

Receiving treatment was a significant predictor of reduced symptom frequency (partial  $\eta^2 = .27$ ). To assess the safety of exercise therapy we counted the number of reported MS relapses in the people receiving exercise therapy and in people in a non-exercise group and did not find a significant difference. The electronic database search retrieved 1883 published articles on fatigue in MS (1061), stroke (474), TBI (113), and PD (235). There were no significant interactions between group and any of the secondary outcome variables, with both groups showing improvements over time on all measures. We found 45 trials, involving 2250 people with MS, assessing the effect of exercise therapy using self-reported fatigue. These results collectively contribute to the overall understanding of the impact of fatigue on individuals with MS and the ongoing efforts to address this significant symptom. Fatigue, functional capacity, and fitness were significantly better after exercise than after flexibility treatment. Results present various findings and insights throughout the document related to the relationship between fatigue and cognitive function, motor function, pathogenic mechanisms, treatment approaches, and the need for further research in understanding and managing fatigue in multiple sclerosis (MS). The ES adjusted for baseline values indicated substantial reductions in symptom frequency for the treatment group ( $ES_{\text{treatment}} = .27$  vs  $ES_{\text{waitlist}} = -.32$ ). Results also indicated that both groups showed clinically significant decreases in fatigue defined as fatigue levels equivalent or less than those reported by a non-fatigued healthy comparison group. Overall, 56 studies (22 systematic reviews/meta analyses, 32 RCTs, 2 CCT) fulfilled the inclusion criteria for this review. There were no statistically significant differences among groups regarding functional status, but there appeared to be less loss of functional status in the treatment group compared with the waiting list group ( $ES_{\text{treatment}} = -.07$  vs  $ES_{\text{waitlist}} = -.70$ ). High-dose cooling produced a small improvement in the MSFC (0.076, 0.66,  $p = 0.007$ ), whereas low-dose cooling produced only a trend toward improvement (0.053, 0.031,  $p = 0.09$ ), but the difference between conditions was not significant ( $ES = .26$ ) at the 1-year follow-up.