Contents

Supplementary material S1: Table of baseline patient characteristics in matched vs unmatched cohorts 2
Table S1.1: MSIS: all eligible patients 2
Table S1.2: MSIS: matched patients 2
Table S1.3: EQ5D: all eligible patients 2
Table S1.4: EQ5D: matched patients 3
Table S1.5: EDSS: all eligible patients 3
Table S1.6: EDSS: matched patients 3
Supplementary material S2: Sensitivity analysis: Modelling longitudinal outcomes with all available data (patients are not propensity matched to early vs late cohorts) 4
Table S2.1: MSIS physical subscore (generalised linear mixed model with gamma log link) 4
Table S2.2: MSIS psychological subscore (generalised linear mixed model with gamma log link) 4
Table S2.3: EQ5D (linear mixed model) 5
Table S2.4: EDSS (linear mixed model) 5
Supplementary material S3: First DMT used by patients in the early vs late groups for each outcome analysis (matched cohorts) 6
S3.1: MSIS analysis 6
S3.2: EQ5D analysis 7
S3.3: EDSS analysis 8
Supplementary material S4: Full model specifications for main analyses 9
S4.1: Analysis of MSIS after early vs late DMT 9
S4.2: Analysis of EQ5D after early vs late DMT 10
S4.3: Analysis of EDSS after early vs late DMT 11

He A, *et al. J Neurol Neurosurg Psychiatry* 2023; 94:284–289. doi: 10.1136/jnnp-2022-330169

SUPPLEMENTARY MATERIAL S1: TABLE OF BASELINE PATIENT CHARACTERISTICS IN MATCHED VS UNMATCHED COHORTS

Table S1.1: MSIS: all eligible patients

	Early	Late	p	SMD
n	1913	130		
sex = Man (%)	590 (30.8)	34 (26.2)	0.306	0.104
Age at onset (mean (SD))	33.65 (9.62)	34.49 (8.85)	0.333	0.091
Calendar year of onset (median [IQR])	2011 [2008, 2013]	2009 [2007, 2011]	<0.001	0.482
Baseline EDSS (median [IQR])	1.50 [1.00, 2.25]	1.50 [0.56, 2.00]	0.434	0.044
Number of relapses in first 2 years of disease (mean (SD))	0.88 (1.11)	0.75 (0.94)	0.218	0.120
Onset to first DMT, years (mean (SD))	0.67 (0.52)	2.63 (0.57)	<0.001	3.604

Table S1.2: MSIS: matched patients

	Early	Late	p	SMD
n	650	130		
sex = Man (%)	177 (27.2)	34 (26.2)	0.885	0.024
Age at onset (mean (SD))	34.36 (9.52)	34.49 (8.85)	0.884	0.014
Calendar year of onset (median [IQR])	2011 [2009, 2013]	2009 [2007, 2011]	<0.001	0.551
Baseline EDSS (median [IQR])	1.50 [0.81, 2.00]	1.50 [0.56, 2.00]	0.858	0.003
Number of relapses in first 2 years of disease (mean (SD))	0.72 (0.94)	0.75 (0.94)	0.708	0.036
Onset to first DMT, years (mean (SD))	0.69 (0.53)	2.63 (0.57)	<0.001	3.531

Table S1.3: EQ5D: all eligible patients

	Early	Late	p	SMD
n	1764	115		
sex = Man (%)	540 (30.6)	32 (27.8)	0.600	0.061
Age at onset (mean (SD))	33.77 (9.60)	34.32 (8.75)	0.551	0.060
Calendar year of onset (median [IQR])	2011 [2009, 2013]	2009 [2007, 2012]	NA	0.494
Baseline EDSS (median [IQR])	1.50 [1.00, 2.06]	1.50 [1.00, 2.00]	NA	0.012
Number of relapses in first 2 years of disease (mean (SD))	0.88 (1.12)	0.72 (0.82)	0.129	0.164
Onset to first DMT, years (mean (SD))	0.67 (0.52)	2.62 (0.56)	<0.001	3.608

He A, *et al. J Neurol Neurosurg Psychiatry* 2023; 94:284–289. doi: 10.1136/jnnp-2022-330169

	Early	Late	p	SMD
n	575	115		
sex = Man (%)	172 (29.9)	32 (27.8)	0.737	0.046
Age at onset (mean (SD))	33.72 (8.54)	34.32 (8.75)	0.500	0.068
Calendar year of onset (median [IQR])	2012 [2009, 2013]	2009 [2007, 2012]	<0.001	0.552
Baseline EDSS (median [IQR])	1.50 [0.62, 2.00]	1.50 [1.00, 2.00]	0.978	0.025
Number of relapses in first 2 years of disease (mean (SD))	0.68 (0.86)	0.72 (0.82)	0.661	0.045
Onset to first DMT, years (mean (SD))	0.64 (0.51)	2.62 (0.56)	<0.001	3.658

Table S1.4: EQ5D: matched patients

Table S1.5: EDSS: all eligible patients

	Early	Late	p	SMD
n	2340	179		
sex = Man (%)	734 (31.4)	50 (27.9)	0.383	0.075
Age at onset (mean (SD))	34.18 (9.84)	35.23 (9.37)	0.167	0.109
Calendar year of onset (median [IQR])	2010 [2007, 2013]	2008 [2005, 2011]	<0.001	0.495
Baseline EDSS (median [IQR])	1.5 [1.0, 2.25]	1.0 [0.0, 2.0]	0.025	0.134
Number of relapses in first 2 years of disease (mean (SD))	0.92 (1.23)	0.79 (0.95)	0.186	0.113
Onset to first DMT, years (mean (SD))	0.70 (0.52)	2.65 (0.55)	<0.001	3.609

Table S1.6: EDSS: matched patients

	Early	Late	p	SMD
n	886	179		
sex = Man (%)	256 (28.9)	50 (27.9)	0.866	0.021
Age at onset (mean (SD))	35.32 (9.99)	35.23 (9.37)	0.913	0.009
Calendar year of onset (median [IQR])	2010 [2007, 2013]	2008 [2005, 2011]	<0.001	0.476
Baseline EDSS (median [IQR])	1.50 [0.50, 2.00]	1.00 [0.00, 2.00]	0.463	0.010
Number of relapses in first 2 years of disease (mean (SD))	0.84 (1.10)	0.79 (0.95)	0.636	0.041
Onset to first DMT, years (mean (SD))	0.70 (0.52)	2.65 (0.55)	<0.001	3.612

He A, *et al. J Neurol Neurosurg Psychiatry* 2023; 94:284–289. doi: 10.1136/jnnp-2022-330169

SUPPLEMENTARY MATERIAL S2: SENSITIVITY ANALYSIS: MODELLING LONGITUDINAL OUTCOMES WITH ALL AVAILABLE DATA (PATIENTS ARE NOT PROPENSITY MATCHED TO EARLY VS LATE COHORTS)

Table S2.1: MSIS physical subscore (generalised linear mixed model with gamma log link)

	Estimate	95% CI lower limit	95%CI upper limit
(Intercept)	13.86	10.28	18.68
Onset to DMT time (years)	1.11	1.05	1.18
Disease duration (years)	0.99	0.96	1.02
Age at onset (years over 18)	1.02	1.01	1.02
Male sex	0.77	0.71	0.85
Calendar year at index (years over 2000)	0.95	0.95	0.97
Number of relapses in first 2 years of disease	1.02	0.99	1.06
Baseline EDSS (in first 2 years of disease)	1.30	1.25	1.34

N=2043 patients (see table S1.1 for baseline characteristics of this cohort)

This indicates for every additional year of delay to DMT (between 0 to 4 years), severity of physical symptoms during followup (between 4-10 years) increases by 11% (95%CI 5, 18).

Other variables that were associated with worse physical symptoms during followup include older age at onset, female sex, earlier calendar year at onset, and higher baseline EDSS.

Disease duration was not associated with change in physical symptoms.

Table S2.2: MSIS psychological subscore (generalised linear mixed model with gamma log link)

	Estimate	95% CI lower limit	95%CI upper limit
(Intercept)	29.95	22.94	39.09
Onset to DMT time (years)	1.06	1.01	1.12
Disease duration (years)	0.98	0.95	1.00
Age at onset (years over 18)	1.00	1.00	1.01
Male sex	0.78	0.72	0.84
Calendar year at index (years over 2000)	0.98	0.96	0.99
Number of relapses in first 2 years of disease	1.01	0.98	1.05
Baseline EDSS (in first 2 years of disease)	1.14	1.11	1.17

N=2043 patients (see table S1.1 for baseline characteristics of this cohort)

This indicates that for every additional year of delay to DMT (between 0 to 4 years), severity of psychological symptoms during followup (between 4-10 years) increases by 6% (95%CI 1, 12).

Other variables that were associated with worse psychological symptoms during followup include female sex, earlier calendar year at onset, and higher baseline EDSS.

He A, *et al. J Neurol Neurosurg Psychiatry* 2023; 94:284–289. doi: 10.1136/jnnp-2022-330169

Disease duration was not associated with change in psychological symptoms.

Table S2.3: EQ5D (linear mixed model)

	Estimate	95% CI lower limit	95%CI upper limit
(Intercept)	75.4	71.0	79.9
Onset to DMT time (years)	-0.8	-1.9	0.3
Disease duration (years)	0.3	0.0	0.5
Age at index (years over 18)	-0.2	-0.3	-0.1
Male sex	1.5	-0.1	3.1
Calendar year at index (years over 2000)	0.6	0.3	0.9
Number of relapses in first 2 years of disease	-0.3	-1.0	0.4
Median EDSS in first 2 years of disease	-3.8	-4.4	-3.2

N=1879 patients (see table S1.3 for baseline characteristics of this cohort)

This indicates that there is no significant difference to health related quality of life with delay to treatment.

Variables that were associated with worse general health related quality of life during followup include older age at onset, earlier calendar year at onset, and higher baseline EDSS.

Disease duration was not associated with change in health related quality of life.

Table S2.4: EDSS (linear mixed model)

	Estimate	95% CI lower limit	95%CI upper limit
(Intercept)	0.09	-0.11	0.29
Onset to DMT time (years)	0.19	0.12	0.26
Disease duration (years)	0.05	0.05	0.06
Age at index (years over 18)	0.03	0.03	0.04
Male sex	0.03	-0.07	0.13
Calendar year at index (years over 2000)	-0.04	-0.06	-0.03
Number of relapses in first 2 years of disease	0.02	-0.03	0.06
Median EDSS in first 2 years of disease	0.65	0.62	0.69

N=2519 patients (see table S1.5 for baseline characteristics of this cohort)

This indicates that every year of delay to DMT (between years 0-4) is associated with a worse clinical disability as measured by higher EDSS, during followup (between years 4-10) by 0.19 points (95%CI 0.12, 0.26).

Other variables that were associated with worse EDSS during following include older age at onset, earlier calendar year at onset, and higher baseline EDSS. Disease duration was associated with worsening EDSS (0.05 points per year of disease, 95%CI 0.05, 0.06)

He A, *et al. J Neurol Neurosurg Psychiatry* 2023; 94:284–289. doi: 10.1136/jnnp-2022-330169

SUPPLEMENTARY MATERIAL S3: FIRST DMT USED BY PATIENTS IN THE EARLY VS LATE GROUPS FOR EACH OUTCOME ANALYSIS (MATCHED COHORTS)

S3.1: MSIS analysis

First DMT (MSIS analysis)	Early	Late
Alemtuzumab	0.3%	0.0%
Glatiramer acetate	6.8%	4.6%
Dimethylfumarate	10.3%	9.2%
Fingolimod	2.5%	0.8%
Haematopoietic stem cell transplantation	0.3%	0.0%
Interferon	56.8%	56.2%
Mitoxantrone	0.0%	0.8%
Natalizumab	13.7%	13.8%
Ocrelizumab	0.5%	0.8%
Rituximab	7.9%	13.1%
Teriflunomide	0.9%	0.8%

First DMT category (MSIS analysis)	Early	Late	p	SMD
n	650	130		
First DMT, n(%)			0.243	0.177
High-efficacy *	147.0 (25.3)	37.0 (31.4)		
Oral therapies*	22.0 (3.8)	2.0 (1.7)		
Injectables*	412.0 (70.9)	79.0 (66.9)		

* High-efficacy therapies are Alemtuzumab, Daclizumab, haematopoietic stem cell therapy, Mitoxantrone, Natalizumab, Ocrelizumab, Rituximab. Oral therapies are Dimethylfumarate, Fingolimod and Teriflunomide. Injectable therapies are Glatiramer acetate and all Interferons

He A, *et al. J Neurol Neurosurg Psychiatry* 2023; 94:284–289. doi: 10.1136/jnnp-2022-330169

S3.2: EQ5D analysis

First DMT (EQ5D analysis)	Early	Late
Alemtuzumab	0.2%	0.0%
Glatiramer acetate	6.3%	5.3%
Daclizumab	0.2%	0.0%
Dimethylfumarate	11.1%	9.6%
Fingolimod	1.9%	0.9%
Haematopoietic stem cell transplantation	0.2%	0.0%
Interferon	55.9%	55.3%
Mitoxantrone	0.0%	0.9%
Natalizumab	14.3%	11.4%
Ocrelizumab	0.0%	0.9%
Rituximab	8.7%	14.9%
Teriflunomide	1.2%	0.9%

First DMT category (EQ5D analysis)	Early	Late	p	SMD
n	575	115		
First DMT, n(%)			0.488	0.134
High-efficacy *	135.0 (26.5)	32.0 (31.1)		
Oral therapies*	18.0 (3.5)	2.0 (1.9)		
Injectables*	357.0 (70.0)	69.0 (67.0)		

* High-efficacy therapies are Alemtuzumab, Daclizumab, haematopoietic stem cell therapy, Mitoxantrone, Natalizumab, Ocrelizumab, Rituximab. Oral therapies are Dimethylfumarate, Fingolimod and Teriflunomide. Injectable therapies are Glatiramer acetate and all Interferons

S3.3: EDSS analysis

First DMT (EDSS analysis)	Early	Late
Alemtuzumab	0.5%	0.0%
Glatiramer acetate	8.8%	6.9%
Daclizumab	0.1%	0.0%
Dimethylfumarate	7.0%	8.0%
Fingolimod	2.3%	0.0%
Haematopoietic stem cell transplantation	0.2%	0.0%
Interferon	62.2%	61.7%
Mitoxantrone	0.1%	0.6%
Natalizumab	11.2%	10.9%
Ocrelizumab	0.1%	0.6%
Rituximab	6.7%	10.9%
Teriflunomide	0.8%	0.6%

First DMT category (EDSS analysis)	Early	Late	p	SMD
n	886	179		
First DMT, n(%)			0.093	0.216
High-efficacy *	165.6 (20.2)	40.0 (24.8)		
Oral therapies*	26.7 (3.3)	1.0 (0.6)		
Injectables*	626.4 (76.5)	120.0 (74.5)		

* High-efficacy therapies are Alemtuzumab, Daclizumab, haematopoietic stem cell therapy, Mitoxantrone, Natalizumab, Ocrelizumab, Rituximab. Oral therapies are Dimethylfumarate, Fingolimod and Teriflunomide. Injectable therapies are Glatiramer acetate and all Interferons

SUPPLEMENTARY MATERIAL S4: FULL MODEL SPECIFICATIONS FOR MAIN ANALYSES

S4.1: Analysis of MSIS after early vs late DMT (same model for physical and psychological subscales)
Model type: Generalized linear mixed model fit by maximum likelihood
Family: Gamma (log-link)
Formula: MSIS score ~ late + year + (1 | clinic_id) + (1 | id)

Note that for all model formulae, "late" is a factor variable referring to the late treatment group (compared to reference group of early treatment); "year" is a numeric variable referring to disease duration in years, "clinic ID" is a factor variable referring to the treating clinic (stratifying variable) and "id" is a factor variable referring to the individual patient (stratifying variable).
All models are weighted to account for the variable one-to-many match ratio between patients in the early vs late treated groups.

Model output: MSIS physical

	outcome.gamma		
Predictors	*Estimates*	*CI*	*p*
(Intercept)	17.78	13.39 – 23.60	**<0.001**
late	1.31	1.09 – 1.58	**0.004**
year	0.99	0.95 – 1.03	0.664
Random Effects			
σ^2	1.25		
$\tau_{00\ id}$	0.00		
$\tau_{00\ clinic\_id}$	0.00		
N_{clinic_id}	43		
N_{id}	780		
Observations	2761		
Marginal R^2 / Conditional R^2	0.009 / NA		

Model output: MSIS psychological

	outcome.gamma		
Predictors	*Estimates*	*CI*	*p*
(Intercept)	26.41	20.71 – 33.68	**<0.001**
late	1.14	0.97 – 1.34	0.102
year	0.99	0.96 – 1.03	0.693
Random Effects			
σ^2	0.76		
$\tau_{00\ id}$	0.00		
$\tau_{00\ clinic\_id}$	0.00		
N_{clinic_id}	43		
N_{id}	779		
Observations	2755		
Marginal R^2 / Conditional R^2	0.003 / NA		

S4.2: Analysis of EQ5D after early vs late DMT
Generalized linear mixed model fit by maximum likelihood
Family: Gamma (log)
Formula: EQ5D VAS ~ late + year + (1 | clinic_id) + (1 | id)

Model output: EQ5D visual analogue scale

	outcome.gamma		
Predictors	*Estimates*	*CI*	*p*
(Intercept)	71.63	67.02 – 76.56	**<0.001**
late	0.93	0.85 – 1.01	0.089
year	1.00	0.99 – 1.01	0.814
Random Effects			
σ^2	0.04		
$\tau_{00\ id}$	0.03		
$\tau_{00\ clinic\_id}$	0.00		
ICC	0.43		
N_{clinic_id}	42		
N_{id}	681		
Observations	2037		
Marginal R^2 / Conditional R^2	0.010 / 0.435		

S4.3: Analysis of EDSS after early vs late DMT
Linear mixed model fit by maximum likelihood
Formula: EDSS ~ late + year + (1 | clinic_id) + (1 | id)

		edss	
Predictors	*Estimates*	*CI*	*p*
(Intercept)	1.27	1.12 – 1.42	**<0.001**
late	0.35	0.10 – 0.59	**0.005**
year	0.07	0.06 – 0.08	**<0.001**
Random Effects			
σ^2	0.36		
$\tau_{00\ id}$	2.17		
$\tau_{00\ clinic\_id}$	0.04		
ICC	0.86		
N_{clinic_id}	46		
N_{id}	1065		
Observations	4620		
Marginal R^2 / Conditional R^2	0.013 / 0.861		