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Sunlight is associated with decreased multiple sclerosis risk: no interaction with human leukocyte antigen-DRB1*15

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Background: Both insufficient exposure to sunlight and vitamin D deficiency have been associated with an increased risk for multiple sclerosis (MS). An interaction between human leukocyte antigen HLA-DRB1*15 and vitamin D in MS was recently proposed. We investigated the association between previous exposure to ultraviolet radiation (UVR), vitamin D status at inclusion in the study, and MS risk including the interaction of these factors with HLA-DRB1*15.

Methods: A population-based case–control study involving 1013 incident cases of MS and 1194 controls was performed in Sweden during 2005–2010. Subjects were classified according to their UVR exposure habits, vitamin D status, and HLA genotypes. The associations between different sun exposure habits/vitamin D levels and MS were calculated as odds ratios (OR) with 95% confidence intervals (CI) using logistic regression. Potential interaction was evaluated by calculating the attributable proportion due to interaction.

Results: Subjects with low UVR exposure had a significantly increased risk of MS compared with those who reported the highest exposure (OR 2.2, 95% CI 1.5–3.3). Similarly, subjects who had 25-hydroxy-vitamin D levels less than 50 nM/l had an increased risk for MS (OR 1.4, 95% CI 1.2–1.7). The association between UVR exposure and MS risk persisted after adjustment for vitamin D status. There was no interaction with HLA-DRB1*15 carriage.

Conclusions: UVR and vitamin D seem to affect MS risk in adults independently of HLA-DRB1*15 status. UVR exposure may also exert a protective effect against developing MS via other pathways than those involving vitamin D.

Introduction

Multiple Sclerosis (MS) is an inflammatory demyelinating disease in which the etiology involves both genetic and environmental factors. Ultraviolet radiation (UVR) exposure/vitamin D status [1,2] are considered to be major lifestyle/environmental factors influencing MS risk, along with smoking [3–6] and Epstein-Barr virus infection [7,8].

There is evidence suggesting that frequent exposure to UVR confers a protective effect against developing MS [9–11] and vitamin D has been proposed to be the major mediator of this protective effect [5,12]. Sun exposure and vitamin D were recently reported by Lucas *et al.* [13] to be independent risk factors for CNS demyelination, suggesting partly different pathways for influencing MS risk. This finding may have vast clinical consequences in terms of preventive intervention, and its replication is therefore important.

A gene–environment interaction involving vitamin D and the most important genetic risk factor in MS, HLA-DRB1*15, was suggested based on an *in vitro* study in which a vitamin D response element (VDRE) was identified in the promoter region of the HLA-DRB1*15 allele [14]. It may also thus be of importance to include HLA-DRB1*15 in the analysis of the association between UVR exposure/vitamin D and MS[1]. In the current population-based study of incident MS patients and matched controls, we examined the association between previous exposure to UVR, vitamin D levels at inclusion in the study, and occurrence of MS, including interaction of these factors with HLA-DRB1*15.

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Subjects and methods

This study is based on the Epidemiological Investigation of Multiple Sclerosis (EIMS), an ongoing case–control study performed in geographically defined parts of Sweden and comprising the general population aged 16–70 years. The present report analyzed incident cases and controls included between April 2005 and March 2010. In all, 35 hospital-based neurology units recruited cases to the study.

Standard protocol approvals, registrations, and patient consents

Each participant provided written informed consent and the study was approved by the Regional Ethical Review board at Karolinska Institutet.

Case identification and selection of controls

A case was defined as a person in the study base who for the first time received a diagnosis of MS according to the McDonalds criteria [15]. All cases were diagnosed by a neurologist at the unit where the case was entered in the study. For each case, two controls were randomly selected from the national population register frequency matched by age (predetermined 5-year age groups), gender, and residential area.

Data collection and exposure information

Information regarding environmental exposures amongst cases and controls was collected using questionnaires that were filled in at home. Completed questionnaires were obtained from 1233 cases and 2685 controls, corresponding to a participation proportion of 93% for the cases and 73% for the controls. The questions about exposure to ultraviolet radiation (measured as exposure to sunny weather, visits to sunny countries, and use of sunbed) are presented in detail as supporting information (online only) and regarded UVR exposure during the last 5 years before inclusion in the study. Subjects of non-Scandinavian origin (170 cases and 459 controls) were excluded in this report as analysis of 25-hydroxy-vitamin D in relation to MS risk should preferably be performed within each ethnic group because of differences in skin color and HLA allele distribution [1].

25-hydroxy-vitamin D in plasma

Vitamin D status was measured as levels of 25-hydroxy-vitamin D in samples included between April 2005 and December 2009. We received blood samples from 95% of the Scandinavian cases who answered the questionnaire and from 54% of the corresponding controls. The blood samples were collected from the cases at the corresponding neurology clinic and the controls donated blood at their primary health care center. The samples are stored at the KI BioBank at Karolinska Institutet and were analyzed using a chemiluminescent immunoassay from Diasorin (Diasorin AB, Sundbyberg, Sweden) and a LIAISON® instrument provided by Diasorin AB with equimolar measurement of both 25-hydroxy-vitamin D_2 and D_3.

For 1013 cases and 1194 controls, we had information for both exposure to UVR and 25-hydroxy-vitamin D levels.

Genotyping

Samples included in the study between April 2005 and November 2009 were available for HLA typing. Unfortunately, a fraction of the samples submitted was lost as a result of failures in the DNA preparation at the central BioBank at the Karolinska Institutet. In total, 890 cases and 1040 controls of Scandinavian origin were genotyped for HLA-DRB1 alleles. DRB1 genotypes were determined using sequence-specific primers [16] and OLERUP SSP™ HLA kits (Qiagen, Hilden, Germany).

Statistical analysis

We used logistic regression analysis to estimate the odds of being a MS case for subjects with different UVR exposure habits, compared with that in subjects who reported the highest exposure, by calculating odds ratios with 95% confidence intervals (and similarly for different levels of 25-hydroxy-vitamin D). Each question related to UVR exposure was analyzed separately. We also constructed an index based on the three questions regarding exposure to UVR. Each answer alternative was given a number ranging from 1 to 4, where 1 was assigned to the lowest exposure alternative and 4 to the highest. By adding the numbers corresponding to each answer, we thus calculated a value between 3 and 12 for each individual. This index was then categorized into the following group intervals: 3; 4–5; 6; 7–8; 9–12. In addition to the analysis based on all subjects, women and men were analyzed separately and a separate analysis restricted to subjects with the first symptoms of the disease within the last 2 years before inclusion in the study was also performed.

The optimal 25-hydroxy-vitamin D level for nervous system and immune functions has not yet been determined, although 75 nM/l is considered an important physiological threshold [2,17]. In dichotomous analyses, we used 75 nM/l as well as 50 nM/l as cutoff. We also analyzed 25(OH) D levels in quintiles.

The potential interaction between HLA-DRB1*15 and UVR exposure, as well as between HLA-DRB1*15 and 25-hydroxy-vitamin D deficiency, was analyzed using departure from additivity of effects as criterion of interaction and was evaluated by calculating attributable proportion due to interaction (AP) together with a 95% confidence interval [18,19]. AP is the proportion of the incidence amongst individuals exposed to two interacting factors that are attributable to the interaction *per se*, thus an AP greater than 0 indicates presence of interaction. In the analyses of interaction UVR exposure was dichotomized into low/high exposure (index value ≤ 6 or >6), and 25-hydroxy-vitamin D levels in plasma were dichotomized into vitamin D deficiency or not (<50 or ≥ 50 nM/l).

All analyses were adjusted for the design variables (age, gender, and residential area), smoking (ever/never), and current body mass index ($\geq$ or <25 kg/m^2). We additionally adjusted for socioeconomic status using an established socio-economical classification [20] (using five categories), but this adjustment had only minor influence on the results and was not retained in the final analyses.

Analyses of the association between vitamin D and MS were adjusted for month of blood donation. To study to what extent the effect of UVR exposure is mediated by vitamin D, the association between UVR exposure and MS was further adjusted for vitamin D status, sampling month, intake of fatty fish (more or less than once a week), and vitamin supplement use during the last 5 years (ever/never). However, the two last-mentioned adjustments had minor influences on the results and were not retained in the final analyses. All analyses were conducted using Statistical Analysis System (SAS) version 9.2 (SAS Institute AB, Solna, Sweden).

Results

Our analyses regarding UVR exposure/vitamin D and MS risk included 1013 cases and 1194 controls. The mean duration between disease onset and inclusion in the study was 4.5 years (median 3 years) (Table 1). 476 cases (47%) were included in the study within 2 years after disease onset and 64% (652) within 4 years. The mean expanded disability status scale (EDSS) at inclusion was 1.8.

Ultraviolet radiation exposure and risk of developing MS

For each of the questions concerning exposure to UVR, a statistically significant inverse relationship between exposure to UVR and risk of developing MS was observed (Table 2). The results remained mainly unchanged when adjusting each type of UVR exposure (each question) for the other UVR-related exposures.

Analyses based on the constructed UVR index revealed that subjects who reported low exposure to UVR

Table 1 Characteristics of cases and controls

Characteristics	Cases (*N*/%)	Controls (*N*/%)
Women	742 (73)	891 (75)
Men	271 (27)	303 (25)
Total	1013 (100)	1194 (100)
Mean age at first symptom of MS (years)	34.5 (SD 10.4)	
Duration from first symptoms to diagnosis (years)		
Mean	3.9 (SD 5.7)	
Median	2.0	
EDSS at inclusion in the study		
Mean	1.8 (SD 1.5)	
Median	1.5	
BMI		
Mean	24.7 (SD 4.5)	24.7 (SD 4.1)
Smoker	555 (55)	563 (47)
Non-smoker	458 (45)	631 (53)
Intake of fat fish weekly		
Yes	189 (19)	265 (22)
No	824 (81)	928 (78)
Socioeconomic status		
Unskilled manual worker	180 (18)	188 (16)
Skilled manual worker	128 (13)	165 (14)
Assistant non-manual employees	144 (14)	159 (13)
Intermediate non-manual employees	187 (18)	233 (20)
Higher non-manual employees	175 (17)	217 (18)
Missings	54 (5)	74 (6)
Not classified[a]	145 (14)	158 (13)[a]

[a]Maternity leave, sick leave. SD, standard deviation; EDSS, expanded disability status scale.

Table 2 Odds ratio (OR) with 95% confidence interval (CI) of developing multiple sclerosis associated with different UVR-related exposures

N = 2207 (1013/1194)	ca/co[a]	OR (95% CI)[b]	OR (95% CI)[c]	OR (95% CI)[d]
Voluntary sun exposure				
No exposure	154/154	1.7 (1.2–2.4)	1.7 (1.2–2.4)	1.6 (1.1–2.3)
Monthly exposure	403/433	1.5 (1.1–2.1)	1.5 (1.1–2.1)	1.5 (1.1–2.0)
Weekly exposure	372/466	1.3 (1.0–1.8)	1.3 (1.0–1.8)	1.3 (1.0–1.8)
Daily exposure	84/141	1.0 (–)	1.0 (–)	1.0 (–)
Visits to sunny countries				
Never	262/264	2.0 (1.4–2.7)	2.0 (1.5–2.7)	1.9 (1.4–2.6)
Less than once a year	364/420	1.7 (1.2–2.2)	1.7 (1.3–2.3)	1.7 (1.2–2.2)
Once a year	297/341	1.6 (1.2–2.2)	1.7 (1.3–2.3)	1.7 (1.2–2.3)
More than once a year	90/169	1.0 (–)	1.0 (–)	1.0 (–)
Using a tanning bed				
Never	623/709	1.6 (1.2–2.0)	1.6 (1.3–2.0)	1.5 (1.2–1.9)
Less than once a year	166/130	2.2 (1.6–2.9)	2.1 (1.6–2.9)	2.1 (1.5–2.8)
Once a year	59/84	1.2 (0.8–1.7)	1.2 (0.8–1.7)	1.1 (0.8–1.7)
More than once a year	165/271	1.0 (–)	1.0 (–)	1.0 (–)

[a]Number of cases and controls.
[b]Adjusted for age, gender, residential area.
[c]Adjusted for age, gender, residential area, body mass index, and smoking.
[d]Adjusted for age, gender, residential area, body mass index, smoking, vitamin D level, and sampling month.

Table 3 Odds ratio (OR) with 95% confidence interval (CI) of developing multiple sclerosis associated with different categories of the constructed UVR index

N = 2207 (1013/1194) UVR category	ca/co[a]	OR (95% CI)[b]	OR (95% CI)[c]	OR (95% CI)[d]
Index 3	69/61	2.2 (1.5–3.3)	2.2 (1.5–3.3)	2.0 (1.3–3.1)
Index 4–5	286/308	1.8 (1.4–2.3)	1.8 (1.4–2.4)	1.7 (1.3–2.2)
Index 6	204/215	1.8 (1.4–2.4)	1.8 (1.4–2.4)	1.8 (1.3–2.3)
Index 7–8	293/329	1.6 (1.3–2.1)	1.7 (1.3–2.2)	1.7 (1.3–2.2)
Index 9–12	161/281	1.0 (–)	1.0 (–)	1.0 (–)
Women				
Index 3	38/38	2.0 (1.2–3.3)	2.0 (1.2–3.3)	1.8 (1.1–3.1)
Index 4–5	189/194	1.9 (1.4–2.5)	1.9 (1.4–2.6)	1.7 (1.3–2.4)
Index 6	152/163	1.8 (1.3–2.4)	1.9 (1.3–2.5)	1.7 (1.2–2.3)
Index 7–8	224/255	1.6 (1.2–2.1)	1.6 (1.2–2.2)	1.6 (1.2–2.3)
Index 9–12	139/241	1.0 (–)	1.0 (–)	1.0 (–)
Men				
Index 3	31/23	2.6 (1.2–5.7)	2.5 (1.1–5.5)	2.4 (1.1–5.4)
Index 4–5	97/114	1.7 (0.9–3.0)	1.8 (1.0–3.3)	1.8 (0.9–3.3)
Index 6	52/52	1.9 (1.0–3.7)	2.2 (1.1–4.3)	2.1 (1.0–4.2)
Index 7–8	69/74	1.8 (0.9–3.3)	1.9 (1.0–3.6)	1.9 (1.0–3.6)
Index 9–12	22/40	1.0 (–)	1.0 (–)	1.0 (–)

[a]Number of cases and controls.
[b]Adjusted for age, residential area, and gender when appropriate.
[c]Adjusted for age, residential area, body mass index, smoking, and gender when appropriate.
[d]Adjusted for age, residential area, body mass index, smoking, vitamin d level, sampling month, and gender when appropriate.

had an increased risk for MS. It is noteworthy that adjustment for vitamin D, considered as a mediator, only marginally changed the estimated associations between UVR and MS (Table 3).

When restricting the analyses to subjects with disease onset within two years prior to inclusion, the results remained quite similar (data not included).

Vitamin D in plasma and MS status

The mean values of 25-hydroxy-vitamin D were 62.9 nM/l amongst the cases and 66.3 nM/l amongst the controls (mean difference 3.4 nM/l, 95% CI 1.2–5.6). There was a significant correlation between exposure to ultraviolet radiation (UVR index) and 25-hydroxy-vitamin D level with r = 0.34 for women (95% CI

Table 4 Association between different levels of vitamin D (nM/l) and multiple sclerosis (OR with 95% CI)

N = 2207 (1013/1194)	ca/co[a]	OR (95% CI)[b]	OR (95% CI)[c]	OR (95% CI)[d]
Vitamin D ≥ 50	659/864	1.0 (–)	1.0 (–)	1.0 (–)
Vitamin D < 50	354/330	1.4 (1.2–1.7)	1.4 (1.2–1.7)	1.2 (1.1–1.5)
Vitamin D ≥ 75	285/397	1.0 (–)	1.0 (–)	1.0 (–)
Vitamin D < 75	728/797	1.3 (1.1–1.6)	1.3 (1.1–1.6)	1.1 (0.9–1.4)
Quintiles of 25(OH) D				
>85–≥250	188/254	1.0 (–)	1.0 (–)	1.0 (–)
>68–≥85	166/254	0.9 (0.7–1.2)	0.9 (0.7–1.2)	0.9 (0.6–1.1)
>56–≥68	201/239	1.2 (0.9–1.6)	1.2 (0.9–1.6)	1.1 (0.8–1.4)
≥42–≥56	231/247	1.3 (1.0–1.7)	1.3 (1.0–1.7)	1.1 (0.8–1.5)
<42	227/300	1.6 (1.2–2.2)	1.6 (1.2–2.1)	1.3 (1.0–1.8)
P for trend		<0.0001	0.0002	0.03

[a]Number of cases and controls
[b]Adjusted for age, gender, residential area, and sampling month.
[c]Adjusted for age, gender, residential area, sampling month, body mass index, and smoking.
[d]Adjusted for age, gender, residential area, sampling month, body mass index, smoking, and sun exposure habits.

0.29–0.38) and r = 0.23 for men (95% CI 0.15–0.30). Compared with subjects with 25-hydroxy-vitamin D levels 50 nM/l or higher, the OR was 1.4 (95% CI 1.2–1.7) for subjects with levels less than 50 nM/l and the corresponding OR when using cutoff level 75 nM/l was 1.3 (1.1–1.6) (Table 4). Adjustment for a series of confounding factors did not affect the strength of the association apart from adjustment for UVR exposure habits which caused a decrease of the estimated OR (Table 4).

*Analysis of interaction between HLA-DRB1*15 and UVR and vitamin D level, respectively, with regard to MS status*

There was no interaction between HLA-DRB1*15 and UVR exposure regarding risk of developing MS nor between HLA-DRB1*15 and 25-hydroxy-vitamin D deficiency and MS at study inclusion (Tables 5 and 6).

Table 5 Adjusted odds ratio (OR) with 95% confidence interval (95% CI) of developing MS for subjects exposed to different combinations of sun exposure habits and HLA-DRB1*15 alleles. Attributable proportion owing to interaction (AP)

N = 1930 (890/1040) UVR Exposure	DRB1*15	ca/co[a]	OR[b]	OR[c]
High	No	161/390	1.0 (–)	1.0 (–)
Low	No	211/353	1.5 (1.2–1.9)	1.5 (1.1–2.0)
High	Yes	243/144	4.1 (3.1–5.4)	4.1 (3.1–5.4)
Low	Yes	275/153	4.6 (3.5–6.0)	4.6 (3.5–6.1)
AP	0.01 (−0.3–0.3)			

UVR exposure categories: high = UVR index > 6 (reference category) and low = UVR index ≤ 6.
[a]Number of cases and controls.
[b]Adjusted for age, gender, residential area.
[c]Adjusted for age, gender, residential area, body mass index, and smoking.

Discussion

The findings in this large population-based case–control study of MS provide further support to the notion of an association between UVR exposure/vitamin D status and MS risk. Adjusting for 25-hydroxy-vitamin D regarded as a mediator of the protective effect of UVR only marginally changed the estimated association between UVR and MS. Our results are thus consistent with the hypothesis that UVR exposure contributes to decreasing the risk of MS independently of its effects on vitamin D levels. In addition, there were no signs of interaction between UVR exposure and HLA-DRB1*15, or between 25-hydroxy-vitamin D and HLA-DRB1*15 with regard to occurrence of MS in this adult population.

Table 6 Adjusted odds ratio (OR) with 95% confidence interval (95% CI) of developing MS for subjects exposed to different combinations of vitamin D levels and HLA-DRB1*15 alleles. Attributable proportion due to interaction (AP)

N = 1930 (890/1040) Vit D < 50	DRB1*15	ca/co[a]	OR[b]	OR[c]
No	No	233/547	1.0 (–)	1.0 (–)
Yes	No	139/196	1.7 (1.3–2.2)	1.6 (1.2–2.1)
No	Yes	342/216	3.7 (3.0–4.7)	3.8 (3.0–6.5)
Yes	Yes	176/81	5.2 (3.8–7.1)	5.1 (3.7–7.1)
AP	−0.1 (−0.1–0.4)			

[a]Number of cases and controls.
[b]Adjusted for age, gender, residential area, and sampling month.
[c]Adjusted for age, gender, residential area, sampling month, body mass index, and smoking.

With regard to the potential biases in our study, there is a potential selection bias (response proportion for cases 93% and for controls 73%). However, we find it unlikely that the probability to participate would be related to UVR exposure for several reasons. First, the possible association between UVR exposure/vitamin D and MS was not publicly known when the subjects in this report were recruited. Secondly, there was no confounding from socioeconomic status (likely to be associated with different sun exposure habits).

Access to medical care is available at low cost in Sweden and almost all cases of MS are referred to public neurological units. We consider it unlikely that the unidentified cases that may exist would cause a substantial bias in our calculations as the main reason for not being invited to participate in our study is likely to be of administrative nature.

The questionnaire asked for information regarding UVR exposure habits during the previous 5 years. The rationale behind this wording of questions was to minimize recall error. However, heat sensitivity is a common problem in MS and even if most cases were recruited close to diagnosis the exposure information partly corresponded to time with disease. Recently, an explorative survey on heat sensitivity amongst 256 prevalent MS patients with a mean disease duration of 13 years was published [21] where 58% of MS patients reported this symptom. The results we present herein could thus partly be explained by reverse causation, as people with MS may tend to avoid UVR exposure owing to heat-related fatigue or restricted mobility. In the survey of Flensner *et al*., the proportion of people with heat sensitivity was larger amongst those with higher EDSS than amongst those with normal neurological condition (but numbers were small). This may indicate that the phenomenon of heat sensitivity becomes more common with longer duration of disease (and greater handicap) and consequently would be less in recently diagnosed cases as in our study with in general low EDSS values indicating low handicap. An Australian survey of self-reported factors influencing health amongst MS patients suggested that solar heat, and not solar light, was a negative factor [22]. This might indicate that change of sun exposure habits occurs to a lesser degree amongst MS patients in Sweden because of the fairly moderate summer temperatures in this country. In our study, when the analyses were restricted to those that had experienced the first symptoms of the disease within 2 years prior to inclusion (and who were therefore less likely to report exposure biased by MS-related behavior change and less likely to have a great handicap), the results remained mainly unchanged. Furthermore, according to the results in the study by Lucas *et al*. [13], recent sun exposure (during the last 3 years) and not only childhood exposure was associated with decreased risk for a first demyelinating event, in agreement with our own study results.

In our study we also had the opportunity to consider a number of potential confounding factors, such as age, gender, residential area, smoking, body mass index, socioeconomic status, sampling month, fatty fish consumption, and vitamin D supplementation. We further addressed if carriage of the strongest MS risk gene, HLA-DRB1*15, had any influence on the studied associations, and none of the above mentioned factors influenced the results. In summary, taking various potential sources of bias into consideration, we believe our findings add to the notion of an MS-protective effect of exposure to sunlight. With regard to the temporality of the sun exposure, the observed association could either be owing to recent sun exposure (as asked) or alternatively be owing to exposure in childhood, provided sun exposure habits are relatively stable during the life course.

Vitamin D can be regarded as a mediator between UVR exposure and MS risk. However, the estimated association between UVR exposure and MS risk was only marginally influenced when we adjusted for vitamin D status. As vitamin D was measured after disease onset and it is known that levels decline after MS onset [23,24], it is possible that the measured levels do not reflect the circumstances during the etiologically relevant time-period. A consequence of this potential reversed causality would be an overestimation of the association between low vitamin D levels and MS.

Declining vitamin D levels after disease onset may also introduce bias owing to misclassification of this mediator in the analysis of the association between UVR exposure and MS risk. To shed light on this, we simulated different scenarios. For the association between low UVR exposure and increased MS risk to be entirely caused by vitamin D deficiency, 450 cases (68%) who in our analyses were determined to have adequate vitamin D levels would have had vitamin D deficiency before the disease onset. This seems highly unlikely as vitamin D levels rather decrease than increase after MS onset.

Exposure to UVR leads to the release of a number of secondary mediators capable of suppressing cell-mediated immunity. However, as UVR also modulates immune responses by stimulating endogenous production of vitamin D, it is not obvious whether the low MS risk associated with high UVR exposure, and *vice versa,* observed in earlier studies is attributable specifically to UVR, vitamin D, or to both.

Both UVR and the active form of vitamin D suppress disease in EAE models (experimental autoimmune encephalitis) [25,26]. The levels of $1,25(OH)_2D_3$ that are

required to suppress EAE are above those that can be physiologically produced by exposure to UVR and complete disease suppression by $1,25(OH)_2D_3$ only occurs using doses that cause severe hypercalcemia [27]. However, it was recently demonstrated that continuous treatment with UVB suppresses EAE without altering serum calcium levels [25], which may indicate that UVR suppresses disease independent of vitamin D production.

There are a number of pathways whereby UVR may affect immune functions that are independent of vitamin D production [28]. UVB appears to up-regulate the secretion of TNF-α, IL-10, and regulatory T cells [29], and UVA radiation has a complex dose-related immunomodulating effect where the underlying mechanism is not fully investigated [30].

Previous data [13,25,29] and the findings in our study are consistent with the hypothesis that the association between UVR exposure and risk of developing MS cannot be fully explained by vitamin D-mediated mechanisms.

In conclusion, in this population-based case–control study we observed an association between UVR exposure and risk of MS. This association seemed only to be mediated by vitamin D to a limited extent. Vitamin D supplementation alone as a preventive approach for MS may thus not have the capacity to completely compensate for insufficient UVR exposure. There were no signs of interaction between vitamin D status and the HLA-DRB1*15 allele which has previously been suggested.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Exposure to ultraviolet radiation/sunlight: information gathered through questionnaire.

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