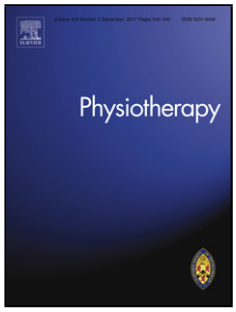

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The effect of exercise on high-level mobility in individuals with neurodegenerative disease: a systematic literature review.

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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).

Contribution of paper

- 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.

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 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 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 with regards to 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 (figure 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].

[Insert figure 1 here]

Study population

A total of 909 participants were included in the review with sample sizes for individual studies ranging from 10-110 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 4.5-18 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 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.

[Insert table 1 here]

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 (figure 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.

[Insert figure 2 here]

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 4-48 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 3-104 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 10-60 minutes. Measures of exercise intensity were commonly not reported (table 2). There were no significant adverse effects of any intervention reported.

[Insert table 2 here]

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 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 2 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.

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Declaration of interest

The authors report no conflicts of interest.

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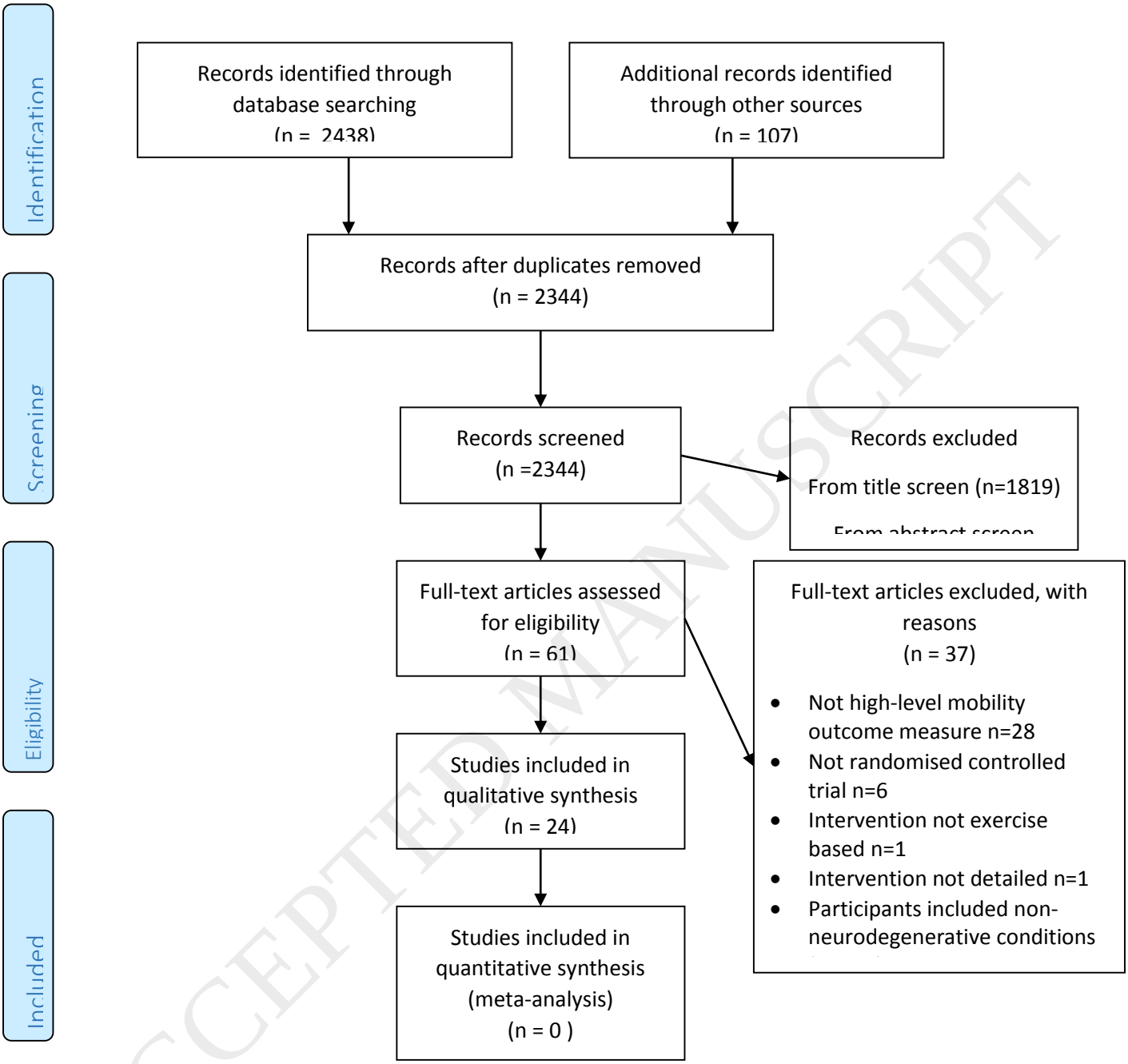

Figure 1. PRISMA flow diagram [24]

Figure 2: Cochrane risk of bias tool

	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							
Cakit et al, 2007 [36]	?	?	+	?	-	+	+
Duncan & Earhart, 2012 [48]	+	?	+	+	-	+	?
Duncan & Earhart, 2014 [49]	?	?	+	+	+	+	?
Hackney & Earhart, 2008 [50]	+	-	+	+	+	+	?
Hackney & Earhart, 2009 [51]	+	-	?	+	-	+	+
Kurtais et al, 2008 [37]	?	?	+	+	+	+	+
Landers et al, 2016 [52]	+	?	-	-	+	+	+
Liao et al, 2015 [38]	+	+	+	+	?	+	+
Song et al, 2018 [53]	+	+	+	+	-	+	+
Multiple sclerosis							
Cakit et al, 2010 [32]	+	?	+	+	-	+	?
Cattaneo et al, 2007 [33]	+	?	-	-	+	+	+
Dalgas et al, 2009 [39]	?	+	+	?	+	+	+
Hayes et al, 2011 [40]	?	?	?	?	-	+	+
Kjolhede et al, 2015 [47]	+	+	?	-	-	+	+
Lord et al, 1998 [41]	+	+	-	+	-	+	?
Nilsagard et al, 2013 [34]	+	+	+	+	+	+	?
Pfalzer & Fry, 2011 [42]	-	?	+	+	+	?	+
Salhofer-Polanyi et al, 2013 [43]	?	?	+	+	?	+	+
Samaei et al, 2016 [44]	+	+	+	+	+	+	+
Straudi et al, 2014 [35]	+	?	+	+	-	+	+
Tarakci et al, 2013 [46]	+	+	+	+	+	+	+
Wiles et al, 2001 [45]	+	+	+	+	+	+	?
Huntington's disease							
Kloos et al, 2013 [54]	-	-	+	+	-	+	+
Degenerative cerebellar disease							
Miyai et al, 2012 [55]	+	+	+	+	+	+	+

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

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
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)	EG: treadmill/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≤0.05

		CG= 5.4 (1.2)						
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).
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
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)	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

		EDSS Mean (SD) 4.9 (0.5)						
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 * (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 * (score)**	Three-way ANCOVA 90% power for 1 unit difference at α=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
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

* Primary outcome measure

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.

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	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. Stretching exercises	No incline	NA	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	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	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	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	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	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	NA	6 reps of balance course	Balance tasks progressed with equipment modifications.
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	EG1: NR EG2: strengthening 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	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	NA	EG1: 12 successful sets at cycle workload then ↑ by 10W increments

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:"conventional therapy" not aimed at balance	3 weeks	3-4 x week / 10-12 sessions	45 minutes	NR	NA	Individualised	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 1-4: 3 sets; weeks 5-10: 4 sets; weeks 11-12: 3 sets.	Weeks 1-2: 10 reps of 15RM; weeks 3-6: 12 reps at 12RM; weeks 7-8: 10 reps at 10RM; weeks 9-12 8 reps at 8RM.	Weeks 1-2: 10 reps of 15RM; weeks 3-6: 12 reps at 12RM; weeks 7-8: 10 reps at 10RM; weeks 9-12 8 reps at 8RM.
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 "somewhat hard'	NA	Standard exercise training: 1 set	Standard exercise training - upper limb resistance: 10RM	Eccentric stepper: weeks 1-2: 1-5 minutes; weeks 3-12 maximum 14 minutes. Progression with RPE.
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 1-6: 3 sets; weeks 7-12: 4 reps; weeks 13-14: 3 reps; weeks 15-22: 4 reps; weeks 23-24: 5 reps.	weeks 1-2: 10 reps of 15RM; weeks 3-4: 12 reps of 15RM; weeks 5-6: 10 reps of 12RM; weeks 7-8: 10 reps of 10 RM; weeks 9-10: 8 reps of 8 RM;	weeks 1-2: 10 reps of 15RM; weeks 3-4: 12 reps of 15RM; weeks 5-6: 10 reps of 12RM; weeks 7-8: 10 reps of 10 RM; weeks 9-10: 8 reps of 8 RM;

										weeks 11-12: 6 reps of 6RM; weeks 13-14: 10 reps of 12RM; weeks 15-18: 10 reps of 10RM; weeks 19-20: 8 reps pf 8RM; weeks 21-24 6 reps of 6RM.	weeks 11-12: 6 reps of 6RM; weeks 13-14: 10 reps of 12RM; weeks 15-18: 10 reps of 10RM; weeks 19-20: 8 reps pf 8RM; weeks 21-24 6 reps of 6RM.
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	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	NR	Wii Fit games ranked for difficulty and used as 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	15	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	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	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	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	NR
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	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	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	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