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Factors affecting the risk of relapsing-onset and progressive-onset multiple sclerosis

Anna Karin Hedström ¹, Jan Hillert,¹ Tomas Olsson,¹ Lars Alfredsson²

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¹Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
²Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

Correspondence to

Dr Anna Karin Hedström, Karolinska Institutet, Stockholm, Stockholm, Sweden; anna.hedstrom@ki.se

TO and LA contributed equally.

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ABSTRACT

Objective It has been debated whether the different clinical disease courses in multiple sclerosis (MS) are the consequence of different pathogenic mechanisms, with distinct risk factors, or if all MS clinical phenotypes are variations of similar underlying disease mechanisms. We aimed to study environmental risk factors and their interactions with human leucocyte antigen DRB1*15:01 with regards to relapsing-onset and progressive-onset MS.

Methods We used two Swedish population-based case–control studies, including 7520 relapsing-onset cases, 540 progressive-onset cases and 11 386 controls matched by age, sex and residential area. Logistic regression was used to estimate ORs with 95% CIs for associations between the different MS phenotypes and a number of environmental and lifestyle factors. Interaction between the DRB1*15:01 allele and environmental risk factors was evaluated on the additive scale.

Results All environmental and lifestyle factors associated with risk of developing MS apply to both relapsing-onset and progressive-onset disease. Smoking, obesity and Epstein-Barr virus nuclear antigen-1 (EBNA-1) antibody levels were associated with increased risk of both MS phenotypes, whereas snuff use, alcohol consumption and sun exposure were associated with reduced risk. Additive interactions between DRB1*15:01 and smoking, obesity, EBNA-1 antibody levels and sun exposure, respectively, occurred to increase MS risk regardless of the clinical phenotype.

Interpretation Our finding that the same environmental and lifestyle factors affect both relapsing-onset and progressive-onset MS supports the notion that the different clinical phenotypes share common underlying disease mechanisms.

INTRODUCTION

Multiple sclerosis (MS) is the most frequent demyelinating disease, characterised by a highly variable and mostly unpredictable disease course. MS typically starts as a relapsing remitting (RR) disease, characterised by recurring clinical symptoms followed by complete or partial recovery. Ultimately, the disease becomes progressive in a majority of patients and the clinical symptoms slowly cause progressive deterioration (secondary progressive MS). In a subset of patients, the disease is progressive from onset without distinct relapses (primary progressive MS) or with occasional superimposed relapses (progressive relapsing MS).¹ Progressive-onset MS does not show the female

predominance seen with relapsing onset MS² and the onset of disease usually occurs later.³

It has long been debated whether the different clinical disease courses are due to different pathogenic mechanisms or whether they present variants of a common disease process.^{4–7} The relapses in the RR disease course are believed to be the result of focal inflammatory demyelinating lesions, whereas the progressive course is dominated by diffuse grey and white matter atrophy and cortical demyelination.⁸ It is unclear whether the focal inflammatory lesions trigger the progressive phase of the disease or whether other mechanisms are responsible for the more subtle processes dominating the progressive phase.

The substantial differences in clinical presentation have also led to the question whether the disease courses have distinctive risk factors. Genetic variance is a proposed determinant of MS disease course, but no definite genetic differences have been found between relapsing and progressive onset MS.⁹ It has also been suggested that other factors than genetics may underlie the differences between the clinical phenotypes. However, few studies have investigated risk factors for MS by disease course.¹⁰ In the present report, we aimed to study environmental risk factors and their interactions with the main MS risk gene, the human leucocyte antigen (HLA)-DRB1*15:01 allele, with regards to relapsing-onset and progressive-onset MS.

METHODS**Study design and data collection**

Epidemiological investigation of multiple sclerosis (EIMS) and genes and environment in multiple sclerosis (GEMS) are population-based, case–control studies with the main purpose to investigate the influence of genetic and environmental risk factors for MS. The study base comprised the Swedish general population aged 16–70 years. In EIMS, cases with newly diagnosed MS were recruited from neurology clinics throughout the country, including all university hospitals. All cases were examined and diagnosed by a neurologist according to the McDonald criteria.^{11 12} For each case, we randomly selected two controls from the national population register, frequency matched for the case's age in 5-year age strata, sex and residential area. Reminders were sent to cases and controls who had not answered the questionnaire within 2, 4 and 6 weeks. Before a person was recorded as a non-responder, he or she was also contacted by phone. The study period was April 2005 to June 2015.



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Table 1 Number of cases and controls in EIMS and GEMS

Case-control status	Included	Data on disease course, smoking, alcohol and snuff use	Data on disease course and sun exposure	Data on disease course and adolescent BMI (index age >19 years)	Data on disease course, DRB1 and smoking	Data on disease course, DRB1 and adolescent BMI	Data on disease course, DRB1 and EBNA-1 antibody levels
Relapsing-onset MS	8965	7520	6840	7206	6109	5899	4419
Progressive-onset MS		540	489	517	456	439	398
Controls	11 479	11 386	10 590	10 351	6683	6526	5144

BMI, body mass index; EBNA-1, Epstein-Barr virus nuclear antigen-1; EIMS, epidemiological investigation of multiple sclerosis; GEMS, genes and environment in multiple sclerosis; MS, multiple sclerosis.

In GEMS, cases who fulfilled the McDonald criteria^{11 12} were identified from the Swedish National MS registry¹³ and one control per case was randomly selected from the national population register matched for age, sex and residential area at the time of disease onset. Those who did not respond were recorded as nonresponders. No reminders were sent out. The study participants, distinct from those in EIMS, were recruited between November 2009 and November 2011. Ethical approval for both EIMS (04-252/1f and 2012/359-32) and GEMS (2008/1617-31/2 and 2017/1378-31) was obtained from the Regional Ethical Review Board at Karolinska Institutet. All participants provided their informed consent.

In both studies, information regarding environmental exposures and lifestyle factors was collected using a standardised questionnaire. The response rate was 93% for cases and 73% for controls in EIMS and 82% for cases and 66% for controls in GEMS. All participants in both studies were asked to provide blood samples for genetic and serologic analyses. Blood samples were available for 81% of the cases and 59% of the controls. Epstein-Barr virus nuclear antigen-1 (EBNA-1) antibody status was available for participants who had been recruited before August 2013. Table 1 presents the number of cases and controls in each study, and online supplemental table 1 provides further information regarding missing data.

Definition of self-reported exposures

Smoking

Information regarding smoking was obtained by asking about current and previous smoking habits. The year of disease onset in cases was defined as the index year and the corresponding controls were given the same index year. Cases and controls were categorised into current smokers (those who smoked during the index year), previous smokers (those who had stopped smoking prior to the index) and never smokers (those who had never smoked before or during the index year). We also calculated the number of pack years as a measure of the cumulated dose of smoking before the index year. One pack year is defined as 20 cigarettes smoked daily for 1 year.

Snuff use

Subjects provided information regarding current and previous snuff use. Subjects who reported that they had never smoked, but used snuff before or during the index year was defined as exclusive snuff users. The total number of packages of snuff consumed before the index year was calculated as a measure of the cumulative dose of snuff.

Alcohol consumption

Incident cases and controls in EIMS were defined as drinkers if they reported alcohol consumption during the year before study inclusion and those who did not drink alcohol were defined as nondrinkers. Prevalent cases and controls in GEMS were categorised into drinkers and nondrinkers based on their alcohol consumption at disease onset. We further categorised the drinkers into the following subgroups based on the sex-specific distribution of alcohol intake in gram per week; nondrinkers, low consumption (below or equal to the median), moderate consumption (above the median, but below or equal to the 75th percentile) and high consumption (above the 75th percentile). Low alcohol consumption was defined as <24 g/week among women and <60 g/week among men; moderate alcohol consumption as 24–89 g/week among women and 60–114 g/week among men and high alcohol consumption as >89 g/week among women and >114 g/week among men.

Adolescent body mass index

Information was obtained regarding current height and body weight at age 20. We calculated body mass index (BMI) at age 20, by dividing weight in kilograms by height in metres squared. Adolescent BMI was categorised into normal weight (<25 kg/m²), overweight (25–30 kg/m²) and obesity (>30 kg/m²).

Sun exposure

Sun exposure during the index year was estimated as high or low during the time period (5-year period in EIMS and 10-year period in GEMS) that included the index year. Based on three questions regarding sun exposure (frequency of sun bathing, travelling to a sunnier country and frequency of use of sunbeds) where each answer alternative was reported on a four-point scale, we created a sun exposure index by adding the numbers together, acquiring a value between 3 (the lowest exposure) and 12 (the highest exposure) (online supplemental table 2). Sun exposure was dichotomised into high or low based on the 25th percentile among controls (5).

Genotyping and serologic analyses

HLA-A and HLA-DRB1 alleles were determined at four-digit resolution, using the MS replication chip,¹⁴ an Illumina exome chip to which approximately 90 000 custom markers were added, and HLA was then imputed with HLA*IMP:02.¹⁵ Population stratification was determined by PCA of ancestral informative markers using EIGENSTRAT, and population outliers were removed.

Multiplex serology was used to detect IgG antibodies against the EBNA-1 peptide segment (aa 385–420),^{16 17} which was

selected from our previous study as the main targeted fragment associated with MS.¹⁸ Dual-laser flow-based detection was used to quantify the antibodies as units of median fluorescence intensity (MFI). EBNA-1 antibodies were quantified as units of median seroreactivity among controls (4920 MFI) defining groups with high and low EBNA-1 antibody levels.

Statistical analysis

Each risk factor was analysed separately. Using logistic regression models, exposed and unexposed subjects were compared with regards to relapsing-onset and progressive-onset MS, respectively, by calculating OR with 95% CIs with adjustment for the matching factors.¹⁹ We performed both conditional and unconditional analyses of the data. We were able to include a higher number of controls in the unconditional analyses, which, therefore, had increased statistical power. Only the results from the unconditional analyses are presented since these were in close agreement with those from the conditional analyses but had higher precision in terms of more narrow CIs.

We also performed the analyses by study, and measures of association derived from each study were then combined. Specifically, ORs were combined by calculating a weighted average of the study-specific adjusted ORs, where weights were proportional to the inverse of the variance for each OR.

For each risk factor, a trend test for a dose–response relationship regarding exposure level and risk of relapsing and progressive onset MS was performed by using a continuous or categorical variable, as described in the section Definitions of exposures, in a logistic regression model.

Sufficient-cause interactions between DRB1*15:01 and smoking, obesity, high EBNA-1 antibody levels and sun exposure, respectively, were evaluated by estimating departure from additivity of effects using attributable proportion (AP) due to interaction.^{20,21} Statistical interaction is scale dependent and presence of interaction on one scale does not necessarily mean presence of interaction on the other. Presence of *no* interaction between two risk factors (with OR larger than 1) on the additive scale implies negative interaction on the multiplicative scale and presence of *no* interaction between two risk factors on the multiplicative scale implies that there is positive interaction on the additive scale. Interaction on the additive scale is thought to be more informative from a public health perspective than multiplicative interaction. Further, the sufficient-cause concept that was developed by Rothman *et al*²⁰ and later expanded by VanderWheele²¹ has improved the understanding between disease causation and interaction, in that, presence of interaction between two causal factors on the additive scale implies that there exists a pathway towards disease where the presence of both risk factors is needed. The AP between two interacting factors reflects the joint effect beyond the sum of the independent effects. Factors associated with reduced risk of disease should be recoded as risk factors when conducting analyses of interaction.²² We also calculated the product terms for the interactions between DRB1*15 and each environmental factor in logistic regression models in order to present the interactions on the multiplicative scale.

All analyses were adjusted for study, year of enrollment, age, sex, residential area and ancestry. Residential area was defined as the Swedish county (1 of 21) in which the participant lived, and the variable was dichotomised into conurbations (Stockholm, Göteborg, Malmö) and smaller cities. Ancestry was dichotomised into Nordic versus non-Nordic origin. Participants born in Sweden, Norway or Denmark, whose parents had not immigrated from outside these countries, were classified as Nordic.

When examining the impact of a risk factor on relapsing and progressive onset MS, the remaining risk factors were assessed as potential confounding factors. The factors that had no influence on the main results were not included in the final model.

As a sensitivity analysis, we used principal component analysis (PCA) vectors based on 3736 ancestrally informative markers to adjust for population stratification. In this analysis, population outliers were excluded, as were related participants in order to avoid cryptic relatedness. All analyses were conducted using SAS V.9.4.

RESULTS

Our analyses of risk factors for relapsing-onset and progressive-onset MS included 8060 cases and 11 386 controls matched by age, sex and residential area. Among cases with progressive-onset MS (n=540), disease-onset occurred later by approximately a decade, as compared with those with relapsing-onset MS. Characteristics of cases and controls are presented in table 2 and online supplemental table 3.

Environmental factors associated with relapsing-onset and progressive-onset MS

Smoking

Ever smoking was associated with increased risk of both relapsing-onset MS (OR 1.6, 95% CI 1.5 to 1.7) and progressive-onset MS (OR 1.9, 95% CI 1.6 to 2.3). With regards to both clinical phenotypes, current smoking had a greater impact on disease risk than previous smoking (table 3). There were significant trends showing increasing risk of both relapsing-onset and progressive-onset MS with cumulative dose of smoking (p values for trend <0.0001).

Snuff use

Exclusive snuff use was associated with reduced risk of both relapsing-onset MS (OR 0.7, 95% CI 0.6 to 0.9) and progressive-onset MS (OR 0.6, 95% CI 0.4 to 0.9).

Alcohol consumption

When subjects were categorised by their weekly alcohol consumption, those who reported a consumption exceeding the 75th percentile among controls had a 20% reduced risk of relapsing-onset MS (OR 0.8, 95% CI 0.7 to 0.9) and a 50% reduced risk of progressive onset MS (OR 0.5, 95% CI 0.4 to 0.7) (table 4). The risk of both relapsing-onset and progressive-onset MS decreased with increasing alcohol consumption (p values for trend <0.0001 and 0.009, respectively).

Overweight/obesity

Overweight was associated with a small increased risk of relapsing-onset MS (OR 1.3, 95% CI 1.2 to 1.4) and progressive-onset MS (OR 1.2, 95% CI 0.8 to 1.6), whereas obesity had a more pronounced impact on the risk of disease (OR 1.7, 95% CI 1.4 to 2.0 for relapsing-onset MS and OR 1.8, 95% CI 1.0 to 3.2 for progressive-onset MS). There were trends showing that the risks increased with increasing adolescent BMI (p values for trends 0.007 and 0.01, respectively).

Sun exposure

Low exposure to sun was associated with increased risk of relapsing-onset MS (OR 1.3, 95% CI 1.2 to 1.4) and progressive-onset MS (OR 1.3, 95% CI 1.1 to 1.6). The risk of developing either of the clinical phenotypes of MS increased with decreasing exposure to the sun (p values for trend <0.0001).

Table 2 Characteristics of cases and controls

Exposure	Relapsing-onset MS	Progressive-onset MS	Controls
N	7520	540	11 386
Females, n (%)	5501 (73)	321 (59)	8278 (73)
Nordic	6645 (88)	490 (91)	9974 (86)
Non-Nordic European	501 (7)	41 (8)	875 (8)
Non-European	374 (5)	10 (2)	767 (7)
Ever smoking, n (%)	4108 (55)	332 (61)	5106 (45)
Current smoking, n (%)	2670 (36)	190 (35)	2984 (26)
Past smoking, n (%)	1438 (19)	142 (26)	2122 (19)
Cumulative dose of smoking, pack years (SD)	7.6 (8.5)	12.3 (11)	7.2 (8.6)
Exclusive snuff users, n (%)	316 (4.3)	21 (4.0)	604 (5.4)
No alcohol consumption, n (%)	2009 (27)	152 (28)	3000 (26)
Low alcohol consumption, n (%)	1438 (19)	110 (20)	2102 (18)
Moderate alcohol consumption, n (%)	3156 (42)	217 (40)	4679 (41)
High alcohol consumption, n (%)	917 (12)	61 (11)	1605 (14)
Normal weight, kg/m ² (SD)	6200 (89)	461 (86)	9720 (89)
Overweight, n (%)	772 (7.7)	40 (11)	969 (8.9)
Obesity, n (%)	234 (3.1)	16 (3.3)	226 (2.1)
Mean sun exposure index (SD)	6.1 (1.8)	5.8 (1.7)	6.4 (1.8)
Low sun exposure, n (%)	1818 (25)	156 (30)	2127 (19)
Mean EBNA-1 antibody levels (SD)	6821 (3079)	6232 (3173)	4894 (3245)
Median EBNA-1 antibody levels	6838	6166	4915
High EBNA-1 antibody levels	3463 (78)	280 (70)	2718 (53)
DRB1*15:01 positive	3411 (58)	246 (56)	1843 (28)
A*02:01 negative	3371 (57)	237 (54)	2927 (45)
Age at disease onset (SD)	32.9 (10.0)	42.3 (11.0)	

EBNA-1, Epstein-Barr virus nuclear antigen-1; MS, multiple sclerosis.

EBNA-1 antibody levels

High EBNA-1 antibody levels were associated with increased risk of relapsing-onset MS (OR 3.0, 95% CI 2.7 to 3.3) and

progressive-onset MS (OR 2.0, 95% CI 1.6 to 2.5). The risk increased with increasing levels of EBNA-1 antibodies (p values for trend <0.0001).

Gene-environment interactions in the development of relapsing-onset and progressive-onset MS

Overall, carriers of the DRB1*15:01 allele had an increased risk of developing relapsing-onset MS (OR 3.5, 95% CI 3.3 to 3.8) and progressive-onset MS (3.3, 95% CI 2.6 to 4.0). Additive interactions occurred between DRB1*15:01 and both smoking, obesity, EBNA-1 antibody levels and sun exposure with regards to both relapsing-onset and progressive-onset MS (table 5).

The interactions were evaluated by calculating the AP. An AP of, for example, 0.5 indicate that the combined effect of two risk factors was 50% higher than the sum of the individual effects or, equivalently, that 50% of the cases among the double exposed are due to the interaction *per se*.

Combined and pooled analyses of data rendered similar results. The results from the pooled analyses are presented in online supplemental tables 3-6. Terms for multiplicative interaction between DRB1*15:01 and each environmental factor are presented in online supplemental table 7.

All findings remained similar when the analyses included all subjects, and when they were restricted to participants with Nordic and European ancestry, respectively. Furthermore, our results remained almost identical after excluding population outliers and adjusting the analyses for PCA vectors.

DISCUSSION

Our findings imply that all environmental and lifestyle factors associated with increased risk of developing MS apply to both relapsing-onset and progressive onset disease. Additive interactions between DRB1*15:01 and environmental factors increase MS risk regardless of the clinical phenotype, indicating that the different phenotypes share common underlying disease mechanisms.

The aetiology and pathogenesis of MS are still not resolved. It has long been debated whether the different clinical disease courses in MS are the consequence of different pathogenic mechanisms, with distinct risk factors, or if all MS clinical phenotypes are variations of a similar underlying pathology, with inflammation and neurodegeneration occurring throughout the disease spectrum.⁴⁻⁷ Increasing evidence support the latter hypothesis.

Although a vast majority of MS risk alleles are immunological genes, no definite genetic differences have been found between relapsing and progressive onset MS, indicating that the different clinical phenotypes may be opposite ends of the same disease spectrum, rather than different diseases.⁹ Our observation that the DRB1*15:01 allele is comparably distributed in patients

Table 3 OR with 95% CI of developing relapsing-onset and progressive-onset MS among subjects with different smoking habits

Smoking	Relapsing-onset MS			Progressive-onset MS		
	ca/co*	aOR (95% CI)†	aOR (95% CI)‡	Ca/co*	aOR (95% CI)†	aOR (95% CI)‡
Never smoking	3412/6280	1.0 (reference)	1.0 (reference)	208/6280	1.0 (reference)	1.0 (reference)
Ever smoking	4108/5106	1.5 (1.4 to 1.6)	1.6 (1.5 to 1.7)	332/5106	1.7 (1.4 to 2.0)	1.9 (1.6 to 2.3)
Current smoking	2670/2984	1.7 (1.6 to 1.8)	1.7 (1.6 to 1.8)	190/2984	2.0 (1.7 to 2.5)	2.3 (1.9 to 2.8)
Past smoking	1438/2122	1.3 (1.2 to 1.5)	1.4 (1.3 to 1.5)	142/2122	1.3 (1.1 to 1.7)	1.5 (1.2 to 1.9)

*Number of exposed cases and controls.

†Adjusted for study, year of enrolment, age, sex, residential area and ancestry.

‡Adjusted for study, year of enrolment, age, sex, residential area, ancestry, obesity, alcohol consumption, sun exposure habits and snuff use. The analyses are based on 7520 relapsing-onset MS cases, 540 progressive-onset MS cases and 11 386 controls.

aOR, adjusted OR; MS, multiple sclerosis.

Multiple sclerosis

Table 4 OR with 95% CI of developing relapsing-onset and progressive-onset MS, among subjects with different alcohol consumption habits

Alcohol consumption	Relapsing-onset MS			Progressive-onset MS		
	ca/co*	aOR (95% CI)†	aOR (95% CI)‡	Ca/co*	aOR (95% CI)†	aOR (95% CI)‡
None	2009/3000	1.0 (reference)	1.0 (reference)	152/3000	1.0 (reference)	1.0 (reference)
Low	1438/2102	1.0 (0.9 to 1.1)	1.0 (0.9 to 1.1)	110/2102	0.7 (0.5 to 0.9)	0.8 (0.6 to 1.0)
Moderate	3156/4679	0.9 (0.8 to 1.0)	0.9 (0.8 to 1.0)	217/4679	0.7 (0.6 to 0.9)	0.7 (0.6 to 1.0)
High	917/1605	0.7 (0.6 to 0.9)	0.8 (0.7 to 0.9)	61/1605	0.5 (0.4 to 0.7)	0.5 (0.4 to 0.7)

*Number of exposed cases and controls.

†Adjusted for study, year of enrolment, age, sex, residential area and ancestry.

‡Adjusted for study, year of enrolment, age, sex, residential area, ancestry, obesity, smoking, sun exposure habits and snuff use. The analyses are based on 7520 relapsing-onset MS cases, 540 progressive-onset MS cases and 11 386 controls.

aOR, adjusted OR; MS, multiple sclerosis.

with relapsing-onset, and progressive MS is in accordance with these results.

According to our findings, environmental and lifestyle risk factors for MS, and their interaction with the DRB1*15:01 allele, also contribute to MS development regardless of the

clinical phenotype. This further supports the notion that the different phenotypes share common underlying disease mechanisms. A peripheral immune response targeting the CNS is likely to initiate the disease process, and factors modulating the adaptive immune response may increase or decrease the risk of

Table 5 OR with 95% CI of developing relapsing-onset and progressive-onset MS among subjects categorised by DRB1*15:01 and environmental factors

Interaction between DRB1*15:01 and smoking								
DRB1*15:01		Relapsing-onset MS			Progressive-onset MS			
		Smoking	ca/co*	aOR (95% CI)†	aOR (95% CI)‡	ca/co*	aOR (95% CI)†	aOR (95% CI)‡
–	–	–	1109/2543	1.0 (reference)	1.0 (reference)	71/2543	1.0 (reference)	1.0 (reference)
–	+	–	1478/2248	1.6 (1.4 to 1.8)	1.7 (1.5 to 1.8)	132/2248	1.8 (1.4 to 2.5)	2.0 (1.5 to 2.9)
+	–	–	1626/1002	3.8 (3.4 to 4.2)	3.6 (3.3 to 4.1)	96/1002	3.4 (2.5 to 4.8)	3.2 (2.3 to 4.4)
+	+	–	1896/890	5.2 (4.6 to 5.8)	5.3 (4.7 to 5.9)	157/890	5.5 (4.1 to 7.5)	6.0 (4.4 to 8.2)
AP		–		0.2 (0.1 to 0.3)	0.2 (0.1 to 0.3)		0.2 (0.02 to 0.4)	0.3 (0.1 to 0.5)
Interaction between DRB1*15:01 and obesity								
DRB1*15:01		Obesity	ca/co*	aOR (95% CI)†	aOR (95% CI)‡	ca/co*	aOR (95% CI)†	aOR (95% CI)‡
–	–	–	2422/4595	1.0 (reference)	1.0 (reference)	187/4595	1.0 (reference)	1.0 (reference)
–	+	–	66/88	1.4 (1.0 to 1.9)	1.4 (1.0 to 1.9)	6/88	1.7 (0.7 to 4.3)	1.6 (0.6 to 4.1)
+	–	–	3293/1818	3.5 (3.2 to 3.7)	3.4 (3.1 to 3.6)	238/1818	3.2 (2.6 to 4.0)	3.1 (2.5 to 3.8)
+	+	–	118/25	8.7 (5.6 to 13.4)	8.4 (5.4 to 12.9)	8/25	8.0 (3.4 to 18.8)	7.4 (2.9 to 17.8)
AP		–		0.6 (0.4 to 0.8)	0.5 (0.3 to 0.8)		0.5 (0.1 to 1.0)	0.5 (0.01 to 1.0)
Interaction between DRB1*15:01 and EBNA-1 antibody levels								
DRB1*15:01		EBNA-1 IgG levels	ca/co*	aOR (95% CI)†	aOR (95% CI)‡	ca/co*	aOR (95% CI)†	aOR (95% CI)‡
–	–	Low	510/1836	1.0 (reference)	1.0 (reference)	67/1836	1.0 (reference)	1.0 (reference)
–	–	High	1284/1832	2.5 (2.2 to 2.9)	2.5 (2.2 to 2.8)	110/1832	1.7 (1.2 to 2.3)	1.6 (1.2 to 2.2)
+	–	Low	446/590	2.8 (2.3 to 3.2)	2.9 (2.4 to 3.4)	51/590	2.1 (1.7 to 3.6)	2.4 (1.6 to 3.6)
+	–	High	2179/886	8.9 (7.9 to 10.1)	9.1 (8.0 to 10.3)	170/886	5.5 (4.1 to 7.5)	5.5 (4.1 to 7.5)
AP		–		0.5 (0.4 to 0.6)	0.5 (0.4 to 0.6)		0.4 (0.3 to 0.6)	0.4 (0.3 to 0.6)
Interaction between DRB1*15:01 and sun exposure								
DRB1*15:01		Sun exposure	Relapsing-onset MS			Progressive-onset MS		
–	–	High	1921/3864	1.0 (reference)	1.0 (reference)	155/3864	1.0 (reference)	1.0 (reference)
–	–	Low	666/927	1.4 (1.3 to 1.6)	1.4 (1.3 to 1.6)	48/927	1.2 (0.8 to 1.7)	1.1 (0.8 to 1.6)
+	–	High	2628/1516	3.5 (3.2 to 3.8)	3.4 (3.1 to 3.7)	166/1516	2.7 (2.2 to 3.5)	2.7 (2.1 to 3.4)
+	–	Low	894/376	4.8 (4.2 to 5.5)	4.8 (4.1 to 5.4)	87/376	5.3 (3.9 to 7.1)	4.8 (3.4 to 6.2)
AP		–		0.2 (0.1 to 0.4)	0.2 (0.1 to 0.3)		0.4 (0.3 to 0.6)	0.4 (0.2 to 0.6)

*Number of exposed cases and controls.

†Adjusted for study, year of enrolment, age, sex, residential area and ancestry.

‡Adjusted for study, year of enrolment, age, sex, residential area, ancestry, obesity, alcohol consumption, sun exposure habits, snuff use, HLA-A*02:01 and EBNA-1 antibody status.

§Adjusted for study, year of enrolment, age, sex, residential area, ancestry, smoking, alcohol consumption, sun exposure habits, snuff use, HLA-A*02:01 and EBNA-1 antibody status.

¶Adjusted for study, year of enrolment, age, sex, residential area, ancestry, smoking, obesity, alcohol consumption, sun exposure habits, snuff use and HLA-A*02:01.

**Adjusted for study, year of enrolment, age, sex, residential area, ancestry, smoking, obesity, alcohol consumption, snuff use, HLA-A*02:01 and EBNA-1 antibody status.

aOR, adjusted OR; AP, Attributable proportion due to interaction; MS, multiple sclerosis.

disease initiation. Potential biological mechanisms behind the association of specific environmental factors with MS risk have been discussed in detail elsewhere.^{23–25}

Clinically silent lesions on MRI are often found in patients at the time of the first symptoms of disease, indicative of a preclinical phase of MS of unknown duration. A study of subjects identified by MRI as having asymptomatic disease, who later experienced symptoms consistent with PPMS, showed that the preprogressive phase is characterised by active lesion development that is similar to that in relapsing-remitting MS.²⁶

New data also reveal that silent progression, associated with brain atrophy, during the relapsing-remitting phase is common, and independent of relapse activity.²⁷ The onset of the clinical progressive phase in MS is dependent on age rather than on the presence or absence of preceding clinical relapses.⁷ Although it remains unexplained why MS would manifest clinically as relapses in some patients, but not in others, patients with progressive onset MS may have had subclinical disease activity at similar ages as patients with preceding clinical relapses.

Our studies were designed as case-control studies and information regarding exposures and lifestyle factors was collected retrospectively. In order to reduce the risk of recall bias, EIMS primarily recruited incident cases of MS, whereas GEMS recruited prevalent cases. However, the relationship between MS and most of the investigated environmental factors had not been investigated to a large extent when our original results were published,^{28–30} and the quality of the reported information would probably not differ between cases and controls. In a validation study among women in the Nurses' Health Study, high correlations were found between recalled and measured weight, with a mean difference of 1.4 kg.³¹ A possible underreporting of weight in our study would probably not differ by case-control status, especially since there is no association between BMI at disease onset and MS risk.³²

Since the participants were asked to estimate their sun exposure habits by answering three questions using a four-point scale, we did not have specific information regarding intensity or duration of sun exposure by season, neither did we have information regarding the use of sunscreen. Our categorisation by sun exposure habits is, thus relatively imprecise.

Selection bias was minimised by the population-based design. Since the public healthcare system in Sweden provides equal free of charge access to medical services for all citizens, cases of MS are referred to neurological units, making them eligible to be included in EIMS. Selection bias among controls is probably modest because the prevalence of life style factors, such as smoking and socioeconomic status, among the controls was in close agreement with that of the general population.³³ The synergistic effects with risk genes also argue against biases in the interpretation of the lifestyle factors, since the HLA alleles are unlikely to determine exposure habits. We, thus, believe that our findings are not affected by bias to a large extent. Since we used a case-control study design, we only show associations between environmental exposures and disease, without being able to confirm causality. Further studies are needed in order to investigate biological mechanisms behind our findings.

In summary, our finding that the same environmental and lifestyle factors affect both relapsing-onset and progressive-onset MS supports the notion that the different clinical MS phenotypes share common underlying disease mechanisms.

Contributors AKH: conception and design of the study, acquisition and analysis of data, drafting the manuscript. JH, TO and LA: conception and design of the study. All authors revised the manuscript and approved the final draft.

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Data availability statement Data are available upon reasonable request. Anonymised data will be shared by request from any qualified investigator that wants to analyse questions that are related to the published article.

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ORCID iD

Anna Karin Hedström <http://orcid.org/0000-0002-6612-4749>

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Supplementary table 1. Presentation of missing data.

	N	Missing	Comment
Included cases	8965	-	
Data on disease course, smoking, alcohol, and snuff use	8060	10%	
Data on disease course and sun exposure	7329	18%	
Data on disease course & adolescent BMI (index age >19 years)	7723	7%	8307 of included cases have index age >19 years
Data on disease course, DRB1 and smoking	6565	27%	
Data on disease course, DRB1 and adolescent BMI	6338	24%	8307 of included cases have index age >19 years
Data on disease course, DRB1 and EBNA-1 antibody levels	4817	~ 27%	Based on cases included before Aug 2013
Included controls	11479	-	
Data on disease course, smoking, alcohol, and snuff use	11386	1%	
Data on disease course and sun exposure	10590	8%	
Data on disease course & adolescent BMI (index age >19 years)	10351	3%	10657 of included controls have index age >19 years
Data on disease course, DRB1 and smoking	6683	42%	
Data on disease course, DRB1 and adolescent BMI	6526	40%	10657 of included cases have index age >19 years
Data on disease course, DRB1 and EBNA-1 antibody levels	5411	~ 42%	Based on controls included before Aug 2013

Supplementary table 2. Questions regarding sun exposure habits.

Questions regarding sun exposure in EIMS.

1. How often, during the last 5 years, have you used a sun-bed?

Never A few times a year Once a month Once a week

2. How often, during the last 5 years, have you visited a country that is sunnier than Sweden?

Never More seldom Once a year More than once a year

3. If the weather is sunny, how often do you usually sunbathe?

Never A few times a month A few times a week Daily

Questions regarding sun exposure in GEMS.

1. How often, during each period, have you used a sun-bed?

	Never	A few times a year	Once a month	Once a week
15-19 years				
20-29				
30-39				
40-49				
50-				

2. How often, during each period, have you visited a country that is sunnier than Sweden?

	Never	More seldom	Once a year	More than once a year
15-19 years				
20-29				
30-39				
40-49				
50-				

3. How often, during each period, have you sunbathed if the weather was sunny?

	Never	A few times a month	A few times a week	Daily
15-19 years				
20-29				
30-39				
40-49				
50-				

Supplementary table 3. Characteristics of cases and controls by study.

Exposure	Relapsing-onset MS		Progressive-onset MS		Controls	
	EIMS	GEMS	EIMS	GEMS	EIMS	GEMS
Study						
N	2662	4858	79	461	6119	5267
Women, n (%)	1911 (72)	3590 (74)	52 (66)	269 (58)	4365 (71)	3913 (74)
Ever smoking, n (%)	1385 (52)	2723 (56)	55 (69)	277 (60)	2599 (42)	2507 (48)
Current smoking, n (%)	777 (29)	1893 (39)	38 (48)	152 (33)	1418 (23)	1566 (30)
Past smoking, n (%)	608 (23)	830 (17)	17 (22)	125 (27)	1181 (19)	941 (18)
Exclusive snuff users, n (%)	127 (4.8)	189 (4.0)	2 (2.5)	19 (4.3)	375 (6.1)	229 (4.4)
Alcohol consumption						
None, n (%)	868 (33)	1141 (23)	27 (34)	125 (27)	1858 (30)	1142 (22)
Low, n (%)	542 (20)	896 (18)	15 (19)	95 (21)	1118 (18)	984 (19)
Moderate, n (%)	941 (35)	2215 (46)	30 (38)	187 (41)	2223 (36)	2456 (47)
High, n (%)	311 (12)	606 (12)	7 (8.9)	54 (12)	920 (15)	685 (13)
Normal weight, kg/m ² (SD)	2031 (82)	4169 (88)	67 (86)	394 (90)	5026 (88)	4694 (90)
Overweight, n (%)	347 (14)	425 (9.0)	5 (6.4)	35 (8.0)	558 (9.8)	411 (7.9)
Obesity, n (%)	108 (4.3)	126 (2.7)	6 (7.7)	10 (4.5)	139 (2.4)	87 (1.7)
Mean sun exposure index (SD)	6.1 (1.8)	6.1 (1.7)	5.7 (1.7)	5.7 (1.6)	6.4 (1.8)	6.2 (1.6)
Low sun exposure, n (%)	535 (20)	684 (19)	22 (28)	78 (22)	1007 (16)	502 (15)
EBNA-1 antibody levels						
Mean (SD)	7715 (3017)	6577 (3051)	7322 (2707)	6129 (3201)	5195 (3318)	4780 (3209)
Median	7937	6570	7875	6049	5394	4744
DRB1*15:01 positive	1039 (55)	2157 (59)	39 (58)	189 (54)	802 (28)	968 (29)
A*02:01 negative	1122 (59)	2080 (57)	34 (51)	186 (53)	1324 (46)	1501 (44)
Age at disease onset (SD)	34 (11)	32 (10)	38 (12)	43 (11)		

Supplementary table 4. Pooled ORs with 95% CI of developing relapsing- and progressive-onset MS among subjects with different smoking habits.

Smoking	Relapsing-onset MS			Progressive-onset MS		
	ca/co ¹	aOR (95% CI) ²	aOR (95% CI) ³	ca/co ¹	aOR (95% CI) ²	aOR (95% CI) ³
Never smoking	3412/6280	1.0 (reference)	1.0 (reference)	208/6280	1.0 (reference)	1.0 (reference)
Ever smoking	4108/5106	1.5 (1.4-1.6)	1.5 (1.4-1.6)	332/5106	1.6 (1.3-1.9)	1.8 (1.5-2.0)
Current smoking	2670/2984	1.6 (1.4-1.7)	1.6 (1.4-1.7)	190/2984	1.9 (1.4-2.2)	2.1 (1.6-2.6)
Past smoking	1438/2122	1.4 (1.3-1.5)	1.4 (1.3-1.5)	142/2122	1.3 (1.0-1.5)	1.5 (1.0-1.9)

¹ number of exposed cases and controls; ²adjusted for study, year of enrollment, age, sex, residential area, and ancestry; ³adjusted for study, year of enrollment, age, sex, residential area, ancestry, obesity, alcohol consumption, sun exposure habits, and snuff use.

Supplementary table 5. Pooled ORs with 95% CI of developing relapsing- and progressive-onset MS, among subjects with different alcohol consumption habits.

Alcohol consumption	Relapsing-onset MS			Progressive-onset MS		
	ca/co ¹	OR (95% CI) ²	aOR (95% CI) ³	ca/co ¹	OR (95% CI) ²	aOR (95% CI) ³
None	2009/3000	1.0 (reference)	1.0 (reference)	152/3000	1.0 (reference)	1.0 (reference)
Low	1438/2102	0.9 (0.8-1.0)	0.9 (0.8-1.0)	110/2102	0.7 (0.5-0.9)	0.6 (0.5-0.8)
Moderate	3156/4679	0.9 (0.8-1.0)	0.9 (0.8-1.0)	217/4679	0.6 (0.5-0.8)	0.6 (0.5-0.8)
High	917/1605	0.8 (0.7-0.9)	0.7 (0.6-0.8)	61/1605	0.5 (0.3-0.7)	0.4 (0.2-0.6)

¹ number of exposed cases and controls; ²adjusted for study, year of enrollment, age, sex, residential area, and ancestry; ³adjusted for study, year of enrollment, age, sex, residential area, ancestry, smoking, obesity, sun exposure habits, and snuff use.

Supplementary table 6. Pooled OR with 95% CI of developing relapsing- and progressive-onset MS among subjects categorized by DRB1*15:01 and environmental factors.

Interaction between DRB1*15:01 and smoking							
DRB1*15:01	Smoking	Relapsing-onset MS			Progressive-onset MS		
		ca/co ¹	aOR (95% CI) ²	aOR (95% CI) ³	ca/co ¹	aOR (95% CI) ²	aOR (95% CI) ³
-	-	1109/2543	1.0 (reference)	1.0 (reference)	71/2543	1.0 (reference)	1.0 (reference)
+	-	1478/2248	1.6 (1.4-1.7)	1.7 (1.4-1.8)	132/2248	1.7 (1.2-2.4)	1.9 (1.4-2.6)
-	+	1626/1002	3.7 (3.3-4.1)	3.7 (3.3-4.0)	96/1002	3.6 (2.7-4.8)	3.4 (2.4-4.8)
+	+	1896/890	5.0 (4.5-5.6)	5.2 (4.7-5.9)	157/890	5.1 (3.8-7.0)	5.6 (5.0-6.7)
AP			0.2 (0.1-0.3)	0.3 (0.2-0.4)		0.6 (0.3-0.9)	0.6 (0.5-0.9)
Interaction between DRB1*15:01 and obesity							
DRB1*15:01	Obesity	ca/co ¹	aOR (95% CI) ²	aOR (95% CI) ⁴	ca/co ¹	aOR (95% CI) ²	aOR (95% CI) ⁴
-	+	2422/4595	1.0 (reference)	1.0 (reference)	187/4595	1.0 (reference)	1.0 (reference)
+	+	66/88	1.5 (1.1-2.0)	1.4 (1.0-1.9)	6/88	2.7 (1.0-7.2)	2.1 (0.8-5.8)
-	-	3293/1818	3.3 (3.1-3.7)	3.4 (3.2-3.7)	238/1818	3.7 (2.2-5.9)	3.1 (2.5-3.9)
+	-	118/25	9.1 (5.9-14.0)	8.7 (5.6-13.6)	8/25	8.9 (3.7-21.4)	7.9 (3.2-19.6)
AP			0.6 (0.5-0.8)	0.6 (0.4-0.8)		0.5 (0.3-0.9)	0.6 (0.3-0.9)
Interaction between DRB1*15:01 and EBNA-1 antibody levels							
DRB1*15:01	EBNA-1 IgG levels	ca/co ¹	aOR (95% CI) ²	aOR (95% CI) ⁵	ca/co ¹	aOR (95% CI) ²	aOR (95% CI) ⁵
-	-	510/1836	1.0 (reference)	1.0 (reference)	67/1836	1.0 (reference)	1.0 (reference)
+	-	1284/1832	2.6 (2.2-3.0)	2.5 (2.2-2.8)	110/1832	1.8 (1.3-2.5)	1.7 (1.3-2.4)
-	+	446/590	2.7 (2.3-3.2)	2.8 (2.4-3.4)	51/590	2.5 (1.7-3.7)	2.4 (1.6-3.6)
+	+	2179/886	9.2 (8.1-10.4)	9.3 (8.1-10.6)	170/886	6.1 (4.4-8.3)	6.0 (4.4-8.1)
AP			0.54 (0.52-0.56)	0.52 (0.47-0.58)		0.5 (0.4-0.6)	0.5 (0.4-0.7)
Interaction between DRB1*15:01 and sun exposure							
DRB1*15:01	Sun exposure	Relapsing-onset MS			Progressive-onset MS		
		ca/co ¹	aOR (95% CI) ²	aOR (95% CI) ⁶	ca/co ¹	aOR (95% CI) ²	aOR (95% CI) ⁶
-	High	1921/3864	1.0 (reference)	1.0 (reference)	155/3864	1.0 (reference)	1.0 (reference)
-	Low	666/927	1.4 (1.2-1.6)	1.4 (1.2-1.6)	48/927	1.2 (0.8-1.8)	1.1 (0.7-1.7)
+	High	2628/1516	3.5 (3.2-3.8)	3.4 (3.1-3.7)	166/1516	2.8 (2.1-3.6)	2.7 (2.1-3.5)

+	Low	894/376	4.5 (3.8-5.3)	4.4 (3.7-5.2)	87/376	5.2 (3.7-7.5)	4.6 (3.2-6.6)
AP			0.2 (0.1-0.3)	0.2 (0.1-0.3)		0.5 (0.4-0.7)	0.4 (0.3-0.6)

¹number of exposed cases and controls; ²adjusted for study, year of enrollment, age, sex, residential area, and ancestry; ³adjusted for study, year of enrollment, age, sex, residential area, ancestry, obesity, alcohol consumption, sun exposure habits, snuff use, HLA-A*02:01 and EBNA-1 antibody status; ⁴adjusted for study, year of enrollment, age, sex, residential area, ancestry, smoking, alcohol consumption, sun exposure habits, snuff use, HLA-A*02:01 and EBNA-1 antibody status; ⁵adjusted for study, year of enrollment, age, sex, residential area, ancestry, smoking, obesity, alcohol consumption, sun exposure habits, snuff use, and HLA-A*02:01. ⁶adjusted for study, year of enrollment, age, sex, residential area, ancestry, smoking, obesity, alcohol consumption, snuff use, HLA-A*02:01 and EBNA-1 antibody status.

Supplementary table 7. Term for multiplicative interaction with 95% CI between DRB1*15:01 and each environmental factor.

		Relapsing-onset MS		Progressive-onset MS	
		Interaction term ¹	Interaction term ²	Interaction term ¹	Interaction term ²
DRB1*15:01	Smoking	0.9 (0.8-1.1)	0.9 (0.8-1.0) ³	0.9 (0.6-1.3)	0.9 (0.6-1.4) ³
DRB1*15:01	Obesity	1.8 (1.1-3.2)	1.8 (1.0-3.2) ⁴	1.5 (0.4-5.4)	1.7 (0.5-6.5) ⁴
DRB1*15:01	High EBNA-1 antibody levels	1.3 (1.1-1.6)	1.7 (1.6-1.9) ⁵	1.3 (0.8-2.1)	1.4 (0.9-2.3) ⁵
DRB1*15:01	Low sun exposure	1.0 (0.8-1.1)	1.0 (0.8-1.2) ⁶	1.5 (1.0-2.5)	1.4 (1.0-2.4) ⁶

¹adjusted for study, year of enrollment, age, sex, residential area, and ancestry; ²adjusted for study, year of enrollment, age, sex, residential area, ancestry, alcohol consumption, snuff use, and HLA-A*02:01; ³further adjusted for obesity, EBNA-1 status and sun exposure; ⁴further adjusted for smoking, EBNA-1 status and sun exposure; ⁵further adjusted for smoking, obesity and sun exposure; ⁶further adjusted for smoking, obesity and EBNA-1 status.