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Review article

Mobility and balance rehabilitation in multiple sclerosis: A systematic review and dose-response meta-analysis

Chiara Corrini [a], Elisa Gervasoni [a,*], Gloria Perini [a], Carola Cosentino [b], Martina Putzolu [b], Angelo Montesano [a], Elisa Pelosin [b], Luca Prosperini [c], Davide Cattaneo [a,d]

[a] LaRiCE lab: Gait and Balance Disorders Laboratory, Department of Neurorehabilitation, IRCSS Fondazione Don Carlo Gnocchi, Via Capecelatro 66, Milano 20148, Italy
[b] Department of Neuroscience, Rehabilitation, Ophtalmology, Genetics and Maternal Child Health, University f Genova, Genova, Italy
[c] Multiple Sclerosis Center, Neurology Unit S. Camillo-Forlanini Hospital, C.ne Gianicolense 87, 00152 Rome, Italy
[d] Department of Physiopathology and Transplants, University of Milan, Milan 20100, Italy

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ABSTRACT

Objective: To assess the benefits of neurological rehabilitation and the dose-response relationship for the treatment of mobility and balance in multiple sclerosis.

Methods: We included studies investigating the effects of neurological rehabilitation on mobility and balance with the following eligibility criteria for inclusion: Population, People with Multiple Sclerosis (PwMS); Intervention, method of rehabilitation interventions; Comparison, experimental (specific balance intervention) vs control (no intervention/no specific balance intervention); Outcome, balance clinical scales; Study Design, randomised controlled trials. We conducted a random effects dose-response meta-analysis to assess linear trend estimations and a one stage linear mixed effects meta-regression for estimating dose-response curves.

Results: We retrieved 196 studies from a list of 5020 for full text review and 71 studies (n subjects=3306) were included. One study was a cross-over and 70 studies were randomized controlled trials and the mean sample size per study was 46.5 ± 28.6 (mean±SD) with a mean age of 48.3 ± 7.8years, disease duration of 11.6 ± 6.1years, and EDSS of 4.4 ± 1.4points. Twenty-nine studies (40.8%) had the balance outcome as the primary outcome, while 42 studies (59.1%) had balance as secondary outcome or did not specify primary and secondary outcomes. Thirty-three trials (46.5%) had no active intervention as comparator and 38 trials (53.5%) had an active control group.

Individual level data from 20 studies (n subjects=1016) were analyzed showing a medium pooled effect size for balance interventions (SMD=0.41; 95% CIs 0.22 to 0.59). Moreover, we analyzed 14 studies (n subjects=696) having balance as primary outcome and BBS as primary endpoint yielding a mean difference of 3.58 points (95% CIs 1.79 to 5.38, $p<0.0001$).

Finally, we performed meta regression of the 20 studies showing an association between better outcome, log of intensity defined as minutes per session (β=1.26; SEβ=0.51; $p = 0.02$) and task-oriented intervention (β=0.38; SEβ=0.17; $p = 0.05$).

Conclusion: Our analyses provide level 1 evidence on the effect of balance intervention to improve mobility. Furthermore, according to principles of neurological rehabilitation, high intensity and task-specific interventions are associated with better treatment outcomes.

1. Introduction

Balance impairments, defined as the difficulties in maintaining the upright position during static, challenging, and reactive conditions of postural control, are common in People with Multiple Sclerosis (PwMS) (Cameron and Nilsagard, 2018; Cameron and Lord, 2010; Scholz et al., 2021) leading to falls in 46% of PwMS over six months (Beghi et al., 2018).

Balance disorders and falls highlighted the importance of balance rehabilitation (Comber et al., 2018), setting of intervention, disability,

* Corresponding author.
E-mail address: egervasoni@dongnocchi.it (E. Gervasoni).

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and type of treatment, can modulate the effects of balance rehabilitation, however treatment approaches and dose of intervention are two key factors. In recent decades, several rehabilitation approaches have been developed to improve balance in PwMS (Khan et al., 2017). Gunn et al. reported that the effect on balance outcomes was higher in interventions incorporating gait, balance, and functional training compared to other types of interventions (Gunn et al., 2015), while Paltamaa et al. reported that progressive resistance and aerobic interventions have positive effects on mobility and balance in PwMS (Paltamaa et al., 2012).

Even though several rehabilitation approaches have proven to be effective, it is important to understand the magnitude of mobility and balance improvement gained by increasing therapeutic dose (Dijkers et al., 2014). The dose can be defined as "the amount of active ingredient (s) expected to produce the desired effect and the frequency and duration at which the agent is taken" (Lang et al., 2015). Dose is a critical complex element that contributes to the effectiveness of the therapeutic interventions including frequency, intensity, duration, and timing of interventions (Kwakkel, 2006).

Understanding the optimal dose of a given therapeutic intervention is critical to the implementation of evidence-based practice and to increase the effectiveness of interventions. The challenge of finding the best dose for rehabilitation is that the active ingredients, their targets and mechanisms of action remain unclear hampering the development of theoretical models on rehabilitation (Dijkers et al., 2014).

Evidence about the appropriate dose of rehabilitation interventions is sorely lacking for neurological diseases. Only a few studies on stroke rehabilitation and brain injury have been carried out supporting contradictory results about the dose-response relationship between high intensity of practice and better outcome (Kwakkel, 2006; Shiel et al., 2001; Chen et al., 2002; Lohse et al., 2014; Kwakkel et al., 2004). However, a review by Lohse et al. showed a strong positive relationship between dose and response, demonstrating that time spent in therapy is a robust predictor of recovery across different types of interventions in people with Stroke (Lohse et al., 2014).

International clinical guidelines of rehabilitation in multiple sclerosis stress the lack of an appropriate dose for rehabilitation interventions. To our knowledge, only two reviews on balance intervention in PwMS suggest that rehabilitation programs achieving a high dose of challenging balance exercise may lead to the greatest benefit in balance outcomes (Khan et al., 2017; Gunn et al., 2015), although a formal analysis investigating dose-response relationship in mobility and balance interventions in PwMS is missing.

Hence, our systematic review is aimed at: (i) evaluating the effectiveness of balance interventions, (ii) evaluating the relationship between dose and rehabilitation effect on balance outcomes, (iii) uncovering variables that may influence balance interventions in PwMS.

2. Methods

2.1. Protocol and registration

This systematic review was performed according to the Cochrane group recommendations (Higgins and Green, 2008). We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA2020) statement for the reporting (Liberati et al., 2009). We also registered the protocol and details of this review into the International Prospective Register of Systematic Reviews—PROSPERO (https://www.crd.york.ac.uk/prospero/; register number CRD42020187247) that are publicly available.

2.2. Eligibility criteria

We included studies eligible according to the following PICOs:

- (P) Population: participants who had a diagnosis of Multiple Sclerosis (MS) according to McDonald criteria (Thompson et al., 2018) without concomitant neurological pathologies
- (I) Intervention; specific balance intervention, defined as all the interventions used in MS rehabilitation that specifically target balance and coordination using specific function-based activities to improve balance and stability (Bowman et al., 2021)
- (C) Comparison: no intervention or no specific balance intervention, defined as any type of intervention, passive stretching, and general exercises (Bowman et al., 2021)
- (O) Outcomes clinical scales whose area of assessment includes "balance (non-vestibular)" according to the Rehabilitation Measure Database (https://www.sralab.org/rehabilitation-measures);
- (s) Study design: Randomised Controlled Trials (RCTs) and crossover

Additionally, we included only RCTs published in English when one or more independent variables (e.g., intensity and/or duration of training) were specified in the paper; conversely, we excluded non-randomized and non-controlled pre-experimental studies, protocols, conference papers, or unpublished materials and studies including multiple diagnoses without separate analysis of MS.

2.2.1. Search strategy

We conducted a literature search from inception to January 2021 through the following databases: MEDLINE, Embase, Cochrane Library (CENTRAL database), Scopus, Web of Science, and PEDro Database. Suitable keywords and MeSH headings were generated through discussions amongst the study authors. Search strategies for each database were available in Supplementary Table 1.

We also performed a manual search in the reference list of included articles and previously published reviews, to retrieve articles not covered by the databases search. The literature search was supplemented by examining citation lists of returned articles and through Google Scholar searches.

2.3. Study selection

Two reviewers (GP and CC) independently screened all the titles and abstracts of the articles. After this step, potentially relevant articles were retrieved for full-text assessment, and the same reviewers independently evaluated all the potential full-text papers to identify eligible studies. In the event of disagreement, a third reviewer (EG) evaluated the article to achieve a joint consensus.

2.4. Data extraction and quality assessment

Studies were summarized by two authors (GP and CC). A planned spreadsheet was used to extract the following data:

- The publication year and the first author's name
- Sample size (n° of participants in the experimental group and the control group and drops out)
- Clinical and demographic characteristics of the sample (Mean age, MS type, EDSS score, Disease duration)
- Experimental and control intervention description
- Intervention characteristics [setting, duration, frequency, intensity, and dose of intervention]
- Timing of follow-up assessments
- Balance related outcome measures (primary and secondary outcomes)

In case of unavailable data, we sent an e-mail to the authors or we estimated required data when possible, otherwise, the study was excluded from meta-analysis. If data were presented as median and interquartile range, median was assimilated to mean and standard

deviation (SD) was calculated considering that inter-quartile range = 1.35 × SD, (Higgins and Green, 2008) and clinical relevance was differently judged depending on the minimally clinically important difference (MCID) of the measured outcomes (McGlothlin and Lewis, 2014). The study with a crossover design was analyzed as parallel group RCT, by calculating effects before the point of crossover.

2.5. Categories of balance intervention

According to previous studies on the definition and classification of balance intervention (Horak, 2006; Forbes et al., 2018; Cosentino et al., 2020; Heine et al., 2015; Shumway-Cook and Woollacott, 2012), we defined and classified rehabilitation intervention of the selected studies in eight categories:

1) Task-oriented training: individualized, client-centered, and functional-based interventions focused on motor relearning principles;
2) Gaming exercises program: active console game interventions, exergames;
3) General exercises program: general exercises challenging balance;
4) Mixed exercises program: more than one intervention in the same group;
5) Core stability training: yoga and pilates trained by a physical therapist;
6) Aerobic and resistance training;
7) Vibration therapy: vibration therapy
8) Other types of training (e.g. aquatic training and hippotherapy)

2.6. Risk of bias assessment

We assessed the methodological quality of the studies using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2.0, version of 15 March 2019) (Sterne et al., 2019). Bias arising from the: randomization process, deviations from intended intervention (effect of assignment and adhering to intervention), missing outcome data, outcome measurement. The selection of the reported studies was considered for risk-of-bias assessment and labeled as "low risk of bias," "high risk of bias," or "some concerns" by two independent reviewers (GP, CC). Disagreements were resolved by a third author (EG). Traffic light plots of the domain-level judgments for each individual result and weighted bar plots of the distribution of risk-of-bias judgments within each bias domain are formated according to the risk-of-bias assessment tool and built up through RobVis.

2.7. Data synthesis and analysis

According to PICOs, all studies have been considered in a qualitative synthesis of the results (see Table 1). To limit heterogeneity, we did not include studies where the balance outcomes were assessed only by instruments (e.g. static and dynamic posturography) providing a wide range of instrumented variables.

We included in the meta-analysis all the studies with available data comparing the experimental group (specific balance intervention classified into 8 categories) versus the control group (no intervention or no specific balance intervention). For each study, we entered only post-intervention scores to account for the expected heterogeneity between studies and outcome measures, as recommended by the Cochrane collaboration. In the case of two or more experimental groups, we considered only the balance group. Consequently, in the case of two experimental (balance) groups belonging to one of the eight categories listed above, we combined the experimental interventions into a single group. Conversely, in case of two experimental groups belonging to different categories, we examined the experimental group considered as the main active principle of efficacy by the authors.

2.8. Statistical analysis

Random-effects models weighted by inverse variance were used to calculate the pooled effect size (ES) according to the DerSimonian and Laird procedure. Each study included in this meta-analysis was handled as a statistical unit.

We estimated the pooled ES of interventions either as mean difference (MD) to summarize studies using the same balance scale or as standardized mean difference (SMD) to summarize studies using different balance scales. Given the small sample size of included studies, we applied the bias-corrected Hedges' g to estimated SMD. This is equivalent to a Cohen's d with an additional correction factor for small samples, thus providing more conservative results. Positive ESs indicated greater improvement in balance with the experimental intervention than the control intervention. ESs were graded as small ($g = 0.20$), medium ($g = 0.50$) and large ($g = 0.80$).

Between-study variance and heterogeneity were assessed by the Cochran's Q-value and I^2 index, respectively; we considered an $I^2 \leq 40\%$ as marginal, 30 to 60% as moderate, and 50 to 90% as substantial heterogeneity. The risk of publication bias was assessed by the Egger's test of asymmetry and the Orwin's fail-safe N test for estimating the number of missing studies to be incorporated to make the observed ES trivial, on the assumption that studies demonstrating a lack of benefit might not have been published. We performed a sensitivity analysis to confirm our results when the balance was not set as the primary endpoint.

Meta-regression analyses were run to explore which covariates or factors were associated (if any) with a greater ES of experimental interventions.

We identified the following study variables as continuous (log10-transformed) covariates: mean age of participants, duration (overall treatment length in weeks), frequency (number of sessions per week), intensity (minutes spent in a single session) of intervention, and dose (total time rehabilitation intended as a product of duration, frequency and intensity in hours) as defined by Lohse et al. (2014) or as categorical factors: setting (home-based or hospital-based), type of experimental intervention (non task-oriented or task-oriented), type of control intervention (none or alternative).

Two-tailed p values less than 0.05 were considered significant. Data were analyzed by using the freeware software Revman 5.3 and JASP version 0.14 (JASP Team, 2020; www.jasp-stats.org).

2.9. GRADE

The Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) system was employed to score the overall quality of evidence (Guyatt et al., 2011). An initially assumed high level of evidence was downgraded according to the following pre-defined criteria (Andrews et al., 2013): risk of bias (limitations in study design and execution or methodological quality); inconsistency (significant between-study heterogeneity and $I^2 \geq 40\%$); indirectness (> 50% of the participants were outside the target population); imprecision (< 400 participants,); publication/selection bias (asymmetry of the funnel plot). Consequently, the evidence could be ranked into four levels: very low, low, moderate, and high.

3. Results

3.1. Study selection

The literature search identified a total of 5020 results, among which 1591 duplicates were removed, and 3233 studies were rejected according to title and abstract. A total of 196 unique full-text articles were assessed for eligibility. At the end of the screening phase, 125 studies were excluded (reasons for exclusion are reported in Fig. 1), and then 71 studies were included in systematic review (Fig. 1).

Table 1
Summary of included studies.

First Author [Ref], Year	Specified balance as primary outcome (Y/N)	Sample size (drop out)	Participant Characteristics	Experimental intervention	Control intervention	Balance-related outcome measures	Setting	Duration, weeks	Frequency, sessions per week	Intensity, min per session	Dose, H tot	FU, weeks
Abasıyanık, 2020	N	EG: 21 (5)										
CG: 21 (4)	Mean age: 45.5 MS type: RR, SP EDSS: 3.15 Disease duration: 11.84	Clinical Pilates	Home exercise program	TUG, ABC, FES-I, Posturography	Out	8	3	57.5	23	/		
Afrasiabifar, 2018	Y	EG1: 25 (1) EG2: 25 (2) CG: 25 (0)	Mean age: 32.7 MS type: RR, SP, PP EDSS: not specified Disease duration: 27.6	EG1: Cawthorne–Cooksey treatment EG2: Frenkel treatment	Routine care	BBS	Out	12	3	60	36	6
Aidar, 2018	N	EG: 13 (2) CG: 13 (1)	Mean age:43.2 MS type:not specified EDSS <7.5 Disease duration: not specified	Resistance training	No physiotherapy	BBS, TUG	Out	12	3	52.5	31.5	/
Aidar, 2018	N	EG: 14 (1) CG: 14 (1)	Mean age: 43.2 MS type: not specified EDSS <7.5 Disease duration: not specified	Aquatic exercises	No physiotherapy	BBS, TUG	Out	12	3	52.5	31.5	/
Amiri, 2019	N	EG: 36 (1) CG: 36 (2)	Mean age: 31.61 MS type: RR EDSS: 3.84 Disease duration: not specified	Core stability training	Conventional programs (not include training of balance function)	Posturography	Out	10	3	60	30	/
Armutlu, 2001	Y	EG: 13 (0) CG: 13 (0)	Mean age: 33.61 MS type: PP, SP EDSS: 4.7 Disease duration: 6.07	Johnstone Pressure Splint in addition to neuromuscular rehabilitation	Neuromuscular rehabilitation, mat activities with PNF techniques combined with balance training	Posturography	In	4	3	Not specified	Not specified	/
Arntzen, 2019	Y	EG: 40 (1) CG: 40 (0)	Mean age:50.1 MS type:not specified EDSS:2.36 Disease duration:10.36	Group-based, comprehensive core stability intervention	Standard care on balance and trunk control	Mini-BESTest, Posturography	Out	6	3	60	18	12, 24
Aydin, 2014	N					BBS		12	5	40	40	/

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Table 1 (*continued*)

		EG: 20 (4) CG: 20 (0)	Mean age: 32.83 MS type: not specified EDSS: 3.5 Disease duration: 6.97	Hospital-based calisthenic and relaxation exercises	Home-based calisthenic and relaxation exercises		EG: In CG: Home					
Brichetto_1, 2013	Y	EG: 18 (0) CG: 18 (0)	Mean age: 41.95 MS type: not specified EDSS: 4.1 Disease duration: 11.75	Wii exercises	Balance rehabilitation	BBS, Posturography	Out	4	3	60	12	/
Brichetto_2, 2015	Y	EG: 16 (0) CG: 16 (0)	Mean age: 50.5 MS type: RR, SP, PP EDSS: 3.7 Disease duration: 10.5	Sensory system impairment rehabilitation	Balance rehabilitation	BBS, Posturography	Out	4	3	60	12	/
Broekmans, 2010	N	EG: 11 (0) CG: 14 (2)	Mean age: 47.9 MS type: RR, SP, PP EDSS: 4.3 Disease duration: not specified	Leg muscle training on a vibration platform	No physiotherapy	BBS, TUG	Out	20	5	50	83.5	/
Bulguroglu, 2017	N	EG1: 12 EG2: 13 CG: 13 (7 drop out, groups not specified)	Mean age: 40.6 MS type: not specified EDSS: 1.6 Disease duration: 4.16	EG1: Mat Pilates EG2: Reformer Pilates	Home-based relaxation and respiration exercises	TUG, ABC	EG1,2: Out CG: Home	8	2	60	16	/
Cakt, 2010	N	EG1: 15 (1) EG2: 15 (5) CG: 15 (6)	Mean age: 37.9 MS type: not specified EDSS: not specified Disease duration: 7.3	EG1: progressive resistance training on a bicycle ergometer and balance exercise EG2: home-based lower-limb strengthening and balance exercise	No physiotherapy	TUG, DGI	EG1: Out EG2: Home	8	2	123	32.8	/
Calabrò, 2017	Y	EG: 20 (0) CG: 20 (0)	Mean age:42.5 MS type: RR EDSS: 4.57 Disease duration: 11.5	Robotic-assisted gait training +VR	Robotic-assisted gait training	BBS, TUG	Out	8	5	70	46.6	/
Callesen, 2019	Y	EG1: 23 (6) EG2: 28 (4) CG: 20 (2)	Mean age: 52 MS type: RR, SP, PP EDSS: 3.5 Disease duration: 17	EG1: Progressive resistance training of the lower extremities EG2: Balance and Motor Control Training that challenges gait function	No physiotherapy	SSST, Mini-BESTest, ABC, Posturography	Out	10	2	60	20	/
Carling, 2017	Y	EG: 25 (2) CG: 26 (0)	Mean age: 58 MS type: RR, SP, PP EDSS: 6	Core stability exercises, dual tasking and sensory strategies + tailored home exercise program	No physiotherapy	BBS, FES-I, TUG, Posturography	Out + Home	7	2	60	14	/

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Table 1 (*continued*)

			Disease duration: 20.85									
Cattaneo_1, 2007	Y	EG1:23 (3) EG2:12 (1) CG:15 (2)	Mean age:46 MS type:RR,SP, PP EDSS:not specified Disease duration:13.8	EG1: Balance rehabilitation to improve motor and sensory strategies EG2: Balance rehabilitation to improve motor strategy	Conventional therapy, treatments not specifically aimed at improving balance	BBS, DGI, ABC	In	3	3.5	45	7.8	/
Cattaneo_2, 2014	N	EG: 25 (2) CG: 28 (7)	Mean age: 48.35 MS type: RR, SP, PP EDSS: 5 Disease duration: not specified	Balance rehabilitation aimed at improving motor and sensory strategies	Rehabilitation treatment which did not include training of sensory strategies	Posturography	Out	3	3	45	6.7	/
Conroy, 2017	N	EG: 26 (10) CG: 25 (17)	Mean age: 52.7 MS type: RR, SP, PP EDSS:not specified Disease duration: 13.3	Internet-based module, tele-management home exercise	Home-based exercises	BBS	Home	24	7	Not specified	Not specified	/
DeBolt, 2004	Y	EG: 19 (1) CG: 17 (0)	Mean age: 50.7 MS type: RR, SP, PP EDSS: 3.78 Disease duration: 14.09	Lower-extremity resistance training.	No physiotherapy	TUG, Posturography	Home	10	3	42.5	21.2	/
Eftekharsadat, 2015	N	EG: 15 (0) CG: 15 (0)	Mean age: 35.2 MS type: RR, SP EDSS:not specified Disease duration: 7.1	Postural stability training program using the Biodex Balance System SD	No physiotherapy	BBS, TUG, Posturography	Out	12	2	20	8	/
Fjeldstad-Pardo, 2018	N	EG: 10 (1) CG1:10 (0) CG2: 10 (0)	Mean age: 54.7 MS type: RR, SP, PP EDSS: 4.3 Disease duration: not specified	Home based exercises program plus in-person physical therapy at foundation	CG1: Remote physical therapy supervised via audio/visual real-time telecommunication CG2: Unsupervised home based exercises program	BBS, ABC, Posturography	EG: Home+out CG1,2: Home	8	7	Not specified	Not specified	/
Forsberg, 2016	Y	EG: 44 (9) CG: 43 (5)	Mean age: 54.14 MS type: RR, SP, PP EDSS:not specified Disease duration:15.5	Group-based balance exercises	No physiotherapy	BBS, TUG, ABC, FSST, Posturography	Out	7	2	55	12.8	/
Freitas, 2018	N	EG: 9 (0) CG: 12 (0)	Mean age:46.5 MS type: RR EDSS: not specified Disease	Whole-body vibration	Sham whole-body vibration	BBS, TUG, Posturography	Out	5	1	2.5	0.2	/

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Table 1 (*continued*)

			duration: not specified									
Frevel, 2015	Y	EG: 9 (1) CG: 9 (1)	Mean age: 45.5 MS type: RR, SP EDSS: 3.8 Disease duration: 19	Internet-based home training (balance, postural control and strenght training)	Hippotherapy	BBS, DGI, TUG	EG: Home CG: Out	12	2	25	10	/
Gandolfi_1, 2014	Y	EG: 12 (2) CG: 14 (2)	Mean age: 50.5 MS type: RR, SP EDSS: 4.2 Disease duration: 14.2	Specific balance exercises aimed at improving the ability to integrate multisensory inputs during balance responses	End-effector system training and stretching exercises	BBS, ABC, Posturography	Out	6	2	50	10	4
Gandolfi_2, 2015	Y	EG: 39 (7) CG: 41 (5)	Mean age:48.38 MS type:RR EDSS:3.3 Disease duration:13.74	Specific training to improve central integration of afferent sensory inputs	Conventional rehabilitation	BBS, ABC, Posturography	Out	5	3	50	12.5	4
Hayes, 2011	N	EG: 11 (2) CG: 11 (1)	Mean age: 49 MS type: not specified EDSS: 5.24 Disease duration: 12.15	Standard exercises and Renew training (high intensity lower extremity eccentric ergometric resistance exercise)	Standard therapy: aerobic training, lower extremity stretching, upper extremity strenght training and balance exercises	TUG, BBS	Out	12	3	52.5	31.5	/
Hebert_1, 2011	Y	EG1: 12 (0) EG2: 13 (0) CG: 13 (0)	Mean age: 46.53 MS type: RR, SP EDSS: not specified Disease duration: 6.9	EG1: Vestibular rehabilitation EG2: Bicycle endurance and stretching exercises	No physiotherapy	Posturography	Out	6	2	60	12	4, 8
Hebert_2, 2018	Y	EG:44 (6) CG:44 (6)	Mean age:44.75 MS type:not specified EDSS:3.42 Disease duration:7.16	Vestibular rehabilitation	No physiotherapy	Posturography	Out	14	7	Not specified	Not specified	/
Hoang, 2016	Y	EG: 28 (5) CG: 22 (1)	Mean age: 52.4 MS type: RR, SP, PP EDSS:4.15 Disease duration:12.5	Step training with two interactive exergames	No physiotherapy	TUG, Posturography	Out	12	2	30	12	/
Hogan, 2014	N	EG1: 66 (18) EG2: 45 (10) EG3: 16 (3) CG: 19 (4)	Mean age: 52 MS type: RR, SP, PP EDSS: not specified Disease duration: 14	EG1: Group-based physiotherapy (balance and strengthening exercises) EG2: Individual physiotherapy EG3: Yoga	No physiotherapy	BBS	Out	10	1	60	10	/
Kalron_1, 2016	N	EG: 16 (1) CG: 16 (1)	Mean age: 45.6 MS type: RR EDSS: 4.2 Disease duration: 11	VR balance rehabilitation	Stretching exercises, static postural control, weight shifting and perturbations exercises	BBS, FSST, Posturography	Out	6	2	30	6	/
Kalron_2, 2017	N	EG:25 (3) CG:25 (2)	Mean age:43.2 MS type:RR EDSS:4.3	Pilates intervention + home exercise program	Physiotherapy sessions + home exercise program	BBS, TUG, FSST	Out	12	1	30	6	/

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Table 1 (*continued*)

			Disease duration:11.85									
Kargarfard, 2018	N	EG: 20 (3) CG: 20 (5)	Mean age: 36.4 MS type: RR EDSS: 3.6 Disease duration: 6.2	Aquatic training program	No physiotherapy	BBS	Out	8	3	52.5	21	/
Keser, 2013	N	EG: 10 CG: 10 (3 drop out, groups not specified)	Mean age: 38.6 MS type: not specified EDSS: 2.82 Disease duration: 6.35	Posture, mat, coordination, balance, walking, stepping and movement control, and strengthening exercises and trunk exercises based on the Bobath concept	Routine neurorehabilitation program (posture, mat, coordination, balance, walking, stepping and movement control, and strengthening exercises)	BBS	Out	8	3	60	24	/
Khalil, 2018	N	EG: 20 (4) CG: 20 (4)	Mean age: 37.37 MS type: RR EDSS: 3 Disease duration: 9.04	VR training	Home-based traditional balance exercises without the VR	BBS, TUG	EG: Out CG: Home	6	3	12	3.6	/
Kramer, 2014	Y	EG1:21 EG2:20 CG:20 (9 drop out, groups not specified)	Mean age: 47 MS type: not specified EDSS: 3 Disease duration: not specified	EG1: Exergame EG2: Posturomed training	Conventional training group	Posturography	Out	3	3	30	4,5	/
Kucuk, 2016	N	EG: 11 (8) CG: 9 (4)	Mean age: 48.45 MS type: not specified EDSS: 3 Disease duration: 14.5	Pilates	Usual care (traditional exercise program; strength, balance and coordination exercises)	BBS, TUG	Out	8	2	52.5	14	/
Lord, 1998	N	EG: 12 (16) CG: 11 (9)	Mean age: 53,1 MS type: RR, PP EDSS: not specified Disease duration: 16.15	Facilitation (impairments-based) approach	Task-oriented treatment for walking and functional mobility	BBS	Out	6	2.5	60	15	/
Lozano-Quilis, 2014	N	EG: 6 (0) CG: 5 (1)	Mean age: 44,82 MS type: RR, SP EDSS: not specified Disease duration: 9.77	Virtual rehabilitation	Usual care (standard balance and gait rehabilitation exercises)	BBS, TUG, POMA	Out	10	1	60	10	/
Mansour, 2013	N	EG: 12 (0) CG: 12 (0)	Mean age: 41.04 MS type: RR EDSS: 2,85 Disease duration: not specified	Treadmill training	Treadmill training with 40% partial body weight support	TUG	Out	6	3	30	9	/
Martini, 2018	N	EG: 20 (0) CG: 20 (0)	Mean age: 55.4 MS type: not specified EDSS: 6	Task-oriented training	Usual medical care	TUG, FSST, ABC	Out	6	1	40	4	/

(*continued on next page*)

Table 1 (*continued*)

			Disease duration: not specified								
McAuley, 2015	N	EG: 24 (2) CG: 24 (0)	Mean age: 59,7 MS type: RR, SP, PP EDSS: not specified Disease duration: 18,97	DVD exercise intervention focusing on balance, strength, and flexibility	Watch the 85-minute DVD documentary and continue with their normal day to-day lives	SPPB	Home	24	3	Not specified	Not specified	/
Monjezi, 2017	N	EG: 23 (4) CG: 24 (5)	Mean age: 36 MS type: RR EDSS: 2,8 Disease duration: 7,35	Dual-task balance training	Single-task balance training	ABC, BBS	Out	4	3	45	9	6
Negahban, 2013	N	EG: 12 (0) CG: 12 (0)	Mean age: 36,62 MS type: RR, SP EDSS: 3,7 Disease duration: 9,4	EG 1:Swedish massage EG 2: Exercise therapy (strength, stretch, endurance treadmill and balance training exercises) EG 3: Exercise therapy plus massage	Standard medical care	BBS, TUG	Out	5	3	30	7,5	/
Nilsagård, 2012	Y	EG: 42 (1) CG: 42 (3)	Mean age: 49,7 MS type: RR, SP, PP EDSS: not specified Disease duration: 12,35	Balance exercise using Nintendo Wii Fit Plus®	No physiotherapy	TUG, FSST, DGI, ABC	Home	6.5	2	30	6,5	/
Novotna, 2019	Y	EG: 23 (0) CG: 16 (0)	Mean age: 40,69 MS Type: not specified EDSS: 3,8 Disease duration: 14,76	Tailored exercise training using Homebalance®	No physiotherapy	BBS, Mini-BESTest, TUG (part of Mini-BESTest), ABC, FES-I	Home	4	7	15	7	4
Ortiz Gutié rrez 2013	N	EG: 25 (1) CG: 25 (2)	Mean age: 41,23 MS type: RR EDSS: 3,3 Disease duration: 10,27	Telerehabilitation treatment using the Xbox 360®	Physiotherapy treatment (stretching, low-loads strength exercises, propioception exercises and gait facilitation exercises)	BBS, POMA	Home	10	EG: 4 CG: 2	EG: 20 CG: 40	13.3	/
Ozgen, 2016	Y	EG: 20 (0) CG: 20 (0)	Mean age: 41 MS Type: RR, SP, PP EDSS: 3,5 Disease duration: 7,7	Customized vestibular rehabilitation	Usual medical care	ABC, TUG, BBS, DGI, Posturography	Out	8	6	55	44	/
Ozkul_1, 2020	N	EG1: 17 (4) EG2: 17 (4) CG: 17 (4)	Mean age: 32,33 MS type: RR EDSS: 1,3 Disease duration: 4	EG 1: Virtual reality Pilates EG 2: Pilates and balance training group	Relaxation exercises	BBS, TUG, Posturography	EG 1,2: Out CG: Home	8	2	EG: 60 CG: 20	EG: 16 CG: 5.3	/
Ozkul_2, 2020	N	EG: 12 (2) CG: 11 (1)	Mean age: 43,75 MS Type: RR,	Task-oriented circuit training	Relaxation exercises	BBS, ABC, TUG, Posturography	Out	6	2	60	12	/

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Table 1 (*continued*)

			PP EDSS: 3,87 Disease duration: 14,75									
Pavlikova, 2020	N	EG: 114 (19) CG: 64 (9)	Mean age: 46,63 MS type: RR, SP, PP EDSS: 5,1 Disease duration: 13,6	Balance specific physiotherapy (motor program activating therapy and sensory motor integration training	Vojta and conventional dynamic strengthening exercises	BBS, TUG	EG: In + Out CG: In + Out	9	2	40	12	/
Peruzzi, 2017	N	EG: 16 (2) CG: 15 (4)	Mean age: 42,8 MS Type: RR EDSS: 3,8 Disease duration: 12,1	VR Treadmill training	Virtual reality-based treadmill training	BBS, TUG, FSST	Out	6	3	45	13.5	/
Prokopiusova, 2020	Y	EG: 22 CG: 22 (5 drop out, groups not specified)	Mean age: 48,5 MS type: RR, SP, PP EDSS: 4,7 Disease duration: 12,8	Functional Electric Stimulation in Posturally Corrected Position	Neuroproprioceptive facilitation and inhibition physiotherapy	BBS, TUG, DGI, ABC, FSST	Out	8	7	60	56	/
Prosperini, 2013	N	EG: 18 (1) CG: 18 (1)	Mean age: 36,2 MS type: RR, SP EDSS: 3,25 Disease duration: 10,75	Balance exercise using Nintendo Wii Fit Plus	No physiotherapy	FSST, Posturography	Home	12	5	30	30	21
Robinson, 2015	Y	EG1: 20 (0) EG2: 18 (1) CG: 18 (3)	Mean age: 52 MS type: not specified EDSS: not specified Disease duration: not specified	EG 1: Balance exercise using the Nintendo Wii Fit™ EG2: Traditional balance training	No physiotherapy	Posturography	In	4	2	50	7	4
Russo, 2017	N	EG: 30 (0) CG: 15 (0)	Mean age: 41,5 MS type: RR EDSS: 5 Disease duration: 11,69	Lokomat-Pro + traditional training	Usual care (general conditioning exercises, warming up, strengthening, gait and postural control)	TUG, POMA	Out	18	3	60	54	/
Salci, 2017	N	EG1: 16 (2) EG2: 16 (2) CG: 16 (2)	Mean age: 35,67 MS type: RR, SP, PP EDSS: 3,5 Disease duration: 7	EG 1: Balance training (sensory and motor strategy facilitation techniques) EG 2: Lumbar stabilization exercises in addition to balance training	Task-oriented training (Nine workstations: sit to stand, stepping, reaching, walking, running, hitting a ball)	BBS, Posturography	Out	6	3	45	13.5	/
Samaei, 2011	Y	EG: 17 (1) CG: 17 (2)	Mean age: 33 MS type: RR EDSS: not specified Disease duration: 4,65	Downhill or uphill treadmill walking	Downhill or uphill treadmill walking	TUG, Posturography	Out	4	3	30	6	4
Sangelaji, 2014	N	EG: 42 (7) CG: 30 (10)	Mean age: 32,55 MS Type: not specified	Combination exercises (stretching, strengthening aerobics and balancing exercises	Not specified	BBS	Out	10	3	75	37.5	/

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Table 1 (*continued*)

			EDSS: 1,83 Disease duration: not specified								
Sangelaji, 2016	N	EG1: 10 (0) EG2: 10 (0) EG3: 10 (0) CG: 10 (0)	Mean age: 33,66 MS type: RR EDSS: 1,78 Disease duration: 2	Aerobic exercise training and resistance exercise training sessions in different ratios	No physiotherapy	BBS, TUG	Out	8	4	Not specified	Not specified	/
Schuhfried, 2005	N	EG: 6 (0) CG: 6 (0)	Mean age: 47,1 MS type: not specified EDSS: 3,8 Disease duration: not specified	Whole-body vibration	Sham whole-body vibration	TUG, Posturography	Out	1	1	9	0.15	2
Silkwood-Sherer, 2007	Y	EG: 9 (0) CG: 6 (0)	Mean age: 44,53 MS type: RR, SP, PP EDSS: not specified Disease duration: 11,03	Hippo-therapy sessions	No physiotherapy	BBS, POMA, Posturography	Out	14	1	30	7	/
Spina, 2016	Y	EG: 10 (1) CG: 10 (0)	Mean age: 47,5 MS type: RR, SP, PP EDSS: 3,8 Disease duration: 6,97	Whole-body vibration	Sham whole-body vibration	BBS, DGI, Posturography	In	3	5	60	15	3
Stephens, 2001	N	EG: 6 (not specified) CG: 6 (not specified)	Mean age: 54 MS Type: not specified EDSS: 4,75 Disease duration: 7,61	Awareness through movements training	Educational classes on acupuncture treatment, new medications, benefits of exercise	ABC, Posturography	Out	10	Not specified	EG:180 CG: 90	Not specified	/
Tarakci, 2013	Y	EG: 55 (4) CG: 57 (7)	Mean age: 40,57 MS type: RR, SP, PP EDSS: 4,29 Disease duration: 8,71	Flexibility, range of motion, strengthening, core stabilization, balance and coordination exercises and functional activities	No physiotherapy	BBS	Out	12	3	60	36	/
Thomas, 2017	N	EG: 15 (1) CG: 15 (0)	Mean age: 49,3 MS type: RR, SP, PP EDSS: not specified Disease duration: not specified	Balance exercise using the Nintendo Wii Fit™ (Wii Sports, Sports Resort and Fit Plus software)	Usual medical care	TUG	EG: Home + Out CG: Out	EG: 48	2	Not specified	Not specified	/
Tramontano, 2018	N	EG: 15 (2) CG: 15 (7)	Mean age: 48,2 MS Type: not specified EDSS: 6,5	VR treatment (VRG): postural stability in standing position on a foam cushion	Standard neurorehabilitation (stretching, postural alignment, mobilizations and neuromuscular facilitations,	BBS, POMA	Out	4	5	EG: 100 CG: 80	EG: 33.3 CG: 26.7	4

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Table 1 (*continued*)

			Disease duration: 14		balance training in standing and dynamic tasks)							
Vermohlen, 2018	Y	EG: 32 (2) CG: 38 (1)	Mean age: 51 MS type: not specified EDSS: 5,4 Disease duration: 17	Hippotherapy and standard care	Standard therapy	BBS	Out	12	EG: 1	30	6	/
Yazgan, 2020	Y	EG1: 16 (1) EG2: 16 (4) CG: 15 (0)	Mean age: 43,73 MS type: RR, SP, PP EDSS: 4,01 Disease duration: 12,67	EG 1: Balance exercise using Nintendo Wii Fit™ EG 2: Balance Trainer	No physiotherapy	BBS, TUG	Out	8	2	60	16	/

3.2. Studies characteristics

The total number of participants is sufficiently high (n = 3306), however, we observed a great heterogeneity of the sample size among the studies ranging from 12 to 178 participants with a mean (mean ± SD) sample size per study of 46.5 ± 28.6 participants. The mean age was 48.3 ± 7.8 years with a disease duration of 11.6 ± 6.1 years and an Expanded Disability Status Scale (EDSS) score of 4.4 ± 1.4 points.

Thirteen studies (18.3%) (Afrasiabifar et al., 2018; Arntzen et al., 2019; Gandolfi et al., 2014; Gandolfi et al., 2015; Hebert et al., 2011; Monjezi et al., 2017; Novotna et al., 2019; Prosperini et al., 2013; Robinson et al., 2015; Samaei et al., 2016; Schuhfried et al., 2005; Spina et al., 2016; Tramontano et al., 2018) had follow-up assessment including 843 participants. Timing of follow-up assessments ranged from 4 to 24 weeks.

A comprehensive summary of the trials and participants' characteristics is reported in Table 1. All 71 studies included were randomized controlled studies: one (1.4%) (Prosperini et al., 2013) was crossover and 70 (98.6%) (Afrasiabifar et al., 2018; Arntzen et al., 2019; Gandolfi et al., 2014; Gandolfi et al., 2015; Hebert et al., 2011; Monjezi et al., 2017; Novotna et al., 2019; Prosperini et al., 2013; Robinson et al., 2015; Samaei et al., 2016; Schuhfried et al., 2005; Spina et al., 2016; Tramontano et al., 2018; Khalil et al., 2018; Abasıyanık et al., 2020; FJ Aidar et al., 2018; FJ Aidar et al., 2018; Amiri et al., 2019; Armutlu et al., 2001; Aydın et al., 2014; Brichetto et al., 2013; Brichetto et al., 2015; Broekmans et al., 2010; Bulguroglu et al., 2017; Cakt et al., 2010; Calabrò et al., 2017; Callesen et al., 2020; Carling et al., 2017; Cattaneoet al., 2007; Cattaneoet al., 2014; Conroy et al., 2018; DeBolt and McCubbin, 2004; Eftekharsadat et al., 2015; Fjeldstad-Pardo et al., 2018; Forsberg et al., 2016; Freitas et al., 2018; Frevel and Mäurer, 2015; Hayes et al., 2011; Hebert et al., 2018; Hoang et al., 2016; Hogan et al., 2014; Kalron et al., 2016; Kalron et al., 2017; Kargarfard et al., 2018; Keser et al., 2013; Kramer et al., 2014; Küçük et al., 2016; Lord et al., 1998; Lozano-Quilis et al., 2014; Mansour et al., 2013; Martini et al., 2018; McAuley et al., 2015; Negahban et al., 2013; Nilsagård et al., 2013; Ortiz-Gutiérrez et al., 2013; Ozgen et al., 2016; C Ozkul et al., 2020; C Ozkul et al., 2020; Pavlikova et al., 2020; Peruzzi et al., 2017; Prokopiusova et al., 2020; Russo et al., 2017; Salcı et al., 2017; Sangelaji et al., 2014; Sangelaji et al., 2016; Silkwood-Sherer and Warmbier, 2007; Stephens et al., 2001; Tarakci et al., 2013; Thomas et al., 2017; Vermöhlen et al., 2018; Yazgan et al., 2019) had a parallel design.

Twenty-nine studies (40.8%) (Afrasiabifar et al., 2018; Arntzen et al., 2019; Gandolfi et al., 2014; Gandolfi et al., 2015; Hebert et al., 2011; Monjezi et al., 2017; Novotna et al., 2019; Prosperini et al., 2013; Robinson et al., 2015; Samaei et al., 2016; Spina et al., 2016; Armutlu et al., 2001; Brichetto et al., 2013; Brichetto et al., 2015; Calabrò et al., 2017; Callesen et al., 2020; Carling et al., 2017; Cattaneoet al., 2007; DeBolt and McCubbin, 2004; Forsberg et al., 2016; Frevel and Mäurer, 2015; Hebert et al., 2018; Hoang et al., 2016; Kramer et al., 2014; Nilsagård et al., 2013; Ozgen et al., 2016; Prokopiusova et al., 2020; Tarakci et al., 2013; Vermöhlen et al., 2018; Yazgan et al., 2019) had the balance outcome as the primary outcome, while 42 studies (59.1%) (Prosperini et al., 2013; Schuhfried et al., 2005; Tramontano et al., 2018; Khalil et al., 2018; Abasıyanık et al., 2020; FJ Aidar et al., 2018; FJ Aidar et al., 2018; Amiri et al., 2019; Aydın et al., 2014; Broekmans et al., 2010; Bulguroglu et al., 2017; Cakt et al., 2010; Cattaneoet al., 2014; Conroy et al., 2018; Eftekharsadat et al., 2015; Fjeldstad-Pardo et al., 2018; Forsberg et al., 2016; Freitas et al., 2018; Hayes et al., 2011; Hogan et al., 2014; Kalron et al., 2016; Kalron et al., 2017; Kargarfard et al., 2018; Keser et al., 2013; Küçük et al., 2016; Lord et al., 1998; Lozano-Quilis et al., 2014; Mansour et al., 2013; Martini et al., 2018; McAuley et al., 2015; Negahban et al., 2013; Ortiz-Gutiérrez et al., 2013; C Ozkul et al., 2020; C Ozkul et al., 2020; Pavlikova et al., 2020; Peruzzi et al., 2017; Russo et al., 2017; Salcı et al., 2017; Sangelaji et al., 2014; Sangelaji et al., 2016; Silkwood-Sherer and Warmbier, 2007; Stephens

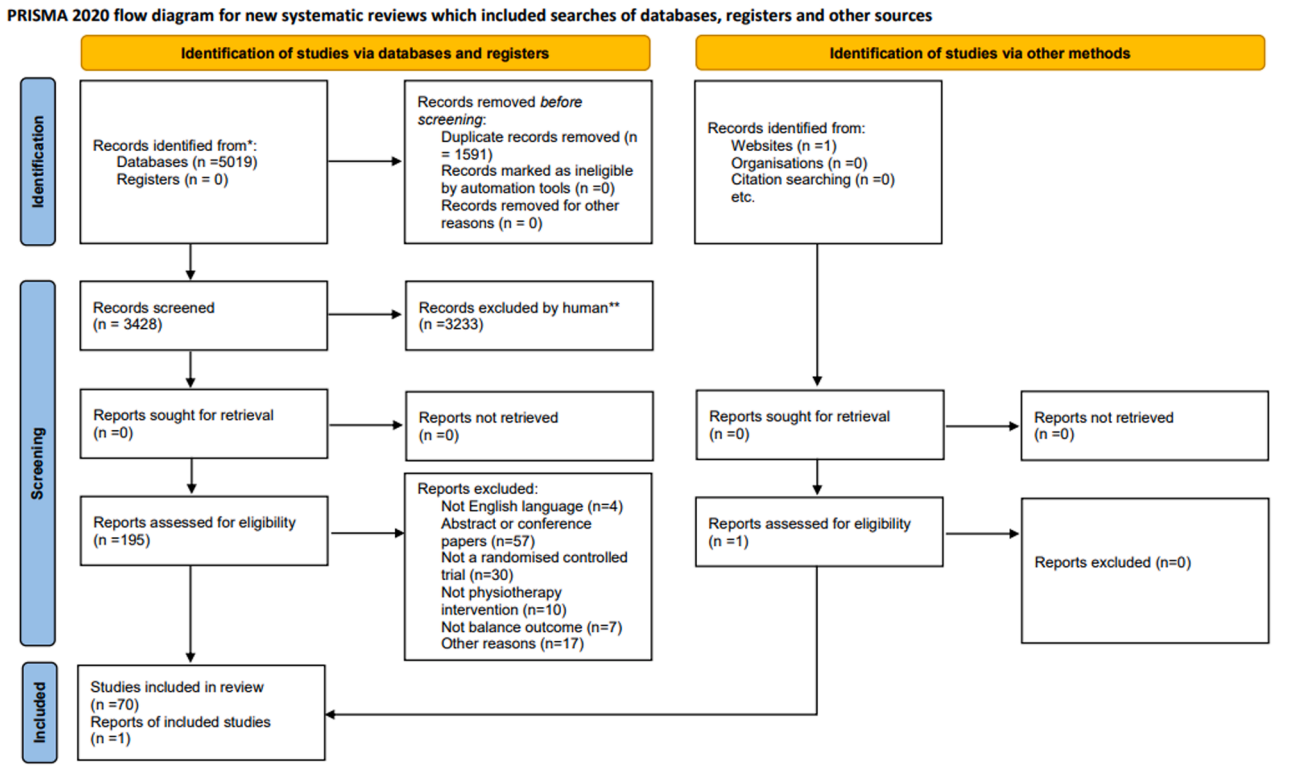

Fig. 1. PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) 2009 flow diagram (www.prisma-statement.org).

et al., 2001; Thomas et al., 2017) had balance outcome as the secondary outcome or did not specify primary and secondary outcomes.

Thirty-three trials (46.5%) (Hebert et al., 2011; Novotna et al., 2019; Prosperini et al., 2013; Robinson et al., 2015; Schuhfried et al., 2005; Spina et al., 2016; FJ Aidar et al., 2018; FJ Aidar et al., 2018; Broekmans et al., 2010; Bulguroglu et al., 2017; Cakt et al., 2010; Callesen et al., 2020; Carling et al., 2017; DeBolt and McCubbin, 2004; Eftekharsadat et al., 2015; Forsberg et al., 2016; Freitas et al., 2018; Hebert et al., 2018; Hoang et al., 2016; Hogan et al., 2014; Kargarfard et al., 2018; Martini et al., 2018; McAuley et al., 2015; Negahban et al., 2013; Nilsagård et al., 2013; C Ozkul et al., 2020; C Ozkul et al., 2020; Sangelaji et al., 2016; Silkwood-Sherer and Warmbier, 2007; Stephens et al., 2001; Tarakci et al., 2013; Vermöhlen et al., 2018; Yazgan et al., 2019) had no active intervention as comparator and 38 trials (53.5%) (Afrasiabifar et al., 2018; Arntzen et al., 2019; Gandolfi et al., 2014; Gandolfi et al., 2015; Monjezi et al., 2017; Samaei et al., 2016; Tramontano et al.,

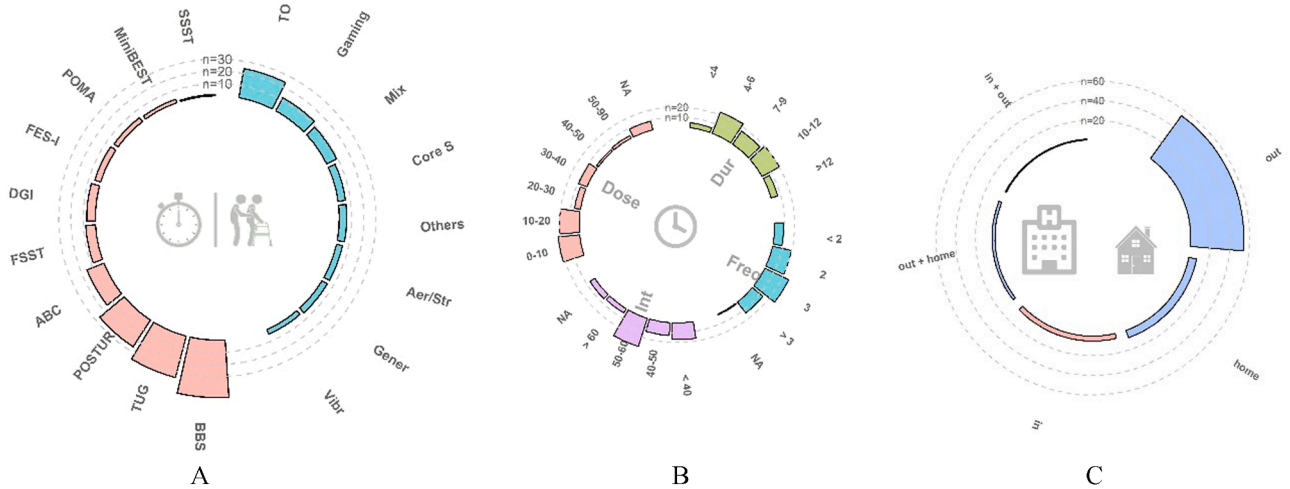

Fig. 2. A: Studies characteristics in terms of treatment type and outcome measures, data are reported as counts.

Fig. 2. B: Studies characteristics in terms of dose, duration, frequencies and intensity

Dose =dose (split into bins of ten hours); Dur=duration (split into bins of 3 weeks); Freq=frequency (number of sessions per week); Int=intensity (split into bins of 10 min). *n*=number of studies.

Fig. 2. C: Studies characteristics in terms of setting of the interventions.

Out: outpatients; Home: home rehabilitation; In: Inpatients; Out+home: mix of outpatients and home rehabilitation; In+out: inpatients and outpatients. *n*=number of studies.

2018; Khalil et al., 2018; Abasıyanık et al., 2020; Amiri et al., 2019; Armutlu et al., 2001; Aydın et al., 2014; Brichetto et al., 2013; Brichetto et al., 2015; Calabrò et al., 2017; Cattaneoet al., 2007; Cattaneoet al., 2014; Conroy et al., 2018; Fjeldstad-Pardo et al., 2018; Frevel and Mäurer, 2015; Hayes et al., 2011; Hoang et al., 2016; Kalron et al., 2017; Keser et al., 2013; Kramer et al., 2014; Küçük et al., 2016; Lord et al., 1998; Lozano-Quilis et al., 2014; Mansour et al., 2013; Ortiz-Gutiérrez et al., 2013; Ozgen et al., 2016; Pavlikova et al., 2020; Peruzzi et al., 2017; Prokopiusova et al., 2020; Russo et al., 2017; Salcı et al., 2017; Sangelaji et al., 2014; Thomas et al., 2017) had an active control group (Table 1).

Fig. 2A-C summarize studies' assessment and treatment type (2A), dose (2B), and setting (2C) of the interventions.

Treatment type(blue bars): TO=task-oriented interventions; Gaming=active console game interventions; Mix= Mixed interventions Core *S*=trunk stability interventions; Aer/Str=strength and aerobic resistance training; Gener=general exercises, usual care; Vibr=vibration. *n*=number of study

Outcome (red bars): BBS=Berg Balance Scale; TUG=timed up-and-go test; Platf=stabilometric platform; ABC=Activities-specific Balance Confidence Scale; FSST=Four-Step Square Test; DGI=Dynamic Gait Index; FES=Falls Efficacy scale; POMA=Performance Oriented Mobility Assessment; M_BEST=Mini-Balance Evaluation Systems Test. *n*=number of studies

According to balance intervention (see the method section), we reported the types of intervention in the 71 selected trials (Fig. 2A): 23 studies (32.4%) (Afrasiabifar et al., 2018; Arntzen et al., 2019; Gandolfi et al., 2014; Gandolfi et al., 2015; Hebert et al., 2011; Monjezi et al., 2017; Novotna et al., 2019; Samaei et al., 2016; Brichetto et al., 2015; Calabrò et al., 2017; Callesen et al., 2020; Cattaneoet al., 2007; Cattaneoet al., 2014; Eftekharsadat et al., 2015; Forsberg et al., 2016; Hebert et al., 2018; Kalron et al., 2016; Keser et al., 2013; Mansour et al., 2013; Martini et al., 2018; Nilsagård et al., 2013; Ozgen et al., 2016; C Ozkul et al., 2020; Peruzzi et al., 2017)provided task-oriented training, 12 studies (16.9%) (Prosperini et al., 2013; Robinson et al., 2015; Tramontano et al., 2018; Khalil et al., 2018; Brichetto et al., 2013; Hoang et al., 2016; Kramer et al., 2014; Lozano-Quilis et al., 2014; Ortiz-Gutiérrez et al., 2013; C Ozkul et al., 2020; Thomas et al., 2017; Yazgan et al., 2019) gaming exercises program, 4 studies (5.6%) (Conroy et al., 2018; Fjeldstad-Pardo et al., 2018; Lord et al., 1998; Tarakci et al., 2013) general exercises program, 10 studies (14.1%) (Cakt et al., 2010) (Carling et al., 2017; Hayes et al., 2011; Hogan et al., 2014; Negahban et al., 2013; Pavlikova et al., 2020; Russo et al., 2017; Salcı et al., 2017; Sangelaji et al., 2014; Vermöhlen et al., 2018) mixed exercises program, 6 studies (8.4%) (Arntzen et al., 2019; Abasıyanık et al., 2020; Amiri et al., 2019; Bulguroglu et al., 2017; Kalron et al., 2017; Küçük et al., 2016) core stability training, 4 studies (5.6%) (FJ Aidar et al., 2018; Aydın et al., 2014; DeBolt and McCubbin, 2004; Sangelaji et al., 2016) strength exercises program, 8 studies (11.2%) (FJ Aidar et al., 2018; Armutlu et al., 2001; Frevel and Mäurer, 2015; Kargarfard et al., 2018; McAuley et al., 2015; Prokopiusova et al., 2020; Silkwood-Sherer and Warmbier, 2007; Stephens et al., 2001) others type of training (e.g. aquatic training and hippo therapy), and 4 studies (5.6%) (Schuhfried et al., 2005; Spina et al., 2016; Broekmans et al., 2010; Freitas et al., 2018) vibration program.

3.3. Dose of the interventions

The duration, frequency, and intensity of balance intervention for each trial significantly differed among the studies. The dose varies greatly from less than 1 hour in two studies (2.8%) (Schuhfried et al., 2005; Freitas et al., 2018) to 83 h in one study (1.4%) (Broekmans et al., 2010), with a median of 12 h. Eight studies (11.3%) (Armutlu et al., 2001; Conroy et al., 2018; Fjeldstad-Pardo et al., 2018; Hebert et al., 2018; McAuley et al., 2015; Sangelaji et al., 2016; Stephens et al., 2001; Thomas et al., 2017) provide information only about duration and/or frequency of intervention making it impossible to calculate the total dose. Due to the high heterogeneity of dose, we grouped studies into categorical subgroups (Fig. 2B). For the vast majority of the reports (n = 60, 84.5%) (Afrasiabifar et al., 2018; Arntzen et al., 2019; Gandolfi et al., 2014; Gandolfi et al., 2015; Monjezi et al., 2017; Novotna et al., 2019; Prosperini et al., 2013; Robinson et al., 2015; Samaei et al., 2016; Tramontano et al., 2018; Khalil et al., 2018; Abasıyanık et al., 2020; FJ Aidar et al., 2018; FJ Aidar et al., 2018; Amiri et al., 2019; Armutlu et al., 2001; Aydın et al., 2014; Brichetto et al., 2013; Brichetto et al., 2015; Bulguroglu et al., 2017; Cakt et al., 2010; Calabrò et al., 2017; Callesen et al., 2020; Carling et al., 2017; DeBolt and McCubbin, 2004; Eftekharsadat et al., 2015; Fjeldstad-Pardo et al., 2018; Forsberg et al., 2016; Freitas et al., 2018; Frevel and Mäurer, 2015; Hayes et al., 2011; Hebert et al., 2018; Hoang et al., 2016; Hogan et al., 2014; Kalron et al., 2016; Kalron et al., 2017; Kargarfard et al., 2018; Keser et al., 2013; Kramer et al., 2014; Küçük et al., 2016; Lord et al., 1998; Lozano-Quilis et al., 2014; Mansour et al., 2013; Martini et al., 2018; Negahban et al., 2013; Nilsagård et al., 2013; Ortiz-Gutiérrez et al., 2013; Ozgen et al., 2016; C Ozkul et al., 2020; C Ozkul et al., 2020; Pavlikova et al., 2020; Peruzzi et al., 2017; Prokopiusova et al., 2020; Salcı et al., 2017; Sangelaji et al., 2014; Sangelaji et al., 2016; Stephens et al., 2001; Tarakci et al., 2013; Vermöhlen et al., 2018; Yazgan et al., 2019) rehabilitation intervention lasted from 4 to 12 weeks, while frequency was around of 2/3 times per week in 48 studies (67.6%) (Afrasiabifar et al., 2018; Arntzen et al., 2019; Gandolfi et al., 2014; Gandolfi et al., 2015; Hebert et al., 2011; Monjezi et al., 2017; Robinson et al., 2015; Samaei et al., 2016; Khalil et al., 2018; Abasıyanık et al., 2020; FJ Aidar et al., 2018; FJ Aidar et al., 2018; Amiri et al., 2019; Armutlu et al., 2001; Brichetto et al., 2013; Brichetto et al., 2015; Broekmans et al., 2010; Bulguroglu et al., 2017; Cakt et al., 2010; Calabrò et al., 2017; Callesen et al., 2020; Carling et al., 2017; Cattaneoet al., 2014; DeBolt and McCubbin, 2004; Eftekharsadat et al., 2015; Forsberg et al., 2016; Frevel and Mäurer, 2015; Hayes et al., 2011; Hebert et al., 2018; Hoang et al., 2016; Kalron et al., 2016; Kargarfard et al., 2018; Keser et al., 2013; Kramer et al., 2014; Küçük et al., 2016; Lord et al., 1998; Mansour et al., 2013; McAuley et al., 2015; Negahban et al., 2013; Nilsagård et al., 2013; C Ozkul et al., 2020; C Ozkul et al., 2020; Pavlikova et al., 2020; Peruzzi et al., 2017; Russo et al., 2017; Salcı et al., 2017; Sangelaji et al., 2014; Tarakci et al., 2013; Thomas et al., 2017; Yazgan et al., 2019) and intensity ranged from 30 to 60 min in 53 studies (74.6%) (Afrasiabifar et al., 2018; Arntzen et al., 2019; Gandolfi et al., 2014; Gandolfi et al., 2015; Hebert et al., 2011; Monjezi et al., 2017; Prosperini et al., 2013; Robinson et al., 2015; Samaei et al., 2016; Spina et al., 2016; Tramontano et al., 2018; Abasıyanık et al., 2020; FJ Aidar et al., 2018; FJ Aidar et al., 2018; Amiri et al., 2019; Armutlu et al., 2001; Aydın et al., 2014; Brichetto et al., 2013; Brichetto et al., 2015; Broekmans et al., 2010; Bulguroglu et al., 2017; Callesen et al., 2020; Carling et al., 2017; Cattaneoet al., 2007; Cattaneoet al., 2014; DeBolt and McCubbin, 2004; Forsberg et al., 2016; Hayes et al., 2011; Hebert et al., 2018; Hoang et al., 2016; Hogan et al., 2014; Kalron et al., 2016; Kalron et al., 2017; Kargarfard et al., 2018; Keser et al., 2013; Kramer et al., 2014; Küçük et al., 2016; Lord et al., 1998; Lozano-Quilis et al., 2014; Mansour et al., 2013; Martini et al., 2018; Negahban et al., 2013; Nilsagård et al., 2013; Ozgen et al., 2016; C Ozkul et al., 2020; C Ozkul et al., 2020; Pavlikova et al., 2020; Peruzzi et al., 2017; Prokopiusova et al., 2020; Russo et al., 2017; Salcı et al., 2017; Silkwood-Sherer and Warmbier, 2007; Tarakci et al., 2013; Vermöhlen et al., 2018; Yazgan et al., 2019). Detailed information is presented in Supplementary Table 2.

3.4. Setting

In 54 studies (76.0%)30 (Arntzen et al., 2019; Gandolfi et al., 2014; Gandolfi et al., 2015; Hebert et al., 2011; Monjezi et al., 2017; Samaei et al., 2016; Schuhfried et al., 2005; Tramontano et al., 2018; Khalil et al., 2018; Abasıyanık et al., 2020; FJ Aidar et al., 2018; FJ Aidar et al., 2018; Amiri et al., 2019; Brichetto et al., 2013; Brichetto et al., 2015;

Broekmans et al., 2010; Bulguroglu et al., 2017; Cakt et al., 2010; Calabrò et al., 2017; Callesen et al., 2020; Cattaneoet al., 2014; Eftekharsadat et al., 2015; Forsberg et al., 2016; Freitas et al., 2018; Frevel and Mäurer, 2015; Hayes et al., 2011; Hebert et al., 2018; Hoang et al., 2016; Hogan et al., 2014; Kalron et al., 2016; Kalron et al., 2017; Kargarfard et al., 2018; Keser et al., 2013; Kramer et al., 2014; Küçük et al., 2016; Lord et al., 1998; Lozano-Quilis et al., 2014; Mansour et al., 2013; Martini et al., 2018; Negahban et al., 2013; Ozgen et al., 2016; C Ozkul et al., 2020; C Ozkul et al., 2020; Peruzzi et al., 2017; Prokopiusova et al., 2020; Russo et al., 2017; Salcı et al., 2017; Sangelaji et al., 2014; Sangelaji et al., 2016; Silkwood-Sherer and Warmbier, 2007; Stephens et al., 2001; Tarakci et al., 2013; Vermöhlen et al., 2018; Yazgan et al., 2019) (Fig. 2C) rehabilitation interventions were provided for outpatients, while 8 studies (11.2%) (Novotna et al., 2019; Prosperini et al., 2013; Conroy et al., 2018; DeBolt and McCubbin, 2004; Frevel and Mäurer, 2015; McAuley et al., 2015; Nilsagård et al., 2013; Ortiz-Gutiérrez et al., 2013) performed home based treatments. In 5 studies (7.0%) (Robinson et al., 2015; Spina et al., 2016; Armutlu et al., 2001; Aydın et al., 2014; Cattaneoet al., 2007) interventions were provided for inpatients and 3 studies (4.2%) (Carling et al., 2017; Fjeldstad-Pardo et al., 2018; Thomas et al., 2017) performed outpatient plus home interventions, while in only 1 study (1.4%) (Pavlikova et al., 2020) interventions were provided for both inpatients and outpatients.

3.5. Outcome measures

Static balance was assessed by Berg Balance Scale (BBS) in 47 studies (66.2%) (Afrasiabifar et al., 2018; Arntzen et al., 2019; Gandolfi et al., 2014; Gandolfi et al., 2015; Monjezi et al., 2017; Novotna et al., 2019; Spina et al., 2016; Tramontano et al., 2018; Khalil et al., 2018; Abasıyanık et al., 2020; FJ Aidar et al., 2018; FJ Aidar et al., 2018; Aydın et al., 2014; Brichetto et al., 2013; Brichetto et al., 2015; Broekmans et al., 2010; Calabrò et al., 2017; Carling et al., 2017; Cattaneoet al., 2007; Conroy et al., 2018; Eftekharsadat et al., 2015; Fjeldstad-Pardo et al., 2018; Forsberg et al., 2016; Freitas et al., 2018; Frevel and Mäurer, 2015; Hayes et al., 2011; Hogan et al., 2014; Kalron et al., 2016; Kalron et al., 2017; Kargarfard et al., 2018; Keser et al., 2013; Küçük et al., 2016; Lord et al., 1998; Lozano-Quilis et al., 2014; Negahban et al., 2013; Ortiz-Gutiérrez et al., 2013; Ozgen et al., 2016; C Ozkul et al., 2020; C Ozkul et al., 2020; Pavlikova et al., 2020; Peruzzi et al., 2017; Prokopiusova et al., 2020; Salcı et al., 2017; Sangelaji et al., 2014; Sangelaji et al., 2016; Silkwood-Sherer and Warmbier, 2007; Tarakci et al., 2013; Vermöhlen et al., 2018; Yazgan et al., 2019) (Fig. 2A). Dynamic balance was assessed by the Timed Up & Go test in 36 studies (50.7%) (Novotna et al., 2019; Samaei et al., 2016; Schuhfried et al., 2005; Khalil et al., 2018; Abasıyanık et al., 2020; FJ Aidar et al., 2018; FJ Aidar et al., 2018; Broekmans et al., 2010; Bulguroglu et al., 2017; Cakt et al., 2010; Calabrò et al., 2017; Callesen et al., 2020; Carling et al., 2017; DeBolt and McCubbin, 2004; Eftekharsadat et al., 2015; Forsberg et al., 2016; Freitas et al., 2018; Frevel and Mäurer, 2015; Hayes et al., 2011; Hoang et al., 2016; Kalron et al., 2017; Küçük et al., 2016; Lozano-Quilis et al., 2014; Mansour et al., 2013; Martini et al., 2018; Negahban et al., 2013; Nilsagård et al., 2013; Ozgen et al., 2016; C Ozkul et al., 2020; C Ozkul et al., 2020; Pavlikova et al., 2020; Peruzzi et al., 2017; Prokopiusova et al., 2020; Russo et al., 2017; Sangelaji et al., 2016; Thomas et al., 2017; Yazgan et al., 2019), by the Four Square Step Test (FSST) in 8 studies (11.3%) (Prosperini et al., 2013; Forsberg et al., 2016; Kalron et al., 2016; Kalron et al., 2017; Martini et al., 2018; Nilsagård et al., 2013; Peruzzi et al., 2017; Prokopiusova et al., 2020), and by the Dynamic Gait Index (DGI) in 7 studies (9.8%) (Spina et al., 2016; Cakt et al., 2010; Cattaneoet al., 2007; Frevel and Mäurer, 2015; Nilsagård et al., 2013; Ozgen et al., 2016; Prokopiusova et al., 2020) static and dynamic balance were assessed by comprehensive tests such as the Performance-Oriented Mobility Assessment (Tinetti scale) in 5 studies (7.0%) (Tramontano et al., 2018; Lozano-Quilis et al., 2014; Ortiz-Gutiérrez et al., 2013; Russo et al., 2017; Silkwood-Sherer and Warmbier, 2007) and by the Mini-Best Test in 3 studies (4.2%) (Arntzen et al., 2019; Novotna et al., 2019; Callesen et al., 2020).

Finally, patient-reported outcomes assessed subjective balance improvement by the Activities-Specific Balance Confidence Scale (ABC) in 16 studies (22.5%) (Gandolfi et al., 2014; Gandolfi et al., 2015; Monjezi et al., 2017; Novotna et al., 2019; Abasıyanık et al., 2020; Bulguroglu et al., 2017; Callesen et al., 2020; Cattaneoet al., 2007; Fjeldstad-Pardo et al., 2018; Forsberg et al., 2016; Martini et al., 2018; Nilsagård et al., 2013; Ozgen et al., 2016; C Ozkul et al., 2020; Prokopiusova et al., 2020; Stephens et al., 2001) while fear of falling was measured by the Fall Efficacy Scale International (FES-I) in 3 RCTs (4.2%) (Novotna et al., 2019; Abasıyanık et al., 2020; Carling et al., 2017). Details of outcome measures are reported in Table 1.

3.6. Country of origin of the studies

Thirteen studies (18.3%) (Abasıyanık et al., 2020; Armutlu et al., 2001; Aydın et al., 2014; Bulguroglu et al., 2017; Cakt et al., 2010; Keser et al., 2013; Küçük et al., 2016; Ozgen et al., 2016; C Ozkul et al., 2020; C Ozkul et al., 2020; Salcı et al., 2017; Tarakci et al., 2013; Yazgan et al., 2019) were carried out in Turkey, 11 studies (15.5%) in Italy (Gandolfi et al., 2014; Gandolfi et al., 2015; Prosperini et al., 2013; Spina et al., 2016; Tramontano et al., 2018; Brichetto et al., 2013; Brichetto et al., 2015; Calabrò et al., 2017; Cattaneoet al., 2007; Cattaneoet al., 2014; Russo et al., 2017) and in USA (Hebert et al., 2011; Conroy et al., 2018; DeBolt and McCubbin, 2004; Fjeldstad-Pardo et al., 2018; Freitas et al., 2018; Hayes et al., 2011; Hebert et al., 2018; Martini et al., 2018; McAuley et al., 2015; Silkwood-Sherer and Warmbier, 2007; Stephens et al., 2001), 9 (12.7%) (Afrasiabifar et al., 2018; Monjezi et al., 2017; Samaei et al., 2016; Amiri et al., 2019; Eftekharsadat et al., 2015; Kargarfard et al., 2018; Negahban et al., 2013; Sangelaji et al., 2014; Sangelaji et al., 2016) in Iran, and 27 studies (38.0%) (Arntzen et al., 2019; Novotna et al., 2019; Robinson et al., 2015; Schuhfried et al., 2005; Khalil et al., 2018; FJ Aidar et al., 2018; FJ Aidar et al., 2018; Broekmans et al., 2010; Callesen et al., 2020; Carling et al., 2017; Forsberg et al., 2016; Frevel and Mäurer, 2015; Hoang et al., 2016; Hogan et al., 2014; Kalron et al., 2016; Kalron et al., 2017; Kargarfard et al., 2018; Keser et al., 2013; Kramer et al., 2014; Lord et al., 1998; Lozano-Quilis et al., 2014; Mansour et al., 2013; Nilsagård et al., 2013; Ortiz-Gutiérrez et al., 2013; Pavlikova et al., 2020; Peruzzi et al., 2017; Prokopiusova et al., 2020; Thomas et al., 2017; Vermöhlen et al., 2018) elsewhere (Fig. 3).

3.7. Risk of bias 2.0

The risk of bias graph is reported in Fig. 4. Nine of the studies (12.7%) had a low risk of bias for all domains. Briefly, the majority of the studies (more than 50%) present low risk of bias in the randomization process (Domain 1), effect of assignment to intervention (Domain 2), missing outcome data (Domain 3), outcome measurement (Domain 4). Regarding the effect of adhering to intervention (Domain 2), almost half of the studies (49.3%) present some concerns in the adherence to intervention, furthermore, the majority of the studies (more than 50%) were not registered on a clinical trial register (Domain 5). The most frequent methodological weaknesses were the lack of double-blindness and the lack of intention-to-treat analysis, and, considering the overall risk of bias, most of the studies present “some concerns risk of bias” (Fig. 4). Details of the results for each included study are reported in the Supporting Material (Supplementary Fig. 1).

3.8. Meta-analysis

3.8.1. Analysis of the studies pooling together different balance outcomes

The pooled ES of interventions on balance on 1016 participants was almost medium (SMD = 0.41; 95% CIs 0.22 to 0.59, $p < 0.0001$) after including all identified studies ($n = 20$, Fig. 5).

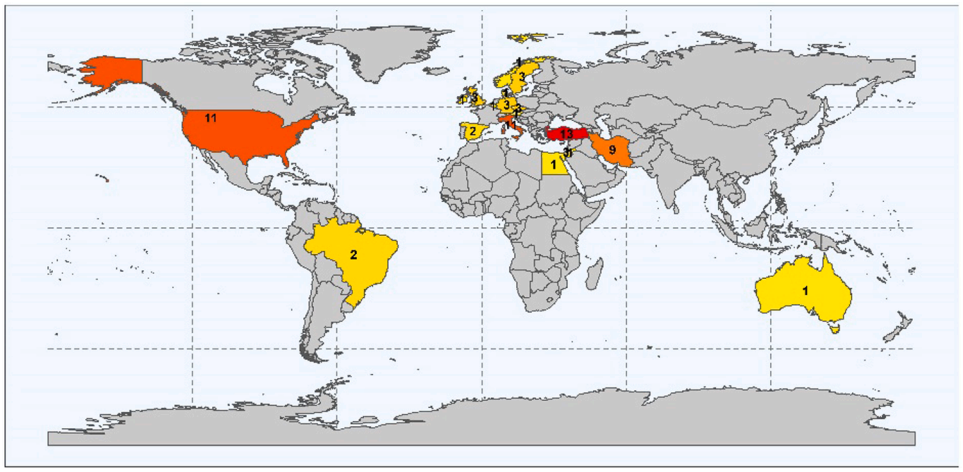

Fig. 3. Origin of the studies.

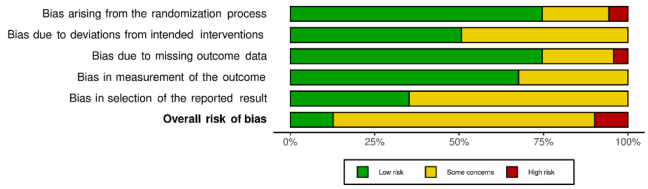

Fig. 4. Summary of risk of bias assessment across all included randomised controlled trials.

Subgroup analysis on 418 participants on the two most prevalent interventions showed good results for the task-oriented approach (Fig. 6) with a standardized mean difference of 0.63 (95% CIs 0.32 to 0.95, p <0.0001) without important differences when its effect was compared with active or no interventions. Conversely, the pooled effect of the four studies (n participants = 239) using gaming (Fig. 7) showed a smaller and not statistically significant effect (SMD = 0.10; 95% CIs −0.19 to 0.38, $p = 0.51$).

We observed moderate to substantial heterogeneity between the included studies in all meta-analyses (Q >24, p ⟨ 0.001, I^2 ⟩ 53%), but there was no publication bias (Egger p-values >0.37). The Orwin's fail-safe N analysis showed that >375 studies with a mean effect size of 0 would be required to alter the significant difference found between the active group and the control group on balance.

Notably, the pooled ES was not driven by the type of control intervention, as revealed by a subgroup analysis showing superiority of active intervention as in studies where the control group received no intervention ($n = 10$) (SMD = 0.33, 95% CIs 0.06 to 0.59; $p < 0.02$) as in studies where an alternative training was administered to the control group ($n = 9$) (SMD = 0.55, 95% CIs 0.23 to 0.88; $p = 0.007$). However, the larger ES found in studies with alternative training than in those with no intervention was also associated with more heterogeneity ($I^2 = 62\%$ versus $I^2 = 56\%$).

3.8.2. *Analysis of the studies considering specific balance outcomes*

Limiting the analysis only to the 14 studies where the BBS (n participants = 696) was set as endpoint (Fig. 8) yielded a MD of 3.58 (95% CIs 1.79 to 5.38) points in favor of interventions (p <0.0001) while the analysis on dynamic balance, measured by the timed up and go test

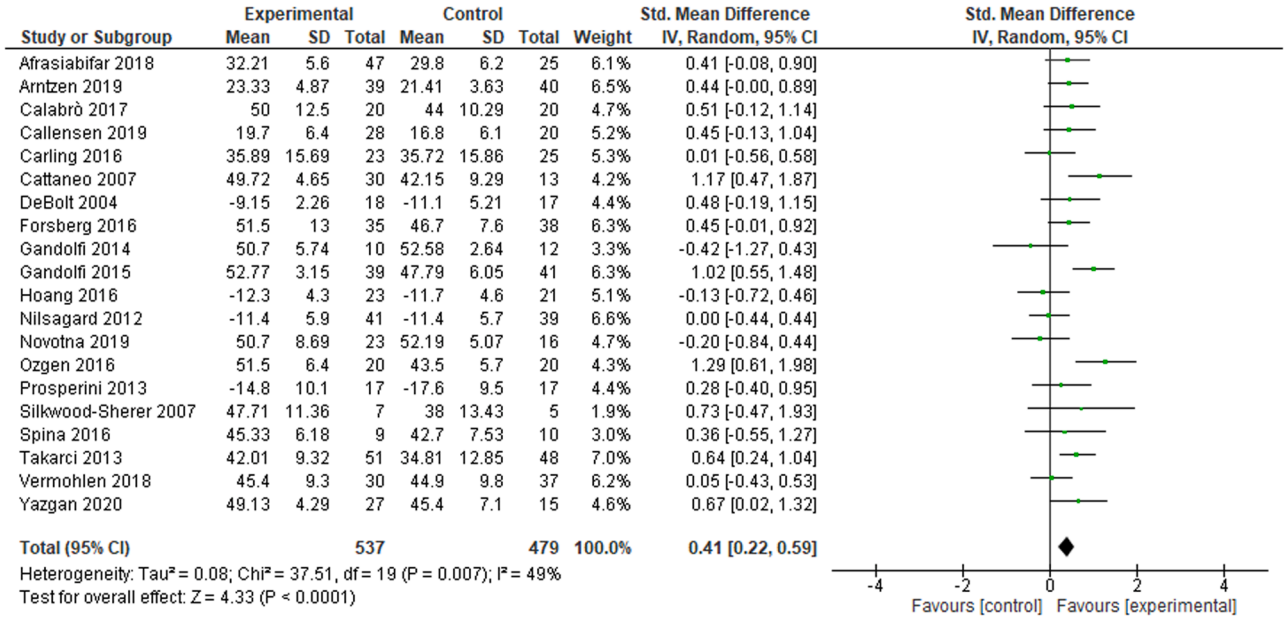

Fig. 5. Random effects meta-analysis of randomised controlled trials examining the association between mobility and balance interventions and balance improvements in balance outcome. (Std. Mean difference and CIs=confidence intervals).

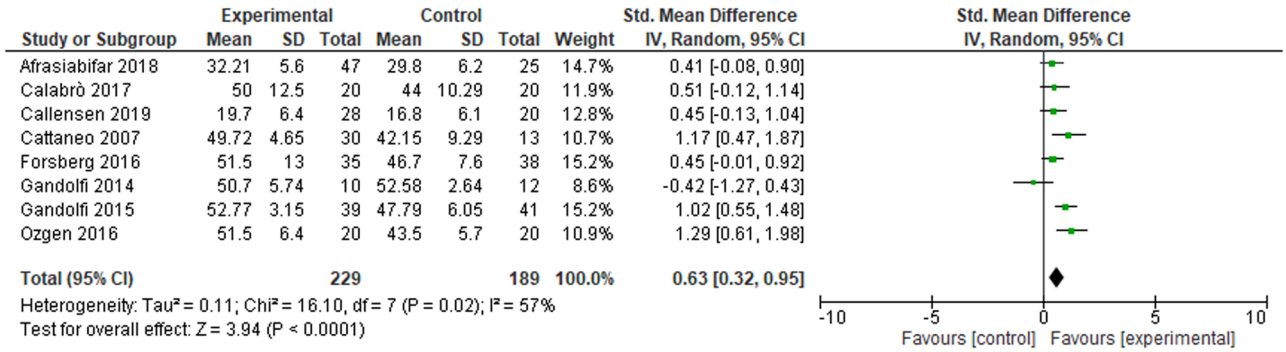

Fig. 6. Random effects meta-analysis of subgroup analysis: task-oriented approach (SMD) CIs=confidence intervals.

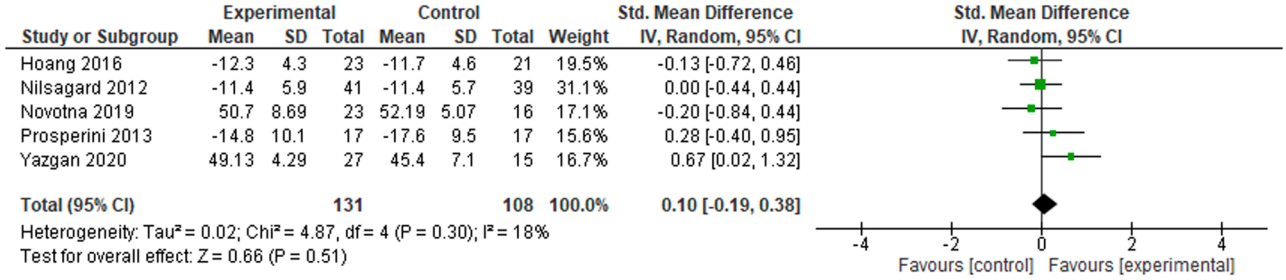

Fig. 7. Random effects meta-analysis of subgroup analysis: gaming (SMD) CIs=confidence intervals.

(Fig. 9) resulted in a not statistically significant improvement of 0.42 s (95% CIs −1.09 to 1.93 s, $p = 0.38$) favoring the experimental group.

3.8.3. *Publication bias*

The Funnel's plot of included studies (Fig. 10A) revealed the absence of significant asymmetry.

No publication bias was found when the analysis was limited only to studies with BBS or TUG as endpoints (Fig. 10B-C). Leave-one-out tests showed that estimates did not change even after removing one study at time, thus confirming our findings were not driven by any single study (data not shown).

2.9. *Sensitivity analyses*

To explore whether different inclusion criterion could affect our results, we included 37 additional studies where the balance was not set as the primary endpoint. This sensitivity analysis on 62 RCTs revealed a small ES (SMD = 0.32; 95% CIs 0.18 to 0.47, $p < 0.001$) in favor of interventions.

Limiting the sensitivity analysis only to the 47 studies where the BBS was set as endpoint yielded a MD of 2.26 (95% CIs 1.18 to 3.34, $p < 0.001$) points in favor of interventions.

We observed substantial heterogeneity (Table 2) between the included studies in both sensitivity analyses ($Q > 139$, $p < 0.001$, $I^2 > 59\%$), but there was no publication bias (Egger p-values >0.38). The Orwin's fail-safe N analysis showed that >845 studies with a mean effect size of 0 would be required to alter the significant difference found between the active group and the control group on balance.

3.9.1. *Meta-regressions*

We found larger ES for studies based on higher training log of intensity ($\beta = 1.26$, $p = 0.02$) and on task-oriented interventions rather than studies on non-specific interventions ($\beta = 0.38$, $p = 0.05$). The ES of interventions was not influenced by age of participants, duration,

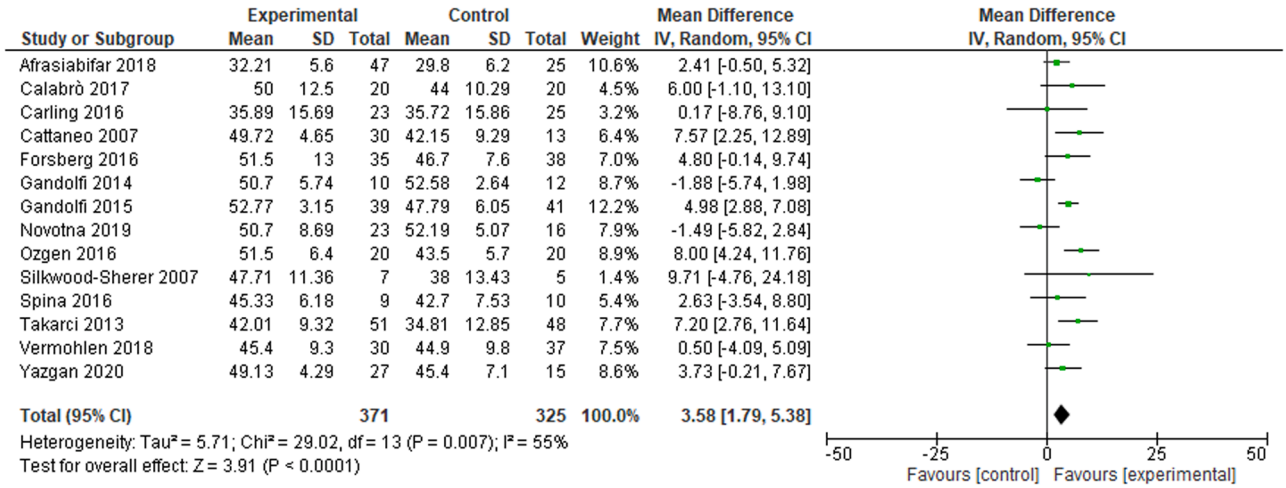

Fig. 8. Random effects meta-analysis of subgroup analysis: BBS as primary endpoint (MD) CIs=confidence intervals.

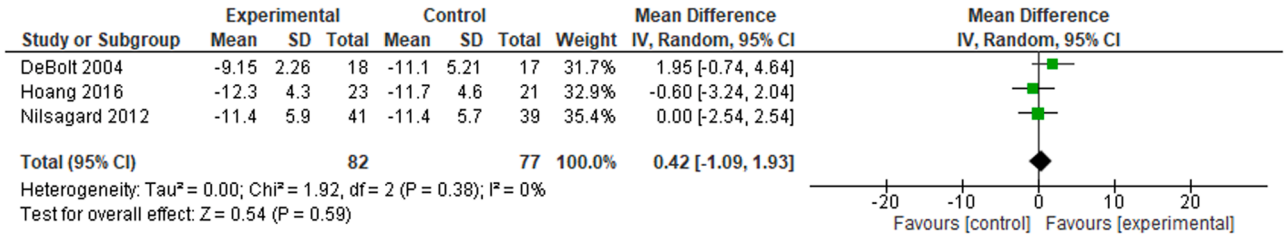

Fig. 9. Random effects meta-analysis of subgroup analysis: TUG (MD) CIs=confidence intervals.

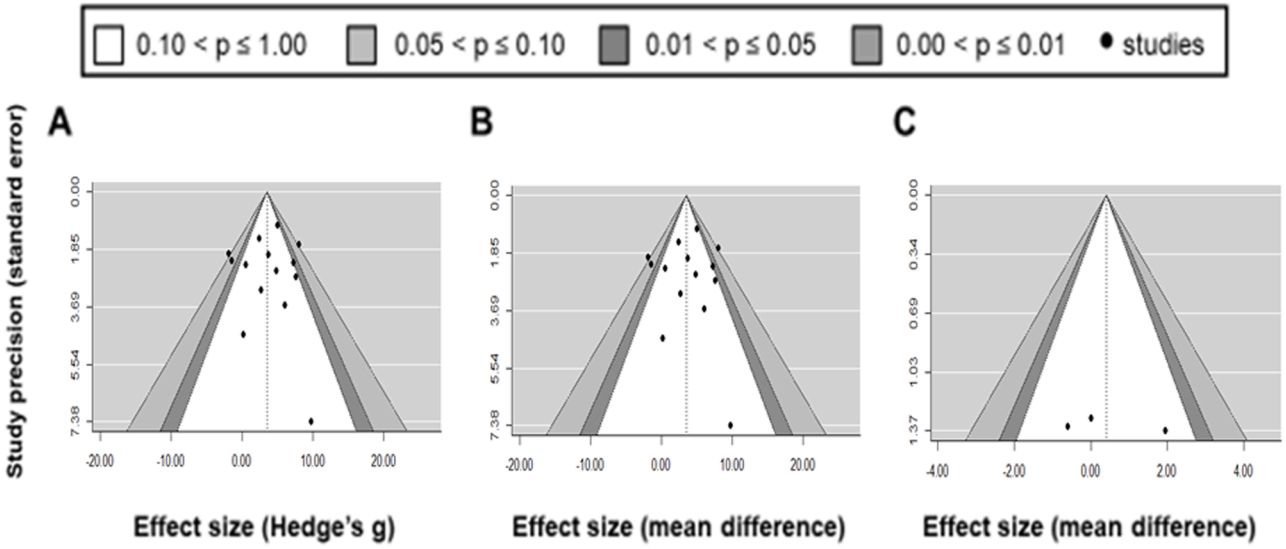

Fig. 10. A-C. Contour-enhanced funnel plots of all included studies (A), of studies where BBS was the main study endpoint (B), and of studies where TUG was the main study endpoint (C); all funnel plots showed a very low risk of publication bias.

Table 2
Heterogeneity and publication bias of Meta-analyses examining the effect of rehabilitation on balance.

	Heterogeneity			Publication bias	
	Q	P	I2	Egger's p-value	Orwin's Fail-safe N
Studies where balance scale was set as primary endpoint					
Any balance scale	50.04	<0.001	54%	0.46	457
Only Berg balance scale	24.08	<0.001	58%	0.77	376
Sensitivity analyses: studies where the balance was not set as primary endpoint					
Any balance scale	146.53	<0.001	59%	0.43	1181
Only Berg balance scale	139.89	<0.001	68%	0.38	845

frequency and setting of experimental interventions (Table 3). Limiting the analysis only to study with available BBS score showed consistent results regarding the effect of training intensity (β = 9.36, p = 0.08), whereas intervention type had no effect.

Visual inspection of the bubble plots (Fig. 11A and B) revealed that, on average, an intervention of at least 40 min was associated with the largest ES (based on the lower bound of 95% CIs). Indeed, a subgroup analysis by intensity of interventions showed that the pooled ES was mainly driven by studies with interventions ≥40 min (n = 14) (SMD = 0.55, 95% CIs 0.36 to 0.75; p < 0.00001) whereas the ES of studies with interventions <40 min (n = 6) failed to reach the statistical significance (SMD = 0.03, 95% CIs −0.21 to 0.27; p = 0.82). Additionally, the subgroup analysis of studies only with available BBS scores and interventions ≥40 min (n = 11) revealed an average improvement of approximately 4 points (95% CIs 2.42 to 6.05; p < 0.00001), whereas there was no gain for interventions <40 min (n = 3).

Additionally, we ran multivariable meta-regressions by duration × frequency × intensity into the model (including all the selected studies, n = 20) revealing a significant intensity effect (β = 1.29, p = 0.001).

Table 3
Meta-regression (univariate) analyses identifying variables that influence the effect of rehabilitation on balance.

	Main analysis (n = 20)				Only BBS (n = 14)			
	β	SE	T	p-value	β	SE	T	p-value
Age of participants (years) [log]	−1.65	1.51	−1.10	0.29	−8.95	15.12	−0.59	0.56
Duration (weeks) [log]	−0.32	0.53	−0.59	0.56	1.82	4.70	0.38	0.70
Frequency (sessions per week) [log]	0.58	0.45	1.29	0.21	3.12	4.03	0.77	0.45
Intensity (minutes per session) [log]	1.26	0.51	2.45	0.02	9.36	4.93	1.90	0.08
Total dose (hours) [log]	0.62	0.32	1.95	0.07	5.71	2.74	1.97	0.06
Type of interventions								
Task-oriented vs. non-specific training	0.38	0.17	2.18	0.05	1.75	1.86	0.94	0.37
Setting of interventions								
In-hospital vs. home-based	0.39	0.23	1.75	0.10	–	–	–	–

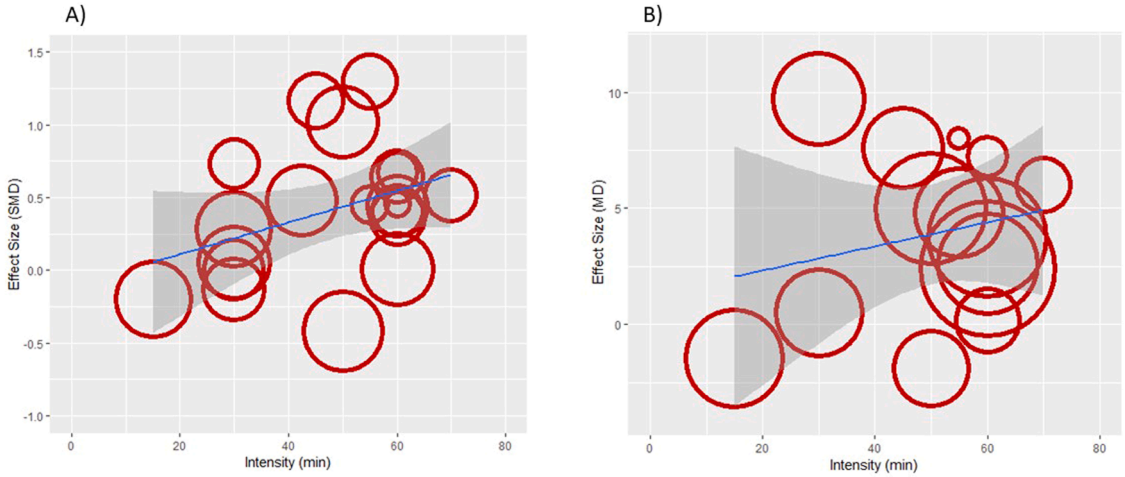

Fig. 11. A-B. Bubble plots of all included studies (A) and of studies where BBS was available as main study endpoint (B) showed a direct correlation between the intensity of intervention and its effect size.

3.9.2. GRADE assessment

According to the GRADE criteria, an initially assumed high level of evidence was downgraded once, because of the presence of inconsistencies due to significant between-study heterogeneity ($I^2 \geq 40\%$). Despite the inconsistencies, our meta-analysis exhibited directness (all participants were affected by balance dysfunction due to MS disease), precision (more than 1000 participants), and was free from publication/selection bias across included studies.

4. Discussion

4.1. Summary of main results

To the best of our knowledge, this is the first systematic review and meta-analysis of randomized controlled trials aimed at investigating the overall effects of balance intervention on mobility and balance performances and quantifying the dose–response relationships of balance intervention for different dose characteristics (intensity, duration, and frequency) in PwMS.

This review provides evidence on the short-term efficacy of physiotherapy for the treatment of multiple sclerosis suggesting that balance interventions have a medium effect on balance outcomes.

Although most of the differences between the two treatment groups were medium, we observed clinically important improvements in the Berg Balance Scale.

Our first meta-regression analysis revealed a strong relationship in intensity-balance outcomes, suggesting stronger effects in trials having treatment sessions lasting more than 40 min. Moreover, not all treatment approaches lead to similar effects: intervention satisfying task-oriented guidelines (Bayona et al., 2005) were the most effective in improving mobility and balance in PwMS (Callesen et al., 2020).

4.2. Effectiveness of balance intervention

Results on the 20 RCTs with 'a priori' defined balance-based endpoint showed an almost medium effect size (SMD = 0.41) favoring interventions focused on improving mobility and balance skills corroborating findings from a previous meta-analysis on PwMS showing a SMD of 0.55 (Gunn et al., 2015). A closer analysis of the studies using BBS as primary outcome showed clinically meaningful improvement according to the 3-points BBS cut-off score defined by Gervasoni et al. (2017) and Baert et al. (2018) as minimally clinically important difference. Results are less clear for dynamic balance measured by TUG, showing a between-group difference of around 1.2 s. This seems to be a consistent improvement considering the total duration of the test ranges between 7 and 25 s for PwMS, (Baert et al., 2018) however measurement variability was large to provide a precise estimation of MD and no cut-off score is available to define a clinically meaningful improvement.

Taken together the results suggest that a physiotherapy intervention may have a clinically significant effect on balance during transfers and static postures, however, more studies are needed to better understand the impact of rehabilitation on dynamic balance, quality of life, social participation, depression, and anxiety that are outcomes often neglected in RCT.

Noteworthy, we found a small effect size and no clinically meaningful changes when the balance was not set as the primary outcome suggesting the specificity of the intervention is a key determinant of balance intervention effectiveness. This was already pointed out in a preceding study showing that specificity of intervention increases 5 times the likelihood of a clinically meaningful improvement on the BBS compared to unspecific treatment (Cattaneoet al., 2020). This highlights the importance of specific and tailored treatment as compared with generic exercises.

Although, steps have been taken to provide best practice consensus on multiple sclerosis rehabilitation over the past decade, (Anon, 2022) no clear suggestions have been provided on how to treat this complex condition tailoring interventions to fit a specific person's complaints, lifestyle, and person's interests, as opposed to a "one size fits all" approach.

4.3. Effectiveness of task-oriented balance intervention

Regarding specificity of intervention this review highlights the variety of physiotherapy interventions being used in the treatment of multiple sclerosis and shows evidence of differences in the effectiveness between the different treatment approaches. Task-oriented interventions seem to be more effective to improve balance in PwMS with respect to other interventions as confirmed by previous clinical trials and reviews (Khan et al., 2017; Ozgen et al., 2016; Gates et al., 2008; Boyd et al., 2010; Nathan et al., 2012).

Neuroscience and rehabilitation literature are converging to strongly support the idea that task-oriented practice is a key active ingredient targeting specificity and salience of the intervention, repetition, and intensity of the training (Gates et al., 2008). Specific practice of a challenging task-oriented movement can produce behavioral changes in motor learning and long-lasting physiological changes in motor neural networks (Prosperini and Di Filippo, 2019), as demonstrated for several decades in both human and animal studies (Boyd et al., 2010; Nathan

et al., 2012; Karni et al., 1995; Nudo et al., 1999; Pascual-Leone et al., 1994). However, our comparisons between different approaches were based on indirect comparisons, and should be interpreted with caution. Therefore, physiotherapy interventions should be compared against each other to determine the best approaches and to provide therapists with a set of strategies to individualized interventions.

4.4. Dose–response relationship following balance intervention

Overall, we found that intense treatments lasting at least 40′ were associated with a better and more clinically meaningful improvement, and greater results can be reached when rehabilitation is provided over a short period (duration) and for a few sessions per week (frequency) (Lang et al., 2015; Kwakkel, 2006; Santiago de Araújo Pio et al., 2017). Our findings support the claim that more is better as suggested by two reviews on stroke (Lohse et al., 2014) and cardiac rehabilitation (Santiago de Araújo Pio et al., 2017) and are in agreement with studies on animals demonstrating that intensive training induces neural plasticity with long-term potentiation and increases number of synapses within motor cortex (Lisman and Spruston, 2005; Kleim et al., 2002). Moreover, studies on people with neurological conditions showed that high-dose rehabilitation protocols with extended training hours induce neuroplasticity as well as stimulate specific neural pathways to reorganize and increase motor output (Liepert et al., 2000; Veerbeek et al., 2014; Kwakkel et al., 2015; Fritz et al., 2011).

4.5. Strengths and limitations

The strengths of this study were the gathering of all evidence related to the association of mobility and balance improvements in PwMS with a dose of rehabilitation treatment, and the inclusion of 20 RCTs with more than 1000 participants, providing a detailed analysis of data related to program content, structure, format, and dose.

However, some limitations deserved to be discussed. We found a wide range of treatment modalities hampering the classification of interventions. Indeed, a different categorization may have led to different results on the specificity of the intervention suggesting the development of a new treatment taxonomy based upon the common theoretical basis. Indeed, when both the intervention and control group received an intervention that targeted balance, we assumed that the experimental treatment (indicated by the authors) was the main active principle of efficacy, thus we examined the experimental group as specific and the control group as unspecific. All the studies included in the review used valid outcomes to assess the impact of mobility and balance rehabilitation. However, multiple sclerosis is a complex, time-varying multidimensional disease, and many important outcomes were either poorly or not reported. We saw a little focus on patient-reported outcomes, without which studies cannot necessarily capture the difficulties experienced by PwMS in activities of daily living or their opinions on treatment acceptability.

When needed, we transformed data reported of one study (Ozgen) as median and interquartile range to mean and standard deviation in accordance to Cochrane methodology, this may have biased the results. To assess the impact of this transformation we rerun the analyses removing that specific study, fortunately results were unchanged.

Moreover, despite the moderate effect of balance interventions, there was still considerable clinical and statistical heterogeneity of included RCTs and follow-up periods were not considered in most of them. Thus, more carefully designed studies with longer follow-up are needed in trial to determine how long the beneficial effect of balance intervention lasts after their discontinuation.

We assessed the association between dose and response across studies having the same dosages in the experimental and control group. However, conclusions about differences in effect due to differences in dose are stronger if participants are randomized to one dose or another within a study. Moreover, the dose was simply calculated in minutes failing to recognize the potentially important contribution of the level of participant effort while undertaking an exercise to program outcome and the workload intensity of the different types of intervention (e.g. Balance training). Thus, our result should be taken with caution, and trials are warranted to verify the effects of dose-response relationship with a more comprehensive assessment of exercise intensity and effort.

Conclusions and future direction

The results of our review provide level I evidence on the effects of balance intervention to improve mobility and balance in people with MS. Therefore, it is critical to prescribe and deliver physiotherapy to improve mobility and balance in PwMS, who often present with mobility impairments and falls.

Our results agree with two main principles of neurological rehabilitation stating that specificity of intervention and the amount of practice (dosage) are two pillars of motor recovery. It seems that a high dosage of rehabilitation interventions lasting more than 40 min should be specifically delivered to improve balance impairments according to task-oriented principles.

Further high-quality experimental studies with large samples and longer follow ups are needed to develop balance and gait treatment recommendations for clinicians treating PwMS. Additionally, a new taxonomy of rehabilitation intervention would facilitate the classification of balance interventions.

Contributor and guarantor information

CCor, PG, EG, and DC conceptualised the idea for the article and performed the literature search, PG, CCor, EG and DC conducted the systematic review and wrote the article, CCos, MP, AM, EP read and reviewed the draft, DC checked for methodology, LP was involved in statistical analysis and DC is the guarantor.

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Supplementary materials

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