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Outdoor activities and diet in childhood and adolescence relate to MS risk above the Arctic Circle

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Abstract *Background* A relationship between the latitude-related distribution of multiple sclerosis (MS) and exposure to sunlight has long been considered. Higher sun exposure during early life has been associated with decreased risk of MS. *Objective* Since Norway is an exception to the latitude gradient of MS prevalence, we tested here whether sunlight exposure or vitamin D-related dietary factors in childhood and adolescence are associated with the risk of MS. *Methods* Retrospective recall questionnaire data from 152 MS patients and 402 population controls born at and living at latitudes 66–71°N were analysed by means of conditional logistic regression analysis accounting for the matching variables age, sex, and place of birth. *Results* Increased outdoor activities during summer in early life were associated with a decreased risk of MS, most pronounced at ages 16–20 years (odds ratio (OR) 0.55, 95% CI 0.39–0.78, p = 0.001, adjusted for intake of fish and cod-liver oil). A protective effect of supplementation with cod-liver oil was suggested in the subgroup that reported low summer outdoor activities (OR 0.57, 95% CI 0.31–1.05, p = 0.072). Consumption of fish three or more times a week was also associated with reduced risk of MS (OR 0.55, 95% CI 0.33–0.93, p = 0.024). *Conclusions* Summer outdoor activities in childhood and adolescence are associated with a reduced risk of MS even north of the Arctic Circle. Supplemental cod-liver oil may be protective when sun exposure is less, suggesting that both climate and diet may interact to influence MS risk at a population level.

Key words MS · epidemiology · vitamin D · UV-radiation · Sami

Introduction

Multiple sclerosis (MS) risk is determined by an interaction between genetic and environmental factors. Studies of familial aggregation show that environmental factors determining the individual's MS risk act at a population level rather than in the familial microenvironment [8, 9]. The marked geographical gradient with prevalence formerly increasing with distance from the equator [2, 17, 32] has been attributed to differences in regional levels of ambient UV(ultraviolet)-radiation [1, 14, 30]. This observation and the fact that UV-B radiation is essential in vitamin

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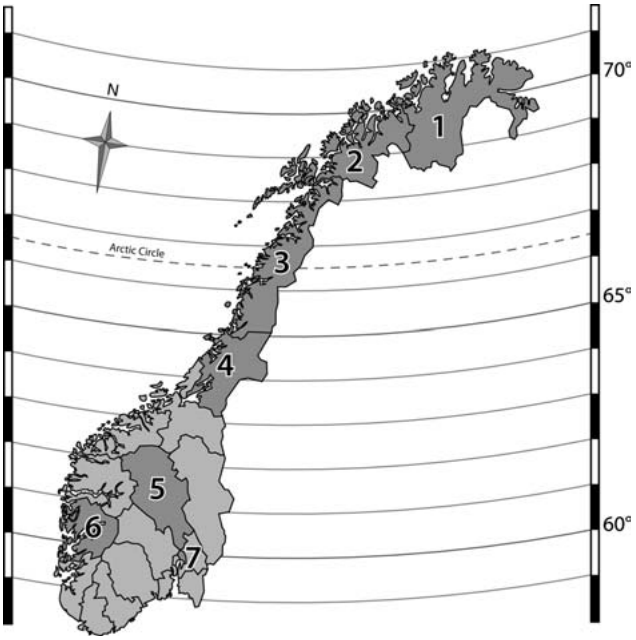

County	Cases/10^5 inhabitants	Date (January 1)
1 Finnmark[a]	>86	2003
2 Troms[a]	>104	2003
3 Nordland	106	2000
4 Nord-Trøndelag	164	2000
5 Oppland	190	2002
6 Hordaland	151	2003
7 Oslo[b]	154	2005

Fig. 1 MS prevalence in Norway by county [16, 24]

D production in the skin, have played an important role for the UV-radiation/vitamin D hypothesis for MS [18].

The association of exposure to solar UV-radiation or vitamin D intake with MS has been assessed in several epidemiologic studies [7, 29]. A case-control study in Tasmania at latitudes 41–43°S found a protective effect of higher sun exposure between age 6 and 15 years on the risk of MS [31]. It has also been suggested that the maternal parent of origin effect [10] and the unexplained excess of MS in those born in May in Scotland, Denmark, Sweden, and Canada might be related to maternal vitamin D deficiency [33]. In the experimental autoimmune encephalomyelitis (EAE) model of MS, treatment of mice with vitamin D hormone completely inhibited EAE induction and progression [6], and a recent pilot study suggested there may be some relapse rate reduction in MS patients supplemented with a vitamin D analogue [34].

Solar radiation may provide the essential amount of vitamin D through synthesis in the skin, and protect genetically susceptible individuals from developing MS at lower latitudes. Above the Arctic Circle, winter-sunlight is not sufficient for production of vitamin D for about four months [11], and in a colder climate less outdoor activities and more outdoor clothing even in summer will further decrease UV-radiation exposure. Norway spans latitudes 58–71°N, which is higher than all other areas from which MS prevalence data have been reported. Approximately 375,000 inhabitants live north of the Arctic Circle (66°33′N), including an estimated 30,000 Samis, an MS-resistant ethnic group [15]. The large increase of MS prevalence with increasing latitude that is well-documented in the Australian population [30] is not observed in Norway (Fig. 1).

Epidemiological research in the 1950s revealed that the incidence of MS in Norway was considerably lower in the coastal fishing areas than in the inland farming and dairy areas [28], and several studies have shown that diets high in meat and dairy products and low in fish were associated with increased prevalence of MS [21]. This finding may be due to a protective effect of vitamin D (from fatty fish and fish oil) or marine omega-3 polyunsaturated fatty acids [7, 27].

In this study we assessed exposure to sunlight and vitamin D-related dietary factors during the first two decades of life during which an individual's risk of MS probably is established [17]. A questionnaire was mailed to MS patients and matched population controls born at latitudes 66–71° N to collect data on outdoor activities, sun exposure, diet, and use of cod-liver oil supplement.

Methods

Participants

The Department of Neurology, University Hospital of North Norway manages more than 95% of MS patients in a population of 225,000 living in the two northernmost counties of Norway, Troms and

Table 1 Characteristics of patients and controls

Characteristics	Patients n = 152	Controls n = 402
Female, %	64	67
Year of birth		
median	1956	1954
range	1931–1980	1931–1980
Sami ancestry[a]		
one Sami-speaking grandparent, n (%)	3 (2)	11 (3)
four Sami-speaking grandparents, n (%)	0 (0)	12 (3)
Age at first symptoms, y, median (range)	30 (12–58)	
Age at diagnosis, y, median (range)	36 (18–58)	
Duration of MS since first symptoms[b], y, median (range)	14 (2–44)	

[a] Data not available for 1 patient and 4 controls. 12 incomplete responses, in most cases father unknown; [b] at the time of this study (2003)

Finnmark (Fig. 1). We identified persons with a diagnosis of MS according to the diagnostic criteria of Poser or McDonald [22, 26] who had been seen in the hospital during 2001 and 2002 from electronic hospital records. In March 2003, questionnaires were mailed to 233 patients born between 1931 and 1980. The questionnaire was returned by 194 (83%) MS-patients. All respondents who were born north of the Arctic Circle (n = 164) were matched for age, sex, and place of birth with population controls residing in Troms and Finnmark. In the drawing procedure from the National Population Register no controls were matched to eight of the patients due to a software error. Questionnaires were mailed to 624 controls in March 2004 and completed by 407 subjects (65%), providing at least one matched control for 152 of the cases. Five controls had to be excluded. One person had been diagnosed with MS. Control subjects with diagnoses of early-onset insulin dependent diabetes mellitus (n = 1) and rheumatoid arthritis (n = 3) were excluded because of a possible protective role for UV-radiation in these diseases [25]. Analyses in this study are based on data provided by 152 MS-patients and 402 controls.

The study was approved by the Regional Committee for Research Ethics and data were licensed by the Norwegian Data Inspectorate.

Questionnaire

Patients reported age at first symptom of MS and age at diagnosis. Questions on outdoor activities (as used in a previous study [31]) and sun exposure referred to ages 6–10, 11–15, and 16–20 years, and included also queries on sunbathing vacations, sunbed use, ability to tan, and tendency to sunburn. Data on diet consisted of information on commonly consumed dinner dishes and use of cod-liver oil supplement before the subjects left home for good. Sami ethnicity was defined as having at least one grandparent who had Sami as first language [20].

Statistical analysis

Data were double entered and analysed by use of SPSS 12.0.1 for Windows (SPSS Inc. Chicago, IL 60606).

Descriptive analyses – We calculated frequencies, proportions, medians, and ranges.

Comparisons between groups – Chi-square test or Mann-Whitney test were applied for comparisons between groups. A *p* value less than 0.05 was considered statistically significant.

Regression analyses – Odds ratios (ORs) between patients and controls were calculated using conditional logistic regression analysis accounting for the matching variables age, sex, and place of birth. Ordinal variables reflecting outdoor activities showed a significant linear trend and were entered into the model as continuous variables. Variables for "dinner dishes" were dichotomised.

Unconditional logistic regression was performed in subgroup analysis (use of cod-liver oil supplement stratified for outdoor activities).

Results

Characteristics of cases and controls

Characteristics of cases and controls are shown in table 1. There were no statistically significant differences between the groups.

Outdoor activities and sun exposure

More time spent on outdoor activities in summertime was associated with a decreased risk of MS. This effect was most pronounced at ages 16–20 with a 45% reduction in odds of MS per one unit change (table 2). Adjustment for winter outdoor activities slightly strengthened the effect of outdoor activities summertime (age 16–20: OR 0.50, 95% CI 0.33–0.77, p = 0.001). The association between winter outdoor activities and MS disappeared when adjusting for summer outdoor activities (age 16–20: OR1.13, 95% CI 0.74–1.71, p = 0.576). Adjustment for use of cod-liver oil supplement and fish consumption made no important difference to the results (table 2). When all available cases were included, the association between summer outdoor activities and risk of MS (unadjusted odds ratio) was slightly strengthened for age 11–15 (120 patients, 279 controls, p = 0.013) and age 6–10 (122 patients, 281 controls, p = 0.004). Patients with first symptom of MS before age 21 were excluded from all analyses regarding outdoor activities because the questions referred specifically to ages 6–20.

Table 2 Odds ratios for MS and summer outdoor activities

	Unadjusted odds ratio		p value	Adjusted odds ratio[a]		p value
	OR[b]	95% CI		OR[b]	95% CI	
Summer outdoor activities						
Age 16–20	0.54	0.38–0.75	<0.0001	0.55	0.39–0.78	0.001
Age 11–15	0.70	0.52–0.96	0.025	0.74	0.54–1.01	0.055
Age 6–10	0.69	0.51–0.93	0.013	0.71	0.52–0.96	0.025

Regression analysis included 111 patients (first symptom of MS after age 20) and 246 controls with complete data for all variables. [a] Adjusted for use of cod-liver oil supplement and dinner dishes of boiled or fried fish. [b] Odds ratio per one unit change in summer outdoor activities (four levels: not that often; a moderate amount; quite a lot; virtually all the time)

Table 3 Distribution of outdoor activities, fish consumption, and use of cod-liver oil supplement

	Patients		Controls	
	%	No[a]	%	No[a]
Outdoor activities				
In summer, how much did your activities (playing, sports, walking, working) take you outside? (age 16–20)		149		334
not that often	13	19	5	16
a moderate amount	44	66	33	110
quite a lot	32	48	50	166
virtually all the time	11	16	13	42
P < 0.001 for linear trend				
In winter, how much did your activities (playing, sports, walking, working) take you outside? (age 16–20)		145		335
not that often	19	27	12	41
a moderate amount	53	77	49	164
quite a lot	22	32	32	107
virtually all the time	6	9	7	23
P = 0.047 for linear trend				
Diet before you left home for good				
Dishes of boiled or fried fish (dichotomised)[b]		148		398
< 3 per week	55	81	45	177
≥ 3 per week	45	67	56	221
P = 0.030 (Chi-square)				
Other fish dishes (dichotomised)[c]		142		377
< 1 per week	33	47	27	102
≥ 1 per week	67	95	73	275
P = 0.169 (Chi-square)				
Porridge or pancakes (dichotomised)[c]		145		388
< 1 per week	36	52	45	174
≥ 1 per week	64	93	55	214
P = 0.065 (Chi-square)				
Meat dishes (dichotomised)[c]		142		385
< 1 per week	52	74	51	198
≥ 1 per week	48	68	49	187
P = 0.968 (Chi-square)				
Were you given cod-liver oil when growing up?		146		377
Yes	69	101	75	284
No	31	45	25	93
P = 0.160 (Chi-square)				

[a] Total numbers vary due to missing data; [b] Frequency choices "boiled or fried fish": never, 1- 11/year, 1/month, 2–3/month, 1–2/week, 3–4/week, ≥5/week; [c] Frequency choices other dinner dishes: never, 1–11/year, 1/month, 2–3/month, 1/week, 2/week, ≥3/week

In table 3 the questions asked in the questionnaire are specified and frequency data are given for ages 16–20.

Patients and controls did not differ in ability to tan (p = 0.998), tendency to sunburn (p = 0.460), or time spent on sunbathing vacations (p = 0.944). Therefore, these variables were not included in the regression models.

Cod-liver oil supplement use

We found no significant association between use of cod-liver oil supplement and MS risk in the matched analysis (table 4). In the subgroup that reported low summer outdoor activities, however, use of cod-liver oil supplement had a possible protective effect against MS, p = 0.072 (table 4). This association was com-

Table 4 Odds ratios for MS and use of cod-liver oil supplement

	No of patients/controls[a]	OR	95% CI	*p* value
Matched analysis[b]	132/295	0.73	0.44–1.21	0. 222
Subgroup analysis[c]				
Low outdoor activities[d]	81/118	0.57	0.31–1.05	0.072
High outdoor activities[d]	63/196	1.18	0.57–2.46	0.657

[a] Lower numbers in matched analysis due to missing data; [b] conditional logistic regression; [c] unconditional logistic regression, adjustment for age and sex, stratification for summer outdoor activities age 16–20; [d]low outdoor activities = not that often/a moderate amount; high outdoor activities = quite a lot/virtually all the time

pletely unchanged by adjustment for fish consumption (OR 0.57, 95% CI 0.31–1.05, p = 0.073).

Fish consumption

The proportion of respondents who had eaten boiled or fried fish three or more times a week was significantly (p = 0.030) higher among controls than among patients. Regression analysis included 119 patients and 251 controls with complete data for all variables. High fish consumption was associated with a reduced risk of MS (unadjusted OR 0.56, 95% CI 0.34–0.91, p = 0.020). This effect was unchanged by adjustment for other dinner dishes that were commonly consumed at least once a week as specified in table 3 (OR 0.55, 95% CI 0.33–0.92, p = 0.022). Also, when use of cod-liver oil supplement was entered into the model the association was sustained (OR 0.55, 95% CI 0.33–0.93, p = 0.024). Additional adjustment for summer outdoor activities age 16–20 reduced the effect of fish consumption on MS risk (OR 0.61, 95% CI 0.36–1.03, p = 0.065).

Discussion

The impetus to this study was provided by the anomalous distribution of MS in Norway, where the north-south gradient is almost inverted. Prevalence figures from formal studies in the southern part of Norway are similar to but not higher than those reported from the UK [13]. Although the published prevalence figures from Norway have been obtained using different ascertainment schemes, there is reason for confidence in the general pattern. Case ascertainment in the northernmost regions of Norway is advantaged by centralised medical services.

In a population living north of the Arctic Circle we found that outdoor activities (as a measure of UV-exposure) during summer in childhood and adolescence reduce the risk of MS. In the same age-groups, supplementation with cod-liver oil seems to decrease the risk of MS in those with the least sunlight exposure, and a diet high in fish may also be protective. North Norway is exceptional in that exposure to sunlight is low [11] and fish consumption is high [3, 28]. Data for this study were collected in a small but unselected patient population attending the Neurology clinic at the only Medical School north of the Arctic Circle. The study focused on the age-range during which an individual's risk of MS probably is established. Controls were matched on place of birth to accommodate local variations in UV-radiation, life style (urban vs. rural), diet (coast vs. inland), and to a certain extent socioeconomic status. Although a cause-and-effect relationship between MS risk and all three factors that were associated with risk of MS in this study is biologically plausible [7, 27, 29] and evidence is accumulating in favour of the UV-radiation/vitamin D hypothesis for MS, our findings do not prove causality. Neither can we exclude confounding by unknown variables.

Our data confirm the association of higher UV-radiation exposure during childhood and adolescence with a reduced risk of developing MS, implied by migration studies. In the first case-control study to report an association between UV-exposure and MS risk in Tasmania [31], patient recall was supported by objective measures of skin sun exposure. It is highly unlikely that the MS-patients in our study were aware of the hypothesis, as data were collected before publication of the latter study. In Tasmania at latitudes 41–43°S, higher UV-exposure in winter was more important than higher exposure in summer which is in agreement with results from a population-based epidemiological study at latitudes 30°–47°N [1]. We found that more time spent on outdoor activities summertime was associated with a lower risk of MS. At latitudes 66–71° N, any significant effect of UV-radiation has to occur in summer, because solar radiation wintertime is extremely low and insufficient for vitamin D synthesis for about four months [11]. The association was strongest for ages 16–20, which is within the age-range of risk of developing MS that has been reported from migration to Australia [17]. We found no association between MS and reported tendency to sunburn or tan, which is in agreement with the findings in Tasmania [31]. The finding of a protective effect of outdoor activities on MS risk in the north of Norway seems to be in conflict with the absence of a latitude gradient for MS prevalence in the country. Vitamin D production in the skin is the primary source of vitamin D in humans [29] and the total population is exposed to UV-radiation to a varying degree. A larger number of subjects and more accurate measures of vitamin D intake might be needed to precisely assess the relative importance of dietary vitamin D.

Supplementation with cod-liver oil, an important source of vitamin D, seemed to prevent MS in the subgroup of respondents with low summer outdoor activities. Though not statistically significant, the result is suggestive, and it is consistent with a study in 271 women living at 65–71°N showing a significant positive correlation between dietary vitamin D intake and plasma 25(OH) vitamin D level only in subjects with low sun exposure [4]. Our finding of a possible protective effect of cod-liver oil supplementation in those with the least sunlight exposure is consistent with these data and supports the UV-radiation/vitamin D hypothesis for MS. In the Nurses' Health Study, supplemental vitamin D intake in adults was associated with a decreased risk of MS [23], but the doses taken were small, and the epidemiological evidence indicates that the environmental impact on risk occurs before the third decade.

Consumption of boiled or fried fish three or more times a week was associated with reduced risk of MS. This finding is interesting, but it has to be interpreted with caution. Patients' recall of food intake when growing up may be biased by the publicity surrounding fish consumption and MS. In the Norwegian diet, fish provides half of the total intake of very-long-chain n-3 fatty acids [19]. Marine omega-3 polyunsaturated fatty acids have potent anti-inflammatory and immunomodulatory properties, and it is biologically plausible that a diet rich in fish has a protective effect on the risk of developing MS [7, 27]. In a comparison of six dietary patterns, "traditional fish eaters" also had the highest intake of vitamin D [12]. Individuals consuming a diet rich in fish are likely to eat a fish dish consisting of cod, cod roe, and cod-liver oil served during the winter months. One such meal contains about ten times the advised daily intake of vitamin D. Once a tradition determined by availability, this dish still is commonly consumed in North Norway, especially in the fishing villages [5].

We report findings which support the UV-radiation/vitamin D hypothesis for MS: a significant association between time spent outdoor in summer with reduced MS risk, and a possible protective effect of cod-liver oil supplementation when sun exposure is less, suggesting that both climate and diet may interact to influence MS risk at a population level. A relationship to vitamin D requirements provides one possible common pathway which would accommodate these observations and may help explain the apparently anomalous prevalence-latitude data in Norway.

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