



Exercise-Associated Fatigue Modulation in Multiple Sclerosis: A Meta-Analysis of MFIS Outcomes Within a Proposed Extracellular Vesicle Framework

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Abstract

Context: Fatigue in multiple sclerosis (MS) affects three domains: physical, mental, and social. Exercise holds therapeutic promise because of its potential benefits for health and well-being. However, the biological mechanisms underlying these effects remain poorly understood, particularly with respect to extracellular vesicles (EVs). Moreover, little is known about the interaction between exercise and EVs, or the potential role of EVs in mediating exercise-related health benefits. This systematic review and meta-analysis synthesizes current evidence on how various types of exercise modulate fatigue in MS, assessed using the Modified Fatigue Impact Scale (MFIS), with a focus on EV-driven neurofunctional adaptations.

Evidence Acquisition: This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Eleven randomized controlled trials (RCTs) involving 665 participants were included. Subgroup analyses and random-effects modeling were performed using Stata 15 to assess domain-specific effects and modality-based differences.

Results: Exercise interventions significantly reduced fatigue across all MFIS domains. The largest effects were observed for physical fatigue (pooled effect size [ES]: -4.486; 95% confidence interval [CI]: -5.502 to -3.470), followed by cognitive fatigue (-2.792; 95% CI: -3.810 to -1.775) and psychosocial fatigue (-0.938; 95% CI: -1.226 to -0.650). Aquatic and coordination-based exercises showed the most consistent and substantial improvements.

Discussion: This meta-analysis highlights the therapeutic role of exercise in alleviating MS-related fatigue, with modality-specific benefits suggesting distinct underlying biological mechanisms. Integrating MFIS outcomes with emerging EV literature may provide a hypothesis-generating framework for future mechanism-oriented rehabilitation research in multiple sclerosis.

Keywords: Exercise Therapy, Extracellular Vesicles, MFIS, Multiple Sclerosis, Fatigue, Rehabilitation

1. Introduction

Fatigue in multiple sclerosis (MS) can cause substantial functional impairment, may be resistant to rest, and can affect energy (1), cognition, and social functioning (2, 3). Exercise may improve strength and modulate brain-body signaling pathways related to fatigue through biological

adaptations (4-6). Extracellular vesicles (EVs) are membrane-bound particles that can be released during exercise (7). These vesicles may contribute to fatigue modulation by carrying messages between neurons and immune cells, thereby supporting intercellular communication relevant to fatigue and recovery (8, 9). Physical activity remains a cornerstone of fatigue

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management, likely because of its accessibility and its simultaneous engagement of physical and cognitive processes in neurorehabilitation (10). Certain modalities, such as water therapy, coordination-based exercises, and mindfulness-infused movement, have significant effects on the physical, cognitive, and psychosocial domains, in addition to enhancing overall fitness (11). Researchers use validated instruments such as the Modified Fatigue Impact Scale (MFIS) (12) and the Fatigue Severity Scale (FSS), the latter originally introduced by Krupp et al., to detect multidimensional changes in fatigue perception among individuals with MS (3, 13). Emerging research highlights biological messengers, particularly exercise-induced EVs, as potential mediators that may explain why certain modalities yield stronger effects (14). Recent evidence also highlights the role of exercise-induced exerkines and extracellular signaling molecules in modulating neuroinflammation and neuroprotection in MS (15). Exercise-induced EVs may contribute to neurofunctional adaptation through immune regulation, intercellular signaling, and modulation of neuroinflammatory pathways in MS. Fatigue assessment in MS extends beyond measuring tiredness; it reflects how disrupted energy affects thinking, movement, and social engagement (16, 17). The MFIS delineates these effects across domains, illustrating how physical, cognitive, and social functioning interact; for example, brain fog can slow movement, whereas social withdrawal can deepen tiredness (11, 18). As evidence accumulates, more nuanced approaches to fatigue management are needed (19, 20). Although many studies confirm the benefits of exercise, only a handful investigate how different types affect fatigue in distinct ways, particularly via EV-related pathways (21-23). These vesicles, released during exertion, may help explain how fatigue responses shift across interconnected systems (24). By integrating MFIS assessments with findings on EV signaling, researchers can identify patterns that move beyond nonspecific interventions toward more individualized approaches rooted in biological mechanisms (25). This study analyzed existing data on exercise-based interventions for managing fatigue in MS, using the MFIS to evaluate outcomes across physical, cognitive, and psychosocial domains. By synthesizing the most recent research, it aims to provide a comprehensive assessment of the effectiveness of these techniques in reducing MS-related tiredness. Through meta-analysis, it evaluates the effectiveness of different exercise modalities while considering how emerging EV-related mechanisms might contribute to neurofunctional adaptation. The goal is to provide clinicians and researchers with a biologically grounded framework for tailoring exercise programs that address the complex nature of fatigue in MS.

2. Evidence Acquisition

2.1. Search Strategy and Study Selection

This systematic review and meta-analysis were conducted in accordance with PRISMA guidelines. A comprehensive, structured search was conducted on October 1, 2025, across five major sources: PubMed/Medline, Scopus, ScienceDirect, the WHO International Clinical Trials Registry Platform (ICTRP), and ClinicalTrials.gov. The search strategy was designed to identify studies involving individuals with multiple sclerosis (MS) in whom fatigue was assessed using the MFIS and in which the intervention comprised physical activity or exercise-induced modulation, with consideration of extracellular vesicle signaling. The full search syntax is provided in Appendix 1 in the Supplementary File.

In total, 10,018 records were initially identified. After automated duplicate removal, 7,342 records remained for screening. Titles and abstracts were manually reviewed, and full texts were retrieved for 151 studies. Articles were excluded if they lacked a control group, involved non-exercise-based interventions (e.g., pharmacological, dietary, or purely psychological), or were not published in English. Only randomized controlled trials reporting MFIS outcomes in adults with MS were included. After full-text assessment, 11 studies met the inclusion criteria and were retained for quantitative synthesis. The study selection process is illustrated in the PRISMA flow diagram (Figure 1). This review was not prospectively registered in PROSPERO. At study initiation, it was conceived as an exploratory synthesis integrating exercise-related fatigue outcomes with emerging EV literature, and the analytical framework was refined during protocol development. Nevertheless, the eligibility criteria, search strategy, outcomes, and analytical methods were predefined before study screening and data extraction. To promote transparency and reproducibility, the full review protocol and all methodological decisions are provided as supplementary material and are reported in accordance with PRISMA 2020 recommendations.

2.2. Eligibility Criteria

A predefined internal review protocol was developed before study screening and data extraction. Formal prospective registration was not completed because the conceptual framework of the review underwent iterative refinement during the early development phase, particularly regarding the integration of extracellular vesicle signaling with MFIS-based fatigue outcomes.

Eligibility criteria were defined according to a PICO framework. The population comprised adults diagnosed

Table 1. Characteristics of Studies Included in the Meta-Analysis ^a

Author (Year)	Country	Study Type	Sample Size	Intervention Group(s)	Control Group	Variables Examined	Duration
Escudero-Urbe et al. (26)	Spain	Randomized Controlled Trial	48	Whole-Body Vibration (WBV) + (BT) + Standard Exercise	Wait-list control	MFIS	12 weeks
Fillis et al. (27)	Brazil	Randomized Clinical Trial	17	Shiatsu + Physical Therapy	Maintain usual activities	MFIS	8 weeks
Garrett et al. (28)	Ireland	Assessor-blind Randomized Controlled Trial	179	Physiotherapy + physical activity	No change in exercise habits	MFIS	10 weeks
Hebert et al. (29)	USA	Examiner-blinded Randomized Controlled Trial (Class I evidence)	88	Balance and Eye-Movement Exercises (BEEMS)	Wait-listed control	MFIS	14 weeks 6 weeks
Hvid et al. (30)	Denmark	Randomized Controlled Trial	62	Walking Exercise Therapy	Habitual Lifestyle	MFIS	7 weeks
Kargarfard et al. (31)	Iran	Randomized Controlled Trial	32	Aquatic Exercise Training	Usual care	MFIS	8 weeks
Kooshar et al. (32)	Iran	Randomized Controlled Clinical Trial	37	Aquatic Exercise	Normal treatments	MFIS	8 weeks
Langeskov-Christensen et al. (33)	Denmark	Randomized Controlled Trial (Single-blinded)	86	Progressive Aerobic Exercise (PAE)	Waitlist	MFIS	24 weeks 12 weeks
Mikuláková et al. (34)	Slovak Republic	Randomized Controlled Trial	65	Individualized Rehabilitation Program	Wait-list control	MFIS	12 weeks
Skovgaard et al. (35)	Denmark	Randomized Controlled Trial	28	Tension and Trauma Releasing Exercises	Usual care	MFIS	8 weeks
Torkhani et al. (36)	France	Randomized Controlled Pilot Trial	23	Mindfulness + Physical Activity	Physical Activity only	MFIS	8 weeks

^a Abbreviations: WBV, Whole-Body Vibration; BT, Balance Training; MFIS, Modified Fatigue Impact Scale; BEEMS, Balance and Eye-Movement Exercises; PAE, Progressive Aerobic Exercise.

with multiple sclerosis, regardless of MS phenotype. Eligible interventions consisted of structured exercise or physical activity programs, including aerobic, aquatic, coordination-based, psychophysical, and rehabilitation-oriented interventions. Comparators included usual care, wait-list controls, no-exercise conditions, or standard treatment. Outcomes were required to include fatigue assessment using the MFIS. Only randomized controlled trials published in peer-reviewed journals were included. Studies involving pharmacological, dietary, or exclusively psychological interventions without an exercise component were excluded.

Conference abstracts, preprints, unpublished studies, dissertations, and other forms of grey literature were not included due to concerns regarding methodological consistency, incomplete outcome reporting, and peer-review status.

2.3. Data Extraction and Management

All relevant data were manually extracted by the research team. A structured Excel file was used to capture key study characteristics, including the author, year, country, sample size, duration, intervention and control conditions, and MFIS outcomes. Reference management and initial screening were performed using EndNote software. The completed dataset was organized in Excel

and then imported into Stata version 15 (StataCorp, College Station, TX, USA) for statistical analysis.

2.4. Risk of Bias Assessment

The risk of bias in each included study was independently assessed using the Cochrane Risk of Bias 2.0 (RoB 2.0) methodology. This framework evaluates five key domains: the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results. Each domain was rated as “low risk,” “some concerns,” or “high risk,” and an overall judgment was assigned accordingly. The results of this assessment are summarized in Figure 2. Overall, most included studies were judged to present either low risk of bias or some concerns according to the RoB 2.0 framework. The most common concerns were related to the blinding of participants and personnel, deviations from intended interventions, and incomplete outcome reporting, which are frequently encountered in exercise-based rehabilitation trials. No study was judged to have a level of bias that warranted exclusion from the quantitative synthesis.

2.5. Statistical Analysis

Meta-analytic computations were performed using Stata 15. For each MFIS domain (physical, cognitive, and

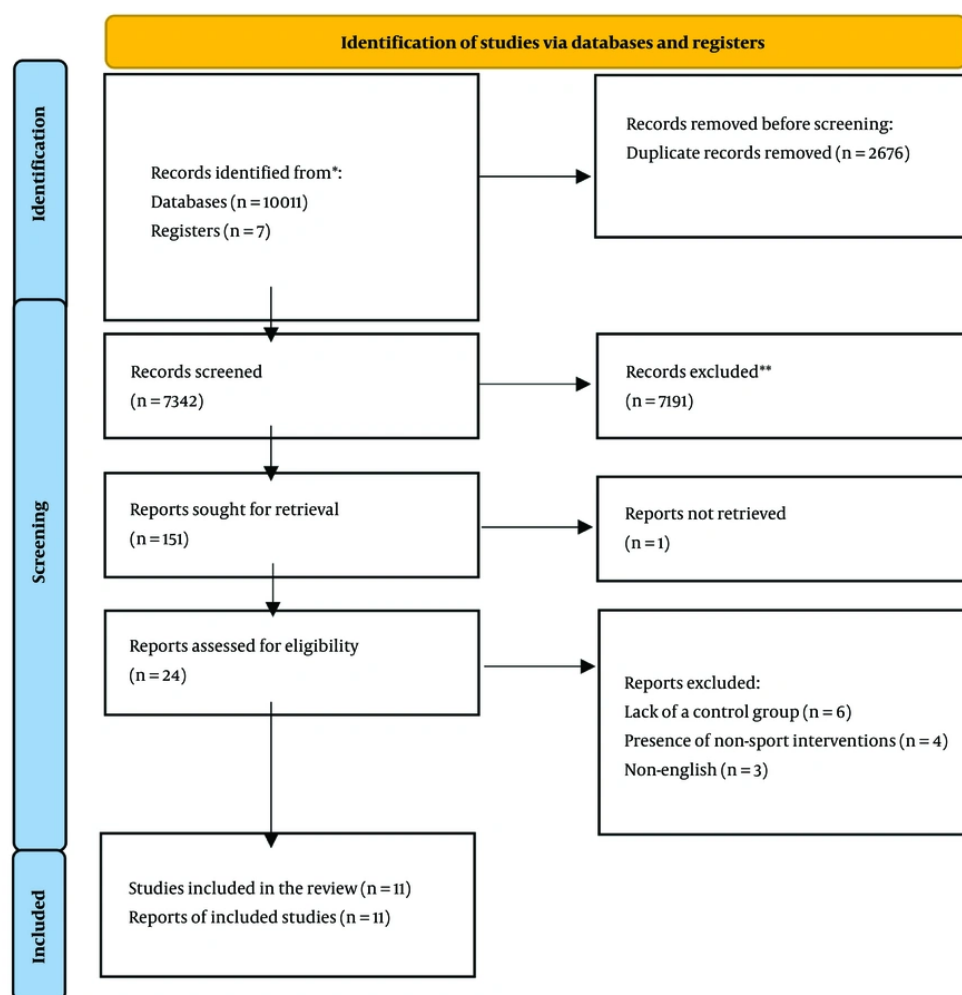


Figure 1. PRISMA flow diagram of studies included in this systematic review and meta-analysis

psychosocial), pooled effect estimates were calculated using mean differences (MDs) between intervention and control groups, as all included studies used the same MFIS scoring framework and outcome scale. Post-intervention MFIS subscale scores were preferentially extracted for quantitative synthesis. For studies reporting multiple intervention arms or more than one eligible comparison, outcomes were included separately only when data were reported independently, without overlap in participant allocation within the same comparison. When multiple follow-up assessments were available, the endpoint immediately after completion of the intervention period was selected for analysis to ensure methodological

consistency across studies. Statistical heterogeneity was evaluated using the I^2 statistic and Cochran's Q test. Heterogeneity thresholds were interpreted according to conventional meta-analytic recommendations, with I^2 values above 50% considered indicative of substantial between-study heterogeneity. Given the expected clinical and methodological diversity across exercise modalities, intervention durations, comparator conditions, and participant characteristics, random-effects modeling using the DerSimonian-Laird method was applied to analyses demonstrating moderate-to-high heterogeneity to account for between-study variability. When standard errors or confidence intervals were not directly reported, they were

Study	Randomization Process	Deviations from Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of Reported Results	Overall Risk of Bias
Escudero-Uribe et al. (2017)	● Low risk	● Low risk	● Low risk	● Low risk	● Some concerns	● Low risk
Fillis et al. (2022)	● Some concerns	● Low risk	● Low risk	● Some concerns	● Some concerns	● Some concerns
Garrett et al. (2013)	● Low risk	● Low risk	● Low risk	● Some concerns	● Low risk	● Low risk
Hebert et al. (2018)	● Low risk	● Low risk	● Low risk	● Low risk	● Low risk	● Low risk
Hvid et al. (2025)	● Low risk	● Low risk	● Low risk	● Low risk	● Low risk	● Low risk
Kargarfard et al. (2018)	● Low risk	● Low risk	● Low risk	● Low risk	● Low risk	● Low risk
Kooshia et al. (2015)	● Low risk	● Low risk	● Low risk	● Some concerns	● Low risk	● Low risk
Langeskov-Christensen et al. (2022)	● Low risk	● Low risk	● Low risk	● Low risk	● Low risk	● Low risk
Mikuláková et al. (2018)	● Low risk	● Low risk	● Low risk	● Low risk	● Some concerns	● Low risk
Skovgaard et al. (2025)	● Some concerns	● Low risk	● Some concerns	● Some concerns	● Some concerns	● Some concerns
Torkhani et al. (2021)	● Some concerns	● Low risk	● Low risk	● Some concerns	● Some concerns	● Some concerns

Legend: ● = Low risk ● = Some concerns

Figure 2. Risk of bias assessment for included studies using the Cochrane RoB 2.0 tool (26-36)

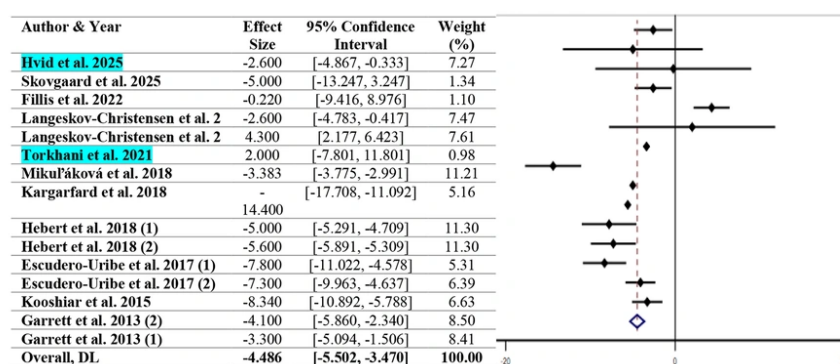


Figure 3. Impact of exercise interventions on physical fatigue in multiple sclerosis (26-36)

calculated from available means, standard deviations, and sample sizes using standard meta-analytic procedures implemented in Stata 15. Subgroup analyses included aquatic, coordination-based, psychophysical, and standard physiotherapy modalities to examine differences across

fatigue domains. Funnel plots were generated to assess potential publication bias and small-study effects.

2.6. PICO Framework

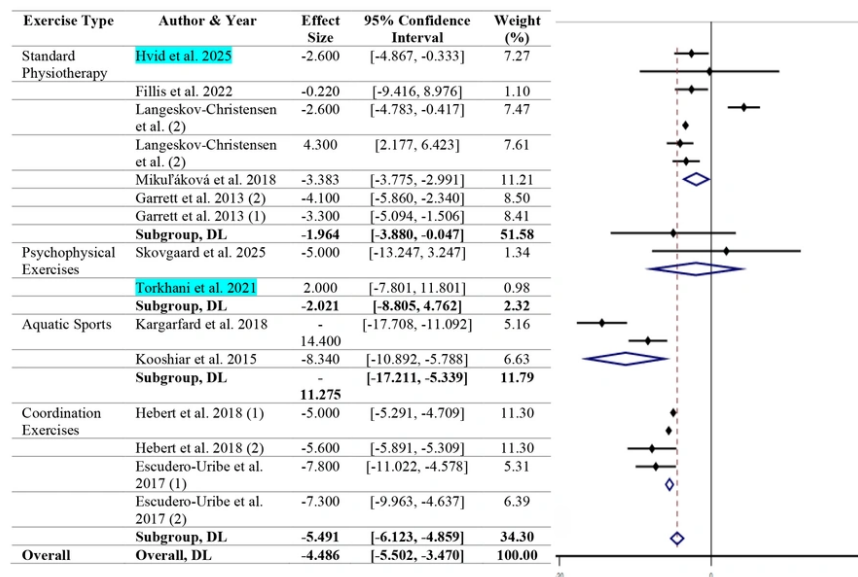


Figure 4. Impact of exercise interventions on physical fatigue in multiple sclerosis (subgroup analysis) (26-36)

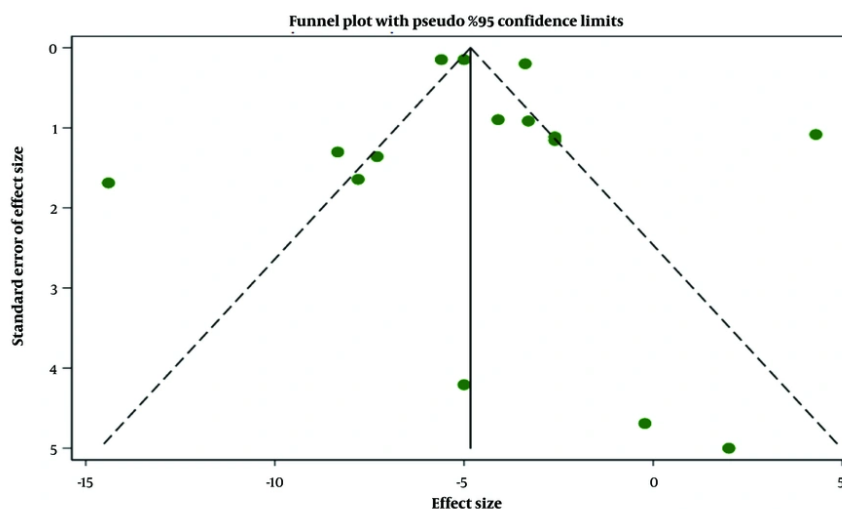


Figure 5. Funnel plot with pseudo 95% confidence limits for the MFIS-Physical subscale

Population (P): Adults diagnosed with multiple sclerosis, irrespective of disease phenotype, sex, or disability status.

Intervention (I): Structured exercise-based interventions, including aerobic exercise, aquatic exercise, coordination training, psychophysical exercise,

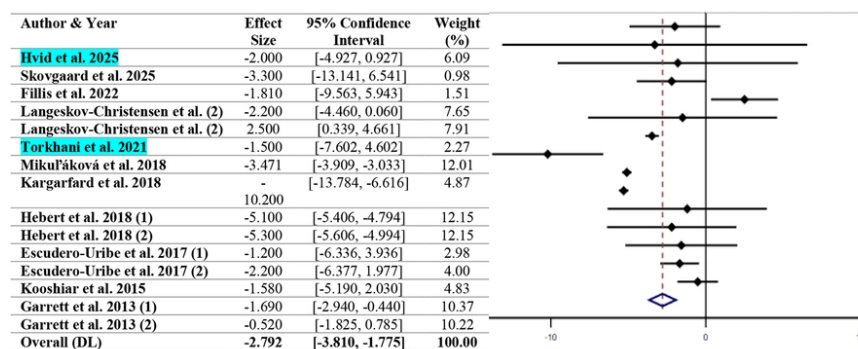


Figure 6. Impact of exercise interventions on MFIS-Cognitive in multiple sclerosis (26-36)

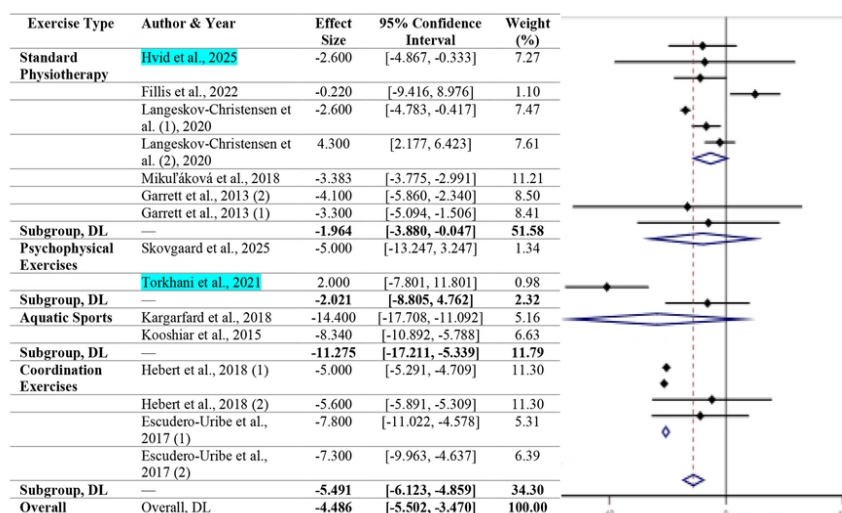


Figure 7. Impact of exercise interventions on MFIS-Cognitive in multiple sclerosis (subgroup analysis) (26-36)

rehabilitation programs, and multimodal physical activity interventions.

Comparator (C): Usual care, wait-list controls, no-exercise conditions, standard treatment, or alternative non-exercise control interventions.

Outcome (O): Fatigue outcomes assessed using the MFIS, including physical, cognitive, and psychosocial subscale scores.

3. Results

A total of 11 randomized controlled trials comprising 665 participants were included in this meta-analysis. The detailed characteristics of these studies, including author, year, country, sample size, intervention, control condition, and duration, are summarized in Table 1.

The overall reduction in physical fatigue is depicted in the forest plot (Figure 3), and the differential effects of exercise modalities are shown in the subgroup analysis (Figure 4). Potential publication bias for physical fatigue outcomes was assessed using a funnel plot (Figure 5), which demonstrated a symmetrical distribution of studies.

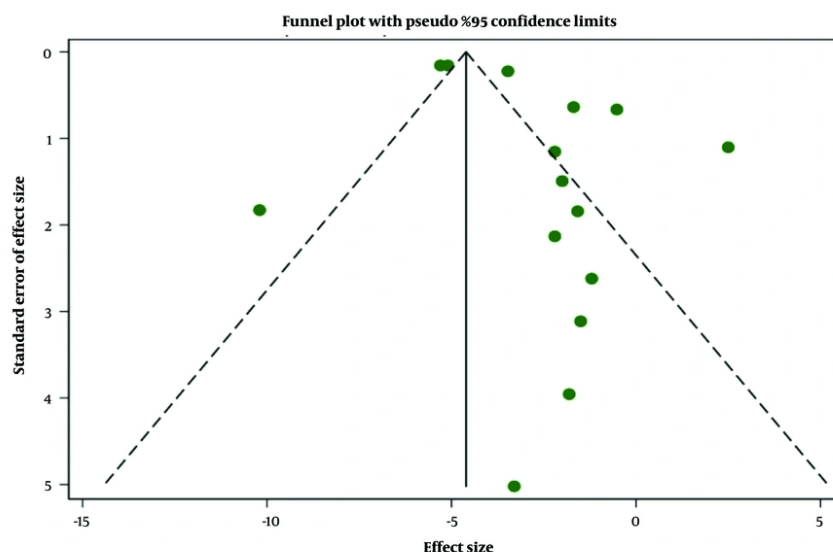


Figure 8. Funnel plot with pseudo 95% confidence limits for the MFIS-Cognitive subscale

Figure 3 summarizes the effect sizes of individual studies assessing the impact of exercise interventions on the physical subscale of the MFIS in patients with multiple sclerosis. Each horizontal line reflects the 95% confidence interval (CI) for the effect size (ES) reported in a study, and the central marker denotes the point estimate. Studies with CIs not crossing the vertical line of no effect are considered statistically significant. The diamond at the bottom of the plot reflects the pooled effect size and its CI, derived from a DerSimonian-Laird (DL) random-effects model. The accompanying table presents the author/year, ES, CI, and relative weight of each study in the meta-analysis. Overall, the analysis indicates a significant reduction in physical fatigue following exercise-based interventions.

Figure 4 presents a subgroup meta-analysis of exercise modalities targeting physical fatigue in individuals with multiple sclerosis, based on the physical subscale of the MFIS. The forest plot illustrates effect sizes and 95% confidence intervals across four distinct exercise categories: standard physiotherapy, psychophysical exercises, aquatic sports, and coordination-based interventions. Each subgroup is pooled using a DerSimonian-Laird random-effects model, with the overall estimate shown at the bottom. The vertical line at zero represents the line of no effect, while the dashed red line indicates the overall pooled effect.

This plot shows the relationship between study effect sizes and their standard errors to assess potential publication bias. The central vertical line marks the pooled effect estimate, while the dashed boundaries represent pseudo 95% confidence limits. The visual distribution of studies did not show obvious asymmetry; however, interpretation of funnel plots should be approached cautiously given the limited number of included studies for physical fatigue outcomes.

Figure 6 presents a forest plot summarizing the impact of different exercise modalities on cognitive fatigue in multiple sclerosis, based on MFIS scores. Each line shows the 95% confidence interval for individual studies, and blue diamonds represent subgroup pooled estimates. Coordination and aquatic exercises showed the strongest effects, while the overall analysis (DL method) revealed a significant reduction in cognitive fatigue (effect size, -2.792 ; 95% CI, -3.810 to -1.775). Detailed modality-specific results are provided in Figure 7. The corresponding funnel plot (Figure 8) shows a symmetrical distribution, with no obvious visual asymmetry for cognitive fatigue outcomes.

Figure 7 presents a subgroup meta-analysis of exercise modalities targeting cognitive fatigue in individuals with multiple sclerosis, based on the cognitive subscale of the MFIS. The forest plot illustrates effect sizes and 95% confidence intervals across four distinct exercise categories: standard physiotherapy, psychophysical

exercises, aquatic sports, and coordination-based interventions. Each subgroup is pooled using a DerSimonian-Laird random-effects model, with the overall estimate shown at the bottom. The vertical line at zero represents the line of no effect, while the dashed red line indicates the overall pooled effect. Coordination and aquatic exercises showed the strongest reductions. The overall analysis (DL method) indicated a significant improvement ($ES = -2.792$; 95% CI: -3.810 to -1.775).

This plot displays the distribution of study effect sizes against their standard errors to evaluate potential publication bias. The funnel plot did not demonstrate obvious visual asymmetry; however, interpretation remains limited by the relatively small number of included studies, and inferences regarding publication bias should therefore be made cautiously.

Figure 9 summarizes the impact of exercise interventions on psychosocial fatigue in multiple sclerosis, based on the psychosocial subscale of the MFIS. Each horizontal line reflects the 95% confidence interval for the effect size from an individual study, while the central marker indicates the point estimate. Studies with CIs crossing the vertical line of no effect are considered non-significant. The diamond at the bottom of the plot represents the pooled ES and its CI, derived from a DerSimonian-Laird random-effects model. The accompanying table details the author/year, ES, CI, and relative weight of each study in the meta-analysis. Overall, the analysis indicates a modest but significant reduction in psychosocial fatigue following exercise-based interventions. Most studies reported negative effect estimates, indicating improvement. The overall pooled estimate (DL method) was -0.938 (95% CI: -1.226 to -0.650), indicating a modest but statistically significant reduction in psychosocial fatigue. These results are visualized in the forest plot (Figure 9) and further detailed by exercise type in the subgroup analysis (Figure 10). The funnel plot for psychosocial fatigue (Figure 11) also demonstrates symmetry, with no obvious visual asymmetry.

Figure 10 illustrates the pooled effects of exercise interventions on psychosocial fatigue in individuals with multiple sclerosis, based on the MFIS psychosocial subscale. Aquatic and coordination exercises demonstrated the most consistent and substantial reductions (pooled ES values of -2.285 and -1.253 , respectively), with narrow confidence intervals indicating high precision. In contrast, standard physiotherapy and psycho-physical modalities showed mixed or non-significant effects. The overall pooled estimate from the DerSimonian-Laird random-effects model was -0.938 [95% CI: -1.226 to -0.650], suggesting a modest but statistically

significant improvement in psychosocial fatigue following exercise interventions.

This funnel plot shows study effect sizes against their standard errors to assess potential publication bias. No major visual asymmetry was observed in the funnel plot; however, conclusions regarding publication bias should be interpreted cautiously due to the limited number of available studies.

4. Discussion

Across the 11 included trials, exercise interventions reduced fatigue in people with multiple sclerosis (MS). Experimental evidence also suggests that modulation of neuroinflammatory pathways and nitric oxide signaling may contribute to behavioral improvements in experimental models of multiple sclerosis, further supporting the biological plausibility of fatigue-related interventions (37). Coordination-based and aquatic exercises demonstrated the most substantial effects, suggesting that exercise modality is an important determinant of fatigue reduction. These modality-specific effects may hypothetically relate to differences in EV-associated neuroimmune signaling pathways described in previous mechanistic literature; however, direct EV measurements were not assessed in the included randomized trials.

Although physical fatigue showed the greatest improvement, the cognitive and psychosocial MFIS domains also improved (6). These findings may reflect meaningful improvements in daily functioning and participation.

Other non-exercise approaches to MS-related fatigue have also been reviewed, including pulsed electromagnetic field therapy (38) and non-invasive neuromodulation (39). A recent network meta-analysis further demonstrated that resistance and coordination-based training may provide superior improvements in MS-related fatigue, particularly in long-term interventions (5). Exercise-induced EVs may modulate neuroimmune signaling and, according to Nederveen et al. (40) and Maggio et al. (41), their profiles vary by exercise regimen, with reported differences in inflammatory signaling profiles (40-44). Recent mechanistic findings further indicate that EV-associated microRNAs (miRNAs) (45) may participate in exercise-induced cellular adaptation and intercellular communication, potentially influencing neuroplasticity and immune regulation (46). These biological insights align with our subgroup findings, in which these modalities yielded the strongest fatigue reductions.

From a behavioral standpoint, Burschka et al. (47) found that mindfulness-based movements, such as Tai Chi,

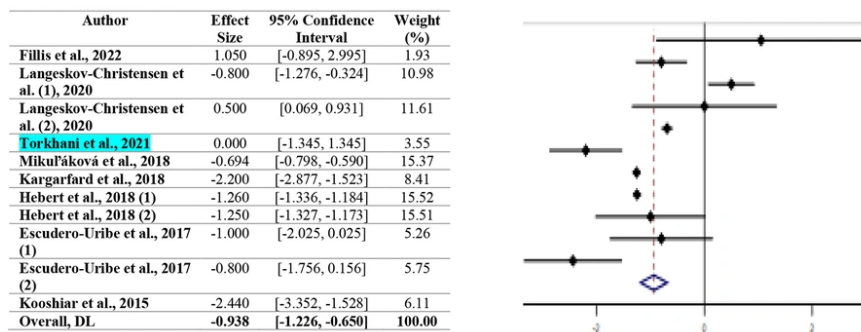


Figure 9. Impact of exercise interventions on MFIS-Psychosocial in multiple sclerosis (26-36)

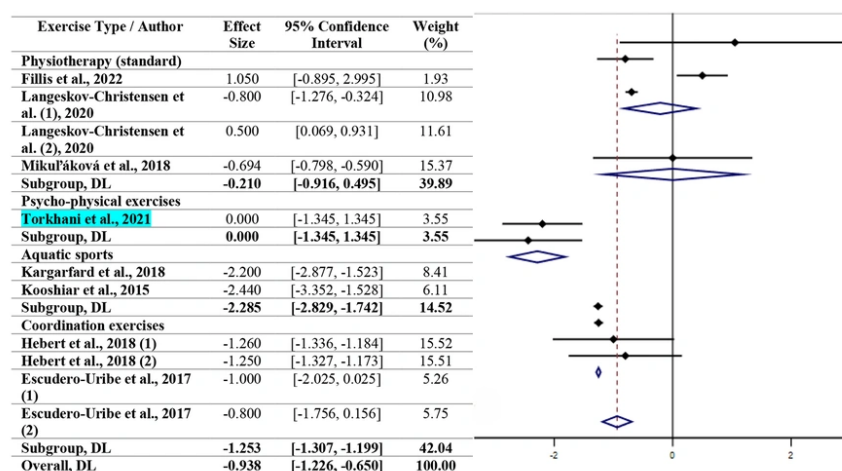


Figure 10. Impact of exercise interventions on MFIS-Psychosocial in multiple sclerosis (subgroup analysis) (26-36)

significantly improved fatigue and coordination in patients with MS. This supports our inclusion of psychophysical interventions and may explain the modest gains observed in psychosocial fatigue (47, 48). Additionally, Moon and van Praag (49) proposed that EVs mediate exercise-induced neuroplasticity, offering a plausible mechanism for the cognitive improvements observed in our analysis (49, 50).

The clinical relevance of these findings lies in their potential to support fatigue management in MS rehabilitative practice. Clinicians may benefit from adopting more individualized, modality-specific rehabilitation strategies. For instance, aquatic therapy not

only reduces physical fatigue through low-impact resistance but also enhances mood and balance (51), as reported by Naeimi et al. (52). Coordination exercises improve both physical and mental abilities, according to Blázquez-Fernández et al. (53), with related evidence from Ivaldi et al. (54). Furthermore, the use of the MFIS allows practitioners to monitor fatigue across the physical, cognitive, and psychosocial levels, enabling fine-tuned adaptations (55, 56). Rehabilitation approaches can shift from symptom management to mechanism-informed treatment by incorporating scientific findings, such as the role of exercise-induced extracellular vesicles in neuroimmune signaling (57). This shift empowers

clinicians to treat fatigue not merely as a barrier but as a modifiable outcome shaped by biological signaling responses associated with exercise adaptation (15).

While this meta-analysis offers valuable insights into the relationship between exercise modalities and fatigue perception in MS, several limitations warrant consideration. First, heterogeneity in intervention protocols, ranging from duration and intensity to delivery format, may have influenced effect sizes and reduced comparability across studies. Second, although the MFIS offers a comprehensive perspective on fatigue, it relies primarily on self-report and may not fully capture neurobiological changes. Third, none of the included randomized trials directly measured extracellular vesicles, precluding mechanistic conclusions about EV-mediated effects across exercise modalities. Additionally, several studies raised some concerns regarding blinding procedures and deviations from intended interventions, which may have influenced self-reported MFIS outcomes; however, the overall consistency in effect direction across studies supports the general stability of the findings. Moreover, limited sample sizes in certain trials and the underrepresentation of progressive MS phenotypes may further restrict generalizability. Future research should prioritize standardized intervention frameworks and incorporate objective biomarkers such as EV profiling, neuroimaging, or inflammatory markers (58) to complement subjective fatigue assessments (59). Longitudinal designs with larger, more diverse cohorts will be essential to evaluate sustained effects and modality-specific neuroadaptations (60). Ultimately, incorporating individualized exercise prescriptions based on fatigue subtype and biological responsiveness may help advance precision rehabilitation in MS.

4.1. Conclusions

The findings of this meta-analysis highlight the complexity of fatigue in multiple sclerosis and support exercise as a biologically active intervention that can improve fatigue in all three domains: physical, cognitive, and psychosocial. By integrating MFIS-based assessments with emerging insights into extracellular vesicle signaling, the study moves beyond symptom tracking toward a mechanistic understanding of how movement influences neurofunctional recovery. The differential impact of exercise modalities, particularly aquatic and coordination-based interventions, may reflect underlying neurobiological adaptations associated with exercise and its effects on intercellular signaling. These findings advocate for a paradigm shift in MS rehabilitation that emphasizes individualized programs informed by patient-reported outcomes and, when available, biological

responses. In conclusion, coupling subjective fatigue metrics with objective biomarkers may pave the way for precision rehabilitation in which exercise is not only therapeutic but also tailored to the neuroimmune profile of each person living with MS.

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Supplementary Material

Supplementary material(s) is available [here](#) [To read supplementary materials, please refer to the journal website and open PDF/HTML].

Footnotes

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Authors' Contribution: All authors contributed equally to this article.

Conflict of Interests Statement: The authors declare that there is no conflict of interest regarding the publication of this manuscript.

Data Availability: The dataset presented in the study is available on request from the corresponding author. The data are not publicly available due to copyright restrictions on the original publications and ethical/privacy considerations related to individual participant data.

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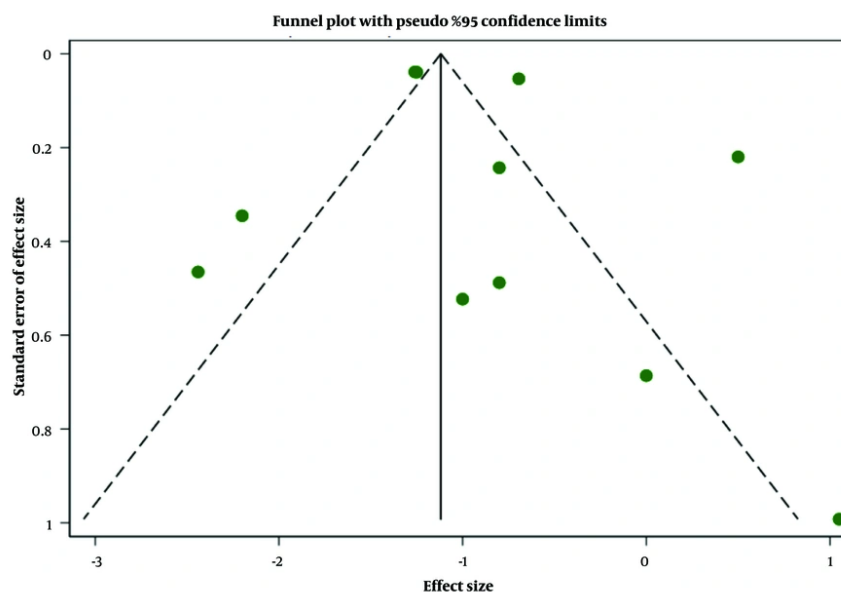


Figure 11. Funnel plot with pseudo 95% confidence limits for the MFIS-Psychosocial subscale

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