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**Title:**

Determinants of therapeutic lag in multiple sclerosis

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## **ABSTRACT** (250 words)

**Objective:** Explore the associations of patient and disease characteristics with the duration of therapeutic lag for relapses and disability progression.

**Background:** Therapeutic lag represents the delay from initiation of therapy to attainment of full treatment effect. Understanding the determinants of therapeutic lag provides valuable information for personalised choice of therapy in multiple sclerosis (MS).

**Methods:** Data from MSBase, a multinational MS registry, and OFSEP, the French MS registry, were used. Patients diagnosed with MS, minimum 1-year exposure to MS treatment, minimum 3-year pre-treatment follow up and yearly review were included in the analysis. We studied incidence of relapses and 6-month confirmed disability progression. Therapeutic lag was calculated by identifying the first local minimum of the first derivative after treatment start in subgroups stratified by patient and disease characteristics. Therapeutic lag under specific circumstances was then estimated in subgroups defined by combinations of individual clinical and demographic determinants.

**Results:** High baseline disability scores (EDSS), annualised relapse rate (ARR)  $\geq 1$  and male sex were associated with longer therapeutic lag on disability progression ( $T_d$ ) in sufficiently populated groups: females with EDSS $<6$  and ARR $<1$  had mean  $T_d$  of 26.6 weeks (95%CI 18.2-34.9), males with EDSS $<6$  and ARR $<1$  31.0 weeks (95%CI 25.3-36.8), females with EDSS $<6$  and ARR $\geq 1$  44.8 weeks (95%CI 24.5-65.1), and females with EDSS $\geq 6$ , ARR $<1$  54.3 weeks (95%CI 47.2-61.5).

**Conclusions:** We have utilised a novel method for the quantification of clinical therapeutic lag in different patient groups. EDSS and ARR at the commencement of an MS therapy are the most important determinants of therapeutic lag.



## **INTRODUCTION**

The goal of treatment in multiple sclerosis (MS) is prevention of long-term disability. After starting a disease modifying therapy (DMT), there is however a delay to full clinically apparent treatment effect, referred to as 'therapeutic lag'.<sup>1</sup> As treatment decisions are often made in the face of ongoing disease activity, accurate expectations of timing of treatment effect is clinically relevant.<sup>2</sup> Using an objective, differential calculus-derived method, the duration of therapeutic lag has recently been estimated to range between 12-30 weeks for relapses and 30-70 weeks for disability progression.(Roos et al. under review) Moreover, normalisation of brain atrophy rates (a marker of neuroaxonal loss) have been delayed up to 3 years after the commencement of natalizumab.<sup>3</sup>

It has been suggested that the duration of therapeutic lag is not uniform amongst patients, and may increase proportionate to the degree of pre-existing disability.<sup>4</sup> A randomised placebo-controlled trial of interferon beta-1b in primary progressive MS failed to detect a beneficial treatment response after 2 years.<sup>5</sup> However, when patient outcomes were revisited at year 7, after a 5-year treatment free period, cognitive and upper limb outcomes in patients initially randomised to interferon beta-1b were superior to those randomised to placebo.<sup>6</sup> This suggests that in patients with progressive MS, therapeutic lag may obscure a detectable effect of therapy if not accounted for analytically. As yet, therapeutic lag has not been incorporated into clinical trial design. Understanding the effect of individual disease characteristics on the duration of therapeutic lag might aid personalised DMT decision-making.

In this study, we apply an objective, externally validated method to measure the duration of therapeutic lag with respect to disability progression and relapses. We aim to explore the associations of the duration of therapeutic lag with patient and disease characteristics.

## **METHODS**

### **Ethics statement**

The MSBase registry<sup>7</sup> (registered with WHO ICTRP, ID ACTRN12605000455662) was approved by the Melbourne Health Human Research Ethics Committee, and by the local ethics committees in all participating centres (or exemptions granted, according to applicable local laws and regulations). Written informed consent was obtained from enrolled patients as required. The Observatoire Français de la Sclérose en Plaques (OFSEP) cohort<sup>8</sup> (registered with WHO ICTRP, ID NCT02889965) was collected with approval from and in accordance with French *Commission Nationale Informatique et Libertés* and French law relative to observational research.

### **Population and data collection**

Longitudinal clinical and demographic data were extracted from the MSBase registry (125 centres in 37 countries) and OFSEP registry (39 French centres) in December 2018. Inclusion criteria for this study consisted of: diagnosis of MS as per the 2005<sup>9</sup> or 2010<sup>10</sup> McDonald Criteria, commencement of and persistence on a DMT for at least 12 months, minimum 3-year pre-treatment follow up, yearly visits during the treatment epoch (defined below) and availability of the minimum dataset. The minimum dataset consisted of patient age, sex (dichotomised as male and female), disease phenotype, disability (quantified by the Expanded Disability Status Scale (EDSS)) at baseline and two subsequent timepoints at least 6 months apart, MS duration, relapses recorded during the follow up period, and date of treatment start and cessation (where applicable).

The prospective follow up period was defined as time from first to the last available EDSS. Study baseline was defined as the start of the index DMT. All DMTs were eligible for study inclusion. A treatment epoch was defined as time including three years prior to baseline and one year (for the effect of relapses) and three years (for the effect on disability; see below) after baseline. In patients in whom multiple eligible baselines were identified, multiple eligible treatment epochs per patient were studied. Each treatment epoch was treated as independent.

All data were prospectively collected during routine clinical care predominantly from tertiary multiple sclerosis centres and entered near real-time (at the time of a clinic visit) into the iMed patient record or online data entry system for MSBase or EDMUS patient record for OFSEP. Standardised data quality processes were applied as previously described.<sup>11</sup>

## Study outcomes

This study evaluated the time from treatment start to its full clinically manifest effect ('therapeutic lag') on disability progression and relapses in subgroups of patients with MS.

Disability progression was defined as an EDSS score increase of 1 point (1.5 points where EDSS is 0, 0.5 points if EDSS  $\geq 6$ ), confirmed over  $\geq 6$  months (in the absence of a relapse in the 30 days prior to confirmation), and sustained for the remainder of the treatment epoch.<sup>12</sup> Relapses were defined as new symptoms or exacerbation of existing symptoms for at least 24 hours, in the absence of a concurrent illness or fever, and occurring at least 30 days after a previous relapse.<sup>13</sup>

**The first episode of demyelination was considered a relapse.** For analysis of disability outcomes, patients were treated for at least one year, and all disability progression events recorded during a 3-year period were analysed, irrespective of treatment status. For the analysis of relapses patients required one year on-treatment follow up, and relapses recorded during this year were included in the analysis. Differences in analytical approaches are motivated by observations that the effect of DMTs on relapses is more immediate than the effect on disability (Roos et al).

Classification of MS phenotype was analysed as documented by the treating physician. Additionally, secondary progressive MS (SPMS) was analysed as defined by an objective algorithm, which identifies SPMS with 87% accuracy in a timely manner.<sup>14</sup> Annualised relapse rate (ARR) was calculated as the annualized number of recorded relapses in the three years before baseline. MS duration and onset were calculated from the first MS symptom.

By separately plotting the incidence of relapses and disability progression events in subgroups stratified by patient and disease characteristics, the duration of therapeutic lag was calculated by identifying the first local minimum of the first derivative after treatment start (Roos et al.). This local minimum represents the timepoint at which stabilisation of the effect of treatment is reached on disability progression ( $T_d$ ) and relapses ( $T_r$ ). Estimates of therapeutic lag were recalculated by non-parametric bootstrap with 10,000 repetitions, without replacement.

### **Statistical analysis**

Statistical analysis was conducted by IR using *R* (version 3.5.3). Point and interval estimates of distribution were expressed as means with 95% confidence intervals, or medians with quartiles, as appropriate.

Therapeutic lag ( $T_d$  and  $T_r$ ) was calculated for patient subgroups stratified by their demographic and clinical characteristics. As discussed elsewhere (Roos et al.), a critical number of events are required to identify a stable, reliable estimate of therapeutic lag. Therefore, we only considered results from subgroups in whom more than 300 events were recorded (disability progression events or relapses), and for which  $T_d$  or  $T_r$  was identified in more than 80% of the bootstrap repetitions. Categorisation of continuous variables was performed by first computing quantiles and then aggregating the overlapping quantiles (Supplementary Table 1).

Studied potential baseline determinants of therapeutic lag were selected based on the results of prior studies<sup>1 4 15-17</sup>: sex, age at start of index DMT, age at MS onset, ARR, MS duration, EDSS, pyramidal score, presence/absence of 6-month confirmed disability progression in the 3 years before baseline, slope of the disability trajectory (the regression line projected over the EDSS/time points), treatment with MS-specific DMT in the 6 months before baseline and reason for discontinuation of preceding DMT (as reported by the treating neurologist) if applicable. A prior analysis explored therapeutic lag in different DMTs: time to treatment effect for disability progression ranged between 30-52 weeks for all included therapies apart from interferon beta-1a IM (mean 70.4, 95% confidence interval [95%CI] 59.8-81.0) and time to treatment

effect for relapses ranged between 9.4-19.8 weeks for all included therapies apart from dimethyl fumarate (mean 30.2, 95%CI 26.6-33.7).(Roos et al.) Therefore, treatment identity was not considered to be a confounder of the estimated therapeutic lag and its effect on therapeutic lag was not evaluated in this study, unless dimethyl fumarate or interferon beta-1a IM were over-represented in any studied subgroup. In this circumstance the analysis was repeated after the exclusion of dimethyl fumarate (relapses) or interferon beta-1a (disability progression) treatment epochs.

Second, the patient characteristics identified by the above analysis as relevant determinants of  $T_d$  and  $T_r$  were included in pairwise analyses, in which therapeutic lag was estimated in groups defined by combinations of two characteristics. Third, combinations of determinants that consistently drove differences in therapeutic lag duration in the pairwise analyses were included in the final set of analyses in which groups were defined by combinations of multiple relevant patient characteristics. As mentioned above, we only considered results from sufficiently represented subgroups.

## **RESULTS**

### **Patients and follow-up**

A total of 5,415 patients (3,473 MSBase, 1,492 OFSEP) were included in the analysis of determinants of therapeutic lag for disability progression and 10,192 patients (6,051 MSBase, 4,141 OFSEP) in the determinants for relapses (figure 1). Characteristics of the study population are shown in Table 1 and the number of patients per contributing centre in Supplementary Table 2.

In the disability progression cohort, the index therapy was continued for a median duration of 3.6 years (2.4-5.3). Although population characteristics were largely similar between registries, more patients in MSBase were commenced on an injectable therapy at baseline than those in OFSEP (disability cohort: MSBase 51.7%, OFSEP 41.4%; relapse cohort: MSBase 44.6%, OFSEP 33.1%). In both

registries, the most common preceding DMT was an injectable therapy. Lack of efficacy was the most commonly reported reason for discontinuation of the preceding DMT. Details of the index DMT for each of the studied determinants of therapeutic lag are shown in Supplementary Table 3.

Table 1: Characteristics of the study population

Source	Disability Progression Cohort			Relapse Cohort		
	Overall <i>n</i> = 5415	MSBase <i>n</i> = 3473	OFSEP <i>n</i> = 1492	Overall <i>n</i> = 10192	MSBase <i>n</i> = 6051	OFSEP <i>n</i> = 4141
Female, <i>n</i> (%)	4142 (76)	2570 (74)	1134 (76)	7583 (74)	4478 (74)	3105 (75)
Treatment epochs, <i>n</i>	6551	4304	2247	12553	7606	4947
Age of MS onset, years <sup>a</sup>	27.9 (8.6)	27.8 (8.6)	28.2 (8.5)	28.4 (8.7)	28.2 (8.7)	28.6 (8.7)
Age at start of index DMT, years <sup>a</sup>	40.0 (9.5)	39.7 (9.4)	40.7 (9.7)	40.8 (9.7)	40.3 (9.6)	41.5 (9.9)
Disease duration, years <sup>b</sup>	10.6 [6.9, 15.7]	10.5 [6.7, 15.4]	10.9 [7.1, 16.1]	10.8 [6.9, 16.1]	10.5 [6.7, 15.7]	11.2 [7.4, 16.6]
Disability, EDSS step <sup>b</sup>	3.0 [2.0, 4.5]	3.0 [2.0, 4.0]	3.5 [2.0, 4.5]	3.0 [1.5, 4.0]	2.5 [1.5, 4.0]	3.0 [2.0, 4.5]
Pyramidal score, step <sup>a</sup>	1.8 (1.2)	1.8 (1.2)	1.6 (1.3)	1.7 (1.2)	1.8 (1.2)	1.6 (1.2)
Annualised relapse rate <sup>b</sup>	0.7 [0.3, 1.0]	0.7 [0.3, 1.0]	0.7 [0.3, 1.0]	0.3 [0.0, 1.0]	0.3 [0.3, 1.0]	0.3 [0.0, 1.0]
Disease course (%)						
Clinically isolated syndrome	82 (1.3)	43 (1.0)	39 (1.7)	195 (1.6)	85 (1.1)	110 (2.2)
Relapsing-remitting	5646 (86.2)	3780 (87.8)	1866 (83.0)	10819 (86.2)	6715 (88.3)	4104 (83.0)
Secondary progressive	745 (11.4)	419 (9.7)	326 (14.5)	1378 (11.0)	691 (9.1)	687 (13.9)
Primary progressive	78 (1.2)	62 (1.5)	16 (0.7)	161 (1.3)	115 (1.5)	46 (0.9)
DMT started at baseline (%)						
Injectable therapies	3159 (48.2)	2228 (51.7)	931 (41.4)	5030 (40.1)	3393 (44.6)	1637 (33.1)
Oral therapies	1747 (26.7)	1130 (32.5)	617 (27.5)	4677 (37.3)	2718 (35.7)	1959 (39.6)
Infusion therapies	1645 (25.1)	946 (22.0)	699 (31.1)	2846 (20.0)	1495 (24.7)	1351 (27.3)
DMT in 6 months preceding baseline (%)						
None	1507 (23.0)	955 (22.2)	552 (24.6)	2753 (21.9)	1630 (21.4)	1123 (22.7)
Injectable therapies	3914 (59.7)	2640 (61.3)	1274 (56.7)	7107 (56.6)	4578 (60.2)	2529 (51.2)
Infusion therapies	878 (13.4)	514 (11.9)	364 (16.2)	1695 (13.5)	839 (13.9)	856 (20.7)

Oral therapies	252 (3.9)	195 (4.5)	57 (2.5)	998 (8.0)	559 (7.3)	439 (10.6)
Reason for discontinuation of preceding DMT (%)						
No Preceding Treatment	1507 (23.0)	955 (22.2)	552 (24.6)	2753 (21.9)	1630 (21.4)	1123 (22.7)
Convenience	231 (3.5)	131 (3.0)	100 (4.5)	564 (4.5)	275 (3.6)	289 (5.8)
Lack of efficacy	1680 (25.6)	1042 (24.2)	638 (28.4)	3014 (24.0)	1710 (22.5)	1304 (26.4)
Lack of tolerance	882 (13.5)	455 (10.6)	427 (19.0)	1805 (14.4)	873 (11.5)	932 (18.8)
Pregnancy (including planned)	82 (1.3)	51 (1.2)	31 (1.4)	185 (1.5)	100 (1.3)	85 (1.7)
Scheduled stop	589 (9.0)	292 (6.8)	297 (13.2)	1213 (9.7)	547 (7.2)	666 (13.5)
Other	47 (0.7)	10 (0.2)	37 (1.6)	142 (1.1)	36 (0.5)	106 (2.1)
Reason not available	1533 (23.4)	1368 (31.8)	165 (7.3)	2877 (22.9)	2435 (32.0)	442 (8.9)
<sup>a</sup> Mean (standard deviation)	<sup>b</sup> Median [quartiles]					

DMT = disease modifying therapy; MS = multiple sclerosis

Injectable therapies: glatiramer acetate, interferon beta-1b IM, interferon beta-1b SC, interferon beta-1b

Oral therapies: fingolimod, dimethyl fumarate, teriflunomide, cladribine

Infusion therapies: natalizumab, ocrelizumab, alemtuzumab, rituximab, mitoxantrone

Clinically isolated syndrome: patients classified as clinically isolated syndrome at the start of their treatment, with  $\geq 3$  year follow up from their first symptoms.

Patient disposition is summarised per treatment epoch at the start of treatment. In patients with multiple eligible treatments, multiple epochs were studied.



## Therapeutic lag for disability progression

We have identified three potential determinants of the duration of therapeutic lag for disability progression: disability (EDSS<6, 17.2 weeks, 13.6-20.5 [mean, 95% confidence interval]; EDSS≥6, 47.5, 23.7-71.3), relapse frequency (ARR<1, 29.2, 21.1-37.2; ARR≥1, 52.4, 38.9-65.9) and sex (female, 31.8, 26.2-37.5; male 55.8, 45.6-66.0) (figure 2). Patient and disease characteristics which did not influence  $T_d$  are shown in supplementary figure 1. Interferon beta-1a IM was not markedly over- or under-represented in any patient groups (supplementary table 3a) and therefore DMT choice at baseline was not included among the examined potential determinants of  $T_d$ . All three individual determinants (EDSS, ARR and sex) contributed to differences in  $T_d$  when combined in pairwise analyses (supplementary table 4) and were then included in the final set of analyses exploring all combinations of the three determinants. In these final models,  $T_d$  was successfully calculated in 4 groups in whom the number of disability progression events was sufficient, ≥300 (figure 3). In females with ARR<1 and EDSS<6 the mean  $T_d$  was 26.6 weeks (95%CI 18.2-34.9). This was 27.7 weeks shorter than the mean  $T_d$  among females with ARR<1 and EDSS≥6 (54.3, 95%CI 47.2-61.5), and not substantially different from males with ARR<1 and EDSS<6 (31.0, 95%CI 25.3-36.8). In females with ARR≥1 and EDSS<6, mean  $T_d$  was 44.8 weeks (24.5-65.1).

## Therapeutic lag for relapses

Baseline EDSS (EDSS<2, 9.2 weeks, 7.0-11.4 [mean, 95% confidence interval]; EDSS≥2 and <6, 12.1, 11.1-13.2; EDSS ≥6, 16.9, 13.8-19.9), ARR (ARR<2, 14.9, 13.4-16.4; ARR≥2, 11.1, 9.3-12.8), sex (female, 14.3, 12.7-15.9; male, 9.8, 7.2-12.4), physician-defined MS phenotype (physician RRMS: 9.6, 7.5-11.6; physician SPMS: 14.7, 10.8-18.6) and algorithm-defined MS phenotype (algorithm RRMS: 10.0, 8.0-12.0; algorithm SPMS: 14.8, 11.8-17.7) were identified as potential determinants of  $T_r$  (figure 4); determinants which did not influence  $T_r$  are shown in supplementary figure 2.  $T_r$  was estimated in patients with RRMS and SPMS but not in patients with CIS or PPMS due to low total number of relapses (195 and 192 respectively). As  $T_r$  estimates for the algorithm-defined MS phenotype showed less overlap than for physician-defined MS phenotype, the former were used in

subsequent analyses. Dimethyl fumarate was neither markedly over- nor under-represented in any patient groups (supplementary table 3b) and therefore index DMT was not included in the estimation of  $T_r$ . Pairwise analyses of the individual determinants suggested that baseline EDSS, ARR and MS phenotype were independently associated with  $T_r$  (supplementary table 5) and were included in the set of analyses exploring all combinations of the four determinants. In these final models,  $T_r$  was calculated in 7 groups in whom the number of relapses was  $\geq 300$  (figure 5). Most notably,  $T_r$  was shorter in patients with RRMS and an EDSS $<6$  compared to the other represented groups. In patients with RRMS and an ARR $<2$ ,  $T_r$  was approximately 5 weeks shorter in patients with an EDSS $<6$  compared to  $\geq 6$ . Detailed estimates of  $T_r$  in patient groups are shown in figure 5.

## DISCUSSION

This study from the two largest MS registries, MSBase and OFSEP, showed that the time from commencing MS immunotherapy to its full clinically manifest effect (here termed therapeutic lag) is prolonged especially in patients with greater disability. Other contributing factors include low relapse frequency prior to commencement of therapy (associated with shorter therapeutic lag for disability progression events ~~but longer lag to maximum effect on relapses~~) and sex (with a mildly shorter time to maximum treatment effect on disability progression among females). Therapeutic lag for relapses was mildly prolonged in SPMS.

In contrast with evidence that DMTs reduce long term disability progression in RRMS, results in progressive MS have been comparatively disappointing. Beyond the pathologic differences in each disease stage, proposed methodological reasons have included patient selection, outcome selection, clinical trial design and therapeutic lag. Therapeutic lag was anecdotally observed when differences in disability outcomes occurred at year 7, but not year 2, of a randomised double-blind placebo-controlled trial of interferon beta-1b in PPMS.<sup>6</sup> Our results show that  $T_r$  and  $T_d$  increase with baseline EDSS. Similarly, a post-hoc analysis of the SPECTRIMS (interferon beta-1a in SPMS)<sup>18</sup> and PROMISE (interferon beta-1a in PPMS)<sup>19</sup> trials reported that treatments influenced disability progression with a 2-2.5-year delay and that therapeutic lag duration increased with baseline EDSS.<sup>4</sup> Whilst these findings

mirror our own, there were important differences in the methodology used to estimate lag duration. Whereas the post-hoc analysis of the two clinical trials approximated the duration of *therapeutic lag (years) = baseline EDSS - 3 years*, we used an objective method based on differential calculus, suitable for calculation of therapeutic lag in sufficiently large subgroups, which we have validated in 2 non-overlapping registries (Roos et al., 2020, manuscript under review).

Treatments in MS predominantly act by modifying the inflammatory processes, to which the loss of nervous tissue is secondary.<sup>20</sup> Therefore, prevention of further axonal damage, through the immunosuppressive/immunomodulatory action of DMTs occurs by definition with a delay. There are a number of factors that can define a duration of such delay. For instance, the influence of EDSS on therapeutic lag is consistent with the hypothesis that the CNS possesses a degree of functional reserve capacity that can mask the true extent of axonal loss early in MS.<sup>1</sup> Functional reserve reduces with increasing EDSS as illustrated by incomplete relapse recovery in subjects with an EDSS  $\geq 3$ .<sup>17</sup> In cases with higher EDSS, when the reserve has been exhausted, it is suggested that any therapeutic effects would only become apparent once the degeneration of already damaged and vulnerable axons is complete.<sup>1</sup> This manifests as therapeutic lag.

The role of MS phenotype in therapeutic lag was explored using both physician- and algorithm-defined definitions of SPMS; both definitions of MS phenotype led to similar estimates of lag. In the “multivariable” model that accounted for interactions among the individual determinants of  $T_r$ , the addition of MS phenotype contributed only minimally to the differences in the duration of  $T_r$  within the sufficiently populated groups - i.e.  $T_r$  was only 5 weeks longer in secondary progressive compared to relapsing-remitting patients with EDSS 2-6 and ARR  $\leq 2$ . MS phenotype did not significantly contribute to the duration of  $T_d$ . The observation that therapeutic lag duration was influenced by EDSS more consistently than MS phenotype supports the hypothesis that MS is a continuum, with elements of neuroaxonal loss and progression throughout its disease course, rather than a disease consisting of clearly separable phases.<sup>21-24</sup>

Whereas one prior study<sup>15</sup> showed no difference in the time to the effect of natalizumab on relapses between patients with and without highly active MS ( $\geq 2$  relapses in the year before baseline), ARR was a significant modifier of therapeutic lag for both disability progression and relapses in our analysis. Patients with  $ARR \geq 2$  had a mean 4-week shorter  $T_r$  than those with  $ARR < 2$ . Considering the anti-inflammatory and immunomodulatory mechanisms of current DMTs for MS, it is not unexpected that they show more pronounced, and earlier, effect on the absolute drop in relapse incidence in patients with higher pre-treatment ARR - a clinical presentation of episodic, therapeutically modifiable inflammatory activity.<sup>16</sup> Conversely, our observation that higher pre-treatment ARR prolongs therapeutic lag for disability progression is consistent with previous research that showed a positive association between high ARR and worse disability outcomes in MS.<sup>25 26</sup> Therefore, lowering of relapse activity below the critical level to enable stabilisation of (or recovery from) disability is expected to be prolonged among patients in whom the pre-treatment level of relapse activity was high.

Whilst male sex is associated with faster disability accrual<sup>12 27-30</sup>, the role of sex in therapeutic lag has not previously been explored. Male sex was weakly associated with longer  $T_d$ , but sex was not found to consistently drive differences in  $T_r$ .

Studies of observational data are subject to a number of potential limitations and biases. Variable data quality was controlled through the use of a validated data quality control process.<sup>11</sup> Selection and reporting bias was addressed through the inclusion of two largely non-overlapping data sources from predominantly academic MS centres (MSBase, a global registry, and OFSEP, a national cohort) with near-real time data acquisition and prospectively defined observational plans.  $T_d$  and  $T_r$  was only estimated for subgroups in which more than 300 relapses or progression events occurred as the underlying method is dependent on a critical mass of events to consistently identify the first local minimum of the first derivative of relapse incidence (Roos et al., 2020, under review). Where an insufficient number of events were present analyses were discontinued. There are therefore groups of determinants, particularly in the assessment of  $T_d$  in groups defined by multiple interacting patient characteristics, for which therapeutic lag could not be calculated. In an effort to maximise analytical power, we have combined data from the two largest MS

registries. It is also reassuring that the sufficiently powered groups included in the analysis represent the most common clinical scenarios encountered in practice. Because the method requires that therapeutic lag is estimated within discrete groups, we have categorised continuous determinants. While this may lead to some loss of information, we have ensured that the groups defined on categorised variables are internally consistent with regards to the duration of therapeutic lag.

DMT as a determinant of therapeutic lag was explored in a previous analysis (Roos et al. 2020, under review). Whilst  $T_r$  and  $T_d$  did not differ between most therapies, therapeutic lag tended to be relatively prolonged in dimethyl fumarate ( $T_r$ ) and interferon beta-1a IM ( $T_d$ ). Neither of these therapies were represented disproportionately within any of the groups defined by relevant determinants of therapeutic lag, and were therefore unlikely to obscure or inflate the observed therapeutic lag.

As this study did not include patients treated within 3 years of MS onset, or patients treated for less than 1 year, our conclusions cannot be generalised to these patient groups. Reassuringly, neither MS duration nor the reported reason for discontinuation of the preceding DMT were found to influence  $T_r$  or  $T_d$ . In addition, too few patients with PPMS or CIS were included to explore the duration of therapeutic lag in these MS phenotypes; our conclusions can therefore not be extended to these groups.

The EDSS has a number of limitations as a marker of disability progression<sup>31</sup>; we have utilised this disability scale due to its widespread use and availability in registry data, enabling combining information from two separate registries. We have aimed at improving intra- and inter-rater reliability by using specialist neurologist EDSS raters<sup>32</sup> and a robust definition of disability progression.<sup>12</sup> Only clinical markers of therapeutic lag have been studied in this analysis as observational data, with semiquantitative imaging information acquired at varying intervals, is not suited to assess the radiological onset of treatment effect.

MS is a heterogenous disease, and it is highly desirable to personalise treatment based on patients' individual characteristics - demographic and clinical.<sup>33</sup> In the present study, we identified disability and relapse activity immediately prior to commencing a new MS immunotherapy as factors that most consistently influence the duration of therapeutic lag for disability progression and relapses. Sex has

additional influence on the lag of the effect of therapy on disability progression, and MS phenotype contributes to the duration of therapeutic lag with regards to relapses. This knowledge will contribute to the therapeutic decisions in response to reactivation of MS early after patients commenced a new immunotherapy. It is also of relevance to future reanalysis of clinical trials in patients with more advanced disease and design of future clinical trials in progressive MS. Treatment outcomes in cohorts enriched with patients with higher disability scores and relapse activity should be interpreted with the expected duration of therapeutic lag in sight.

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The authors have received research support, support to attend conferences, speaker honoraria and fees for participation at advisory boards from Actelion, Almirall, Bayer-Schering, Biogen, BioCSL, Celgene, EMD, Geneuro, Medday, Merck, Myalin, Novartis, Roche, Sanofi-Genzyme, Teva, WebMD Global outside the submitted work.

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### **DATA AVAILABILITY STATEMENT**

MSBase is a data processor, and warehouses data from individual principal investigators who agree to share their datasets on a project-by-project basis. Data access to external parties can be granted upon reasonable request at the sole discretion of each OFSEP and MSBase Principal Investigator (the data controllers), who will need to be approached individually for permission.

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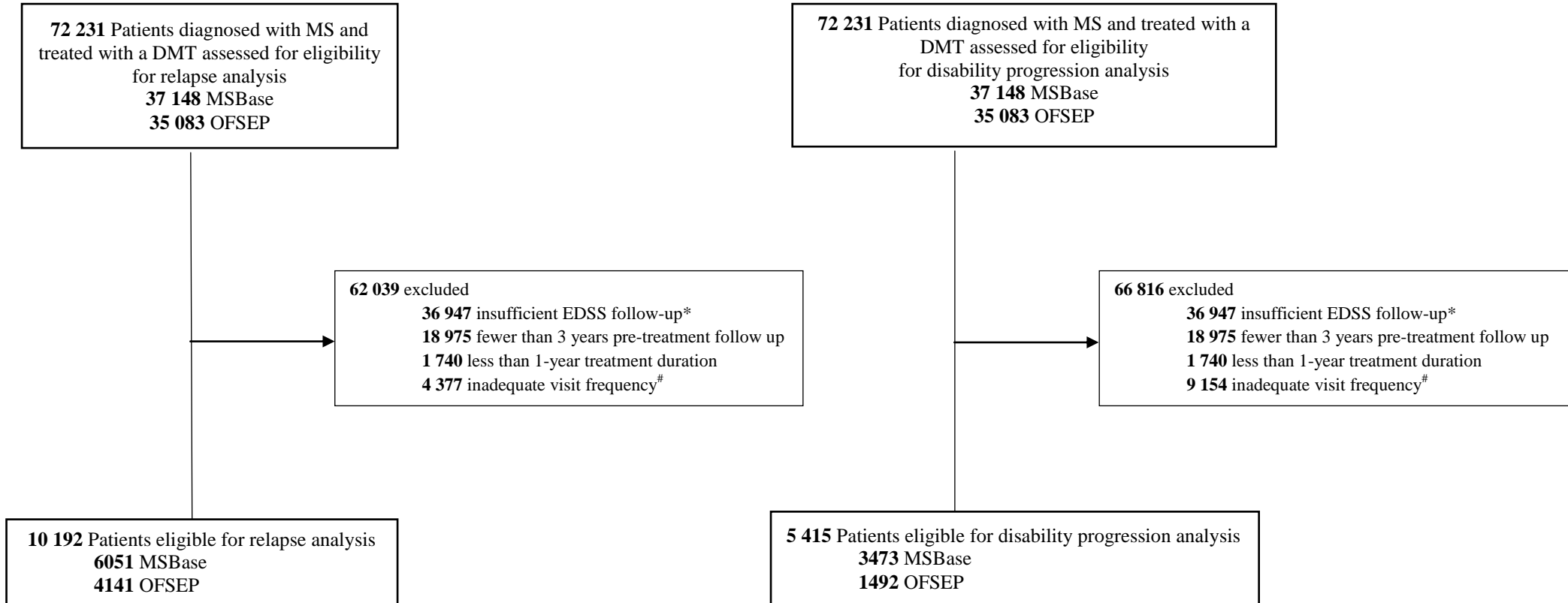
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## FIGURE LEGENDS

Figure 1: CONSORT Diagram



\*Patients excluded owing to “insufficient EDSS follow-up” did not have a baseline visit with a recorded EDSS measurement within 6 months pre or 1-month post therapy commencement or had fewer than 2 post baseline visits 6 or more months apart.

#Patients excluded due to “inadequate visit frequency” did not have at least yearly visits with EDSS recorded during the treatment epoch. A treatment epoch was defined as time including three years prior to treatment start and one year (for the effect on relapses) and three years (for the effect on disability) after treatment start.

MS multiple sclerosis; RRMS relapsing relapsing MS; CIS clinically isolated syndrome; DMT disease modifying therapy

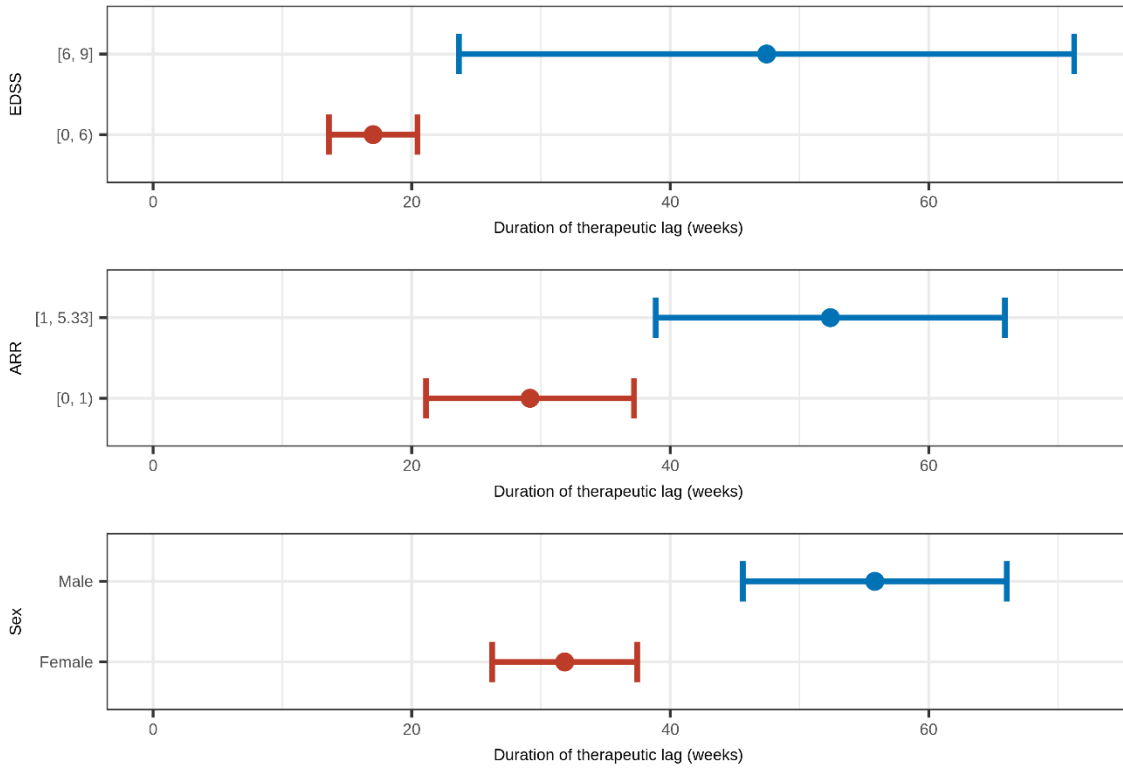


Figure 2

Individual determinants of therapeutic lag for disability progression

EDSS: expanded disability status scale; ARR: annualised relapse rate

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) = exclusive bracket

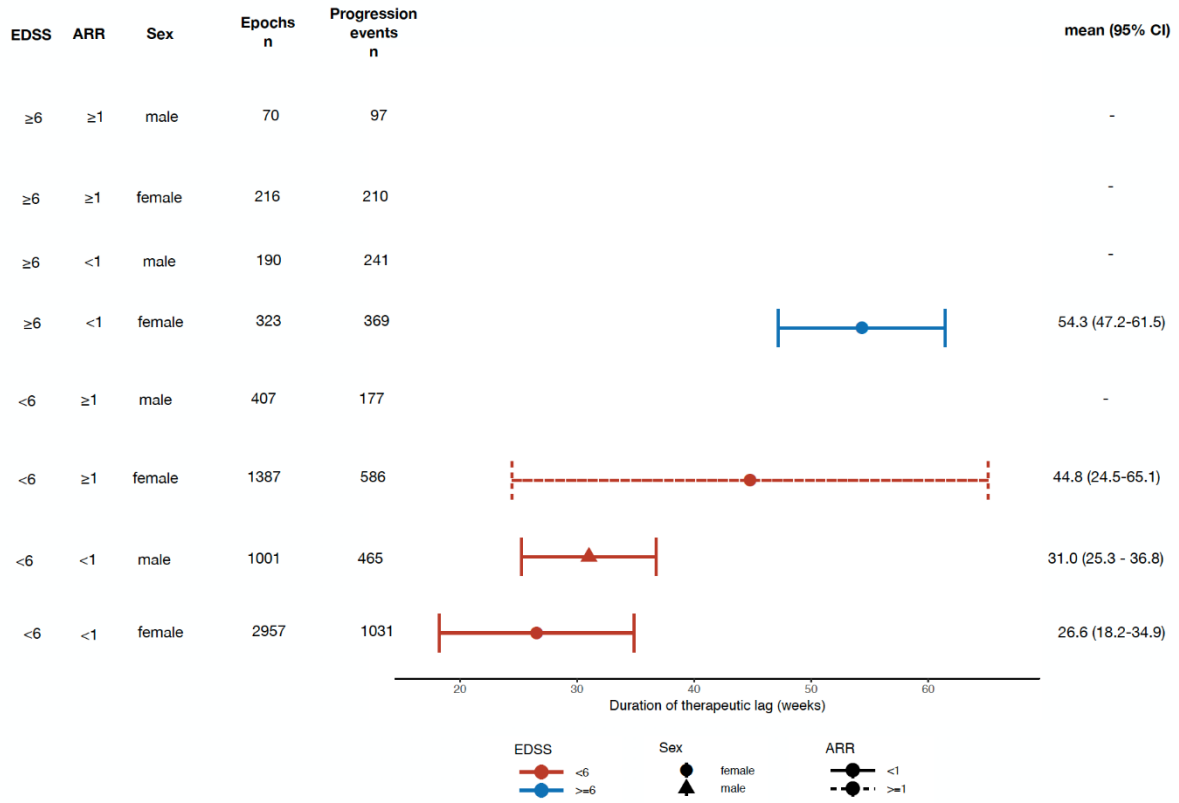


Figure 3

Interactions among the three determinants of therapeutic lag for disability progression ( $T_d$ )

-  $T_d$  was not calculated in groups of determinants with fewer than 300 progression events

EDSS: expanded disability status scale; ARR: annualised relapse rate; CI: confidence interval

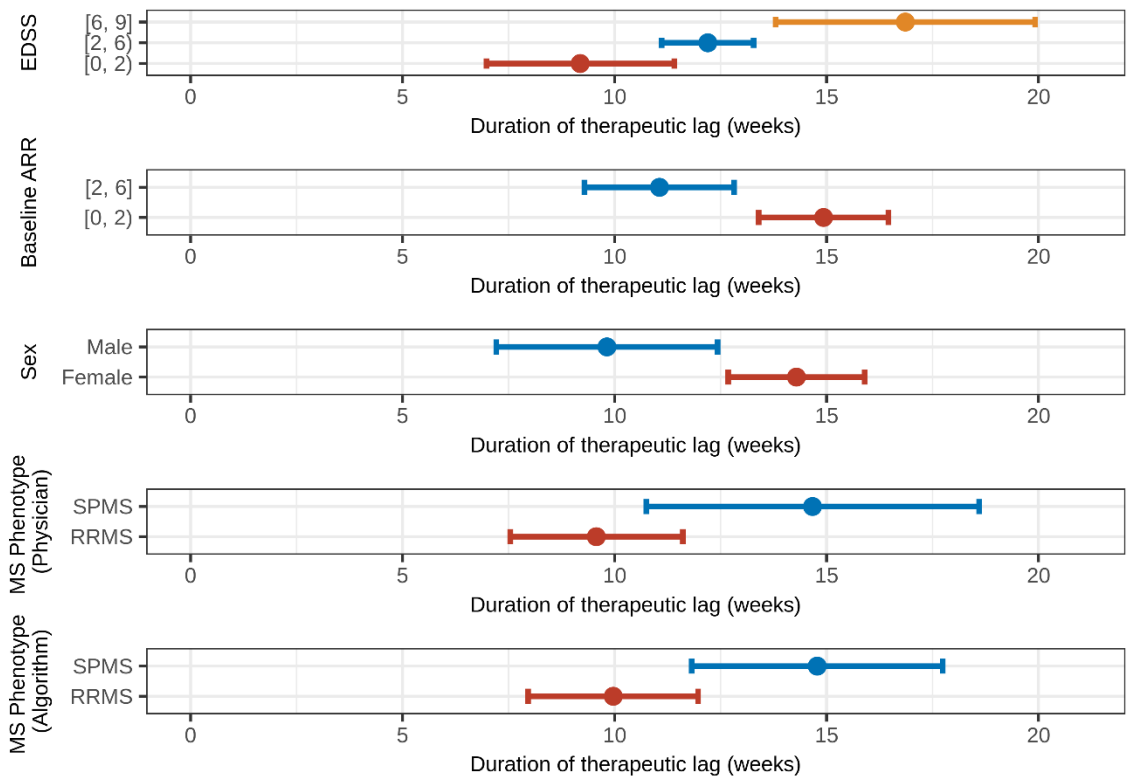


Figure 4  
Individual determinants of therapeutic lag for relapses

EDSS: expanded disability status scale; ARR: annualised relapse rate; RRMS: relapsing remitting MS; SPMS: secondary progressive MS  
[: inclusive bracket; ): exclusive bracket

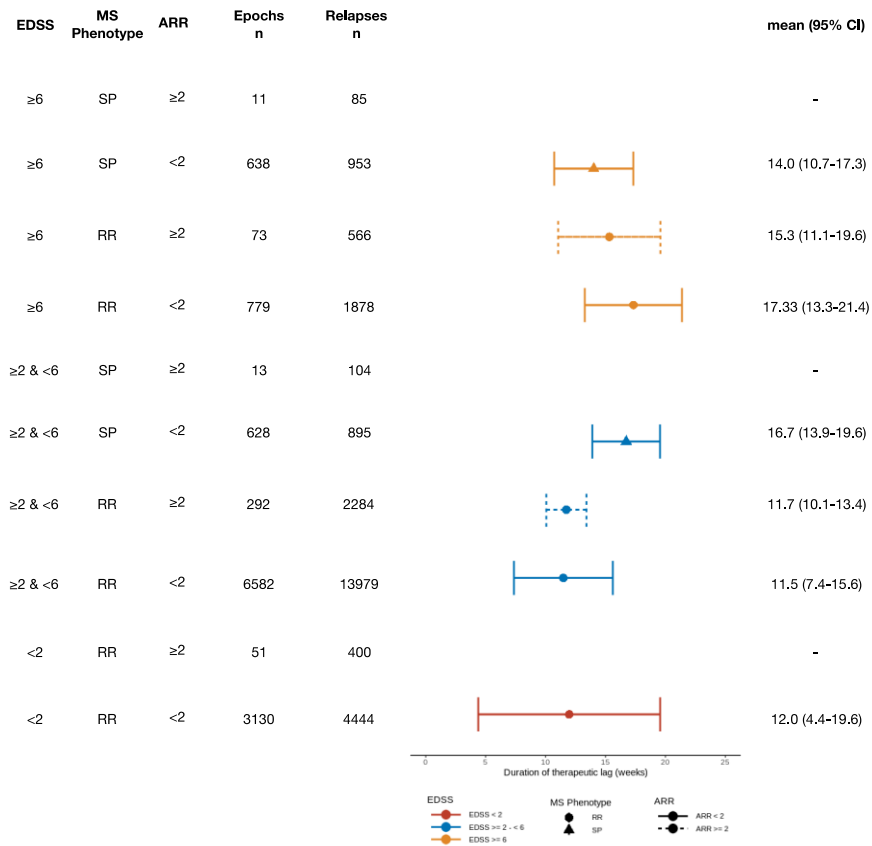


Figure 5

Interactions among the three determinants of therapeutic lag for relapses

-  $T_r$  was not calculated in groups of determinants with fewer than 300 relapses or in which  $T_r$  was not identified in more than 80% of bootstrap replications.

EDSS: expanded disability status scale; SP: secondary progressive; RR: relapsing-remitting; ARR: annualised relapse rate; CI: confidence interval





