Past exposure to sun, skin phenotype, and risk of multiple sclerosis: case-control study

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Abstract

Objective To examine whether past high sun exposure is associated with a reduced risk of multiple sclerosis.
Design Population based case-control study.
Setting Tasmania, latitudes 41-3°S.
Participants 136 cases with multiple sclerosis and 272 controls randomly drawn from the community and matched on sex and year of birth.
Main outcome measure Multiple sclerosis defined by both clinical and magnetic resonance imaging criteria.
Results Higher sun exposure when aged 6-15 years (average 2-3 hours or more a day in summer during weekends and holidays) was associated with a decreased risk of multiple sclerosis (adjusted odds ratio 0.31, 95% confidence interval 0.16 to 0.59). Higher exposure in winter seemed more important than higher exposure in summer. Greater actinic damage was also independently associated with a decreased risk of multiple sclerosis (0.32, 0.11 to 0.88 for grades 4-6 disease). A dose-response relation was observed between multiple sclerosis and decreasing sun exposure when aged 6-15 years and with actinic damage.
Conclusion Higher sun exposure during childhood and early adolescence is associated with a reduced risk of multiple sclerosis. Insufficient ultraviolet radiation may therefore influence the development of multiple sclerosis.

Introduction

Multiple sclerosis is a chronic demyelinating disease of the central nervous system. Contributing factors include a defect in immunological self tolerance resulting in a T helper cell type 1 mediated attack on myelin proteins.[1] One of the most striking epidemiological features of multiple sclerosis is a gradient of increasing prevalence with latitude.[2] An inverse association between solar radiation and prevalence of multiple sclerosis was first observed in 1960.[3] Recent photoimmunological work has rekindled interest in this observation because ultraviolet radiation can attenuate T helper cell type 1 mediated immune responses through several mechanisms.[4] Also, administration of ultraviolet radiation or 1,25-dihydroxycholecalciferol, the active form of vitamin D_3, which is produced under the influence of ultraviolet radiation,[5] has shown protective effects against the induction or progression of experimental allergic encephalomyelitis.[6 7]

In humans, ultraviolet radiation or vitamin D may also protect against multiple sclerosis. A strong ecological association between regional levels of ultraviolet radiation and prevalence of multiple sclerosis is evident in Australia ($r = -0.91$).[8] In a death certificate based case-control study, high residential or occupational exposure to sunlight was negatively associated with mortality from multiple sclerosis.[9] Exposure to ultraviolet radiation early in life may alter immunological development during a critical developmental phase. However, the finding of a strong latitudinal gradient of prevalence of multiple sclerosis in Australia even among immigrants from the United Kingdom and Ireland (70% who migrated after age 15) suggests that cumulative exposure to ultraviolet radiation or exposure later in life might also be important.[10]

Tasmania, the island state of Australia, is located at latitudes 41-3°S and has a high prevalence of multiple sclerosis at 75.6 per 100 000 population.[11] We conducted a case-control study in Tasmania to examine whether high past sun exposure was associated with a reduced risk of multiple sclerosis.

Participants and methods

Our source population consisted of people aged under 60 years who were residents of Tasmania and who had at least one grandparent who was born in Tasmania. Written consent was obtained from all participants.

Cases

Cases were members of the source population who had a diagnosis of multiple sclerosis. To recruit participants, information evenings were held for members of the local multiple sclerosis societies, and information packs were sent out to neurologists, general physicians, general practitioners, and pharmacists, who were encouraged to publicise the posters and to inform people with multiple sclerosis about the programme. Neurologists in the south of the state sent letters to eligible patients inviting them to participate and verbally encouraged newly diagnosed patients to participate. In total, 169 people responded. We included 136 cases in the final sample: 30 people (18%) did not meet the study criteria for diagnosis of multiple sclerosis, one

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person refused a neurological assessment, one person died before interview, and one person deteriorated and was unable to take part. Respondents were interviewed and examined by one of the participating neurologists. Magnetic resonance images subsequently confirmed the diagnosis for 134 cases (99%), and for the other two cases we obtained the reports of previous scans. Eligible cases had cerebral abnormalities on magnetic resonance imaging consistent with multiple sclerosis, as defined by Paty et al, and definite multiple sclerosis using the criteria of Poser et al.[12 13] Cases with a classification of primary progressive multiple sclerosis had to exhibit progressive neurological disability for at least one year, had to have no other better explanation for the clinical features, and had to have relevant spinal cord abnormalities and changes on cerebral magnetic resonance imaging consistent with demyelination. The cases were also included in a genetic study, for which a haplotype analysis was conducted on the human leucocyte antigen region.[14]

Controls

Controls were selected from the source population using the roll of registered electors, a comprehensive listing of the population maintained by the state electoral office of Tasmania. We randomly selected two controls for each case and matched them to the index case on sex and year of birth. Overall, 272 of 359 eligible controls participated (response rate 76%). In an unmatched design, we required at least 100 cases and 200 controls to detect an odds ratio of 2.0 or 0.5 for the effect of a dichotomous exposure where 40% of the controls were exposed.

Measurements

Time in sun

Two research assistants conducted all interviews and measurements between March 1999 and June 2001. Participants were asked about the amount of time they would normally have spent in the sun during weekends and holidays in winter and summer ("time in the sun" question), using questions validated for teenagers in this climate.[15] Answers to the time in the sun question for winter predict levels of serum 25-hydroxycholecalciferol in 8 year old Tasmanian children.[16] The standardised questionnaire included questions on measures to protect against the sun, use of vitamin D supplements at ages 10-15 years, medical history (including infections and immunisations), and other factors suggested by past work to be associated with multiple sclerosis. For the timing of exposures we obtained either the exact age or the five year age range in which the exposure occurred.[17] Before interview, participants were asked to fill in a lifetime calendar for each year of their life. During the interview, participants answered the time in the sun question for summer only for each year of their life, and from the information in the calendar we identified blocks of years where time in the sun was constant or not. The κ statistic (95% confidence interval) between the questionnaire based measure and the calendar measure (using the mean value) for ages 6-10, 11-15, and 16-20 years was 0.54 (0.47 to 0.61), 0.51 (0.44 to 0.58), and 0.44 (0.37 to 0.50), respectively. No difference in agreement was found between cases and controls.

Actinic damage

Silicone casts of the skin surface of the hand, measuring actinic damage, were used as an objective marker of cumulative lifetime sun exposure. This measure has been associated with living in a location with high ultraviolet radiation, lifetime exposure to sun, outdoor occupations and leisure activities, solar keratosis, and basal and squamous cell cancer.[18–21] Silicone liquid was mixed with catalyst and applied to the dorsum of the participant's left hand. After seven minutes, the cast was removed. The lines on the underside of the cast were examined under a low power dissecting microscope and graded by one observer from 1 (undamaged skin) to 6 (severe deterioration).[22] By age 14 up to 70% of Australians show detectable skin damage caused by the sun.[18] In Nambour (latitude 27°S), Queensland, 72% of men and 47% of women had moderate to severe deterioration of the skin by their 30s.[20] Age and sex have also been shown to be strong predictors of the amount of actinic damage, and we controlled for these two factors through our matched design.[18 20 21]

Skin phenotype

Skin phenotype was assessed with a spectrophotometer at the upper inner arm and buttock-body sites usually not exposed to sunlight. Cutaneous melanin density was estimated from the skin reflectance of light centred at 400 nm and 420 nm.[23] Skin colour at the upper inner arm was also assessed visually by the research assistants. The standardised questionnaire included a question on lifetime sunburns where the pain lasted more than two days, a measure that reflects both skin phenotype and sun exposure behaviour. The research assistant also recorded the number of naevi greater than 5 mm on the left arm, hair and eye colour, height, and weight.

Data analysis

Pearson correlations were calculated as measures of linear association. Odds ratios and 95% confidence intervals were estimated by conditional logistic regression (STATA 7.0). Tests for trend of categorical variables were undertaken by replacing the binary predictors with a single predictor, taking category rank scores. The scaled variables for melanin and naevi were dichotomised at previously used cut-off points.[24] Analysis of actinic damage was restricted to 323 high quality casts. The recording of year by year exposure by the lifetime calendar allowed an estimation of average exposure at any age. We did this for ages 6-10, 11-15, and 16-20 and for ages 6-10, 6-15, 6-20, and so on. To aggregate and then average annual exposure, the categories were assigned rank scores. For each age span in the figure the average sun exposure was dichotomised at 2-3 hours a day. For table 4 and the figure, the sample was limited to cases and their matched controls who had not experienced any symptoms of multiple sclerosis before or during the age span. To take account of duration of disease, we stratified by time elapsed since the first symptom of multiple sclerosis: 0-5, 6-10, 11-15, 16-20, and >20 years. A test of interaction was conducted using the coefficient and standard error of a product term of exposure to sun and duration of disease. In analysis, controls were given the years of duration or the age at onset (age at first symptom) of their case pair. Proportional hazard

regression was used among cases to assess the effect of sun exposure and skin phenotype on the age at onset of disease.

Results

Overall, 68% (n=92) of the cases were female, and most of the cases and controls were born in Tasmania and living there at age 10 (table 1). Sixty five per cent of the cases had relapsing remitting multiple sclerosis (table 2) Although only of borderline significance, the odds of having light skin colour (<2% melanin) was 1.59 times higher for cases than for controls. Skin colour assessed by the research assistant showed a significant relation with multiple sclerosis, but reported tendency to burn or tanning ability did not (table 2).

Childhood sun exposure

People with multiple sclerosis were less likely to report severe sunburn episodes during their lifetime, despite their fairer skin (table 3). We observed a strong inverse association between sun exposure in childhood and adolescence and multiple sclerosis (table 4). For example, cases were less likely than controls to report higher levels (>1 hour a day) of exposure during winter at age 6-10 years (odds ratio 0.47, 95% confidence interval 0.26 to 0.84). This inverse association was observed for exposure both in winter and in summer (see table 4). Compared to bivariate analysis, including both summer and winter questionnaire based measures for exposure as dichotomised terms in the model left the estimated effect of exposure in winter almost unchanged (adjusted odds ratio 0.52, 0.28 to 0.95 at age 6-10 years), but greatly reduced the effect of exposure in summer (0.63, 0.30 to 1.35 at age 6-10 years). This was found irrespective of the age at exposure.

We then estimated the effect of average sun exposure at age 6-15 years on multiple sclerosis from the year by year calendar (table 5) taking into account other factors that related to multiple sclerosis (low melanin density at the upper inner arm, smoking, history of glandular fever, no immunisation for rubella in early life, high education, exposure to fibreglass and resin before age 17, exposure to smoke fumes before age 17, and exposure to smoke fumes between age 17 and the age of diagnosis). Intake of vitamin D supplements at age 10-15 years was not associated with multiple sclerosis. After controlling for smoking and melanin density at the upper inner arm, the adjusted odds ratio was 0.31 (0.16 to 0.59) for high sun exposure at age 6-15 years. Additional adjustment for the other factors made no important difference to the results (see table 5).

Table 1 Personal characteristics of cases and controls

Characteristics	Cases (n=136)	Controls (n=272)
No (%) female	92 (68)	184 (68)
No (%) male	44 (32)	88 (32)
Female to male ratio	2.1:1	2.1:1
Mean (SD) age (years)	43.5 (9.3)	43.6 (9.2)
No (%) born in Tasmania	131 (96)	258 (95)*
No (%) living in Tasmania at age 10	131 (96)	265 (97)
Mean (SD) height (cm)	166.9 (9.0)	166.1 (8.9)
Mean (SD) weight (kg)	72.9 (14.4)	76.2 (16.1)

*Unknown for one participant.

Table 2 Disease specific characteristics of cases. Values are numbers (percentages) of cases unless stated otherwise

Characteristics	Cases (n=136)
Mean (SD) age at diagnosis	34.6 (9.1)
Mean (SD) age at first symptoms	31.0 (9.1)
Mean (SD) duration of multiple sclerosis since diagnosis (years)	9.4 (7.5)
Mean (SD) duration of multiple sclerosis since first symptoms (years)	12.1 (8.0)
Mean (SD) EDSS score	3.5 (2.2)
Frequency of DRB1*1501—DQB1*0602 haplotype	66 (54)
Type of multiple sclerosis:	
Relapsing remitting	89 (65)
Secondary progressive	35 (27)
Primary progressive	10 (8)

Frequency of DRB1*1501-DQB1*0602 not available for 13 cases. Type of multiple sclerosis not available for two cases.

Table 3 Odds ratios for multiple sclerosis and measures of skin phenotype, history of sunburn, and skin naevi

Factor	No (%) of cases exposed	No (%) of controls exposed	Unadjusted odds ratio (95% CI)
Melanin density at upper inner arm (<2% *v* ≥2%)	69/127 (54)	104/236 (44)	1.59 (0.99 to 2.55)
Skin colour* (fair or medium to fair *v* olive to medium or olive)	87/132 (66)	142/264 (54)	1.62 (1.05 to 2.51)
Tendency to burn (burn within 1 h *v* burn after >1 h)	81/136 (60)	151/272 (56)	1.19 (0.77 to 1.83)
Ability to tan (light or no tan *v* dark or medium tan)	48/136 (35)	91/272 (34)	1.11 (0.68 to 1.80)
Lifetime sunburn (any *v* none)	104/135 (77)	232/272 (85)	0.55 (0.32 to 0.96)
No of naevi >5 mm on left arm (≥3 *v* <3)	25/129 (19)	51/263 (19)	0.94 (0.54 to 1.63)

*At upper inner arm, assessed by research assistant.

Lifetime sun exposure

The figure shows the odds ratios for higher sun exposure by age using the calendar data. The odds ratio estimates of the apparent protective effect of higher exposure were greatest for age spans before 15 (6-10 years: 0.43, 0.21 to 0.88; 6-15 years: 0.40, 0.20 to 0.80). Inclusion of later years into the cumulative lifespan measure diluted the effect. We repeated the analysis on a subgroup of participants who had indicated on a checklist before interview that they did not believe that climatic factors such as sun exposure were an important cause of multiple sclerosis. For this group, the protective effect of past exposure was even stronger than for the total group (figure).

Greater levels of actinic damage were also associated with a reduced risk of multiple sclerosis (grades 4-6 *v* grade 3: 0.32, 0.11 to 0.88) with evidence of a dose-response relation (table 6). We adjusted for melanin density at the upper inner arm because it was associated with less actinic damage. Doing so increased the magnitude of the odds ratios. We also adjusted for total sun exposure after onset of multiple sclerosis to remove the contribution of this factor to the observed associations. Duration of disease was not strongly associated with past sun exposure (for example, correlation with exposure to age 15, r= −0.08) or actinic damage after adjustment for age (r= −0.02). Moreover, the relative risk estimates for neither exposure to age 15 nor actinic damage differed by duration of disease, and the protective effects were also observed among cases of recent (≤5 years) onset (adjusted odds ratio 0.58 for 2-3 hours or more of exposure a day before age 15; 0.50 for grades 4-6 actinic damage), although the estimates were more imprecise. We then assessed whether higher exposure before age 15 and greater actinic

Table 4 Odds ratios for multiple sclerosis and reported measures of sun exposure in childhood and adolescence

Sun exposure	Age 6-10			Age 11-15			Age 16-20		
	No (%) of cases	No (%) of controls	Unadjusted odds ratio (95% CI)	No (%) of cases	No (%) of controls	Unadjusted odds ratio (95% CI)	No (%) of cases	No (%) of controls	Unadjusted odds ratio (95% CI)
In winter, by questionnaire									
Time in sun (h/day):									
<1	26 (19.1)	27 (10.0)	1	22 (16.3)	28 (10.3)	1	29 (21.3)	37 (13.6)	1
1-2	29 (21.3)	61 (22.7)	0.50 (0.24 to 1.00)	29 (21.5)	69 (25.4)	0.55 (0.27 to 1.10)	37 (27.2)	84 (30.9)	0.59 (0.32 to 1.07)
2-3	26 (19.1)	64 (23.8)	0.43 (0.21 to 0.87)	30 (22.2)	65 (23.9)	0.61 (0.30 to 1.22)	26 (19.1)	53 (19.5)	0.63 (0.32 to 1.24)
3-4	14 (10.3)	34 (12.6)	0.44 (0.19 to 1.01)	22 (16.3)	37 (13.6)	0.76 (0.36 to 1.61)	17 (12.5)	39 (14.3)	0.56 (0.26 to 1.22)
>4	41 (30.2)	83 (30.9)	0.50 (0.26 to 0.98)	32 (23.7)	73 (26.8)	0.57 (0.28 to 1.14)	27 (19.9)	59 (21.7)	0.60 (0.30 to 1.17)
Linear trend			P=0.18			P=0.45			P=0.22
Dichotomised (≥1-2 *v* <1)			0.47 (0.26 to 0.84)			0.60 (0.33 to 1.09)			0.59 (0.35 to 1.01)
In summer, by questionnaire									
Time in sun (h/day):									
<1	6 (4.4)	8 (3.0)	1	3 (2.2)	2 (0.7)	1	11 (8.1)	13 (4.8)	1
1-2	15 (11.0)	15 (5.6)		13 (9.6)	26 (9.6)		19 (14.0)	37 (13.6)	
2-3	20 (14.7)	39 (14.4)	0.59 (0.27 to 1.28)	20 (14.7)	37 (13.6)	0.94 (0.40 to 2.17)	22 (16.0)	64 (23.6)	0.55 (0.28 to 1.10)
3-4	17 (12.5)	48 (17.8)	0.39 (0.17 to 0.88)	27 (19.9)	61 (22.4)	0.77 (0.35 to 1.68)	26 (19.1)	61 (22.5)	0.71 (0.38 to 1.35)
>4	78 (57.4)	160 (59.3)	0.55 (0.30 to 1.03)	73 (53.7)	146 (53.7)	0.88 (0.44 to 1.74)	58 (42.7)	96 (35.4)	1.00 (0.57 to 1.78)
Linear trend			P=0.15			P=0.72			P=0.56
Dichotomised (≥2-3 *v* ≤1-2)			0.50 (0.24 to 1.02)			0.86 (0.44 to 1.66)			0.79 (0.47 to 1.33)
In summer, by calendar									
Time in sun (h/day):									
<1	2 (1.5)	2 (0.7)	1	4 (2.9)	2 (0.7)	1	6 (4.4)	8 (2.9)	1
1-2	17 (12.5)	14 (5.2)		11 (8.1)	12 (4.4)		20 (14.7)	47 (17.3)	
2-3	18 (13.2)	23 (8.5)	0.63 (0.23 to 1.73)	27 (19.9)	40 (14.7)	0.65 (0.26 to 1.61)	27 (19.9)	58 (21.3)	0.99 (0.50 to 1.95)
3-4	19 (14.0)	44 (16.3)	0.35 (0.14 to 0.88)	22 (16.2)	53 (19.5)	0.39 (0.16 to 0.95)	30 (22.1)	55 (20.2)	1.16 (0.59 to 2.26)
>4	80 (58.8)	187 (69.3)	0.34 (0.16 to 0.74)	72 (52.9)	165 (60.7)	0.40 (0.18 to 0.89)	53 (39.0)	104 (38.2)	1.09 (0.60 to 1.97)
Linear trend			P<0.01			P=0.01			P=0.70
Dichotomised (≥2-3 *v* ≤1-2)			0.36 (0.17 to 0.76)			0.44 (0.20 to 0.94)			1.07 (0.63 to 1.85)

damage were each important in predicting the risk of multiple sclerosis. Compared to bivariate analysis, including both in the same model as linear terms left the effect of each factor almost unchanged.

Table 5 Odds ratios for multiple sclerosis and average time in sun in summer during weekends and holidays at age 6-15 years using calendar measure

Sun exposure	No (%) of cases	No (%) of controls	Unadjusted odds ratio (95% CI)	Adjusted odds ratio* (95% CI)
Time in sun (h/day):				
<1	4 (3.0)	4 (1.5)		
1-2	16 (11.9)	14 (5.2)	1	1
2-3	22 (16.3)	39 (14.4)	0.51 (0.22 to 1.17)	0.42 (0.16 to 1.09)
3-4	30 (22.0)	65 (24.1)	0.40 (0.18 to 0.89)	0.32 (0.13 to 0.80)
>4	63 (46.7)	148 (54.8)	0.37 (0.18 to 0.76)	0.26 (0.11 to 0.60)
Linear trend			P=0.01	P<0.01
Dichotomised (≥2-3 *v* ≤1-2)			0.39 (0.22 to 0.70)	0.31 (0.16 to 0.59)

*Adjusted for melanin density at upper inner arm and whether ever smoked before age of diagnosis.

Table 6 Odds ratios for multiple sclerosis and levels of actinic damage on dorsum of hand

Actinic damage	No (%) of cases	No (%) of controls	Unadjusted odds ratio (95% CI)	Adjusted odds ratio* (95% CI)
Grade 3	18 (17.1)	21 (9.6)	1	1
Grade 4	34 (32.4)	59 (27.1)	0.47 (0.19 to 1.13)	0.32 (0.10 to 0.98)
Grade 5	41 (39.0)	78 (35.8)	0.37 (0.15 to 0.90)	0.33 (0.12 to 0.96)
Grade 6	12 (11.4)	60 (27.5)	0.14 (0.05 to 0.42)	0.17 (0.05 to 0.60)
Linear trend			P<0.01	P<0.01
Dichotomised (grades 4-6 *v* grade 3)			0.39 (0.17 to 0.90)	0.32 (0.11 to 0.88)

*Adjusted for melanin density at upper inner arm, whether ever smoked before age of diagnosis and amount of sun exposure after onset of disease.

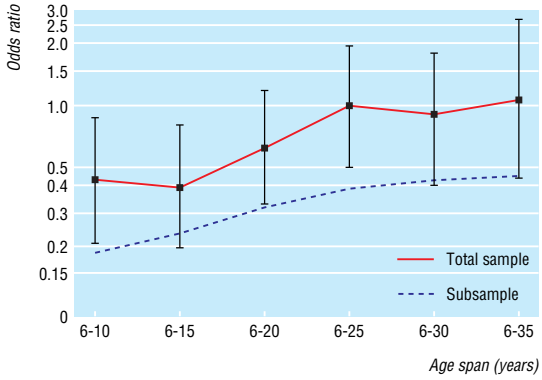
Age at onset

To assess the effect of sun exposure at a specific time immediately before onset of disease, we created variables of the participants' exposure at particular years before the onset of multiple sclerosis by using the calendar. The odds ratios (95% confidence intervals) for 2-3 hours or more exposure to the sun in summer during weekends and holidays were 0.95 (0.55 to 1.64), 0.92 (0.55 to 1.54), and 1.06 (0.65 to 1.74) for 10 years, five years, and one year before the onset of multiple sclerosis, respectively. Thus, in contrast to the inverse association between sun exposure in early life or actinic damage and multiple sclerosis, there was no evidence that exposure at these particular years in the decade before the onset of disease was important.

Finally, we examined age at onset of multiple sclerosis among cases. No evidence was found that increasing exposure from age 6-15 years or lifetime actinic damage were associated with earlier onset of disease. However, skin phenotype did relate to age at onset. Low melanin density at the buttock and fair skin were associated with earlier onset of disease.

Discussion

Higher sun exposure during childhood and early adolescence and greater actinic damage are associated with a decreased risk of multiple sclerosis. Both exhibited a dose-response relation with multiple sclerosis. The inverse association between past exposure to ultraviolet radiation and multiple sclerosis was consistently found regardless of whether exposure was measured by questionnaire, calendar, or actinic damage. These findings are consistent with other work



Association between sun exposure and multiple sclerosis for different age spans. Odds ratios and 95% confidence intervals for higher (average 2-3 hours or more a day) sun exposure in summer during weekends and holidays. Subgroup is participants who did not believe that sun exposure was an important cause of multiple sclerosis

indicating that ultraviolet radiation may be beneficial against multiple sclerosis. A strong negative association was also found in a death certificate based case-control study among outdoor workers, where the adjusted odds ratios (95% confidence intervals) for low, medium, and high regional sunlight for multiple sclerosis were 0.89 (0.64 to 1.22), 0.52 (0.38 to 0.71), and 0.24 (0.15 to 0.38) compared with indoor workers with low ambient sunlight.[9] Both ultraviolet radiation and vitamin D_3 have been found to suppress T helper cell type 1 immune responses through cytokine signalling.[6 25 26] Clinical symptoms of experimental allergic encephalomyelitis—an animal model of multiple sclerosis—can be prevented or delayed by providing ultraviolet radiation or 1,25-dihydroxycholecalciferol (the active form of vitamin D_3) at the time of immunisation.[6 7 27] A strong inverse correlation ($r = -0.79$) between concentrations of serum 25-hydroxycholecalciferol in a population and mean lesional activity among people with multiple sclerosis has also been reported.[28] Vitamin D deficiency has been noted among people with multiple sclerosis,[29] and a small vitamin D and mineral intervention study in patients with multiple sclerosis showed that less than half the number of exacerbations occurred after one or two years compared with the expected number based on patient case histories.[30] Ultraviolet radiation or vitamin D may also relate to other T helper cell type 1 related autoimmune diseases such as type 1 diabetes. In a Finnish birth cohort, regular supplementation with vitamin D in the first year of life was associated with a reduced risk of subsequent disease (rate ratio 0.12, 0.03 to 0.51).[31]

The case sample seemed similar to other populations with multiple sclerosis of north European ancestry for disease related features such as type of disease, age at diagnosis, and sex ratio.[11 32 33] Also, the phenotypic frequency of the human leucocyte antigen haplotype DRB1*1501-DQB1*0602 was similar.[34 35] Tasmania provides a good setting for this type of study. Unlike northern Australia, the region has relatively low levels of ambient ultraviolet radiation in winter, and exposure to sun in winter is a major determinant of serum 25-hydroxycholecalciferol concentration in humans living in this location.[16] Participation rates were high, reducing non-response bias, but it is possible that some selection bias may have occurred. The use of measures of past time in the sun could have led to substantial misclassification of the measurement of past exposure if participants had resided in locations with varying levels of ambient ultraviolet radiation, but a high proportion of participants had lived in Tasmania for most of their life and their estimated exposure to ultraviolet radiation would not be confounded by past residence. A possible weakness of our study was that prevalent, not incident, cases were studied. It is unlikely that recall bias fully explains the observed strong reported associations. The inverse association between estimated average sun exposure in early life and multiple sclerosis did not seem to be caused by the participants' knowledge of the hypothesis. In fact, the odds ratios for exposure were more protective for the participants who had indicated that they did not believe climatic factors such as sun exposure were an important cause of multiple sclerosis. Also, if the results were caused by recall bias, we would expect this to affect the results of exposure after age 20 or exposure immediately before the age at onset in a similar manner, but this was not the case. In addition, actinic damage, an objective marker of past exposure, also showed an inverse association with multiple sclerosis, and this objective marker is free of recall bias. Disease related changes in behaviour also did not explain the findings because (*a*) the protective effect of greater actinic damage or exposure to sun in childhood and early adolescence was evident even among the group with recent onset of multiple sclerosis, (*b*) the strong inverse association between actinic damage and multiple sclerosis persisted after adjustment for differences in sun exposure that occurred after onset of multiple sclerosis, and (*c*) the association did not differ by duration of disease.

The levels of skin pigmentation in indigenous populations have evolved to optimise the amount of ultraviolet radiation absorbed by the skin for the balance of biological benefits and risks.[36] It would be expected that if a host's response to ultraviolet radiation were part of the causal pathway for multiple sclerosis, risk would vary by levels of skin pigmentation. Here, fair skin was associated with an increased risk of multiple sclerosis. Genotypes associated with fair skin may partially contribute to the higher rate of multiple sclerosis observed in Scottish and northern European populations.[37]

We found that higher sun exposure in winter was particularly important. In our region, the daily levels of ambient ultraviolet radiation are more than 10-fold lower in mid-winter than they are in mid-summer, compounded by less time spent outdoors.[38] This suggests that, in winter in particular, minimum threshold requirements for sufficient ultraviolet radiation and vitamin D may not have been met.

The apparent protective effect seemed to be greatest for sun exposure during childhood and early adolescence. However, we can only address the timing issue through self reported data, because actinic damage measures cumulative damage but cannot provide data on timing of sun exposure. The finding of no association between sun exposure in the decade before onset of multiple sclerosis may indicate that the timing

What is already known on this topic

Multiple sclerosis shows a gradient of increasing prevalence with latitude

This has been attributed to differences in regional levels of ultraviolet radiation

Ultraviolet radiation may have a protective role in T helper cell type 1 mediated autoimmune disease

What this study adds

Higher sun exposure during childhood and early adolescence and greater actinic damage are associated with a reduced risk of multiple sclerosis

These associations persisted after adjustment for fair skin and exposure after onset of disease

Insufficient ultraviolet radiation or vitamin D, or both, may influence the development of multiple sclerosis

of low exposure may relate more to age related immunological development than to onset of disease. In conclusion, higher sun exposure seems to be associated with a reduced risk of multiple sclerosis, which is consistent with insufficient ultraviolet radiation influencing the development of multiple sclerosis.

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Contributors: A-LP, TD, and RS designed the study. IvdM coordinated the study and TK, HB, and BVT were the neurologists responsible for the clinical diagnosis of the cases. IvdM conducted the statistical analysis in conjunction with A-LP, LB, and TD. The main contributors to the writing of the report were IvdM, A-LP, LB, and TD, but others provided important feedback at a later stage. All authors approved the final document.

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