Title
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Journal
Neurology, 98(3)

ISSN
0028-3878

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Publication Date
2022-01-18

DOI
10.1212/wnl.0000000000013045

Peer reviewed

RESEARCH ARTICLE

Association Between Time Spent Outdoors and Risk of Multiple Sclerosis

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Neurology® 2022;98:e267-e278. doi:10.1212/WNL.0000000000013045

Abstract

Background and Objectives

This study aims to determine the contributions of sun exposure and ultraviolet radiation (UVR) exposure to risk of pediatric-onset multiple sclerosis (MS).

Methods

Children with MS and controls recruited from multiple centers in the United States were matched on sex and age. Multivariable conditional logistic regression was used to investigate the association of time spent outdoors daily in summer, use of sun protection, and ambient summer UVR dose in the year before birth and the year before diagnosis with MS risk, with adjustment for sex, age, race, birth season, child's skin color, mother's education, tobacco smoke exposure, being overweight, and Epstein-Barr virus infection.

Results

Three hundred thirty-two children with MS (median disease duration 7.3 months) and 534 controls were included after matching on sex and age. In a fully adjusted model, compared to spending <30 minutes outdoors daily during the most recent summer, greater time spent outdoors was associated with a marked reduction in the odds of developing MS, with evidence of dose-response (30 minutes–1 hour: adjusted odds ratio [AOR] 0.48, 95% confidence interval [CI] 0.23–0.99, $p = 0.05$; 1–2 hours: AOR 0.19, 95% CI 0.09–0.40, $p < 0.001$). Higher summer ambient UVR dose was also protective for MS (AOR 0.76 per 1 kJ/m^2, 95% CI 0.62–0.94, $p = 0.01$).

Discussion

If this is a causal association, spending more time in the sun during summer may be strongly protective against developing pediatric MS, as well as residing in a sunnier location.

MORE ONLINE

Infographic
links.lww.com/WNL/B738

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

US Network of Pediatric Multiple Sclerosis Centers coinvestigators are listed in the appendix 2 at the end of the article.

Glossary

AOR = adjusted odds ratio; **BMI** = body mass index; **CI** = confidence interval; **EBV** = Epstein-Barr virus; **IgG** = immunoglobulin G; **MOG** = myelin oligodendrocyte glycoprotein; **MS** = multiple sclerosis; **25(OH)D** = 25-hydroxyvitamin D; **UVR** = ultraviolet radiation; **VCA** = EBV viral capsid antigen.

Multiple sclerosis (MS) onset typically occurs between the ages of 20 and 50 years; however, 3% to 5% of individuals with MS begin experiencing symptoms before 18 years of age.[1] Pediatric-onset MS typically exhibits a highly inflammatory disease course initially but subsequently takes longer to progress to irreversible disability than adult-onset MS, although disability landmarks are still reached on average ≈10 years earlier.[2]

MS etiology is understood to be a combination of genetic predisposition, infectious exposures, and other environmental and behavioral risk factors.[3] In particular, low sun exposure, low ultraviolet radiation (UVR) exposure, and low vitamin D status have been well characterized as environmental risk factors for adult-onset MS,[4-6] with a particular increase in risk associated with insufficient sun exposure in childhood.[7,8] However, to date, research on sun/UVR exposure in MS has been limited to mostly adult populations.

In this study, we analyze data from a multicenter case-control study that investigated environmental risk factors for pediatric MS. Our objective was to examine the associations of sun exposure (measured as time spent outdoors) and UVR exposure (measured as ambient UVR dose) with risk of pediatric MS. Based on the known associations of these factors with risk of adult-onset MS, our hypothesis was that low sun exposure and low UVR exposure would be associated with greater risk in this pediatric population.

Methods

Study Population

Case participants were recruited from 16 MS centers at pediatric hospitals within the United States (University of California San Francisco, Stony Brook Children's Hospital, Children's Hospital of Philadelphia, Texas Children's Hospital, Children's Hospital Colorado/University of Colorado, Children's Dallas/University of Texas Southwestern, State University of New York Buffalo, Loma Linda University, Mayo Clinic, University of Alabama at Birmingham, Ann and Robert Lurie Children's Hospital of Chicago, University of Utah, Boston Children's Hospital, Massachusetts General Hospital, New York University Langone Health, Washington University St. Louis, and Children's National Medical Center in Washington, DC). These sites are considered to be secondary or tertiary referral centers for pediatric MS and see patients from large catchment areas. Case participants were 4 to 22 years of age and eligible for inclusion if they had either MS or clinically isolated syndrome onset before the age of 18 years and were within 4 years of symptom onset. Control participants were patients or siblings of patients recruited from primary care and non-MS pediatric clinics at the same institutions from which the cases were recruited. Controls were 3 to 22 years of age and had no personal history of autoimmune disease, severe health conditions or treatment with immunosuppressants, and no parental history of MS.

Participants or their parents/guardians completed a questionnaire providing data on demographic characteristics (including age, sex, and race), medical history, location of residence (at birth and most recently), environmental exposures, and behaviors related to sun exposure. Participants also provided a blood sample. Blood was separated, divided into aliquots, and stored at −80°C until study completion. Serum levels of 25-hydroxyvitamin D [25(OH)D] were measured with batched chemiluminescent assay (Heartlands Assay, Inc, Ames, IA).[9] Serum immunoglobulin G (IgG) against Epstein-Barr virus (EBV) viral capsid antigen (VCA) was measured by ELISA (Wampole Laboratories, Princeton, NJ).[10] Serum anti-myelin oligodendrocyte glycoprotein (MOG) IgG was measured at the Mayo Clinic by live cell–based fluorescence-activated cell sorting assay, with titer ≥1:20 confirming positivity.[11]

Children with MS were matched to controls based on age and sex. The case:control ratio was unfixed and ranged from 1:1 to 1:16, with most matched sets having a ratio of 1:5 or less. The R package matchit was used to first match each case with the most appropriate control. Remaining controls were subsequently iteratively matched with suitable cases. Age matching was within 6 months for participants <8 years of age, within 1 year for those 8 to 14 years of age, and within 2 years for those >14 years of age. Twenty cases and 26 controls could not be matched according to these criteria and were excluded.

Exposures of Interest

Sun exposure was measured with several metrics, including time spent outdoors and use of sun protection, and UVR exposure was measured as ambient UVR dose.

Time spent outdoors was self-reported through questions on time spent outdoors daily during weekends and holidays in each of spring, summer, and autumn at <1, 1 to 2, 3 to 5, 6 to 10, and 11 to 15 years of age, and in the most recent year. Data were recorded in 5 categories: <30 minutes, 30 minutes to 1 hour, 1 to 2 hours, 2 to 3 hours, and >3 hours. This study focuses on time spent outdoors in the present/most recent summer on weekends and during holidays and in the summer during the first year of life because these had the most complete data.

Table 1 Characteristics of Cases With Pediatric MS and Age- and Sex-Matched Controls (Including Imputed Data)

	Control (N = 534)	Case (N = 332)
Sex, n (%)		
Male	219 (41.0)	122 (36.7)
Female	315 (59.0)	210 (63.3)
Age, y		
Median (IQR)	15.4 (5.3)	15.9 (3.3)
Race, n (%)		
White	366 (68.5)	246 (74.1)
Black	87 (16.3)	46 (13.9)
Asian	36 (6.7)	15 (4.5)
Other	45 (8.4)	25 (7.5)
Season of birth, n (%)		
Winter	123 (23.0)	71 (21.4)
Spring	130 (24.3)	78 (23.5)
Summer	136 (25.5)	90 (27.1)
Autumn	145 (27.2)	93 (28.0)
Mother's highest education at child's birth, n (%)		
Secondary school or less	237 (44.4)	196 (59.0)
Trade certificate or other	237 (44.4)	99 (29.8)
University qualification	60 (11.2)	37 (11.1)
Parental smoking during child's first year of life, n (%)		
No	466 (87.3)	273 (82.2)
Yes	68 (12.7)	59 (17.8)
Child's skin color, n (%)		
Dark	41 (7.7)	22 (6.6)
Olive	115 (21.5)	80 (24.1)
Fair	378 (70.8)	230 (69.3)
Did a doctor ever say that the child was overweight?, n (%)		
No	458 (85.8)	253 (76.2)
Yes	76 (14.2)	79 (23.8)
Serum anti-VCA level, optical density		
Median (IQR)	2.2 (3.5)	3.7 (1.8)

Abbreviations: IQR = interquartile range; MS = multiple sclerosis; VCA = Epstein-Barr virus viral capsid antigen.

Use of sun protection was based on questions on the 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 (corresponding to 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, similar to the validated Sun Protection Behavior Scale,[12] as follows: overall use of sun protection = sunscreen + sunglasses + hat + clothes covering arms and legs − clothes exposing forearms and legs.

Ambient UVR Dose

We assigned latitude and longitude to the locations of residence of each participant over their lifetime. We obtained data on average daily ambient UVR from orbiting satellites (National Aeronautics and Space Administration Ozone Monitoring Instrument[13]) for the period from 2000 to 2018. For each participant, according to their approximate location of residence, date of birth, and age at the point of recruitment into the study, we then derived estimates of daily ambient UVR dose for 3-month intervals coinciding with the following time periods: last summer before birth, last winter before birth, 6 months before birth, last summer before recruitment, last winter before recruitment, and 6 months before recruitment.

Vitamin D Status

Vitamin D status measured as the serum concentration of 25(OH)D (nanograms per milliliter) was modeled as a continuous variable.

Other Measures

Race was self-reported by participants as White, Black/African American, American Indian/Alaskan Native, Asian or Pacific Islander, other, mixed race, and do not know. Participants selected 1 and only 1 of the above racial categories. We categorized participants' self-reported race as White, Black, Asian, or other.

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

Overweight was based on the question, "Did a doctor ever say that the child was overweight?" (yes/no).

Although we had access to body mass index (BMI) data for most participants, we did not use BMI in the main analyses because of the number of missing or implausible values.

Mother's highest education attainment was collapsed to 3 categories: secondary school or below, trade certificate or other, or university qualification.

Sun sensitivity of both the child participant and their mother was represented by self-reported eye color, hair color, skin color, presence/absence of freckles, skin sensitivity to sun, and propensity to tan. From these, child's reported skin color (categorized as dark, olive, or fair) was selected as a marker of

Table 2 Sun Exposure, UVR Dose, and Serum 25(OH)D Concentration in Cases With Pediatric MS and Age- and Sex-Matched Controls (Including Imputed Data)

	Control (N = 534)	Case (N = 332)
Time spent in the sun during the summer in the first year of life, n (%)		
<30 min	265 (49.6)	200 (60.2)
30 min–1 h	137 (25.7)	86 (25.9)
1–2 h	71 (13.3)	30 (9.0)
2–3 h	30 (5.6)	8 (2.4)
>3 h	31 (5.8)	8 (2.4)
Time spent in the sun during weekends in the present or most recent summer, n (%)		
<30 min	33 (6.2)	62 (18.7)
30 min–1 h	68 (12.7)	72 (21.7)
1–2 h	132 (24.7)	61 (18.4)
2–3 h	122 (22.8)	62 (18.7)
>3 h	179 (33.5)	75 (22.6)
Time spent in the sun during holidays in the present or most recent summer, n (%)		
<30 min	43 (8.1)	55 (16.6)
30 min–1 h	65 (12.2)	78 (23.5)
1–2 h	116 (21.7)	54 (16.3)
2–3 h	130 (24.3)	62 (18.7)
>3 h	180 (33.7)	83 (25.0)
UVR dose in the winter before enrolment, kJ/m^2		
Median (IQR)	1.2 (0.7)	1.0 (0.7)
UVR dose in the summer before enrolment, kJ/m^2		
Median (IQR)	4.9 (1.5)	4.8 (1.6)
UVR dose 6 mo before enrolment, kJ/m^2		
Median (IQR)	2.6 (2.4)	2.8 (2.3)
Sun protection behavior index		
Mean (SD)	5.9 (2.5)	5.5 (2.5)
Serum 25(OH)D concentration, ng/mL		
Median (IQR)	23.7 (11.9)	27.7 (17.5)

Abbreviations: IQR = interquartile range; MS = multiple sclerosis; 25(OH)D = 25-hydroxyvitamin D; UVR = ultraviolet radiation.

sun sensitivity, according to the amount of missing data and correlation with the other variables. While race and skin color are closely related, they are not synonymous because race is a social construct incorporating many factors other than skin color. Hence, both race and skin color were included as covariates in this study.

EBV seropositivity, measured as serum antibody titer against EBV VCA (optical density), was modeled as a continuous variable.

Statistical Analysis

Statistical analyses were performed with the R statistical package (version 4.0.2) and RStudio (version 1.0.153, R Foundation for Statistical Computing, Vienna, Austria). Missing values (representing <3% of all data) were multiply imputed in 3 separate complete datasets with the R package mice and aggregated (with the R command merge_imputations) into a single complete dataset. In post hoc analyses, we tested variations in this imputation method (eTable 1, links.lww.com/WNL/B653), confirming the superiority of the reported method. Diagnostic tests using logistic regression analyses of missingness against the covariates suggested that the missing data were missing completely at random, confirming that multiple imputation was appropriate. For numerical variables, outlier values (defined as >2.5 SDs from the mean) were adjusted in a manner that brought them closer to the mean but preserved their numerical order (eAppendix 1).[14] No more than 3.5% of values were adjusted in this manner for any given numerical variable. Correlation between covariates was tested with the Pearson correlation.

Multivariable conditional logistic regression was performed with the R package clogit to test associations between exposures of interest and case-control status, with adjustment for sex, age, race, birth season, child's skin color, mother's education, smoke exposure, being overweight, and antibodies against EBV VCA. We ran several multivariable conditional logistic regression models: the initial models tested time spent outdoors as the exposure of interest; sun protection behavior and ambient UVR dose were added in subsequent models. Because serum 25(OH)D levels were postdiagnostic, limiting any conclusions about their association with MS risk, we did not include 25(OH)D in the main analyses. Model fit statistics were compared with analysis of variance. Results are reported as adjusted odds ratios (AORs) with 95% confidence intervals (95% CIs) for a 1-unit increment in the exposure variable(s). Statistical significance was set at $p < 0.05$. In interpreting ORs, a potential protective effect is indicated by an AOR < 1, with (1 – AOR) × 100 used to provide a percentage reduction in odds.

We undertook multiple sensitivity analyses, restricting the dataset to participants for whom accurate BMI data were available; children with MS onset in the year before enrollment and their matched controls; and children diagnosed with MS who had a negative anti-MOG IgG screen and their matched controls.

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the Human Research Protection Institutional Review Board of all the participating centers,

Table 3 Use of Sun Protection in Cases With Pediatric MS and Age- and Sex-Matched Controls (Including Imputed Data)

	Control (N = 534)	Case (N = 332)
Use of sunscreen during the present or most recent summer, n (%)		
Never	85 (15.9)	72 (21.7)
<50% of the time	167 (31.3)	135 (40.7)
≥50% of the time	199 (37.3)	94 (28.3)
Always	83 (15.5)	31 (9.3)
Use of sunglasses during the present or most recent summer, n (%)		
Never	192 (36.0)	115 (34.6)
<50% of the time	187 (35.0)	118 (35.5)
≥50% of the time	117 (21.9)	70 (21.1)
Always	38 (7.1)	29 (8.7)
Use of a hat during the present or most recent summer, n (%)		
Never	214 (40.1)	162 (48.8)
<50% of the time	197 (36.9)	117 (35.2)
≥50% of the time	101 (18.9)	37 (11.1)
Always	22 (4.1)	16 (4.8)
Use of clothes covering arms and legs during present or most recent summer, n (%)		
Never	206 (38.6)	147 (44.3)
<50% of the time	231 (43.3)	141 (42.5)
≥50% of the time	83 (15.5)	35 (10.5)
Always	14 (2.6)	9 (2.7)
Use of clothes exposing at least half of forearms during the present or most recent summer, n (%)		
Never	14 (2.6)	8 (2.4)
<50% of the time	77 (14.4)	47 (14.2)
≥50% of the time	257 (48.1)	151 (45.5)
Always	186 (34.8)	126 (38.0)
Use of clothes exposing at least half of legs during the present or most recent summer, n (%)		
Never	15 (2.8)	21 (6.3)
<50% of the time	90 (16.9)	57 (17.2)
≥50% of the time	243 (45.5)	141 (42.5)
Always	186 (34.8)	113 (34.0)
Sun protection behavior index		
Mean (SD)	5.9 (2.5)	5.5 (2.5)

Abbreviation: MS = multiple sclerosis.

including the University of California San Francisco (protocol No. 10-05039). Before participation, parents/guardians provided written informed consent on behalf of participants <18 years of age; older participants provided written informed consent on their own behalf.

Data Availability

Data used in this study are available from the corresponding author on request.

Results

The study sample included 332 children with MS and 534 controls after matching on sex and age. Median disease duration for children with MS was 7.3 months. Participants' characteristics are presented in Table 1, and participants' exposure measures are presented in Tables 2 and 3. Children with MS did not differ from controls on race, birth season, or skin color. Among children with MS, the proportion whose mother's education level was secondary school or less was higher and trade certificate or other was lower compared to controls. Children with MS were more likely than controls to have been exposed to tobacco smoke during their first year of life and more likely to ever have been overweight. Children with MS spent less time outdoors during summer and were less likely to use sun protection than controls but were exposed to similar ambient UVR doses. Serum levels of 25(OH)D and antibodies against EBV VCA were higher among children with MS compared to controls.

Correlations among exposures and covariates are presented in the Figure. There were significant correlations among the various measures of time spent outdoors (Pearson correlation coefficients [r] ranging from 0.25–0.84, $p < 0.001$) and among the ambient UVR measures ($r = 0.76$, $p < 0.001$), although time outdoors was inversely correlated with ambient UVR dose in the most recent summer ($r = -0.15$ and -0.17, $p < 0.05$). Levels of antibodies against EBV VCA were correlated with age ($r = 0.23$, $p < 0.001$); being overweight was inversely correlated with serum 25(OH)D concentration ($r = -0.15$, $p = 0.001$). Serum 25(OH)D concentration was correlated with mother's education ($r = 0.15$, $p < 0.001$), child's skin color ($r = 0.15$, $p < 0.001$), and time outdoors in the most recent summer ($r = 0.13$, $p < 0.05$).

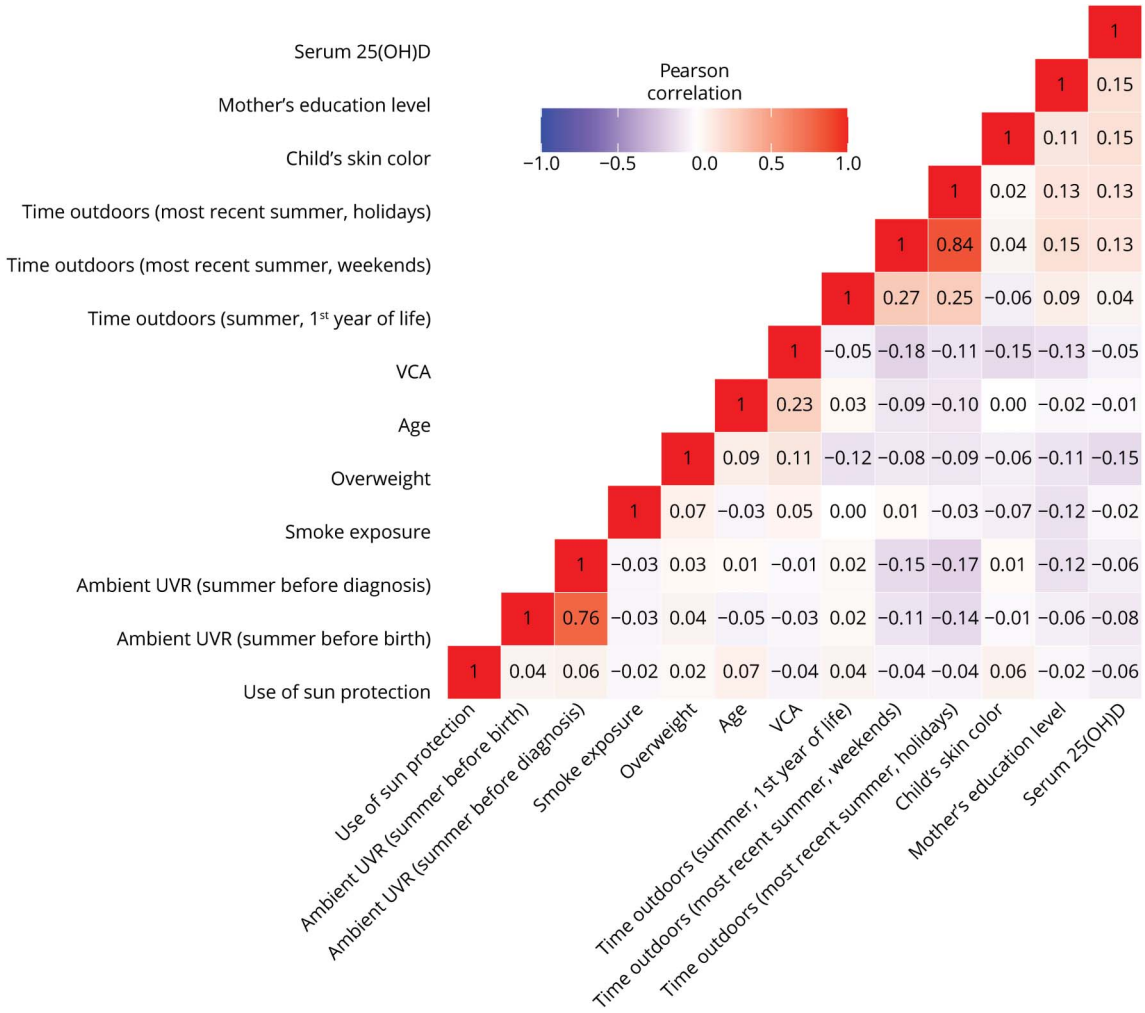
Sun Exposure

The results of the multivariable conditional logistic regression models testing associations between time spent outdoors during summer, use of sun protection during summer, and ambient summer UVR dose and MS case-control status are presented in Table 4.

Time Spent Outdoors

Greater time spent outdoors during the present/most recent summer on weekends was associated with significantly lower odds of MS, with evidence of a dose-dependent response (Table 4, model 1; eTable 2, links.lww.com/WNL/B653, model 2). Compared to spending <30 minutes outdoors daily,

Figure Heat Map Showing Pearson Correlation Between Markers of Sun Exposure, UVR Dose, Serum 25(OH)D Level, and Other Covariates for All Study Participants



25(OH)D = 25-hydroxyvitamin D; UVR = ultraviolet radiation; VCA = antibodies against Epstein-Barr virus viral capsid antigen.

spending 30 minutes to 1 hour had a clinically relevant 50% lower odds of MS, although this observation did not reach statistical significance (AOR 0.50, 95% CI 0.24–1.03, p = 0.06). Spending 1 to 2 hours reduced MS odds by 78% (AOR 0.22, 95% CI 0.11–0.44, $p < 0.001$); spending >2 hours did not provide any additional benefit. Adding time spent outdoors as a predictor explained an additional 2.5% of the variance and significantly improved model fit compared to a base model with only covariates (eTable 2) ($p < 0.001$). Greater time spent outdoors in the present/most recent summer during holidays, and in the first year of life, was also associated with lower odds of MS but with smaller effect estimates (eTable 2, models 3 and 4).

Sun Protection

Use of sun protection in the most recent summer was not significantly associated with the odds of MS (eTable 3, links.lww.com/WNL/B653, model 3). Adding both time spent outdoors and use of sun protection as predictors to the same model did not improve model fit compared to the model with only time spent outdoors (Table 4, model 2).

Ambient UVR Dose

Greater ambient UVR dose in the most recent summer (in a model not including time outdoors and sun protection behaviors) was associated with lower odds of MS, but this observation did not reach statistical significance (AOR 0.83, 95% CI 0.68–1.00, p = 0.05) (eTable 3, links.lww.com/WNL/B653, model 4). Similarly, ambient UVR doses in the most recent winter, 6 months before enrollment, summer before birth, winter before birth, and 6 months before birth were not associated with MS case-control status, although ambient UVR dose in the summer before birth approached statistical significance (AOR 0.83, 95% CI 0.68–1.01, p = 0.06) (eTable 4).

Finally, time spent outdoors, use of sun protection, and ambient UVR dose were added as predictors in the same model

Table 4 Multivariable Conditional Logistic Regression Analysis for the Association Between Time Spent Outdoors, Ambient Summer UVR Dose, and Pediatric MS Risk.

	Model 1	Model 2	Model 3
	AOR (95% CI) *p*	AOR (95% CI) *p*	AOR (95% CI) *p*
Time spent outdoors (present/most recent summer, weekends)			
<30 min	Reference	Reference	Reference
30 min–1 h	0.50	0.49	0.48
	(0.24–1.03)	(0.24–1.01)	(0.23–0.99)
	$p = 0.06$	$p = 0.05$	$p = 0.05$
1–2 h	0.22	0.21	0.19
	(0.11–0.44)	(0.10–0.43)	(0.09–0.40)
	$p < 0.001$	$p < 0.001$	$p < 0.001$
2–3 h	0.28	0.28	0.26
	(0.14–0.58)	(0.13–0.57)	(0.12–0.54)
	$p < 0.001$	$p < 0.001$	$p < 0.001$
>3 h	0.24	0.23	0.20
	(0.12–0.48)	(0.11–0.47)	(0.10–0.42)
	$p < 0.001$	$p < 0.001$	$p < 0.001$
Use of sun protection		0.94	0.94
		(0.87–1.01)	(0.88–1.01)
		$p = 0.09$	$p = 0.11$
Ambient UVR (kJ/m^2) dose in the summer before enrollment			0.76
			(0.62–0.94)
			$p = 0.01$

Adjusted for sex, age, race, birth season, child's skin color, mother's education, tobacco smoke exposure, being overweight, and antibodies against EBV VCA.
Abbreviations: AOR = adjusted odds ratio; EBV VCA = Epstein-Barr virus viral capsid antigen; CI = confidence interval; MS = multiple sclerosis; UVR = ultraviolet radiation.
Model 1 is a multivariable conditional logistic regression model testing the association between time spent outdoors in the present/most recent summer on weekends and MS case vs control status (risk of pediatric MS), adjusted for sex, age, race, birth season, child's skin color, mother's education, tobacco smoke exposure, being overweight, and antibodies against EBV VCA. Model 2 is the same as Model 1 with use of sun protection in the most recent summer as an additional predictor. Model 3 is the same as model 2 with ambient summer UVR dose (in the summer before enrollment in the study) as an additional predictor. Results are presented as AORs with 95% CIs.

(Table 4, model 3). Including all 3 sun-related predictors in the same model improved model fit compared to models including any 1 of them alone ($p < 0.01$). In this fully adjusted model, compared to spending <30 minutes outdoors daily during summer, spending 30 minutes to 1 hour was associated with a 52% reduction in MS odds (AOR 0.48, 95% CI 0.23–0.99, $p = 0.05$), and spending 1 to 2 hours was associated with a 81% reduction (AOR 0.19, 95% CI 0.09–0.40, $p < 0.001$). Use of sun protection was not associated with the odds of having MS; however, greater ambient UVR dose was associated with significantly lower odds of MS (AOR 0.76 per 1 kJ/m^2, 95% CI 0.62–0.94, $p = 0.01$).

To better illustrate this ambient UVR result, we selected 2 arbitrary locations—Florida (28°N) and New York (40°N)—and computed ambient summer UVR doses at these locations and the associated predicted comparison in odds of having MS. We estimate that an individual residing in Florida would be exposed to an ambient summer UVR dose that is ≈0.9 kJ/m^2 higher compared to that of an individual residing in New York; this represents a 21% reduction in the odds of developing MS (AOR 0.79, 95% CI 0.67–0.95).

In the fully adjusted model, higher levels of antibodies against EBV VCA were associated with greater odds of MS (AOR 1.45 per unit, 95% CI 1.30–1.62, $p < 0.001$). Tobacco smoke exposure during the first year of life was also associated with greater odds of MS but did not reach statistical significance (AOR 1.67, 95% CI 0.99–2.82, $p = 0.06$) (eTable 3, links.lww.com/WNL/B653, model 7).

Table 5 Summary of Sensitivity Analyses Undertaken in Testing the Association of Sun Exposure and UVR Exposure With Risk of Pediatric MS

	Sensitivity analysis restricted to:		
	Participants with reliable BMI data	Children with MS onset within prior year and their matched controls	Patients with MOG IgG-negative MS and their matched controls
	AOR (95% CI) *p*	AOR (95% CI) *p*	AOR (95% CI) *p*
Time outdoors:			
<30 min	Reference	Reference	Reference
30 min–1 h	0.79	0.48	0.43
	(0.21–3.07)	(0.17–1.38)	(0.19–0.99)
	p = 0.74	*p* = 0.17	*p* = 0.05
1–2 h	0.17	0.22	0.19
	(0.04–0.68)	(0.07–0.65)	(0.08–0.43)
	p = 0.01	*p* = 0.01	*p* < 0.001
2–3 h	0.14	0.26	0.22
	(0.03–0.65)	(0.09–0.78)	(0.10–0.51)
	p = 0.01	*p* = 0.02	*p* < 0.001
>3 h	0.14	0.26	0.18
	(0.03–0.60)	(0.09–0.76)	(0.08–0.40)
	p = 0.01	*p* = 0.01	*p* < 0.001
Use of sun protection	0.96	1.00	0.92
	(0.83–1.11)	(0.90–1.11)	(0.85–1.00)
	p = 0.58	*p* = 0.99	*p* = 0.05
Ambient UVR dose in the summer before recruitment	0.65	0.71	0.76
	(0.45–0.94)	(0.52–0.97)	(0.6–0.97)
	p = 0.02	*p* = 0.03	*p* = 0.03
Observations, n	405	529	742
Case participants, n	173	221	293
Control participants, n	232	308	449

Abbreviations: AOR = adjusted odds ratio; BMI = body mass index; CI = confidence interval; IgG = immunoglobulin G; MOG = myelin oligodendrocyte glycoprotein; MS = multiple sclerosis; UVR = ultraviolet radiation.
Multivariable conditional logistic regression models testing the association between time spent outdoors daily in the most recent summer on the weekends, use of sun protection in the most recent summer, ambient UVR dose in the summer before recruitment, and MS case vs control status (risk of pediatric MS). All models are adjusted for sex, age, race, birth season, child's skin color, mother's education, tobacco smoke exposure, and antibodies against Epstein-Barr virus viral capsid antigen. Model 1 is additionally adjusted for BMI, and models 2 and 3 are adjusted for overweight (yes/no). Results are presented as AORs with 95% CIs.

Vitamin D Status

Higher serum 25(OH)D concentration (postdiagnostic) was associated with greater odds of MS (AOR 1.06 per ng/mL, 95% CI 1.04–1.08, $p < 0.001$) (eTable 5, links.lww.com/WNL/B653, model 3). When time spent outdoors, use of sun protection, ambient summer UVR dose, and serum 25(OH)D concentration were included as predictors in the same model, higher serum 25(OH)D concentration remained associated with greater odds of MS (AOR 1.07 per ng/mL, 95% CI 1.05–1.09, $p < 0.001$) (eTable 5, model 3). We tested for interaction effects between time outdoors, use of sun protection, ambient UVR levels, and serum 25(OH)D but did not detect any significant interactions.

Sensitivity Analyses and Post Hoc Analyses

We conducted several sensitivity analyses, restricting the dataset to participants with accurate BMI data; children with MS onset in the year before enrollment and their matched controls; and children diagnosed with MS who had a negative anti-MOG antibody screen and their matched controls (Table 5 and eTables 6–8, links.lww.com/WNL/B653). All sensitivity analyses produced results very similar to results

from the main analyses, with some attenuation of effect size owing to smaller sample sizes.

In a post hoc analysis restricting the dataset to children with MS onset <4 months before enrollment and their matched controls, higher serum 25(OH)D levels remained associated with greater odds of MS, but the effect was not statistically significant. When the dataset was further restricted to children diagnosed <2 months prior and their matched controls, higher serum 25(OH)D concentration was associated with lower odds of MS, although the effect was not statistically significant, likely due to the reduced sample size (eTable 9, links.lww.com/WNL/B653).

Discussion

In this matched case-control study testing the association of sun exposure–related factors with pediatric MS, we found that spending more time outdoors during summer and residing in an area with higher ambient summer UVR were associated with reduced odds of pediatric MS. Our findings suggest that low sun exposure and UVR dose may be important environmental risk factors for pediatric MS and that even 30 minutes of sun exposure daily during summer could substantially reduce MS risk. The finding that sun exposure in the first year of life is associated with MS risk, if shown to be causal, suggests that early life exposures may influence subsequent MS risk, although a cumulative dose effect during subsequent years is also possible.

There are few studies testing the effect of environmental exposures on the risk of developing pediatric MS, a form of the disease that occurs on average 20 to 30 years earlier than in adults. While the effect of sun exposure in pediatric MS has not been investigated previously, our findings are consistent with the large body of work on the relationship between sun/UVR exposure and adult-onset MS, with comparable effect sizes.[4,6,8] Several studies have also reported that greater sun exposure in childhood and adolescence is associated with reduced risk of subsequent adult-onset MS.[15-17]

Providing guidance on optimal UVR exposure (and use of sunscreen), weighing benefits against risks, is challenging. Ambient UVR varies by location and time of year, and doses required to incur both risks and benefits are poorly defined. The World Health Organization has introduced the UV Index to overcome the need for different messages for different locations (the UV Index and its use are reviewed in reference 18). This is a measure of the instantaneous UV irradiance that is contained within weather reports in many countries. The World Health Organization recommends that sun protection is required when the UV Index is ≥3, and algorithms are available to calculate the maximum time outdoors at any UV Index to avoid a minimal sunburn.

Several previous studies have implicated low vitamin D status as a risk factor for the onset and progression of pediatric MS.[5,19-21] However, we found that higher serum 25(OH)D concentration was associated with greater odds of MS. We excluded the 25(OH)D analyses from the main results because of the high likelihood of reverse causality, with routine vitamin D supplementation likely to have occurred shortly after diagnosis. In support of this view, we observed that serum 25(OH)D was inversely correlated with the odds of having MS when comparing children diagnosed with MS very recently (<2 months) and their matched controls. We were unable to explore this further because data on current/recent vitamin D supplementation were unavailable.

Our study used a robust multifactorial approach to measure sun exposure, incorporating self-reported time spent outdoors and use of sun protection, as well as satellite data on ambient UVR dose during various time periods. The cohort was large, racially diverse, perfectly matched on sex, closely matched on age, and recruited from multiple study centers. The criteria for defining cases and the questionnaire used in this study have previously been validated.[22] Most of the case participants had a short disease duration at the time of enrollment in the study. We were able to replicate all our key findings in multiple sensitivity analyses. Measurement bias is unlikely because procedures for data collection were identical for cases and controls.

Recall error is a possible limitation because data on sun exposure and use of sun protection were retrospectively obtained. However, there is no reason to expect that recall of sun exposure differs between cases and controls, so recall error would be expected to cause underestimation of the true effect rather than overestimation. Controls were patients and siblings of patients presenting to non-MS pediatric clinics at the same study centers as case participants; that is, they came from the same source population as the cases. Nevertheless, there is potential for selection bias. We cannot rule out reverse causality in the sun exposure findings because children in the MS prodrome may have spent less time outdoors during the most recent summer due to increased heat sensitivity. This is unlikely, however, because greater sun exposure in the first year of life was also associated with lower odds of MS. We could not account for differences in physical activity; individuals with MS may be more sedentary and therefore less likely to spend time outdoors. Lack of data on vitamin D supplementation and our reliance on a single serum 25(OH)D measurement obtained after diagnosis precluded our ability to investigate fully vitamin D status as a risk factor.

Further work is needed to accurately evaluate vitamin D status as a risk factor for pediatric MS; longitudinal studies are necessary to avoid the risk of reverse causality. Clinical trials are required to determine whether increasing sun exposure or vitamin D supplementation can prevent the development of MS or alter the disease course after diagnosis. Given the rarity of pediatric MS and the length of follow-up required, such studies are more feasible in relation to disease progression after diagnosis rather than disease onset. The mechanisms

underlying a protective effect of sun exposure, UVR exposure, and vitamin D, including any potential vitamin D–independent effects of sun exposure, remain unclear.

Low sun exposure and/or low vitamin D status have been linked to a range of other neurologic diseases, including Parkinson disease, Alzheimer disease and other forms of dementia, as well as mental health conditions such as schizophrenia (reviewed in reference 12). However, unlike the relatively consistent evidence of a protective effect of higher sun exposure for risk of MS,[6,15,23-26] much of the evidence for other neurologic diseases derives from animal or ecologic human studies,[12] and there is considerable conflict in the research findings. These differences in association with other neurologic diseases are hardly surprising and may relate to their very different pathophysiology compared to MS.

The investigation of pediatric MS offers a valuable opportunity to understand MS etiology, especially the effect of environmental exposures, because the window between exposure and onset of disease is narrower compared to adult-onset MS. Clarifying the causal effect of modifiable risk factors such as sun exposure and vitamin D status could reduce the disease burden associated with MS. Our findings suggest that advising regular time in the sun of at least 30 minutes daily during summer, using sun protection as needed, especially for first-degree relatives of patients with MS, may be a worthwhile intervention to reduce the incidence of pediatric MS.

Acknowledgment

The authors thank the study coordinators at the participating sites, the study participants, and their families.

Study Funding

This study was funded by the NIH (R01NS071463, E.W.) and the National MS Society (HC0165, C.C.).

Disclosure

P. Sebastian, N. Cherbuin, and L. Barcellos report no disclosures relevant to the manuscript. S. Roalstad and C. Casper report grants from National MS Society, during the conduct of the study. J. Hart reports no disclosures relevant to the manuscript. G. Aaen reports grants from National Pediatric MS Society and grants from NIH, during the conduct of the study. L. Krupp reports grants from National Multiple Sclerosis Society, during the conduct of the study; personal fees from Sanofi-Aventis; grants and personal fees from Biogen; personal fees and nonfinancial support from Novartis; nonfinancial support from Celgene; and personal fees from EMD Serono, Allergan, Tesaro, Eisai, Roche, and Janssen, outside the submitted work. L. Benson reports grants from NIH, during the conduct of the study; other from Alexion Pharmaceuticals; personal fees from Department of Public Health, Massachusetts, and Vaccine Injury Compensation Program; and grants from ROHHAD Fight, Inc and Shore Foundation, outside the submitted work. M. Gorman reports grants from National Multiple Sclerosis Society and National Institute of Neurologic Disorders and Stroke, during the conduct of the study, and grants from Biogen, Novartis, and Roche, outside the submitted work. M. Candee reports no disclosures relevant to the manuscript. T. Chitnis reports consulting fees from Biogen Idec, Novartis, Sanofi, Bayer, Celgene, and Genentech, as well as grants from Novartis, Octave Bioscience, EMD Serono, and Verily Life Sciences, all outside the submitted work. M. Goyal reports no disclosures relevant to the manuscript. B. Greenberg reports grants from NIH, during the conduct of the study' personal fees from Novartis, EMD Serono, and Alexion; grants from Guthy Jackson Charitable Foundation; grants and other from Siegel Rare Neuroimmune Association; and grants from NMSS and Clene Nanomedicine, outside the submitted work. S. Mar, M. Rodriguez, J. Rubin, T. Schreiner, and A. Waldman report no disclosures relevant to the manuscript. B. Weinstock-Guttman reports grants and personal fees from Biogen, Novartis, Genentech, and Genzyme & Sanofi, as well as personal fees from Abbvie and Bayer, outside the submitted work. J. Graves reports personal fees from Alexion and Celgene and grants from Biogen and Octave, outside the submitted work. E. Waubant reports personal fees from MS@TheLimit, MS curriculum, PRIME, DBV, Emerald, Jazz Pharma, and The Corpus, outside the submitted work. R. Lucas reports no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* March 23, 2021. Accepted in final form October 19, 2021.

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Appendix 1 *(continued)*

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Appendix 2 *(continued)*

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