

eTable 1. Number of cases and controls in EIMS and GEMS.

Study		Included in the study	HLA genotype available	Datasets for analysis		
				Data on genotype and smoking.	Data on genotype and EBNA-1 antibody levels	Data on genotype and adolescent BMI
EIMS	Cases	2880	2070	2070	986	1968
	Controls	6122	2899	2899	1417	2783
GEMS	Cases	6085	5161	5161	4284	5017
	Controls	5357	3833	3833	3770	3786
Total	Cases	8965	7231	7231	5270	6985
	Controls	11479	6732	6732	5187	6569

eTable 2. OR with 95% CI of developing MS among subjects categorized by *HLA-DRB1*15:01* and smoking habits. N=7231 cases and 6732 controls.

<i>DRB1*15:01</i>	Smoking	ca/co ^a	OR (95% CI) ^b	OR (95% CI) ^c	AP (95% CI)	Exponentiated interaction term ^d
0	-	1326/2572	1.0 (reference)	1.0 (reference)		
0	+	1767/2258	1.5 (1.4-1.7)	1.5 (1.4-1.7)		
1	-	1525/904	3.3 (3.0-3.7)	3.9 (3.4-4.4)		
1	+	1881/815	4.5 (4.1-5.1)	5.6 (4.9-6.3)	0.3 (0.2-0.4)	0.9 (0.8-1.1)
2	-	364/106	6.7 (5.4-8.6)	8.3 (6.5-10.8)		
2	+	368/77	9.1 (7.1-11.9)	11.6 (8.8-15.3)	0.3 (0.02-0.6)	0.9 (0.7-1.3)

^anumber of exposed cases and controls; ^badjusted for study, age, sex, residential area, and ancestry;

^cadjusted for study, age, sex, residential area, ancestry, EBNA1 status, adolescent BMI, rs9277565, rs2229092, *DRB1*03:01*, *DRB1*13:03*, *DRB1*08:01*, *A*02:01*, *B*44:02*, *B*38:01*, *B*55:01*,

*DQA1*01:01*, *DQB1*03:02*, and *DQB1*03:01*. Homozygote correction for *DRB1*03:01* and *A*02:01*.

AP=attributable proportion due to interaction. ^dinteraction term related to multiplicative interaction.

eTable 3. OR with 95% CI of developing MS among subjects categorized by *HLA-DRB1*15:01* and EBNA-1 status. N=5270 cases and 5187 controls.

<i>DRB1*15:01</i>	Anti-EBNA-1 IgG	ca/co ^a	OR (95% CI) ^b	OR (95% CI) ^c	AP (95% CI)	Exponentiated interaction term
0	Low	693/1955	1.0 (reference)	1.0 (reference)		
0	High	1474/1747	2.5 (2.2-2.8)	2.6 (2.3-2.9)		
1	Low	514/584	2.5 (2.1-2.9)	3.2 (2.7-3.8)		
1	High	2033/758	8.0 (7.0-9.0)	10.0 (8.6-11.5)	0.5 (0.4-0.6)	1.0 (0.8-1.2)
2	Low	111/56	5.6 (4.0-7.8)	7.7 (5.4-11.0)		
2	High	445/87	15.2 (11.8-19.4)	19.5 (14.8-25.6)	0.5 (0.4-0.7)	1.0 (0.7-1.5)

^anumber of exposed cases and controls; ^badjusted for study, age, sex, residential area, and ancestry;

^cadjusted for study, age, sex, residential area, ancestry, smoking, adolescent BMI, rs9277565,

rs2229092, *DRB1*03:01*, *DRB1*13:03*, *DRB1*08:01*, *A*02:01*, *B*44:02*, *B*38:01*, *B*55:01*,

*DQA1*01:01*, *DQB1*03:02*, and *DQB1*03:01*. Homozygote correction for *DRB1*03:01* and *A*02:01*.

AP=attributable proportion due to interaction. ^dinteraction term related to multiplicative interaction.

eTable 4. OR with 95% CI of developing MS among subjects categorized by HLA-DRB1*15:01 and adolescent BMI status. N=6985 cases and 6569 controls.

DRB1*15:01	Adolescent BMI	ca/co ^a	OR (95% CI) ^b	OR (95% CI) ^c	AP (95% CI)	Exponentiated interaction term
0	≤25	2584/4252	1.0 (reference)	1.0 (reference)		
0	>25	392/467	1.4 (1.2-1.6)	1.4 (1.2-1.6)		
1	≤25	2851/1509	3.1 (2.9-3.4)	3.7 (3.3-4.1)		
1	>25	450/164	4.7 (3.9-5.6)	5.4 (4.4-6.7)	0.3 (0.1-0.4)	0.9 (0.8-1.1)
2	≤25	621/162	6.2 (5.2-7.5)	8.1 (6.5-10.0)		
2	>25	87/15	10.0 (5.7-17.3)	12.5 (6.9-21.6)	0.3 (-0.1-0.7)	0.9 (0.6-1.3)

^anumber of exposed cases and controls; ^badjusted for study, age, sex, residential area, and ancestry;

^cadjusted for study, age, sex, residential area, ancestry, smoking, EBNA1 status, rs9277565,

rs2229092, *DRB1*03:01*, *DRB1*13:03*, *DRB1*08:01*, *A*02:01*, *B*44:02*, *B*38:01*, *B*55:01*,

*DQA1*01:01*, *DQB1*03:02*, and *DQB1*03:01*. Homozygote correction for *DRB1*03:01* and *A*02:01*.

AP=attributable proportion due to interaction. ^dinteraction term related to multiplicative interaction.

Participants with age <20 years at the index year were excluded.

eTable 5. OR with 95% CI of developing MS among subjects categorized by DRB1*15:01, HLA-A*02:01, and smoking.

DRB1*15:01	A*02:01	Smoking	ca/co ^a	OR (95% CI) ^b	OR (95% CI) ^c
0	1-2	-	510/1402	1.0 (reference)	1.0 (reference)
0	0	-	816/1170	2.0 (1.7-2.3)	1.8 (1.6-2.1)
1	1-2	-	655/501	3.6 (3.1-4.2)	4.0 (3.3-4.8)
1	0	-	870/403	6.0 (5.1-7.0)	6.8 (5.7-8.2)
2	1-2	-	173/57	8.3 (6.0-11.4)	10.9 (7.6-15.4)
2	0	-	191/49	10.9 (7.8-15.3)	12.6 (8.7-18.2)
0	1-2	-	722/1217	1.6 (1.4-1.9)	1.6 (1.4-1.9)
0	0	+	1045/1041	2.8 (2.4-3.2)	2.6 (2.2-3.0)
1	1-2	+	865/473	5.1 (4.4-5.9)	5.7 (4.8-6.7)
1	0	+	1016/342	8.2 (7.0-9.6)	9.3 (7.7-11.1)
2	1-2	+	175/48	9.8 (7.0-13.8)	11.5 (8.0-16.5)
2	0	+	193/29	18.0 (12.0-27.0)	20.0 (13.1-30.5)

^anumber of exposed cases and controls; ^badjusted for study, age, sex, residential area, and ancestry;

^cadjusted for study, age, sex, residential area, ancestry, EBNA-1 status, adolescent BMI, rs9277565, rs2229092, DRB1*03:01, DRB1*13:03, DRB1*08:01, B*44:02, B*38:01, B*55:01, DQA1*01:01, DQB1*03:02, and DQB1*03:01. Homozygote correction for DRB1*03:01 and A*02:01.

eTable 6. OR with 95% CI of developing MS among subjects categorized by DRB1*15:01, A*02:01 status, and EBNA-1 status.

DRB1*15:01	A*02:01	Anti-EBNA-1 IgG	ca/co ^a	OR (95% CI) ^b	OR (95% CI) ^c
0	1-2	Low	306/1081	1.0 (reference)	1.0 (reference)
0	0	Low	387/874	1.6 (1.3-1.9)	1.4 (1.1-1.6)
1	1-2	Low	260/342	2.7 (2.1-3.3)	3.2 (3.2-4.0)
1	0	Low	254/242	3.7 (2.9-4.6)	4.2 (3.4-5.4)
2	1-2	Low	58/31	6.6 (4.2-10.4)	8.5 (5.3-13.7)
2	0	Low	53/25	7.5 (4.6-12.3)	8.8 (5.3-14.8)
0	1-2	High	566/980	2.1 (1.8-2.5)	2.2 (1.8-2.6)
0	0	High	908/767	4.3 (3.7-5.1)	4.2 (3.5-4.9)
1	1-2	High	881/424	7.7 (6.5-9.2)	8.9 (7.4-10.8)
1	0	High	1152/334	12.7 (10.6-15.2)	14.9 (12.4-18.3)
2	1-2	High	208/52	14.7 (10.5-20.4)	17.8 (12.5-25.3)
2	0	High	237/35	25.2 (17.3-36.8)	28.7 (19.3-42.7)

^anumber of exposed cases and controls; ^badjusted for study, age, sex, residential area, and ancestry;

^cadjusted for study, age, sex, residential area, ancestry, smoking, adolescent BMI, rs9277565, rs2229092, DRB1*03:01, DRB1*13:03, DRB1*08:01, B*44:02, B*38:01, B*55:01, DQA1*01:01, DQB1*03:02, and DQB1*03:01. Homozygote correction for DRB1*03:01 and A*02:01.

eTable 7. OR with 95% CI of developing MS in subjects categorized by DRB1*15:01, A*02:01 status, and adolescent BMI.

DRB1*15:01	A*02:01	Adolescent BMI	ca/co ^a	OR (95% CI) ^b	OR (95% CI) ^c
0	1-2	<25	1021/2295	1.0 (reference)	1.0 (reference)
0	0	<25	1563/1957	1.8 (1.6-2.0)	1.6 (1.5-1.8)
1	1-2	<25	1248/864	3.2 (2.9-3.6)	3.6 (3.2-4.1)
1	0	<25	1603/645	5.6 (5.0-6.3)	6.2 (5.4-7.2)
2	1-2	<25	301/90	7.4 (5.8-9.5)	9.2 (7.0-12.1)
2	0	<25	320/72	9.8 (7.5-12.9)	11.3 (8.4-15.2)
0	1-2	≥25	161/72	1.3 (1.1-1.7)	1.3 (1.0-1.6)
0	0	≥25	231/199	2.8 (2.2-3.4)	2.5 (2.0-3.1)
1	1-2	≥25	221/89	5.8 (4.5-7.5)	6.0 (4.6-8.0)
1	0	≥25	229/75	7.1 (5.4-9.4)	8.0 (6.0-10.7)
2	1-2	≥25	39/12	7.2 (3.7-13.8)	8.2 (4.1-16.2)
2	0	≥25	48/3	40.0 (12.4-129)	44.3 (13.5-145)

^anumber of exposed cases and controls; ^badjusted for study, age, sex, residential area, and ancestry;

^cadjusted for study, age, sex, residential area, ancestry, smoking, EBNA-1 status, rs9277565, rs2229092, DRB1*03:01, DRB1*13:03, DRB1*08:01, B*44:02, B*38:01, B*55:01, DQA1*01:01, DQB1*03:02, and DQB1*03:01. Homozygote correction for DRB1*03:01 and A*02:01.