

3 ORIGINAL ARTICLE

4 Early versus late initiation of high-efficacy
5 disease-modifying therapies in relapsing-
6 remitting multiple sclerosis: a systematic
7 review and meta-analysis

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12 ABSTRACT

13 **Background:** Relapsing-remitting multiple sclerosis (RRMS) is a chronic immune-mediated disorder of the cen-
14 tral nervous system associated with recurrent inflammatory activity and long-term disability accumulation.
15 Although escalation therapy has traditionally been used, early initiation of high-efficacy disease-modifying
16 therapies (HE-DMTs) may provide stronger inflammatory control and improve long-term outcomes.

17 **Objective:** This systematic review and meta-analysis aimed to compare early initiation of HE-DMTs with esca-
18 lation or delayed treatment strategies in adults with relapsing-remitting MS.

19 **Methods:** PubMed, Scopus, and Web of Science were systematically searched. Eligible studies included adults
20 with RRMS treated with either early HE-DMTs or escalation/delayed strategies. Outcomes included annualized
21 relapse rate (ARR), Expanded Disability Status Scale (EDSS) change, and delta-Expanded Disability Status Scale
22 (Δ EDSS). Study quality was assessed using the Newcastle-Ottawa Scale, and pooled analyses were performed
23 using random-effects models.

24 **Results:** Ten observational cohort studies were included. Early initiation of high-efficacy treatment was
25 associated with a lower ARR than escalation therapy. Disability findings remained uncertain. The pooled
26 EDSS-change analysis was not statistically significant and showed considerable heterogeneity. Only one eligi-
27 ble study reported an adjusted Δ EDSS comparison; therefore, this outcome was reported narratively and was
28 not meta-analyzed. Nonrandom treatment allocation and potential confounding by indication limit causal
29 interpretation.

30 **Conclusion:** Early initiation of high-efficacy disease-modifying therapy was associated with lower relapse
31 activity in observational RRMS cohorts. The available disability evidence does not establish a causal advantage
32 of either treatment strategy and requires cautious interpretation.

33 **Keywords:** Relapsing-remitting multiple sclerosis, high-efficacy disease-modifying therapy, early intensive
34 treatment, escalation therapy, meta-analysis.

35 Introduction

36 Multiple sclerosis (MS) is a chronic immune-mediated
37 inflammatory disorder of the central nervous system
38 characterized by demyelination, axonal injury, and
39 progressive neurodegeneration [1]. It is a leading cause
40 of non-traumatic neurological disability among young
41 adults [2]. Relapsing-remitting multiple sclerosis

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46	(RRMS) is characterized by relapses followed by	The protocol for this systematic review and meta-analysis	101
47	partial or complete remission [1], although neuroaxonal	was registered in the international Prospective Register	102
48	damage and subclinical disease activity may begin before	of Systematic Reviews (PROSPERO; registration	103
49	sustained clinical progression becomes apparent [3].	number: CRD420261456933; https://www.crd.york.ac.uk/PROSPERO/view/CRD420261456933)	104
50	Disease-modifying therapies (DMTs) aim to reduce		105
51	inflammatory and magnetic resonance imaging		
52	(MRI) activity and delay disability accumulation [2],	Eligibility Criteria (PICO Framework)	106
53	substantially improving disease control and long-term		
54	prognosis [4]. Moderate-efficacy therapies include	Population (P)	107
55	interferon beta and glatiramer acetate, whereas high-	Studies involving adult patients diagnosed with RRMS,	108
56	efficacy therapies include natalizumab, ocrelizumab, and	according to the McDonald criteria or equivalent	109
57	alemtuzumab [5]. The traditional escalation approach	diagnostic definitions used by the individual studies,	110
58	begins with moderate-efficacy therapy and introduces	were included.	111
59	more potent agents when disease activity persists [6],		
60	partly because of the established safety profiles of first-	Intervention (I)	112
61	line therapies [5]. However, this approach may allow	The intervention of interest is early initiation of high-	113
62	ongoing subclinical inflammation and irreversible	efficacy disease-modifying therapies, defined as either:	114
63	neurological damage [3].		
64	Early initiation of high-efficacy therapy has therefore	1. Initiation of a HE-DMT within ≤ 2 years of diagnosis.	115
65	gained attention [7]. Rapid suppression of inflammatory		
66	activity may limit cumulative central nervous system	2. Use of a HE-DMT as first-line/upfront therapy in	116
67	damage and improve long-term outcomes [3].	treatment-naïve patients, according to study-specific	117
68	Observational studies have associated early intensive	definitions.	118
69	treatment (EIT) with lower relapse and radiological	High-efficacy therapies of interest include natalizumab,	119
70	activity [6], delayed disability progression, and a lower	alemtuzumab, anti-CD20 therapies (ocrelizumab,	120
71	risk of conversion to secondary progressive MS [6].	ofatumumab, rituximab), cladribine, and other agents	121
72	Nevertheless, the evidence remains heterogeneous because	categorized as high-efficacy or early intensive therapies	122
73	of differences in study design, treatment definitions,	by the included studies.	123
74	outcomes, and follow-up duration [7]. Uncertainty also		
75	remains regarding patient selection, treatment timing,	Comparator (C)	124
76	and the balance between efficacy and safety [4]. Because	The comparator group included escalation or delayed	125
77	previous reviews have often lacked quantitative synthesis	treatment strategies, defined as:	126
78	[7], this systematic review and meta-analysis evaluated		
79	the effects of early high-efficacy therapy compared with	1. Initial treatment with platform or moderate-efficacy	127
80	delayed or escalation strategies on relapse activity and	DMTs (e.g., interferon-beta, glatiramer acetate,	128
81	disability-related outcomes in RRMS [3].	teriflunomide, or dimethyl fumarate), followed by	129
82		escalation to a HE-DMT when clinically indicated.	130
83	Methodology		
84		2. Delayed initiation of a HE-DMT after an initial	131
85	Study objectives	treatment period with lower-efficacy therapies.	132
86	To systematically review and quantitatively synthesize		
87	the available evidence comparing early initiation of	Outcomes (O)	133
88	high-efficacy disease-modifying therapies (HE-DMTs)	The outcomes of interest were measures of disease	134
89	with escalation or delayed treatment strategies in adults	activity and disability progression in patients with	135
90	with RRMS, focusing on relapse activity and disability-	RRMS. Clinical outcomes included annualized relapse	136
91	related outcomes.	rate (ARR), changes in disability measured using the	137
92		Expanded Disability Status Scale (EDSS), and delta-	138
93	Study design	EDSS (Δ EDSS).	139
94	This study was conducted as a systematic review and		
95	meta-analysis in accordance with the Preferred Reporting	Study designs	140
96	Items for Systematic Reviews and Meta-Analyses	Eligible studies included randomized controlled trials,	141
97	guidelines. The review aimed to synthesize available	post hoc analyses of randomized trials, prospective	142
98	evidence comparing early initiation of HE-DMTs with	cohort studies, retrospective cohort studies, and registry-	143
99	escalation or delayed treatment approaches in patients	based observational studies.	144
100	with relapsing MS.		
	Where appropriate, quantitative synthesis (meta-analysis)	The following study types were excluded: Case reports	145
	was performed using pooled effect estimates derived	and case series, Narrative reviews and editorials,	146
	from eligible studies reporting comparable outcomes.	Cross-sectional studies without longitudinal follow-up,	147
		Conference abstracts or poster presentations lacking	148
		sufficient data, Studies not stratifying patients according	149
		to treatment timing or escalation strategy (ESC),	150
		and studies focused exclusively on pediatric MS or	151

152	progressive-onset MS subtypes without relapsing disease	206
153	activity.	207
154	Information Sources and Search Strategy	208
155	A comprehensive literature search was conducted using	209
156	the following electronic databases: PubMed, Scopus, and	210
157	Web of Science.	211
158	The search included studies published from database	212
159	inception to the most recent search date. Only studies	213
160	published in English were considered eligible.	214
161	Additionally, reference lists of included studies and	
162	relevant reviews were manually screened to identify	
163	potentially eligible articles not captured through the	
164	database search.	
165	The search strategy combined Medical Subject Headings	
166	and free-text keywords related to RRMS, high-efficacy	
167	therapies, treatment timing, escalation strategies, and	
168	clinical outcomes.	
169	The main search terms included: “relapsing multiple	
170	sclerosis” “RRMS” “high-efficacy” “highly effective”	
171	“natalizumab” “alemtuzumab” “ocrelizumab”	
172	“ofatumumab” “rituximab” “cladribine” “early treatment”	
173	“first-line” “upfront therapy” “late initiation” “escalation	
174	therapy” “annualized relapse rate” “ARR” “Expanded	
175	Disability Status Scale” “EDSS” “MRI” “NEDA”.	
176	The Boolean search strategy included combinations of the	
177	following structure: (“relapsing multiple sclerosis” OR	
178	RMS OR RRMS) AND (“high-efficacy” OR natalizumab	
179	OR ocrelizumab OR alemtuzumab OR rituximab OR	
180	cladribine) AND (“early treatment” OR “first-line” OR	
181	“upfront therapy” OR “escalation therapy” OR “late	
182	initiation”) AND (ARR OR EDSS OR relapse OR MRI	
183	OR NEDA OR disability progression).	
184	Study selection	
185	All retrieved records were imported into Rayyan, and	
186	duplicate records were removed prior to screening.	
187	Two independent reviewers performed title and abstract	
188	screening according to the predefined eligibility criteria.	
189	Studies deemed potentially eligible subsequently	
190	underwent full-text review.	
191	Disagreements between reviewers at any stage of the	
192	screening process were resolved by a third reviewer for	
193	final decision-making.	
194	Data extraction	
195	Data were extracted independently by two reviewers	
196	using a standardized data extraction form. Extracted	
197	variables included study characteristics such as author,	
198	year of publication, country, journal, study design, study	
199	duration, follow-up period, sample size, and inclusion	
200	and exclusion criteria.	
201	Quality assessment (ROB)	
202	The methodological quality and risk of bias of the	
203	included observational cohort studies were assessed	
204	using the Newcastle–Ottawa Scale (NOS) [8]. Studies	
205	were evaluated across three domains: selection	
	(maximum 4 points), comparability (maximum 2 points),	206
	and outcome (maximum 3 points), with a maximum total	207
	score of 9 points. For this review, NOS scores of 8-9 were	208
	interpreted as low risk of bias, scores of 6-7 as moderate	209
	risk of bias, and scores of 5 or fewer as high risk of bias.	210
	Overall judgments were expressed more conservatively	211
	when important residual confounding or selection bias	212
	was considered likely. The assessment was performed by	213
	three reviewers.	214
	Statistical analysis	215
	Cochrane Review Manager 5.3 was used to perform a	216
	meta-analysis. The mean difference with 95% confidence	217
	interval (CI) was used for continuous outcomes. A	218
	random-effects model was used to account for between-	219
	study heterogeneity. Statistical heterogeneity was	220
	assessed using the I^2 statistic. A leave-one-out sensitivity	221
	test was performed to assess the robustness of the pooled	222
	estimates and explore heterogeneity. In terms of values,	223
	we interpreted the I-square as follows: not significant for	224
	0%–40%, moderate heterogeneity for 30%–60%, and	225
	substantial heterogeneity for 50%–90%, following the	226
	Cochrane Handbook chapter nine. Funnel plots were	227
	used to assess publication bias.	228
	Quantitative pooling was undertaken only when	229
	outcome definitions, follow-up scales, treatment-contrast	230
	directions, and measures of variance were sufficiently	231
	comparable. Outcomes reported by only one eligible	232
	study or outcomes that could not be harmonized reliably	233
	were synthesized narratively.	234
	Results	235
	Screening of the included studies	236
	A literature search of PubMed, Scopus, and Web of Science	237
	identified 3,691 records. After removing 977 duplicates,	238
	2,714 studies were screened, and 2,600 were excluded.	239
	Of 114 full-text reports sought, 10 were unavailable and	240
	104 were assessed. Following full-text review, 94 articles	241
	were excluded for secondary progressive multiple	242
	sclerosis inclusion ($n = 12$), inappropriate design ($n =$	243
	45), unavailable data ($n = 26$), or irrelevant populations or	244
	outcomes ($n = 11$). Ultimately, 10 studies were included	245
	in the systematic review and meta-analysis (Figure 1).	246
	Characteristics of included studies	247
	Ten comparative observational cohort studies were	248
	included. The studies were conducted across European,	249
	Australian, and multinational registry settings. Sample	250
	sizes ranged from 195 to 4,878 participants. Most	251
	participants were female, constituting around 62%–81%.	252
	Mean age ranged from 29 to 39 years (Table 1).	253
	Abbreviations: CDA, confirmed disability accrual; EDSS,	254
	Expanded Disability Status Scale; EIT, early intensive	255
	treatment; ESC, escalation strategy; HEET, high-efficacy	256
	early therapy; LEET, low-efficacy early therapy; NOS,	257
	Newcastle-Ottawa Scale; PIRA, progression independent	258
	of relapse activity; RAW, relapse-associated worsening;	259
	RoB, risk of bias. AZA, azathioprine; AZM, alemtuzumab;	260
	CLAD, cladribine; DMF, dimethyl fumarate; DMT,	261

262 disease-modifying therapy; EIT, early intensive treatment;
 263 ESC, escalation strategy; FTY, fingolimod; GA, glatiramer
 264 acetate; HEET/heDMT, high-efficacy early/high-efficacy
 265 DMT; IPW, inverse probability weighting; LEET/
 266 meDMT, low-/moderate-efficacy early DMT; NR, not
 267 reported; NTZ, natalizumab; OCR, ocrelizumab; OZA,
 268 ozanimod; RTX, rituximab; TERI, teriflunomide; TOP,
 269 Tysabri Observational Program.

270 Risk of bias

271 All ten included comparative studies were observational
 272 cohorts and were assessed using the NOS (Table 2).
 273 Four studies scored 8 of 9 and were judged to have
 274 low-to-moderate risk of bias, five studies scored 7 of 9
 275 and were judged to have moderate risk of bias, and one
 276 study scored 6 of 9 and was judged to have moderate-
 277 to-high risk of bias. The most frequent limitations were
 278 nonrandom treatment allocation, potential confounding
 279 by indication, baseline imbalance, treatment switching,
 280 incomplete MRI or safety data, and variable follow-
 281 up intensity. The main methodological strengths were
 282 registry-based sampling, neurologist-assessed EDSS and
 283 relapse outcomes, propensity-score matching or inverse

probability weighting in several studies, and long-term
 outcome assessment in multiple cohorts.

Abbreviations: CDA, confirmed disability accrual;
 EDSS, Expanded Disability Status Scale; EIT, early
 intensive treatment; ESC, escalation strategy; HEET,
 high-efficacy early therapy; LEET, low-efficacy
 early therapy; NOS, Newcastle-Ottawa Scale; PIRA,
 progression independent of relapse activity; RAW,
 relapse-associated worsening; RoB, risk of bias.

Primary outcomes

1. Change in EDSS

The pooled mean difference in EDSS change, calculated as
 ESC minus EIT, was 0.55 (95% CI -0.82-1.92; $p = 0.43$),
 with considerable heterogeneity ($I^2 = 99\%$; Figure 2). The
 CI was compatible with differences in either direction
 and does not establish equivalence between the strategies.
 After exclusion of Prosperini et al. [17] in the sensitivity
 analysis, the pooled estimate was 1.06 (95% CI 0.12-2.00;
 $p = 0.03$), while heterogeneity remained considerable (I^2
 $= 92\%$; Figure 3). The change in statistical significance
 indicates sensitivity to study inclusion; therefore, this

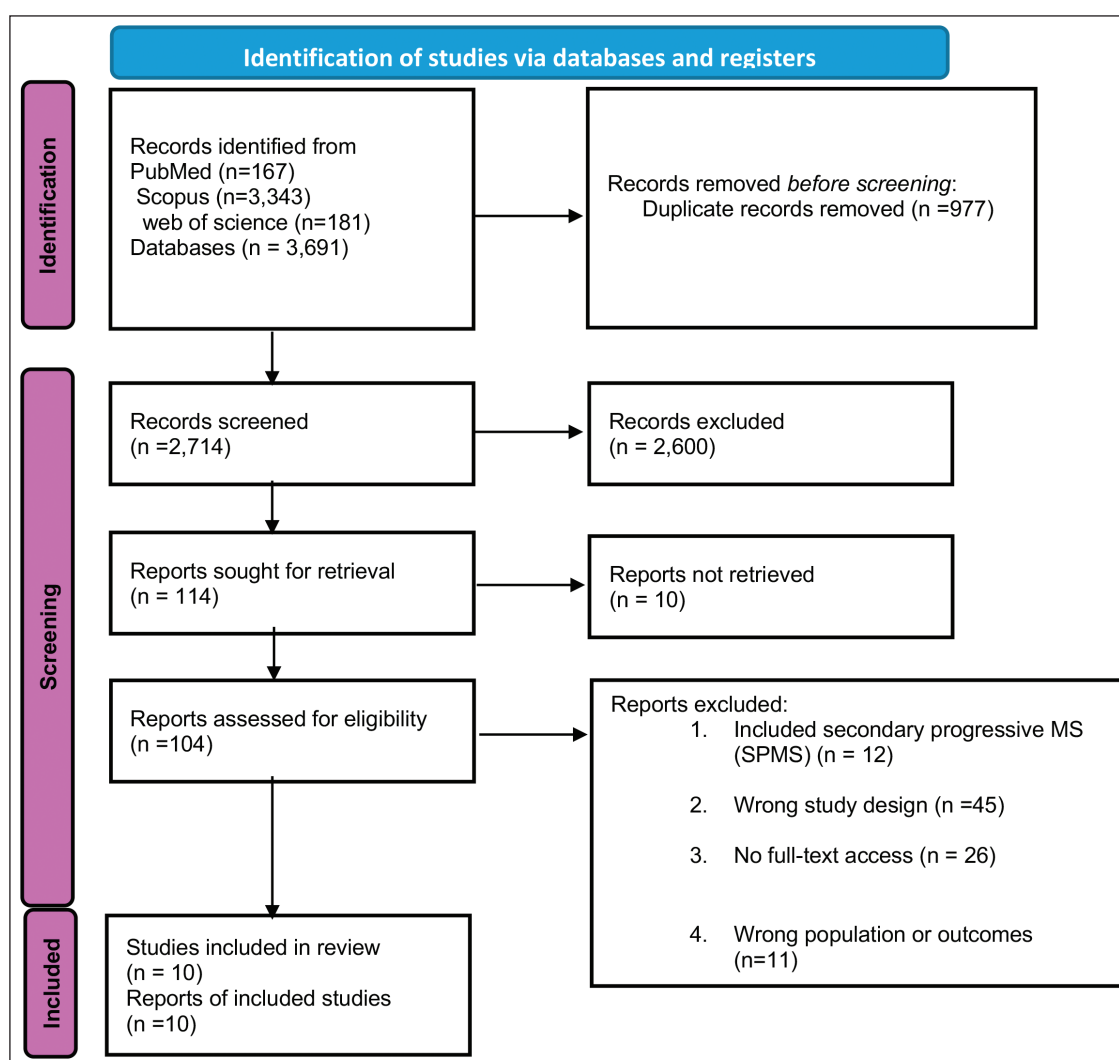


Figure 1. PRISMA chart of the included studies.

Table 1. The summary characteristics of the included studies.

Study	Setting ng	Design	Analysis sample (n)	Treatment comparison	Age, years	Female (n/N, %)
Spelman et al. [10]	Denmark; Sweden	Registry cohort	4,861 (Denmark 2161; Sweden 2700)	Denmark: predominantly escalation strategy; Sweden: more frequent initial high-efficacy DMT	Denmark 37.3 (9.4); Sweden 36.1 (9.5)	Denmark 1,472/2,161 (68.1%); Sweden 1867/2700 (69.2%)
Iaffaldano et al. [27]	Italy	Retrospective registry cohort	2,702 (ESC 2337; EIT 365)	EIT: initial FTY/NTZ/ mitoxantrone/CLAD; ESC: initial IFN-beta/GA/AZA followed by a high-efficacy DMT	ESC 29.37 (9.22); EIT 31.13 (10.06)	ESC 1,541/2,337 (65.94%); EIT 240/365 (65.75%)
Iaffaldano et al. [11]	Italy	Retrospective registry cohort	4,878 (ESC 3964; EIT 914)	EIT: initial high-efficacy DMT; ESC: moderate-efficacy DMT for at least 1 year followed by a high-efficacy DMT	ESC 31.15 (10.07); EIT 32.46 (10.84)	ESC 2,633/3,964 (66.42%); EIT 608/914 (66.52%)
Harding et al. [4]	United Kingdom	Observational cohort	592 (EIT 104; ESC 488)	EIT: initial alemtuzumab or NTZ; ESC: initial moderate-efficacy DMT followed by escalation	EIT 34.0 (9.0); ESC 38.5 (9.7)	EIT 79/104 (76%); ESC 346/488 (71%)
David et al. [28]	France (Caribbean)	Multicenter retrospective cohort	195 (EIT 66; ESC 129)	EIT: initial mitoxantrone/NTZ/ FTY/OCR/RTX; ESC: initial IFN-beta/DMF/GA/TERI	EIT 31 (24–40); ESC 38 (28–43)	EIT 54/66 (81.8%); ESC 98/129 (76.0%)
Guger et al. [9]	Austria	Registry cohort with IPW	IPW effective n = 955 (EIT 491; ESC 464)	EIT: initial AZM/CLAD/FTY/NTZ/ OCR/OZA; ESC: DMF or TERI followed by a high-efficacy DMT	EIT 36.1 (11.3); ESC 35.9 (10.2)	EIT 315/491 (64.2%); ESC 306/464 (65.9%)
Butzkueven et al. [29]	International (MSBase)	Retrospective matched cohort	710 (NTZ 355; BRACETD 355)	Initial NTZ versus initial BRACETD; subsequent switching or escalation was permitted	NTZ 34.19 (10.70); BRACETD 34.88 (10.78)	NTZ 218/355 (61.4%); BRACETD 218/355 (61.4%)
Spelman et al. [30]	International (MSBase/ TOP)	Propensity-matched cohort	732 (NTZ 366; IFN-beta/GA 366)	Initial NTZ versus initial IFN-beta or GA	NTZ 33 (27–42); IFN-beta/GA 37 (30–44)	Count NR; NTZ 70% (n = 366), IFN-beta/GA 72% (n = 366)
Prosperini et al. [17]	Italy	Multicenter observational cohort	813 (ESC 738; induction 75)	Initial induction therapy versus escalation from moderate-efficacy therapy	ESC 32.2 (8.4); induction 35.6 (9.3)	ESC 526/738 (71.3%); induction 51/75 (68.0%)
Hänninen et al. [31]	Finland	Population-based propensity-matched cohort	1,925 (heDMT 154; meDMT 1,771)	Initial heDMT (NTZ/AZM/OCR/ RTX) versus initial meDMT (injectables/TERI/DMF), with escalation as indicated	heDMT 32.2 (9.40); meDMT 35.4 (9.69)	heDMT 109/154 (70.8%); meDMT 1,293/1,771 (73.0%)

Note: Values refer to the baseline analysis cohort reported by each study. Age is mean (SD) at DMT/treatment initiation unless stated otherwise; David 2025 and Spelman 2016 report median (IQR). Guger et al. [9] reports IPW effective sample sizes and weighted baseline values so that all denominators align. BRACETD includes interferon beta, glatiramer acetate, teriflunomide, and dimethyl fumarate.

sensitivity analysis should not be interpreted as robust evidence of EIT benefit. These observational estimates remain susceptible to confounding by indication. The funnel plot for change in EDSS is presented in Figure 4 and was interpreted cautiously in view of the limited number of contributing studies.

2. ARR

The pooled mean difference in ARR, calculated as ESC minus EIT, was 0.16 (95% CI 0.08-0.23; $p < 0.0001$), favoring EIT, with considerable heterogeneity ($I^2 = 95\%$; Figure 5). After exclusion of Guger et al. [9], the pooled estimate remained statistically significant (MD = 0.12, 95% CI 0.05-0.19; $p = 0.0004$), while heterogeneity remained considerable ($I^2 = 93\%$; Figure 6). The funnel plot for ARR is presented in Figure 7 and was interpreted cautiously because of the limited number of contributing studies.

3. Delta-EDSS findings

One eligible study reported an adjusted Δ EDSS comparison. Iaffaldano et al. [11] reported an adjusted

between-strategy difference of -0.16 points at year 1 (95% CI -0.25 to -0.07), favoring EIT. Because only one eligible study contributed to this outcome, no meta-analysis was performed. This observational estimate remains susceptible to confounding by indication, residual baseline differences, and variation in follow-up and EDSS assessment.

Discussion

The disability findings require cautious interpretation. The EDSS-change estimate was imprecise, showed considerable heterogeneity, and was sensitive to the exclusion of one study. Δ EDSS was reported by one eligible study and was therefore summarized narratively. Accordingly, these observational findings do not establish a causal or clinically definitive disability advantage for either strategy. The ARR result is consistent with recent real-world evidence. Guger et al. [9] reported a lower adjusted ARR with EIT than ESC in an Austrian cohort [9]. A Swedish and Danish registry comparison similarly associated earlier highly effective treatment with better disability outcomes [10], while the Italian MS Register reported long-term disability advantages with

Table 2. *Newcastle-Ottawa Scale risk of bias assessment.*

Study	Design	Tool	Selection/4	Comparability/2	Outcome/3	Total/9	Overall RoB	Main concerns
Spelman et al. [10]	Observational cohort	NOS cohort	4	2	2	8	Low to moderate	Country-level nonrandomized comparison and possible differences in EDSS assessment frequency between registries.
Spelman et al. [30]	Observational cohort	NOS cohort	3	1	2	6	Moderate to high	Cross-registry comparison, shorter follow-up, residual confounding, indication bias, selection or ascertainment bias, incomplete MRI and safety data.
Iaffaldano et al. [27]	Observational cohort	NOS cohort	4	2	2	8	Low to moderate	Registry design, decreasing EDSS availability over time, lack of MRI covariates in matching, EDSS measurement limitations.
Iaffaldano et al. [11]	Observational cohort	NOS cohort	4	2	2	8	Low to moderate	Retrospective registry design, EDSS-only CDA, PIRA, and RAW definitions, no systematic MRI, possible EDSS assessment-density bias.
David et al. [28]	Observational cohort	NOS cohort	3	1	3	7	Moderate	Small EIT subgroup, shorter EIT follow-up, baseline age imbalance, no propensity matching, residual indication bias.
Guger et al. [9]	Observational cohort	NOS cohort	4	2	2	8	Low to moderate	Nonrandom treatment allocation, possible indication bias, no follow-up MRI data, residual unmeasured registry confounding.
Butzkueven et al. [29]	Observational cohort	NOS cohort	3	2	2	7	Moderate	Residual confounding, treatment switching, missing discontinuation reasons, no MRI adjustment, product-specific rather than pure strategy comparison.
Prosperini et al. [17]	Observational cohort	NOS cohort	3	2	2	7	Moderate	Small induction group, nonrandom assignment, selection and indication bias, incomplete matching, higher serious adverse event rate.
Harding et al. [4]	Observational cohort	NOS cohort	4	1	2	7	Moderate	EIT selected for worse prognostic features, no propensity matching, nonuniform imaging and safety data, residual confounding.
Hänninen et al. [31]	Observational cohort	NOS cohort	3	2	2	7	Moderate	Small matched samples, retrospective design, missing MRI data preventing MRI matching, selection bias, incomplete adverse event reporting.

Note: NOS interpretation used for this manuscript: 8–9 stars = low risk of bias; 6–7 stars = moderate risk of bias; 5 or fewer stars = high risk of bias. Overall judgements were expressed conservatively when major residual confounding or selection bias was likely.

early intensive therapy [11]. Together, these findings support the potential benefit of earlier inflammatory disease control. This benefit is biologically plausible. Natalizumab reduces immune-cell migration across the blood-brain barrier and reduced relapse and disability progression in the AFFIRM trial [12]. Ocrelizumab reduced ARR and disability progression compared with interferon beta-1a in OPERA I and II [13], while ofatumumab reduced ARR compared with teriflunomide in ASCLEPIOS I and II [14]. The nonsignificant pooled EDSS-change result does not demonstrate an absence of disability benefit. EDSS is weighted toward ambulation and may not fully capture cognitive, visual, upper-limb, or MRI-related disease effects. Harding et al. [4] associated EIT with better five-year EDSS outcomes, and Brown et al. [6] associated initial high-efficacy treatment with a lower risk of conversion to secondary progressive MS. Disability differences may therefore

require longer follow-up or more sensitive outcome measures. Confounding by indication remains important because patients selected for EIT frequently have more active disease at baseline. Treatment strategies are influenced by baseline risk, safety considerations, and treatment access [15]. The potential benefits of EIT must also be balanced against safety and variation in disease activity [16]. The adjusted Δ EDSS finding should therefore be interpreted as a supportive observational association rather than definitive evidence of treatment superiority. Differences in treatment era, follow-up, baseline activity, drug availability, and the definitions of EIT and ESC likely contributed to heterogeneity. Some studies classified fingolimod as high efficacy, whereas others focused on monoclonal antibodies or immune-reconstitution therapies. Earlier induction studies also used agents that may not be directly comparable with contemporary EIT strategies [17]. The results are

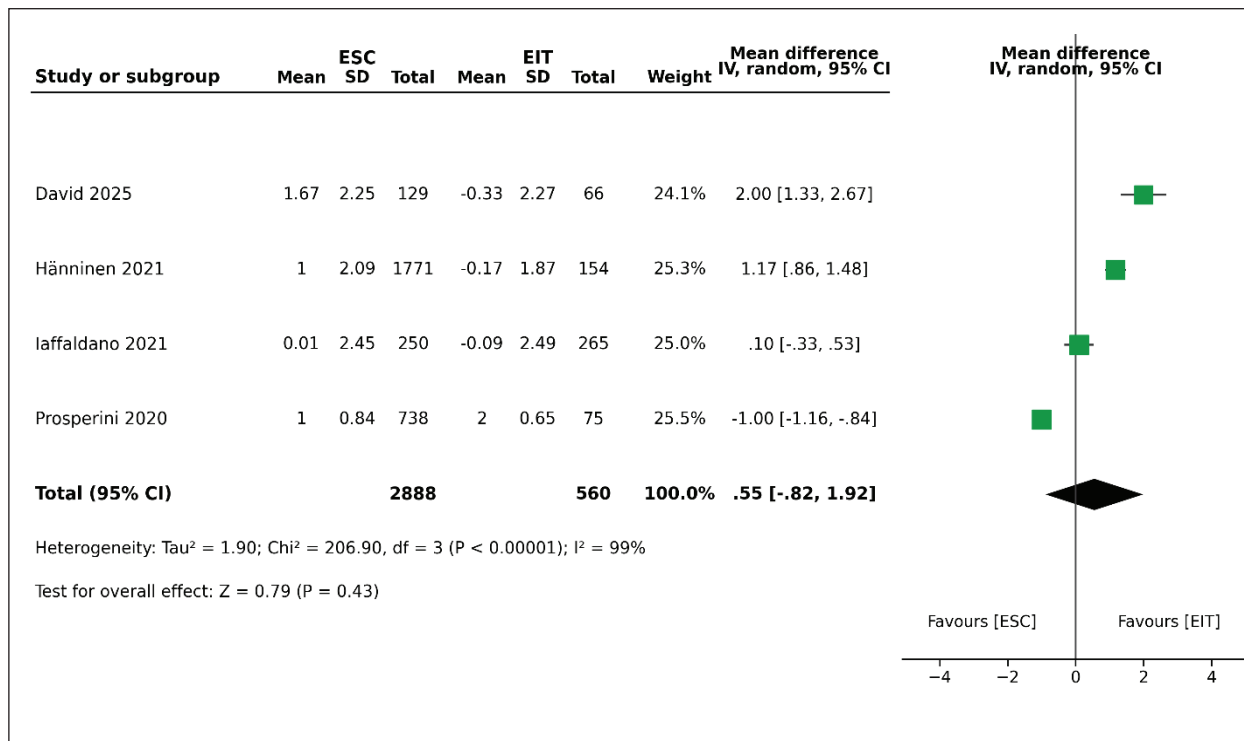


Figure 2. Forest plot of Change in EDSS outcome.

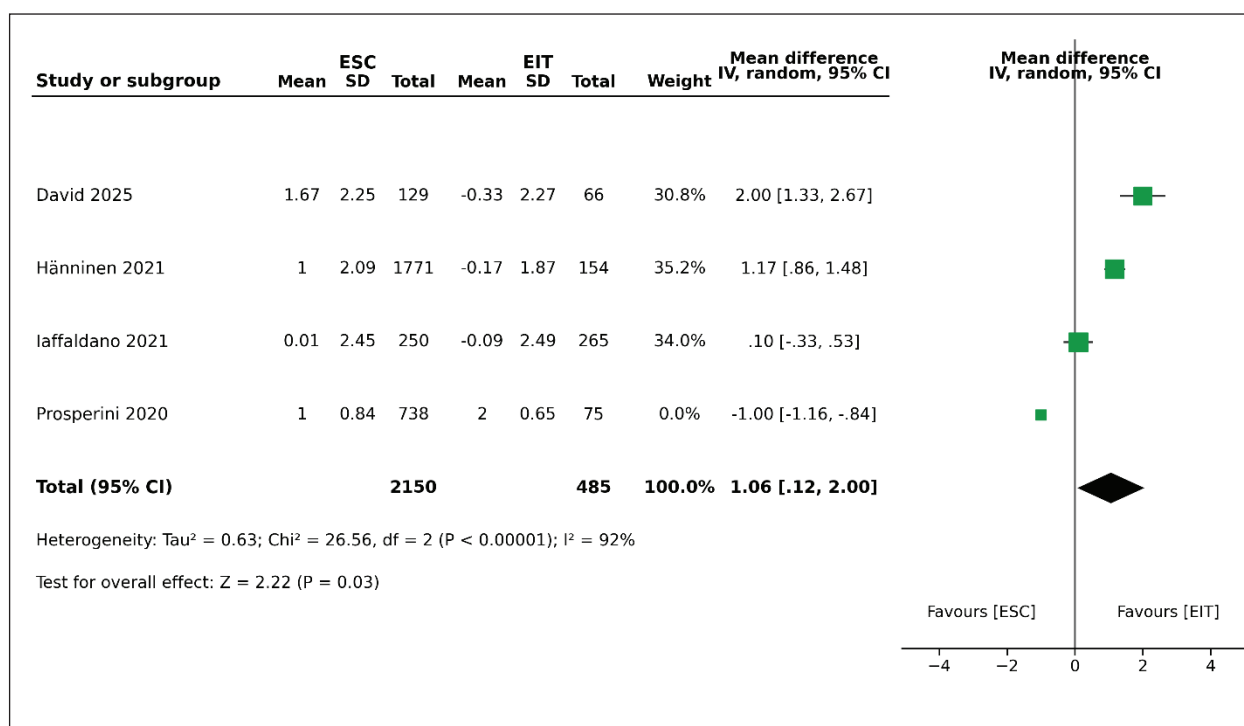


Figure 3. Sensitivity analysis of change in EDSS after exclusion of Prosperini 2020.

consistent with the proposed therapeutic window in early RRMS, during which controlling inflammatory injury may help preserve neurological reserve. Filippi et al. [18] argued that early high-efficacy treatment may alter the long-term disease course by preventing irreversible early injury. Early treatment may offer a favorable risk-benefit profile, particularly in younger patients with

active disease and limited established disability [19]. Disability progression is not entirely relapse-dependent. Progression independent of relapse activity reflects chronic disease mechanisms and may be affected by silent MRI activity and incomplete relapse recovery [20]. This may explain why ARR showed a clearer benefit than EDSS change in the present analysis.

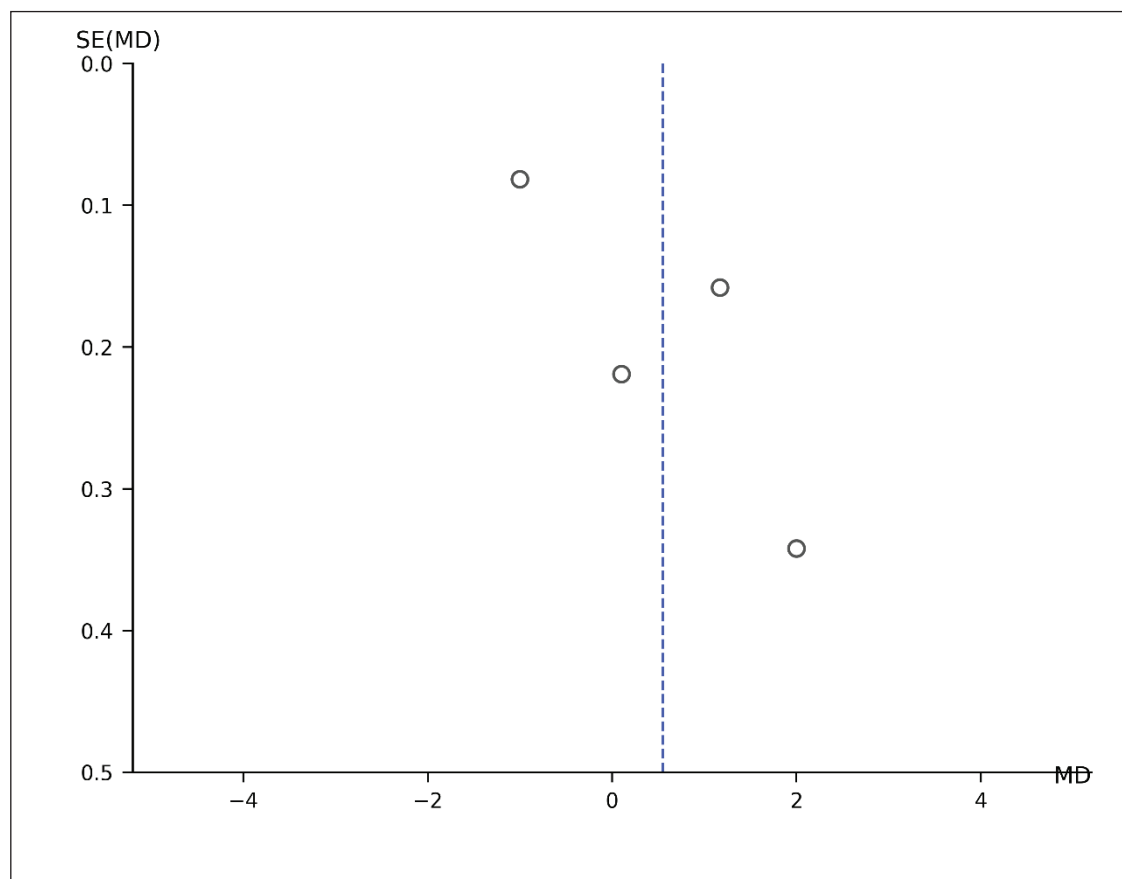


Figure 4. Funnel plot of change in EDSS outcome.

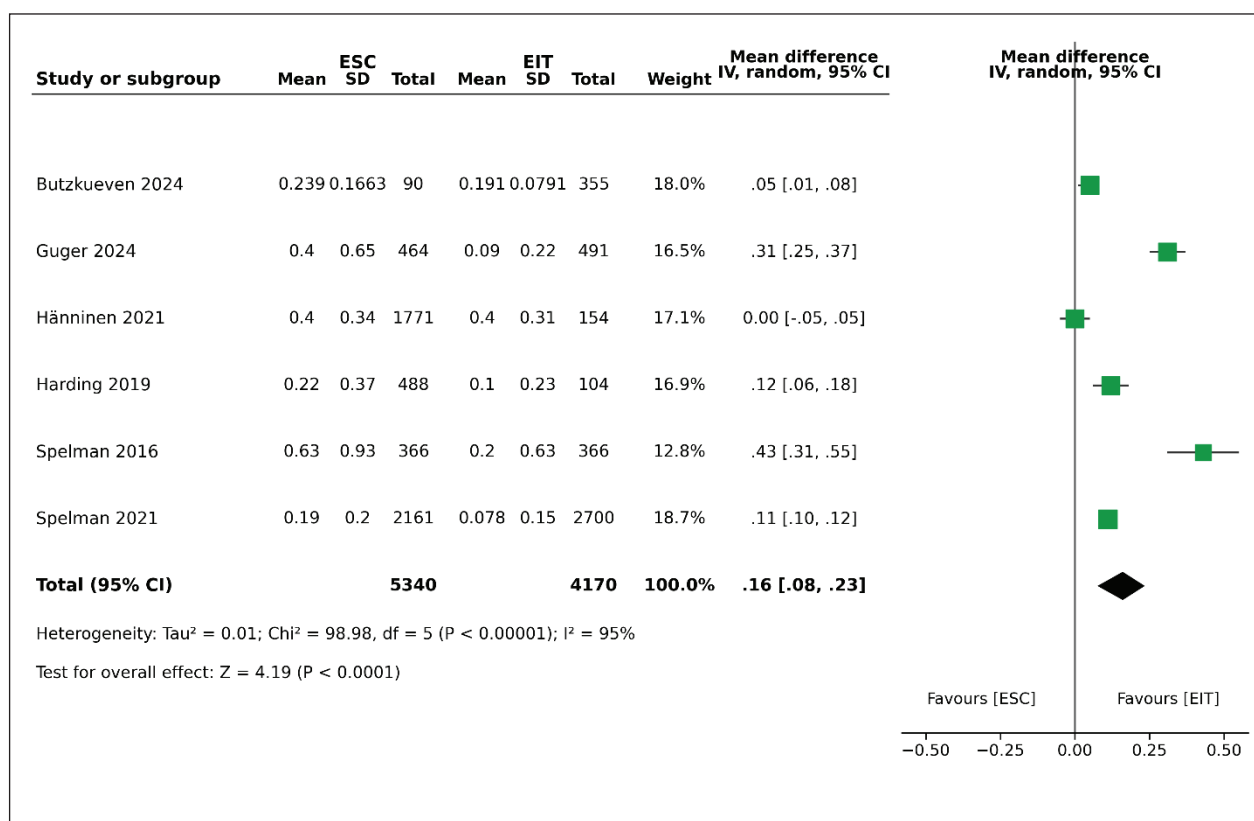


Figure 5. Forest plot of ARR outcome.

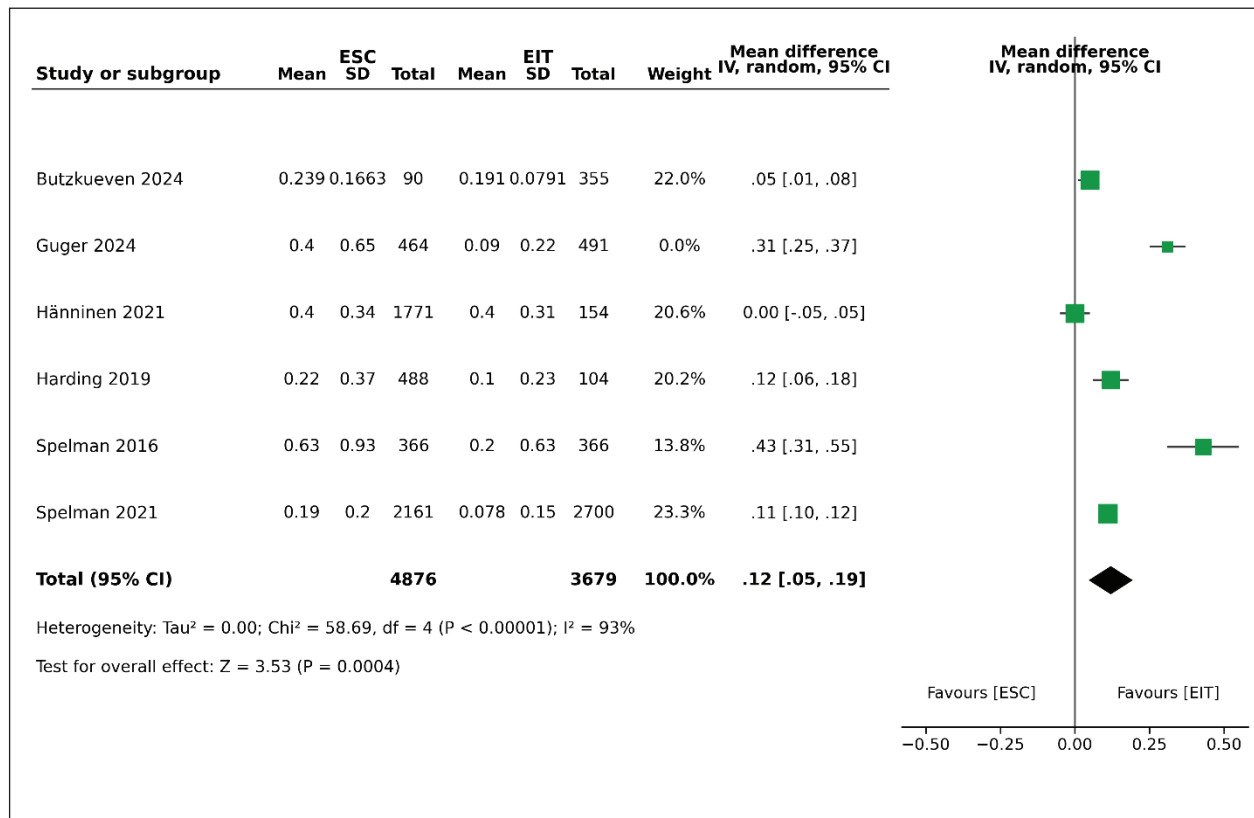


Figure 6. Sensitivity plot of ARR outcome.

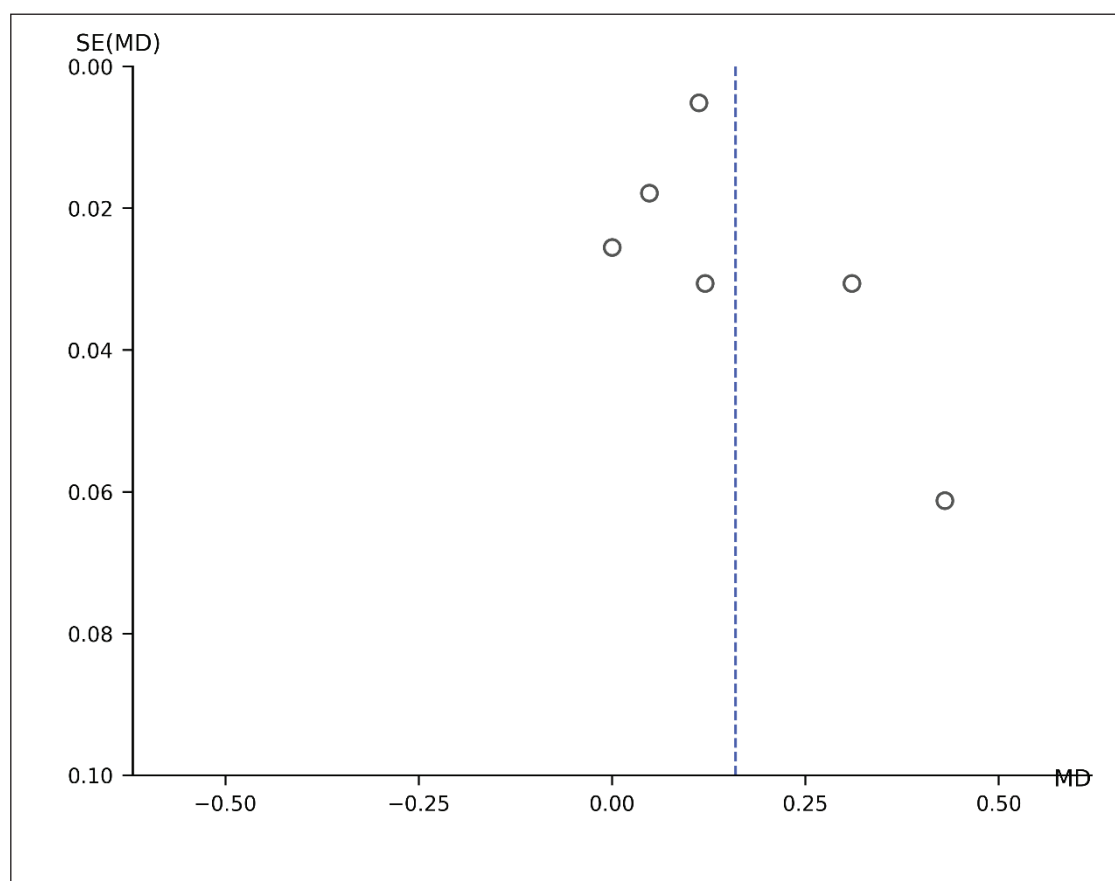


Figure 7. Funnel plot of ARR outcome.

Clinically, these findings support considering early high-efficacy treatment for patients with active or high-risk RRMS while maintaining individualized decision-making. Treatment selection should account for infection risk, monitoring, pregnancy planning, vaccination, cost, and patient preferences. Natalizumab requires progressive multifocal leukoencephalopathy risk assessment, particularly in patients with JC virus positivity [21]. DMT sequencing similarly requires consideration of efficacy, safety, disease activity, and patient preference [22].

Limitations

This review has limitations that should be considered when interpreting its findings. All included studies were observational cohorts; therefore, residual confounding, including confounding by indication, cannot be fully excluded despite the use of statistical adjustment, propensity-score matching, or weighting methods in several studies. Differences in baseline disability, treatment selection, follow-up duration, EDSS assessment, relapse definitions, and MRI surveillance may have contributed to between-study variation. The EDSS-change analysis showed considerable heterogeneity, while only one eligible study reported an adjusted Δ EDSS comparison; accordingly, the latter outcome was synthesized narratively rather than quantitatively. Funnel-plot findings were also interpreted cautiously in view of the number of contributing studies. These considerations primarily limit causal interpretation of the disability outcomes rather than the value of systematically synthesizing the available real-world evidence. The inclusion of large registry-based cohorts, formal risk-of-bias assessment, adjusted estimates, and sensitivity analysis supports the clinical relevance and transparency of this review. Consistent with the ECTRIMS/EAN guideline, treatment decisions should integrate evolving evidence across different therapies and clinical contexts; therefore, the present findings should be interpreted as informative observational associations rather than definitive evidence of treatment superiority [23].

Future directions

Future studies should use standardized definitions of EIT and ESC, report time from diagnosis to treatment, separate relapse-associated worsening from progression independent of relapse activity, and include MRI activity, brain volume loss, spinal cord lesions, cognition, quality of life, serum neurofilament light chain, and treatment discontinuation. Serum neurofilament light chain is increasingly studied as a biomarker of neuroaxonal injury and may help connect inflammatory control with tissue protection [24]. Pragmatic trials such as DELIVER-MS and TREAT-MS are especially important because they directly compare early highly effective strategies with escalation in treatment-naïve patients [25,26]. These trials will complement the comparative real-world evidence provided by the additional cohorts included in this review [27–31].

Conclusion

This systematic review and meta-analysis, including large real-world RRMS cohorts, found that early initiation of high-efficacy therapy was associated with a lower ARR than escalation therapy, supporting its potential value in controlling inflammatory disease activity. Disability outcomes were less consistent and should be interpreted cautiously because of between-study heterogeneity, limited Δ EDSS evidence, and the possibility of residual confounding. Overall, this review provides clinically relevant comparative evidence supporting early high-efficacy treatment while highlighting the need for prospective studies with standardized disability outcomes.

List of Abbreviations

ARR	Annualized Relapse Rate	
DMTs	Disease-Modifying Therapies	
EDSS	Expanded Disability Status Scale	
EIT	Early Intensive Treatment	
ESC	Escalation Strategy	
HE-DMTs	High-Efficacy Disease-Modifying Therapies	
MS	Multiple Sclerosis	
NOS	Newcastle-Ottawa Scale	
RRMS	Relapsing-Remitting Multiple Sclerosis	

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None.

Data availability statement

This systematic review and meta-analysis used data from published studies cited in the article. The extracted data and analysis files supporting the findings are available from the corresponding author upon reasonable request.

Conflict of interest

The authors declare that they have no conflicts of interest related to this manuscript.

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Consent to participate

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Ethics approval

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Use of Artificial Intelligence

AI-assisted tools were used during manuscript preparation solely for language refinement and improvement of paragraph wording. AI tools were not used to generate or analyze study data, conduct statistical analysis, interpret the findings, or make scientific or clinical decisions. All AI-assisted text was reviewed and verified by the authors, who take full responsibility for the accuracy, originality, and integrity of the final manuscript.

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