Effect of serious games over conventional therapy in the rehabilitation of people with multiple sclerosis – A systematic review and meta-analysis

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Abstract

Purpose: This meta-analysis aimed to quantify the effect of serious games over conventional therapy on upper-limb activity, balance, gait, fatigue, and cognitive functions in people with multiple sclerosis.

Materials and methods: Search strategies were developed for PubMed, Embase, Cochrane Library, and Scopus. Studies were selected if participants were adults with multiple sclerosis; the intervention consisted of a virtual reality serious game-based program; the control group received conventional therapy; outcomes included upper limb activity, balance, gait, fatigue, or cognitive functions; and used a randomized controlled trial design. Data were synthesized using a standardized mean difference with a random-model effect.

Results: From 2532 studies, seventeen trials were selected (n=740). Overall, serious games programs effect on upper limb activity, gait, verbal memory, verbal fluency and attention seemed neutral. Balance functions appeared to be improved by semi-immersive virtual reality serious games (SMD=0.48;95%CI=0.12–0.84;p=0.01;I^2=0%), fatigue by treadmill serious games (SMD=0.80;95%CI=0.40–1.20;p<0.001) and visuo-spatial memory by semi-immersive virtual reality general cognitive serious games (SMD=0.35;95%CI=0.04–0.65;p=0.03;I^2=0%).

Conclusion: This review suggests, with a very-low-to-low certainty of evidence, that while some specific serious games may improve balance, fatigue and visuo-spatial memory, their overall effect on upper limb activity, gait, fatigue, and other cognitive functions appears neutral.

Keywords: Multiple Sclerosis; Exergame; Upper Extremity; Neurological Rehabilitation; Virtual Reality; Telemedicine

Introduction

Multiple sclerosis (MS), also known as immune-mediated demyelinating disease, is a complex central nervous system disease that is frequently associated with several symptoms including fatigue, weakness, incontinence, visual and sensory impairment, emotional disturbances, mobility problems, and balance disorders [1,2].

The number of people living with MS was estimated at 2.8 million cases worldwide in 2020, representing a significant increase from the 2.3 million cases in 2013 [3-5]. A new case of MS is predicted to be diagnosed every 5 minutes, with a threefold increase in mortality when compared to the non-MS people [5,6] and responsible as neurology disorders primarily in young and middle-age adults [7].

As the disease progresses and relapses, certain functions deteriorate more prominently, particularly mobility limitations due to balance and gait impairments, causing disruption in daily living activities (ADLs) [8]. Upper limb dysfunction, accompanied by muscle weakness, numbness, and poor coordination, is also frequently associated with an inability to perform ADLs, or functional disability [9]. Furthermore, in addition to functional disability on physical performance, cognitive impairment is a common complication in the early stages of MS, resulting in slow cognitive processing in 50%-60% of individuals [10]. At this point, people may experience memory and cognitive deficits, impaired verbal fluency, and decreased alertness [11].

The prevalence of negative outcomes after MS highlights the importance of rehabilitation in improving and maintaining individuals' function and well-being [12]. Since MS is a chronic and degenerative condition, maintaining engagement in rehabilitation is particularly challenging. Although rehabilitation has been shown to play a crucial role in preventing disease progression, this importance is not always fully recognized. In fact, MS rehabilitation is described as a complex process that necessitates a lengthy procedure, potentially contributing to lower participant engagement and adherence to treatment [13,14]. Therefore, the development of an effective and sustainable method to increase people's participation and motivation in the lengthy rehabilitation process is necessary. Providing rehabilitation in innovative ways could also enhance MS people’s perception of its importance, further improving engagement and adherence [15]. In recent years, technological innovations, such as serious games, have been developed with the intention of managing the deterioration function in people with MS [16]. Serious games are defined as games whose main purpose is for learning rather than entertainment [17,18]. In rehabilitation, serious games are intended for training and education rather than pure entertainment. These games often comply with a range of characteristics that are not typical of commercial entertainment and off-the-shelf games [17], and are designed to be interactive, meaningful and challenging [19]. Some of these can even update the game difficulty according to the user’s performance and handle failure with relevant cues and feedbacks [20]. Typically, serious games have the potential to respect key neurorehabilitation and motor learning principles [21,22], thus favoring neuroplasticity [23]. In this regard, serious games may help to contribute to the improvements of motor, sensitive and cognitive functions in people suffering from neurological disorders. Serious games can also help to motivate, increase participation, and improve adherence to the treatment regimen. Serious games are frequently combined with virtual reality, computer devices, or gamified robots in MS people in order to optimize regimen and health outcomes [24,25].

Several trials have been published to investigate the efficacy of serious games in improving the performance of upper limb, balance, gait, fatigue, and cognitive functions in MS people [26-28]. However, owing for their mixed results, the relatively small sample sizes (compared to large randomized controlled trials) and the heterogeneity in the outcomes and scales used, the findings of previous trials on health outcomes may appear inconclusive, thereby clouding the true effectiveness of serious games on MS people. Therefore, to better understand the differences and validate the findings, a pooled analysis of several studies measuring a specific outcome seems necessary.

While numerous relevant reviews have been undertaken to synthesize virtual reality effectiveness in improving upper limb and lower limb functions of people with MS [29-36], the resultant effect of serious games remains underexplored. Current reviews often include studies using commercial entertainment and off-the-shelf gaming interventions, which complicates the analysis of the truth effectiveness of serious games. For instance, in the work of Calafiore et al., 2021, studies covering the use of virtual reality serious and non-serious games involving activity exercises were both included [31].

Moreover, since the publication of these works, several serious games trials have been published, calling for further analyses with larger sample sizes. In addition, among the current reviews only one assessed the certainty of evidence [32], which limits the reliability of their conclusion. As a result, the aim of this study was to specifically assess the effectiveness of serious games, over conventional therapy, on upper limb activity, gait, balance, fatigue and cognitive functions of people with MS.

Methods

This review was undertaken following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Cochrane Handbook recommendations (see Supplement Material 1) [37]. The protocol was registered in PROSPERO (CRD42021259008) prior to the start of the study. Deviations from the original protocol, with reasons, are explained in Supplement Material 2.

Criteria for considering studies for this review

To be included in this review, trials had to fulfil the following PICOs criteria: (P) people were adults suffering from MS (age > 18 years); (I) the intervention group followed serious games-based programs (programs involving the use of a game whose main purpose is rehabilitation, exercise or education rather than entertainment [18]) displayed on virtual reality devices (in addition to or in substitution of conventional therapy; no restrictions in terms of intensity, duration, route or timing); (C) the control group followed a conventional therapy (therapy recommended by most recent guidelines and aiming to improve or maintain motor and cognitive functions of people with multiple sclerosis,); (O) relevant outcomes were measured to assess upper-limb activity, gait, balance, fatigue and cognitive functions (verbal memory, visuo-spatial memory, verbal fluency, executive functions and attention) according to the International Classification of Functioning, Disability and Health – World Health Organisation (ICF-WHO) directly after the intervention; (s) the study was a randomized controlled trial (RCT) written in English, French, or Spanish, published before February 2024, and with a PEDro score ≥ 5. Studies not matching all these PICOs criteria were excluded.

Trials whose interventions involved the use of commercial entertainment (games with entertainment as primary goal) or off-the-shelf games (recreational games that can be purchased by anybody) were excluded.

Outcome measures

We chose eligible studies that documented at least one of the specified outcome measures. In cases where multiple scales were employed to assess a particular outcome, we followed a hierarchical order. We here present the prioritized scales first, with additional ones listed by order of preference.

For upper limb activity outcomes, we chose the Box and Block Test [38], the Action Research Arm Test [39], the Nine Hole Peg Test [40], and the Purdue Pegboard Test [41]. For gait parameters, we chose gait speed, the 10 Meter Walk Test [42], the Six Minute Walk Test [43], the Timed-25 foot walk test [44], and the Two Minute Walk Test [45]. For balance outcomes, we did not aim to isolate specific aspects of balance (e.g., dynamic and static) but rather aimed to evaluate overall balance performance. We therefore selected the Berg Balance Scale [46], the Mini-BESTest (global score) [47], posturography kinematics, the Four Square Step Test [48], and the Tinetti-balance scale [49]. For fatigue, we chose the Fatigue Severity Scale [50] and the modified Fatigue Impact Scale [51]. For verbal memory, we chose the Selective Reminding Test [52] and the California Verbal Learning Test [53]. For visuo-spatial memory, we chose the Spatial Recall Test [54], the Brief Visuospatial Memory Test [55] and the Rey-Osterrieth Complex Figure-Delayed Recall Test [56]. For verbal fluency, we selected the Word List Generation [57] and the Greek Verbal Fluency Test [58]. For attention, we chose the Stroop Word Color Task, the Trail Making Test Part A [59], the Paced Auditory Serial Addition Test [60] and the Symbol Digit Modalities Test [61].

Search methods

Search strategies were first developed according to the PICO format for PubMed and then adapted for other databases Embase, Cochrane Library, and Scopus (see Table 1).

In addition, handsearching was performed by examination of the reference list of included studies and relevant systematic reviews, and exploration of PEDro and grey literature (Google Scholar).

Selection of studies

All references were stored in Zotero, a reference management software. After removal of duplicates, two researchers (WG and GE) screened and selected the trials based on titles and abstract. This first selection was performed independently according to the eligibility criteria. A second (independent) screening was then undertaken by reading full text of the pre-selected trials. Pooling agreement was organized during an online meeting. Disagreements were resolved through discussion. If no consensus was reached, a third researcher was involved (J-PL).

Data extraction and management

Following data was collected from each study using a data extraction form: number of people, age, degree of neurologic impairment (according to the Expanded Disability Status Scale [62]), male and female proportions, type of MS, frequency, duration, setting and content of the intervention and control programs (type and focus of rehabilitation, device used), scales and questionnaire used for the reported outcomes, and main findings of the study.

Assessment of risk of bias in included studies

Methodological quality of each study was assessed by two authors using the Cochrane Risk of Bias 2 (GE and WG) [63]. This tool allows for the assessment of risk of bias for each outcome. We assessed the impact of assignment for the following outcomes: upper limb activity, balance, gait, fatigue and all cognitive functions. The following domains were covered: bias arising from the randomization process (domain 1), bias due to deviations from intended interventions (domain 2), bias due to missing outcome data (domain 3), bias in measurement of the outcome (domain 4), and bias in selection of the reported result (domain 5). For each domain, we classified the overall risk of bias for each outcome as low, high, or with some concerns using the Excel tool (available at riskofbiasinfo.org).

Measures of treatment effect

For continuous outcomes, if the studies included in our analysis utilized identical scales for measuring the outcome, we presented the treatment effect using mean differences (MDs) along with their corresponding 95% confidence intervals (CIs). However, if different measurement scales were employed to assess the same outcome, we evaluated treatment effectiveness by calculating a standardized mean difference (SMD) along with its 95% CI [64]. For each SMD, the magnitude of effect was categorized as low (SMD ≤ 0.5), moderate (0.5 < SMD ≤ 0.8) or large (SMD > 0.8) according to Cohen's conventions [65]. Our analysis focused on comparing post-intervention outcomes at the conclusion of treatment. To ensure the accuracy of numerical data, we cross-referenced the direction of effect observed in terms of relative MD, or SMD with the findings reported in the included studies.

In instances where trial authors were unable to furnish the mean and standard deviations (SDs) directly, we adopted Wan's approach to convert medians and their quartiles into means and SDs [66]. Additionally, when confidence intervals (CIs) and standard errors of the means were provided, we converted them to SDs utilizing the methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions.

Assessment of heterogeneity

We quantified between-study statistical heterogeneity using the I^2 statistic. We interpreted it as low (I^2 between 0% and 40%), moderate (I^2 between 40% and 60%), substantial (I^2 between 50% and 90%), or considerable (I^2 between 75% and 100%), according to the Cochrane Handbook recommendations. We also assessed heterogeneity by visual inspection of forest plots, and with Chi^2 tests.

We assessed clinical heterogeneity using the characteristics of included studies tables to compare the population, interventions, comparisons, and outcomes. If the studies were sufficiently similar, we pooled the data.

We assessed methodological heterogeneity using sensitivity analyses, to see whether including studies at a high risk of bias affected our conclusions.

Assessment of reporting bias

To assess reporting biases, we compared the information outlined in each trial's published protocol, available in clinical trials registers, with the details provided in the methods and results sections of the corresponding publication. Additionally, if more than 10 studies reported the same outcome, we employed funnel plots to examine for small study effects, potentially indicative of publication bias. In case of asymmetry or outliers, indicating substantial differences in intervention effect estimates among studies, if more than 10 studies reported the same outcome, we conducted the Egger regression test to quantify the influence of publication bias on each result [67]. When less than 10 studies were reported, we looked for potential unpublished studies in trials registries.

Data synthesis

Based on the clinical heterogeneity assessment, if the studies were deemed sufficiently similar, we synthesized serious games-based programs effectiveness in rehabilitating people with MS' upper limb activity, balance, gait, fatigue and cognitive functions using a meta-analysis. All eligible studies were included in this meta-analysis. When the rehabilitation content of the included studies varied significantly, for each motor and cognitive outcome, we conducted subgroup (for n studies $\geq$ 10) or separate analyses (for n studies < 10) based on the specific rehabilitation content, settings and objectives. Specifically, we pooled studies that used a common device (robotic, non-immersive VR, semi-immersive VR, immersive VR, treadmill, or motion platform) and aimed to rehabilitate the same function(s) or body part(s), such as upper limb function, gait, lower limb function, balance, attention, visuo-spatial memory, overall cognition, or multiple functions.

RevMan software was utilized for all statistical analyses and forest plots. A random-effects model was employed due to expected heterogeneity between studies. However, if fewer than two studies were included for one given outcome, or if the heterogeneity was considerable (I^2 > 75%) after removing outliers, we summarized the results using a narrative synthesis.

Sensitivity analyses

We performed sensitivity analyses to assess the robustness of the decision we made 1) not to limit forest-plots to studies at low risk of bias and those with some concerns (analyses excluding studies with high risk of bias), 2) not to limit forest-plot to studies conducted in substitution of conventional therapy (analyses excluding studies conducted in addition to conventional therapy).

Summary of findings and assessment of the certainty of the evidence

We made a summary of findings table focusing on the comparison between serious games-based programs and conventional therapy for people with MS. Table 4 outlines the following outcomes: upper limb activity, balance, gait, fatigue, visuo-spatial memory and attention.

In this table, we provided details regarding the study population and settings, the interventions (in experimental and control groups), and the specified health outcomes. Each outcome is accompanied by its respective measure (MD or SMD) along with corresponding 95% CIs, the magnitude of effect, the numbers of participants and studies, and the overall certainty of the body of evidence.

We assessed the certainty of evidence for each outcome using the GRADE approach. This method categorizes the certainty of evidence as high, moderate, low, or very low based on various factors such as study limitations, inconsistency, indirectness, imprecision, and publication bias [68].

For each domain, we lowered the certainty of evidence by one level for serious concerns and by two levels for very serious concerns. This adjustment was made to account for any significant limitations or biases identified within the body of evidence.

Results

Results of the search

Search strategies produced a total of 2532 studies. After removal of duplicates (n = 626), 1906 different trials were screened (Figure 1). During the first selection process, 54 studies were retained leading to the exclusion of 1852 trials. At the end of the second screening, a total of 17 RCTs [26-28,69-82], with a total number of 740 people, met the inclusion criteria.

[insert Figure 1 here]

Sample characteristics

Participant's mean age ranged from 26.4 (3.45) to 60.6 (13.70) years. Their average Expanded Disability Status Scale score was of 4.75 [3.69; 5.28]. Characteristics of the included studies and people are presented in Table 2 and Table 3.

[insert Table 2 here]

Females and males were represented in all studies except one [77]. This study included 45 females with MS. Six trials included people with relapsing-remitting MS only [28,71-74,78], one people with secondary progressive MS only [82], two people with relapsing-remitting or secondary progressive MS [75,76], one people with primary or secondary progressive MS [80], and five people with either one of the three types of MS [26,27,69,70,81]. Two studies did not really specify people's type of MS [77,79].

Majority of trials (n = 10) disclosed being supported by a grant [27,28,69,71-73,75,77,79,81]. Four trials were multicentric [27,69,71,81]. Two RCTs were conducted in three different countries (one in Belgium, Italy and Israel, and another in Israel, USA and Germany) [71,81]. Other studies were undertaken in Italy (n = 6) [28,74,76,79,80,82], Spain (n = 4) [26,27,69,75], Iran (n = 1) [77], Belgium (n = 1) [70], Israel (n = 1) [72], Jordan (n = 1) [73] and Turkey (n = 1) [78].

Most serious games were provided using specific non-immersive virtual reality devices such as gaming consoles (n = 10) [26-28,69,71-73,75,77,81]. Four serious game-based programs were delivered using a semi-immersive virtual reality device [74,76,79,83] and another using a full-immersive virtual reality device [78]. Two studies combined their serious game with an interactive robotic device [70,80]. The content of the rehabilitation varied between trials. Two studies mainly focused on the rehabilitation of upper limb function [27,77], four on cognition and upper limb function [26,69,70,80], three on cognition and gait functions [28,71,81], three on balance functions [72,73,78], one on balance and upper limb function [75], three on cognition (involving UL interaction) [74,76,82] and one on general motor and cognitive rehabilitation [79]. Most studies involved seeing patients on an outpatient basis and more than half of trials' interventions were designed to be conducted in addition to conventional therapy [26,27,69,70,75-78,80,82].

Control group interventions comprised traditional upper limb motor training (n=5) [26,27,69,77,80], traditional gait and balance exercises (n = 3) [75,78,81], traditional balance exercises (n = 2) [72,73], treadmill training [28,71], general motor-cognitive training (n = 3) [76,79,82], traditional cognitive training (n = 1) [74] or non-specific multidisciplinary standard clinical cares (n = 1) [70].

Intervention duration was of ten weeks in two studies [69,75], eight weeks in nine studies [26,27,70,74,76-78,81,82], six weeks in five studies [28,71-73,79], and four weeks in one study [81]. In most studies (n = 8), sessions were provided two times a week [26,27,69,72,73,77,78,81]. Six studies involved interventions that were delivered three times a week [28,71,74,76,80,82], two studies involved interventions that were delivered at least five times a week [70,79] and one study involved an intervention that was delivered only once a week [75].

[insert Table 3 here]

Reported outcome measures

Upper limb activity was measured in seven different trials [26,27,69,70,77,79,80]. The Box and Block Test was used in four studies [26,27,69,79], the Action Research Arm Test in one [70], the Nine Hole Peg Test in five [26,69,77,79,80], and the Purdue Pegboard Test in one [69].

Gait outcomes were evaluated in five different trials [28,71,73,75,81]. Gait speed was evaluated in two studies [28,71], the 10 Meter Walk Test was used in three [28,73,75], the Six Minute Walk Test in one [28], the Timed-25 foot walk test in one [81], and the Two Minute Walk Test in one [81].

Balance was measured in seven different studies [28,72,73,75,76,78,79]. The Berg Balance Scale was used in five studies [28,72,73,75,78], the Mini-BESTest in one [79], postugraphy kinematics in three [72,78,79], the Four Square Step Test in two [28,72], and the Tinetti-balance scale in one [76].

Fatigue was measured in eight different studies [27,69,71,73,78-81]. The Fatigue Severity Scale was used in five studies [27,69,78-80] and the modified Fatigue Impact Scale in three studies [71,73,81].

Regarding cognitive functions, verbal memory was measured in three different studies [71,74,79]. The Selective Reminding Test was used in two studies [74,79] and the California Verbal Learning Test in one study [71]. Visuo-spatial memory was measured in five different studies [71,74,76,79,83]. The Spatial Recall Test was used in four studies [71,74,76,79], the Brief Visuospatial Memory Test in one study [71], and the Rey-Osterrieth Complex Figure-Delayed Recall Test in two studies [76,83]. Verbal fluency was measured in three different studies [71,74,79]. The Word List Generation test was used in three studies [71,74,79]. Attention was measured in six studies [26,71,74,76,79,81]. The Stroop Word Color Task was used in one study [26], the Trail Making Test Part A was used in two studies [26,71], the Paced

Auditory Serial Addition Test was used in three studies [74,76,79] and the Symbol Digit Modalities Test was used in three studies [74,79,81].

Risk of bias in included studies

Detailed results of outcome assessment per domain is available in Supplement Material 3.

For upper limb activity outcomes, overall risk of bias was found to be low for one study [26], with some concerns for four studies [27,69,70,79] and high for two studies [77,80].

For gait outcomes, overall risk of bias was found to be low for two studies [71,73], with some concerns for two studies [28,81], and high for one study [75].

For balance outcomes, overall risk of bias was found to be low for one study [73], with some concerns for four studies [28,72,78,79] and high for two studies [75,76].

For fatigue outcomes, overall risk of bias was found to be low for three studies [69,71,73], with some concerns for four studies [27,78,79,81] and high for one study [80].

Regarding cognitive outcomes, for verbal memory, overall risk of bias was found to be low for one study [71] and with some concerns for two studies [74,79]. For visuo-spatial memory, overall risk of bias was found to be low for one study [71], with some concerns for three studies [74,79,83] and high for one study [76]. For verbal fluency, overall risk of bias was found to be low for one study [71] and with some concerns for two [74,79]. For attention, overall risk of bias was found to be low for two studies [26,71], with some concerns for three studies [74,79,81] and high for one study [76].

Effect of serious games on upper limb activity

One study did not provide quantitative data for upper limb activity outcomes [77]. Due to population bias suspicions (possible overlapped series), two other studies were removed from the analysis [27,69]. Owing for the heterogeneity in the content of interventions, separate analyses were conducted for serious games-based interventions comprising robotic upper limb training, non-immersive virtual reality upper limb training and general semi-immersive virtual reality training (not particularly focused on upper limb).

As presented in Figure 2, no significant difference was observed between the effect of robotic upper limb serious-games based programs and conventional therapy (SMD = 0.00; 95% CI = -0.56 – 0.57; p = 0.99). Between-studies statistical heterogeneity was found to be low (Chi^2 = 0.11 (p = 0.74); I^2 = 0%). As presented in Supplement Material 4, sensitivity analysis, involving removal of one additional study from the analysis [80], due to high risk of bias concerns, did not change the result (SMD = 0.00; 95% CI = -0.56 – 0.57; p = 0.99 vs SMD = 0.13; 95% CI = -0.80 – 1.05; p = 0.79; test for difference : p = 0.85).

[insert Figure 2 here]

Similarly, non-immersive virtual reality upper limb serious games (SMD = -0.17; 95% CI = -1.03 – 0.69; p = 0.69) and general semi-immersive virtual reality serious games did not lead to increased benefits over conventional programs (SMD = -0.03; 95% CI = -0.54 – 0.48; p = 0.91).

Due to the overall risk of bias in included studies and the limited number of observations, the strength of the body evidence was downgraded by two (see Table 4). Consequently, the certainty of evidence regarding the effect of serious games over conventional therapy on upper limb activity in people with multiple sclerosis was considered as low.

Effect of serious games on gait

Owing for the heterogeneity in the content of interventions, separate analyses were conducted interventions comprising the use of treadmill serious games, and non-immersive virtual reality serious games targeting lower limb and balance functions. Meta-analysis suggest that treadmill serious games-based programs did not lead to increased gait benefits over conventional therapy

(SMD = 0.06; 95% CI = -0.30 – 0.42; $p = 0.74$) (see Figure 3). Between-studies statistical heterogeneity was found to be low ($Chi^2 = 0.13$ ($p = 0.72$); $I^2 = 0\%$).

[insert Figure 3 here]

No significant difference was observed between the effect of non- or semi-immersive virtual reality serious games targeting balance and lower limb functions and conventional therapy (SMD = 0.29; 95% CI = -0.15 – 0.72; $p = 0.20$). Between-studies statistical heterogeneity was also found to be low ($Chi^2 = 1.23$ ($p = 0.54$); $I^2 = 0\%$). As presented in Supplement Material 5, sensitivity analysis, involving removal of one study from the analysis [75], due to high risk of bias and intervention design concerns (provided in addition to conventional therapy), did not change the result (SMD = 0.29; 95% CI = -0.15 – 0.72; $p = 0.20$ vs SMD = 0.38; 95% CI = -0.09 – 0.85; $p = 0.11$; test for difference: $p = 0.77$).

Due to the overall risk of bias in included studies and the limited number of observations, the strength of the body evidence was downgraded by two (see Table 4). Consequently, the certainty of evidence regarding the effect of serious games over conventional therapy on gait in people with multiple sclerosis was considered as low.

Effect of serious games on balance

Owing for the heterogeneity in the content of interventions, separate analyses were conducted for interventions comprising the use of motion platforms serious games targeting balance functions, immersive virtual reality serious games targeting balance functions, treadmill serious games, non-immersive virtual reality serious games targeting lower limb and balance functions, and general semi-immersive virtual reality serious games (not particularly focused on upper or lower limb).

As presented in Figure 4, when compared to conventional therapy, the effect of motion platform serious games (SMD = 0.56; 95% CI = -0.17 – 1.30; $p = 0.13$), immersive virtual reality serious games targeting balance impairments (SMD = 0.02; 95% CI = -0.75 – 0.79; p = 0.96), and treadmill serious games (SMD = 0.00; 95% CI = -0.79 – 0.79; p = 1.00) did not lead to increased balance benefits.

[insert Figure 4 here]

Contrastingly, a marginal but significant effect was found between non-immersive virtual reality serious games targeting lower limb and balance functions, and conventional therapy (SMD = 0.62; 95% CI = -0.00 – 1.23; p = 0.05). Between studies statistical heterogeneity was non-significant (Chi^2 = 0.64 (p = 0.42); I^2 = 0%). Sensitivity analysis involving removal of one study [75] from the analysis due to high risk of bias and intervention design concerns (provided in addition to conventional therapy), did not change the result (SMD = 0.62; 95% CI = -0.00 – 1.23; p = 0.05 vs SMD = 0.77; 95% CI = 0.05 – 1.49; p = 0.04; test for difference: p = 0.75) (see Supplement Material 6).

Meta-analysis also suggests a significant effect of general semi-immersive virtual reality serious games over conventional therapy on balance outcomes (SMD = 0.48; 95% CI = 0.12 – 0.84; p = 0.01). Between-studies statistical heterogeneity was found to be low (Chi^2 = 0.06 (p = 0.81); I^2 = 0%) so as the observed effect size ($0.2 < SMD \leq 0.5$). However, sensitivity analysis involving removal of one study from the analysis [76], due to risk of bias and intervention design concerns (provided in addition to conventional therapy), did change the result but not statistically (SMD = 0.48; 95% CI = 0.12 – 0.84; p = 0.01 vs SMD = 0.43; 95% CI = -0.08 – 0.95; p = 0.10; test for difference: p = 0.89) (see Supplement Material 7).

Due to the overall risk of bias in included studies and the limited number of observations, the strength of the body evidence was downgraded by two (see Table 4). Consequently, the certainty of evidence regarding the effect of serious games over conventional therapy on balance in people with multiple sclerosis was considered as low.

Effect of serious games on fatigue

Due to publication bias suspicions, one study was removed from the analysis [27]. In addition, owing for the heterogeneity in the content of interventions, separate analyses were conducted for interventions comprising the use of robotic upper limb serious games, non-immersive virtual reality upper limb serious games, immersive virtual reality serious games targeting balance functions, non-immersive virtual reality serious games targeting lower limb and balance functions, treadmill serious games, and general semi-immersive virtual reality serious games (not particularly focused on upper or lower limb).

Meta-analysis, presented in Supplement Material 8, showed that robotic upper limb serious games (SMD = -0.41; 95% CI = -1.13 – 0.32; p = 0.27) and non-immersive upper limb virtual reality serious games (SMD = -0.19; 95% CI = -0.91 – 0.53; p = 0.61) were not significantly superior to conventional therapy to improve fatigue outcomes.

Similarly, the effect of interventions targeting balance and lower limb functions using immersive (SMD = -0.25; 95% CI = -1.02 – 0.52; p = 0.52) and non-immersive virtual reality serious games (SMD = 0.31; 95% CI = -1.00 – 1.62; p = 0.64) were not superior to conventional therapy (see Supplement Material 8). For the latter, between-studies statistical heterogeneity was found to be substantial (Chi² = 7.35; p = 0.007; I^2 = 86%). However, the removal of outlier results issued from one study [73], did not change the result (SMD = 0.31; 95% CI = -1.00 – 1.62; p = 0.64 vs SMD = -0.35; 95% CI = -0.97 – 0.28; p = 0.28; test for group difference: p =) and, by default, improved heterogeneity (Supplement Material 9).

Contrastingly, a significant and positive effect was found in favor of treadmill serious games over conventional therapy (SMD = 0.80; 95% CI = 0.40 – 1.20; p <0.001) (Supplement Material 8). The effect size was moderate (0.5 < SMD ≤ 0.8).

Lastly, no significant difference was found between the effect of general semi-immersive virtual reality serious games and conventional therapy (SMD = -0.04; 95% CI = -0.55 – 0.46; p = 0.86) (Supplemental Material 8).

Due to the overall risk of bias in included studies, the limited number of observations, and the considerable statistical heterogeneity, the strength of the body evidence was downgraded by three (see Table 4). Consequently, the certainty of evidence regarding the effect of serious games over conventional therapy on fatigue in people with multiple sclerosis was considered as very low.

[insert Table 3 here]

Effect of serious games on verbal memory

One study was removed from the analysis due to publication bias suspicion [74]. In addition, owing for the heterogeneity in the content of interventions, separate analyses were conducted for treadmill serious games targeting attentional and visuo-spatial memory functions and semi-immersive virtual reality general cognitive serious games.

As presented in Supplement Material 10, no significant difference was observed between the effect of treadmill attentional and visuo-spatial memory serious-games and conventional therapy (SMD = 0.01; 95% CI = -0.37 – 0.39; p = 0.96) nor between the effect of semi-immersive virtual reality general cognitive serious games and conventional therapy (SMD = 0.34; 95% CI = -0.17 – 0.85; p = 0.19).

Effect of serious games on visuo-spatial memory

Two studies were removed from the analysis due to publication bias suspicion [74,76]. Owing for the heterogeneity in the content of interventions, separate analyses were conducted for treadmill serious games targeting attentional and visuo-spatial memory functions and semi-immersive virtual reality general cognitive serious games.

Meta-analysis results suggest that, when compared to conventional therapy, treadmill attentional and visuo-spatial memory serious games did not lead to superior benefits (SMD = 0.00; 95% CI = -0.38 – 0.38; p = 1.00) (see Figure 5).

Contrastingly, the effect of semi-immersive virtual reality general serious games was found to be significantly superior to this of conventional therapy (SMD = 0.35; 95% CI = 0.04 – 0.65; p = 0.03). Between-studies statistical heterogeneity was found to be low (Chi^2 = 0.24 (p = 0.63); I^2 = 0%) so as the observed effect size ($0.2 < SMD \leq 0.5$). However, sensitivity analysis involving removal of one study from the analysis [82], due to intervention design concerns (provided in addition to conventional therapy), did change the result (SMD = 0.35; 95% CI = 0.04 – 0.65; p = 0.03 vs SMD = 0.25 ; 95% CI = -0.26 – 0.75; p = 0.34; test for group difference: p = 0.74) (see Supplement Material 11).

[insert Figure 5 here]

Due to the overall risk of bias in included studies, and the limited number of observations, the strength of the body evidence was downgraded by two (see Table 4). Consequently, the certainty of evidence regarding the effect of serious games over conventional therapy on visuo-spatial memory in people with multiple sclerosis was considered as low.

Effect of serious games on verbal fluency

One study was removed from the analysis due to publication bias suspicion [74]. Owing for the heterogeneity in the content of interventions, separate analyses were conducted for treadmill serious games targeting attentional and visuo-spatial memory functions and semi-immersive virtual reality general cognitive serious games.

As presented in Supplement Material 12, no significant difference was observed between the effect of treadmill attentional and visuo-spatial memory serious games and conventional therapy (SMD = -0.02; 95% CI = -0.40 – 0.37; p = 0.93) nor between the effect of semi-immersive virtual reality general serious games and conventional therapy (SMD = 0.13; 95% CI = -0.38 – 0.64; p = 0.61).

Effect of serious games on attention

One study was removed from the analysis due to publication bias suspicion [74]. Owing for the heterogeneity in the content of interventions, separate analyses were conducted for treadmill serious games targeting attentional and visuo-spatial memory functions and semi-immersive virtual reality general cognitive serious games.

As presented in Figure 6, no significant difference was observed between the effect of treadmill attentional and visuo-spatial memory serious games and conventional therapy (SMD = 0.06; 95% CI = -0.32 – 0.45; p = 0.74).

[insert Figure 6 here]

Similarly, when compared to conventional therapy, the effect of semi-immersive virtual reality general cognitive serious games did not lead to significant benefits (SMD = 0.10; 95% CI = -0.40 – 0.61; p = 0.68). However, for the latter, between-studies statistical heterogeneity was found to be substantial (Chi^2 = 8.25 (p = 0.04); I^2 = 64%). First sensitivity analysis involving removal of one study from the analysis [76], due to high risk of bias, did not change the result (SMD = 0.10; 95% CI = -0.40 – 0.61; p = 0.68 vs SMD = -0.16; 95% CI = -0.51 – 0.20; p = 0.39; test for group difference: p = 0.41) and improved statistical heterogeneity (Chi^2 = 0.70 (p = 0.40); I^2 = 0%) (see Supplement Material 13). Second sensitivity analysis involving removal of one study from the analysis [26], due to intervention design concerns (provided in addition to conventional therapy), did not change the result (SMD = 0.10; 95% CI = -0.40 – 0.61; p =

0.68 vs SMD = 0.16; 95% CI = -0.46 – 0.50; p = 0.61; test for group difference: p = 0.89) (see Supplement Material 14).

Due to the overall risk of bias in included studies, the limited number of observations, and the considerable statistical heterogeneity, the strength of the body evidence was downgraded by three (see Table 3). Consequently, the certainty of evidence regarding the effect of serious games over conventional therapy on attention in people with multiple sclerosis was considered as very low.

Discussion

The current meta-analysis included a total of 17 trials with 740 participants. Because of the diversity in clinical approaches and methodologies, as well as a deficiency in evaluating various reported outcomes, there were limited opportunities for us to combine data. Results of the current work suggest, with a very low to low certainty of evidence, that overall, all serious games and conventional therapy programs are equally effective to improve upper limb activity, gait, fatigue, as well as cognitive functions such as verbal memory, verbal fluency and attention. According to our separate analyses, some serious games programs showed superior effectiveness to conventional therapy on balance, fatigue and visuo-spatial memory. As presented in Table 5, balance functions appeared to be improved by semi-immersive virtual reality serious games, fatigue by treadmill serious games and visuo-spatial memory by semi-immersive virtual reality general cognitive serious games.

[insert Table 5 here]

Comparison with prior reviews

The present study contradicts previous reviews underlining that the aggregate effect of virtual reality and serious games had a greater benefit in improving upper limb outcomes [34], in individuals with MS. Several explanations for the inconclusive findings might be proposed.

First, the severity of upper limb disability and its prevalence since the onset of the disease can vary significantly among individuals [84]. This variability may influence the overall effectiveness of serious games interventions. In particular, the level of disability could play a crucial role, as individuals with more advanced upper limb impairment may respond differently to serious games compared to those with milder symptoms. Second, the inability of serious games to improve upper limb activity in people with MS may be due to different subtypes of the disease, such as relapsing-remitting and secondary progressive MS, in which some symptoms steadily worsen and progress to a worsening stage, resulting in disability accumulation without intermittent recovery [85,86]. Until recently, there was no effective treatment to prevent the disability from worsening [87]. In addition, as underlined in Table 2, most of the included studies recruited individuals with different types of MS (relapsing-remitting, primary and secondary progressive MS) making it difficult to draw conclusions for each subtype of the pathology. Moreover, the fact that, in our review, not all included trials used serious games-based programs that were specifically developed to improve one particular outcome such as manual dexterity or muscle strength might be partially responsible for the lack of significance in the present study. For example, Feys et al., [70] Tramontano et al., [80] and Cuesta-Gomez et al., [26] provided games focused on upper limb function, whereas Pagliari et al., [79] focused on both general motor and cognitive functions. Additionally, reported scales such as the Nine-Hole Peg Test assess finer manual abilities compared to other outcome measures considered for upper limb functionality. These tests are sensitive to subtle changes in dexterity and coordination [88], which may not be adequately captured by broader assessments. Therefore, variations in the specific measures used to evaluate upper limb function could contribute to the differences in observed outcomes.

Regarding balance outcomes, our results partially align with prior reviews suggesting the beneficial effects of virtual reality and serious games in improving balance outcomes in people with MS [29,31,33,35]. The observed superior effect of non-immersive virtual reality and semi-immersive virtual reality serious games programs is unlikely solely due to intervention duration or design, as evidenced by the composition of the trials analyzed. Specifically, half of the trials (2 out of 4) incorporated serious games as a replacement for conventional therapy, while the remaining half (2 out of 4) utilized them as an additional therapy. The superior effectiveness of serious games in improving balance may stem from the diverse training provided to the intervention group, encompassing activities such as gait and balance training, treadmill exercises, and Pilates within the gaming framework. Notably, these exercises are recognized for their efficacy in enhancing balance and coordination outcomes [89]. However, it seems important to highlight that only one low risk of bias study independently demonstrated a significant effect on balance outcomes [73]. This study's intervention employed a virtual reality serious game to target balance deficits. This may highlight the potential of incorporating an intervention with an interactive device such as virtual reality to specifically rehabilitate balance functions [90]. In addition, virtual reality is a popular serious game delivery system that has been shown to improve participant enjoyment, engagement, and adherence in rehabilitation [91,92].

Neutral effect of serious games on gait outcomes

Gait deficiency is one of the most common adverse outcomes affecting disability in MS people [93]. Our findings suggest that serious games effectiveness was not superior to conventional therapy in improving gait outcomes. This lack of significant improvement may be explained by several factors. First, while some specific serious games can effectively target some aspects of balance and coordination, they may not sufficiently address the complexity of gait mechanics and patterns, which are influenced by various factors such as muscle strength, joint flexibility, motor control, and cognitive function. Virtual reality environments, including treadmill-based systems, may struggle to fully replicate the dynamic and multidimensional nature of real-world walking. In a virtual reality setup, users can be limited in terms of space and movement, which can restrict natural gait patterns and fail to engage the complex motor and cognitive processes involved in walking. Additionally, virtual reality environments may lack the sensory inputs and environmental cues present in real-world settings that are critical for adaptive gait control, such as uneven surfaces, and varying terrain. The absence of these elements can lead to an oversimplification of gait mechanics, thus limiting the potential for rehabilitation gains. Furthermore, individual variability in response to serious games interventions and differences in baseline gait impairments or motor control deficits could also contribute to the neutral effect observed. Finally, it is plausible that the neutral effect could also be attributed to the effectiveness of the control interventions employed in the included trials, which may have also produced positive outcomes in gait measures, thereby mitigating the potential additional benefits offered by the serious gaming interventions. In 80% of the included trials (4 out of 5), control interventions were specifically designed to improve gait parameters whereas only 60% of these trials (3 out of 5) comprised serious games targeting gait functions.

Serious games effect on cognitive functions

The meta-analysis findings reveal that while some specific serious games programs (in semi-immersive virtual reality), in comparison to conventional therapy, notably enhanced visuo-spatial memory among individuals with MS, no significant improvements were observed in verbal memory, verbal fluency, or attention. The differential impact observed on various cognitive domains may stem from the inherent differences in the cognitive processes targeted by serious games interventions. For instance, visuo-spatial memory may be particularly responsive to the visual and spatial stimuli inherent in semi- to fully immersive virtual reality environments, whereas verbal memory, verbal fluency, and attention may require different modalities or cognitive strategies that may not be as effectively stimulated through serious games alone. Additionally, individual variability in cognitive profiles and the specific design of the serious games interventions may also contribute to the varied outcomes across cognitive domains. These findings underscore the importance of tailoring interventions to target specific cognitive functions and the need for further research to elucidate the mechanisms underlying the differential effects of serious games on cognition in MS. Furthermore, these inconsistent results might also be attributable to the limited number of studies included in the separate analyses for each cognitive outcome, highlighting the need for additional research with larger sample sizes to provide more robust conclusions regarding the efficacy of serious games interventions on various aspects of cognitive function in MS.

Separate analyses findings and their implications

Isolating programs that target specific outcomes or integrate specific exercises is instrumental to draw more precise conclusions about which types of serious games are beneficial for rehabilitation goals. The separate analyses based on the specific rehabilitation content and objectives of the interventions may offer valuable insights into the varying effectiveness of serious games for different outcomes. In our review, we identified significant benefits in certain areas, such as the improvements in balance and visuo-spatial memory observed with semi-immersive virtual reality and the improvements of fatigue with treadmill training. Other areas, like upper limb function and gait, showed more neutral effects, irrespective of the interventions provided.

Semi-immersive virtual reality serious games appear particularly effective for balance and visuo-spatial memory rehabilitation, possibly due to their unique combination of immersive experience and practical usability. They strike a "golden mean" between non-immersive and fully immersive virtual reality, offering a more realistic environment than non-immersive setups, while avoiding the complexity and potential drawbacks associated with fully immersive systems, such as cybersickness [94]. Semi-immersive virtual reality allows users to interact with virtual elements in a 3D space while enabling interaction with practitioners, allowing for immediate feedback and guidance, which is crucial for tailoring the rehabilitation process to individual needs. This interaction may ensure that while participants benefit from a realistic 3D environment, they also receive real-time feedback, which has been shown to be important for cognitive rehabilitation [95]. Several studies recommend the use of semi-immersive virtual reality serious games for these reasons, as it provides the immersive qualities needed for engaging and realistic practice without the overstimulation that can come with full immersion [94,96]. The observed effectiveness of semi-immersive virtual reality serious games identified in our review may also stem from the fact the programs involved were mostly general, focusing on overall motor and cognitive improvements. Combining cognitive and motor challenges appears to be particularly beneficial for rehabilitation outcomes [97,98]. By challenging both cognitive processing and motor coordination, these programs may stimulate neuroplasticity, enhancing the brain's ability to reorganize and form new neural connections [99]. This process is further supported by the physical activity involved, which promotes increased blood flow to key brain areas, such as the hippocampus, and boosts the release of neurotrophic factors that facilitate learning and memory [100].

Similarly, the observed effectiveness of treadmill-based serious games in improving fatigue outcomes may be attributed to the combined physical and cognitive engagement involved in these interventions. Walking or running on a treadmill challenges the cardiovascular system and increases overall physical activity levels, which has been shown to reduce fatigue in various populations, including individuals with neurological conditions [101,102]. This physical activity boosts circulation, promotes the release of endorphins, and in the long term, enhances energy levels, which can directly counteracts fatigue [103,104]. In addition, treadmill-based serious games often include cognitive elements that require focus, decision-making, and task completion. Engaging in these dual-task activities may not only challenge motor coordination but also stimulate cognitive processing, potentially contributing to mental alertness and reducing perceived fatigue. This may also help to sustain motivation, making the exercise more enjoyable and reducing the mental drain that can accompany prolonged physical activity.

However, despite their advantages, nuances should be considered when interpreting the findings of these separate analyses. The limited number of studies in some categories may affect the robustness of our conclusions, potentially leading to uncertainty in areas where results were not statistically significant. The variability in study designs and outcome measures also complicates the generalization of findings across different types of serious games.

Impact of publication bias on findings

Publication bias is a concern as it can overrepresent positive outcomes in systematic reviews. Typically, funnel plots are used to assess this bias, but the Cochrane Handbook advises against using them when fewer than 10 studies are included. Since none of our outcomes included more than 10 studies, we could not conduct a meaningful assessment of publication bias.

Despite this limitation, several observations from our analyses suggest that the potential for publication bias may be low. Notably, across most outcomes, we found a mix of studies reporting negative, neutral, and positive effects of serious games on multiple sclerosis rehabilitation. This balance indicates that studies with varying results have been published and included in our review, reducing the likelihood that only positive findings were selectively reported. Moreover, we conducted a thorough search of trial registries for unpublished studies. Our search did not uncover any relevant unpublished studies, which further supports the notion that our review has not excluded significant negative or neutral findings that would otherwise alter the overall conclusions. While these observations suggest a lower risk of publication bias in our review, we acknowledge that the possibility cannot be entirely ruled out.

Certainty of evidence and applicability of findings

The evidence generated in this review, despite showing some benefits of serious games in specific outcomes like balance, visuo-spatial memory and fatigue, remains of low to very low certainty due to the overall risk of bias and the limited sample size of included studies. These factors should be considered when interpreting the results and their potential applicability to clinical practice. The heterogeneity between trials, both in terms of intervention design and outcome measures, adds to the complexity of generalizing these findings across different settings.

However, while the low certainty of evidence might limit immediate clinical applicability, it should not entirely deter the integration of serious games into rehabilitation programs for individuals with MS. To better support clinical decision-making, we conducted sensitivity analyses to determine whether excluding high-risk studies would impact the overall conclusions. These analyses indicated that the removal of studies with a high risk of bias did not substantially alter the results, reinforcing the robustness of our findings despite the low certainty of evidence. Nevertheless, future research with higher methodological rigor and larger sample sizes is necessary to increase the confidence in these conclusions and to more clearly define the role of serious games in rehabilitation for individuals with MS.

Implications for practice

Although, the very low to low certainty of evidence warrants further research to draw conclusion on serious games effectiveness, our findings suggest that most programs may not be inferior to conventional therapy in enhancing upper limb activity, gait, balance, fatigue and cognition. More importantly, the meta-analysis suggests a beneficial effect of some of these programs on balance, visuo-spatial memory and fatigue.

Given the current evidence, serious games should not be used to replace conventional approaches but should rather be considered as an alternative and encouraging adjunct therapy to supplement conventional approaches in the rehabilitation of individuals with MS. By providing engaging and interactive interventions, serious games have the potential to enhance participation and adherence to long-term rehabilitation regimens among certain segments of the MS population. The immersive nature of serious games platforms may help alleviate some of the barriers to engagement commonly encountered in conventional therapy settings, thereby fostering greater enthusiasm and commitment to rehabilitation activities. The interactive and gamified elements can also motivate MS people to adhere to their rehabilitation programs more consistently. Clinicians can leverage this by incorporating serious games into home-based rehabilitation programs, allowing MS people to continue their therapy outside clinical settings. This can be particularly beneficial for people who may have difficulty attending frequent in-person sessions due to mobility issues or geographical constraints.

Moreover, the flexibility and adaptability of serious gaming interventions may cater to the diverse needs and preferences of individuals with MS, allowing for personalized and targeted rehabilitation approaches. Clinicians should assess patient-specific factors such as the type of MS, severity of symptoms, and individual preferences when selecting serious game interventions. Tailoring the choice of serious games to the MS person’s specific rehabilitation goals can optimize outcomes and enhance the overall effectiveness of the therapy. For example, people with more severe balance and visuo-spatial memory issues might benefit from general semi-immersive virtual reality serious games, while those with fatigue deficits may benefit more from treadmill serious games. In fact, our work highlights that serious games involving general semi-immersive virtual reality interventions showed superior effectiveness for balance and visuo-spatial memory outcomes. Similarly, for fatigue, treadmill-based serious games demonstrated superior effectiveness. Clinicians may therefore consider integrating these specific types of serious games for MS people who particularly need improvement in these areas. Moreover, given the current evidence for these outcomes, clinicians might also integrate serious games into their practice for combined cognitive and motor rehabilitation, potentially improving functional benefits [105].

Nevertheless, for effective clinical implementation, clinicians should receive training on the use of serious games and virtual reality in therapy. Understanding the technical aspects of these tools and how to integrate them with traditional rehabilitation methods is essential. Additionally, clinicians should monitor people progress regularly to adjust the interventions as needed and ensure that the serious games are providing the intended therapeutic benefits.

The potential benefits of serious games may also vary depending on the type of MS a person has. People with relapsing-remitting MS may benefit the most from serious games, as these tools can be particularly effective during remission periods to help regain lost functions and maintain physical and cognitive abilities. In our review, most studies that showed a superior effectiveness of serious games over conventional programs were conducted among people with relapsing-remitting MS [71,73,76]. For people with primary progressive MS, serious games may offer a consistent and adaptable form of rehabilitation that can help maintain functionality and slow the progression of disability. Customizable difficulty levels may ensure that these people remain appropriately challenged and engaged. For people with secondary progressive MS, the tailored interventions provided by serious games may help to address their changing needs as they transition from a relapsing-remitting course to a more steadily progressive phase. A recent large randomized controlled trial involving 106 participants with secondary progressive MS demonstrated that serious games programs had a superior effect on attentional functions compared to conventional therapy [82].

In addition, factors such as age, cognitive function, depression, disease duration and comorbidities, may significantly influence people with MS's commitment to serious games interventions. Younger patients may have a higher affinity for technology, making them more engaged with serious games. Those with mild cognitive impairments are likely to navigate the cognitive challenges effectively, while individuals experiencing lower disease severity can participate more actively due to better physical capabilities. Additionally, patients with fewer comorbidities may face fewer barriers to engagement, and those who express positive treatment satisfaction are generally more open to exploring supplementary therapies.

Limits of the work

However, some concerns with the current study need to be taken into consideration. First, some relevant studies may have been missed due to the language restriction in the selection process. However, according to the findings of a recent work, the omission of non-English studies does not really affect the overall conclusion [106]. Second, results concerning the effect of serious games was limited by the specificity of the scales that were used to assess cognitive functions. Third, because of the limited number of studies available, this study was unable to conduct subgroup analyses. This limitation affected our ability to explore whether specific characteristics, such as patient demographics, MS severity, or the design of serious game interventions, might influence outcomes more distinctly, resulting in more generalized findings. While our separate analyses offer insights into the differential effectiveness of serious games for specific outcomes, future research should prioritize studies with larger sample sizes and more consistent reporting of participant characteristics and intervention specifics to enable meaningful subgroup analyses. Additionally, future studies could directly compare the same program between patients with different MS subtypes, such as relapsing-remitting, primary progressive, and secondary progressive MS, or evaluate the effects of different serious games on patients with similar profiles. Subgroup analyses could also have been valuable in evaluating the differences in effect between serious games used as adjunct therapy and those used as therapy substitutes. Nevertheless, our sensitivity analyses suggest that the inclusion of studies where serious games were provided in addition to conventional therapy alongside those where serious games substituted conventional therapy did not significantly affect the overall outcomes. Fourth, the studies' small participant numbers and their varied risk of bias resulted in evidence of very low to low certainty. While our sensitivity analyses suggested that findings were not influenced by the inclusion of studies with a high risk of bias, there was one notable exception. Specifically, when it came to balance outcomes, removing studies identified as having a high risk of bias shifted the impact of semi-immersive serious games from a beneficial effect to a neutral one. This limitation prevents us from making definitive statements about the effectiveness of serious games. It is likely that the low number of studies included in this analysis contributed to this issue. A small sample size increases the influence of individual studies with varying levels of quality. As a result, even a single study with a high risk of bias can disproportionately affect the overall findings. Lastly, due to the limited number of studies (fewer than 10 for each outcome), we could not assess publication bias using funnel plots. However, the inclusion of studies with negative, neutral, and positive outcomes, along with a thorough search for unpublished studies, suggests that the risk of publication bias may be low.

Conclusion

This review, involving 17 different randomized controlled trials, suggest that while some specific serious games may improve balance, fatigue and visuo-spatial memory, overall, serious games effect on upper limb activity, gait and other cognitive functions remains neutral. The certainty of evidence was very low to low owing for the heterogeneity between trials, their respective risk of bias, and the limited amount of data.

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Declaration of interest

The authors report there are no competing interests to declare.

Data availability

The data that support the findings of this study are available on request from the corresponding author, GE.

Authors contributions

WG and GE independently conducted the selection process and extracted data and performed analyses. GE and IS wrote the manuscript. CSB and JPL contributed to data interpretation and manuscript revisions. All authors read and approved the final manuscript.

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Tables

Table 1. Search strategies

Database	Search strategy
PubMed	(Multiple Sclerosis[MeSH Terms] OR multiple sclerosis[Title/Abstract] OR "disseminated sclerosis"[Title/Abstract] OR "insular sclerosis"[Title/Abstract] OR "sclerosis multiplex"[Title/Abstract] OR "sclerosis disseminated"[Title/Abstract] OR "sclerosis insular"[Title/Abstract] OR "sclerosis multiple"[Title/Abstract] OR "chronic progressive sclerosis"[Title/Abstract] OR "relapsing remitting sclerosis"[Title/Abstract] OR "relapsing-remitting sclerosis"[Title/Abstract] OR "secondary progressive sclerosis"[Title/Abstract]) AND (virtual reality[MeSH Terms] OR virtual reality exposure therapy[MeSH Terms] OR therapy, computer assisted[MeSH Terms] OR artificial intelligence[MeSH Terms] OR serious game*[Title/Abstract] OR video game*[Title/Abstract] OR computer game*[Title/Abstract] OR TV game*[Title/Abstract] OR television game*[Title/Abstract] OR "portable software app"[Title/Abstract] OR "portable software apps"[Title/Abstract] OR portable software application*[Title/Abstract] OR mobile application*[Title/Abstract] OR "mobile app"[Title/Abstract] OR "mobile apps"[Title/Abstract] OR virtual realit*[Title/Abstract] OR immersive[Title/Abstract] OR interactive[Title/Abstract] OR computer assisted therap*[Title/Abstract] OR exergam*[Title/Abstract])
Scopus	(TITLE-ABS-KEY ({multiple sclerosis}) OR TITLE-ABS ({disseminated sclerosis}) OR TITLE-ABS ({insular sclerosis}) OR TITLE-ABS ({sclerosis multiplex}) OR TITLE-ABS ({sclerosis disseminated}) OR TITLE-ABS ({sclerosis insular}) OR TITLE-ABS ({sclerosis multiple}) OR TITLE-ABS ({chronic progressive sclerosis}) OR TITLE-ABS ({relapsing remitting sclerosis}) OR TITLE-ABS ({relasping-remitting sclerosis}) OR TITLE-ABS ({secondary progressive sclerosis})) AND (TITLE-ABS-KEY ("video gam*") OR TITLE-ABS-KEY ({virtual reality}) OR TITLE-ABS-KEY ({therapy computer assisted}) OR TITLE-ABS-KEY ({artificial intelligence}) OR TITLE-ABS-KEY ({serious game}) OR TITLE-ABS-KEY ({serious games}) OR TITLE-ABS ("computer game*") OR TITLE-ABS ("mobile application*") OR TITLE-ABS ("virtual realit*") OR TITLE-ABS ("computer assisted therap*") OR TITLE-ABS ("exergam*") OR TITLE-ABS ("television gam*") OR TITLE-ABS ("TV gam*") OR TITLE-ABS ("portable software application*"))
Embase	('multiple sclerosis'/exp OR 'ms (multiple sclerosis)':ti,ab,kw OR 'disseminated sclerosis':ti,ab,kw OR 'insular sclerosis':ti,ab,kw OR 'multiple sclerosis':ti,ab,kw OR 'sclerosis, disseminated':ti,ab,kw OR 'sclerosis, insular':ti,ab,kw OR 'sclerosis, multiple':ti,ab,kw OR 'relapsing remitting multiple sclerosis'/exp OR 'rrms (relapsing remitting multiple sclerosis)':ti,ab,kw OR 'multiple sclerosis, relapsing-remitting':ti,ab,kw OR 'relapsing remitting multiple sclerosis':ti,ab,kw OR 'relapsing-remittent (rr) multiple sclerosis':ti,ab,kw OR 'relapsing-remittent ms':ti,ab,kw OR 'relapsing-remittent multiple sclerosis':ti,ab,kw OR 'relapsing-remitting (rr) multiple sclerosis':ti,ab,kw OR 'relapsing-remitting ms':ti,ab,kw OR 'relapsing-remitting multiple sclerosis':ti,ab,kw OR 'remittent-relapsing ms':ti,ab,kw OR 'remittent-relapsing multiple sclerosis':ti,ab,kw OR 'remitting-relapsing ms':ti,ab,kw OR 'remitting-relapsing multiple sclerosis':ti,ab,kw OR 'progressive multiple sclerosis'/exp OR 'chronic progressive ms':ti,ab,kw OR 'chronic progressive multiple sclerosis':ti,ab,kw OR 'multiple sclerosis, chronic progressive':ti,ab,kw OR 'primary progressive multiple sclerosis':ti,ab,kw OR 'progressive ms':ti,ab,kw OR 'progressive multiple sclerosis':ti,ab,kw OR 'secondary progressive multiple sclerosis':ti,ab,kw) AND ('virtual reality'/exp/mj OR 'virtual reality':ti,ab OR 'serious game'/exp/mj OR 'serious game'/exp OR 'video game':ti,ab OR 'video game'/exp OR 'tv games':ti,ab,kw OR 'computer game':ti,ab,kw OR 'computergame':ti,ab,kw OR 'television game':ti,ab,kw OR 'video game':ti,ab,kw OR 'video games':ti,ab,kw OR 'videogame':ti,ab,kw OR 'videogames':ti,ab,kw OR 'mobile application'/exp OR 'mobile app':ti,ab,kw OR 'mobile application':ti,ab,kw OR 'mobile applications':ti,ab,kw OR 'mobile apps':ti,ab,kw OR 'portable software app':ti,ab,kw OR 'portable software application':ti,ab,kw OR 'portable software

	applications':ti,ab,kw OR 'portable software apps':ti,ab,kw OR 'tablet application':ti,ab,kw)
Cochrane Library	"Multiple Sclerosis" OR "disseminated sclerosis" OR "insular sclerosis" OR "sclerosis multiplex" OR "sclerosis disseminated" OR "sclerosis insular" OR "sclerosis multiple" OR "chronic progressive sclerosis" OR "relapsing remitting sclerosis" OR "relapsing-remitting sclerosis" OR "secondary progressive sclerosis" in Title Abstract Keyword AND "virtual reality" OR "virtual reality exposure therapy" OR "therapy computer assisted" OR "artificial intelligence" OR "serious game" OR "video game" OR "computer game" OR "TV game" OR "television game" OR "portable software app" OR "portable software apps" OR "portable software application" OR "mobile application" OR "mobile app" OR "mobile apps" OR "virtual reality" OR "computer assisted therapy" OR "exergame" in Title Abstract Keyword

Table 2. Characteristics of included studies

Studies	N	Mean age (SD)	Mean EDSS (SD)	Gender (F/M)	Type of MS (RR/SP/PP)	Location	Fundings
Cuesta-Gomez et al., 2022 [26]	21	50.9 (2.79)	5.7 (0.33)	9/12	11/8/2	Spain	No grant
Cuesta-Gomez et al., 2020 [69]	30	46.2 (2.8)	5.4 (0.33)	12/18	11/13/6	Spain	ROBOESPAS, RoboCity2030-DIH-CM Madrid Robotics Digital Innovation Hub
Feys et al., 2015 [70]	17	60.6 (13.7)	7.6 (0.26)	7/10	1/14/2	Belgium	ns
Galperin et al., 2023 [71]	124	49.1 (9.9)	3.8 (2.22)	89/35	124/0/0	Israel, USA, Germany	RG-1507-05433 National Multiple Sclerosis Society
Kalron et al., 2016 [72]	30	45.6 (10.1)	4.2 (1.45)	19/11	30/0/0	Israel	PP2208 (pilot research award national MS Society)
Khalil et al., 2018 [73]	32	37.8 (10.87)	3 (1.25)	22/10	32/0/0	Jordan	AR-42 (EU Commission)
Leonardi et al., 2021 [74]	30	54.6 (1)	4.8 (1.4)	12/18	30/0/0	Italy	ns
Lozano-Quilis et al., 2014 [75]	11	44.8 (10.1)	ns	4/7	RR & SP (ns)	Spain	Generalitat Valenciana, Fundación Antonio Gargallo
Maggio et al., 2022 [76]	60	50 (11.4)	>7	29/31	RR & SP (ns)	Italy	ns
Maggio et al., 2023 [82]	106	51 (11.8)	4.8 (1.0)	48/58	0/106/0	Italy	ns
Marcos-Anton et al., 2023 [27]	30	48.3 (7.17)	6 (1.85)	16/14	15/10/5	Spain	I + D projects for young doctors at Rey Juan Carlos University, stimulation program for young researchers provided by the Community of Madrid (Ref.: A483-3921), panish Ministry of Economy and Competitiveness (PID2020-113508RB-I00)
Norouzi et al., 2021 [77]	45	26.39 (3.45)	2.15 (1.38)	45/0	ns	Iran	Urmia University
Ozkul et al., 2020 [78]	39	33.77 (10.37)	1.73 (1.54)	20/6	39/0/0	Turkey	No grant
Pagliari et al., 2024 [79]	70	50.3 (9.5)	4.8 (1.85)	36/24	ns	Italy	Italian Ministry of Health
Peruzzi et al., 2016 [28]	25	42.9 (11)	3.84 (4.08)	15/10	25/0/0	Italy	Fondazione Italiana Sclerosi Multipla, 10.13039/100007366 [FISM 2013/R/10]
Tramontano et al., 2020 [80]	30	49.7 (7.73)	6.91 (1.37)	18/12	13/0/7	Italy	ns
Veldkamp et al., 2019 [81]	40	52.4 (9.25)	3.55 (1.1)	23/17	26/7/7	Belgium, Italy & Israel	RIMS by Novartis AG, MS Society Flanders, Swedish Promobilia Foundation and SailingChallenge4MS

F = female, M = male, N = number of people, ns = not specified, , PP = primary progressive, RR = relapsing-remitting, SP = secondary progressive.

Table 3. Interventions of included studies and reported outcomes

Studies	Type of intervention	Type of control intervention	Upper limb activity	Gait	Balance	Fatigue	Cognitive functions
Cuesta-Gomez et al., 2022 [26]	Non-immersive VR targeting cognition and UL function (8 weeks; 2 sessions/week; 20 min/session) + UL rehabilitation (8 weeks; 2 sessions/week; 20 min/session)	UL motor rehabilitation therapy (8 weeks; 2 sessions/week; 40 min/session)	BBT[1] NHPT	/	/	/	SWCT[8] TMT-A
Cuesta-Gomez et al., 2020 [69]	Non-immersive VR targeting cognition and UL function (10 weeks; 2 sessions/week; 45 min/session) + UL rehabilitation (10 weeks; 2 sessions/week; 15 min/session)	UL motor rehabilitation therapy (10 weeks; 2 sessions/week; 60 min/session)	BBT NHPT PPT	/	/	FSS[4]	/
Feys et al., 2015 [70]	Robotic non-immersive VR serious game targeting UL movements and cognition (8 weeks; 3 sessions/week 30 min/session) + Multidisciplinary conventional rehabilitation (8 weeks; potentially every day; 2 hours/day)	Multidisciplinary conventional therapy (8 weeks; potentially every day; 2 hours/day)	ARAT[1]	/	/	/	/
Galperin et al., 2023 [71]	Treadmill training within a non-immersive VR environment projected on a TV screen targeting visuo-spatial memory, attentional memory and gait improvements (6 weeks; 3 sessions/week; session time ns)	Treadmill training alone (6 weeks; 3 sessions/week; session time ns)	/	Gait speed[2]	/	mFIS[4]	CVLT[5] BVMT[6] SPART WLG[7] TMT-A[8]
Kalron et al., 2016 [72]	Motion platform training within a non-immersive VR environment projected on a TV screen; mainly targeting	Traditional stretching and balance exercises (6 weeks; 2 sessions/week; 30 min/session)	/	/	BBS[3] Posturography kinematics FSST	/	/

	balance improvements (6 weeks; 2 sessions/week; 30 min/session)						
Khalil et al., 2018 [73]	Balance board training using a depth sensor camera; mainly targeting balance deficits (6 weeks; 2 sessions/week; session time ns)	Traditional balance exercises (6 weeks; 2 sessions/week; session time ns)	/	10MWT[2]	BBS[3]	mFIS[4]	/
Leonardi et al., 2021 [74]	Non-immersive VR comprehensive cognitive rehabilitation (involving UL movements) with an interactive tablet (8 weeks; 3 sessions/week; session time ns)	Comprehensive cognitive training (8 weeks; 3 sessions/week; session time ns)	/	/	/	/	SRT SPART WLG SDMT PASAT
Lozano-Quilis et al., 2014 [75]	Non immersive VR training mainly targeting balance and UL function (10 weeks; 1 session/week; 15 min/session) + Conventional gait and balance rehabilitation (10 weeks; 1 session/week; 15 min/session)	Traditional balance and gait rehabilitation exercises (10 weeks; 1 session/week; 1 hour/session)	/	10MWT[2]	BBS[3]	/	/
Maggio et al., 2022 [76]	Semi-immersive VR cognitive rehabilitation involving UL movements in ecological scenario (8 weeks; 3 sessions/week; session time ns) + Standard physical treatment (8 weeks; 3 sesions/week; 30 min/session)	Conventional and general cognitive rehabilitation + Standard physical treatment (8 weeks; 3 sesions/week; 30 min/session)	/	/	Tinetti-balance[3]	/	SPART ROCF-DRT PASAT[8]
Maggio et al., 2023 [82]	Semi-immersive VR cognitive rehabilitation involving UL movements in ecological scenario (8 weeks; 3 sessions/week; session time ns)	Conventional and general cognitive rehabilitation + Standard physical treatment (8 weeks; 3 sessions/week; 30 min/session)	/	/	/	/	ROCF-DRT[6]

	+ Standard physical treatment (8 weeks; 3 sessions/week; 30 min/session)						
Marcos-Anton et al., 2023 [27]	Non-immersive VR training mainly targeting UL function using an EMG armband detector (8 weeks; 2 sessions/week; 45 min/session) + UL conventional rehabilitation (8 weeks; 2 sessions/week; 15 min/session)	UL conventional rehabilitation (8 weeks; 2 sessions/week; 15 min/session)	BBT	/	/	FSS	/
Norouzi et al., 2021 [77]	<u>Group 1:</u> Non-immersive VR mainly targeting UL function and coordination using a joystik (8 weeks; 2 sessions/week; 30 min/session) <u>Group 2:</u> Non-immersive VR mainly targeting UL function and coordination using a joystik (8 weeks; 2 sessions/week; session time ns) + UL conventional rehabilitation targeting coordination (8 weeks; 2 sessions/week; session time ns)	UL conventional rehabilitation targeting coordination (8 weeks; 2 sessions/week; 30 min/session)	NHPT	/	/	/	/
Ozkul et al., 2020 [78]	Immersive VR training targeting balance impairments (8 weeks; 2 sessions/week; 20 min/session) + Pilates exercises (8 weeks; 2 sessions/week; 30 min/session)	<u>Group 1:</u> Balance exercises (8 weeks; 2 sessions/week; 20 min/session) + Pilates exercises (8 weeks; 2 sessions/week; 30 min/session) <u>Group 2:</u> Jacobson's progressive relaxation training (8 weeks; 2 sessions/week;	/	Posturography kinematics	BBS[3]	FSS[4]	/

		20 min/session)					
Pagliari et al., 2024 [79]	Cognitive semi-immersive VR telerehabilitation involving general motor and cognitive exercises (6 weeks; 5 sessions/week; 45 min/session)	Home-based motor and cognitive rehabilitation training	BBT[1] NHPT	/	MiniBESTest[3] Posturography kinematics	FSS[4]	SRT[5] SPART[6] WLG[7] PASAT[8] SDMT
Peruzzi et al., 2016 [28]	Treadmill training within a non-immersive VR environment projected on a TV screen targeting cognition and gait improvements (6 weeks; 3 sessions/week; 45 min/session)	Treadmill training alone (6 weeks; 3 sessions/week; 45 min/session)	/	Gait speed[2] 10MWT 6mWT	BBS[3] FSST	FSS	/
Tramontano et al., 2020 [80]	Robotic non-immersive VR serious game targeting UL function and cognition (4 weeks; 3 sessions/week; 40 min/session) + Conventional neuro-rehabilitation (4 weeks; 3 sessions/week; session time ns)	UL sensori-motor training (4 weeks; 3 sessions/week; 40 min/session) + Conventional neuro-rehabilitation (4 weeks; 3 sessions/week; session time ns)	NHPT[1]	/	/	FSS[4]	/
Veldkamp et al., 2019 [81]	Non-immersive VR training provided in a tablet and targeting cognition and gait impairments (8 weeks; 2-3 sessions/week; 45 min/session)	Traditional gait and balance dynamic exercises (8 weeks; 2-3 sessions/week; 45 min/session)	/	T25WT[2] 2mWT	/	mFIS[4]	SDMT[8]

ARAT = Action Research Arm Test ; BBS = Berg Balance Scale ; BBT = Box and Block Test ; BVMT = Brief Visuospatial Memory Test ; CVLT = California Verbal Learning Test ; FSS = Fatigue Severity Scale ; FSST = Four Square Step Test ; mFIS : modified Fatigue Impact Scale ; GVFT = Greek Verbal Fluency Test ; NHPT = Nine Hole Peg Test ; ns = not specified ; PASAT = Paced Auditory Serial Addition Test ; PPT = Purdue Pegboard Test ; ROCF-DL = Rey-Osterrieth Complex Figure-Delayed Recall Test ; SDMT = Symbol Digit Modality Test; SPART = Spatial Recall Test ; SRT = Selective Reminding Test ; TMT-A = Trail Making Test Part A; TUG = Timed-Up and Go Test ; T25W = Timed-25 foot Walk Test ; UL = upper limb ; VR = virtual reality ; 10MWT = Ten Meter Walk Test ; WLG = Word List Generation test ; 6mWT = Six Minute Walk Test ; 2mWT = Two Minute Walk Test. [1] = Scales used for upper limb activity meta-analysis ; [2] = Scales used for gait meta-analysis ; [3] = Scales used for balance meta-analysis ; [4] = Scales used for fatigue meta-analysis ; [5] = Scales used for verbal memory meta-analysis ; [6] = Scales used for visuo-spatial memory meta-analysis ; [7] = Scales used for verbal fluency meta-analysis ; [8] = Scales used for attention meta-analysis.

Table 4. Summary of findings

<table>
<tr><th colspan="4">Serious games programs compared with conventional therapy for multiple sclerosis rehabilitation</th></tr>
<tr><td colspan="4">Population: People with multiple sclerosis
Settings: Hospital, clinic or home
Intervention: Serious games-based programs
Comparison: Conventional therapy</td></tr>
<tr><th>Outcome</th><th>Effect size and direction of effect (95% CI)</th><th>Number of participants (studies)</th><th>Certainty of the Body of Evidence</th></tr>
<tr><td>UL Activity</td><td>1. Robotic UL SG
No significant difference found on UL activity:
SMD = 0.00 (-0.56 – 0.57)

2. Non-immersive VR UL SG
No significant difference found on UL activity:
SMD = -0.17 (-1.03 – 0.69)

3. Global semi-immersive VR SG
No significant difference found on UL activity:
SMD = -0.03 (-0.54 – 0.48)</td><td>129
(4)</td><td>Low[a,b]</td></tr>
<tr><td>Gait</td><td>1. Treadmill SG
No significant difference found on gait:
SMD = 0.06 (-0.30 – 0.42)

2. Non-immersive SG targeting balance/LL functions
No significant difference found on gait:
SMD = 0.29 (-0.15 – 0.72)</td><td>203
(5)</td><td>Low[a,b]</td></tr>
<tr><td>Balance</td><td>1. Motion platform SG targeting balance functions
No significant difference found on balance:
SMD = 0.56 (-0.17 – 1.30)

2. Immersive VR SG targeting balance functions
No significant difference on balance:
SMD = 0.02 (-0.75 – 0.79)

3. Treadmill SG
No significant difference on balance:
SMD = 0.00 (-0.79 – 0.79)

4. Non-immersive VR SG targeting balance/LL functions
Significant but marginal difference found in favour of SG:
SMD = 0.62 (-0.00 – 1.23)

5. Global semi-immersive VR SG
Significant difference found in favour of SG:
SMD = 0.48 (0.12 – 0.84)</td><td>244
(7)</td><td>Low[a,b]</td></tr>
</table>

Fatigue	1. Robotic UL SG No significant difference found on fatigue: SMD = -0.41 (-1.13 – 0.32) 2. Non-immersive VR UL SG No significant difference found on fatigue: SMD = -0.19 (-0.91 – 0.53) 3. Immersive VR SG targeting balance functions No significant difference found on fatigue: SMD -0.25 (-1.02 – 0.52) 4. Non-immersive VR SG targeting balance/LL functions No significant difference found on fatigue: SMD 0.31 (-1.00 – 1.62) 5. Treadmill SG Significant difference found in favour of SG: SMD = 0.80 (0.40 – 1.20) 6. Global semi-immersive VR SG No significant difference found on fatigue: SMD = -0.04 (-0.55 – 0.46)	322 (7)	Very low[a,b,c]
Visuo-spatial memory	1. Treadmill attentional and visuo-spatial memory SG No significant difference found on visuo-spatial memory: SMD = 0.00 (-0.38 – 0.38) 2. Semi-immersive VR overall/comprehensive cognitive SG Significance difference found in favour of SG SMD = 0.35 (0.04 – 0.65)	270 (3)	Low[a,b]
Attention	. 1. Treadmill attentional and visuo-spatial memory SG No significant difference found on attention: SMD = 0.06 (-0.32 – 0.45) 2. Semi-immersive VR overall/comprehensive cognitive SG No significant difference found on attention: SMD = 0.10 (-0.40 – 0.61)	285 (5)	Very low[a,b,c]

[a] = Downgraded one level due to Risk of Bias in included studies' overall Risk of Bias; [b] = Downgraded one level due to imprecision related to small sample size; [c] = Downgraded one level due to inconsistency related to considerable between-studies statistical heterogeneity; UL = upper limb; LL = lower limb; VR = virtual reality; SG = serious games; n = number of participants; N = number of trials; RCT = randomized controlled trial.

Table 5. Overall conclusions

Outcome	Interventions	Conclusion
UL activity	• Robotic UL serious games • Non-immersive VR serious games • General semi-immersive VR serious games	When compared to conventional rehabilitation, **all serious games interventions** were found to have a **neutral effect** on UL activity
Gait	• Treadmill serious games • Non-/ semi-immersive VR serious games targeting LL/balance functions	When compared to conventional rehabilitation, **all serious games interventions** were found to have a **neutral effect** on gait outcomes
Balance	• Motion platform serious games targeting balance functions • Immersive VR serious games targeting balance functions • Treadmill serious games • Non-immersive VR serious games targeting LL/balance functions • General semi-immersive VR serious games	When compared to conventional rehabilitation, **motion platform, immersive VR** and **treadmill serious games** were found to have a **neutral effect** on balance outcomes When compared to conventional rehabilitation, **non-immersive VR targeting LL/balance functions** and **general semi-immersive VR serious games** were found to have a **positive effect** on balance outcomes
Fatigue	• Robotic UL serious games • Non-immersive VR serious games • Immersive VR serious games targeting balance functions • Non-immersive VR serious games targeting LL/balance functions • Treadmill serious games • General semi-immersive VR serious games	When compared to conventional rehabilitation, **robotic UL, non-immersive VR UL, immersive and non-immersive VR targeting LL/balance functions** were found to have a neutral effect on fatigue

		When compared to conventional rehabilitation, **treadmill serious games and general semi-immersive VR serious games** were found to have a **positive effect** on fatigue
Verbal memory	• Treadmill attentional and visuo-spatial memory serious games • Semi-immersive VR general cognitive serious games	When compared to conventional rehabilitation, **treadmill attentional and visuo-spatial memory, and semi-immersive VR general cognitive serious games** were found to have a **neutral effect** on verbal memory
Visuo-spatial memory	• Treadmill attentional and visuo-spatial memory serious games • Semi-immersive VR general cognitive serious games	When compared to conventional rehabilitation, **treadmill attentional and visuo-spatial memory serious games** were found to have a **neutral effect** on visuo-spatial memory When compared to conventional rehabilitation, **semi-immersive VR general cognitive serious games** were found to have a **positive effect** on visuo-spatial memory
Verbal fluency	• Treadmill attentional and visuo-spatial memory serious games • Semi-immersive VR general cognitive serious games	When compared to conventional rehabilitation, **treadmill attentional and visuo-spatial memory and semi-immersive VR general cognitive serious games** were found to have a **neutral effect** on verbal fluency
Attention	• Treadmill attentional and visuo-spatial memory serious games	When compared to conventional rehabilitation,

	• Non-/semi-immersive VR general cognitive serious games	**treadmill attentional and visuo-spatial memory and non-/semi-immersive VR general cognitive serious games** were found to have a **neutral effect** on attentional functions

UL = upper limb; LL = lower limb; VR = virtual reality; SG = serious games

Appendices

Supplement Material 1. PRISMA guidelines

Supplement Material 2. PROSPERO protocol deviations and rationale

Supplement Material 3. Risk of bias per outcome

Supplement Material 4. Sensitivity analysis – Upper limb activity

Supplement Material 5. Sensitivity analysis – Gait outcomes

Supplement Material 6. Sensitivity analysis – Balance outcomes 1

Supplement Material 7. Sensitivity analysis - Balance outcomes 2

Supplement Material 8. Forest plot representing the effect of serious games over conventional therapy on fatigue.

Supplement Material 9. Sensitivity analysis – Fatigue outcomes

Supplement Material 10. Forest plot representing the effect of serious games over conventional therapy on verbal memory.

Supplement Material 11. Sensitivity analysis – Visuo-spatial memory

Supplement Material 12. Forest plot representing the effect of serious games over conventional therapy on verbal fluency.

Supplement Material 13. Sensitivity analysis – Attention 1

Supplement Material 14. Sensitivity analysis – Attention 2

Figures

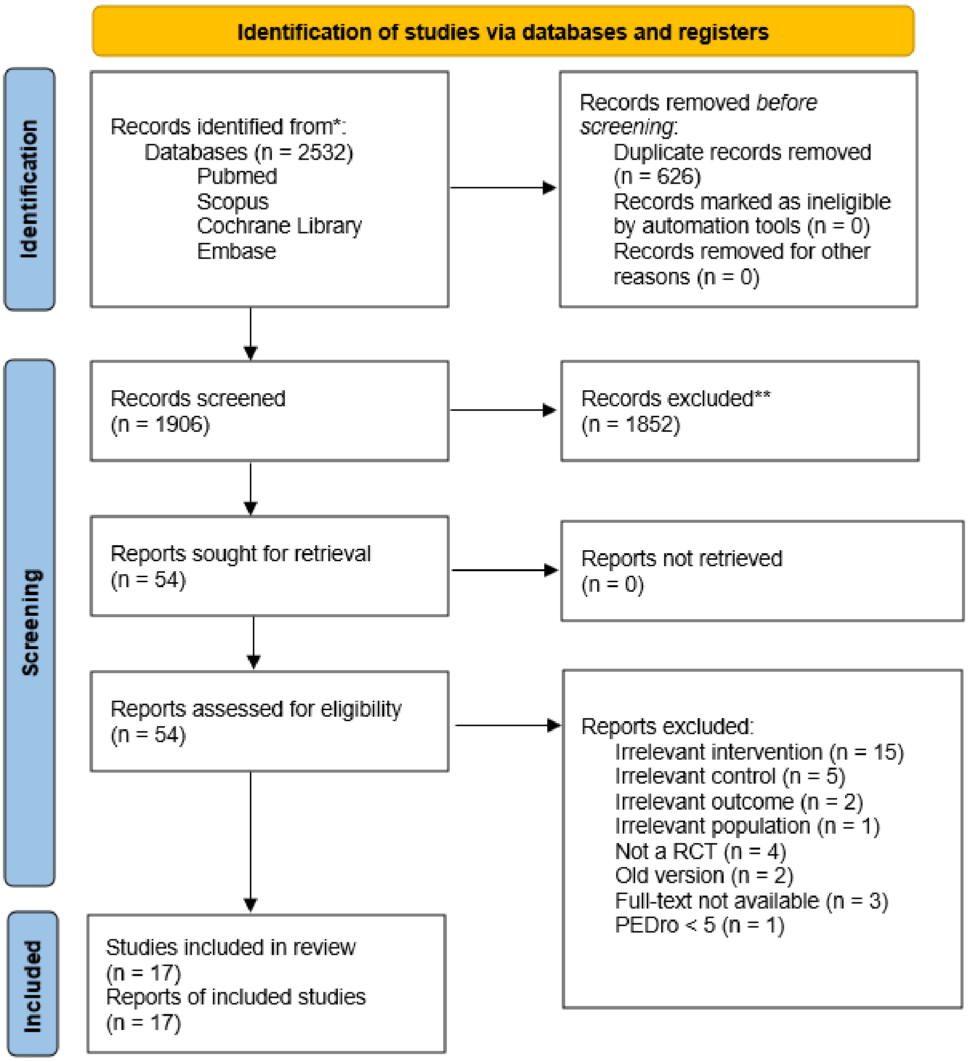

Figure 1. Flow chart diagram of the included studies

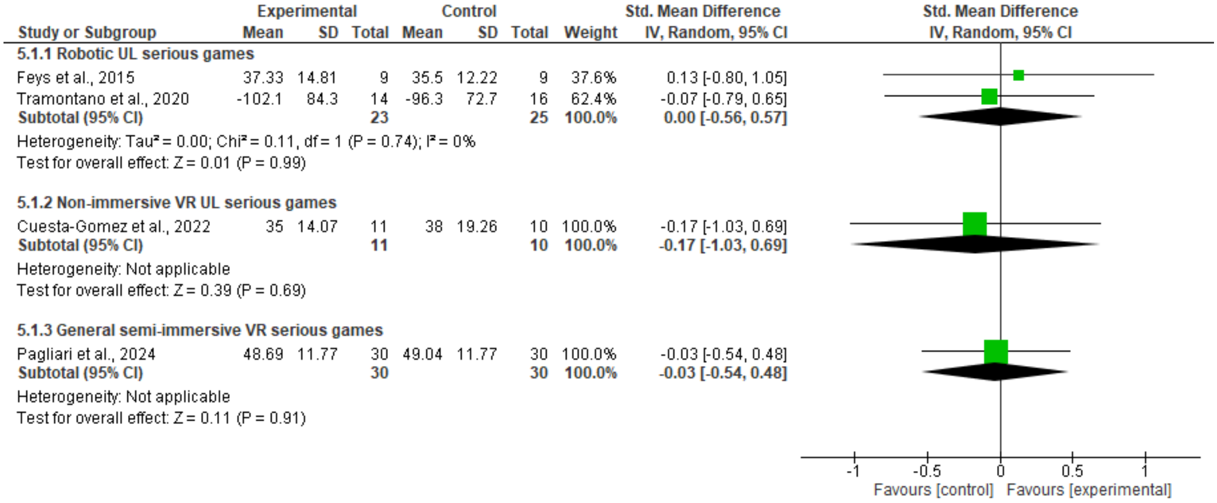

Figure 2. Forest plot representing the effect of serious games over conventional therapy on upper limb activity.

UL = upper limb; VR = virtual reality

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
5.3.1 Treadmill serious games								
Galperin et al., 2023	115	31	53	114	41	42	79.3%	0.03 [-0.38, 0.43]
Peruzzi et al., 2016	1.09	0.26	14	1.04	0.25	11	20.7%	0.19 [-0.60, 0.98]
Subtotal (95% CI)			**67**			**53**	**100.0%**	**0.06 [-0.30, 0.42]**
Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 1 (P = 0.72); I² = 0%								
Test for overall effect: Z = 0.33 (P = 0.74)								
5.3.2 Non/semi-immersive VR serious games targeting LL/balance functions								
Khalil et al., 2018	-11.35	2.66	16	-19.69	27.23	16	38.4%	0.42 [-0.28, 1.12]
Lozano-Quilis et al., 2014	-16.469	5.77	6	-14.49	4.597	5	13.1%	-0.34 [-1.54, 0.86]
Veldkamp et al., 2019	-5.3	1.2	20	-6	2.5	20	48.4%	0.35 [-0.28, 0.97]
Subtotal (95% CI)			**42**			**41**	**100.0%**	**0.29 [-0.15, 0.72]**
Heterogeneity: Tau² = 0.00; Chi² = 1.23, df = 2 (P = 0.54); I² = 0%								
Test for overall effect: Z = 1.29 (P = 0.20)								

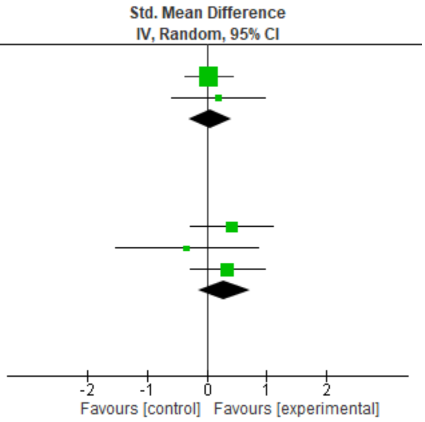

Figure 3. Forest plot representing the effect of serious games over conventional therapy on gait outcomes.

VR = virtual reality; LL = lower limb

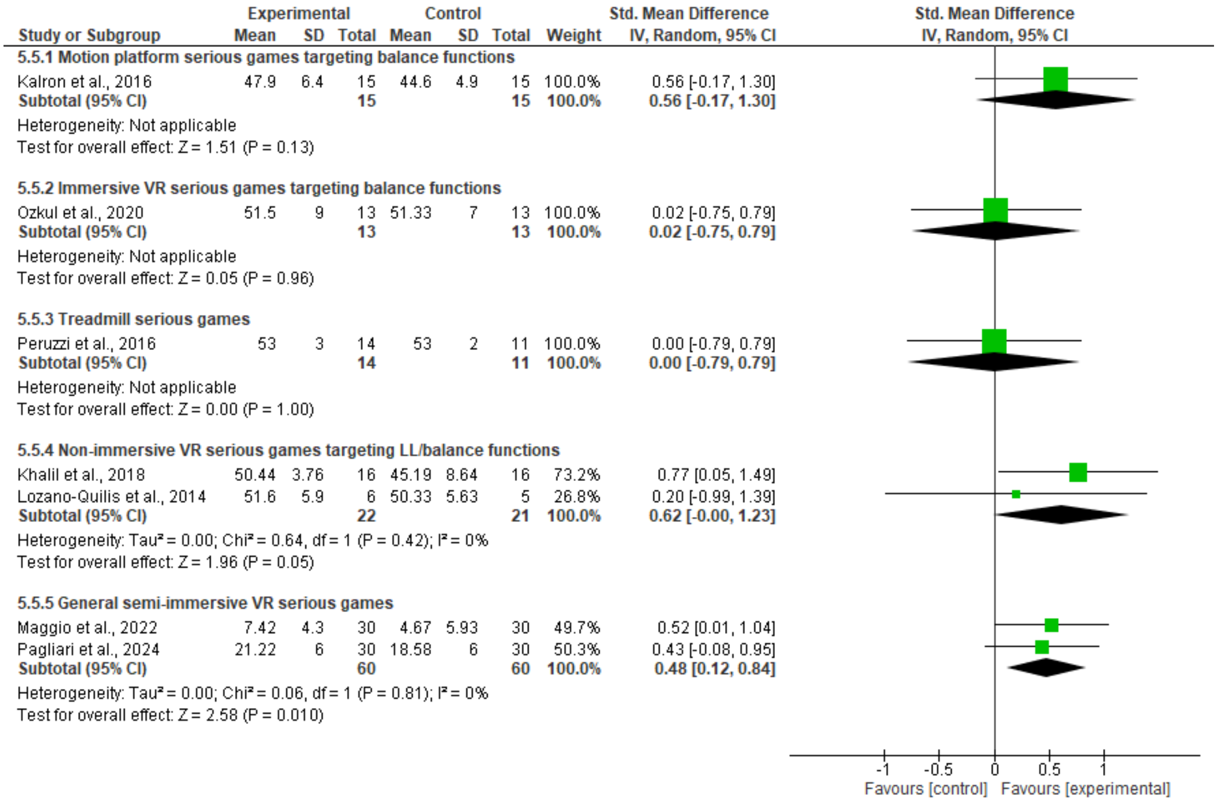

Figure 4. Forest plot representing the effect of serious games over conventional therapy on balance outcomes.

VR = virtual reality

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
5.14.1 Treadmill attentional and visuo-spatial memory serious games								
Galperin et al., 2023	8	8.148	53	8	8.148	51	100.0%	0.00 [-0.38, 0.38]
Subtotal (95% CI)			**53**			**51**	**100.0%**	**0.00 [-0.38, 0.38]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
5.14.2 Semi-immersive VR general serious games								
Maggio et al., 2023	12.67	7.1	53	10.43	3.185	53	63.6%	0.40 [0.02, 0.79]
Pagliari et al., 2024	7.05	2.96	30	6.3	3.07	30	36.4%	0.25 [-0.26, 0.75]
Subtotal (95% CI)			**83**			**83**	**100.0%**	**0.35 [0.04, 0.65]**
Heterogeneity: Tau² = 0.00; Chi² = 0.24, df = 1 (P = 0.63); I² = 0%								
Test for overall effect: Z = 2.21 (P = 0.03)								

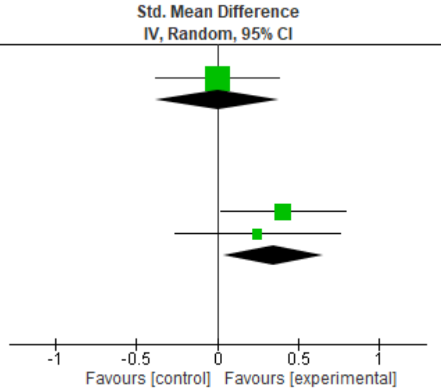

Figure 5. Forest-plot representing the effect of serious games over conventional therapy on visuo-spatial memory.

VR = virtual reality

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
5.17.1 Treadmill attentional and visuo-spatial memory serious games								
Galperin et al., 2023	91.89	140.44	53	83.33	124.81	51	100.0%	0.06 [-0.32, 0.45]
Subtotal (95% CI)			**53**			**51**	**100.0%**	**0.06 [-0.32, 0.45]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.33 (P = 0.74)								
5.17.2 Non/semi-immersive VR general cognitive serious games								
Cuesta-Gomez et al., 2022	30	12.59	11	31.5	5.185	10	18.6%	-0.15 [-1.00, 0.71]
Maggio et al., 2022	29.3	15.852	30	17.37	16.296	30	28.0%	0.73 [0.21, 1.26]
Pagliari et al., 2024	40.57	18.29	30	46.19	19.061	30	28.5%	-0.30 [-0.81, 0.21]
Veldkamp et al., 2019	48.8	14.7	20	48.2	10.5	20	25.0%	0.05 [-0.57, 0.67]
Subtotal (95% CI)			**91**			**90**	**100.0%**	**0.10 [-0.40, 0.61]**
Heterogeneity: Tau² = 0.17; Chi² = 8.25, df = 3 (P = 0.04); I² = 64%								
Test for overall effect: Z = 0.41 (P = 0.68)								

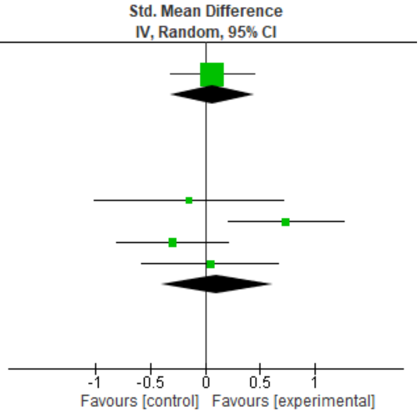

Figure 6. Forest-plot representing the effect of serious games over conventional therapy on attention.

VR = virtual reality