Exercise in patients with multiple sclerosis

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Exercise can be a beneficial rehabilitation strategy for people with multiple sclerosis to manage symptoms, restore function, optimise quality of life, promote wellness, and boost participation in activities of daily living. However, this population typically engages in low levels of health-promoting physical activity compared with adults from the general population, a fact which has not changed in the past 25 years despite growing evidence of the benefits of exercise. To overcome this challenge, the main limitations to promoting exercise through the patient–clinician interaction must be addressed. These limitations are the inadequate quality and scope of existing evidence, incomplete understanding of the mechanisms underlying the beneficial effects of exercise in people with multiple sclerosis, and the absence of a conceptual framework and toolkit for translating the evidence into practice. Future research to address those limitations will be essential to inform decisions about the inclusion of exercise in the clinical care of people with multiple sclerosis.

Introduction

Multiple sclerosis is often described as a chronic, immune-mediated disease of the CNS, although neurodegenerative processes are increasingly being recognised in its pathogenesis.[1] The disease manifests as symptoms (eg, fatigue and depression) and dysfunction (eg, mobility and cognitive impairment) that compromise quality of life and participation in activities of daily living. Multiple sclerosis is typically treated with disease-modifying drugs that target immunological signalling proteins (eg, interferons and cytokines) or populations of immune cells (eg, lymphocytes). This approach substantially controls inflammatory activity, but not neurodegenerative processes, and does not cure the disease, so people with multiple sclerosis often experience residual symptoms and dysfunction.

Participation in physical activity, particularly exercise training (panel), has increasingly been recommended for patients with multiple sclerosis to manage symptoms, restore function, optimise quality of life, promote wellness, and boost participation in activities of daily living.[3] Thus, exercise can be a beneficial rehabilitation approach for addressing the multifaceted aspects of multiple sclerosis. Nevertheless, over the past 25 years, this population typically has engaged in low levels of health-promoting physical activity compared with adults from the general population,[4] despite growing evidence of the benefits of exercise.[5] This observation presents a conundrum: exercise and physical activity offer wide-ranging benefits, but people with multiple sclerosis are not sufficiently physically active.

In this Personal View, we discuss limitations to the widespread adoption of exercise as a rehabilitation strategy in people with multiple sclerosis. These limitations include inadequate quality and scope of existing evidence, incomplete understanding of the mechanisms underlying the beneficial effects of exercise in multiple sclerosis, and the absence of a conceptual framework and toolkit for translating the evidence into practice. Overcoming these limitations and narrowing the gap between research and clinical practice are both timely and important given the deleterious effect of low-level participation in exercise and physical activity in people with multiple sclerosis.

Panel: **Definitions of physical activity, exercise, and fitness**[2]

Physical activity
Any bodily movement produced by contraction of skeletal muscles that results in a substantial increase in energy expenditure over resting levels

Exercise
A subset of physical activity that is planned, structured, and repetitive with the objective of improving or maintaining physical fitness

Physical fitness
A set of characteristics or attributes that people have or achieve that describe the capacity for performing physical activity

Effects of exercise

In this section, we review the evidence on the effects of exercise training and participation in physical activity on physical fitness, walking mobility, balance, cognition, fatigue, depressive symptoms, and quality of life, consistent with the order of constructs within the International Classification of Functioning, Disability and Health model for multiple sclerosis.[3] The evidence comes from meta-analyses; Cochrane reviews; and systematic or narrative reviews (table) of exercise effects on outcomes in multiple sclerosis. The size of exercise effects on specific outcomes were interpreted relative to standard guidelines[20] of small (Cohen's d=0·2), medium (d=0·5), or large (d=0·8) effects. Clinical meaningfulness was discussed when guidelines were available for specific outcomes.

Physical fitness

One systematic review[6] and two meta-analyses[7,8] have summarised the effects of exercise training on physical-fitness outcomes in people with multiple sclerosis. These outcomes are crucial given the deleterious effects of physiological deconditioning on walking impairment and cognition in multiple sclerosis.[21] Evidence exists of small improvements in lower-extremity muscle strength (Cohen's d=0·27) after resistance exercise training[8] and moderate improvements in cardiorespiratory fitness (Cohen's d=0·47–0·63) after aerobic exercise training[7,8] (table). The improvement in aerobic fitness is seemingly large enough for secondary health benefits and, therefore, is considered clinically meaningful.[7] The systematic reviews and meta-analyses showed that many of the studies were underpowered; did not mask participants, therapists, and assessors; did not do intention-to-treat analyses; and often predominantly involved people with relapsing-remitting multiple sclerosis.[6–8]

Walking mobility

Two meta-analyses[9,10] have examined the effects of exercise training on walking-mobility outcomes in people with multiple sclerosis. The studies showed small (Cohen's d=0·25)[10] but beneficial (and clinically-meaningful) effects for exercise training on walking speed and walking endurance (table). Such effects were reasonably homogeneous across modes of exercise training (ie, aerobic *vs* resistance). These analyses confirmed the results of an earlier meta-analysis,[22] which reported small (d=0·19)

	Study design	Study aim	Number of studies	Primary outcome and effect sizes*	Quality indices	Limitations of included studies
Physical fitness						
Kjølhede et al (2012)[6]	Systematic review	Effects of resistance exercise on outcomes of muscular strength	16	7–21% improvement in lower-limb maximal voluntary contraction (*d*=NR); 20–50% improvement in lower-limb one-repetition maximum (*d*=NR)	5·0†	Small sample sizes (risk of type II error); absence of masked assessors
Langeskov-Christensen et al (2015)[7]	Meta-analysis	Effects of exercise on aerobic capacity	17	Moderate improvements in peak oxygen consumption (*d*=0·63)	5·5†	No inclusion of people with severe disability
Platta et al (2016)[8]	Meta-analysis	Effects of exercise training on fitness	20	Improvements in muscular fitness (*d*=0·27) and cardiorespiratory fitness (*d*=0·47)	6·6 for combined aerobic and resistance exercise; 7·2 for aerobic exercise; 6·7 for resistance exercise†	Overall scarcity of studies reporting fitness measures; low-quality outcome measures (eg, manual dynamometry); no inclusion of people with severe disability; intervention allocation not concealed; participants, assessors, and therapists not masked; few intention-to-treat analyses
Walking mobility						
Pearson et al (2015)[9]	Meta-analysis	Effects of exercise on mobility	13	Overall clinically meaningful improvements (based on percentage change) in 10 m walking test (17% improvement) and 2 min walking test (19% improvement; *d*=NR); overall significant but non-clinically meaningful improvements in timed 25 ft walking and 6 min walking tests (*d*=NR)	6·0†	Heterogeneous interventions; no dose-response studies; few comparisons between exercise modes
Learmonth et al (2016)[10]	Meta-analysis	Effects of physiotherapy treatment on walking performance	21	Small improvements in walking outcomes (*d*=0·25); similar across treatment protocols	6·0†	Heterogeneous treatment protocols
Balance						
Paltamaa et al (2012)[11]	Meta-analysis	Effects of physiotherapy interventions on balance outcomes	7	Small improvements in balance (*d*=0·34)	4·4‡	Small, underpowered studies; no blinding; no reporting of intervention and randomisation protocols
Cognition						
Sandroff et al (2016)[12]	Systematic review	Effects of exercise, physical activity, and physical fitness on cognition	26	No clear evidence for exercise effects	7·0 for exercise; 6·0 for physical activity; NA for physical fitness†	Cognition not included as primary outcome; poorly developed exercise interventions; no inclusion of people with cognitive impairment
Fatigue						
Pilutti et al (2013)[13]	Meta-analysis	Effects of exercise training on fatigue	17	Consistent, moderate reductions in fatigue (*d*=0·45)	6·0§	Heterogeneous interventions; no inclusion of participants with progressive multiple sclerosis; participants not preselected for fatigue; no masking of assessors; few intention-to-treat analyses
Asano et al (2015)[14]	Meta-analysis	Effects of exercise, education, and pharmacotherapy on fatigue	25 (of which ten were of exercise)	Moderate reductions in fatigue (*d*=0·57); similar to effects of educational interventions (*d*=0·54)	PEDro score (NR)	Heterogeneous interventions; no prescreening for people with fatigue; selection bias; no concealed allocation; incomplete or selective outcome reporting
Heine et al (2015)[15]	Cochrane review	Effects of exercise therapy on fatigue	45	Moderate reductions in fatigue (*d*=0·53); the effect was deemed heterogeneous	5·2†	Underpowered studies; recruitment not based on having severe fatigue; absence of therapies targeting fatigue

(Table continues on next page)

	Study design	Study aim	Number of studies	Primary outcome and effect sizes*	Quality indices	Limitations of included studies
(Continued from previous page)						
Depressive symptoms						
Ensari et al (2014)[16]	Meta-analysis	Effects of exercise training on depressive symptoms	13	Small, consistent improvements in depressive symptoms (*d*=0·36)	5·8†	No masked assessors; depression not primary focus of interventions; no prescreening for depression
Dalgas et al (2015)[17]	Meta-analysis	Effects of exercise training on depressive symptoms	12	Small, consistent improvements in depressive symptoms (*d*=0·37)	5·6†	Heterogeneous interventions; depression not primary outcome; no studies of major depressive disorder; few people with progressive multiple sclerosis; no control for antidepressants
Adamson et al (2015)[18]	Meta-analysis	Effects of exercise training on depressive symptoms in people with neurological disorders	23 (of which 13 were of multiple sclerosis)	Small, consistent improvements in depressive symptoms (*d*=0·28); larger effects when interventions met physical activity guidelines (*d*=0·38) than when interventions did not meet guidelines (*d*=0·19)	5·5† (for studies of multiple sclerosis only)	Few studies of major depressive disorder; no masking of participants, therapists, and assessors; inadequate reporting of adverse events; inclusion of people without depression
Quality of life						
Latimer-Cheung et al (2013)[19]	Systematic review	Effects of exercise training on fitness, mobility, fatigue, and health-related quality of life	26	Insufficient evidence for effects on quality of life (d=NR)	7·5 for aerobic exercise; 8·5 for resistance exercise; 7·7 for combined aerobic and resistance exercise; 7·0 for other exercise†	Overall poor reporting on safety of exercise training; heterogeneous interventions; unequal monitoring of people in exercise or control conditions

PEDro scores of 6·0 or higher are indicative of good methodological study quality. *d*=Cohen's *d*. NR=not reported. NA=not applicable. PEDro=Physiotherapy Evidence Database. *Effect sizes were interpreted as small, medium, or large based on Cohen's *d* values of 0·2, 0·5, and 0·8, respectively. †Mean PEDro score. ‡Mean van Tulder scale score. §Median PEDro score.

***Table:* Reviews and meta-analyses of the effects of exercise training in people with multiple sclerosis**

but beneficial effects for exercise on walking outcomes in multiple sclerosis. However, the more recent meta-analyses[9,10] reported substantial heterogeneity between exercise training protocols, which might reduce the ability of clinicians to prescribe patients with a specific exercise programme for selective improvement of mobility in multiple sclerosis.

Balance

One meta-analysis[11] has analysed the effects of exercise training on balance outcomes in people with multiple sclerosis, and concluded that exercise training had a small (Cohen's *d*=0·34) but significant beneficial effect on balance outcomes in this population (table). However, studies included small samples and were underpowered for detection of meaningful balance improvements, and randomised trials did not adequately report intervention details or randomisation procedures for reproduction of the research.[11] Results from a series of preliminary studies[23,24] showed that balance exercise training improved postural control and, possibly, integrity of cerebellar white and grey matter.

Cognition

One systematic review[12] has examined the effects of exercise, physical activity, and physical fitness on cognitive outcomes in people with multiple sclerosis; no meta-analyses focused on this outcome have been done (table). The study found no clear evidence regarding a beneficial effect for exercise training on cognition. This finding might be attributable to several shortcomings in the methods of exercise trials (ie, phase 1 and 2 trials); for example, no inclusion of cognition as a primary outcome, poorly designed exercise interventions, and no inclusion of people with cognitive impairment. However, other evidence supports possible beneficial effects for physical activity and exercise training on cognition in this population.[25–27]

Fatigue

Two meta-analyses[13,14] and one Cochrane review[15] have examined the overall effects of exercise on fatigue outcomes in people with multiple sclerosis. These quantitative syntheses have reported overall moderate reductions in fatigue (Cohen's *d*=0·45–0·57) after exercise training (table). One meta-analysis[13] reported that the overall effects were reasonably consistent across studies, whereas the Cochrane review[15] reported overall heterogeneity in the effects of exercise interventions on fatigue outcomes. All three studies[13–15] noted the absence of prescreening of participants for severe fatigue associated with multiple sclerosis, such that the trials did not examine exercise as a possible treatment for fatigue in multiple sclerosis. Other limitations included underpowered studies, selective reporting of outcomes, and heterogeneous exercise interventions across studies.

Depressive symptoms

Three meta-analyses[16–18] have examined the effects of exercise training on depressive symptoms in people with multiple sclerosis. The meta-analyses reported small (Cohen's d=0·28–0·37) but consistent beneficial effects for exercise on depressive symptoms in this population (table). One meta-analysis[18] reported that the benefits of exercise on depressive outcomes were larger if the intervention met physical activity guidelines than if it did not (d=0·38 *vs* d=0·19). As with the studies of the effects of exercise on fatigue in people with multiple sclerosis, prescreening for individuals with worsened depressive symptoms or major depressive disorder was infrequent. Thus, studies[16–18] could only report on the effects of exercise on depressive symptoms, and not on exercise as a possible treatment for major depressive disorder in multiple sclerosis.

Quality of life

One systematic review[19] has examined the effects of exercise training on quality-of-life outcomes in people with multiple sclerosis (table), and reported insufficient evidence for a conclusion. This finding is not consistent with the results of an earlier meta-analysis,[28] which reported small (Cohen's d=0·23) but beneficial improvements in quality of life in this population. One issue that might contribute to the mixed evidence is the inconsistent outcome measures used across studies (for example, general *vs* disease-specific quality-of-life outcomes and composite quality-of-life outcomes *vs* subscales).[19]

Other outcomes

Other studies of exercise in people with multiple sclerosis have suggested that exercise might have effects on the hippocampus,[29,30] sleep quality,[31] and cardiovascular and metabolic comorbidity.[32,33] Exercise has been associated with reduced incidence of relapses[34,35] and slowed disability progression.[36] The safety profile (occurrence of adverse and serious adverse events) for exercise in people with multiple sclerosis is similar to that for the general adult population.[34] Additionally, exercise has been recognised as a primary strategy for restoration of physical function[37] and perhaps even for modification of the disease.[38,39] The evidence base has led to the development of guidelines for prescribing exercise behaviour to people with multiple sclerosis who have mild or moderate neurological disability,[19,40] which can be used within comprehensive care for multiple sclerosis.[41]

Factors affecting exercise participation

The evidence for exercise training suggests small-to-moderate effects on fitness, symptoms, and function in people with multiple sclerosis. However, people with multiple sclerosis engage in substantially less physical activity than healthy individuals from the general population, but similar amounts to those with other chronic diseases.[4,42] Evidence from waist-worn accelerometry has shown that people with multiple sclerosis engage in less moderate-to-vigorous physical activity than the general population[43] and that physical activity levels decrease over time as the disease develops.[44] Data also suggest that less than 20% of people with multiple sclerosis in the USA engage in recommended amounts of moderate-to-vigorous physical activity necessary for health benefits, compared with 40% of healthy, control populations;[43,45] the level of physical activity is also low for people with mild multiple sclerosis who do not have severe disability.[43] This disconnect between the evidence and levels of participation in physical activity is seemingly not associated with compliance to specific exercise programmes; more than 80% of people with multiple sclerosis who were enrolled in randomised trials of structured, supervised exercise training completed the prescribed regimen.[34]

The extent to which people with multiple sclerosis participate in physical activity might reflect physical limitations associated with ambulatory disability, symptoms of multiple sclerosis (eg, depression, fatigue), environmental barriers (eg, poor access to facilities), or psychosocial factors related to behaviour change (eg, self-monitoring, self-efficacy, goal setting, social support).[46] There has also been interest in the use of behaviour-change theory to study determinants of physical activity behaviour in people with multiple sclerosis, and such research has mainly focused on variables from social cognitive theory.[47,48] Social cognitive theory recognises interactions between individuals and environments (physical and social) when considering behavioural changes, identifying environmental facilitators that permit successful use of programmes for behaviour change.

We propose that the low participation in physical activity by people with multiple sclerosis—despite evidence of its benefits—can be overcome by ameliorating three key limitations in exercise research: inadequate quality and scope of existing evidence, incomplete understanding of the mechanisms underlying the beneficial effects of exercise in patients with multiple sclerosis, and the absence of a conceptual framework and toolkit for translating the evidence into practice.

Quality and scope of existing evidence

Evidence from phase 1 and 2 clinical trials has supported that exercise has substantial benefit for people with multiple sclerosis.[49] However, the limitations of this evidence restrict translation of the knowledge gained into clinical practice (table). First, no effectiveness trials (ie, phase 3 clinical trials) of exercise in multiple sclerosis have been done, and only a few studies[50,51] have focused on the dose-response association between exercise-training parameters (intensity, frequency) and multiple sclerosis outcomes. Second, studies have not pre-screened individuals for the presence of a specific symptom or dysfunction associated with multiple sclerosis. For example, although meta-analyses have shown that exercise training improves measures of fatigue[13] or depressive symptoms,[16] only a few studies included patients with severe fatigue and clinical depression or major depressive disorder.[15,17] This limitation is important given the high prevalence and burden of fatigue and depression in multiple sclerosis,[52] which might affect the high incidence of physical inactivity in this population.[53]

Third, the outcomes of exercise training might vary according to the type of multiple sclerosis, yet such heterogeneity has not been systematically examined in the literature. Studies have often included patietns with relapsing-remitting multiple sclerosis or mild-to-moderate disability related to multiple sclerosis,[13,15,49] or who are reasonably healthy without comorbid conditions common to multiple sclerosis.[54] Evidence is substantially weaker for progressive forms of multiple sclerosis and for those with severe disability,[55–57] although people with progressive multiple sclerosis and severe ambulatory disability are much less physically active than people with relapsing-remitting multiple sclerosis[43] and thus might benefit the most from exercise training.[49] The absence of specific guidelines for these populations is a limitation that must be overcome, because most disease-modifying drugs are not approved for progressive multiple sclerosis or are ineffective in later stages of relapsing-remitting multiple sclerosis (eg, an Expanded Disability Status Scale score of 4·0 or higher).[58,59]

Fourth, clearly defined primary endpoints are missing from many studies; for example, in studies of the effects of exercise training on depression, only one of 12 randomised trials specified depression as a primary endpoint.[17] The absence of symptom-specific primary endpoints might result in the effects of exercise being underestimated in randomised trials, and so warrants further study. However, there is no consensus regarding a symptom-specific set of validated, core outcomes for inclusion in exercise trials. Increasingly, emphasis is on identifying whether the changes in outcomes signal an improvement that has value in a patient's life (ie, clinical relevance based on benchmarks of meaningful change), yet few randomised trials[49–51] of exercise training have properly reflected on this value. If these limitations are addressed in future research, it might become easier to translate evidence into clinical practice.

Numerous other problems beset the quality of the existing research. For example, evidence is scarce regarding the durability or sustainability of exercise effects on outcomes of multiple sclerosis,[49,60] which brings into question whether or not exercise can exert meaningful, long-term disease-modifying changes in fitness, symptoms, and function. Other limitations include underpowered studies[16] with small sample sizes (the mean sample size for randomised trials was 50 patients [range 14–130] in one review[5]), no use of masked assessors or intention-to-treat analyses,[13,15,17] and no focus on metrics in the RE-AIM framework[61] when designing and analysing trials. The principles of the RE-AIM framework are reach (number, proportion, or representativeness of participants), effectiveness (change in appropriate outcomes, including quality of life), adoption (number, proportion, or representativeness of settings or clinicians), implementation (extent, time, and costs of consistent programme delivery), and maintenance (long-term effects and attrition).

Other issues restrict the scope of the available evidence on exercise and multiple sclerosis. For example, most people with relapsing-remitting multiple sclerosis take a disease-modifying drug, yet such information is not systematically collected, reported, or statistically accounted for in trials of exercise training. Similar problems exist for symptomatic agents and other rehabilitation therapies. This issue means that no clear understanding of the benefits of exercise in the context of disease-modifying-drug use is available when considering prescribing exercise to people with multiple sclerosis.

A role for exercise training as an add-on or stepped-care therapy in multiple sclerosis has not yet been considered. For example, cognitive behavioural therapy is commonly used for management of depression in people with multiple sclerosis, but it is not always effective alone[62] and exercise could be added as a stepped-care approach for therapy. Additionally, little is known about exercise within the context of relapses,[63] and many aspects must be considered such as discontinuation of exercise during a relapse for safety, when and how exercise should be reinitiated after resolution of a relapse, and if exercise is only suitable after certain types of relapses. High-quality research in this area should provide stronger evidence such that health-care providers would be more likely to prescribe exercise alongside adjuvant pharmacological or other rehabilitative therapies for improvement of function in this population.

Another issue associated with the quality and scope of evidence is inadequate knowledge of how to maximise adherence to and compliance with exercise training programmes.[5,34] Future research might consider integrating approaches—on the basis of behaviour-change theories such as social cognitive theory[5,47,48]—within exercise training programmes to maximise adherence, compliance, and long-term maintenance. Such approaches could inform the patient–clinician interaction by providing guidance as to how patients can optimally initiate and maintain physical activity behaviour over time.

Mechanisms underlying the effects of exercise

Almost all research on the outcomes of exercise training has focused on symptoms, functions, and quality of life, whereas little research has focused on the mechanisms underlying the effects of exercise training in patients with multiple sclerosis. Investigation of the biological factors involved in exercise-training effects in this population is crucial to increase the confidence of health-care providers in prescribing exercise to patients. Increasingly, studies are examining the neural and molecular mechanisms of exercise and physical activity in animal models of multiple sclerosis.[64] However, these animal studies are often inconclusive, difficult to interpret, and might not translate to studies in human beings, which might undermine the promotion of exercise by clinicians.

Some efforts have been made toward studying the mechanisms of exercise effects in people with multiple sclerosis by focusing on immune cells and neurotrophic factors in peripheral blood samples;[3] the assumption being that peripheral blood samples reflect the ongoing pathophysiology in the CNS. However, the evidence is inconclusive[3] and these studies did not consider that multiple sclerosis is typically an acute, episodic disease that involves intermittent bursts of inflammation, although ongoing, chronic inflammation is also observed.[1] Therefore, future clinical trials might overcome these limitations by collecting peripheral blood samples after acute exercise and during relapses (a period when the blood–brain barrier is disrupted, allowing migration of lymphocytes into the CNS) or collecting CSF during long-term exercise training.

Evidence is emerging that exercise might promote neuroplasticity in people with multiple sclerosis. Several cross-sectional studies[65,66] have suggested that aerobic fitness or physical activity are positively associated with increased volumes of subcortical grey matter structures, such as the hippocampus and basal ganglia, in people with multiple sclerosis. Other case studies[29,30] have indicated that aerobic exercise training might increase hippocampal volume and integrity in this population. These structural brain observations might explain exercise training effects on ambulation and cognition,[67] although no evidence is available from phase 2 randomised trials and ontological mechanisms explaining why the structural changes occur are unknown. This absence of evidence probably represents a key limitation in the clinical translation of exercise research, because health-care providers seek mechanistically-derived evidence when making recommendations regarding any treatment of multiple sclerosis, and patients might seek a mechanistic explanation or rationale before engaging in exercise.

Conceptual framework and toolkit for translating the evidence

Development of high-quality clinical evidence that is supported by research into mechanisms, and with substantial scope for use across types of multiple sclerosis, is the first step in achieving exercise behaviour in people with multiple sclerosis. A detailed understanding of the patient–clinician interaction (a conceptual framework) and an associated toolkit for use by health-care providers to translate knowledge about exercise into practice is also needed. For example, the patient–clinician interaction might represent an opportunity to discuss benefits, barriers, and facilitators to engagement in exercise (eg, to promote change in exercise behaviour in a patient for management of fatigue).

The translation of evidence into practice might be a key factor determining the adoption and maintenance of exercise behaviours. Research has shown that people with multiple sclerosis seek information about behavioural approaches for management of their symptoms and optimisation of wellness, particularly exercise[50] and diet.[68] One survey-based study[69] of 930 people with multiple sclerosis in the USA showed that 34–50% of people, depending on the health-care setting (greater interest at health maintenance organisations than at independent practice associations), wanted substantially more information about exercise and nutrition in the context of health-care services. Qualitative data from two studies[70,71] of the same 50 people with multiple sclerosis in the USA showed a need for information, particularly through face-to-face interactions,[71] about the benefits of exercise and its prescription; materials supporting home and community exercise; and tools for initiating and maintaining exercise behaviour through interactions with health-care providers across levels of disability and physical activity. Qualitative data from 44 neurologists, occupational therapists, physical therapists, and nurses in the USA showed that health-care providers were able to identify opportunities for exercise promotion through the health-care system and comprehensive team during clinical appointments.[72] Health-care providers also seek professional and service training for information about the benefits of exercise, provision of protocols for exercise promotion, and prescriptive exercise guidelines for promotion of behaviour change in people with multiple sclerosis.[72] Thus, health-care providers, including neurologists, neuropsychologists, nurses, and occupational and physical therapists, are strategically positioned to address issues around exercise adoption and adherence,[41] yet health-care providers might not have the knowledge, models, tools, or resources to capitalise on this opportunity. Focusing on the health-care provider for promotion of exercise is not necessarily a new idea in general medicine,[73] but it is a fresh perspective in the care of people with multiple sclerosis that seems particularly suitable given the importance of ongoing, comprehensive care through the patient–clinician interaction in this population.

The results of qualitative research are consistent with a participatory action framework in which patients and health-care providers are involved in the formation of an action plan for promotion of exercise through the patient–clinician interaction.[74,75] The information must be organised into a framework through concept mapping (ie, a diagram that represents associations between ideas) to yield a toolkit that supports knowledge translation consistent with implementation science (ie, study of methods for uptake of research findings into routine health care in clinical contexts). Focus on a conceptual model and toolkit is particularly important given the recent emphasis on the putative benefits of exercise in people with multiple sclerosis; previously, clinicians prescribed rest for improving function and symptoms in this population.[76] Indeed, despite reasonably weak evidence, energy conservation techniques to reduce fatigue are still commonly prescribed in rehabilitation settings for people with multiple sclerosis.[77] Perhaps the view of exercise as fatiguing will shift to considering exercise as a means to reduce fatigue as evidence supporting the benefits of exercise in this population increases.[13–15] Such a shift in clinical practice would mirror that occurring in people with stroke.[78] Carefully completed, evidence-based practice guidelines supporting exercise in people with multiple sclerosis are crucial for the development of toolkits for exercise promotion by health-care providers.

Translating knowledge into clinical practice

Five main questions surround knowledge translation,[79] concerning what information should be transferred; how, to whom, and by whom should it be transferred; and with what effect when transferred (ie, does it work?). Addressing the three key limitations in research on exercise training for people with multiple sclerosis will advance our knowledge about four of the five questions regarding knowledge translation. Tackling the first (poor quality and scope of evidence) and second (unknown mechanisms for the benefits of exercise in people with multiple sclerosis) limitations of exercise research will be necessary to address the question of what information should be transferred, whereas targeting the first limitation will be required to identify to whom research knowledge should be transferred. Focusing on the third limitation (absence of a conceptual framework and toolkit for translating the evidence into clinical practice) will provide direction on how and by whom research knowledge should be transferred. The three key limitations are interconnected and could be addressed through formation of an international collaborative research network to improve the translational research pipeline, as done for stroke.[80] Collaboration with implementation scientists will be essential to address the fifth theme regarding an approach and process for assessing the effect of knowledge translation on increasing exercise behaviour in multiple sclerosis. This multifaceted approach will be crucial to facilitate and support integration of research of exercise into clinical practice.

Search strategy and selection criteria

We identified references for this Personal View by searches of PubMed, Google Scholar, Scopus, and CINAHL between Jan 1, 2012, and July 31, 2017, and by searching the reference lists of retrieved articles. The search terms were "multiple sclerosis", "exercise", "physical activity", "physical fitness", and "rehabilitation". We focused on meta-analyses, Cochrane reviews, and narrative or systematic reviews to capture the broad scope and overall effects of exercise on various outcomes of multiple sclerosis. We did not focus on individual studies because to separately review more than 60 individual clinical trials of exercise in multiple sclerosis would have been beyond the scope of this Personal View. We only reviewed papers that were published in English. The final reference list was generated on the basis of relevance to the focus of this Personal View.

Conclusions and future directions

Exercise can be a beneficial rehabilitation approach for people with multiple sclerosis to manage symptoms, restore function, optimise quality of life, promote wellness, and boost participation in activities of daily living. Nevertheless, a disconnect exists between the evidence of benefits from exercise training and the low level of participation in physical activity in this population. Although this conundrum is probably multifactorial, the patient–clinician interaction is an understudied and crucial platform for promoting participation in physical activity and increasing the likelihood that people with multiple sclerosis experience exercise-related benefits in fitness, symptoms, and function. Addressing the three main limitations to promotion of exercise through the patient–clinician interaction could, in turn, affect other causes of inadequate exercise participation in this population.

Future research should improve the quality and scope of evidence on the benefits of exercise training in people with multiple sclerosis, to better inform clinical care, by addressing priorities identified in a 2015 paper.[51] For example, future study participants should be pre-screened according to the primary outcome, because disease-related symptoms are common and highly burdensome in this population (eg, pre-screen for severe fatigue when investigating an exercise intervention for reducing fatigue). To truly understand the effect of exercise training on outcomes, more specific, targeted exercise interventions for representative populations of patients with multiple sclerosis might need to be designed. Future research might also attempt to delineate how to optimise adherence and compliance within the context of a given intervention, so that people with multiple sclerosis can maximise the benefits of exercise training. Addressing these and other limitations could improve promotion of exercise via the patient–clinician interaction.

In this Personal View, we have underscored the importance of knowledge translation and implementation science for bridging the gap between the data arising from exercise research and clinical practice. This focus includes better equipping both health-care providers and patients with strategies and resources for adoption of exercise behaviour to manage the numerous debilitating consequences of multiple sclerosis.

Contributors

RWM contributed to the conceptual design, literature search, drafting of the manuscript, and critical revision of the manuscript. BMS contributed to the conceptual design, literature search, and critical revision of the manuscript. GK, UD, AF, CH, PF, and AJT contributed to the conceptual design and critical revision of the manuscript.

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