Participation in exercise and sport for individuals with minimal disability from multiple sclerosis

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Chapter	Title	Contribution
Chapter 1	Introduction	Concept: MS Writing: MS Draft review/revisions: RB & GW
Chapter 2	The effect of exercise on high-level mobility in individuals with neurodegenerative disease	Concept: MS Study design: MS, RB, GW & RG Search and appraisal: MS & JC Data extraction: MS Manuscript writing: MS Draft review/revisions: RB, GW, JC & RG
Chapter 3	A qualitative study of active participation in sport and exercise for individuals with multiple sclerosis	Concept: MS Study design: MS, RB & GW Data collection: MS & BN Data analysis: MS & BN Manuscript writing: MS Draft review/revisions: RB, GW, BN & MB

Chapter 4	Development of a study protocol to find the right balance with participation in sport and exercise for individuals with multiple sclerosis	Concept: MS Study design: MS, RB & GW Manuscript writing: MS Draft review/revisions: RB & GW
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Abstract

Multiple sclerosis (MS) is commonly diagnosed between 20-40 years of age. At this stage in life, it is not uncommon to have a young family, be working in a demanding job, and be participating in an active lifestyle that includes sport or exercise for health, work or leisure. Participation in an active lifestyle demands high-level mobility, such as running, jumping, bounding and exercise. Paradoxically, interventions to enhance participation in high-level mobility activities for individuals with MS are lacking. To maximise the likelihood that individuals with MS can continue with an active lifestyle, it is imperative to optimise their capacity to participate in sport or exercise.

Exercise is known to be beneficial for individuals with MS because it addresses impairments such as muscle weakness, fatigue and balance, and improves activities such as walking. Exercise may also have a neuroprotective effect by changing the balance between pro- and anti-inflammatory cytokines, reducing the inflammatory response and the subsequent damage to the nerve structures. However, further research is required to determine whether exercise can have a disease-modifying effect.

The aim of this thesis was to develop an exercise intervention program, driven by consumers, that would optimise participation in sport and exercise for individuals with MS with minimal disability. Specifically, the objectives of the thesis were to (a) review the literature on the effect of exercise on high-level mobility in individuals with neurodegenerative disease, including MS; (b) explore the experience of participation in sport and exercise for individuals with MS; (c) develop an exercise participation program for individuals with MS with minimal disability, underpinned by their preferences and the scientific literature; and (d) test the feasibility of the exercise participation program, the feasibility of conducting a future trial and the acceptability of the exercise program from the perspective of individuals with MS.

To achieve the aim of this thesis, five studies were conducted. Study 1 involved a systematic review of the literature, including 33 randomised controlled trials. The review found that sport and exercise involving high-level mobility were not commonly investigated, and that high-level mobility was rarely assessed for individuals with MS, even for those with minimal disability. These findings highlighted the need to create an exercise intervention incorporating the high-level mobility required for a normal active lifestyle for individuals with minimal disability from MS.

Study 2 was a qualitative study with 16 individuals with MS that explored, via focus groups, the experience of participation in sport and exercise. The findings revealed that individuals with MS wanted to participate in activities that demanded a high level of mobility, such as running or squash. In addition, they wanted support from health professionals to help them find the right balance with sport and exercise.

In Study 3, the views of the individuals with MS from the qualitative study were coupled with the findings of the systematic review to develop a protocol for a flexible exercise participation program (FEPP) for individuals with minimal disability from MS. Conducted independently in the community, the FEPP is a 12-week program designed to enable individuals with MS to participate and progress in an exercise or sport of their choice. The FEPP is underpinned by guidelines on aerobic exercise for individuals with MS and is supported by a physiotherapist using behaviour change techniques.

Study 4 assessed the feasibility of the FEPP and the feasibility of a larger trial with 11 participants with MS with minimal disability. The FEPP was deemed safe and feasible for use, confirmed by participants' ability to participate in their regular exercise program and weekly coaching sessions as planned. Further, participants were able to use the FEPP flow chart to modify and progress their exercise to achieve their personal goals, with some able to exceed the MS aerobic exercise guidelines. Following the 12-week program, overall high-level mobility had improved, vitality had not changed and cytokine responses were suggestive of an anti-inflammatory response to exercise. Based on assessment of process, resources, management and scientific outcomes, Study 4 also demonstrated that a larger trial to demonstrate the effectiveness of the FEPP was feasible, safe and warranted.

Study 5 explored the acceptability of the FEPP from the participants' perspective. Using a mixed-methods approach, a quantitative survey was followed by a series of focus groups with participants. The FEPP was found to be highly acceptable to participants, who all valued the individualised nature and flexibility of the program. The ability to choose their own exercise mode enabled participation across a wide variety of sport and exercise, much of which demanded a high level of mobility. Health professional support, via a weekly telephone coaching session using behaviour change techniques, facilitated exploration of exercise boundaries and enabled self-efficacy with exercise participation. Participants recommended improvement of the FEPP by measuring energy daily and including peer support as part of the FEPP.

Individuals with minimal disability from MS showed that with health professional support, they could push the boundaries with sport and exercise and progress beyond current exercise guidelines. Health professionals can set the bar high and enable individuals with MS to maximise their potential in exercise and sport. The FEPP as a mechanism to help provide this support is safe, feasible and highly acceptable to individuals with minimal disability from MS. A larger-scale Phase II trial is now warranted to determine the efficacy of the FEPP and the possibilities for neuroprotection. The FEPP has potential for use with individuals with MS who have moderate disability and with individuals with other chronic diseases. With the possibility of integration into healthcare, the FEPP can help individuals find the right balance with participation in exercise and sport.

Publications

Smith, M., Barker, R., Williams, G., Carr, J., & Gunnarsson, R. (2020). The effect of exercise on high-level mobility in individuals with neurodegenerative disease: A systematic literature review. *Physiotherapy*, *106*, 174–193. https://doi.org/10.1016/j.physio.2019.04.003

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Smith, M., Neibling, B., Williams, G., Birks, M., & Barker, R. (2021). Consumer experience of a flexible exercise participation program (FEPP) for individuals with multiple sclerosis: A mixed-methods study. *Physiotherapy Research International*, *26*(4), Article e1922. https://doi.org/10.1002/pri.1922

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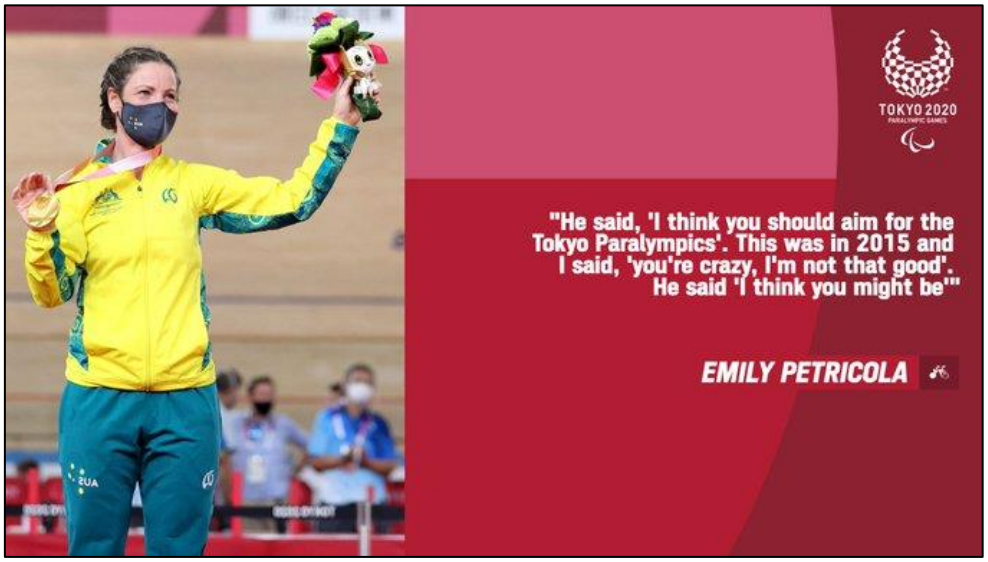
List of Abbreviations

BCT	Behaviour change techniques
CIS	Clinically isolated syndrome
CG	Control group
CSF	Cerebrospinal fluid
CNS	Central nervous system
DCD	Degenerative cerebellar disease
DGI	Dynamic gait index
EDSS	Expanded disability status scale
EG	Exercise group
FEPP	Flexible exercise participation program
FAC	Functional ambulation category
FGA	Functional gait assessment
GAS	Goal attainment scale
HiMAT	High-level mobility assessment tool
HD	Huntington's disease
ICF	International Classification of Functioning, Disability and Health
IFN	Interferon
(IgG)	Immunoglobulin G
IL	Interleukin
IQR	Interquartile range
MDC	Minimal detectable change
MHR	Maximum heart rate
MRI	Magnetic resonance imaging

MS	Multiple sclerosis
PD	Parkinson's disease
Pg/mL	Picograms per millilitre
PPMS	Primary progressive multiple sclerosis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RMI	Rivermead mobility index
RM	Repetition maximum
RPE	Rating of perceived exertion
RRMS	Relapsing-remitting multiple sclerosis
SPMS	Secondary progressive multiple sclerosis
SVS	Subjective vitality scale
TNF	Tumour necrosis factor
WHO	World Health Organisation

Chapter 1: Introduction



Paralympic Games (2021)

Emily Petricola seized gold for Australia at the Tokyo 2020 Paralympic Games in the women's cycling C4 3000m individual pursuit and set a new world record qualifying time (ABC News, 2021). Emily's other cycling credentials include winning the 2020 Individual Pursuit World Champion and the 2019 Road Time Trial World Champion (Olympics, 2021).

The Paralympic gold medallist has multiple sclerosis (MS). Spurred on by the support and belief of her coaching team and other Olympic athletes, Emily achieved the gold medal through dedication to her training and sport. With training as demanding and strenuous as it is for able-bodied cyclists, Emily also deals with 'MS roadblocks', which she problem solves with others to negotiate the additional challenges (Athletes Voice, 2021). Multiple sclerosis affects Emily's grip strength, and she is currently working with Paralympics Australia to create better bike hand grips (MS Australia, 2021a). Emily is also affected by heat sensitivity and manages it with fans, cooling towels and ice vests (MS Australia, 2021a). With commitment and support, Emily has continued to problem solve, push forward and achieve gold.

As is the case with Emily, onset of MS occurs at a prime period in an individual's life, commonly between 20 and 40 years of age (Ahmad et al., 2018). During this time, individuals may be starting a family, working in a demanding job and participating in an active lifestyle that includes exercise or sport. Optimising the capacity and potential for participation in sport or exercise as part of an active lifestyle for individuals with MS is prudent and requires

investigation. With Emily as inspiration, the focus of this PhD thesis is on creating opportunities for individuals with MS to strive for and achieve success with exercise and sport.

1.1 Multiple sclerosis

1.1.1 Prevalence and aetiology

MS is a neurodegenerative disease that affects 25,600 people in Australia and 2.8 million people worldwide (Ahmad et al., 2018; MS Australia, 2020; MS International Federation, 2020). The most recent data indicate a prevalence of 104 per 100,000 in Australia (MS International Federation, 2020). Overall prevalence in Australia increased by 8.2 per 100,000 people between 2010 and 2017 (Ahmad et al., 2018). Increasing prevalence is reportedly a result of increased survival and increased diagnostic ability (Ahmad et al., 2018). Areas with the highest prevalence are located at higher latitudes in the northern and southern hemispheres (Simpson et al., 2019). This latitudinal gradient is evident in Australia, where prevalence in Tasmania (139 per 100,000) is higher than in Queensland (75 per 100,000) (Ahmad et al., 2018; MS International Federation, 2020). The increased prevalence is correlated with a reduced exposure to sunlight and vitamin D at these latitudes (Simpson et al., 2018; Simpson et al.,2019).

Multiple sclerosis primarily affects young adults and is commonly diagnosed between the ages of 20 and 40 (Lane & Yadav, 2020; MS Australia, 2020). More common in females than males, the gender ratio is reported as close to 3:1 (F:M) (Dobson & Giovannoni, 2019; MS Australia, 2020). The aetiology of the disease is heterogenous, with genetic and environmental/lifestyle factors determining risk (Amato et al., 2017; Leddy & Dobson, 2020). Genetically, the risk for MS is higher in individuals with the HLA-DRB1*1501-DRB5*0101 haplotype, particularly Caucasians (Amato et al., 2017). The presence of other factors, such as smoking, obesity, Epstein–Barr virus seropositivity and low vitamin D, can affect disease development and the degree of disease activity as a result of interaction with the HLA risk genes (Amato et al., 2017; Olsson et al., 2017; Rosso & Chitnis, 2020; Simpson et al., 2018). Some of these lifestyle risk factors are modifiable, such as smoking and diet (including low vitamin D); therefore, there is potential for prevention, particularly for those at risk (Olsson et al., 2017). Environmentally, individuals who migrate from an area with low risk of MS to an area of high risk before the age of 15 will assume the risk of the new area (Leddy & Dobson, 2020). This interaction between genetic and environmental factors is particularly complex and continues to be explored (Amato et al., 2017; Dobson & Giovannoni, 2019).

1.1.2 Pathophysiology

Multiple sclerosis is a neurodegenerative, inflammatory disease that results in damage to the oligodendrocytes and insulating myelin sheath of neurons in the central nervous system (CNS) (Haase & Linker, 2021). Triggered by an autoimmune response, a cascade of inflammatory activity occurs driven by T lymphocyte and B lymphocyte cells (Haase & Linker, 2021; Lane & Yadav, 2020). T lymphocyte cells are the most numerous lymphocytes in the MS brain and are responsible for the production of pro- and anti-inflammatory cytokines (Lassmann, 2018). These cytokines are proteins that influence the proliferation, differentiation and function of the immune cells (Negaresh et al., 2018. In MS, the normal balance between pro- and anti-inflammatory cytokines changes as a result of a greater presence of pro-inflammatory cytokines and a reduction in anti-inflammatory cytokines (Lassmann, 2018; Negaresh et al., 2018) (see also section 1.3.1 for further detail). The increased presence of pro-inflammatory cytokines in the cerebrospinal fluid (CSF) and blood intensifies the demyelination process and axonal damage in the CNS (Lane & Yadav, 2020; Negaresh et al., 2018). Activation of macrophages and microglia in the clean-up process, as part of the inflammatory response, leads to further myelin damage and scarring or sclerosis of the neuron (Lassmann, 2018; Lassmann et al., 2007). In addition, apoptosis of oligodendrocytes during the autoimmune response reduces the capacity for neural remyelination, although it can occur (Lassmann, 2018).

Damage occurring in the CNS can be focal in the grey or white matter and can later present as widespread neurodegeneration (Cortese et al., 2019; Lassmann, 2018). In the early stages of the disease, new white matter lesions are identified via magnetic resonance imaging (MRI) indicating areas of demyelination and active inflammation (Cortese et al., 2019). These early focal lesions are commonly identified in the perivenous areas of the CNS as a result of the inflammatory response occurring at the blood brain barrier (Lassmann, 2018). As the disease progresses, new active lesions are less common, but more diffuse changes in the white matter are noted, including areas of lower perfusion (Lassmann, 2018). Brain volume reduction occurs as a result of grey matter demyelination and atrophy, which is associated with increasing disability and progression of the disease (Cortese et al., 2019).

1.1.3 Classification

Multiple sclerosis is classified into three main clinical courses with key descriptors: (i) relapsing-remitting MS (RRMS), (ii) secondary progressive MS (SPMS) and iii) primary progressive MS (PPMS) (Lublin et al., 2014). Relapsing-remitting MS is classified by

episodes of acute worsening of neurological function (relapses) followed by complete or partial recovery (remission) (Lublin et al., 2014). This is the most common classification of the disease, with 85% of individuals diagnosed with RRMS, (Ahmad et al., 2018; MS International Federation, 2020). Approximately 50% of individuals with RRMS will develop secondary progressive MS within 10–15 years of MS onset (Inojosa et al., 2019). Secondary progressive MS is characterised by progressive worsening of symptoms, with or without relapse. Some periods of stabilisation may occur. Primary progressive MS is characterised by progressive worsening of symptoms from the onset of the disease (Lublin et al., 2014). There are no periods of remission or recovery with this type of MS, and 10–15% of individuals with MS are diagnosed with PPMS (Ahmad et al., 2018; Lublin et al., 2014).

Diagnosis and classification of MS is dependent on the integration of clinical findings, CSF analysis and diagnostic imaging such as MRI. Clinical findings include examination of the periods and frequency of acute neurological worsening experienced by the individual. However, given the nature of the disease, clinical signs and symptoms can be transient and may not always be evident on examination. Laboratory analysis of CSF explores the presence of oligoclonal immunoglobulin G (IgG) bands indicating an immune disorder suggestive of MS. This band patterning in the CSF occurs in 95% of individuals with MS; however, it can be present in other diseases and is not a conclusive diagnostic test in isolation (Halbgebauer et al., 2016). Magnetic resonance imaging scans allow the detection and mapping of the dissemination of lesions in the CNS over time and space (Cortese et al., 2019), yet MS can be diagnosed in the absence of lesions (Thompson et al., 2018). Therefore, a combination of diagnostic factors is assessed to provide a definitive diagnosis using the McDonald criteria as the gold standard tool (Thompson et al., 2018) (see Appendix A). This tool provides a means for comparing and contrasting positive diagnostic features of MS and determining a clinical diagnosis. The McDonald criteria are widely used in clinical practice and research (Thompson et al., 2018). Originally developed in 2001, and most recently revised in 2017, the McDonald criteria now provide greater diagnostic accuracy, particularly in the early stages of the disease (McDonald et al., 2001; Thompson et al., 2018).

1.1.4 Degree of disability

Evaluation of the degree of disability and subsequent progression of MS is commonly measured using the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983; Zurawski et al., 2019) (see Appendix B). The EDSS is a 0–10-point composite scale with 0.5 incremental steps ranging from 0 (normal) to 10 (death due to MS). The EDSS is based on the analysis of

functional systems that may be affected by the disease, namely, pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral (mental) or other functions (Zurawski et al., 2019). The EDSS steps 0–3.5 indicate minimal–moderate disability in the functional system(s) with no limitations in walking. Greater disability is evident from step 4 and above due to functional and progressive limitations in walking ability.

Other disability measures of MS include the Patient Determined Disease Steps (PDDS) and the Multiple Sclerosis Functional Composite (MSFC). The PDDS is similar to the EDSS with a key focus on mobility and is also scored on an ordinal scale ranging from 0 (normal) to 8 (bedridden). In contrast to the EDSS, the PDSS is a patient reported rather than clinician reported outcome measure, thereby it affords greater flexibility for use in research. The MSFC is a multidimensional assessment that provides a composite measure across the domains of cognition, leg function/ambulation and arm/hand function, however a trained examiner is required. Psychometrically, all three disability measures display good reliability and validity (Goodkin et al., 1992; Learmonth et al., 2013; Meyer-Moock et al., 2014). The EDSS has some weakness in sensitivity to change, whereas the MSFC has some limitations due to learning effects (Meyer-Moock et al., 2014). Internationally, the EDSS is the most widely used measure of MS disability, enabling cross-study comparisons (Meyer-Moock et al., 2014).

Functioning and disability can also be measured using the International Classification of Functioning, Disability and Health (ICF), which is a framework developed by the World Health Organisation (WHO, 2001) to provide a standard language for the description of health. The ICF identifies functioning as an outcome of the interaction between health conditions and contextual factors (see Figure 1). Under the health condition banner are the domains of body function/structure, activity and participation, which detail the functioning of the individual. Contextual factors include environmental and personal factors that affect functioning in day-to-day life. The ICF is a biopsychosocial model that provides perspective on the biological, individual and social aspects of health and functioning (WHO, 2001).

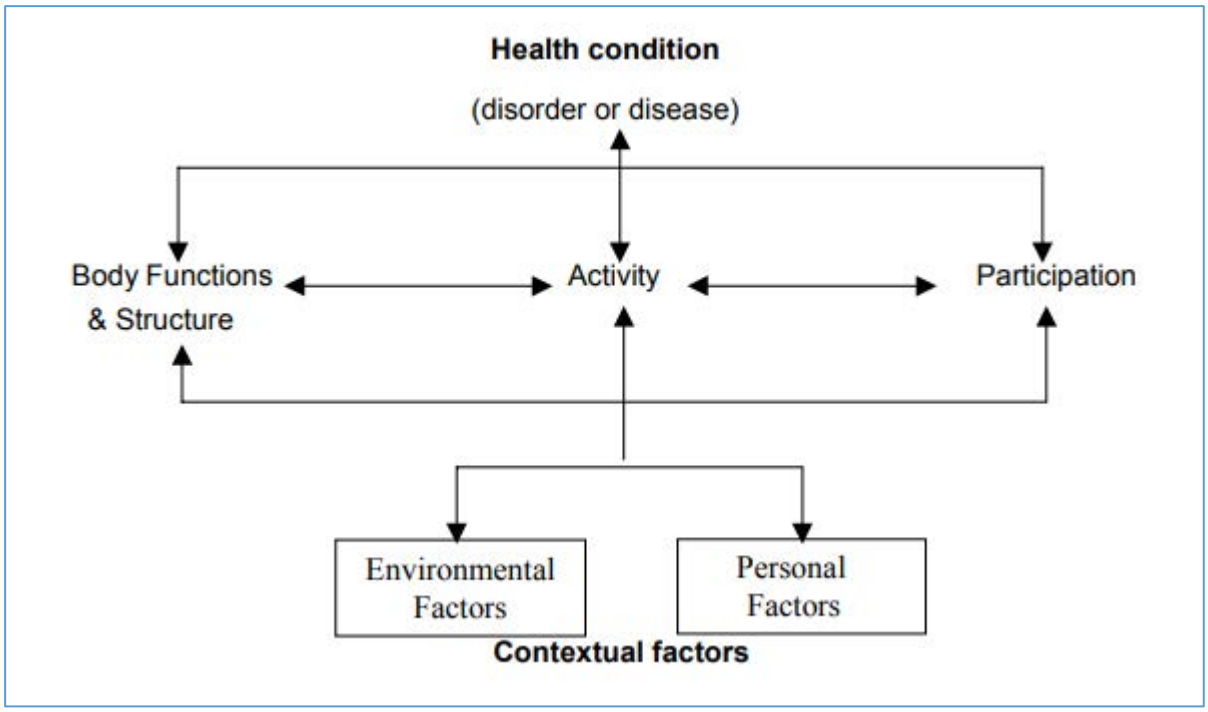


Figure 1. International Classification of Functioning, Disability and Health (WHO, 2001)

1.1.5 Effect of multiple sclerosis on body structures and functions

The effect of MS on body structures and functions is significant. The development of areas of demyelination and plaque (scarring) formation leads to changes in the conduction of the nerve. Prolonged conduction times, extended nerve latencies and nerve conduction asymmetries are evident when comparing individuals with MS with those without the disease (Mamoei et al., 2020). Ephaptic transmission between denuded neurons in proximity can cause dysregulated neural activity (Compston & Coles, 2008). The degree of altered nerve conduction in the CNS correlates with the increasing degree of disability experienced by the individual with MS (Mamoei et al., 2020). The resultant effect includes muscle weakness, somatosensory loss, vestibular dysfunction, spasticity, fatigue, altered bladder and bowel control (Lane & Yadav, 2020; Leddy & Dobson, 2020; Manjaly et al., 2019). In addition, disruption to cognitive function and alterations in mood (e.g. depression) can arise (Benedict et al., 2020; Whitehouse et al., 2019).

1.1.6 Effect of multiple sclerosis on activity

The onset of impairments such as weakness, somatosensory loss, vestibular dysfunction and altered cognitive function can lead to limitations in activities of daily living (e.g. washing, dressing and feeding) (Cattaneo et al., 2017; Conradsson et al., 2021). Other activity limitations include changes to functional mobility such as the sit-to-stand movement

(Khalil et al., 2021), walking ability (Hvid et al., 2020) and jogging (Kalron et al., 2014). For example, compared with healthy controls, individuals with MS have slower rise times from sit-to-stand as a result of lower limb weakness (Bowser et al., 2015). In regard to gait, there is an accelerated deterioration in walking capacity compared with individuals without the disease (Hvid et al., 2020). In addition, the oxygen cost of walking is significantly higher in individuals with MS, particularly those with greater disability, compared with healthy control populations (Rooney et al., 2021). Balance can be impaired for individuals with MS, reducing stability during walking and increasing the likelihood of falls (Nilsagård et al., 2014). Multiple sclerosis can affect higher levels of mobility such as jogging, with increases in step width, stance phase and double-support phase evident compared with individuals without the disease, these changes may serve to increase stability (Kalron et al., 2014). Notably, the study by Kaltron et al. (2014) was the first to report jogging spatio-temporal findings in the MS population and no further exploration of this has been published since then.

1.1.7 Effect of multiple sclerosis on participation

Participation restrictions for individuals with MS may involve difficulties in some domains such as home integration (cooking, cleaning), work (employment, caring roles) and social pursuits (relationships, outings, sport and leisure) (Cattaneo et al., 2017; Conradsson et al., 2021). As disability level increases, so do participation restrictions (Cattaneo et al., 2017). Changes in participation may lead to a reduction in socioeconomic status and quality of life. Changes in employment as a result of MS can affect the individual's socioeconomic status if they have cause to shift from full-time to part-time work, retire early, change occupation or lose days to illness (Ahmad et al., 2018; Marck, Aitken et al., 2020). The loss of wages for individuals with MS in Australia in 2017 was estimated at $21,858 per person (Ahmad et al., 2018). In addition, the total annual direct costs of MS (which include medication, healthcare services and home/car adaptations) in 2017 were $68,382 per person (Ahmad et al., 2018). Twenty-two per cent of the total annual direct costs were estimated to be met by the individual with MS (Ahmad et al., 2018). Changes in financial and employment status can significantly affect quality of life (Marck, Aitken et al., 2020). In particular, retiring due to disability from MS, compared to being in full-time employment, is associated with a greater decline in mental health quality of life (Marck, Aitken et al., 2020). Other drivers for a reduction in quality of life include the changing dimensions of independent living, relationships and mental health, which can result in reduced social interaction (Ahmad et al., 2018; Yalachkov et al., 2019; Zhang et al., 2020).

1.1.8 Maintaining or improving participation in an active lifestyle

Participation in an active lifestyle is important for well-being, physical and mental health and is a normal part of life for most people (Australian Government Department of Health, 2021; Schuch & Stubbs, 2019). Maintaining participation in an active lifestyle frequently requires a high level of mobility, where high-level mobility is defined as more challenging than independent level walking (Williams et al., 2005). For example, employment may demand speed of movement in the workplace, as well as climbing and negotiating difficult terrain. Playing with children in a parenting role may demand running, chasing and playing outdoor games. Sport and leisure require running, jumping, bounding, climbing and altered terrain negotiation. Individuals with mild MS have indicated that the ability to run and not just walk is important (Kalron et al., 2020), yet running is not commonly targeted with this population. One study has explored running in the MS population with a community-based start-to-run program, whilst outcomes of aerobic capacity, walking ability and fatigue were measured, high-level mobility outcomes were not (Feys et al., 2019).

Investigation of high-level mobility in the early stages of MS is warranted to delay onset or maximise prevention of impairment, activity limitations and participation restrictions. The use of exercise and sport to target high-level mobility as part of an active lifestyle, as a proactive approach to maintaining or improving participation in the early stages of MS, requires investigation.

1.2 Benefits of exercise

Exercise is defined as a subset of physical activity that is planned structured and repetitive with the aim of improving and/or maintaining physical fitness (American College of Sports Medicine [ACSM], 2018). Sport is also a subset of physical activity and is defined as an activity involving physical effort and skill governed by a set of rules (Australian Sport Commission, n.d.). The health benefits of regular exercise or sport for the general population, including individuals with MS, are substantial and consist of improvement in physical function, psychosocial benefits and prevention or management of chronic disease (Australian Government Department of Health, 2021).

1.2.1 Physical benefits

Physical benefits of exercise include improvement in cardiovascular and respiratory function. Cardiovascular changes resulting from regular exercise include a lower resting heart rate and lower systolic/diastolic blood pressure (Nystoriak & Bhatnagar, 2018). Respiratory

changes consist of decreased minute ventilation and increased maximal oxygen uptake (ACSM, 2018). These cardiorespiratory changes enable improved physical fitness (ACSM, 2018).

Improvements in musculoskeletal function are evident with exercise. Increased muscular fitness consists of enhanced muscle power, strength and endurance (Garber et al., 2011). Improvements in bone density and structure are evident with dynamic loading and resistance training (Bolam et al., 2013; Kemmler et al., 2020; Weaver et al., 2016). Collectively, these physical benefits of exercise are important across the lifespan.

1.2.2 Psychosocial benefits

Psychosocial benefits of exercise include enhanced quality of life, improved well-being and decreased anxiety or depression (Bize et al., 2007; Schuch & Stubbs, 2019). Exercise is known to reduce the risk of poor mental health, which is often attributed to psychological and neurophysiological mechanisms (Stubbs et al., 2018). Psychological mechanisms include increased self-efficacy, self-esteem and distraction from stressful stimuli through exercising (Chan et al., 2019). Neurophysiological mechanisms include increased endorphins, elevated body temperatures and subsequent changes in serotonin levels affecting mood (Chan et al., 2019). Exercise sessions of 10–30 minutes' duration have been reported as sufficient to improve mood (Chan et al., 2019). In addition, higher levels of physical activity are associated with greater health-related quality of life (Bize et al., 2007).

1.2.3 Prevention and management of chronic disease

Exercise plays a critical role in the prevention and management of many chronic diseases (Australian Government Department of Health, 2021). The uptake of regular exercise and physical activity is associated with a reduced incidence of cardiovascular disease, diabetes, osteoporosis, stroke and some forms of cancer (ACSM, 2018; Febbraio, 2017; Nystoriak & Bhatnagar, 2018; Pinheiro et al., 2020). Exercise can also reduce cardiovascular mortality by reducing blood pressure, improving insulin sensitivity and improving plasma lipoprotein profile (Nystoriak & Bhatnagar, 2018). The role of exercise in secondary prevention following cardiac events (Salzwedel et al., 2020) or stroke is also well established (Prior & Suskin, 2018). In addition, exercise can be used as an effective means of disease management for chronic conditions such as pulmonary disease (Lacasse et al., 2007), kidney disease (Barcellos et al., 2015) and cancer (Stout et al., 2017).

1.2.4 Exercise and physical activity guidelines

Given the effect of exercise on health and disease prevention, international guidelines exist for the prescription of exercise and physical activity (WHO, 2020). The WHO (2020) recommends that adults aged 18–64 undertake 150–300 minutes of moderate-intensity exercise or 75–150 minutes of vigorous-intensity exercise (or a combination of both) each week. In addition, muscle-strengthening activities should take place two days per week. These guidelines have been widely adopted internationally, including Australia (Australian Government Department of Health, 2021), the United States (Piercy et al., 2018) and the United Kingdom (Department of Health and Social Care, 2020). The guidelines exist to signpost a way for the general population to be sufficiently active and to work towards the prevention and management of non-communicable diseases (WHO, 2020). Alternative guidelines are available for children and adults over the age of 64 (WHO, 2020).

1.3 Exercise and multiple sclerosis

Exercise was once viewed as potentially detrimental to individuals with MS. Exercise is now known to be safe and beneficial in preserving body structures, functions, activity and participation for individuals with MS (Pilutti et al., 2014). Exercise can be promoted by healthcare professionals and there are conceptual models available to assist with the process, however, further education of health professionals may be required to maximise this opportunity (Motl et al., 2018).

1.3.1 Effects of exercise on body structures and functions for individuals with multiple sclerosis

Exercise shows potential as a disease-modifying and as a preventative intervention (Dalgas et al., 2019; Kalb et al., 2020). Exercise can decrease neural apoptosis, neurodegeneration and may stimulate neuroplasticity (Mahalakshmi et al., 2020). The mechanism for the potential neuroprotective effect of exercise on MS is debated and has been explored in several animal studies, however less so in human studies (Benson et al., 2015; Gentile et al., 2019; Pryor et al., 2015; Xie et al., 2019). One proposed mechanism is that exercise may increase the presence of brain-derived neurotrophic factor, which plays a role in the neuroprotection and neuroregeneration of the CNS (Campos et al., 2016; Diechmann et al., 2021; Negaresh et al., 2019). Indeed, increases in cortical thickness have been identified following progressive resistance training programs for individuals with MS, suggestive of neuroregeneration (Kjolhede et al., 2018). Another potential mechanism is that exercise may

normalise the balance between pro- and anti-inflammatory cytokines, reducing the overall level of inflammation (Negaresh et al., 2018).

As previously mentioned in section 1.1.2, there is an increased presence in MS of pro-inflammatory cytokines such as tumour necrosis factor (TNF)-α, interferon (INF)-γ and interleukin (IL)6 (Negaresh et al., 2018; Palle et al., 2017). In contrast, there is a reduction in the presence of anti-inflammatory cytokines such as IL-10 and IL-4 (Lane & Yadav, 2020; Negaresh et al., 2018; Palle et al., 2017). Collectively, this amounts to an inflammatory environment that intensifies the demyelination of the neurons (Lane & Yadav, 2020). Exercise may improve the balance between pro- and anti-inflammatory cytokine levels; however, a review of the small pool of studies investigating this identifies conflicting results (Negaresh et al., 2018). Some of this inconsistency may be a result of small sample sizes, a lack of standardisation in testing and the inclusion of individuals with high-ranging EDSS scores (0–6.5) whereby the capabilities of the participants were hugely variable (Faramarzi et al., 2020; Negaresh et al., 2018). Further research is required in this important field to identify whether exercise affects cytokine levels in MS and, if so, whether it represents a disease-modifying effect.

The timeframe for the introduction of exercise may also have an effect in relation to neuroprotection. Much of the research in exercise to date has focused on individuals with an established disease, which means that exercise interventions in the early stages of the disease have not been sufficiently investigated (Riemenschneider et al., 2018). To explore the neuroprotective capacity and potential primary prevention model, analysis of exercise interventions in the early stages of the disease (where there is minimal or no disability) is required. Early application of disease-modifying medical therapies is effective in reducing disease progression (Ziemssen et al., 2016), and early administration of exercise therapy also warrants investigation as a means to reduce the onset and progression of MS (Riemenschneider et al., 2018).

Exercise is also known to improve impairments of body function associated with MS and is supported by several meta-analyses and network meta-analyses (Harrison et al., 2021; Pearson et al., 2015; Platta et al., 2016; Razazian et al., 2020; Taul-Madsen et al., 2021). Improvements in strength and aerobic capacity have been established following interventions such as progressive resistance training and aerobic exercise (Motl et al., 2017; Taul-Madsen et al., 2021). Balance, gait and functional training programs provide improvements in balance

(Gunn et al., 2015). Significant reductions in fatigue are also evident following exercise interventions for individuals with MS (Harrison et al., 2021; Razazian et al., 2020). While this symptomatic intervention (tertiary prevention) is important, the possibility of exercise as a disease-modifying intervention (secondary prevention) and a potentially preventative intervention (primary prevention) is an exciting prospect that requires evaluation (Dalgas et al., 2019; Kalb et al., 2020). Exploration of the cytokine response to exercise is one such option.

1.3.2 Effects of exercise on activity for individuals with multiple sclerosis

The effect of exercise on the activity of individuals with MS has predominantly focused on walking (Latimer-Cheung, Pilutti et al., 2013; Motl et al., 2017). To date, exercise has shown small improvements in walking, including increased endurance and distance (Learmonth et al., 2016; Pearson et al., 2015). Further investigation is required into the exercise modalities that enable the greatest change in walking ability (Callesen et al., 2019). Changes in high-level mobility such as running and jumping appear to be largely unreported. Hence, changes in capacity for high-level mobility and its effect on participation in exercise, sport and leisure activities requires further investigation, particularly in the early stages of the disease.

1.3.3 Effects of exercise on participation for individuals with multiple sclerosis

Participation restrictions for individuals with MS are closely associated with a number of variables, including fatigue, pain, depression and increased dependency in activities of daily living (Conradsson et al., 2021; Yorkston et al., 2012). Exercise can have a positive effect on these variables (Demaneuf et al., 2019; Motl & Sandroff, 2020) and, as such, may influence participation. Participation is important for quality of life, which is compromised in individuals with MS (Motl et al., 2020). Exercise interventions have been shown to improve quality of life and participation for individuals with and without neurodegenerative disease, including MS (Bize et al., 2007; Dauwan et al., 2019; Edwards et al., 2021; Motl et al., 2017). While improvement is welcome, it may be more prudent to examine the initiation of early exercise interventions to prevent participation restrictions.

1.4 Towards achieving participation in exercise and sport

1.4.1 Facing the barriers

Despite the known benefits of exercise, participation in exercise is low for individuals with MS compared with those without the disease (Marck, Learmonth et al., 2020).

Participation in exercise is influenced by both environmental and personal factors, as illustrated by the ICF (WHO, 2001) (see Figure 1). These contextual factors are often viewed as modifiable determinants of participation in exercise and sport for individuals with MS (Learmonth & Motl, 2016; Riemann-Lorenz et al., 2019). Environmental factors include access to facilities and healthcare professionals (Learmonth et al., 2017; Learmonth et al., 2020). Personal factors include disability level, exercise history, motivation and self-efficacy for individuals with MS (Riemann-Lorenz et al., 2019; Streber et al., 2016).

Health professionals have a role to play in addressing some of these barriers and are ideally placed to support individuals with MS to commence or maintain participation in exercise or sport (Motl et al., 2018). Mechanisms of support include behaviour change techniques (BCTs), which have been used successfully with the general population (Schwartz et al., 2019) to support commencement and maintenance of exercise participation. Behaviour change theories such as social cognitive theory (Bandura, 2004) and the transtheoretical model of change (Prochaska et al., 2009) explain health behaviour, underpin BCTs and are commonly used in healthcare (Davis et al., 2015). Recently, social cognitive theory–based techniques have been shown to improve exercise participation for individuals with MS (e.g. via goal setting and addressing self-efficacy) (Motl et al., 2018). The logistics of when and how BCTs are introduced and integrated into the management of MS requires further investigation to optimise support to engage with and sustain exercise participation (Donkers et al., 2020; Kim et al., 2020; Sangelaji et al., 2016).

Behaviour change techniques may be an important intervention for some; however, for those already participating in exercise or sport, health professional support may be required to address individual concerns about exercise participation in relation to MS (e.g. fatigue, harm, exercise progression) (Kayes et al., 2011; Learmonth et al., 2020). Access to health professional support is often limited because of funding or location (Learmonth et al., 2020). Therefore, there is a need to identify efficient and effective methods to provide this support for individuals with MS (Donkers et al., 2020).

1.4.2 Implementing guidelines

To encourage participation in exercise, physical activity guidelines for individuals with MS (mild to moderate disability) were developed in 2013 as a tool to guide and improve exercise prescription (Latimer-Cheung, Martin Ginis et al., 2013). These guidelines recommended a minimum of 30 minutes of moderate-intensity aerobic activity twice per

week and resistance training twice per week. While these guidelines provided an important minimum level for individuals with MS, the level proposed was below the WHO physical activity guidelines for adults to prevent chronic disease (WHO, 2020).

In 2019, new MS exercise training guidelines were developed that provided a more detailed prescription and a scaling up of exercise to include strengthening, general aerobic exercise and advanced aerobic exercise guidelines (Kim et al., 2019). The inclusion of advanced aerobic exercise promotes a higher level of activity—five days a week of aerobic exercise with a duration approaching 40 minutes and intensity approaching 15 on the 20-point rating of perceived exertion (RPE) scale (Kim et al., 2019). Support to push beyond the general or advanced exercise guidelines for MS (Kim et al., 2019) may be required for individuals with MS to reach their full potential in sport and exercise, yet exploration of this is largely unreported. Efficient and effective methods to provide this support for individuals with MS are required (Donkers et al., 2020). Telehealth may provide an opportunity to do this by providing care remotely, thereby potentially addressing issues with funding and service provision; however, this requires further investigation (Learmonth et al., 2020; Xiang & Bernard, 2021).

Mechanisms to best support individuals with MS to participate in exercise and sport are required. These mechanisms need to assist with engagement, maintenance and suitable progression of exercise participation, while supporting concerns that individuals with MS may have about undertaking sport and exercise.

1.4.3 Person-centred approach

To engage individuals with MS in exercise and sport, a person-centred approach may be required. Such an approach would focus on the exercise or sport that the individual is interested in, that is suitably challenging and that is appropriate for their age and stage in life. To date, clinical trials in exercise and MS have typically focused on targeting body functions and structures (see Figure 1), such as strength and cardiovascular fitness, rather than participation in sport and exercise. Interventions have commonly consisted of progressive resistance training and aerobic exercise programs that are often seated (e.g. cycle ergometry, gym resistance equipment) (Dennett et al., 2020) rather than outdoor running or team sports that demand a high level of mobility. These interventions may not be in line with the individual's goals or interests.

The recently developed advanced aerobic exercise guidelines (Kim et al., 2019) introduce more challenging exercise options for individuals with MS including, running and road cycling. However, the evidence to support these modes was based on treadmill or cycle ergometry outcomes rather than outdoor running or cycling (Kim et al., 2019). That noted, the inclusion of different exercise modes that demand a high level of mobility demonstrates a broadening in the approach to exercise for individuals with MS. Exploration of different exercise and sport options is required to widen the possibilities for individuals with MS and facilitate a more person-centred approach to participation in exercise and sport. Given the age of onset for this population and the longevity of the disease, the importance of exploring ways to enable active participation in exercise and sport for individuals with MS should not be understated.

1.5 Statement of issue

With the onset of MS occurring at the age of 20–40 years (Ahmad et al., 2018), individuals with MS are potentially living an active lifestyle that demands participation in sport, exercise, employment and family play. With sport, this may include engaging in team activities that require a high level of mobility, such as running or outdoor cycling. However, the effect of exercise on a high level of mobility for individuals with MS and other neurodegenerative diseases is largely unexplored. Therefore, methods are required to explore maintaining or improving a high level of mobility as part of active participation in exercise and sport that fulfills potential and is person-centred.

Exercise is beneficial for individuals with MS, with known gains in strength, aerobic capacity, balance and mental health (Marck, Learmonth et al., 2020; Motl et al., 2020). Importantly, early intervention with exercise may be neuroprotective—the potential neuroprotective mechanism requires further exploration. Effective methods of supporting, progressing and sustaining participation in suitably challenging exercise and sport are required at an early stage in the disease process. Understanding the experience of participating in sport and exercise may assist in finding mechanisms for health professionals to best support individuals with MS to exercise. Novel ways are required to initiate and progress exercise or sport that will enable individuals with MS to participate in an active, person-centred lifestyle, for as long as possible.

1.6 Research aim and objectives

The aim of this research was to develop an exercise participation program to optimise exercise participation by individuals with MS with minimal disability. The research objectives were to:

1. review the literature on the effect of exercise on high-level mobility (i.e. mobility more advanced than independent level walking) in individuals with neurodegenerative disease including MS
2. explore the experience of participation in sport and exercise for individuals with MS in relation to:
    i. key factors that influence participation in sport and exercise
    ii. recommendations made by individuals with MS to enable or enhance their participation in sport and exercise for as long as possible
3. develop an exercise participation program for individuals with MS with minimal disability, underpinned by their preferences and the scientific literature
4. test the feasibility of the newly developed exercise participation program for individuals with MS with minimal disability
5. explore the experience of participation in the exercise participation program, its acceptability and recommendations for improvement from the perspective of individuals with MS.

1.7 Thesis structure

Chapter 1 of this thesis outlines the need to explore participation in exercise or sport for individuals in the early stages of MS to maintain or improve participation in an active lifestyle for as long as possible. Chapter 2 explores what is already known about participation in exercise and sport for individuals with MS through a systematic review of the literature on the effect of exercise on high-level mobility in individuals with neurodegenerative disease including MS. Chapter 3 investigates the experience of participating in sport and exercise from the perspective of individuals with MS in a qualitative study. Based on the findings of the scientific literature in Chapter 2 and the perspectives of individuals with MS in Chapter 3, Chapter 4 contains a research protocol for a flexible exercise participation program (FEPP) for individuals with MS with minimal disability to support them to find the right balance with participation in exercise and sport. Chapter 5 reports on the feasibility of the FEPP, and Chapter 6 reports on the acceptability of the FEPP from the perspective of the participants.

The thesis concludes with Chapter 7, a discussion of the findings and implications for future research. A concept model of the thesis is detailed in Figure 2.

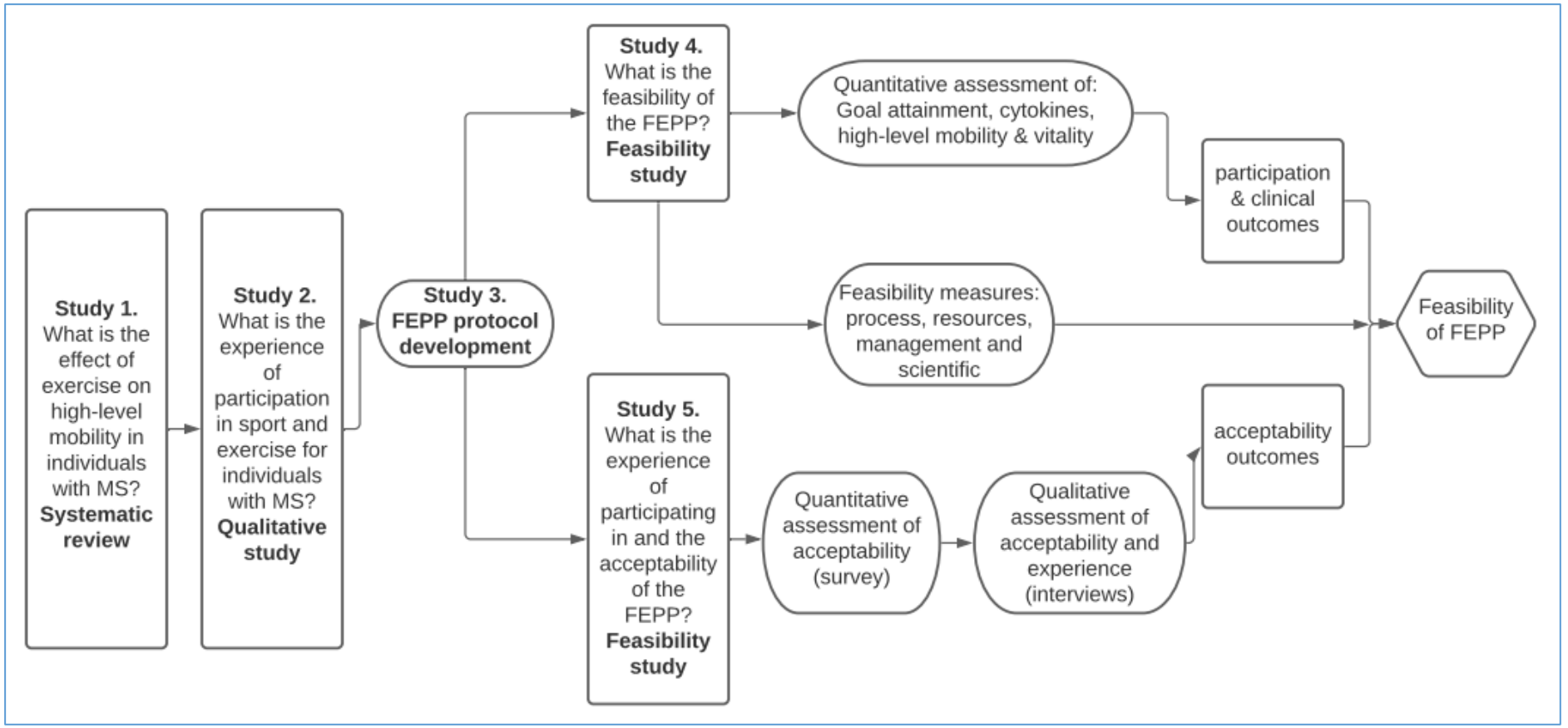
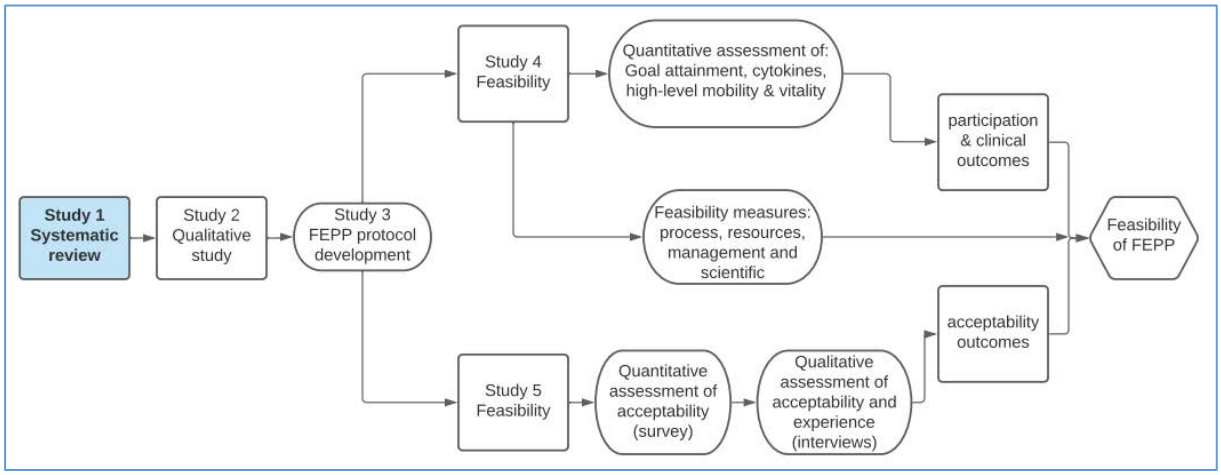


Figure 2. Thesis concept model

Key: FEPP = Flexible Exercise Participation Program

Chapter 2: The Effect of Exercise on High-Level Mobility in Individuals with Neurodegenerative Disease



2.1 Overview of the study

Chapter 1 provided a rationale for why participation in an active lifestyle requires more than just walking; a higher level of mobility is required, such as running or jumping. To that end, exercise options that have been offered to individuals with MS required exploration to identify whether they include high-level activities and what effect each option may have on high-level mobility. Given that MS is a neurodegenerative disease, it was pertinent to broadly explore exercise interventions targeted at individuals with different neurodegenerative diseases because of the overlap in pathophysiology and clinical presentation (Dauwan et al., 2019).

The aim of the systematic review in this chapter was to investigate the effect of exercise on high-level mobility (i.e. mobility more advanced than independent level walking) in individuals with neurodegenerative disease. A systematic review was required to identify interventions used to address high-level mobility for a range of neurodegenerative diseases, recognising that some interventions could be applicable to MS and could subsequently guide the intervention protocol to be developed as part this research.

2.2 Publication—systematic review

This systematic review has been published as:

Smith, M., Barker, R., Williams, G., Carr, J., & Gunnarsson, R. (2020). The effect of exercise on high-level mobility in individuals with neurodegenerative disease: A systematic literature review. *Physiotherapy*, *106*, 174–193. https://doi.org/10.1016/j.physio.2019.04.003

This publication is included below with the addition of an updated search to include relevant literature published between 1 May 2018 and 31 August 2021. Permission to reproduce this paper was provided by the publisher (Elsevier). The published paper is available online at https://www.sciencedirect.com/science/article/pii/S0031940618301639.

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Review

The effect of exercise on high-level mobility in individuals with neurodegenerative disease: a systematic literature review

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Abstract

Objective To investigate the effect of exercise on high-level mobility (i.e. mobility more advanced than independent level walking) in individuals with neurodegenerative disease.

Data sources A systematic literature search was conducted in Medline, CINAHL, Scopus, SportDiscus and PEDro.

Study selection Randomised controlled trials of exercise interventions for individuals with neurodegenerative disease, with an outcome measure that contained high-level mobility items were included. High-level mobility items included running, jumping, bounding, stair climbing and backward walking. Outcome measures with high-level mobility items include the High Level Mobility Assessment Tool (HiMAT); Dynamic Gait Index; Rivermead Mobility Index (RMI) or modified RMI; Functional Gait Assessment and the Functional Ambulation Category.

Study appraisal Quality was evaluated with the Cochrane Risk of Bias Tool.

Results Twenty-four studies with predominantly moderate to low risk of bias met the review criteria. High-level mobility items were included within primary outcome measures for only two studies and secondary outcome measures for 22 studies. Eight types of exercise interventions were investigated within which high-level mobility tasks were not commonly included. In the absence of outcome measures or interventions focused on high-level mobility, findings suggest some benefit from treadmill training for individuals with multiple sclerosis or Parkinson's disease. Progressive resistance training for individuals with multiple sclerosis may also be beneficial. With few studies on other neurodegenerative diseases, further inferences cannot be made.

Conclusion Future studies need to specifically target high-level mobility in the early stages of neurodegenerative disease and determine the impact of high-level mobility interventions on community participation and maintenance of an active lifestyle.

Systematic review registration number PROSPERO register for systematic reviews (registration number: CRD42016050362).

Keywords: Neurodegenerative; Multiple sclerosis; Parkinson's disease; High-level mobility; Exercise; Systematic review

Introduction

High-level mobility can be defined as mobility more advanced than independent level walking [1]. High-level mobility can be lost by individuals in the early stages of a neurodegenerative disease, such as multiple sclerosis (MS), Parkinson's (PD) and Huntington's disease (HD), as progressive dysfunction of the neurons in the central nervous

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system occurs [2]. Mobility typically relates to the ability to stand up and walk about for day-to-day function. High-level mobility is more advanced and includes running, jumping, leaping, bounding, backward walking and stair climbing. Participation in active sports, employment of a physical nature and engagement with young family members typically require high-level mobility. Accordingly, older individuals approaching retirement regularly seek a lifestyle with active leisure pursuits that demand high-level mobility [3]. Hence, for individuals with neurodegenerative disease, maintaining high-level mobility for as long as possible is important for participation and quality of life [4–7].

Deterioration in mobility due to neurodegenerative disease occurs as a result of different pathological processes across the spectrum of the diseases e.g. basal ganglia dysfunction in PD and HD; interruption of neural transmission in MS and cerebellar degeneration in cerebellar ataxias [8–10]. These pathological processes lead to primary and secondary impairments in motor control, balance, coordination and strength [11–13] leading to a decline in mobility. Although age of onset, physical impairments and disease progression vary across the neurodegenerative diseases, the commonality is that these individuals are typically active and mobile at diagnosis. The challenge therefore, is to maintain high-level mobility for as long as possible to maintain participation and to maintain an active lifestyle [14,15] to avoid progressive reduction in physical activity and associated risk of chronic lifestyle diseases such as cardiovascular disease, diabetes and obesity [16,17].

To date, exercise interventions designed for individuals with neurodegenerative diseases have been shown to increase strength, aerobic capacity and balance [18,19]. In addition, recent research findings suggest that exercise can prevent or reduce disease progression for individuals with some neurodegenerative diseases [11,20]. However, the impact of exercise interventions on basic mobility such as walking speed and stride length is unclear due to conflicting research findings [18,19,21–23]. Interestingly, little consideration has been given to high-level mobility nor its impact on community participation and physical activity levels. Consequently, the purpose of this systematic review was to investigate the effect of exercise interventions on high-level mobility in individuals with neurodegenerative disease.

Methodology

Protocol and registration

A systematic review was conducted in accordance with the PRISMA statement [24] and was registered on the PROSPERO register for systematic reviews (registration number: CRD42016050362).

Eligibility criteria

Randomised controlled trials (RCTs) exploring exercise interventions and their effect on high-level mobility in adults (≥18 years of age) with a neurodegenerative disease were included in this review. Studies that utilised an objective measure of mobility that contained high-level mobility items (i.e. running, jumping, leaping, bounding, backwards walking or stair climbing) analysed either as a single item or as part of a composite outcome measure, were included. Composite outcome measures usually combine performance on a range of mobility tasks to provide an overall score. Composite outcome measures, such as the High Level Mobility Assessment Tool (HiMAT) [25]; Dynamic Gait Index (DGI) [26]; Rivermead Mobility Index (RMI) [27]; modified RMI (mRMI) [28]; Functional Gait Assessment (FGA) [29] or the Functional Ambulation Category (FAC) [30] were included if they contained any high-level mobility items.

Studies were excluded if they were not written in English, involved participants with co-existing neurological diseases such as stroke, or if they only included multi-dimensional composite outcome measures in which the primary focus was not mobility (e.g. Functional Independence Measure).

Data sources

Medline, CINAHL, Scopus, SportDiscus and PEDro databases were searched from the commencement period of each database to April 2018. Search terms used, keywords, MeSH terms and truncation symbols were applied as appropriate for each database (online supplementary information). Boolean operators were specifically used to connect a range of degenerative disease types and outcome measures containing high-level mobility items.

Study selection

Database searches were conducted by one reviewer (MS). Two reviewers (MS and JC) independently screened titles and abstracts, reviewed full text articles and decided if a study was to be included. Disagreements were resolved by consensus with a third reviewer if required (RB). Reference lists were screened and a citation search conducted on eligible full-text articles.

Data collection and assessment of risk of bias

Data extracted included participant diagnosis; participant characteristics; intervention; outcome measures and results. Information regarding risk of bias was independently collected using the Cochrane risk of bias tool [31] with data extracted on six domains of bias: selection bias; performance bias; detection bias; attrition bias; reporting bias and other bias. The Cochrane risk of bias tool allowed identification of high, low or unclear bias in each of these domains [31]. Where risk of bias was high in three or more domains, the

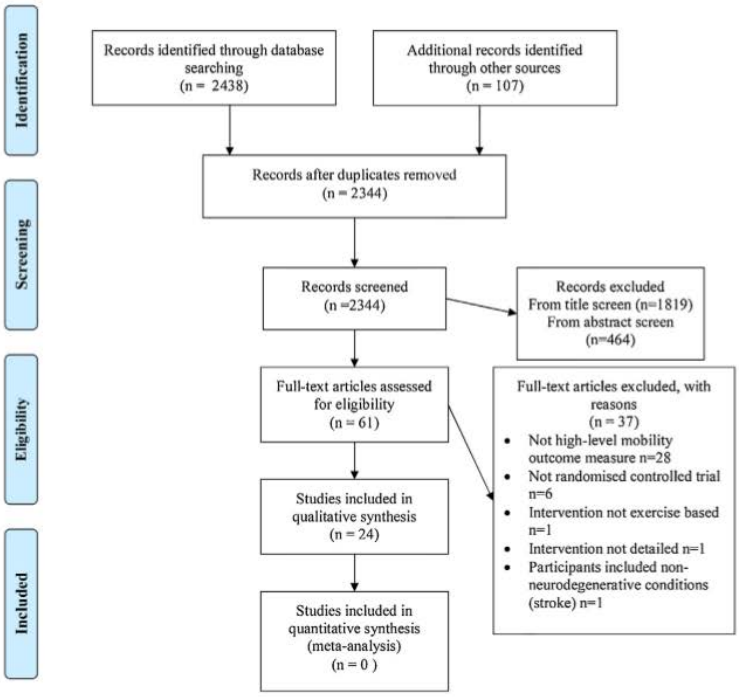

Fig. 1. PRISMA flow diagram [24].

study was classified as high risk of bias. Conversely, low risk of bias was classified by low risk of bias in all domains. The remainder of studies falling between these classifications were of moderate risk of bias. Disagreements or discrepancies were discussed and resolved by consensus (MS and JC) with a third reviewer if required (RB).

Synthesis of study findings

Studies included in the systematic review were divided into subsets according to disease type. Common themes concerning the intervention were identified across the different neurodegenerative diseases and explored. Use of outcome measures containing high-level mobility items as a primary or secondary measure within each study was identified. Statistical significance for each outcome measure was reported and a meta-analysis of suitable data planned.

Results

Study selection

The search resulted in 2344 studies following removal of duplicates (Fig. 1). After abstract screening, 61 studies were deemed eligible for full text review, 37 of which were excluded with a total of 24 studies included in this review (Table 1). A meta-analysis of the data was deemed unsuitable due to the heterogeneity between studies in terms of disease severity, intervention and outcome measures utilised. Where similar outcome measures were used, the interventions varied [32–35] conversely, where interventions were similar the outcome measures varied [36–38].

Study population

A total of 909 participants were included in the review with sample sizes for individual studies ranging from 10 to 110 participants with an age range of 23–89 years. Fifty-nine percent of participants were female. Across the 24 studies, 13 studies reported exercise interventions for individuals with MS (mean age 46; range 23–69 years) [32–35,39–47], nine for PD (mean age 68; range 48–89 years) [36–38,48–53], one for HD (mean age 51; range 23–75 years) [54] and one for degenerative cerebellar disease (DCD) (mean age 63; range 40–82 years) [55].

Studies on MS included participants with different types of MS i.e. relapse-remitting MS (RRMS), secondary progressive MS (SPMS) or primary progressive MS (PPMS). Mean disease duration ranged from 4.5 to 18 years for participants with MS, 5.8–11 years for participants with PD, 1–30 years for the participants with DCD and ≤14 years for participants with HD.

Disease severity varied across studies from minimal to severe however all studies included participants with moderate disease severity (Table 1). Moderate disease

Table 1
Summary of included randomised controlled trials.

Author/Year	*n*	Disease type/ chronicity	Intervention	Intervention duration	Follow up	High-level mobility outcome measure	Between group comparison	Outcome
Parkinson's Disease								
Cakit et al, 2007 [36]	54	Hoehn & Yahr 2-3. Mean duration years (SD) 5.6 (2.9)	EG: treadmill $n=27$ CG: no intervention $n=27$	8 weeks	No follow up	**DGI (score)**	Mann–Whitney U-test	Significant between group improvement in favour of EG $p<0.01$
Duncan & Earhart, 2012 [48]	62	Hoehn & Yahr (SD) EG = 2.6 (0.1) CG = 2.5 (0.1) Mean duration years (SE) EG = 5.8 (1.1) CG = 7.0 (1.0)	EG: Argentine tango $n=32$ CG: no intervention $n=30$	12 months	No follow up	**GAITRite. backward walking velocity (m/s)**	Repeated measures ANOVA with group and time. Tukey-Kramer between groups at given time	No significant between group differences $p>0.05$
Duncan & Earhart, 2014 [49]	10	Hoehn & Yahr 2-3. Mean duration years (SE) EG = 6.6 (7.5) CG = 11 (3.9)	EG: Argentine tango $n=5$ CG: no intervention $n=5$	24 months	No follow up	**GAITRite. backward walking velocity (m/s)**	Repeated measures ANOVA with group and time Tukey-Kramer between groups at given time	No significant main effects or between group differences $p>0.05$
Hackney & Earhart, 2008 [50]	33	Hoehn & Yahr 1.5-3. Mean duration years (SE) EG = 8.7 (4.7) CG = 5.5 (3.3)	EG: Tai Chi $n=17$ CG: no intervention $n=16$	13 weeks	No follow up	**GAITRite. backward walking velocity (m/s) backward stride length (m)**	Independent t-tests Mann–Whitney Rank sum	**Backward velocity** Non-significant between group difference in $p=0.06$ **Backward stride length** Non-significant between group difference $p=0.08$
Hackney & Earhart, 2009 [51]	58	Hoehn & Yahr 1-3. Mean duration years (SD) EG1 = 9.2 (1.5) EG2 = 6.9 (1.3) CG = 5.9 (1.0)	EG1: waltz/foxtrot $n=19$ EG2: tango $n=19$ CG: no intervention $n=20$	13 weeks	No follow up	**GAITRite. backward walking velocity (m/s) backward stride length (m)**	Repeated measures ANOVA with group and time. Holm-Sidak post-hoc tests	**Backward velocity** No significant between group difference $p>0.05$ **Backward stride length** Significant between group difference $p=0.05$: EG1 & EG2 increased backward stride length, CG reduced backward stride length. Time $p=0.008$

Table 1 (*Continued*)

Author/Year	*n*	Disease type/ chronicity	Intervention	Intervention duration	Follow up	High-level mobility outcome measure	Between group comparison	Outcome
Kurtais et al, 2008 [37]	27	Hoehn & Yahr (SD) EG = 2.5 (0.7) CG = 2.2 (0.8) Mean duration years (SD) EG = 5.3 (0.8) CG = 5.4 (1.2)	EG: tread-mill/flexibility $n = 13$ CG: flexibility exercises $n = 14$	6 weeks	No follow up	**Ascending/ descending stairs, (seconds)**	Mann-Whitney U test	Significant between group improvement in favour of EG $p \leq 0.05$
Landers et al, 2016 [52]	49	Hoehn & Yahr scale range 1.5-4	EG1: balance external focus $n = 12$ EG2: balance internal focus $n = 13$ EG3: balance no attentional focus $n = 12$ CG: no intervention $n = 12$	4 weeks	2 and 8 weeks post intervention	**DGI (score)**	Repeated measures ANOVA with group and time. Secondary analysis of combined EG (EG1, EG2, EG3) compared to CG	No statistically significant between group differences $p = 0.40$ No statistically significant between group difference of combined EG (EG1, EG2, EG3) and control $p = 0.6$
Liao et al, 2015 [38]	36	Hoehn & Yahr (SD) EG1 = 2.0 (0.7) EG2 = 2.0 (0.8) CG = 1.9 (0.8) Mean duration years (SD) EG1 = 7.9 (2.7) EG2 = 6.9 (2.8) CG = 6.4 (3.0)	EG1: Wii Fit & treadmill $n = 12$ EG2: exercise & treadmill $n = 12$ CG: falls prevention education $n = 12$	6 weeks	30 days post intervention	**FGA (score)**	One-way ANOVA Tukey post hoc test	Statistically significant between improvement for EG1 & EG2 vs CG $p < 0.05$ No statistically significant difference between EG1 & EG2 $p > 0.05$
Song et al, 2018 [53]	60	Hoen & Yahr NR Mean duration years (SD) EG = 7 (4) CG = 9 (6)	EG: video dance game $n = 31$ CG: no intervention $n = 29$	12 weeks	No follow-up	**FGA (score)**	repeated measures ANOVA	No statistically significant between group differences $p = 0.52$
Multiple Sclerosis								
Cakit et al, 2010 [32]	45	RRMS SPMS Mean duration years (SD) 7.7 (4.1) EDSS ≤ 6	EG1: cycling PRT & exercise $n = 15$ EG2: exercise $n = 15$ CG: no intervention $n = 15$	8 weeks	No follow up	**DGI (score)**	One-way ANOVA Tukey post hoc test	Significant between group difference in favour of EG1: EG1-EG2 $p < 0.001$ EG2-CG NS EG1-CG $p < 0.01$).

Table 1 (*Continued*)

Author/Year	*n*	Disease type/ chronicity	Intervention	Intervention duration	Follow up	High-level mobility outcome measure	Between group comparison	Outcome
Cattaneo et al, 2007 [33]	50	RRMS; SPMS OR PPMS. Mean duration years (SD) 13.8 (8.1) EDSS NR	EG 1: balance rehab motor/sensory $n=23$; EG 2: balance rehab motor $n=12$ CG: conventional non-balance $n=15$.	3 weeks	No follow up	**DGI (score)**	One-way ANOVA Newman-Keuls post hoc test	Statistically significant between group differences in favour of EG1 $p=0.04$ compared to CG. No significant between group difference for EG1 vs EG2 $p=0.08$
Dalgas et al, 2009 [39]	38	RRMS. Mean duration years: EG = 6.6 CG = 8.1 EDSS range 3.0–5.5	EG: PRT lower limb $n=19$ CG: no intervention $n=19$	12 weeks	12 weeks post intervention	**Ascending stair climbing test (seconds)**	Unpaired t-test Follow-up: paired t-test	Significant between group difference in favour of EG $p<0.05$, maintained at follow-up
Hayes et al, 2011 [40]	22	MS. Mean duration years (SD) 2.2 (8.1) EDSS mean (SD) 5.24 (0.96)	EG1: eccentric resistance training plus standard exercise $n=11$ CG: standard exercise $n=11$	12 weeks	No follow up	**Stair ascent Stair descent (seconds)**	Repeated measures ANOVA with group and time.	Significant between group difference, CG improved, EG did not $p=0.02$
Kjolhede et al, 2015 [47]	35	RRMS. Median duration years (range): 5 (0.5–28) EDSS range 2–4	EG: PRT upper and lower limbs CG: no intervention	24 weeks	48 weeks	**Ascending stair climbing test (seconds)**	Two way repeated measures ANOVA	Significant between group difference in favour of EG $p<0.01$, maintained at follow-up
Lord et al, 1998 [41]	23	Progressive or RRMS. Mean duration years (SD) EG1 = 14 (8.1) EG2 = 18.3 (7.0) EDSS NR	EG1: task oriented $n=11$ EG2: facilitation $n=12$	5–7 weeks	No follow up	**Rivermead Mobility Index (score)**	Mann–Whitney U test Student's unrelated t-test	Significant improvement in EG1 & EG2 $p<0.05$. No significant difference between groups $p>0.05$
Nilsagard et al, 2013 [34]	84	RRMS , SPMS; PPMS Mean duration years (SD) EG = 12.5 (8.0) CG 12.2 (9.2) EDSS NR	EG: Wii Fit balance $n=42$ CG: no intervention $n=42$	6-7 weeks	No follow up	**DGI (score)**	Mann–Whitney U test	No statistically significant between group difference $p=0.21$ ES=0.34
Pfalzer & Fry, 2011 [42]	46	RRMS, SPMS, PPMS EDSS range 2–6.5	EG: inspiratory muscle training $n=23$ CG: no intervention $n=23$	10 weeks	No follow up	**Functional stair test (seconds)**	Repeated measures ANOVA	No statistically significant between group differences $p=0.06$, observed power 0.46

Table 1 (*Continued*)

Author/Year	*n*	Disease type/ chronicity	Intervention	Intervention duration	Follow up	High-level mobility outcome measure	Between group comparison	Outcome
Salhofer-Polanyi, 2013 [43]	21	RRMS, SPMS; PPMS Mean duration years (SD) EG = 17.6 (10.0) CG = 15.9 (11.9) EDSS range 4–6.5	EG: task specific training, balance & strength $n = 10$ CG: no intervention $n = 9$ 2 exclusions: group allocation not provided	3 weeks	No follow up	**Rivermead mobility index (score)**	Mann–Whitney U test	No statistically significant between group differences $p = 0.35$
Samaei, 2016 [44]	34	RRMS Mean duration years (SD) EG1 = 4.8 (3.3) EG2 = 4.5 (2.8) EDSS NR	EG1: downhill treadmill $n = 17$ EG2: uphill treadmill $n = 17$	4 weeks	4 weeks post intervention	**mRMI (score)**	Repeated measures ANOVA Tukey post hoc test	Significant improvement in EG1 $p = 0.009$ & EG2 $p = 0.038$. Between groups EG1 improved more than EG2 at post intervention $p = 0.005$ and at follow-up $p = 0.009$
Straudi, 2014 [35]	24	RRMS, SPMS; PPMS Mean duration years (SD) EG = 12.2 (6.9) CG 18.25 (9.46) EDSS Mean (SD) 4.9 (0.5)	EG: task specific training & home exercise $n = 12$ CG: no intervention $n = 12$	Intervention i) 3 weeks. Intervention ii) 3 months	post intervention i) 3 month follow up	**DGI (score)**	Post hoc analysis only performed if significant within group differences	No significant change over time $p > 0.05$ for either group
Tarakci et al, 2013 [46]	110	RRMS, SPMS; PPMS Mean duration years (SD) EG = 9 (4.7) CG = 8.4 (5.4) EDSS range 2–6.5	EG: group task specific training, balance and strength CG: no intervention	12 weeks	no follow up	**Ascending stair climbing test**[a] **(seconds)**	Student's t test	statistically significant between group difference in favour of EG $p < 0.05$
Wiles, 2001 [45]	42	MS Mean duration years (SD) 12.3 (8.4) EDSS range 0–10	42 patients per group (crossover trial) EG1: home based task-oriented approach EG2: hospital outpatient – facilitation techniques CG: no intervention	8 weeks	No follow up	**Rivermead mobility index**[a] **(score)**	Three-way ANCOVA 90% power for 1 unit difference at $\alpha = 0.05$	Statistically significant between group difference: EG1 & EG2 improved compared to CG $p < 0.001$. No statistically significant between group difference for E1 & E2 $p = 0.77$

Table 1 (*Continued*)

Author/Year	*n*	Disease type/ chronicity	Intervention	Intervention duration	Follow up	High-level mobility outcome measure	Between group comparison	Outcome
Huntington's Disease								
Kloos et al, 2013 [54]	24	UHDRS motor score: ≤ 42 *n* = 10 UHDRS motor score >42 *n* = 8 Mean duration years (SD) 5 (4)	EG: video dance game *n* = 13 CG: sedentary handheld game *n* = 11	6 weeks	No follow up	**GAITRite. backward walking velocity (m/s)** **backward stride length (m)** **backward double support percentage** (%)	linear regressions model	Statistically significant between group change in backward double support percentage, EG improved compared to CG $p = 0.01$. No statistically significant between group difference for backward stride length $p = 0.4$ or velocity $p = 0.8$
Degenerative cerebellar ataxia								
Miyai et al, 2012 [55]	42	spinocerebellar ataxia: SCA type 6 *n* = 20 SCA type 31 *n* = 6 idiopathic cerebellar ataxia *n* = 16. Mean duration years (SE) 9.8 (1.0) SARA mean (SE) EG:12.2 (0.7) CG: 11.0 (0.8)	EG: task specific training, balance and strength *n* = 21 CG: delayed entry *n* = 21	4 weeks	4, 12 & 24 weeks post intervention	**FAC(score)**	Wilcoxon rank-sum test	Statistically significant between group difference in favour of EG after 4 weeks $p < 0.05$, maintained at 12 week follow-up $p < 0.01$

KEY: ANOVA = analysis of variance; ANCOVA = analysis of covariance; CG = control group; DGI = dynamic gait index; EDSS = Expanded Disability Status Scale; EG = exercise group; FAC = functional ambulation category; FGA = functional gait assessment; m = metres; mRMI = modified Rivermead mobility index; m/s = metres per second; n = number of participants; NR = not reported; NS = non-significant; PPMS = primary progressive multiple sclerosis; PRT = progressive resistance training; RRMS = relapse remitting multiple sclerosis; SARA = Scale for Rating and Assessment of Ataxia; SCA = spinocerebellar ataxia; SD = standard deviation; SE = standard error; SPMS = secondary progressive multiple sclerosis; UHDRS = Unified Huntington's Disease Rating Scale.

[a] Primary outcome measure.

severity can be defined as an Expanded Disability Status Scale (EDSS) ≥ 3 for MS; Hoehn and Yahr stage 2–3 for PD; Unified Huntington's Disease Rating Scale (UHDRS) motor > 42; Scale for Assessment and Rating of Ataxia (SARA) ≤ 11.5 for DCD.

Quality assessment

Methodological quality of the included studies varied with three studies demonstrating a low risk of bias in all categories of the Cochrane risk of bias tool (Fig. 2) [44,46,55]. Most studies were classified as having a moderate risk of bias. High risk of bias was evident in one study [54]. The most common issue was attrition bias, which was evident in ten studies. Only ten of the 24 studies reported a power calculation to inform sample size [38–40,45–48,52,53,55]. Two studies failed to use adequate randomization and 14 studies had either unclear allocation concealment or no concealment. One study evaluating dance in PD [49] was a subset of a larger trial [48]. Lowest risk of bias was evident in MS studies, which supported use of treadmill training and task specific training [44,46]. The only study on individuals with DCD [55] also demonstrated low risk of bias.

Outcome measures

Outcome measures designed specifically to assess high-level mobility e.g. the High Level Mobility Assessment Tool (HiMAT) [25], were not used in any of the included studies. Only two studies used a primary outcome measure that contained items of high-level mobility, one of which used timed stair ascent as part of a battery of measures [46], and the other a composite measure of mobility that included a high-level mobility item (Rivermead Mobility Index (RMI)) [45]. In the remaining 22 studies, secondary outcome measures that included high-level mobility items were either single-item measures or composite measures with a ceiling effect for high-level mobility items [56,57]. Single item measures included timed stair ascent/descent in five studies [37,39,40,42,47] and backward walking in five studies [48–51,54]. Composite measures of mobility were used in 12 studies, six of which used the Dynamic Gait Index (DGI) [32–36,52], three used the Rivermead Mobility Index (RMI) or modified RMI (mRMI) [41,43,44], two used the Functional Gait Assessment (FGA) [38,53] and one used the Functional Ambulation Category (FAC) [55]. Outcome measures were recorded at baseline and post intervention in all studies and at follow up assessments in seven studies [35,38,39,44,47,52,55] with a follow up period ranging from 4 to 48 weeks.

Fifteen studies compared an experimental group (EG) with a control group (CG) [34–37,39,40,42,43,46–50,53,55]. Six studies compared two experimental groups (EG1, EG2) with a control group [32,33,38,45,51,52] and three studies compared two different experimental groups (Table 1) [41,44,54].

Intervention types

Eight different intervention types in total were identified: task specific training, progressive resistance training, treadmill training, dance, video exercise gaming, balance rehabilitation, tai chi and inspiratory muscle training (Tables 1 and 2). Only nine of the 24 studies included high-level mobility tasks within their intervention and these tasks consisted of stair climbing [35,41,45], plyometrics [32] or dance [48,49,51,53,54].

Duration of intervention programs ranged from 3 to 104 weeks with a median duration of eight weeks. Intervention frequency ranged from twice per week to daily, with twice per week most commonly applied [32,34,36,38,39,45,48–51,54]. Where individual intervention session time was reported, session time ranged from 10 to 60 minutes. Measures of exercise intensity were commonly not reported (Table 2). There were no significant adverse effects of any intervention reported.

Task specific training (functional mobility)

Two studies compared task-specific training (gait and stair retraining) to a facilitation approach (trunk mobilisation, stretching, and facilitation techniques) in individuals with MS [41,45] with one study also comparing to no intervention [45]. Both approaches were individualised to participants and demonstrated significantly greater improvements on timed stair ascent [45] and RMI [41,45] than no intervention with neither approach demonstrating greater benefit over the other. Location of intervention varied with one study conducted in a hospital outpatient setting [41] and the other study in a hospital outpatient setting for the task-specific training and the home environment for the facilitation techniques [45]. No significant differences were identified based on location of the intervention.

Task specific training plus balance training and strengthening

Task specific training was combined with balance and strength training, compared to no intervention in one study for DCD [55] and three studies for MS [35,43,46]. Task specific training addressed gait, stair practice and functional activities of daily living. Statistically significant between group differences in the FAC were found in the DCD study and these improvements were maintained at 12-week follow up [55]. The three MS studies had conflicting results as one study demonstrated a statistically significant improvement in timed stair ascent [46], while the other two studies displayed no difference on the RMI [35,43] and DGI [35,43].

Progressive resistance training

Four studies investigated progressive resistance training in individuals with MS compared with a standardised exercise

Table 2
Summary of interventions used in included trials.

Author/ Year	Intervention	Additional intervention detail	Randomised comparison	Intervention duration	Frequency/ total sessions	Duration	Intensity	Inline/ decline	Sets and Repetitions	Progression
Parkinson's disease										
Cakit et al, 2007 [36]	EG: treadmill training		CG: no intervention	8 weeks	2 x week / 16 sessions	30 ± 5 minutes	5 minute warm up at 50% maximum walking speed. ↑ by 0.6km/hr every 5 mins. Max safe speed for 5 mins, ↓ by 0.6km/hr. Maintain until session complete.	No incline	NA	↑ speed by 0.6km/hr next session if max walking speed achieved
Duncan & Earhart, 2012 [48]	EG: Argentine tango classes	Leading and following roles. Frequent partner change.	CG: no intervention	12 months	2 x week / 104 sessions	60 minutes	NR	NA	NA	Learning new steps, integration of new steps.
Duncan & Earhart, 2014 [49]	EG: Argentine tango classes		CG: no intervention	24 months	2 x week / 208 sessions	60 minutes	NR	NA	NA	NR
Hackney & Earhart, 2008 [50]	EG: Tai Chi.	First and second circles of Yang Short Style of Cheng Manching	CG: no intervention	10-13 weeks	2x week / 20 sessions	60 minutes	NR	NA	NA	NR
Hackney & Earhart, 2009 [51]	EG1: dance waltz/foxtrot EG2: Dance tango	Leading and following roles. Closed practice position	CG: no intervention	10-13 weeks	2 x week / 20 sessions	60 minutes	NR	NA	NA	NR
Kurtais et al, 2008 [37]	EG: treadmill training & home flexibility exercises	Home flexibility exercise NR	CG: home flexibility exercises	6 weeks	3 x week / 18 sessions	40 minutes	70-80% MHR	Gradual incline or speed progression	NA	Gradual incline or speed progression
Landers et al, 2016 [52]	EG1: balance training + external focus instructions; EG2: balance training +internal focus instructions; EG3: balance training + no attentional focus instructions.	Balance training: 10 minutes treadmill; 10 minutes obstacle negotiation; 10 minutes balance training tasks in harness.	CG: no intervention	4 weeks	3 x week / 12 sessions	45 minutes	NR	NR	6 reps of balance course	Balance tasks progressed with equipment modifications.

Table 2 (*Continued*)

Author/ Year	Intervention	Additional intervention detail	Randomised comparison	Intervention duration	Frequency/ total sessions	Duration	Intensity	Inline/ decline	Sets and Repetitions	Progression
Liao et al, 2015 [38]	EG1: virtual reality Wii exercise & treadmill training EG2: exercise & treadmill training	EG1: 10 minutes yoga; 15 minutes strengthening; 20 minutes balance game; 15 minutes treadmill training. EG2: 10 minutes stretching; 15 minutes strengthening - gross lower limb movements; 20 minutes dynamic balance activities, 15 minutes treadmill training	CG: falls prevention education	6 weeks	2 x week / 12 sessions	45 minutes	Treadmill: 80% comfortable walking speed. ↑ 0.2km/hr per 5 minutes as tolerated	NR	EG1; NR EG2: strengthening 3 sets 10 reps	EG 1 & 2 strengthening: 1kg ankle weight progressed to 2kg weight
Song et al, 2018 [53]	EG: video dance game	EG: step activated dance pad following 6 multi-directional arrows.	CG: no intervention	12 weeks	3 x week/ 36 sessions	15 minutes		NA	NA	4 levels of difficulty: novice, easy, medium and hard
Multiple sclerosis										
Cakit et al, 2010 [32]	EG1: cycling progressive resistance training plus exercise program. EG 2: exercise program	EG1: progressive resistance training on cycle ergometer. EG1 & 2: exercise programme: 5 minutes warm up; 20-25 minutes dynamic balance exercise - balance board, plyometrics; 5 minutes whole body stretching	CG: no intervention	8 weeks	2 x week / 16 sessions	60 minutes cycling; 30 minutes exercise program	EG1: 2 mins high-resistance pedalling (40% TMW); 2 mins low resistance (30-40 W) or rest	NA	EG1: 15 sets of cycle program EG1 & 2: exercise program individualised	EG1: 12 successful sets at cycle workload then ↑ by 10W increments

Table 2 (*Continued*)

Author/ Year	Intervention	Additional intervention detail	Randomised comparison	Intervention duration	Frequency/ total sessions	Duration	Intensity	Inline/ decline	Sets and Repetitions	Progression
Cattaneo et al, 2007 [33]	EG 1: balance rehabilitation using motor and sensory strategies. EG 2: balance rehabilitation motor strategies.	Motor strategies: dynamic standing tasks, limits of stability and biofeedback. Sensory strategies: dynamic standing tasks with manipulation of vision/ proprioception/ vestibular systems.	CG: ĉonventional therapyñot aimed at balance	3 weeks	3-4 x week/ 10-12 sessions	45 minutes	NR	NA	Individualised	Progress from body stability to gait exercises in a variable environment
Dalgas et al, 2009 [39]	EG: progressive resistance lower limb training	5 minutes stationary cycle warm up. Fast concentric and slow eccentric exercises: leg press, knee extension; hip flexion; hamstring curl; hip extension.	CG: no intervention.	12 weeks	2 x week / 24 sessions	NR	NR	NA	Weeks 1-2: 3 sets of 10 reps of 15RM; weeks 3-4: 3 sets of 12 reps at 12RM; weeks 5-6: 4 sets of 12 reps at 12RM; weeks 7-8: 4 sets of 10 reps at 10RM; weeks 9-10: 4 sets of 8 reps at 8RM; weeks 11-12: 3 sets of 8 reps at 8RM	as indicated by sets/reps
Hayes et al, 2011 [40]	EG: lower extremity eccentric ergometric resistance training plus standard exercise training	EG: eccentric recumbent stepper plus: standard exercise training: 15 minutes recumbent stepper; lower limb stretching; upper limb resistance exercises; dynamic balance exercises	CG: standard exercise training as per EG	12 weeks	3 x week / 36 sessions	45-60 minutes	Borg scale RPE 13/20 ŝomewhat hard'	NA	Standard exercise training - upper limb resistance: 1 set 10RM	Eccentric stepper: weeks 1-2: 1-5 minutes; weeks 3-12 maximum 14 minutes. Progression with RPE.

Table 2 (*Continued*)

Author/ Year	Intervention	Additional intervention detail	Randomised comparison	Intervention duration	Frequency/ total sessions	Duration	Intensity	Inline/ decline	Sets and Repetitions	Progression
Kjolhede et al, 2015 [47]	EG: PRT upper and lower limbs	Lower limb exercises: leg press, hip flexion, leg extension, prone hamstring curl. Upper limbs: cable pull down, cable triceps extension.	CG: no intervention	24 weeks	3 x week / 72 sessions	NR	NR	NA	Weeks 1-2: 3 sets of 10 reps of 15RM; weeks 3-4: 3 sets of 12 reps of 15RM; weeks 5-6: 3 sets of 10 reps of 12RM; weeks 7-8: 4 sets of 10 reps of 10 RM; weeks 9-10: 4 sets of 8 reps of 8 RM; weeks 11-12: 4 sets of 6 reps of 6RM; weeks 13-14: 3 sets of 10 reps of 12RM; weeks 15-18:4 sets of 10 reps of 10RM; weeks 19-20: 4 sets of 8 reps pf 8RM; weeks 21-22: 4 sets of 6 reps of 6RM; weeks 23-24: 5 sets of 6 reps of 6RM.	as indicated by sets/reps
Lord et al, 1998 [41]	EG1: task-orientated approach.	EG1: task specific training – gait, dynamic stepping, stairs EG2: facilitation; dynamic gait re-education; dynamic stretch; mobilisation.	EG2: facilitation approach	5-7 weeks	3 x week / 15 sessions	60 minutes	NR	NA	Individualised	Individualised progression of activity, repetitions and difficulty.
Nilsagard et al, 2013 [34]	EG: Wii Fit balance exercises	Video exercise game of balance, yoga, strength and aerobics	CG: no intervention	6-7 weeks	2 x week / 12 sessions	30 minutes	NR	NA	NR	Wii Fit games ranked for difficulty and used as progression

Table 2 (*Continued*)

Author/ Year	Intervention	Additional intervention detail	Randomised comparison	Intervention duration	Frequency/ total sessions	Duration	Intensity	Inline/ decline	Sets and Repetitions	Progression
Pfalzer & Fry, 2011 [42]	EG: inspiratory muscle training	Threshold inspiratory muscle training device	CG: no intervention	10 weeks	daily	10-15 minutes	NR	NA	3 sets of 15 reps	NR
Salhofer-Polanyi, 2013 [43]	EG: task specific training and exercise	Session 1: individualised physiotherapy. Session 2: treadmill training. Session 3: functional gait & balance exercise. Session 4: strength-training ergometry. Session 5: occupational therapy	CG: no intervention	3 weeks	4-5 sessions 5 x week / 20 sessions	each session 30 minutes maximum, full daily program between 2-2 ½ hours	NR	NR	Individualised	Individualised
Samaei, 2016 [44]	EG1: downhill eccentric treadmill training		EG2: uphill concentric treadmill training	4 weeks	3 x week / 12 sessions	30 minutes	55% - 85% MHR	EG1: 10% decline EG2: 10% incline	NA	Progression for 55%-85% MHR over duration of program
Straudi, 2014 [35]	EG: intervention i) progressive task oriented circuit training. intervention ii) home exercise	Intervention i) circuit: step ups; slalom; tandem walking; step targets; obstacles; long steps; treadmill 30 minutes. ii) independent home exercise: gait training, stretching, strengthening	CG: no intervention	Intervention i) 3 weeks. Intervention ii) 3 months	Intervention i) 5 x week/ 10 sessions. Intervention ii) 3 x week	Intervention i) 120 minutes. Intervention ii) 60 minutes	Self-selected walking speed for treadmill (0.9-2.9 km/hr)	NR	Individualised	↑ reps per station; ↑ treadmill speed
Tarakci et al, 2013 [46]	EG: group task specific training	EG: flexibility, lower limb strengthening, balance, coordination, functional activities	CG: no intervention	12 weeks	3 x week / 36 sessions	60 minutes	Borg scale RPE 13/20 ‘somewhat hard’	NA	NR	NR

Table 2 (*Continued*)

Author/ Year	Intervention	Additional intervention detail	Randomised comparison	Intervention duration	Frequency/ total sessions	Duration	Intensity	Inline/ decline	Sets and Repetitions	Progression
Wiles, 2001 [45]	EG1: physio at home - functional task-oriented approach EG2: physio hospital outpatient - facilitation techniques	Individualised problem solving approach. EG1: functional activities: stairs, mobility, community access. EG2: facilitation techniques; mobilisations.	CG: no intervention	8 weeks	2 x week / 16 sessions	45 minutes	NR	NA	NA	Individualised
Huntington's Disease										
Kloos et al, 2013 [54]	EG: video game dance exercise	EG: step activated dance pad following 4 multi-directional arrows in time to music. CG: bingo; blackjack or solitaire	CG: hand held sedentary video/ board game	6 weeks	2 x week / 12 sessions	45 minutes	NR	NA	NA	Speed ↑ in 25% increments when top level achieved
Degenerative cerebellar ataxia										
Miyai et al, 2012 [55]	EG: task specific active exercise for balance, gait and coordination activities.	General conditioning; stretching; strengthening; balance exercise; spine mobilisation; ADL functions; coordination tasks.	CG : no intervention	4 weeks	11 sessions week / 44 sessions	60 minutes	NR	NA	NR	NR

Key: ADL = activities of daily living; MHR = maximum heart rate; NR = not reported; NA = not applicable; RM = repetitions maximum; RPE = rating of perceived exertion; TMW = tolerated maximum workload; W = watts.

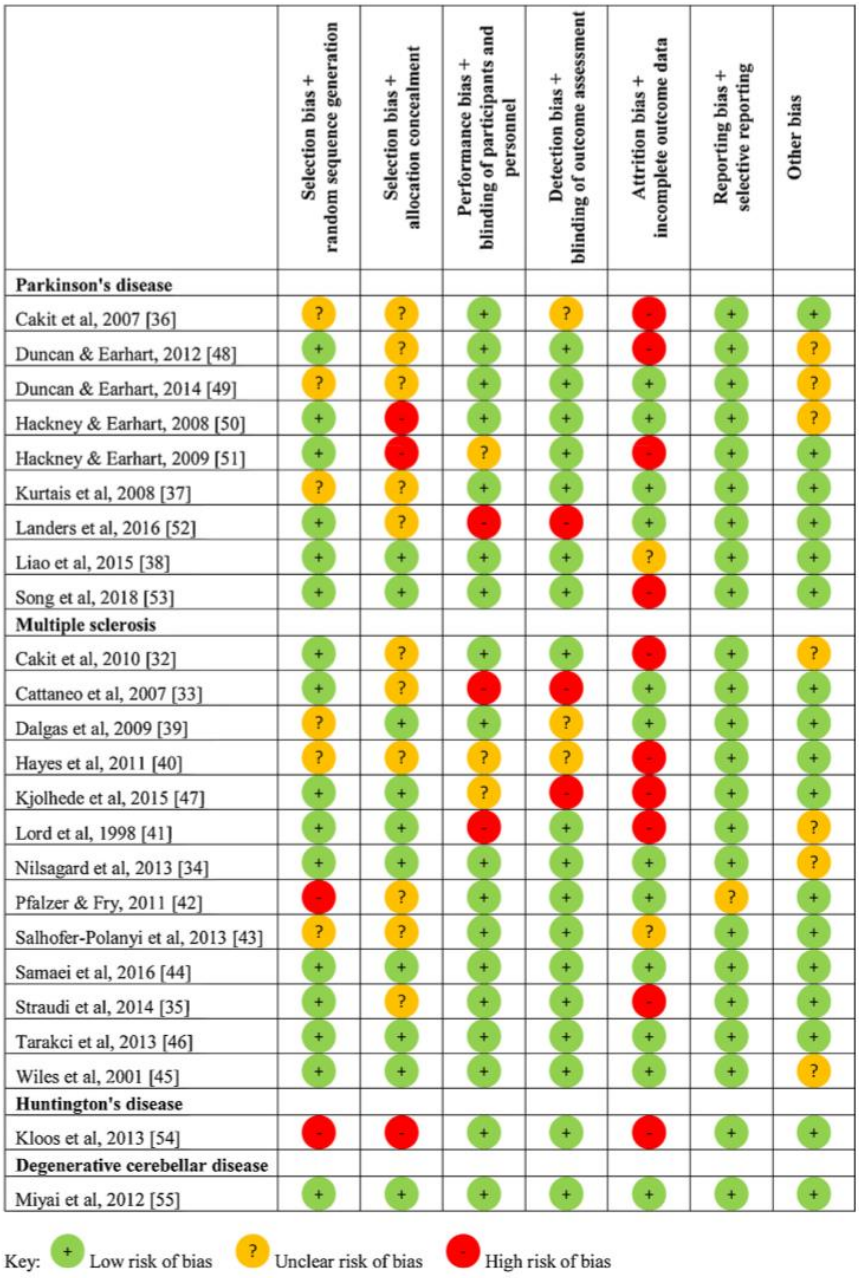

Fig. 2. Cochrane risk of bias tool.

program [40], no-intervention [39,47], or both comparators [32]. Two studies used ergometric devices for the progressive resistance training – one utilised a cycle ergometer and plyometric exercise [32] and another [40] used an eccentric ergometer recumbent stepper. The remaining studies used weights for progressive resistance training [39,47] with one study using fast concentric and slow eccentric control [39]. Three studies found statistically significant differences in favour of progressive resistance training groups in DGI [32] and timed stair ascent [32,39,47] with gains in stair ascent maintained in two studies at 12 and 48 week follow up respectively [39,47]. Contrary to this, another MS study found that those who received the standardised exercise program improved significantly more for the timed stair ascent than those who received progressive resistance training [40].

Treadmill training

Treadmill training was investigated in two studies for PD [36,37] and one for MS [44] with progression of the intervention *via* incremental increases in speed in all three studies and treadmill incline in two of the studies [37,44]. All studies found statistically significant improvements in mRMI [44], DGI [36] and timed stair ascent and descent [37]. Treadmill training was compared to no intervention in one PD study using DGI scores [36] and compared to flexibility exercise using timed stair ascent/descent in the other PD study [37]. In the MS study, downhill decline resulted in significantly greater improvement than uphill incline on mRMI with changes maintained at four-week follow up [44].

Dance

Dance was explored in three studies with individuals with PD with all three studies sharing one common author [48,49,51]. Two studies reviewed Argentine tango compared to no intervention however, one study was a subset of the larger trial [48,49]. The remaining study compared the effects of Argentine tango and American ballroom [51]. There was no difference between groups for backward walking velocity [48,49,51] but one study did identify a significant increase in backward stride length for both types of dance (tango and ballroom), compared to no intervention [51].

Video exercise gaming

The effect of video exercise gaming was assessed in four studies [34,38,53,54]. Two utilized the Wii Fit for balance, strength and yoga with MS and PD participants [34,38] and two used a video dance game with PD and HD participants [53,54]. In MS, there was no difference in DGI score between video exercise gaming and no intervention [34]. In PD, there was a statistically significant difference in FGA with use of video exercise gaming compared to a falls education control group but no difference compared to conventional exercise (stretching, strengthening and balance exercise) [38]. Improvements made with video exercise gaming and conventional exercise were maintained at one month follow up. Video dance gaming for PD participants did not improve FGA compared to no intervention [53]. In HD, video dance gaming led to a significant reduction in double support percentage in backward walking compared to handheld sedentary games but no difference in the change in backward velocity or stride length [54].

Balance rehabilitation

Balance exercises such as shifting centre of mass, altering base of support and dynamic activities during gait were assessed in two studies for participants with MS and PD [33,52]. In the MS study, a statistically significant difference in the DGI was found for the combined use of motor and sensory strategies compared with motor strategies alone or a conventional non-balance therapy control group [33]. In the PD study, no statistically significant differences were found on any of the outcome measures between no intervention and three intervention groups: i) an internal attentional focus ii) an external attentional focus iii) no attentional focus. The trial was halted at mid-point following an interim futility analysis [52].

Discussion

This systematic review is the first to investigate the effect of exercise interventions on high-level mobility in individuals with neurodegenerative disease. Across the 24 RCTs included in this review, high-level mobility was not the focus for measurement, and exercise interventions that were employed did not commonly include high-level mobility tasks. Furthermore, interventions were trialed with individuals across the spectrum of disease severity (EDSS 0–10), many of which would not have been capable of performing high-level mobility tasks. Hence, review findings highlight that to date, exercise interventions for individuals with neurodegenerative conditions have not targeted high-level mobility nor have they specifically focused on participants who were capable of participating in and benefiting from high-level mobility tasks.

Outcome measures

High-level mobility was not exclusively assessed as a primary outcome in any of the studies in this review. Instead, just two studies included high-level mobility items within one of a number of primary outcome measures, with one study including a single item measure and [46] the second study using a composite score of mobility [45]. As composite outcome measures (e.g. DGI, FAC, and RMI) include a range of low and high-level items, significant improvement on these measures could have been achieved in the absence of improvement on the high-level items. For example, improvement in level walking and independence will increase the DGI score without a change in high-level mobility. The low representation of high-level mobility items within most composite measures renders them susceptible to a ceiling effect, therefore, an outcome measure that exclusively targets high-level mobility is recommended [56–58]. The only outcome measure that appears to be currently available that focuses on high-level mobility for populations with neuromusculoskeletal conditions, is the HiMAT [25]. Originally designed for use in traumatic brain injury, the psychometric properties of the HiMAT are yet to be investigated for individuals with neurodegenerative diseases. Recognising that the purpose of a high-level exercise intervention would be to increase or maintain community participation and an active lifestyle, inclusion of corresponding measures of community participation and physical activity levels would be indicated [59].

Interventions

Exercise interventions designed for individuals with neurodegenerative diseases appear to overlook the requirements for high-level mobility. Improving strength, control and skill acquisition in high-level mobility and sport is typically achieved *via* part-practice and task-specific practice [60]. In order to achieve transference to specific high-level mobility activities, interventions need to address relevant components of the high-level mobility activity such as running, jumping and stair climbing. Running was not an intervention in any studies; stair climbing was used in only three studies [35,41,45] and jumping (plyometrics) in one study [32]. High-level mobility tasks such as dancing were included however, although outcome measurement was limited to backwards walking, which is unlikely to have fully represented changes in high-level mobility.

Unpacking exercise interventions that have shown benefit for people with neurodegenerative diseases for even single items of high-level mobility (e.g. timed stair ascent/descent) may provide some insight into potentially effective interventions. Treadmill training, progressive resistance training and task-specific training are such examples for individuals with MS or PD [37,39,46,47]. Treadmill training and progressive resistance training incorporated eccentric muscular strengthening (downhill walking, plyometric training and weighted resistance) indicating potential strength gain transference to high-level mobility [32,37,39,44,47]. Task-specific training customised to the individual had a positive effect for participants with MS [41,45]. Due to the clinical heterogeneity of individuals with MS, this approach may have been effective because the participant was challenged at an appropriate level and on tasks relevant to their lifestyle. This customisation is important especially when considering the different classifications of MS and hence different functional capability of participants.

Intervention intensity across included studies was commonly not reported (Table 2) making it difficult to identify whether participants were working at an appropriate intensity in order to facilitate maximum change in high-level mobility. In addition, it is not possible to determine whether participants engaged in sufficient physical activity to meet the recommendations for prevention of chronic disease [17]. Challenging individuals at sufficient intensity with an appropriate exercise intervention requires assessment of risk. In the included studies there were no significant adverse effects reported which would indicate interventions were safe and feasible to provide. In the future, if interventions are modified to specifically target high-level mobility at the optimum intensity, then an assessment of feasibility and safety with this population will be required.

Disease status

Inclusion of individuals at different stages of a disease, reflecting different functional levels will have reduced the probability of demonstrating a significant group difference in high-level mobility. For example, some MS studies included individuals with a range of classifications including RRMS, SPMS and PPMS or with different disease severity (EDSS). Similarly, PD participants varied in disease severity between stages I–IV Hoehn and Yahr scores. Participants with a lower functional level would not have been able to perform tasks that could be expected to improve high-level mobility. Additionally, to demonstrate efficacy, wide variability in a sample requires a much larger sample size than when variability is low [61]. An outcome measure is also required that has sufficient range to exclude the possibility of a ceiling or floor effect yet has the sensitivity to reveal significant change in any one individual in the study. Thus to demonstrate the impact of exercise interventions on high-level mobility, individuals targeted for inclusion in a trial need to have the capacity to benefit from high-level mobility interventions and outcome measures used need the necessary sensitivity to detect change in high-level mobility.

Strengths and limitations

This comprehensive review has provided a broad view of what is known about the impact of exercise interventions on high-level mobility within the population of people with neurodegenerative diseases. Included studies showed a large heterogeneity in disease severity (e.g. EDSS 0–10), interventions and outcome measures. Where similar outcome measures were used, the interventions varied [32–35] conversely, where interventions were similar the outcome measures varied [36–38]. Hence, a meta-analysis was deemed unsuitable due to the design and population heterogeneity of the included studies.

Studies were limited for neurodegenerative diseases of lower prevalence (e.g. DCD and HD) with several neurodegenerative diseases not featured at all (e.g. Friedreich's ataxia, spinal muscular atrophy).

Overall, studies included were of moderate to low risk of bias, with risk of bias largely limited by attrition. The probability of demonstrating benefits for high-level mobility was low as many included studies would not have been sufficiently powered due to smaller sample sizes (range $n = 10–110$), and because power calculations would have been based on basic mobility (primary outcome measure) rather than high-level mobility. Power would also have been limited by high variability in disease severity, and therefore performance, coupled with use of measures that lacked the sensitivity to detect changes in high-level mobility [61]. While RCTs were selected in order to utilise level two evidence [62] inclusion of lower levels of evidence may have identified potential beneficial interventions or more challenging assessment of high-level mobility. In addition, non-English papers were excluded which creates the potential for selection bias.

Future directions

High-level mobility is important for community participation, subsequent quality of life and prevention of sedentary behaviours associated with chronic diseases [16,17,63]. Hence for individuals with neurodegenerative disease, there are three key considerations for future research. Primarily, exercise interventions need to be designed specifically to target high-level mobility, ideally in the early stage of the disease where participants have minimal impairment and are still able to actively participate in high-level tasks. Secondly, outcome measures are required that can detect changes in high-level mobility, community participation and physical activity levels as well as slowing of disease progression. Finally, further exploration of interventions for neurodegenerative diseases of low prevalence is required.

Conclusion

To date, exercise interventions for individuals with neurodegenerative disease have rarely included high-level mobility tasks, nor measured the impact of interventions on high-level mobility particularly in the early stage of disease when high-level mobility interventions would be most feasible. Accordingly, future high quality studies need to specifically target high-level mobility in the early stages of neurodegenerative disease and determine the impact on high-level mobility, community participation and levels of physical activity.

Key messages

Studies of interventions for individuals with neurodegenerative disease have not focussed on high-level mobility.

Little is known about the effectiveness of interventions for high-level mobility in the early stages of neurodegenerative disease.

Treadmill training and progressive resistance training may improve high-level mobility in neurodegenerative disease.

;1;

Conflicts of interest: None declared.

Ethical Approval: no ethical approval was required.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.physio.2019.04.003.

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2.3 Systematic review update (1 May 2018 to 31 August 2021)

2.3.1 Methods

2.3.1.1 Search strategy

The original systematic review (Smith, Barker et al., 2020) was published in 2020, with the search completed on 30 April 2018. To provide a review update that included any new literature, the search was repeated using the original search strategies and databases. The database search was limited to the period of 1 May 2018 to 31 August 2021. The systematic review update was reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 statement (Page et al., 2021).

2.3.1.2 Study selection

The original reviewer (MS) conducted the database searches, screened the titles and abstracts, and reviewed the full-text articles. Studies were included if they met the criteria identified in the original review (Smith, Barker et al., 2020). Where required, the second original reviewer (JC) confirmed the inclusion or exclusion of articles according to the review criteria. Reference lists of relevant articles were screened, and a forward citation search was conducted on eligible full-text articles.

2.3.1.3 Data collection and assessment of risk of bias

In accordance with the original review, data were extracted and tabulated using the same table formats. The Cochrane risk-of-bias tool (Higgins et al., 2011) was completed using the same risk of bias classification. One reviewer (MS) conducted the data extraction and the risk-of-bias assessment, with a second reviewer (JC) to clarify and confirm where required.

2.3.2 Results

2.3.2.1 Study selection

The PRISMA flow diagram (Page et al., 2021) (see Figure 3) summarises the search and study selection for the systematic review update. Eighteen full-text articles from the database screen were reviewed for eligibility, with nine studies suitable for inclusion in the review update (Barbuto et al., 2020; Calabrò et al., 2019; da Silva & Israel, 2019; da Silva Rocha Paz et al., 2019; Helgerud et al., 2020; Rocha et al., 2018; Santos et al., 2019; Szefler-Derela et al., 2020; Tollar et al., 2019). No studies were eligible from the citation search. As

per the original systematic review, meta-analysis was unsuitable because of heterogeneity in disease severity, exercise intervention and outcome measures across the studies.

2.3.2.2 Study population

A total of 324 participants were included across the nine studies of the review update, and the sample size per study was relatively low (median n = 28). Participant ages ranged from 40 to 80 years, and 55% of participants were male. Exercise interventions were reported for individuals with Parkinson's disease (PD) in eight studies (Calabrò et al., 2019; da Silva & Israel, 2019; da Silva Rocha Paz et al., 2019; Helgerud et al., 2020; Rocha et al., 2018; Santos et al., 2019; Szefler-Derela et al., 2020; Tollar et al., 2019) and degenerative cerebellar disease (DCD) in one study (Barbuto et al., 2020) (see Table 1). Participants with PD varied widely in disease severity (Hoehn and Yahr stages 1–4), with mean disease duration ranging from 4.9 to 8.8 years. Individuals with DCD experienced moderate disease severity, with a mean SARA score of 9.6 (SD = 3.1) and a mean disease duration of 5.4 years (SD = 3.6). No studies were found for individuals with MS or other neurodegenerative diseases.

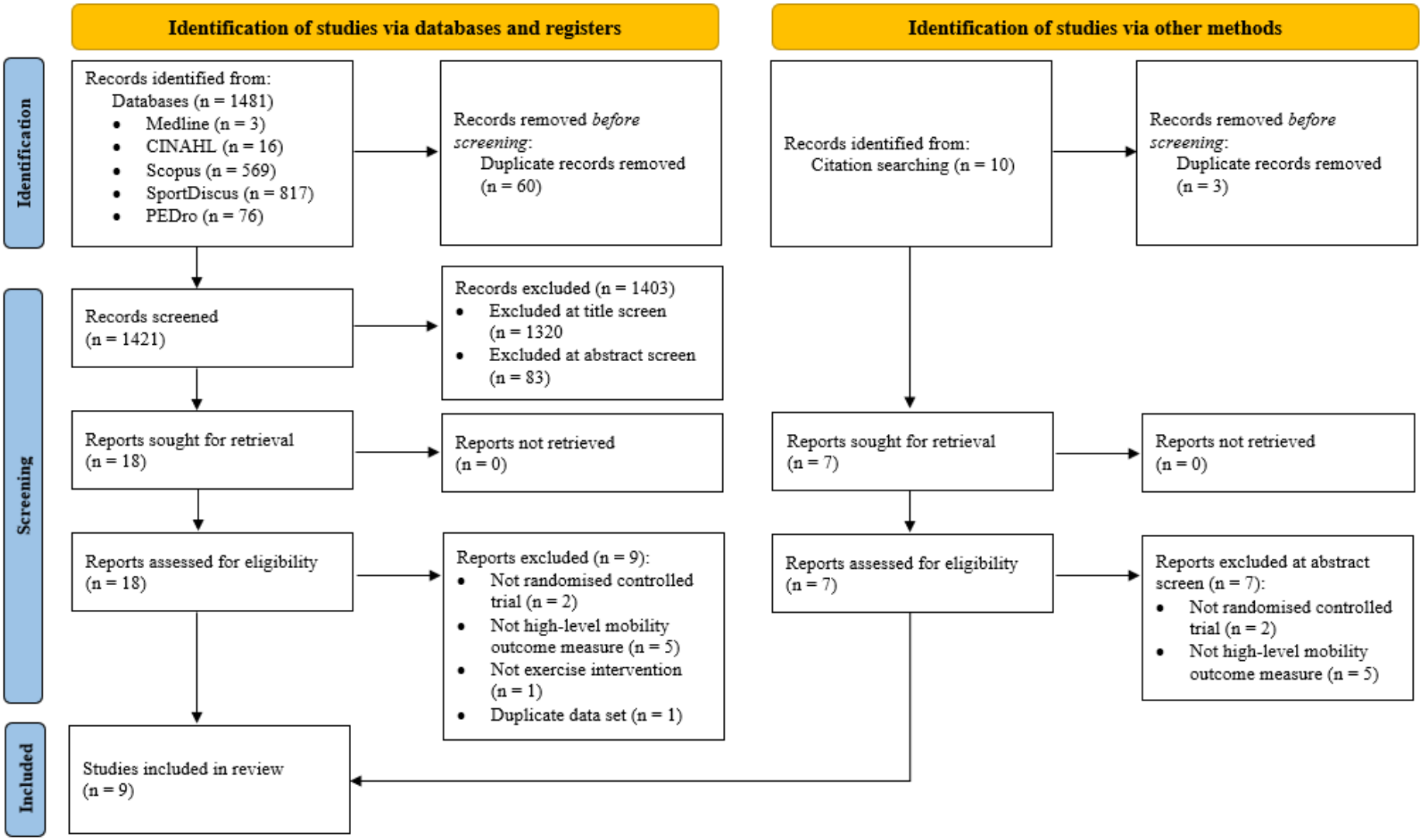


Figure 3. PRISMA flow diagram (Page et al., 2021)

2.3.2.3 Quality and risk of bias

Two studies (Rocha et al., 2018; Santos et al., 2019) demonstrated low risk of bias across all categories in the Cochrane risk-of-bias tool, demonstrating high methodological quality (see Figure 4). The remaining studies demonstrated a moderate risk of bias, mostly because of unclear allocation concealment and unclear or unreported blinding of participants and personnel. However, because of the nature of the studies, it is not always possible to blind participants or personnel. Three studies reported the use of a power calculation to inform the sample size (da Silva & Israel, 2019; Santos et al., 2019; Tollar et al., 2019). No studies were deemed to be at a high risk of bias.

	Selection bias + random sequence generation	Selection bias + allocation concealment	Performance bias + blinding of participants and personnel	Detection bias + blinding of outcome assessment	Attrition bias + incomplete outcome data	Reporting bias + selective reporting	Other bias
Parkinson's disease							
Calabrò et al. (2019)	?	?	?	+	+	+	+
da Silva Rocha Paz et al. (2019)	?	?	?	?	?	+	+
Helgerud et al. (2020)	?	?	?	?	+	+	+
Rocha et al. (2018)	+	+	+	+	+	+	+
Santos et al. (2019)	+	+	+	+	+	+	+
da Silva & Israel (2019)	+	+	?	+	-	+	+
Szefler-Derela et al. (2020)	?	?	?	+	+	+	+
Tollar et al. (2019)	+	?	?	+	+	+	+
Degenerative cerebellar disease							
Barbuto et al. (2020)	+	?	+	+	+	+	+

Key: + ***Low risk of bias*** ? ***Unclear risk of bias*** - ***High risk of bias***

Figure 4. Cochrane risk of bias tool (1 May–31 August 2021)

2.3.2.4 Outcome measures

Similar to the original systematic review, no outcome measures specifically designed to assess high-level mobility (e.g. HiMAT [High-Level Mobility and Assessment Tool]) were used in any of the included studies. Only one study (Calabrò et al., 2019) used a primary outcome measure that contained items of high-level mobility—namely, the Functional Gait Assessment (FGA), which includes assessment of backwards walking and stairs. Secondary outcome measures in the remaining studies included single-item measures (ascending/ descending stairs; da Silva Rocha Paz et al., 2019; Helgerud et al., 2020) and composite measures (FGA; Rocha et al., 2018) and Dynamic Gait Index (DGI), which includes stair assessment (Barbuto et al., 2020; da Silva & Israel, 2019; Santos et al., 2019; Szefler-Derela et al., 2020; Tollar et al., 2019)). All studies measured outcome pre- and post-intervention, with only one study (da Silva & Israel, 2019) conducting a follow-up review at 12 weeks.

Five studies compared an experimental group with an alternative intervention control group (Calabrò et al., 2019; da Silva Rocha Paz et al., 2019; Helgerud et al., 2020; Santos et al., 2019; Szefler-Derela et al., 2020). Two studies compared an experimental group to a control group with no intervention (Barbuto et al., 2020; da Silva & Israel, 2019). One study compared two exercise interventions (Rocha et al., 2018), and the remaining study compared two exercise intervention groups with a no-intervention control group (Tollar et al., 2019) (see Table 1).

2.3.2.5 Intervention types

Seven different exercise interventions were explored: treadmill training, video exercise gaming, dance, maximal strength training, aquatic exercise, Nordic walking and aerobic training (see Tables 1 and 2). Only two high-level mobility tasks were included as interventions: dance (Rocha et al., 2018) and backwards walking in aquatic therapy. Intervention programs ranged from 4 to 14 weeks of exercise (median duration: eight weeks). Sessions commonly took place twice per week (da Silva & Israel, 2019; da Silva Rocha Paz et al., 2019; Rocha et al., 2018; Santos et al., 2019; Szefler-Derela et al., 2020) (range 2–5), with session times ranging from 30 to 90 minutes. Intensity of exercise was measured in four studies using different methods (i.e. RPE, percentage 1RM; percentage MHR) (see Table 2). No serious adverse events were reported.

2.3.2.6 Treadmill training

Two studies explored the use of treadmill training for individuals with PD. One study compared treadmill training plus rhythmic auditory stimulation with treadmill training alone (Calabrò et al., 2019). Another compared treadmill training plus kinesiotherapy (exercise training) with conventional physiotherapy (da Silva Rocha Paz et al., 2019). Both studies showed improvements, with FGA (Calabrò et al., 2019) and ascending/descending stairs (da Silva Rocha Paz et al., 2019) that were significantly greater following treadmill training compared with control groups.

2.3.2.7 Video exercise gaming

Video exercise gaming was used in two studies for individuals with PD. One study (Santos et al., 2019) compared video exercise gaming plus conventional exercise with a control group of video exercise gaming only, and a secondary control of conventional exercise only. Another study (Tollar et al., 2019) compared video exercise gaming with an exercise group with stationary cycling and a control group with no intervention. No significant between-group differences were found in either study with the DGI following the interventions.

Table 1. Summary of included randomised controlled trials (1 May 2018 to 31 August 2021)

Author/Year	n	Disease severity/ chronicity	Intervention	Intervention duration	Follow-up	High-level mobility outcome measure	Between-group comparison	Outcome
Parkinson's Disease								
Calabrò et al. (2019)	50	Hoehn & Yahr 1–2 Mean (SD) EG = 3 (1) CG = 3 (1)	EG: treadmill & rhythmic auditory stimulation n = 25 CG: treadmill only n = 25	8 weeks	No follow-up	**FGA***	Repeated measures ANOVA with group and time	Significant between-group improvement in favour of EG $p < 0.001$
da Silva Rocha Paz et al. (2019)	24	Hoehn & Yahr 1–3 Mean (SD) EG = 1.9 (0.9) CG = 2 (0.7) Mean duration years (SD) EG = 4.9 (3.9) CG = 6.4 (6.9)	EG: treadmill & kinesiotherapy n = 12 CG: conventional physiotherapy n = 12	14 weeks	No follow-up	**Ascending/ descending stairs, (seconds)**	Student's t-test	Significant between-group improvement in favour of EG $p < 0.05$
Helgerud et al. (2020)	22	Hoehn & Yahr Mean (SD) EG = 2.3 (1.0) CG = 2.7 (0.7) Mean duration years (SD) EG = 8.8 (4.9) CG = 7.3 (2.5)	EG: maximal strength training & conventional rehabilitation n = 15 CG: conventional rehabilitation n = 7	4 weeks	No follow-up	**Ascending/ descending stairs, (seconds)**	Two-way repeated measures ANOVA Tukey's post hoc test	No significant between-group differences $p > 0.05$
Rocha et al. (2018)	21	Hoehn & Yahr 1–4 Mean duration years (SD) EG = 7.2 (4.9) CG = 8.4 (5.2)	EG1: Argentine tango n = 10 EG2: mixed-genre dance n = 11	8 weeks	No follow-up	**FGA**	Repeated measures ANOVA with group and time	No significant between-group differences $p > 0.05$
Santos et al. (2019)	45	Hoehn & Yahr 1–3 Mean duration years (SD) 7.1 (0.5)	EG: virtual reality Wii & conventional exercise n = 15 CG1: virtual reality Wii n = 15 CG2: conventional exercise n = 15	8 weeks	No follow-up	**DGI**	Repeated measures ANOVA with group and time	No significant between-group differences $p = 0.28$
da Silva & Israel (2019)	28	Hoehn & Yahr 1–4 Mean duration years (SD) 7.1 (0.5)	EG: aquatic exercise CG: no intervention	10 weeks	12 weeks post-intervention	**DGI**	Repeated measures ANOVA with group and time Bonferroni post hoc test	Significant between-group improvement in favour of EG at post-intervention $p = 0.001$ and follow-up $p = 0.003$

Author/Year	n	Disease severity/ chronicity	Intervention	Intervention duration	Follow-up	High-level mobility outcome measure	Between-group comparison	Outcome
Szefler-Derela et al. (2020)	40	Hoehn & Yahr 1–3 Median duration years (range) EG = 6.0 (3–18) CG = 5.0 (2–14)	EG: Nordic walking n = 20 CG: conventional rehabilitation n =20	6 weeks	No follow-up	**DGI**	Mann–Whitney U test	No significant between-group differences p = 0.06
Tollar et al. (2019)	74	Hoehn & Yahr 2–3 Mean duration years (SD) EG1: 7.5 (1.8) EG2: 7.5 (2.2) CG: 7.3 (2.2)	EG1: agility exer-gaming n = 25 EG2: stationary cycling n = 25 CG: no intervention n = 24	5 weeks	No follow-up	**DGI**	Repeated measures ANOVA	No significant between-group difference p = 0.77
Degenerative cerebellar disease								
Barbuto et al. (2020)	20	SARA Mean (SD) 9.6 (3.1) Mean duration years (SD) 5.4 (3.6)	EG: aerobic training n = 10 CG: no intervention n = 10	4 weeks	No follow-up	**DGI**	Mixed effect model with group and time	Significant between-group improvement in favour of EG p = 0.006

* Primary outcome measure

Key: ANOVA = analysis of variance; CG = control group; DGI = Dynamic Gait Index; EG = exercise group; FGA = Functional Gait Assessment; n = number of participants; SARA = Scale for Rating and Assessment of Ataxia; SD = standard deviation.

Table 2. Summary of interventions used in included trials (1 May 2018 to 31 August 2021)

Author/Year	Intervention	Additional intervention detail	Randomised comparison	Intervention duration	Frequency/ total sessions	Duration	Intensity	Treadmill inline/ decline	Sets and repetitions	Progression
Parkinson's disease										
Calabrò et al. (2019)	EG: treadmill & rhythmic auditory stimulation	Acoustic cues for stepping cadence	CG: treadmill only	8 weeks	5 x week 40 sessions	30 minutes	NR	NR	NA	Gradual increase of acoustic beat frequency to 120 bpm
da Silva Rocha Paz et al. (2019)	EG: treadmill & kinesiotherapy	EG: treadmill, circuit training, exercise bike CG: stretching, strengthening, mobility& balance training, relaxation	CG: conventional physiotherapy	14 weeks	2 x week 28 sessions	EG:50 minutes (treadmill 20 minutes; circuits 20 minutes; exercise bike 20 minutes) CG: 50 minutes	EG: 3–7 on Borg scale CG: NR	NR	NR	NR
Helgerud et al. (2020)	EG: maximal strength training & conventional rehabilitation	EG: Leg press & chest press CG: Body weight exercise, exercise in water, Nordic walking (plus leg & chest press at < 50% IRM)	CG: conventional rehabilitation	4 weeks	5 x week 20 sessions	CR: 60 minutes	90% IRM	NA	4 sets of 4 reps	↑ leg press by 5 kg and chest press by 2.5 kg once able to complete > 4 reps per set
Rocha et al. (2018)	EG: Argentine tango & home dance program		EG2: Mixed-genre dance & home dance program	8 weeks	1 x week class 1 x week home 16 sessions	60 minutes dance class 40 minutes home dance program	NR	NA	NA	Learning new steps
Santos et al. (2019)	EG: virtual reality Wii exercise & conventional exercise	Virtual reality: Wii Fit & Wii Sport games Conventional exercises: proprioceptive neuromuscular facilitation and gait training	CG1: virtual reality Wii CG2: Conventional exercise	8 weeks	2 x week 16 sessions	50 minutes	NR	NA	NA	NR

Author/Year	Intervention	Additional intervention detail	Randomised comparison	Intervention duration	Frequency/ total sessions	Duration	Intensity	Treadmill inline/ decline	Sets and repetitions	Progression
da Silva & Israel (2019)	EG: aquatic exercise	Forward and backward walking, balance and strengthening exercise in water	CG: no intervention	10 weeks	2 x week 20 sessions	50 minutes	NR	NA	NR	↑ complexity of movement plus dual tasking
Szefler-Derela et al. (2020)	EG: Nordic walking	CG: general exercises	CG: conventional rehabilitation	6 weeks	2 x week 12 sessions	EG:90 minutes CG:45 minutes	NR	NA	NR	↑ intensity and distance of walking
Tollar et al. (2019)	EG1: agility exer-gaming EG2: cycling	EG1: Xbox dance and spatial orientation exercises EG2: cycle ergometry	CG: no intervention	5 weeks	5 x week 25 sessions	60 minutes	HR 110–140 bpm 12–13 RPE	NA	NA	NR
Degenerative cerebellar disease										
Barbuto et al. (2020)	EG: aerobic training	Stationary cycling	CG: no intervention	4 weeks	5 x week 20 sessions	30 minutes	65–80% MHR	NA	NA	↑ intensity by 5% each week until 80% MHR maintained for 30 minutes

Key: bpm = beats per minute; CG = control group; EG = exercise group; HR = heart rate; MHR = maximum heart rate; NR = not reported; NA = not applicable; RM = repetitions maximum; RPE = rating of perceived exertion

2.3.2.8 Dance

Argentinian tango was compared with mixed-genre dancing for individuals with PD in one study (Rocha et al., 2018). No significant between-group differences were found with the FGA in this study.

2.3.2.9 Maximal strength training

Maximal strength training plus conventional rehabilitation demonstrated a statistically significant improvement in ascending/descending stair outcome compared with conventional rehabilitation alone for individuals with PD (Helgerud et al., 2020).

2.3.2.10 Aquatic exercise

A 10-week aquatic exercise program demonstrated a statistically significant improvement in the DGI outcome for individuals with PD compared with no intervention (da Silva & Israel, 2019). Improvements were maintained at 12-week follow-up.

2.3.2.11 Nordic walking

There were no significant between-group differences in DGI for individuals with PD when comparing Nordic walking with conventional rehabilitation (Szefler-Derela et al., 2020).

2.3.2.12 Aerobic training—stationary cycling

Four weeks of aerobic training was compared with a no-intervention control group for individuals with DCD (Barbuto et al., 2020). A significant between-group difference in the DGI was found in favour of the exercise group following the intervention.

2.3.3 Discussion

Consistent with the original review, the findings of the systematic review update confirmed that high-level mobility interventions were not commonly used, and high-level mobility outcomes were not the focus of assessments. Interventions were trialled across studies, with significant differences in participants' disease severity (e.g. Hoehn & Yahr stage 1–4), yet the ability to engage in challenging high-level activities may only be appropriate for those at stage 1–2 and unlikely at stage 3–4. Interventions that challenge and assess high-level mobility for individuals with mild to moderate disability from neurodegenerative disease are still lacking.

2.3.3.1 Outcome measures

No new outcome measures of high-level mobility were used in the studies included in this review update compared with the original systematic review. The DGI and FGA were used as composite measures that included a component of high-level mobility, and timed ascent/descent of stairs was used as a standalone measure of mobility. The absence of a comprehensive high-level mobility outcome measure such as the HiMAT, or individual measures of high-level mobility such as running and jumping, highlights the lack of focus in assessing and targeting high-level mobility for individuals with neurodegenerative disease.

2.3.3.2 Interventions

New modes of exercise included in the updated review were aquatic exercise and Nordic walking, with only aquatic exercise possibly of benefit to high-level mobility for people with PD. Interventions investigated that were similar to those in the original systematic review were treadmill training, video exercise gaming, dance, stationary cycling and strengthening programs. In the absence of outcome measures or interventions focused on high-level mobility, the findings suggest some support for the use of treadmill walking training for individuals with PD, and strength (Helgerud et al., 2020) and aerobic training (Barbuto et al., 2020) for individuals with PD and DCD respectively. Of note, interventions were structured, providing a prescribed program for participants. No studies involved the participants in selecting or tailoring their own exercise intervention.

Across the included studies, most exercise interventions still only required a low level of mobility. While this may be appropriate for those at a later stage in the disease process, it is likely that those in the early stages of disease have the capacity to work at a higher level of mobility. For example, jogging, running and cycling, which are among the top five sporting activities participated in by adults in Australia (Australian Sports Commission, 2020), can form part of a normal active lifestyle. Across all studies, activities such as running, outdoor cycling and team sports were not represented. Without the challenge, it is difficult to interpret the full capability of the individual with neurodegenerative disease and the effect of exercise, particularly in the early stages.

2.3.3.3 Strengths and limitations

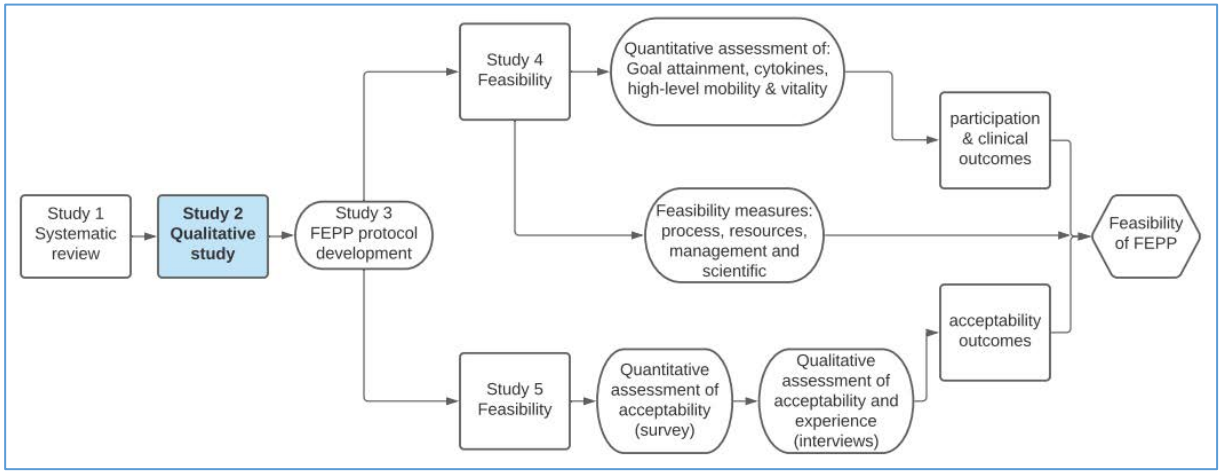
This systematic review update provides some support for treadmill training and new evidence of the benefits of aquatic therapy for people with PD. Some support is also demonstrated for the use of aerobic exercise for individuals with DCD. However, there was no further evidence regarding the effect of exercise on individuals with MS or other neurodegenerative diseases, such as Huntington's disease or Friedreich's ataxia. With the heterogeneity in disease severity, interventions and outcome measures, meta-analysis of the data was not possible.

Studies were of moderate to low risk of bias. Risk of bias in the original review was mostly reflective of attrition, whereas updated studies were limited by reporting of allocation concealment or blinding of participants/personnel, potentially affecting the results. With only three of the nine studies in the review update using a power calculation to inform the sample size, many of the studies would have been underpowered to detect change in high-level mobility.

2.3.4 Summary

This review update confirms the conclusions of the original review that exercise interventions that include high-level mobility activities for individuals with neurodegenerative disease are yet to be investigated. Enabling individuals to maintain participation in an active lifestyle for as long as possible requires exploration of exercise interventions early in the disease process. Adequate assessment of high-level mobility is required to monitor change and the effectiveness of interventions that could maintain or potentially improve high-level mobility. Further, investigation of exercise interventions to address high-level mobility for neurodegenerative diseases of low prevalence is required.

Chapter 3: A Qualitative Study of Active Participation in Sport and Exercise for Individuals with Multiple Sclerosis



3.1 Overview of the study

In Chapter 2, the need to investigate high-level mobility activities for individuals with neurodegenerative disease was highlighted. It was important to begin by understanding the experience of participation in sport and exercise for individuals with MS, where sport is defined as an activity involving physical effort and skill governed by a set of rules (Australian Sport Commission, n.d.), and exercise is defined as a subset of physical activity that is planned, structured and repetitive with the aim of improving and/or maintaining physical fitness (ACSM, 2018). Accordingly, Chapter 3 consists of a qualitative study in which the key factors that influenced participation in sport and exercise were explored from the perspective of individuals with MS. An additional aim of the study was to determine the support required, as identified by individuals with MS, to participate in their choice of sport and exercise. The aim was to use the findings from the systematic review and the qualitative study to develop an exercise program to optimise exercise participation for individuals with minimal disability from MS.

3.2 Publication—qualitative study

This qualitative study has been published as:

Smith, M., Neibling, B., Williams, G., Birks, M., & Barker, R. (2019). A qualitative study of active participation in sport and exercise for individuals with multiple sclerosis. *Physiotherapy Research International*, *24*(3), Article e1776. https://doi.org/10.1002/pri.1776

The published paper is available online at: https://onlinelibrary.wiley.com/doi/10.1002/pri.1776

Supporting information for this publication is provided in Section 3.4. Ethical approval is provided in Appendix D.

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RESEARCH ARTICLE

WILEY

A qualitative study of active participation in sport and exercise for individuals with multiple sclerosis

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Abstract

Objective: The aim of this study was to explore the experience of participation in sport and exercise for individuals with multiple sclerosis (MS) with minimal disability. The objectives were to gain an understanding of key factors that influence participation in sport and exercise and to determine support required by individuals with MS to participate in their choice of sport and exercise for as long as possible.

Methods: A qualitative, descriptive study utilizing three focus groups was conducted. Data were analysed thematically aided by NVivo software. Participants were individuals with MS who had an Expanded Disability Status Scale score of 0–4, indicating full ambulation. All participants were living in northern Queensland, Australia.

Results: Sixteen individuals participated; 63% of whom regularly participated in sport or exercise. All participants viewed sport and exercise positively and identified inherent benefits of exercise. Five key themes emerged to describe the experience of participating in sport and exercise: "personally engaging with exercise," "influencing barriers and enablers of exercise," "sustaining independence," "integrating exercise into lifestyle," and "getting the balance right." Most participants felt that advice and guidance from health professionals about the optimum mode and dose (how much and how often) of exercise was lacking.

Conclusions: Participation in sport and exercise was valued by individuals with MS with minimal disability for sustaining independence and an active lifestyle. Personalized exercise advice from health professionals was the key support identified by participants to assist them to maintain an active lifestyle for as long as possible.

KEYWORDS

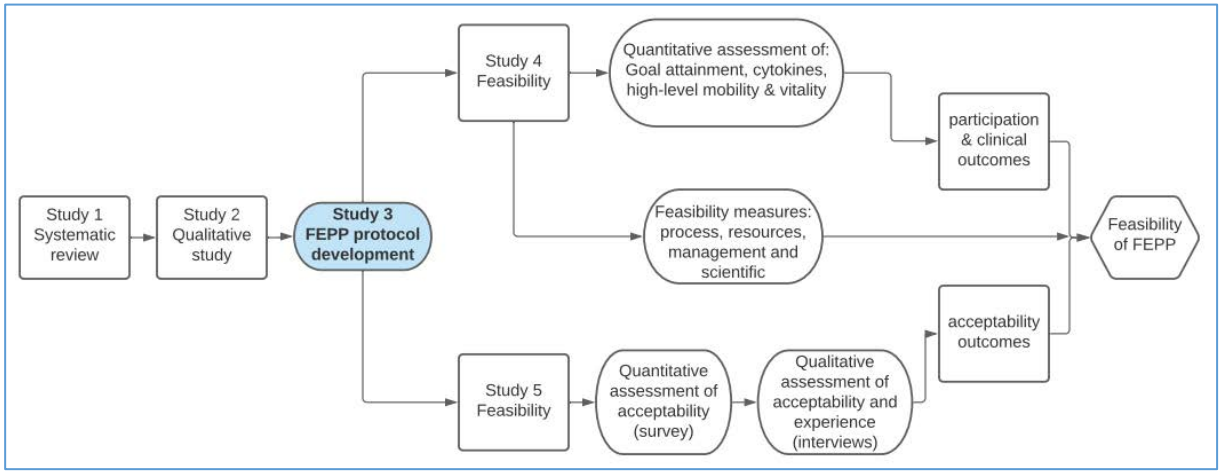
exercise, multiple sclerosis, qualitative research

3.3 Supporting information

Table 3. Interview domains and questions

Domain	**Topic questions**
Introductions	Tell the group who you are and about life with multiple sclerosis?
Physical activity	Tell me about physical activity and what you do?
High-level mobility and sport	Tell me about what high-level mobility/sport/exercise you do? How often do you do this activity, why and who with?
Barriers and enablers to exercise/sport	What stops you from participating in sport/exercise? What enables you to participate in sport/exercise?
Diagnosis	Once diagnosed with multiple sclerosis, did you change your approach to sport/exercise?
Advice or assistance	What advice/ assistance have you had about participating in sport/exercise (if any)? How has this influenced your participation (positively or negatively) in sport/exercise?
Lifestyle	What role (if any) does sport/exercise play in your outdoor/indoor lifestyle? What is important about this role?
Future directions	In the ideal world, what would assist you in your current community in participating in sport/exercise?

Chapter 4: Development of a Study Protocol to Find the Right Balance with Participation in Sport and Exercise for Individuals with Multiple Sclerosis



4.1 Overview of the study

Chapter 3 revealed that individuals with MS wanted to participate in sport and exercise of their choice and that they wanted health professional support to do so. Study participants' choices included high-level mobility activities such as trail running and playing squash. Specifically, they wanted health professional support to assist them with finding the right balance with exercise (i.e. suitable progression/regression) and information on management of exercise with MS. In this chapter, the perspective of individuals with MS (see Chapter 3) and the findings of the systematic review (see Chapter 2) were combined to develop a flexible exercise participation program (FEPP). Chapter 4 includes details of the FEPP protocol together with the rationale behind its development.

4.2 Publication—study protocol

This study protocol has been published as:

Smith, M., Williams, G., & Barker, R. (2020). Finding the right balance with participation in exercise and sport for individuals with multiple sclerosis: Protocol for a pre and post intervention feasibility study. *BMJ Open, 10*(3), Article e035378. https://doi.org/10.1136/bmjopen-2019-035378

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Open access Protocol

BMJ Open

Finding the right balance with participation in exercise and sport for individuals with multiple sclerosis: protocol for a pre and post intervention feasibility study

Moira Smith ,[1] Gavin Williams,[2] Ruth Barker[3]

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ABSTRACT

Introduction Individuals with minimal disability from multiple sclerosis (MS) requested advice on finding the right balance, between too much and too little exercise, when participating in their choice of sport or exercise. To optimise exercise participation during the early stages of the disease, a flexible exercise participation programme (FEPP) has been developed. The FEPP is novel because it provides guidance and support for individuals with MS to participate and progress in their *preferred* sport or exercise. The primary objective was to assess the feasibility of the FEPP. The secondary objective was to assess the feasibility of a larger trial to demonstrate the efficacy of the FEPP.

Methods and analysis A stage I feasibility study of the FEPP, using a single group preintervention/post-intervention design, will be conducted with 16 participants with minimal disability from MS (Expanded Disability Status Scale level of 0–3.5). The 12-week FEPP will guide participants to independently participate in their preferred sport or exercise at a location of their choice. Exercise progression will be guided by individual energy levels and a weekly telephone coaching session with a physiotherapist. Participation in exercise or sport will be recorded in parallel with assessment of disease biomarkers (plasma cytokines interleukin (IL)-2, IL-4, IL-6, IL-10, interferon (IFN)-γ and tumour necrosis factor (TNF)), subjective vitality and high-level mobility. Acceptability of the FEPP will be assessed using a sequential explanatory mixed methods design where the findings of a participant survey will inform the interview guide for a series of focus groups.

Feasibility of a larger trial will be assessed via process, resources, management and scientific metrics. Progression to a larger trial will depend on the achievement of specified minimum success criteria.

Ethics and dissemination Ethical approval has been obtained for this study from the James Cook University Human Research Ethics Committee (H7956). Dissemination of findings is planned via peer-reviewed journals, conference presentations and media releases. The protocol date was 21 December 2019, V.1.

Trial registration number The trial is registered with Australian New Zealand Clinical Trials Registry (ANZCTR), ACTRN12620000076976.

Strengths and limitations of the study

- The flexible exercise participation programme (FEPP) is a consumer-driven programme for individuals with multiple sclerosis.
- Consumer preference for sport or exercise mode is central to the FEPP.
- Active participation in exercise or sport is focused on participation rather than impairment.
- Study findings will inform the design of a larger trial.
- This study without a control group demonstrates feasibility rather than efficacy.

INTRODUCTION

Individuals with minimal disability from multiple sclerosis (MS), have recently reported participating in, or wanting to participate in, sport or high-level exercise, such as running, squash or road cycling.[1] While their preference was to undertake their choice of sport/exercise independently at a time suitable to them, they also wanted advice on finding the correct balance between too much activity, which may exacerbate symptoms, and too little activity, which could unnecessarily limit participation. Yet few study participants had received any such advice, nor had they been given their choice of exercise.[1] Commonly, exercise interventions for individuals with MS are provided in a clinical or home-based setting where the individual follows a prescribed activity or exercise programme. High-level mobility activities such as running, sport or outdoor leisure pursuits are not typically targeted.[2] Instead, exercise interventions prescribed include progressive resistance training, balance training and stationary cycling, addressing impairments such as strength and balance.[3–5] Functional outcomes are typically focused on walking[6 7] with no attention to the benefits for

high-level mobility, even for those who are higher functioning.[2] Benefits of participation in regular sport and exercise according to the preference of individuals with MS have not been reported.

Empowering individuals with the autonomy to manage their own exercise prescription, according to their individual goals, is an important concept in exerting control over the impact of the disease. Previous interventions examined in clinical trials for MS have not commonly allowed for this diversity. Therefore, exploration of ways to adapt and modify personal exercise choices to improve or maintain participation is required. To address this need, a flexible exercise participation programme (FEPP) has been developed to offer individuals choice and to guide their mode and dose of exercise. The FEPP has been based on existing recommendations for general and advanced aerobic exercise for individuals with MS.[8] It has also been informed by the guidelines for healthy individuals proposed by the American College of Sports Medicine and equivalent version by the Australian Government Department of Health, which aim to reduce the risk of chronic disease.[9 10] The FEPP is a stepping stone supported pathway to move from low levels of aerobic exercise towards meeting or exceeding advanced aerobic exercise guidelines for individuals with MS. The aim of the FEPP is to assist individuals with minimal disability from MS in finding the right balance between too little and too much exercise, and to maximise the benefits of exercise for individuals with MS. The FEPP provides a personally tailored programme to achieve exercise participation goals specific to the individual and is guided by the individual's perceived energy levels. By monitoring and responding to energy levels, participants are using a pacing technique, which is a method for managing energy effectively,[11] thereby enabling participation. The FEPP provides a framework for a graded response to exercise rather than an 'all-or-nothing' approach. Support is provided on a weekly basis, by a physiotherapist, using recognised behaviour change techniques to enable individuals to vary their physical activity.[12] It is evident that individuals with MS need support to increase and maximise participation in their *choice* of exercise.[1]

Many individuals with mild to moderate disability from MS do not meet recommended levels of physical activity required to obtain fitness benefits[13] despite guideline recommendations.[8 14] For those who do, the guidelines provide a baseline for exercise,[8] but the maximum safe dose is not yet known.[14] Manipulation of the exercise dose is required to determine the optimum level, which maximises benefits and is free from negative consequences, for each individual with MS. Historically, concerns existed around the possibility of exercise increasing fatigue for individuals with MS.[15] Even though evidence now suggests otherwise,[16] levels of fatigue continue to guide practice.[14] In the FEPP, a shift away from such impairment-based assessment is proposed with assessment of perceived energy levels prior to exercise to guide selection of exercise dose. Energy conservation approaches for individuals with MS are important tools for planning and pacing activities in order to manage fatigue in daily life.[11 17] Attention to available energy prior to exercise may enable an informed decision on whether to progress, maintain or regress exercise dose, and assist in finding the right balance between too much and too little activity. Measurement of vitality following a period of regular participation in exercise may also serve to demonstrate long-term benefits of exercise.[18]

Physiological benefits of exercise include improvements in aerobic capacity, balance and muscle strength.[19–21] In addition, it has been proposed that exercise may have a neuroprotective and disease-modifying effect on MS.[22 23] Biomarkers that may serve as indicators of exercise-induced neural changes in MS include neurotrophic factors and cytokines.[24] Neurotrophic factors can increase as a result of exercise, such as brain-derived neurotrophic factor, which has a role in neurogenesis and neuroprotection of the central nervous system.[22 25] Cytokine levels have also shown change following exercise in individuals with MS.[26 27] Cytokines assist in regulating the immune response.[28] In MS, there is an imbalance between the levels of proinflammatory and anti-inflammatory cytokines, with higher levels of proinflammatory cytokines linked to the demyelination process.[28] Reduction in proinflammatory cytokines can occur following exercise.[26] However, the evidence is inconsistent as to whether the change in cytokine profile is the mechanism for physiological improvement following exercise and hence requires further investigation.[29] Furthermore, the effects of exercise dose (ie, frequency, intensity, duration and mode) on cytokine levels remains unknown.[29 30]

The purpose of this study was to assess the feasibility of the FEPP, a novel sport and exercise intervention for individuals with MS. Individuals with minimal disability from MS will be invited to participate in their preferred exercise. Response to exercise dose will be assessed using disease biomarkers, subjective vitality, as a measure of energy, high-level mobility, and subjective reporting. The objectives of the study were to

1. Assess the feasibility of the FEPP for individuals with minimal disability from MS.
   a. Does the FEPP enable achievement of goals for participation in exercise and sport for individuals with MS?
   b. What is the best method to describe and report on the exercise or sport intervention?
   c. Is there a relationship between the level of participation in exercise and clinical/physiological outcomes?
      - Plasma cytokine levels (IL-2, IL-4, IL-6, IL-10, IFN-γ and TNF).
      - Vitality (energy levels measured via the Subjective Vitality Scale).
      - High-level mobility (measured via the High-Level Mobility Assessment Tool (HiMAT)).
   d. Is the FEPP acceptable from the perspective of individuals with MS?

2. Assess the feasibility of a larger clinical trial against the following minimum success criteria:
   a. No reports of serious adverse events as a result of completing the FEPP.
   b. A minimum of 80% of participants able to modify exercise participation using the FEPP.
   c. A minimum of 80% of participants report satisfaction with the FEPP.
   d. A minimum of 20% attrition from the 12-week FEPP.
   e. A minimum of 75% recruitment of the intended 16 participants.
   f. A minimum of 75% completion of each outcome measure.

METHODS AND ANALYSIS

Study design

This stage I feasibility study will involve a single group preintervention/post-intervention design to explore implementation of a 12-week FEPP with individuals with minimal disability from MS. Participation in exercise or sport will be recorded in parallel with assessment of disease biomarkers, subjective vitality and high-level mobility.

Acceptability of the FEPP to participants will be assessed using a sequential explanatory mixed methods design.[31] Perceived effective/ineffective elements of the FEPP and potential adaptations will be explored to guide refinement of the FEPP. Assessment of feasibility metrics (process, resources, management and scientific) will inform the suitability of a larger trial.

Study setting

Data collection will occur in the James Cook University (JCU), Australia, in January 2020. The intervention will occur according to each participant's preferred mode of exercise and preferred setting, for example, sports centre, gym or outdoor pursuit in his/her local environment.

Participants

Individuals with MS who meet the following inclusion criteria will be invited to participate: (1) diagnosis of relapsing remitting MS as defined by the 2017 McDonald criteria[32]; (2) independent mobility as defined by Expanded Disability Status Scale level 0–3.5[33]; (3) stability, that is, not worsening in the past 3 months on disease-modifying drugs (e.g. alemtuzamab, natalizumab and ocrelizumab)[34]; (4) 18 years of age or over; and (5) ability to provide informed consent. Potential participants will be excluded if they have (1) any concomitant neurological condition or (2) an additional health condition that would prohibit their participation in aerobic exercise or sport.

Recruitment

Participants will be recruited via (1) media: television, newspaper and social media; (2) flyer distributed by MS Queensland and by consultant neurologists; (3) flyer displayed in community settings (eg, community notice boards and medical practices; (4) JCU website and social media; and (v) snowballing. Potential participants will be advised to contact the primary researcher by email or telephone for further information. Once contacted, the primary researcher will screen potential participants in person or via telephone against the inclusion/exclusion criteria.

All potential participants who meet the eligibility criteria will be provided with an information letter and a consent form, either electronically or via post with a reply-paid envelope, according to their preference. Those who wish to participate will be advised to return the signed consent form in person, electronically or via post. Participants can withdraw from the study at any time without explanation or prejudice.

Sample size

Sixteen participants will be recruited, allowing for a 25% dropout rate. A sample size of 12 participants has been recommended for feasibility studies.[35] As this study is designed to assess the feasibility of a larger trial, a formal sample size calculation will not be required.

Intervention

All 16 participants will undertake the FEPP, a 12-week programme, in which participants choose their preferred mode of exercise as well as the time and location for exercise. Exercise will be performed independently by the participant (ie, not supervised by the research team). The FEPP is illustrated in flowchart format in figures 1 and 2. The FEPP flowchart will guide the participant to incrementally progress, maintain or regress their activity level based on performance feedback. The FEPP has two streams (table 1) to enable progression of activity level relative to the individual's baseline activity level.

Stream 1 is for participants who do not meet the MS general aerobic exercise guidelines of at least 30 min of moderate intensity aerobic exercise three times per week.[8] Moderate intensity exercise is defined as 40%–59% of heart rate reserve and can be scored as 12–13 on a 6–20 rating of perceived exertion (RPE) scale.[9] Participants progress through the stream modifying frequency and duration of exercise, as guided by the FEPP, until they reach the MS general aerobic exercise guidelines.[8] Participants can opt to maintain this activity level for the remainder of the programme if they are satisfied with their participation in their chosen sport or exercise in accordance with their goals. Alternatively, participants can progress through stream 2.

Stream 2 is for participants who meet MS general aerobic exercise guidelines. This stream is designed to incrementally progress exercise towards meeting or exceeding the MS advanced aerobic exercise guidelines.[8] These guidelines recommend an exercise duration approaching 40 min; frequency approaching 5 days per week and intensity approaching 15 on an RPE scale of 6–20 points.[8] Participants progress through the stream by modifying frequency, intensity and duration of exercise

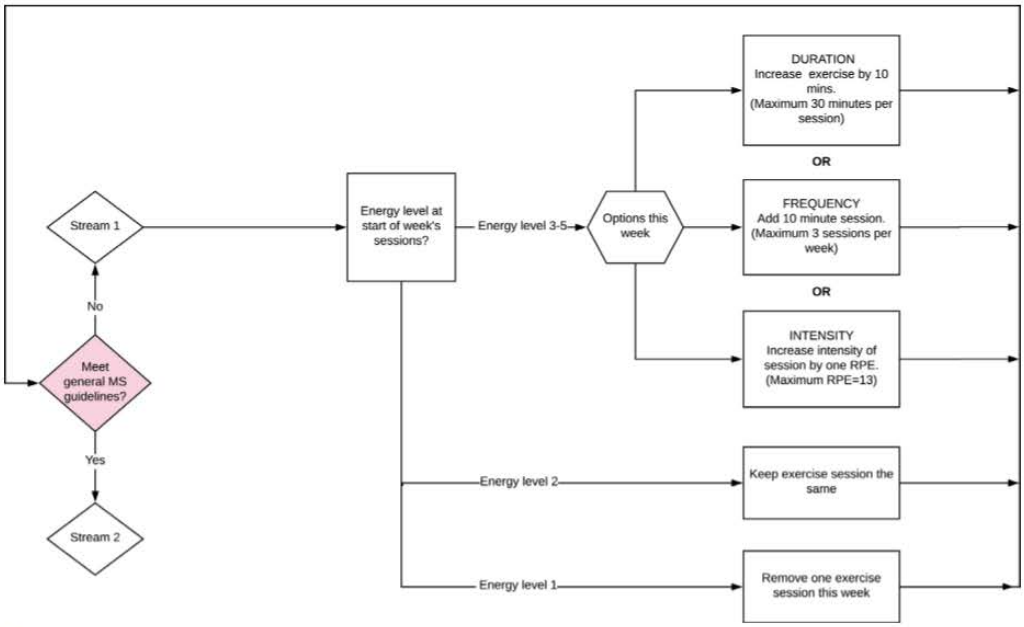

Figure 1 FEPP stream 1.

until they are satisfied with their participation in their chosen sport or exercise in accordance with their goals. This may be below, at or above MS advanced aerobic exercise guidelines. Participants continue with their optimum participation for the duration of the programme.

Each participant will begin the FEPP with an individual interview conducted by a physiotherapist (MS) to identify and discuss their goals for participation in sport or exercise. The participant determines their mode of exercise or sport, whether performed individually, with others or as part of a team, and indoors or outdoors. This information will be recorded in the participant database and exercise diary. Exercise progression will be guided by the FEPP. The FEPP stream allocation will be determined by the participant's baseline activity level recorded on entry to the programme.

Progression through the FEPP for both streams will be determined by the participant's rating of perceived energy levels over the course of each week. A single question, 'How

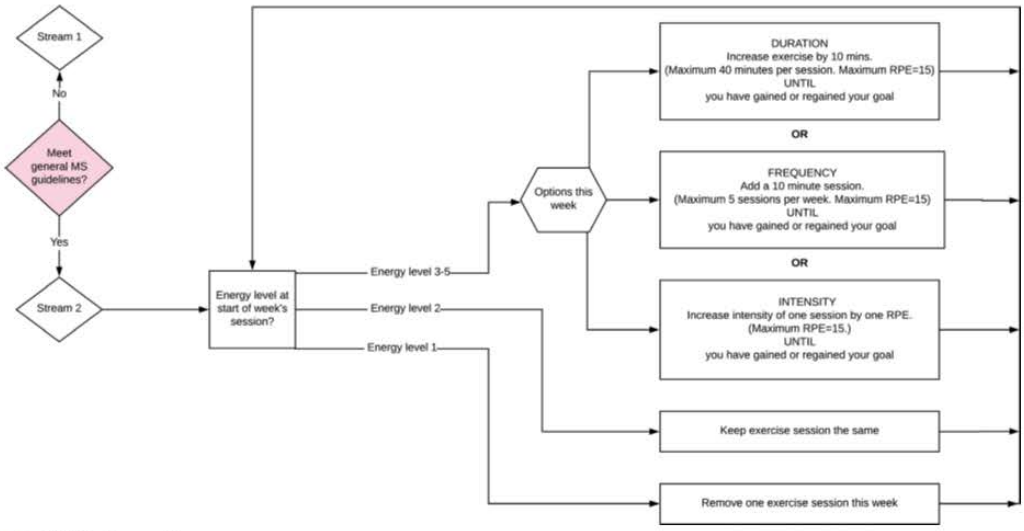

Figure 2 FEPP stream 2.

Table 1 FEPP streams

	Current aerobic exercise	Intervention	Outcome
Stream 1 Does not meet MS general aerobic exercise guidelines	Less than 30 min moderate intensity three times per week	FEPP stream 1	MS general aerobic exercise guidelines are achieved, with progress to stream 2.
Stream 2 Meets MS general aerobic exercise guidelines	30 min or more of moderate intensity three times per week	FEPP stream 2	Exercise participation goals are satisfied, which may be below, at or above MS advanced aerobic exercise guidelines.

FEPP, flexible exercise participation programme; MS, multiple sclerosis.

would you rate your overall energy levels this week?', will be scored by participants using the Energy Monitoring Tool, a 5-point energy Likert scale ranging from no energy to maximum energy (figure 3). Single-item questions such as this are used commonly to provide a quick response to self-rated health status.[36] The Energy Monitoring Tool will guide incremental progressions or regressions using manipulation of frequency, intensity, time and type of exercise, that is, the FITT principle of exercise prescription,[9] as indicated on the FEPP (figures 1 and 2).

Prior to and throughout the 12-week period, participants will be supported to participate in exercise or sport via a coaching session with a physiotherapist, once each week, via telephone. Behaviour change techniques known to assist with participation in exercise and sport[12] will be used as listed in table 2, together with their definition[12] and planned application.

Outcome measures and data collection

Data collection will take place via face-to-face visits, telephone interviews, email or post. Outcome measurement will occur face-to-face at JCU, Australia. The timeline for data collection of each outcome measure is displayed in table 3.

Feasibility outcomes

The primary objective of the study was to assess the feasibility of implementing the FEPP for individuals with MS, in accordance with stage I feasibility trials specific to MS.[37] Process, resources, management and scientific feasibility outcomes will be assessed. Process measures will include participant recruitment, eligibility, refusals, retention and attrition. Resources and management refer to the administrative aspects of the study such as data entry, finance and communication time with participants and staff. Scientific feasibility outcomes address aspects of safety, adverse events, compliance and potential treatment effects. This process of recording feasibility metrics has been used in other feasibility studies with MS populations.[38 39]

Clinical outcomes

Clinical outcomes will include the three domains of the International Classification of Functioning, Disability and Health framework,[40] which are body structures/functions, activities and participation.

Primary outcome

Participation

The primary clinical outcome is participation goals in sport and exercise according to the participant's choice measured by the Goal Attainment Scale (GAS).[41 42] The GAS measures goal achievement (positive or negative) on a 5-point scale and can be quantified as a single aggregated goal attainment score for analysis.[42] The GAS is a responsive measure for individuals with MS.[43]

During the preintervention interview with the primary researcher, participants will be asked to identify their goals for participation in exercise and sport. The participant will be guided to set specific, measurable, achievable, relevant and timed (SMART) goals,[44] for example, to cycle to work three times per week by the final 2 weeks of the FEPP. One to three goals will be set to represent the participant's key priorities.[42] Reassessment of goals by the

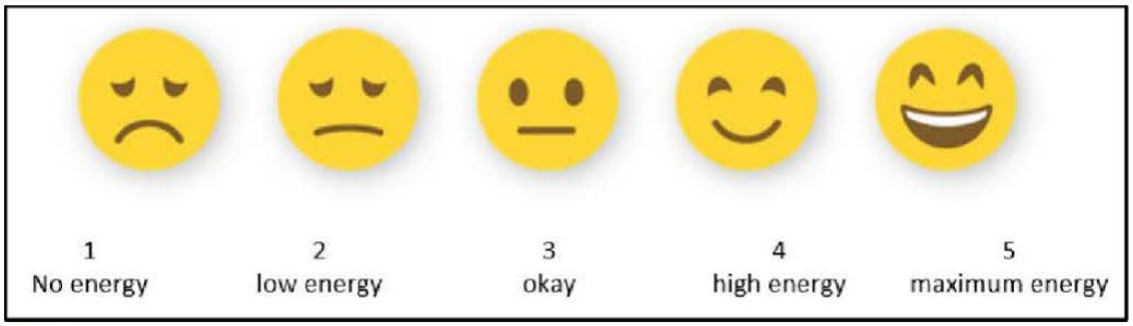

Figure 3 Energy Monitoring Tool.

Table 2 Behaviour change techniques, definitions and application framework

Technique	Taxonomy definition (brief)	Application framework
Goal setting (outcome)	The person is encouraged to set a goal that can be achieved by behavioural means but is not defined in terms of behaviour.	Exercise and sport participation goals will be set by the participant following consultation with the physiotherapist. Session: initial interview.
Action planning	Involves detailed planning of what the person will do, including, as a minimum, when, in which situation and/or where to act. 'When' may describe frequency or duration.	Guidance on the application of the FEPP to ensure appropriate and correct usage. Session: initial interview and weekly coaching.
Barrier identification/ problem solving	The person is prompted to think about potential barriers and to identify the ways of overcoming them. Barriers may include competing goals in specified situations. This may be described as 'problem solving'. Examples of barriers may include behavioural, cognitive, emotional, environmental, social and/or physical barriers.	Discussion of barriers to participating in sport and exercise and potential ways of overcoming them. Session: weekly coaching.
Prompt review of outcome goals	Involves a review or analysis of the extent to which previously set outcome goals were achieved.	Discussion of progress towards participation goals. Session: weekly coaching.
Prompt self-monitoring of behaviour	The person is asked to keep a record of specified measures expected to be influenced by the behaviour change, for example, blood pressure, blood glucose, weight loss and physical fitness.	Completion and submission of exercise diary each week. Session: weekly coaching.
Provide feedback on performance	This involves providing the participant with data about their own recorded behaviour.	Discussion and feedback on activity recorded in exercise diary. Session: weekly coaching.

FEPP, Flexible exercise participation programme.

participant will take place during the postintervention interview with the primary researcher.

Secondary outcomes

Body structures and function: plasma cytokines

To identify the effects of exercise on cytokines, a 4 mL blood sample will be collected from each participant via pathology services during the week preintervention and postintervention, which is in accordance with similar studies.[26 27 45] Blood samples will be collected between 08:00 and 09:30, following an overnight fast of at least 10 hours. Samples will be collected in the morning to prevent any circadian changes in gene expression and to allow for a more meaningful comparison.[46] Blood will be collected in 4 mL EDTA vacutainers. Following collection, blood samples will be chilled and immediately transferred to the JCU Molecular and Cell Biology Department for processing. The samples will be centrifuged, plasma collected and stored at −80°C until all samples are ready for analysis. Cytokine levels (IL-2, IL-4, IL-6, IL-10, IFN-γ and TNF) will then be tested, following manufacturer's instructions, using the commercially available kit: BD Cytometric Bead Array (CBA) Hu Th1/Th2 Cytokine Kit II.

Body functions: vitality

Perceptions of vitality will be self-reported by participants using the six-item version of the Subjective Vitality Scale, which has been validated for use with the general population[47] and has previously been used with the MS population.[48] The Subjective Vitality Scale assesses the experience of being full of energy and alive, via six questions rated on a 7-point scale from 'not at all true' to 'very true', and provides an overall score of participants' energy.[47] The primary researcher will collect these data at four time periods across the study: baseline and 4, 8 and 12 weeks (completion) via face-to-face or telephone interview.

Activities: high-level mobility

High-level mobility (ie, running or jumping) will be measured using the HiMAT[49] to explore the relationship between high-level mobility and participation in exercise for individuals with MS. The HiMAT assesses high-level mobility across 13 items, such as running, jumping and climbing stairs, with a total point score of 54 and higher scores indicating higher levels of mobility. The HiMAT is a valid and reliable tool for assessing high-level mobility.[50] A physiotherapist, who is independent of the intervention that has been trained in the use of the HiMAT, will assess the participants during the 1-week preintervention and postintervention period.

Participation

Participation in sport or exercise during the intervention period will be measured using an exercise diary. The participant will record the frequency, intensity, time and type of exercise undertaken each week in an electronic exercise diary and email it to the primary researcher on a weekly basis. Where participants do not have access to email, a paper format will be provided, together with a reply-paid envelope. FITT data will provide a record

Table 3 Data collection and outcome measures

Outcome measures		Collection procedure	Baseline evaluation	During intervention	Post intervention evaluation
Feasibility measures					
Process	▶ Recruitment. ▶ Eligibility. ▶ Refusals. ▶ Retention. ▶ Attrition. ▶ Adherence.	Documentation of ▶ All contacts with potential participants. ▶ Participant flow through study. ▶ Adherence via exercise diary.	√	Daily	√
Resources	▶ Communication. ▶ Finance.	Documentation of ▶ Duration and frequency of communication between participants/ staff (email, telephone and face-to-face contact). ▶ Communication difficulties. ▶ All costs associated with the study.	√	Daily	√
Management	▶ Data management. ▶ Staff management.	Documentation of ▶ Data collection times. ▶ Data entry and checking of data. ▶ Staffing requirements.	√	Daily	√
Scientific	▶ Safety. ▶ Adverse events. ▶ Compliance. ▶ Treatment effect.	Documentation of adverse and serious adverse events ▶ Via exercise diary. ▶ Via weekly check-in with physiotherapist. ▶ Via reporting safety concerns and adverse events as per university policy. Documentation of compliance ▶ Via exercise diary and weekly check-in. Treatment effect ▶ Documentation of clinical outcome measures preintervention/ postintervention.	√	Daily	√
Participation outcome					
Goal attainment scale		Face-to-face or telephone data collection	√		√
Clinical outcomes					
Cytokines		Collection at the James Cook University pathology site	√		√
Subjective Vitality Scale		Face-to-face or telephone data collection	√	Weeks 4 and 8	√
HiMAT		Face-to-face assessment and data collection	√		√
Exercise diary		Electronic or paper-based collection	√	Weekly	
Subjective acceptability outcomes					
Participant survey		Electronic data collection			√
Focus group interviews		Face-to-face recorded interviews			√

of change in aerobic activity across the duration of the study. Specifically, comparisons will be made on a week-by-week basis as to whether participants meet or exceed MS general and advanced aerobic exercise guidelines.

Acceptability of the FEPP

Participant survey

A participant survey will provide an initial assessment of the acceptability of the intervention to the participants. Three key areas (satisfaction, usability and suitability) will be explored in a short survey using a 5-point Likert scale (online supplementary file) based on similar surveys used with individuals with MS.[38 51] The survey will be provided electronically to each participant on completion of the study via the survey platform Qualtrics.[52] If participants are unable to access the survey electronically, it will be provided in paper format. Survey responses will remain anonymous.

Focus group interviews

Focus group interviews will take place during the 6-week postintervention period to gain greater insight into participants' perceptions of the FEPP than the survey alone. Question design will be based on participant survey results regarding acceptability and recommendations for improvement of the FEPP. In addition, the focus groups

Table 4 Acceptability of the FEPP to participants: methods for data collection

Data collection method	Questions
Participant survey	Acceptability of intervention: ► Satisfaction. ► Usability. ► Suitability.
Focus group	Acceptability of intervention ► Participant survey results will guide the questions. Effectiveness of the FEPP ► Changes in participation in physical activity, exercise or sport during the programme. ► Changes in energy levels during the programme. ► Changes in high-level mobility during the programme. ► Long-term changes in participation in physical activity, exercise or sport. Goals ► Goal setting. ► Achievement /non-achievement of goals. Finding the balance Plans to continue with physical activity, exercise or sport Suggestions to improve the FEPP or the process. ► Participant survey results will guide the questions.

will explore the participants' perspectives on the effects of the programme. The focus group study will adopt an exploratory qualitative descriptive methodology in order to gain a rich description of participants' experiences of the FEPP and to produce authentic reporting of the participants' experience.[53 54]

All participants will be invited to attend the focus group interviews. Each group will contain a minimum of three and a maximum of six participants per group, depending on participant availability. Where participants are unable to attend a focus group interview, they will be offered a one-to-one interview.

Methods used to determine FEPP acceptability are outlined in table 4.

Data management

On entry to the study, participants will be allocated a unique identifying code which will then be recorded on all datasets pertaining to that individual. The confidential coding system will be held in a file separate from the other datasets. All data will be stored on the primary researcher's computer, which is password protected. A secondary copy will be stored on a secure research storage platform. When in use, all data will be saved to the computer and backed up daily. On completion, data will be stored in the JCU institutional repository for a minimum of 15 years.

Patient and public involvement

A qualitative study on active participation in sport and exercise informed the development of this protocol.[1] Participants with minimal disability from MS highlighted that they want to participate in their preferred exercise or sport at a time that suits them. Importantly, participants identified that they need assistance in determining the dose of exercise they should undertake. This is the premise for the current feasibility study.

DATA ANALYSIS

Data analysis will occur in accordance with the objectives of the study: to assess the feasibility of the FEPP for individuals with MS and to assess the feasibility of conducting a larger clinical trial.

Feasibility data analysis

Descriptive statistics will be used to report on the process, resources, management and scientific feasibility domains of this study. The process domain (eg, recruitment and retention) will inform the feasibility of achieving the sample size required for a larger trial. The resources and management domains will inform the financial and administrative requirements for a larger trial. The scientific domain will identify the suitability of the outcome measures and any risk management required for a larger trial. In addition, the scientific domain will provide preliminary data on the effect and acceptability of the FEPP for individuals with MS and hence the feasibility of the FEPP.

Clinical data analysis

Clinical outcomes will be analysed descriptively rather than through formal hypothesis testing, as is the nature of feasibility trial data.[55] Change from pre-FEPP to post-FEPP will be described based on the (1) GAS; (2) exercise frequency, intensity and duration of exercise; (3) Subjective Vitality Scale; (4) HiMAT; and (5) cytokine levels. Changes in cytokine levels will be analysed with conventional flow cytometry analysis software by gating on the appropriate bead clusters and measuring the phycoerythrin median value for the bound analyte.

FEPP acceptability data analysis

Participant survey responses will be analysed descriptively using frequency distribution, central tendency and dispersion. Focus group data will be analysed in accordance with the exploratory qualitative descriptive methodology. Following reading and rereading of the dataset, each line of data will be coded, using a short title or word enabling clear identification of topics within the data.[56] Inductive thematic analysis will be used to analyse the patterns, with similar codes brought together to identify emergent themes from the bottom up.[54 57] Themes will subsequently be reviewed to check that they work in relation to the coded extracts by checking and rechecking the data; analysis will continue until themes are refined

and a thematic map is created.[57] Codes and patterns from one focus group dataset will be reviewed by a secondary researcher to check and verify, or to identify error, as part of quality assurance.[58] In addition, member checking will take place with one member from each focus group to ensure appropriate representation of participant experiences.

Interpretation of the data through thematic analysis will enable a well-organised descriptive evaluation of the FEPP from the perspective of the participants. The final analysis will involve exploration of how the focus group data explain the quantitative participant survey data in accordance with the sequential explanatory mixed methods design.[31]

Data analysis summary

Collectively, the data will provide a comprehensive analysis of the feasibility of conducting a larger trial to assess the effectiveness of using the FEPP with individuals with MS. Progression to a larger trial will be dependent on the logistics of implementing the trial (process and resource metrics), together with the feasibility of the FEPP. Feasibility of the FEPP will be dependent on participants' safety, ability to modify exercise prescription with minimal supervision, preliminary effectiveness and participant acceptability with the intervention. Progression to a larger trial will be dependent on achievement of specified minimum success criteria.

Ethics and dissemination

Ethical approval has been obtained for this study protocol from the JCU Human Research Ethics Committee (H7956). The research team will be briefed on the requirements for conduct of this study in accordance with the National Statement on Ethical Conduct in Human Research.[59]

This novel approach to participation in exercise in sport has been guided and driven by individuals with MS who have minimal disability. This approach has the potential to empower individuals with MS to independently engage in and optimise their participation in exercise according to their own preferences. The results of this study will inform future research in finding the balance between too much and too little participation in exercise and sport, for people with MS. Dissemination of study findings is planned via peer-reviewed journals, national and international conferences and associated media releases.

Contributors MS is the principal investigator. MS, GW and RB conceived and designed the study. MS wrote the first draft of the manuscript with subsequent revisions from all authors. MS will lead the operation of the study with support from GW and RB.

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Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. As this is a protocol paper there are currently no data.

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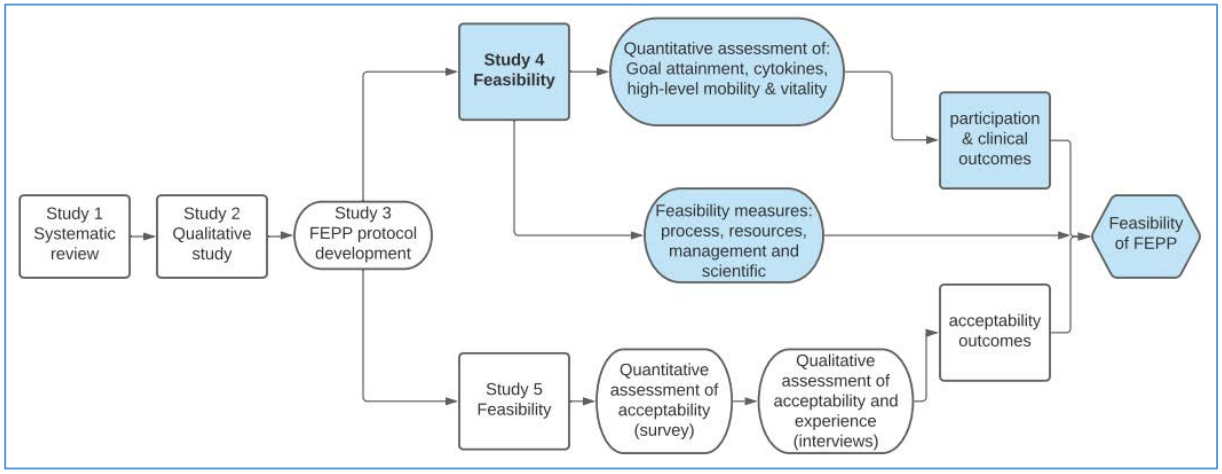
Chapter 5: The Feasibility of a Flexible Exercise Participation Program for Individuals with Multiple Sclerosis



5.1 Overview of the study

Chapter 4 contains the details of the FEPP protocol and rationale. Moving forward, the aim of Chapter 5 was to assess the feasibility of the FEPP for individuals with minimal disability from MS and the feasibility of conducting a larger trial to assess the efficacy of the FEPP. Feasibility of the FEPP was explored by assessing exercise participation, high-level mobility, vitality and cytokine biomarkers for inflammation. Feasibility of conducting a larger trial was assessed via process, resources, management and scientific outcomes. In this chapter, the feasibility of the FEPP is reported, and in Chapter 6 the acceptability of the FEPP (a component of feasibility) is reported.

5.2 Publication—feasibility qualitative study

This study has been submitted to *Physiotherapy Theory and Practice* and is under review:

Smith, M., Williams, G., Jordan, M., Willson, A., & Barker, R. (2021). The feasibility of a flexible exercise participation program (FEPP) for individuals with multiple sclerosis. *Physiotherapy Theory and Practice*. Under review.

5.3 Introduction

Multiple sclerosis hits at a point in life when many people are engaged in employment, family activities, sport and exercise, with diagnosis occurring between 20-40 years (MS International Federation, 2020; Lane & Yadav, 2020). Individuals with MS wishing to have an active lifestyle seek to fit different forms of exercise into their routine, including sporting activities such as running, cycling and squash (Akbar et al., 2021; Smith et al., 2019). However, they want health professional support to ensure they achieve a balance between too much and too little exercise (Learmonth et al., 2017; Smith et al., 2019).

A flexible exercise participation program was developed to enable individuals with minimal disability from MS to participate in an exercise or sport of their choice with remote health professional support to achieve personal exercise participation goals (Smith, Williams et al., 2020). The FEPP was underpinned by four key concepts. The first involves obtaining the MS general aerobic exercise guidelines, the MS advanced aerobic guidelines (Kim et al., 2019) and support to safely exercise beyond the advanced guidelines in the sport or exercise of their choice. Second, the FEPP provides a method to self-monitor energy levels and allay concerns expressed by individuals with MS around fatigue during or after exercise (Gullo et al., 2019; Smith et al., 2019). Third, BCTs grounded in social cognitive theory underpin the health professional support provided to enable exercise participation (Bandura, 2004; Motl et al., 2018). Fourth, the concept of a person-centred program with exercise choice is an important component of the FEPP. Rather than fitting individuals to a predetermined program, the program is fitted to individuals' priorities and goals.

Exercise participation has important health and lifestyle benefits (Motl et al., 2020), but may also have a neuroprotective effect and slow the rate of neuronal atrophy for individuals with MS (Dalgas et al., 2019). The mechanism of neuroprotection is not yet known, but may be linked to changes in biomarkers (Faramarzi et al., 2020; Negaresh et al., 2018; Negaresh et al., 2019). With MS, there is an increased presence of pro-inflammatory cytokines such as TNF, IFN-γ and IL-6 (Negaresh et al., 2018; Palle et al., 2017) (noting that IL-6 also has anti-inflammatory properties) (Scheller et al., 2011), and a reduction in anti-inflammatory cytokines IL-10 and IL-4 (Negaresh et al., 2018; Palle et al., 2017). This creates a pro-inflammatory environment, which may intensify myelin destruction and prevent remyelination (Negaresh et al., 2018). There is some evidence that exercise may improve the cytokine balance (i.e. reduce pro-inflammatory and increase anti-inflammatory cytokines),

hence reducing the overall inflammation. However, further research is required (Negaresh et al., 2018).

Given the potential for exercise to affect the disease process, it is essential to explore programs for engaging and sustaining exercise participation. Thus, the objectives of this study were to:

1) assess the feasibility of the FEPP for individuals with minimal disability from MS
2) assess the feasibility of a larger clinical trial to evaluate the impact of the FEPP.

5.4 Methods

5.4.1 Study design

This feasibility study consisted of a single group pre-/post-intervention design. Ethical approval was granted by the James Cook University Human Research Ethics Committee (H7956) (see Appendix D), and the study was registered with the Australian New Zealand Clinical Trials Registry, ACTRN12620000076976 (see Appendix E). The study was conducted according to the published FEPP protocol (Smith, Williams et al., 2020), with one minor deviation that allowed email instead of telephone contact if a participant could not be contacted for the weekly coaching call.

5.4.2 Participants

Participants were recruited in northern Queensland, Australia via MS Queensland, local neurologists and media sources (i.e. television, social media). Inclusion criteria were (i) diagnosis of RRMS as defined by the 2017 McDonald criteria (Thompson et al., 2018), (ii) independent mobility as defined by EDSS level 0–3.5 (Kurtzke, 1983), (iii) stable (i.e. not worsening) in past three months (Lublin, 2014), (iv) aged > 18 years and (v) able to provide informed consent. Potential participants were excluded if they had (i) any concomitant neurological condition or (ii) an additional health condition that prohibited participation in exercise. Written informed consent was provided.

5.4.3 Intervention

Participants engaged in the 12-week FEPP (Smith, Williams et al., 2020), in which they chose their preferred exercise or sport, set goals for exercise participation and completed the exercise at a time and place suitable to them. Progression towards their goals was guided using a FEPP flowchart (Smith, Williams et al., 2020), and their perceived energy levels each week were measured using a 5-point Likert scale (where 1 indicated no energy and 5 indicated maximum energy). Participants were allocated into one of two streams: Stream 1 for

participants who did not meet the exercise participation levels in the MS general aerobic exercise guidelines (Kim et al., 2019); and Stream 2 for participants who did. Each stream involved graded progression towards meeting or exceeding the respective MS exercise guidelines or maintaining their exercise participation in accordance with their goals.

Participants were supported remotely by a physiotherapist via a weekly coaching telephone call over the 12-week intervention period. To promote self-management of exercise, coaching sessions focused on BCTs drawn from the behaviour change taxonomy (Michie et al., 2011). Techniques included goal setting, problem solving and action planning (Table 4), which are known to assist with participation in exercise and sport for individuals with MS (Silveira et al., 2021).

Table 4. Behaviour change techniques, definitions and application framework

Technique	**Taxonomy Definition (brief)**	**Application Framework**
Goal setting (outcome)	The person is encouraged to set a goal that can be achieved by behavioural means but is not defined in terms of behaviour.	Exercise and sport participation goals will be set by the participant following consultation with the physiotherapist. Session: Initial interview.
Action planning	Involves detailed planning of what the person will do including, as a minimum, when, in which situation and/or where to act. 'When' may describe frequency or duration.	Guidance on application of the FEPP to ensure appropriate and correct usage. Session: Initial interview and weekly coaching.
Barrier identification/problem solving	The person is prompted to think about potential barriers and identify the ways of overcoming them. Barriers may include competing goals in specified situations. This may be described as 'problem solving'. Examples of barriers may include behavioural, cognitive, emotional, environmental, social and/or physical barriers.	Discussion of barriers to participating in sport and exercise and potential ways of overcoming them. Session: Weekly coaching.
Prompt review of outcome goals	Involves a review or analysis of the extent to which previously set outcome goals were achieved.	Discussion of progress towards participation goals. Session: Weekly coaching.
Prompt self-monitoring of behaviour	The person is asked to keep a record of specified measures expected to be influenced by the behaviour change, e.g. blood pressure, blood glucose, weight loss, physical fitness.	Completion and submission of exercise diary each week. Session: Weekly coaching.
Provide feedback on performance	This involves providing the participant with data about their own recorded behaviour	Discussion and feedback on activity recorded in exercise diary. Session: Weekly coaching.

5.4.4 Measurement—trial feasibility

Feasibility of a larger trial of the FEPP was assessed by measures of process (recruitment and retention), resources, management (communication time and data entry) and scientific feasibility (safety, compliance, serious adverse events/effects and adverse events/effects). The a priori minimum success criteria were:

1) a minimum of 75% recruitment of the intended 16 participants
2) a minimum of 20% attrition from the 12-week FEPP
3) a minimum of 80% of participants able to modify exercise participation using the FEPP
4) a minimum of 75% completion of each outcome measure
5) no reports of serious adverse events or effects as a result of completing the FEPP
6) a minimum of 80% of participants report satisfaction with the FEPP.

5.4.5 Measurement—Flexible Exercise Participation Program feasibility

Feasibility of the FEPP was assessed in relation to its suitability to enable exercise participation, its potential relationship with clinical outcomes and its acceptability via the following primary and secondary outcomes obtained at baseline (week 0) and post-intervention (week 13).

5.4.5.1 Primary outcome measure

The primary outcome was achievement of exercise participation goals as measured by the Goal Attainment Scale (GAS) (Turner-Stokes, 2009), which measures goal achievement on a 5-point scale, quantified as a single aggregated goal attainment score (GAS T-score) for analysis (Turner-Stokes, 2009).

5.4.5.2 Secondary outcome measures

Exercise participation was recorded by participants using a weekly exercise diary to detail frequency, intensity, duration and mode of exercise. This information identified whether the participant met, did not meet or exceeded the MS aerobic exercise guidelines in their stream each week.

High-level mobility was measured using the HiMAT to assess 13 items important for sport, such as running, jumping and bounding (Williams et al., 2004). Scored out of 54, higher scores indicate higher levels of mobility. The minimal detectable change (MDC) is

indicated by an improvement of ≥ 4 points or a deterioration of ≥ 2 points (Williams et al., 2006).

Vitality was self-reported by participants using the Subjective Vitality Scale (SVS) at weeks 0, 4, 8 and 12 (Bostic et al., 2000). This six-question survey was rated using a 7-point Likert scale and provided an average score of participants' energy (out of 7), with higher scores indicating greater energy.

Cytokine response to exercise was assessed via blood plasma samples collected from each participant pre- and post-intervention, as per the published protocol (Smith, Williams et al., 2020). Cytokine levels IL-2, IL-4, IL-6, IL-10, IFN-γ and TNF were tested following the manufacturer's protocol using the commercially available kit BD Cytometric Bead Array Hu Th1/Th2 Cytokine Kit II (BD Biosciences). Manufacturer-reported detection limits were 2.6 pg/mL (IL-2), 2.6 pg/mL (IL-4), 3.0 pg/mL (IL-6), 2.8 pg/mL (IL-10), 2.8 pg/mL (TNF) and 7.1 pg/mL (IFN-γ). Increased TNF and IFN-γ is indicative of a pro-inflammatory response, and an increase in IL-4 or IL-10 indicates an anti-inflammatory response. IL-2 and IL-6 can exert either a pro- or anti-inflammatory response (Boyman & Sprent, 2012; Scheller et al., 2011).

Acceptability of the FEPP by participants was assessed using a sequential explanatory mixed-methods design (Creswell & Plano Clark, 2018). Participants completed an online survey at the end of the 12-week program via the survey platform Qualtrics (QualtricsXM, 2019). The survey explored satisfaction, usability and suitability using a 5-point Likert scale (where 1 indicated low satisfaction/agreement and 5 indicated high satisfaction/agreement). Survey results were used to develop a question guide for interviews with participants during the six-week period post-intervention. Interviews were conducted individually or in focus groups.

5.4.6 Data analysis

Participant characteristics were summarised using descriptive statistics. Feasibility of a larger trial was assessed by comparing a priori minimum success criteria to measures of process, resources, management and scientific safety using descriptive statistics.

Changes from pre- to post-intervention for the GAS, HiMAT and SVS were described quantitatively and compared using the Wilcoxon signed-rank test (statistical significance set at $p < 0.05$). Exercise participation was categorised into number of sessions completed below, between or beyond the exercise guidelines and reported as a percentage for each category.

Changes from pre- to post-intervention for cytokine levels were described quantitatively and compared using a paired t-test (statistical significance set at $p < 0.05$). A one-sample Kolmogorov–Smirnov test was used to check for normal distribution of the data.

Survey responses on acceptability of the FEPP were analysed descriptively. Inductive thematic analysis was used to identify emergent themes from the interview data (Braun & Clarke, 2006; Stanley, 2015). Survey and interview findings were integrated to allow greater explanation of the survey findings and extraction of recommendations for improvement of the FEPP.

Statistical analyses were conducted using SPSS Statistics version 27 (IBM Corp). Cytokine analyses and graphs were generated in GraphPad version 9.1.2 (Prism). Thematic analysis was managed using NVivo software version 12 (QSR International Pty Ltd).

5.5 Results

5.5.1 Participants

Eleven participants enrolled in the study, of whom nine were female, with a mean age of 47 years (SD: 9.9; range 30–65). Mean EDSS was 1.8 (SD: 0.5; range 1.5–3) and mean duration of MS was 11 years (SD: 7.3 range 0.33–24). Participants chose to participate in a range of exercises and sport including walking, running, dancing, aerobic gym sessions, cycling, golf, swimming, water aerobics and touch football. At baseline, three participants (27%) were exercising below the general aerobic exercise guidelines, six (55%) between the general and advanced exercise guidelines, and two (18%) beyond the advanced exercise guidelines.

5.5.2 Trial feasibility

5.5.2.1 Process

Recruitment commenced in January 2020 and was affected by the onset of the COVID-19 pandemic in February 2020. By March 2020 a hard lockdown was in place for two months in Queensland, limiting access to gyms and sporting activities, with restrictions gradually easing across the remainder of the year. Participant flow through the trial is presented in Figure 5. Eighty-five per cent of the total eligible participants consented to enrol in the study. Retention was high at 91%, with only one participant withdrawing at week 4 because of the personal effect of the COVID-19 restrictions.

5.5.2.2 Resources and management

Coaching sessions with each participant included an in-person baseline interview with a mean duration of 39 minutes (SD: 6.6, range 30–50 minutes), and telephone coaching with a mean duration of 10 minutes (SD: 3.8, range 3–26) per week. Eighty-nine per cent of the coaching calls made were received by participants, with the remaining 11% conducted via email contact. Time spent on data collection and entry for outcome measures by the researcher included face-to-face contact time per participant (pre-intervention plus post-intervention) with a mean time of 44 minutes (SD: 2.1, range 42–49).

5.5.2.3 Scientific safety and compliance

No serious adverse events or effects occurred. Two adverse events were reported, with two participants experiencing a fall during their exercise participation for the study. Both participants sustained minor injuries and were able to continue with the study within two days. Compliance with electronic submission of the exercise diary each week reached 99%.

5.5.2.4 A priori minimum success criteria

All criteria were met except for criteria i) a minimum of 75% recruitment of the intended 16 participants (11 participants were recruited). Recruitment was affected by the COVID-19 pandemic as a result of lockdown during the data collection period of March to May 2020.

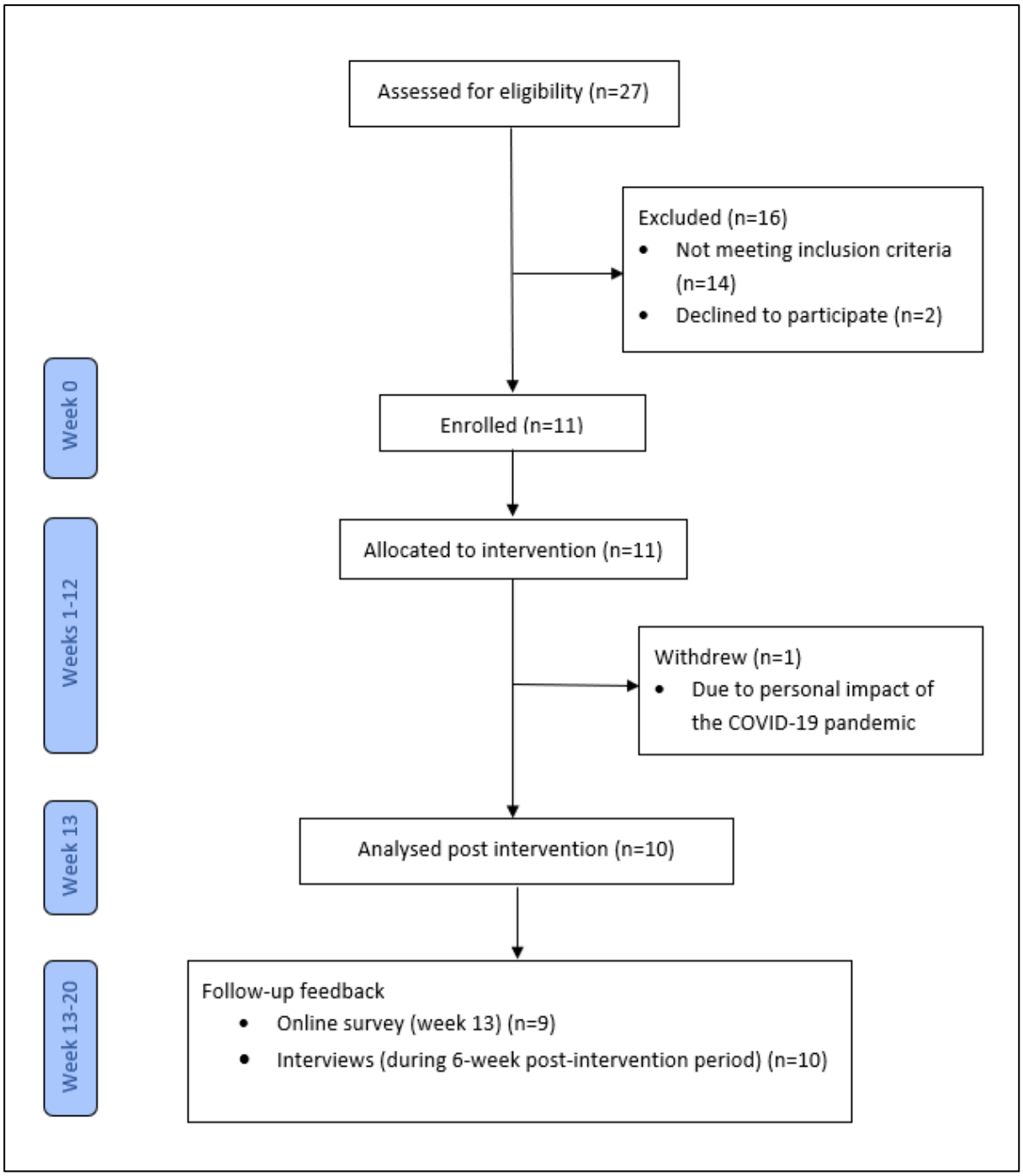


Figure 5. Participant flow diagram

5.5.3 Flexible Exercise Participation Program feasibility

5.5.3.1 Primary outcome

GAS T-scores increased significantly, indicating achievement of exercise participation goals ($z = 2.68$, $p = 0.01$). The median change in the GAS T-score was 11.4 (IQR: 8.0–18.2), with 16 out of 26 goals achieved (see Table 5).

Table 5. Pre- and post-intervention clinical outcomes

				Wilcoxon signed-rank test	
Outcome measure	**Pre-intervention: median (IQR)**	**Post-intervention: median (IQR)**	**Median difference: median (IQR)**	**z**	**p**
GAS	36.3 (36.3–38.4)	50.0 (44.3–54.6)	11.4 (8.0–18.2)	2.68	<0.01*
HiMAT	36.0 (24.0–46.0)	40.5 (26.5–47.5)	2.5 (0.8–5.0)	2.50	0.01*
SVS	5.5 (4.4–6.0)	5.6 (5.0–6.3)	0.3 (−0.2–0.9)	1.36	0.17

Key: GAS = Goal Attainment Scale; HiMAT = High-level Mobility Assessment Tool; SVS=Subjective Vitality Scale; IQR = interquartile range; * Statistically significant

5.5.3.2 Secondary outcomes

Exercise participation recorded each week indicated that 7 out of 10 participants achieved beyond the advanced exercise guidelines. Importantly, participants were able to safely advance their exercise participation. Table 6 provides a breakdown of the weekly exercise participation for each participant and whether it fell below, between or beyond the aerobic exercise guidelines.

Table 6. Number of weeks spent in each exercise participation category, per participant

		Number of weeks in each exercise participation category		
Participant	**Baseline exercise level (week 0)**	**Below general**	**Between general & advanced**	**Beyond advanced**
1	Below general	1	9	2
2	Below general	0	1	11
3	Between general and advanced	0	0	12
4	Between general and advanced	3	9	0
5	Between general and advanced	5	7	0
6	Between general and advanced	1	1	10
7	Between general and advanced	4	8	0
8	Between general and advanced	0	0	12
9	Beyond advanced	0	0	12
10	Beyond advanced	0	0	12
Total sessions in each category		14 (12%)	35 (29%)	71 (59%)

HiMAT scores improved significantly from pre- to post-intervention (z = 2.50, p = 0.01) (see Table 5), indicating an improvement in high-level mobility. Eight out of 10 participants improved their HiMAT scores, with three demonstrating an improvement greater than the MDC score. There was no difference in SVS pre- to post-intervention (z = 1.36, p = 0.17) (see Table 5).

Cytokine concentrations of IL-2 significantly increased post-intervention (t(9) = 2.5; p = 0.03), which may indicate a pro- or anti-inflammatory response due to its dual action. The trend for the remaining interleukins (IL-4, IL-6, IL-10) was to increase post-intervention and for TNF to decrease, which may indicate an anti-inflammatory response; however, statistical significance was not reached (see Figure 6). Concentrations of IFN-γ fell below the level of detection and were not reported.

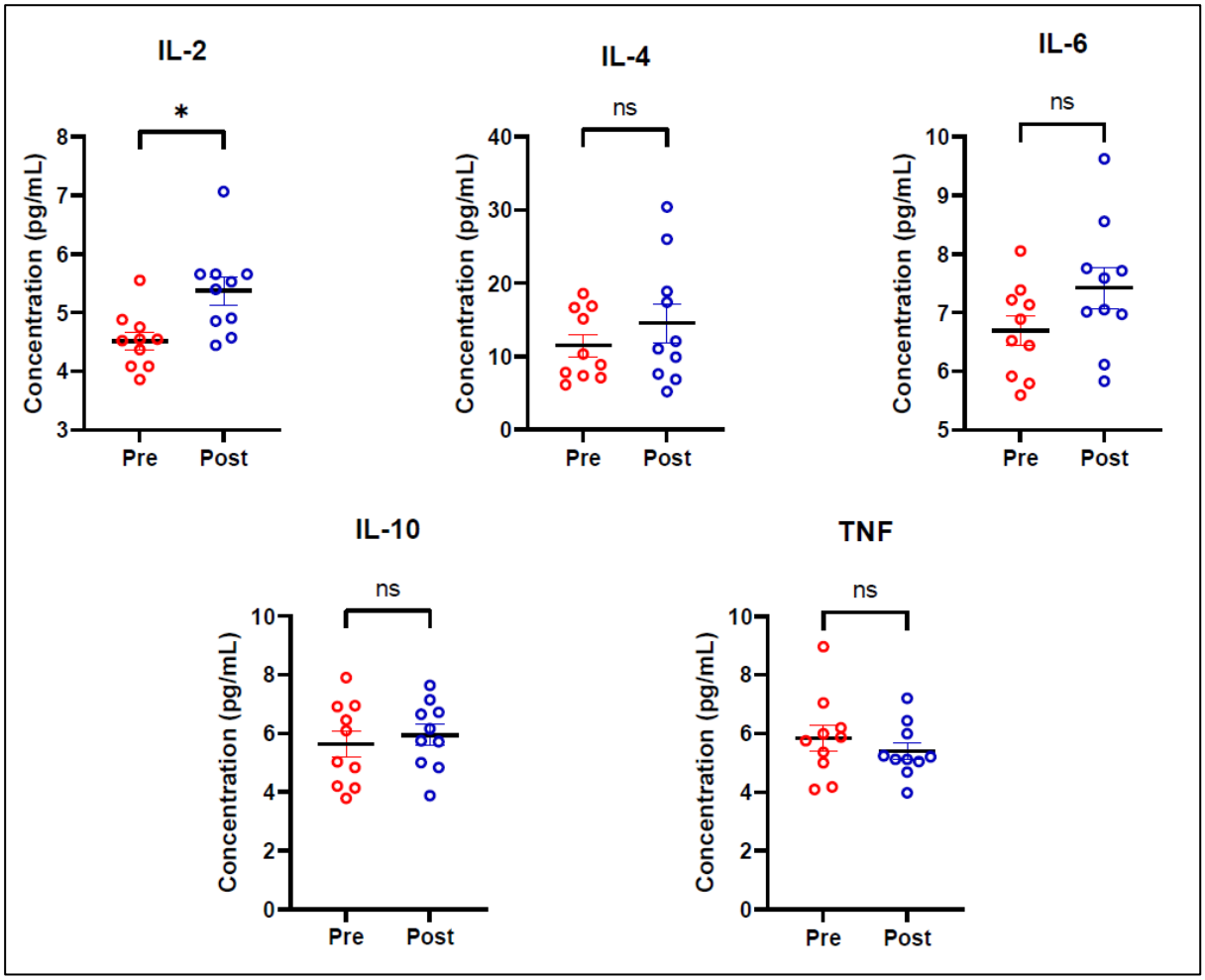


Figure 6. Cytokine responses to exercise (pg/ml)

*Data presented pre and post 12-week FEPP as individual values, group mean ± SE. Wilcoxon signed-rank test statistical significance set at *p < 0.05; ns = not significant.*

The FEPP acceptability survey was returned electronically by 9 out of 10 participants. Overall, participants were satisfied with the FEPP, its utility and its suitability, with a median score of 5 out of 5 (see Table 7). Ten participants were interviewed and reported that the flexibility of the FEPP was highly valued in conjunction with coaching from the physiotherapist. Participants recommended that the recording of energy level could be improved by measuring pre- and post-exercise and calculating an average energy level for the week to guide exercise progression. The participants' experience of the FEPP has been published elsewhere (Smith et al., 2021) (see Chapter 6).

Table 7. Acceptability of the FEPP, survey results

Topic area	**Question content**	**Survey score (1–5)**	
		Median (IRQ)	**Range**
Satisfaction	FEPP overall	5 (5–5)	4–5
	Telephone contact—amount	5 (5–5)	5–5
	Telephone contact—advice	5 (5–5)	5–5
Utility	FEPP flowchart	5 (5–5)	4–5
	Energy monitoring tool	5 (4.5–5)	3–5
	Exercise diary	5 (5–5)	4–5
Suitability	Fitness level	5 (5–5)	5–5
	Time requirement	5 (5–5)	5–5
	Exercise progression	5 (5–5)	5–5

Key: FEPP = Flexible Exercise Participation Program; IQR = interquartile range

5.6 Discussion

This study demonstrated that the FEPP is feasible, safe and highly acceptable for individuals with MS with minimal disability. This novel intervention enabled individuals with MS to participate in an exercise or sport of interest to them, that fitted with their lifestyle, and that often demanded a high level of mobility, such as running, dancing or football. In essence, the FEPP was individually tailored and led to personal goal achievement. Further, the findings suggest that a larger clinical trial to evaluate the effect of the FEPP is feasible and warranted.

The FEPP is the first exercise program for individuals with MS to involve challenging high-level exercise of their choice and to demonstrate improvement in high-level mobility, which is not commonly assessed or targeted in this population (Smith, Barker et al., 2020). The FEPP enabled the progression of exercise at a rate that was acceptable to the individual depending on their personal goals, and that met or exceeded the MS aerobic exercise

guidelines (Kim et al., 2019). With 59% of weekly sessions completed beyond the advanced aerobic exercise guidelines, the capacity and desire of some individuals with MS to push the boundaries of exercise participation was evident. Exploring the capacity to exercise, particularly in the early stages of the disease process, is essential to identify any relationship with neuroprotection and to provide early implementation of an optimal exercise prescription (Dalgas et al., 2019; Riemenschneider et al., 2021; Riemenschneider et al., 2018).

Multiple sclerosis exercise guidelines (Kim et al., 2019; Latimer-Cheung, Martin Ginis et al., 2013) recommend a gradual progression of exercise, whereas the FEPP provides an individualised approach to safe progression and regression with greater specificity, depending on the energy levels of the participant each week. Finding the right balance with exercise can be difficult for people with MS (Smith et al., 2019); therefore, provision of a tool to navigate periods of low energy is a novel approach encouraging self-efficacy. This enabled variability in the program on a weekly basis to fit the individual while still addressing the need for exercise to combat fatigue (Motl & Sandroff, 2020; Razazian et al., 2020). Measurement of energy levels on a daily rather than weekly basis will be included in future versions of the FEPP.

Cytokine data were cautiously suggestive of an anti-inflammatory response to exercise. IL-2 demonstrated a significant increase post-exercise, which may indicate an anti-inflammatory response (stimulation of regulatory T cells) or a pro-inflammatory response (stimulation of cytotoxic T cells) (Boyman & Sprent, 2012). Given the trend towards an anti-inflammatory response from the other cytokines (decrease in TNF, increase in IL-4, IL-10 and IL-6), it is possible that IL-2 was activating an anti-inflammatory response. An anti-inflammatory response to exercise has been identified in healthy adults with an increase in IL-10 and IL-6 post-exercise (Sharif et al., 2018). In previous studies with people with MS, findings have been inconsistent (Negaresh et al., 2018). However, increases in IL-6 (Berkowitz et al., 2019; Devasahayam et al., 2021) and IL-10 (Barry et al., 2019) have been identified post-exercise, similar to trends in this study. Findings from this study cautiously suggest an anti-inflammatory response to exercise, however, a larger sample size and controlled trial are required to explore the neuroprotective benefits of the FEPP.

A larger clinical trial to evaluate the effect of the FEPP is feasible and warranted given that all a priori minimum success criteria were met, except for recruitment, which was halted, and the target sample size was not met because of COVID-19 government restrictions. Data

have been collected on process, resources and management to guide the requirements of a larger trial. Preliminary findings suggest that this intervention is safe, acknowledging two falls during exercise as adverse events.

5.6.1 Study limitations

This feasibility study had a small sample size and no control group; hence, the findings regarding the FEPP outcomes should be interpreted with caution. Volunteer bias may have occurred because the FEPP likely attracted individuals with an interest in exercise. In addition, participants were only recruited from and exercised within the environment of regional northern Queensland and therefore may not be representative of the general population. A larger, sufficiently powered randomised controlled trial with longer-term follow-up is feasible and warranted to confirm the efficacy and sustainability of the FEPP.

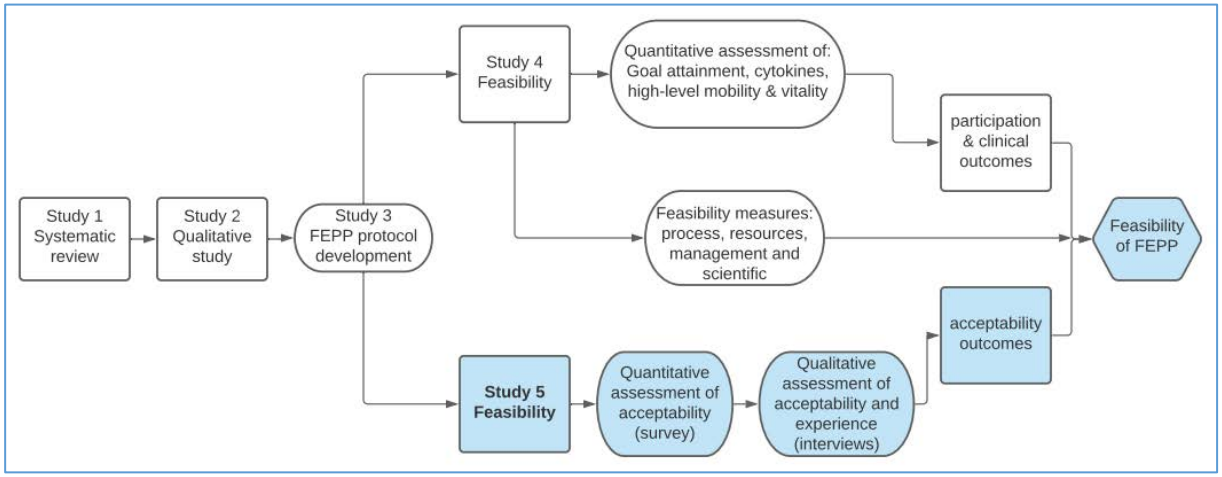
5.7 Conclusion

The FEPP was highly acceptable, safe and feasible for use with individuals with MS with minimal disability. FEPP participants achieved their personal exercise participation goals across a variety of exercises and sport while monitoring energy levels. A larger trial is both feasible and warranted to evaluate the effect of FEPP and the neuroprotective effects, and to enable individuals with MS to find the right balance with participation in exercise and sport.

Highlights

- The FEPP is feasible, safe and acceptable for people with MS.
- People with MS can engage in exercise beyond the MS advanced exercise guidelines.
- A larger trial to assess the effectiveness of the FEPP is feasible and warranted.

Chapter 6: Consumer Experience of a Flexible Exercise Participation Program for Individuals with Multiple Sclerosis: A Mixed-Methods Study



6.1 Overview of the study

In Chapter 5, the FEPP was reported to be safe and feasible for individuals with minimal disability from MS. In Chapter 6, the experience of participating in the FEPP is reported as a mixed-methods study. The aims of this study were to determine the acceptability of the FEPP and recommendations for improvement from the perspective of the FEPP participants. This study was an integral part of determining the overall feasibility of the FEPP.

6.2 Publication—feasibility mixed-methods study

This study has been published as:

Smith, M., Neibling, B., Williams, G., Birks, M., & Barker, R. (2021). Consumer experience of a flexible exercise participation program (FEPP) for individuals with multiple sclerosis: A mixed-methods study. *Physiotherapy Research International*, *26*(4), Article e1922. https://doi.org/10.1002/pri.1922

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RESEARCH ARTICLE

WILEY

Consumer experience of a flexible exercise participation program (FEPP) for individuals with multiple sclerosis: A mixed-methods study

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Abstract

Background and Purpose: The flexible exercise participation program (FEPP) is a novel intervention developed to enable individuals with multiple sclerosis (MS) participate and progress in an exercise or sport of their choice. The FEPP is underpinned by guidelines on aerobic exercise for individuals with MS and is supported by a physiotherapist using behaviour change techniques. As part of a FEPP feasibility trial, the aim of this nested study was to explore the experience of participation in the FEPP from the perspective of individuals with MS. The objectives were to (i) determine the acceptability of the FEPP and (ii) identify recommendations for improvement.

Methods: A mixed methods study using a sequential explanatory design was conducted. Part I consisted of a quantitative participant survey. Survey data were analysed descriptively using SPSS and informed the protocol for part II – qualitative interviews. Interview data were analysed thematically using NVivo. Part III consisted of integration of quantitative and qualitative data to allow greater explanation of survey responses. Individuals with MS who had participated in the FEPP feasibility trial were invited to take part in the study.

Results: The FEPP was highly acceptability to the 10 participants. Five themes emerged to describe the experience of participating in the FEPP: (i) exploring exercise boundaries, (ii) measuring energy, (iii) acknowledging accountability, (iv) adjusting to exercising in a pandemic and (v) sustaining participation. Recommendations for improving the FEPP included changes to energy level monitoring and incorporation of peer support mechanisms.

Discussion: Participants found the FEPP highly acceptable and valued the flexibility to choose their own activity and the health professional support. Based on participant recommendations, future versions of the FEPP will include daily rather than weekly monitoring of exercise and peer support to further enable individuals with MS to find the right balance with exercise and sport.

KEYWORDS
behavioural change techniques, COVID-19, exercise, multiple sclerosis

Chapter 7: Discussion and Conclusions

This chapter provides a broad overview of the aims and outcomes of each of the studies in this thesis. Detailed discussions of each study, as well as their strengths and limitations, are reported in the respective chapters. In this overview, the clinical implications of the findings from each chapter in the thesis are discussed, together with future directions for research that arise from the thesis.

7.1 Overview

Young active individuals with MS, such as Emily Petricola, provided the impetus and inspiration for this research. Hence, the focus of this PhD thesis has been on creating opportunities for individuals with MS to strive for and achieve success with exercise and sport. Multiple sclerosis commonly occurs between 20-40 years of age (MS International Federation, 2020), when life is generally active and busy with parenting, and pursuing career and sporting goals. Participation in sport and exercise, whether for health, competition, work or leisure, is part of a normal active lifestyle. Achieving participation in an active lifestyle demands mobility greater than walking, such as running, jumping, bounding, sport and exercise. However, interventions to support and progress participation in high-level mobility activities for individuals with MS were lacking.

The aim of this thesis was to develop an exercise program to optimise sport and exercise participation by individuals with minimal disability from MS. The overarching objective was to enable individuals with MS to participate in and maintain an active lifestyle for as long as possible.

7.2 Synthesis and key findings

7.2.1 Study 1: Systematic review—exercise and high-level mobility

This thesis began with a systematic review that demonstrated that sport and exercise activities involving high-level mobility were not commonly targeted or assessed with individuals with MS (Smith, Barker et al., 2020). Running, outdoor pursuits and sport did not feature as interventions for individuals with MS. This highlighted a need to create opportunities to target and explore the benefits of high-level mobility as part of participation in a normal active lifestyle for individuals with minimal disability from MS.

7.2.2 Study 2: A qualitative study of active participation in exercise and sport

The next step in the thesis was to explore the perspective of individuals with MS on participation in exercise and sport through a qualitative study (Smith et al., 2019). Key

findings included requests from individuals with MS for support to participate in the sport or exercise of their choosing, and at a time and place that suited them. Individuals with MS wanted to participate in activities that demanded a high level of mobility, such as trail running and outdoor cycling. In addition, they wanted health professional support to help them find the right balance with sport and exercise (i.e. how to appropriately scale exercise up or down to optimise the outcome). Thus, a demand for something different was evident. Accordingly, the views and opinions of individuals with MS from the qualitative study were coupled with the findings of the systematic review to develop a consumer-driven exercise intervention for individuals with minimal disability from MS.

7.2.3 Study 3: Development of the Flexible Exercise Participation Program

In the third study in this thesis, the FEPP (Smith, Williams et al., 2020) was created in response to the requests made by individuals with MS (Smith et al., 2019). The FEPP is a 12-week exercise program that enables individuals with MS to participate in their chosen sport or exercise with weekly telephone coaching support from a physiotherapist. Choosing their own sport ensures that individuals with MS can undertake a sport or exercise of interest to them, that is suitably challenging. FEPP participants work towards personal and meaningful exercise participation goals. Scaling progression or regression of exercise in the FEPP is determined by monitoring energy levels and making changes according to the FEPP flowchart, which is based on the MS aerobic exercise guidelines (Kim et al., 2019).

7.2.4 Study 4: Feasibility of the Flexible Exercise Participation Program

Determining the feasibility of the FEPP and of conducting a larger trial to evaluate the effectiveness of the FEPP became the next important step in the thesis. Feasibility of the FEPP was confirmed by participants' ability to modify and progress exercise participation using the FEPP, and achievement of exercise participation goals. High-level mobility improved, vitality remained unchanged and cytokine responses were suggestive of an anti-inflammatory response to exercise following the 12-week program.

The feasibility of conducting a larger trial was assessed across four domains of process, resource, management and scientific outcomes. All a priori minimum success criteria were met except for recruitment (n = 11), which was affected by the COVID-19 pandemic restrictions. However, 11 participants were deemed adequate for the feasibility study. By design, feasibility studies are limited in sample size and are not intended to be generalisable

or to demonstrate effectiveness. Instead, the feasibility study demonstrated that a larger trial to demonstrate the effectiveness of the FEPP was feasible, safe and warranted.

7.2.5 Study 5: Acceptability of the Flexible Exercise Participation Program

The final study in this thesis verified that the FEPP was highly acceptable from the perspective of the individuals with MS who participated in the FEPP trial (Smith et al., 2021). Participants valued the flexibility and the individualised nature of the program. The ability to choose their own exercise mode enabled participation across a wide variety of sports and exercise, much of which demanded a high level of mobility. Recommendations made by participants for improvement of the FEPP included monitoring energy on a daily basis and the possibility of including peer support mechanisms during the program.

Overwhelmingly, the FEPP was perceived to be safe, feasible and highly acceptable to individuals with minimal disability from MS. The FEPP supported individuals with MS to find the right balance with participation in exercise and sport.

7.3 Key contributions and implications

7.3.1 Overview

It is clear from this thesis that individuals with MS have not been challenged to engage in sport or exercise that demands a high level of mobility, and high-level mobility has not been proactively measured. The bar needs to be set higher, and health professionals can facilitate this. Individuals with MS requested support to engage in a challenging sport or exercise of their choice, and when challenged and supported to step up to the challenge, they were able to participate in exercise and sport that demanded a high level of mobility, and they were able to maintain or increase their high-level mobility skills. In addition, changes in cytokine levels following the 12-week FEPP suggested that the participants had an anti-inflammatory response to exercise, which is an important consideration for neuroprotection. Collectively, there is a need to shift away from limiting exercise and instead challenge exercise participation by breaking boundaries to enable individuals with MS to reach their full potential.

Emily Petricola achieved gold in the women's cycling C4 3000m individual pursuit at the 2021 Tokyo Paralympics (Olympics, 2021). She was 14 years post-MS diagnosis at the time. Emily set out to achieve her full potential and, in so doing, she smashed the boundaries for sport and exercise for individuals with MS. While not all individuals with MS will set their sights as high as Emily, the FEPP can provide stepping stones for each individual with

minimal disability from MS to engage with sport and exercise to achieve their own personal goals and explore their own potential.

7.3.2 Breaking exercise boundaries

The FEPP was novel in that it enabled the progression of exercise participation beyond the MS aerobic exercise guidelines (Kim et al., 2019). When the participants had difficulty knowing how hard to push themselves, the FEPP provided a framework that was based on the MS aerobic guidelines and delivered the support to progress beyond them. Many participants chose to progress beyond the MS advanced aerobic guidelines, which demonstrated their capacity and highlighted their ability to progress without adverse effects. This is an important outcome to share with the MS community, particularly given that individuals with MS have been known to limit exercise participation in fear of exacerbating symptoms (Smith et al., 2019). Participants could break exercise boundaries in relation to the MS exercise guidelines and break their own personal pre-existing exercise boundaries. Now it is up to health professionals to support individuals with MS to challenge their limits and achieve success in sport and exercise.

Another important breakthrough in this thesis was that individuals with minimal disability from MS demonstrated that they could engage in exercise and sport that demanded a high level of mobility. Participants in the FEPP feasibility trial chose challenging activities such as touch football, running and outdoor cycling and showed that the capacity was there. This suggests that health professionals can lift expectations and support individuals with minimal disability from MS to engage in challenging activities of their choice. The FEPP feasibility trial demonstrated that improvements in high-level mobility were possible with participation in exercise and sport. Now it is essential to determine whether high-level mobility can be improved and maintained as part of a normal active lifestyle through participation in exercise and sport.

7.3.3 Neuroprotection

The idea that exercise may have a neuroprotective effect is an exciting concept. The findings from this thesis are cautiously suggestive of an anti-inflammatory cytokine response following participation in the 12-week FEPP. However, further investigation with a larger, adequately powered trial is required. Evidence around this topic of cytokine response to exercise is variable and can be conflicting (Negaresh et al., 2018). It is unclear whether changes in cytokines following exercise are a mechanism for neuroprotection in MS.

However, the FEPP provides an opportunity to explore this hypothesis further while providing individuals with MS with a sustainable pathway for active participation in exercise and sport. It is important to explore the implementation and evaluation of exercise interventions early in the disease process to maximise potential opportunities for neuroprotection.

7.4 Strengths and limitations of the thesis

7.4.1 Strengths

The FEPP enabled individuals with MS to participate in exercise and sport because of the person-centred approach of this research. The strength of the person-centred approach was constructed from four key pillars.

First, the FEPP was informed by the needs of individuals with MS. Consultation with people with lived experience is an important part of research and should guide development, particularly to ensure buy-in from the population it serves (National Health and Medical Research Council, 2016). By determining the needs of individuals with MS in advance, the FEPP was developed in accordance with those needs to facilitate participation in exercise and sport.

Second, individuals with MS were central to the FEPP intervention. Their personal choice around exercise mode was linked to appropriate, relevant and meaningful exercise participation goals. The FEPP was geared to the individual, which was in contrast to standard clinical trials, where the participant fits to the intervention. A one-size-fits-all model is not always conducive to management of exercise participation (Bouca-Machado et al., 2020). By being person-centred, the FEPP addressed individuals' specific needs and preferences. It ensured engagement with activities that were interesting, appropriate for the participants' mobility level and sufficiently challenging. In addition, the responsibility to complete the activity, with control and flexibility of the participation time, date, activity and location, matched their circumstances and enabled them to sustain participation. Having control and choice is known to increase motivation and perseverance with exercise (Wilson & Brookfield, 2009), which was apparent with the FEPP.

Third, support to negotiate challenges with exercise participation for individuals with MS was provided via advice and behavioural change coaching from a physiotherapist. By working together, there was a greater propensity to solve problems, develop action plans and

meet individual goals (Franklin et al., 2019). The provision of advice and use of BCTs enabled self-efficacy and helped to sustain participation in exercise and sport.

Last, the FEPP adopted a strengths-based approach, which addressed what participants could do, rather than an impairments-based approach, which focuses on what they cannot do; thus, it empowered individuals with MS. A reminder of the achievements of Emily Petricola (the Australian Paralympian athlete with MS), whose ability to participate in exercise and sport while negotiating MS challenges, demonstrated the scope and capacity to exercise when a strengths-based approach is taken.

The combination and interaction of the four pillars of the person-centred approach was important in enabling and sustaining participation with exercise and sport over the 12-week FEPP program. At the end of the FEPP, the perspectives of the participants with MS were again considered to determine pertinent modifications that would enhance and further strengthen the program. The FEPP is a valued program and continues to be shaped by individuals with MS. As stakeholders, a degree of ownership and investment in the program may be key to enhancing and sustaining motivation. Given that participation in exercise is low in individuals with MS, mechanisms to support and maintain exercise participation are necessary (Marck, Learmonth et al., 2020). The unique approach of the FEPP is applicable and potentially translatable to clinical practice to support individuals with MS to find the right balance with participation in exercise and sport.

7.4.2 Limitations

Limitations of individual studies have been detailed in the respective chapters, and limitations of the thesis are outlined in this section.

7.4.2.1 Participant locality

Study participants resided in northern Queensland, Australia, and therefore may not be representative of the general population. In addition, participants were typically residing in a regional or rural area; therefore, their views may not reflect the views of those in metropolitan areas. However, the successful recruitment of participants is significant given the difficulties often encountered with recruitment to clinical trials in rural and regional areas (McMahon et al., 2011). Coupled with the requirement to engage in exercise in a region dominated by heat and humidity, the trial was successful and the FEPP feasible, despite the environmental challenges. The opportunity for a larger trial encompassing other regions will broaden the lens and the potential for participation in exercise and sport for individuals with MS.

7.4.2.2 Exercise bias and motivation

Motivational bias may exist, whereby those who volunteered may have been more motivated to exercise (Barreto et al., 2013). In addition, individuals with MS who are more physically active have greater self-directed and self-capable motivations towards exercise than those who are less active (Learmonth & Heritage, 2020). Across the studies involving individuals with MS (see Chapters 3, 5 and 6), most participants were engaging in regular sport or exercise, where regular was defined as a minimum of one exercise session per week. This may account for the positive perspective towards exercise across all studies and the ability to persist with exercise across the 12-week FEPP. However, each study also included participants who were not engaging in any exercise or who were undertaking less exercise than the MS aerobic general exercise guidelines (Kim et al., 2019). The FEPP may have actually assisted motivation to exercise, possibly because of its person-centred approach, whereby the participant was integral in defining the exercise mode and the exercise participation goals. With the flexibility to conduct the exercise when and where they wanted to, perhaps the FEPP design facilitated motivation to complete the 12-week program.

7.4.2.3 COVID-19 pandemic

Some limitations were evident as a result of the COVID-19 pandemic. As previously mentioned, the lockdown restrictions may have affected recruitment. In addition, the lockdown placed restrictions on available options for exercise participation (e.g. closure of gyms and cancellation of team sports and exercise events). However, participants were able to problem solve and demonstrate resilience in finding alternative means to exercise. Contingency plans were developed in preparation for the possibility that outcome measures could not be implemented face-to-face, however due to the easing of restrictions this was not necessary. It should be emphasised that the FEPP model endured during the particularly significant disruption of the COVID-19 pandemic, which is a testament to its flexibility and sustainability.

7.4.2.4 Long-term effects

The long-term effect of the FEPP is yet unknown. While the mixed-methods study (see Chapter 6) provided some insights into the participants' ability to sustain participation in exercise and sport following completion of the FEPP, long-term follow-up of clinical outcomes was not possible. However, this feasibility study has laid the foundation for a larger clinical trial that will enable long-term follow-up.

The FEPP also has potential for long-term application. Although it is a 12-week program, the design is such that the program may be suitable for long-term use and could become a routine part of an active lifestyle.

7.5 Future directions

7.5.1 Reaching potential

A shift in focus towards enabling individuals with minimal disability with MS to reach their full potential with sport and exercise is required. Engaging with exercise that is challenging and that demands a high level of mobility is possible for individuals with MS. Pushing beyond the MS advanced aerobic guidelines is possible. Health professionals can adopt a strengths-based approach to exercise that enables individuals with MS to monitor, modify and progress their exercise accordingly using energy level as a positive tool. Health professionals are ideally placed to provide the necessary support for this approach, which aims to assist individuals with MS to manage their own exercise effectively and ensure it fits in with their lifestyle. A FEPP training program for health professionals may be a useful addition to the FEPP package to enable health professionals to implement the FEPP effectively and encourage its use. Critically, to maximise and reach the full potential for the individual with MS, health professionals need to assess changes in high-level mobility. In addition, further exploration of high-level mobility measures is required for the MS population.

7.5.2 Building an evidence base to support the Flexible Exercise Participation Program

Neuroprotection is a possibility that needs to be explored further. The FEPP feasibility study has provided the important groundwork to test this hypothesis in a larger clinical trial. Now with a robust protocol, the next stage of this research is planning a Phase II clinical trial to assess the effectiveness and impact of the FEPP (National Health and Medical Research Council, 2015). This is an important milestone in preparation for rolling out the FEPP to clinical practice. The feasibility trial has provided information to assist with the calculation of a suitable sample size to assess the efficacy of the FEPP. The size of the trial will also be dependent on funding and location, with Queensland-wide or Australia-wide as location options. A randomised controlled trial would enable the comparison of individuals with MS against a wait-list control of individuals with MS to assess the efficacy of the FEPP. In addition, a comparison to healthy individuals without MS would be beneficial to compare changes in the cytokine response to exercise. Cytokine levels are dependent on several factors, including age, sex and time of day. By matching participants with MS with healthy

controls, in-depth analyses of the changes to cytokine levels in response to exercise can be identified. In addition, the larger sample size would allow analysis of any correlation of cytokine change with the level, intensity or volume of exercise performed, which may provide a clearer indication of the possibilities for neuroprotection.

A larger trial could also allow for economic analysis of the FEPP. Analysis of cost and effectiveness would identify whether it was economically feasible to translate this knowledge into practice. Depending on cost, effectiveness and suitability, there may be opportunities to integrate the FEPP into healthcare. In the context of the Australian healthcare system, options include public healthcare (Medicare), private healthcare and the National Disability Insurance Scheme (Australian Government Department of Health, 2019). Other options include integration into charity services that provide care and advice, such as MS Australia (MS Australia, 2021b).

7.5.3 Applying the Flexible Exercise Participation Program to a wider audience

The FEPP will ideally evolve and strengthen over time to provide a solid framework for individuals with MS. One potential opportunity is the inclusion of the MS general resistance exercise guidelines in the FEPP. General resistance exercise guidelines for MS are 2–3 days per week, 1–3 sets of 8–15 repetitions of major/large muscle groups (5–10 exercises) (Kim et al., 2019). Current options in the FEPP include changing frequency, duration or intensity. The addition of a 'load' option would allow participants to add or progress resistance training in line with the guidelines. This potential addition would allow for a more rounded framework for individuals with MS by specifically addressing strength and aerobic capacity according to the goals of the individual with MS.

The FEPP has been targeted towards individuals with minimal disability from MS and those classified with RRMS. There is also an opportunity to extend the FEPP to individuals with moderate disability and other classifications of MS such as SPMS. While the general MS guidelines can be used as an initial framework, exercise participation in the community for individuals with moderate disability would require additional consideration of participant safety. Exercise participation is limited in this population; therefore, opportunities to support an increase are required (Marck, Learmonth et al., 2020).

The FEPP could also be considered for modification and use for individuals with other health conditions, where engagement with exercise and sport presents a challenge. Participation in exercise and sport is limited for many individuals with chronic diseases such

as neurodegenerative disease or stroke (Simpson et al., 2017; van Nimwegen et al., 2011), prompting the development of global guidelines on physical activity for adults with disability (Carty et al., 2021). There are more detailed exercise guidelines available, which follow a similar format to the MS guidelines, for adults with mild to moderate disability, such as stroke and Parkinson's disease (Kim et al., 2019). The FEPP could be easily modified to facilitate exercise participation incorporating the relevant guidelines. Barriers to exercise participation are similar across other health conditions such as fear, fatigue, lack of support and environmental issues (Débora Pacheco et al., 2021; Zaman et al., 2021). The FEPP model of health professional support and behavioural change techniques to assist with problem solving and action planning could therefore be appropriate. There is evidence to suggest that behavioural coaching from health professionals is applicable for these populations (Stretton et al., 2017). Similar to the proposed inclusion of individuals with SPMS, the inclusion of individuals with other health conditions would require relevant safety considerations.

7.6 Conclusions

This thesis was the first to identify that individuals with MS are yet to be challenged to engage in sport or exercise that demands a high level of mobility. Individuals with MS wanted assistance to do this and identified that support from health professionals was lacking. Mechanisms that enable greater engagement with, or maintenance of, an active lifestyle were required early in the disease process and could open up possibilities for neuroprotection.

As such, the FEPP was developed. A feasibility study showed that the FEPP enabled exercise participation, enabled the progression of high-level mobility and may provoke an anti-inflammatory response. This program was highly acceptable to participants and enabled them to achieve meaningful exercise participation goals within or beyond the MS aerobic exercise guidelines.

There is now a need for health professionals to set the bar high for participation in exercise and sport for individuals with MS by supporting challenging personal exercise goals. Possibilities include support to progress beyond the MS advanced aerobic exercise guidelines, exploring the degree of high-level mobility that can be achieved and, importantly, exploring the potential of exercise as a neuroprotector. The outcomes from this thesis will aid the design of a larger clinical trial to test the efficacy of the FEPP and shape its future evolution. With potential for integration into healthcare, the FEPP can enable individuals with MS to find the right balance with participation in exercise and sport.

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Appendix A: Summary of the 2017 McDonald Criteria

Adapted from National Multiple Sclerosis Society (2017)

CLINICAL PRESENTATION	ADDITIONAL CRITERIA TO MAKE MS DIAGNOSIS
In an individual who has experienced a typical attack/clinically isolated syndrome at onset	
Two or more attacks and clinical evidence of two or more lesions	Nil
Two or more attacks and clinical evidence of one lesion with clear historical evidence of prior attack involving lesion in different location	Nil
Two or more attacks and clinical evidence of one lesion	Dissemination in space (DIS) shown by one of these criteria: • additional clinical attack implicating different CNS site • one or more MS-typical T2 lesions in two or more areas of CNS (periventricular, cortical, juxtacortical, infratentorial or spinal cord)
One attack and clinical evidence of two or more lesions	Dissemination in time (DIT) shown by one of these criteria: • additional clinical attack • simultaneous presence of both enhancing and non-enhancing MS-typical MRI lesions, or new T2 or enhancing MRI lesion compared with baseline scan (without regard to timing of baseline scan) • CSF oligoclonal bands
One attack and clinical evidence of one lesion	Dissemination in space (DIS) shown by one of these criteria: • additional attack implicating different CNS site • one or more MS-typical T2 lesions in two or more areas of CNS (periventricular, cortical, juxtacortical, infratentorial or spinal cord) **AND** DIT shown by one of these criteria: • additional clinical attack

	• simultaneous presence of both enhancing and non-enhancing MS-typical MRI lesions, or new T2 or enhancing MRI lesion compared with baseline scan (without regard to timing of baseline scan) • CSF oligoclonal bands
In an individual with steady progression of disease since onset	
1 year of disease progression (retrospective or prospective)	DIS shown by at least two of these criteria: • One or more MS-typical T2 lesions (periventricular, cortical, juxtacortical or infratentorial) • Two or more T2 spinal cord lesions • CSF oligoclonal bands

CNS = central nervous system; CSF = cerebrospinal fluid; DIS = dissemination in space; DIT = dissemination in time; T2 lesion = hyperintense lesion on T2-weighted MRI

Appendix B: Expanded Disability Status Scale (EDSS)

Adapted from Multiple Sclerosis Trust (2020)

Score	Description
0	Normal neurological exam, no disability in any FS.
1.0	No disability, minimal signs in one FS.
1.5	No disability, minimal signs in more than one FS.
2.0	Minimal disability in one FS.
2.5	Minimal disability in two FS.
3.0	Moderate disability in one FS, or mild disability in three or four FS. No impairment to walking.
3.5	Moderate disability in one FS and more than minimal disability in several others. No impairment to walking.
4.0	Significant disability but self-sufficient and up and about some 12 hours a day. Able to walk without aid or rest for 500 m.
4.5	Significant disability but up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance. Able to walk without aid or rest for 300 m.
5.0	Disability severe enough to impair full daily activities and ability to work a full day without special provisions. Able to walk without aid or rest for 200 m.
5.5	Disability severe enough to preclude full daily activities. Able to walk without aid or rest for 100 m.
6.0	Requires a walking aid—cane, crutch, brace—to walk about 100 m with or without resting.
6.5	Requires two walking aids—pair of canes, crutches—to walk about 20 m without resting.
7.0	Unable to walk beyond approximately 5 m even with aid. Essentially restricted to wheelchair; though wheels self in standard wheelchair and transfers alone. Up and about in wheelchair some 12 hours a day.
7.5	Unable to take more than a few steps. Restricted to wheelchair and may need aid in transferring. Can wheel self but cannot carry on in standard wheelchair for a full day and may require a motorised wheelchair.
8.0	Essentially restricted to bed or chair or perambulated in wheelchair. May be out of bed itself much of the day. Retains many self-care functions. Generally has effective use of arms.
8.5	Essentially restricted to bed much of day. Has some effective use of arms retains some self-care functions.
9.0	Confined to bed. Can still communicate and eat.
9.5	Confined to bed and totally dependent. Unable to communicate effectively or eat/swallow.
10.0	Death due to MS.

Appendix C: PROSPERO Registration

NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

Are exercise interventions effective in maintaining or regaining high-level mobility in individuals with neurodegenerative diseases?

Moira Smith, Gavin Williams, Ronny Gunnarsson, Ruth Barker, Jennifer Carr

Citation

Moira Smith, Gavin Williams, Ronny Gunnarsson, Ruth Barker, Jennifer Carr. Are exercise interventions effective in maintaining or regaining high-level mobility in individuals with neurodegenerative diseases?. PROSPERO 2016 CRD42016050362 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42016050362

Review question

To identify exercise interventions designed to maintain or regain high-level mobility in individuals with neurodegenerative diseases
To examine the effectiveness of exercise interventions on high-level mobility in individuals with neurodegenerative diseases

Searches

The following databases will be searched for this systematic review: MEDLINE, CINAHL, SCOPUS, SPORTDiscus and PEDRO.
The search strategy will include terms relating to neurodegenerative diseases and measures of high-level mobility.
There will be no timeframe restrictions or language restrictions applied

Types of study to be included

Randomised controlled trials will be included in the review

Condition or domain being studied

All neurodegenerative conditions (e.g. multiple sclerosis, Parkinson's disease, Huntington's disease, spinocerebellar degenerations). Exercise interventions addressing high level mobility.

Participants/population

Inclusion: Individuals with neurodegenerative disease, no age limitations

Intervention(s), exposure(s)

Interventions will include any form of physical activity or exercise that aims to address high level mobility. Examples include: progressive resistance training; plyometric exercise; running and cycling

Comparator(s)/control

Randomised controlled trials selected, any comparator considered

Main outcome(s)

Primary outcome measures are those which identify a change in high-level mobility. Examples include: HIMAT; Dynamic gait index; and Rivermead mobility index

* Measures of effect

Pre, post and follow up intervention measures as above

Additional outcome(s)

None

* Measures of effect

Not applicable

Data extraction (selection and coding)
From the search results, two authors will independently screen the titles and abstracts of the studies in order to determine eligibility for inclusion in the review. Any disagreement in terms of eligibility of the study will be discussed and if consensus is not reached this will be resolved by referral to a third reviewer. Potentially relevant studies will have the full text reviewed by both authors in order to ensure that inclusion/exclusion criteria are met.

Risk of bias (quality) assessment
Risk of bias of the selected articles will be assessed by two independent authors using the Cochrane Collaboration's risk of bias tool. Authors will be contacted if further clarification is required in relation to their study. Any conflict of opinion will be resolved through discussion or referral to a third party if necessary

Strategy for data synthesis
Study details extracted will include the following: year, author, title, participants, intervention, randomised comparator, method of randomisation, allocation concealment, blinding, dropouts and follow up period. Outcomes reported will be categorised to high level mobility descriptors as previously described.

Analysis of subgroups or subsets
None planned

Contact details for further information
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Ms Moira Smith. James Cook University
Dr Gavin Williams. University of Melbourne
Dr Ronny Gunnarsson. James Cook University
Dr Ruth Barker. James Cook University
Ms Jennifer Carr. James Cook University

Type and method of review
Systematic review

Anticipated or actual start date
22 September 2016

Anticipated completion date
30 June 2017

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This review is independently researched with no funding supplied

Conflicts of interest
None known

Language
English

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Australia

Stage of review
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NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

Details of final report/publication(s) or preprints if available

Smith, Moira, Barker, Ruth, Williams, Gavin, Carr, Jennifer, and Gunnarsson, Ronny (2020) The effect of exercise on high-level mobility in individuals with neurodegenerative disease: a systematic literature review. Physiotherapy, 106. pp. 174-193. https://doi.org/10.1016/j.physio.2019.04.003

https://www.ScienceDirect.com/science/article/pii/S0031940618301639?dgcid=author

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Exercise; Exercise Therapy; Humans; Neurodegenerative Diseases

Date of registration in PROSPERO

28 October 2016

Date of first submission

11 February 2020

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Revision note

This sytematic review is now complete and published

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

28 October 2016
20 October 2020

Appendix D: Human Research Ethics Approvals

Human research ethics approval H7227 (Study 2)

This administrative form has been removed

Human research ethics approval H7956 (Studies 4 and 5)

This administrative form has been removed

Appendix E: Clinical Trial Registration

This administrative form has been removed