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Virtual reality for multiple sclerosis rehabilitation (Review)

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TABLE OF CONTENTS

[Intervention Review]

Virtual reality for multiple sclerosis rehabilitation

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ABSTRACT

Background

Multiple sclerosis (MS) is the most common neurological disease in young adults. Virtual reality (VR) offers a promising rehabilitation tool by providing controllable, personalised environments for safe, adaptable and engaging training. Virtual reality can be tailored to patients' motor and cognitive skills, enhancing motivation through exciting scenarios and feedback.

Objectives

Primary objective

To assess the effects of virtual reality interventions compared with an alternative or no intervention on lower limb and gait function, and balance and postural control in people with MS.

Secondary objective

To assess the effects of virtual reality interventions compared with an alternative or no intervention on upper limb function, cognitive function, fatigue, global motor function, activity limitation, participation restriction and quality of life, and adverse events in people with MS.

Search methods

We identified relevant articles through electronic searches of CENTRAL, MEDLINE, Embase, PEDro, CINAHL and Scopus. We also searched trials registries (ClinicalTrials.gov and the WHO ICTRP search portal) and checked reference lists. We carried out all searches up until August 2022.

Selection criteria

We included only (quasi-)randomised controlled trials (RCTs) that assessed virtual reality interventions, defined as "an artificial, computer-generated simulation or creation of a real-life environment or situation allowing the user to navigate through and interact with", in people with MS. The primary outcomes were lower limb and gait function, and balance and postural control. Secondary outcome measures were upper limb function, cognitive function, fatigue, global motor function, activity limitation, participation and quality of life, and adverse events. Eligible participants were people with MS who were 18 years or older.

Data collection and analysis

Two review authors independently screened the studies based on pre-specified criteria, extracted study data and assessed the risk of bias of the included studies. We used the risk of bias 2 tool (RoB 2). A third review author was consulted to resolve conflicts.

Main results

We included 33 RCTs with 1294 people with MS. The sample sizes of the included studies were relatively small and there was considerable heterogeneity between studies regarding the virtual reality devices and the outcome measures used. The control group either received no intervention, conventional therapy or an alternative intervention (an intervention that does not fit the description of conventional therapy for the rehabilitation of people with MS). We most frequently judged the risk of bias as 'some concerns' across domains, leading to an overall high risk of bias in the majority of included studies for all outcome measures.

Primary outcomes

When compared with no intervention, virtual reality interventions may result in no difference in lower limb and gait function (Timed Up and Go, mean difference (MD) -0.43 sec, 95% confidence interval (CI) -0.85 to 0.00; 6 studies, 264 participants; low-certainty evidence) or balance and postural control (Berg Balance Scale, MD 0.29 points, 95% CI -0.1 to 0.68; 4 studies, 137 participants; very low-certainty evidence).

When virtual reality interventions are compared to conventional therapy, results for lower limb and gait function probably do not differ between interventions (Timed Up and Go, MD -0.2 sec, -1.65 to 1.25; 4 studies, 107 participants; moderate-certainty evidence). However, virtual reality interventions probably improve balance and postural control (Berg Balance Scale, MD 2.39 points, 95% CI 1.22 to 3.57; 7 studies, 201 participants; moderate-certainty evidence), almost reaching the clinically important difference (3 points).

Secondary outcomes

Compared to no intervention, the use of virtual reality may also improve upper limb function (9-Hole Peg Test, MD -4.19 sec, 95% CI -5.86 to -2.52; 2 studies, 84 participants; low-certainty evidence), almost reaching the clinically important difference (4.38 points) and participation and quality of life, but the evidence is very uncertain (MS International QoL, MD 9.24 points, 95% CI 5.76 to 12.73; 2 studies, 82 participants; very low-certainty evidence).

Compared to conventional therapy, virtual reality interventions may improve participation and quality of life (Falls Efficacy Scale-1, MD -3.07 points, 95% CI -5.99 to -0.15; 3 studies, 101 participants; low-certainty evidence), but not upper limb function (9-Hole Peg Test, MD 0.10 sec, 95% CI -1.70 to 1.89; 3 studies, 93 participants; low-certainty evidence). For other key secondary outcome measures, i.e. global motor function and adverse events, there were no data available as these were not measured in the studies.

Authors' conclusions

We found evidence that the use of virtual reality may be more effective than no intervention in improving upper limb function and participation and quality of life. Training with virtual reality may be superior to conventional therapy for improving balance and postural control, and participation and quality of life. For the other outcomes, there was no clear difference between virtual reality and conventional therapy. There was insufficient evidence to reach conclusions about the effect of virtual reality on global motor function, activity limitations and adverse events. Additional high-quality, large-scale studies are needed to expand and confirm these findings.

PLAIN LANGUAGE SUMMARY

Are virtual reality interventions more effective than an alternative or no intervention for the rehabilitation of people with multiple sclerosis?

Key messages

- Virtual reality might improve balance and postural control, upper limb function, and participation and quality of life, but the overall quality of the evidence is limited.
- Since these results are based on few studies of lower quality, they should be interpreted with caution.

What is multiple sclerosis?

Multiple sclerosis is the most common neurological disease in young adults. People with multiple sclerosis can have a variety of symptoms, such as fatigue, and sensory, cognitive and sexual dysfunction, but also muscle weakness and co-ordination problems.

How can virtual reality help people with multiple sclerosis?

Virtual reality has been proposed as a new rehabilitation tool and is increasingly being used for the rehabilitation of neurological patients. Virtual reality interventions use computer programs that allow users to navigate in and interact with a virtual environment. The use of virtual reality in rehabilitation offers several advantages, such as providing fully controllable, personalised environments and situations that are too dangerous, expensive or impossible in real life. Moreover, the level of difficulty and intensity can be adapted to the skills of the

patient, and virtual reality has the potential to increase patients' motivation by creating more exciting training environments and providing feedback.

What did we want to find out?

The purpose of this review was to assess the effectiveness of virtual reality interventions for the rehabilitation of people with multiple sclerosis. We wanted to find out whether training with virtual reality resulted in more improvement of lower limb function and gait, balance and postural control, upper limb function, cognition, fatigue, global motor function, activity limitations, participation and quality of life, and the occurrence of adverse (harmful or unwanted) events. We compared virtual reality training to 1) no intervention and 2) conventional therapy or an alternative therapy.

What did we do?

We identified 33 studies with a total of 1294 people with multiple sclerosis, who on average (based on 22 studies) had a significant disability but were able to walk without an aid for 500 metres. A lot of different virtual reality devices and programs were used. Almost 91% (30) of the included studies used non-immersive virtual reality systems (e.g. TV screens), two studies used semi-immersive virtual reality devices (e.g. big screens) and one study used a full-immersive head-mounted display. Most virtual reality interventions aimed to improve balance and gait function.

What did we find?

Ten studies assessed whether virtual reality can be used to improve gait and balance function and found that the use of virtual reality may not result in better function for most outcome measures when compared to no intervention (we are very uncertain about these results). When compared to conventional therapy, the gains in terms of lower limb and gait function were probably not greater for the virtual reality interventions. However, virtual reality is probably superior in improving balance and postural control compared to conventional therapy. Two trials tested whether virtual reality would lead to more improvements in upper limb function compared to no intervention, and found that this may be the case. Virtual reality may be more effective in improving upper limb function than conventional therapy. Studies that assessed participation and quality of life may indicate positive effects in favour of virtual reality, both when compared to no intervention and conventional therapy (we are very uncertain about these results). We were unable to assess the effect of virtual reality interventions on global motor function and adverse events.

What are the limitations of the evidence?

Overall, we have moderate to low or very low confidence in evidence. This was mainly due to the small numbers of participants in the included studies and the poor quality of the studies. Moreover, due to the nature of the included studies, the evidence is mainly limited to people with a relatively low degree of physical disability and virtual reality technology that has a limited degree of immersion. Furthermore, the methods used in the studies varied; for example, regarding the types of outcomes measured and the design of the interventions.

How up-to-date is this evidence?

The evidence is current to August 2022.

Summary of findings 1. Summary of findings table - Virtual reality versus no intervention for adults with multiple sclerosis

Virtual reality versus no intervention for adults with multiple sclerosis

Patient or population: adults with multiple sclerosis
Setting: hospital, clinic or home
Intervention: virtual reality
Comparison: no intervention

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no intervention	Risk with virtual reality				
Lower limb and gait function (TUG) assessed with: Timed Up and Go (in seconds, lower scores represent benefit) follow-up: range 4 weeks to 6 months	The mean lower limb and gait function was **0.01 sec higher**	MD **0.43 lower** (0.85 lower to 0)	-	264 (6 RCTs)	⊕⊕⊖⊖ Low[a,b]	Virtual reality may result in little to no difference in lower limb and gait function.
Balance and postural control (BBS) assessed with: Berg Balance Scale (in points, higher scores represent benefit) Scale from: 0 to 56 follow-up: range 4 weeks to 12 weeks	The mean balance and postural control was **0.42 points higher**	MD **0.29 higher** (0.1 lower to 0.68 higher)	-	137 (4 RCTs)	⊕⊖⊖⊖ Very low[c,d,e]	Virtual reality may have little to no effect on balance and postural control but the evidence is very uncertain.
Upper limb function (9-HPT) assessed with: 9-Hole Peg Test (in seconds, lower scores represent benefit) follow-up: range 8 weeks to 12 weeks	The mean upper limb function was **1.3 sec higher**	MD **4.19 lower** (5.86 lower to 2.52 lower)	-	84 (2 RCTs)	⊕⊕⊖⊖ Low[b,e]	Virtual reality may improve upper limb function, almost reaching the clinically important difference of 4.38 points.
Global motor function	See comment			80 (2 RCTs)	⊕⊖⊖⊖ Very low[b,f,g]	One study reported significantly better motor function in the intervention group (P = 0.01) on the MS Functional Composite Score and one study reported no dif-

						ference between groups (P > 0.05) on the Modified Ashworth Scale. These results could not be pooled.
Participation and quality of life (MSIQOL) assessed with: MS International QoL (in points, higher scores represent benefit) Scale from: 0 to 100 follow-up: range 8 weeks to 8 weeks	The mean participation and quality of life was **1.38 points lower**	MD **9.24 higher** (5.76 higher to 12.73 higher)	-	82 (2 RCTs)	⊕⊖⊖⊖ Very low[b,e,h]	Virtual reality may improve participation and quality of life but the evidence is very uncertain.
Adverse events	See comment			30 (1 RCT)	⊕⊕⊖⊖ Low[b,i]	No serious adverse events were reported for both groups. Adverse events were reported descriptively for the intervention (leg pain, backache, discomfort, aggravating pre-existing condition, near/falls), but not reported for the control.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_431750496042143828.

[a] Downgraded one level for inconsistency due to moderate heterogeneity levels (60%) and non-overlapping CIs.
[b] Downgraded one level for imprecision due to low sample size.
[c] Downgraded one level for inconsistency due to high heterogeneity levels (92%) and non-overlapping CIs.
[d] Downgraded one level for imprecision due to low sample size and including the possibility of no effect.
[e] Downgraded one level for high risk of publication bias.
[f] Downgraded one level due to overall uncertain and high risk of bias in the two studies.
[g] Downgraded one level for different outcome measure used.
[h] Downgraded one level due to some concerns in 4 out of 5 domains of the risk of bias in both studies.
[i] Downgraded one level due to high risk of bias.

Summary of findings 2. Summary of findings table - Virtual reality versus conventional therapy for adults with multiple sclerosis

Virtual reality versus conventional therapy for adults with multiple sclerosis

Patient or population: adults with multiple sclerosis
Setting: hospital, clinic or home
Intervention: virtual reality
Comparison: conventional therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with conventional therapy	Risk with virtual reality				
Lower limb and gait function (TUG) assessed with: Timed Up and Go (in seconds, lower scores represent benefit) follow-up: range 6 weeks to 10 weeks	The mean lower limb and gait function was **1.04 sec lower**	MD **0.2 lower** (1.65 lower to 1.25 higher)	-	107 (4 RCTs)	⊕⊕⊕⊖ Moderate[a]	Virtual reality likely results in little to no difference in lower limb and gait function.
Balance and postural control (BBS) assessed with: Berg Balance Scale (in points, higher scores represent benefit) Scale from: 0 to 56 follow-up: range 4 weeks to 10 weeks	The mean balance and postural control was **2.1 points higher**	MD **2.39 higher** (1.22 higher to 3.57 higher)	-	201 (7 RCTs)	⊕⊕⊕⊖ Moderate[b]	Virtual reality likely improves balance and postural control, almost reaching the clinically important difference of 3 points.
Upper limb function (9-HPT) assessed with: 9-Hole Peg Test (in seconds, lower scores represent benefit) follow-up: range 1 months to 8 weeks	The mean upper limb function was **1.91 sec lower**	MD **0.1 higher** (1.7 lower to 1.89 higher)	-	93 (3 RCTs)	⊕⊕⊖⊖ Low[a,c]	Virtual reality may result in little to no difference in upper limb function.
Global motor function	See comment			93 (3 RCTs)	⊕⊖⊖⊖ Very low[b,d,e]	Two studies reported no difference within and between groups on the Expended Disability Status Scale (within: exp P = 0.15 - contr P = -; between: P = 0.781) and at the Modified Ashworth Scale (within: exp P =

						0.2 - contr P = 0.2; P = 0.017). One study reported significant improvement within group (exp P = 0.038; contr P = 0.011) and better motor function in the exp group on the Rivermead Mobility Index. These results could not be pooled.
Participation and QoL (FES-I) assessed with: Falls Efficacy Scale-I (in points, lower scores represent benefit) Scale from: 0 to 64 follow-up: range 6 weeks to 6 weeks	The mean participation and QoL was **5.81 points lower**	MD **3.07 lower** (5.99 lower to 0.15 lower)	-	101 (3 RCTs)	⊕⊕⊖⊖ Low[b,c]	Virtual reality may improve participation and QoL. FES-I was used as the MusiQoL was not available for this comparison and the authors considered fear of falling to be the most important contributor to participation.
Adverse events - not reported	-	-	-	-	-	No results were available for this outcome.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_431861003357295697.

[a] Downgraded one level for imprecision due to small sample size and including the possibility of no effect.
[b] Downgraded one level for imprecision due to small sample size.
[c] Downgraded one level for high risk of publication bias.
[d] Downgraded one level due to unclear (1 study) and high (2 studies) risk of bias.
[e] Downgraded one level for different outcome measures used.

BACKGROUND

Description of the condition

Multiple sclerosis (MS) is the most common neurological disease in young adults (Koch-Henriksen 2010). The cause of MS is still poorly understood, but current evidence suggests that it is an autoimmune and neurodegenerative disorder, characterised by demyelinating lesions of the central nervous system (CNS) (Kubsik-Gidlewska 2017), triggered by environmental and genetic factors (Garg 2015; Kubsik-Gidlewska 2017). MS is three times more prevalent in women than in men and there is evidence that this ratio is increasing (Bishop 2015). Other risk factors include low levels of vitamin D, Epstein-Barr virus in childhood and smoking (Garg 2015).

The World Health Organization (WHO) estimates that more than two million people worldwide have MS (GBD 2019). The prevalence of the disease varies across countries, ranging from 15 per 100,000 to 250 per 100,000, and is higher in Northern Europe and in more temperate regions such as Canada, the USA and Australia (Bishop 2015; Garg 2015; GBD 2019). The incidental peak of this chronic disease is around the age of 30 years (Maggio 2019), but initial symptoms are most often seen between 20 and 50 years of age (Bishop 2015; Garg 2015). Multiple sclerosis is categorised into four subtypes: primary progressive multiple sclerosis (PPMS), secondary progressive multiple sclerosis (SPMS), relapsing-remitting multiple sclerosis (RRMS) and progressive-relapsing multiple sclerosis (RPMS). Clinically, most patients are diagnosed with RRMS in early disease stages and around 60% to 80% of these cases convert to SPMS with time (Maggio 2019).

Symptoms of MS vary depending on the location and size of the CNS lesions. Besides feeling fatigued and experiencing sensory, cognitive (e.g. information processing speed and attention and memory deficits) and sexual dysfunction, MS often induces symptoms such as spasticity, tremor and diminished strength and co-ordination (Bishop 2015; Maggio 2019). Moreover, the chronicity of these motor symptoms can cause irreversible disability. Given this wide variety of symptoms, multidisciplinary rehabilitation is required, involving both pharmacology and neurorehabilitation (Bishop 2015; Kubsik-Gidlewska 2017). The key components of such rehabilitation are: reducing the difficulties related to MS symptoms, re-educating motor and cognitive functions, and increasing cognitive abilities (Maggio 2019).

Description of the intervention

Virtual reality can be defined as “an application that, in very near real time, allows a user to navigate through and interact with a virtual environment” (Baus 2014). Key concepts related to virtual reality are level of immersion and presence. Based on the degree of immersion, virtual reality systems and devices can be classified into three categories: fully immersive, semi-immersive and non-immersive virtual reality (Rose 2018). Full-immersive virtual reality systems (e.g. a head-mounted display) integrate the user completely into the virtual environment by blocking out perception of the real world. Semi-immersive virtual reality systems (e.g. large screen monitors, projections or multiple television screens) and non-immersive virtual reality systems (e.g. a single television screen) let the user perceive both the real world and a part of the virtual environment. It is known that the degree of immersion has an impact on users’ virtual reality experience and affects their sense of presence (i.e. the feeling of being physically present in the virtual world) (Rose 2018), with stronger feelings of ‘being physically present’ during exposure with more immersive virtual environments (Tieri 2018).

Virtual reality is a relatively new tool emerging in the field of physical rehabilitation (Dockx 2016; Tieri 2018), and may improve both the quality and quantity of rehabilitation treatments (Tieri 2018). There are a broad variety of virtual reality applications that can be used for rehabilitation. Video gaming consoles — such as the Nintendo Wii or Sony PlayStation — are often used in rehabilitation centres (Tieri 2018). These low-cost commercial gaming applications were originally designed for entertainment purposes but can be adapted to provide therapeutic activities in rehabilitation. More advanced virtual reality systems — such as the Gait Real-time Analysis Interactive Lab (GRAIL) or Computer Assisted Rehabilitation Environment (CAREN) system and head-mounted displays — are also slowly finding their way to the rehabilitation settings. The downside of these systems is that they are expensive.

Virtual reality applications for physical rehabilitation of neurological disorders are being used to improve both upper and lower limb function, cognitive function, balance and gait training (De Keersmaecker 2019; Dockx 2016; Laver 2017; Maggio 2019; Massetti 2016; Thomson 2014). Virtual reality can be added to therapies with repetitive tasks to increase the patient’s active participation and motivation during training. For example, virtual reality applications can be used alongside a treadmill or with robotic exoskeletons for the lower and upper limbs (e.g. the Lokomat gait exoskeleton and the AMADEO finger and hand rehabilitation robot).

How the intervention might work

The use of virtual reality may be important in the rehabilitation of people with MS (Maggio 2019), since it has the potential to increase relevant concepts of neural plasticity (e.g. repetition, intensity, individualisation and task specificity) by providing training in more interactive and motivating environments. Virtual reality can offer several advantages in physical rehabilitation programmes. Firstly, it can simulate environments and situations that are too dangerous, expensive or impossible in real life (e.g. crowded areas, uneven surfaces, etc.). Secondly, virtual environments are fully controllable by therapists and researchers, enabling the opportunity to practise functional tasks (e.g. grasping, opening and closing the hand, etc.) and to introduce real-life environments or situations (e.g. doing grocery shopping in a supermarket) into the hospital or rehabilitation centre (Tieri 2018). Thirdly, virtual environments are artificially made and can therefore easily be changed, creating the possibility to personalise environments and therapies (Teo 2016; Tieri 2018). Moreover, the level of difficulty and intensity can be adapted to the motor and cognitive skills of the patient. Lastly, virtual reality has the potential to increase patients’ motivation by creating more exciting training environments and providing feedback, resulting in more repetitions and longer training durations, and ultimately improving patients’ treatment compliance (Howard 2017; Massetti 2016; Tieri 2018).

Despite its utility in neurorehabilitation, the effectiveness of the use of virtual reality for motor and cognitive training in MS is still unclear. Moreover, it is also worth exploring these new technologies across the disability spectrum of MS. In other central neurological diseases, such as stroke, it is suggested that the disability of the

disease can influence the effect of the use of virtual reality during rehabilitation (Laver 2017). It will be interesting to investigate whether the disability level of patients with MS (in terms of Expanded Disability Status Scale (EDSS) score) has an influence on the effect of virtual reality.

Why it is important to do this review

As technology becomes more affordable and accessible, it is likely that virtual reality applications will become more widely used during rehabilitation in patients with neurological disorders such as MS. Therefore, it is important to investigate the effectiveness of virtual reality for physical rehabilitation in order to guide the future use and design of virtual reality applications.

Previous research shows that virtual reality seems to be a feasible strategy to improve motor and cognitive function in several neurological populations, such as stroke or Parkinson's disease (De Keersmaecker 2019; Dockx 2016; Laver 2017). There are now some reviews examining the effect of virtual reality for rehabilitation in people with MS (Maggio 2019; Massetti 2016), and more specifically for balance and gait rehabilitation (Casuso-Holgado 2018). The review by Massetti and colleagues examined the effect of virtual reality for both the motor and cognitive rehabilitation of people with MS (Massetti 2016). It included 10 studies providing evidence about the use of virtual reality in MS. The more recent review by Maggio and colleagues evaluated the role of virtual reality tools in the motor and cognitive rehabilitation of people with MS (Maggio 2019). The authors identified 28 studies and, once again, concluded that virtual reality could be an effective tool to improve traditional motor and cognitive rehabilitation for people with MS, but further studies with larger sample sizes are needed to investigate the real impact. However, neither review was systematic (i.e. with assessment of methodological quality) or included a meta-analysis. Casus-Holgado and colleagues conducted a systematic review and meta-analysis of the effectiveness of virtual reality only for gait and balance training in people with MS (Casuso-Holgado 2018). The authors included 11 studies, of which nine were randomised controlled trials and two were controlled clinical trials. The authors concluded that virtual reality for gait and balance training is at least as effective as conventional training and more effective than no intervention. To improve the strength of evidence, future studies need to be large randomised controlled trials.

Currently, there is no recent, complete systematic review with meta-analysis regarding the effects of virtual reality on the rehabilitation of people with MS. Moreover, only studies performed until 2017 were sought in previous research. Given that this is a rapidly growing area, updates on the effects of virtual reality in MS rehabilitation are warranted, both now and in the future. Therefore, this Cochrane review will provide an overview of the effectiveness of the use of virtual reality applications for gait and balance function (primary outcome), as well as upper limb function, cognitive function, fatigue, global motor function, activity limitation, participation restriction and quality of life (secondary outcomes) in people with MS.

OBJECTIVES

Primary objective

To assess the effects of virtual reality interventions compared with alternative or no intervention in people with multiple sclerosis (MS) on:

1. lower limb and gait function;
2. balance and postural control.

Secondary objective

To assess the effects of virtual reality interventions compared with alternative or no intervention in people with MS on:

1. upper limb function;
2. cognitive function;
3. fatigue;
4. global motor function;
5. activity limitation;
6. participation restriction and quality of life;
7. adverse events.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials or quasi-randomised controlled trials (e.g. studies where allocation is made by medical record number). We looked for studies that compared virtual reality interventions with either an alternative intervention or no intervention. Multi-arm studies (studies that compared different types of virtual reality with a control group) were also included. We did not include cross-over trials.

Types of participants

We included studies of adult participants (aged 18 years or older) with a confirmed diagnosis of any type of MS (primary progressive, secondary progressive, relapsing-remitting and progressive-relapsing MS), with any level of disability and at any stage of the disease. Current diagnostic criteria for MS are the revised McDonald Criteria (Thompson 2018). Depending on the type of MS, different weights are attributed to different types of information (e.g. clinical history, neurological examination, lumbar puncture, magnetic resonance imaging, evoked potentials) in order to make the diagnosis. The relative weight of these information types has changed over time with different versions of the diagnostic criteria. What has not changed is that MS is in principle a clinical diagnosis, made by a clinical neurologist. We included studies with a mixed sample of participants if they reported data on people with MS as a separate subgroup.

Types of interventions

We included studies using virtual reality interventions that met the following definition: "an artificial, computer-generated simulation or creation of a real-life environment or situation allowing the user to navigate through and interact with" (Baus 2014). We included studies that used any form of non-immersive, semi-immersive or full-immersive virtual reality, and studies using

commercially available gaming consoles. We included all virtual reality interventions that used more than one treatment session and evaluated any intensity and duration of virtual reality. We classified the virtual reality interventions based on the level of immersion (full-, semi- and non-immersive) and the dosage of intervention (≤ 10 hours and > 10 hours).

The comparison group received either an alternative intervention or no intervention. Since there is a broad range of alternative interventions, we considered these to be any intervention designed to be therapeutic at the impairment, activity or participation level without the use of virtual reality (https://richtlijnendatabase.nl/richtlijn/multiple_sclerose_ms/startpagina_addendum_multiple_sclerose.html).

Types of outcome measures

The expected time points of evaluation of the outcomes were as follows:

1. Within one week prior to the start of the intervention (pre-outcome measures)
2. Within one week after the end of the intervention (post-outcome measures)
3. Follow-up measurements (more than one week after the intervention)

Primary outcomes

1. Lower limb and gait function: including assessments such as walking distance, gait speed, Tinetti Assessment Tool and the Timed Up and Go test (TUG).
2. Balance and postural control: including assessments such as the Berg Balance Scale (BBS) and Functional Reach Test (FRT).

In the case of multiple outcome measures assessing the same outcome, we prioritised the TUG test for 'lower limb and gait function' and the BBS for 'balance and postural control', as these are part of core outcome sets and the most commonly used outcome measures in clinical settings (Calafiore 2021; Paul 2014; Truijen 2022).

Secondary outcomes

1. Upper limb function: including assessments such as grip strength, the Box and Block Test (BBT) and Jebsen-Taylor Hand Function Test.
2. Cognition: including assessments such as the Brief Repeatable Battery of Neuropsychological tests (BRB-N), the minimal assessment of cognitive function in MS (MACFIMS) and the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS), the Paced Auditory Serial Addition Test (PASAT) and the Symbol Digit Modalities Test (SDMT).
3. Global motor function: including assessments such as the Expanded Disability Status Scale (EDSS).
4. Activity limitation: including assessments such as the Barthel Index and Functional Independence Measurement (FIM).
5. Participation and quality of life: including assessments such as the Health Status Questionnaire (SF-36), MS Quality of Life Inventory (MSQLI), Falls Efficacy Scale-International (FES-I) and MS Quality of Life-54 (MSQLI-54).
6. Fatigue: including assessments such as the Modified Fatigue Impact Scale (MFIS), the Fatigue Severity Scale (FSS) and the Fatigue Scale for Motor and Cognitive Functions (FSMC).
7. Adverse events: including motion sickness, pain and injury.

In the case of multiple measures assessing the same outcome, we prioritised measures that were specifically designed for MS and target the outcome directly and not as surrogates.

We included summary of findings tables for the following comparisons: 1) virtual reality compared to no intervention, and 2) virtual reality compared to conventional therapy. The tables included the primary outcomes (gait and balance function) as well as upper limb function, global motor function, quality of life and adverse events.

Search methods for identification of studies

Electronic searches

In March 2021, the Information Specialist of Cochrane Multiple Sclerosis and Rare Diseases of the Central Nervous System performed our search. In June 2022, the search string was updated, and the new search was completed in August 2022. Trials were identified through systematic searches of the following electronic bibliographic databases:

1. MEDLINE (PubMed, 1966 to 29 July 2022) (Appendix 1);
2. PEDro (1999 to 2 August 2022) (Appendix 2);
3. Scopus (searched 22 June 2022) (Appendix 3);
4. Cochrane Central Register of Controlled Trials (CENTRAL; 2022, Issue 7), in the Cochrane Library (searched 1 August 2022) (Appendix 4);
5. Embase (1980 to 3 August 2022) (Appendix 5);
6. CINAHL (1984 to 3 August 2022) (Appendix 6).

The search strategy for MEDLINE (PubMed) was adapted for use in the other databases. We also conducted a search of ClinicalTrials.gov (www.ClinicalTrials.gov) (Appendix 7) and the WHO International Clinical Trials Registry Platform (ICTRP) search portal (apps.who.int/trialsearch/) (Appendix 8) on 2 August 2022. We imposed no restrictions on publication date, status or language.

Searching other resources

In an effort to identify trials potentially missed through the database searches, ongoing and planned trials, and trials from the 'grey literature', we performed an expanded search, which included:

1. checking the reference lists of all included studies, texts and any relevant reviews on this topic;
2. contacting authors and researchers active in this field;
3. the use of Cited Reference Search (Web of Science and PubMed) for forward-tracking of important articles;
4. the use of Google Scholar alerts for new results matching our search.

Data collection and analysis

Selection of studies

With the use of Covidence, two review authors (EDK and ES or LD) independently screened the titles and abstracts of the search results to identify studies for possible inclusion. If there were

any disagreements, a third author was asked to arbitrate (DB). The same two authors then independently assessed the eligibility of studies based on the full text. We documented the reasons for excluding reports. We resolved any disagreement through discussion or, if required, we consulted a third person (DB). We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Liberati 2009).

Data extraction and management

Two review authors (EDK and ES or LD) independently extracted study characteristics from the included studies using a pre-described data extraction form. We contacted the primary authors of potentially eligible studies to provide data and clarification if the required data were absent, ambiguous or reported insufficiently. If data remained missing after these efforts, we assessed the impact in terms of introducing bias to our analyses, and either rejected the study or solely included sufficiently reported elements.

We extract the following study characteristics:

1. Methods: study design, funding source, declaration of interest
2. Participant details: in - and exclusion criteria, sample sizes, number of dropouts, descriptive characteristics including age, sex, type of MS, disease duration, severity of condition (disability according to Kurtzke's Expanded Disability Status Scale (EDSS) score (Kurtzke 1982))
3. Interventions: description of the intervention and comparison
4. Outcomes: outcomes specified and collected, time points reported, adverse events
5. Level of immersion

Two review authors (EDK and ES or LD) independently extracted outcome data from included studies with a pre-described data extraction form. We double-checked if data were entered correctly by comparing the two data extraction forms and resolved disagreements by consensus or by involving a third person (DB). One review author (EDK) transferred data into the Review Manager (RevMan) 5 file (RevMan 2020).

Assessment of risk of bias in included studies

Two review authors (EDK and ES) independently assessed the risk of bias for each study using version two of the Cochrane risk of bias tool (RoB 2), as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022). Disagreements between authors were resolved by discussion or by involving another author (DB). We assessed the risk of bias for a specific result of a trial according to the following domains:

1. Bias arising from the randomisation process
2. Bias due to deviations from intended interventions
3. Bias due to missing outcome data
4. Bias in measurement of the outcome
5. Bias in selection of the reported result
6. Overall bias

We used the signalling questions and algorithms in the RoB 2 tool to rate each domain as 'low risk of bias', 'some concerns' or 'high risk of bias'. We provided information from the study, together with a justification for our risk of bias judgement, in the risk of bias table.

The response options for the overall risk of bias judgement are the same as for individual domains ('low risk of bias', 'some concerns' or 'high risk of bias'), and were considered as follows:

1. 'low' if the study was judged to be at low risk of bias for all domains;
2. 'high' if the study was judged to be at high risk of bias in at least one domain, or if the study had some concerns for multiple domains;
3. 'some concerns' if the study was judged to raise some concerns in at least one domain, but not to be at high risk of bias for any domain.

We assessed the risk of bias for each outcome category (see Types of outcome measures). The effect of interest was 'the effect of assignment'. We managed the risk of bias assessment by using the RoB 2 Microsoft Excel tool (available at www.riskofbias.info) and made the consensus decisions for the signalling questions available online.

Measures of treatment effect

Two review authors (EDK and ES or LD) independently classified the outcome measures in terms of the domain assessed (gait function, balance function, upper limb function, cognitive function, fatigue, global motor function, activity limitation, participation restriction and quality of life, and adverse events). Outcomes measured during the virtual reality intervention were not included. If a study presented more than one outcome measure for the same domain, we included all outcome measures. We performed an analysis for all outcome measures that were reported in two or more studies. If relevant, we combined different outcome measures for the same domain. We analysed dichotomous data as risk ratios (RR) with 95% confidence intervals (CI), and continuous data as mean difference (MD) or standardised mean difference (SMD) with 95% CI.

Unit of analysis issues

We considered one unit of analysis issue in this review: the inclusion of studies with more than two intervention groups. If trials included multiple intervention groups, we combined all relevant experimental intervention groups of the study into a single group, and all relevant comparator intervention groups into a single comparator group. To avoid double-counting, we pooled the groups by combining the sample size and number of events for dichotomous outcomes and the means and standard deviations (SDs) for continuous outcomes, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020).

Dealing with missing data

We contacted investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data if necessary. Where possible, we used the Cochrane Excel calculator to calculate missing standard deviations using other data from the trial, such as confidence intervals, based on the methods outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019). In particular, to derive standard deviations we used a standard error or a confidence interval. These were calculated from within-group data or from a t-test comparing the mean scores or mean difference between groups.

Assessment of heterogeneity

We assessed heterogeneity by visual inspection of forest plots. We used both the Chi^2 test and I^2 statistic to quantify inconsistency among the trials in each analysis. We considered the presence of substantial heterogeneity to be indicated by an I^2 value greater than 50%. If we identified substantial heterogeneity, we reported it and explored possible causes using prespecified subgroup analysis.

Assessment of reporting biases

If sufficient data were available, we created and examined a funnel plot to explore possible publication bias. Our comprehensive search strategy, which also included searching clinical trial registers, unpublished studies and 'grey literature', assisted in minimising publication bias. We investigated reporting bias by comparing trials with their preregistered protocol or, when the protocol was not available, by comparing the outcomes described in the methods section of trials with the results reported.

Data synthesis

We performed meta-analyses only where this was meaningful, i.e. if the treatments, participants and underlying clinical question were similar enough for pooling to make sense. Where there were acceptable levels of heterogeneity, we conducted a meta-analysis with appropriate data using a fixed-effect model in RevMan 5. If, due to unacceptable heterogeneity, meta-analysis was not appropriate, we presented a narrative summary of the study results. Results of dichotomous (or binary) data were reported as a RR with 95% CI. For continuous data, we reported the treatment effect using the SMD with 95% CI where different scales were used for assessing the same outcome, and the MD with 95% CI when studies used the same scales.

Subgroup analysis and investigation of heterogeneity

We performed subgroup analyses to determine whether outcomes varied according to the disability level of MS (i.e. EDSS score ≤ 6; EDSS score > 6), the type of intervention (i.e. level of immersion: non-immersive, semi-immersive, full-immersive) and the dosage of the intervention (i.e. total dose of intervention ≤ 10 hours, > 10 hours). However, not all of these analyses were possible due to the homogeneity of trial participants or interventions. We compared subgroups using the test for subgroup differences in RevMan 5.

Sensitivity analysis

We conducted sensitivity analyses by excluding results with an overall assessment of 'high risk of bias'. We also conducted sensitivity analyses to determine whether there was a difference in using a fixed-effect model or a random-effects model. We considered and discussed the results of these analyses in comparison to the overall findings.

Summary of findings and assessment of the certainty of the evidence

We created summary of findings tables for the following comparisons: 1) virtual reality compared to no intervention, and 2) virtual reality compared to conventional therapy. The tables included outcomes that were considered clinically important: the primary outcomes (gait and balance function) as well as upper limb function, global motor function, quality of life and adverse events.

We used GRADE to interpret the findings and used GRADEpro GDT to create our summary of findings tables. The tables provide outcome-specific information about the overall certainty of evidence of the included studies. GRADE has four levels of certainty: high, moderate, low, very low. The body of evidence for randomised trials begins with a high-certainty rating. Based on five domains (risk of bias, consistency of effect, imprecision, indirectness and publication bias), the certainty of the evidence for a specific outcome can be downgraded. The reasons for downgrading were always documented and classified as 'no limitation' (not important enough for downgrading), 'serious' (downgrading by one level) and 'very serious' (downgrading by two levels).

RESULTS

Description of studies

See Characteristics of included studies; Characteristics of excluded studies.

Results of the search

Electronic and manual searches identified 4342 references with our search string (search in 2021: 2846 references (449 PubMed, 25 Embase, 296 CINAHL, 485 CENTRAL, 1975 Scopus, 34 Pedro, 95 ClinicalTrials.gov, 79 WHO ICTRP); search in 2022: 1496 references (659 PubMed, 1149 Embase, 443 CINAHL, 561 CENTRAL, 2319 Scopus, 16 Pedro, 27 ClinicalTrials.gov, 24 WHO ICTRP)).

After removing duplicates, we screened 4218 records on title and abstract. Of these, we retrieved 210 full-text articles for assessment of their full text. Finally, we included 33 studies in this review. See study flow chart (Figure 1).

Figure 1.

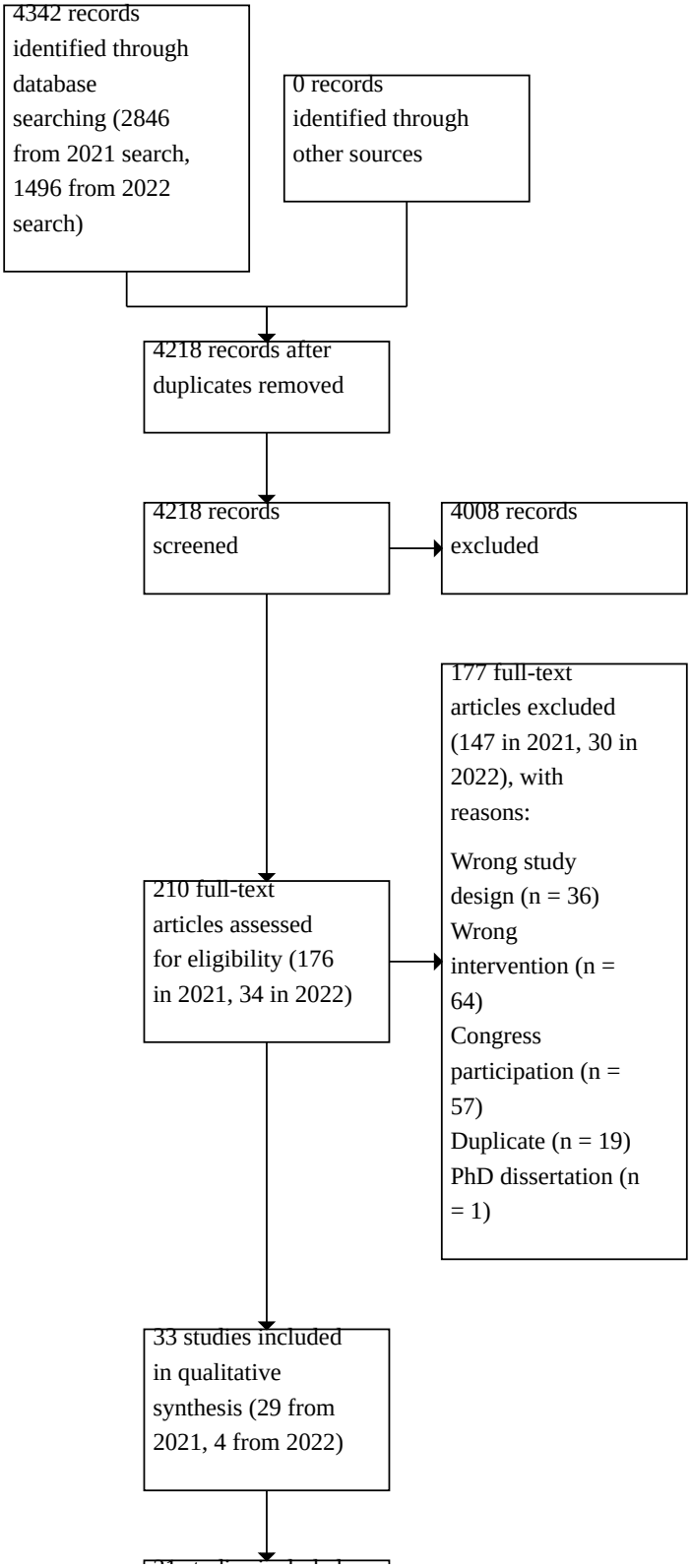
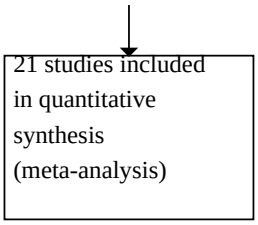


Figure 1. (Continued)



We contacted seven groups of authors via email for missing and/or inconsistent data (Calabrò 2017; Cuesta-Gómez 2020; Feys 2015; Jonsdottir 2018a; Maggio 2022; Ortiz-Gutiérrez 2013; Ozkul 2020). Two authors answered and provided the necessary data (Feys 2015; Jonsdottir 2018).

Included studies

In total, 33 RCTs with a total of 1294 participants met the inclusion criteria and were included in this review. Of the 33 included studies, 29 studies (with 1128 participants) were included after the first search and four (with 166 participants) after the updated search in 2022.

Participants

More detailed information about participants' characteristics, including inclusion/exclusion criteria and baseline demographics, are presented in the Characteristics of included studies table.

All studies were published between 2012 and 2022. Sample sizes of the included studies were small, ranging from 6 to 42 participants per group. Only six studies included more than 20 participants in each group (Bove 2021; Hoang 2015; Maggio 2022; Nilsagård 2012; Ortiz-Gutiérrez 2013; Pagliari 2021). A total sample size of 1294 participants with MS were included in the trials. As expected, the majority of participants were female; almost 70% of the total sample size were women. The mean age of participants ranged from 29 to 61 years, with a mean age of 44.51 years, and the mean time since diagnosis ranged from 4 to 25 years, with a mean of 11.97 years. Only 16 studies reported the type of MS of the included participants. The majority of included participants (405) had a relapsing-remitting course of MS, 149 participants were diagnosed with secondary progressive MS and 54 participants with primary progressive MS. The disability level of MS was reported with the EDSS score in 22 studies (ranging from 1 to 8 with a mean score of 3.95), and one study used the Adapted Patient Determined Disease Steps (APDDS) score (Thomas 2017).

Interventions

Experimental interventions

Three different intervention approaches were distinguished: lower limb, balance and gait training, upper limb training and cognitive training. Eighteen trials focused on lower limb, balance and gait training (Brichetto 2013; Calabrò 2017; Eftekharsadat 2015; Hoang 2015; Kalron 2016; Khalil 2018; Kramer 2014; Lozano-Quilis 2014; Molhemi 2021; Munari 2020; Nilsagård 2012; Novotna 2019; Ortiz-Gutiérrez 2013; Ozkul 2020; Peruzzi 2017; Robinson 2015; Tollár 2019; Yazgan 2019). Six trials involved upper limb training (Cuesta-Gómez 2020; Feys 2015; Jonsdottir 2018; Norouzi 2021; Tramontano 2020; Waliño-Paniagua 2019). Four trials focused on cognitive training (Bove 2021; Janssen 2015; Leonardi 2021; Maggio 2022). Two trials involved all three intervention approaches (Ozdogar 2022; Pagliari 2021). One trial focused on both cognition and lower limb and gait (Molhemi 2022). One trial involved both balance and upper limb training (Ozdogar 2020). One trial involved activity levels, well-being and vitality and had a more comprehensive approach (Thomas 2017).

Several virtual reality hardware systems and/or sensors were used. Eighteen studies (55%) used commercially available systems including the Nintendo Wii (Balance Board), Kinect, Xbox360 or Leap Motion Controller (Brichetto 2013; Cuesta-Gómez 2020; Jonsdottir 2018; Khalil 2018; Kramer 2014; Lozano-Quilis 2014; Molhemi 2021; Molhemi 2022; Nilsagård 2012; Norouzi 2021; Novotna 2019; Ortiz-Gutiérrez 2013; Ozdogar 2020; Ozdogar 2022; Robinson 2015; Thomas 2017; Tollár 2019; Yazgan 2019) combined with a television screen or tablet. Two studies used a gait exoskeleton (Lokomat and G-EO) with a screen (Calabrò 2017; Munari 2020), two studies used an upper limb robotic device (PABLO, HapticMaster) with a screen (Feys 2015; Tramontano 2020), one study the CAREN system (treadmill with motion capture system and projector) (Kalron 2016), two studies used the VR Rehabilitation System (VRRS) (Leonardi 2021; Pagliari 2021), and one study the BTS Nirvana system (two infrared sensors with a camera and projector) (Maggio 2022), devices that are available for rehabilitation centres to purchase. One study used the head-mounted display from Oculus (Ozkul 2020), and one study a tablet (Bove 2021). The remaining studies used a screen in combination with the Biodex Balance system (Eftekharsadat 2015), the StepMania mat (Hoang 2015), a joystick (Janssen 2015), two inertial sensors (Peruzzi 2017) and video capturing of the upper limb (Waliño-Paniagua 2019). With regard to the software used in the virtual reality interventions, only seven studies used customised environments/games (Bove 2021; Cuesta-Gómez 2020; Feys 2015; Munari 2020; Norouzi 2021; Ozkul 2020; Peruzzi 2017). The remaining studies used commercially available games that came with the hardware used (Brichetto 2013; Calabrò 2017; Eftekharsadat 2015; Hoang 2015; Janssen 2015; Jonsdottir 2018; Kalron 2016; Khalil 2018; Kramer 2014; Lozano-Quilis 2014; Maggio 2022; Molhemi 2021; Molhemi 2022; Nilsagård 2012; Novotna 2019; Ortiz-Gutiérrez 2013; Ozdogar 2020; Ozdogar 2022; Robinson 2015; Thomas 2017; Tollár 2019; Tramontano 2020; Waliño-Paniagua 2019; Yazgan 2019).

Almost 91% (30 studies) of the included studies used non-immersive virtual reality systems (e.g. TV screens). Two studies used semi-immersive virtual reality devices: the CAREN system (Kalron 2016) and the BTS Nirvana system (Maggio 2022). One study

used the full-immersive head-mounted display from Oculus (Ozkul 2020).

Comparison interventions

Fifteen studies compared the virtual reality intervention with conventional therapy (Brichetto 2013; Cuesta-Gómez 2020; Kalron 2016; Khalil 2018; Leonardi 2021; Lozano-Quilis 2014; Maggio 2022; Molhemi 2021; Molhemi 2022; Norouzi 2021; Ortiz-Gutiérrez 2013; Ozdogar 2022; Peruzzi 2017; Tramontano 2020). Three studies compared the virtual reality intervention with an alternative intervention that did not fit the description of conventional therapy for the rehabilitation of people with MS: a tablet-based placebo game (Bove 2021), robot-assisted gait training with the Lokomat (Calabrò 2017) and G-EO system (Munari 2020). Six studies investigated the effect of virtual reality when compared to no intervention (Eftekharsadat 2015; Hoang 2015; Janssen 2015; Nilsagård 2012; Novotna 2019; Thomas 2017) and two studies when used as an adjunct (Feys 2015; Waliño-Paniagua 2019), leading to an unequal amount of therapy between the intervention and control groups. One study compared two virtual reality interventions (Jonsdottir 2018). Six studies were multi-arm studies with three groups: three studies compared the virtual reality intervention with conventional therapy and no intervention (Ozdogar 2020; Robinson 2015; Tollár 2019), one study compared the virtual reality intervention with conventional therapy and an alternative intervention (Kramer 2014), one study compared the virtual reality intervention with an alternative intervention and no intervention (Ozkul 2020) and the last study compared two virtual reality interventions with no intervention (Yazgan 2019).

Dosage of the interventions

There was a wide variety of therapy dosages between studies. Only one study provided less than five hours of total therapy (Kramer 2014). Thirteen studies provided between 6 and 10 hours of therapy (Eftekharsadat 2015; Jonsdottir 2018; Kalron 2016; Lozano-Quilis 2014; Molhemi 2022; Munari 2020; Nilsagård 2012; Norouzi 2021; Novotna 2019; Ozdogar 2020; Robinson 2015; Tramontano 2020; Waliño-Paniagua 2019). Twelve studies provided between 11 and 20 hours of therapy (Bove 2021; Brichetto 2013; Cuesta-Gómez 2020; Feys 2015; Hoang 2015; Janssen 2015; Leonardi 2021; Molhemi 2021; Ortiz-Gutiérrez 2013; Ozkul 2020; Peruzzi 2017; Yazgan 2019). Four studies provided more than 20 hours of therapy (Calabrò 2017; Maggio 2022; Pagliari 2021; Tollár 2019).

Outcomes

Given the broad scope of this review, a wide range of outcome measures were used. Outcome measures for each of the predefined outcome categories are shown in Table 1. It was not possible to include all the outcome measures in the analyses due to heterogeneity (Table 2). Regarding the assessment points, one study collected data within seven days after the intervention (Hoang 2015) and one study within two weeks (Janssen 2015). The remaining studies measured the outcomes immediately after the intervention was finished. Eight studies included a follow-up assessment, ranging from one month to three months after the intervention (Bove 2021; Cuesta-Gómez 2020; Molhemi 2021; Molhemi 2022; Munari 2020; Norouzi 2021; Novotna 2019; Ozdogar 2022).

Excluded studies

We excluded 177 trials after screening of the full text. The reasons for exclusion are listed in the Characteristics of excluded studies table.

Risk of bias in included studies

We used version two of the Cochrane risk of bias tool (RoB 2), as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022). The completed RoB 2 tool with responses to all assessed signalling questions is available online at https://doi.org/10.5281/zenodo.7457264. Below, we briefly summarise the overall risk of bias per outcome. Risk of bias assessments for all domains and for studies used in the analyses are located in the risk of bias section beside each of the forest plots. More detailed information about the study characteristics is presented in the Characteristics of included studies table.

Risk of bias by outcome

The following section summarises the overall risk of bias per outcome category for all included studies.

Lower limb and gait function

Twenty-one studies reported lower limb and gait-related outcomes. We had some concerns regarding the risk of bias for five studies because no pre-specified analysis plan was available (Calabrò 2017; Eftekharsadat 2015; Molhemi 2021; Molhemi 2022; Tollár 2019). In the remaining 16 studies, we detected high risk of bias because multiple domains raised some concerns (Hoang 2015; Khalil 2018; Kramer 2014; Lozano-Quilis 2014; Maggio 2022; Munari 2020; Nilsagård 2012; Novotna 2019; Ozdogar 2020; Ozdogar 2022; Ozkul 2020; Pagliari 2021; Peruzzi 2017; Robinson 2015; Thomas 2017; Yazgan 2019).

Balance and postural control

Twenty-two studies reported balance and postural control-related outcomes. We assessed five studies as having 'some concerns' about risk of bias because no pre-specified analysis plan was available (Brichetto 2013; Calabrò 2017; Eftekharsadat 2015; Molhemi 2021; Tollár 2019). In the remaining 17 studies, we detected high risk of bias because multiple domains raised some concerns (Hoang 2015; Kalron 2016; Khalil 2018; Kramer 2014; Lozano-Quilis 2014; Maggio 2022; Munari 2020; Nilsagård 2012; Novotna 2019; Ortiz-Gutiérrez 2013; Ozdogar 2020; Ozkul 2020; Pagliari 2021; Peruzzi 2017; Robinson 2015; Thomas 2017; Yazgan 2019).

Upper limb function

Upper limb function was assessed in 12 studies. Two studies raised some concerns about risk of bias because no pre-specified analysis plan was available (Eftekharsadat 2015; Norouzi 2021). The remaining 10 studies had some concerns in multiple domains, and we rated them as high risk of bias (Cuesta-Gómez 2020; Feys 2015; Hoang 2015; Jonsdottir 2018; Ozdogar 2020; Ozdogar 2022; Pagliari 2021; Thomas 2017; Tramontano 2020; Waliño-Paniagua 2019).

Cognition

Seventeen studies assessed cognition. Four studies raised some concerns about risk of bias because no pre-specified analysis plan was available (Bove 2021; Calabrò 2017; Molhemi 2021; Molhemi

2022). In the remaining 13 studies, we detected high risk of bias because multiple domains raised some concerns (Hoang 2015; Janssen 2015; Kramer 2014; Leonardi 2021; Maggio 2022; Munari 2020; Nilsagård 2012; Novotna 2019; Ozdogar 2020; Ozdogar 2022; Ozkul 2020; Pagliari 2021; Peruzzi 2017).

Global motor function

Five studies assessed global motor function. Two studies raised some concerns about risk of bias because no pre-specified analysis plan was available (Calabrò 2017; Eftekharsadat 2015). We detected high risk of bias in the remaining three studies, because multiple domains raised some concerns (Hoang 2015; Peruzzi 2017; Tramontano 2020).

Activity limitations

One of the three studies that assessed activity limitations raised some concerns because no pre-specified analysis plan was available (Calabrò 2017). We assessed the remaining two studies as having high risk of bias due to deviations from intended interventions and having no pre-specified analysis plan available (Thomas 2017; Tramontano 2020).

Participation and quality of life

Twenty-two studies reported participation and quality of life-related outcomes. Five studies raised some concerns about risk of bias because no pre-specified analysis plan was available (Bove 2021; Calabrò 2017; Eftekharsadat 2015; Molhemi 2021; Tollár 2019), while the remaining 17 studies had a high risk of bias due to multiple domains that raised some concerns (Cuesta-Gómez 2020; Hoang 2015; Jonsdottir 2018; Kalron 2016; Khalil 2018; Leonardi 2021; Maggio 2022; Munari 2020; Nilsagård 2012; Novotna 2019; Ozdogar 2020; Ozdogar 2022; Pagliari 2021; Robinson 2015; Thomas 2017; Tramontano 2020; Yazgan 2019).

Fatigue

Fatigue was assessed in 11 studies. Two studies raised some concerns about risk of bias because no pre-specified analysis plan was available (Bove 2021; Brichetto 2013). We detected high risk of bias in the remaining nine studies because multiple domains raised some concerns (Cuesta-Gómez 2020; Khalil 2018; Ozdogar 2020; Ozdogar 2022; Ozkul 2020; Pagliari 2021; Thomas 2017; Tramontano 2020; Yazgan 2019).

Adverse events

The study Thomas 2017 was the only study that reported adverse events. The study had a high risk of bias due to deviations from intended interventions and having no pre-specified analysis plan available.

Effects of interventions

See: **Summary of findings 1** Summary of findings table - Virtual reality versus no intervention for adults with multiple sclerosis; **Summary of findings 2** Summary of findings table - Virtual reality versus conventional therapy for adults with multiple sclerosis

See Summary of findings 1 and Summary of findings 2 for the main comparisons. For comparisons that were planned in the protocol, but for which data from at least two studies were not available (activity limitation, adverse events and global motor function), we did not perform meta-analysis, and they are therefore not included in this section. See Table 2 for the outcomes that were not included in the meta-analysis, with details and results from the RCTs. For two studies we obtained unpublished data to include in the meta-analysis (Feys 2015; Jonsdottir 2018). We did not undertake subgroup analyses because of the small number of studies included in all the analysed comparisons (always fewer than 10) (Deeks 2022).

Virtual reality versus no intervention

Primary outcomes

Lower limb and gait function

Results are presented for the Timed Up and Go, MS Walking Scale-12, walking endurance and walking speed. All outcomes were taken within days of the end of the intervention programme.

Comparison 1.1: Timed Up and Go

Six studies (with 264 participants) used the Timed Up and Go test and were pooled for meta-analysis (Eftekharsadat 2015; Hoang 2015; Nilsagård 2012; Novotna 2019; Thomas 2017; Yazgan 2019). Pooled data showed no effect of virtual reality on the Timed Up and Go (mean difference (MD) -0.43, 95% confidence interval (CI) -0.85 to -0.00; 6 studies, 264 participants; low-certainty evidence) (Analysis 1.1). Statistical heterogeneity was substantial (I^2 = 60%). We were unable to obtain data in a suitable format for pooling for one study (Ozkul 2020). The study reported an improvement in the Timed Up and Go for the virtual reality intervention group.

Sensitivity analyses for comparison 1.1

Excluding those studies judged to be at high risk of bias left only one study (Eftekharsadat 2015). The study also reported no effect of virtual reality on the Timed Up and Go test (MD 0.46, 95% CI -0.20 to 1.12; 1 study, 30 participants). We conducted a sensitivity analysis using a random-effects model. The difference was minor (MD -0.56, 95% CI -1.38 to 0.26; 6 studies, 264 participants).

Comparison 1.2: MS Walking Scale-12

Four studies (with 194 participants) used the MS Walking Scale-12 and were pooled for meta-analysis (Nilsagård 2012; Novotna 2019; Ozdogar 2020; Robinson 2015). Virtual reality had no effect on the MS Walking Scale-12 (MD -1.16, 95% CI -4.04 to 1.72; 4 studies, 194 participants) (Analysis 1.2). There was no statistical heterogeneity (I^2 = 0%).

Comparison 1.3: Walking endurance

Four studies presented results for walking endurance in a form suitable for inclusion in the meta-analysis (141 participants) (Hoang 2015; Thomas 2017; Tollár 2019; Yazgan 2019). Pooled data showed no effect of virtual reality on walking endurance (standardised mean difference (SMD) 0.34, 95% CI -0.00 to 0.68; 4 studies, 141 participants) (Analysis 1.3). Statistical heterogeneity was moderate (I^2 = 54%).

Sensitivity analyses for comparison 1.3

Excluding those studies judged to be at high risk of bias left only one study (Tollár 2019). The result showed an effect of virtual reality on walking endurance (SMD 0.97, 95% CI 0.15 to 1.80; 1 study, 26 participants). We conducted a sensitivity analysis using a random-

effects model. The difference was minor (SMD 0.38, 95% CI -0.13 to 0.89; 4 studies, 141 participants).

Comparison 1.4: Gait speed

Five studies presented results for gait speed in a form suitable for inclusion in the meta-analysis (238 participants) (Hoang 2015; Nilsagård 2012; Novotna 2019; Ozdogar 2020; Robinson 2015). The result showed an effect of virtual reality on gait speed (SMD 0.39, 95% CI 0.13 to 0.65; 5 studies, 238 participants) (Analysis 1.4). Statistical heterogeneity was considerable (I^2 = 79%).

Sensitivity analyses for comparison 1.4

We conducted a sensitivity analysis using a random-effects model. The result was a higher SMD than found in the original analysis (SMD 0.48, 95% CI -0.11 to 1.08; 5 studies, 238 participants).

Balance and postural control

Results are presented for the Berg Balance Scale. All outcomes were taken within days of the end of the intervention programme.

Comparison 2.1: Berg Balance Scale

Four studies (with 137 participants) used the Berg Balance Scale and were pooled for meta-analysis (Eftekharsadat 2015; Novotna 2019; Tollár 2019; Yazgan 2019). Overall, there was no effect of virtual reality on the Berg Balance Scale (MD 0.29, 95% CI -0.10 to 0.68; 4 studies, 137 participants; very low-certainty evidence) (Analysis 2.1). Statistical heterogeneity was considerable (I^2 = 92%). We were unable to obtain data in a suitable format for pooling for one study (Ozkul 2020). The study reported no effect of virtual reality on the Berg Balance Scale.

Sensitivity analyses for comparison 2.1

Excluding those studies judged to be at high risk of bias left two studies (Eftekharsadat 2015; Tollár 2019). The result also showed no effect of virtual reality on the Berg Balance Scale (MD 0.13, 95% CI -0.28 to 0.53; 2 studies, 56 participants). We conducted a sensitivity analysis using a random-effects model. The result was a higher MD than found in the original analysis (MD 2.74, 95% CI -0.55 to 6.02; 4 studies, 137 participants).

Secondary outcomes

Upper limb function

Comparison 3.1: 9-Hole Peg Test

Two studies (with 84 participants) used the 9-Hole Peg Test and were pooled for meta-analysis (Hoang 2015; Ozdogar 2020). Virtual reality had an effect on the 9-Hole Peg Test (MD -4.19, 95% CI -5.86 to -2.52; 2 studies, 84 participants; low-certainty evidence) (Analysis 3.1). There was no statistical heterogeneity (I^2 = 0%). We were unable to obtain data in a suitable format for pooling for one study (Thomas 2017). The study reported no effect of virtual reality on the 9-Hole Peg Test.

Cognition

Comparison 4.1: Timed Up and Go dual task

Three studies (with 163 participants) used the Timed Up and Go with a dual task and were pooled for meta-analysis (Hoang 2015; Nilsagård 2012; Novotna 2019). Virtual reality had no effect on the Timed Up and Go with dual task (MD -0.87, 95% CI -2.23 to 0.48; 3 studies, 163 participants) (Analysis 4.1). There was no statistical heterogeneity (I^2 = 0%). We were unable to obtain data in a suitable format for pooling for one study (Ozkul 2020). The study reported an effect of virtual reality on the Timed Up and Go dual task.

Comparison 4.2: Symbol Digit Modalities Test

Three studies (with 112 participants) used the Symbol Digit Modalities Test and were pooled for meta-analysis (Hoang 2015; Janssen 2015; Ozdogar 2020). Virtual reality had an effect on the Symbol Digit Modalities Test (MD 6.70, 95% CI 3.22 to 10.18; 3 studies, 112 participants) (Analysis 4.2). Statistical heterogeneity was found not to be important (I^2 = 47%).

Participation and quality of life

Comparison 5.1: Activities-specific Balance Confidence (ABC) scale

Three studies (with 159 participants) used the ABC scale and were pooled for meta-analysis (Nilsagård 2012; Novotna 2019; Ozdogar 2020). Virtual reality had no effect on the ABC scale (MD 1.13, 95% CI -3.54 to 5.81; 3 studies, 159 participants) (Analysis 5.1). There was no statistical heterogeneity (I^2 = 0%).

Comparison 5.2: Beck Depression Inventory

Two studies (with 66 participants) used the Beck Depression Inventory and were pooled for meta-analysis (Ozdogar 2020; Tollár 2019). There was no effect of virtual reality on the Beck Depression Inventory (MD -0.63, 95% CI -2.51 to 1.24; 2 studies, 66 participants) (Analysis 5.2). Statistical heterogeneity was moderate (I^2 = 55%).

Sensitivity analyses for comparison 5.2

Excluding those studies judged to be at high risk of bias left only one study (Tollár 2019). The result also showed no effect of virtual reality (MD 0.20, 95% CI -1.97 to 2.37; 1 study, 26 participants). We conducted a sensitivity analysis using a random-effects model. The result was a higher MD than found in the original analysis (MD -1.06, 95% CI -4.17 to 2.04; 2 studies, 66 participants).

Comparison 5.3: MS International Quality of Life Questionnaire

Two studies (with 82 participants) used the MS International QoL questionnaire and were pooled for meta-analysis (Ozdogar 2020; Yazgan 2019). Virtual reality had an effect on the MS International QoL questionnaire (MD 9.24, 95% CI 5.76 to 12.73; 2 studies, 82 participants; very low-certainty evidence) (Analysis 5.3). There was no statistical heterogeneity (I^2 = 0%).

Primary outcomes

Lower limb and gait function

Results are presented for the Timed Up and Go, MS Walking Scale-12, walking endurance and gait speed. All outcomes were taken within days of the end of the intervention programme.

Comparison 6.1: Timed Up and Go

Four studies (with 107 participants) used the Timed Up and Go test and were pooled for meta-analysis (Khalil 2018; Lozano-Quilis 2014; Molhemi 2021; Peruzzi 2017). Overall, pooled data showed no difference in Timed Up and Go between participants receiving

virtual reality interventions versus conventional therapy (MD -0.20, 95% CI -1.65 to 1.25; 4 studies, 107 participants; moderate-certainty evidence) (Analysis 6.1). There was no statistical heterogeneity (I^2 = 0%). We were unable to obtain data in a suitable format for pooling for one study (Maggio 2022). The study reported a difference between groups in favour of virtual reality.

Comparison 6.2: MS Walking Scale-12

Four studies (with 138 participants) used the MS Walking Scale-12 and were pooled for meta-analysis (Molhemi 2021; Ozdogar 2020; Ozdogar 2022; Robinson 2015). Pooled data showed no difference in the MS Walking Scale-12 between participants receiving virtual reality interventions versus conventional therapy (MD 1.01, 95% CI -2.00 to 4.02; 4 studies, 138 participants) (Analysis 6.2). There was no statistical heterogeneity (I^2 = 0%). We were unable to obtain data in a suitable format for pooling for one study (Pagliari 2021). The study reported no differences between groups for the MS Walking Scale-12.

Comparison 9.3: Walking endurance

Four studies presented results for walking endurance in a form suitable for inclusion in the meta-analysis (111 participants) (Khalil 2018; Ozdogar 2022; Peruzzi 2017; Tollár 2019). When we pooled the data, there was no difference in walking endurance between participants receiving virtual reality interventions versus conventional therapy (SMD 0.10, 95% CI -0.28 to 0.48; 4 studies, 111 participants) (Analysis 6.3). Statistical heterogeneity was found not to be important (I^2 = 35%).

Comparison 6.4: Gait speed

Eight studies presented results for gait speed in a form suitable for inclusion in the meta-analysis (247 participants) (Khalil 2018; Kramer 2014; Lozano-Quilis 2014; Molhemi 2021; Ozdogar 2020; Ozdogar 2022; Peruzzi 2017; Robinson 2015). Pooled results showed no difference in gait speed between participants receiving virtual reality interventions versus conventional therapy (SMD 0.03, 95% CI -0.22 to 0.29; 8 studies, 247 participants) (Analysis 6.4). Statistical heterogeneity was substantial (I^2 = 61%).

Sensitivity analyses for comparison 6.4

Excluding those studies judged to be at high risk of bias left only one study (Molhemi 2021). The result showed a difference between groups in favour of the conventional therapy (SMD -0.76, 95% CI -1.42 to -0.11; 1 study, 39 participants). We conducted a sensitivity analysis using a random-effects model. The difference was minor (SMD 0.03, 95% CI -0.39 to 0.45; 8 studies, 247 participants).

Balance and postural control

Results are presented for the Berg Balance Scale, Tinetti test and Four Square Step Test. All outcomes were taken within days of the end of the intervention programme.

Comparison 7.1: Berg Balance Scale

Seven studies (with 201 participants) used the Berg Balance Scale and were pooled for meta-analysis (Brichetto 2013; Kalron 2016; Khalil 2018; Lozano-Quilis 2014; Molhemi 2021; Peruzzi 2017; Tollár 2019). Pooled data showed a difference in the Berg Balance Scale between participants receiving virtual reality interventions versus conventional therapy in favour of virtual reality (MD 2.39, 95% CI 1.22 to 3.57; 7 studies, 201 participants; moderate-certainty evidence) (Analysis 7.1). There was no statistical heterogeneity (I^2 = 0%). We were unable to obtain data in a suitable format for pooling for one study (Ortiz-Gutiérrez 2013). The study reported a difference between groups in favour of virtual reality.

Comparison 7.2: Tinetti Test

Two studies (with 39 participants) used the Tinetti Test and were pooled for meta-analysis (Lozano-Quilis 2014; Tollár 2019). Pooled results showed no difference in the Tinetti Test between participants receiving virtual reality interventions versus conventional therapy (MD 0.98, 95% CI -0.50 to 2.47; 2 studies, 39 participants) (Analysis 7.2). There was no statistical heterogeneity (I^2 = 0%). We were unable to obtain data in a suitable format for pooling for one study (Ortiz-Gutiérrez 2013). The study reported a difference between groups in favour of virtual reality.

Comparison 7.3: Four Square Step Test

Two studies (with 55 participants) used the Four Square Step Test and were pooled for meta-analysis (Lozano-Quilis 2014; Tollár 2019). When we pooled the data, there was no difference in the Four Square Step Test between participants receiving virtual reality interventions versus conventional therapy (MD -0.60, 95% CI -3.21 to 2.01; 2 studies, 55 participants) (Analysis 7.3). There was no statistical heterogeneity (I^2 = 0%).

Secondary outcomes

Upper limb function

Comparison 8.1: 9-Hole Peg Test

Three studies (with 93 participants) used the 9-Hole Peg Test and were pooled for meta-analysis (Ozdogar 2020; Ozdogar 2022; Tramontano 2020). Pooled data showed no difference in the 9-Hole Peg Test between participants receiving virtual reality interventions versus conventional therapy (MD 0.10, 95% CI -1.70 to 1.89; 3 studies, 93 participants; low-certainty evidence) (Analysis 8.1). There was no statistical heterogeneity (I^2 = 0%). We were unable to obtain data in a suitable format for pooling for two studies (Cuesta-Gómez 2020; Pagliari 2021). The study Cuesta-Gómez 2020 reported no differences between groups, while the study Pagliari 2021 reported a difference in the 9-Hole Peg Test between groups in favour of virtual reality.

Participation and quality of life

Comparison 9.1: Activities-specific Balance Confidence (ABC) scale

Two studies (with 76 participants) used the ABC scale and were pooled for meta-analysis (Molhemi 2021; Ozdogar 2020). Pooled data showed no difference in the ABC scale between participants receiving virtual reality interventions versus conventional therapy (MD -1.97, 95% CI -10.05 to 6.10; 2 studies, 76 participants) (Analysis 9.1). Statistical heterogeneity was found not to be important (I^2 = 34%).

Comparison 9.2: Beck Depression Inventory

Two studies (with 65 participants) used the Beck Depression Inventory and were pooled for meta-analysis (Ozdogar 2020; Tollár 2019). Results showed no difference in the Beck

Depression Inventory between participants receiving virtual reality interventions versus conventional therapy (MD -0.57, 95% CI -2.13 to 1.00; 2 studies, 65 participants) (Analysis 9.2). There was no statistical heterogeneity (I^2 = 0%). We were unable to obtain data in a suitable format for pooling for one study (Maggio 2022). The study also reported no differences between groups.

Comparison 9.3: Falls Efficacy Scale-1

Three studies (with 101 participants) used the Falls Efficacy Scale-1 and were pooled for meta-analysis (Kalron 2016; Khalil 2018; Molhemi 2021). Overall, pooled data showed a difference in the Falls Efficacy Scale-1 between participants receiving virtual reality interventions versus conventional therapy in favour of virtual reality (MD -3.07, 95% CI -5.99 to -0.15; 3 studies, 101 participants; low-certainty evidence) (Analysis 9.3). There was no statistical heterogeneity (I^2 = 0%).

Fatigue

Comparison 10.1: fatigue

Five studies presented results for fatigue in a form suitable for inclusion in the meta-analysis (161 participants) (Brichetto 2013; Khalil 2018; Ozdogar 2020; Ozdogar 2022; Tramontano 2020). Pooled data showed a difference in fatigue between participants receiving virtual reality interventions versus conventional therapy in favour of virtual reality (SMD -0.40, 95% CI -0.72 to -0.09; 5 studies, 161 participants) (Analysis 10.1). Statistical heterogeneity was moderate (I^2 = 48%). We were unable to obtain data in a suitable format for pooling for two studies (Cuesta-Gómez 2020; Pagliari 2021). Both studies reported no differences between groups.

Virtual reality versus alternative intervention

Secondary outcomes

Cognition

Comparison 11.1: Paced Auditory Serial Addition Test (PASAT)

Two studies (with 52 participants) used the PASAT and were pooled for meta-analysis (Bove 2021; Munari 2020). There was no effect of virtual reality on the PASAT (MD 0.41, 95% CI -3.50 to 4.32; 2 studies, 52 participants) (Analysis 11.1). There was no statistical heterogeneity (I^2 = 0%).

DISCUSSION

Summary of main results

This review included 33 studies with 1294 participants in total. All studies were published in the last 10 years, illustrating how the use of virtual reality in rehabilitation has been emerging in recent years. The main results are presented in Summary of findings 1 and Summary of findings 2.

Virtual reality versus no intervention

Ten studies compared the effects of virtual reality interventions with no intervention on our primary outcomes 'lower limb and gait function' and 'balance and postural control'. A variety of virtual reality interventions were used, but the majority used non-immersive, commercially available gaming consoles. Only one study used a fully immersive head-mounted display. For the outcome measures Timed Up and Go (six studies) and Berg Balance Scale (four studies), no differences were found between the virtual reality intervention and no intervention.

For some secondary outcome measures of the category 'upper limb function' and 'participation and quality of life', results could also be pooled. We found an effect in favour of the virtual reality intervention for the outcome 'upper limb function', as measured by the 9-Hole Peg Test (two studies) and for the outcome 'participation and quality of life' when measured by the MS International QoL questionnaire (two studies).

Virtual reality versus conventional therapy

Twelve studies compared the effect of virtual reality interventions with conventional therapy on 'lower limb and gait function'. Again, the majority of the included studies used non-immersive, commercially available gaming consoles. Only one study used a semi-immersive virtual reality system. Results showed no superiority of virtual reality interventions over conventional therapy for 'lower limb and gait function' when measured by the Timed Up and Go test.

Thirteen studies compared the effect of virtual reality interventions with conventional therapy on 'balance and postural control'. Two studies used semi-immersive virtual reality devices, while the remaining 11 studies used non-immersive systems, of which the majority were commercially available gaming consoles. Results showed that virtual reality was more effective than conventional therapy when measured by the Berg Balance Scale (seven studies).

For some secondary outcome measures of the category 'upper limb function' and 'participation and quality of life', results could also be pooled. Virtual reality interventions were found to be more effective than conventional therapy for improving the Falls Efficacy Scale-1 (three studies). No differences were found for 'upper limb function' when measured by the 9-Hole Peg Test (three studies),

Overall completeness and applicability of evidence

Our findings must be interpreted with caution. This review identified 33 RCTs with relatively small sample sizes (between 6 and 42 participants). There was a considerable amount of heterogeneity between the included studies, especially with regard to the variety of outcome measures used, which limited our ability to pool results. As a consequence, the majority of our meta-analyses are based on a limited number of studies. Hence, additional research including studies with larger sample sizes is needed to provide a more firm body of evidence.

It was not possible to perform subgroup analyses regarding characteristics of the participant or the intervention, due to bad reporting or lack of studies. Mainly mild to moderately disabled people with MS were included in these studies (EDSS score < 6), thereby raising questions about how applicable virtual reality interventions could be for more severely disabled people with MS. Furthermore, the mean age of included participants was relatively low (45 years). Therefore, information about the applicability and acceptability of this technology in an older population is still missing. Since the majority of the included studies used non-immersive virtual reality systems, it was not possible to investigate the effect of the level of immersion. Given the upcoming use of more immersive virtual reality devices, such as head-mounted displays, it might be possible to provide more information about the effect of the level of immersion in the future.

Quality of the evidence

All 33 studies included in this review had small sample sizes, and studies with larger sample sizes are needed to confirm our findings. Using the GRADE approach, we assessed the certainty of the evidence and found moderate to low or very low-certainty evidence across the outcomes of interest. This means that there is a high degree of uncertainty about the observed effects. As the number of studies included in the analyses was below four, we did not undertake a formal assessment of reporting bias using a funnel plot.

We noticed that the risk of bias was judged to be similar across outcomes. Most frequently, we assessed the overall risk of bias as 'high risk'. None of the included studies had an overall low risk of bias. The overall high risk of bias was often caused by an unclear randomisation process, lack of intention-to-treat analysis and the unavailability of a pre-registered analysis plan.

Potential biases in the review process

Despite having carried out an extensive literature search, we acknowledge the possibility that we did not identify all relevant studies. Selection bias was minimised by conducting a comprehensive search using a wide range of databases. Cochrane Multiple Sclerosis and Rare Diseases of the Central Nervous System assisted us in ensuring a robust search strategy. We checked the references of relevant systematic reviews to see if any studies were missed. To minimise the potential bias associated with the collection, selection and extraction of study data, two review authors independently performed these steps. We also independently entered data into the Excel sheet with a double entry process, to minimise errors related to data entry.

Agreements and disagreements with other studies or reviews

Several systematic reviews regarding virtual reality and people with MS have recently been published. To the best of our knowledge, in total seven systematic reviews, published in peer-reviewed journals, have addressed the effectiveness of virtual reality technologies for rehabilitation in people with MS (Calafiore 2021; Casuso-Holgado 2018; Cortés-Pérez 2021; Maggio 2019; Massetti 2016; Nascimento 2021; Webster 2021). Some reviews specifically focused on one outcome domain: balance and gait (Calafiore 2021; Casuso-Holgado 2018), and upper limb function (Webster 2021). In contrast, other studies performed a more comprehensive review with multiple outcome domains: cognition and motor function (Maggio 2019; Massetti 2016), fatigue, MS impact and quality of life (Cortés-Pérez 2021), and functional mobility, quality of life, fatigue and balance (Nascimento 2021). In general, our review agrees with the results of the previous reviews. The various reviews reported that virtual reality can be considered to be as effective as conventional therapy, and more effective than no intervention, for several motor and cognitive functions. Positive effects of the use of virtual reality were mainly found for upper limb function, balance and gait, fatigue and quality of life. For these outcome measures, our review also found effects. However, the reviews also agree that additional research is necessary to obtain more robust evidence, and to find out which virtual reality approaches are most effective, for example in terms of virtual reality devices, optimal duration and intensity, and characteristics of the virtual reality environment.

The results of our review are also in line with the results of two other Cochrane reviews on the effects of virtual reality for the rehabilitation of people post-stroke (Laver 2017) and people with Parkinson's disease (Dockx 2016). These authors also concluded that virtual reality interventions could be at least as effective as conventional therapy, but the evidence is of low quality and more research is needed.

AUTHORS' CONCLUSIONS

Implications for practice

In general, we found that when compared to no intervention, virtual reality training led to improvements in the level of upper limb function, and participation and quality of life. Moreover, when virtual reality training was compared to conventional therapy, we found that virtual reality training was superior in improving balance and postural control, and participation and quality of life. The clinical relevance of these findings remains to be established for most outcome measures. For balance function (virtual reality training compared to conventional training) and upper limb function (virtual reality training compared to no intervention), the lower limit of the minimal clinically important difference was almost reached (2.39 versus 3 points on the Berg Balance Scale and 4.19 versus 4.38 seconds for the 9 Hole Peg Test, respectively) (Gervasoni 2017; Hervault 2017). At the moment, there is no evidence that virtual reality interventions are inferior in terms of clinical yields compared to conventional therapy.

When using virtual reality, there is a big difference in experience between non-immersive, semi-immersive and full-immersive virtual reality systems. Nevertheless, the added value of an increased level of immersion is not clear due to the limited body of research using more immersive virtual reality devices such as head-mounted displays. Almost all included studies used a television screen or a small projection screen.

Overall, MS patients included in the studies in this review had limited disability (EDSS score below 6). Hence, it is not clear whether the conclusions are extendable to patients with higher levels of disability (EDSS above 6). Importantly, in this review, the mean age of the study population was around 45 years old. It is possible that in elderly MS populations, the use of rehabilitation technology, including virtual reality, is more challenging. Symptoms related to the disease, but also co-morbidities, can affect the rehabilitation process and strategy, e.g. vision and cognitive problems.

None of the other studies included in this review mentioned any serious adverse events such as motion sickness, headache or nausea. This could indicate that the therapy is well tolerated by the patients. Based on this information and the results of this review, we can conclude that if therapists have virtual reality devices available, these systems can be considered effective and safe devices during the rehabilitation of physical and cognitive symptoms in people with MS. The use of virtual reality can also be a relevant tool to increase motivation of patients during the training and can positively influence therapy adherence (Howard 2017). However, healthcare professionals should always keep in mind their therapeutic goal, the possibilities and the preference of the patient.

Implications for research

Despite promising results of several studies included in this review, clear evidence regarding the effect of virtual reality training in multiple sclerosis is still missing. Overall, methodological quality is limited, and sample sizes are small. Studies should also consider including people with MS of increased age and with higher levels of disability.

Virtual reality applications, like many other technological applications within rehabilitation, are costly and therefore not available to everyone worldwide. For example, low-income countries have less access to these technologies and the studies included in this review are from mid- and high-income countries. It will be important to conduct future research in these low-income countries to evaluate the global application of virtual reality.

More standardisation in outcome measures, duration and frequency of training, and follow-up periods should improve the evidence. Outcome measures should be clearly defined and should be on the level of functioning, participation and quality of life, including physical and cognitive outcomes.

Almost all studies used non-immersive types of virtual reality and the virtual environments were diverse (e.g. type and quality of the design, the implementation of a game element or not, difficulty of the exercises and first or third person view). Due to the enormous increase in the use and implementation of virtual reality in practice and research in recent years, in the next update of this Cochrane review, we hope to be able to perform sub-analyses related to the type of virtual reality device and environment.

The data from this study are of clinical importance, but also relevant to guide future development and design of virtual reality protocols and applications.

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The following people conducted the editorial process for this article:

- Sign-off Editor (final editorial decision): Robert Boyle, Imperial College London;
- Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Samuel Hinsley, Cochrane Central Editorial Service;
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- Peer reviewers (provided comments and recommended an editorial decision): Sinéad M. Hynes, University of Galway, Ireland (clinical/content review); Brian Duncan (consumer review); Jennifer Hilgart, Cochrane (methods review); Steve McDonald, Cochrane Australia (search review); Patricia Sánchez-Herrera Baeza, Occupational Therapist, King Juan Carlos University, Madrid, Spain (clinical/content review).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bove 2021

Study characteristics	
Methods	Study design: RCT (2 groups)

Bove 2021 *(Continued)*

Participants	Inclusion criteria: adults with written SDMT z-scores between -2 and 1, who had WiFi at home, and a visual acuity of 20/50 OU or better Exclusion criteria: moderate to severe depression based on self- or clinician-report and clinical relapse within prior 30 days Sample size: VR group: 23 Control group: 21 Number of dropouts: VR group: 3 Control group: 1 Age, mean years (SD): VR group: 52.9 (14.0) Control group: 49.2 (10.9) Sex (F/M): VR group: 17/6 Control group: 18/3 Type of MS: VR group: 19 RR, 3 SP, 1 PP Control group: 14 RR, 4 SP, 1 PP, 1 CIS, 1 undetermined Years since MS diagnosis, mean years (SD): VR group: 11.2 (7.9) Control group: 16.1 (7.8) Disease severity, EDSS score, median (IQR): VR group: 3.0 (2.5 to 4.5) Control group: 3.5 (2.5 to 4.0)
Interventions	VR group (AKL-T03 group): in-home, tablet-based, videogame-like digital treatment. AKL-T03 is an investigational digital therapeutic that uses a proprietary algorithm designed to improve attention and related cognitive control processes, by training interference management at an adaptive and personalised high degree of difficulty. Interference is instantiated through a video game-like interface displaying two tasks that are to be done in parallel (multitasking): a perceptual discrimination targeting task in which users respond to the instructed stimulus targets and ignore the stimulus distractors (similar to a Go–No-Go task) and a sensory motor navigation task in which users continuously adjust their location to interact with or avoid positional targets. Dose: 30 sessions (5 sessions of 25 min per week for 6 weeks) Control group (AKL-T09 group): active tablet-based placebo control. AKL-T09 is a game in which the aim is to connect letters on a grid to spell as many words as possible. The active placebo control was used to provide similar time on task and engagement. Dose: 30 sessions (5 sessions of 25 min per week for 6 weeks)

Bove 2021 *(Continued)*

Outcomes	Primary outcome: SDMT score Secondary outcomes: Cognition: PASAT, BVMT-R, CVLT-II Patient-reported outcomes: PDQ-5, CESD, STAI-S, STAI-T, MFIS Assessment points: baseline, post-intervention (6 weeks), follow-up (8 weeks)
Level of immersion	Non-immersive
Notes	Funding source: supported by an unrestricted grant from Akili Interactive. Akili Interactive provided AKL-T03 and AKL-T09 without charge for the study. Declaration of interest:R.B. has received research support from the National Multiple Sclerosis Society, the Hilton Foundation, the California Initiative to Advance Precision Medicine, the Sherak Foundation, and Akili Interactive. R.B. has also received personal compensation for consulting from Alexion, Biogen, EMD Serono, Novartis, Pear Therapeutics, Roche Genentech, and SanofiGenzyme. D.L. has participated in speaker bureau for Bayer, Merck, Almirall, Execemed, TEVA, Roche, Novartis, Biogen, and Sanofi; has had consultancy from Novartis, Bayer, Merck, Biogen, TEVA, and Sanofi; has had research grants from Bayer, Merck, Novartis, and Biogen. R.H. has received research support from Roche, Genentech, and MedDay and personal compensation for consulting from Roche, Novartis, and Sanofi. A.G. is cofounder, shareholder, BOD member, and advisor for Akili Interactive Labs, a company that manufactures investigational digital treatments delivered through a video game–like interface. A.G. has a patent for a game-based cognitive intervention on which the tool (AKL-T03) that was used in this study was based. A.F. reports research support from the MS Society of Canada and the Progressive MS Alliance; speaker's honoraria from Sanofi-Genzyme, Merck-Serono, Novartis, Biogen, and Teva; and consultancy from Akili Interactive

Brichetto 2013

Study characteristics	
Methods	Study design: RCT (2 groups)
Participants	Inclusion criteria: MS defined following McDonald criteria, fear of falling or a history of falls (defined by at least one fall within the last year), participants who were in a stable phase of the disease (without relapses or worsening in the last 3 months), able to walk with at the maximum an aid such as a cane or single crutch, an Expanded Disability Status Scale (EDSS) ≤ 6 and an Ambulation Index (AI) ≤ 4 Exclusion criteria: psychiatric disorders, blurred vision, or severe cognitive impairment Sample size: VR group: 18 Control group: 18 Number of dropouts: 0 Age, mean years (SD): VR group: 40.7 (11.5) Control group: 43.2 (10.6) Sex (F/M):

Brichetto 2013 *(Continued)*

	VR group: 10/8 Control group: 12/6 Years since MS diagnosis, mean years (SD): VR group: 11.2 (6.4) Control group: 12.3 (7.2) Disease severity, EDSS score, mean (SD): VR group: 3.9 (1.6) Control group: 4.3 (1.6)
Interventions	VR group: 1 hour of supervised Nintendo® Wii® Balance Board® sessions, with the following games: soccer heading, slalom skiing, table tilt, snowboarding, tightrope walking and zazen, which were randomly presented to the participant at each training session. Dose: 12 sessions (3 sessions of 60 min per week for 4 weeks) Control group: training consisting of static and dynamic exercises in both a single-leg and double-leg stance, with or without an equilibrium board and half kneeling exercises of increasing difficulty, tailored to the ability level of each participant. Dose: 12 sessions (3 sessions of 60 min per week for 4 weeks)
Outcomes	Primary outcome: BBS Secondary outcomes: MFIS, open-eye and closed-eye stabilometry (sway area) Assessment point: baseline, post-intervention (4 weeks)
Level of immersion	Non-immersive
Notes	Funding source: none Declaration of interest: none

Calabrò 2017

Study characteristics	
Methods	Study design: RCT (2 groups)
Participants	Inclusion criteria: age 18 to 65 years; moderate to severe walking disability with Expanded Disability Status Score between 4.0 and 5.5 (pyramidal sub-item ≥ 3); Montreal Cognitive Assessment score ≥ 24; absence of concomitant neurological or orthopaedic conditions that may interfere with ambulation; stable pharmacological therapy for at least 6 months Exclusion criteria: MS relapse during the 3 months prior to recruitment; presence of paroxysmal vertigo; lower limb botulinum toxin injections within the previous 12 weeks; cardiorespiratory instability; high risk of spontaneous fracture (assessed by computerised bone mineralometry score); lower-limb skin lesions and phlebitis/thrombosis; > 130 kg body weight; visual acuity and visual perception impairment Sample size: RAGT + VR group: 20

Calabrò 2017 *(Continued)*

	RAGT – VR group: 20 Number of dropouts: 0 Age, median years (range): RAGT + VR group: 44 (40 to 48) RAGT – VR group: 41 (38 to 47) Sex (F/M): RAGT + VR group: 13/7 RAGT – VR group: 12/8 Years since MS diagnosis, median years (range): RAGT + VR group: 11.5 (8 to 16) RAGT – VR group: 11.5 (8 to 14) Disease severity, EDSS score, median (range): RAGT + VR group: 4.4 (4 to 4.9) RAGT – VR group: 4.75 (4.1 to 5.5)
Interventions	All the patients underwent a standard physical treatment programme, consisting of general conditioning exercises (5 min of warming up, e.g. calf, shoulder and hand passive range of motion exercises; 5 min of lower and upper extremity strengthening; 20 min of postural control exercise with maintenance of standing and shifting the weight loads to the paretic side). After 15 min of rest, both the study groups received RAGT by means of Lokomat exoskeleton. RAGT + VR group: RAGT with the Augmented Feedback Module projecting patient's avatar while walking on a screen. Participants were required to pass obstacles or catch objects appearing on the trail, thus being forced to change walking direction, and this was achieved by changing the force exerted by a lower limb as compared to the other. Dose: 40 sessions (5 sessions of 40 min per week for 8 weeks) RAGT – VR group: RAGT with visual feedback (a smiling face) Dose: 40 sessions (5 sessions of 40 min per week for 8 weeks)
Outcomes	Primary outcomes: TUG, BBS, COPE Secondary outcomes: FIM, MAS, HRSD, hip and knee flexion/extension force Assessment point: baseline, post-intervention (8 weeks)
Level of immersion	Non-immersive
Notes	Authors contacted for missing and/or inconsistent data. No response received. This study was not included in MA because of insufficient reporting of outcomes data. Funding source: none Declaration of interest: none

Cuesta-Gómez 2020

Study characteristics	
Methods	Study design: RCT (2 groups)
Participants	Inclusion criteria: a diagnosis of MS according to the McDonald criteria with over 2 years evolution; a score of between 3.5 and 7.5 on the Kurtzke Expanded Disability Status Scale (EDSS); with stable medical treatment during at least the 6 months prior to the intervention; muscle tone in the upper limbs not greater than two points on the modified Ashworth Scale; as well as a score of four points or less in the "Pyramidal Function" section of the EDSS functional scale; absence of cognitive decline; with the ability to understand instructions and obtaining a score of 24 or more in the Mini-Mental Test; and a score of two points or less in the "Mental Functions" section of the EDSS. Exclusion criteria: a diagnosis of another neurological illness or musculoskeletal disorder different to MS; the diagnosis of a cardiovascular, respiratory, or metabolic illness or other conditions which may interfere with the study; suffering a flare-up or hospitalisation in the last 3 months prior to commencement of the assessment protocol or during the process of the therapeutic intervention; receiving a cycle of steroids, either intravenously or orally, 6 months prior to the commencement of the assessment protocol and within the study period of intervention; receiving treatment with botulinum toxin in the 6 months prior to the beginning of the study; or the presence of visual disorders non-corrected by optical devices. Sample size: VR group: 16 Control group: 14 Number of dropouts: 0 Age, mean years (SD): VR group: 49.86 (2.46) Control group: 42.66 (3.14) Sex (F/M): VR group: 9/7 Control group: 9/5 Type of MS: VR group: 4 RR, 8 SP, 4 PP Control group: 7 RR, 5 SP, 2 PP Years since MS diagnosis, mean years (SD): VR group: 15.20 (2.43) Control group: 10.91 (2.19) Disease severity, EDSS score, mean (SD): VR group: 5.43 (0.31) Control group: 5.45 (0.36)
Interventions	Control group: received a specific UL intervention by two physical therapists based on conventional motor rehabilitation therapy based on shoulder, elbow, wrist and finger mobilisation, strengthening of UL extensor muscles and stretching exercises for UL flexor muscles and with functional task practice trying to imitate the movements of the serious games designed for the experimental

Cuesta-Gómez 2020 *(Continued)*

	group (i.e. reaching movements, dexterity, grasping and pincer grasp movements using objects of daily living, such as coins, keys, balls, cups, plates) Dose: 20 sessions (2 sessions of 60 min per week for 10 weeks) VR group: received the same conventional motor rehabilitation therapy (45 min) + Leap Motion Controller (LMC) (15 min). Six serious games (piano game, reach game, sequence game, grasp game, pinch game, flip game) were developed. The Leap Motion sensor was employed to capture the user's hand movements, and different virtual environments were created using Unity3D Game Engine software. The games were performed firstly unilaterally (each hand separately) and then bilaterally (both hands at the same time). Dose: 20 sessions (2 sessions of 45 min + 15 min VR per week for 10 weeks)
Outcomes	Grip strength, BBT, PPT, NHPT, FSS, MSIS-29 Assessment point: baseline, post-intervention (10 weeks), follow-up (1 month)
Level of immersion	Non-immersive
Notes	Authors contacted for missing and/or inconsistent data. No response received. This study was not included in MA because of insufficient reporting of outcomes data. Funding source: the ROBOHEALTH-A project (DPI2013–47944-C4–1-R) funded by the Spanish Ministry of Economy and Competitiveness Declaration of interest: none

Eftekharsadat 2015

Study characteristics	
Methods	Study design: RCT (2 groups)
Participants	Inclusion criteria: ambulatory patients with relapsing-remitting or secondary-progressive types of MS Exclusion criteria: a background of diabetes mellitus, myasthenia gravis, myopathies, metabolic or toxic neuropathies, degenerative disorders of the musculoskeletal system, past history of trauma or surgery in the lower extremities, previous cerebrovascular accidents, or major cardiopulmonary disease Sample size: VR group: 15 Control group: 15 Number of dropouts: 0 Age, mean years (SD): VR group: 33.4 (8.1) Control group: 37.0 (8.3) Sex (F/M): VR group: 10/5 Control group: 12/3

Eftekharsadat 2015 *(Continued)*

	Years since MS diagnosis, mean years (SD): VR group: 5.8 (3.9) Control group: 8.3 (4.3)
Interventions	VR group: All participants in the intervention group performed postural stability training (PST) using the Biodex Balance System SD. Postural stability training simulates specific movement patterns or strategies by placing markers on specific locations on the screen grid. In each session, the participants attempted to touch targets nine times using an on-screen cursor, which is manoeuvred by the participants' legs on the device's platform. The platform stability was set to 6 (moderately stable). Dose: 24 sessions (2 sessions of 20 min per week for 12 weeks) Control group: no intervention
Outcomes	MMT (wrist, hip, knee), TUG, MAS (knee, hip), Romberg test, BBS, overall stability index, fall risk index Assessment point: baseline, post-intervention (12 weeks)
Level of immersion	Non-immersive
Notes	Funding source: Physical Medicine and Rehabilitation Research Center, Tabriz University of Medical Sciences, Iran Declaration of interest: none

Feys 2015

Study characteristics	
Methods	Study design: RCT (2 groups)
Participants	Inclusion criteria: patients with MS diagnosed according to the McDonald criteria and upper limb weakness determined by the Motricity Index (MI; score < 85) Exclusion criteria: participants with (nearly) total paralysis of both upper limbs based on the Motricity Index, participants with visual, cognitive and cerebellar dysfunctions, having a relapse in the last month before study onset or receiving relapse-related glucocorticosteroid treatment Sample size: VR group: 9 Control group: 8 Number of dropouts: VR group: 0 Control group: 1 Age, median years (IQR): VR group: 58 (56 to 65) Control group: 61 (47 to 75) Sex (F/M):

Feys 2015 *(Continued)*

	VR group: 3/6 Control group: 4/4 Type of MS: VR group: 1 RR, 8 SP Control group: 1 RR, 7 SP Years since MS diagnosis, median years (IQR): VR group: 25 (14 to 27) Control group: 14 (9 to 19.5) Disease severity, EDSS score, median (IQR): VR group: 8 (8 to 8) Control group: 7.3 (6.9 to 7.6)
Interventions	VR group (I-TRAVLE): conventional therapy + robot-supported training. I-TRAVLE consists of using interfaces for evaluation of arm movements and performance of 3D exercises in a custom-built virtual learning environment. The virtual learning environment enables therapeutic-based training of motor function by gradually changing the amplitude, speed, accuracy requirements and knowledge of performance while providing feedback by the means of haptic, visual and auditory stimuli. It permits playing of serious games, which can be defined as games that are designed for a primary purpose other than of pure entertainment. The developed serious games (penguins, arkanoid, chicken run and watering the flowers) incorporated simultaneous training of multiple skill components combined with cognitive distractors and challenges. Dose: 24 sessions (3 sessions of 30 min per week for 8 weeks) + 2 h multidisciplinary treatment per day Control group: conventional therapy including 30 min physiotherapy, 30 min occupational therapy and 60 min group physiotherapy, speech therapy or psychotherapy depending on the needs of the participant Dose: 2 h multidisciplinary treatment per day
Outcomes	Motricity Index, hand grip strength, FM-UL, ARAT, MAL Assessment point: baseline, post-intervention (8 weeks)
Level of immersion	Non-immersive
Notes	Authors contacted for inconsistent data. Results in the form of mean and standard deviation have been provided. This study was not included in MA because it introduced a different comparison. Funding source: not mentioned Declaration of interest: none

Hoang 2015

Study characteristics	
Methods	Study design: RCT (2 groups)

Hoang 2015 *(Continued)*

Participants	Inclusion criteria: a clinical diagnosis of MS as defined by the modified McDonald criteria, an expanded disability status scale (EDSS) score of 2 to 6, age 18 to 65 years, no apparent cognitive impairment (i.e. ability to provide written informed consent and understand and follow instructions), and no exacerbation of MS in the past 3 months. Exclusion criteria: presence of conditions that preclude stepping exercise, such as severe spasticity that prevented a person taking a full step (from one panel on the mat to another), excessive fatigue or exercise intolerance (judged by the physiotherapist who performed the baseline testing) Sample size: VR group: 28 Control group: 22 Number of dropouts: VR group: 5 Control group: 1 Age, mean years (SD): VR group: 53.4 (10.7) Control group: 51.4 (12.8) Sex (F/M): VR group: 21/7 Control group: 17/5 Type of MS: VR group: 15 RR, 5 SP, 8 PP Control group: 11 RR, 7 SP, 2 PP, 2 unknown Years since MS diagnosis, mean years (SD): VR group: 11.6 (9.1) Control group: 13.4 (6.9) Disease severity, EDSS score, median (IQR): VR group: 4.1 (1.4) Control group: 4.2 (1.2)
Interventions	Intervention group: a home-based step training programme. The exercises involved two interactive exergames. The first used Stepmania open source software (www.stepmania.com) to develop a rhythm video game that required participants to step as accurately as possible, both in terms of direction and timing, while synchronising their step responses to stimuli presented on the television screen. To enhance compliance, participants could choose music from a list of songs. Choice Stepping Reaction Time (CSRT) training comprised the second game that required quick, accurate steps with both legs. Dose: 24 sessions (at least 2 sessions of 30 min per week for 12 weeks) Control group: no intervention, continued their usual physical activity
Outcomes	Primary outcome: choice stepping reaction time (CSRT) total time, the Stroop stepping test time

Hoang 2015 *(Continued)*

	Secondary outcomes: Balance and mobility: CSRT decision time, CSRT movement time, postural sway eyes open-closed, TUG single task, 10MWT, 6MWT, fall history Cognitive function: TUG dual task, trail making test, symbol digit modalities test Upper limb function: 9HPT MS Functional Composite score Assessment point: baseline, within 7 days post-intervention (12 weeks)
Level of immersion	Non-immersive
Notes	Funding source: partly funded by Multiple Sclerosis Research Australia and National Health and Medical Research Council (NHMRC) Australia Declaration of interest: none

Janssen 2015

Study characteristics	
Methods	Study design: RCT (2 groups)
Participants	Inclusion criteria: individuals with RRMS, 20/40 visual acuity or better; dominant right-handedness as measured by the Edinburgh Handedness Inventory; absence of depression as measured by a score of 18 or less on the Beck Depression Inventory–II; absence of relapse and corticosteroid use for the last 30 days; age 30 to 59 years; a score higher than 23 on the Mini Mental Status Examination, videogame usage of less than 4 hours/week; absence of any other neurological or psychological disorders; and a score greater than 1 on the Expanded Disability Status Scale Exclusion criteria: — Sample size: VR group: 17 Control group: 17 Number of dropouts: VR group: 3 Control group: 3 Age, mean years (SD): VR group: 49.43 (6.4) Control group: 44.93 (8.8) Sex (F/M): VR group: 10/4 Control group: 11/3 Years since MS diagnosis, mean years (SD): VR group: 13.00 (6.7)

Janssen 2015 *(Continued)*

	Control group: 10.93 (7.4) Disease severity, EDSS score, mean (SD): VR group: 2.86 (1.3) Control group: 2.68 (1.4)
Interventions	Intervention group: received 20 one-hour sessions with the Space Fortress game over 8 weeks. The player, using a joystick, navigates their spaceship in a frictionless environment, shooting missiles at the Space Fortress to destroy it, while simultaneously monitoring and collecting bonus points that appear at the bottom of the screen and constantly dealing with diamond-shaped foe or friend mines that appear on the screen. The first 10 one-hour training sessions required participants to practice part-task training. This learning approach divided the Space Fortress game into 14 part tasks, each about 2 min long, which focused on different aspects of the game. The next 10 one-hour sessions consisted of a variable priority training (VPT) strategy. This strategy highlighted different aspects of the game, with varying emphasis on each subscore to minimise overall cognitive load, while integrating previously trained part-tasks. Dose: 20 sessions of 60 min over 8 weeks Control group: waitlist control group
Outcomes	PASAT, SRT, 10/36 Spatial Recall Test, SDMT, Word List Generation Task Assessment point: baseline, within 2 weeks post-intervention (8 weeks)
Level of immersion	Non-immersive
Notes	Funding source: not mentioned Declaration of interest: none

Jonsdottir 2018

Study characteristics	
Methods	Study design: RCT (2 groups)
Participants	Inclusion criteria: persons with MS established according to McDonald's criteria with upper extremity motor deficits but able to flex shoulder and elbow at least 45 degrees, able to comprehend and follow directions Exclusion criteria: persons with MS wearing pace-makers, epilepsy and with other comorbidities of the arm Sample size: Serious games group: 10 Exergames group (control group): 6 Number of dropouts: 0 Age, mean years (SD): Serious games group: 55.4 (7.7) Exergames group (control group): 53.5 (13.3) Sex (F/M):

Jonsdottir 2018 *(Continued)*

	Serious games group: 7/3 Exergames group (control group): 6/0 Disease severity, EDSS score, n: Serious games group: 5.5 (n = 1), 6.5 (n = 5), 7 (n = 2), 7.5 (n = 1), 8 (n = 1) Exergames group (control group): 6 (n = 1), 6.5 (n = 2), 7 (n = 2), 7.5 (n = 1) Years since MS diagnosis, mean years (SD): Serious games group: 20.7 (9.3) Exergames group (control group): 17.3 (6.3)
Interventions	Serious games group: played using the Kinect. The system consisted of a camera and a depth sensor. The gaming environment included a calibration of individual active range of motion and so the virtual environment could be adapted to the participant's ability irrespective of disability level. Six arm rehabilitation games were available to be played and all had adjustable difficulty levels and required different activity of arms and hands. Games were played in sitting or standing, depending on the participants' balance ability. Dose: 12 sessions (4 to 5 sessions of 40 min per week) Exergames group (control group): played various games of their choice available from the Nintendo Wii gaming console. Games came from the Nintendo Wii package that offers games enabling users to work on timing, dexterity, hand-eye co-ordination, perceptual skills and spatial awareness. Games were played in sitting or standing, depending on the participants' balance ability. Dose: 12 sessions (4 to 5 sessions of 40 min per week)
Outcomes	Primary outcome: 9HPT, BBT Secondary outcomes: EQ-5D visual analogue scale, short form SF-12 Assessment point: baseline, post-intervention
Level of immersion	Non-immersive
Notes	Authors contacted for inconsistent data. Results in the form of mean and standard deviation have been provided. This study was not included in MA because it introduced a different comparison. Funding source: not reported Declaration of interest: none

Kalron 2016

Study characteristics	
Methods	Study design: RCT (2 groups)
Participants	Inclusion criteria: diagnosis of definite relapsing-remitting MS according to the revised McDonald criteria 2010, (2) 25–55 years of age, (3) moderate neurological disability as scored by the expanded disability status scale (EDSS), ranging from 3.0 to 6.0 inclusive with a pyramidal functional score of at least 3 Exclusion criteria: (1) MS clinical relapse or treatment with corticosteroid therapy within 6-months prior to examination, (2) patients experiencing major depression or cognitive decline, (3) orthope-

Kalron 2016 *(Continued)*

	dic disorders that could negatively affect balance, (4) pregnancy, (5) blurred vision, or (6) cardiovascular disorders. Sample size: VR group: 16 Control group: 16 Number of dropouts: VR group: 1 Control group: 1 Age, mean years (SD): VR group: 47.3 (9.6) Control group: 43.9 (10.6) Sex (F/M): VR group: 10/5 Control group: 9/6 Years since MS diagnosis, mean years (SD): VR group: 11.6 (7.7) Control group: 10.4 (6.5) Disease severity, EDSS score, mean (SD): VR group: 4.5 (1.6) Control group: 3.9 (1.3)
Interventions	VR group: participants trained with the CAREN system and had to keep their balance in response to changes in the slope or direction of a road projected on a screen in front of them. The VR training included a secondary task: intercepting 18 moving targets (a colored ball of 12.5 cm diameter) appearing above the road. Dose: 12 sessions (2 sessions of 30 min per week for 6 weeks) Control group: 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. Dose: 12 sessions (2 sessions of 30 min per week for 6 weeks)
Outcomes	Posturography eyes open/closed (CoP length, sway rate, ellipse sway area, pressure distribution difference), FRT, BBS, FSST, FES-I questionnaire Assessment point: baseline, post intervention (6 weeks)
Level of immersion	Semi-immersive
Notes	Funding source: a Pilot Research Award from the National Multiple Sclerosis Society (PP2208) Declaration of interest: none

Khalil 2018

Study characteristics	
Methods	Study design: RCT (2 groups)
Participants	Inclusion criteria: 1) a neurologist's confirmed diagnosis of MS according to the revised McDonald criteria, 2) relapsing remitting type of MS, 3) age of above 18 years, 4) Expanded Disability Status Scale (EDSS) score of 3 to 6.5, 5) being relapse free for 30 days prior to participation or to completing testing, 6) able to follow simple instruction Exclusion criteria: 1) diagnoses of any other condition affecting the central nervous system, 2) the presence of any medical condition for which the individual has been advised to refrain from undertaking physical activity, severe uncorrected visual impairments, or uncorrected hearing deficits Sample size: VR group: 20 Control group: 20 Number of dropouts: VR group: 4 Control group: 4 Age, mean years (SD): VR group: 39.88 (12.75) Control group: 34.87 (8.98) Sex (F/M): VR group: 12/4 Control group: 10/6 Years since MS diagnosis, mean years (SD): VR group: 8.38 (5.49) Control group: 10.43 (6.10) Disease severity, EDSS score, mean (SD): VR group: 2.9 (1.4) Control group: 3.1 (1.1)
Interventions	VR group: practised with 5 games targeting several exercises (standing from chair, squatting, reaching, stepping over virtual object, weight shifting, rising on toes) played with the Kinect or Wii balance board. Participants began with one set of 1 minute per virtual reality based exercise and then progressed to complete the other 3 sets of 1 minute per exercise. Participants were asked to come 2 times per week for 6 weeks. In addition to these 2 clinic-based VR exercise sessions, participants were asked to complete one session of balance exercises similar to those of the VR exercise at home. Dose: 18 sessions (3 sessions per week for 6 weeks): 2 in lab/1 at home Control group: performed balance exercises (2 instructional sessions in clinic with physiotherapist, afterwards exercise sheet) similar to the ones promoted by the virtual reality at home 3 times a week over the intervention period

Khalil 2018 *(Continued)*

	Dose: 18 sessions (3sessions per week for 6 weeks)
Outcomes	BBS, TUG, 3MWD, 10MWT, FES-I, MFIS, SF-36 Assessment point: baseline, post intervention (6 weeks)
Level of immersion	Non-immersive
Notes	Funding source: EU commission Support to Research and Technological Development & Innovation initiatives and Strategies in Jordan scheme (grant number: AR- 42) Declaration of interest: none

Kramer 2014

Study characteristics	
Methods	Study design: RCT (3 groups)
Participants	Inclusion criteria: an EDSS ≤ 6, no relapse in the past 3 months and the recommendation from the physiotherapists that the patient needed balance training Exclusion criteria: — Sample size: Exergame group: 21 Posturomed group: 20 Conventional group: 20 Number of dropouts: 0 Age, mean years (SD): Total sample: 47 (9) Sex (F/M): Total sample: 44/17 Type of MS: Total sample: 74% RR, 23% SP, 3% PP Years since MS diagnosis, mean years (SD): Total sample: 8 (7) Disease severity, EDSS score, mean (SD): Total sample: 3 (1)
Interventions	Exergame training group: playing Wii Sports/Sports Resort/Fit games that require arm movements (tennis, table tennis, boxing, archery and sword fight) or displacements of the whole body to control the game avatar (ski slalom, balance bubble, penguin picnic, soccer heading, tilt city and perfect ten). While playing these games, the patients stood on an unstable surface (the Posturomed) that swings when the patient moves his limbs or is not in balance.

Kramer 2014 *(Continued)*

	Posturomed training group: also trained on the Posturomed, but performed about 5 ST balance exercises of a pool of 15 exercises with increasing difficulty, ranging from standing on the Posturomed on both legs as still as possible to standing on your toes or heels to standing on one leg while moving one arm quickly as if hitting a tennis ball. Conventional training group: conventional balance training of the Schmieder rehabilitation clinic, which consisted of various exercises on the floor: Romberg stance, tandem stance, standing on the toe or the heel, walking forwards and backwards on a line, tandem walk and one-leg stance on an aerobic mat. Dose: 9 sessions (3 sessions of 30 min per week for 3 weeks)
Outcomes	Balance tests on force plates: Romberg eyes open/closed, one-leg stance eyes open/closed/addition task, one leg stance non-preferred leg Balance tests on Posturomed: normal stance on both legs and one-leg stance on the preferred leg, once without an additional task and once with an additional task Gait analysis: velocity with and without an additional task, step-to-step CV with and without an additional task Assessment point: baseline, post intervention (3 weeks)
Level of immersion	Non-immersive
Notes	Accepted manuscript, no final PDF version Funding source: not mentioned Declaration of interest: not mentioned

Leonardi 2021

Study characteristics	
Methods	Study design: RCT (2 groups)
Participants	Inclusion criteria: diagnosis of MS based on the latest reviews of McDonald's criteria, patients who were stable on therapy for at least 6 months before entering the study, presence of mild to moderate cognitive impairment (Montreal Cognitive Assessment – MoCA range 18 to 27) Exclusion criteria: severe medical and psychiatric illness potentially interfering with the training, disabling sensory alterations (i.e. auditory and visual disturbances), age > 75 or < 18 years, clinical and/or neuroradiological relapse of MS in the 6 months preceding the enrolment, EDSS > 7 Sample size: VR group: 15 Control group: 15 Number of dropouts: not mentioned Age, mean years (SD): VR group: 57.4 (7.9) Control group: 51.8 (1.2) Sex (F/M):

Leonardi 2021 *(Continued)*

	VR group: 7/8 Control group: 5/10 Type of MS: VR group: 15 RR Control group: 15 RR Disease severity, EDSS score, mean (SD): VR group: 4.6 (1.3) Control group: 5.0 (1.6)
Interventions	VR group: The intervention group received cognitive rehabilitation using the VRRS. The exercises can be classified into 2 main categories: 1) 2D exercises, in which the patient interacts with objects and scenarios through the touchscreen or through a particular magnetic tracking sensor coupled with a compressible object, thus emulating mouse-like interaction skills; 2) 3D exercises, where patients interact with 3D on immersive scenarios and virtual objects through a magnetic tracking sensor generally positioned above the hand. In each session, specific cognitive domains were trained in a specific order: attention, verbal and visuo-spatial memory exercises and executive function training. The exercises were presented with increasing difficulty and implemented according to the response to the treatment (i.e. when 9 out of 10 correct answers were achieved) and the number of errors (number of errors < 1). Dose: 24 sessions (3 sessions of 45 min per week for 8 weeks) Control group: The control group received traditional cognitive rehabilitation, which consisted of a face-to-face approach between the patient and the therapist in the individual sessions. In each session, specific cognitive domains were trained in a specific order: attention, verbal and visuo-spatial memory exercises and executive function training. The tasks were presented using a pencil and paper method and were designed to stimulate specific cognitive skills. The type and level of exercises were progressively and randomly changed to avoid the learning effect. Dose: 24 sessions (3 sessions of 45 min per week for 8 weeks)
Outcomes	Cognition: MOCA, SRT, SPART, SDMT, PASAT, SRD, SPART-D, WLG QoL: BDI, MSQoL-54 Assessment point: Baseline, post-intervention (8 weeks)
Level of immersion	Non-immersive
Notes	This study was not included in MA because it introduced a different comparison. Funding source: not mentioned Declaration of interest: none

Lozano-Quilis 2014

Study characteristics	
Methods	Study design: RCT (2 groups)
Participants	Inclusion criteria: (1) men and women between 18 and 65 years old, (2) patients have relapsing-remitting and secondary-progressive MS, (3) patients have a minimum score of 6 on all items of the

Lozano-Quilis 2014 *(Continued)*

	domain of the Functional Independence Measure (FIM), (4) patients do not need assistive devices for ambulation or at most a cane, and (5) patients do not have cognitive impairments Exclusion criteria: (1) patients with flare-up symptoms, or (2) patients that cannot physically complete all rehabilitation sessions Sample size: VR group: 6 Control group: 6 Number of dropouts: VR group: 0 Control group: 1 Age, mean years (SD): VR group: 48.33 (10.82) Control group: 40.60 (9.24) Sex (F/M): VR group: 3/3 Control group: 1/4 Years since MS diagnosis, mean years (SD): VR group: 14.00 (12.69) Control group: 4.70 (3.11)
Interventions	VR group: performed the same exercises as the control group for 45 min and during the last 15 minutes of the session, they performed the Kinect-based virtual rehabilitation exercises. The VR exercises consisted of 3 games: touch ball, take ball and step ball. Participants had to touch, take or step over the virtual balls that are presented in the virtual environment. Dose: 10 sessions (1 sessions of 45 min + 15 min VR per week for 6 weeks) Control group: performed standard balance and gait rehabilitation exercises Dose: 10 sessions (1 session of 60 min per week for 6 weeks)
Outcomes	Non-immersive
Level of immersion	BBS, Tinetti Balance Scale, Single Leg Balance Test, 10MWT, TUG Assessment point: baseline, post intervention (10 weeks)
Notes	Funding source: partially funded by the Generalitat Valenciana (projecte GV/2012/069) and by the Fundación Antonio Gargallo (proyecto 2013/B001) Declaration of interest: none

Maggio 2022

Study characteristics

Maggio 2022 *(Continued)*

Methods	Study design: RCT (2 groups)
Participants	Inclusion criteria: 1) MS diagnosis according to the last revisions of the McDonald criteria; 2) patients that are stable in therapy least for at least 6 months before the study entry; 3) presence of mild/moderate cognitive impairment (Montreal Cognitive Assessment – MoCA >18); 4) absence of severe medical and psychiatric illness potentially interfering with the VRT; and 5) absence disabling sensory alterations (i.e. auditory and visual disturbances) Exclusion criteria: 1) age > 75 or < 18 years; 2) presence of severe medical and psychiatric illness according to the DSM-V and International Classification of Disease; 3) MS clinical and/or neuroradiological relapse in the 6 months before enrolment; (iv) EDSS > 7 Sample size: VR group: 30 Control group: 30 Number of dropouts: 0 Age, mean years (SD): VR group: 51.9 (9.9) Control group: 48.2 (12.2) Sex (F/M): VR group: 12/18 Control group: 17/13
Interventions	VR group: received VR training, which consisted of providing the patient with cognitive rehabilitation in the semi-immersive VR system "BTS-Nirvana". The BTS-N system consists of computerised software, two infrared sensors without markers, a video camera and a projector connected to a large screen. This device allows reproducing multiple exercises; the patient performs the exercises interacting with virtual scenarios and audio-visual stimuli through movement, thus permitting a greater awareness of the performance and movements, and permitting the total sensory involvement with positive repercussions for the rehabilitation outcomes. Dose: 24 sessions (3 sessions of 60 min per week for 8 weeks) Control group: a traditional rehabilitation training, which consisted of a face-to-face approach between the patient and the therapist in individual sessions. The tasks were presented using a pencil-and-paper method, and these were designed to stimulate specific cognitive skills. Dose: 24 sessions (3 sessions of 60 min per week for 8 weeks)
Outcomes	TUG, Tinetti, TCT, MoCA, 10/36 spatial recall test, Rey-Osterrieth Complex figure, PASAT, MSQOL-54, BDI Assessment point: baseline, post-intervention (8 weeks)
Level of immersion	Semi-immersive
Notes	Authors contacted for missing and/or inconsistent data. No response received. This study was not included in MA because of insufficient reporting of outcomes data. Funding source: none Declaration of interest: none

Molhemi 2021

Study characteristics	
Methods	Study design: RCT (2 groups)
Participants	Inclusion criteria: confirmed diagnosis of relapsing-remitting or secondary progressive MS according to the McDonald criteria by a neurologist specialised in treating MS, age 18 to 64 years, EDDS < 6, and Berg Balance Scale lower than 53 Exclusion criteria: had exacerbation of symptoms in the past 3 months, cognitive impairment determined by Mini-Mental State Examination below 24, any neurologic or musculoskeletal diagnosis except MS that negatively affected their gait and balance, uncorrected visual or auditory impairments, or pregnancy Sample size: VR group: 19 Control group: 20 Number of dropouts: VR group: 3 Control group: 4 Age, mean years (SD): VR group: 36.8 (8.4) Control group: 41.6 (8.4) Sex (F/M): VR group: 12/7 Control group: 12/8 Type of MS: VR group: 14 RR, 5 SP Control group: 16 RR, 4 SP Years since MS diagnosis, mean years (SD): VR group: 7.7 (3.6) Control group: 11.2 (6.8) Disease severity, EDSS score, median (IQR): VR group: 4.8 (0.9) Control group: 4.7 (1.1)
Interventions	VR group: progressive balance exercises with the use of the Xbox360 with Microsoft's Kinect games: Light Race, Stack'em Up and 20000 Leaks Dose: 18 sessions (3 sessions of 35 min per week for 6 weeks) Control group: standing exercises (multidirectional stepping and single – and double-leg standing), walking exercises (forward, backward, and side walking), weight-shifting exercises (lunge, half-squat, leaning, reaching).

Molhemi 2021 *(Continued)*

	Dose: 18 sessions (3 sessions of 35 min per week for 6 weeks)
Outcomes	Limits of stability, TUG (ST/DT), 10MWT (ST/DT), dual-task costs, BBS, MS Walking Scale-12, FES-I, ABC scale Assessment point: baseline, post-intervention (6 weeks), follow-up (3 months)
Level of immersion	Non-immersive
Notes	Funding source: supported by Ahvaz Jundishapur University of Medical Sciences (grant no PHT-9617) Declaration of interest: none

Molhemi 2022

Study characteristics	
Methods	Study design: RCT (2 groups)
Participants	Inclusion criteria: people with a definitive neurologist diagnosis of relapsing-remitting or secondary-progressive MS, 18 to 64 years of age and EDSS higher than 2 and lower than 6 Exclusion criteria: MS relapse in the past 3 months, apparent cognitive impairment (Mini-Mental State Examination below 24), uncorrected visual or auditory impairments, and pregnancy Sample size: VR group: 18 Control group: 18 Number of dropouts: VR group: 1 (post-intervention), 1 (follow-up) Control group: 2 (post-intervention), 1 (follow-up) Age, mean years (SD): VR group: 37.00 (8.64) Control group: 41.33 (8.83) Sex (F/M): VR group: 11/7 Control group: 10/8 Type of MS: VR group: 13 RR, 5 SP Control group: 14 RR, 4 SP Years since MS diagnosis, mean years (SD): VR group: 7.33 (3.29) Control group: 11.28 (7.19)

Molhemi 2022 *(Continued)*

	Disease severity, EDSS score, mean (SD): VR group: 4.83 (1.00) Control group: 4.86 (1.16)
Interventions	VR group: The intervention group performed 3 exergame exercises using the Xbox360 with Microsoft's Kinect which required multidirectional timed stepping, weight-shifting and walking in different directions. Progression of exercises was individualised for each participant. Dose: 18 sessions (3 sessions of 35 min per week for 6 weeks) Control group: The control group performed matched conventional exercises in terms of type, form and duration. Progression of exercises was individualised for each participant. Dose: 18 sessions (3 sessions of 35 min per week for 6 weeks)
Outcomes	Cognition: TMT, CSRT (reaction time (RT), movement time (MVT), and total response time (TRT)) Lower limb and gait: SSST Assessment point: baseline, post-intervention (6 weeks), follow-up (3 months)
Level of immersion	Non-immersive
Notes	This study was not included in MA because it introduced a different comparison. Funding source: This study was supported by Ahvaz Jundishapur University of Medical Sciences under the Grant Number: PHT-9642. Declaration of interest: none

Munari 2020

Study characteristics	
Methods	Study design: RCT (2 groups)
Participants	Inclusion criteria: diagnosis of primary progressive, secondary progressive, relapsing-remitting MS; Expanded Disability Status Scale (EDSS) score between 3 and 6; Mini Mental State Examination score > 24; age > 18 years and < 65 years Exclusion criteria: MS relapse during the 3 months prior to recruitment; any rehabilitation training in the 6 months prior to recruitment; participants with psychiatric disorders and/or drugs/alcohol abuse; changes in disease-modifying and symptomatic therapy for MS during the study period; contraindications to RAGT such as inability to sit without trunk support, inability to stand for at least 10 seconds with support; other neurological or orthopaedic conditions involving the lower limbs (musculoskeletal diseases, severe osteoarthritis, peripheral neuropathy, joint replacement); cardiovascular co-morbidity (recent myocardial infarction, heart failure, uncontrolled hypertension, orthostatic hypotension); and concurrent participation in other clinical studies Sample size: VR group: 8 Control group: 9 Number of dropouts: 0 Age, mean years (SD):

Munari 2020 *(Continued)*

	VR group: 57 (5.83) Control group: 51.7 (10.24) Sex (F/M): VR group: 5/3 Control group: 5/4 Type of MS: VR group: 1 RR, 7 SP Control group: 2 RR, 7 SP Years since MS diagnosis, mean years (SD): VR group: 17.7 (9.62) Control group: 13.9 (9.23) Disease severity, EDSS score, mean (SD): VR group: 5.4 (0.9) Control group: 5 (1.01)
Interventions	VR group: received RAGT with the G-EO system + non-immersive VR (video screen). Visual scenario was a simulation of a walking trial in a natural park, which was synchronised with the movements of the footplates of the G-EO. Dose: 12 sessions (2 sessions of 40 min per week for 6 weeks) Control group: received RAGT with the G-EO system Dose: 12 sessions (2 sessions of 40 min per week for 6 weeks)
Outcomes	Primary outcomes: PASAT, 2MWT Secondary outcomes: Phonemic Fluency test, Novel task, Digit Symbol, MSQOL-54, 10MWT, BBS, gait analysis and stabilometric assessment Assessment point: baseline, post-intervention (6 weeks), follow-up (1 month)
Level of immersion	Non-immersive
Notes	Uncorrected author proof – no final PDF version Funding source: none Declaration of interest: none

Nilsagård 2012

Study characteristics	
Methods	Study design: RCT (2 groups)
Participants	Inclusion criteria: (a) reported, subjectively perceived impaired balance function in standing or walking activities; and (b) the ability to walk 100 m without resting

Nilsagård 2012 *(Continued)*

	Exclusion criteria: (a) cognitive or linguistic problems with understanding instructions or filling in self-administered outcome measures; (b) ongoing exacerbation of MS; (c) other disease interfering with either intervention or testing procedures; (d) a weight > 140 kg (due to restrictions stated by the producer of the Nintendo Wii Fit® balance platform) Sample size: VR group: 42 Control group: 42 Number of dropouts: VR group: 1 Control group: 3 Age, mean years (SD): VR group: 50.0 (11.5) Control group: 49.4 (11.1) Sex (F/M): VR group: 32/10 Control group: 32/10 Type of MS: VR group: 26 RR, 13 SP, 3 PP Control group: 28 RR, 13 SP, 1 PP Years since MS diagnosis, mean years (SD): VR group: 12.5 (8.0) Control group: 12.2 (9.2)
Interventions	VR group: individual PT-supervised sessions of balance exercise using Nintendo Wii Fit Plus®. The Wii Fit Plus® is a video exercise game containing balance games, yoga poses, strength training and aerobics. Games in the Wii Fit Plus® that targeted balance were selected by the authors and ranked, in order to standardise the progression of exercises. The first session started with the games categorised as easier (Penguin Slide, Ski Slalom, Perfect 10, Heading, Table Tilt). During all sessions, the PTs encouraged the participants to progress to more difficult games (Tightrope Tension, Balance Bubble, Snowboard Slalom, Skateboard Arena, Table Tilt+, Balance Bubble+). Dose: 12 sessions (2 sessions of 30 min per week for 6 to 7 weeks) Control group: no intervention
Outcomes	Primary outcome: TUG Secondary outcomes: TUG cognitive, FSST, 25FWT, DGI, MS walking scale 12, ABC scale, timed chair stand test Assessment point: baseline, post-intervention
Level of immersion	Non-immersive
Notes	Funding source: the Uppsala-Örebro Regional Research Council, the Research Committee of Örebro County Council and the Norrbacka-Eugenia Foundation

Nilsagård 2012 *(Continued)*

	Declaration of interest: none

Norouzi 2021

Study characteristics	
Methods	Study design: RCT (3 groups)
Participants	Inclusion criteria: (1) female with MS; (2) age between 20 and 30 years; (3) right-handed (assessed by the Edinburgh Handedness Inventory); (4) a diagnosis of poor fine manual dexterity (based on the Nine Hole Peg Test (NHPT) criteria); (5) signed written informed consent; (6) normal vision based on the Snellen Chart Test and (7) self-reported normal audition Exclusion criteria: (1) psychiatric issues, as ascertained by a brief psychiatric interview (M.I.N.I; Mini International Neuropsychiatric Interview); (2) intake of mood- and arousal-medications or substances; (3) orthopaedic problems; (4) pregnancy; and (5) patients with underlying somatic diseases such as diabetes Sample size: VR group: 15 Conventional group: 15 Combination group: 15 Number of dropouts: 0 Age, mean years (SD): Total sample: 26.39 (3.45) Sex (F/M): Total sample: 45/0 Disease severity, EDSS score, mean (SD): Total sample: 2.15 (1.38)
Interventions	VR group: participants practised to co-ordinate the movement of both their hands with the movements of a visual stimulus. The visual stimulus reflected the participants' hands in the shape of a two-handed animation presented on the screen. A Kinect camera captured the hand movements of the participants. This technical set-up enabled participants to control an avatar, which interacts with an activity presented on a screen. Several games and activities were available to train participants' bimanual co-ordination task (e.g. grasping cup with two hands, putting dishes away, performing wrist flection and extension, reaching apples with two hands). Dose: 16 sessions (2 sessions of 30 min per week for 8 weeks) Conventional group: participants received instructions to keep the pace of a bimanual coordination task with a metronome by performing a complete cycle of in–out-in handle displacements in time with the beat. The metronome paced the required speed or frequency of limb movements, beginning at a slow speed equivalent to a frequency of 58 bpm for 20 s. After completion of the 20-second trial at slow speed, the same co-ordination task was paced at a medium metronome frequency (90 bpm), and finally at a fast metronome frequency (152 bpm). Dose: 16 sessions (2 sessions of 30 min per week for 8 weeks) Combination group: participants received general guidance on the task. The task required them to grasp two handles attached to moving slides and displace them horizontally in the left-right dimen-

Norouzi 2021 *(Continued)*

	sion. While grasping the two handles, participants produced a 180° relative phase (anti-phase) pattern. For the anti-phase pattern, participants were instructed to move their hands together in an iso-directional fashion. The metronome was also used for increasing the speed or frequency of bimanual co-ordination task. This condition provided the visual (VR screen), proprioception (grasping bimanual handles) and auditory (VR game voice) feedback of motor control.
Outcomes	Bimanual co-ordination accuracy and consistency Assessment point: baseline, post-intervention (8 weeks), follow-up (4 weeks)
Level of immersion	Non-immersive
Notes	Only data from the VR group and conventional group included. This study was not included in MA because it introduced a different comparison. Funding source: Urmia University Declaration of interest: none

Novotna 2019

Study characteristics	
Methods	Study design: RCT (2 groups)
Participants	Inclusion criteria: (1) clinically stable, without relapse or worsening in the previous 3 months; (2) aged 18–60 years with; (3) ability to walk with or without a walking aid for at least 5 m (EDSS 1–7); and (4) ability to maintain a standing position for at least 10 minutes, to be able to perform exercise (assessed by physiotherapist) Exclusion criteria: (1) inpatient rehabilitation programme during the previous 3 months; (2) orthopaedic problems or other conditions affecting balance and gait performance; (3) blurred vision; (4) severe cognitive impairment or psychiatric disorders; (5) pregnancy; (6) weight over 150 kg (to be able to use the exercise platform) Participants who were receiving other physiotherapy targeting balance problems or were having any other changes in lifestyle prior to or during the study. Sample size: VR group: 23 Control group: 16 Number of dropouts: 0 Age, mean years (SD): VR group: 39.39 (9.68) Control group: 42.56 (10.63) Sex (F/M): VR group: 17/6 Control group: 12/4 Years since MS diagnosis, mean years (SD): VR group: 14.95 (8.59)

Novotna 2019 *(Continued)*

	Control group: 14.5 (9.88) Disease severity, EDSS score, mean (SD): VR group: 3.93 (1.91) Control group: 3.62 (1.89)
Interventions	VR group: home-based balance exercise training using Homebalance for at least 15 min daily for 4 weeks. There were two therapeutic games available: (a) a chessboard—where the therapeutic task can be set to different positions/directions; (b) planets—where the therapeutic task is to increase the limits of stability combined with cognitive training (remember the order of the planets) Dose: 28 sessions (daily 15 min for 4 weeks) Control group: wait list group
Outcomes	Primary outcomes: BBS Secondary outcomes: mini-BESTest, TUG, TUG dual task, spatiotemporal parameters, FES, ABC scale, MS Walking Scale 12. Assessment point: baseline, post-intervention (4 weeks), follow-up (4 weeks)
Level of immersion	Non-immersive
Notes	No adverse events Funding source: grant provided by Czech Ministry of Education PROGRES Q27/LF 1 and part of research grant SGS17/206/OHK4/3T/17 “Complex monitoring of the patient during the virtual reality based therapy” provided by the Czech Technical University in Prague Declaration of interest: none

Ortiz-Gutiérrez 2013

Study characteristics	
Methods	Study design: RCT (2 groups)
Participants	Inclusion criteria: 1) age between 20 and 60 years; 2) confirmed diagnosis of MS for over 2 years based on McDonald criteria; 3) medically stable during the 6 months prior to baseline; 4) Impaired balance associated with demyelinated lesions in the cerebellum and its connections demonstrated by Magnetic Resonance Imaging; 5) Expanded Disability Status Scale (EDSS) score ranging from 3 to 5; 6) Hauser ambulatory index value higher than 4; 7) absence of cognitive impairment according to the mini mental state examination test (MMES≥24); 8) no visual deficits; 9) internet connection at home Exclusion criteria: 1) diagnosed with another disease or pathological condition that affects balance; 2) had a relapse in the month prior to baseline or during the intervention process, 3) received an intravenous or oral steroid cycle prior to beginning the evaluation protocol and within the 4-month duration of the project intervention Sample size: VR group: 25 Control group: 25 Number of dropouts:

Ortiz-Gutiérrez 2013 *(Continued)*

	VR group: 1 Control group: 2 Age, mean years (SD): VR group: 39.69 (8.13) Control group: 42.78 (7.38) Sex (F/M): VR group: 13/11 Control group: 14/9 Type of MS: VR group: 16 RR, 3 SP, 5 PP Control group: 15 RR, 6 SP, 2 PP Years since MS diagnosis, mean years (SD): VR group: 9.68 (6.76) Control group: 10.86 (5.40) Disease severity, EDSS score: VR group: score 3 (n = 4), score 4 (n = 17), score 5 (n = 3) Control group: score 3 (n = 5), score 4 (n = 14), score 5 (n = 4)
Interventions	VR group: received individual TR treatments using the Xbox360® console with Microsoft® Kinect following a protocol specifically designed for this purpose. The treatment gaming protocol consisted of three games: Kinect Sports®, Joy Ride® and Adventures®. A physiotherapist monitored and supervised all interventions using online meetings via videoconferencing to avoid adverse events. Dose: 40 sessions (4 sessions of 20 min per week for 10 weeks) Control group: received physiotherapy treatment based on low-load strength exercises (10 min per session), proprioception exercises on unstable surfaces and gait facilitation exercises (20 min per session) and muscle-tendon stretching (10 min per session). Dose: 20 sessions (2 sessions of 40 min per week for 10 weeks)
Outcomes	CDP (SOT, MCT), BBS, Tinetti Assessment point: baseline, post intervention (10 weeks)
Level of immersion	Non-immersive
Notes	Authors contacted for missing and/or inconsistent data. No response received. This study was not included in MA because of insufficient reporting of outcomes data. Funding source: none Declaration of interest: none

Ozdogar 2020

Study characteristics	
Methods	Study design: RCT (3 groups)
Participants	Inclusion criteria: having relapsing-remitting or secondary progressive type of MS, being able to walk at least 100 m without resting, being able to stably stand for half an hour, relapse-free period of 3 months, willing to participate in the study Exclusion criteria: having another neurological disorder, a relapse during the study period, orthopaedic surgery history covering the ankle-foot, knee, hip, or spine, affecting balance, and diagnosed severe cognitive and/or psychiatric impairment Sample size: VR group: 21 Conventional group: 19 Control group (no intervention): 20 Number of dropouts: VR group: 1 Conventional group: 2 Control group (no intervention): 0 Age, mean years (SD): VR group: 39.2 (8.6) Conventional group: 43.6 (10.5) Control group (no intervention): 37.9 (12.4) Sex (F/M): VR group: 16/5 Conventional group: 12/6 Control group (no intervention): 15/5 Type of MS: VR group: 18 RR, 3 SP Conventional group: 18 RR Control group (no intervention): 18 RR, 2 SP Years since MS diagnosis, mean years (SD): VR group: 7.5 (4.5) Conventional group: 6.43 (5.9) Control group (no intervention): 5.93 (4.2) Disease severity, EDSS score, mean (SD): VR group: 2.7 (1.8) Conventional group: 2.11 (0.9)

Ozdogar 2020 *(Continued)*

	Control group (no intervention): 2.25 (1.2)
Interventions	VR group: The video-based exergaming was applied using a game console (Microsoft Xbox One and Kinect motion sensor). Participants played the Kinect Sports Rivals game, which included bowling, Jet Ski racing, rock climbing, football, tennis and target shooting Dose: 8 sessions (1 session of 45 min per week for 8 weeks) Conventional group: received a patient-specific rehabilitation programme, including balance, arm and core stability exercises. The sessions had warming and cool-down periods for 5 to 10 min, which consisted of posture and stretching exercises. The programme difficulty was progressed by increasing the number of repetitions and then the number of sets. Dose: 8 sessions (1 session of 45 min per week for 8 weeks) Control group: no intervention
Outcomes	Primary outcomes: 9HPT Secondary outcomes: Manual Ability Measurement-36, BICAMS, ABC scale, Sit-to-stand test, curl up test, T25FW, MS walking scale-12, Six Spot Step Test, BDI, MFIS, MS International Quality of Life questionnaire. Assessment point: baseline, post-intervention (8 weeks)
Level of immersion	Non-immersive
Notes	Funding source: a grant from the Multiple Sclerosis Research Association to get the game console, games and TV used in the study Declaration of interest: none

Ozdogar 2022

Study characteristics	
Methods	Study design: RCT (2 groups)
Participants	Inclusion criteria: MS diagnosis (2017 McDonald criteria), receiving corticosteroid treatment, an Expanded Disability Status Scale (EDSS) score of ≤ 6 and the ability to stand erect for at least half an hour. Exclusion criteria: having neurological disorders other than MS or orthopaedic surgery on ankle-foot, knee, hip or spine, affecting balance, and cognitive or psychiatric impairment confirmed by a physician that is so severe that it is impossible to perform cognitive testing Sample size: VR group: 15 Control group: 15 Number of dropouts: VR group: 3 Control group: 1 Age, mean years (SD): VR group: 37.5 (10.4)

Ozdogar 2022 *(Continued)*

	Control group: 37.7 (13.1) Sex (F/M): VR group: 11/4 Control group: 10/5 Type of MS: VR group: 13 RR, 2P Control group: 13 RR, 2P Years since MS diagnosis, mean years (SD): VR group: 8.7 (8.7) Control group: 9.8 (9.6) Disease severity, EDSS score, mean (SD): VR group: 3.6 (1.3) Control group: 3.4 (1.2)
Interventions	VR group: all patients received intravenous methylprednisolone (IVMP) infusions 1 g per day between 5 and 10 days, and rehabilitation was applied before daily IVMP treatment. The intervention group received exergaming as a rehabilitation method with the Microsoft Xbox One, a Kinect motion sensor and TV screen (A 50-inch 4K Ultra HD LED TV). The Kinect Sports Rivals game was chosen from the commercial market. All games required core stabilisation, balance, and arm and leg function. The game type was selected according to the physical fitness of the participant. The games and difficulty ratings were changed considering participants' performance. Dose: 45 min per session in a day during the hospitalisation period Control group: all patients received intravenous methylprednisolone (IVMP) infusions 1 g per day between 5 and 10 days, and rehabilitation was applied before daily IVMP treatment. A patient-specific rehabilitation programme was applied, including balance, gait, upper extremity and core stability exercises. Each session started with warming and ended with cooling down periods consisting of posture and stretching exercises for 5 to 10 minutes. Exercise and set repetitions were used to control the difficulty level. Dose: 45 min per session in a day during the hospitalisation period
Outcomes	Upper limb: N-HPT, MAM-36 Lower limb and gait: T25FWT, 2MWT, SSST, MSWS-12 Fatigue: MFIS QoL: MusiQoL, ESS, HADS Cognition: BICAMS, PASAT Assessment point: baseline, post-intervention (at discharge), follow-up (1 month)
Level of immersion	Non-immersive
Notes	Funding source: none Declaration of interest: none

Ozkul 2020

Study characteristics	
Methods	Study design: RCT (3 groups)
Participants	Inclusion criteria: (1) the diagnosis of definite relapsing-remitting MS according to the revised McDonald criteria 2010, (2) 18 to 65 years of age, (3) an Expanded Disability Status Scale (EDSS) score under 6 Exclusion criteria: (1) patients suffering from relapses in the last 3 months, (2) having a disease in which exercise was contraindicated, (3) having orthopaedic, vision, hearing or perception problems Sample size: VR group: 17 Control group 1 (non VR): 17 Control group 2 (no intervention): 17 Number of dropouts: VR group: 4 Control group 1 (non VR): 4 Control group 2 (no intervention): 4 Age, median years (IQR): VR group: 29 (25 to 41) Control group 1 (non VR): 34 (25.5 to 45.5) Control group 2 (no intervention): 34 (32 to 42.5) Sex (F/M): VR group: 9/4 Control group 1 (non VR): 11/2 Control group 2 (no intervention): 10/3 Years since MS diagnosis, median years (IQR): VR group: 4 (4 to 6.5) Control group 1 (non VR): 4 (3 to 6.5) Control group 2 (no intervention): 4 (2.5 to 14.5) Disease severity, EDSS score, median (IQR): VR group: 1 (1 to 3) Control group 1 (non VR): 1 (0.75 to 3) Control group 2 (no intervention): 2 (1 to 2.5)
Interventions	VR group: Pilates based core stability training + exercises in the virtual world created with HMD that have three-dimensional images (Oculus VR goggle). The system (RAGU) included two games for improving balance: the football game (keeping balls out of a goal) and the guillotine game (avoiding the guillotine by bending the body).

Ozkul 2020 *(Continued)*

	Dose: 16 sessions (2 sessions of 30 min Pilates + 20 min VR training per week for 8 weeks) Control group 1: Pilates based core stability training + exercises that consisted of similar movements required for VR games (20 min, 2 times a week for 8 weeks): hitting and avoiding balls that were thrown by the PT Dose: 16 sessions (2 sessions of 30 min Pilates + 20 min balance training per week for 8 weeks) Control group 2: received 1 session of the Jacobson's progressive relaxation exercise and were asked to practise this at home Dose: 16 sessions (2 sessions of 15 to 20 min per week for 8 weeks)
Outcomes	BBS, postural sway (eyes open/closed, firm/foam surface, right/left foot), limits of stability, TUG, FSS Assessment point: baseline, post intervention (8 weeks)
Level of immersion	Fully-immersive
Notes	Authors contacted for missing and/or inconsistent data. No response received. This study was not included in MA because of insufficient reporting of outcome data. Funding source: none Declaration of interest: none

Pagliari 2021

Study characteristics	
Methods	Study design: RCT (2 groups)
Participants	Inclusion criteria: aged 25 to 70 years, Italian mother language, education ≥ 8 years, right-handedness, EDSS score ≤ 6.5 points as determined by a neurologist. Exclusion criteria: clinical relapses and/or steroid treatment (3 months prior to study entry), and evidence of visual acuity or acoustic perception problems that would impair performance in rehabilitation activities. Sample size: VR group: 35 Control group: 35 Number of dropouts: VR group: 3 (during intervention), 2 (follow-up) Control group: 3 (during intervention), 2 (follow-up) Age, mean years (SD): VR group: 48.33 (9.66) Control group: 52.23(9.34) Sex (F/M): VR group: 18/12

Pagliari 2021 *(Continued)*

	Control group: 18/12 Years since MS diagnosis, mean years (SD): VR group: 12.68 (6.72) Control group: 15.36 (7.17) Disease severity, EDSS score, median (25thto 75th): VR group: 5.00 (3.50 to 6.00) Control group: 4.50 (3.50 to 6.00)
Interventions	VR group: the intervention in the VR group consisted of an integrated and intensive telerehabilitation approach, including digital motor and cognitive rehabilitation activities. The exercises were performed at home by the patient using a dedicated VRRS home-based kit in an asynchronous TR modality with digital contents and offline remote monitoring by the therapist. Dose: 30 sessions (5 sessions of 45 min per week for 6 weeks) Control group: the control group received an active comparator treatment, which consisted of a written home-based self-administrated booklet with conventional motor and cognitive exercises tailored for patients with MS. Dose: 30 sessions (5 sessions of 45 min per week for 6 weeks)
Outcomes	QoL: MSQOL-54; BDI; RESE; STAI Fatigue: FSS Lower limb and gait: MSWS-12 Balance and postural control: Mini-BESTest Upper limb: BBT; 9-HPT Cognition: MoCA; SDMT; SRT-LTS; SRT-CLTR; 10/36 SPART; PASAT 3; SRT-DR; D-10/36-SPART; WLG Assessment point: baseline, post-intervention (6 weeks)
Level of immersion	Non-immersive
Notes	This study was not included in MA because it introduced a different comparison. Funding source: the Italian Ministry of Health (Ricerca Corrente and Rete IRCCS Delle Neuroscienze e Della Neuroriabilitazione – Teleneuroriabilitazione). Declaration of interest: none

Peruzzi 2017

Study characteristics	
Methods	Study design: RCT (2 groups)
Participants	Inclusion criteria: (a) a diagnosis of relapsing remitting multiple sclerosis, (b) an expanded disability status scale – EDSS score between 3 and 5.5 and (c) a mini-mental state examination score of 26 or above, (d) no relapses within the 6 months prior to the study

Peruzzi 2017 *(Continued)*

	Exclusion criteria: chronic medical illnesses, severe visual deficits, severe ataxia or severe depression, patients who received botulinum toxin injection within the past 4 months or functional surgery in the past 6 months Sample size: VR group: 16 Control group: 15 Number of dropouts: VR group: 2 Control group: 4 Age, mean years (SD): VR group: 43.6 (10.2) Control group: 42.0 (12.0) Sex (F/M): VR group: 8/6 Control group: 7/4 Years since MS diagnosis, mean years (SD): VR group: 11.8 (6.8) Control group: 12.4 (4.0) Disease severity, EDSS score, mean (SD): VR group: 4.1 (1.0) Control group: 3.5 (0.8)
Interventions	VR group: virtual reality-based treadmill training. Participants walked on the treadmill while watching a virtual tree-lined trail. They were asked to pass the obstacles appearing on the trail. Dose: 18 sessions (3 sessions of 45 min per week for 6 weeks) Control group: treadmill training Dose: 18 sessions (3 sessions of 45 min per week for 6 weeks)
Outcomes	Gait analysis under single and dual task conditions, 6MWT, 10MWT, TUG, BBS, FSST, EDSS Assessment point: baseline, post-intervention (6 weeks)
Level of immersion	Non-immersive
Notes	Funding source: Fondazione Italiana Sclerosi Multipla, 10.13039/100007366 [FISM 2013/R/10] Declaration of interest: none

Robinson 2015

Study characteristics

Robinson 2015 *(Continued)*

Methods	Study design: RCT (3 groups)
Participants	Inclusion criteria: male or female, aged 18 to 65 years, clinical diagnosis of MS, self-reported ability to walk 100 metres with or without resting with the use of one stick or crutch (equivalent to an Expanded Disability Status Scale score of 6), able to read and comprehend written and spoken English Exclusion criteria: acute exacerbation and/or relapse of MS symptoms within the last 3 months, diagnoses of any other condition affecting the central nervous system, any musculoskeletal injury or receiving physical therapy Sample size: VR group: 20 Conventional group: 16 Control group (no intervention): 15 Number of dropouts: VR group: 0 Conventional group: 1 Control group (no intervention): 4 Age, mean years (SD): VR group: 52.6 (6.1)) Conventional group: 53.9 (6.5) Control group (no intervention): 51.9 (4.7) Sex (F/M): VR group: 14/6 Conventional group: 12/7 Control group (no intervention): 12/5
Interventions	VR group: subject performed following Wii Fit™ exercises: Soccer Heading, Ski Slalom, Table Tilt, Tightrope Walk, Rhythm Boxing, Basic Step and Hula Hoop. These games were each completed 3 times per session. The games Torso Twist and Rowing Squats were completed only once per session. Dose: 8 sessions (2 sessions of 40 to 60 min per week for 4 weeks) Conventional group: received comparable traditional balance exercises Dose: 8 sessions (2 sessions of 40 to 60 min per week for 4 weeks) Control group 2: no intervention
Outcomes	Primary outcomes: postural sway, gait Secondary outcomes: MS walking scale-12, WHO Disability Assessment Schedule 2.0 questionnaire Assessment point: baseline, post-intervention (4 weeks)
Level of immersion	Non-immersive

Robinson 2015 *(Continued)*

Notes	Funding source: North Tees and Hartlepool NHS Foundation Trust and Teesside University for funding the research by way of a doctoral scholarship Declaration of interest: none

Thomas 2017

Study characteristics	
Methods	Study design: RCT (2 groups)
Participants	Inclusion criteria: (1) a clinically definite diagnosis of MS; (2) aged 18 years or above; (3) satisfied a risk assessment; (4) relatively physically inactive (active for a period of 30 min or more on fewer than 5 days per week); (5) having a suitable television at home Exclusion criteria: (1 Adapted Patient Determined Disease Steps (APDDS) scale score of 1 or ≥ 6 (equivalent to an Expanded Disability Status Scale score of 1 or ≥ 6); (2) a relapse within the past 3 months that required treatment with corticosteroids and/or a hospital admission; (3) already participating in exercise or rehabilitation research; (4) a medical condition placing an individual at risk from exercise participation; (5) owns a Wii and is currently using it on a weekly basis or more; (6) unwilling or unable to comply with the protocol (e.g. long vacation planned) Sample size: Immediate VR group: 15 Delayed VR group (control group): 15 Number of dropouts: VR group: 1 Delayed VR group (control group): 0 Age, mean years (SD): Immediate VR group: 50.9 (8.08) Delayed VR group (control group): 47.6 (9.26) Sex (F/M): Immediate VR group: 14/1 Delayed VR group (control group): 13/2 Type of MS: Immediate VR group: 12 RR, 3 SP Delayed VR group (control group): 9 RR, 2 SP, 1 PP, 1 benign, 2 unknown Years since MS diagnosis, mean years (SD): Immediate VR group: < 1 year (n = 1), 1 to 5 years (n = 7), 6 to 10 years (n = 3), 11 to 15 years (n = 2), > 16 years (n = 2) Delayed VR group (control group): < 1 year (n = 2), 1 to 5 years (n = 4), 6 to 10 years (n = 4), 11 to 15 years (n = 1), > 16 years (n = 4) Disease severity, APDDS score:

Thomas 2017 *(Continued)*

	Immediate VR group: 2 (n = 3), 4 (n = 5), 5 (n = 6), 6 (n = 1) Delayed VR group (control group): 2 (n = 2), 3 (n = 1), 4 (n = 2), 5 (n = 10)
Interventions	Immediate VR group: Mii-vitaliSe intervention (personalised exercises performed with the Wii) for 12 months Delayed VR group (control group): Mii-vitaliSe intervention (personalised exercises performed with the Wii) for 6 months after a delay of 6 months
Outcomes	Adverse events Physical activity: Godin Leisure Time Exercise Questionnaire, accelerometer Psychosocial well-being, QoL: HADS, EQ-5D-5L, MSIS-29, Fatigue Symptom Inventory, SF-36 Self-efficacy: SCI-Exercise Self-Efficacy Scale, MS Self-Efficacy Scale Balance/gait/mobility: 2MWT, Step test, Steady Stance Test, i-TUG, gait stride-time rhythmicity, static posturography Hand dexterity/co-ordination: 9HPT Assessment point: baseline, 6 months, post-intervention (12 months)
Level of immersion	Non-immersive
Notes	Included part of the data: VR vs no intervention (only data of T0 and T1). This is the only included study for which the SDs have been calculated Funding source: project grant awarded by the MS Society in the UK (ref no. 933/10). It is included in the National Institute of Health Research. Clinical Research Network (NIHR CRN) portfolio (ID 13130) Declaration of interest: none

Tollár 2019

Study characteristics	
Methods	Study design: RCT (5 groups)
Participants	Inclusion criteria: male or female sex, age ≥ 30 years, EDSS score of 4 to 6, a relapse frequency ≤ 1 per year over the past 5 years to minimise a change in medication and Mini-Mental State Examination score ≥ 24 Exclusion criteria: steroid therapy currently or during the past month, acute exacerbation of MS within 3 months of starting the programme, radiological change in disease progression over the past 2 years, a substantial change in medication over the past year, use of a cane or walker, depression (Beck Depression Inventory (BDI) score > 40), a serious unstable medical condition, severe cardiac disease (i.e. congestive heart failure, ischaemic disease, pacemaker, orthostatic hypotension), uncontrolled diabetes, history of stroke, traumatic brain injury, an epileptic seizure within a year, or current participation in a self-directed or formal group exercise programme Sample size: EXE (VR) group: 14 BAL group: 14

Tollár 2019 *(Continued)*

CYC group: 14

PNF group: 14

CON group: 12

Number of dropouts: 0

Age, mean years (SD):

EXE (VR) group: 48.2 (5.48)

BAL group: 46.9 (6.46)

CYC group: 48.1 (5.65)

PNF group: 46.9 (5.57)

CON group: 44.4 (6.76)

Sex (female, %):

EXE (VR) group: 86

BAL group: 86

CYC group: 93

PNF group: 93

CON group: 92

Type of MS:

EXE (VR) group: 7 RR, 7 PP

BAL group: 9 RR, 5 PP

CYC group: 9 RR, 5 PP

PNF group: 9 RR, 5 PP

CON group: 8 RR, 4 PP

Years since MS diagnosis, mean years (SD):

EXE (VR) group: 12.1 (2.68)

BAL group: 13.6 (4.07)

CYC group: 13.2 (4.42)

PNF group: 12.7 (4.25)

CON group: 14.0 (4.11)

Disease severity, EDSS score, median (range):

EXE (VR) group: 5.0 (5 to 6)

BAL group: 5.0 (5 to 6)

CYC group: 5.0 (5 to 6)

PNF group: 5.0 (5 to 6)

CON group: 5.0 (5 to 6)

Tollár 2019 *(Continued)*

Interventions	EXE group (VR group): received sensorimotor and visuomotor agility training using each of the 3 modules of the Xbox 360 core system BAL group: received training that consisted of dynamic and static balance and stepping exercises performed in multiple directions. CYC group: received spinning class PNF group: PNF intervention delivered by a PNF-trained physical therapist CON group: waitlisted group that continued their standard physical therapy and habitual activity Dose: 25 sessions (5 sessions of 60 min per week for 5 weeks)
Outcomes	Primary outcomes: MSIS-29 Secondary outcomes: EQ5D, BDI, Tinetti Assessment Tool, BBS, 6MWT, COP path length Assessment point: baseline, post intervention (5 weeks)
Level of immersion	Non-immersive
Notes	Only data from the EXE (VR) group, BAL group and CON group included. Funding source: none Declaration of interest: none

Tramontano 2020

Study characteristics	
Methods	Study design: RCT (2 groups)
Participants	Inclusion criteria: aged between 30 and 70 years with the diagnosis of MS according to the McDonald criteria, upper limb deficits and disability between 5 and 8.5 on the EDSS Exclusion criteria: Modified Ashworth Scale > 3 at the upper limb, cognitive deficits affecting the ability to understand task instructions (MMSE < 24), MRC scale with score 0 or 5, presence of clinically evaluated severe comorbidities, pregnancy, participants with artificial pacemaker, participants involved in other studies Sample size: VR group: 15 Control group: 16 Number of dropouts: VR group: 1 Control group: 0 Age, mean years (SD): VR group: 46.7 (10.4) Control group: 52.3 (5.4) Sex (F/M):

Tramontano 2020 *(Continued)*

	VR group: 8/6 Control group: 10/6 Type of MS: VR group: 10 SP, 4 PR Control group: 13 SP, 3 PR Years since MS diagnosis, mean years (SD): VR group: 17.3 (7.06) Control group: 22.4 (9.50) Disease severity, EDSS score, mean (SD): VR group: 6.7 (1.8) Control group: 7.1 (1.0)
Interventions	VR group: performed upper limb training with PABLO-Tyromotion. The training consisted of interactive games-based on virtual reality which allowed a task-oriented approach and neurocognitive feedback. Dose: 12 sessions (3 sessions of 40 min per week for 4 weeks) Control group: performed upper limb sensory-motor training, without robotic support. Specific exercises were performed aimed to recovery global upper limb functions, to control hand grasp and to improve the hand's fine movements. Dose: 12 sessions (3 sessions of 40 min per week for 4 weeks)
Outcomes	Primary outcomes: 9HPT Secondary outcomes: modified Barthel Index, MSQoL-54, Rivermead Mobility Index, Fatigue Severity Scale, MRC upper limb Assessment point: baseline, post-intervention (1 month)
Level of immersion	Non-immersive
Notes	Funding source: none Declaration of interest: not reported

Waliño-Paniagua 2019

Study characteristics	
Methods	Study design: RCT (2 groups)
Participants	Inclusion criteria: a diagnosis of MS according to the McDonald criteria with over 2 years evolution; a score of between 3.5 and 6 on the EDSS; with stable medical treatment during at least the 6 months prior to the intervention; muscle tone in the upper limbs not greater than 2 points on the modified Ashworth Scale; as well as a score of 4 points or less in the "Pyramidal Function" section of the EDSS functional scale; absence of cognitive decline; with the ability to understand instructions and obtaining a score of 24 or more in the Mini-Mental Test; and a score of 2 points or less in the "Mental Functions" section of the EDSS.

Waliño-Paniagua 2019 *(Continued)*

	Exclusion criteria: a diagnosis of another neurological illness or musculoskeletal disorder different to MS; the diagnosis of a cardiovascular, respiratory or metabolic illness or other conditions which may interfere with the study; suffering a flare-up or hospitalisation in the last 3 months prior to commencement of the assessment protocol or during the process of the therapeutic intervention; receiving a cycle of steroids, either intravenously or oral, 6 months prior to the commencement of the assessment protocol and within the study period of intervention; receiving treatment with botulinum toxin in the 6 months prior to the beginning of the study; or the presence of visual disorders not corrected by optical devices Sample size: VR group: 13 Control group: 13 Number of dropouts: VR group: 5 Control group: 5 Age, mean years (SD): VR group: 46.75 (9.31) Control group: 46.13 (9.49) Sex (F/M): VR group: 4/4 Control group: 4/4
Interventions	VR group: received VR treatment in addition to their conventional treatment. They received 20 VR treatment sessions via the online and free website motiongamingconsole.com, during which they performed exercises with video capture of the upper limb movements via the performance of functional and manual dexterity activities based on the following games: Flip Out, Air Hockey, Particles, Dunk It, Counting Fish and Robo Maro. Dose: 20 sessions of conventional treatment (2 sessions of 30 min per week for 10 weeks) + 20 sessions of VR training (2 sessions of 20 min per week for 10 weeks) Control group: received conventional occupational therapy Dose: 20 sessions of conventional treatment (2 sessions of 30 min per week for 10 weeks)
Outcomes	Purdue Pegboard Test, Jebsen-Taylor Hand Function Test, Grooved Pegboard Test Assessment point: baseline, post-intervention (10 weeks)
Level of immersion	Non-immersive
Notes	No adverse events. This study was not included in MA because it introduced a different comparison. Funding source: not reported Declaration of interest: none

Yazgan 2019

Study characteristics	
Methods	Study design: RCT (3 groups)
Participants	Inclusion criteria: participants who were ambulatory and volunteered to participate in the study, who were in a stable phase of the disease, without relapses or worsening in the last 3 months, with an EDSS between 2.5 and 6 and aged between 25 and 60 years Exclusion criteria: a diagnosis of any other disorder affecting the central nervous system, musculoskeletal disorder, pregnancy, blurred vision, psychiatric problems or severe cognitive impairment Sample size: VR group 1: 16 VR group 2: 16 Control group: 15 Number of dropouts: VR group 1: 1 VR group 2: 4 Control group: 0 Age, mean years (SD): VR group 1: 47.46 (10.53) VR group 2: 43.08 (8.74) Control group: 40.66 (8.82) Sex (F/M): VR group 1: 13/2 VR group 2: 12/0 Control group: 13/2 Type of MS: VR group 1: 11 RR, 1 SP, 1 PP, 2 PR VR group 2: 8 RR, 1 SP, 3 PR Control group: 14 RR, 1 PR Years since MS diagnosis, mean years (SD): VR group 1: 12.06 (6.56) VR group 2: 14.91 (6.54) Control group: 11.06 (5.70) Disease severity, EDSS score, mean (SD): VR group 1: 4.16 (1.37) VR group 2: 3.83 (1.49)

Yazgan 2019 *(Continued)*

	Control group: 4.06 (1.26)
Interventions	VR group 1 (Nintendo Wii Fit): the training protocol comprised games such as Penguin Slide, Table Tilt, Ski Slalom, Heading and Balance Bubble, all selected from the Wii Fit Plus balance games section. Dose: 16 sessions (2 sessions of 60 min per week for 8 weeks) VR group 2 (Balance Trainer): the training protocol consisted of Collect Apples, Outline, Paddle War and Evaluation of Movement games, which were included in the device software and allowed the patients to perform balance exercises in different directions. Dose: 16 sessions (2 sessions of 60 min per week for 8 weeks) Control group: waitlist group
Outcomes	Primary outcomes: BBS Secondary outcomes: TUG, 6MWT, FSS, MS international QoL questionnaire Assessment point: baseline, post-intervention (8 weeks)
Level of immersion	Non-immersive
Notes	Funding source: TUBITAK 1002- Short Term R&D Funding Program (Project number: 315S276) and TUBITAK BIDEB2211-A National Scholarship Program for Ph.D. student Declaration of interest: none

10/36 SPART: 10/36 Spatial Recall Test; 10MWT: 10-Metre Walk Test; 25FWT: 25-Foot Walk Test; 2MWT: 2-Minute Walk Test; 3MWT: 3-Minute Walk Test; 6MWT: 6-Minute Walk Test; 9HPT: 9-Hole Peg Test; ABC: Activities-specific Balance Confidence scale; ARAT: Action Research Arm Test; BAL: Balance Assessment Laboratory; BBS: Berg Balance Scale; BBT: Box and Block Test; BDI: Beck Depression Inventory; BICAMS: Brief International Cognitive Assessment for Multiple Sclerosis; BVMT-R: Brief Visuospatial Memory Test-Revised; CDP: computerised dynamic posturography; CESD: Center for Epidemiological Studies Depression Scale; CIs: confidence intervals; CON: control group; COP: centre of pressure; COPE: Coping Orientation to Problems Experienced Inventory; CSRT: choice stepping reaction time; CVLT-II: California Verbal Learning Test, Second Edition; CYC: cycling group; D-10/36-SPART: Delayed 10/36 Spatial Recall Test; DGI: Dynamic Gait Index; DSM-V: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; EDSS: Expanded Disability Status Scale; ESS: Epworth Sleepiness Scale; EXE: exercise group; F: female; FES-I: Falls Efficacy Scale-International; FES: Functional Electrical Stimulation; FIM: Functional Independence Measure; FM-UL: Fugl-Meyer Assessment of Upper Limb; FSS: Fatigue Severity Scale; FSST: Four Square Step Test; h: hours; HADS: Hospital Anxiety and Depression Scale; HRSD: Hamilton Rating Scale for Depression; IQR: interquartile range; IVMP: intravenous methylprednisolone; M: male; MA: meta-analysis; MAL: Motor Activity Log; MAM-36: Manual Ability Measure-36; MAS: Modified Ashworth Scale; MCT: Motor Control Test; MFIS: Modified Fatigue Impact Scale; MI: Motricity Index; MMT: Manual Muscle Testing; MOCA: Montreal Cognitive Assessment; MS: multiple sclerosis; MSIS-29: Multiple Sclerosis Impact Scale-29; MSQoL-54: MS Quality of Life-54; MSWS-12: Multiple Sclerosis Walking Scale-12; MusiQoL: Multiple Sclerosis International Quality of Life Questionnaire; MVT: movement time; N-HPT: Nine-Hole Peg Test; NHPT: Nine-Hole Peg Test; OU: Oculus Unit; PASAT 3: Paced Auditory Serial Addition Test 3-second version; PASAT: Paced Auditory Serial Addition Test; PDQ-5: Perceived Deficits Questionnaire-5; PNF: Proprioceptive Neuromuscular Facilitation; PP: primary progressive; PPT: Physical Performance Test; QoL: quality of life; RAGT: Robot-Assisted Gait Training; RCT: randomised controlled trial; RESE: Regulatory Emotional Self-Efficacy Scale; RR: relapsing-remitting; RRMS: relapsing-remitting multiple sclerosis; RT: reaction time**;** SD: standard deviation; SDMT: Symbol Digit Modalities Test; SF-36: Health Status Questionnaire; SOT: Sensory Organization Test; SP: secondary progressive; SPART-DSRD: Spatial Recall Test-Delayed Spatial Recall Delay; SPART: Spatial Recall Test; SRT-CLTR: Selective Reminding Test-Consistent Long-Term Retrieval; SRT-DR: Selective Reminding Test-Delayed Recall; SRT-LTS: Selective Reminding Test-Long-Term Storage; SRT: Selective Reminding Test; SSST: Six Spot Step Test; STAI-S: State-Trait Anxiety Inventory-State; STAI-T: State-Trait Anxiety Inventory-Trait; T25FWT: Timed 25-Foot Walk Test; TCT: Trunk Control Test; TRT: total response time; TUG: Timed Up and Go test; UL: upper limb; VR: virtual reality; VRRS: virtual reality rehabilitation system; WLG: Word List Generation

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Akinwuntan 2012	Congress participation
Akinwuntan 2014	Not considered to be properly randomised
Allen 1998	Study design: single group
Al-Sharman 2019	Study design: MS versus healthy controls
Altinkaya 2012	Congress participation
Amato 2012	Congress participation
Amato 2013	Did not meet the definition of a VR intervention
Amato 2014	Did not meet the definition of a VR intervention (computer-assisted rehab)
Amiri 2022	Study design: single group
Arian Darestani 2020	Did not meet the definition of a VR intervention (RehaCom software)
Arsoy 2018	Did not meet the definition of a VR intervention (computer-assisted rehab)
Babaei-Ghazani 2013	Congress participation
Baram 2006	Augmented reality
Baram 2010	Augmented reality
Baram 2013	Augmented reality
Barker 2019	Did not meet the definition of a VR intervention (computer-assisted rehab)
Blair 2021	Did not meet the definition of a VR intervention (computer-assisted rehab)
Bonavita 2015	Did not meet the definition of a VR intervention (computer-assisted rehab)
Bove 2018	Congress participation
Bove 2019	Study design: single group
Bove 2019b	Congress participation
Bove 2021a	Duplicate
Cadorin 2015	Congress participation
Calabro 2017	Duplicate
Campbell 2015	Congress participation
Campbell 2015a	Congress participation
Campbell 2015b	Congress participation
Campbell 2016	Did not meet the definition of a VR intervention (RehaCom software)

Study	Reason for exclusion
Cano Porras 2019	Study design: retrospective, mixed population
Cerasa 2012	Duplicate
Cerasa 2013	Did not meet the definition of a VR intervention (computer-assisted rehab)
Cerezo-Garcia 2018	Congress participation
Charvet 2015	Did not meet the definition of a VR intervention
Charvet 2015b	Congress participation
Charvet 2016	Congress participation
Charvet 2017	Did not meet the definition of a VR intervention (computer-assisted rehab)
Chiaravalloti 2018	Did not meet the definition of a VR intervention
Chiaravalloti 2018a	Duplicate
Chmelarova 2020	Did not meet the definition of a VR intervention (computer-assisted rehab)
Cooper 2011	Did not meet the definition of a VR intervention (computer-assisted rehab)
Cooper 2012	Did not meet the definition of a VR intervention
Corrini 2017	Congress participation
Cuesta-gomez 2022	Did not meet the definition of a VR intervention
Dana 2019	Did not meet the definition of a VR intervention
De Giglio 2013	Congress participation
De Giglio 2014	Congress participation
De Giglio 2015	Did not meet the definition of a VR intervention
De Giglio 2015a	Congress participation
De Giglio 2016	Did not meet the definition of a VR intervention
De Giglio 2016a	Letter to the editor
De Luca 2019	Did not meet the definition of a VR intervention
De Luca 2021	Did not meet the definition of a VR intervention (computer-assisted rehab)
Di Tella 2020	Study design: mixed population
Erratum	Correction for article
Eshaghi 2015	Congress participation
Filippi 2012	Did not meet the definition of a VR intervention (RehaCom software)

Study	Reason for exclusion
Fjeldstad-Pardo 2018	Did not meet the definition of a VR intervention (telerehabilitation)
Flachenecker 2017	Did not meet the definition of a VR intervention
Forsberg 2015	Study design: qualitative research, interviews
Francavilla 2015	Congress participation
Glusman 2020	PhD dissertation
Güçlü Altun 2015	Study design: single group
Guidi 2013	Letter to the editor
Gutierrez 2013	Duplicate
Hancock 2012	Congress participation
Hancock 2015	Did not meet the definition of a VR intervention
Hebert 2016	Congress participation
Hebert 2018	Did not meet the definition of a VR intervention
Hildebrandt 2007	Did not meet the definition of a VR intervention
Hind 2010	Study design: qualitative research, interviews
Hojjatollah 2012	Did not meet the definition of a VR intervention
Hortobagyi 2022	Duplicate
Hsu 2020	Congress participation
Hubacher 2015	Study design: case-based
Iaffaldano 2015	Congress participation
Iaffaldano 2016	Congress participation
Janssen 2014	Congress participation
Jonsdottir 2018a	Duplicate
Kahraman 2020	Did not meet the definition of a VR intervention: telerehabilitation
Kalron 2012	Study design: single session, single group
Kalron 2016a	Congress participation
Kavaklioglu 2017	Congress participation
Kazemi 2022	Did not meet the definition of a VR intervention
Keytsman 2019	Did not meet the definition of a VR intervention

Study	Reason for exclusion
Khalil 2019	Duplicate
Khalil 2019a	Duplicate
Koubiyr 2018	Congress participation
Lamargue 2020	Did not meet the definition of a VR intervention
Lamargue-Hamel 2017	Congress participation
Leocani 2007	Study design: single session
Lo 2011	Cross-over design
Maggio 2022a	Duplicate
Manca 2018	Congress participation
Manca 2021	Did not meet the definition of a VR intervention (network-based rehab)
Manglani 2020	Did not meet the definition of a VR intervention
Mangone 2012	Congress participation
Mäntynen 2014	Did not meet the definition of a VR intervention
Maris 2018	Cohort study
Mattioli 2010	Did not meet the definition of a VR intervention (RehaCom software)
Menascu 2021	Did not meet the definition of a VR intervention
Mendozzi 1998	Did not meet the definition of a VR intervention (RehaCom software)
Messinis 2015	Congress participation
Messinis 2017	Did not meet the definition of a VR intervention
Messinis 2019	Congress participation
Messinis 2020	Did not meet the definition of a VR intervention
Mishra 2013	Did not meet the definition of a VR intervention
Mitolo 2015	Congress participation
Molhemi 2018	Congress participation
Molhemi 2018a	Duplicate
Molhemi 2020	Duplicate
Molhemi 2021a	Duplicate
Moustafaa 2022	Did not meet the definition of a VR intervention

Study	Reason for exclusion
Munari 2018	Congress participation
Naeeni Davarani 2020	Did not meet the definition of a VR intervention
Naeeni Davarani 2022	Did not meet the definition of a VR intervention (RehaCom software)
Norouzi 2021a	Duplicate
Nurova 2014	Congress participation
Nurova 2014a	Congress participation
Ozdogar 2017	Congress participation
Ozdogar 2018	Congress participation
Ozdogar 2021	Congress participation
Ozkul 2020a	Duplicate
Pardo 2016	Congress participation
Parisi 2012	Congress participation
Parisi 2012a	Duplicate
Parisi 2014	Did not meet the definition of a VR intervention (RehaCom software)
Pau 2015	Study design: single group
Paul 2019	Did not meet the definition of a VR intervention
Penasco-Martin 2010	Review
Perez 2016	Congress participation
Perez-Martin 2017	Did not meet the definition of a VR intervention
Peruzzi 2015	Congress participation
Peruzzi 2016	Study design: single group
Peruzzi 2017a	Duplicate
Pilutti 2014	Did not meet the definition of a VR intervention
Plohmann 1994	Congress participation
Poettgen 2015	Congress participation
Pöttgen 2022	Did not meet the definition of a VR intervention
Prosperini 2010	Cross-over design
Prosperini 2014	Cross-over study

Study	Reason for exclusion
Prouskas 2019	Congress participation
Pusswald 2014	Did not meet the definition of a VR intervention
Rahmani 2020	Did not meet the definition of a VR intervention
Russo 2018	Duplicate
Sastre-Garriga 2011	Study design: MS vs healthy
Scanlan 2013	Synopsis
Schättin 2021	Study design: not a RCT
Schwartz 2012	Did not meet the definition of a VR intervention
Severini 2017	Study design: single session
Shahrbanian 2017	Congress participation
Sharifi 2019	Did not meet the definition of a VR intervention (computer-assisted rehab)
Shatil 2010	Did not meet the definition of a VR intervention
Shaw 2019	Congress participation
Solari 2004	Did not meet the definition of a VR intervention
Solari 2004a	Correction for article
Solaro 2020	Did not meet the definition of a VR intervention
Solaro 2020a	Duplicate
Stough 2016	Congress participation
Streicher 2018	Retrospective chart review
Stuifbergen 2011	Study design: qualitative research
Stuifbergen 2011a	Duplicate
Stuifbergen 2012	Did not meet the definition of a VR intervention
Stuifbergen 2018	Did not meet the definition of a VR intervention (computer-assisted rehab)
Stuifbergen 2018a	Duplicate
Thomas 2017a	Duplicate
Tiozzo 2010	Congress participation
Topcular 2011	Congress participation
Tuzun 2018	Congress participation

Study	Reason for exclusion
Vilou 2020	Did not meet the definition of a VR intervention (computer-assisted rehab)
Vogt 2008	Did not meet the definition of a VR intervention
Vogt 2009	Did not meet the definition of a VR intervention
Winter 2021	Study design: healthy vs MS or stroke
Yazgan 2019a	Duplicate
Yazgan 2020	Duplicate
Zare 2019	Did not meet the definition of a VR intervention
Zenginler 2016	Congress participation
Zenginler 2017	Congress participation

MS: multiple sclerosis; RCT: randomised controlled trial; VR: virtual reality

RISK OF BIAS

Legend: ✓ Low risk of bias ✗ High risk of bias ~ Some concerns

Risk of bias for analysis 1.1 TUG

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Eftekharsadat 2015	✓	✓	✓	✓	~	~
Hoang 2015	✓	~	✓	✓	~	✗
Nilsagård 2012	✓	~	✓	✓	~	✗
Novotna 2019	~	✓	✓	~	~	✗
Thomas 2017	✓	~	✓	✓	~	✗
Yazgan 2019	~	~	✓	~	~	✗

Risk of bias for analysis 1.2 MS Walking Scale - 12

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Nilsagård 2012	✓	~	✓	✓	~	✗
Novotna 2019	~	✓	✓	~	~	✗
Ozdogar 2020	~	~	✓	~	~	✗
Robinson 2015	~	✓	✓	✓	~	✗

Risk of bias for analysis 1.3 Walking endurance

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Hoang 2015	✓	~	✓	✓	~	✗
Thomas 2017	✓	~	✓	✓	~	✗
Tollár 2019	✓	✓	✓	✓	~	~
Yazgan 2019	~	~	✓	~	~	✗

Risk of bias for analysis 1.4 Gait speed

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Hoang 2015	✓	~	✓	✓	~	✗
Nilsagård 2012	✓	~	✓	✓	~	✗
Novotna 2019	~	✓	✓	~	~	✗

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Ozdogar 2020	~	~	✓	~	~	✗
Robinson 2015	~	✓	✓	✓	~	✗

Risk of bias for analysis 2.1 BBS

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Eftekharsadat 2015	✓	✓	✓	✓	~	~
Novotna 2019	~	✓	✓	~	~	✗
Tollár 2019	✓	✓	✓	✓	~	~
Yazgan 2019	~	~	✓	~	~	✗

Risk of bias for analysis 3.1 9HPT

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Hoang 2015	✓	~	✓	✓	~	✗
Ozdogar 2020	~	~	✓	~	~	✗

Risk of bias for analysis 4.1 TUG - cognitive

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Hoang 2015	✓	~	✓	✓	~	✗
Nilsagård 2012	✓	~	✓	✓	~	✗
Novotna 2019	~	✓	✓	~	~	✗

Risk of bias for analysis 4.2 Symbol Digit Modalities Test

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Hoang 2015	✓	~	✓	✓	~	✗
Janssen 2015	✓	~	✓	✓	~	✗
Ozdogar 2020	~	~	✓	~	~	✗

Risk of bias for analysis 5.1 ABC scale

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Nilsagård 2012	✓	~	✓	✓	~	✗
Novotna 2019	~	✓	✓	~	~	✗
Ozdogar 2020	~	~	✓	~	~	✗

Risk of bias for analysis 5.2 BDI

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Ozdogar 2020	~	~	✓	~	~	✗
Tollár 2019	✓	✓	✓	✓	~	~

Risk of bias for analysis 5.3 MS International QoL

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Ozdogar 2020	~	~	✓	~	~	✗
Yazgan 2019	~	~	✓	~	~	✗

Risk of bias for analysis 6.1 TUG

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Khalil 2018	✓	~	✓	✓	~	✗
Lozano-Quilis 2014	~	~	✓	~	~	✗
Molhemi 2021	✓	✓	✓	✓	~	~
Peruzzi 2017	~	~	✓	✓	~	✗

Risk of bias for analysis 6.2 MS Walking Scale - 12

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Molhemi 2021	✓	✓	✓	✓	~	~
Ozdogar 2020	~	~	✓	~	~	✗
Ozdogar 2022	~	✓	✓	✓	~	✗
Robinson 2015	~	✓	✓	✓	~	✗

Risk of bias for analysis 6.3 Walking endurance

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Khalil 2018	✓	~	✓	✓	~	✗
Ozdogar 2022	~	✓	✓	✓	~	✗
Peruzzi 2017	~	~	✓	✓	~	✗
Tollár 2019	✓	✓	✓	✓	~	~

Risk of bias for analysis 6.4 Gait speed

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Khalil 2018	✓	~	✓	✓	~	✗
Kramer 2014	~	✓	✓	✓	~	✗

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Lozano-Quilis 2014	~	~	✓	~	~	✗
Molhemi 2021	✓	✓	✓	✓	~	~
Ozdogar 2020	~	~	✓	~	~	✗
Ozdogar 2022	~	✓	✓	✓	~	✗
Peruzzi 2017	~	~	✓	✓	~	✗
Robinson 2015	~	✓	✓	✓	~	✗

Risk of bias for analysis 7.1 BBS

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Brichetto 2013	✓	✓	✓	✓	~	~
Kalron 2016	✓	~	✓	✓	~	✗
Khalil 2018	✓	~	✓	✓	~	✗
Lozano-Quilis 2014	~	~	✓	~	~	✗
Molhemi 2021	✓	✓	✓	✓	~	~
Peruzzi 2017	~	~	✓	✓	~	✗
Tollár 2019	✓	✓	✓	✓	~	~

Risk of bias for analysis 7.2 Tinetti Test

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Lozano-Quilis 2014	~	~	✓	~	~	✗
Tollár 2019	✓	✓	✓	✓	~	~

Risk of bias for analysis 7.3 FSST

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Kalron 2016	✓	~	✓	✓	~	✗
Peruzzi 2017	~	~	✓	✓	~	✗

Risk of bias for analysis 8.1 9HPT

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Ozdogar 2020	~	~	✓	~	~	✗
Ozdogar 2022	~	✓	✓	✓	~	✗
Tramontano 2020	✓	~	✓	✓	~	✗

Risk of bias for analysis 9.1 ABC scale

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Molhemi 2021	✓	✓	✓	✓	~	~
Ozdogar 2020	~	~	✓	~	~	✗

Risk of bias for analysis 9.2 BDI

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Ozdogar 2020	~	~	✓	~	~	✗
Tollár 2019	✓	✓	✓	✓	~	~

Risk of bias for analysis 9.3 FES-1

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Kalron 2016	✓	~	✓	✓	~	✗
Khalil 2018	✓	~	✓	✓	~	✗
Molhemi 2021	✓	✓	✓	✓	~	~

Risk of bias for analysis 10.1 Fatigue

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Brichetto 2013	✓	✓	✓	✓	~	~
Khalil 2018	✓	~	✓	✓	~	✗
Ozdogar 2020	~	~	✓	~	~	✗
Ozdogar 2022	~	✓	✓	✓	~	✗
Tramontano 2020	✓	~	✓	✓	~	✗

Risk of bias for analysis 11.1 PASAT

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Bove 2021	~	✓	✓	✓	✓	~
Munari 2020	✓	~	✓	✓	~	✗

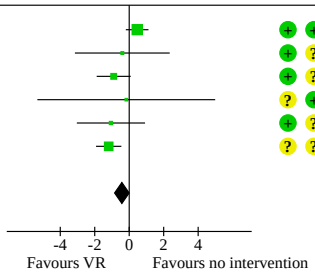
DATA AND ANALYSES

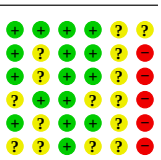
Comparison 1. VR vs no intervention - lower limb and gait function

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.1 TUG	6	264	Mean Difference (IV, Fixed, 95% CI)	-0.43 [-0.85, -0.00]
1.2 MS Walking Scale - 12	4	194	Mean Difference (IV, Fixed, 95% CI)	-1.16 [-4.04, 1.72]
1.3 Walking endurance	4	141	Std. Mean Difference (IV, Fixed, 95% CI)	0.34 [-0.00, 0.68]
1.4 Gait speed	5	238	Std. Mean Difference (IV, Fixed, 95% CI)	0.39 [0.13, 0.65]

Analysis 1.1. Comparison 1: VR vs no intervention - lower limb and gait function, Outcome 1: TUG

Study or Subgroup	VR Mean	VR SD	VR Total	No intervention Mean	No intervention SD	No intervention Total	Weight	Mean Difference IV, Fixed, 95% CI
Eftekharsadat 2015	0.66	0.72	15	0.2	1.08	15	41.2%	0.46 [-0.20 , 1.12]
Hoang 2015	-0.8	5.01	23	-0.4	4.29	21	2.4%	-0.40 [-3.15 , 2.35]
Nilsagård 2012	-0.8	2.4	41	0.1	2.1	39	18.3%	-0.90 [-1.89 , 0.09]
Novotna 2019	-0.62	10.79	23	-0.45	5.46	16	0.7%	-0.17 [-5.33 , 4.99]
Thomas 2017	-0.53	2.82	14	0.53	2.6	15	4.5%	-1.06 [-3.04 , 0.92]
Yazgan 2019	-1.14	1.33	27	0.05	1.06	15	33.0%	-1.19 [-1.92 , -0.46]
Total			**143**			**121**	**100.0%**	**-0.43 [-0.85 , -0.00]**



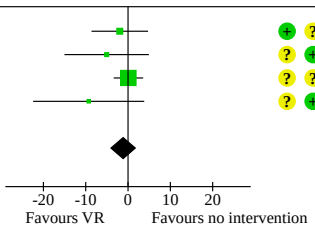


Test for overall effect: Z = 1.98 (P = 0.05)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 12.44, df = 5 (P = 0.03); I² = 60%

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.2. Comparison 1: VR vs no intervention - lower limb and gait function, Outcome 2: MS Walking Scale - 12

Study or Subgroup	VR Mean	VR SD	VR Total	No intervention Mean	No intervention SD	No intervention Total	Weight	Mean Difference IV, Fixed, 95% CI
Nilsagård 2012	-5.9	11.5	41	-3.95	18.1	39	18.6%	-1.95 [-8.63 , 4.73]
Novotna 2019	-1.61	16.58	23	3.44	14.95	16	8.3%	-5.05 [-15.03 , 4.93]
Ozdogar 2020	-0.9	7.4	20	-1	2.9	20	68.3%	0.10 [-3.38 , 3.58]
Robinson 2015	-5.5	16.59	20	3.8	21.6	15	4.8%	-9.30 [-22.43 , 3.83]
Total			**104**			**90**	**100.0%**	**-1.16 [-4.04 , 1.72]**

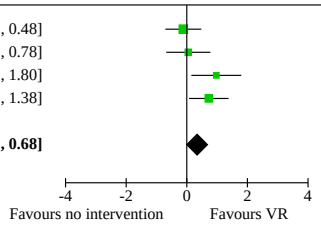


Test for overall effect: Z = 0.79 (P = 0.43)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 2.62, df = 3 (P = 0.45); I² = 0%

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.3. Comparison 1: VR vs no intervention - lower limb and gait function, Outcome 3: Walking endurance

Study or Subgroup	VR Mean	VR SD	VR Total	No intervention Mean	No intervention SD	No intervention Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Hoang 2015	2	89.37	23	13	99.86	21	33.3%	-0.11 [-0.71 , 0.48]	+ ? + + ? −
Thomas 2017	0.56	18.05	14	-0.64	27.51	15	22.0%	0.05 [-0.68 , 0.78]	+ ? + + ? −
Tollár 2019	57.4	52.09	14	6.3	49.27	12	17.2%	0.97 [0.15 , 1.80]	+ + + + ? ?
Yazgan 2019	34.06	30.91	27	7.59	43.3	15	27.5%	0.73 [0.07 , 1.38]	? ? + ? ? −
Total			**78**			**63**	**100.0%**	**0.34 [-0.00 , 0.68]**	

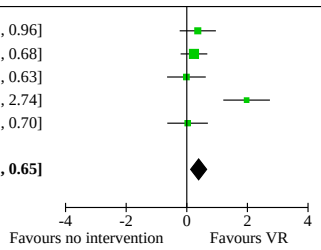


Test for overall effect: Z = 1.95 (P = 0.05)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 6.50, df = 3 (P = 0.09); I² = 54%

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.4. Comparison 1: VR vs no intervention - lower limb and gait function, Outcome 4: Gait speed

Study or Subgroup	VR Mean	VR SD	VR Total	No intervention Mean	No intervention SD	No intervention Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Hoang 2015	2	4.58	23	0.3	4.63	21	19.6%	0.36 [-0.23 , 0.96]	+ ? + + ? −
Nilsagård 2012	0.3	1.1	41	0	1.4	39	36.0%	0.24 [-0.20 , 0.68]	+ ? + + ? −
Novotna 2019	5.41	44.25	23	5.91	34.86	16	17.1%	-0.01 [-0.65 , 0.63]	? + + ? ? −
Ozdogar 2020	2.6	1.9	20	-0.6	1.2	20	11.8%	1.97 [1.20 , 2.74]	? ? + ? ? −
Robinson 2015	11.9	28.04	20	11.1	32.3	15	15.5%	0.03 [-0.64 , 0.70]	? + + + ? −
Total			**127**			**111**	**100.0%**	**0.39 [0.13 , 0.65]**	



Test for overall effect: Z = 2.90 (P = 0.004)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 19.42, df = 4 (P = 0.0006); I² = 79%

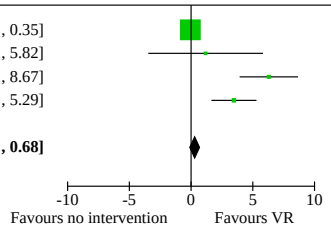
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 2. VR vs no intervention - balance and postural control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 BBS	4	137	Mean Difference (IV, Fixed, 95% CI)	0.29 [-0.10, 0.68]

Analysis 2.1. Comparison 2: VR vs no intervention - balance and postural control, Outcome 1: BBS

Study or Subgroup	VR Mean	VR SD	VR Total	No intervention Mean	No intervention SD	No intervention Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Eftekharsadat 2015	0.2	0.41	15	0.26	0.7	15	91.9%	-0.06 [-0.47 , 0.35]	+ + + + ? ?
Novotna 2019	1.87	9.09	23	0.69	5.69	16	0.7%	1.18 [-3.46 , 5.82]	? + + ? ? -
Tollár 2019	6.1	3.52	14	-0.2	2.62	12	2.8%	6.30 [3.93 , 8.67]	+ + + + ? ?
Yazgan 2019	4.4	4.38	27	0.93	1.53	15	4.7%	3.47 [1.65 , 5.29]	? ? + ? ? -
Total			**79**			**58**	**100.0%**	**0.29 [-0.10 , 0.68]**	



Test for overall effect: Z = 1.44 (P = 0.15)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 39.39, df = 3 (P < 0.00001); I² = 92%

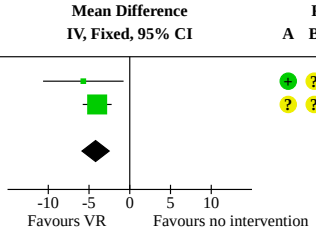
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 3. VR vs no intervention - upper limb function

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 9HPT	2	84	Mean Difference (IV, Fixed, 95% CI)	-4.19 [-5.86, -2.52]

Analysis 3.1. Comparison 3: VR vs no intervention - upper limb function, Outcome 1: 9HPT

Study or Subgroup	VR Mean	VR SD	VR Total	No intervention Mean	No intervention SD	No intervention Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Hoang 2015	-3.6	7.85	23	2.1	8.78	21	11.4%	-5.70 [-10.64 , -0.76]	+ ? + + ? -
Ozdogar 2020	-3.5	3.4	20	0.5	2.2	20	88.6%	-4.00 [-5.77 , -2.23]	? ? + ? ? -
Total			**43**			**41**	**100.0%**	**-4.19 [-5.86 , -2.52]**	



Test for overall effect: Z = 4.92 (P < 0.00001)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.40, df = 1 (P = 0.53); I² = 0%

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

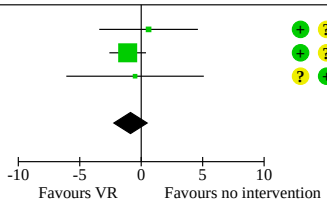
Comparison 4. VR vs no intervention - cognition

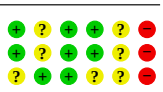
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 TUG - cognitive	3	163	Mean Difference (IV, Fixed, 95% CI)	-0.87 [-2.23, 0.48]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2 Symbol Digit Modalities Test	3	112	Mean Difference (IV, Fixed, 95% CI)	6.70 [3.22, 10.18]

Analysis 4.1. Comparison 4: VR vs no intervention - cognition, Outcome 1: TUG - cognitive

Study or Subgroup	VR Mean	VR SD	VR Total	No intervention Mean	No intervention SD	No intervention Total	Weight	Mean Difference IV, Fixed, 95% CI
Hoang 2015	-2	6.43	23	-2.6	7.09	21	11.4%	0.60 [-3.41 , 4.61]
Nilsagård 2012	-1.9	4.2	41	-0.8	2.4	39	82.7%	-1.10 [-2.59 , 0.39]
Novotna 2019	-1.66	11.54	23	-1.16	6.14	16	5.9%	-0.50 [-6.09 , 5.09]
Total			**87**			**76**	**100.0%**	**-0.87 [-2.23 , 0.48]**



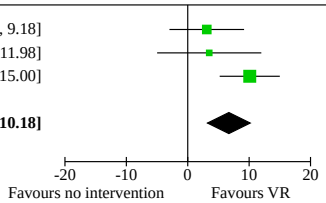


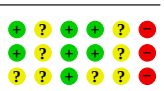
Test for overall effect: Z = 1.26 (P = 0.21)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.62, df = 2 (P = 0.73); I² = 0%

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.2. Comparison 4: VR vs no intervention - cognition, Outcome 2: Symbol Digit Modalities Test

Study or Subgroup	VR Mean	VR SD	VR Total	No intervention Mean	No intervention SD	No intervention Total	Weight	Mean Difference IV, Fixed, 95% CI
Hoang 2015	2.2	10.05	23	-0.9	10.47	21	32.7%	3.10 [-2.98 , 9.18]
Janssen 2015	1.28	11.89	14	-2.22	11	14	16.8%	3.50 [-4.98 , 11.98]
Ozdogar 2020	4.8	7.2	20	-5.3	8.54	20	50.5%	10.10 [5.20 , 15.00]
Total			**57**			**55**	**100.0%**	**6.70 [3.22 , 10.18]**





Test for overall effect: Z = 3.78 (P = 0.0002)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 3.75, df = 2 (P = 0.15); I² = 47%

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

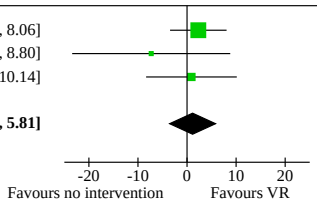
Comparison 5. VR vs no intervention - participation and QoL

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 ABC scale	3	159	Mean Difference (IV, Fixed, 95% CI)	1.13 [-3.54, 5.81]
5.2 BDI	2	66	Mean Difference (IV, Fixed, 95% CI)	-0.63 [-2.51, 1.24]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.3 MS International QoL	2	82	Mean Difference (IV, Fixed, 95% CI)	9.24 [5.76, 12.73]

Analysis 5.1. Comparison 5: VR vs no intervention - participation and QoL, Outcome 1: ABC scale

Study or Subgroup	VR Mean	VR SD	VR Total	No intervention Mean	No intervention SD	No intervention Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Nilsagård 2012	5	14.4	41	2.7	11.8	39	66.0%	2.30 [-3.46 , 8.06]	+ ? + + ? −
Novotna 2019	-4.84	25.47	23	2.46	25.08	16	8.4%	-7.30 [-23.40 , 8.80]	? + + ? ? −
Ozdogar 2020	-1.2	14.5	20	-2.1	15.3	20	25.6%	0.90 [-8.34 , 10.14]	? ? + ? ? −
Total			**84**			**75**	**100.0%**	**1.13 [-3.54 , 5.81]**	

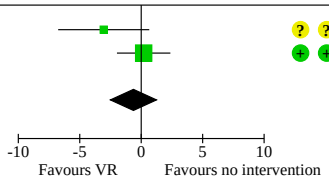


Test for overall effect: Z = 0.47 (P = 0.64)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 1.21, df = 2 (P = 0.55); I² = 0%

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 5.2. Comparison 5: VR vs no intervention - participation and QoL, Outcome 2: BDI

Study or Subgroup	VR Mean	VR SD	VR Total	No intervention Mean	No intervention SD	No intervention Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Ozdogar 2020	-3.9	7.1	20	-0.85	4.59	20	25.6%	-3.05 [-6.76 , 0.66]	? ? + ? ? −
Tollár 2019	-0.2	2.67	14	-0.4	2.94	12	74.4%	0.20 [-1.97 , 2.37]	+ + + + ? ?
Total			**34**			**32**	**100.0%**	**-0.63 [-2.51 , 1.24]**	

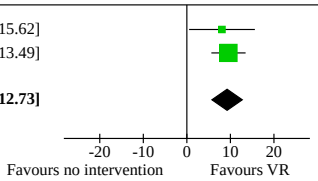


Test for overall effect: Z = 0.66 (P = 0.51)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 2.20, df = 1 (P = 0.14); I² = 55%

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 5.3. Comparison 5: VR vs no intervention - participation and QoL, Outcome 3: MS International QoL

Study or Subgroup	VR Mean	VR SD	VR Total	No intervention Mean	No intervention SD	No intervention Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Ozdogar 2020	5.5	13.3	20	-2.57	10.95	20	21.3%	8.07 [0.52 , 15.62]	? ? + ? ? −
Yazgan 2019	9.37	6.662	27	-0.19	5.97	15	78.7%	9.56 [5.63 , 13.49]	? ? + ? ? −
Total			**47**			**35**	**100.0%**	**9.24 [5.76 , 12.73]**	



Test for overall effect: Z = 5.20 (P < 0.00001)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.12, df = 1 (P = 0.73); I² = 0%

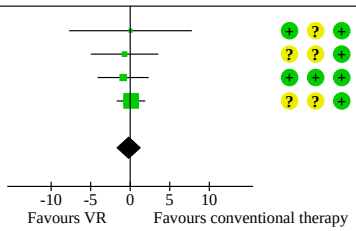
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 6. VR vs conventional therapy - lower limb and gait function

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
6.1 TUG	4	107	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-1.65, 1.25]
6.2 MS Walking Scale - 12	4	138	Mean Difference (IV, Fixed, 95% CI)	1.01 [-2.00, 4.02]
6.3 Walking endurance	4	111	Std. Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.28, 0.48]
6.4 Gait speed	8	247	Std. Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.22, 0.29]

Analysis 6.1. Comparison 6: VR vs conventional therapy - lower limb and gait function, Outcome 1: TUG

Study or Subgroup	VR Mean	VR SD	VR Total	Conventional therapy Mean	Conventional therapy SD	Conventional therapy Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Khalil 2018	-0.55	5.49	16	-0.59	14.85	16	3.5%	0.04 [-7.72 , 7.80]	+ ? + + ? −
Lozano-Quilis 2014	-2.374	3.02	6	-1.66	4.02	5	11.6%	-0.71 [-4.99 , 3.56]	? ? + ? ? −
Molhemi 2021	-2.1	2.81	19	-1.2	6.78	20	20.3%	-0.90 [-4.13 , 2.33]	+ + + + ? ?
Peruzzi 2017	-0.6	2.36	14	-0.7	2.23	11	64.7%	0.10 [-1.71 , 1.91]	? ? + + ? −
Total			**55**			**52**	**100.0%**	**-0.20 [-1.65 , 1.25]**	

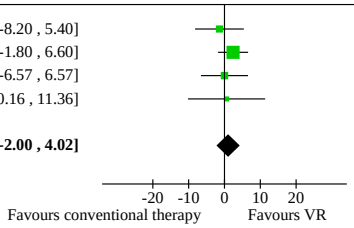


Test for overall effect: Z = 0.27 (P = 0.79)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.35, df = 3 (P = 0.95); I² = 0%

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 6.2. Comparison 6: VR vs conventional therapy - lower limb and gait function, Outcome 2: MS Walking Scale - 12

Study or Subgroup	VR Mean	VR SD	VR Total	Conventional therapy Mean	Conventional therapy SD	Conventional therapy Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F
Molhemi 2021	-12.2	10.66	19	-10.8	11.01	20	19.6%	-1.40 [-8.20 , 5.40]	+	+	+	+	?	?
Ozdogar 2020	-0.9	7.4	20	-3.3	5.6	17	51.5%	2.40 [-1.80 , 6.60]	?	?	+	?	?	−
Ozdogar 2022	-4.93	8.62	12	-4.93	8.4	14	21.0%	0.00 [-6.57 , 6.57]	?	+	+	+	?	−
Robinson 2015	-5.5	16.59	20	-6.1	16.2	16	7.8%	0.60 [-10.16 , 11.36]	?	+	+	+	?	−
Total			**71**			**67**	**100.0%**	**1.01 [-2.00 , 4.02]**						

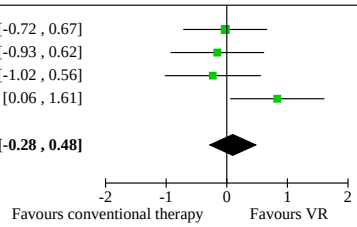


Test for overall effect: Z = 0.66 (P = 0.51)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 1.00, df = 3 (P = 0.80); I² = 0%

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 6.3. Comparison 6: VR vs conventional therapy - lower limb and gait function, Outcome 3: Walking endurance

Study or Subgroup	VR Mean	VR SD	VR Total	Conventional therapy Mean	Conventional therapy SD	Conventional therapy Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F
Khalil 2018	-6.44	61.84	16	-4.75	67.17	16	29.7%	-0.03 [-0.72 , 0.67]	+	?	+	+	?	−
Ozdogar 2022	6.4	10.54	12	8.93	18.94	14	23.9%	-0.16 [-0.93 , 0.62]	?	+	+	+	?	−
Peruzzi 2017	34	58.64	14	50	76.74	11	22.7%	-0.23 [-1.02 , 0.56]	?	?	+	+	?	−
Tollár 2019	57.4	52.09	14	19.2	35.4	14	23.6%	0.83 [0.06 , 1.61]	+	+	+	+	?	?
Total			**56**			**55**	**100.0%**	**0.10 [-0.28 , 0.48]**						

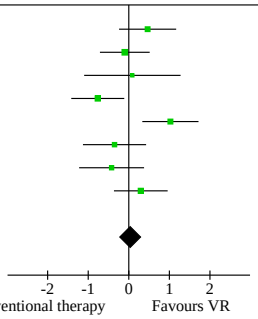


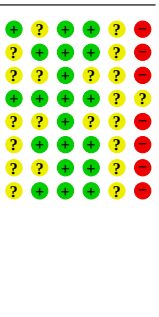
Test for overall effect: Z = 0.52 (P = 0.61)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 4.63, df = 3 (P = 0.20); I² = 35%

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 6.4. Comparison 6: VR vs conventional therapy - lower limb and gait function, Outcome 4: Gait speed

Study or Subgroup	VR Mean	VR SD	VR Total	Conventional therapy Mean	Conventional therapy SD	Conventional therapy Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Khalil 2018	1.08	2.77	16	-7.58	25.58	16	13.2%	0.46 [-0.24 , 1.17]
Kramer 2014	0.14	0.19	21	0.16	0.21	20	17.4%	-0.10 [-0.71 , 0.51]
Lozano-Quilis 2014	2.693	6.05	6	2.135	5.48	5	4.6%	0.09 [-1.10 , 1.28]
Molhemi 2021	-0.2	0.2	19	0	0.3	20	15.3%	-0.76 [-1.42 , -0.11]
Ozdogar 2020	2.6	1.9	20	1	0.9	17	13.6%	1.03 [0.33 , 1.72]
Ozdogar 2022	0.18	0.75	12	0.456	0.77	14	10.8%	-0.35 [-1.13 , 0.43]
Peruzzi 2017	-0.18	0.19	14	-0.08	0.27	11	10.2%	-0.42 [-1.22 , 0.38]
Robinson 2015	11.9	28.04	20	4.1	22.55	16	14.9%	0.30 [-0.37 , 0.96]
Total			**128**			**119**	**100.0%**	**0.03 [-0.22 , 0.29]**





Test for overall effect: Z = 0.26 (P = 0.79)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 18.05, df = 7 (P = 0.01); I² = 61%

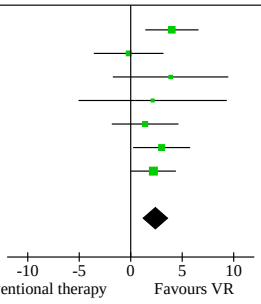
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 7. VR vs conventional therapy - balance and postural control

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
7.1 BBS	7	201	Mean Difference (IV, Fixed, 95% CI)	2.39 [1.22, 3.57]
7.2 Tinetti Test	2	39	Mean Difference (IV, Fixed, 95% CI)	0.98 [-0.50, 2.47]
7.3 FSST	2	55	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-3.21, 2.01]

Analysis 7.1. Comparison 7: VR vs conventional therapy - balance and postural control, Outcome 1: BBS

Study or Subgroup	VR Mean	VR SD	VR Total	Conventional therapy Mean	Conventional therapy SD	Conventional therapy Total	Weight	Mean Difference IV, Fixed, 95% CI
Brichetto 2013	5	4.25	18	1	3.64	18	20.7%	4.00 [1.41 , 6.59]
Kalron 2016	1.1	4.2	15	1.3	5.2	15	12.1%	-0.20 [-3.58 , 3.18]
Khalil 2018	6.75	5.72	16	2.88	9.91	16	4.4%	3.87 [-1.74 , 9.48]
Lozano-Quilis 2014	2.333	6.01	6	0.2	6.11	5	2.7%	2.13 [-5.06 , 9.33]
Molhemi 2021	5.8	3.38	19	4.4	6.52	20	13.2%	1.40 [-1.84 , 4.64]
Peruzzi 2017	4	4.36	14	1	2.65	11	18.0%	3.00 [0.23 , 5.77]
Tollár 2019	6.1	3.52	14	3.9	2.25	14	28.9%	2.20 [0.01 , 4.39]
Total			**102**			**99**	**100.0%**	**2.39 [1.22 , 3.57]**

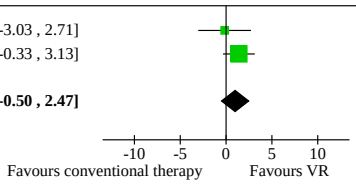


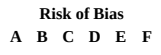
Test for overall effect: Z = 3.99 (P < 0.0001)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 4.59, df = 6 (P = 0.60); I² = 0%

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 7.2. Comparison 7: VR vs conventional therapy - balance and postural control, Outcome 2: Tinetti Test

Study or Subgroup	VR Mean	VR SD	VR Total	Conventional therapy Mean	Conventional therapy SD	Conventional therapy Total	Weight	Mean Difference IV, Fixed, 95% CI
Lozano-Quilis 2014	0.84	2.5	6	1	2.35	5	26.7%	-0.16 [-3.03 , 2.71]
Tollár 2019	3.1	2.71	14	1.7	1.9	14	73.3%	1.40 [-0.33 , 3.13]
Total			**20**			**19**	**100.0%**	**0.98 [-0.50 , 2.47]**



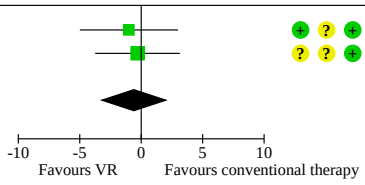


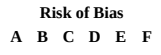
Test for overall effect: Z = 1.30 (P = 0.19)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.83, df = 1 (P = 0.36); I² = 0%

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 7.3. Comparison 7: VR vs conventional therapy - balance and postural control, Outcome 3: FSST

Study or Subgroup	VR Mean	VR SD	VR Total	Conventional therapy Mean	Conventional therapy SD	Conventional therapy Total	Weight	Mean Difference IV, Fixed, 95% CI
Kalron 2016	-4.5	5	15	-3.5	6.1	15	42.7%	-1.00 [-4.99 , 2.99]
Peruzzi 2017	-1.7	2.97	14	-1.4	5.2	11	57.3%	-0.30 [-3.74 , 3.14]
Total			**29**			**26**	**100.0%**	**-0.60 [-3.21 , 2.01]**





Test for overall effect: Z = 0.45 (P = 0.65)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² = 0%

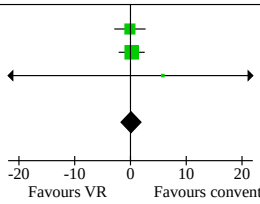
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 8. VR vs conventional therapy - upper limb function

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 9HPT	3	93	Mean Difference (IV, Fixed, 95% CI)	0.10 [-1.70, 1.89]

Analysis 8.1. Comparison 8: VR vs conventional therapy - upper limb function, Outcome 1: 9HPT

Study or Subgroup	VR Mean	VR SD	VR Total	Conventional therapy Mean	Conventional therapy SD	Conventional therapy Total	Weight	Mean Difference IV, Fixed, 95% CI
Ozdogar 2020	-3.5	3.4	20	-3.4	5	17	40.8%	-0.10 [-2.91 , 2.71]
Ozdogar 2022	-1.61	3.57	12	-1.83	2.22	14	59.1%	0.22 [-2.11 , 2.55]
Tramontano 2020	102.1	84.3	14	96.3	72.1	16	0.1%	5.80 [-50.75 , 62.35]
Total			**46**			**47**	**100.0%**	**0.10 [-1.70 , 1.89]**



Test for overall effect: Z = 0.10 (P = 0.92)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.07, df = 2 (P = 0.97); I² = 0%

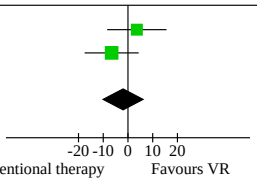
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

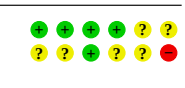
Comparison 9. VR vs conventional therapy - participation and QoL

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
9.1 ABC scale	2	76	Mean Difference (IV, Fixed, 95% CI)	-1.97 [-10.05, 6.10]
9.2 BDI	2	65	Mean Difference (IV, Fixed, 95% CI)	-0.57 [-2.13, 1.00]
9.3 FES-1	3	101	Mean Difference (IV, Fixed, 95% CI)	-3.07 [-5.99, -0.15]

Analysis 9.1. Comparison 9: VR vs conventional therapy - participation and QoL, Outcome 1: ABC scale

Study or Subgroup	VR Mean	VR SD	VR Total	Conventional therapy Mean	Conventional therapy SD	Conventional therapy Total	Weight	Mean Difference IV, Fixed, 95% CI
Molhemi 2021	21.4	19.53	19	17.8	18.64	20	45.4%	3.60 [-8.39 , 15.59]
Ozdogar 2020	-1.2	14.5	20	5.4	18.7	17	54.6%	-6.60 [-17.53 , 4.33]
Total			**39**			**37**	**100.0%**	**-1.97 [-10.05 , 6.10]**



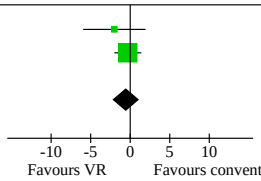


Test for overall effect: Z = 0.48 (P = 0.63)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 1.52, df = 1 (P = 0.22); I² = 34%

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 9.2. Comparison 9: VR vs conventional therapy - participation and QoL, Outcome 2: BDI

Study or Subgroup	VR Mean	VR SD	VR Total	Conventional therapy Mean	Conventional therapy SD	Conventional therapy Total	Weight	Mean Difference IV, Fixed, 95% CI
Ozdogar 2020	-3.9	7.1	20	-1.9	5.1	17	15.7%	-2.00 [-5.94 , 1.94]
Tollár 2019	-0.2	2.67	14	0.1	1.86	14	84.3%	-0.30 [-2.00 , 1.40]
Total			**34**			**31**	**100.0%**	**-0.57 [-2.13 , 1.00]**

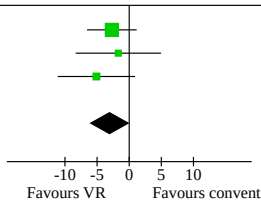


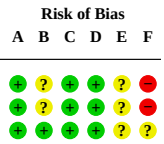
Test for overall effect: Z = 0.71 (P = 0.48)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.60, df = 1 (P = 0.44); I² = 0%

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 9.3. Comparison 9: VR vs conventional therapy - participation and QoL, Outcome 3: FES-1

Study or Subgroup	VR Mean	VR SD	VR Total	Conventional therapy Mean	Conventional therapy SD	Conventional therapy Total	Weight	Mean Difference IV, Fixed, 95% CI
Kalron 2016	-7	4.3	15	-4.3	6.3	15	57.2%	-2.70 [-6.56 , 1.16]
Khalil 2018	-8.94	8.57	16	-7.24	10.49	16	19.3%	-1.70 [-8.34 , 4.94]
Molhemi 2021	-11	9.92	19	-5.9	9.24	20	23.5%	-5.10 [-11.12 , 0.92]
Total			**50**			**51**	**100.0%**	**-3.07 [-5.99 , -0.15]**





Test for overall effect: Z = 2.06 (P = 0.04)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.64, df = 2 (P = 0.73); I² = 0%

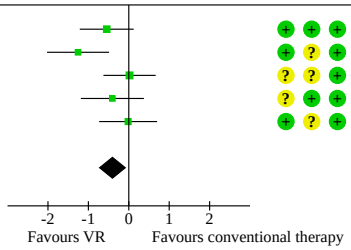
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 10. VR vs conventional therapy - fatigue

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Fatigue	5	161	Std. Mean Difference (IV, Fixed, 95% CI)	-0.40 [-0.72, -0.09]

Analysis 10.1. Comparison 10: VR vs conventional therapy - fatigue, Outcome 1: Fatigue

Study or Subgroup	VR Mean	VR SD	VR Total	Conventional therapy Mean	Conventional therapy SD	Conventional therapy Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Brichetto 2013	-10.1	13.01	18	-2.2	15.21	18	22.7%	-0.55 [-1.21 , 0.12]	+ + + + ? ?
Khalil 2018	-11	11.5	16	4.75	12.91	16	17.1%	-1.26 [-2.02 , -0.49]	+ ? + + ? -
Ozdogar 2020	-7.5	16.8	20	-7.8	14	17	24.1%	0.02 [-0.63 , 0.67]	? ? + ? ? -
Ozdogar 2022	-11.93	17.5	12	-5.67	12.32	14	16.5%	-0.41 [-1.19 , 0.37]	? + + + ? -
Tramontano 2020	-2	10.01	14	-1.8	13.68	16	19.6%	-0.02 [-0.73 , 0.70]	+ ? + + ? -
Total			**80**			**81**	**100.0%**	**-0.40 [-0.72 , -0.09]**	



Test for overall effect: Z = 2.50 (P = 0.01)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 7.68, df = 4 (P = 0.10); I² = 48%

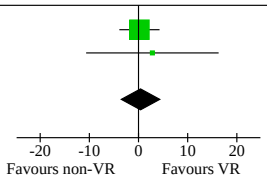
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 11. VR vs alternative intervention - cognition

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 PASAT	2	52	Mean Difference (IV, Fixed, 95% CI)	0.41 [-3.50, 4.32]

Analysis 11.1. Comparison 11: VR vs alternative intervention - cognition, Outcome 1: PASAT

Study or Subgroup	VR Mean	VR SD	VR Total	Alternative intervention Mean	Alternative intervention SD	Alternative intervention Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Bove 2021	2.72	5.41	18	2.53	7.19	19	91.6%	0.19 [-3.90 , 4.28]	? + + + + ?
Munari 2020	5.25	12.42	8	2.43	13.99	7	8.4%	2.82 [-10.65 , 16.29]	+ ? + + ? -
Total			**26**			**26**	**100.0%**	**0.41 [-3.50 , 4.32]**	



Test for overall effect: Z = 0.21 (P = 0.84)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.13, df = 1 (P = 0.71); I² = 0%

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

ADDITIONAL TABLES

Table 1. Used outcome measures of the included trials

Author and year	Lower limb and gait function	Balance and postural control	Upper limb function	Cognition	Global motor function	Activity limitation	Participation and quality of life (QoL)	Fatigue	Adverse events
Bove 2020	-	-	-	Symbol Digit Modalities Test, Paced Auditory Serial Addition Test, Brief Visuospatial Memory Test, California Verbal Learning Test	-	-	Center for Epidemiologic Studies Depression Scale, State Trait Anxiety Inventory, Perceived Deficits Questionnaire-5	Modified Fatigue Impact Scale	-
Brichetto 2013	-	Berg Balance Scale, Stabilometry eyes open/closed	-	-	-	-	-	Modified Fatigue Impact Scale	-
Calabro 2017	Timed Up and Go, Knee & Hip force	Berg Balance Scale	-	Coping orientation to problem experienced	Modified Ashworth Scale	Functional Independence Measure	Hamilton Rating Scale for Depression		-
Cuesta-Gomez 2020	-	-	Grip strength, Box and Blocks Test, Purdue Pegboard Test, 9 Hole Peg Test,	-	-	-	MS Impact Scale	Fatigue Severity Scale	-
Eftekharsadat 2015	Timed Up and Go, Manual Muscle Test hip/knee	Romberg Test, Berg Balance Scale, overall Stability Index	Manual muscle Test wrist	-	Modified Ashworth Scale	-	Fall Risk Index		-
Feys 2015	-	-	Motricity Index, Grip strength, Fugl Meyer – upper	-	-	-	-		-

Table 1. Used outcome measures of the included trials *(Continued)*

			limb, Action Research Arm Test, Motor Activity Log						
Hoang 2015	Timed Up and Go, 10-Metre Walk Test, 6-Minute Walk Test	Choice Stepping Reaction Time (CSRT), CSRT decision time, CSRT movement time, postural sway eyes open/closed	9 Hole Peg Test	Timed Up and Go dual task, Trail Making test, Symbol Digit Modalities Test, Stroop Stepping Test	MS Functional Composite Score	-	Fall history		-
Janssen 2015	-	-	-	Paced Auditory Serial Addition Test, Selective Reminding Task, 10/36 Spatial Recall Test, Symbol Digit Modalities Test, Word List Generation Task	-	-	-		-
Jonsdottir 2018	-	-	9 Hole Peg Test, Box and Blocks Test	-	-	-	EQ-5D visual analogue scale, SF-12		-
Kalron 2016	-	Posturography eyes open/closed, Functional Reach Test, Berg Balance Scale, Four Step Square Test	-	-	-	-	Falls Efficacy Scale International		-
Khalil 2018	Timed Up and Go, 3-Minute Walk Distance, 10-Metre Walk Test	Berg Balance Scale	-	-	-	-	Falls Efficacy Scale International, SF-36	Modified Fatigue Impact Scale	-

Table 1. Used outcome measures of the included trials *(Continued)*

Kramer 2014	Gait analysis	Centre of force displacement, platform displacement	-	Centre of force displacement Dual task, platform displacement Dual task, gait analysis Dual task	-	-	-	-
Leonardi 2021	-	-	-	Montreal Cognitive Assessment, Spatial Recall Test, Selective Reminding Test, Symbol Digit Modalities Test, Paced Auditory Serial Addition Test, Word List Generation Task	-	-	Beck Depression Inventory, MS Quality of Life-54	-
Lozano-Quilis 2014	Timed Up and Go, 10-Metre Walk Test	Berg Balance Scale, Single Leg Balance Test, Tinetti Balance Scale	-	-	-	-	-	-
Maggio 2020	Timed Up and Go	Trunk Control Test, Tinetti Balance and Gait Scale	-	Montreal Cognitive Assessment, 10/36 Spatial Recall Test, Rey-Osterrieth Complex figure, Paced Auditorial Serial Addition Test	-	-	Beck Depression Inventory, MS Quality of Life-54	-
Molhemi 2020	Timed Up and Go, 10-Metre Walk Test, Multiple Sclerosis Walking Scale-12	Limits of Stability, Berg Balance Scale	-	Dual Task Costs – Timed Up and Go and 10-Metre Walk Test	-	-	Falls Efficacy Scale International, Activities-specific Balance Confidence Scale, number of falls	-
Molhemi 2022	Six Spot Step Test	-	-	Trail Making Test, Choice Stepping Reaction Time	-	-	-	-
Munari 2020	2-Minute Walk Test, 10-Metre Walk Test, Gait analysis	Berg Balance Scale, stabilometric assessment	-	Paced Auditory Serial Addition Test, Phonemic Fluency test, Rivermead Behavioral Memory Test Novel task, Digit Symbol	-	-	MS Quality Of Life-54	-

Table 1. Used outcome measures of the included trials *(Continued)*

Nilsagard 2012	Timed Up and Go, 25-Foot Walk Test, Dynamic Gait Index, MS Walking Scale-12	Four Square Step Test, Timed Chair Stand Test	-	Timed Up and Go Dual task	-	-	Activities-specific Balance Confidence Scale		-
Norouzi 2020	-	-	Bimanual co-ordination accuracy and consistency	-	-	-	-		-
Novotna 2019	Timed Up and Go, Spatiotemporal parameters, MS Walking Scale-12	Berg Balance Scale, mini-BESTest	-	Timed Up and Go Dual task	-	-	Activities-specific Balance Confidence Scale, Falls Efficacy Scale International		-
Ortiz-Gutierrez 2013	-	Berg Balance Scale, Sensory Organisation Test, Motor Control Test, Tinetti Test	-	-	-	-	-		-
Ozdogar 2020	25-Foot Walk, MS Walking Scale-12, Six Spot Step Test, Sit-to-Stand Test	Curl-up Test	9 Hole Peg Test, Manual Ability Measurement-36	Brief International Cognitive Assessment in Multiple Sclerosis	-	-	Activities-specific Balance Confidence Scale, Beck Depression Inventory, MS International Quality of Life	Modified Fatigue Impact Scale	-
Ozdogar 2022	MS Walking Scale-12, 25 Foot Walk, Six Spot Step Test, 2-Minute Walk Test	-	9 Hole Peg Test, Manual Ability Measurement-36	Brief Visuospatial Memory Test, California Verbal Learning, Symbol Digit Modalities Test, Paced Auditory Serial Addition Test	-	-	Hospital Anxiety and Depression Scale, MS Internation Quality of Life, Epworth Sleepiness Scale	Modified Fatigue Impact Scale	-

Table 1. Used outcome measures of the included trials *(Continued)*

Ozkul 2020	Timed Up and Go	Berg Balance Scale, Postural Sway, Limits of Stability	-	Timed Up and Go Dual task	-	-	-	Fatigue Severity Scale	-
Pagliari 2021	MS Walking Scale-12	mini-BESTest, postural control	Box and Block Test, 9 Hole Peg Test	Montreal Cognitive Assessment, Symbol Digit Modalities Test, Selective Reminding Test, Spatial Recall Test, Paced Auditory Serial Addition Test, Word List Generation Task	-	-	Beck Depression Inventory, regulatory emotional self-efficacy, state-trait anxiety, MS Quality of Life-54	Fatigue Severity Scale	-
Peruzzi 2017	Gait analysis, 6-Minute Walk Test, Timed Up and Go, 10-Metre Walk Test	Berg Balance Scale, Four Square Step Test	-	Gait analysis Dual task	Expended Disability Status Scale	-	-		-
Robinson 2015	Gait analysis, MS Walking Scale-12, Functional Ambulation Profile	Postural sway unipedal/ bipedal	-	-	-	-	WHO Disability Assessment Schedule 2.0 questionnaire		-
Thomas 2017	2-Minute Walk Test, Timed Up and Go, Gait Stride-time Rhythmicity, Step Test	Steady balance test, static posturography	9 Hole Peg Test	-	-	Godin Leisure-Time Exercise Questionnaire	Hospital Anxiety and Depression Scale, EuroQol-5 Dimensions-5 Levels, MS Impact Scale, SF-36, SCI-Exercise Self-Efficacy Scale, MS Self-Efficacy Scale	Fatigue Symptom Inventory	Adverse events
Tollar 2019	6-Minute Walk Test	Berg Balance Scale, centre of pressure path length, Tinetti Test	-	-	-	-	MS Impact Scale, EuroQol Five Dimensions Questionnaire, Beck Depression Inventory		-

Table 1. Used outcome measures of the included trials *(Continued)*

Tramontano 2020	-	-	9 Hole Peg Test, upper limb strength	-	Rivermead Mobility Index	Modified Barthel Index	MS Quality of Life-54	Fatigue Severity Scale	-
Walino-Paniagua 2019	-	-	Purdue Pegboard Test, Jebsen-Taylor Hand Function Test, Grooved Pegboard Test	-	-	-	-		-
Yazgan 2020	Timed Up and Go, 6-Minute Walk Test	Berg Balance Scale	-	-	-	-	MS International Quality of Life Questionnaire	Fatigue Severity Scale	-

Table 2. Outcomes not included in meta-analysis

Study ID	Outcome measure	Time point(s)	Results	Reason for exclusion from MA
Activity limitations				
Calabro 2017	Functional Independence Measure	8 weeks	No difference within (RAGT-VR P = 0.3; RAGT + VR P = 0.4) and between group(s) (P = 0.5)	Data reported as median and IQR
Thomas 2017	Godin Leisure-Time Exercise Questionnaire	6 (*Immediate*) or 12 (*Delayed*) months	*Immediate*: mean score 28.00 (24.61) *Delayed*: mean score 18.17 (17.57)	The only study assessing physical activity limitations
Tramontano 2020	Modified Barthel Index	4 weeks	Significant improvement of activity within group (exp P = 0.027; contr P = 0.011). No between-group difference (P = 0.053)	The only study assessing upper limb activity limitations
Global motor function				
Calabro 2017	Modified Ashworth Scale	8 weeks	No difference within (RAGT-VR P = 0.2; RAGT + VR P = 0.2) and between groups (P = 0.4)	Data reported as median and IQR
Eftekharsadat 2015	Modified Ashworth Scale	12 weeks	No between-group difference (P > 0.05)	The only study comparing the effects of VR vs no intervention for balance and postural control
Hoang 2015	MS Functional Composite Score	12 weeks	Significantly better motor function in the exp group (P = 0.001)	The only study comparing the effects of VR vs no intervention for gait function
Peruzzi 2017	Expended Disability Status Scale	6 weeks	No difference within (exp P = 0.15; contr P = -) and between groups (P = 0.781)	The only study comparing the effects of VR vs active training for gait function
Tramontano 2020	Rivermead Mobility Index	4 weeks	Significant improvement of motor function within group (exp P = 0.038; contr P = 0.011). Significantly better motor function in the exp group (P = 0.017).	The only study assessing upper limb motor function
Adverse events				
Thomas 2017	Number of adverse events	6 (*Immediate*) or 12 (*Delayed*) months	No SAEs reported for both groups. AEs reported descriptively (leg pain, backache, discomfort, aggravating pre-existing condition, near/falls)	The only study assessing adverse events

IQR: interquartile range; SAE: serious adverse event; RAGT: robot-assisted gait training; VR: virtual reality

APPENDICES

Appendix 1. PubMed search strategy (29 July 2022)

	Search term	Hits 29/07/22
1.	"Multiple Sclerosis"[Mesh]	67097
2.	"multiple sclerosis"[TIAB]	86535
3.	MS[TI]	42072
4.	"disseminated sclerosis"[TIAB]	639
5.	"Demyelinating Autoimmune Diseases, CNS"[Mesh:NoExp]	534
6.	"Demyelinating Diseases"[Mesh:NoExp]	12690
7.	"demyelinating disease*"[TIAB]	7809
8.	"demyelinating disorder*"[TIAB]	1549
9.	"Myelitis, Transverse"[Mesh]	5344
10.	"transverse myelitis"[TIAB]	2631
11.	"Optic Neuritis"[Mesh]	9957
12.	"optic neuritis"[TIAB]	6790
13.	"Neuromyelitis Optica"[Mesh]	3945
14.	"neuromyelitis optica"[TIAB]	5189
15.	"Devic disease"[TIAB]	64
16.	"Encephalomyelitis, Acute Disseminated"[Mesh]	2428
17.	adem[TIAB]	1,224
18.	"acute disseminated encephalomyelitis"[TIAB]	2062
19.	"clinically isolated syndrome"[TIAB]	1569
20.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19	155957
21.	"Virtual Reality"[Mesh] OR "Virtual Reality Exposure Therapy"[Mesh] OR "Computers"[Mesh] OR "Computer Simulation"[Mesh] OR "Computer Graphics"[Mesh] OR "Computer-Assisted Instruction"[Mesh] OR "User-Computer Interface"[Mesh] OR "Therapy, Computer-Assisted"[Mesh] OR "Video Games"[Mesh]	473141
22.	"virtual realit*"[TIAB]	14559

(Continued)

23.	"virtual rehabilitation*"[TIAB] OR "virtual therap*"[TIAB] OR "virtual treatment*"[TIAB]	427
24.	"virtual environment*"[TIAB] OR "virtual simulation*"[TIAB] OR "virtual world*"[TIAB] OR "virtual object*"[TIAB]	6020
25.	"virtual system*"[TIAB] OR "virtual program*"[TIAB]	248
26.	computer*[TIAB]	335214
27.	simulation*[TIAB]	423530
28.	"user interface*"[TIAB]	8082
29.	videogame*[TIAB] OR "video gam*"[TIAB] OR "serious gam*"[TIAB] OR "interactive gam*"[TIAB] OR "exergam*"[TIAB] OR gaming[TIAB]	10638
30.	#21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29	1019704
31.	"randomized controlled trial"[PT]	574574
32.	"controlled clinical trial"[PT]	664628
33.	randomized[TIAB]	620610
34.	placebo[TIAB]	236803
35.	"drug therapy"[sh]	2512551
36.	randomly[TIAB]	388590
37.	trial[TIAB]	717998
38.	groups[TIAB]	2417665
39.	#31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38	5493638
40.	"Animals"[Mesh] NOT "Humans"[Mesh]	5029415
41.	#39 NOT #40	4790011
42.	#20 AND #30 AND #41	659

Appendix 2. PEDro search strategy (2 August 2022)

#	SEARCH	Hits 20220802
1	"multiple sclerosis" and virtual in Title and Abstract	28
2	"multiple sclerosis" and videogame* in Title and Abstract	0

(Continued)

3	"multiple sclerosis" and computer* in Title and Abstract	15
4	"multiple sclerosis" and gam* in Title and Abstract	16

Appendix 3. Scopus search strategy (22 July 2022)

	Search term	Hits 20220622
1.	TITLE-ABS-KEY("multiple sclerosis" OR "disseminated sclerosis" OR (demyelinating W/1 disorder*) OR (demyelinating W/1 disease*) OR "transverse myelitis" OR "optic neuritis" OR "neuromyelitis optica" OR "Devic disease" OR "adem" OR "acute disseminated encephalomyelitis" OR "clinically isolated syndrome")	157,294
2.	TITLE-ABS-KEY((virtual W/1 (realit* OR rehabilitation* OR therap* OR treatment* OR environment* OR simulation OR world* OR object* OR system* OR program*)) OR gaming OR exergam OR computer* OR videogame* OR "interactive gam*" OR "serious gam*" OR "video gam*")	5,333,270
3.	KEY("clinical trials" OR "Clinical trials as topic" OR "randomized controlled trial" OR "Randomized Controlled Trials as Topic" OR "controlled clinical trial" OR "Controlled Clinical Trials" OR "random allocation" OR "Double-Blind Method" OR "Single-Blind Method" OR "Cross-Over Studies" OR "Placebos" OR "multicenter study" OR "double blind procedure" OR "single blind procedure" OR "crossover procedure" OR "clinical trial" OR "controlled study" OR "randomization" OR "placebo")	8,272,274
4.	#1 AND #2 AND #3	2,319

Appendix 4. CENTRAL search strategy (Issue 7, 2022)

	Search term	Hits 1/08/22
1.	MeSH descriptor: [Multiple Sclerosis] explode all trees	3965
2.	"multiple sclerosis":ti,ab,kw	11334
3.	MS:ti	2073
4.	"disseminated sclerosis":ti,ab,kw	2
5.	MeSH descriptor: [Demyelinating Autoimmune Diseases, CNS] this term only	5
6.	MeSH descriptor: [Demyelinating Diseases] this term only	85
7.	(demyelinating NEXT disease*):ti,ab,kw	452
8.	(demyelinating NEXT disorder*):ti,ab,kw	37

(Continued)

9.	MeSH descriptor: [Myelitis, Transverse] explode all trees	63
10.	"transverse myelitis":ti,ab,kw	51
11.	MeSH descriptor: [Optic Neuritis] explode all trees	197
12.	"optic neuritis":ti,ab,kw	470
13.	MeSH descriptor: [Neuromyelitis Optica] explode all trees	52
14.	"neuromyelitis optica":ti,ab,kw	277
15.	"Devic disease":ti,ab,kw	3
16.	MeSH descriptor: [Encephalomyelitis, Acute Disseminated] explode all trees	3
17.	"acute disseminated encephalomyelitis":ti,ab,kw	22
18.	adem:ti,ab,kw in Trials	16
19.	"clinically isolated syndrome":ti,ab,kw	181
20.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19	12719
21.	MeSH descriptor: [Virtual Reality] explode all trees	521
22.	MeSH descriptor: [Virtual Reality Exposure Therapy] explode all trees	229
23.	MeSH descriptor: [Computers] explode all trees	2087
24.	MeSH descriptor: [Computer Simulation] explode all trees	2218
25.	MeSH descriptor: [Computer Graphics] explode all trees	517
26.	MeSH descriptor: [Computer-Assisted Instruction] explode all trees	1267
27.	MeSH descriptor: [User-Computer Interface] explode all trees	1292
28.	MeSH descriptor: [Therapy, Computer-Assisted] explode all trees	2443
29.	MeSH descriptor: [Video Games] explode all trees	825
30.	(virtual NEXT realit*):ti,ab,kw	4719
31.	(virtual NEXT rehabilitation*):ti,ab,kw OR (virtual NEXT therap*):ti,ab,kw OR (virtual NEXT treatment*):ti,ab,kw	131
32.	(virtual NEXT environment*):ti,ab,kw OR (virtual NEXT simulation*):ti,ab,kw OR (virtual NEXT world*):ti,ab,kw OR (virtual NEXT object*):ti,ab,kw	770
33.	(virtual NEXT system*):ti,ab,kw OR (virtual NEXT program*):ti,ab,kw	25
34.	computer*:ti,ab,kw	53566
35.	simulation*:ti,ab,kw	13911

(Continued)

36.	(user NEXT interface*):ti,ab,kw	241
37.	videogame*:ti,ab,kw OR (video NEXT gam*):ti,ab,kw OR (serious NEXT gam*):ti,ab,kw OR (interactive NEXT gam*):ti,ab,kw OR exergam*:ti,ab,kw OR gaming:ti,ab,kw	3232
38.	#21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37	71037
39.	#20 AND #38	561

Appendix 5. Embase search strategy (3 August 2022)

	Search term	Hits 3/8/22
1.	'multiple sclerosis'/exp	151161
2.	'multiple sclerosis':ti,ab,kw	136724
3.	MS:ti	58045
4.	'disseminated sclerosis':ti,ab,kw	626
5.	'demyelinating disease'/exp	202946
6.	'demyelinating disease*':ti,ab,kw	12233
7.	'demyelinating disorder*':ti,ab,kw	2679
8.	'transverse myelitis'/exp	885
9.	'transverse myelitis':ti,ab,kw	4767
10.	'optic neuritis'/exp	12535
11.	'optic neuritis':ti,ab,kw	11384
12.	'myelooptic neuropathy'/exp	11272
13.	'neuromyelitis optica':ti,ab,kw	9828
14.	'Devic disease':ti,ab,kw	108
15.	'acute disseminated encephalomyelitis'/exp	3416
16.	'acute disseminated encephalomyelitis':ti,ab,kw	3210
17.	adem:ti,ab,kw	2397
18.	'clinically isolated syndrome':ti,ab,kw	3534
19.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18	278481

(Continued)

20.	'video game'/exp OR 'computer assisted therapy'/exp OR 'computer interface'/exp OR 'computer graphics'/exp OR 'computer simulation'/exp OR 'virtual reality'/exp OR 'virtual reality exposure therapy'/exp OR 'computer'/exp	366527
21.	(virtual NEAR/1 (realit* OR rehabilitation* OR therap* OR treatment* OR environment* OR simulation OR world* OR object* OR system* OR program*)):ti,ab,kw	24440
22.	computer*:ti,ab,kw OR simulation*:ti,ab,kw	817313
23.	(user NEAR/1 interface*):ti,ab,kw	9832
24.	((video NEAR/1 gam*):ti,ab,kw) OR ((serious NEAR/1 gam*):ti,ab,kw) OR ((interactive NEAR/1 gam*):ti,ab,kw) OR gaming:ti,ab,kw OR exergam*:ti,ab,kw	12152
25.	#20 OR #21 OR #22 OR #23 OR #24	1027149
26.	'randomized controlled trial'/de	722877
27.	'controlled clinical trial'/de	437555
28.	random*:ti,ab,tt	1817710
29.	'randomization'/de	94486
30.	'intermethod comparison'/de	288040
31.	placebo:ti,ab,tt	345535
32.	(compare:ti,tt OR compared:ti,tt OR comparison:ti,tt)	594302
33.	((evaluated:ab OR evaluate:ab OR evaluating:ab OR assessed:ab OR assess:ab) AND (compare:ab OR compared:ab OR comparing:ab OR comparison:ab))	2540615
34.	(open NEXT/1 label):ti,ab,tt	98333
35.	((double OR single OR doubly OR singly) NEXT/1 (blind OR blinded OR blindly)):ti,ab,tt	261175
36.	'double blind procedure'/de	197971
37.	(parallel NEXT/1 group*):ti,ab,tt	29807
38.	(crossover:ti,ab,tt OR 'cross over':ti,ab,tt)	117817
39.	((assign* OR match OR matched OR allocation) NEAR/6 (alternate OR group OR groups OR intervention OR interventions OR patient OR patients OR subject OR subjects OR participant OR participants)):ti,ab,tt	424717
40.	(assigned:ti,ab,tt OR allocated:ti,ab,tt)	453815
41.	(controlled NEAR/8 (study OR design OR trial)):ti,ab,tt	423045
42.	(volunteer:ti,ab,tt OR volunteers:ti,ab,tt)	271641
43.	'human experiment'/de	588101

(Continued)

44.	trial:ti,tt	371371
45.	#26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44	5900487
46.	(((random* NEXT/1 sampl* NEAR/8 ('cross section*' OR questionnaire* OR survey OR surveys OR database or databases)):ti,ab,tt) NOT ('comparative study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt OR 'randomly assigned':ti,ab,tt))	2897
47.	('cross-sectional study'/de NOT ('randomized controlled trial'/de OR 'controlled clinical study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt OR 'control group':ti,ab,tt OR 'control groups':ti,ab,tt))	338810
48.	('case control*':ti,ab,tt AND random*:ti,ab,tt NOT ('randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt))	20025
49.	('systematic review':ti,tt NOT (trial:ti,tt OR study:ti,tt))	216834
50.	(nonrandom*:ti,ab,tt NOT random*:ti,ab,tt)	17948
51.	'random field*':ti,ab,tt	2713
52.	('random cluster' NEAR/4 sampl*):ti,ab,tt	1570
53.	(review:ab AND review:it) NOT trial:ti,tt	1001829
54.	('we searched':ab AND (review:ti,tt OR review:it))	42899
55.	'update review':ab	122
56.	(databases NEAR/5 searched):ab	59179
57.	((rat:ti,tt OR rats:ti,tt OR mouse:ti,tt OR mice:ti,tt OR swine:ti,tt OR porcine:ti,tt OR murine:ti,tt OR sheep:ti,tt OR lambs:ti,tt OR pigs:ti,tt OR piglets:ti,tt OR rabbit:ti,tt OR rabbits:ti,tt OR cat:ti,tt OR cats:ti,tt OR dog:ti,tt OR dogs:ti,tt OR cattle:ti,tt OR bovine:ti,tt OR monkey:ti,tt OR monkeys:ti,tt OR trout:ti,tt OR marmoset*:ti,tt) AND 'animal experiment'/de)	1167850
58.	('animal experiment'/de NOT ('human experiment'/de OR 'human'/de))	2449548
59.	#46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58	4041483
60.	#45 NOT #59	5225082
61.	#19 AND #25 AND #60	1149

Appendix 6. CINAHL search strategy (3 August 2022)

	Search term	Hits 20220803

(Continued)

1.	MH "Demyelinating Autoimmune Diseases, CNS+" Expanders - Apply equivalent subjects	22,773
2.	TI "multiple sclerosis" OR AB "multiple sclerosis" Expanders - Apply equivalent subjects	19445
3.	TI "MS" Expanders - Apply equivalent subjects	5,937
4.	TI "disseminated sclerosis" OR AB "disseminated sclerosis" Expanders - Apply equivalent subjects	21
5.	MH "Demyelinating Diseases" Expanders - Apply equivalent subjects	2271
6.	TI "demyelinating disease*" OR AB "demyelinating disease*" Expanders - Apply equivalent subjects	855
7.	TI "demyelinating disorder*" OR AB "demyelinating disorder*" Expanders - Apply equivalent subjects	270
8.	TI "transverse myelitis" OR AB "transverse myelitis" Expanders - Apply equivalent subjects	616
9.	MH "Optic Neuritis+" Expanders - Apply equivalent subjects	930
10.	TI "optic neuritis" OR AB "optic neuritis" Expanders - Apply equivalent subjects	1021
11.	TI "neuromyelitis optica" OR AB "neuromyelitis optica" Expanders - Apply equivalent subjects	1054
12.	TI "Devic disease" OR AB "Devic disease" Expanders - Apply equivalent subjects	11
13.	TI "adem" OR AB "adem" Expanders - Apply equivalent subjects	276
14.	TI "acute disseminated encephalomyelitis" OR AB "acute disseminated encephalomyelitis" Expanders - Apply equivalent subjects	514
15.	TI "clinically isolated syndrome" OR AB "clinically isolated syndrome" Expanders - Apply equivalent subjects	369
16.	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15	32431
17.	(MH "Computer Simulation") OR (MH "Virtual Reality Exposure Therapy") OR (MH "Virtual Reality+") Expanders - Apply equivalent subjects	25522
18.	(MH "Computer Graphics") OR (MH "User-Computer Interface+") OR (MH "Therapy, Computer Assisted+")) Expanders - Apply equivalent subjects	33989
19.	TI (virtual realit*) OR AB (virtual realit*) OR TI ((virtual rehabilitation*) OR (virtual therap*) OR (virtual treatment*)) OR AB ((virtual rehabilitation*) OR (virtual therap*) OR (virtual treatment*)) OR TI ((virtual environment*) OR (virtual simulation*) OR (virtual world*) OR (virtual object*)) OR AB ((virtual environment*) OR (virtual simulation*) OR (virtual world*) OR (virtual object*)) OR TI ((virtual system*) OR (virtual program*)) AND AB ((virtual system*) OR (virtual program*)) Expanders - Apply equivalent subjects	7154

(Continued)

20.	TI (computer* or simulation*) OR AB (computer* or simulation*) OR TI (user interface*) OR AB (user interface*) OR TI (Videogame* OR (video gam*) OR (serious gam*) OR (interactive gam*) OR exergam* OR gaming) OR AB (Videogame* OR (video gam*) OR (serious gam*) OR (interactive gam*) OR exergam* OR gaming) Expanders - Apply equivalent subjects	111922
21.	S17 OR S18 OR S19 OR S20	155488
22.	S16 AND S21	443

Appendix 7. ClinicalTrials.gov search strategy (2 August 2022)

#	SEARCH in Other terms	Hits 20220802
1	"multiple sclerosis" AND virtual	27
2	"multiple sclerosis" and computer*	0
3	"multiple sclerosis" and videogame*	0
4	"multiple sclerosis" and gam*	0

Appendix 8. ICTRP WHO search strategy (2 August 2022)

#	SEARCH	Hits 20220802
1	"multiple sclerosis" AND virtual	13
2	"multiple sclerosis" and computer*	3
3	"multiple sclerosis" and videogame*	0
4	multiple sclerosis" and gam*	8

HISTORY

Protocol first published: Issue 12, 2020

CONTRIBUTIONS OF AUTHORS

Emma De Keersmaecker was involved in conceiving, designing and co-ordinating the review, designing the search strategy, screening the search results, organising retrieval of papers, screening the papers for inclusion, performing the risk of bias assessment, extracting data from the papers, writing to study authors for additional information, managing and entering data in Review Manager 5, analysing and interpreting the data, creating summary of findings tables and assessing the certainty of the evidence, and writing the review.

Stefania Guida was involved in extracting data from the papers, managing and entering data in Review Manager 5, analysing and interpreting the data, adding information to the summary of findings tables and assessing the certainty of the evidence, and writing the review.

Stijn Denissen was involved in designing the search strategy, analysing and interpreting the data, and writing the review.

Luna Dewolf was involved in screening the search results, organising retrieval of the papers, screening the papers for inclusion, and extracting data from the papers.

Guy Nagels was involved in designing the search strategy, analysing and interpreting the data, and writing the review.

Bart Jansen was involved in analysing and interpreting the data, and writing the review.

David Beckwée was involved in designing the search strategy, analysing and interpreting the data, and writing the review.

Eva Swinnen was involved in designing the search strategy, screening the search results, organising retrieval of the papers, screening the papers for inclusion, performing risk of bias assessment, extracting data from the papers, analysing and interpreting the data, and writing the review.

DECLARATIONS OF INTEREST

Emma De Keersmaecker is a Strategic Basic Research Fellow funded by the Research Foundation – Flanders (FWO) (1S58419N).

Stefania Guida: none known.

Stijn Denissen is funded by an industrial doctoral grant for a PhD trajectory in collaboration with icometrix NV, appointed by Flanders Innovation and Entrepreneurship (HBC.2019.2579, www.vlaio.be). However, this does not cause a conflict of interest with regard to the day-to-day business of icometrix.

Luna Dewolf: none known.

Guy Nagels is a Senior Clinical Investigator Fellow funded by the Research Foundation – Flanders (FWO) (1805620N). He is also a minority shareholder of icometrix NV. However, this does not cause a conflict of interest with regard to the day-to-day business of icometrix.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

To be intelligible for readers and in view of future updates, we changed the primary outcome categories 'gait function' and 'balance function', as written in the protocol, into 'lower limb and gait function' and 'balance and postural control' in the review.

For the assessment of risk of bias using the RoB 2 tool, we focused on the main outcomes of the review, including the results contributing to the review's summary of findings tables.

Due to the low number of included randomised controlled trials in this version of the review, we could not perform all the analyses planned in the protocol:

- In the summary of findings tables, we compared virtual reality to no intervention and to conventional therapy, but we were not able to compare virtual reality with usual care (i.e. where VR was provided as an additional therapy).

- We used a fixed-effect model instead of a random-effects model. We did perform a sensitivity analysis to determine whether there was a difference between the models.
- We performed no subgroup analyses for level of immersion due to the low number of included randomised controlled trials that used semi- or full-immersive virtual reality devices.

INDEX TERMS

Medical Subject Headings (MeSH)

Bias; Cognition; Fatigue [etiology] [rehabilitation]; *Gait; Lower Extremity; *Multiple Sclerosis [rehabilitation]; *Postural Balance; *Quality of Life; *Randomized Controlled Trials as Topic; Upper Extremity; *Virtual Reality

MeSH check words

Adult; Humans; Middle Aged