Childhood sun exposure influences risk of multiple sclerosis in monozygotic twins

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ABSTRACT Objective: To address the role of childhood sun exposure on the risk of multiple sclerosis (MS) after controlling for genetic susceptibility, we investigated the association between sun exposure and MS comparing disease-discordant monozygotic (MZ) twins. **Method:** Twins with MS were sought by yearly newspaper advertisements throughout North America from 1980 to 1992. Diagnosis was verified by updated medical documentation through 2005. This analysis was restricted to 79 disease- and exposure-discordant monozygotic twin pairs who had ranked themselves before 1993 in relation to each of nine childhood sun exposure activities. A sun exposure index (SI) was defined as the sum of those exposures for which one twin ranked higher than his or her co-twin. The SI difference within each twin pair was calculated by subtracting the SI value of the affected twin from the SI value of the unaffected twin (range −9 to +9). The results were then analyzed using conditional logistic models. **Result:** Each of the nine sun exposure–related activities during childhood seemed to convey a strong protection against MS within MZ twin pairs. Depending on the activity, the odds ratio (OR) ranged from 0.25 to 0.57. For example, the risk of subsequent MS was substantially lower (OR 0.40, 95% CI 0.19 to 0.83) for the twin who spent more time suntanning in comparison with the co-twin. For each unit increase in SI, the relative risk of MS decreased by 25%. **Conclusion:** Early sun avoidance seems to precede the diagnosis of multiple sclerosis (MS). This protective effect is independent of genetic susceptibility to MS. **NEUROLOGY 2007;69:381–388**

Multiple sclerosis (MS) is an autoimmune disease of the CNS with a complex etiology. Despite a strong genetic component and substantial concordance (approximately 20%) among monozygotic (MZ) twins,[1] environmental determination is suggested by the incidence gradient according to latitude,[2] and the effect of migration within genetically uniform groups.[2]

We have observed that concordance for MS among identical twins diminishes as latitude decreases and have observed that this effect seems to depend on both genetic and environmental factors.[3] Solar flux is one latitude-dependent environmental exposure that is also (inversely) related to MS incidence and prevalence. In an environment with uniformly low solar flux, both twins are likely to receive relatively little sunlight, whereas in sunny regions, behavioral variation is likely to result in exposure discordancy. Sun exposure therefore offers a possible explanation for latitudinal differences in disease concordance among identical twins.

Initially, a possible protective role of sun exposure was hypothesized on the basis of an ecological study of World War II veterans in the 1960s.[4] Recently, a strong protective role of childhood sun exposure has been observed in Tasmania.[5] In a well-controlled case–control study, Tasmanians with 2 to 3 hours of youthful sun exposure on average per week were found to have nearly a 60% reduction in MS risk. Using actinic damage of the hand as a biomarker for lifetime exposure, a similar association was observed. It was suggested that the immunomodulatory effect of sun exposure is responsible for this apparent protective effect.

Supplemental data at www.neurology.org

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The International Twin Study is a large registry of North American twins who have been diagnosed with any of several chronic diseases, including MS.[6] It provides an opportunity to investigate the association between MS and relative exposure to the sun, as reflected by the childhood activities of paired identical twins, one member of each pair having symptomatic MS. Such subjects permit the effect of sun exposure to be assessed without confounding by genotype. Furthermore, because the exposure data were collected before 1993, when sun exposure was not considered to be an important factor in MS etiology, the possibility of recall bias is minimal.

METHODS

Study population. Twins with MS and other chronic diseases were ascertained by annual advertisements in periodicals throughout North America from 1980 to 1992. The details of the recruitment process and a description of the representativeness of the twin MS cases have been provided earlier.[3,6] In brief, ascertainment of the original cohort of subjects was designed to capture pairs of twins in whom at least one member had physician-diagnosed MS. In this process, 1,149 pairs, including 418 MZ pairs with at least one member of the pair with MS, approximately 27% of the North American twin cases prevalent at any time during the period of ascertainment, were identified. Basic items of information, including address, sex, the date and place of birth, perceived zygosity, and the date and place of MS diagnosis, were collected. No concordant pairs were doubly ascertained. Discordancy for the disease in pairs so identified was verified based on the neurologic health of the unaffected co-twin, most often by direct contact; discordant pairs were followed through the period of risk (see below). Among the complete set of affected twin volunteers, the ratio of female to male cases is 3.0, the ratio of affected fraternal to identical twins overall is 1.7, and that among like-sex pairs is 1.0. Excepting the slight excess of female volunteers, each of these ratios is consistent with what would be expected based on the pattern of cases and of twins in the United States.

The diagnoses of 94.6% of the twin cases occurred between ages 15 and 50 years, and roughly two-thirds were diagnosed between ages 20 and 40 years. The diagnoses were self-reported, and because the cases resided all over North America, they could not be confirmed by direct neurologic examination. The validity of the diagnoses has been discussed previously,[3] and here we will address the issue briefly. An early sample of cases was validated by expert record review, and fewer than 2% cases were considered to be "not MS." Virtually all cases have provided the names of their providers, and cases have been followed and screened for diagnostic errors by periodic follow-up and review by telephone interview, questionnaire, and record review. The average interval between diagnosis and study entry was 10 years; after entry, the subjects have been followed on average for 13 years. Follow-up of roughly a thousand cases for 23 years on average has identified only 17 syndromes now considered not to be MS.

A detailed 60-page questionnaire exploring possible etiologic factors and opinions about MS etiology was sent to each living member of an affected pair. Completed questionnaires were received before 1993 from the members of 292 MZ pairs (70%), of which 42 were disease concordant and 250 were disease discordant. Of the latter, 193 pairs (77%) were represented by instruments completed by both members. Death of a twin was a more common feature of nonresponding pairs (26.8% compared with 17.2%) and of pairs with a single respondent (33.3% compared with 12.4%).

Diagnostic validation. With written permission from cases, providers were asked to provide medical documentation for each diagnosis and to update each diagnostic status. Academic MS neurologists (L. Weiner, W. Weiderholt) reviewed the records of an early sample of cases (both MZ and dizygotic [DZ]). Applying the Schumacher criteria[7] (formulated to identify MS cases with CNS lesions disparate in both time and space, using only the clinical findings from sequential episodes [at least 1 month apart, lasting at least 24 hours, over a period of at least 6 months], for which no more credible alternative explanation is available), they judged that 141 of the 145 cases (97%) initially accepted to represent probable MS. (The remaining 4 were excluded.) As follow-up has proceeded to the present, 7 symptomatic twins indicated that their physicians now favored an alternative diagnosis, and a review of the diagnostic basis of 161 (MZ and DZ) pairs lost to subsequent follow-up identified 6 additional cases for which objective evidence either was lacking or provided support for an alternative diagnosis. These 13 pairs have also been excluded. Over this period, 17 originally unaffected co-twins have developed confirmed MS.

Zygosity. Twins' perception of zygosity repeatedly has been shown to be more than 95% accurate,[8,9] and the zygosity assignment of each pair was based on the twins' own assessment. We ourselves have assessed the perceptions of more than 150 previous twin pairs using molecular biologic methods,[10,11] confirming self-reported zygosity in all but one pair. On the basis of HLA-DR2 validation, self-assessment by 7 of the 360 pairs was erroneous (1.9%).

Exposure measurement. Information regarding the twins' ranked outdoor activities in childhood was obtained from the completed questionnaires. Each twin was asked to specify whether he or she or the co-twin spent more time outdoors "during hot days," "during cold days," "during summer," "spring," "winter," and "fall," and which one spent more time in "suntanning," "going to the beach," and "participating in team sports." Thus, the measures of exposure were comparative rather than absolute in nature. For the present purposes, informative pairs consisted solely of those pairs discordant for both disease and exposure. For any given question, only those pairs who were in agreement about the ranked assessment were accepted for analysis.

To address the issue of global sun exposure, a sun exposure index (SI) was calculated for each twin member, the index representing the total number of responses for which that twin's exposure exceeded that of the co-twin. There being nine questions, the possible range of the index was 0 to 9. To assess risk according to levels of exposure, the pairwise difference in SI was then calculated by subtracting the SI value for the affected twin from the value for the unaffected

Table 1 Baseline characteristics of exposure-discordant and exposure-concordant MS-discordant MZ twin pairs

Characteristic	Exposure-discordant pairs,* N = 79, n (%)	Exposure-concordant pairs,† N = 114, n (%)	*p* Value‡
Male	13 (16.5)	29 (25.4)	0.13
Born in Canada or an adjacent state	34 (43.0)	43 (37.7)	0.48
North European ancestry	13 (16.5)	15 (13.2)	0.52
Age at diagnosis < 30 years	38 (46.8)	54 (47.4)	0.94

* Multiple sclerosis (MS)–discordant monozygotic (MZ) pairs who were discordant for at least one of the nine sun exposure–related activities.
† MS-discordant MZ pairs who were concordant for each of the nine sun exposure–related activities (114).
‡ The reported *p* values were from chi-square tests; testing for difference between exposure-concordant and -discordant MZ pairs.

co-twin. Thus, the range of pairwise difference in SI could range from −9 to +9.

Other exposures. The history of childhood infections (chickenpox, red measles, German measles, hepatitis, polio, and mumps) and of infectious mononucleosis for each twin was obtained. Those smoking at least 100 cigarettes before MS diagnosis were considered to be smokers, and the age at menarche of each female twin was recorded. Comparative questions were also asked about exposures thought at the time to be pertinent.

Twins born in Canada and adjacent US states at or above 41 to 42 °N were considered to be northern born, and those with at least one grandparent of Scandinavian or Celtic origin were considered to be of "North European ancestry." MS cases diagnosed before age 29.3 years (median age at diagnosis for MZ twins) were considered to have been diagnosed "early."[3]

Analysis. To assess the possible redundancy between different measures of sun exposure, Spearman correlation statistics were calculated, separately for affected and unaffected co-twins. Because the discordant MZ twin pairs represent 1:1 matched case–control pairs, tests of association between exposure and disease were performed using the McNemar test as well as by conditional logistic regression. All models were tested for possible confounding and effect modification by personal smoking, childhood infection, history of infectious mononucleosis, and age at menarche. Because birthplace, year of birth, age, sex, and North European ancestry are always the same for both twins, those were assessed only for effect-magnitude modification.

The difference in SI value between affected and unaffected twins was tested using a paired *t* test. The strength of the link to MS per unit of SI was calculated using logistic regression models, with assessment of confounding and effect modification. Potential confounders (as listed above) were added to the logistic model one at a time and assessed on the basis of at least a 10% change in the SI parameter estimate. Appropriate interaction terms were used to test for effect modification by those factors. Sensitivity analysis was conducted by stratifying the analysis by frequency of contact between twins and restricting the analysis to twins with detailed medical records. All analyses were performed using SAS 9.1, and all findings were assessed allowing for two-sided significance at the 0.05 level.

RESULTS

Baseline characteristics. Of the 193 disease-discordant pairs with both twins completing the questionnaire, the twins in 114 pairs considered themselves to be identically exposed with respect to each of the nine exposures. The remaining 79 were discordant on at least one of the sun exposure–related activities. Most twins were female, born in the Northern states, and of North European ancestry (table 1). The demographic features of the exposure-discordant pairs did not differ from those of the 114 exposure-concordant pairs. Moreover, no difference of those demographic features was observed between twins with (250) or without (112) completed questionnaires, nor between single (57) and double (193) respondent pairs (tables E-1 and E-2 on the *Neurology* Web site at www.neurology.org).

Twin pairs were categorized according to whether the twins communicated with each other at least once a month. Most exposure-concordant (90%) as well as most exposure-discordant pairs (87%) had kept in such close contact. Most cases had been diagnosed at least 10 years before study entry, usually after age 29 years. Subjects were asked to speculate about the causes of MS, and the members of only three pairs perceived aspects of climate or weather to be a potential determinant.

Independence of the measures of sun exposures. Although the relative frequencies of outdoor exposures by season were moderately correlated (tables 2 and 3), the relative frequency of specific activities was largely independent of the seasonal exposures and of each other. The pattern of correlations between the different measures was similar among affected (table 2) and unaffected co-twins (table 3).

Measures of sun exposure and MS risk. Considering the individual measures separately, the risk of

Table 2 Correlation (Spearman coefficients) between different measures of outdoor exposure among affected MZ twins

	Summer	Fall	Winter	Spring	Hot day	Cold day	Suntan	Beach	Team sports
Summer	1.00	0.72	0.63	0.69	0.36	0.34	0.05*	0.11*	0.12
Fall		1.00	0.70	0.72	0.38	0.36	0.03*	0.07*	0.15
Winter			1.00	0.57	0.39	0.45	0.08*	0.10*	0.19
Spring				1.00	0.32	0.25	0.05*	0.05*	0.17
Hot day					1.00	0.66	0.24	0.17	0.16
Cold day						1.00	0.24	0.14	0.15
Suntan							1.00	0.36	0.26
Beach								1.00	0.29
Team sports									1.00

* All correlations were significant except those marked.
MZ = monozygotic.

MS decreased with each of the nine exposures investigated (table 4). Although the number of discordant pairs was limited, significant associations were seen for spending more hours outdoors during spring (odds ratio [OR] 0. 25, 95% CI 0.07 to 0.89), during hot days (OR 0.40, 95% CI 0.18 to 0.91), while suntanning (OR 0.40, 95% CI 0.19 to 0.80), and while at the beach (OR 0.42, 95% CI 0.18 to 0.96). Other exposures addressed in the questionnaire proved independent of the MS diagnosis, including those considered etiologically suspect at the time, such as fish consumption (OR 1.0) and close contact with dogs (OR 0.7).

Sun exposure index and MS risk. The histogram in the figure shows the distribution of cumulated pairwise differences in SI. Under the null hypothesis, the expected mean of SI is zero, and the calculated mean value of SI of 1.0 is significantly different from that null value (p value from paired t test = 0.0013). Further, the distribution of differences in the index is shifted to the right with a substantial right tail. This pattern supports the conclusion that affected twins had less overall sun exposure than their unaffected co-twins.

Moreover, increased risk of MS was associated with a lower SI value (table 5). One unit increase in the SI difference was associated with 25% reduction in the risk of MS ($\beta = -0.28$, OR = 0.75, $p = 0.004$). This trend persisted after stratifying on the potentially modifying characteristics of birthplace, age at diagnosis, sex, and North European ancestry. No significant interaction was noted for any variable.

We could identify no factor confounding the observed protective effect of past sun exposure against MS risk. The association between sun exposure and MS was neither confounded (table 6) nor modified (data not shown) by factors such as childhood infection, incidence of infectious mononucleosis, personal smoking, diet, and age at menarche (for female twins). With the possibility that some of the team sports might be played

Table 3 Correlation (Spearman coefficients) between different measures of outdoor exposure among unaffected MZ co-twins

	Summer	Fall	Winter	Spring	Hot day	Cold day	Suntan	Beach	Team sports
Summer	1.00	0.72	0.68	0.74	0.59	0.46	0.22	0.17	0.12
Fall		1.00	0.72	0.87	0.49	0.48	0.18	0.10	0.13
Winter			1.00	0.71	0.52	0.67	0.19	0.16	0.06*
Spring				1.00	0.46	0.46	0.17	0.10	0.12
Hot day					1.00	0.72	0.26	0.25	0.04*
Cold day						1.00	0.22	0.19	0.04*
Suntan							1.00	0.36	0.26
Beach								1.00	0.28
Team sports									1.00

* All correlations were significant except those marked.
MZ = monozygotic.

Table 4 Odds ratios and 95% CIs linking MS to various measures of relative outdoor exposure

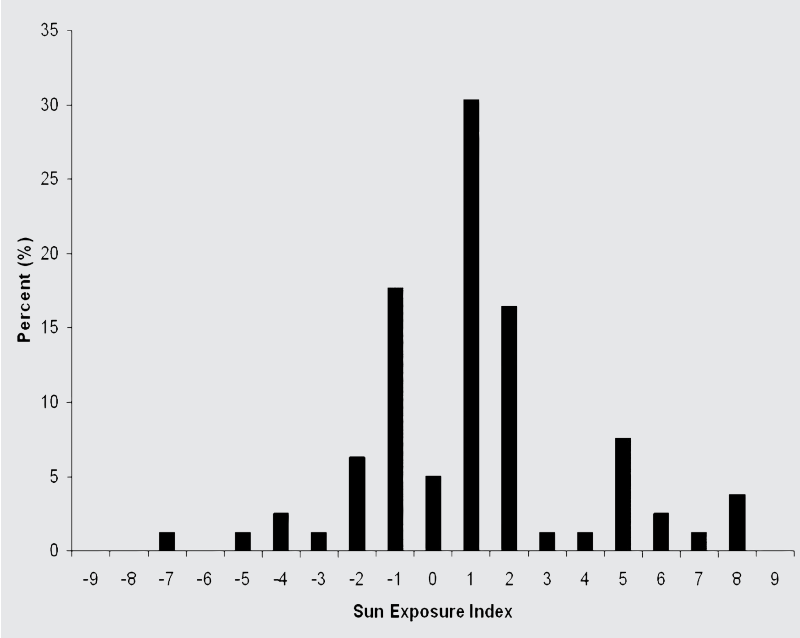
Exposure group	n*	MZ twins OR (95% CI)	p Value†
Seasonal outdoor exposure			
Summer	6/15	0.40 (0.15–1.03)	0.06
Fall	4/7	0.57 (0.17–1.95)	0.37
Winter	5/11	0.45 (0.16–1.31)	0.14
Spring	3/12	0.25 (0.07–0.89)	0.03
Temperature-related outdoor exposure			
Hot day	8/20	0.40 (0.18–0.91)	0.03
Cold day	9/17	0.53 (0.24–1.19)	0.12
Sun exposure–related activities			
Suntanning	10/25	0.40 (0.19–0.83)	0.01
Beach	8/19	0.42 (0.18–0.96)	0.03
Team sports	8/18	0.44 (0.19–1.02)	0.06

* Number of multiple sclerosis (MS)–affected twins exposed/number of control twins exposed.
† McNemar test for the association between sun exposure–related activity and MS among the monozygotic (MZ) twins.
OR = odds ratio.

indoors, in a subanalysis we restricted our analysis to the other eight exposures. However, the finding remained unchanged (OR 0.75, 95%CI 0.62 to 0.90).

Validation of the findings. We searched for other possible artifacts. To learn whether the results might have been influenced by the degree of contact between co-twins, we stratified the twin pairs into two groups based on the above frequency-of-contact criterion. No significant difference in the association between SI and MS was noted between pairs with more (OR 0.62, 95% CI 0.43 to 0.91) or less (OR 0.86, 95% CI 0.77 to 1.06) contact. To address the impact of errors in MS diagnosis, we restricted the analysis to pairs for whom detailed medical records were available (n = 56) or pairs who were followed up to the present (n = 70). The ORs from both subanalyses were similar to the original (available records: OR 0.75, 95% CI 0.59 to 0.93; complete follow-up: OR 0.73, 95% CI 0.58 to 0.89). To address the issue of possible delayed diagnosis in a co-twin, we restricted the analysis to pairs with a current age of 60+ years and still observed a similar effect (OR 0.69, 95% CI 0.49 to 0.90). We also considered age at and interval since diagnosis of MS as potential confounders because those diagnosed very early or those long affected might falsely characterize themselves as less exposed to sun exposure activities during childhood. Restricting the analysis to cases who completed the questionnaire within 3 years of diagnosis (30% of the population; SI OR 0.78, 95% CI 0.51 to 1.17) or within 14 years of diagnosis (75% of the population; SI OR 0.79, 95% CI 0.62 to 0.97) did not substantially alter our estimates. Of all the 14 pairs who had SI values above 5, all were diagnosed as adults. Thus, this high-exposure group does not represent a group with very young-onset MS. Exclusion of the 3 pairs who considered climate to be a determinant of MS also did not materially affect the association.

Figure Distribution of intrapair difference in the sun exposure index in multiple sclerosis–discordant monozygotic pairs



The difference in the sun exposure index (SI) for each monozygotic pair was calculated by subtracting the SI value of the affected twin from that of the unaffected co-twin. The skewed distribution to the right denotes higher SI values (more sun exposure) for the unaffected twins compared with the affected twins.

Table 5 Odds ratios and 95% CIs* for the association between the sun exposure index and MS, stratified on known risk factors

	OR	95% CI	*p* Value	EM†
All MZ twins	0.75	0.62–0.90	0.004	
Birth location‡				0.29
Southern states	0.63	0.38–0.92	0.04	
Northern states and Canada	0.80	0.63–0.98	0.03	
Ancestry§				0.34
No North European ancestry	0.96	0.60–1.47	0.83	
North European ancestry	0.71	0.55–0.87	0.004	
Age at diagnosis‖				0.41
≥29.3 years	0.66	0.42–0.90	0.02	
<29.3 years	0.80	0.62–0.99	0.05	
Sex				0.09
Male–male	1.02	0.68–1.56	0.92	
Female–female	0.69	0.53–0.86	0.003	

* Odds ratios (ORs) and 95% CIs are derived from conditional logistic regression models.
† *p* Value reported from likelihood ratio test, testing for possible effect modification (EM).
‡ Twins born in Canada and adjacent US states at or above 41 to 42 °N were considered to be northern born.
§ Twins with at least one grandparent of Scandinavian or Celtic origin were considered to be of "North European ancestry."
‖ Multiple sclerosis (MS) cases were stratified by the median age at diagnosis for monozygotic (MZ) twins (29.3 years).

Additionally, we compared exposures between the affected twin and his or her unaffected co-twin without restricting the analysis to pairs from whom both responses were received, or to pairs who were in agreement. Considering the responses individually, despite the substantial number of pairs who disagreed ($\kappa < 0.40$ for each measure), a similar protective effect of sun exposure was observed for each measure. For example, the OR for more frequent suntanning was 0.48 (95% CI 0.25 to 0.93) based on responses from cases and 0.38 (95% CI 0.19 to 0.76) based on responses from unaffected co-twins (for further detail, see table E-3).

Table 6 Odds ratios and 95% CIs for the association between sun exposure index and MS, adjusted for possible confounders*

Adjustment factor	OR	95% CI	*p* Value
Unadjusted base model	0.75	0.62–0.90	0.004
Childhood infection†	0.76	0.62–0.91	0.007
Infectious mononucleosis‡	0.76	0.62–0.90	0.004
Smoking§	0.75	0.60–0.90	0.004
Age at menarche‖	0.69	0.57–0.85	0.002

* Each factor is separately fitted in the logistic model.
† History of any childhood infection (chickenpox, red measles, German measles, hepatitis, polio, and mumps).
‡ History of infectious mononucleosis.
§ History of smoking at least 100 cigarettes before multiple sclerosis (MS) diagnosis.
‖ Age at menarche from the questionnaire response.
OR = odds ratio.

DISCUSSION To summarize, we found a strong inverse association between the relative frequency of sun exposure and the appearance of MS within pairs of monozygotic twins. There was a linear trend of decreasing MS risk with increasing disparity between the paired sun exposures. The observed incremental reduction in risk of 25% for each unit of SI was independent of birthplace and age at diagnosis. The disease risk estimates for time outdoors and sun-specific activity questions were similar, suggesting that all of these variables might be capturing a similar underlying association. Our use of the SI was aimed at capturing a variety of activities that could plausibly predict differences in underlying sun exposure between cases and controls. This reduction of risk associated with SI should not be considered as the joint effect of different sun exposure–related activities, but rather a cumulative effect of overall sun exposure.

A similarly strong protective effect of childhood (6 to 15 years) sun exposure in relation to MS has been found in a standard case–control study of prevalent MS cases conducted in Tasmania.[5] In that study, the OR for MS among children averaging 2 or more hours of sun exposure per week, compared with less than 2 hours, was 0.31 (95% CI 0.16 to 0.59). An earlier study of outdoor

and indoor workers found a dose-dependent protective effect of sun exposure on MS-related mortality.[12] However, sun exposure could result from heritable factors influencing tolerance to solar flux, and neither of these investigators could assess genetic susceptibility. An association demonstrated within pairs of identical twins could not reflect inheritance.

In addition to eliminating confounding by genetic factors, this design provides other benefits. We were able to simultaneously control age, sex, latitude of birth, skin color, socioeconomic status, and family history as well as genotype. Identical twins are representative of the population in terms of both genetic susceptibility and environmental exposure, because MZ twinning is not influenced by environmental and genetic factors[13] and MZ twins are not at higher risk of MS.[14] Given the 1.9% error rate in self-classification of zygosity, no more than 2 of the 79 seemingly identical discordant pairs might actually be fraternal. They would be less likely to agree on the difference in exposure, but even presuming otherwise, the negligible error introduced by the confounding effect of genetic difference within these 2 pairs would not alter the results. Although this analysis was limited to the 69% of MZ twin pairs from which both questionnaires were available, we did not detect any substantial difference between those pairs with double and those with single responses, or between pairs with and without any questionnaire responses with respect to sex, ancestry, age at diagnosis, or birthplace (tables E-1 and E-2). In fact, the most frequent reason for nonresponse from one member of a pair or twin pair was death of one of the members.

We therefore focused concern on the validity of the diagnoses and the meaningfulness of the comparative exposure measurement. Neither offers a credible explanation for the results.

The exclusion of twin pairs with incomplete medical records or incomplete follow-up did not change our estimates. Residual diagnostic inaccuracy after repeated follow-up of relatively well-educated persons with such a serious diagnosis is unlikely to be substantial. Although recollection of the sequence of diagnosis and exposure might be less accurate for subjects diagnosed at an early age or long affected by MS, analyses stratified by age at diagnosis did not produce different results. Finally, there is no reason to assume that misdiagnosis would be nonrandomly associated with sun exposure.

We reasoned that responses might be less independent if twins remained in especially close contact. In this regard, the informative pairs were representative of all pairs, and the observed associations were independent of the degree of close contact.

Because we used relative exposure within pairs and were unable to directly quantify exposure, we made no attempt to estimate the level of exposure that might confer protection. Such estimates would be inaccurate under any circumstance. Conventional subjective estimates of time spent "out in the sun" or "in outdoor activities" involve substantial recall bias and measurement error, especially given the long interval between exposure and disease, and are highly influenced by variations in weather and behavior. By using the independent recollections of both twins, we limited both measurement error and recall bias, because any difference must have been sufficiently notable that both members could recollect and agree upon it even after many years. In addition, the validating perceptions from the unaffected co-twins reduces the likelihood that recollections from cases were biased by their sensitivity to heat intolerance. Moreover, at the time subjects completed their responses, sun exposure was not considered to be an important etiologic factor, whereas no associations were found between MS and those exposures popularized at the time. Restricting the analyses to pairs in which neither member perceived "weather" as a risk factor for MS had no effect on the result.

Exposure to sunlight, i.e., ultraviolet radiation (UVR), might induce protection against an autoimmune disease by any of several immunosuppressive mechanisms. UVR exposure can exert its immunosuppressive effect directly by producing cytokines[15,16] and reducing natural killer cell activity, thus affecting innate immunity.[17] Animal studies have shown that UV-radiated keratinocytes produce an array of cytokines including interleukin (IL)-10 and IL-4 through a prostaglandin E2–induced pathway.[18] IL-10, a potent immunosuppressor,[19] alters antigen presentation and interferon (IFN)-γ secretion by antigen presenting cells and thus prevents TH0 to TH1 conversion and TH1 activation.[20,21] UVR can also reduce natural killer cell activity and thus affect innate immunity.[15]Alternatively, solar flux can act indirectly by producing vitamin D and suppressing melatonin secretion,[22] with the resultant effects on Th1–Th2 balance. This effect is probably achieved by activated vitamin D suppressing the production of cytokines associated with MS activity, such as IL-2, IFN-γ, and tumor necrosis

factor α,[23] and stimulating opposing cytokines, such as tumor growth factor β1 and IL-4.[24]

The observation that the protective effect of sun exposure was only observed among female twin pairs and not among male pairs is intriguing. A recent animal study noted that vitamin D is protected against experimental autoimmune encephalomyelitis only among female mice.[25] It is possible that the protective effect of sun exposure–related activity represents vitamin D mediated sex-specific immunomodulation. However, with the small numbers of male–male pairs and the resultant nonsignificant interaction (table 5), we must view this novel finding with caution.

The demonstration of a protective effect of sun exposure on MS risk among MZ twins supports the similar findings observed by van der Mei et al.[5] The demonstration of a similar reduction of risk from two methodologically different studies conducted in two widely disparate populations emphasizes the possible importance of sun exposure in MS etiology. Moreover, our finding notes the importance of sun exposure among individuals with identical genetic risk for MS. Studies of the pathway by which sun exposure reduces MS risk should receive high priority if we are to unravel the mystery of MS etiology.

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