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The MoxFo initiative – outcomes: Outcome measures in studies of exercise training in multiple sclerosis; scoping review of reviews and classification according to the ICF Framework

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Abstract

Background: The number of published studies of exercise training in multiple sclerosis (MS) has grown exponentially with increasing numbers of outcomes capturing exercise effects. This has complicated the selection of relevant indicators and interpretation of intervention effects. **Objectives:** The Outcomes subgroup of the MoXFo initiative aimed to: 1) identify outcome measures and biomarkers in studies of exercise training in MS; 2) systematically map retrieved outcomes to International Classification of Functioning, Disability and Health (ICF) categories; 3) identify gaps where relevant ICF categories have been omitted. **Methods:** Electronic databases and registers were searched from 2010 to July 2020 to identify systematic reviews or meta-analyses of controlled trials of exercise training on any outcome in MS. Retrieved outcomes/biomarkers were mapped to the corresponding ICF category. **Results:** 81 review articles reporting 235 different outcomes were included. The outcomes corresponded to 15 chapters and 45 categories within the ICF. Outcomes mapped primarily to body function (30 categories) and activities and participation (9 categories) components. Few outcomes mapped to body structures (2 categories) or environmental factors (1 category). **Conclusion:** This sets the stage to develop a resource for researchers/clinicians that will aid in the selection of appropriate outcomes/biomarkers when examining exercise effects in MS.

Introduction

There is increasingly compelling evidence for the beneficial effects of exercise for people with multiple sclerosis (MS) based on a proliferation of research over the past two decades (1). Such benefits occur across multiple domains and are captured by numerous, heterogeneous outcome measures (2). No single outcome measure is sufficient to capture the complex presentation of MS. In research, outcome measures are chosen depending on the study aims and often on the preferences/previous experience of the research team. Outcomes can be classified as clinical outcomes with direct importance to patients (e.g. measures of fatigue) or as biomarkers that are biological indicators of the pathophysiology (e.g. cytokines, brain volume) (3). For this review, clinical outcome measures and biomarkers will be considered as outcome measures.

The International Classification of Functioning, Disability and Health (ICF) is the World Health Organisation's (WHO) framework for describing and measuring disability and health (4). The ICF provides a framework for defining functioning and disability associated with health conditions and includes four components: 'body functions and body structures', 'activities and participation', 'environmental factors' and 'personal factors'. The ICF is increasingly adopted for a common narrative of rehabilitation outcomes across disciplines and may also serve as a common framework for clinical outcomes for exercise interventions in MS.

It is challenging to characterize the overall effects of exercise training on ICF domains in persons with MS considering that there is significant heterogeneity in outcome measures used in exercise studies/clinical trials. Such heterogeneity, even for similar constructs, makes comparisons across study results difficult and complicates the selection of outcomes in future trials. To overcome such an issue, in 2020, the MoXFo (Moving exercise research in MS forward) initiative highlighted that improving the outcomes and

reporting in exercise trials in MS represents a priority area for advancing the research to better understanding the pleiotropic effects of exercise training in this population (5).

To that end, this review represents the initial step of the MoXFo Outcomes and Reporting Group, focusing on outcome measures for advancing the evidence base on exercise effects in MS. We identified an eight-stage process for doing so (Fig 1) and this paper collectively embodies the first three stages of the process.

The aims of this study were to: 1) extract and catalogue the outcome measures (clinical outcomes and biomarkers) used in studies of exercise training in MS through a scoping review of systematic reviews and meta-analyses published from 2010 to July 2020; 2) map these outcome measures to the relevant ICF categories; and 3) identify potential gaps where relevant ICF categories have not been reported in reviews of exercise studies in MS. We performed a scoping review as, being the initial step, the aim was to explore the existing literature (reviews) and identify gaps, not to evaluate the strength of existing evidence(6) nor the efficacy of interventions on outcomes. Rather the aim was to provide researchers and clinicians with the ICF-based overview of the clinical scales and/or biomarkers that have been used as endpoints in exercise trials. For selection in future trials, outcome measures/biomarkers should align with the research question/hypothesis guiding the trial and be verified on psychometric properties.

Methods

Search Strategy.

This scoping review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) statement and guidelines (Appendix 1) (7). Electronic databases and registers (Embase, EBSCO

(Academic Search Complete, AMED, Biomedical Reference Collection, CINAHL, Medline, PsycInfo, SPORTDiscus), Cochrane Database of Systematic Reviews, and Prospero) were searched from 2010 to 3 July, 2020 for relevant systematic review articles published in English. These databases were chosen based on their relevance to the topic and previous use in reviews of exercise training in MS. Search terms were categorized into three distinct themes: 'review', 'exercise', and 'multiple sclerosis' (Table 1, Supplementary Appendix 2). The electronic searches were conducted by two members of the team (BC and LP). Search results were imported into Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) for article management, deduplication, and screening.

Eligibility Criteria and Screening.

Guided by a PICOS framework, included articles were published systematic reviews or meta-analyses of controlled trials of exercise training interventions on any outcome in people with MS (Table 2). In line with the MOXFO initiative definitions paper, exercise was defined as physical activity that is planned, structured, repetitive, and purposive in the sense that improvement or maintenance of one or more components of physical fitness is an objective (8). Review articles were excluded if they were unavailable in English, conference presentations/abstracts, or if they involved similar information published by the same research group. Of note, a review article was not excluded if it involved a mixed sample wherein data on persons with MS could be extracted.

Following automated deduplication, two independent reviewers (BC and LP) initially conducted screening for relevant review articles at the title and abstract level. Full-text screening was then conducted by six independent reviewers (LP, BC, BMS, LAP, PF, JB), who screened each review article for inclusion in pairs. To minimize potential bias *a priori*, reviewers did not screen review articles in which

they were authors. Any discrepancies regarding review article inclusion were resolved by consensus or evaluation by a third, independent reviewer.

Data Extraction.

The full-texts of review articles that met the eligibility criteria were comprehensively reviewed by seven independent reviewers (LP, JB, BMS, LAP, PF, ZA, CR), who reviewed in pairs using the aforementioned rules for preserving independence and systematically minimizing bias *a priori*. The data that were extracted from each eligible systematic review/meta-analysis included: primary study aim, demographic/clinical characteristics, details on the primary dependent variable (i.e., construct of the primary dependent variable, specific outcome measures representing that construct), other variables assessed, exercise modalities represented, review results, and conclusions. Any discrepancies in data extraction were subsequently resolved by consensus; if consensus was not reached, a third, independent reviewer resolved any conflicts. Data were extracted into a pre-determined data-charting form.

Data synthesis.

The ICF classifies health and health-related states. The unit of classification is, therefore, categories within health and health-related domains organized in chapters for each component (i.e., body structure, body function, activities and participation, environmental and personal factors) (4). CR and JB assigned all extracted outcomes to a corresponding ICF component (i.e., body structure, body function, activities and participation, environmental and personal factors) based on defined linking criteria (9) and consultation with the ICF browser at WHO (https://apps.who.int/classifications/icfbrowser/). Agreement regarding the corresponding ICF chapters and categories were made between the two authors (CR and JB) with consultation of a third author (PF) if needed. If an outcome measure could not be mapped directly to a specific ICF category, outcomes were mapped to the category that best matched the outcome measure.

Results

A total of 3844 records were imported into Covidence with 1888 duplicates subsequently removed. 1956 abstracts and titles were screened with 1742 excluded, resulting in 214 articles that were eligible for full-text screening. Of the 214 articles that underwent full-text screening, 133 were excluded, resulting in 81 review articles that underwent data extraction and were included in the analyses (Figure 2). A third independent reviewer was required to reach consensus on the extracted data on three occasions.

Outcomes.

Outcomes across 81 review articles were assigned into ICF components of body functions and body structures (Table 3), activities and participation, environmental and personal factors (Table 4). Overall, 235 different outcomes were reported, capturing 15 chapters and 45 categories of the ICF. Body function was the most commonly captured ICF component (154 outcomes across 30 categories and 5 chapters). Fifteen outcomes were reported for body structures component (capturing 2 categories and 2 chapters). 62 outcomes were reported for the activities and participation component (9 categories covering 3 chapters). Only one category (one outcome) was captured for environmental factors and three outcomes for personal factors.

Body Functions (Table 3)

Concerning the outcomes capturing the categories of mental functions (b1), one outcome was reported for global psychosocial functions (b122) while fourteen outcomes were included in the energy and drive functions (b130) related to fatigue. In addition, specific mental functions such as attention (b140), memory (b144), emotion (b152) and high-level cognitive functions (b164) were investigated by 36

outcomes reported in the review articles. The outcomes assessing anxiety, depression and fatigue were all patient reported outcomes (PROs). Conversely, specific mental functions regarding cognition (i.e., attention, memory and high-level cognitive functions) were mainly objective neuropsychological tests. Across the review articles, only five outcomes were reported for the category of mental function of sequencing complex movements (e.g., dual-task tests of cognitive-motor interference (b176)).

Few (six) outcomes were used to assess sensory functions and pain (b2). Only one outcome was used to evaluate general sensory functions (i.e., Nottingham sensory Assessment). Concerning specific sensory functions, outcomes were only reported for visual, vestibular and proprioceptive functions (five outcomes in total). Pain was evaluated by the brief pain inventory, VAS and the short-form McGill pain questionnaires.

Regarding functions of the cardiovascular, haematological, immunological and respiratory systems (b4), outcomes were mainly biomarkers and included a variety of serum markers such as interleukins, neurotrophic factors, tryptophan-kynurenine pathway and blood- brain barrier markers (e.g., s100 calcium-binding protein B, Neuron-specific enolase). Exercise tolerance functions (b455) were mainly represented by the physiological cost index (PCI), physical work capacity (Watts/min) and peak power (Watts). Outcomes of oxygen consumption and the oxygen uptake (i.e., $VO_{2,Max}/_{peak}$) were extensively used and were related to the category of additional functions of the cardiovascular and respiratory systems (b469).

Only two PROs captured genitourinary and reproductive functions (b6), specifically the categories of urinary and sexual functions.

The majority of identified outcomes (32), were related to the neuromusculoskeletal and movement-related functions (b7). Joint mobility (b710), muscle power (b730), muscle endurance (b740), involuntary movement reaction (b755) and gait pattern (b770) (e.g., spatiotemporal parameters) were all assessed by objective measures, with muscle power and gait having the most outcomes. Concerning muscle tone (b735) and motor reflex functions (b750), outcomes encompassed ratings from clinicians based on manual tests.

Body Structures (Table 3)

Few outcomes (15) addressed the body structures components. Review articles evaluated structures related to the brain (s110) or structures related to movement (s7) such as muscle, skin and other related structures. Outcomes (biomarkers) that relate to structures of the brain included neuroimaging outcomes: i) whole brain volume; ii) volumes of cortical and sub-cortical regions of interest and iii) white matter integrity (i.e., structural connectivity) based on diffusion tensor imaging.

Outcomes associated with other bodily structures were related to movement and only focused on the structure of lower extremity (s750) using ultrasound scanning and muscle biopsy to quantify cross-sectional area and identify muscle fiber type.

Activities and Participation (Table 4)

The categories related to mobility (d4) reported two clinician-rated outcomes (Rivermead Mobility Index and Functional independence measure – Motor). There was only one outcome regarding changing basic body position (d410). For the categories of maintaining a body position (d415), a variety of objective assessments (i.e. Berg Balance Scale) and PROs (e.g. Activities-specific Balance Confidence scale) were used. Outcomes for arm and hand use were mainly objective tests (e.g. Nine-Hole Peg Test) related to

fine hand use (d440). Concerning the outcomes in the categories of walking and moving (d450-d469), short and long walking tests, as well as functional mobility such as the Timed Up-and-Go test were extensively reported.

Interpersonal interactions and social life described in the chapter of major life areas (d8) were not widely investigated with only two outcomes (i.e., Social Provisions Scale and Work and Social Adjustment Scale) being reported. Regarding community, social and civic life chapter (d9), seven physical activity questionnaires were reported as outcomes along with accelerometers, sensors and pedometers to investigate the impact of physical exercises on recreation and leisure category (d920). Regarding environmental factors, only outcomes related to the category of attitudes, unspecified (e499) were reported.

Disability and QOL outcomes (Table 5)

As overall disability and QOL were measured with composite ratings or PROs capturing several categories in the body function component, as well as the impact of the disease on a broad range of categories from the activities and participation component, disability/QOL outcomes were not allocated into a specific ICF component (Table 5). Concerning disability-related scales, five outcomes were reported including functional system score, disability scales and functional and independence assessment. Regarding the PROs investigating perceived generic disability, fifteen outcomes were used to capture the effects of exercise on disability from the patient perception. The PROs related to QOL were also extensively investigated by the review articles (nine outcomes).

Personal factors. In terms of personal factors there were two outcome measures for self-efficacy (Exercise self-efficacy scale - ESES, (26) and the Multiple Sclerosis Self Efficacy Scale – MSSE (37)) and

one in relation to outcome expectations (Multidimensional Outcome Expectancies for Exercise Scale MOEES (26).

Exercise Interventions. Within the systematic reviews and meta-analyses, there were various exercise training interventions that were described across included RCTs (Supplementary Table 2). Overall, interventions mostly involved aerobic and resistance exercise training paradigms.

Discussion

This study, as the foundational step of the MoXFo agenda on outcomes and reporting of exercise trials in MS addressed the first three stages of Figure 1. The primary results involved a large number (n=236) of different outcome measures to document the effects of exercise on various domains of functioning in this population (15 chapters and 45 categories).

The second aim was to map these outcome measures against the relevant ICF domains (Stage 2; Fig 1). When mapped to the ICF, outcomes were primarily associated with body function (30 categories) (Table 3) or activity and participation (9 categories) components (Table 4). By comparison, there were fewer outcomes related to body structures (2 categories) and environmental factors (1 category). The only outcome related to attitudes was the Exercise Benefits and Barriers Scale. These factors can significantly impact an individual's engagement with an exercise programme, and its outcomes. Environmental factors such as lack of support and lack of a positive attitude of healthcare providers, have been reported as barriers to persons with MS taking part in exercise (84) and warrant further inquiry. Self-efficacy and outcome expectations were the only specific outcomes relating to personal factors, although personal factors may also have been encompassed within the disability and QOL measures

(discussed below).

There were numerous instances wherein a large number of outcome measures mapped to a single ICF category. For example, in b130 'Energy and Drive Functions' there were 14 different fatigue measures reported in the included systematic reviews; but only one measure of muscle fatigability. Similarly, in b152 Emotional Functions, there were 11 different anxiety and depression measures. There were 10 different categories related to walking (d450), some of which related to gait speed, others to endurance. Although the aim was not to recommend specific outcome measures, this demonstrates the high degree of heterogeneity in outcome measures in specific ICF categories in relation to exercise studies in MS.

Measures of overall disability and QOL were also commonly reported in systematic reviews and meta-analyses of exercise in persons with MS (Table 5). These are multi-component assessments that reflect a number of different categories across ICF domains within the one outcome. For instance, the MSIS-29 includes questions related to body functions as well as activities and participation issues. Within the scope of this study, we considered these measures separately. However, it would be possible to map to the level of individual scale items/components to the specific ICF category. Nevertheless, there too was substantial heterogeneity in the assessments of disability and QOL, with 15 different PROs reported for the measure of disability and nine for QOL (Table 5).

The third aim (Stage 3; Fig 1) was to identify gaps where ICF domains have not been captured in the reviews/meta-analyses of exercise studies in MS. There were several ICF categories of common signs and symptoms of MS that rarely mapped to outcome measures reported in the systematic reviews and meta-analyses. For instance, there was little evidence on the effects of exercise training on measures of vision, vestibular function and proprioception. Similarly, pain was rarely reported as a study outcome (four outcomes), despite its prevalence and burden in MS (85) and no outcomes in relation to

autonomic (dys)function or changes in cerebral blood flow with exercise (b415). There was a notable paucity of outcomes specifically capturing bladder and bowel function in persons with MS (b6), although this may have been a component of disability measures (discussed below) and in relation to vocation (d825) or remunerative employment (d850), as unemployment represents a major burden associated with the disease. As these are common in persons with MS, future research on exercise effects on those functions might consider adopting more comprehensive and/or rigorous batteries, given the paucity of research in this area. This scoping review presents a comprehensive overview of the outcome measures, and ICF categories, which have been used in studies of exercise in MS, and highlights ICF categories not commonly captured as outcomes in exercise studies in MS. This knowledge will support researchers to choose outcome measures to address their research question.

This review has a number of limitations: First, we did not count the frequency of use of each outcome measure. This was not practical, as there was significant overlap in terms of the individual studies included in each of the 81 review articles. Second, as the unit of analysis was the systematic review/meta-analysis and not individual RCTs, we were unable to articulate which outcomes are most frequently used in trials. Furthermore, the aim of this work was not to examine exercise-related changes in the outcomes relative to a control condition as that was outside the scope of this review. Third, it was challenging to map outcomes to a single category as they could have been mapped to a number of related categories and judgement was required. This was particularly the case with multi-component, disability and QOL outcomes that were considered separately. In addition, although there are a number of tools available to assess the quality of systematic reviews, including AMSTAR (https://amstar.ca/index.php), such an endeavor extends beyond the scope of this work. Finally as this was a scoping review there is no publicly available protocol.

The next stages of this programme of work, within the MOXFO and other initiatives, needs Patient and Public Involvement to determine the relevance and importance of the identified ICF categories for patients and other stakeholders. Concurrently an assessment of the quality of the outcome measures through an evaluation of the measurement properties (reliability, validity and responsiveness) of the outcome is required. This assessment should also consider the feasibility of implementation of the outcome measure in practice. Although this is a substantial piece of work, existing resources can be used. Consideration of outcome measures in terms of their use for persons with MS across different phenotypes or disability levels is also required. The goal is to reach consensus to an MS stage-adapted and intervention-goal adapted minimal outcome set applied in studies to enable meta-analytic work and definite conclusions.

The final stages will involve dialogue and consultation with a wide range of international stakeholders that may involve an international stakeholder consensus meeting with consensus building using Delphi techniques. The findings then need to be disseminated and regularly evaluated and updated as the field moves forward.

Conclusion

Whilst the aim of this work was not to recommend specific outcomes, we demonstrated a large number of clinical outcomes and biomarkers that are used in reviews/meta-analyses of exercise studies in MS. We identified major gaps in MS exercise studies where relevant ICF categories have not been considered. These findings, the first three steps in a proposed eight step programme of work, provide resources for researchers, clinicians and health educators who prescribe exercise for people with MS to select appropriate outcomes, which may be a combination of e.g. biomarkers and clinical scales, that address specific exercise-related hypotheses based on a scientific rationale and clinical relevance.

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Table 1. Search strategy themes and keywords.

Review keywords	**Exercise keywords**	**Multiple sclerosis keywords**
"systematic" OR "review" OR "meta-analysis"	“exercise” OR “physical activity” OR “exercise prescription” OR “exercise therapy” OR “training” OR “fitness” OR “aerobic” OR “strength” OR “resist” OR “ambulatory activity” OR “walk” OR “workout” OR “physical fitness”	“Multiple sclerosis” OR “MS”

Table 2. PICOS framework and inclusion criteria for article selection.

PICOS characteristic	**Inclusion criteria**
Population	People with MS; Studies with mixed populations where data on people with MS could be extracted.
Intervention	Any exercise intervention defined as physical activity that is planned, structured, repetitive, and purposive in the sense that improvement or maintenance of one or more components of physical fitness is an objective. (8)
Comparison	Any non-active or active control condition that did not include exercise (e.g., usual care, wait-list, attention/social contact conditions).
Outcomes	Any clinical outcome or biomarker.
Study design	Systematic reviews or meta-analyses of randomised controlled trials (RCTs) and/or quasi-RCTs of intervention studies. Systematic review criteria (9): • Search strategy of at least one electronic database • Clear research question • Detailed inclusion/exclusion criteria • Clear process of selecting/screening

Table 3. Outcomes related to the categories of the ICF Body Functions and Body Structures domains. (PRO) PRO/ratings (patient reported, mostly ordinal rating scales and then total score) or single-item ratings by interval; (PER) Performance Measure (usually instructed by a health care provider or researcher); (PM) Physiological or structural marker; (ObS) Observational scale (to quantify the level of disability).

ICF - Chapter/code	Outcomes
Body Functions	
b1 mental functions	
b122 Global psychosocial functions	Mental Health Inventory (MHI) (10) (PRO)
b130 Energy and drive functions	Fatigue Severity Scale (FSS) (11-31) (PRO)
	Modified Fatigue Impact Scale (MFIS) (12-14, 16-21, 23-26, 28-30, 32-34) (PRO)
	Fatigue Scale of Motor and Cognitive Function (FSMC) (13, 20, 27, 29, 33) (PRO)
	Fatigue Impact Scale (FIS) (13, 20, 35, 36) (PRO)
	Fatigue Index (FI) (14) (PER)
	Multidimensional Fatigue Inventory score (14, 21, 23, 25, 30) /MFI-20 (29) (PRO)
	Würzburger Erschöpfungs Inventar (15, 37) (PRO)
	Global Fatigue Severity subscale of the fatigue Assessment Inventory (GFS) (20) (PRO)
	Chronic Fatigue Scale (CFS) (20) (PRO)
	CIS20 fatigue subscale (20) (PRO)
	Visual Analog Fatigue Scale (21) (PRO)
	Multidimensional Fatigue Index (28) (PER)
	Flow State Scale (FSS) (34) (PRO)
b139 Global mental functions, other specified and unspecified	Global cognition (38) (PRO)/(PER)
Specific mental functions (b140-b189)	
b140 Attention functions	Test Battery of Attention (39) (PER)
	Attention, Tonic alertness (33) (PER)
b144 Memory functions	California Verbal Learning Test-II (CVLT-II) (39-41) (PER)
	Attention and working memory (A&WM) (38, 42) (PER)
	Weschler Memory Scale III (28, 39, 43) (PRO)
	Brief Visual Memory Test–Revised (BVMT-R) (39-41) (PER)
	Verbal Learning Memory Test, recall 1–5 (VLMT) (33, 36, 44) (PER)
	Selective Reminding Test (SRT) (41) (PER)
	Trail Making Test (TMT) (37, 40, 45) (PER)
	Spatial Recall Test (40) (PER)
	Verbal LM Test (39) (PER)
b147 Psychomotor functions	Psychomotor speed (PS) (38) (PER)
b152 Emotional functions	Profile of Mood States (POMS) (11, 12, 18, 22, 24, 28, 29, 42, 46-49) (PRO)
	Hamilton Rating Scale for Depression (HRSD) (11, 42) (PRO)
	Beck Depression Inventory Score (BDI) (12, 17, 19, 26, 42, 46, 48, 49)/ BDI-II (26, 28, 48) (PRO)
	Beck Anxiety Inventory (BAI) (28, 50) (PRO)
	Centre for Epidemiologic Studies Depression Scale (CESD) (12, 28, 46, 49) (PRO)
	Inventory of Depressive Symptomatology (33, 36, 46, 48, 49) (PRO)
	Hospital Anxiety, Depression Scale (HADS) (26, 46, 48-50) (PRO)
	Ontgomery Asberg Depression Rating Scale (MADRS)(42) (PRO)
	Geriatric Depression Scale (GDS)(42) (PRO)
	Major Depression Inventory (MDI) (10, 14, 26, 27, 33, 36, 37, 48, 49) (PRO)
	State-Trait Anxiety Inventory (STAI) (28, 50) (PRO)
b164 Higher-level cognitive functions	Symbol Digit Modality Test (SDMT) (12, 27, 37, 39-41, 44, 45, 51-53) (PER)
	Stroop Test (28, 39, 43) (PER)
	Paced Auditory Serial Addition Test (PASAT) (18, 19, 28, 37, 39-41, 43, 54) (PER)
	Word List generation (WLG) (37, 41) (PER)
	Verbal fluency (VF) (38, 42) (PER)
	Achievement Testing System (39) (PER)
	Executive functioning (EF) (38, 54) (PER)
	Digit Span (38, 39) (PER)
	DKEFS, Delis-Kaplan Executive Function System (26) (PER)
	Trail Making Test (TMT) (26, 27, 37, 40, 45) (PER)

	Wechsler Adult Intelligence Scale (28, 43) (PRO)
	TOL -Tower of London Test (28, 43) (PER)
	Digit Symbol Substitution Test (DSST) (40, 41) (PER)
b167 Mental functions of language	Regensburger Verbal Fluency Test (RWT) (39, 40) (PER)
b176 Mental function of sequencing complex movements	Dual task performance; Both-leg postural sway in dual task condition (54) (PER)
	TUG Dual-task (26, 45, 54, 55) (PER)
	Stroop Stepping Test (SST) (26, 45) (PER)
	Choice stepping reaction time (CSRT) (26, 37, 45) (PER)
b198 Mental functions, other specified	Achievement Testing System (39) (PER)
b2 Sensory functions and pain	Nottingham sensory Assessment (56) (PER)
b229 Seeing and related functions, other specified and unspecified	Dynamic Visual Acuity Test (DVAT) (57) (PER)
	Gaze Stabilization Test (GST) (57) (PER)
b235 Vestibular functions	Dizziness Handicap Inventory (57) (PRO)
b260 Proprioceptive function	Paresthesia VAS (PRO); Verbal analog scale – sensory (PRO); vibration threshold Neurothesiometer (PER) (26)
Pain (b280-b289)	
b280 Sensation of pain	Brief Pain Inventory (58) (PRO)
	Visual analog Scale (VAS) (15) (PRO)
b289 Sensation of pain, other specified and unspecified	pain questionnaire (SF-MPQ) (26, 53) (PRO)
b4 functions of the cardiovascular, haematological, immunological and respiratory systems	
b410 Heart functions	Resting heart rate: Systolic, Diastolic at rest (10, 12, 27, 31, 59) (PM)
b420 Blood pressure functions	Blood pressure (12, 27, 59) (PM)
b439 Functions of the haematological and immunological systems, other specified and unspecified	Blood lipids: total cholesterol; triglyceride; high-density lipoprotein (HDL); low-density lipoprotein (LDL); and very-low-density lipo- protein (VLDL) (11, 12) (PM)
	IL: interleukin / IL-4, IL 10, IL-2, IL-6; TNF-α; C-reactive protein; IFN-interferon (12, 19, 44, 60-62) (PM)
	Lactate; ACTH: adrenocorticotropic hormone; cortisol; Nor- and epinephrine; sIL-6R: soluble IL-6 receptor (12, 44, 60-62) (PM)
	BDNF: brain-derived neurotrophic factor (12, 16, 33, 44, 60, 62) (PM)
	Serotonin; Trp, tryptophan; Kyn, kynurenine; Kyn/Trp ratio), NGF: nerve growth factor (12, 27, 33, 44, 60, 62) (PM)
	Serum Irisin, IL-6 (12, 33, 44, 60) (PM)
	Vitamin D (18) (PM)
	AUC from OGTT; Fasting glucose concentration (27) (PM)
	Blood-brain barrier function Markers: s100 calcium-binding protein B; Neuron-specific enolase; Matrixmetalloprotinease-2/9 (MMP-2,9) (44) (PM)
Additional functions and sensations of the cardiovascular and respiratory systems (b450-b469)	
b455 Exercise tolerance functions	Physiological Cost Index (PCI) (11, 12) (PM)
	Physical Work Capacity (W/min) (24) (PER)
	Watt peak (53) (PER)
	Fatigue Index - Knee extension/Knee flexion (24) (PER)
b469 Additional functions and sensations of the cardiovascular and respiratory systems, other specified and unspecified	VO2Max / VO2peak (10-12, 16, 24, 26, 27, 33, 36, 39, 47, 53, 63) (PM)
	Energy cost of walking (Oxygen consumption in mL/kg/min) (60) (PM)
b6 Genitourinary and reproductive functions	
b620 Urination functions	Bladder/bowel control (10) (PRO)
b640 Sexual functions	Sexual satisfaction (10) (PRO)
b7 Neuromusculoskeletal and movement related functions	
b710 Mobility of joint functions	Goniometric measurements for passive and active range of motion (64) (PER)
	Kinematics (10) (PER)

	Minimum pelvic rotation, hip flexion at heel strike; maximum hip extension and flexion, Hip total sagittal plane excursion (15) (PER)
b730 Muscle power functions	Maximum Voluntary Contraction (i.e., isometric, dynamic) lower limbs (11, 12, 15, 17-19, 24, 26, 27, 35, 40, 47, 53, 56, 65-68) (PER)
	1 Repetition Maximum (1RM) (10, 12, 17, 18, 26, 47, 59, 63, 65-67) (PER)
	Power (65) (PER)
	Grip strength (10, 24, 27, 33, 36, 51, 63) (PER)
	5-Sit to Stand Test (26, 40, 57) (PER)
	Chair Rise (34) (PER)
	Pinch Grip (63) (PER)
	Upper limb strength - Shoulder, Ellbow (63) (PER)
	Leg Power (W/kg); Leg Power (W) (24) (PER)
b735 Muscle tone functions	Quantitative Myometry Assessment (11) (PER)
	Modified Ashworth Scale (12, 15, 26, 56) (PRO)
	Pendulum test for muscle tone, ankle clonus score and patellar tendon reflex scale (64) (PRO)
	Penn Spasm Frequency Score (PSFS) (64) (PRO)
	Multiple Sclerosis Spasticity Scale-88 (MSSS-88) (56, 64) (PRO)
	Spasticity, Tremor Severity Scale (TSS) (63) (PRO)
	Visual Analog Scale Spasticity (56) (PRO)
b740 Muscle endurance functions	Upper extremity endurance (51) (PER)
	Muscular endurance (10) (PER)
	Movement rate at maximum velocity (RATE-MV); Movement rate at spontaneous velocity (RATE-SV) (63) (PER)
b749 Muscle functions, other specified and unspecified	Electromyography (EMG) (11, 17, 24, 31, 64) (PER)
b755 Involuntary movement reaction functions	Force platform - postural sway (anterior-posterior, mediolateral) and sway velocity (11, 24, 26, 34, 35, 45, 55, 57, 65, 69) (PER)
	Functional Reach Test (17, 19, 26, 35, 65, 69, 70) (PER)
	Both-leg postural sway in dual task condition (54) (PER)
	Rivermead Mobility Index (RMI)/modified RMI; Numeric Rating Scale on difficulty carrying a drink while walking (26) (PRO)
b770 Gait pattern functions	The Dynamic Gait Index (DGI) (10, 34, 44, 55, 70-74) (PER)
	Spatiotemporal gait parameters (10, 12, 15, 16, 26, 34-36, 60, 68, 75) (PER)
	Functional ambulation profile (FAP) (26, 60) (PER)
	Gait analyses, power generated and smoothness of movement (64) (PER)
Body Structure	
s1 Structures of the nervous system	
s110 Structure of brain	White matter integrity of cerebellar peduncles, Whole brain volume, Hippocampal viscoelasticity (shear stiffness, damping ratio), Thalamocortical resting-state functional connectivity (RSFC) (40, 44) (PM)
	Cortical thickness of 74 exploratory regions of interest (ROI); Volumes of subcortical ROI; RSFC of the bilateral hippocampus (40) (PM)
	Plaque Volume in Brain (18) (PM)
s7 Structures related to movement	
s750 Structure of lower extremity	Ultrasound scan: cross-sectional area (CSA) of thigh muscles (17, 18, 27, 66) (PM)
	Thigh circumference (10) (PM)
	Biopsies: muscle fibre type, satellite cell, myonuclei and central nuclei analysis, muscle tissue fibrosis and lipid content (27) (PM)

Table 4. Outcomes related to the categories of the ICF Activities and Participation, and Environmental factors domains. (PRO) PRO/ratings (patient reported, mostly ordinal rating scales and then total score) or single-item ratings by interval; (PER) Performance Measure (usually instructed by a health care provider or researcher); (PM) Physiological or structural marker; (ObS) Observational scale (to quantify the level of disability).

ICF - Chapter/code	Outcomes
Activities and Participations	
d4 Mobility	Rivermead Mobility Index (10, 15, 73) (PRO)/(ObS) Modified Rivermead Mobility Index (73) (PRO)/(ObS) Northwick Park ADL index (51) (ObS) Circulation, Transfer ability (self-reported) (10) (PRO)
Changing and maintaining body position (d410-d429)	
d410 Changing basic body position	Timed transfer (11) (PER)
d415 Maintaining a body position	Activities-specific balance confidence scale (ABC) (10, 14, 15, 19, 26, 34, 35, 55, 57, 70, 74) (PRO) Berg Balance Scale (BBS) (10, 14, 15, 19, 26, 34, 35, 37, 40, 44, 55, 57, 63, 69, 70, 74, 76, 77) (PER) /(ObS) Mini-BESTest (10, 26) (PER) /(ObS) Modified Dizziness Handicap Inventory (mDHI) (14, 74) (PRO) Sensory Organization Balance Test (SOBT) (15, 26, 44, 57, 70) (PER) Computerised Dynamic Posturography-Sensory Organisation Test (CDP-SOT) (57) (PER) Four Square Step Test (FSST) (26, 45, 55, 69) (PER) Single leg Standing Test (19, 69, 77) (PER) Equiscale (26, 69) (PER) /(ObS) Composite Equilibrium Score (34) (PER) Tinetti Balance Test (34, 55) (PER) Balance and coordiantion tasks - series of 14 balance tasks and 10 coordination tasks - reference/validation in German (70) (PER)
Carrying, moving and handling objects (d430-d449)	
d440 Fine hand use	9-Hole Peg Test (9HPT) (10, 12, 14, 16, 27, 33, 36, 40, 45, 51, 52, 63) (PER) Block and Box Test (10, 27, 33, 36, 51, 63) (PER) Jebson Test for Hand Function (JTHF) (51, 63) (PER) Action Reach Arm Test (ARAT); Functional Dexterity Test (FDT) Fugl Meyer Total/proximal Score; Two-Point Discrimination Test (TPD); Motor Ability Log (MAL); Wolf Motor Function Test - Fuctional Ability (WMFT-FA); Wolf Motor Function Test - Performance Time (WMFT-PT); Activities of Daily Living (ADL): Manual ability for adults with upper limb impairment (ABILHAND) (63) (PER)
d445 Hand and arm use	Upper extremity endurance (10, 51) (PER)
Walking and moving (d450-d469)	
d450 Walking	10-meter timed walk (10mW) (11, 12, 15-17, 24, 26, 28, 31, 34, 36, 37, 45, 47, 56, 60, 65, 66, 70-72, 76-78) (PER) 50-meter walk (50mW) (11, 78) (PER) 2-minutes walking test (2MWT) (10, 12, 15-17, 19, 24, 26-28, 35, 40, 44, 45, 53, 57, 60, 65-67, 70-72, 78) (PER) The timed 25 foot walk (T25FW) (10, 12, 15-18, 24, 26, 28, 34, 36, 37, 40, 45, 47, 51-53, 55, 57, 65-68, 70, 71, 75, 76, 78) (PER) 6-minutes walking test (6MWT) (12, 14-19, 26-28, 31, 33-36, 40, 45, 57, 60, 65-68, 70-72, 75-78) (PER) 20-meter walk (20mW) (68, 75, 76) (PER) 3-meter walk (3mW) (75, 76) (PER) 500-meter walking test (500mW) (12, 24, 26, 60, 66) (PER) 3-minute walking test (3MWT) (36) (PER) 10-minute walking (10MW) / Self- and Maximal-pace (70) (PER) Pedometer steps-per-day (18, 26, 45, 79-81) (PER) Energy expenditure and steps/day (80) (PER)

d455 Moving around	Number of Falls (36) (PRO) Hauser's Ambulation Index (HAI) (11) (PER)/(ObS) Multiple Sclerosis walking scale (MSWS-12) (10, 15, 19, 26, 34, 37, 53) (PRO) International Physical Activity Questionnaire (IPAQ) (59, 79) (PRO) Physical Activity Scale for Individuals with Physical Disabilities (PASPID) (27, 59, 81) (PRO) Health-Promoting Lifestyle Profile II (HPLP-II) (59, 81) (PRO) BAECKE - activity questionnaire (11, 24, 59, 81) (PRO) 7-Day Physical Activity Recall (PAR) (59, 71) (PRO) MET hrs/week (27, 81) (PER) Accelerometers and sensors (15, 32, 59) (PER)
d469 Walking and moving, other specified and unspecified	TUG (11, 12, 14, 15, 17, 19, 24, 27, 34, 35, 47, 53, 55-57, 60, 65, 67, 70-72, 74, 76-78) (PER) Four Square Step Test (19, 26, 34, 35, 65) (PER) Six Spot Step Test (19, 77) (PER) Timed stair ascent (12, 17, 26, 70, 73) (PER) Stair descent (70, 73) (PER)
d8 Major life areas	Social Provisions Scale (SPS) (26) (PRO) Work and Social Adjustment Scale (wSAS) (20) (PRO)
d9 Community, social and civic life	
d920 Recreation and leisure	The Godin Leisure-Time Exercise Questionnaire (GLTEQ) (18, 26, 27, 32, 37, 59, 71, 79, 81) (PRO) Sitting Time Questionnaire (min/day) (81) (PRO)
Environmental factors	
e499 Attitudes, unspecified	EBBS - Exercise Benefits and Barriers Scale (26) (PRO)

Table 5. Outcomes reported to investigate the effects of exercise interventions on disability and on Patient-reported outcomes (PROs) for generic disability and quality of life in pwMS. [PRO] PRO/ratings (patient reported, mostly ordinal rating scales and then total score) or single-item ratings by interval; [PER] Performance Measure (usually instructed by a health care provider or researcher); [PM] Physiological or structural marker; [ObS] Observational scale (to quantify the level of disability).

Rater-based outcomes of Disability	Patient-reported outcomes (PROs) of disability	Patient-reported outcomes (PROs) of Quality of life
Expanded Disability Status Scale (EDSS) (12, 26, 36, 52, 56, 68, 75) [ObS]	Multiple Sclerosis Impact Scale-29 (MSIS-29) (15, 17, 21, 26-28, 32-34, 37, 38, 44, 45, 47, 51, 53) [PRO]	8-Items Short Form Health Survey (SF-8 QOL) (82) [PRO]
Functional System Score (51) [ObS]	Short form health survey-36 (SF-36) (11, 12, 15, 17, 18, 21, 22, 26-28, 30, 38, 47, 57, 58, 82, 83) [PRO]	Multiple sclerosis quality of life (MSQOL) (12, 47, 58) [PRO]
Guys neurological disability scale (12, 51, 52) [ObS]	Functional assessment in multiple sclerosis (FAMS) (12, 38, 47, 82) [PRO]	MSQOL-54 (15, 19, 21, 22, 26, 28, 30, 32, 33, 38, 47, 57, 82, 83) [PRO]
Functional Independence Measure (FIM) (10, 12, 51, 52) [ObS]	Patient Health Questionnaire-9 (PHQ-9) (37, 42) [PRO]	Hamburg Quality of Life Questionnaire (HAQUAMS) (12, 21, 24, 30, 37, 38, 47) [PRO]
	Late-life function and disability inventory (LLFDI) (26) [PRO]	General life (15, 22) [PRO]
	Rehabilitation Institute of Chicago-Functional Assessment Scale (51) [PRO]	WHO Quality of Life BREF questionnaire (17, 82, 83) [PRO]
	Symptom Checklist-90 (SCL-90) (10) [PRO]	Single Term Quality of Life (21, 38) [PRO]
	Social support, Visual impairment impact (10) [PRO]	Leeds MS Quality of Life Scale (LMSQOL) (26, 38) [PRO]
	Perceived Deficits Questionnaire (PDQ) (57) [PRO]	Euro-QoL-5D (EQ5D) (26, 38, 45) [PRO]
	Research and Development Cooperation-25 item (RAND-25; RAND-36)(15) [PRO]	
	Satisfaction with Life Scale (21) [PRO]	
	Sickness Impact Profile (SIP) (21, 24, 30) [PRO]	
	MS-related Symptom Checklist (MSRSC) (22) [PRO]	
	Unified Theory of Acceptance and Use of Technology (34) [PRO]	
	World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) (34) [PRO]	
	Northwick Park ADL index (51) [ObS]	

Figure 1 Eight stage programme of work to determine specific and acceptable outcome measures in studies of exercise training in MS

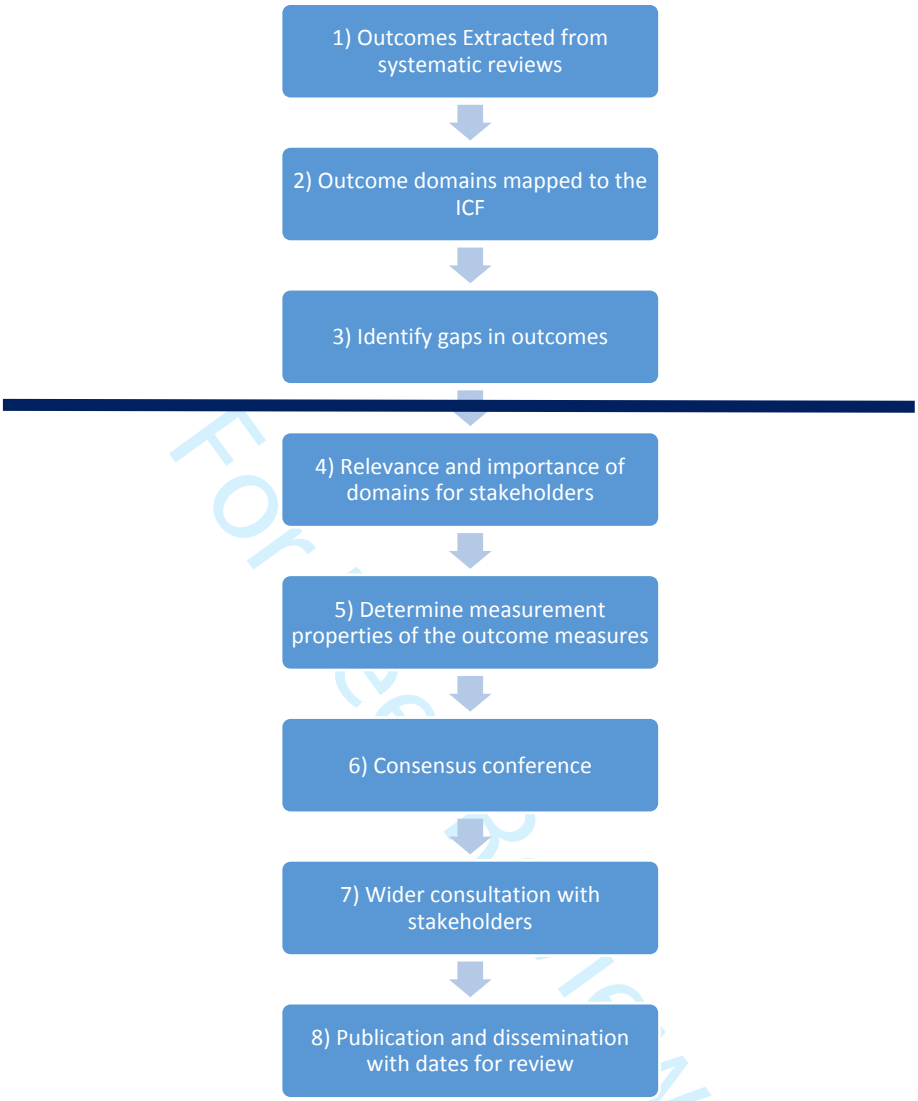
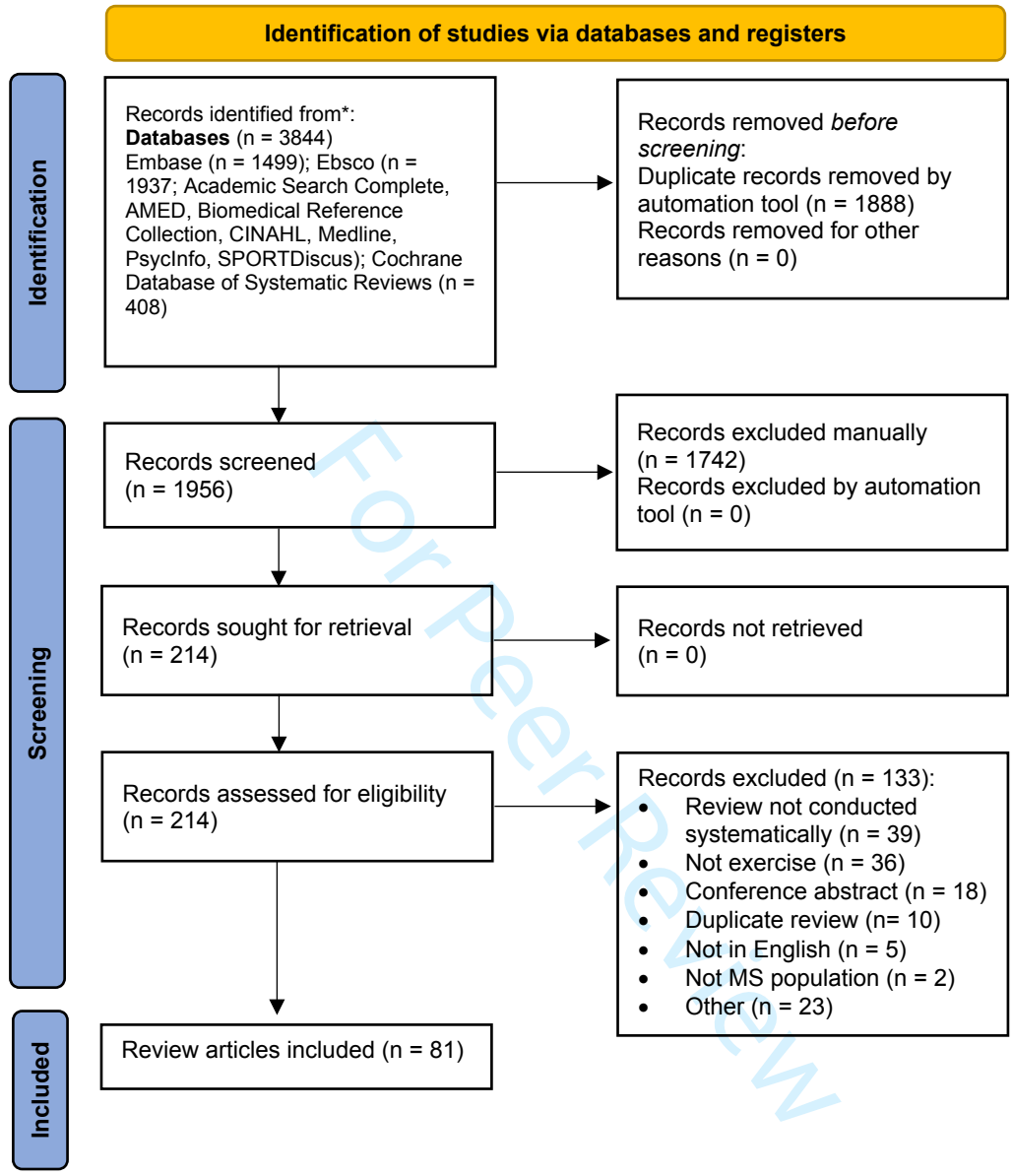


Figure 1

Legend – Stages 1-3 involve reviewing outcomes used previously in studies of exercise in MS, mapping them to the ICF and identifying gaps (presented in this paper). Stages 4-8 include reviewing the psychometric properties of the outcomes and discussing the relevance and usability of the outcomes with stakeholder, primarily people with MS, before broader consultation with the MS research and clinical community and further dissemination.

Figure 2 PRISMA diagram



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Supplementary table 1 Example Search Strategy

Example Search Strategy: Medline (EBSCO)	
AB ("systematic" OR "review" OR "meta-analysis") AND AB (“exercise” OR “physical activity” OR “exercise prescription” OR “exercise therapy” OR “training” OR “fitness” OR “aerobic” OR “strength” OR “resist” OR “ambulatory activity” OR “walk” OR “workout” OR “physical fitness”) AND AB (“Multiple sclerosis” OR “MS”)	Limiters- English Language

Supplementary table 2. Interventions included in the review studies.

Type of Intervention	Exercises
AEROBIC TRAINING	• Walking (e.g., over ground, treadmill, home-based walking training, electromechanical gait trainer, body-weight support treadmill training, recumbent stepping, downhill and uphill treadmill training) • Cycling (e.g., leg ergometry cycling, high-intense cycling, interval training, high-intensity interval training, functional electrical stimulation and cycling, arm ergometry cycling) • Rowing • Swimming and aqua aerobics
RESISTANCE TRAINING	• Free weights lifting • Weights machines • Resistance bands • Plyometrics
COMBINED TRAINING	• Aerobic + resistance exercises • Aquatic + resistance exercises • Aerobic cycling + Pilates • Aerobic + physiotherapy • Aerobic + resistance + balance exercises
BALANCE TRAINING	• Static balance • Dynamic balance • Walking with objects
OTHERS INTERVENTIONS	• Active console games (e.g., Nintendo WII, exergaming) • Yoga • Pilates • Tai Chi • Sports climbing • Robot-based Exercises • Hydrotherapy • Hippotherapy