

**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 <sup>2</sup> (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 <sup>1</sup>	aOR (95% CI) <sup>2</sup>	aOR (95% CI) <sup>3</sup>	ca/co <sup>1</sup>	aOR (95% CI) <sup>2</sup>	aOR (95% CI) <sup>3</sup>
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)

<sup>1</sup> number of exposed cases and controls; <sup>2</sup>adjusted for study, year of enrollment, age, sex, residential area, and ancestry; <sup>3</sup>adjusted 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 <sup>1</sup>	OR (95% CI) <sup>2</sup>	aOR (95% CI) <sup>3</sup>	ca/co <sup>1</sup>	OR (95% CI) <sup>2</sup>	aOR (95% CI) <sup>3</sup>
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)

<sup>1</sup> number of exposed cases and controls; <sup>2</sup>adjusted for study, year of enrollment, age, sex, residential area, and ancestry; <sup>3</sup>adjusted 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 <sup>1</sup>	aOR (95% CI) <sup>2</sup>	aOR (95% CI) <sup>3</sup>	ca/co <sup>1</sup>	aOR (95% CI) <sup>2</sup>	aOR (95% CI) <sup>3</sup>
-	-	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 <sup>1</sup>	aOR (95% CI) <sup>2</sup>	aOR (95% CI) <sup>4</sup>	ca/co <sup>1</sup>	aOR (95% CI) <sup>2</sup>	aOR (95% CI) <sup>4</sup>
-	+	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 <sup>1</sup>	aOR (95% CI) <sup>2</sup>	aOR (95% CI) <sup>5</sup>	ca/co <sup>1</sup>	aOR (95% CI) <sup>2</sup>	aOR (95% CI) <sup>5</sup>
-	-	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 <sup>1</sup>	aOR (95% CI) <sup>2</sup>	aOR (95% CI) <sup>6</sup>	ca/co <sup>1</sup>	aOR (95% CI) <sup>2</sup>	aOR (95% CI) <sup>6</sup>
-	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)

<sup>1</sup>number of exposed cases and controls; <sup>2</sup>adjusted for study, year of enrollment, age, sex, residential area, and ancestry; <sup>3</sup>adjusted 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; <sup>4</sup>adjusted 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; <sup>5</sup>adjusted for study, year of enrollment, age, sex, residential area, ancestry, smoking, obesity, alcohol consumption, sun exposure habits, snuff use, and HLA-A\*02:01. <sup>6</sup>adjusted 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 <sup>1</sup>	Interaction term <sup>2</sup>	Interaction term <sup>1</sup>	Interaction term <sup>2</sup>
DRB1*15:01	Smoking	0.9 (0.8-1.1)	0.9 (0.8-1.0) <sup>3</sup>	0.9 (0.6-1.3)	0.9 (0.6-1.4) <sup>3</sup>
DRB1*15:01	Obesity	1.8 (1.1-3.2)	1.8 (1.0-3.2) <sup>4</sup>	1.5 (0.4-5.4)	1.7 (0.5-6.5) <sup>4</sup>
DRB1*15:01	High EBNA-1 antibody levels	1.3 (1.1-1.6)	1.7 (1.6-1.9) <sup>5</sup>	1.3 (0.8-2.1)	1.4 (0.9-2.3) <sup>5</sup>
DRB1*15:01	Low sun exposure	1.0 (0.8-1.1)	1.0 (0.8-1.2) <sup>6</sup>	1.5 (1.0-2.5)	1.4 (1.0-2.4) <sup>6</sup>

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