Table S1 – Significant correlation of epigenetic markers with clinical and demographic variables

		r	p	n
	Correlations of global levels of epigenetic markers with AGE			
a)	**5mC**	**r**	**p**	**n**
	Total of participants	-0.339	0.0014	86
	Healthy controls	-0.456	0.0130	29
	RRMS patients	-0.265	0.047	57
	Female participants	-0.359	0.009	52
	Female controls	-0.507	0.027	19
	Normal weight participants	-0.353	0.030	38
	Normal weight controls	-0.552	0.033	15
	Overweight female patients	-0.642	0.033	11
	Participants ≤40 years old	-0.288	0.050	47
	AcH3	**r**	**p**	**n**
	Total of participants	-0.223	0.039	86
	Female participants	-0.316	0.021	53
	Overweight female	-0.576	0.015	17
	Obese female	-0.9	0.037	5
	AcH4	**r**	**p**	**n**
	Total of participants	-0.236	0.028	87
	RRMS patients	-0.308	0.020	57
	Female participants	-0.34	0.012	54
	Female participants	-0.411	0.017	33
	Overweight female	-0.584	0.014	17
	Treated patients	-0.286	0.042	51
	IFN-β treated patients	-0.52	0.008	25
b)	**Correlations of global levels of epigenetic markers with BMI**			

5hmC	r	p	n
Healthy controls	0.681	< 0.0001	29
Female healthy controls	0.585	0.011	18
Normal weight healthy controls	0.581	0.029	14
Control ≤40 years old	0.581	0.023	15
Control >40 years old	0.694	0.012	12
GA treated patients	-0.45	0.027	24
AcH4	**r**	**p**	**n**
Normal weight healthy controls	0.786	0.021	8
AcH3	**r**	**p**	**n**
Overweight healthy controls	0.37	0.024	37

Correlations of global levels of epigenetic markers with disease evolution			
5mC	**r**	**p**	**n**
Obese patients	-0.755	0.03	8
<8 years of RRMS evolution	-0.494	0.008	28
>8 years of RRMS evolution	-0.439	0.017	29
5hmC	**r**	**p**	**n**
<8 years of RRMS evolution	-0.379	0.047	28
<10 years of RRMS evolution	-0.42	0.015	33

c)

Correlations of global levels of epigenetic markers with time of DMT use			
5mC	**r**	**p**	**n**
<8 years of RRMS evolution	-0.546	0.005	25
<10 years of RRMS evolution	-0.444	0.016	29
<5 years of DMT use	-0.627	0.003	20
5hmC	**r**	**p**	**n**
Overweight patients	0.45	0.047	20
AcH3	**r**	**p**	**n**
<8 years of RRMS evolution	-0.416	0.039	25
<5 years of DMT use	-0.458	0.042	20

d)

e)	Correlations of global levels of epigenetic markers with EDSS			
	5mC	*r*	*p*	*n*
	Male patients	-0.474	0.019	24
	Overweight male patients	-0.626	0.039	11
	5hmC	*r*	*p*	*n*
	Female patients	0.431	0.017	30
	Normal weight female patients	0.585	0.036	13
	AcH4	*r*	*p*	*n*
	Normal weight patients	-0.563	0.010	20
	Normal weight female patients	-0.585	0.046	12
f)	Correlations of global levels of epigenetic markers with MSSS			
	5mC	*r*	*p*	*n*
	Overweight male patients	-0.702	0.016	11
	5hmC	*r*	*p*	*n*
	Female patients	0.364	0.048	30
	AcH4	*r*	*p*	*n*
	Normal weight patients	-0.513	0.021	20
	Normal weight female patients	-0.629	0.028	12

Table S2 – Summary of the correlations found in the subgroups of patients and controls

	5mC (%)	5hmC (%)	AceH3 (O.D.)	AceH4 (O.D.)	BMI	Age (years)	EDSS	MSSS	EMRR evolution (years)	Time of DMT (years)
5mC (%)	#subgroups Direction significance									
5hmC (%)	8 (+) 0.01 & 0.05	#subgroups Direction significance								
AceH3 (O.D.)			#subgroups Direction significance							
AceH4 (O.D.)	2 (-) 0.05			#subgroups Direction significance						
BMI		6 (+, -) 0.0001–0.05	1 (+) 0.05	1 (+) 0.05	#subgroups Direction significance					
Age (years)	9 (-) 0.01 & 0.05		4 (-) 0.05	7 (-) 0.01 & 0.05	3 (+) 0.05	#subgroups Direction significance				
EDSS	2 (-) 0.05	2 (+) 0.05		2 (-) 0.05	1 (-) 0.05	5 (+) 0.01 & 0.05	#subgroups Direction significance			
MSSS	1 (-) 0.05	1 (+) 0.05		2 (-) 0.05	3 (-) 0.05	4 (+) 0.01 & 0.05	22 (+) 0.0001–0.01	#subgroups Direction significance		
EMRR evolution (years)	2 (-) 0.01 & 0.05	2 (-) 0.05				3 (+) 0.01 & 0.05		5 (+, -) 0.01 & 0.05	#subgroups Direction significance	
Time of DMT (years)	4 (-) 0.01 & 0.05	1 (+) 0.05	2 (-) 0.05			1 (+) 0.05		6 (-) 0.01	20 (+) 0.0001–0.01	#subgroups Direction significance

#subgroups, number of subgroups with that specific significant correlation; Direction, positive (+) or negative (-) correlation; significance, significant p values found across de subgorups.

Table S3 – Comparison of epigenetic marker levels in patients with RRMS and controls, stratified by sex.

Var.	Subgroup		n	M±SD	p
%5mC	RRMS Patient	Female	33	14.01 ± 5.6	0.102[a]
		Male	24	15.5 ± 7.56	
	Controls	Female	19	20.04 ± 11.16	
		Male	10	20.46 ± 7.73	
Var.	**Subgroup**		**n**	**M±SD**	**p**
%5hmC	RRMS Patients	Female	32	0.0017 ± 0.0008	0.018*[a]
		Male	24	**0.0014 ± .0007[†]**	
	Controls	Female	20	0.0015 ± .0012	
		Male	10	**0.0024 ± 0.0007[†]**	
Var.	**Subgroup**		**n**	**M±SD**	**P**
AcH3 (O.D.)	RRMS Patients	Female	33	0.1145 ± .039	0.065[a]
		Male	24	0.11 ± 0.032	
	Controls	Female	20	0.1217 ± 0.043	
		Male	9	0.1097 ± 0.069	
Var.	**Subgroup**		**N**	**M±SD**	**P**
AcH4 (O.D.)	RRMS Patients	Female	36	0.101 ± 0.02	0.189[a]
		Male	24	0.1024 ± 0.02	
	Controls	Female	20	0.0951 ± 0.013	
		Male	9	0.1027 ± 0.01	

Data are expressed as M ± SD. ([a]p ≤ 0.05, Kruskal-Wallis test; [†]p <0.01, Dunn's test). RRMS, relapsing-remitting multiple sclerosis. %5mC, percentage of 5-methylcytosine; %5hmC, percentage of 5-hydroxymethylcytosine; O.D., optical density; AcH3, Histone H3 acetylation; AcH4, Histones H4 acetylation.*