Table F.1.a. People with multiple sclerosis, relationship between physical activity and health-related outcomes

Questions: What is the association between **physical activity** and health-related outcomes?
Population: People with multiple sclerosis
Exposure: Greater volume, duration, frequency, or intensity of physical activity
Comparison: No physical activity or lesser volume, duration, frequency, or intensity of physical activity
Outcome: Risk of co-morbid conditions (including disease progression and symptoms of disease), physical function, cognitive function, health-related QOL

Outcome	Systematic review evidence / Review credibility	No. of studies/ Study design / No. of participants	Quality Assessment					Description of evidence / Summary of findings	Certainty	US PAGAC evidence (39)
			Risk of bias	Inconsis-tency	Indirectness†	Imprecision	Other			
Risk of co-morbid conditions	No systematic review identified									No review evidence Insufficient evidence is available to determine the relationship between physical activity and risk of comorbid conditions in adults with multiple sclerosis. **PAGAC Grade: Not Assignable**.
Physical function[a]	Campbell 2018 (5) Low	5 RCTs 2 before-after N = 249	No serious risk of bias	No serious inconsistency	Serious indirectness	No serious imprecision	None	Five studies included participants that were predominantly mildly disabled (EDSS < 4.0), one study recruited moderately disabled persons (EDSS 4.0-6.0), and one recruited those who were more severely disabled (EDSS 6.0-8.0). All studies conducted HIIT, in a supervised setting, on a cycle ergometer or upper limb ergometer. Four studies compared HIIT to a form of continuous training, one compared HIIT and in-patient rehabilitation to just in-patient rehabilitation, and two studies had no comparator. 6/7 studies found improvements in measures of cardiorespiratory fitness (VO$_2$peak or VO$_2$max, HRMax, peak power) or muscle strength following 3-12 weeks of HIIT using cycle ergometry; however, minimal information on between-group differences for HIIT vs. control results.	HIGH[b]	12 ESRs Strong evidence demonstrates that physical activity—particularly aerobic and muscle-strengthening activities—improves physical function, including walking speed and endurance, in adults with multiple sclerosis. **PAGAC Grade: Strong**. .
	Manca 2019 (24) Moderate	11 RCTs N = 426	No serious risk of bias	Serious inconsistency	Serious indirectness	Serious imprecision	Possible publica-tion bias	Median EDSS score was 3.9. Mean age ranged from 33.1 to 53.0 years. Strength training programs training whole lower limb (8 studies), knee extensor muscles (2 studies), or ankle plantar flexors (1 study). No study focused on upper limb strength.	LOW[c]	

								Average training duration was 13.2 weeks. All control groups received no intervention. Pooled analyses found increased strength by 23.1% (95% CI, 11.8 to 34.4) among those in strength training group compared with control groups (ES = 0.37 [95% CI, 0.16 to 0.57] (11 RCTs, n=366) as measured by isokinetic dynamometer and 1RM testing. No statistically significant differences in strength outcomes when limited dynamometer and 1RM measures separately.		
	Patterson 2018 *(28)* Moderate	1 case reports 1 before-after N = 9	No serious risk of bias	No serious inconsistency	Serious indirectness	No serious imprecision	None	One case study reported improved functional mobility following a dance intervention and the other reported improved balance after the intervention.	VERY LOW[d]	
Cognitive function	No systematic review included[e]										1 ESR Moderate evidence indicates that moderate-to-vigorous physical activity can have beneficial effects on cognition in individuals with diseases or disorders that impair cognitive function, including attention deficit hyperactivity disorder, schizophrenia, multiple sclerosis, Parkinson's disease, and stroke. **PAGAC Grade: Moderate.** Results regarding the efficacy of interventions to improve cognitive function in individuals with MS are conflicting. However, interventions show the largest effects on executive function, learning, memory, and processing speed *(39)*.
Health-related QOL	Alphonsus 2019 *(1)* Low	12 RCTs 6 obs N = 725	No serious risk of bias	Serious inconsistency	Serious indirectness	Serious imprecision	None	Participant characteristics (age, disability status) NR. Seven studies tested aerobic exercise interventions, 4 tested anaerobic exercise studies, 3 tested a yoga intervention, 3 used physiotherapy, and 5 studies tested combinations of exercises. Aerobic exercise had small statistically significant effect on physical (ES = 0.35 [95% CI, 0.08 to 0.62], *p*=0.01), mental (ES = 0.42 [95% CI, 0.11 to 0.72], *p*=0.007), and social (ES = 0.42 [95% CI, 0.15 to	VERY LOW[f]	11 ESRs Limited evidence suggests that physical activity improves quality of life, including symptoms of fatigue and depressive symptoms, in adults with

| | | | | | | | 0.69], *p*=0.002) domains of QOL. Anaerobic exercise, combinations of exercise, and yoga did not have a significant effect on measures of QOL. Medium to large effects associated with physical and social domains of QOL were seen for physiotherapy, though few studies (3) measured this relationship. | multiple sclerosis. **PAGAC grade: Limited.** |

Abbreviations: 1RM = 1 repetition maximum; CI = confidence interval; EDSS = Expanded Disability Status Scale; ERS = existing systematic review; ES = effect size; HIIT = high-intensity interval training; NR = not reported; obs = observational study design; PAGAC = Physical Activity Guidelines Advisory Committee; QOL = quality-of-life; RCT = randomized clinical trial

[†] Serious indirectness indicates measurement of intermediate/indirect outcomes or heterogeneity in exposures and comparisons assessed; certainty of evidence was not always downgraded for indirectness if it was not judged to impact the certainty in the findings for the outcome evaluated in the review

[a] One review *(6)* was identified by rated as very low credibility and was not included.
[b] Certainty of evidence not downgraded due to indirectness in outcome measures; the SOE indicates the certainty in measures of cardiorespiratory fitness or muscle strength
[c] Certainty of evidence downgraded due to substantial degree of heterogeneity (I^2=62%) in pooled analyses, serious imprecision given wide confidence intervals around estimates of effects, and possible publication bias serious inconsistency, indirectness, imprecision, and possible publication bias
[d] Certainty of evidence not upgraded
[e] Two reviews *(27, 34)* were identified but were rated as very low credibility and were not included.
[f] Certainty of evidence downgraded for serious unexplained inconsistency (moderate heterogeneity (I2>50%) in most pooled analyses; individual study effects include benefit and no benefit), serious indirectness (lack of detail regarding populations and interventions), and imprecision (wide confidence intervals around measures of effect)