Table S1: interaction effect estimates for interaction between HLA status and EBNA titre – subgroup analysis based on method of HLA genotyping.

PCR-based HLA genotyping			
	Estimate	SE	P.value
AP	0.600626	0.080903	1.14E-13
RERI	5.848862	1.473361	7.20E-05
Log(Synergy index)	0.8520740	0.29822258	4.274305e-03
Multiplicative interaction	1.771796	1.030103	0.453711
Tag SNP HLA genotyping			
	Estimate	SE	P.value
AP	0.148602	0.209132	0.477353
RERI	0.988962	1.947507	0.611587
Log(Synergy index)	0.1139513	0.2786410	0.6825735
Multiplicative interaction	0.446705	1.320622	0.675241

Table S2: interaction effect estimates for interaction between smoking status and EBNA titre – subgroup analysis with one study excluded due to second-hand smoke exposure being used as the exposure, and one for using serum cotinine as a proxy measure for smoking.

Excluding study assessing second-hand smoke			
	Estimate	SE	P.value
AP	0.188255	0.127964	0.14125
RERI	0.39963	0.372714	0.283623
Log(Synergy index)	0.2422447	0.2503367	0.3332064
Multiplicative interaction	1.179697	0.781378	0.818112
Excluding study using cotinine as proxy for smoking			
	Estimate	SE	P.value
AP	0.159765	0.158914	0.314724
RERI	0.377317	0.477298	0.429221
Log(Synergy index)	0.1489028	0.2585146	0.5646194
Multiplicative interaction	1.263166	0.888417	0.767063

Supplementary figure legends

Supplementary figure 1: (a)-(d) Graphs as per figure 2, analysis restricted to studies using tagging SNPs to determine HLA genotype. (e) - (h) Graphs as per figure 2, analysis restricted to studies using PCR-based methods to determine HLA genotype.

Study	ln(OR)	SE(ln(OR))	Weight	OR [95% CI]
De Jager 2008	2.21	0.5595	14.1%	9.08 [3.03; 27.20]
Lucas 2011	2.99	0.6144	13.1%	19.84 [5.95; 66.15]
Simon_NHS 2010	1.55	0.8790	9.2%	4.70 [0.84; 26.32]
Simon_Tas 2010	0.79	0.3275	18.6%	2.20 [1.16; 4.18]
van der Mei 2010	2.95	0.5526	14.2%	19.17 [6.49; 56.62]
van der Mei 2010	1.49	0.5101	15.0%	4.43 [1.63; 12.04]
Van der Mei 2016	1.76	0.4684	15.8%	5.81 [2.32; 14.55]
Total (95% CI)			**100.0%**	**6.77 [3.43; 13.37]**

Heterogeneity: Tau^2 = 0.5421; Chi^2 = 18.32, df = 6 (P < 0.01); I^2 = 67%

(a)
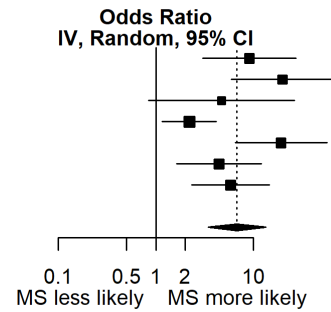
Study	ln(OR)	SE(ln(OR))	Weight	OR [95% CI]
De Jager 2008	1.20	0.7406	12.4%	3.30 [0.77; 14.10]
Lucas 2011	.	.	0.0%	
Simon_NHS 2010	0.47	0.1339	29.6%	1.60 [1.23; 2.08]
Simon_Tas 2010	1.59	1.2141	6.1%	4.90 [0.45; 52.92]
van der Mei 2010	2.40	0.5803	16.1%	11.04 [3.54; 34.43]
van der Mei 2010	1.00	0.5086	18.1%	2.71 [1.00; 7.34]
Van der Mei 2016	1.11	0.5246	17.7%	3.02 [1.08; 8.44]
Total (95% CI)			**100.0%**	**3.15 [1.63; 6.07]**

Heterogeneity: Tau^2 = 0.3614; Chi^2 = 13.28, df = 5 (P = 0.02); I^2 = 62%

(b)
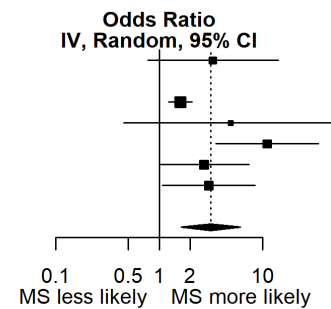
Study	ln(OR)	SE(ln(OR))	Weight	OR [95% CI]
De Jager 2008	1.47	0.5602	20.8%	4.35 [1.45; 13.05]
Lucas 2011	.	.	0.0%	
Simon_NHS 2010	.	.	0.0%	
Simon_Tas 2010	.	.	0.0%	
van der Mei 2010	1.86	0.5958	18.5%	6.43 [2.00; 20.67]
van der Mei 2010	1.55	0.4802	28.0%	4.69 [1.83; 12.02]
Van der Mei 2016	0.69	0.4426	32.7%	2.00 [0.84; 4.76]
Total (95% CI)			**100.0%**	**3.70 [2.23; 6.16]**

Heterogeneity: Tau^2 = 0.0106; Chi^2 = 3.12, df = 3 (P = 0.37); I^2 = 4%

(c)

(d)

Odds Ratio
IV, Random, 95% CI
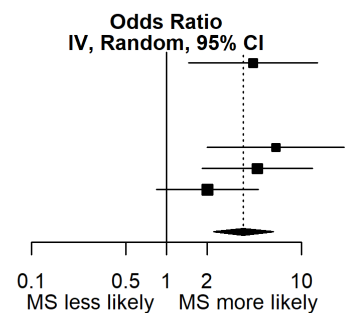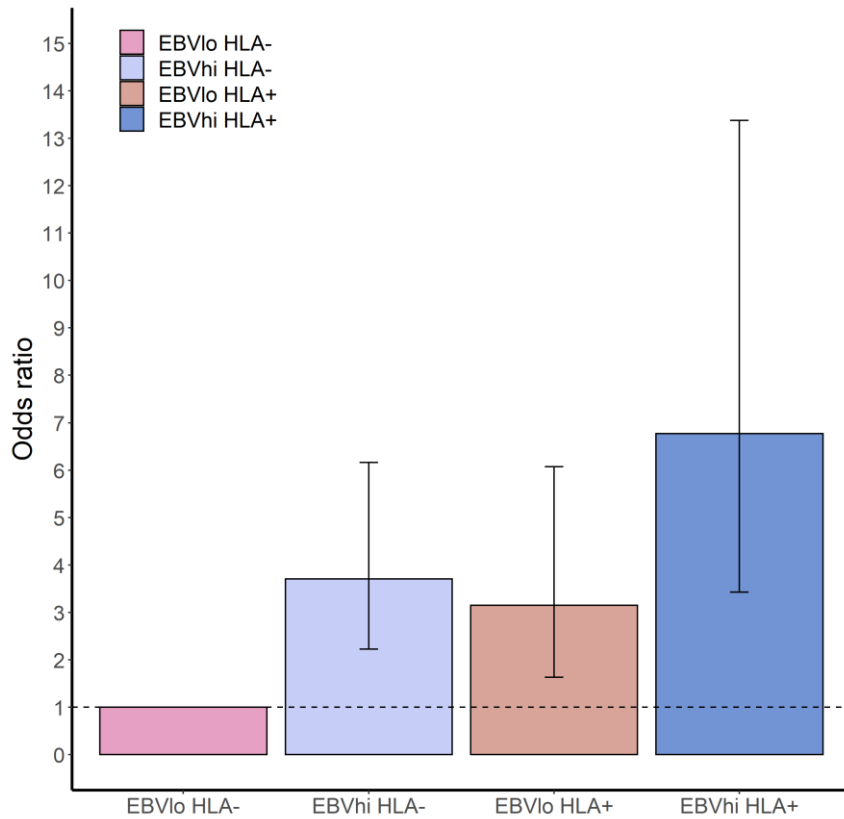
Study	ln(OR)	SE(ln(OR))	Weight	OR [95% CI]
Pandit 2013	1.78	0.6031	16.1%	5.96 [1.83; 19.42]
Simon_Swedish 2010	0.96	0.6675	14.7%	2.60 [0.70; 9.62]
Sundqvist 2011	2.34	0.2068	25.9%	10.40 [6.93; 15.59]
Sundqvist 2012	1.20	0.1683	26.6%	3.31 [2.38; 4.60]
Sundstrom 2008	2.77	0.5837	16.6%	15.98 [5.09; 50.17]
Total (95% CI)			**100.0%**	**6.13 [2.97; 12.68]**

Heterogeneity: $Tau^2 = 0.4868$; $Chi^2 = 23.17$, df = 4 (P < 0.01); $I^2 = 83\%$

0.1 0.5 1 2 10
MS less likely   MS more likely

(e)

Odds Ratio
IV, Random, 95% CI
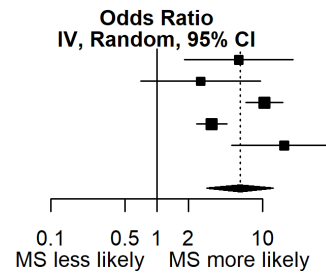
Study	ln(OR)	SE(ln(OR))	Weight	OR [95% CI]
Pandit 2013	0.19	0.6162	5.8%	1.21 [0.36; 4.04]
Simon_Swedish 2010	1.34	0.8003	3.4%	3.80 [0.79; 18.24]
Sundqvist 2011	0.86	0.2574	31.0%	2.36 [1.43; 3.91]
Sundqvist 2012	1.10	0.1886	54.2%	3.01 [2.08; 4.36]
Sundstrom 2008	1.81	0.6231	5.6%	6.11 [1.80; 20.72]
Total (95% CI)			**100.0%**	**2.78 [2.08; 3.72]**

Heterogeneity: $Tau^2 = 0.0054$; $Chi^2 = 4.16$, df = 4 (P = 0.39); $I^2 = 4\%$

0.1 0.5 1 2 10
MS less likely   MS more likely

(f)
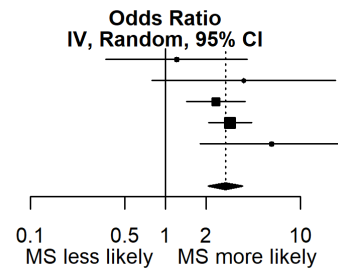
Study	ln(OR)	SE(ln(OR))	Weight	OR [95% CI]
Pandit 2013	0.17	0.4046	32.1%	1.19 [0.54; 2.63]
Simon_Swedish 2010	.	.	0.0%	
Sundqvist 2011	1.02	0.2010	44.9%	2.77 [1.87; 4.10]
Sundqvist 2012	.	.	0.0%	
Sundstrom 2008	1.79	0.5805	23.0%	6.01 [1.93; 18.74]
Total (95% CI)			100.0%	2.52 [1.21; 5.24]

Heterogeneity: Tau^2 = 0.2704; Chi^2 = 5.88, df = 2 (P = 0.05); I^2 = 66%
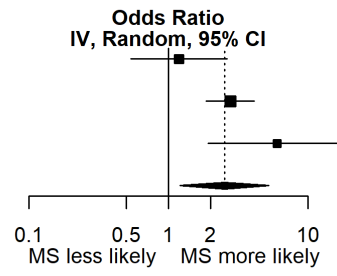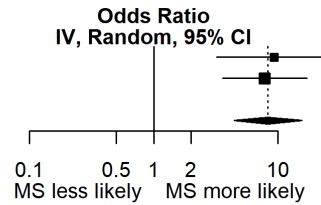

(g)
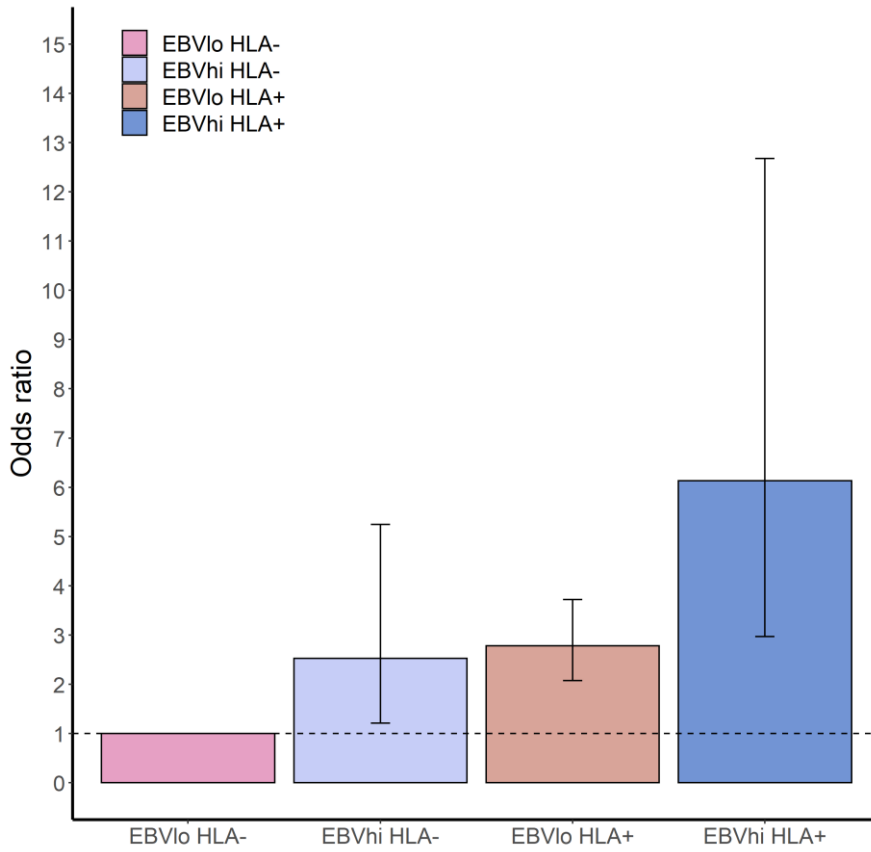
(h)

Supplementary figure 2: (a)-(d) Graphs as per figure 3, analysis restricted to studies using tagging SNPs to determine HLA genotype. (e) - (h) Graphs as per figure 3, analysis restricted to studies using PCR-based methods to determine HLA genotype.

Study	In(OR)	SE(In(OR))	Weight	OR [95% CI]
De Jager 2008	2.23	0.5436	34.7%	9.28 [3.20; 26.94]
Van der Mei 2016	2.06	0.3964	65.3%	7.83 [3.60; 17.03]
Total (95% CI)			**100.0%**	**8.31 [4.43; 15.56]**

Heterogeneity: Tau^2 = 0; Chi^2 = 0.06, df = 1 (P = 0.80); I^2 = 0%

Odds Ratio
IV, Random, 95% CI

0.1   0.5 1   2   10
MS less likely   MS more likely

(a)

Study	In(OR)	SE(In(OR))	Weight	OR [95% CI]
De Jager 2008	1.40	0.4755	44.0%	4.05 [1.60; 10.29]
Van der Mei 2016	0.42	0.3339	56.0%	1.52 [0.79; 2.92]
Total (95% CI)			**100.0%**	**2.34 [0.90; 6.08]**

Heterogeneity: Tau^2 = 0.3117; Chi^2 = 2.85, df = 1 (P = 0.09); I^2 = 65%

Odds Ratio
IV, Random, 95% CI

0.1   0.5   1   2   10
MS less likely   MS more likely

(b)
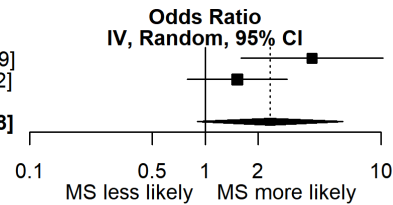
Study	In(OR)	SE(In(OR))	Weight	OR [95% CI]
De Jager 2008	0.85	0.2263	57.3%	2.35 [1.51; 3.66]
Van der Mei 2016	0.83	0.2621	42.7%	2.29 [1.37; 3.83]
Total (95% CI)			**100.0%**	**2.32 [1.66; 3.25]**

Heterogeneity: Tau^2 = 0; Chi^2 = 0.00, df = 1 (P = 0.94); I^2 = 0%

Odds Ratio
IV, Random, 95% CI

0.5   1   2
MS less likely   MS more likely

(c)

(d)
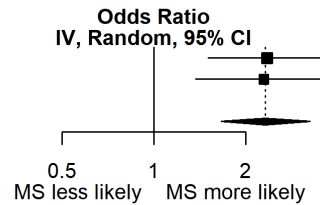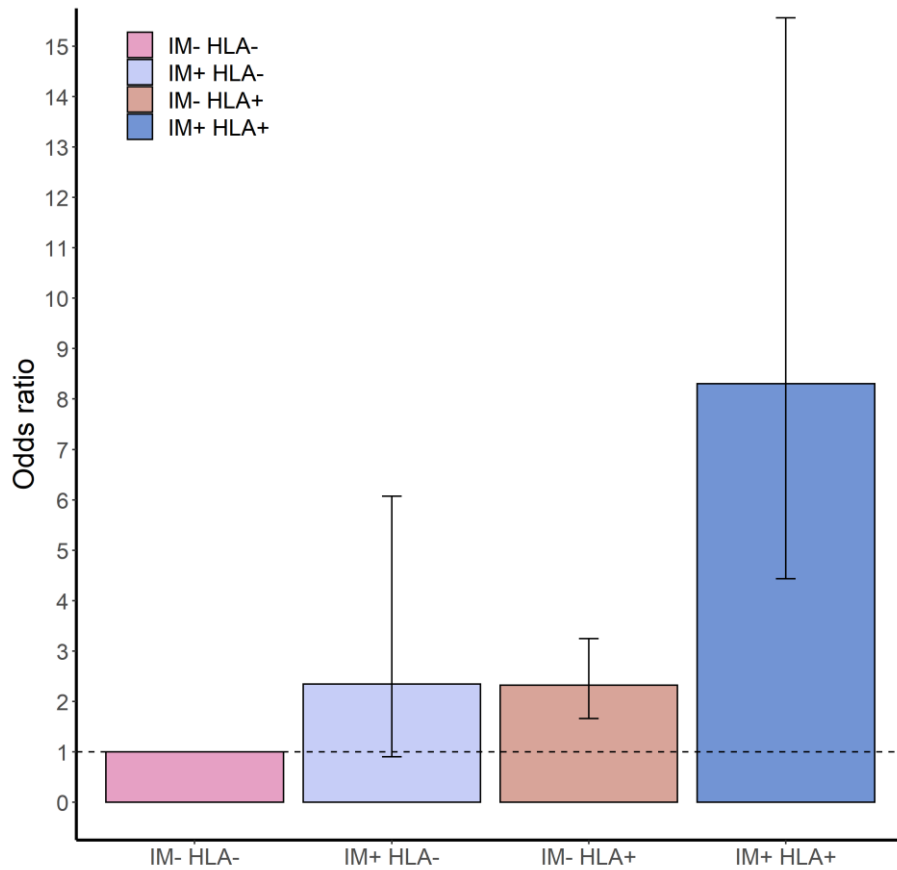
Study	ln(OR)	SE(ln(OR))	Weight	OR [95% CI]
Nielsen 2009	0.36	0.3088	49.6%	1.43 [0.78; 2.61]
Sundqvist 2011	2.01	0.2695	50.4%	7.49 [4.42; 12.70]
Total (95% CI)			100.0%	3.29 [0.65; 16.70]

Heterogeneity: $Tau^2 = 1.2900$; $Chi^2 = 16.36$, df = 1 (P < 0.01); $I^2 = 94\%$

Odds Ratio
IV, Random, 95% CI

0.1   0.5   1   2   10
MS less likely   MS more likely

(e)
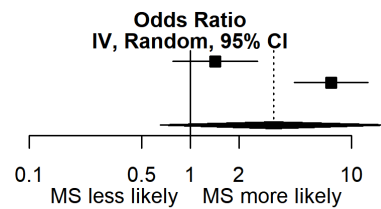
Study	ln(OR)	SE(ln(OR))	Weight	OR [95% CI]
Nielsen 2009	-1.59	0.2553	49.9%	0.20 [0.12; 0.34]
Sundqvist 2011	0.66	0.2439	50.1%	1.94 [1.20; 3.12]
Total (95% CI)			100.0%	0.63 [0.07; 5.71]

Heterogeneity: $Tau^2 = 2.4705$; $Chi^2 = 40.64$, df = 1 (P < 0.01); $I^2 = 98\%$

Odds Ratio
IV, Random, 95% CI

0.2   0.5   1   2   5
MS less likely   MS more likely

(f)
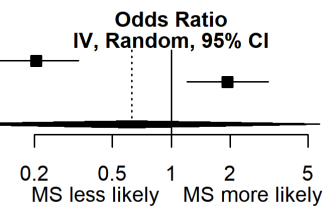
Study	ln(OR)	SE(ln(OR))	Weight	OR [95% CI]
Nielsen 2009	0.89	0.1069	51.5%	2.43 [1.97; 3.00]
Sundqvist 2011	1.36	0.1348	48.5%	3.88 [2.98; 5.06]
Total (95% CI)			100.0%	3.05 [1.93; 4.83]

Heterogeneity: $Tau^2 = 0.0945$; $Chi^2 = 7.39$, df = 1 (P < 0.01); $I^2 = 86\%$

Odds Ratio
IV, Random, 95% CI

0.2   0.5   1   2   5
MS less likely   MS more likely
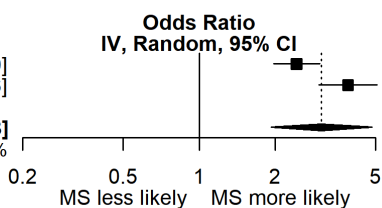
(g)
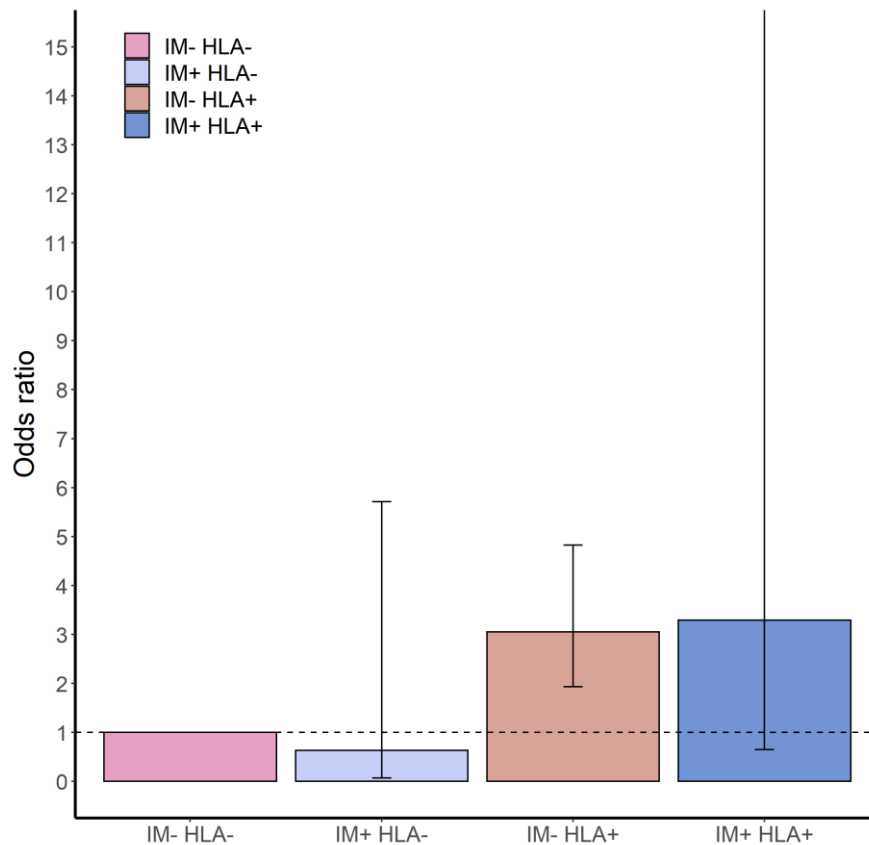
(h)

Supplementary References

References for EBV seropositivity and MS
(i) Adults:
[1][2][3][4][5][6][7][8][9][10][11][12][13][14][15][16][17][18][19][20][21][22][23][24][25][26][27][28][29][30][31][32][33][34][35][36][37][38][39][40][41][42][43][44][45][46][47][48]

(ii) Paediatric MS
[49][50][51][52][53][54][55][56][57][58]

References for IM and MS
[59][60][61][16][28][62][63][64][65][66][67][68][69][70][71][72][73][74][75]

References examining EBV DNA detectable by PCR
[2][76][25][37][44][77][78][79][80][81][82][83][84][85][86][87][88][89]

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