Virtual Reality

Dropout rate in randomised controlled trials of balance and gait rehabilitation in multiple sclerosis: is it expected to be different for virtual reality-based interventions? A systematic review with meta-analysis and meta-regression

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Corresponding Author:	Cristina García-Muñoz Universidad de Cádiz Cadiz, Andalucía SPAIN
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Universidad de Cádiz
Corresponding Author's Secondary Institution:	
First Author:	María Jesús Casuso-Holgado
First Author Secondary Information:	
Order of Authors:	María Jesús Casuso-Holgado
	Cristina García-Muñoz
	Rocío Martín-Valero
	David Lucena-Anton
	Jose A. Moral-Munoz
	María-Dolores Cortés-Vega
Order of Authors Secondary Information:	
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Dear Daniel Ballin
Editor in Chief
Virtual Reality
Ref.: Submission ID VIRE-D-22-00088R1
Manuscript entitled: *"Dropout rate in randomised controlled trials of balance and gait rehabilitation in multiple sclerosis: is it expected to be different for virtual reality-based interventions? A systematic review with meta-analysis and meta-regression".*

Dear Daniel Ballin,

On behalf of my co-authors, I would like to express our gratitude for the comments and suggestions made by the reviewers on our manuscript entitled "*Dropout rate in randomised controlled trials of balance and gait rehabilitation in multiple sclerosis: is it expected to be different for virtual reality-based interventions? A systematic review with meta-analysis and meta-regression".* In line with the reviewer's comments, we have thoroughly reviewed the text to solve the repeated information and errors of in-text citations. Also, the manuscript has been professionally proof-reader to solve the typographical errors and unclear expressions. The professional proofreading certificate was attached to the submission platform.

Finally, we remain at your disposal for any further information you may need.

Yours sincerely,

Prof. Cristina García-Muñoz

ID VIRE-D-22-00088R1

Manuscript entitled: *"Dropout rate in randomised controlled trials of balance and gait rehabilitation in multiple sclerosis: is it expected to be different for virtual reality-based interventions? A systematic review with meta-analysis and meta-regression".*

Guest Editor's comments: Thank you for your hard work on the revised mansucript and thorough answers to all reviewers comments. The manuscript has been accepted for publication, however, one of the reviewers brouht to our attention that the revised manuscript contains several typographical errors, unclear expressions and some errors of in-text citations. I therefore would like to ask you to conduct a thorough review of the final wording and citations and to provide a proper proof reading before publication of your manuscript.

Response to Guest Editor´s Comments: On behalf of all my co-authors, I would like to thank you and the reviewers your nice work and comments that helped us to improve our manuscript. A tracked changes and clean version of the manuscript was attached to the submission platform. In line with the reviewer's comments, we have thoroughly reviewed the text to solve the repeated information and errors in-text citations. Also, the manuscript has been professionally proof-reader to solve the typographical errors and unclear expressions. The professional proofreading certificate was attached to the submission platform. Thank you.

Reviewer #2:

I am happy to see that all my comments and suggestions have been considered and have improved the manuscript.

Response to Reviewer#2: Thank you, your comments helped us to improve our manuscript.

Reviewer #3:

I think the authors have done a very good job in reacting to all the comments.

Response to Reviewer#3: Thank you, your comments helped us to improve our manuscript.

Reviewer #4:

The manuscript has improved with the revisions submitted and I believe the authors have adequately addressed the reviewers' comments. However, there are some language and typographical errors in the manuscript which need to be corrected. Some sentences are unclear and there are instances where information is repeated between sentences. In addition, some errors are still present with the in-text citations. A thorough review and proof-reading of the manuscript is required.

Response to Reviewer#4:

On behalf of all the authors we are grateful for your comments, which helped us to improve the manuscript, and it to obtain the current form. In line with your comment, we have thoroughly reviewed the text to solve the repeated information and errors in-text citations. Also, the manuscript has been professionally proof-reader to solve the typographical errors and unclear expressions. The professional proofreading certificate was attached to the submission platform.

Title page

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Running Head

Dropouts in multiple sclerosis for virtual reality

Author's information:

María Jesús Casuso-Holgado [1]. https://orcid.org/0000-0002-4217-6827

Cristina García-Muñoz[2]. https://orcid.org/0000-0003-2621-2098

Rocío Martín-Valero[3]. https://orcid.org/0000-0002-1664-3647

David Lucena-Anton[2]. https://orcid.org/0000-0003-2441-5342

Jose A. Moral-Munoz[2, 4]. https://orcid.org/0000-0002-6465-982X

María-Dolores Cortés-Vega[1]. https://orcid.org/0000-0002-9514-8811

1. Department of Physiotherapy, University of Seville, Sevilla, Spain
2. Department of Nursing and Physiotherapy, University of Cadiz, Cadiz, Spain
3. Department of Physiotherapy, University of Malaga, Malaga, Spain
4. Institute of Research and Innovation in Biomedical Sciences of the Province of Cadiz (INiBICA), University of Cadiz, Cadiz, Spain

Correspondence to: Dr. Cristina García Muñoz; cristina.garciamunoz@uca.es

ABSTRACT (258 words)

Aim: To assess and meta-analyse the pooled dropout rate in absolute and comparative terms of randomised control trials using virtual reality for balance or gait rehabilitation in people with multiple sclerosis.

Design: A systematic review of randomized control trials with meta-analysis and meta-regression.

Data sources: A search was conducted in PubMed, Scopus, Web of Science, the Physiotherapy Evidence Database, the Cochrane Database, CINHAL, LILACS, ScienceDirect, and ProQuest. It was last updated in July 2022.

Review Methods: After the selection of studies, a quality appraisal was carried out using the PEDro Scale and the Revised Cochrane risk-of-bias tool for randomised trials. A descriptive analysis of main characteristics and dropout information was performed. An overall proportion meta-analysis calculated the pooled dropout rate. Odds ratio meta-analysis compared the dropout likelihood between interventions. The meta-regression evaluated the influence of moderators related to dropout.

Results: Sixteen studies with 656 participants were included. The overall pooled dropout rate was 6.6% and 5.7% for virtual reality and 9.7% in control groups. The odds ratio (0.89, $p = 0.46$) indicated no differences in the probability of dropouts between the interventions. The number, duration, frequency, and weeks of sessions, intervention, sex, multiple sclerosis phenotype, Expanded Disability Status Scale score, and PEDro score were not moderators ($p > 0.05$). Adverse events were not reported and could not be analysed as moderators.

Conclusions: Dropouts across the virtual reality and control comparators were similar without significant differences. Nonetheless, there is a slight trend that could favour virtual reality. Standardisation in reporting dropouts and adverse events is recommended for future trials.

PROSPERO database, registration number ID
CRD42021284989

Keywords
Dropout rate; multiple sclerosis; adherence; virtual reality; attrition.

Statements and declarations
The authors declare no conflicts of interest.

Competing interests
This research received no external funding.

1. Introduction

Different types of virtual reality technology (e.g., non-immersive, semi-immersive, or fully immersive) have emerged as an useful tool in neurorehabilitation with promising results for physical and cognitive rehabilitation (Voinescu et al. 2021). In this way, virtual reality-based interventions have been enhanced as a technological solution for telerehabilitation at the time of the COVID-19 pandemic (Matamala-Gomez et al. 2021). Furthermore, previous literature has proposed that virtual reality strategies present higher adherence in patients with neurological disorders (Asadzadeh et al. 2021; Dalmazane et al. 2021). Multitask training, patient motivation, safety, and the low cost of commercial devices are some of the benefits of using virtual reality for neurological rehabilitation (Forsberg et al. 2015; Gustavsson et al. 2021; Moan et al. 2021). Nonetheless, some undesired effects (e.g., headache, sickness, or nausea) (Massetti et al. 2018), as well as the difficulty of transferring the complex skills trained in virtual environments to the real world and the lack of ecological validity in a neurologically-impaired population (Levac et al. 2019), were reported. Specifically for balance training, the time of latency, the underestimation of perceived distances, and the dependence on specific systems (e.g., balance board) and virtual contexts were proposed as potential weaknesses of virtual reality environments (Morel et al. 2015).

Multiple sclerosis is a global neurodegenerative disease affecting approximately three million people in the world (Tafti et al. 2022). Balance disorders, gait impairments, and fatigue are the main symptoms in patients with multiple sclerosis that obtain positive effects with physical therapy intervention (Amedoro et al. 2020; Abou et al. 2022). Particularly, virtual reality-based physical rehabilitation showed benefits for balance and gait training (Casuso-Holgado et al. 2018; García-Muñoz et al. 2021; Nascimento et al. 2021); however, fatigue is a significant barrier to participation in physical activity, which influences the participants' adherence (Moore et al. 2022). A recent systematic review has summarised dropout data from randomised control clinical trials about exercise interventions in people with multiple sclerosis, concluding that mean age, the proportion of females, and intervention duration were moderators inversely associated with adherence (Dennett et al. 2020). Therefore, these findings could impact the sample size calculation, promoting an under- or overestimation. Furthermore, this could influence the differential dropout rate, which is how the degree of dropout differs between the intervention and comparator conditions after randomisation (Crutzen et al. 2015). It might affect the power of research and could present a risk of bias for randomised control clinical trials (Cooper et al. 2018). In view of this background, setting accurate expected dropout rates in virtual reality studies for rehabilitation in multiple sclerosis could help future trials to avoid problems in their internal or external validity. In addition, the identification of factors specifically associated with dropout in virtual reality trials could help clinicians when translating research into practice.

As far as we are concerned, no previous systematic reviews were found reporting dropout in virtual reality interventions for balance and gait rehabilitation in this population. Thus, the present systematic review and meta-analysis aimed to: (1) systematically assess and meta-analyse the overall pooled dropout rate of randomised controlled trials using virtual reality as an intervention for balance or gait training in people with multiple sclerosis in both absolute and comparative terms; (2) analyse whether any participant or intervention factors are related to dropout; and (3) identify adverse events that could be the reason for dropouts.

2. Methods

2.1 Data sources and search strategy

This systematic review was carried out following the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher 2009). The review protocol was registered in the PROSPERO database (Registration number: CRD42021284989).

Two independent reviewers (M.J.C.-H., C.G.-M.) conducted an electronic search in MEDLINE (PubMed), Scopus, Web of Science (WOS), the Physiotherapy Evidence Database (PEDro), the Cochrane Database of Systematic Reviews (CDSR), CINHAL, LILACS, ScienceDirect, and ProQuest. The search was performed between July and November 2021. Neither language nor date filters were applied in the different databases. Key terms concerning intervention (*'virtual reality'*, *'game'*, *'gaming'*, *'exergaming'*, and *'interactive'*), balance (*'balance'* or '*postural control'*), gait (*'gait'*, *'walking'*, and *'ambulation'*), and *'multiple sclerosis'* were combined as search terms in the strategies. The search strategy is shown in detail in Supplemental Material 1.

2.2 Research question and study selection

The participants, interventions, comparisons, outcomes, and study design (PICOS) model was considered to set the following research questions: what dropout data are reported during the intervention and follow-up period by randomised control clinical trials conducting virtual reality intervention to improve balance or gait in multiple sclerosis and what are the possible moderators affecting dropout in these studies?

Participants included in the review were female or male, aged between 18 and 65 years old, with any diagnosis of multiple sclerosis phenotype meeting the revised McDonald criteria (Thompson et al. 2018). Walking ability was preservedaccording to the Expanded Disability Status Scale (EDSS) score (EDSS $\leq$ 6). Included interventions involved any type of virtual reality systems aimed at improving balance or gait compared to other interventions based-on physical activity with or without external aid use. Furthermore, studies that reported dropout event information were included.

2.3 Data extraction and quality assessment

First, two independent reviewers (C.G.-M. and M.J.C.-H.) identified potential articles in databases to be included in the systematic review through the title and abstract information. Next, duplicates were removed, and an exhaustive analysis of articles was carried out based on their full-text reading. This step was particularly focused on the selection criteria assessment, ensuring that the inclusion criteria were met before selecting suitable studies. In the case of disagreement, a third reviewer (M.-D.C.-V.) was consulted to decide on the inclusion of the documents.

Once articles were selected, the quality assessment was conducted using the PEDro scale (Maher et al. 2003) and the Revised Cochrane risk-of-bias tool for randomised trials (RoB-2) (Higgins et al. 2019). PEDro is a reliable tool of 11 items that evaluates the inner validity of a clinical trial. If studies score above 6 points, they are classified as level I evidence (6–8: good; 8–10: excellent). If the score is below 5, they are classified as level II (4–5: deficient; <4: poor). ROB-2 allows the evaluation of bias in randomised control trials, comprising five domains (bias arising from the randomisation process, due to deviations from the intended interventions, to missing outcome data, in the measurement of the outcome, and in the selection of the reported result) that are qualified as a low or high risk of bias with some concerns (Sterne et al. 2019).

Next, reviewers recorded the data for qualitative and quantitative synthesis. The extracted data were country, multiple sclerosis phenotype and disability status, female and male percentages, age, experimental and comparator group intervention characteristics, number of participants recruited and analysed, retention rate, dropout rates (for the experimental and control groups), reasons for dropout (in each group), and adverse events. Disagreements in data were solved by consensus with a third reviewer. Information provided by the included studies allowed us to calculate dropout rates in all cases, so no corresponding authors were contacted.

2.4 Data analysis

Dropout rate was calculated as the number of participants who did not complete the intervention and follow-up period divided by the total number of participants that underwent the randomisation process. Moreover, retention rate was the total number of participants that concluded the intervention, showing the adherence rate to treatment. For those studies that included more than two groups of intervention, comparison between groups was analysed separately two by two.

To conduct the meta-analysis, the R Studio software (version 4.0.0) and its packages *meta*, *metafor*, and *dmetar* were used (Viechtbauer 2010; Balduzzi et al. 2019; Harrer et al. 2021). The proportion meta-analysis was performed through the *metaprop* function to determine the estimated dropout rate in virtual reality intervention, the control comparator, and all arms. Proportions were transformed using the logit transformation (Schwarzer et al. 2019).

A binary meta-analysis based on odds ratios (ORs) was conducted to examine whether the probability of dropouts is higher in the virtual reality or in the comparator interventions. To assess the effect measure in binary outcomes, the OR with a 95% confidence interval (95%CI) was calculated, and the inverse variance method was used to adjust pooling estimations to sparse data (considering that dropouts are a rare event). Likewise, the Hartung-Knapp adjustment for a random effects model was implemented. Focusing on ORs, if the value is 1, there are no differences in dropouts between the experimental and comparator groups. In contrast, if the OR is greater than 1, a higher dropout rate was registered for the experimental group. The restricted maximum-likelihood estimator for tau^2 was selected to estimate the between-study variance (Viechtbauer 2005). As some studies could present zero events in the experimental and/or comparator arm, a 0.5 continuity correction was added to all meta-analyses, as suggested by Gart and Zweifel (1967).

Heterogeneity between studies was assessed through I^2, tau^2, and Cochrane's Q ($p < 0.05$ indicates heterogeneity). When I^2 presents a value above 50%, it means that large heterogeneity is found across studies (Higgins et al. 2021). A random effects model was employed considering the possible degree of heterogeneity between the included studies.

Forest plots were used to show the outcomes of proportions and binary meta-analyses. The prediction interval was added as a red line to the forest plot to provide a measure of reliability of future treatment effects in new studies (Nagashima et al. 2019). Depending on the level of immersion of the subject within the virtual environment, virtual reality was classified as non-immersive, semi-immersive, and fully immersive for subgroup analysis.

A sensitivity analysis was carried out to assess the influence of studies on the overall binary meta-analysis results. The influence was explored to detect the presence of outlier data and whether there were studies that contributed to heterogeneity or bias pooled results. A Baujat plot, a L'Abbé plot, and influence graphs were created to represent influential cases in meta-analysis. The influence graphs showed the studies that significantly influenced the pooled effect size in red. In addition, an exploratory graphical analysis of data was performed to examine whether there is a clear trend of effect size related to independent variables.

Meta-regression was conducted to evaluate possible associations between participants or study characteristics which could vary in the presence of dropout events. Studies with no available data were excluded from the meta-regression analysis. Moreover, to run the meta-regression, at least three studies with the predictor were needed. The analysed moderators were interventions, number, duration, frequency and weeks of sessions, EDSS score, multiple sclerosis phenotype, and sex.

Publication bias and small study effects were evaluated through a contour enhanced-funnel plot adjusted by the Duval and Tweedie trim and fill method (Shi and Lin 2020). Asymmetry in the funnel plot indicated the effect of small studies in the pooled results. To confirm the absence of asymmetry, a p-value greater than 0.05 must be reached in the Harbord's test (Harbord et al. 2006) and the Egger bias test (Egger et al. 1997).

3. Results

3.1 Study selection and methodological quality assessment

In total, 7,024 articles were identified through the initial database search based on titles and abstracts. After that, duplicates were removed, obtaining 5,995 articles. Once the studies underwent the screening and eligibility steps, 16 randomised control trials were included for the qualitative synthesis and quantitative analysis. There was no disagreement between reviewers in the study selection process. Figure 1 showed the PRISMA flowchart detailing the selection procedure [insert Figure 1]. Excluded studies and their reasons were detailed in Supplemental Material 2.

Regarding the quality assessments, the PEDro scale results are shown in Supplemental Material 3. PEDro scores were reported from the included studies: thirteen with level I evidence (Lozano-Quilis et al. 2014; Hoang et al. 2016; Kalron et al. 2016; Calabrò et al. 2017; Peruzzi et al. 2017; Russo et al. 2018; Khalil et al. 2019; Munari et al. 2020; Ozkul et al. 2020; Tollar et al. 2020; Molhemi et al. 2021; Pagliari et al. 2021; Molhemi et al. 2022) and three with level II (Brichetto et al. 2015; Robinson et al. 2015; Yazgan et al. 2020). Most studies were single blinded, with the assessor being blinded to participant allocation. In addition, the ROB-2 overall score reported that most studies presented some concerns, but only three studies (Robinson et al. 2015; Ozkul et al. 2020; Yazgan et al. 2020) had a 'high risk' of bias (Fig. 2) [insert Figure 2]. Disagreements between reviewers occasionally occurred for domain 2, but consensus was always reached without the participation of the third reviewer.

3.2 Study design and population characteristics

The main characteristics of the participants and the interventions were shown in Table 1. The randomised pooled population obtained from the reviewed studies reached a total of 656 participants with a mean EDSS score of 4.22 (95%CI 4.15–4.30). The mean age was 45.12 (95%CI 44.66–45.59) and 65.57% of the population were female. All studies involved patients with relapsing-remitting type, except for three studies which did not specify the phenotype of multiple sclerosis (Robinson et al. 2015; Kalron et al. 2016; Pagliari et al. 2021). Furthermore, eight studies (Lozano-Quilis et al. 2014; Brichetto et al. 2015; Hoang et al. 2016; Munari et al. 2020; Tollar et al. 2020; Yazgan et al. 2020; Molhemi et al. 2021, 2022) involved participants with any type of multiple sclerosis (relapsing-remitting, secondary progressive, and primary progressive) without subgroup analysis.

Concerning the immersion of the virtual reality systems, 14 studies employed non-immersive virtual reality as the main experimental intervention and four of them used the Wii Fit system (Brichetto et al. 2015; Robinson et al. 2015; Khalil et al. 2019; Yazgan et al. 2020). Only two trials used fully immersive virtual reality (Kalron et al. 2016; Ozkul et al. 2020).

Most studies compared the virtual reality intervention to improve balance or gait to conventional balance training (n = 13, 81.25%) (Lozano-Quilis et al. 2014; Brichetto et al. 2015; Robinson et al. 2015; Hoang et al. 2016; Kalron et al. 2016; Peruzzi et al. 2016; Calabrò et al. 2017; Russo et al. 2018; Khalil et al. 2019; Ozkul et al. 2020; Molhemi et al. 2021, 2022; Pagliari et al. 2021), followed by robotic-assisted gait training (n = 3, 18.75%) (Calabrò et al. 2017; Peruzzi et al. 2017; Munari et al. 2020). The lowest number of sessions performed was 8 (Robinson et al. 2015), while the highest was 54 (Russo et al. 2018). Most authors proposed a frequency of intervention of 2 times per week with a minimum time per session of 30 minutes (Hoang et al. 2016; Kalron et al. 2016) and a maximum of 85 minutes (Calabrò et al. 2017).

The mean number of dropout events for the experimental group was 1.61 cases and 1.88 for the comparator group. The highest number of dropouts in the virtual reality groups were registered by Hoang et al. (2016) and Pagliari et al. (2021). The reasons reported by the authors for dropout in both groups were: difficulties

reaching the research centre, transportation problems, scheduling problems, moving to another city, refusal to participate, personal or familial issues, lack of motivation or time, loss of data due to administrative problems, exacerbation of symptoms, disease relapse, work intensity, and illness/medical reasons/hospitalisation not related to multiple sclerosis. Three studies did not report any dropout events during the intervention or follow-up period (Brichetto et al. 2015; Calabrò et al. 2017; Russo et al. 2018).

3.3 Meta-analysis of proportions

A total of 18 arms (k) from 16 studies were included in the proportion and binary meta-analysis, since one of the randomised control trials presented three study groups (Tollar et al. 2020). From a total of 638 participants, 63 cases of dropouts were reported. The forest plot showed an overall pooled dropout rate of 6.6% (95%CI 3.2%–12.9%) without heterogeneity between studies (tau^2 = 1.18, Q = 10.07, df = 17, I^2 = 0%, 95%CI 0%–50%, p = 0.90) (Fig. 3) [insert Figure 3]. The dropout rate for the virtual reality-based interventions was 5.7% (95%CI 2.3%–13.6%) against the 9.7% (95%CI 5.7%–16.02%) in the comparator groups (Supplemental Material 4). Conversely, the retention rate for the virtual reality and comparator groups were 94.3% and 90.3%, respectively. None of the prediction intervals calculated across the meta-analysis suggested that the intervention would achieve the same effects in the future.

3.4 Binary meta-analysis (OR)

The main results showed a slightly lower probability that dropouts occurred in the virtual reality-based interventions than in the comparator groups, but a significant difference was not obtained (OR = 0.89, 95%CI 0.64–1.24, p = 0.46). No significant heterogeneity between studies was found (tau^2 = 0, Q = 5.6, df = 17, I^2 = 0%, 95%CI 0%–50%, p = 0.99) (Fig. 4) [insert Figure 4]. The prediction interval confirmed that the same effects would not happen in future studies. A subgroup meta-analysis according to the immersion level of the virtual reality was not carried out because the number of studies using immersive systems did not reach the minimum required (3 studies).

A post-hoc sensitive analysis using the L'Abbé and Baujat plots and influence graphs (Supplemental Material 5) showed that none of the included studies influenced heterogeneity or bias for the pooled effect size, and no outliers were found. Additionally, no small study effects or publication bias were shown in the contour-enhanced funnel plot (Fig. 5) [insert Figure 5], the Harbord test (p = 0.37), or the Egger bias test (p = 0.34).

3.5 Meta-regression

The meta-regression revealed that the type of intervention, number, frequency, and duration of session, weeks of intervention, EDSS score, multiple sclerosis phenotype, sex, and methodological quality could not be related to the dropout events. A detailed description of the analysis was shown in Table 2.

4. Discussion

A total of 16 randomised control trials reporting dropouts were meta-analysed to calculate the overall pooled dropout rate of virtual reality-based interventions for the improvement of balance and gait in patients with multiple sclerosis. The main clinical implication of the results of our study was that the virtual reality-based training for balance and gait in people with multiple sclerosis was highly accepted with a low dropout rate and high adherence during the study period. Torous et al. (2020) suggested that the retention in research contexts could change when experimental approaches are translated into a clinical setting. This could be especially important for long rehabilitation programmes in chronic conditions. A recent study (Hortobágyi et al. 2022) reported a high adherence rate to a two-year maintenance program including exergaming in

people with multiple sclerosis; however, the sample size was very small, and more research about long-term adherence to virtual reality rehabilitation in this population is needed.

Adherence is one of the main conflicts faced in rehabilitation; the therapeutic approach of multiple sclerosis is not an exception. As a result, looking for rehabilitation therapies that achieve higher participant compliance to treatment is vital (Arafah et al. 2017). If correct adherence is not achieved, the effectiveness of the rehabilitation might be limited and incur additional healthcare costs (Jack et al. 2010; Room et al. 2021). Accordingly, previous literature has proposed that virtual reality strategies presented higher adherence in patients with neurological disorders (Asadzadeh et al. 2021; Dalmazane et al. 2021). Nonetheless, our results suggested lower dropout rates in virtual reality-based interventions, which may be confirmed with larger sample sizes. This idea is supported by the prediction intervals, which stated that our findings could change with future trials. The recent systematic review of Bevens et al. (2021) analysed the dropout rate in people with multiple sclerosis who received digital health interventions, showing no significant differences between experimental and control comparators. Therefore, we can consider that the adherence to virtual reality or other technological approaches were at least similar to other interventions.

During the screening process, several studies were discarded because dropouts were not mentioned. Despite CONSORT guidelines stating the need to report complete data, many authors do not know how to handle dropouts (Bell et al. 2013). To address this issue, it is necessary to standardise the way in which the reason and number of dropouts are described, for example, using the CONSORT flowchart of the study period. Also, further details of dropouts could help to make decisions regarding which interventions to offer to whom (Wright et al. 2021).

Our meta-regression data showed that the type of intervention, number, duration, and frequency of sessions, weeks of intervention, disability score, phenotype, sex, and methodological quality were not predictors of dropouts. Although it seems that a higher frequency of sessions could favour participant dropouts, no significant results were found. Similar results were obtained by Dennett et al. (2020), who stated that there was no relationship between the frequency of exercise-based sessions and dropouts, but duration modified the likelihood of dropouts. Although our protocol included the analysis according to the level of immersion, fully immersive and semi-immersive virtual reality were excluded from the moderator analysis because of the limited number of studies included. Therefore, we suggest to provide a specific dropout rate analysis when the proportion of studies using immersive virtual reality rises, since higher immersion and presence levels are expected to achieve a higher treatment adherence (Rose et al. 2018; Dębska et al. 2019). Additionally, future studies should evaluate enjoyment and motivation with specific measurement scales, allowing researchers to understand whether motivation or enjoyment during the intervention are predictors of dropout or adherence to treatment in the targeted population.

According to the literature (Grover et al. 2021), adverse events due to treatment are considered one of the main causes of dropouts. Nonetheless, we were unable to analyse them as a moderator of dropout rate, since none of the studies included reported the undesired effects of the virtual reality intervention. Two possible explanations behind the low number of studies describing adverse events or side effects because of the intervention were considered: the first is that participants did not actually have adverse effects due to the virtual reality-based intervention, and the second is that the authors decided not to report them. The latter idea is supported by Phillips et al. (2019) and Pitrou et al. (2009), who addressed methodological weaknesses in reporting adverse events in randomised control trials, leading to a misinterpretation of intervention safety.

4.1 Strength and limitations

This is the first meta-analysis to calculate the overall pooled dropout rate for innovative virtual reality-based interventions in patients with multiple sclerosis. The findings of this review could help future randomised control trials to calculate their sample size to avoid dropout bias. Furthermore, no heterogeneity

between the included studies was found in the analysis. The sensitivity analysis did not report any randomised control trial as an outlier that could strongly influence the overall size effect. Moreover, the funnel plot did not show any publication bias.

The main limitation of this review was the small sample size that the randomised control trials included, so a larger overall sample size would make our results more reliable. Another issue was that many studies did not report detailed reasons for dropouts. Furthermore, adverse events were not reported, so it was not possible to determine whether they could be moderators for dropout rate.

5. Conclusion

The overall pooled dropout rate of randomised control trials on virtual reality for balance or gait training in people with multiple sclerosis was 6.6%. Our analysis reported no differences in dropout rate for participants who received virtual reality-based interventions versus other comparators; however, the lower dropout rate in the virtual reality group could indicate that the inclusion of larger sample sizes would show a significant difference in favour of the virtual reality group. The number, duration, frequency, and weeks of sessions, sex, age, phenotype, disability, and methodological quality were not determined to be moderators of dropouts. Adverse events were not reported by the studies included, making it impossible to analyse their influence as moderators.

Future randomised control trials should standardise the description of dropout causes and adverse effects of the rehabilitation treatments. Furthermore, the advantages of virtual reality, such as motivation and enjoyment, should be systematically assessed in clinical trials to determine whether these outcomes are indeed moderators of dropout and adherence.

Authors contribution

Conceptualization, M.J.C-H and C.G-M; methodology, C.G-M, M.J.C-H; software and formal analysis, C.G-M; writing—original draft preparation, M.J.C-H, C.G-M, M.D.C-V, R.M-V, J.A.M-M and D.L-A; writing, review and editing, M.J.C-H and C.G-M.; visualization, M.D.C-V and R.M-V; supervision, M.D.C-V, J.A.M-M and D.L-A ; M.J-C-H and C.G-M contributed equally to this work. All authors have read and agreed to the published version of the manuscript.

Data availability

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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Title page

Title

Dropout rate in randomised controlled trials of balance and gait rehabilitation in multiple sclerosis: is it expected to be different for virtual reality-based interventions? A systematic review with meta-analysis and meta-regression

Running Head

Dropouts in multiple sclerosis for virtual reality

Author's information:

María Jesús Casuso-Holgado [1]. https://orcid.org/0000-0002-4217-6827

Cristina García-Muñoz[2]. https://orcid.org/0000-0003-2621-2098

Rocío Martín-Valero[3]. https://orcid.org/0000-0002-1664-3647

David Lucena-Anton[2]. https://orcid.org/0000-0003-2441-5342

Jose A. Moral-Munoz[2, 4]. https://orcid.org/0000-0002-6465-982X

María-Dolores Cortés-Vega[1]. https://orcid.org/0000-0002-9514-8811

1. Department of Physiotherapy, University of Seville, Sevilla, Spain
2. Department of Nursing and Physiotherapy, University of Cadiz, Cadiz, Spain
3. Department of Physiotherapy, University of Malaga, Malaga, Spain
4. Institute of Research and Innovation in Biomedical Sciences of the Province of Cadiz (INiBICA), University of Cadiz, Cadiz, Spain

Correspondence to: Dr. Cristina García Muñoz; cristina.garciamunoz@uca.es

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~~1.~~ ABSTRACT (2580 words)

Aim: To assess and meta-analyse the pooled dropout rate in absolute and comparative terms of randomised control~~led~~ trials using virtual reality for balance or gait rehabilitation in people with multiple sclerosis.

Design: A systematic review of randomized control~~led~~ trials with meta-analysis and meta-regression.

Data sources: A search was conducted in PubMed, Scopus, Web of Science, the Physiotherapy Evidence Database, the Cochrane Database, CINHAL, LILACS~~ilacs~~, ScienceDirect, and ProQuest. It was last updated in July 2022.

Review Methods: After the selection of studies, a quality appraisal was carried out using the PEDro Scale and the Revised Cochrane risk-of-bias tool for randomised trials ~~(ROB-2)~~. A descriptive analysis of main characteristics and dropout information was performed. An overall proportion meta-analysis calculated the pooled dropout rate. Odds ratio meta-analysis compared the dropout likelihood between interventions. The meta-regression evaluated the influence of moderators related to dropout.

Results: Sixteen~~16~~ studies with 656 participants were included. The overall pooled dropout rate was 6.6 % and 5.7% for virtual reality and 9.7% in control groups. The odds ratio (0.89, p = 0.46) indicated no differences in the probability of dropouts between the interventions. The number, duration, frequency, and weeks of sessions, intervention, sex, multiple sclerosis phenotype, Expanded Disability Status Scale score, and PEDro score were not moderators (p > 0.05). Adverse events were not reported and could not be analysed as moderators.

Conclusions: Dropouts across the virtual reality and control comparators were similar~~,~~ without significant differences. Nonetheless, there is a slight trend that could favour virtual reality. Standardisation in reporting dropouts and adverse events is recommended for future trials.

PROSPERO database, registration number ID
CRD42021284989

Keywords
Dropout rate; ~~M~~multiple sclerosis; ~~A~~adherence; ~~V~~virtual reality; ~~A~~attrition.

Statements and ~~D~~declarations
The authors declare no conflicts of interest.

Competing ~~I~~interests
This research received no external funding.

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2.1. Introduction

Different types of virtual reality technology (e.ge.g., non-immersive, semi-immersive, or fully immersive) haves emerged as an useful tool in neurorehabilitation with promising results for physical and cognitive rehabilitation (Voinescu et al. 2021). MoreoverIn thisat way, virtual reality-based interventions have been enhanced as a technological solution for telerehabilitation at the time of the COVID-19 pandemic (Matamala-Gomez et al. 2021). Furthermore, pPrevious literature has proposed that virtual reality strategies present higher adherence in patients with neurological disorders (Asadzadeh et al. 2021; Dalmazane et al. 2021). Multitask training, patient motivation, safety, and the low cost of commercial devices are some of the benefits of using virtual reality for neurological rehabilitation (Forsberg et al. 2015; Gustavsson et al. 2021; Moan et al. 2021). Nonetheless, Despite these potential benefits, the recent literature has also highlighted some limitations of the use of virtual reality with rehabilitative purposes. These limitations are undesired effects (e.g., headache, sickness, or nausea) (Massetti et al. 2018), along withas well as the difficulty of transferring the complex skills trained in virtual environments to the real world or and thea lack of ecological validity in a neurologically-impaired population (Levac et al. 2019), were reported. Specifically for balance training, the time of latency, the underestimation of perceived distances, and or the dependence ontо specific systems (e.g., balance board) and virtual contexts have beenwere proposed as potential weaknesses of virtual reality environments (Morel et al. 2015).

Multiple sclerosis (MS) is a global neurodegenerative disease affecting approximately three million people in the world (Tafti et al. 2022). Balance disorders, gait impairments, and or fatigue are core the main symptoms in these peoplepatients with multiple sclerosis that, obtaining. The evidence is positive effects regarding the efficacy of with physical therapy intervention for the rehabilitation of patients with multiple sclerosis (Amedoro et al. 2020; Abou et al. 2022). Particularly, for virtual reality-based physical rehabilitation different types of virtual systems have shown showed benefits for balance and gait training (Casuso-Holgado et al. 2018; García-Muñoz et al. 2021; Nascimento et al. 2021; García-Muñoz et al. 2021);. Hhowever, fatigue is a significant barrier to participation in physical activity, which for this population that could influenceinfluencesing the participants'' adherence when they are enrolled to physical interventions (Moore et al. 2022). In that way, aAA recent systematic review has summarised dropout data from randomised controlled clinical trials about exercise interventions in people with multiple sclerosis, concluding that mean age, the proportion of females, and intervention duration were moderators are inversely associated with adherence (Dennett et al. 2020). However, no previous systematic reviews exist for dropout in virtual reality interventions for balance and gait rehabilitation in this population. Therefore, The aforementioned findings these findings could impact on the sample size calculation, promotinge an under- or overestimationed sample size calculation respectively and also differential dropout. Furthermore, this could influence the differential dropout rate, This occurs when in which is how the degree of dropout differs between the intervention and comparator conditions after randomisation (Crutzen et al. 2015). The differential dropout rate might It might affect the power of research and could present a risk of bias for randomised controlled clinical trials (Cooper et al. 2018). In view of this background, Ssetting accurate expected dropout rates in virtual reality studies for rehabilitation in multiple sclerosis could help future trials to avoid problems in their internal or external validity. In addition, the identification of factors specifically associated with dropout in virtual reality trials could help clinicians when translating research into practice.

As far as we are concerned, no previous systematic reviews were found reporting dropout in virtual reality interventions for balance and gait rehabilitation in this population. Thus, the present systematic review and meta-analysis has three aimsaimed to: (1) to systematically assess and meta-analyse the overall pooled dropout rate of randomised controlled trials using virtual reality as an intervention for balance or gait training in people with multiple sclerosis in both absolute and comparative terms; (2) to analyse whether any participant or intervention factors are related to dropout; and (3) to identify adverse events that could be the reason for dropouts.

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3.2. Methods

2.13.1 Data sources and search strategy

This systematic review was carried out following the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher 2009). The review protocol was registered in the PROSPERO database (Registration Nnumber: CRD42021284989).

Two independent reviewers (M.J.C.-H., C.G.-M.) conducted an electronic search in MEDLINE (PubMed), Scopus, Web of Science (WOS), the Physiotherapy Evidence Database (PEDro), the Cochrane Database of Systematic Reviews (CDSR), CINHAL, LILACSilacs, ScienceDirect, and ProQuest. The search was performed between July and November 2021. Neither language nor date filters were applied in the different databases. Key terms concerning intervention (*"virtual reality"*, *"game"*, *"gaming"*, *"exergaming"*, and *"interactive"*), balance (*"balance"* or *"postural control"*), gait (*"gait"*, *"walking"*, and *"ambulation"*), and *"multiple sclerosis"* were combined as search terms in the strategies. The search strategy is displayed shown in detail in Supplementalry Material 1.

23.2 Research question and study selection

To set the research question, The PICOS model (participants, interventions, comparisons, outcomes, and study design (PICOS) model) recommendations werewas considered to set the following research questionsas follows: what dropout data are reported during the intervention and follow-up period by randomised control clinical controlled trials conducting aan intervention through virtual reality intervention to improve balance or gait in multiple sclerosis and what are the possible moderators that affectaffecting dropout in these studies?

Participants included in the review were female or male, aged between 18 and 65 years old, with any diagnosis of multiple sclerosis phenotype meeting the revised McDonald criteria (Thompson et al. 2018). Walking ability is was preservedconserved according to the Expanded Disability Status Scale (EDSS) score (EDSS ≤ 6). Included interventions involved any type of virtual reality systems aimed at improving balance or gait compared to other interventions based-on physical activity with or without an external aid use. Furthermore, those studies thatwhich reported dropout events information were included.

23.3 Data extraction and quality assessment

First, two independent reviewers (C.G.-M. and M.J.C.-H.) identified potential articles in databases to be included in the systematic review through the title and abstract information. Following thisNext, duplicates were removedremoved, and an exhaustive analysis of articles was carried out based on their full-text reading. This step was particularly focused on the selection criteria checking assessment, and both reviewers ensured ensuring that the inclusion criteria were met before selecting suitable studies. In the case of disagreement, a third reviewer (M.-D.C.-V.) was consulted to decide on the inclusion of the documents.

When Once articles were selected, thea quality assessment was conducted using the Physiotherapy Evidence Database PEDro Sscale (PEDro)(Maher et al. 2003) and the Revised Cochrane risk-of-bias tool for randomised trials (RoB-2) (Higgins et al. 2019). PEDro is a reliable tool of 11 items that evaluates the inner validity of a clinical trial. If studies are scored above 6 points on the PEDro Scale, they are considered to have aclassified as level I of evidence (6–8: good; 8–10: excellent), and iIf while level II is when the score is below 5, they are classified as level II (4–5: deficient; <4: poor). ROB-2 is the updated and

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~~improved version of Cochrane ROB and~~ allows the evaluation of bias in randomised control~~led~~ trials. ~~. This tool is cc~~omprising~~ed of~~ five domains (bias arising from the randomisation process, due to deviations from the intended interventions, to missing outcome data, in the measurement of the outcome, and in the selection of the reported result) that are qualified as a low or high risk of bias with some concerns (Sterne et al. 2019).

Next, reviewers recorded the data for qualitative and quantitative synthesis. ~~For both analyses extracted data were~~The extracted data ~~extracted~~ were country, multiple sclerosis phenotype and disability status, female and male percentages, age, experimental and comparator group intervention~~s~~ characteristics, number of participants recruited and analysed, retention rate, dropout rates (for the experimental and control groups), reasons for dropout (~~o~~in each group), and adverse events. Disagreements in data were solved by consensus with a third reviewer. Information provided by the included studies allowed us to calculate~~he calculation of~~ dropout rates in all cases, so no~~ne~~ corresponding author~~s~~ were~~as~~ contacted.

2~~3~~.4 Data analysis

Dropout rate was calculated as the number of participants who did not complete the intervention and follow-up period divided by the total number of participants that underwent the randomisation process. ~~On the other hand~~Moreover, retention rate was the total number of participants that concluded the intervention, showing the adherence rate to treatment. ~~Rates for both conditions were calculated.~~ For those studies that included more than two groups of intervention, comparison between groups ~~have been~~was analysed separately two by two.

To conduct the meta-analysis, the R Studio software (version 4.0.0) ~~was selected~~ and its packages *meta*, *metafor*, and *dmetar* were ~~employed~~ used (Viechtbauer 2010; Balduzzi et al. 2019; Harrer et al. 2021). The proportion meta-analysis was performed through the *metaprop* function~~,~~ to determine the estimated dropout rate in virtual reality intervention, the control comparator, and all arms. Proportions were transformed using the logit transformation (Schwarzer et al. 2019).

A binary meta-analysis based on odds ratios (ORs) was conducted to examine whether the probability of dropouts is higher in the virtual reality or in the comparator interventions. To assess the effect measure in binary outcomes, the OR with a 95% confidence interval (95%CI) was calculated, and the inverse variance method was used to adjust pooling estimations to sparse data (considering that dropouts are a rare event). Likewise, the Hartung-Knapp adjustment for a random effects model was implemented. Focusing on ORs, if the value is 1, there are no differences in dropouts ~~and dropout exist~~ between the experimental and comparator group~~s interventions~~. In contrast, if the OR is greater than ~~></~~1, a higher dropout rate ~~will be~~was registered for the ~~virtual reality intervention~~experimental group. The restricted maximum-likelihood estimator for ~~t~~τ^2 was selected to estimate the between-study variance (Viechtbauer 2005). As some studies could present zero events in the experimental and/or~~/and~~ comparator arm ~~and in both~~, a 0.5 continuity correction was added to all meta-analyses, as suggested by ~~Gart and Zweifel~~ (Gart and Zweifel (1967).

Heterogeneity between studies was assessed through ~~the~~ I^2, ~~t~~τ^2, ~~tau square~~ and Cochrane's Q ($p < 0.05$ indicates heterogeneity). When I^2 presents a value above 50%, it means that large heterogeneity is found across studies (Higgins et al. 2021). A random effects model was employed considering the possible degree of heterogeneity between the included studies.

~~To display the outcomes of proportions and binary meta-analyses, f~~Forest plots were ~~performed~~used to show the outcomes of proportions and binary meta-analyses. The prediction interval was added as a red line to the forest plot to provide a measure of reliability of future treatment effects in new studies (Nagashima et al. 2019). Depending on the level of immersion of the subject within the virtual environment, virtual reality was ~~distinguished in~~classified as~~on~~ non-immersive, semi-immersive, and fully immersive

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for~~r a~~ subgroup analysis. ~~However, immersive virtual reality and semi immersive virtual reality interventions were excluded due to the low number of studies.~~

A sensitivity~~e~~ analysis was carried out to assess the influence of studies on the overall binary meta-analysis results. The influence was explored to detect the presence of outlier data and whether there ~~will be~~were studies that~~which~~ contribute~~d~~ to heterogeneity or bias pooled results. ~~To represent influential cases in meta-analysis, a~~ A ~~-~~Baujat plot, a L'Abbé plot, ~~was carried out~~ and ~~an~~ influence graphs were~~as~~ created to represent influential cases in meta-analysis. ~~where studies which~~ The influence graphs~~last~~ showed the studies that significantly influenced the ~~ed coloured in red the studies influencing significantly the a~~ ~~bias of~~ pooled effect size in red ~~were shown in red~~. ~~Also~~In addition, an exploratory graphical analysis of data was performed to examine whether there is a clear trend of effect size related to independent variables.

Meta-regression~~s~~ was~~ere~~ conducted to evaluate possible associations between participants or study characteristics which could vary in the presence of dropout events. Studies with no available data were excluded from the meta-regression analysis. Moreover, to run the meta-regression, at least three studies with the predictor were needed. The analysed moderators were interventions, number, duration, frequency and weeks of sessions, EDSS ~~Expanded Disability Status Scale~~ score, multiple sclerosis phenotype, and sex.

Publication bias and small study effects were evaluated through a contour enhanced-funnel plot adjusted by the Duval and Tweedie trim and fill method (Shi and Lin 2020). Asymmetry in the funnel plot ~~will~~ indicated the effect of small studies in the pooled results. To confirm the absence of asymmetry, a p-value greater than ~~>~~ 0.05 must be reached in the Harbord's test (Harbord et al. 2006) and ~~in~~ the Egger bias test (Egger et al. 1997).

~~4.~~3. Results

~~3~~4.1 Study selection and methodological quality assessment

In total, 7,024 articles were identified through the initial database search based on titles and abstracts. After that, duplicates were removed, ~~reducing the overall number of results to~~obtaining 5,995 articles. Once the studies underwent the screening and eligibility steps, 16 randomised control~~led~~ trials ~~that met the eligibility criteria~~ were included for the qualitative synthesis and quantitative analysis. There was no disagreement between reviewers in the study selection process. Figure 1 ~~displays~~ showed the PRISMA flowchart ~~which details~~detailing the selection procedure [insert Figure 1.]. Excluded studies and their~~its~~ reasons ~~are~~ were detailed in Supplemental~~ry~~ Material 2.

Regarding ~~to~~ the quality assessments, the PEDro scale results are shown in Supplemental~~ry~~ Material 3. PEDro scores were reported from the included studies:; thirteen with level I evidence (Lozano-Quilis et al. 2014; Hoang et al. 2016; Kalron et al. 2016; Calabrò et al. 2017; Peruzzi et al. 2017; Russo et al. 2018; Khalil et al. 2019; Munari et al. 2020; Ozkul et al. 2020; Tollar et al. 2020; ~~Munari et al. 2020;~~ Molhemi et al. 2021; Pagliari et al. 2021; Molhemi et al. 2022) and three with level II (Brichetto et al. 2015; Robinson et al. 2015; Yazgan et al. 2020). Most ~~of the~~ studies were single blinded, ~~in which the~~with the assessor being~~was~~ blinded to participant allocation. In addition, the ROB-2 ~~summary~~ overall score reported that most ~~of the research~~studies presented some concerns, but only three studies (Robinson et al. 2015; Ozkul et al. 2020; Yazgan et al. 2020) had a ~~"~~high risk~~"~~ of bias (Fig.~~ure~~ 2) [insert Figure 2.]. Disagreements between reviewers occasionally occurred ~~sometimes~~ for domain 2, but consensus was always reached without the participation of the third reviewer.

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34.2 Study design and population characteristics

The main characteristics of the participants and the interventions ~~can be found~~were shown in Table 1. The randomised pooled ~~randomised~~ population obtained from the reviewed studies reached a total of 656 participants with a mean EDSS score~~xpanded Disability Status Scale~~ of 4.22 (95%CI 4.15–4.30). ~~From the overall population, 65.57% of subjects were female.~~ The mean age was 45.12 (95%CI 44.66–45.59) and 65.57% of the population were female. All studies involved patients with relapsing-remitting type, e~~E~~xcept for three studies which did not specify the phenotype of multiple sclerosis (Robinson et al. 2015; Kalron et al. 2016; Pagliari et al. 2021)~~, all studies involved patients with relapsing-remitting type~~. Furthermore, eight studies (Lozano-Quilis et al. 2014; Brichetto et al. 2015; Hoang et al. 2016; Munari et al. 2020; Tollar et al. 2020;~~ Munari et al. 2020;~~ Yazgan et al. 2020; Molhemi et al. 2021, 2022) involved~~,~~ p~~P~~articipants with any type of multiple sclerosis (relapsing-remitting, secondary progressive, and primary progressive) without subgroup analysis~~e multiple sclerosis, were allocated to the two intervention groups in eight studies (Lozano-Quilis et al. 2014; Brichetto et al. 2015; Hoang et al. 2016; Tollar et al. 2020; Munari et al. 2020; Yazgan et al. 2020; Molhemi et al. 2021, 2022).~~

Concerning the immersion of the virtual reality systems, ~~From 16 studies,~~ 14 studies employed non-immersive virtual reality as the main experimental intervention~~,~~ and four 4of them ~~specifically carried out the intervention through~~ used the Wii Fit system (Brichetto et al. 2015; Robinson et al. 2015; Khalil et al. 2019; Yazgan et al. 2020). Only two trials used ~~the~~ fully immersive virtual reality (Kalron et al. 2016; Ozkul et al. 2020).

Most ~~of~~ studies compared the virtual reality intervention to improve balance or gait ~~-~~ to conventional balance training (n = 13, 81.25%) (Lozano-Quilis et al. 2014; Brichetto et al. 2015; Robinson et al. 2015; Hoang et al. 2016; Kalron et al. 2016; Peruzzi et al. 2016; ~~Kalron et al. 2016;~~ Calabrò et al. 2017; Russo et al. 2018; Khalil et al. 2019; Ozkul et al. 2020; Molhemi et al. 2021, 2022; Pagliari et al. 2021~~; Molhemi et al. 2022~~), followed by robotic-assisted gait training (n = 3, 18.75%)~~.~~ (Calabrò et al. 2017; Peruzzi et al. 2017; Munari et al. 2020). The lowest number of sessions performed was 8 (Robinson et al. 2015), while the highest was 54 (Russo et al. 2018). Most authors proposed a frequency of intervention of 2 times per week with a minimum time per session of 30 minutes (Hoang et al. 2016; Kalron et al. 2016) and a maximum of 85 minutes (Calabrò et al. 2017).

The mean number of ~~for~~ dropout events for the ~~EG~~ experimental group was 1.61 cases and 1.88 for the comparator group ~~was 1.88 cases~~. The~~A~~ highest~~r~~ number of dropouts in the virtual reality groups were registered by ~~Hoang et al.~~ (Hoang et al. (2016) and ~~Pagliari et al.~~ (Pagliari et al. (2021). The reasons reported~~Dropout reasons disclosed~~ by the authors for dropout in both ~~experimental and comparator~~ groups were: difficulties reaching the research centre, transportation problems, scheduling~~e~~ problems, moving to another city, refusal to participate, personal or familial issues, lack of motivation or time, loss of data due to administrative problems, exacerbation of symptoms, disease relapse, work intensity, and illness/medical reasons/hospitalisation not related to multiple sclerosis. Three ~~of sixteen~~ studies did not report any dropout events during the intervention or follow-up period (Brichetto et al. 2015; Calabrò et al. 2017; Russo et al. 2018).

34.3 Meta-analysis of proportions

A total of 18 arms (k) from 16 studies were included in the proportion and binary meta-analysis~~; it is because~~, since one of the ~~RTC~~ randomised control~~led~~ trials presented three ~~groups of intervention~~study groups (Tollar et al. 2020). From a total of 638 participants, ~~a total of~~ 63 cases of dropouts were reported. The forest plot ~~indicated~~ showed an overall pooled dropout rate of 6.6% (95%CI 3.2%–12.9%) ~~not due to~~without heterogeneity between studies (tau^2 = 1.18, Q = 10.07, df = 17, I^2 = 0%, 95%CI 0%–50%, p = 0.90) (Fig~~ure~~ 3) [insert Figure 3~~.~~]. The dropout rate for the virtual reality-based interventions was 5.7% (95% CI 2.3%–13.6%) against the 9.7% (95% CI 5.7%–16.02%) ~~registered for participants allocated~~ in the comparator groups~~. The specific forest plots of the dropout rates for virtual reality and comparators are~~

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displayed in (Supplemental Material 4). Conversely, the final retention rate for the virtual reality and comparator groups were 94.3% and 90.3% of adherence, respectively. None of the prediction intervals calculated across the meta-analysis suggested that the treatment intervention would achieve the same effects in the future.

34.4 Binary meta-analysis (ORs)

The likelihood of dropouts between the intervention of virtual reality and control comparators was evaluated by the binary meta-analysis through ORs. The main results showed a slightly lower probability that dropouts occurred in the virtual reality-based interventions than in the comparator groups, but a significant difference was not reached obtained (OR = 0.89, 95%CI 0.64–1.24, p = 0.46). No significant heterogeneity between studies was found (tau^2 = 0, Q = 5.6, df = 17, I^2 = 0%, 95%CI 0%–50%, p = 0.99) (Fig.ure 4) [insert Figure 4.]. The prediction interval failed to confirmed that the same effects would not happen in future studies. A subgroup meta-analysis sort by type ofaccording to the immersion level of the virtual reality was not carried out, because of the number of studies using immersive virtual realitysystems did not reach the minimum required (3 studies).of three studies.

A post-hoc sensitive analysis using the L'Abbé and Baujat plots and influence graphs (Supplemental Material 5) showed that none of the included studies influenced heterogeneity or bias for the pooled effect size (see Supplementary Material 5), and . Also, no outliers were found. Additionally, no small study effects or publication bias were reflected shown in the contour-enhanced funnel plot (Fig.ure 5) [insert Figure 5], the Harbord test (p = 0.37), or theand Egger bias test (p = 0.34) [insert Figure 5].

34.5 Meta- regression

The meta-regression revealed that the type of intervention, number, frequency, and duration of session, weeks of intervention, EDSSxpanded Disability Status Scale score, multiple sclerosis phenotype, sex, and methodological quality could not be related to the dropout events. A detailed description of the analysis is givenwas shown in Table 2.

5.4. Discussion

A total of 16 randomised controlled trials that reportedreporting dropouts were subjected to meta-analysedis to calculate the overall pooled dropout rate of virtual reality-based interventions for the improvement of balance and gait in patients with multiple sclerosis. The main clinical implication highlighted by our resultsof the results of our study is was that the virtual reality-based training for balance and gait in people with multiple sclerosis is was highly accepted with a low dropout rate and high adherence duringto the studyies period. ButIn that way, as Torous et al. (Torous et al. (2020) suggested, that the retention in research contexts could change when experimental approaches are translated into a clinical setting. This could be especially important for long rehabilitation programmes in chronic conditions. A recent study (Hortobágyi et al. 2022) has reported a high adherence rate to a two- years maintenance exercise program including exergaming in people with multiple sclerosis (Hortobágyi et al. 2022);. Hhowever, the sample size was very small, and more research about long-term adherence to virtual reality rehabilitation in this population is needed.

Adherence is one of the main conflicts faced in rehabilitation; the therapeutic approach of multiple sclerosis is not an exception. As a result, looking for rehabilitation therapies that achieve higher participant compliance to treatment is vital (Arafah et al. 2017). If correct adherence is not achieved, the effectiveness of the rehabilitation might be limited and incur additional healthcare costs (Jack et al. 2010; Room et al. 2021). Accordingly, Pprevious literature has proposed that virtual reality strategies presented higher adherence in patients with neurological disorders (Asadzadeh et al. 2021; Dalmazane et al. 2021). Nonetheless, our results suggested lower dropout rates in virtual reality-based interventions, which may be

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confirmed ~~if the sample sizes of the included studies were~~ with larger sample sizes. This idea is ~~enhanced if we consider our calculated~~supported by the prediction intervals, which state~~d~~s that our findings could change with future trials. ~~Thus, a higher number of randomised controlled trials will be necessary to increase the overall sample size and support this hypothesis. In accordance with~~According to ~~our results, t~~The recent systematic review of ~~Bevens et al.(~~Bevens et al. (2021) analysed the dropout rate in people with multiple sclerosis who received digital health interventions~~. This study also~~, showing~~ed~~ no significant differences between experimental and control comparators. Therefore, we can consider that the adherence to virtual reality or other technological approaches were at least similar ~~outcomes from the aforementioned and our review therapies based on~~ to other interventions~~technological approaches present at least a similar adherence to other interventions~~.

During the screening process, ~~a number of~~several studies were discarded because dropouts were not mentioned. Despite ~~the important guidance of~~ CONSORT guidelines statinge~~, which states~~ the need to report complete data, many authors do not know how to handle dropouts (Bell et al. 2013). To address this ~~problem~~issue, it is necessary to standardise the way in which the reason and number of ~~withdrawals~~ dropouts are described~~,~~; for example, using the CONSORT flowchart of the study period ~~from the CONSORT guidelines~~. Also, further details of dropouts could help to make decisions regarding which interventions to offer to whom (Wright et al. 2021).

Our meta-regression data showed that the type of intervention, number, duration, and frequency of sessions, weeks of intervention, disability score, phenotype, sex, and methodological quality were not predictors of dropouts. ~~Even though~~Although it seems that a higher frequency of sessions could favour participant ~~withdrawals~~dropouts, no significant results were ~~reached~~found. ~~The same~~Similar results were obtained by ~~Dennet et al.(~~Dennett et al. (2020), who stated that there was no relationship between the frequency of exercise-based sessions and dropouts, ~~while~~ but duration modifie~~d~~s the likelihood of dropouts. ~~Moreover, a~~Although our protocol included the analysis according to the level of immersion, ~~The~~ fully immersive ~~virtual reality~~ and semi-immersive virtual reality were excluded from the moderator analysis because of the limited number of studies included. Therefore, we suggest to provide a specific dropout rate analysis ~~W~~when the proportion of studies ~~that employ~~using immersive virtual reality rises~~, we suggest a specific dropout rate analysis. One of the reasons for this suggestion is because~~, since ~~a~~ higher immersion and presence ~~obtained~~ levels are expected to achieve a ~~present a~~ higher treatment adherence ~~to the treatment~~ (Rose et al. 2018; Dębska et al. 2019). Additionally, ~~it would be interesting for~~ future studies ~~to~~ should evaluate enjoyment and motivation with specific measurement scales~~, for virtual reality experimental groups compared to comparator groups. This procedure will~~ allowing researchers to understand whether motivation or enjoyment during the intervention are ~~moderators~~ predictors of dropout or~~and~~ adherence to treatment in the target~~ed~~ population.

According to the literature (Grover et al. 2021), ~~The~~ adverse events due to treatment are considered one of the main causes of dropouts ~~(Grover et al. 2021)~~. Nonetheless, we were unable to analyse them as a moderator of dropout rate, ~~because~~ since none of the ~~sixteen~~ studies included reported the undesired effects of the virtual reality intervention. ~~We consider t~~Two possible explanations behind the low number of studies ~~that describe~~describing adverse events or side effects ~~as a result of~~because of the intervention were considered: the ~~the f~~first~~irst~~ is that participants did not actually ~~have~~ have~~d~~ adverse effects due to the virtual reality-based intervention, ~~while~~ and the ~~second~~ second is that the authors decided not to report them. The latter idea is supported by ~~Philip et al.(~~Phillips et al. (2019) and ~~Pitrou et al.(~~Pitrou et al. (2009), who addressed methodological weaknesses in reporting adverse events in randomised control~~led~~ trials, leading to a misinterpretation of intervention safety.

~~4~~5.1 Strength and limitations

This is the first meta-analysis to calculate the overall pooled dropout rate for ~~the~~ innovative virtual reality-based interventions in patients with multiple sclerosis. The ~~data~~ findings of this review ~~can~~ could help future

randomised controlled trials to calculate their sample size to avoid dropout bias. Furthermore, no heterogeneity between the included studies was found in the analysis. Also, tThe sensitivity analysis did not record reported any randomised control trial as an outlier that could values or randomised control trials that could strongly influence the overall size effect, as those recorded in the Baujat plot. Moreover, the funnel plot did not show any publication bias.

The main limitation of this review is was the small sample size due to the limited number of participants from studiesthatof the randomised controlled trials included. A, so a larger overall sample size will would make our results more reliable. Another issue is was that a large number ofmany studies failed to did not report detailed reasons for dropouts. Furthermore, important information like adverse events was were not reportedonly reported by three studies, meaning thatso it was not possible to determine whether these werethey could be moderators for dropout rate.

6.5. Conclusion

The overall pooled dropout rate of randomised controlled trials on virtual reality for balance or gait training in people with multiple sclerosis wasis 6.6%. Our analysis demonstrated reported no differences in dropout rate for participants who received virtual reality--based interventions compared toversus other comparators;. Hhowever, the lower dropout rate in the virtual reality groups could indicate that a the inclusion of larger sample sizes of study will would show a significant difference in favour of the virtual reality group compared with other interventions. The number, duration, frequency, and weeks of sessions, sex, age, phenotype, disability, and methodological quality were not determined to be moderators of dropouts. Adverse events were scarcely not reported by the studies included, so it was not possible to analyse them as moderatorsmaking it impossible to analyse their influence as moderators.

Future randomised controlled trials need should to standardise thea detailed description of dropout causes and adverse effects of the rehabilitation treatments. Furthermore, the advantages of virtual reality, like such as motivation and enjoyment, should be systematically assessed in clinical trials to determine whether these outcomes are truly indeed moderators of dropout and adherence.

Authors contribution

Conceptualization, M.J.C-H and C.G-M; methodology, C.G-M, M.J.C-H; software and formal analysis, C.G-M; writing—original draft preparation, M.J.C-H, C.G-M, M.D.C-V, R.M-V, J.A.M-M and D.L-A; writing, review and editing, M.J.C-H and C.G-M.; visualization, M.D.C-V and R.M-V; supervision, M.D.C-V, J.A.M-M and D.L-A ; M.J-C-H and C.G-M contributed equally to this work. All authors have read and agreed to the published version of the manuscript.

Data availability

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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Figure 1

Click here to access/download;Figure;Figure 1 PRISMA Flowchart.docx

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only

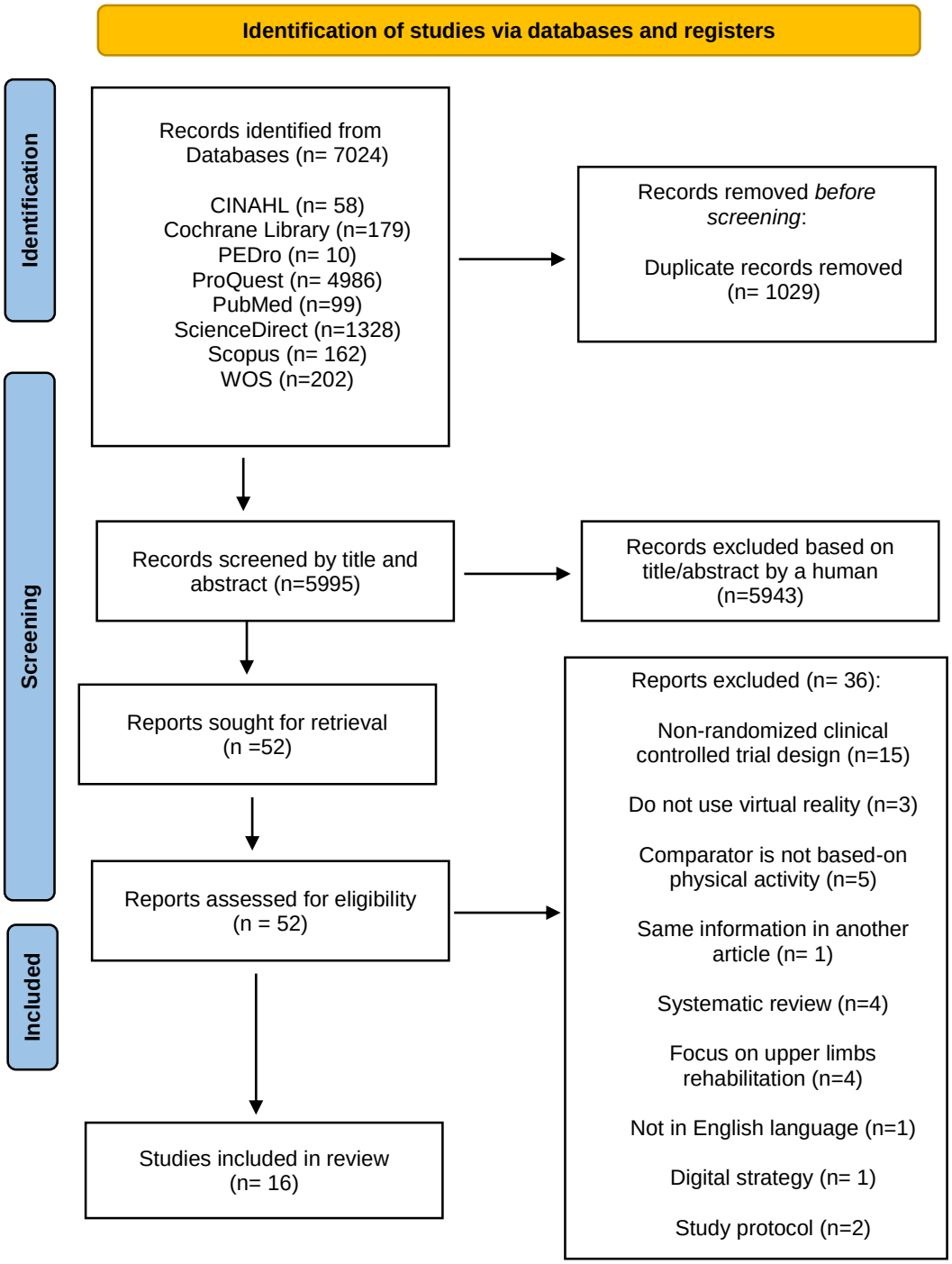

Figure 1. Flow diagram of trials selection based on PRISMA 2020 guidelines.

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only

*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Figure 2

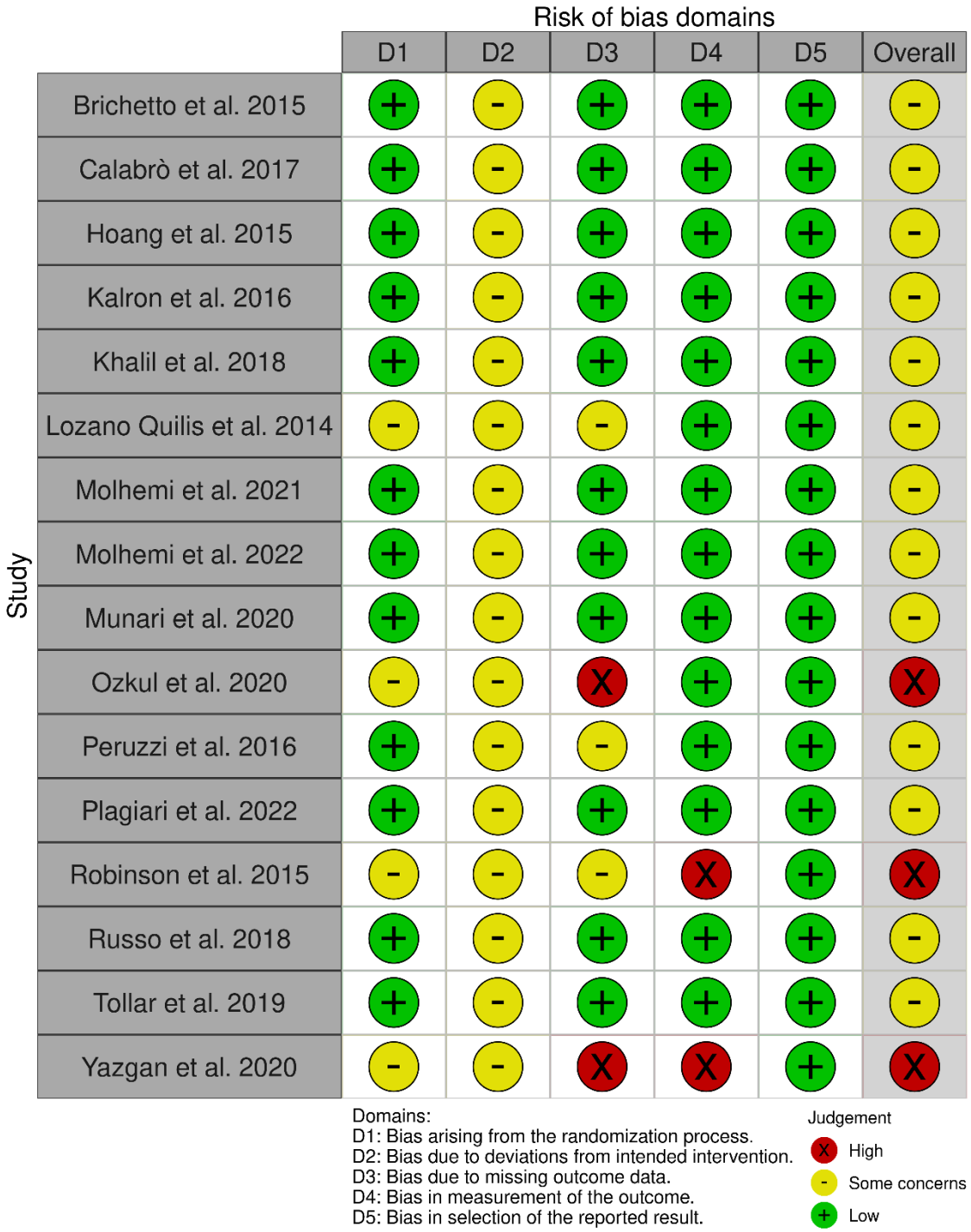

Figure 2. Cochrane risk of bias tool-2 summary.

Figure 3

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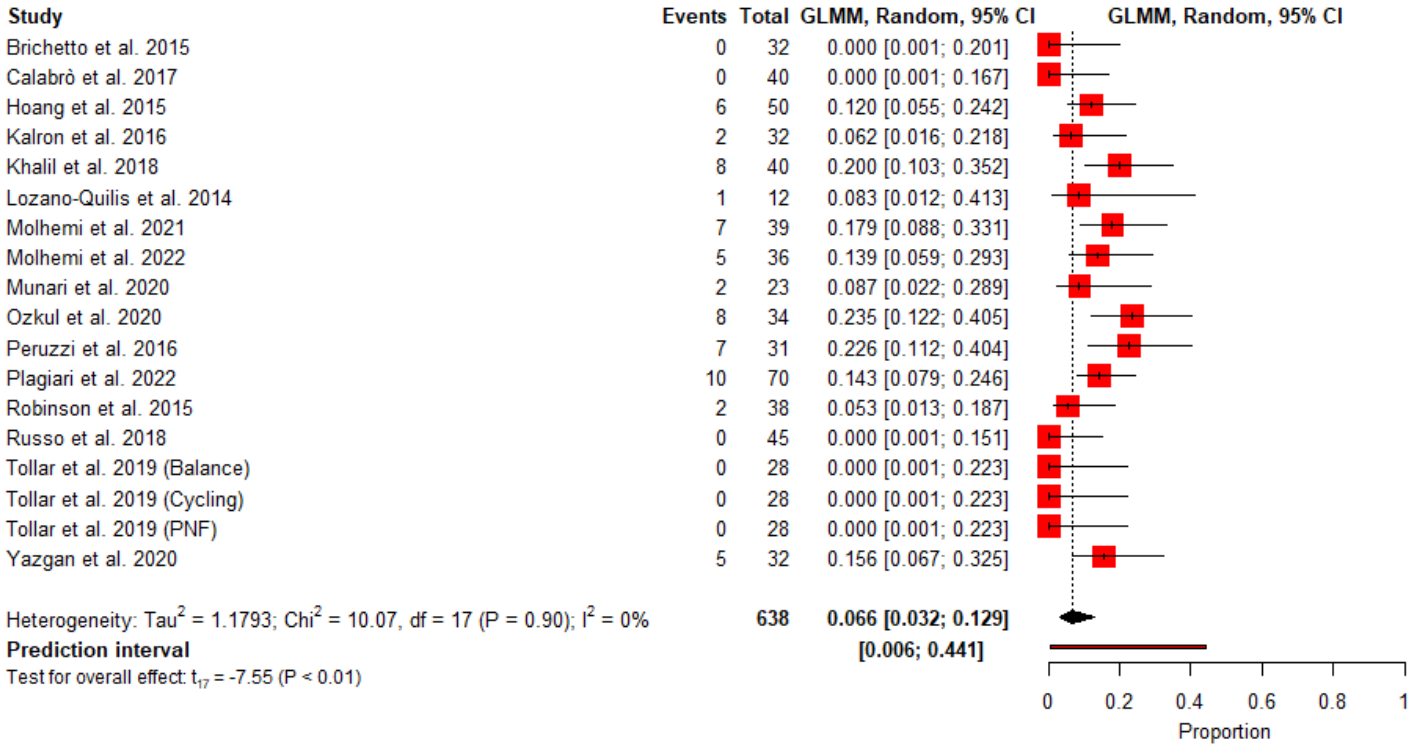

Figure 3. Forest plot of dropout rate for all groups of studies.

Figure 4

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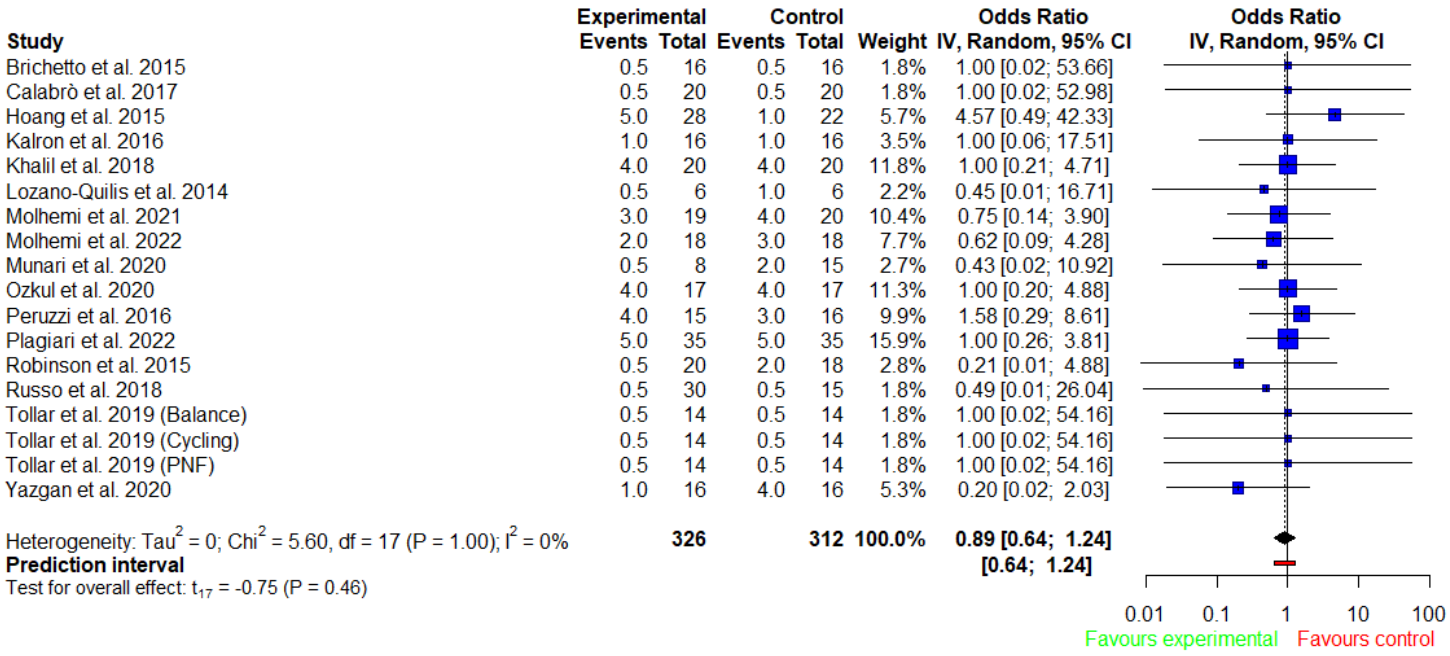

Figure 4. Forest plot of odds ratio comparing attrition from virtual reality intervention and other comparator interventions in people with multiple sclerosis to improve balance or gait.

Figure 5

Click here to access/download;Figure;Figure 5 Funnel plot.docx

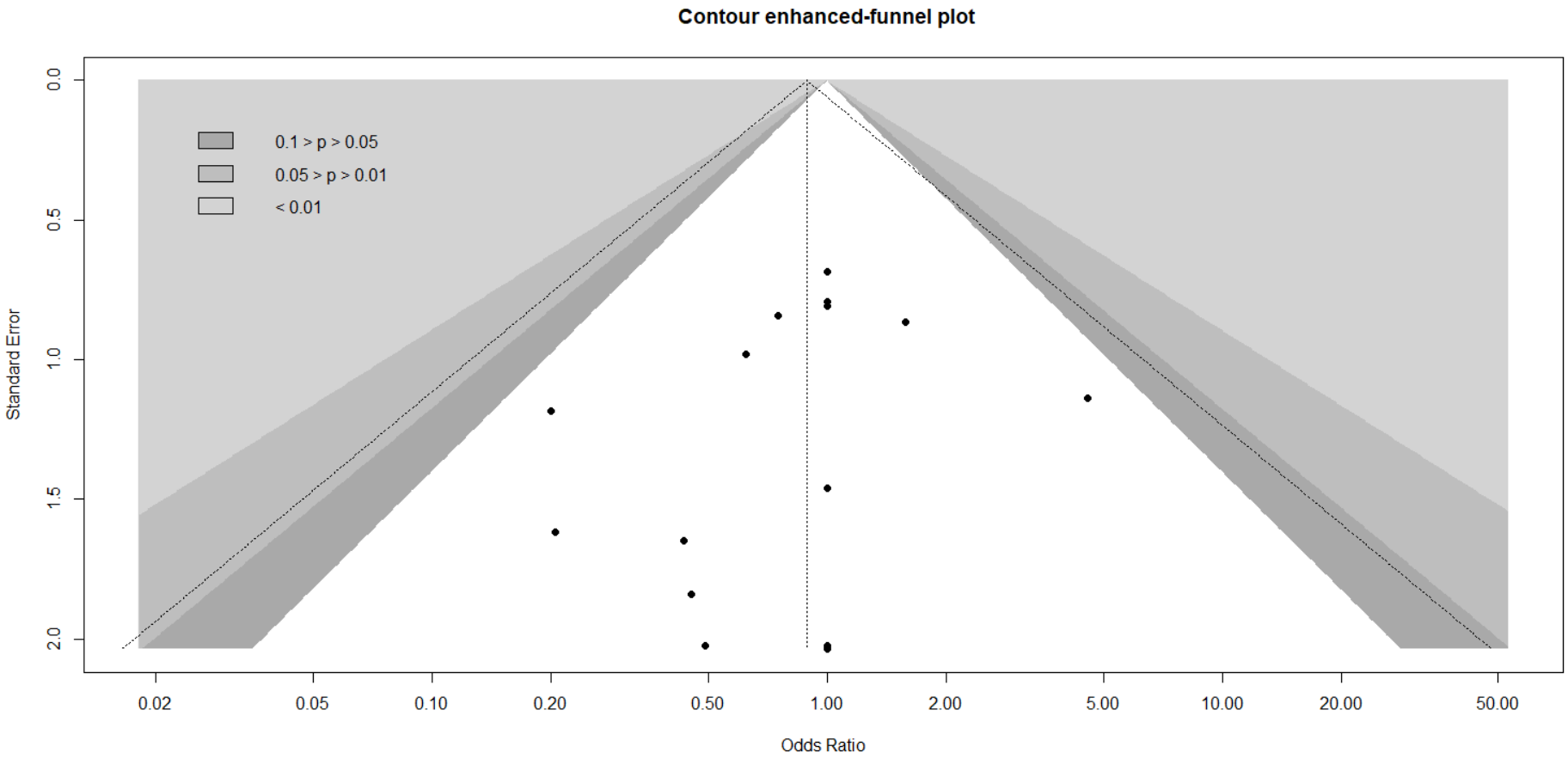

Figure 5. Contour-enhanced funnel plot.

Table 1. Characteristic of studies included in the systematic review

Study/ Country	MS phenotype/ EDSS (mean; SD)	Recruited /Analyzed (n)	% Sex/ Age (mean ± SD)	Experimental intervention	Control group intervention	Retention rate (%)	Dropout rate (%)	Reason for dropouts (EG/CG)	Adverse events
Brichetto et al. 2015 Italy	19 RRMS 9 SPMS 4 PPMS EDSS = 3.7 ± 1.2	EG: 16/16 CG: 16/16	F: 28.13% M: 71.88% 50.5 ± 11.6	12 sessions (60 min and 3 s/w, 4 weeks) Exergaming through Nintendo Wii Fit Balance Board, plus balance exercises in Balance Master Neurocom	12 sessions (60 min and 3 s/w, 4 weeks) Conventional balance training	100 % (32/32)	DOEG: 0% (0/16) DOCG: 0% (0/16)	---	NR
Calabrò et al. 2017 Italy	RRMS EDSS= 4.56	EG: 20/20 CG: 20/20	F: 62.5% M: 37.5 % 42.5	40 sessions (5 s/w, 8 weeks) Standard physical treatment (5 min of warning up, 5 min of strengthening, 20 min of postural control exercises) + 40 min of Lokomat + VR (avoid obstacles or catch objects on the trail)	40 sessions (5 s/w, 8 weeks) Standard physical treatment (5 min of warning up, 5 min of strengthening, 20 min of postural control exercises) + 40 min of Lokomat	100 % (40/40)	DOEG: 0% (0/20) DOCG: 0% (0/20)	----	No adverse or harmful events during the intervention

Hoang et al. 2015 Australia	RRMS: 26 SPMS: 12 PPMS: 10 Unknown: 2 EDSS= 4.15 ± 1.3	EG: 28/23 CG: 22/21	F: 76% M: 24% 52.4 ± 11.75	24 sessions (30 min; 2 s/w, 12 weeks) Exergames (Stepmania and Choice stepping reaction time; Home step training system.)	24 sessions (30 min; 2 s/w, 12 weeks) Conventional balance training + stretching + strength exercises	88% (44/50)	DOEG: 17.9% (5/28) DOCG: 4.5% (1/22)	Discontinued intervention due to personal circumstances (EG), relapse (EG), health problems during reassessment not related to MS (CG)	No adverse or harmful events during the intervention
Kalron et al. 2016 Israel	EDSS= 4.1 ± 1.3	EG: 16/15 CG: 16/15	F: 63.33% M: 36.67% 45.2 ± 11.6	12 sessions (30 min; 2s/w, 6 weeks) Immersive virtual reality system CAREN	12 sessions (30 min; 2s/w, 6 weeks) conventional balance training 10 min of stretching + 20 min of training (static postural control, weight shifting and perturbation exercises)	93.75 % (30/32)	DOEG: 6.3% (1/16) DOCG: 6.3% (1/16)	EG/CG: Difficulties in arrival to the MS center	No adverse or harmful events during the intervention
Khalil et al. 2018 Jordan	RRMS: 40 EDSS= 3 ± 1.25	EG: 20/16 CG: 20/16	F: 68.75% M: 31.25% 37.38 ± 10.87	18 sessions (3s/w, 6 weeks) Exergame through Wii Fit and Microsoft Kinect sensor allows to	18 sessions (3s/w, 6 weeks) Home-base conventional balance training	80% (32/40)	DOEG: 20% (4/20) DOCG: 20% (4/20)	EG: Lack of family support, lack of outcome expectation, need to travel long distance,	No adverse or harmful events during the intervention

				interact with six VR scenarios				CG: not provided reason, lack of time and motivation	
Lozano-Quilis et al. 2014 Spain	RRMS SPMS EDSS = NR	EG: 6/6 CG: 6/5	F: 58.33% M: 41.67% 44.82± 10	10 sessions (45 standard rehabilitation + 15 min of virtual reality training; 1s/w, 10 weeks) RemoviEMVR system	10 sessions (60 min; 1s/w, 10 weeks) Conventional balance and gait training	91.67% (11/12)	DOEG: 0% (0/6) DOCG: 16.7% (1/6)	NR	No adverse or harmful events during the intervention
Molhemi et al. 2021 Iran	RRMS: 30 SPMS: 9 EDSS: 4.8	EG: 19/19 CG: 20/20	F: 61.54% M: 38.46% 39.2 ± 8.4	18 sessions (35 min; 3s/w for 6 weeks) Exergame with Microsoft Kinect	18 sessions (35 min; 3s/w for 6 weeks) Conventional balance training	82.05% (32/39)	DOEG: 15.8% (3/19) DOCG: 20% (4/20)	EG/CG (During-intervention): Difficulties in arrival to the research center, work schedules problems and transport problems, fall data EG: illness and exacerbation of symptoms	Non adverse event during intervention

								CG: interference of treatment time with patient's work hours and moving to another city	
Molhemi et al. 2022 Iran	RRMS: 27 SPMS: 9 EDSS: 4.8	EG:18/18 CG: 18/18	F: 58.33% M: 41.67% 39.2	18 sessions (35 min; 3s/w for 6 weeks) Exergames with Microsoft Kinect	18 sessions (35 min; 3s/w for 6 weeks) Conventional balance training	86.11% (31/36)	DOEG: % (2/18) DOCG: 22.2% (3/18)	EG: Transport problems and exacerbation symptoms CG: Lack of interest, work schedule and personal issue	NR
Munari et al. 2020 Italy	RRMS: 3 SPMS: 14 EDSS: 5.2	EG: 8/8 CG: 9/7	F: 58.82% M: 41.17% 57 ± 8.04	12 sessions (40 min; 2s/w for 6 weeks): Robot-assisted gait training GE-O system + VR environment	12 sessions (40 min; 2s/w for 6 weeks): Robot-assisted gait training GE-O system	88.23% (15/17)	DOEG: 0% (0/8) DOCG: 22.2% (2/15)	CG: Difficulties in arrival to the study place	No adverse or harmful events during the intervention
Ozkul et al. 2020 Turkey	RRMS EDSS= 1.5	EG: 17/13 G1: 17/13 G2: 17/13	F: 58.33% M: 41.67% 32.3	16 sessions (60 min; 2s/w, 8 weeks) 30 min of Pilates + 10 min of rest + 20 min of immersive virtual	G1: 16 sessions (60 min; 2s/w, 8 weeks) 30 min of Pilates + 10 min of rest + 20	76.4% (26/34)	DOEG: 23.5% (4/17)	EG/CG: Work intensity	No adverse or harmful events during the intervention

				reality (HMD). Two supervised exergames in standing position wearing a harness (Football game and Guillotine game)	min of conventional balance training G2: 16 sessions (15-20 min; 2s/w, 8 weeks) Jacobson's progressive relaxation exercise		DOCG: 23.7% (4/17)		
Peruzzi et al. 2016 Italy	RRMS EDSS= 3.8 ± 0.9	EG: 16/14 CG:15/11	F: 60% M: 40% 42.8 ± 11.1	18 sessions (45 min; 3s/w, 6 weeks): supervised treadmill walking 80% 80% of the subject's overground walking speed. Each week speed increased a 10%. Last week the subject removed one or both hands from the handrails + Virtual tree-lined trail in which obstacles have to be passed (also train memory, attention and planning)	18 sessions (45 min; 3s/w, 6 weeks): supervised treadmill walking 80% of the subject's overground walking speed. Each week speed increased a 10%. Last week the subject removed one or both hands from the handrails	77.41% (24/31)	DOEG: 26.7% (4/15) DOCG: 18.8% (3/16)	EG/CG: Personal issues	No adverse or harmful events during the intervention

Pagliari et al. Italy	EDSS= 4.7	EG: 30/35 CG: 30/35	F: 60% M: 40% 50.28	30 sessions (45 min; 5s/w, 6 weeks) VRRS Khymeia telerehabilitation home-based kit + cognitive training	30 sessions (45 min; 5s/w, 6 weeks) Conventional balance training + cognitive training	85.71% (60/70)	DOEG: 14.28% (5/35) DOCG: 14.28% (5/35)	EG/CG: No compliance to intervention EG: problem with internet connection and unrelated comorbidities CG: personal difficulties, moving to new home and unable to come in for follow -up	NR
Robinson et al. 2015 United Kingdom	Phenotypes NR EDSS = 3.5	EG: 20/20 G1: 18/16 G2: 18/15	F: 67.86% M: 32.14% 52 ± 5.8	8 sessions (40 min; 2s/w, 4 weeks) Exergames with Wii Fit	G1: 8 sessions (40 min; 2s/w, 4 weeks) Conventional balance training G2: no intervention	89.3% (50/56)	DOEG: 0% (0/20) DOG1: 11.1% (2/18) DOG2: 22.2% (4/18)	G2: Suspected MS remission, hospitalization (not related to the study) CG: family-matters	NR
Russo et al. 2018	RRMS EDSS= 5	EG: 30/30 CG: 15/15	F: 57.78%	54 sessions (60 min; 3s/w, 18 weeks)	54 sessions (60 min; 3s/w, 18 weeks)	100% (45/45)	DOEG: 0% (0/30)	--	No adverse or harmful events

Italy			M: 42.22% 42 ± 7	6 weeks of Lokomat-PRO sum to VR (2D) + 12 weeks of conventional balance training	Conventional balance training		DOCG: 0% (0/15)		during the intervention
Tollar et al. 2019 Hungary	RRMS:42 PPMS: 26 EDSS= 5	EG: 14/14 G1: 14/14 G2: 14/14 G3: 14/14 G4: 12/12	F: 90% M: 10% 47	25 sessions (60 min; 1-2 s/w, 5 weeks). High- intensity exergaming training	25 sessions (60 min; 1-2 s/w, 5 weeks). G1: high-intensity balance training G2: Cycling G3: Active proprioceptive neuromuscular facilitation (PNF) G4: Standard care wait-listed control group	97.14% (68/70)	DOEG: 0% (0/14) DOG1: 0% (0/14) DOG2:0% (0/14) DOG3: 0% (0/14) DOG4: 16.7% (2/12)	CG: Disease exacerbation and illness	No adverse or harmful events during the intervention
Yazgan et al. 2020 Turkey	RRMS: 33 SPMS: 2 PPMS: 1 Progressive relapsing: 6	EG: 16/15 G1: 16/12 G2: 15/15	F: 82.61% M: 17.39% 43.73 ± 9.36	16 sessions (60 min; 2s/w, 8 weeks) supervised Nintendo Wii Fit exergames in standing position	G1: 16 sessions (60 min; 2s/w, 8 weeks) Collect Apples, Outline, Paddle War, and Evaluation of Movement games	89.4% (42/47)	DOEG: 6.3% (1/16) DOG1: 25% (4/16)	EG/CG: Personal problems CG: transportation problems	No adverse or harmful events during the intervention

	EDSS= 4.02 ± 1.37				G2: waiting list group		DOG2: 0% (0/15)		

CG: control group; DO: dropout; DOCG: dropouts in control group; DOEG: dropouts in experimental group; DOG2: dropouts in the second comparator group; EDSS: Expanded Disability Status Scale; EG: experimental group; F: female; G1: first control intervention; G2: second control intervention; G3: third control intervention; M: male; min: minutes; MS: multiple sclerosis; n: number of participants; NR: no reported; PPMS: primary-progressive multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis; SD: standard deviation; SPMS: secondary-progressive multiple sclerosis; s/w: sessions per week.

Table 2. Meta-regression analysis				
Predictors	**SE**	**t value**	**95%CI**	**p value**
Type of intervention	0.45	-0.30	-1.09,0.82	0.76
Number of sessions	0.02	1.01	-0.02,0.06	0.33
Duration of sessions	0.15	-1.24	-0.05,0.013	0.23
Frequency of sessions	0.15	0.54	-0.23,0.39	0.59
Weeks of intervention	0.07	0.89	-0.08,0.21	0.38
EDSS score	0.15	-0.42	-0.39,0.26	0.68
RRMS	0.38	0.28	-0.70,0.92	0.78
PPMS	0.52	0.40	-0.91,1.32	0.69
SPMS	0.43	-0.20	-1.01,0.84	0.84
Female gender	0.16	0.02	-0.37,0.03	0.86
Male gender	0.16	0.16	-0.03,0.04	0.87
Age	0.03	0.27	-0.046,0.06	0.79
PEDro score	0.14	1.97	-0.02,0.57	0.07
95%CI: 95% Confidence interval; **PPMS:** primary progressive multiple sclerosis; **RRMS:** remittent-recurrent multiple sclerosis; **SPMS:** secondary progressive multiple sclerosis				

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COVER LETTER

Appendix