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Association Between Sun Exposure and Risk of Relapse in Pediatric-Onset Multiple Sclerosis

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Abstract

Background and Objectives

Low sun and ultraviolet radiation (UVR) exposures have been associated with increased risk of developing pediatric-onset multiple sclerosis (MS); however, their effect on disease course has not been well characterized. We primarily investigated whether there was an association between time spent in the sun in early childhood and risk of relapse in pediatric MS. We secondarily investigated the effect of sun exposure during more recent periods on risk of relapse.

Methods

We conducted a multicenter cohort study of participants with pediatric-onset MS recruited from 18 pediatric MS clinics across the United States between November 1, 2011, and July 1, 2017. Relapses were identified prospectively after study enrollment; relapses preceding study enrollment were entered retrospectively. Time spent in the sun at various periods of life was measured using a detailed environmental questionnaire, and ambient UVR exposure was determined using zip codes. Multivariable Cox regression models were used to assess the association between time spent in the sun and UVR dose at specific periods of life and the risk of relapse. Models were adjusted for demographic, clinical, and sun exposure–related characteristics.

Results

In our cohort of 334 children with MS, 206 (62%) experienced at least one relapse from disease onset to the end of the follow-up period. After adjustment, ≥30 minutes of daily sun exposure during the first summer of life was associated with a lower risk of relapse compared with <30 minutes (adjusted hazard ratio [aHR] 0.67, CI 0.48–0.92, $p = 0.01$). Greater time spent in the sun during the second trimester of pregnancy was also associated with reduced risk of relapse (aHR 0.68, CI 0.48–0.97, $p = 0.04$). UVR dose and time spent in the sun later in life were not significantly associated with relapse risk.

Discussion

In this large cohort study of children with MS, greater early childhood and prenatal sun exposure time was associated with lower risk of relapse. Further investigation of sun exposure at other periods is needed to better characterize its impact on disease course and guide potential future interventions.

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Glossary

aHR = adjusted hazard ratio; **CIS** = clinically isolated syndrome; **DMT** = disease-modifying treatment; **MS** = multiple sclerosis; **NMSS** = National Multiple Sclerosis Society; **NPMSC** = Network of Pediatric MS Center; **UVB** = ultraviolet B; **UVR** = ultraviolet radiation.

Introduction

Multiple sclerosis (MS) onset typically occurs between the ages of 20 and 50 years, but 3%–5% of individuals with MS may experience onset before 18 years of age.[1] Compared with those with adult-onset disease, patients with pediatric-onset MS have a higher relapse rate,[2] which may improve the ability to study associations between risk factors and relapse risk. Furthermore, pediatric-onset patients have been shown to reach irreversible disability at a median age 10 years younger compared to patients with adult-onset disease,[3] highlighting the importance of identifying potential risk factors of relapse in this population.

Low sun exposure, low ultraviolet radiation (UVR) exposure, or low vitamin D status have been associated with higher risk of developing MS in both adults and children.[4-10] The effect of these factors on disease course is not well characterized. One prospective cohort study in adults with clinically isolated syndrome (CIS) found that higher UVR exposure at younger ages was associated with a significantly reduced risk of MS conversion and relapse.[7] A survey-based cross-sectional study of adults with relapsing-remitting MS also demonstrated an association between self-reported sun exposure and risk of disability progression.[11] However, the effect of sun exposure on disease course in MS remains poorly understood, especially in children with the disease.

In this multicenter cohort study, we examined the associations between sun exposure at various periods of life and the risk of relapse in pediatric-onset MS. Based on the potential contributions of these risk factors to disease course in adult-onset MS, we hypothesized that higher sun exposure would be associated with lower risk of relapse in this pediatric population.

Methods

Study Population

Study participants were recruited consecutively from 18 pediatric MS clinics across the United States between November 1, 2011, and July 1, 2017. These sites are considered to be secondary or tertiary referral centers for pediatric MS and see patients from large catchment areas. Participants were aged 4–21 years and eligible for inclusion if they had either MS or CIS onset before the age of 18 years and were within 4 years from symptom onset. The diagnosis of MS or CIS was confirmed by at least 2 pediatric MS specialists affiliated with the US Network of Pediatric MS Centers (NPMSC), adhering to the 2010 McDonald Criteria.[12] Participants with complete follow-up information subsequent to enrollment were included in the analysis.

Clinical and Demographic Information

Participants or their parents/guardians completed a questionnaire on study enrollment providing data on demographic characteristics (including binary sex at birth, race, and ethnicity, according to NIH criteria), medical history, location of residence (at birth and most recently), and environmental exposures, including behaviors related to sun exposure. Serum concentrations of 25-hydroxyvitamin D (25(OH)D, in ng/mL) were measured using the batched chemiluminescent assay (Heartlands Assay, Inc., Ames, IA) on blood samples obtained at the time of enrollment and modeled as a continuous variable.[2]

Participants were followed clinically and data entered prospectively from the time of their first clinic visit, which occurred either at or before enrollment in the study; subsequent clinic visits occurred 1–2 times per year, on average. Relapse information preceding study enrollment was entered retrospectively into the US NPMSC database.[13] Relapses were defined as new or recurrent neurologic symptoms localizing to the CNS, lasting for at least 24 hours after a remission of 30 days or more since the previous attack in the absence of an infection or fever.[12] Disease duration at the time of enrollment was calculated from the date of disease onset (first demyelinating event) to the date of study enrollment.

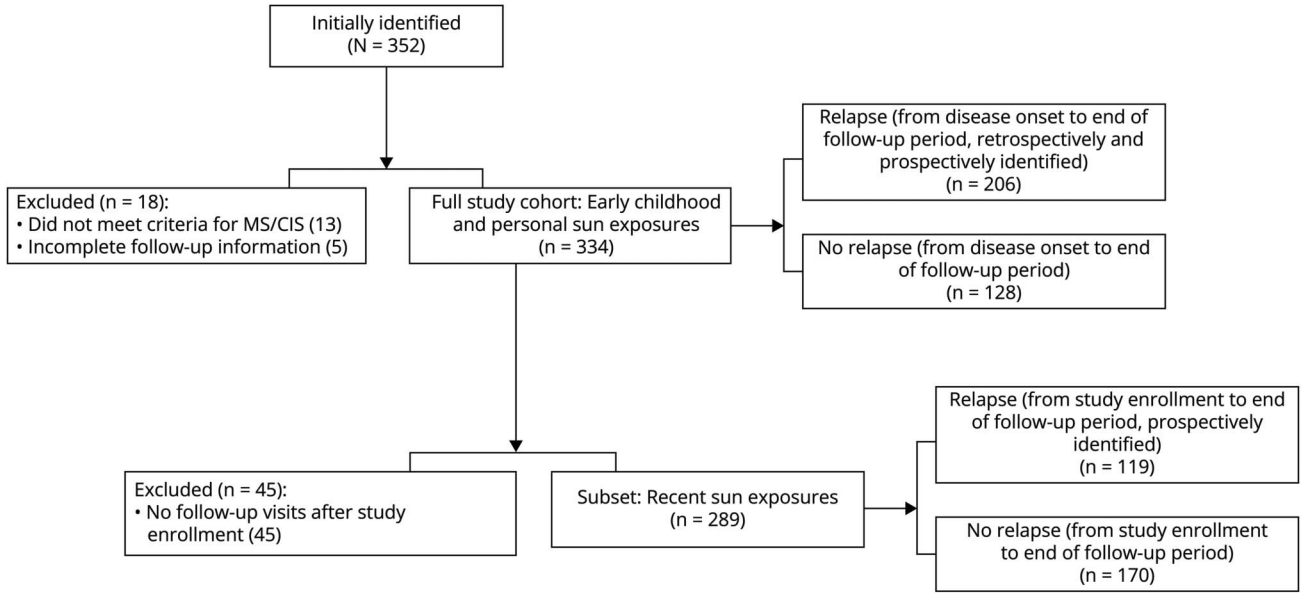
Disease-modifying treatment (DMT) use was categorized into 4 groups based on efficacy[13]: (1) no DMT; (2) interferon β, glatiramer acetate, azathioprine, mycophenolate mofetil, or IV immunoglobulin; (3) fingolimod, dimethyl fumarate, or daclizumab; and (4) natalizumab, rituximab, ocrelizumab, alemtuzumab, cyclophosphamide, or mitoxantrone. Participants who switched treatment during the follow-up period were assigned to the treatment with the longest duration.

Exposures of Interest

Sun exposure was measured as both reported time spent in the sun and ambient UVR dose, at various time points.

Time spent in the sun was based on a detailed environmental questionnaire completed by parents/guardians at the time of study enrollment. We primarily investigated early childhood exposure (duration of time spent in the sun during weekends/holidays in the summer of the first year of life) based on our previous findings of an association between this exposure and risk of MS[8] and because this would allow us to investigate potential association with first relapse since disease onset. We

Figure 1 Flowchart Depicting the Participants Included in Our Analyses



secondarily investigated time spent in the sun during more recent periods (weekends and holidays in the summer preceding study enrollment), which was also previously found to be associated with risk of MS,[8] and during prenatal stages (duration of time that the biological mother spent in the sun daily during each trimester). Data were recorded in 6 categories (never spent time in the sun, <30 minutes, 30 minutes–1 hour, 1–2 hours, 2–3 hours, and >3 hours daily) and analyzed as a dichotomous variable (<30 minutes and ≥30 minutes of daily time spent in the sun), based on the distribution of exposures within our cohort and our previous study, which demonstrated that spending ≥30 minutes in the sun daily during the most recent summer was strongly associated with lower risk of developing MS.[8]

Ambient UVR dose: Determination of ambient UVR dose was previously described.[8] UVR doses for prenatal (6 months before birth) and recent (last summer and 6 months before study enrollment) exposures were categorized into tertiles, with the lowest tertile as the reference.

Other Study Variables and Definitions

Sun protection behavior index was calculated as previously described,[8] based on participant-reported use of sunscreen, sunglasses, hat, clothes fully covering arms and legs, and clothes exposing at least half of the forearms and legs, in the most recent summer. Data were recorded in 4 categories and assigned a numerical score: never (0), <50% of the time (1), ≥50% of the time (2), and always (3). The numerical scores for these self-reported measures were aggregated to produce a single variable, sun protection behavior index, as follows: overall use of sun protection = sunscreen + sunglasses + hat + clothes covering arms and legs–clothes exposing forearms and legs.

Sun protection behavior during the prenatal period was assessed through questions regarding the frequency with which the biological mother wore a hat/veil and sun block and her typical clothing (fully covered to mostly uncovered), in each trimester of pregnancy.

Smoke exposure was based on the question "was the child regularly exposed to tobacco smoke in the first year of life" (yes/no).

Overweight/obese was defined as body mass index ≥85th percentile for age and sex based on Center for Disease Control growth charts, calculated using participant weight and height obtained at the closest visit within 180 days of study enrollment, and represented as a dichotomous variable (overweight/obese vs non-overweight/obese).

Skin tones of the participant and of the participant's biological mother at an unexposed skin site (inner upper arm) were self-reported and included as a marker of sun sensitivity. Skin tone was categorized as dark, olive, or fair.

Maternal education was defined as the highest education obtained by the biological mother and collapsed into 3 categories: completion of secondary school or below, university degree, and trade school or other.

Insurance type was defined as the most recent insurance reported at the time of enrollment and categorized as commercial, Medicaid, and other.

Statistical Analysis

Statistical analyses were performed using Stata version 15.1 (College Station, TX). Demographic and baseline clinical

Table 1 Demographic, Clinical, and Early Childhood Sun Exposure Characteristics of the Full Cohort and Separately According to Relapse/No Relapse

	Total (N = 334)	No relapse (n = 128)	Relapse (n = 206)	*p* Value
Age at onset, yr, median (IQR)	15.2 (13.3–16.5)	15.5 (13.9–17.0)	14.8 (13.0–16.1)	0.004
Female sex, n (%)	210 (62.9)	83 (64.8)	127 (61.7)	0.56
Race, n (%)				0.38
White	232 (69.5)	93 (72.7)	139 (67.5)	
Black	44 (13.2)	13 (10.2)	31 (15.0)	
Asian	14 (4.2)	5 (3.9)	9 (4.4)	
Other	22 (6.6)	6 (4.7)	16 (7.8)	
Hispanic or Latino, n (%)	99 (29.6)	31 (24.2)	68 (33.0)	0.22
Insurance type				0.19
Commercial	192 (57.5)	76 (59.4)	116 (56.3)	
Medicaid	88 (26.3)	27 (21.1)	61 (29.6)	
Other	38 (11.4)	16 (12.5)	22 (10.7)	
Maternal education				0.36
Secondary school or below	185 (55.4)	64 (50.0)	121 (58.7)	
University degree	92 (27.5)	42 (32.8)	50 (24.3)	
Trade school or other	38 (11.4)	15 (11.7)	23 (11.2)	
Overweight/obese status[a], n (%)	164 (51.6)	55 (45.5)	109 (55.3)	0.09
Smoke exposure in first year of life, n (%)	56 (17.9)	19 (15.3)	37 (19.6)	0.34
Follow-up duration, from disease onset, yr, median (IQR)	3.3 (1.7–5.0)	2.4 (1.0–4.0)	3.8 (2.5–5.4)	<0.001
DMT group, n (%)				<0.001
No DMT	35 (10.5)	24 (18.8)	11 (5.3)	
Lower efficacy	153 (45.8)	60 (46.9)	93 (45.1)	
Intermediate efficacy	77 (23.1)	20 (15.6)	57 (27.7)	
Higher efficacy	69 (20.7)	24 (18.8)	45 (21.8)	
Sun protection behavior index, mean (SD)	5.5 (2.5)	5.5 (2.6)	5.5 (2.4)	0.72
Skin tone, n (%)				0.30
Dark	25 (7.5)	8 (6.2)	17 (8.3)	
Olive	70 (21.0)	26 (20.3)	44 (21.4)	
Fair	223 (66.8)	91 (71.1)	132 (64.1)	
Birth season, n (%)				0.23
Winter	75 (22.5)	32 (25.0)	43 (20.9)	
Spring	77 (23.1)	30 (23.4)	47 (22.8)	
Summer	91 (27.2)	27 (21.1)	64 (31.1)	
Fall	91 (27.2)	39 (30.5)	52 (25.2)	
Time spent in the sun daily in the summer of the first year of life, n (%)				<0.001
<30 min	182 (54.5)	64 (50.0)	118 (57.3)	
30 min-1 h	75 (22.5)	41 (32.0)	34 (16.5)	

Continued

Table 1 Demographic, Clinical, and Early Childhood Sun Exposure Characteristics of the Full Cohort and Separately According to Relapse/No Relapse *(continued)*

	Total (N = 334)	No relapse (n = 128)	Relapse (n = 206)	*p* Value
1–2 h	28 (8.4)	14 (10.9)	14 (6.8)	
2–3 h	6 (1.8)	0 (0.0)	6 (2.9)	
>3 h	7 (2.1)	3 (2.3)	4 (1.9)	

Abbreviations: IQR = interquartile range; DMT = disease-modifying therapy.
The following variables displayed missingness: race (6.6%), ethnicity (3.3%), insurance type (4.8%), maternal education (5.7%), overweight/obese status (4.8%), smoke exposure in the first year of life (6.3%), sun protection behavior index (10.2%), participant skin tone (4.8%), and time spent in the sun in the first year of life (10.8%).
[a] Body mass index (BMI) ≥85th percentile for age and sex.

characteristics were summarized by standard descriptive measures and compared between relapse and nonrelapse groups and between sun exposure groups using the χ^2 test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Cox proportional hazard regression models were analyzed to assess the associations between sun exposure variables and time to relapse. For our investigations of early childhood and prenatal sun exposures, the outcome measure was time from disease onset to first relapse. For investigation of more recent sun exposures, the outcome measure was time from study enrollment to the first relapse after enrollment. Kaplan-Meier curves were used to depict the association between sun exposure and time to relapse. To examine early childhood sun exposure, the multivariable Cox proportional hazard regression model was adjusted for age at disease onset, sex, race, ethnicity, insurance type, maternal education, overweight/obese status, tobacco exposure in the first year of life, DMT category, participant's skin tone, sun protection behavior index, and season of birth. Models examining prenatal sun exposure (time spent in the sun each trimester) were adjusted for the same covariates, but we substituted biological mother's skin tone and sun protection behaviors by corresponding trimester in place of participant's skin tone and sun protection behavior index; for the model examining UVR dose in the 6 months before birth, we specifically used second-trimester maternal sun protection behaviors. Models examining recent sun exposures were adjusted for the same covariates as those for early childhood sun exposure, except season of birth, and further adjusted for serum 25(OH)D and disease duration at the time of enrollment. Covariates were chosen because they were known to possibly change risk of relapse or associate with disease activity or were believed to modulate UVR absorption. Notably, although skin tone and race/ethnicity were correlated, they are not identical because race is a social construct and both race and ethnicity carry associations related to social determinants of health; likelihood ratio tests also suggested that the model including all three of these covariates was superior to a model with some or none of these variables. We did not adjust for multiple comparisons because while this decreases the risk of false positives, it also increases the risk of false negatives, particularly when sample sizes are smaller.[14] Multiplicative and additive interactions between sun exposure variables and smoke exposure, as well as between statistically significant sun exposure variables, were also tested; additive interactions were calculated according to the delta method.[15] Multiplicative interactions between sun exposure variables and season of birth were further tested. Model checking, including testing for proportional hazards, was performed. A p value less than 0.05 was considered statistically significant for all analyses.

Multiple imputation using chained equations was used for all multivariable analyses because of over 10% missingness in several variables. Fifteen imputed data sets were created using age, sex, race, ethnicity, insurance type, maternal education, overweight/obese status, smoke exposure, 25(OH)D, disease duration at time of enrollment, follow-up duration, DMT use, birth season, sun protection behavior index, skin tone, maternal skin tone and sun protection behaviors, and sun exposure variables (time spent in the sun and ambient UVR dose). Missing values were imputed for this same set of variables unless a variable had no missingness.

We also performed sensitivity analyses excluding participants with missing data for the sun exposure variables of interest.

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the Human Research Protection Institutional Review Board of all the participating centers including the University of California San Francisco. Before participation, parents/guardians provided written informed consent on behalf of participants aged younger than 18 years; older participants provided written informed consent on their own behalf.

Data Availability

Participant data are securely stored electronically at the Data Coordinating and Access Center of the Network of Pediatric Multiple Sclerosis Centers (NPMSC) registry, which is located at the University of Utah in Salt Lake City, US. Anonymous raw data can be accessed on reasonable request to the corresponding author, subject to approval from the NPMSC steering committee.

Table 2 Prenatal Sun Exposures and Maternal Sun-Related Behaviors

	Total (n = 334)	No relapse (n = 128)	Relapse (n = 206)	*p* Value
UVR dose in the 6 months before birth, n (%)				0.07
Tertile 1[a]	114 (34.1)	36 (28.1)	78 (37.9)	
Tertile 2[b]	110 (32.9)	41 (32.0)	69 (33.5)	
Tertile 3[c]	110 (32.9)	51 (39.8)	59 (28.6)	
First trimester				
Time spent in the sun daily in the first trimester, n (%)				0.61
Never spent time in sun	12 (3.6)	3 (2.3)	9 (4.4)	
<30 min	99 (29.6)	34 (26.6)	65 (31.6)	
30 min-1 h	95 (28.4)	43 (33.6)	52 (25.2)	
1–2 h	52 (15.6)	21 (16.4)	31 (15.0)	
2–4 h	12 (3.6)	3 (2.3)	9 (4.4)	
≥4 h	8 (2.4)	3 (2.3)	5 (2.4)	
Frequency with which the biological mother wore hat/veil, n (%)				0.52
<50% of the time	303 (90.7)	116 (90.6)	187 (90.8)	
≥50% of the time	24 (7.2)	8 (6.2)	16 (7.8)	
Most common type of clothing the biological mother usually wore, n (%)				0.54
Fully covered	44 (13.2)	15 (11.7)	29 (14.1)	
Partly covered	106 (31.7)	37 (28.9)	69 (33.5)	
Mostly covered	83 (24.9)	33 (25.8)	50 (24.3)	
Bathing suit	12 (3.6)	7 (5.5)	5 (2.4)	
Frequency with which the biological mother used sun block, n (%)				0.60
Never	151 (45.2)	54 (42.2)	97 (47.1)	
<50% of the time	88 (26.3)	38 (29.7)	50 (24.3)	
≥50% of the time	47 (14.1)	16 (12.5)	31 (15.0)	
Second trimester				
Time spent in the sun daily in the second trimester, n (%)				0.34
Never spent time in sun	12 (3.6)	3 (2.3)	9 (4.4)	
<30 min	93 (27.8)	28 (21.9)	65 (31.6)	
30 min-1 h	96 (28.7)	45 (35.2)	51 (24.8)	
1–2 h	53 (15.9)	22 (17.2)	31 (15.0)	
2–4 h	21 (6.3)	8 (6.2)	13 (6.3)	
≥4 h	3 (0.9)	1 (0.8)	2 (1.0)	
Frequency with which the biological mother wore hat/veil, n (%)				0.55
<50% of the time	301 (90.1)	115 (89.8)	186 (90.3)	
≥50% of the time	26 (7.8)	9 (7.0)	17 (8.3)	
Most common type of clothing the biological mother usually wore, n (%)				0.89
Fully covered	48 (14.4)	17 (13.3)	31 (15.0)	
Partly covered	100 (29.9)	36 (28.1)	64 (31.1)	

Continued

Table 2 Prenatal Sun Exposures and Maternal Sun-Related Behaviors *(continued)*

	Total (n = 334)	No relapse (n = 128)	Relapse (n = 206)	*p* Value
Mostly covered	87 (26.0)	35 (27.3)	52 (25.2)	
Bathing suit	10 (3.0)	5 (3.9)	5 (2.4)	
Frequency with which the biological mother used sun block, n (%)				0.28
Never	155 (46.4)	55 (43.0)	100 (48.5)	
<50% of the time	85 (25.4)	38 (29.7)	47 (22.8)	
≥50% of the time	46 (13.8)	14 (10.9)	32 (15.5)	
Third trimester				
Time spent in the sun daily in the third trimester, n (%)				0.64
Never spent time in sun	13 (3.9)	4 (3.1)	9 (4.4)	
<30 min	93 (27.8)	33 (25.8)	60 (29.1)	
30 min-1 h	105 (31.4)	48 (37.5)	57 (27.7)	
1–2 h	47 (14.1)	15 (11.7)	32 (15.5)	
2–4 h	13 (3.9)	4 (3.1)	9 (4.4)	
≥4 h	7 (2.1)	3 (2.3)	4 (1.9)	
Frequency with which the biological mother wore hat/veil, n (%)				0.23
<50% of the time	303 (90.7)	118 (92.2)	185 (89.8)	
≥50% of the time	24 (7.2)	6 (4.7)	18 (8.7)	
Most common type of clothing the biological mother usually wore, n (%)				0.44
Fully covered	54 (16.2)	20 (15.6)	34 (16.5)	
Partly covered	89 (26.6)	29 (22.7)	60 (29.1)	
Mostly covered	95 (28.4)	39 (30.5)	56 (27.2)	
Bathing suit	6 (1.8)	4 (3.1)	2 (1.0)	
Frequency with which the biological mother used sun block, n (%)				0.59
Never	161 (48.2)	58 (45.3)	103 (50.0)	
<50% of the time	83 (24.9)	36 (28.1)	47 (22.8)	
≥50% of the time	42 (12.6)	14 (10.9)	28 (13.6)	
Biological mother's skin tone, n (%)				0.09
Dark	30 (9.0)	7 (5.5)	23 (11.2)	
Olive	73 (21.9)	27 (21.1)	46 (22.3)	
Fair	219 (65.6)	92 (71.9)	127 (61.7)	

Abbreviation: UVR = ultraviolet radiation.
The following variables displayed missingness: time spent in the sun in the first trimester (16.8%), second trimester (16.8%), and third trimester (16.8%); amount of time the mother wore hat/veil in the first trimester (2.1%), second trimester (2.1%), and third trimester (2.1%); most common type of clothing worn by the mother in the first trimester (26.6%), second trimester (26.6%), and third trimester (26.9%); frequency with which the mother used sun block in the first trimester (14.4%), second trimester (14.4%), and third trimester (14.4%); and maternal skin tone (3.6%).
[a] 1.1–1.7 kJ/m^2.
[b] 1.7–3.6 kJ/m^2.
[c] 3.7–7.2 kJ/m^2.

Results

Participant Characteristics

The full study cohort comprised 334 children with MS, 206 (62%) of whom experienced at least one relapse from disease onset to the end of the follow-up period (Figure 1). Demographic, clinical, and early childhood sun exposure characteristics are presented in Table 1 for the entire cohort and separately for the group of participants who experienced relapse and for those without relapse. On univariate analyses,

Table 3 Demographic, Clinical, and Sun Exposure Characteristics for the Subset in Which Recent Sun Exposures Were Examined

	Total (n = 289)	No relapse (n = 170)	Relapse (n = 119)	*p* Value
Age at onset, yr, median (IQR)	15.2 (13.4–16.4)	15.2 (13.4–16.4)	15.0 (13.3–16.4)	0.65
Female sex, n (%)	186 (64.4)	113 (66.5)	73 (61.3)	0.37
Race, n (%)				0.96
White	198 (68.5)	114 (67.1)	84 (70.6)	
Black	37 (12.8)	23 (13.5)	14 (11.8)	
Asian	14 (4.8)	8 (4.7)	6 (5.0)	
Other	20 (6.9)	13 (7.6)	7 (5.9)	
Hispanic or Latino, n (%)	91 (31.5)	43 (25.3)	48 (40.3)	0.008
Insurance type				0.13
Commercial	162 (56.1)	96 (56.5)	66 (55.5)	
Medicaid	81 (28.0)	41 (24.1)	40 (33.6)	
Other	33 (11.4)	23 (13.5)	10 (8.4)	
Maternal education				0.35
Secondary school or below	168 (58.1)	94 (55.3)	74 (62.2)	
University degree	78 (27.0)	51 (30.0)	27 (22.7)	
Trade school or other	32 (11.1)	17 (10.0)	15 (12.6)	
Overweight/obese status[a], n (%)	146 (52.9)	83 (51.2)	63 (55.3)	0.51
Smoke exposure in the first year of life, n (%)	47 (17.3)	25 (15.6)	22 (19.8)	0.37
Disease duration at enrollment, yr, median (IQR)	0.6 (0.2–1.2)	0.7 (0.3–1.4)	0.4 (0.2–0.9)	0.001
Follow-up duration, from study enrollment, yr, median (IQR)	2.7 (1.6–4.1)	2.2 (1.2–3.5)	3.7 (2.3–4.9)	<0.001
DMT group, n (%)				0.008
No DMT	21 (7)	18 (11)	3 (3)	
Lower efficacy	127 (44)	78 (46)	49 (41)	
Intermediate efficacy	74 (26)	34 (20)	40 (34)	
Higher efficacy	67 (23)	40 (24)	27 (23)	
Time spent in the sun daily during the most recent summer, during weekends, n (%)				0.87
<30 min	58 (20.1)	33 (19.4)	25 (21.0)	
30 min-1 h	62 (21.5)	35 (20.6)	27 (22.7)	
1–2 h	50 (17.3)	29 (17.1)	21 (17.6)	
2–3 h	45 (15.6)	30 (17.6)	15 (12.6)	
>3 h	60 (20.8)	36 (21.2)	24 (20.2)	
Time spent in the sun daily during the most recent summer, during holidays, n (%)				0.86
<30 min	52 (18.0)	30 (17.6)	22 (18.5)	
30 min-1 h	67 (23.2)	37 (21.8)	30 (25.2)	
1–2 h	43 (14.9)	24 (14.1)	19 (16.0)	
2–3 h	41 (14.2)	27 (15.9)	14 (11.8)	
>3 h	65 (22.5)	38 (22.4)	27 (22.7)	

Continued

Table 3 Demographic, Clinical, and Sun Exposure Characteristics for the Subset in Which Recent Sun Exposures Were Examined *(continued)*

	Total (n = 289)	No relapse (n = 170)	Relapse (n = 119)	*p* Value
UVR dose in the summer before enrollment, n (%)				0.73
Tertile 1[b]	101 (34.9)	57 (33.5)	44 (37.0)	
Tertile 2[c]	92 (31.8)	57 (33.5)	35 (29.4)	
Tertile 3[d]	96 (33.2)	56 (32.9)	40 (33.6)	
UVR dose in the 6 months before enrollment, n (%)				0.09
Tertile 1[e]	94 (32.5)	55 (32.4)	39 (32.8)	
Tertile 2[f]	99 (34.3)	66 (38.8)	33 (27.7)	
Tertile 3[g]	96 (33.2)	49 (28.8)	47 (39.5)	
Serum 25(OH)D concentration (ng/mL), median (IQR)	26.6 (19.4–37.5)	28.4 (20.9–39.7)	23.4 (18.1–36.1)	0.02
Sun protection behavior index, mean (SD)	5.5 (2.5)	5.6 (2.5)	5.4 (2.4)	0.84
Skin tone, n (%)				0.59
Dark	19 (6.6)	12 (7.1)	7 (5.9)	
Olive	66 (22.8)	34 (20.0)	32 (26.9)	
Fair	189 (65.4)	115 (67.6)	74 (62.2)	

Abbreviations: 25(OH)D = 25-hydroxyvitamin D; DMT = disease-modifying therapy; IQR = interquartile range; UVR = ultraviolet radiation.
The following variables displayed missingness: race (6.9%), ethnicity (3.1%), insurance type (4.5%), maternal education (3.8%), overweight/obese status (4.5%), smoke exposure in the first year of life (6.2%), time spent in the sun in the most recent summer weekends (4.8%) and holidays (7.3%), 25(OH)D (4.3%), sun protection behavior index (9.5%), and skin tone (5.2%).
[a] Body mass index (BMI) ≥85th percentile for age and sex.
[b] 2.8–4.0 kJ/m^2.
[c] 4.1–5.3 kJ/m^2.
[d] 5.4–6.8 kJ/m^2.
[e] 0.4–2.2 kJ/m^2.
[f] 2.2–3.6 kJ/m^2.
[g] 3.6–6.5 kJ/m^2.

there were no significant associations between skin tone, race, ethnicity, or sun protection score and early childhood sun exposure (data not shown). Prenatal sun exposure factors are presented in Table 2.

Of the full study cohort, a subset of 289 children (87%) had follow-up beyond study enrollment (Figure 1). This subset was used to study more recent sun exposures and was separated into those who experienced a relapse between study enrollment and the end of the follow-up period (119 children, 41%) and those who did not experience relapse within this period (170 children, 59%). The demographic, clinical, and sun exposure characteristics of this subset are presented in Table 3.

Sun Exposure

Univariable and multivariable associations between all sun exposure variables and time to relapse are shown in Figure 2.

Early Childhood Sun Exposure

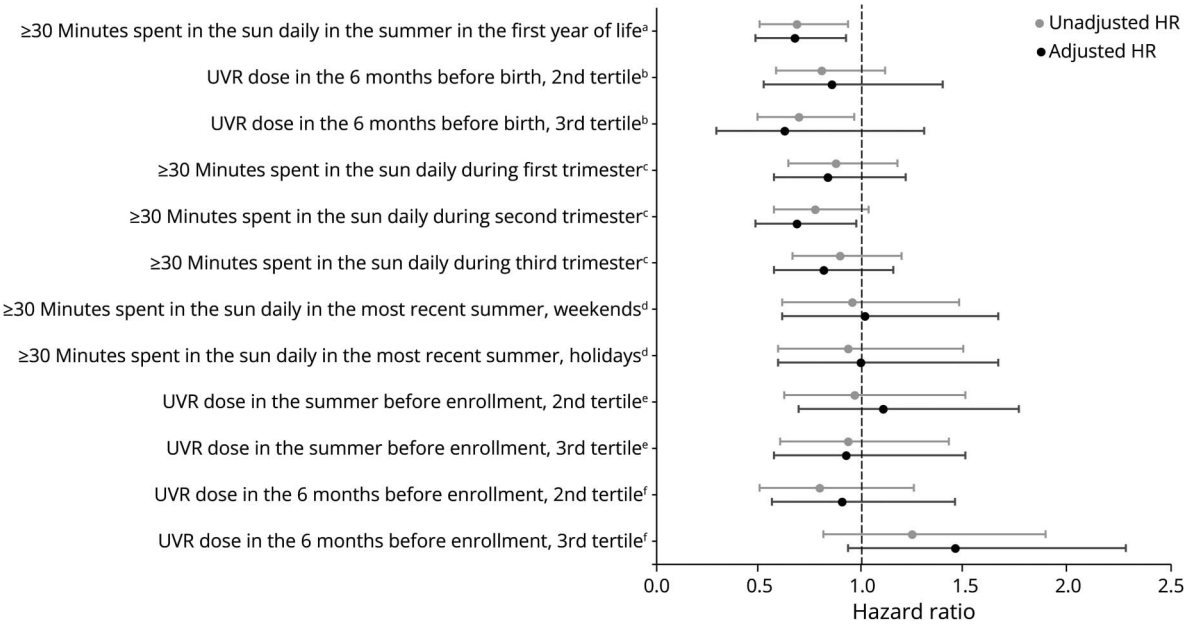
In univariable analysis, spending 30 minutes or more in the sun daily in the summer of the first year of life was associated with a lower risk of relapse compared with spending <30 minutes in the sun (HR 0.65, CI 0.48–0.90, p = 0.008; Figure 3). This finding was retained in the multivariable analysis adjusting for a wide range of demographic and clinical features (adjusted hazard ratio [aHR] 0.67, CI 0.48–0.92, p = 0.01).

Other significant or near-significant factors associated with increased risk of relapse in this model were summer birth season (aHR 1.63, CI 1.09–2.44, p = 0.02; compared with winter birth season) and treatment with mid-efficacy DMT (aHR 1.82, CI 0.93–3.55, p = 0.08; compared with no DMT use) or high-efficacy DMT (aHR 1.83, 0.92–3.64, p = 0.08; compared with no DMT use) (eTable 1, model 1). We did not find significant interaction effect between time spent in the sun in the summer of the first year of life and season of birth or smoke exposure in the first year of life on relapse risk.

Prenatal Sun Exposure

Spending 30 minutes or more in the sun daily during the second trimester of pregnancy was significantly associated with a lower risk of relapse (Figure 4). This relationship remained on multivariable analysis, after adjusting for various covariates (aHR 0.68, CI 0.48–0.97, p = 0.04) (eTable 2, model 2). Time spent in the sun in the first and third

Figure 2 Association Between Sun Exposure at Various Periods of Life and Risk of Relapse



[a]Compared with <30 minutes spent in the sun daily (N = 334); adjusted for age at disease onset, sex, race, ethnicity, insurance type, maternal education, overweight/obese status, tobacco exposure in the first year of life, DMT category, participant's skin tone, sun protection behavior index, and season of birth. [b]Compared with UVR dose in the 6 months before birth, 1st tertile (N = 334); adjusted for age at disease onset, sex, race, ethnicity, insurance type, maternal education, overweight/obese status, tobacco exposure in the first year of life, DMT category, season of birth, biological mother's skin tone, amount of time the biological mother wore hat/veil in the second trimester, most common type of clothing worn by the biological mother in the second trimester, and frequency with which the biological mother used sun block in the second trimester. [c]Compared with <30 minutes in the sun daily during the corresponding trimester (N = 334); adjusted for age at disease onset, sex, race, ethnicity, insurance type, maternal education, overweight/obese status, tobacco exposure in the first year of life, DMT category, season of birth, biological mother's skin tone, amount of time the biological mother wore hat/veil in the corresponding trimester, most common type of clothing worn by the biological mother in the corresponding trimester, frequency with which the biological mother used sun block in the corresponding trimester. [d]Compared with <30 minutes in the sun daily during the most recent summer (weekends, holidays) (N = 289); adjusted for age at disease onset, sex, race, ethnicity, insurance type, maternal education, overweight/obese status, tobacco exposure in the first year of life, DMT category, participant's skin tone, sun protection behavior index, serum 25(OH)D level, and disease duration at the time of study enrollment. [e]Compared with UVR dose in the summer before enrollment, 1st tertile (N = 289); adjusted for age at disease onset, sex, race, ethnicity, insurance type, maternal education, overweight/obese status, tobacco exposure in the first year of life, DMT category, participant's skin tone, sun protection behavior index, serum 25(OH)D level, and disease duration at the time of study enrollment. [f]Compared with UVR dose in the 6 months before enrollment, 1st tertile (N = 289); adjusted for age at disease onset, sex, race, ethnicity, insurance type, maternal education, overweight/obese status, tobacco exposure in the first year of life, DMT category, participant's skin tone, sun protection behavior index, serum 25(OH)D level, and disease duration at the time of study enrollment. HR = hazard ratio; UVR = ultraviolet radiation.

trimesters of pregnancy was not significantly associated with relapse risk. Greater UVR dose in the 6 months before birth (third tertile compared with the first tertile) was associated with a decreased risk of relapse on univariable analysis (HR 0.69, CI 0.49–0.96, $p = 0.03$), although this was not robust to adjustment (aHR 0.62, CI 0.29–1.30, $p = 0.20$) (Figure 2).

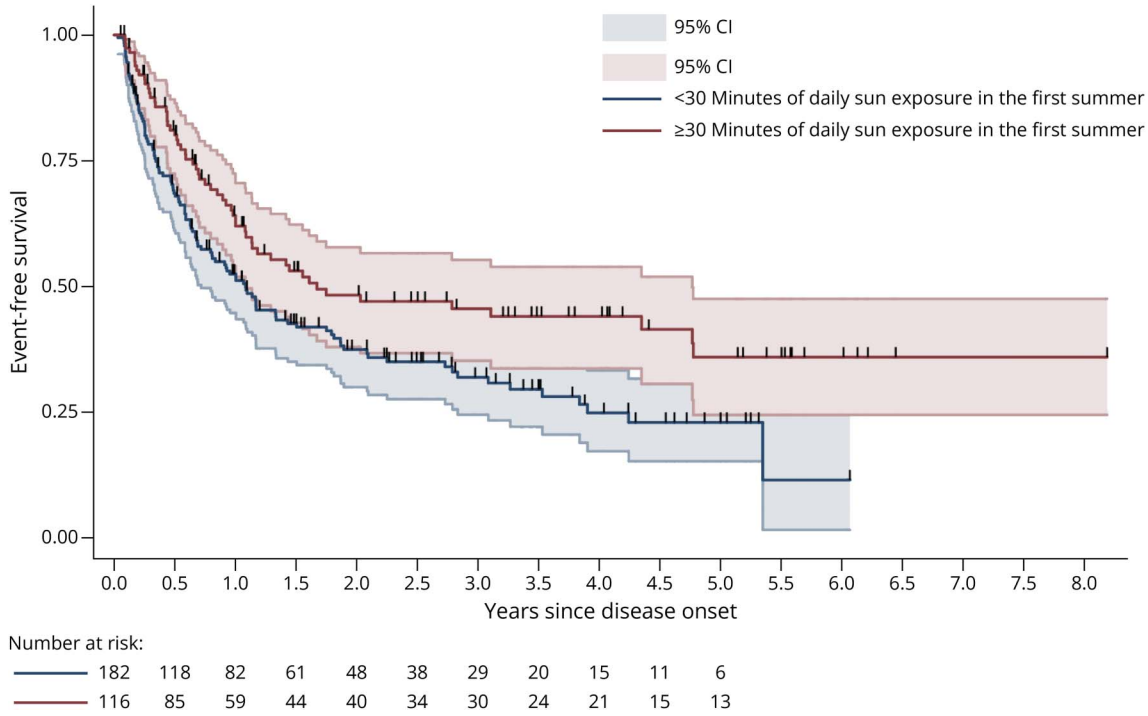
Notably, on Wilcoxon rank-sum testing, there was a significant difference between the median UVR dose in the 6 months before birth for those with <30 minutes of daily sun exposure during the second trimester (median 2.10 kJ/m^2, range 0.463–2.60 kJ/m^2) compared with those with ≥30 minutes of daily sun exposure during the second trimester (median 2.79 kJ/m^2, range 0.113–7.167 kJ/m^2). However, in a multivariable model including both the UVR dose in the 6 months before birth and time spent in the sun during the second trimester, the second trimester sun exposure remained significant (aHR 0.69, CI 0.48–0.99, $p = 0.04$) while UVR dose was not (aHR 0.82, CI 0.57–1.20, $p = 0.30$). There were also no significant multiplicative interactions between these 2 sun exposure variables.

Summer birth season and smoke exposure in the first year of life were significantly associated with increased hazard of relapse in several of these models (eTable 2, models 1–3). There were no multiplicative or additive interactions between time spent in the sun during the second trimester and smoke exposure in the first year of life or birth season on relapse risk. There was also no evidence of interaction between time spent in the sun during the second trimester and time spent in the sun in the first summer of life on relapse risk.

More Recent Sun Exposure

There was no significant association between more recent sun exposure, including time spent in the sun on weekends and holidays in the summer before enrollment and UVR dose in the summer and 6 months before enrollment, and risk of relapse after study enrollment (Figure 2). Among the covariates included in the full multivariable models, disease duration at time of enrollment was found to be protective, with each additional year of disease associated with nearly 40% decreased risk of relapse after study enrollment (eTable 3,

Figure 3 Kaplan-Meier Survival Curve for Time to First Relapse After Disease Onset for Participants With <30 Minutes and ≥30 Minutes of Sun Exposure/Day During the First Summer of Life (Before Multiple Imputation)

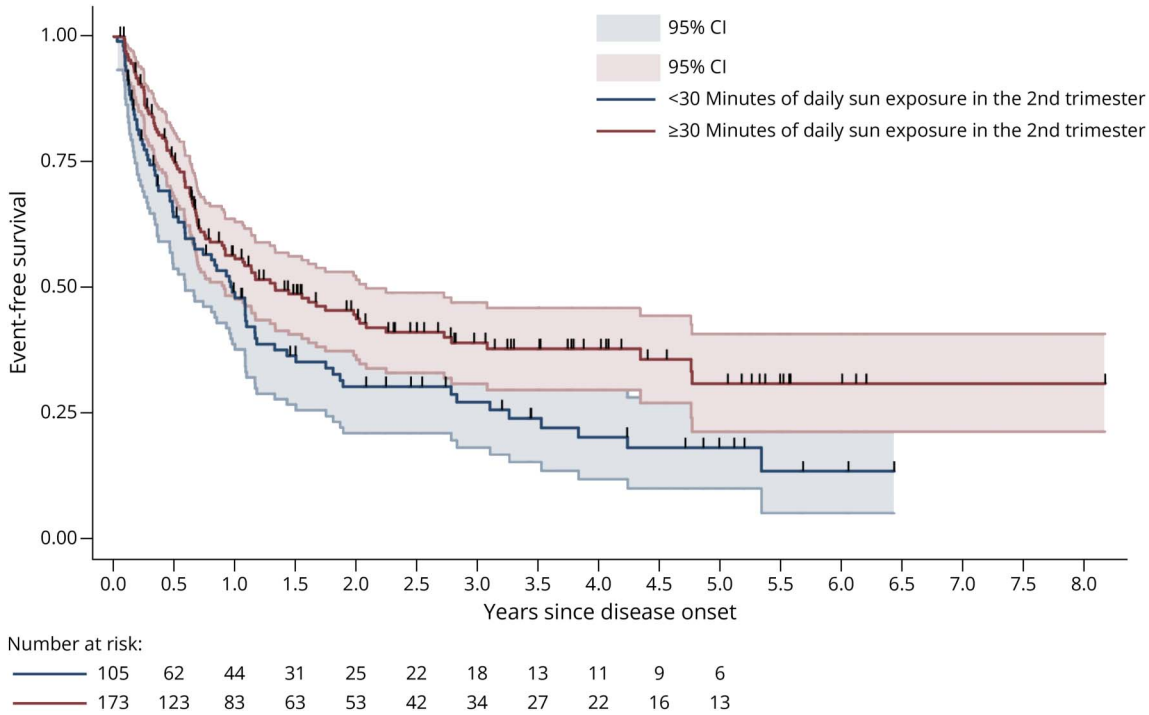


models 1–4). Smoke exposure in the first year of life and 25(OH)D levels were not significantly associated with relapse risk in these models.

Sensitivity Analyses

After excluding participants with missing data for time spent in the sun in the first summer of life (n = 298) and for time

Figure 4 Kaplan-Meier Survival Curve for Time to First Relapse After Disease Onset for Participants With <30 Minutes and ≥30 Minutes of Sun Exposure/Day by the Biological Mother During the Second Trimester of Pregnancy (Before Multiple Imputation)



spent in the sun in the second trimester (n = 278), greater sun exposure in these periods remained significantly associated with decreased risk of relapse (eTable 4).

Additional Analyses

To further test for the potential for recall bias, participants were separated into those who had experienced their first relapse before (n = 135) vs after (n = 71) study enrollment. In χ^2 analyses, there were no significant associations between having experienced first relapse before vs after study enrollment and sun exposure in the first summer of life (<30 minutes vs ≥30 minutes), or with sun exposure during the second trimester of pregnancy (<30 minutes vs ≥30 minutes).

Discussion

In this pediatric cohort study investigating the effect of sun exposure at various life stages on prospective MS course, we found that higher levels of early childhood sun exposure, specifically spending 30 minutes or more (compared with less than 30 minutes) outdoors in the sun in the first summer of life, were associated with a reduced risk of relapse. We found a similarly protective effect with greater sun exposure in the second trimester of pregnancy. These novel findings suggest that sun exposure in early development may have long-lasting benefits on subsequent MS course, possibly through modulation of the immune response.

A prospective cohort study of patients with a first demyelinating event in adulthood found that higher summer UVR loads during childhood and adolescence were significantly associated with reduced risk of conversion to MS.[7] The study also found that higher summer UVR load and absolute durations of sun exposure, specifically at younger ages (6–10 years of age), were associated with a reduced relapse risk, although sun exposure at even younger ages was not available.[7] Our study furthers these observations, demonstrating a significant protective effect of even earlier sun exposures on relapse risk in the pediatric population. As expected, our cohort had overall lower sun exposure in the first summer of life compared with the general population, based on comparison with the control group from our earlier case-control study on sun exposure and MS risk.[8]

We also demonstrated that greater time spent in the sun by the mother during the second trimester of pregnancy was associated with a reduced risk of relapse in the offspring. While it did not reach statistical significance on multivariable analysis, our finding of the protective effect of greater UVR exposure in the 6 months before birth (which would correspond to the second trimester) further supports this finding, through a more direct measurement of sun exposure. Prior studies have examined the effect of prenatal sun exposure on disease risk, though they did not examine effect on disease course. A large Australian cross-sectional study found that greater UVR exposure in the first trimester and early second trimester was associated with a lower risk of adult-onset MS.[16] Our previous case-control study did not find a significant association between UVR exposure before birth and risk of pediatric-onset MS.[8] The mechanism by which second trimester sun exposure would modulate relapse risk is unclear but may be related, for example, to maternal serum vitamin D concentrations or sun-mediated immune effect on dendritic cells and the developing fetal nervous or immune system.[17-19]

We did not find any association between sun exposure just before study enrollment and time to next relapse after enrollment. This may be attributable to the choice of exposures and outcome because both were assessed relative to study enrollment rather than disease onset. Although our cohort had short disease duration at enrollment, it is possible that examining sun exposure just before clinical disease onset and the relationship with time to first relapse from disease onset would be more elucidative and serve to test these hypotheses. Of interest, a study in the adult population similarly found no significant association between UVR exposure during the time after the first demyelinating event and risk of MS conversion or relapse.[7] However, patients who increased their sun exposure during the follow-up period had a significantly reduced risk of MS conversion or relapse compared with those not changing sun exposure behavior, suggesting an overall protective effect on disease course.

The mechanism by which sun exposure modulates relapse risk is unclear. Previous studies have suggested that UVR may have both vitamin D3–dependent and vitamin D3–independent immunomodulating effects.[20-22] In light of the null findings from clinical trials testing vitamin D supplementation for prevention of MS progression,[23-27] UVR exposure may serve as an alternative focus for intervention. The only randomized controlled trial of narrowband ultraviolet B (UVB) radiation to date, for patients with CIS, did not reach its recruitment target but found that 100% of those in the "no phototherapy" arm and 70% of those in the "phototherapy" arm converted to MS within 12 months, although this did not reach statistical significance.[28] Further investigation into the potential for UVB phototherapy to slow MS progression is warranted.

Of interest, we found that summer birth season was associated with a higher risk of relapse, compared with winter birth season. Given our findings on the protective effect of early childhood and second trimester sun exposures, we hypothesize that this may be partly due to patients born in the summer having less overall sun exposure in their first year of life because they may have been intentionally sheltered from direct sunlight because of being a newborn; in addition, the second trimester of pregnancy for patients with summer birthdays would have been in winter, with subsequently less sun exposure. Notably, our findings contrast with the few previous studies in adult-onset MS, which revealed inconsistent results.[29,30]

In studies preceding broad vitamin D supplementation in patients with MS, lower serum 25(OH)D was associated with higher relapse rate in pediatric and adult MS.[31,32] We could

not replicate this finding in our analyses, likely because our serum 25(OH)D measurement was obtained on average more than one year after disease onset and most patients were supplemented. For this reason, we did not include serum 25(OH)D in our models testing early childhood and prenatal sun exposures.

Our finding of lower risk of relapse with longer disease duration at enrollment in our models testing more recent sun exposures may be due to patients with earlier diagnoses having had time to trial different DMTs and optimize efficacy. The association of mid-efficacy and high-efficacy DMTs with increased risk of relapse is likely due to reverse causality because higher efficacy treatment is often reserved for patients with MS with a more aggressive disease course or early clinical or MRI features associated with worse prognosis. Our finding that second-hand smoke exposure was near-significantly associated with relapse risk in several of the models, though with no evidence of interaction with sun exposure, merits further investigation. While exposure to cigarette smoke is a risk factor for development of pediatric-onset MS,[33,34] the association with relapse risk has not been previously described.

Our study possesses several strengths. We used a robust multifactorial approach to measure sun exposure, incorporating self-reported time spent outdoors and satellite data on ambient UVR dose, as well as measures of sun protection and skin tone.[35] The criteria for defining cases and the questionnaire used in this study have been previously validated.[8] Furthermore, our cohort was large, diverse, and recruited from multiple study centers with prospective follow-up, enhancing the generalizability of our findings.

Recall error is a possible limitation because questionnaire data on sun exposure and use of sun protection were retrospectively obtained. Because sun exposure as a risk factor of relapse is not well established, any bias is most likely nondifferential and thus would bias the effect estimate toward the null. Furthermore, in our post hoc analysis, there were no significant associations between experiencing first relapse before vs after study enrollment and time spent in the sun in the first summer of life or during the second trimester, which is reassuring against a major role of recall bias. There were also missing data for several variables, including sun exposure variables; however, we were able to replicate our key findings on sensitivity analyses excluding those participants with missing sun exposure variables. It is possible that maternal sun-related behaviors during pregnancy were similar to those of the family during the participant's early childhood, and thus, our findings may be closely correlated. There is also a possibility that patients changed their sun-related behaviors on MS diagnosis or after enrollment in the study, although there are no current recommendations regarding sun exposure for people with MS. We were not able to fully investigate vitamin D status as a risk factor or confounder because we had only a single serum 25(OH)D level from study enrollment and could not account for vitamin D supplementation. We also could not exclude the effects of other potential confounders, such as exercise. Finally, we were not able to account for the potential effect of MS genetic risk variants.

In summary, this study demonstrated a protective association between early childhood and prenatal sun exposures and pediatric MS relapse risk. Future studies examining ambient UVR dose at these specific early periods would help to validate our findings. Further investigation of sun exposure at other periods, both before disease onset and prospectively after diagnosis, is needed to better characterize the association between sun exposure and disease course and guide future clinical trials.

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Author Contributions

G. Chang: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. P. Sebastian: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. A. Virupakshaiah: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. V.A. Schoeps: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. N. Cherbuin: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. T.C. Casper: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. M.P. Gorman: drafting/revision of the manuscript for content, including medical writing for content. L.A. Benson: drafting/revision of the manuscript for content, including medical writing for content. T. Chitnis: drafting/revision of the manuscript for content, including medical writing for content. M. Rensel: drafting/revision of the manuscript for content, including medical writing for content. A.W. Abrams: drafting/revision of the manuscript for content, including medical writing for content. T. Lotze: drafting/revision of the manuscript for content, including medical writing for content. S.S. Mar: drafting/revision of the manuscript for content, including medical writing for content. T.L. Schreiner: drafting/revision of the manuscript for content, including medical writing for content. Y.S. Wheeler: drafting/revision of the manuscript for content, including medical writing for content. J.W. Rose: drafting/revision of the manuscript for content, including medical writing for content. J. Graves: drafting/revision of the manuscript for content, including medical writing for content. L.B. Krupp: drafting/revision of

the manuscript for content, including medical writing for content. A.T. Waldman: drafting/revision of the manuscript for content, including medical writing for content. R. Lucas: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. E. Waubant: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

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References

1. Cappa R, Theroux L, Brenton JN. Pediatric multiple sclerosis: genes, environment, and a comprehensive therapeutic approach. *Pediatr Neurol*. 2017;75:17-28. doi:10.1016/j.pediatrneurol.2017.07.005
2. Gorman MP, Healy BC, Polgar-Turcsanyi M, Chitnis T. Increased relapse rate in pediatric-onset compared with adult-onset multiple sclerosis. *Arch Neurol*. 2009;66(1):54-59. doi:10.1001/archneurol.2008.505
3. Renoux C, Vukusic S, Confavreux C. The natural history of multiple sclerosis with childhood onset. *Clin Neurol Neurosurg*. 2008;110(9):897-904. doi:10.1016/j.clineuro.2008.04.009
4. Lucas RM, Ponsonby A-L, Dear K, et al. Sun exposure and vitamin D are independent risk factors for CNS demyelination. *Neurology*. 2011;76(6):540-548. doi:10.1212/WNL.0b013e31820af93d
5. Van Der Mei IAF, Ponsonby A-L, Dwyer T, et al. Papers Past exposure to sun, skin phenotype, and risk of multiple sclerosis: case-control study. *BMJ*. 2003;327(7410):316. doi:10.1136/bmj.327.7410.316
6. Tremlett H, Zhu F, Ascherio A, Munger KL. Sun exposure over the life course and associations with multiple sclerosis. *Neurology*. 2018;90(14):E1191-E1199. doi:10.1212/WNL.0000000000005257
7. Simpson S, Van Der Mei I, Lucas RM, et al. Sun exposure across the life course significantly modulates early multiple sclerosis clinical course. *Front Neurol*. 2018;9:16. doi:10.3389/fneur.2018.00016
8. Sebastian P, Cherbuin N, Barcellos LF, et al. Association between time spent outdoors and risk of multiple sclerosis. *Neurology*. 2022;98(3):E267-E278. doi:10.1212/WNL.0000000000013045
9. Banwell B, Bar-Or A, Arnold DL, et al. Clinical, environmental, and genetic determinants of multiple sclerosis in children with acute demyelination: a prospective national cohort study. *Lancet Neurol*. 2011;10(5):436-445. doi:10.1016/S1474-4422(11)70045-X
10. Munger KL, Levin LI, Hollis BW, Howard NS, Ascherio A. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. *JAMA*. 2006;296(23):2832-2838. doi:10.1001/jama.296.23.2832
11. D'Hooghe MB, Haentjens P, Nagels G, Garmyn M, De Keyser J. Sunlight exposure and sun sensitivity associated with disability progression in multiple sclerosis. *Mult Scler*. 2012;18(4):451-459. doi:10.1177/1352458511423778
12. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol*. 2011;69(2):292-302. doi:10.1002/ana.22366
13. Hauser SL, Cree BAC. Treatment of multiple sclerosis: a review. *Am J Med*. 2020;133(12):1380-1390.e2. doi:10.1016/j.amjmed.2020.05.049
14. Rothman KJ. No adjustments are needed for multiple comparisons. *Epidemiology*. 1990;1:43-46. doi:10.1097/00001648-199001000-00010
15. Van Der Weele TJ, Knol MJ. A tutorial on interaction. *Epidemiologic Methods*. 2014;3(1):33-72. doi:10.1515/em-2013-0005
16. Staples J, Ponsonby A-L, Lim L. Low maternal exposure to ultraviolet radiation in pregnancy, month of birth, and risk of multiple sclerosis in offspring: longitudinal analysis. *BMJ*. 2010;340:c1640. doi:10.1136/bmj.c1640
17. Eyles D, Brown J, Mackay-Sim A, McGrath J, Feron F. Vitamin d3 and brain development. *Neuroscience*. 2003;118(3):641-653. doi:10.1016/s0306-4522(03)00040-x

18. Correale J, Ysrraelit MC, Gaitán MI. Immunomodulatory effects of Vitamin D in multiple sclerosis. *Brain*. 2009;132(pt 5):1146-1160. doi:10.1093/brain/awp033
19. Smith SEP, Li J, Garbett K, Mirnics K, Patterson PH. Maternal immune activation alters fetal brain development through interleukin-6. *J Neurosci*. 2007;27(40):10695-10702. doi:10.1523/JNEUROSCI.2178-07.2007
20. Hart PH, Gorman S. Exposure to UV wavelengths in sunlight suppresses immunity. To what extent is UV-induced vitamin D3 the mediator responsible? *Clin Biochem Rev*. 2013;34(1):3-13.
21. Hart PH, Lucas RM, Booth DR, et al. Narrowband UVB phototherapy for clinically isolated syndrome: a trial to deliver the benefits of vitamin D and other UVB-induced molecules. *Front Immunol*. 2017;8:3. doi:10.3389/fimmu.2017.00003
22. Milliken SVI, Wassall H, Lewis BJ, et al. Effects of ultraviolet light on human serum 25-hydroxyvitamin D and systemic immune function. *J Allergy Clin Immunol*. 2012;129(6):1554-1561. doi:10.1016/j.jaci.2012.03.001
23. Cassard SD, Fitzgerald KC, Qian P, et al. High-dose vitamin D3 supplementation in relapsing-remitting multiple sclerosis: a randomised clinical trial. *EClinicalMedicine*. 2023;59:101957. doi:10.1016/j.eclinm.2023.101957
24. Camu W, Lehert P, Pierrot-Deseilligny C, et al. Cholecalciferol in relapsing-remitting MS: a randomized clinical trial (CHOLINE). *Neurol Neuroimmunol Neuroinflamm*. 2019;6(5):e597. doi:10.1212/NXI.0000000000000597
25. Hupperts R, Smolders J, Vieth R, et al. Randomized trial of daily high-dose vitamin D_3 in patients with RRMS receiving subcutaneous interferon β-1a. *Neurology*. 2019;93(20):e1906-e1916. doi:10.1212/WNL.0000000000008445
26. Dörr J, Bäcker-Koduah P, Wernecke K-D, et al. High-dose vitamin D supplementation in multiple sclerosis - results from the randomized EVIDIMS (efficacy of vitamin D supplementation in multiple sclerosis) trial. *Mult Scler J Exp Transl Clin*. 2020;6(1):2055217320903474. doi:10.1177/2055217320903474
27. Butzkueven H, Ponsonby A-L, Stein MS, et al. Vitamin D did not reduce multiple sclerosis disease activity after a clinically isolated syndrome. *Brain*. 2024;147(4):1206-1215. doi:10.1093/brain/awad409
28. Hart PH, Jones AP, Trend S, et al. A randomised, controlled clinical trial of narrowband UVB phototherapy for clinically isolated syndrome: the PhoCIS study. *Mult Scler J Exp Transl Clin*. 2018;4(2):2055217318773112. doi:10.1177/2055217318773112
29. Tremlett HL, Devonshire VA. Does the season or month of birth influence disease progression in multiple sclerosis? *Neuroepidemiology*. 2006;26(4):195-198. doi:10.1159/000092406
30. Koch M, De Keyser J, Tremlett H. Timing of birth and disease progression in multiple sclerosis. *Mult Scler*. 2008;14(6):793-798. doi:10.1177/1352458508090662
31. Mowry EM, Krupp LB, Milazzo M, et al. Vitamin D status is associated with relapse rate in pediatric-onset multiple sclerosis. *Ann Neurol* 2010;67(5):618-624. doi:10.1002/ana.21972
32. Simpson S, Taylor B, Blizzard L, et al. Higher 25-hydroxyvitamin D is associated with lower relapse risk in multiple sclerosis. *Ann Neurol*. 2010;68(2):193-203. doi:10.1002/ana.22043
33. Lavery AM, Collins BN, Waldman AT, et al. The contribution of secondhand tobacco smoke exposure to pediatric multiple sclerosis risk. *Mult Scler*. 2019;25(4):515-522. doi:10.1177/1352458518757089
34. Hempel S, Graham GD, Fu N, et al. A systematic review of modifiable risk factors in the progression of multiple sclerosis. *Mult Scler*. 2017;23(4):525-533. doi:10.1177/1352458517690270
35. Wright CY, Wilkes M, du Plessis JL, Reeder AI. Self-reported skin colour and erythemal sensitivity vs. objectively measured constitutive skin colour in an African population with predominantly dark skin. *Photodermatol Photoimmunol Photomed*. 2015;31(6):315-324. doi:10.1111/phpp.12191