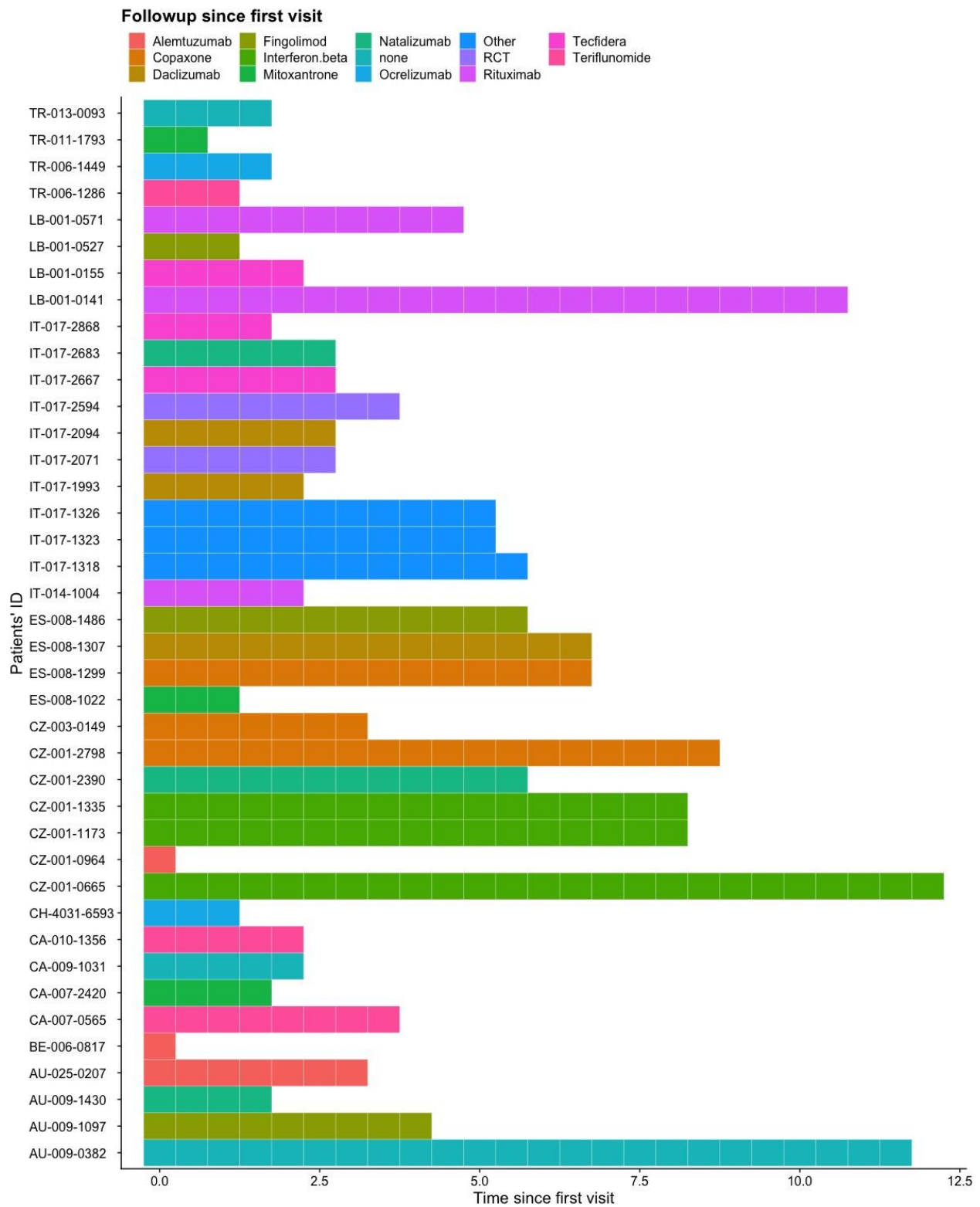


Online supplement**Supplementary Table 1.** Comparison of patients eligible for and excluded from the present study.

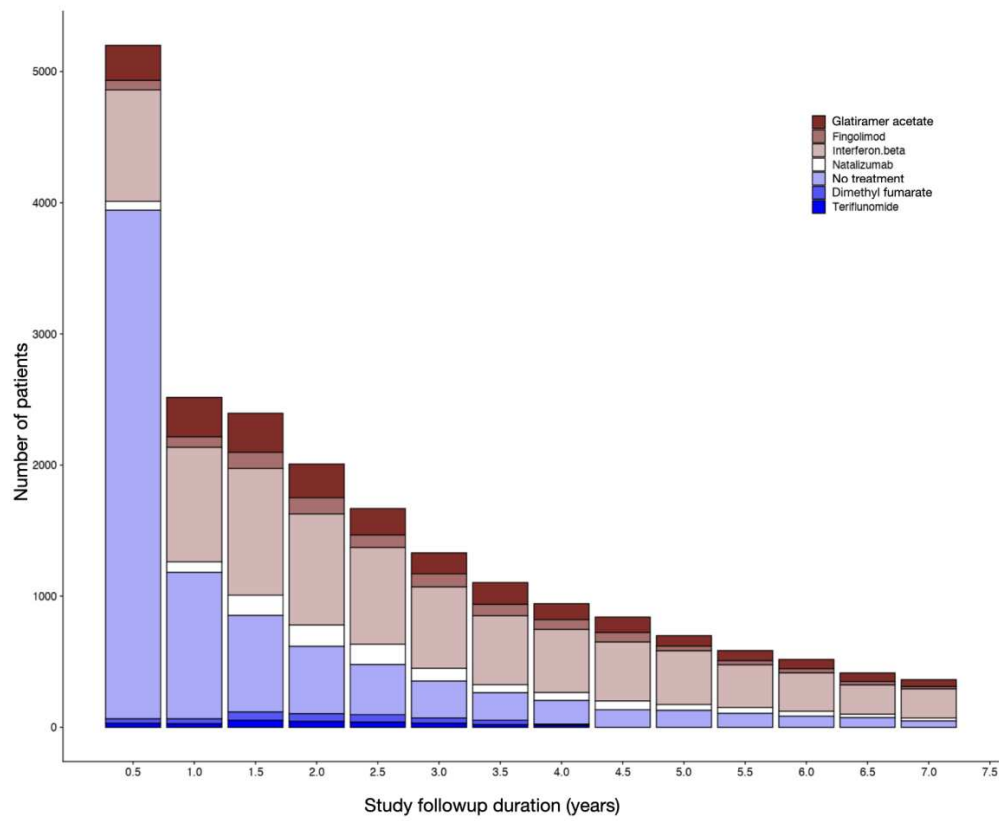
	Excluded (n=38574)	Included (n=23236)
Age first visit, Mean (SD)	39.1 (12.6)	36.3 (10.5)
Female sex	26899 (69.7%)	16685 (71.8%)
MS duration at baseline, Median [Q1, Q3]	7.53 (8.59)	6.21 (6.82)
Disability		
EDSS 0-3.5	22094 (57.3%)	20236 (87.1%)
EDSS 4-5.5	5086 (13.2%)	2230 (9.6%)
EDSS 6-9.5	6087 (15.8%)	770 (3.3%)
Missing	5307 (13.8%)	0 (0%)
Presence of new/enlarging/enhancing cerebral MRI lesions during the last 12 months	913 (2.4%)	1314 (5.7%)
Receiving disease modifying therapy at baseline	9736 (25.2%)	15068 (64.8%)

Supplementary table 2: Summary of the study protocol

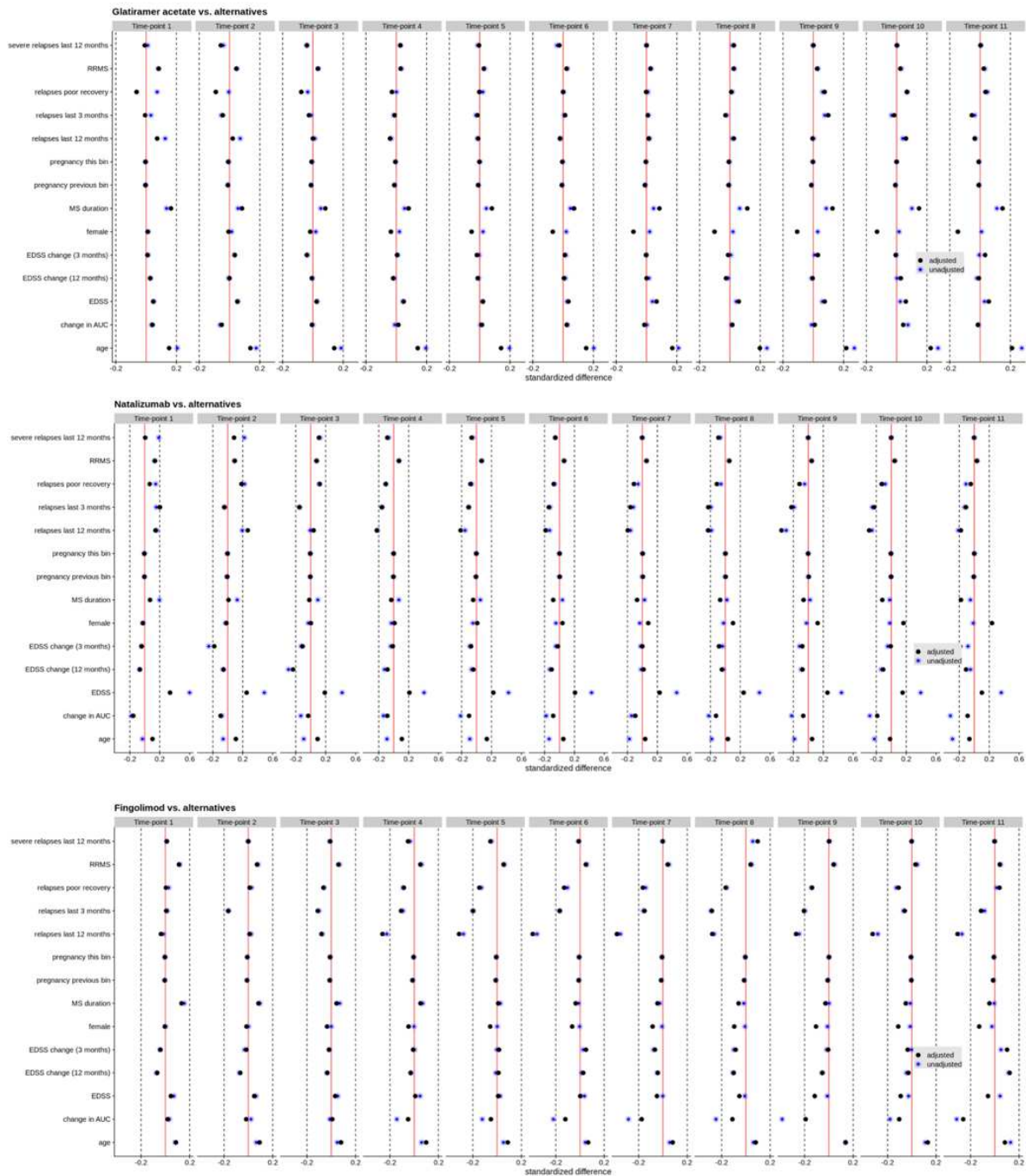
Protocol component	Description
inclusion criteria	clinically isolated syndrome or definite multiple sclerosis
treatment strategies	patients may contribute 6-month periods to either the treated (where exposed to disease modifying therapy for ≥ 15 days during the given period) or the untreated pseudo-cohort (where exposure to disease modifying therapy during the given period < 15 days)
assignment procedures	non-random assignation of therapy by treating neurologists
follow-up period	follow-up ≥ 1 year, ≥ 3 disability scores with ≥ 1 score recorded per year
outcomes	<ul style="list-style-type: none">• 12-month confirmed disability worsening events (increase in EDSS by 1 step; 1.5 step if baseline EDSS=0 and 0.5 steps if baseline EDSS>5.5)• 12-month confirmed disability improvement events (decrease in EDSS by 1 step; 1.5 steps if baseline EDSS≤ 1.5 and 0.5 steps if baseline EDSS>6)• relapses
causal contrast of interest	per-protocol effect
analysis	proportional hazards models of multiple events with robust estimation of variance and inverse probability of treatment weights to adjust for fixed and time-dependent confounders and intermediates of outcomes; this analysis plan implies that data on the adjustment factors are available

Supplementary figure 1. An example of the included follow-up.

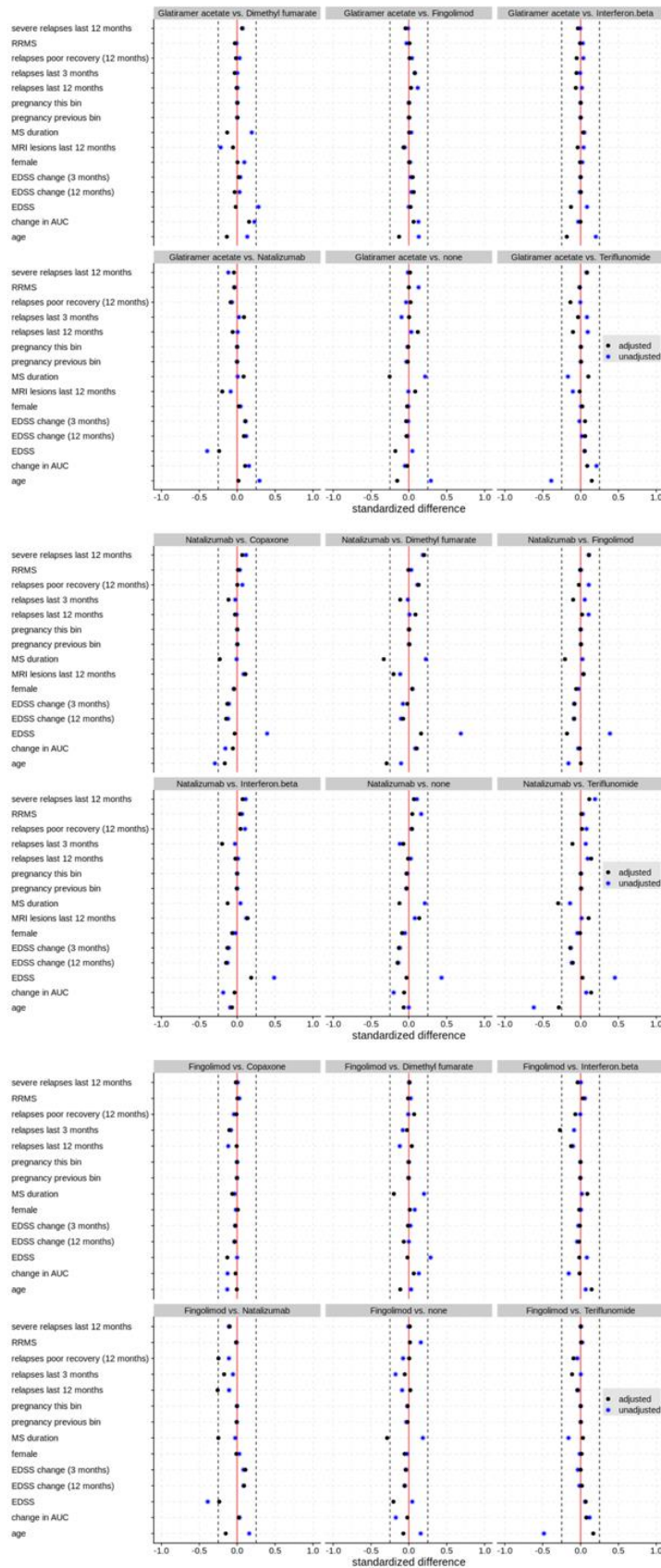
Only patients followed-up with prospective data entry commencing after 1st January 2006 were included. One treated / untreated epoch per patient was included. Patients were censored at the change of their treatment status.

Supplementary figure 2. Attrition of the number of patients over time for each therapy

Supplementary Figure 3: Covariate balance over time, the presented example shows the three reference treatments



Supplementary figure 4: Weighted and unweighted covariate balance measured with standardized difference between glatiramer acetate and alternative treatment groups in an ATT model.



Supplementary figure 5: Comparison of multiple therapies (ATE) among patients with recorded MRI data.

