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REVIEW ARTICLE

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USE OF VIRTUAL REALITY-BASED TRAINING IN DIFFERENT FIELDS OF REHABILITATION: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Objectives: **To analyse the effectiveness of virtual reality-based interventions within several fields of rehabilitation, and to investigate whether the outcomes of virtual reality-based interventions, in terms of upper or lower limb function, gait and balance, differ with respect to the virtual reality system used.**
Methods: **A search of PubMed database resulted in an initial total of 481 records. Of these, 27 articles were included in the study. A final total of 20 articles, with neurological, orthoapedic, geriatric or paediatric patients, published between 2012 and 2019, were included in the study. Two independent reviewers selected potentially relevant articles based on the inclusion criteria for full-text reading. They extracted data, and evaluated the methodological quality of each study.**
Results: **Seventeen studies were included in the meta--analysis. Eight studies analysed upper limb function, with no significant evidence that specialized VR is superior to conventional treatment. Regarding Fugl-Meyer scale results, the effect of specialized virtual reality therapy was found to be significantly better than conventional treatment. No significant differences between specialized VR and conventional treatment were observed in effects on hand dexterity and gait. There was a significant difference in effects on balance in favour of specialized virtual reality as compared to conventional treatment. Gaming virtual reality was significantly better than conventional treatment for upper limb function, but not for hand dexterity, gait and balance.**
Conclusion: **Use of specialized virtual reality and gaming virtual reality can be advantageous for treatment of the upper extremity, but not for hand dexterity and gait in all pathologies considered. Specialized virtual reality can improve balance in neurological patients.**

Key words: virtual reality; rehabilitation; upper limb; hand dexterity; lower limb; gait, balance.

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LAY ABSTRACT

Virtual reality is an innovative technology consisting of interaction between a user and a computer that involves real-time simulation. The objectives of this review were to analyse the effectiveness of virtual reality interventions within several fields of rehabilitation, and to investigate whether the outcomes differ with respect to the type of virtual reality system used. From an initial search of the literature, 481 records were retrieved. Of these, 20 articles were selected for qualitative analysis. Two independent reviewers selected relevant studies based on the inclusion criteria. Furthermore, 17 studies were included for meta-analysis (i.e. quantitative analysis). The results showed that upper limb function can improve with the use of both specialized and gaming virtual reality. Balance disorders improved with specialized virtual reality, but not with gaming virtual reality. However, no improvements were evident in hand dexterity or gait for either specialized or gaming virtual reality. In conclusion, interventions using specialized virtual reality and gaming virtual reality can be advantageous for treatment of the upper extremity, but not for hand dexterity and gait in all pathologies considered. Specialized virtual reality can improve balance in neurological patients.

Virtual reality (VR) is an innovative technology consisting of a high-end user–computer interface that involves real-time simulation and interactions through visual and auditory sensorial channels (1, 2). Computer-based 3-dimensional (3D) environments provide sensory information in a form similar to that received from real-world objects and events. VR allows individuals to experience and interact with or within environments with enhanced feedback (3, 4). The definition of VR is based on a concept of "presence", which refers to the sense of being in a surrounding environment. Four branches are currently defined in relation to VR technology, characterized by their different sense of "presence" within virtual worlds, i.e. non-immersive VR, immersive VR, augmented VR, and mixed VR (3). Thus, what determines the sense of "presence" is the level of immersion provided (i.e. VR interaction level), which in turn depends on the system used.

Since VR technology has been introduced into clinical practice, its importance and usefulness have increased significantly. This meaningful progress in the use of VR systems for patient recovery, which has important favourable results, has led to interest in studying the impact of VR on motor recovery. VR technology is widely

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used in recovery from neurological disease (5), and in paediatrics (e.g. cerebral palsy) (6, 7), orthopaedics, (8) and psychiatry (e.g. for phobia treatment) (9). In the last decade, VR has also been used successfully in telemedicine and telerehabilitation, opening up a new mode of health delivery (10). Furthermore, a wide range of VR systems are available, which can be used for treatment both in clinical and home-based environment. These are grouped as so-called "specialized" VR (i.e. specifically developed therapeutic VR systems) and gaming VR (i.e. commercial VR-game consoles that can be used in clinical practice) (5, 11, 12).

Objectives

The objectives of this systematic review were to analyse the effectiveness of VR-based interventions within several fields of rehabilitation, and to investigate whether the outcomes of VR-based interventions differ, in their effects on upper or lower limb function, gait and balance, with respect to the type of VR system used.

MATERIAL AND METHODS

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting systematic reviews (13).

Search strategy

Studies related to VR training were considered eligible for review. PubMed database was searched for appropriate articles, using the following criteria: ((virtual reality [Title/Abstract] OR virtual environment [Title/Abstract]) OR virtual therapy [Title/Abstract]) AND rehabilitation [Title/Abstract] AND ("loattrfree full text"[sb] AND ("2012/01/01"[PDAT] : "2019/12/31"[PDAT])). Articles were filtered by date of publication, with the aim of including only those published within the last 7 years, due to the large available literature on the topic of VR. Only randomized controlled trials (RCTs) were included. All treatments provided to participants were reported with as much detail as possible. If needed, the trials' author was contacted for clarification and to obtain missing data.

Eligibility of studies

Rehabilitative interventions for the upper and lower limbs in the virtual environment, in different clinical fields (e.g. neurology, orthopaedics, paediatrics, etc.) were considered for review. Both specialized VR and VR gaming systems were included.

Data collection

Screening of research records was conducted by 2 independent reviewers, with the intervention of a third researcher in case of disagreement. A data extraction form was created and applied by the reviewers to extract relevant data. All articles included in the review underwent methodological assessment for risk of bias using Review Manager 5.3 (RevMan) (Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) "Risk of bias" (Appendix 1).

Assessment of risk of bias in included studies

Risk of bias for the included studies was assessed independently by 2 reviewers, who were supported by a third researcher in case of disagreement. Assessment was conducted following the criteria set out by the Cochrane Collaboration in the *Cochrane Handbook for Systematic Reviews of Interventions* (14). The following domains were evaluated: (*i*) selection bias: sequence generation, allocation concealment; (*ii*) detection bias: blinding of outcome assessment; (*iii*) attrition bias: incomplete outcome data; and (*iv*) reporting bias: selective reporting. It was decided to omit the domain that assesses the blinding of participants, as blinding is not possible in most cases and because it was deemed that this domain related to the nature of the intervention, instead of to study quality, as Laver et al. already stated (15). Risk of bias for each domain was coded as "high risk", in case of a high possibility in the occurrence of bias; "low risk", in case of a low possibility of bias; and "unclear risk", when the real incidence of bias could not be defined exactly.

Statistical analysis

A review was conducted using Review Manager 5.3 (RevMan) for statistical analysis. The methodological quality of studies was recorded in the risk of bias tables. Outcome measures were assigned to each domain assessed (upper limb function, hand dexterity, balance and gait) for both specialized and gaming systems. Treatment effect was evaluated using mean difference (MD) in case of homogeneous outcome measures, or standardized mean difference (SMD) when the outcomes were assessed with different scales, and 95% confidence intervals (95% CI) were calculated. A meta-analysis was carried out based on a random-effects model or fixed effect model with 95% CIs.

Heterogeneity was assessed considering intervention and outcome measures, pooling data for the most clinically homogeneous trials. Statistical heterogeneity was assessed with the I^2 statistic, establishing the cut-off value as 50%.

Analysis of subgroups was planned in relation to the different types of rehabilitation (e.g. neurorehabilitation, paediatric rehabilitation) and according to the different aetiologies of motor impairments (i.e. stroke and tetraplegia)

RESULTS

Electronic searching of the PubMed database identified 481 records (Fig. 1). After screening the abstracts, 27 papers were selected for full-text reading. Of these, a final total of 20 papers were included in the review. Of the 20 included studies, 16 (with 518 participants) related to treatment of neurological disorders, 1 (with 30 participants) related to treatment of orthopaedic impairment, 1 (with 70 participants) related to geriatric patients, and 2 (with 128 participants) related to treatment of paediatric patients. Table I shows the characteristics of the included studies. Fig. 2 shows the risk of bias in the included trials.

Summary of included studies

All studies focused on VR treatment for the upper or lower limb. Within the neurological diseases 14 studies assessed the effects of VR treatment in patients after

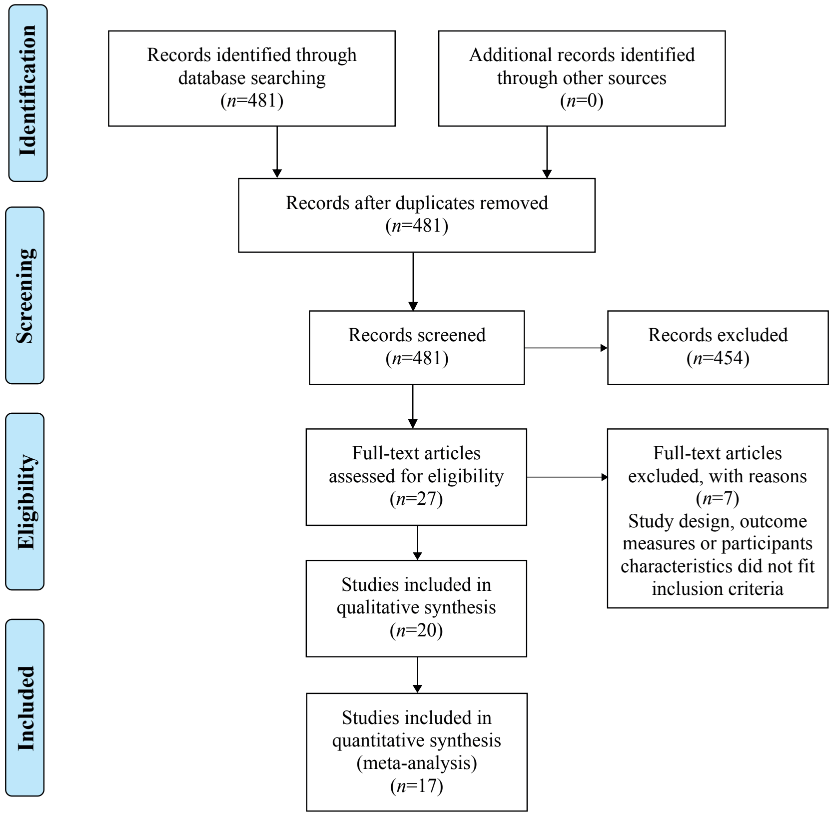

Fig. 1. Study flow diagram.

stroke for both upper and lower limb impairment (12, 16–26). The following studies focused on upper limb recovery (12, 17–19, 21, 23, 25–28). Ballester et al. showed between-group significant improvement in upper limb function in chronic stroke patients in the Fugl-Meyer upper extremity (FMUE) test ($p=0.037$), Chedoke Arm and Hand Activity Inventory ($p<0.552$), Barthel Index ($p<0.241$) and Hamilton Scale ($p<0.05$) (12). Kiper et al. studied kinematics of the upper limb and demonstrated a significant difference between training groups for both kinematic parameters (i.e. time $p=0.008$; peak $p=0.018$; except speed $p=0.140$), and clinical scales (i.e. FMUE $p=0.030$; FIM $p=0.021$). The authors showed that patients after ischaemic or haemorrhagic stroke can benefit similarly from VR training (27), whereas Saposnik et al. did not find statistical differences between VR gaming compared with conventional rehabilitation. Authors suggest that the type of task used in motor rehabilitation post-stroke might have no importance, as long as it is sufficiently intensive and task-specific (25). Another study that assessed the effect of VR on upper limb function was by Shin et al. The authors conclude that combining occupational therapy with specific VR training can be beneficial for hand recovery. However, this was not confirmed by between-group analysis for distal upper limb function, i.e. FMUE ($p>0.05$), Jebsen-Taylor hand

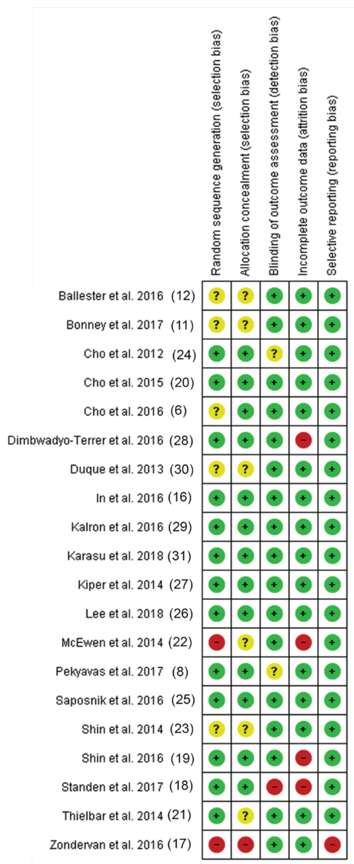

Fig. 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Table I. Characteristics of included studies

Author, (year)	Groups characteristic	*n*	Interventions	VR type	VR system	Outcome measures	Training type	Conclusion	Assessed body part
NEURO-REHABILITATION									
Ballester et al. (2016) (12)	(1) Chronic post-stroke+VR (EG) (2) Chronic post-stroke Control group (CG)	(1) 9 (2) 9	Both groups EG and CG were asked to perform 30 training sessions over the course of six weeks. One session consisted of playing every of three scenarios once for 10 min (30 min in total per training session). Undisclosed to the EG subjects, researchers applied a movement amplification on the virtual representation of the paretic limb that led to a reduced exposure to visuomotor error feedback whereas no such modulation was applied in the CG	Specialized	Rehabilitation Gaming System (manufacture not provided)	Fugl Mayer Assessment for the upper extremities (UE-FM), Chedoke Arm and Hand Activity Inventory (CAHAI-7), Activity of Daily Living (ADLs), Barthel Index (BI), Hamilton Scale	The three training scenarios used: Spheroids, Whack-a-mole and Collector. In the Spheroids and Collector scenarios the patients were required to intercept colored or patterned spheres by performing horizontal lateral arm movement. A bar in the middle of the scenery split the virtual workspace in two sides, herewith forcing the patient to perform ipsilateral movements only. In scenario themed Whack-a-mole, patients executed a horizontal reaching movement to eliminate targets that appeared sequentially on a planar surface	Implicitly reinforcing arm-use by augmenting visuomotor feedback as proposed by RIMT seems beneficial for inducing significant improvement in chronic stroke patients	Upper limb
Cho et al. (2012) (24)	(1) Chronic post-stroke+VR (2) Control group	(1) 11 (2) 11	Both groups participated in a standard rehabilitation program (physical and occupational therapy) for 60 min a day, 5 times a week for 6 weeks. In addition, the VRBT group participated in VRBT for 30 min a day, 3 times a week for 6 weeks	Gaming	Nintendo Wii Fit (Nintendo, Kyoto, Japan)	Posturography (dynamic balance), Berg Balance scale (BBS), Timed Up and Go test (TUG)	Virtual reality balance training was performer using the following games: balance bubble, ski slalom, ski jumping, soccer heading, table tiling and the penguin slide	Virtual reality balance training is feasible and suitable for chronic stroke patients with balance deficit in clinical settings	Lower limb
Cho et al. (2015) (20)	(1) Chronic post-stroke+VR (2) Chronic post-stroke control group	(1) 11 (2) 11	Conventional physical therapy, including exercises for increased trunk stability, lower extremity muscle strength, and gait ability, was performed for 4 weeks. Subjects participated in the Virtual Reality Training with Cognitive Load (VRTCL) for 4 weeks, while subjects in the control group participated in a VR program for 4 weeks. VRTCL consisted of 4, one-week cognitive load tasks	Specialized	The VRTCL was performed using a treadmill (FITEX T-5050) with an overhead harness system (CBJH1) (LINAK, Denmark, 2009)	Walking function (spatio-temporal gait parameters) under single and dual task conditions was measured using the GAITRite walkway system	During the 30-min VRTCL, familiar objects such as an apple, an umbrella, and flowers appeared in the virtual environment video (one object per a minute) and subjects were asked to remember the objects from the virtual environment video and their recollection was tested after the training session. Simple addition and subtraction problems were provided in the virtual environment video. A verbal task that involved citing words that start with letters presented on the screen. Subjects participated in 20 sessions over 4 weeks, which include a total of 30-min walking during each session. Even though rest breaks were upon request, it was not included in the overall walking time	Virtual reality training may be an effective method for the achievement of independent walking in chronic stroke patients	Lower limb (gait)
Dimbwadyo-Terrer etal. (2016) (28)	(1) tetraplegia +VR (2) tetraplegia control group	(1) 16 (2) 15	Experimental group received 15 sessions with Toyra® virtual reality system for 5 weeks, 30 minutes/day, 3 days/week in addition to conventional therapy, while control group only received conventional therapy	Specialized	Virtual reality System Toyra (Xsens Inc., Netherlands)	Manual Muscle Test (MMT), Functional Independence Measure (FIM), Spinal Cord Injury Independence Measure (SCIM), Barthel Index (BI), Motricity Index (MI), Minimal Clinically Important Difference (MCID), Quebec User Evaluation of Satisfaction (QUEST)	The main objective of game was to achieve the maximum degree of autonomy that is possible in basic ADL. The monitor displayed several daily objects (spoon, fork, comb, or sponge), asking the patient to reproduce the movements necessary to perform the corresponding activities (eating, combing hair, or washing the face)	Virtual reality added to conventional therapy produces similar results in upper limb function compared to only conventional therapy. VR rehabilitation appear to produce high motivation during execution of the assigned tasks	Upper limb
In et al. (2016) (16)	(1) Chronic post-stroke+VR+rehabilitation (2) Chronic post-stroke+rehab+VR placebo	(1) 13 (2) 12	The conventional rehabilitation program is patient-specific and consists of neurodevelopmental treatment, physical therapy, occupational therapy, and speech therapy. Participants in the VRRT group additionally received VRRT program, 30 minutes a day, five days a week, for four weeks. The control group performed the placebo VRRT program for the same duration.	Specialized	Virtual reality reflection therapy (VRRT) (manufacture not provided)	Berg Balance Scale (BBS), Functional reaching Test (FRT), Timed Up and Go (TUG), 10-meter walking velocity (10 mWV), postural sway (for static balance ability	Participants in the VRRT group placed their affected lower limb into the VRRT box to observe the projected movement of the unaffected lower limb without visual asymmetry causing tilting of the head and trunk. The unaffected lower limb of each participant was placed so that the center of the camera was over the limb. Participants then adjusted the lower extremities so that the image was projected in the location of the affected lower extremities. When the program started, the participants were asked to watch the movements of the lower limbs on the monitor only	Applying VRRT along with a conventional rehabilitation program for patients with chronic stroke might be even more beneficial than conventional rehabilitation program alone in improving affected lower limb function	Lower limbs
Kalron et al. (2016) (29)	(1) Multiple Sclerosis+VR (2) Multiple Sclerosis Control Group	(1) 15 (2) 15	Each group received balance training sessions for 6 consecutive weeks, two sessions per week, 30 min sessions	Specialized	CAREN Integrated Reality System with D-flow software (Motek Medical BV, Amsterdam, Netherlands)	Posturography –CoP (ellipse sway area, path length, sway rate, pressure distribution), Berg Balance Test (BBT), Four Square Step test (FSST), Fall Efficacy Scale International (FES-I)	The VR training session included a secondary task: intercepting 18 moving targets. In each of the 12 conventional exercise program sessions, the participants underwent 10 min of stretching exercises and 20 min of intervention. The training protocol included a combination of static postural control, weight shifting and perturbations exercises	The balance training based on CAREN device is an effective method of balance training for MS	Lower limb (balance)

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Table I. *Cont.*

Author, (year)	Groups characteristic	*n*	Interventions	VR type	VR system	Outcome measures	Training type	Conclusion	Assessed body part
NEURO-REHABILITATION									
Karasu et al. (2018) (31)	(1) Post-stroke+VR (EG) (2) Post-stroke control group (CG)	(1) 12 (2) 11	Both groups participated in conventional balance rehabilitation for 2-3 h a day, 5 days a week. In addition, the experimental group received 20 min of balance exercise, 5 days a week, for 4 consecutive weeks, with Wii Fit and Wii Balance Board.	Gaming	Nintendo Wii Fit (Nintendo, Kyoto, Japan)	Berg Balance Scale (BBS), Functional Reach Test (FRT), Postural Assessment Scale for Stroke Patients (PASS), Timed Up and Go Test (TUG) and Static Balance Index (SBI)	The Wii Balance Board can sense the transfer of weight in different directions. The balance games included in the Wii Fit package were used during the exercises, selecting those which the hemiplegic patients included in the study would be able to play.	VR exercises with the Nintendo Wii system could represent a useful adjunctive therapy to conventional treatment to improve static and dynamic balance in stroke patients.	Lower limb (balance)
Kiper et al. (2014) (27)	(1) Post-stroke RFVE (2) Post-stroke control group	(1) 23 (2) 11	The RFVE treatment consisted of multidirectional exercises providing augmented feedback provided by virtual reality, while in the TR treatment the same exercises were provided without augmented feedbacks	Specialized	Virtual Reality Rehabilitation System VRRS (VRRS-Khymei aGroup,Ltd.,No ventaPadovana ,Italy)	Fugl-Meyer upper extremity scale (FMUE), Functional Independence Measure Scale (FIM), kinematic parameters (time, speed, peak)	The real object, held by the subject, was matched to the virtual object displayed on the wall screen. In the virtual scenario, the therapist determined the location of the starting position, the target to reach for each task, and the path to follow	These results indicated that some post stroke patients may benefit from Reinforced feedback in Virtual Environment program for the recovery of upper limb motor function	Upper limb
Lee et al. (2018) (26)	(1) subacute post-stroke+VR (EG) (2) subacute post-stroke (CG)	(1) 15 (2) 15	Both the experimental and control groups received a conventional rehabilitation program consisting of physical therapy and occupational therapy. Each type of therapy was performed for 30 minutes per session, twice daily, 5 days each week, for 5 weeks. The patients in the experimental group performed the game-based virtual reality (VR) canoe paddling training for 30 minutes per day, 3 days per week, for 5 weeks.	Gaming	Nintendo Wii Sports Resort game (Nintendo, Kyoto, Japan)	modified Functional Reach Test (mFRT), postural sway test, manual function test (MFT)	The study participants operated the paddle in the direction of the virtual character displayed on an LED TV during the intervention sessions. The intervention consisted of three sessions. The first session was carried out in a 'free practice' mode for 5 minutes. The second session was performed in a 'timed run' mode in which each patient established a personal record of paddling distance during 15 minutes. The third session was performed in a 'competition mode.' during which the patient was motivated to improve their performance by competing with a caregiver or therapist for 10 minutes.	Game-based VR canoe paddling training is an effective rehabilitation therapy that enhances postural balance and upper extremity function in patients with subacute stroke when combined with conventional physical rehabilitation programs	Upper limb Lower limb (balance)
McEwen et al. (2014) (22)	(1) Post-stroke+VR (2) Post-stroke Control group	(1) 30 (2) 29	The treatment group received standard stroke rehabilitation therapy plus a program of VR exercises that challenged balance (eg, soccer goaltending, snowboarding) performed while standing. The control group received standard stroke rehabilitation therapy plus exposure to identical VR environments but whose games did not challenge balance (performed in sitting). VR training consisted of 10 to 12 thirty-minute daily sessions for a 3-week period	Specialized	Interactive Rehabilitation Exercise software (IREX) (Vivid group, Toronto, Canada)	Timed Up and Go Test (TUG), Two-Minute Walk test (TMWT), Chedoke McMaster Stroke Assessment Scale Leg domain (CMSA-Leg)	Participants in the treatment group interacted with the VR games (e.g., soccer goaltending, snowboarding) in a standing position, thereby challenging their balance and weight shifting	This VR exercise intervention for inpatient stroke rehabilitation improved mobility-related outcomes	Lower Limb (balance)
Saposnik et al. (2016) (25)	(1) Post-stroke+VR (2) Post-stroke control group	(1) 47 (2) 54	The VR group played games with goals of enhancing flexibility, range of motion, strength, and coordination of the affected arm. The recreational activity in control group was designed as a customary active control with similar intensity and complexity to simulate the skills required in the VRWii group and favoring motivation	Gaming	Nintendo Wii (Nintendo, Kyoto, Japan)	Wolf Motor Function Test (WMFT), Box and Block Test (BBT), Stroke Impact scale (SIS), Functional Independence Measure (FIM), Barthel Index (BI)	Participants were randomly allocated and receive a programme of structured, task-oriented, upper extremity sessions (ten sessions, 60 min each) of either non-immersive virtual reality using the Nintendo Wii gaming system (VRWii) or simple recreational activities (playing cards, bingo, Jenga, or ball game) as add-on therapies to conventional rehabilitation over a 2-week period	Simple, low-cost and widely available recreational activities might be as effective as innovative non-immersive virtual reality technologies	Upper limb
Shin et al. (2014) (23)	(1) Chronic post stroke+VR (2) Chronic post-stroke control group	(1) 9 (2) 7	The OT was delivered for 20 minutes by trained occupational therapists who were blinded to the protocol in order to provide participants the same OT used in the conventional clinical setting. The rehabilitation games were designed to combine a variety of rehabilitation exercises with gaming elements, thus making the otherwise monotonous practice more competitive, motivating, interesting and enjoyable. Four different types of games that address general UE functional deficits in patients were suggested: Underwater fire, Goalkeeper, Bug hunter, and Rollercoaster	Specialized	RehabMaster (manufacture not provided)	Fugl-Meyer Assessment (FMA), Modified Barthel Index (MBI)	Rehabilitation training simulates arm and trunk movements designed to restore specific functional deficits. The participant is able to practice various movements by copying specific motions made by the RehabMaster avatar. The motions were intended to promote incremental improvement in range of motion and endurance, strength, and deviation from synergistic motion patterns	The RehabMaster in a feasible and safe VR system for enhancing upper extremity function in patients with stroke	Upper limb

Table I. *Cont.*

Author, (year)	Groups characteristic	*n*	Interventions	VR type	VR system	Outcome measures	Training type	Conclusion	Assessed body part
NEURO-REHABILITATION									
Shin et al. (2016) (19)	(1) Post-stroke VR (2) Post-stroke control group	(1) 24 (2) 24	In both groups, the interventions were targeted to the distal upper extremity and standard occupational therapy was administered	Specialized	The RAPAEL Smart Glove (Neofect, Yong-in, Korea)	Fugl-Meyer Assessment (FM), Jebsen-Taylor hanf function test (JTT), Purdue Pegboard Test (PPT), Stroke Impact Scale (SIS)	The intervention programs exclusively focused on the distal upper extremity and were administered by 3 trained occupational therapists who were involved in both the interventions and were exclusively dedicated to this study. Standard OT involved range of motion and strengthening exercises for the affected limb, table-top activities, and training for ADLs	VR-based rehabilitation combined with standard occupational therapy might be more effective than amount-matched conventional rehabilitation for improving distal upper extremity function	Upper limb
Standen et al. (2017) (18)	(1) post-stroke VR (2) post-stroke control group	(1) 9 (2) 9	Eight weeks' use of a low cost home-based virtual reality system employing infra-red capture to translate the position of the hand into game play or usual care	Specialized	The virtual glove (manufacture not provided)	Wolf Motor Function Test (Wolf MFT), Nine-Hole Peg Test (NHPT), Motor Activity Log (MAL), Nottingham Extended Activities of Daily Living (NEADL)	The intervention was developed based on motor learning theory and aimed to increase the number of repetitions of functional movements, whilst providing games that were challenging with feedback on performance. Three games were produced specifically for the project. In order to play them, users had to perform the movements of reach to grasp, grasp and release, pronation and supination that are necessary fort many activities of daily living	To achieve the required sample size, a definitive home-based trial would require additional strategies to boosts recruitment rates adequate for patient support	Upper limb
Thielbar et al. (2014) (21)	(1) Post-stroke VR group (2) Post-stroke control group	(1) 7 (2) 7	The first group performed high intensity, task-oriented occupational therapy centered on fine motor control, dexterity, in-hand manipulation, and finger individuation. The task-oriented protocol utilized was trained the occupational therapists delivering the intervention for this study. The other group (Keypad) trained exclusively with the AVK system to practice movements of different combinations of digits. Two different modes were employed. In one mode, Key Combination, the participant attempted to play the discrete key combinations specified on the computer screen. In the Song Mode, participants attempted to play songs, such as "Ode to Joy" as guided on the computer screen in a manner similar to video games, such as Guitar Hero®	Specialized	Actuated virtual keypad system (AVK) with PneuGlove (Dassault Systemes, France)	Action Research Arm test (ARAT), Jebsen-Taylor Hand Function Test (JTHFT), Upper Extremity Portion of the Fugl-Mayer Motor Assessment (FMUE), Hand subcomponent (FMH), grip strength (GS), lateral pinch strength (LPS), 3-point pinch strength (PPS	The VR group trained exclusively with the AVK system to practice movements of different combinations of digits	Using of VR may prove to be valuable clinical tools for increasing the effectiveness and efficiency of therapy following stroke	Upper limb
Zondervan et al. (2016) (17)	(1) post-stroke Music Glove (2) Post-stroke conventional therapy	(1) 9 (2) 8	The MusicGlove devices used in this study were manufactured by Flint Rehabilitation Devices	Specialized	MusicGlove (manufacture not provided)	Quality of Movement (QOM) and Amount of Use (AOU) subscales of the Motor Activity Log (MAL), the Nine Hole Peg test, Action Research Arm Test (ARAT), Geriatric Depression Scale, the upper-limb section of the Fugl-Meyer score, the National Institutes of Health stroke scale, the modified Ashworth spasticity scale for the wrist	Users were visually cued by scrolling notes on screen to make specific grips in time with popular songs, similar to the video game Guitar Hero. Grips include key pinch grip; pincer grip; and finger-thumb opposition with second, third, and fourth fingers Participants in the conventional therapy group were given a booklet of tabletop exercises for home therapy of the hand developed by experienced occupational therapists and implemented in a prior clinical trial and were instructed on how to correctly perform each hand exercise	MusicGlove therapy was not superior to conventional tabletop exercises for the primary end point but was nevertheless feasible and led to a significantly greater increase in self-reported functional use and quality of movement of the impaired hand than conventional home exercises	Upper limb
ORTHOPEDIC REHABILITATION									
Pekyavas et al. (2017) (8)	Subacromial impingement syndrome (SAIS) (1) EX group (2) Wii group	(1) 15 (2) 15	Home exercise group performer program included posterior, anterior and inferior capsule stretching, pectoral muscle stretching, serratus anterior muscle strengthening, bilateral shoulder elevation, and scapular mobility exercises. Wii group participated in in a supervised virtual reality exergaming program for shoulder movements with Nintendo Wii	Gaming	Nintendo Wii (Nintendo, Kyoto, Japan)	Visual Analogue Scale (based on rest, activity and night pain), Neer and Hawkins Tests, Scapular Retraction Test (SRT), Scapular Assistance Test (SAT), Lateral Scapular Slide Test (LSST) and shoulder disability (Shoulder Pain and Disability Index (SPADI))	Exercise training included bilateral shoulder elevation, boxing, bowling and tennis games accompanied by avatar	VR exergaming programs with these programs were found more effective than home exercise programs at short term in subjects with SAIS	Upper limb

Table I. *Cont.*

Author, (year)	Groups characteristic	*n*	Interventions	VR type	VR system	Outcome measures	Training type	Conclusion	Assessed body part
GERIATRIC REHABILITATION									
Duque et al. (2013) (30)	(1) Older fallers+VR (2) Control group	(1) 30 (2) 40	Both groups received the usual falls prevention care. The BRU-training group attended balance training (two sessions/ week for 6 weeks) using an established protocol. Each training session lasted 30 minutes and consisted of a combination of visual-vestibular rehabilitation and postural training virtual reality exercises	Specialized	Virtual reality system BRU (the Balance Rehabilitation Unit) (manufacture not provided)	Balance parameters (BRU Posturography), Survey of Activities and Fear of Falling In the Elderly (SAFFE) Groningen Elderly Test	The VR exercises consisted of three different postural training games with increasing levels of complexity (maximum of 15 levels), with the goal of reaching at least level 10 in every game by the end of the training period. The levels of complexity were progressively increased as the individual reported higher confidence and demonstrated learning of the correct postural control techniques required to pass to a higher level	Balance Rehabilitation unit training is an effective and well-accepted intervention to improve balance, increase confidence and prevent falls in the elderly	Lower limb
PEDIATRIC REHABILITATION									
Bonney et al. (2017) (11)	(1) Developmental Coordination Disorder (DCD) (2) Control group typically developing individuals (TD)	(1) 56 (2) 54	Children could play several games in random order choosing their preferred games out of 10 preselected Wii Fit balance games	Gaming	Nintendo Wii Fit (Nintendo, Kyoto, Japan)	The Movement Assessment Battery for Childre-2 (MABC-2), Bruininks Oseretsky test of motor proficiency 2 (BOT-2), Functional Strength Measure (FSM) sprinting	The repetitive practice protocol: children could only play the ski slalom game in alternating series of beginners (19 gates) and advanced level (27 gates) Children were offered an opportunity to catch up if they missed a training session, preferably during the same or otherwise the next week	The motor skills acquired in the VR environment, transfers to real world contexts in similar proportion for both TD and DCD children. The type of practice adopted does not seem to influence children's ability to transfer skills acquired in an exergame to life situations, but the number of identical elements does	Upper and lower limbs
Cho et al. (2016) (6)	(1) Celebral palsy+VR treadmill training (VRTT) (2) celebral palsy+treadmill training (TT)	(1) 9 (2) 9	The VRTT group performed treadmill gait training with virtual reality for 30 minutes per day 3 times per week for a total of 8 weeks, while the TT group performed treadmill gait training without virtual reality for the same frequency and period. In addition, all participants received general physical therapy 30 minutes per day 3 times per week for a total of 8 weeks	Gaming	Nintendo Wii Fit Plus (Nintendo, Kyoto, Japan)	Muscle strength, Gross Motor Functional Measure (GMFM), Pediatric Balance Scale (PBS), 10-meter walk test (10MWT), 2-minute walk test (2MWT)	The jogging program from the Nintendo Wii (Nintendo, Tokyo, Japan) was used in the virtual reality program	Virtual Reality Treadmill training programs are effective for improving gait, balance, muscular strength and gross motor function in children with CP	Lower limb (gait)

RAGT, robotic-assisted gait training; VR, virtual reality; EEG, Electroencephalography; EG, experimental group; CG, control group;RIMT, reinforcement-induced movement therapy; VRTT, virtual reality treadmill training; CAREN, computer assisted rehabilitation environment; COP, center of pressure; RFVE, reinforced feedback in virtual environment; OT, occupational therapy; ULC, Upper limb conventional; BRU, Balance Rehabilitation Unit; RGS, rehabilitation gaming system; RGS-E, rehabilitation gaming system with a passive bimanual exoskeleton; RGS-H, rehabilitation gaming system with a haptic interface; HEP, Home Exercise Program; AWVR, Virtual Reality environment based on Alice in Wonderland; VRE, Virtual Reality Environment.

function test ($p>0.05$), Purdue Pegboard Test ($p>0.05$), or Stroke Impact Scale ($p>0.05$) (19), or for whole upper limb assessment, i.e. FMUE ($p<0.61$) and Modified Barthel Index ($p<0.16$) (23). Home-based VR intervention for the upper limb was studied by Standen et al. The authors analysed the feasibility of this training, showing statistically important changes in comparison between VR and control group (Wolf Grip test $p<0.01$, Motor Activity Log $p<0.05$) (18). Thielbar et al. showed statistically significant improvements for both measures of impairment (FMUE: $p=0.048$) and measures of task performance (Jebsen-Taylor Hand Function Test: $p=0.021$). The authors suggest that using VR may increase the effectiveness and efficiency of therapy following stroke (21). Finally, Zondervan et al. showed significantly greater improvements in an experimental group using VR home-based therapy than in conventional exercise in the Motor Activity Log Quality of Movement ($p=0.007$) and Amount of Use ($p=0.04$) (17). The effects of VR therapy on lower limb recovery in stroke survivors were presented by Cho et al., In et al., Karasu et al. and McEwen et al. Specifically, studies by Cho et al. showed that, after 4 weeks of intervention in dual-task conditions, greater improvement in walking function was observed in the VR group than in a control group (gait analysis system $p<0.05$) (20). The authors concluded that VR therapy is also a feasible treatment for patients with chronic stroke in terms of balance improvement (Berg Balance Scale $p<0.05$, Timed Up and Go test $p<0.05$) (24). In et al. assessed the influence of VR environment on gait and balance in people after stroke. The results showed statistically significant improvement between training groups in Berg Balance Scale $p<0.05$, Timed Up and Go test $p<0.05$, Functional Reach Test $p<0.05$, and 10-m walking test $p<0.05$. These results were confirmed by kinematics obtained from the static balance assessment (16). Karasu et al. aimed to evaluate the efficacy of balance gaming system as an adjunctive therapy to conventional rehabilitation in stroke patients (31). The results showed significant improvement in the Berg Balance Scale ($p<0.001$) and Functional Reach Test ($p<0.001$). Finally, McEwen et al. showed that VR balance and mobility exercise are positive additions to inpatient stroke rehabilitation (Timed Up and Go test $p<0.05$, Two-Minute Walk test $p<0.05$, Chedoke McMaster Stroke Assessment Scale Leg domain $p<0.04$) (22). Only Lee et al. investigated the effects of game-based VR training in both upper limb and postural balance (26). They concluded that game-based VR canoe paddling training is an effective rehabilitation therapy that enhances postural balance and upper extremity function in patients with subacute stroke when compared with the control group ($p<0.05$).

One study evaluated upper and lower limb developmental coordination disorder in children (11). The authors showed that the Movement Assessment Battery for Children test ($p<0.0001$), the Bruininks Oseretsky test ($p<0.0001$) and Functional Strength Measure ($p<0.0001$) changed significantly within groups. However, they concluded that skills acquired within VR-game scenarios did not necessarily transfer into the real world (11). One study evaluated VR treatment in relation to cerebral palsy, showing a statistically significant difference between groups in muscular strength flexion and extension ($p<0.05$), in the Pediatric Balance Scale ($p<0.01$), 10-m walking test ($p<0.001$) and 2-min walking test ($p<0.001$). The authors suggest that VR treadmill training is effective for gait and balance improvement (6). One study involved patients affected by multiple sclerosis. Both groups showed a main effect of time on the centre of pressure (CoP) path length with eyes open ($p<0.024$), sway rate with eyes open ($p<0.035$), Functional Reach Test ($p<0.001$), Four Square Step Test ($p<0.031$) and the Fear of Falls self-reported questionnaire ($p<0.023$) (29). One study assessed effects of VR therapy on upper limb impairment in patients with spinal cord injury (SCI). Both groups demonstrated clinical, but no significant, changes related to arm function. Moreover, all patients from the experimental group showed high levels of satisfaction with the VR system (28). Within orthopaedics only one study was included, which assessed the effects of VR therapy in recovery of subacromial impingement syndrome. The authors demonstrated that intensity of pain can be reduced with VR training ($p<0.05$) (8). One study evaluated the effect of VR on lower limb in geriatric patients, showing improvement in balance disorders and fall prevention ($p<0.01$) (30).

The total dose of VR therapy varied between studies. Single sessions lasted from 20 min to 3 h, and a minimum of 10 sessions of training were provided. VR treatments were administered 3–5 times a week. Different types of VR systems were used. Thirteen studies used so-called specialized VR systems (12, 16–23, 27–30), and 7 studies used commercially available gaming consoles (i.e. Nintendo Wii, Nintendo Co., Ltd, Kyoto, Japan) (6, 8, 11, 24–26, 31). Interventions were delivered in inpatient, outpatient, or home settings. Outcome measures were focused on motor skills improvement, and a wide range of clinical scales were used to assess motor and ADL changes (Table I). All studies measured outcomes at the beginning and soon after the interventions were completed. Twelve studies presented outcomes for upper limb function (8, 11, 12, 17–19, 21, 23, 25–28), and 10 presented outcomes for lower limb function (6, 11, 16, 20, 22, 24, 26, 29–31).

Risk of bias in included studies

Fig. 2 shows the risk of bias in the included trials.

Random sequence generation (selection bias). Thirteen studies were assessed as having a low risk of bias for this domain, as the authors described a random component in the sequence-generation process. Five studies did not report information about the randomization process, resulting in an unclear risk of bias. The remaining studies were assessed as having a high risk of bias, with inappropriate randomization methods used.

Allocation concealment (selection bias). Thirteen studies were assessed as having a low risk of bias in this domain, as the allocation methods used were appropriate. Six studies did not report information about the allocation method used, and one study presented a high risk of bias, as therapists were not blinded to the patients' assignment.

Blinding of outcome assessment (detection bias). Seventeen studies were at low risk of bias, as outcome measures were assessed by therapists who differed from those who provided treatment sessions. Two studies did not state whether assessors were blinded, hence the risk of bias was unclear. One study was judged to be at high risk of bias, as evaluations and treatment programmes were both carried out by the same therapist.

Incomplete outcome data (attrition bias). Sixteen studies were at low risk of bias, as most of the participants were included in the final analysis. Four studies reported a high risk of bias due to the large number of drop outs.

Selective reporting (reporting bias). All studies reported all the pre-specified outcomes. Only the study of Zondervan et al. (17) did not publish all outcome measures registered in the study protocol, resulting in a high risk of bias for this domain.

Comparison of conventional treatment vs specialized virtual reality

Upper limb function (all measures). A total of 8 studies, with an overall total of 204 participants, who were divided into subgroup analysis with regard to aetiology, were analysed (i.e. 7 studies with post-stroke patients and one study with patients after SCI. The meta-analysis did not provide significant evidence that specialized VR is superior to conventional treatment. However, it should also be noted that the analysis was influenced

Study or Subgroup	Specialized VR Mean	Specialized VR SD	Specialized VR Total	Conventional Treatment Mean	Conventional Treatment SD	Conventional Treatment Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.1 Stroke								
Ballester et al. 2016 (12)	38.33	17.3	9	43.22	12.62	9	12.5%	-0.31 [-1.24, 0.62]
Kiper et al. 2014 (27)	49.8	12.5	23	49.5	16.2	21	13.6%	0.02 [-0.57, 0.61]
Shin et al. 2014 (23)	51.1	7.8	9	40.7	9.8	7	11.8%	1.13 [0.04, 2.21]
Shin et al. 2016 (19)	58.3	1.7	24	49.6	2.7	22	12.2%	3.83 [2.83, 4.83]
Standen et al. 2017 (18)	2.19	3.1	9	2.47	4.08	9	12.5%	-0.07 [-1.00, 0.85]
Thielbar et al. 2014 (21)	50.4	10.4	7	43.6	8.1	7	11.8%	0.68 [-0.41, 1.77]
Zondervan et al. 2016 (17)	0.7	2.3	9	-0.6	2.9	8	12.3%	0.48 [-0.49, 1.44]
Subtotal (95% CI)			**90**			**83**	**86.7%**	**0.80 [-0.19, 1.80]**
Heterogeneity: Tau² = 1.57; Chi² = 50.24, df = 6 (P < 0.00001); I² = 88%								
Test for overall effect: Z = 1.58 (P = 0.11)								
1.1.2 Tetraplegia								
Dimbwadyo-Terrer et al. 2016 (26)	76.56	13.28	16	78.8	20.27	15	13.3%	-0.13 [-0.83, 0.58]
Subtotal (95% CI)			**16**			**15**	**13.3%**	**-0.13 [-0.83, 0.58]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.36 (P = 0.72)								
Total (95% CI)			**106**			**98**	**100.0%**	**0.68 [-0.18, 1.54]**
Heterogeneity: Tau² = 1.31; Chi² = 53.70, df = 7 (P < 0.00001); I² = 87%								
Test for overall effect: Z = 1.55 (P = 0.12)								
Test for subgroup differences: Chi² = 2.24, df = 1 (P = 0.13), I² = 55.3%								

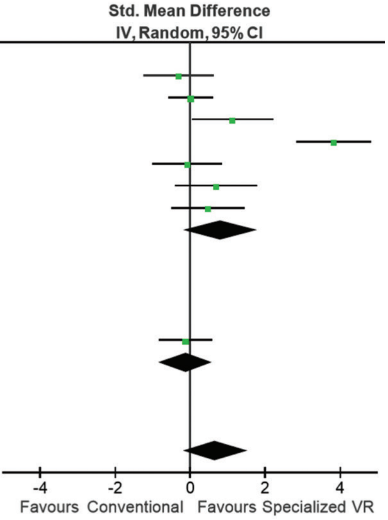

Fig. 3. Upper limb function (all measures): conventional treatment vs specialized virtual reality (VR). SD: standard deviation; 95% CI: 95% confidence interval.

by high heterogeneity. The analyses were performed using standardized mean difference (SMD) with random effects model, since 6 studies used the Fugl-Meyer upper extremity scale, one used the Wolf Motor Function test and one used the Motricity Index. No significant differences were found between specialized VR and conventional treatment in stroke patients (SMD 0.80; 95% CI –0.19 to 1.80, I^2=88%) in SCI patients (SMD –0.13; 95% CI –0.83 to 0.58), or in total comparison (SMD 0.68; 95% CI –0.18 to 1.54, I^2=87%) (Fig. 3).

Upper limb function (Fugl Meyer). A total of 5 studies, with an overall total of 138 stroke survivors, were analysed in relation to upper limb function measured with the Fugl Meyer test. Mean difference (MD) with a fixed effect model was used for analysis. Significant differences (MD 8.41; 95% CI 7.13 to 9.68, I^2=46%) were observed between specialized VR and conventional treatment (Fig. 4).

Upper limb hand dexterity function (all measures). Five studies, with an overall total of 110 post-stroke patients, were analysed in relation to upper limb hand

Study or Subgroup	Specialized VR Mean	Specialized VR SD	Specialized VR Total	Conventional Treatment Mean	Conventional Treatment SD	Conventional Treatment Total	Weight	Mean Difference IV, Fixed, 95% CI
Ballester et al. 2016 (12)	38.33	17.3	9	43.33	12.62	9	0.8%	-5.00 [-18.99, 8.99]
Kiper et al. 2014 (27)	49.8	12.5	23	49.5	16.2	21	2.2%	0.30 [-8.31, 8.91]
Shin et al. 2014 (23)	51.1	7.8	9	40.7	9.8	7	2.1%	10.40 [1.53, 19.27]
Shin et al. 2016 (19)	58.3	1.7	24	49.6	2.7	22	93.2%	8.70 [7.38, 10.02]
Thielbar et al. 2014 (21)	50.4	10.4	7	43.6	8.1	7	1.7%	6.80 [-2.97, 16.57]
Total (95% CI)			**72**			**66**	**100.0%**	**8.41 [7.13, 9.68]**
Heterogeneity: Chi² = 7.42, df = 4 (P = 0.12); I² = 46%								
Test for overall effect: Z = 12.95 (P < 0.00001)								

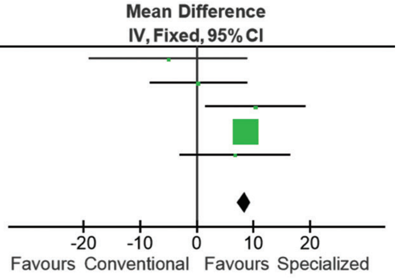

Fig. 4. Upper limb function (Fugl Meyer): conventional treatment vs specialized virtual reality (VR). SD: standard deviation; 95% CI: 95% confidence interval.

Study or Subgroup	Specialized VR Mean	Specialized VR SD	Specialized VR Total	Conventional Treatment Mean	Conventional Treatment SD	Conventional Treatment Total	Weight	Std. Mean Difference IV, Random, 95% CI
Ballester et al. 2016 (12)	33.56	15.08	9	34.22	14.71	9	20.3%	-0.04 [-0.97, 0.88]
Shin et al. 2016 (19)	21.2	0.7	24	17.4	1.1	22	19.8%	4.09 [3.04, 5.14]
Standen et al. 2017 (18)	0.89	3.39	8	0.62	1.14	7	20.0%	0.10 [-0.92, 1.11]
Thielbar et al. 2014 (21)	16.9	5.5	7	13.4	5.7	7	19.7%	0.59 [-0.49, 1.66]
Zondervan et al. 2016 (17)	1.3	6.9	9	-0.2	6	8	20.2%	0.22 [-0.74, 1.18]
Total (95% CI)			**57**			**53**	**100.0%**	**0.98 [-0.51, 2.47]**
Heterogeneity: Tau² = 2.63; Chi² = 44.26, df = 4 (P < 0.00001); I² = 91%								
Test for overall effect: Z = 1.29 (P = 0.20)								

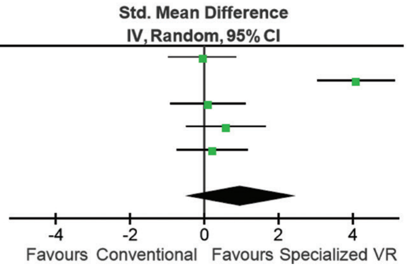

Fig. 5. Upper limb hand dexterity function (all measures): conventional treatment vs specialized virtual reality (VR). SD: standard deviation; 95% CI: 95% confidence interval.

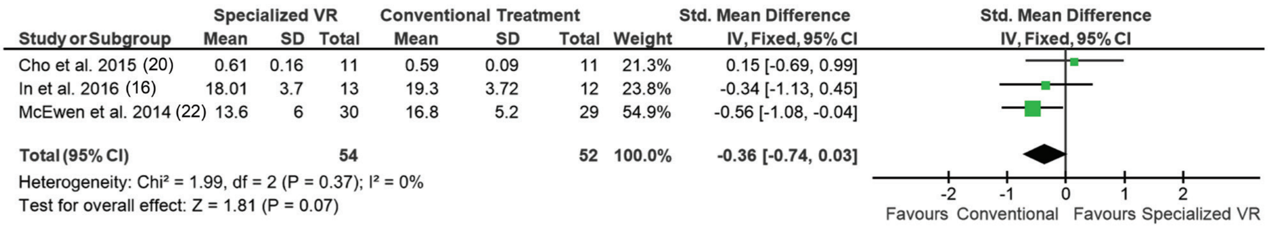

Fig. 6. Lower limb function (gait): conventional treatment vs specialized virtual reality (VR). SD: standard deviation; 95% CI: 95% confidence interval.

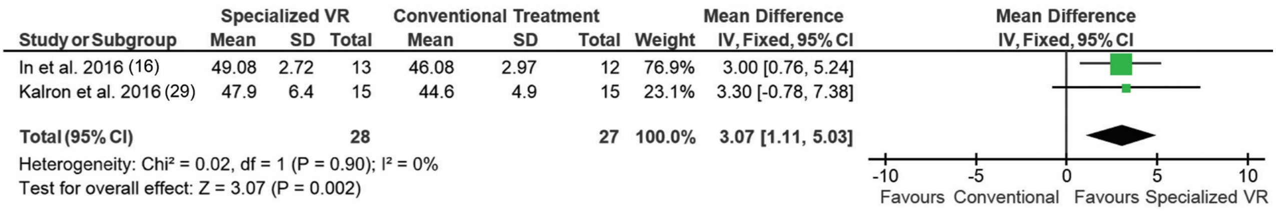

Fig. 7. Lower limb function (balance): conventional treatment vs specialized virtual reality (VR). SD: standard deviation; 95% CI: 95% confidence interval.

dexterity. SMD with random effects model was used for analyses, since 1 study used the Chedoke Arm and Hand Activity Inventory, 2 used the Fugl Meyer upper extremity hand section, and 2 used the Nine Hole Peg Test. No significant differences were found between specialized VR and conventional treatment (SMD 0.98; 95% CI –0.51 to 2.47, I^2=91%) (Fig. 5).

Lower limb function (gait). For gait, 3 studies, with an overall total of 106 post-stroke patients, were analysed. SMD with a fixed effect model was used for analyses, since 2 studies used a Timed Up and Go test, and one used temporal gait speed parameter. No significant differences were found between specialized VR and conventional treatment (SMD –0.36; 95% CI –0.74 to 0.03, I^2=0%) (Fig. 6).

Lower limb function (balance). For balance, 2 studies, with an overall total of 55 patients, were analysed. Mean difference (MD) with a fixed effect model was used for analyses. Significant differences (MD 3.07; 95% CI 1.11–5.03, I^2=0%) were observed between specialized VR and conventional treatment (Fig. 7).

Comparison of conventional treatment vs gaming virtual reality

Upper limb function (all measures). For upper limb function, 2 studies, with an overall total of 171 participants, were analysed. The analysis was performed using SMD with random effects model, one study used Manual Function test and one used Wolf Motor Function. Significant differences (SMD 0.34; 95% CI

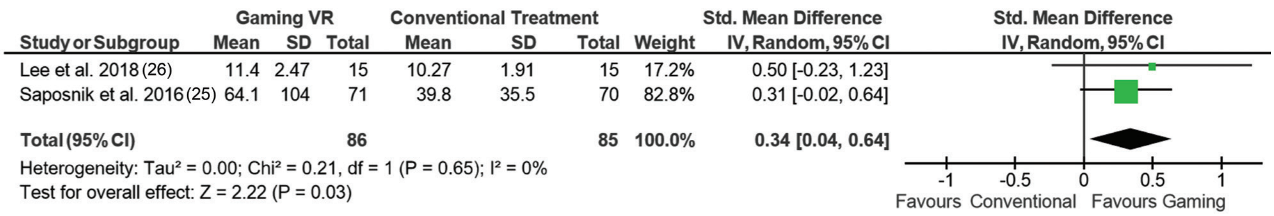

Fig. 8. Upper limb function (all measures): conventional treatment vs gaming virtual reality (VR). SD: standard deviation; 95% CI: 95% confidence interval.

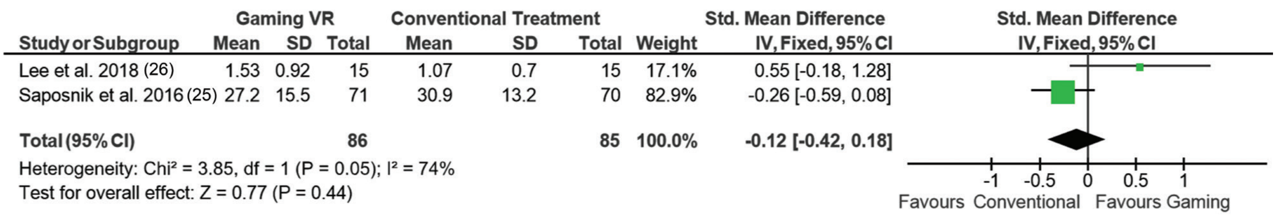

Fig. 9. Upper limb hand dexterity function (all measures): conventional treatment vs gaming virtual reality (VR). SD: standard deviation; 95% CI: 95% confidence interval.

Study or Subgroup	Gaming VR Mean	Gaming VR SD	Gaming VR Total	Conventional Treatment Mean	Conventional Treatment SD	Conventional Treatment Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
2.3.1 Neuro-rehabilitation								
Cho et al. 2012 (24)	20.4	3.19	11	19.08	4.52	11	35.4%	0.32 [-0.52, 1.17]
Karasu et al. 2018 (31)	19.5	9.8	12	24	13.5	11	36.8%	-0.37 [-1.20, 0.46]
Subtotal (95% CI)			**23**			**22**	**72.2%**	**-0.03 [-0.62, 0.56]**
Heterogeneity: Chi² = 1.33, df = 1 (P = 0.25); I² = 25%								
Test for overall effect: Z = 0.10 (P = 0.92)								
2.3.2 Pediatric rehabilitation								
Cho et al. 2016 (6)	0.9	0.2	9	0.7	0.4	9	27.8%	0.60 [-0.35, 1.55]
Subtotal (95% CI)			**9**			**9**	**27.8%**	**0.60 [-0.35, 1.55]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.24 (P = 0.21)								
Total (95% CI)			**32**			**31**	**100.0%**	**0.15 [-0.36, 0.65]**
Heterogeneity: Chi² = 2.56, df = 2 (P = 0.28); I² = 22%								
Test for overall effect: Z = 0.57 (P = 0.57)								
Test for subgroup differences: Chi² = 1.23, df = 1 (P = 0.27), I² = 18.4%								

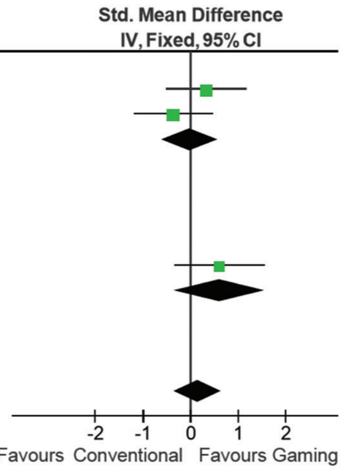

Fig. 10. Lower limb function (gait): conventional treatment vs gaming VR. SD: standard deviation; 95% CI: 95% confidence interval.

0.04–0.64, $I^2=0\%$) were observed between gaming VR and conventional treatment (Fig. 8).

Upper limb hand dexterity function (all measures). For upper limb dexterity function, 2 studies, with an overall total of 171 participants, were analysed. For hand dexterity function, SMD with a fixed effect model was used for analyses, since one study used Manual Function test hand section and one used Box and Block Test. No significant differences were observed between gaming VR and conventional treatment (SMD –0.12; 95% CI –0.42 to 0.18, $I^2=74\%$) (Fig. 9).

Lower limb function (gait). For lower limb function, 8 studies, with an overall total of 63 participants, were analysed, with subgroup analysis in relation to aetiology (i.e. one study with post-stroke patients and one study with cerebral palsy (CP) patients). SMD with a fixed effect model was used for analyses, since 2 studies used the Timed Up and Go test and one used a 10-m walk test. No significant differences were noted between gaming VR and conventional treatment in post-stroke patients (SMD –0.03; 95% CI –0.62 to 0.56, $I^2=25\%$), CP patients (SMD 0.60; 95% CI –0.35 to 1.55) or in total comparison (SMD 0.15; 95% CI –0.36 to 0.65, $I^2=22\%$) (Fig. 10).

Lower limb function (balance). For balance, SMD with random effects model was used for analyses, since 2 studies used the Berg Balance Scale and one used the Pediatric Balance Scale. No significant differences were noted between gaming VR and conventional treatment in post-stroke patients (SMD 0.41; 95% CI –0.75 to 1.57, $I^2=73\%$), CP patients (SMD 0.29; 95% CI –0.64 to 1.22) or in total comparison (SMD 0.37; 95% CI –0.32 to 1.06, $I^2=46\%$) (Fig. 11).

Study or Subgroup	Gaming VR Mean	Gaming VR SD	Gaming VR Total	Conventional Treatment Mean	Conventional Treatment SD	Conventional Treatment Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.4.1 Neuro-rehabilitation								
Cho et al. 2012 (24)	43.09	4.8	11	43.9	4.06	11	35.2%	-0.18 [-1.01, 0.66]
Karasu et al. 2018 (31)	48.9	6.4	12	42.2	6.4	11	33.4%	1.01 [0.13, 1.89]
Subtotal (95% CI)			**23**			**22**	**68.6%**	**0.41 [-0.75, 1.57]**
Heterogeneity: Tau² = 0.51; Chi² = 3.66, df = 1 (P = 0.06); I² = 73%								
Test for overall effect: Z = 0.69 (P = 0.49)								
2.4.2 Pediatric rehabilitation								
Cho et al. 2016 (6)	34.6	13.5	9	30.2	15.6	9	31.4%	0.29 [-0.64, 1.22]
Subtotal (95% CI)			**9**			**9**	**31.4%**	**0.29 [-0.64, 1.22]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.61 (P = 0.54)								
Total (95% CI)			**32**			**31**	**100.0%**	**0.37 [-0.32, 1.06]**
Heterogeneity: Tau² = 0.17; Chi² = 3.69, df = 2 (P = 0.16); I² = 46%								
Test for overall effect: Z = 1.04 (P = 0.30)								
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.87), I² = 0%								

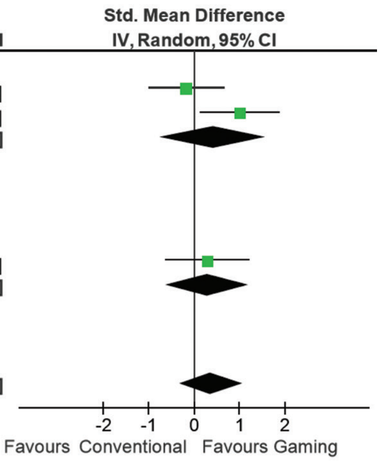

Fig. 11. Lower limb function (balance): conventional treatment vs gaming VR. D: standard deviation; 95% CI: 95% confidence interval.

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DISCUSSION

VR therapy has been shown to result in improvements in analysed parameters, but not with statistical significance for all conditions in comparison with conventional treatment. Significant differences were observed between specialized VR and conventional treatment for upper limb function (Fugl Meyer) and lower limb function (balance). Comparative analysis of conventional treatment vs gaming VR, found significant differences only within upper limb function (all measures).

This review shows that most recipients of VR therapy are patients with neurological disorders, mainly stroke. All studies of patients after stroke showed improvement after VR therapy in comparison with conventional therapy in both upper and lower limbs (11, 14–26). The results of the studies included in this review reveal that stroke patients benefit from this innovative treatment, probably through enhanced stimulation provided by an artificially generated environment leading to the activation of motor learning processes. According to the motor learning paradigms, the efficient movement should be repeated, emulating a reference model as exactly as possible, with the aim of achieving the best motor performance (32). Thus, motor learning paradigms can be seen as a basis for movement re-learning and, according to the results of analysed studies, the VR environment has the potential to stimulate both supervised and reinforcement learning, based on augmented visual, acoustic and sensitive feedback.

VR therapy was also used to treat people with developmental coordination disorder and cerebral palsy, showing improvement in learning new movements from VR environments. VR therapy was also shown to be effective for treating people with multiple sclerosis and SCI. These findings demonstrate a wide range of applications for VR in rehabilitation interventions, and its possible advantage in different clinical settings. In addition, studies included in this review did not find any contraindications to the use of this form of therapy. Only one study was published within the orthopaedic field, in which authors evaluated the effect of a VR programme for recovery of subacromial impingement syndrome (SAIS), showing that the VR training was more effective than home exercise programmes in the short-term in subjects with SAIS (8).

Most of the included studies focused on upper limb treatment, whereas training for the lower limb concentrated mostly on balance. This difference may be due to the complexity of treating upper limb function after stroke, relying on changes in muscle synergies of the upper extremity leading to stereotyped voluntary movements. This change is related to both disrupted motor pathways and altered neural reorganization especially following a stroke. Importantly, approximately 60% of stroke survivors do not recover their upper limb function, conversely less than 25% are unable to walk without full physical assistance (33, 34). Another reason can be related to patient safety during gait or balance treatment, which requires specialized VR systems.

It was observed that the specialized VR systems were used both for treatment and assessment of patients. This was especially common in the neurological field, probably due to the fact that neurological patients require specific and individual training programmes, and only a directed in clinical settings system can be beneficial for these kind of patients. On the other hand, gaming systems were used with children, which can be advantageous because some boring or repetitive exercises can be substituted by more interactive activities. This may help both clinicians and parents to motivate children effectively to comply with their daily therapy.

VR is a growing technology that can provide an important addition to traditional rehabilitation modalities. Research shows that most disabled patients experience not only physical disorders, but also mental health problems (e.g. depression or cognitive impairment) (35, 36). Thus, it could be interesting to combine different motor training aspects with psychological and cognitive ones (e.g. mood improvement, strengthened motivation to active engagement in rehabilitation process, visual-spatial orientation and cognitive stimulation). Future studies should consider this translational aspect for VR therapy.

Study limitations

This study has some limitations that need to be addressed. Firstly, only one database was searched for studies, due to the wide number of publications related to the rehabilitation field. Secondly, only full free-text articles were included, providing an overview of accessible clinical outcomes for a wide audience. In addition, no information was obtained from authors related to *p*-values for the results of included studies.

Conclusion

Implications for clinical practice

Rehabilitation based on VR therapy is emerging as an effective modality for the treatment of balance as well as the upper extremity. VR-based therapy is widely used in the neurological field, especially for rehabilitation after stroke. To date, studies have shown some efficacy of VR-based approach with both specialized and gaming VR systems for gait and hand dexterity; however, this was not significant. Future research into the use of VR in neurological patients should utilize larger samples assessed over time, in order to investigate long-term effects and psychological aspects of the therapeutic intervention. Specialized VR and gaming VR can be advantageous for the upper extremity, but not for balance treatment. There is insufficient evidence across free available articles to reach conclusions about the effects of specialized VR and gaming VR on hand dexterity and gait speed.

Implications for further research

This systematic review highlights the need for further research into VR-based approaches for rehabilitation interventions for gait and hand dexterity. Furthermore, due to the differences in outcome measures, in order to better compare data from different trials specific protocols with equal outcome measures should be developed. Finally, improvements in the methodological quality of evidence are needed, by increasing the number of participants in trials, and correctly randomizing them, in order to minimize the possible effects of confounding factors.

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Appendix 1. Risk of bias in included studies.

Ballester et al., 2016 (12)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of outcome assessment (detection bias)	Low risk	Evaluators blinded to group designation
Incomplete outcome data (attrition bias)	Low risk	Only 2 participants out of 20 dropped out
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported

Bonney et al., 2017 (11)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	no information about randomization method
Allocation concealment (selection bias)	Unclear risk	no information about allocation concealment
Blinding of outcome assessment (detection bias)	Low risk	Evaluators were blinded to outcome assessment and to the protocol the children were assigned to
Incomplete outcome data (attrition bias)	Low risk	All participants included in the analysis
Selective reporting (reporting bias)	Low risk	All expected and pre-specified outcomes were reported

Cho et al., 2012 (24)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was computer-generated by using a basic random number generator
Allocation concealment (selection bias)	Low risk	Random number generator was used to randomize patients
Blinding of outcome assessment (detection bias)	Unclear risk	No information
Incomplete outcome data (attrition bias)	Low risk	1 subject in the training group and 1 subject in the control group withdrew from the training
Selective reporting (reporting bias)	Low risk	All expected and pre-specified outcomes were reported

Cho et al., 2015 (20)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Shuffling envelopes
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessor blinded
Incomplete outcome data (attrition bias)	Low risk	One participant from intervention group and one participant from control group were lost to follow-up. Losses unlikely to affect final results
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported

Cho et al., 2016 (6)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomly allocated by lots
Allocation concealment (selection bias)	Low risk	Participants were allocated by lots
Blinding of outcome assessment (detection bias)	Low risk	The two evaluators were blinded to the group allocation of the participants
Incomplete outcome data (attrition bias)	Low risk	All participants included in the analysis
Selective reporting (reporting bias)	Low risk	All expected and pre-specified outcomes were reported

Dimbwadyo-Terrer et al., 2016 (28)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Shuffling envelopes
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessor blinded
Incomplete outcome data (attrition bias)	High risk	Nine participants lost to follow-up, reasons for losses were disclosed. Losses likely to influence final results
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported

Duque et al., 2013 (30)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of outcome assessment (detection bias)	Low risk	Different physiotherapists with no access to the subjects' data were specifically assigned to perform either assessment or training
Incomplete outcome data (attrition bias)	Low risk	Of the 30 subjects in the BRU-training group, only two withdrew from the program before completing their 6 weeks of BRU training
Selective reporting (reporting bias)	Low risk	All expected and pre-specified outcomes were reported

In et al., 2016 (16)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random allocation software
Allocation concealment (selection bias)	Low risk	Random allocation software
Blinding of outcome assessment (detection bias)	Low risk	the assessors were blinded to the participants' groups
Incomplete outcome data (attrition bias)	Low risk	Missing outcome data balanced in numbers across intervention groups
Selective reporting (reporting bias)	Low risk	All expected and pre-specified outcomes reported

Kalron et al., 2016 (29)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Shuffling envelopes
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessor blinded
Incomplete outcome data (attrition bias)	Low risk	One participant from intervention group and one participant from control group were lost to follow-up. Reasons for losses were disclosed. Losses unlikely to affect final results
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported

Karasu et al., 2018 (31)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A randomization table was used to determine randomization numbers
Allocation concealment (selection bias)	Low risk	The cards showing to which group each patient would be allocated were placed in a series of numbered, sealed, opaque envelopes.
Blinding of outcome assessment (detection bias)	Low risk	An evaluator who was blinded to the groups made assessments.
Incomplete outcome data (attrition bias)	Low risk	All patients who met the inclusion criteria were included in the analysis
Selective reporting (reporting bias)	Low risk	All expected and pre-specified outcomes were reported

Kiper et al., 2014 (27)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization sequence was generated with computerized program (computerized random numbers)
Allocation concealment (selection bias)	Low risk	Allocation sequence was concealed to investigators with sealed envelopes
Blinding of outcome assessment (detection bias)	Low risk	All assessment data were collected by therapists blinded to the treatment allocations
Incomplete outcome data (attrition bias)	Low risk	Only 2 participants out of 46 dropped out
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported

Lee et al., 2018 (26)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomization process was performed using Random Allocation software for parallel group randomized studies
Allocation concealment (selection bias)	Low risk	Random Allocation software for parallel group randomized studies used
Blinding of outcome assessment (detection bias)	Low risk	All assessment data were collected by therapists blinded to the treatment allocations
Incomplete outcome data (attrition bias)	Low risk	Only 1 participant out of 31 dropped out. All 30 participants included in the analysis
Selective reporting (reporting bias)	Low risk	All expected and pre-specified outcomes were reported

McEwen et al., 2014 (22)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	The first 30 participants were randomly assigned through coin-toss method to the control or treatment group, with subsequent participants being allocated using age and Berg Balance Scale scores
Allocation concealment (selection bias)	Unclear risk	Method of concealment not described
Blinding of outcome assessment (detection bias)	Low risk	Evaluators blinded to outcome assessment
Incomplete outcome data (attrition bias)	High risk	74 patients were enrolled, and outcome measures were assessed on 59 (30 treatment and 29 control) immediately after the final training session and on 52 (28 treatment and 24 control) 1 month after the cessation of training
Selective reporting (reporting bias)	Low risk	All expected and pre-specified outcomes were reported

Pekyavas et al., 2017 (8)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Subjects were randomly assigned to groups using an online random allocation software

Allocation concealment (selection bias)	Low risk	Subjects were randomly assigned to groups using an online random allocation software
Blinding of outcome assessment (detection bias)	Unclear risk	No information
Incomplete outcome data (attrition bias)	Low risk	All participants included in the analysis
Saposnik et al., 2016 (25)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly allocated by a computer-generated assignment
Allocation concealment (selection bias)	Low risk	Computer-generated assignment used
Blinding of outcome assessment (detection bias)	Low risk	All investigators assessing outcomes were masked to treatment assignment
Incomplete outcome data (attrition bias)	Low risk	40 participants out of 141 did not complete treatment protocol, but analysis were performed in the intention-to-treat population
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported
Shin et al., 2014 (23)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of outcome assessment (detection bias)	Low risk	Evaluators were blinded to the type of intervention
Incomplete outcome data (attrition bias)	Low risk	All participants included in the analysis
Selective reporting (reporting bias)	Low risk	All expected and pre-specified outcomes were reported
Shin et al., 2016 (19)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomized scheme
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessor blinded
Incomplete outcome data (attrition bias)	High risk	Ten participants lost to follow-up, reasons for losses were disclosed. Losses likely to influence final results
Selective reporting (reporting bias)	Low risk	All primary and most of secondary outcome has been reported. Although, in ClinicalTrial.gov authors' stated Modified Ashworth scale as a secondary outcome measure, which was not reported in the article
Standen et al., 2017 (18)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Web generated list for a two group randomisation sequence which was concealed from the researchers

Allocation concealment (selection bias)	Low risk	The researcher who had collected baseline data phoned the administrator to discover the next unallocated number on the list to determine whether the patient would be allocated to the intervention or control group
Blinding of outcome assessment (detection bias)	High risk	not always possible to ensure the researcher was blind to the allocation of the patient
Incomplete outcome data (attrition bias)	High risk	9 participants out of 27 not included in final analysis
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported
Thielbar et al., 2014 (21)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Drawing of lots
Allocation concealment (selection bias)	Unclear risk	Method of concealment is not described
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessor blinded
Incomplete outcome data (attrition bias)	Low risk	Two participants were lost to follow-up, reasons for losses were disclosed. Losses unlikely to affect final results
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Zondervan et al., 2016 (17)		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Alternate block allocation is a deterministic method that involves open allocation: the person recruiting trial participants knows the next treatment and may be influenced in the recruitment
Allocation concealment (selection bias)	High risk	Alternate block allocation: the person recruiting trial participants knows the next treatment and may be influenced in the recruitment
Blinding of outcome assessment (detection bias)	Low risk	Assessments performed by two blinded evaluators
Incomplete outcome data (attrition bias)	Low risk	Only 1 participant out of 18 lost to follow-up
Selective reporting (reporting bias)	High risk	Not all outcome measures registered in study protocol were published

BRU, Balance Rehabilitation Unit-