Supplementary table 1

Detailed description of study design and data collection

Swedish studies

The ongoing project Epidemiological Investigation of Multiple Sclerosis (EIMS) is a population-based case-control study on environmental and genetic risk factors for MS. The study group comprises the Swedish population aged 16-70 years. In total, there are today 40 neurology clinics that recruit incident cases of MS to the study, including all university hospitals in Sweden. All cases had been diagnosed by their treating neurologist according to the McDonald criteria[1]. For each case, two controls were randomly selected from the national population register, frequency matched for the case's age in 5-year age strata, gender and residential area.

In EIMS, information regarding environmental exposures and life-style factors such as smoking was collected using a standardised questionnaire. The response rate was 93% for cases and 73% for controls. The EIMS replication analysis was restricted to include participants of Nordic origin (Sweden, Norway, or Denmark) recruited between November 2008 and December 2013. A previously published study presenting an interaction between HLA genotype and smoking based on EIMS used study participants recruited between April 2005 and October 2008[2]. When the Nordic studies were combined into one dataset for more detailed analysis, we included EIMS participants of Nordic origin recruited between April 2005 and October 2008.

The time of the initial appearance of MS symptoms was used as an estimate of the disease onset, and the year in which this occurred was defined as the index year. The corresponding

controls were given the same index year. Smoking habits were only considered before the index year. We have previously demonstrated that the increased risk of developing MS associated with smoking slowly abates after smoking cessation. A decade after stopping smoking, there is no longer an association between smoking and MS risk[3]. Therefore, past smokers were excluded. All participants were asked to provide a blood or saliva sample and those who declined to donate blood or saliva were excluded. For EIMS participants included between April 2005 and October 2008, HLA-DRB1 and HLA-A genotypes were obtained as previously described[4]. For EIMS participants recruited between November 2008 and December 2013 genotyping was performed on the MS replication chip[5] which is based on an Illumina exome chip to which approximately 100,000 custom markers were added and HLA was then imputed with HLA*IMP:02[6]. The replication analysis comprised 763 cases and 1037 controls, whereas 1308 cases and 1858 controls were included in the combined Nordic analysis.

The second Swedish study was GEMS (Genes and Environment in Multiple Sclerosis) in which prevalent cases, distinct from those in EIMS, were identified from the Swedish National MS-registry[7] and controls were randomly selected from the national population register matched for age, gender, and residential area at the time of disease onset. Ethical approval was obtained from the relevant ethics committee. All cases fulfilled the McDonald criteria[2].

GEMS used a similar questionnaire as the one used in EIMS, and the questions on smoking habits were identical as those in the EIMS questionnaire. The study participants were recruited between November 2009 and November 2011. The response rate was 82% for the cases and 66% for the controls. The time of the initial appearance of MS symptoms was used as an estimate of the disease onset, and the year in which this occurred was defined as the

index year. The corresponding controls were given the same index year. Those who had stopped smoking before the index year were excluded. Subjects of non-Nordic origin and those who had not answered the questions on smoking habits were excluded, as were those who did not provide a blood sample. Genotyping was performed on the MS replication chip[5] which is based on an Illumina exome chip to which approximately 100,000 custom markers were added and HLA was then imputed with HLA*IMP:02[6]. The part of GEMS used in this report comprised 3272 prevalent cases and 2382 matched controls.

Danish study

Patients fulfilling the McDonald criteria were recruited from Neurology units in Danish hospitals. The majority of patients were recruited in the area of Copenhagen. The control group comprised healthy white Danish blood donors residing in the area of Copenhagen. The participants in the Danish study were not controlled for geographic location since Denmark is a small country with 5 million inhabitant located on a compact geographic location on latitude 54^0-57^0. The controls were matched to the cases by gender and age in five-year age strata at inclusion in the study. Written informed consent was obtained from all MS patients and approved by the local Ethic Committee (KF-01 314009). With regard to the blood donors, informed consent was obtained through their participation in ”The Danish Blood Donor Study” approved by the local Ethics Committee (M-20090237).

All participants in the Danish study filled out a questionnaire on life style and environmental exposures, adapted from the GEMS study. Of the invited cases, 74% accepted participation in the study between October 2009 and December 2014. Controls were recruited as part of

the Danish Blood Donor Study from five major donor locations in the period of October 2012 to December 2014. The participation rate among controls was estimated to be approximately 83%. Subjects of non-Nordic origin were excluded. The time of the initial appearance of MS symptoms was used as an estimate of the disease onset, and the year in which this occurred was defined as the index year. The corresponding controls were given the same index year. Those who had smoked before the index year were excluded. HLA was imputed in the Danish study using the software HLA*IMP:02[6] based on genotypes obtained as described[8]. The part of the Danish study used in this report comprised 1474 prevalent cases and 3466 controls.

Norwegian study

The Norwegian cases were recruited from the Oslo MS Registry[9] and the controls were recruited from the Norwegian Bone Marrow Donor Registry. The cases were diagnosed in accordance with the Poser and/or McDonald criteria[10-11] and informed written consent was obtained from all participants. The controls were matched to the cases by gender and age in five-year age strata at inclusion in the study.

Exposure data in the Norweigan study was collected in 2011 by sending an extensive questionnaire to potential participants. The participation rate was 70% for the cases and 84% for the controls. The time of the initial appearance of MS symptoms was used as an estimate of the disease onset, and the year in which this occurred was defined as the index year. The corresponding controls were given the same index year. Participants of non-Nordic origin were excluded as well as those who had stopped smoking before the index year. Cases who did not provide a blood sample were also excluded. Information regarding HLA

genotype was available for 99% of the controls via the Norwegian Bone Marrow Donor Registry. In the Norwegian study, HLA-DRB1 genotypes were either obtained by a sequence based approach[12] or imputed using HLA*IMP2[5]. The part of the Norwegian study used in this report comprised 211 prevalent cases and 692 controls.

Serbian study

Cases to the Serbian study were recruited at the Military Medical Academy, a military hospital open for civilians as well, and is the largest medical institution in the country. All patients fulfilled the McDonald criteria. Controls comprised of volunteers from employees of the Military Medical Academy (30%) and from the community (70%). Ethical approval was obtained by Ethical Committee of Military Medical Academy.

MS cases cared for at the Military Medical Academy completed a questionnaire by being personally interviewed by medical personnel. All invited patients accepted to participate in the study. Among potential controls, 92% agreed to participate. Controls answered the same questionnaire as the cases but filled it out at home. The recruitment of cases and controls took place during 2009 and 2010. All cases and controls who participated in the study provided a blood sample. Polymerase chain reaction (PCR) amplification with sequence-specific primers (Olerup SSP low resolution typing kits, Olerup SSP AB, Stockholm, Sweden) was used for genotyping participants in the Serbian study. In total, 457 cases and 505 controls from the Serbian study was included in the analysis.

American study

The American case-control study is based on prevalent cases identified among members of

Kaiser Permanente Medical Care Plan, Northern California Region (KPNC) using electronic medical records. All cases fulfilled the McDonald criteria. Controls were randomly selected from KPNC members and were individually matched to cases on gender, birth date, race/ethnicity, and zip code of the case residence. The study protocol was approved by the Institutional Review Boards of the KP Division of Research and the University of California, Berkeley.

Participants completed a computer-assisted telephone interview regarding life-style factors and various exposures. As of the data freeze in August 2014, the study included a total of 1479 cases and 1185 controls. Within this dataset, there were 1163 cases and 1178 matched controls. The study participation proportions were approximately 80% for cases and 66% for controls. Non-Caucasians and study participants who did not provide a blood sample were excluded. Participants from the American study were genotyped as previously described[13]. The part of the KPNC study used in this report comprised 1013 prevalent cases and 794 controls.

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Supplementary table 2.

Description of potential confouding variables adjusted for in EIMS and GEMS

Residential area (county)

Passive smoking; dichotomized into ever or never exposed to passive smoking.

Snuff use; dichotomized into ever or never snuff users.

Alcohol consumption; categorized based on alcohol consumption at the index year (yes, no, or unknown).

Adolescent body mass index; calculated by dividing self-reported weight in kilograms by self-reported height in meters squared and adjusted for as a continuous variable.

Ultraviolet radiation exposure (UVR); based on three questions regarding exposure to UVR where each answer alternative was given a number ranging from 1 (the lowest exposure) to 4 (the highest exposure), we constructed an index by adding the numbers together and thus acquired a value between 3 and 12.

A history of infectious mononucleosis; dichotomized into yes or no.

Educational level; categorized into no post-secondary education, post-secondary education without university degree, or university degree.

Socioeconomic class; the last occupation during the year before the index year was used as a marker for socioeconomic class which was categorized into the following strata: 1, workers in goods production; 2, workers in service production; 3, employees at lower and intermediate levels; 4, employees at higher levels, executives, university graduates, and 5; others such as pensioners, students, and unemployed.

Supplementary table 3. OR with 95% CI of developing MS associated with smoking, absence of HLA-A*02 and HLA-DRB1*15, by study.

	OR[1]	OR[2]	OR[3]	OR[4]	OR[5]	OR6[6]
Smoking	1.5 (1.3-1.8)	1.6 (1.4-1.8)	3.1 (2.7-3.5)	2.2 (1.5-3.1)	2.4 (1.8-3.1)	1.4 (1.1-1.8)
A2-	1.7 (1.5-2.0)	1.8 (1.6-2.0)	1.7 (1.5-2.0)	1.7 (1.2-2.5)	0.9 (0.7-1.2)	1.7 (1.4-2.2)
DR15	3.6 (3.1-4.1)	3.7 (3.3-4.1)	3.4 (3.0-3.9)	5.1 (3.6-7.4)	2.7 (2.0-3.7)	3.1 (2.4-3.9)

1=EIMS, Study 2=GEMS, 3=Danish study, 4=Norwegian study, 5=Serbian study, 6=American study
Each of the three risk factors were adjusted for the other two risk factors, as well as for age and gender.

Supplementary table 4. EIMS April 2005-October 2008

OR with 95% CI of developing MS for subjects categorized by HLA-DRB1*15 and HLA-A*02. Attributable proportion due to interaction between HLA-DRB1*15 and HLA-A*02.

DR15+	A2-	ca/co*	OR (95% CI)#	OR (95% CI)¤	p
-	-	76/321	1.0 (-)	1.0 (-)	
-	+	137/265	2.2 (1.6-3.1)	2.2 (1.6-3.1)	<0.0001
+	-	142/134	4.5 (3.2-6.4)	4.5 (3.2-6.4)	<0.0001
+	+	190/101	8.1 (5.7-11.6)	8.1 (5.7-11.5)	<0.0001
				AP 0.3 (0.07-0.5), p=0.01	

* number of exposed cases and controls; # adjusted for age, gender, and smoking; ¤ adjusted for age, gender, smoking, passive smoking. snuff use, and alcohol habits.

OR with 95% CI of developing MS for subjects categorized by HLA-A*02 and smoking. Attributable proportion due to interaction between HLA-A*02 and smoking.

A2-	Smoking	ca/co*	OR (95% CI)#	OR (95% CI)¤	p
-	-	126/291	1.0 (-)	1.0 (-)	
-	+	92/164	1.3 (0.9-1.8)	1.3 (0.9-1.9)	0.1
+	-	184/250	1.7 (1.3-2.3)	1.7 (1.3-2.3)	0.0003
+	+	143/116	3.2 (2.3-4.5)	3.3 (2.3-4.6)	<0.0001
				AP 0.4 (0.1-0.6), p=0.002	

* number of exposed cases and controls; # adjusted for age, gender, and HLA-DRB1*15; ¤ adjusted for age, gender, HLA-DRB1*15, passive smoking. snuff use, and alcohol habits.

OR with 95% CI of developing MS for subjects categorized by HLA-DRB1*15 and smoking. Attributable proportion due to interaction between HLA-DRB1*15 and smoking.

DR15+	Smoking	ca/co*	OR (95% CI)#	OR (95% CI)¤	p
-	-	114/387	1.0 (-)	1.0 (-)	
-	+	99/199	1.7 (1.2-2.4)	1.7 (1.3-2.4)	0.0008
+	-	196/154	4.4 (3.3-6.0)	4.4 (3.3-6.0)	<0.0001
+	+	136/81	6.1 (4.3-8.6)	6.2 (4.3-8.8)	<0.0001
				AP 0.2 (-0.1-0.5), p=0.3	

* number of exposed cases and controls; # adjusted for age, gender, and HLA-A*02; ¤ adjusted for age, gender, HLA-A*02, passive smoking. snuff use, and alcohol habits.

EIMS November 2008-December 2013

OR with 95% CI of developing MS for subjects categorized by HLA-DRB1*15 and HLA-A*02. Attributable proportion due to interaction between HLA-DRB1*15 and HLA-A*02.

DR15+	A2-	ca/co*	OR (95% CI)#	OR (95% CI)¤	p
-	-	128/332	1.0 (-)	1.0 (-)	
-	+	194/385	1.3 (1.0-1.7)	1.3 (1.0-1.7)	0.05
+	-	193/192	2.6 (2.0-3.5)	2.6 (1.9-3.5)	<0.0001
+	+	248/128	5.0 (3.7-6.8)	5.0 (3.7-6.8)	<0.0001
				0.4 (0.2-0.6), p<0.0001	

* number of exposed cases and controls; # adjusted for age, gender, and smoking; ¤ adjusted for age, gender, smoking, passive smoking. snuff use, and alcohol habits.

OR with 95% CI of developing MS for subjects categorized by HLA-A*02 and smoking. Attributable proportion due to interaction between HLA-A*02 and smoking.

A2-	Smoking	ca/co*	OR (95% CI)#	OR (95% CI)¤	p
-	-	209/385	1.0 (-)	1.0 (-)	
-	+	112/139	1.5 (1.1-2.0)	1.4 (1.0-2.0)	0.03
+	-	286/380	1.5 (1.2-1.9)	1.5 (1.2-1.9)	0.0005
+	+	156/133	2.4 (1.8-3.2)	2.4 (1.8-3.2)	<0.0001
				AP 0.2 (-0.1-0.5), p=0.2	

* number of exposed cases and controls; # adjusted for age, gender, and HLA-DRB1*15; ¤ adjusted for age, gender, HLA-DRB1*15, passive smoking. snuff use, and alcohol habits.

OR with 95% CI of developing MS for subjects categorized by HLA-DRB1*15 and smoking. Attributable proportion due to interaction between HLA-DRB1*15 and smoking.

DR15+	Smoking	ca/co*	OR (95% CI)#	OR (95% CI)¤	p
-	-	212/524	1.0 (-)	1.0 (-)	
-	+	110/193	1.4 (1.1-1.9)	1.4 (1.0-1.8)	0.02
+	-	283/241	3.0 (2.4-3.8)	3.0 (2.4-3.8)	<0.0001
+	+	158/79	5.2 (3.8-7.2)	5.0 (3.6-6.9)	<0.0001
				AP 0.3 (0.1-0.5), p=0.004	

* number of exposed cases and controls; # adjusted for age, gender, and HLA-A*02; ¤ adjusted for age, gender, HLA-A*02, passive smoking. snuff use, and alcohol habits.

EIMS April 2005-December 2013

OR with 95% CI of developing MS for subjects categorized by HLA-DRB1*15 and HLA-A*02. Attributable proportion due to interaction between HLA-DRB1*15 and HLA-A*02.

DR15+	A2-	ca/co*	OR (95% CI)#	OR (95% CI)¤	p
-	-	204/653	1.0 (-)	1.0 (-)	
-	+	331/650	1.6 (1.3-2.0)	1.6 (1.3-2.0)	<0.0001
+	-	335/326	3.3 (2.7-4.1)	3.3 (2.7-4.1)	<0.0001
+	+	438/229	6.2 (5.0-7.8)	6.2 (5.0-7.8)	<0.0001
				AP 0.4 (0.2-0.5), p<0.0001	

* number of exposed cases and controls; # adjusted for age, gender, and smoking; ¤ adjusted for age, gender, smoking, passive smoking. snuff use, and alcohol habits.

OR with 95% CI of developing MS for subjects categorized by HLA-A*02 and smoking. Attributable proportion due to interaction between HLA-A*02 and smoking.

A2-	Smoking	ca/co*	OR (95% CI)#	OR (95% CI)¤	p
-	-	335/676	1.0 (-)	1.0 (-)	
-	+	204/303	1.4 (1.1-1.7)	1.3 (1.1-1.7)	0.009
+	-	470/630	1.6 (1.3-1.9)	1.6 (1.4-1.9)	<0.0001
+	+	299/249	2.8 (2.2-3.5)	2.7 (2.2-3.4)	<0.0001
				0.3 (0.1-0.5), p=0.002	

* number of exposed cases and controls; # adjusted for age, gender, and HLA-DRB1*15; ¤ adjusted for age, gender, HLA-DRB1*15, passive smoking. snuff use, and alcohol habits.

OR with 95% CI of developing MS for subjects categorized by HLA-DRB1*15 and smoking. Attributable proportion due to interaction between HLA-DRB1*15 and smoking.

DR15+	Smoking	ca/co*	OR (95% CI)#	OR (95% CI)¤	p
-	-	326/911	1.0 (-)	1.0 (-)	
-	+	209/392	1.5 (1.2-1.9)	1.5 (1.2-1.9)	<0.0001
+	-	479/395	3.5 (2.9-4.2)	3.5 (2.9-4.2)	<0.0001
+	+	294/160	5.4 (4.3-6.9)	5.4 (4.3-6.9)	<0.0001
				0.3 (0.08-0.4), p=0.005	

* number of exposed cases and controls; # adjusted for age, gender, and HLA-A*02; ¤ adjusted for age, gender, HLA-A*02, passive smoking. snuff use, and alcohol habits.

GEMS

OR with 95% CI of developing MS for subjects categorized by HLA-DRB1*15 and HLA-A*02. Attributable proportion due to interaction between HLA-DRB1*15 and HLA-A*02.

DR15+	**A2-**	**ca/co***	**OR (95% CI)#**	**OR (95% CI)¤**	**p**
-	-	517/971	1.0 (-)	1.0 (-)	1.0 (-)
-	+	700/649	2.0 (1.7-2.4)	2.1 (1.8-2.4)	<0.0001
+	-	977/437	4.2 (3.6-5.0)	4.3 (3.7-5.0)	<0.0001
+	+	1078/325	6.3 (5.4-7.4)	6.4 (5.5-7.6)	<0.0001
				AP 0.2 (0.04-0.3), p=0.01	

* number of exposed cases and controls; # adjusted for age, gender, and smoking; ¤ adjusted for age, gender, smoking, passive smoking. snuff use, and alcohol habits.

OR with 95% CI of developing MS for subjects categorized by HLA-A*02 and smoking. Attributable proportion due to interaction between HLA-A*02 and smoking.

A2-	**Smoking**	**ca/co***	**OR (95% CI)#**	**OR (95% CI)¤**	**p**
-	-	777/890	1.0 (-)	1.0 (-)	
-	+	717/518	1.6 (1.4-1.8)	1.6 (1.4-1.9)	<0.0001
+	-	971/637	1.8 (1.5-2.0)	1.8 (1.6-2.1)	<0.0001
+	+	807/337	2.7 (2.3-3.2)	2.9 (2.4-3.4)	<0.0001
				AP 0.2 (0.008-0.3), p=0.04	

* number of exposed cases and controls; # adjusted for age, gender, and HLA-DRB1*15; ¤ adjusted for age, gender, HLA-DRB1*15, passive smoking. snuff use, and alcohol habits.

OR with 95% CI of developing MS for subjects categorized by HLA-DRB1*15 and smoking. Attributable proportion due to interaction between HLA-DRB1*15 and smoking.

DR15+	**Smoking**	**ca ca/co***	**OR (95% CI)#**	**OR (95% CI)¤**	**p**
-	-	622/1040	1.0 (-)	1.0 (-)	
-	+	595/580	1.7 (1.5-2.0)	1.7 (1.5-2.0)	<0.0001
+	-	1126/487	3.9 (3.4-4.5)	4.0 (3.4-4.6)	<0.0001
+	+	929/275	5.7 (4.8-6.7)	5.8 (4.9-6.9)	<0.0001
				AP 0.2 (0.06-0.3), p=0.005	

* number of exposed cases and controls; # adjusted for age, gender, and HLA-A*02; ¤ adjusted for age, gender, HLA-A*02, passive smoking. snuff use, and alcohol habits.

Danish study

OR with 95% CI of developing MS for subjects categorized by HLA-DRB1*15 and HLA-A*02. Attributable proportion due to interaction between HLA-DRB1*15 and HLA-A*02.

DR15+	A2-	ca/co*	OR (95% CI)#	p	AP
-	-	236/1297	1.0 (-)		
-	+	356/1118	1.8 (1.5-2.2)	<0.0001	
+	-	353/547	3.6 (3.0-4.4)	<0.0001	
+	+	529/504	5.9 (4.9-7.2)	<0.0001	0.3 (0.1-0.4), p=0.0004

* number of exposed cases and controls; # adjusted for age, gender, and smoking;

OR with 95% CI of developing MS for subjects categorized by HLA-A*02 and smoking. Attributable proportion due to interaction between HLA-A*02 and smoking.

A2-	Smoking	ca/co*	OR (95% CI)#	p	AP
-	-	258/1323	1.0 (-)		
-	+	331/521	3.2 (3.6-4.0)	<0.0001	
+	-	414/1185	1.8 (1.5-2.1)	<0.0001	
+	+	471/437	5.4 (4.4-6.6)	<0.0001	0.2 (0.005-0.3), p=0.04

* number of exposed cases and controls; # adjusted for age, gender, and HLA-DRB1*15;

OR with 95% CI of developing MS for subjects categorized by HLA-DRB1*15 and smoking. Attributable proportion due to interaction between HLA-DRB1*15 and smoking.

DR15+	Smoking	ca/co*	OR (95% CI)#	p	AP
-	-	258/1748	1.0 (-)		
-	+	334/667	3.3 (2.7-3.9)	<0.0001	
+	-	414/760	3.6 (3.0-4.3)	<0.0001	
+	+	468/291	10.4 (8.5-12.8)	<0.0001	0.4 (0.3-0.5), p<0.0001

* number of exposed cases and controls; # adjusted for age, gender, and HLA-A*02;

Norwegian study

OR with 95% CI of developing MS for subjects categorized by HLA-DRB1*15 and HLA-A*02. Attributable proportion due to interaction between HLA-DRB1*15 and HLA-A*02.

DR15+	A2-	ca/co*	OR (95% CI)#	p	AP
-	-	34/270	1.0 (-)		
-	+	41/221	1.5 (0.9-2.5)	0.2	
+	-	67/128	4.3 (2.6-7.2)	<0.0001	
+	+	69/73	8.9 (5.3-15.2)	<0.0001	0.5 (0.2-0.7), p=0.0006

* number of exposed cases and controls; # adjusted for age, gender, and smoking;

OR with 95% CI of developing MS for subjects categorized by HLA-A*02 and smoking. Attributable proportion due to interaction between HLA-A*02 and smoking.

A2-	Smoking	ca/co*	OR (95% CI)#	p	AP
-	-	42/247	1.0 (-)	1.0 (-)	
-	+	59/151	2.0 (1.2-3.3)	0.003	
+	-	46/195	1.6 (0.9-2.6)	0.07	
+	+	64/99	3.9 (2.3-6.5)	<0.0001	0.3 (0.0-0.7), p=0.04

* number of exposed cases and controls; # adjusted for age, gender, and HLA-DRB1*15;

OR with 95% CI of developing MS for subjects categorized by HLA-DRB1*15 and smoking. Attributable proportion due to interaction between HLA-DRB1*15 and smoking.

DR15+	Smoking	ca/co*	OR (95% CI)#	p	AP
-	-	33/323	1.0 (-)		
-	+	42/168	2.6 (1.6-4.5)	0.0001	
+	-	55/119	6.0 (3.5-10.3)	<0.0001	
+	+	81/82	11.7 (7.0-19.7)	<0.0001	0.3 (0.05-0.6), p=0.02

* number of exposed cases and controls; # adjusted for age, gender, and HLA-A*02

Serbian study

OR with 95% CI of developing MS for subjects categorized by HLA-DRB1*15 and HLA-A*02. Attributable proportion due to interaction between HLA-DRB1*15 and smoking.

DR15+	A2-	ca/co*	OR (95% CI)#	p	AP
-	-	148/211	1.0 (-)		
-	+	76/34	3.2 (2.0-5.0)	<0.0001	
+	-	141/206	1.0 (0.7-1.3)	0.9	
+	+	92/54	2.4 (1.6-3.6)	<0.0001	-0.3 (-1-0.4), p=0.4

* number of exposed cases and controls; # adjusted for age, gender, and smoking;

OR with 95% CI of developing MS for subjects categorized by HLA-A*02 and smoking. Attributable proportion due to interaction between HLA-A*02 and smoking.

A2-	Smoking	ca/co*	OR (95% CI)#	p	AP
-	-	62/105	1.0 (-)		
-	+	162/140	1.9 (1.3-2.8)	0.0009	
+	-	55/123	0.8 (0.5-1.2)	0.2	
+	+	178/137	2.2 (1.5-3.2)	<0.0001	0.2 (-0.09-0.6), p=0.2

* number of exposed cases and controls; # adjusted for age, gender, and HLA-DRB1*15;

OR with 95% CI of developing MS for subjects categorized by HLA-DRB1*15 and smoking. Attributable proportion due to interaction between HLA-DRB1*15 and smoking.

DR15+	Smoking	ca/co*	OR (95% CI)#	p	AP
-	-	77/187	1.0 (-)		
-	+	212/230	2.2 (1.6-3.1)	<0.0001	
+	-	40/41	2.4 (1.4-4.0)	0.0009	
+	+	128/47	6.5 (4.3-10.0)	<0.0001	0.4 (0.2-0.7), p=0.0005

* number of exposed cases and controls; # adjusted for age, gender, and HLA-A*02

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OR with 95% CI of developing MS for subjects categorized by HLA-DRB1*15 and HLA-A*02. Attributable proportion due to interaction between HLA-DRB1*15 and HLA-A*02.

DR15+	A2-	ca/co*	OR (95% CI)#	p	AP
-	-	169/273	1.0 (-)		
-	+	302/302	1.6 (1.2-2.2)	0.001	
+	-	198/119	2.5 (1.8-3.6)	<0.0001	
+	+	344/100	5.9 (4.1-9.3)	<0.0001	0.5 (0.3-0.7), p<0.0001

* number of exposed cases and controls; # adjusted for age, gender, and smoking

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OR with 95% CI of developing MS for subjects categorized by HLA-A*02 and smoking. Attributable proportion due to interaction between HLA-A*02 and smoking.

A2-	Smoking	ca/co*	OR (95% CI)#	p	AP
-	-	169/231	1.0 (-)		
-	+	198/161	1.9 (1.4-2.7)	0.0004	
+	-	344/244	2.2 (1.6-3.0)	<0.0001	
+	+	302/158	3.1 (2.2-4.3)	<0.0001	0.00 (-0.3-0.3), p=0.97

* number of exposed cases and controls; # adjusted for age, gender, and HLA-DRB1*15;

OR with 95% CI of developing MS for subjects categorized by HLA-DRB1*15 and smoking. Attributable proportion due to interaction between HLA-DRB1*15 and smoking.

DR15+	Smoking	ca/co*	OR (95% CI)#	p	AP
-	-	233/342	1.0 (-)		
-	+	238/233	1.5 (1.1-2.0)	0.01	
+	-	280/133	2.8 (2.1-3.8)	<0.001	
+	+	262/86	5.3 (3.7-7.6)	<0.0001	0.4 (0.1-0.6), p=0.002

* number of exposed cases and controls; # adjusted for age, gender, and HLA-A*02;