and the detailed

TABLE 3 HR with 95% CI of having unfavourable outcomes post-diagnosis, by sun exposure habits at diagnosis, and trend test for the impact of increasing sun exposure.

First clinical disease worsening (CDW)						
Sun exposure	***N***	**Years (SD)**	**Outcome (%)**	**HR (95% CI)[a]**	**HR (95% CI)[b]**	**HR (95% CI)[b,c]**
2	250	5.1 (4.0)	131 (52)	1.36 (1.12–1.66)	1.47 (1.20–1.80)	1.48 (1.21–1.81)
3	452	5.6 (4.0)	203 (45)	1.05 (0.89–1.24)	1.11 (0.94–1.32)	1.12 (0.94–1.33)
4	808	6.0 (4.3)	373 (46)	1.01 (0.88–1.16)	1.06 (0.92–1.22)	1.06 (0.92–1.22)
5	887	6.1 (4.4)	419 (47)	1.0 (reference)	1.0 (reference)	1.0 (reference)
6	636	6.4 (4.5)	277 (44)	0.91 (0.78–1.05)	0.90 (0.78–1.05)	0.90 (0.78–1.05)
7–8	281	6.0 (4.2)	117 (42)	0.91 (0.74–1.12)	0.91 (0.74–1.12)	0.91 (0.74–1.12)
Per 1-unit increase in sun exposure	3314	6.0 (4.3)	1520 (46)	0.94 (0.90–0.97)	0.94 (0.91–0.97)	0.94 (0.91–0.97)
EDSS 3						
2	163	6.1 (4.3)	63 (39)	1.37 (1.04–1.81)	1.33 (1.01–1.77)	1.35 (1.02–1.79)
3	322	6.7 (4.5)	93 (29)	0.94 (0.74–1.20)	0.95 (0.75–1.21)	0.97 (0.75–1.22)
4	622	7.1 (4.7)	172 (28)	0.86 (0.7–1.05)	0.93 (0.76–1.13)	0.94 (0.76–1.13)
5	735	7.2 (4.6)	245 (33)	1.0 (reference)	1.0 (reference)	1.0 (reference)
6	523	7.6 (4.7)	135 (26)	0.75 (0.61–0.93)	0.74 (0.60–0.92)	0.75 (0.60–0.92)
7–8	217	7.0 (4.6)	58 (27)	0.83 (0.62–1.10)	0.79 (0.59–1.06)	0.83 (0.60–1.07)
Per 1-unit increase in sun exposure	2582	7.1 (4.6)	766 (30)	0.95 (0.91–0.99)	0.94 (0.90–0.98)	0.94 (0.90–0.98)
EDSS 4						
2	163	7.7 (4.5)	33 (20)	1.61 (1.09–2.39)	1.48 (1.01–2.21)	1.47 (1.01–2.20)
3	322	7.8 (4.5)	44 (14)	1.07 (0.75–1.52)	1.09 (0.77–1.51)	1.09 (0.76–1.56)
4	622	8.2 (4.5)	76 (12)	0.93 (0.68–1.23)	1.02 (0.76–1.37)	1.01 (0.75–1.34)
5	735	8.7 (4.6)	106 (14)	1.0 (reference)	1.0 (reference)	1.0 (reference)
6	523	8.8 (4.7)	59 (11)	0.79 (0.57–1.08)	0.83 (0.60–1.14)	0.83 (0.60–1.14)
7–8	217	7.9 (4.6)	26 (12)	0.93 (0.60–1.42)	0.96 (0.62–1.47)	0.96 (0.63–1.50)
Per 1-unit increase in sun exposure	2582	8.3 (4.6)	344 (13)	0.93 (0.87–0.99)	0.94 (0.88–1.00)	0.94 (0.88–1.00)
Physical worsening (increased MSIS-29 physical score by 7.5 or more)						
Sun exposure	***N***	**Years (SD)**	**Outcome (%)**	**HR (95% CI)[a]**	**HR (95% CI)[b,d]**	**HR (95% CI)[b–d]**
2	185	4.6 (4.7)	86 (46)	1.24 (0.98–1.58)	1.25 (0.99–1.59)	1.27 (1.00–1.62)
3	351	4.9 (4.4)	147 (42)	1.05 (0.86–1.27)	1.06 (0.87–1.29)	1.06 (0.87–1.29)
4	625	4.8 (4.0)	252 (40)	1.02 (0.86–1.20)	1.05 (0.88–1.24)	1.05 (0.88–1.24)
5	703	5.1 (4.4)	291 (41)	1.0 (reference)	1.0 (reference)	1.0 (reference)
6	510	5.3 (5.2)	214 (42)	0.99 (0.83–1.18)	1.00 (0.83–1.19)	1.00 (0.83–1.19)
7–8	227	4.8 (4.3)	91 (40)	1.03 (0.81–1.30)	1.01 (0.80–1.28)	1.02 (0.81–1.30)
Per 1-unit increase in sun exposure	2601	5.0 (4.5)	1081 (42)	0.98 (0.95–1.02)	0.97 (0.94–1.01)	0.98 (0.94–1.01)

Note: Self-reported sun exposure, quantified on a scale from 2 to 8, reflects participant responses to questions about sunbathing frequency and travel to sunnier countries. The index values capture a spectrum of sun exposure habits, with higher values indicating more frequent and intense exposure.

Abbreviations: CI, confidence interval; EDSS, Expanded Disability Status Scale; HR, hazard ratio; MSIS-PHYS, Multiple Sclerosis Impact Scale 29, physical score.

[a]Crude.

[b]Adjusted for age at diagnosis, sex, residential area, ancestry, disease phenotype, disease duration, baseline EDSS, disease-modifying therapy, use of sunbeds and smoking.

[c]Adjusted for baseline vitamin D status.

[d]Adjusted for baseline MSIS-PHYS.

TABLE 4 HR with 95% CI of having unfavourable outcomes post-diagnosis, by sun exposure habits at diagnosis, and trend test for the impact of increasing sun exposure.

First clinical disease worsening (CDW)						
Sun exposure	***N***	**Years (SD)**	**Outcome (%)**	**HR (95% CI)[a]**	**HR (95% CI)[b]**	**HR (95% CI)[b,c]**
2	82	5.3 (4.0)	51 (62)	1.53 (1.02–2.92)	1.74 (1.14–2.65)	1.71 (1.12–2.60)
3	188	6.6 (4.3)	91 (48)	1.03 (0.71–1.50)	0.97 (0.64–1.40)	0.95 (0.73–1.37)
4	341	6.8 (4.4)	164 (48)	0.95 (0.68–1.33)	0.97 (0.70–1.36)	0.97 (0.69–1.35)
5	366	6.8 (4.5)	198 (54)	1.0 (reference)	1.0 (reference)	1.0 (reference)
6	266	7.2 (4.8)	127 (48)	0.83 (0.59–1.33)	0.82 (0.59–1.16)	0.82 (0.58–1.15)
7–8	17	7.1 (4.5)	8 (47)	1.04 (0.20–9.17)	0.86 (0.11–6.60)	0.82 (0.11–6.30)
Per 1-unit increase in sun exposure	1260	6.7 (4.5)	639 (51)	0.90 (0.82–0.99)	0.89 (0.81–0.98)	0.90 (0.82–0.98)
EDSS 3						
2	54	6.0 (4.1)	30 (56)	1.94 (1.30–2.90)	1.65 (1.10–2.47)	1.62 (1.08–2.43)
3	138	7.6 (4.6)	46 (33)	0.96 (0.67–1.32)	0.91 (0.62–1.23)	0.91 (0.60–1.21)
4	268	8.0 (4.6)	79 (29)	0.79 (0.59–1.04)	0.91 (0.65–1.15)	0.91 (0.64–1.13)
5	307	8.3 (4.8)	119 (39)	1.0 (reference)	1.0 (reference)	1.0 (reference)
6	217	8.8 (4.9)	61 (28)	0.70 (0.51–0.95)	0.74 (0.54–1.01)	0.73 (0.54–1.00)
7–8	9	7.7 (4.6)	2 (22)	0.60 (0.15–2.44)	0.47 (0.11–1.89)	0.48 (0.12–1.90)
Per 1-unit increase in sun exposure	993	8.1 (4.7)	337 (34)	0.88 (0.80–0.96)	0.90 (0.83–0.99)	0.90 (0.83–0.99)
EDSS 4						
2	54	8.6 (4.1)	15 (28)	2.20 (1.23–3.95)	2.05 (1.14–3.70)	1.96 (1.09–3.54)
3	138	9.2 (4.3)	20 (14)	1.07 (0.63–1.81)	1.04 (0.62–1.77)	1.00 (0.57–1.65)
4	268	9.2 (4.2)	35 (13)	0.96 (0.61–1.48)	1.09 (0.70–1.70)	1.03 (0.66–1.60)
5	307	10.2 (4.5)	47 (15)	1.0 (reference)	1.0 (reference)	1.0 (reference)
6	217	10.2 (4.7)	29 (13)	0.87 (0.55–1.39)	0.95 (0.60–1.52)	0.92 (0.58–1.47)
7–8	9	10.4 (4.4)	0	–	–	–
Per 1-unit increase in sun exposure	993	9.7 (4.4)	146 (15)	0.85 (0.74–0.97)	0.86 (0.76–0.99)	0.88 (0.77–1.00)
Physical worsening (increased MSIS-29 physical score by 7.5 or more)						
Sun exposure	***N***	**Years (SD)**	**Outcome (%)**	**HR (95% CI)[a]**	**HR (95% CI)[b,d]**	**HR (95% CI)[b–d]**
2	64	5.3 (6.8)	34 (53)	1.52 (1.04–2.34)	1.48 (1.01–2.16)	1.48 (1.01–2.16)
3	146	5.6 (3.9)	64 (44)	1.11 (0.82–1.51)	1.06 (0.79–1.45)	1.07 (0.79–1.46)
4	255	5.3 (3.7)	95 (37)	0.99 (0.75–1.29)	1.03 (0.79–1.36)	1.04 (0.79–1.36)
5	288	6.0 (4.9)	120 (42)	1.0 (reference)	1.0 (reference)	1.0 (reference)
6	223	6.0 (5.7)	94 (42)	1.02 (0.79–1.34)	1.01 (0.76–1.32)	1.00 (0.76–1.32)
7–8	11	4.7 (4.2)	7 (64)	1.89 (0.88–4.05)	1.67 (0.78–3.59)	1.66 (0.77–3.49)
Per 1-unit increase in sun exposure	987	5.7 (4.8)	414 (42)	0.97 (0.89–1.04)	0.97 (0.90–1.05)	0.97 (0.89–1.05)

Note: Restricted to participants who did not change their sun exposure behaviour during follow-up. Self-reported sun exposure, quantified on a scale from 2 to 8, reflects participant responses to questions about sunbathing frequency and travel to sunnier countries. The index values capture a spectrum of sun exposure habits, with higher values indicating more frequent and intense exposure.

Abbreviations: CI, confidence interval; EDSS, Expanded Disability Status Scale; HR, hazard ratio; MSIS-PHYS, Multiple Sclerosis Impact Scale 29, physical score.

[a]Crude.

[b]Adjusted for age at diagnosis, sex, residential area, ancestry, disease phenotype, disease duration, baseline EDSS, disease-modifying therapy, use of sunbeds and smoking.

[c]Adjusted for baseline vitamin D status.

[d]Adjusted for baseline MSIS-PHYS.

information regarding exposures which makes it possible to consider several potential confounding factors. The patients were followed for up to 15 years by linking baseline information with the nationwide and continuously updated MS registry [33]. Longer follow-up periods offer potential advantages, such as increased statistical power and a more accurate estimation of risk over time. An extended follow-up also provides an opportunity to reveal late-onset effects that may not be evident in shorter-duration studies. Changes in sun exposure habits since baseline could be assessed by the follow-up questionnaire that was sent out in 2021. The response rate was lower in the EIMS follow-up study; however, there were no significant differences in baseline EDSS or at 5 years post-diagnosis amongst those who participated in the follow-up study and those who did not.

Information regarding sun exposure habits collected at baseline should be subjected to limited recall bias. Reverse causation could be a concern if patients with greater disability at inclusion had already developed sun avoidance behaviour which could lead to an overestimation of the inverse association between sun exposure and MS progression. However, the association remained similar when the analysis was restricted to patients who had not changed their sun exposure habits during follow-up. Significant associations between low sun exposure and increased risk of each outcome amongst patients without heat sensitivity at follow-up were also observed. It is therefore believed unlikely that reverse causation would have affected our results to a large extent.

Sunbed use was treated as a potential confounding variable rather than being incorporated into the sun exposure index. This decision was based on the recognition that sunbed exposure differs from natural sunlight exposure, both in terms of intensity and spectrum. Sunbeds omit concentrated ultraviolet radiation, often at levels that surpass natural sunlight. Moreover, the spectrum of ultraviolet radiation emitted by sunbeds may not precisely mimic the complex and varied spectrum of sunlight. By treating sunbed use as a separate variable, the aim was to isolate the effects of natural sunlight exposure on disease progression in MS. It was possible to make adjustments for several clinical and lifestyle variables, including vitamin D status, but since the numbers of patients with vitamin D measurements was relatively small ($n = 1220$), resulting in a large group of unknowns, the adjustment is far from complete. Whilst the subgroup with available vitamin D status exhibited characteristics representative of the overall sample—including similar age at diagnosis, sex ratio, baseline EDSS and sun exposure habits—the challenge of fully disentangling the influence of sun exposure independent of vitamin D is acknowledged. Disease-modifying treatment plays a pivotal role in managing the progression of MS. There was access to comprehensive treatment data spanning from baseline to 2021. In our final analyses, the influence of treatment was accounted for by calculating the proportion of the duration of follow-up spent on disease-modifying therapy and including this variable in the model. The observed results remained consistent even when individuals were excluded who were not receiving treatment.

In conclusion, very low levels of sun exposure seem to be associated with a worse disease progression and health-related quality of life in patients with MS.

AUTHOR CONTRIBUTIONS

Anna Karin Hedström: Conceptualization; investigation; funding acquisition; writing – original draft; writing – review and editing; validation; methodology; formal analysis; supervision. **Jing Wu:** Writing – original draft; visualization; writing – review and editing; validation; methodology; investigation; conceptualization; formal analysis. **Tomas Olsson:** Conceptualization; investigation; funding acquisition; writing – review and editing; validation; methodology. **Lars Alfredsson:** Conceptualization; investigation; funding acquisition; writing – review and editing; validation; methodology.

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CONFLICT OF INTEREST STATEMENT

Wu has nothing to disclose. Alfredsson reports grants from Swedish Research Council, grants from Swedish Research Council for Health, Working Life and Welfare, grants from Swedish Brain Foundation, during the conduct of the study. TO has received lecture/advisory board honoraria, and unrestricted MS research grants from Biogen, Novartis, Sanofi and Merck. Hedström has nothing to disclose.

DATA AVAILABILITY STATEMENT

Anonymized data underlying this article will be shared on reasonable request from any qualified investigator who wants to analyse questions that are related to the published article.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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