Supplemental material

eTable 1. Details on MRI acquisition per protocol.

Protocol (N of patients)	**1** (3)		**2** (13)		**3** (3)		**4** (1)		**5** (3)	
Scanner	Siemens Aera		Siemens Prisma		Siemens Skyra		Siemens Avanto		Siemens Skyra	
Field strength	1.5T		3T		3T		1.5T		3T	
Sequences	T1; MPRAGE	T2; FLAIR	T1; MPRAGE	T2; FLAIR	T1; MPRAGE	T2; FLAIR	T1; MPRAGE	T2; FLAIR	T1; MPRAGE	T2; FLAIR
TR (ms)	1940	5000	1800	5000	2300	5000	2060	5000	2300	5000
TE (ms)	2.69	335	2.28	386	2.32	387	3.10	340	2.32	387
TI (ms)	976	1800	900	1800	900	1800	1100	1800	900	1800
Flip angle (°)	8	120	8	120	8	120	15	120	8	120
Voxel size (mm)	1.00x0.98 x0.98	1.00x1.00x1.00	1.00x1.00x1.00	1.00x1.00x1.00	0.9x0.94 x0.94	0.9x0.45x0.45	1.00x0.49x0.49	1.00x0.51x0.51	0.90x0.94x0.94	0.90x0.45x0.45
Protocol (N of patients)	**6** (4)		**7** (3)		**8** (5)		**9** (12)		**10** (2)	
Scanner	Siemens Avanto		Siemens Aera		Philips Achieva		Philips Achieva		Siemens Prisma	
Field strength	1.5T		1.5T		1.5T		3T		3T	
Sequenses	T1; MPRAGE	T2; FLAIR	T1; MPRAGE	T2; FLAIR	T1; FFE	T2; FLAIR	T1; FFE	T2; FLAIR	T1; MPRAGE	T2; FLAIR
TR (ms)	2200	6000	2200	5000	7.6	4800	8.04	5000	1800	5000
TE (ms)	2.82	358	2.67	335	3.75	338	3.68	386	2.28	385
TI (ms)	900	2200	900	1800		1660		1650	900	1800
Flip angle (°)	8	120	8	120	8	90	8	90	8	120
Voxel size (mm)	1.00x0.98 x0.98	1.00x1.00x1.00	1.00x0.98 x0.98	1.00x1.00x1.00	1.00x0.98 x0.98	1.00x0.98x0.98	1.00x0.46x0.46	0.50x0.73x0.73	1.00x0.50 x0.50	1.00x0.50x0.50
Protocol (N of patients)	**11** (6)		**12** (1)		**13** (2)		**14** (8)		**15** (3)	
Scanner	Philips Ingenia		Toshiba MRT200SP3		Philips Ingenia		Siemens Prisma		Philips Achieva	

Field strength	1.5T		1.5T		3T		3T		1.5T	
Sequenses	T1; FFE	T2; FLAIR	T1; FFE	T2; FLAIR	T1; FFE	T2; FLAIR	T1; MPRAGE	T2; FLAIR	T1; FFE	T2; FLAIR
TR (ms)	25	4800	13.5	1160	11.11	4800	1800	5000	7.1	4800
TE (ms)	9.21	367	5.50	105	6.29	296	2.26	387	2.2	307
TI (ms)		1660		2300		1650	906	1800		1660
Flip angle (°)	30	90	20	90	8	90	8	120	8	90
Voxel size (mm)	1.00x0.94x0.94	0.50x0.74x0.74	0.39x0.65x0.39	0.47x4.0x0.47	0.90x0.67x0.67	0.56x0.98x0.98	1.00x1.000x1.00	1.00x1.000x1.00	1.00x1.00 x1.00	0.76x1.00x1.00

Abbreviations: N=number; T=Tesla; MPRAGE=magnetization-prepared rapid gradient-echo; FLAIR=fluid-attenuated inversion recovery; TR=repetition time; TE=echo time; TI=inversion time; ms=millisecond; mm=millimeter; FFE=fast field echo.

eTable 2 Smoking habits of smokers defined by patient self-reporting (N = 48)				
Current smoker	*Yes:* 27 (56.3%)		*No:* 21 (43.8%)	
Smoking 10 years ago	*Yes:* 47 (97.9%)		*No:* 1 (2.1%)	
Smoking frequency 10 years ago	*1-3 days / month* 2 (4.3%)	*1-2 days / week* 3 (6.4%)	*3-6 days / week* 2 (4.3%)	*Daily* 40 (85.1%)
Daily number of cigarettes 10 years ago	*1-4 / day* 4 (8.5%)	*5-10 / day* 17 (36.2%)	*11-20 / day* 23 (48.9%)	*>20 /day* 3 (6.4%)

Abbreviations: N=number, SD=standard deviation.

eTable 3 MRI and clinical measures in smokers and non-smokers (defined by patient self-reporting) at the 10-year follow-up visit and change in clinical measures between month 24 and the 10-year follow-up visit.

MRI/clinical measure	*Non-smokers (mean, SD)*	*Smokers (mean, SD)*	*Mean difference*	*95% conf. interval*	*p-value*
Total GM volume (mL)	643.48 (57.41)	620.84 (45.45)	22.64	-2.26, 47.53	0.074
Total WM volume (mL)	469.65 (55.90)	433.78 (39.83)	35.87	12.68, 59.07	**0.003**
Total deep GM volume (mL)	58.09 (4.88)	54.37 (5.33)	3.73	1.22, 6.23	**0.004**
Thalamus volume (mL)	8.09 (0.98)	7.66 (1.01)	0.42	-0.06, 0.91	0.086
Mean Cth (mm)	2.55 (0.13)	2.53 (0.13)	0.02	-0.04, 0.09	0.424
T2 Lesion volume (mL)[1]	3.06 (3.28)	6.61 (8.71)			**0.021**
T2 Lesion count	19.56 (7.73)	21.70 (9.70)	-2.14	-6.34, 2.06	0.314
EDSS[1]	2.5 (1.0)	2.5 (2.0)			0.419
Change in EDSS[1]	0.50 (1.50)	0.50 (1.13)			0.474
T25FW[1]	3.88 (1.13)	4.48 (1.32)			**0.005**
Change in T25FW[1]	-0.13 (1.11)	0.43 (1.33)			**0.021**
D9-HPT[1]	20.13 (6.18)	21.15 (5.59)			0.351
Change in D9-HPT[1]	3.10 (2.72)	2.82 (5.90)			0.700
ND9-HPT[1]	20.71 (3.92)	22.40 (8.35)			0.100
Change in ND-9HPT[1]	1.80 (3.78)	4.09 (6.36)			0.069
PASAT	49.30 (7.84)	45.28 (10.91)	4.02	-0.41, 8.45	0.075
Change in PASAT	-3.47 (6.68)	-7.39 (7.03)	3.92	0.67, 7.17	**0.019**

[1]Difference analyzed by Mann-Whitney U test, median and interquartile range reported.
Abbreviations: SD=standard deviation; conf=confidence; GM=gray matter; mL=milliliter; WM=white matter; Cth=cortical thickness; mm=millimeter; EDSS=expanded disability status scale; T25FW=timed 25-foot walk; D9-HPT=dominant hand 9-hole peg test; ND9-HPT=non-dominant hand 9-hole peg test; PASAT=paced auditory serial addition test.

eTable 4 The effect of smoking status (defined by patient self-reporting) on MRI and clinical measures at the 10-year follow-up visit and change in clinical measures between month 24 and the 10-year follow-up visit.

MRI/clinical measure	*N*	*Beta*	*St. Error*	*95% confidence interval*	*p-value*
Total GM volume (mL)	66	-11.002	9.700	-28.825, 6.820	0.263
Total WM volume (mL)	66	-24.918	10.563	-44.326, -5.510	**0.023**
Total deep GM volume (mL)	66	-2.349	1.163	-4.485, -0.213	**0.049**
Thalamus volume (mL)	66	-0.305	0.227	-0.723, 0.112	0.186
Mean Cth (mm)	66	-0.020	0.025	-0.067, 0.027	0.443
LogT2 Lesion volume (mL)[1]	63	0.208	0.087	0.047, 0.368	**0.022**
T2 Lesion count	63	1.969	2.390	-2.448, 6.385	0.415
EDSS	66	0.195	0.288	-0.338, 0.727	0.502
Change in EDSS	64	-0.064	0.312	-0.641, 0.513	0.838
LogT25FW[1]	65	0.050	0.024	0.007, 0.094	**0.039**
LogChange in T25FW[1]	63	0.040	0.020	0.002, 0.078	0.056
LogD9-HPT[1]	63	0.014	0.024	-0.031, 0.058	0.567
LogChange in D9-HPT[1]	61	0.033	0.051	-0.061, 0.126	0.525
LogND9-HPT[1]	63	0.029	0.021	-0.010, 0.069	0.172
LogChange in ND9-HPT[1]	61	0.120	0.062	0.005, 0.234	0.062
PASAT	63	-2.970	2.205	-7.045, 1.105	0.185
Change in PASAT	61	-3.575	1.577	-6.482, -0.667	**0.029**

[1]Dependent variable log transformed due to non-normality (log-linear transformation).

Abbreviations: N=number; St= standard; GM=gray matter; mL=milliliter; WM=white matter; Cth=cortical thickness; mm=millimeter; EDSS=expanded disability status scale; T25FW=timed 25-foot walk; D9-HPT=dominant hand 9-hole peg test; ND9-HPT=non-dominant hand 9-hole peg test; PASAT=paced auditory serial addition test.

eTable 5 Dose-effect relationship between mean cotinine level in smokers and MRI and clinical measures at the 10-year follow-up visit and change in clinical measures between month 24 and the 10-year follow-up visit.

MRI/clinical measure	*N*	*Beta*	*St. Error*	*95% confidence interval*	*p-value*
Total GM volume (mL)	36	-0.023	0.017	-0.053, 0.007	0.211
Total WM volume (mL)	36	-0.006	0.018	-0.038, 0.026	0.741
Total deep GM volume (mL)	36	-0.003	0.002	-0.006, 0.001	0.238
Thalamus volume (mL)	36	-0.001	$3.994*10^{-4}$	-0.001, $3.147*10^{-5}$	0.119
Mean Cth (mm)	36	$-6.990*10^{-5}$	$5.019*10^{-5}$	$-1.582*10^{-4}$, $1.839*10^{-5}$	0.182
LogT2 Lesion volume (mL)[1]	34	$1.593*10^{-4}$	$1.622*10^{-4}$	$-1.241*10^{-4}$, $4.426*10^{-4}$	0.341
T2 Lesion count	34	0.008	0.005	$3.991*10^{-4}$, 0.016	0.085
EDSS	36	$1.147*10^{-4}$	$3.907*10^{-4}$	-0.001, 0.001	0.773
Change in EDSS	35	$-2.540*10^{-4}$	$3.897*10^{-4}$	-0.001, $4.287*10^{-4}$	0.523
LogT25FW[1]	35	$-3.500*10^{-6}$	$3.851*10^{-5}$	$-7.102*10^{-5}$, $6.401*10^{-5}$	0.929
LogChange in T25FW[1]	34	$-2.270*10^{-5}$	$2.141*10^{-5}$	$-6.007*10^{-5}$, $1.472*10^{-5}$	0.305
LogD9-HPT[1]	33	$-4.750*10^{-5}$	$3.925*10^{-5}$	$-1.158*10^{-4}$, $2.079*10^{-5}$	0.245
LogChange in D9-HPT[1]	32	$-1.028*10^{-4}$	$6.805*10^{-5}$	$-2.207*10^{-4}$, $1.509*10^{-5}$	0.153
LogND9-HPT[1]	33	$-1.990*10^{-5}$	$3.789*10^{-5}$	$-8.586*10^{-5}$, $4.597*10^{-5}$	0.606
LogChange in ND9-HPT[1]	32	$-1.032*10^{-4}$	$9.993*10^{-5}$	$-2.763*10^{-4}$, $6.988*10^{-5}$	0.319
PASAT	34	-0.007	0.004	-0.014, $1.642*10^{-4}$	0.106
Change in PASAT	33	-0.001	0.003	-0.006, 0.004	0.771

[1]Dependent variable log transformed due to non-normality (log-linear transformation).

Abbreviations: eTIV=estimated total intracranial volume; N=number; St= standard; GM=gray matter; mL=milliliter; WM=white matter; Cth=cortical thickness; mm=millimeter; EDSS=expanded disability status scale; T25FW=timed 25-foot walk; D9-HPT=dominant hand 9-hole peg test; ND9-HPT=non-dominant hand 9-hole peg test; PASAT=paced auditory serial addition test.