


# Rehabilitation training based on virtual reality for patients with Parkinson's disease in improving balance, quality of life, activities of daily living, and depressive symptoms: A systematic review and meta-regression analysis

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## Abstract

**Objective:** To examine the effectiveness of rehabilitation training based on virtual reality in improving balance, quality of life, activities of daily living, and depressive symptoms of patients with Parkinson's disease.

**Data sources:** PubMed, EMBASE, CINAHL, Scopus, Cochrane Library, PsycINFO, ProQuest, Physiotherapy Evidence Database, IEEE Xplore, China National Knowledge Infrastructure, Wanfang, and VIP Information databases were searched from their inception to October 15, 2020. Trial registries, gray literature, and target journals were also searched.

**Methods:** Eligible randomized controlled trials included studies with patients with Parkinson's disease in rehabilitation training based on virtual reality. Comprehensive Meta-Analysis 3.0 software was used. Physiotherapy Evidence Database Scale and the Grading of Recommendation, Assessment, Development, and Evaluation system were used to assess the methodological quality of individual trials and the overall quality of the evidence, respectively.

**Results:** A total of 22 randomized controlled trials with 836 patients were included. Meta-analysis revealed that training significantly improved balance ( $g=0.66$ ,  $P<0.001$ ), quality of life ( $g=0.28$ ,  $P=0.015$ ), activities of daily living ( $g=0.62$ ,  $P<0.001$ ), and depressive symptoms ( $g=0.67$ ,  $P=0.021$ ) compared to the control group. Subgroup analysis indicated that training should utilize video game consoles. Meta-

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regression analyses showed that age, sessions, and frequency of training had statistically significant impacts on balance scores. Quality of individual trials was high and overall evidence ranged from very low to low. **Conclusion:** Virtual rehabilitation training could be adopted in healthcare institutions as supplementary training for patients with Parkinson's disease.

## Keywords

Parkinson's disease, virtual reality, rehabilitation, systematic review, meta-regression

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## Introduction

Parkinson's disease is the second most common neurodegenerative disorder, affecting approximately 0.021% of the world population.<sup>1</sup> The hallmark symptoms include resting tremors, bradykinesia, stiffness, and postural instability,<sup>2</sup> which have a negative impact on balance,<sup>3</sup> quality of life,<sup>4</sup> activities of daily living,<sup>5</sup> and depressive symptoms.<sup>6</sup> Given the progressive nature of the disease, long-term rehabilitation is necessary to optimize functional ability in order to maintain independence, autonomy, and quality of life.<sup>7,8</sup> However, it is difficult for patients to commit to rehabilitate overtime because the modes of traditional delivery are often perceived as boring and not engaging.<sup>9</sup> Hence, sustainability of rehabilitation training among patients with Parkinson's disease is challenging.

Virtual reality technology, which has advanced at an unprecedented pace, has become an innovative mode of rehabilitation training for Parkinson's disease.<sup>10,11</sup> Virtual reality can promote patients' visual, auditory, and tactile input to simultaneously simulate both motor and cognitive processes.<sup>7</sup> Further, virtual reality features make rehabilitation activities fun, motivating, and interactive, thus improving the likelihood of adherence to training.<sup>12</sup> It is also a safe, convenient, and cost-effective form of training for long-term rehabilitation.<sup>13</sup> A growing number of systematic reviews<sup>7,9-11,13</sup> have supported the effectiveness of rehabilitation training based on virtual reality for patients with Parkinson's disease. However, these reviews are restricted to English language trials,<sup>7,13</sup> few databases,<sup>7,11,13</sup> limited number of trials,<sup>7,11</sup> mixed populations,<sup>9</sup> and narrative synthesis.<sup>13</sup> None of them used meta-regression analysis to examine the effect of covariates on the effect size of trials.

Although some trials in the previous reviews had small sample sizes, none of them adopted Hedges' *g* statistic to measure effect size. Hence, this review aims to synthesize evidence for the effectiveness of rehabilitation training based on virtual reality in improving balance, quality of life, activities of daily living, and depressive symptoms of patients with Parkinson's disease.

## Methods

This systematic review and meta-analysis followed the preferred reporting items for systematic reviews and meta-analysis guidelines.<sup>14</sup> The preferred reporting items for systematic reviews and meta-analysis checklist is presented as Supplemental Material (Table S1). The systematic review protocol was registered in the PROSPERO database at the Centre of Reviews and Dissemination in the United Kingdom with the registration number CRD42020151026.

The Cochrane Database of Systematic Reviews, PubMed Clinical Queries, PROSPERO, and Joanna Briggs Institute were searched for published and ongoing reviews to prevent duplication. A three-step extensive electronic literature search strategy was performed with the assistance of a senior librarian in accordance with the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions.<sup>15</sup> First, the databases of PubMed, EMBASE, CINAHL, Scopus, Cochrane Library, PsycINFO, ProQuest, Physiotherapy Evidence Database, IEEE Xplore, China National Knowledge Infrastructure (a Chinese integrated knowledge resource database), Wanfang (a Chinese medicine premier), and VIP Information (a Chinese scientific journal database) were searched from

**Table 1.** Selection criteria for systematic review.

Criteria	Inclusion criteria	Exclusion criteria
Population	Patient above 18 years old with stage 1 – 4 of Parkinson's disease according to Hoehn and Yahr scales	Any type of dementia, cognitive deficit, or disability
Intervention	Virtual reality-enhanced rehabilitation interventions (use some devices to generate realistic images, sounds, and other sensations that simulate a user's physical presence in a virtual environment and interact with virtual features or items) delivered through one of the following platforms: computers, video, phone, apps, virtual reality devices, etc.	Interventions without virtual reality-enhanced rehabilitation elements
Control	Usual care or exercise therapy	Other rehabilitation interventions
Outcomes	Balance Quality of life Activities of daily living Depressive symptoms	
Type of design	Any type of randomized controlled trials	Non-experimental study, qualitative, reviews, and ongoing studies
Years of publication	No limit	
Publication type	Published primary research titles Unpublished theses	Abstract only Book chapters review Letters Editorials Conference proceedings Other languages
Language	English and Chinese	

their inception to October 15, 2020. The search terms used are included in Supplemental Material (Table S2). Second, unpublished trials from various clinical trial registries were searched. Third, the reference lists of selected trials, gray literature (GreySource and Google Scholar), and target journals were searched manually to maximize the search results. Two reviewers (RZL and YRZ) independently screened the studies on the basis of their titles, abstracts, and full text against the inclusion and exclusion criteria described in Table 1. Any disagreements were resolved by discussion among RZL, YRZ, and YL.

The target population comprised patients above 18 years of age with Stages 1–4 Parkinson's disease assessed using the Hoehn and Yahr scale.<sup>16</sup> The intervention was virtual rehabilitation training that involved interactive sensory stimulation in a virtual environment to promote the recovery of motor functions and activities of daily living. The training was delivered via an individual or group

approach on one of the following devices: computer, video game console, phone, and virtual reality devices. Comparators were usual care, waitlist, or exercise therapy. The outcomes were balance, quality of life, activities of daily living, and depressive symptoms. All types of randomized controlled trials in English and Chinese were included. Publication year was not restricted, and both published and unpublished randomized controlled trials were included to maximize the search. The details are described in Table 1.

A standardized data extraction form based on the Cochrane Handbook for Systematic Reviews of Interventions was developed by RZL.<sup>15</sup> The items included author, year, country, setting, design, mean age, sample size, intervention, control, outcomes, attrition rate, intention-to-treat analysis, missing data management, published protocol, trial registration, and grant support. Training description included the device model, brand, content of training, supportive system (self-help/provider), co-intervention, training

regime (length, session, frequency, and duration), and follow-up assessment. The authors of relevant trials were contacted to retrieve additional information and seek clarification.

The methodological quality of all selected randomized controlled trials was evaluated using the Physiotherapy Evidence Database scale.<sup>17</sup> Each trial is graded on the scale from 0 to 10 based on 11 criteria and the first criterion is not included in the final score. The scale takes into consideration internal validity and sufficiency of the statistical information.<sup>17</sup> Each criterion has a simple yes (1 point) or no (0 point) answer. The scores on all criteria are added, and a score of 6 or above is considered to indicate high methodological quality.<sup>17</sup> Two raters (YL and DA) independently conducted quality assessments, and inter-rater reliabilities of each item of the Physiotherapy Evidence Database scale were calculated using Cohen's  $\kappa$ . In addition, the attrition rate, intention-to-treat, missing data management, trial protocol publication, and registration of clinical trials were investigated in the quality assessment of the evidence.

The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) criteria were used to examine the overall strength of the evidence using GRADEpro 3.6 software.<sup>18</sup> The quality of the evidence was rated as high, moderate, low, and very low on the basis of five criteria of the evidence, namely, risk of bias, inconsistency, indirectness, imprecision, and publication bias. The overall certainty of the evidence was downgraded when sufficient justification for the decision was confirmed. Publication bias was tested if the review included 10 or more trials,<sup>19</sup> using Egger test<sup>20</sup> and funnel plot of precision based on Hedges'  $g$ .

Comprehensive Meta-Analysis software (Version 3)<sup>21</sup> was used to conduct meta-analyses and meta-regression. The random-effects model was adopted because it accounts for the statistical assumption of variation in the estimation of means across all trials.<sup>22</sup> The overall effect was assessed using the  $z$ -statistic at  $P < 0.05$ . Effect sizes were calculated using Hedges'  $g$  because it provides an accurate estimation for small sample sizes.<sup>23</sup> Effect size was interpreted as small (0.2), medium (0.5), large (0.8), and very large (1.2).<sup>24</sup> The inverse-variance statistical method was utilized

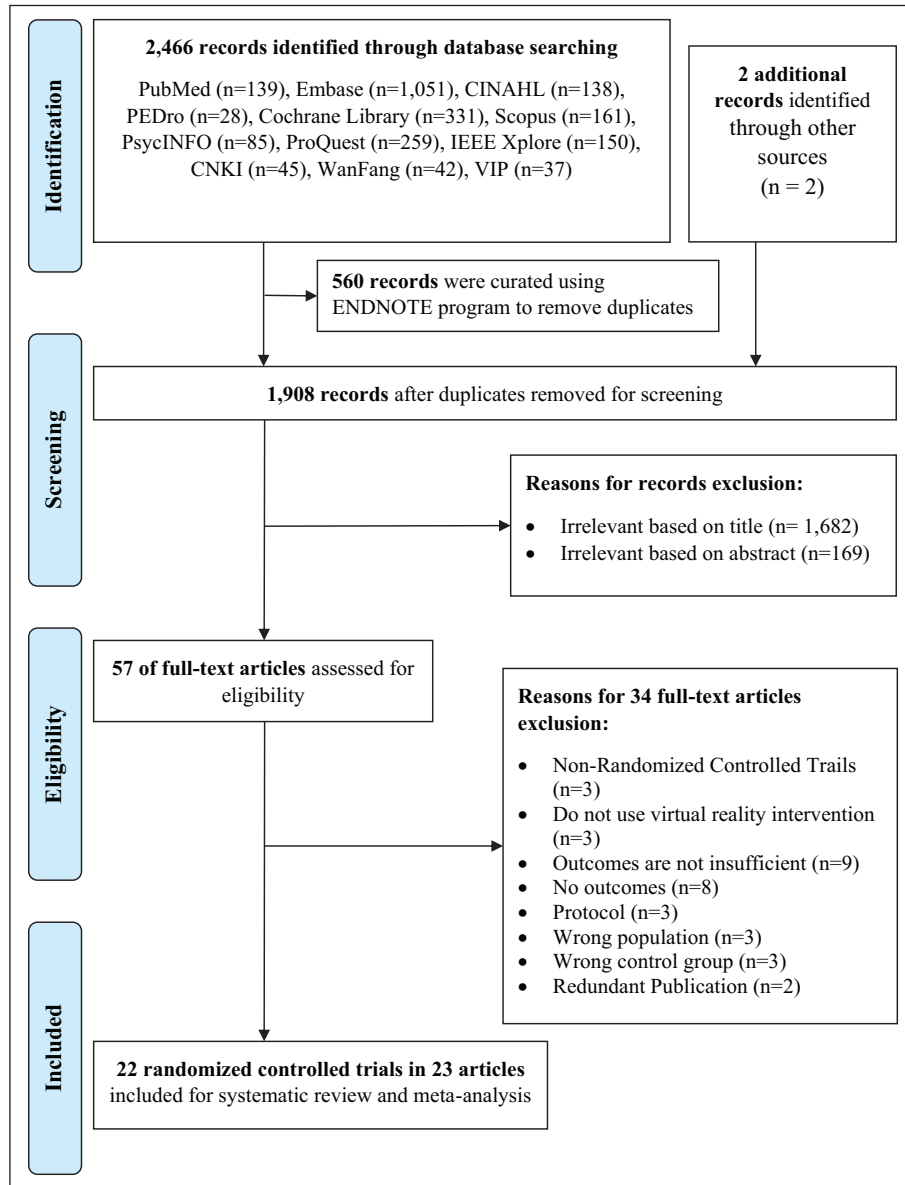
to analyze continuous outcomes.<sup>15</sup> Statistical heterogeneity was evaluated using Cochran's  $Q$  statistic ( $\chi^2$ ), and  $P < 0.10$  was regarded as indicating significant heterogeneity.<sup>15</sup> Heterogeneity was assessed using the  $I^2$  statistic. The estimates of the degree of heterogeneity that were obtained using overlapping intervals for  $I^2$  were interpreted as unimportant (0%–40%), moderate (30%–60%), substantial (50%–90%), and considerable (75%–100%).<sup>15</sup>

Sensitivity analyses were performed to identify heterogeneous trials that were removed to maintain overall homogeneity. Subgroup analyses were conducted to reduce overall heterogeneity across studies ( $I^2 > 40\%$ ). Predefined subgroups included different regions (Asian vs non-Asian), settings (community vs hospital), and devices (video game console vs generic). Univariate and multivariate random-effects meta-regression analyses were used to examine whether any of the following covariates were associated with intervention effectiveness: publication year, mean age of patients, sample size and training regime including length, session, and frequency and duration of intervention. A significance level of  $P < 0.05$  was adopted for random-effects meta-regression analysis.

## Results

Figure 1 illustrates a preferred reporting items for systematic reviews and meta-analysis flow diagram depicting the study selection process. A total of 2468 records were identified. Finally, 22 randomized controlled trials reported by 23 articles<sup>3–6,25–43</sup> were selected for our meta-analysis.

Table 2 summarizes the characteristics of the included trials from 2012 to 2020, comprising 836 participants from Australia, Brazil, China, Italy, Korea, Hungary, and the Netherlands. Four trials had a three-armed design, and the rest had a two-armed design. Sample sizes ranged from 20 to 83. The protocol for only 1 trial was published, and 12 trials were registered in various clinical trial registries. Attrition rate ranged from 0% to 29.55%. Three trials used intention-to-treat analysis and missing data management. Physiotherapy Evidence Database scale scores ranged from 6 to 9 (mean = 7.14, standard deviation = 0.83), indicating



**Figure 1.** Flow chart of the article inclusion process.

high methodological quality of the 22 selected trials (Physiotherapy Evidence Database, 1999). Cohen's  $\kappa$  was 0.88 between the two raters, suggesting an acceptable inter-rater agreement. Physiotherapy Evidence Database item scores and total score for all selected trials are presented in Supplemental Material (Table S3).

A detailed description of the rehabilitation training is shown in Supplemental Material (Table S3). Training platforms involved the use of Nintendo Wii™, Microsoft Xbox 360™ Kinect, tablets, and computers. Contents included 2–10 interactive virtual reality exergames for various rehabilitation trainings. One trial had a co-intervention

**Table 2.** Characteristics of the selected 22 randomized controlled trials.

Authors (year) <sup>Ref</sup>	Country/ setting	Design	Stage* of PD	Age (M ± SD)	Intervention	Control	Sample size	Outcomes (measures)	Attrit (%)	ITT/ MDA	PP/Reg/ GS	PEDro score
Allen et al. (2017) <sup>4</sup>	Australia/ Com	2-arm RCT	NR	I: 67.5 ± 7.3 C: 68.4 ± 8.5	VR exergames training	Usual care	I: 19 C: 19	QoL (PDQ-39)	10.53	Y/Y	N/Y/Y	8/10
Chen et al. (2017) <sup>25</sup>	China/Hosp	2-arm RCT	2-3	I: 62.09 ± 6.11 C: 64.65 ± 5.06	VR balance training	Usual care	I: 23 C: 23	Balance (BBS) DS (HAMDI)	0	N/N	N/N/N	6/10
Feng et al. (2019) <sup>26</sup>	China/Hosp	2-arm RCT	2.5-4	I: 67.47 ± 4.79 C: 66.93 ± 4.64	VR games balance training	Usual care	I: 14 C: 14	Balance (BBS)	0	N/N	N/N/N	7/10
Ferraz et al. (2018) <sup>27</sup>	Brazil/Com	3-arm RCT	2-3	I: 67 ± 1.48 C: 70.67 ± 6.67	VR exergames training	Usual care	I: 22 C: 25	QoL (PDQ-39) DS (GDS-15)	10.64	N/N	N/Y/N	8/10
Gandolfi et al. (2017) <sup>3</sup>	Italy/Com	2-arm RCT	2.5-3	I: 67.45 ± 7.18 C: 69.84 ± 9.41	VR balance training	Usual care	I: 38 C: 38	Balance (BBS)	7.89	N/N	N/N/Y	7/10
Lee et al. (2015) <sup>5</sup>	Korea/Hosp	2-arm RCT	NR	I: 68.4 ± 2.9	VR dance games exercise	Usual care	I: 10	Balance (BBS) ADL (MBI)	0	N/N	N/N/N	6/10
Liao et al. (2015a, 2015b) <sup>28,29</sup>	Taiwan/Hosp	3-arm RCT	1-3	C: 70.1 ± 3.3 I: 67.3 ± 7.1	VR balance therapy	Usual care	C: 10 I: 12	DS (BDI) QoL (PDQ-39)	0	N/N	N/N/N	8/10
Lin et al. (2016) <sup>30</sup>	China/Hosp	2-arm RCT	2.5-4	C: 65.1 ± 6.7 I: 61.4 ± 8.2	VR exergaming balance training	Usual care	I: 18 C: 15	DS (HADS) Balance (BBS)	6.06	N/N	N/N/N	7/10
Liu et al. (2020) <sup>31</sup>	China/Hosp	2-arm RCT	3	C: 62.1 ± 6.3 I: 60.90 ± 7.20	VR exergaming balance training	Usual care	I: 21 C: 21	ADL (MBI) Balance (BBS)	0	N/N	N/Y/Y	6/10
Maggio et al. (2018) <sup>6</sup>	Italy/Hosp	2-arm RCT	1-3	C: 63.90 ± 5.82 T: 69.4 ± 8.2 I: 69.9 ± 6.3	VR cognitive training	Usual care	I: 10	ADL (MBI) DS (GDS-15)	0	N/N	N/N/N	8/10
Pazzaglia et al. (2020) <sup>32</sup>	Italy/Hosp	2-arm RCT	NR	C: 68.9 ± 10.05 I: 72 ± 7	VR exergaming balance training	Usual Care	C: 10 I: 25	Balance (BBS)	0	N/N	N/N/Y	7/10
Pedreira et al. (2013) <sup>33</sup>	Brazil/Com	2-arm RCT	1-3	C: 70 ± 10 I: 61.1 ± 8.2	VR exergames training	Usual care	I: 22 C: 22	QoL (PDQ-39)	29.55	N/N	N/Y/Y	9/10
Pompeu et al. (2012) <sup>34</sup>	Brazil/Com	2-arm RCT	1-2	C: 66.2 ± 8.5 T: 67.4 ± 8.1 I: 68.6 ± 8.0 C: 66.2 ± 8.3	VR global and balance exercises	Usual care	I: 16 C: 16	Balance (BBS) ADL (UPDRS-II)	0	N/N	N/Y/Y	8/10

(Continued)

**Table 2. (Continued)**

Authors (year) <sup>Ref</sup>	Country/ setting	Design	Stage* of PD	Age (M ± SD)	Intervention	Control	Sample size	Outcomes (measures)	Attrit (%)	ITT/ MDA	PP/Reg/ GS	PEdPro score
Qin et al. (2019) <sup>35</sup>	China/Hosp	2-arm RCT	2–3	I: 65.9 ± 4.9 C: 66.1 ± 6.2	VR exergames balance training	Usual care	I: 43 C: 40	Balance (BBS)	4.82	N/N	N/N/N	6/10
Ribas et al. (2017) <sup>36</sup>	Brazil/Com	2-arm RCT	1–3	I: 61.70 ± 6.83 C: 60.20 ± 11.29	VR exergames intervention	Usual care	I: 10 C: 10	QoL (PDQ-39) Balance (BBS)	0	N/N	N/Y/N	7/10
Santos et al. (2019) <sup>37</sup>	Brazil/Hosp	3-arm RCT	1–3	I: 66.6 ± 8.2 C: 64.5 ± 9.8	VR balance training	Usual care	I: 15 C: 15	Balance (BBS) QoL (PDQ-39)	6.67	N/N	N/Y/N	7/10
Shih et al. (2016) <sup>38</sup>	Taiwan/Com	2-arm RCT	1–3	I: 67.5 ± 9.96 C: 68.8 ± 9.67	VR exergaming programs training	Usual care	I: 11 C: 11	Balance (BBS)	9.09	N/N	N/Y/Y	7/10
Tollár et al. (2018) <sup>39</sup>	Hungary/ Hosp	2-arm RCT	NR	I: 67.3 ± 3.4 C: 67.6 ± 4.1	VR exergames training	Usual care	I: 35 C: 20	QoL (PDQ-39) ADL (SE-ADL)	0	N/N	N/N/N	7/10
Tollár et al. (2019) <sup>40</sup>	Hungary/ Hosp	3-arm RCT	2–3	I: 67.6 ± 3.26 C: 67.6 ± 4.08	VR balance training	Usual care	I: 19 C: 20	QoL (PDQ-39) DS (BDI)	0	N/N	N/Y/Y	7/10
van den Heuvel et al. (2014) <sup>41</sup>	Netherlands/ Com	2-arm RCT	2–3	I: 66.3 ± 6.39 C: 68.8 ± 9.68	VR balance training	Usual care	I: 17 C: 16	QoL (PDQ-39) Balance (BBS)	3.03	Y/Y	Y/Y/Y	8/10
Xia et al. (2020) <sup>42</sup>	China/Hosp	2-arm RCT	NR	I: 65.99 ± 4.30 C: 66.00 ± 8.55	VR balance training	Usual care	I: 15 C: 15	Balance (BBS)	14.29	N/N	N/Y/Y	6/10
Yang et al. (2016) <sup>43</sup>	Taiwan/Com	2-arm RCT	2–3	I: 72.5 ± 8.4 C: 75.4 ± 6.3	VR balance board therapy	Usual care	I: 11 C: 12	QoL (PDQ-39) Balance (BBS)	13.04	Y/Y	N/Y/Y	7/10

ADL: activities of daily living; Attrit: attrition rate; BBS: Berg balance scale; BDI: beck depression inventory; C: control; Com: community; DS: depressive symptom; GDS-15: 15-item geriatric depression scale; GS: grant support; HADS: hospital anxiety and depression scale; HAMD: Hamilton depression scale; Hosp: hospital; I: intervention; ITT: intention-to-treat analysis; M: mean; MBI: modified barthel index; MDA: missing data analysis; N: no; NR: not report; PEdPro: physiotherapy evidence database scale; PD: Parkinson's disease; PDQ-39: 39-item Parkinson's disease questionnaire; PP: published protocol; QoL: quality of life; RCT: randomized controlled trial; Reg: registration in clinical trial registry; SD: standard deviation; \*Stage: according to Hoehn and Yahr stage; T: total; UPDRS: the unified Parkinson disease rating scale; VR: virtual reality; Y: yes.

for neurodevelopment treatment and functional electrical stimulations. The majority of the trials were supported by health care providers, and only one trial used the self-help approach. The number of sessions ranged from 10 to 60, and the study duration ranged from 3 to 12 weeks. The follow-up assessment included seven trials.

In 15 trials,<sup>3,5,25,26,30–32,34–38,41–43</sup> balance scores were used as the outcome variable to assess the balance of 551 participants. As shown in Figure 2(a), the meta-analysis performed using the random-effects model revealed that the scores in the intervention groups significantly improved ( $Z=4.41$ ,  $P<0.001$ ) with a medium effect of 0.66. Considering that  $I^2$  was 64.3% and had a  $P$  value of  $\chi^2 < 0.1$ , we conducted a sensitivity analysis to analyze the influence of individual trials by removing included trials individually and identified one heterogeneous trial<sup>25</sup> that utilized a different device. After excluding this trial,<sup>25</sup> the  $I^2$  changed to 24.5% and had a  $P$  value of  $\chi^2 > 0.1$ .

As shown in Table 3, a series of subgroup analyses was conducted on the basis of region, setting, and device for balance scores. We observed that training was more effective using video game console ( $g=0.73$ ,  $P<0.001$ ) than generic devices ( $g=0.37$ ,  $P=0.24$ ) in terms of balance scores. However, no significant subgroup differences ( $P=0.17–0.31$ ) were detected. Univariate and multivariate random-effects meta-regression analyses were performed to examine the impacts of covariates on the effect size of balance scores (Table 4). Covariates that had statistically significant effect on balance scores included frequency of training ( $\beta=-0.47$ ,  $P=0.022$ ) and number of sessions ( $\beta=0.02$ ,  $P=0.042$ ) in univariate random-effect regression analyses. Patients' age was a significant covariate ( $\beta=-0.10$  to  $-0.08$ ,  $P=0.010–0.047$ ) on balance scores in both univariate and multivariate regression analyses. The  $Q$ -value for the multivariate random-effect regression model was 39.20, with  $df=14$  and  $P<0.001$ . Thus, the null hypothesis was rejected, and the effect size was related to the covariate. The explained variance ( $R^2=0.4993$ ) was calculated using the regression model, and it revealed that 49.93% of the variance in true effects could be explained by these covariates. These

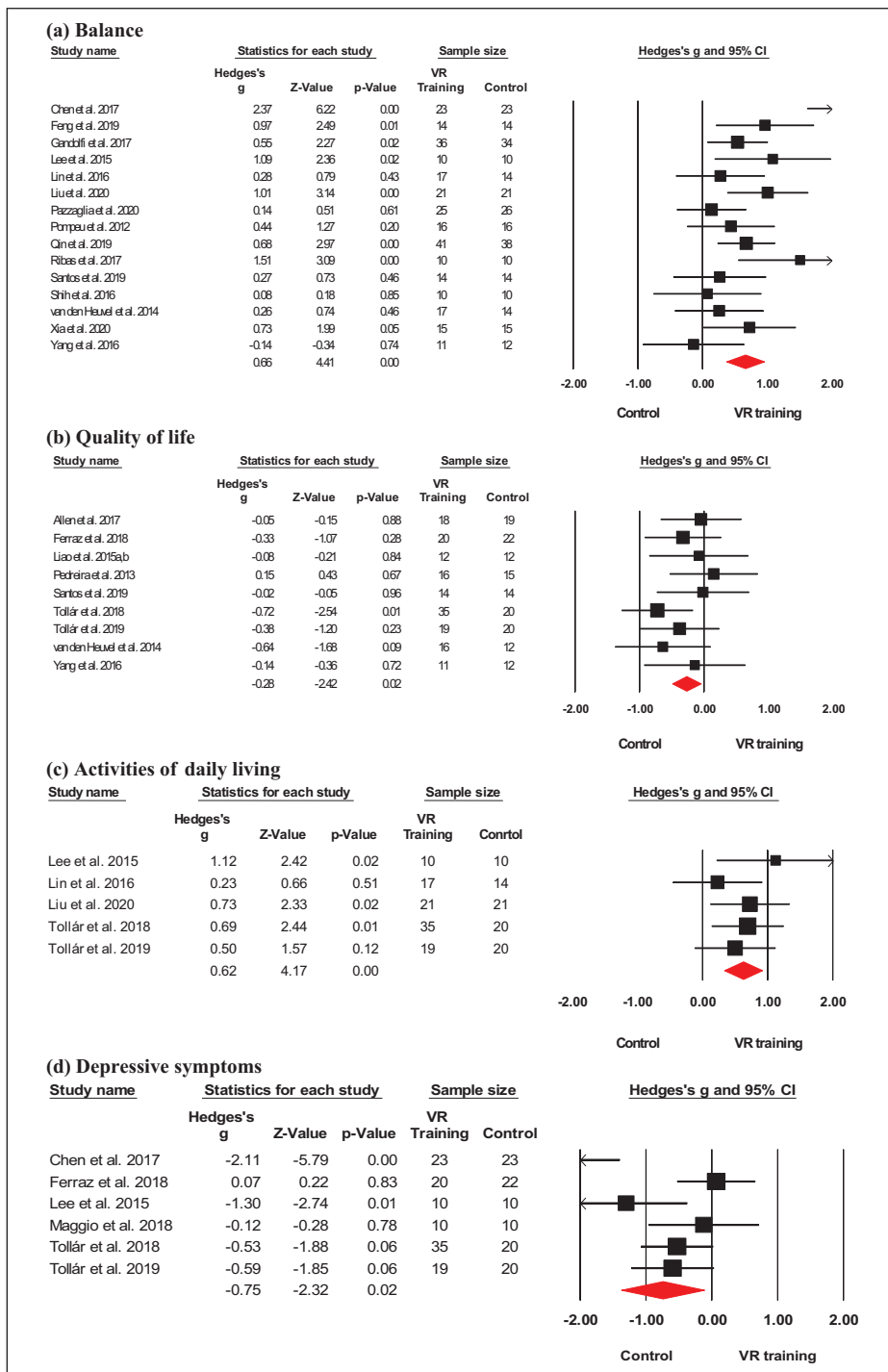
results indicated that rehabilitation training based on virtual reality using long sessions and high intensity was effective in improving balance amongst younger patients. However, we found that publication year, sample size, and duration and length of training had no significant impact on balance scores ( $P>0.05$ ).

Figure 2(b) to (d) revealed significant improvements in quality of life scores in 9 randomized controlled trials<sup>4,27,28,33,37,39–41,43</sup> among 307 patients with a small effect size ( $g=-0.28$ ,  $P=0.02$ ,  $I^2=0\%$ ), activities of daily living scores in five randomized controlled trials<sup>5,30,31,39,40</sup> among 187 patients with a medium effect size ( $g=0.62$ ,  $P<0.001$ ,  $I^2=0\%$ ), and depressive symptom scores in six randomized controlled trials<sup>5,6,25,27,39,40</sup> among 222 patients with a medium effect size ( $g=0.75$ ,  $P=0.02$ ,  $I^2=80.2\%$ ) in rehabilitation training based on virtual reality compared to those in control group. Considering the substantial heterogeneity for depressive symptoms, we performed a sensitivity analysis. After removing two heterogeneous trials that used a different device<sup>25</sup> and were conducted in a different setting,<sup>27</sup>  $I^2$  decreased to 13.7% and had a  $P$  value of  $\chi^2 > 0.1$ .

The overall quality of the evidence among the outcomes of the randomized controlled trials was rated as very low to low in accordance with the Grading of recommendations, assessment, development, and evaluation criteria presented in Supplemental Material (Table S4). Risk of bias was downgraded, as allocation concealment and reporting bias were unclear for a majority of the trials. Imprecision was downgraded because of small size with wide confidence intervals in the selected randomized controlled trials. Publication bias was not detected for randomized controlled trials that reported balance scores, as observed from the symmetrical distribution of the included trials on a funnel plot (Supplemental Material: Figure S1). The  $P$  value of Egger's regression asymmetry test was 0.232, suggesting no evidence of publication bias.

## Discussion

The present review revealed significant improvements in the balance, quality of life, activities of



**Figure 2.** Forest plot of effect size for (a) balance, (b) quality of life, (c) activity of daily living, and (d) depressive symptoms for rehabilitation training based on virtual reality and control group.

**Table 3.** Subgroup analyses of effect size of rehabilitation trainings based on virtual reality on balance scores.

Design	No. of trials <sup>Ref</sup>	Sample size	Hedges' g (95%CI)	Overall effect (P value)	Subgroup differences (P value)	
Region	Asian	9 <sup>5,25,26,30,31,35,38,42,43</sup>	319	0.79 (0.34, 1.23)	Z= 3.48 (P< 0.01**)	Q= 1.56 (P=0.21)
	Non-Asian country	6 <sup>3,32,34,36,37,41</sup>	232	0.45 (0.14, 0.75)	Z= 2.89 (P< 0.01**)	
Setting	Community based	6 <sup>3,34,36,38,41,43</sup>	196	0.42 (0.06, 0.79)	Z= 2.26 (P=0.02*)	Q= 1.92 (P=0.17)
	Hospital based	9 <sup>5,25,26,30-32,35,37,42</sup>	355	0.81 (0.40, 1.23)	Z= 3.85 (P< 0.01**)	
Device	Video game console	12 <sup>3,5,25,30-32,34-38,42</sup>	469	0.73 (0.40, 1.07)	Z= 4.28 (P< 0.01**)	Q= 1.04 (P=0.31)
	Generic	3 <sup>26,41,43</sup>	82	0.37 (-0.25, 0.98)	Z= 1.17 (P=0.24)	

Hedges's g: effect size; CI: confidence interval; Q: Cochran's Q statistic; Z: z-statistics.

\*P < 0.1. \*\*P < 0.01.

**Table 4.** Random-effects univariate and multivariate meta-regression analyses of covariates on balance scores.

Covariates	Univariate meta-regression						Multivariate meta-regression					
	$\beta$	SE	95% lower	95% upper	Z-value	P value	$\beta$	SE	95% lower	95% upper	Z-value	P value
Mean age of patient	-0.10	0.04	-0.18	-0.02	-2.58	<b>0.010*</b>	-0.08	0.04	-0.17	-0.00	-1.99	<b>0.047*</b>
Number of sessions	0.02	0.01	<0.001	0.05	2.03	<b>0.042*</b>	0.02	0.01	-0.01	0.04	1.18	0.239
Frequency of training (times per week)	0.23	0.10	0.03	0.43	2.27	<b>0.023*</b>	0.05	0.13	-0.21	0.31	0.37	0.710
Sample size (n)	<0.001	0.01	-0.01	0.02	0.29	0.774	—	—	—	—	—	—
Length of training (minutes)	<0.001	0.01	-0.02	0.02	0.04	0.970	—	—	—	—	—	—
Year of randomized controlled trials	0.05	0.04	-0.03	0.14	1.17	0.242	—	—	—	—	—	—
Duration of training (week)	0.05	0.07	-0.08	0.18	0.72	0.474	—	—	—	—	—	—

$\beta$ : coefficient; SE: standard error.

\*P < 0.05.

daily living, and depressive symptoms of patients with Parkinson's disease after rehabilitation training based on virtual reality. Subgroup analysis indicated that training should consider the use of video game console in future design. Random-effects meta-regression revealed that younger patients with long and intense sessions showed significant improvements in balance. Our systematic review demonstrated good scientific evidence of selected randomized controlled trials according to

the Physiotherapy Evidence Database scale. However, the majority of randomized controlled trials did not blind the patients or therapists, which may be related to the nature of training because concealing training condition was not possible.

A majority of the selected trials had an unclear risk of selection because allocation concealment<sup>15</sup> was not mentioned in the trials. Considering that allocation concealment aims to prevent exaggerated estimated training effects, future trials should report

the concealment of allocation sequences.<sup>15</sup> A few trials in both clinical registries and published protocols did not provide predefined outcomes and such reporting bias that may reduce the credibility of results.<sup>15</sup> A few trials used intention-to-treat analysis or missing data management that may disrupt prognostic balance among treatment allocation groups and overestimate the treatment effects.<sup>44</sup> In accordance with the Grading of Recommendations, Assessment, Development, and Evaluation criteria, the overall quality of evidence across four outcomes ranged from low to moderate due to small sample sizes and wide confidence intervals, possibly lowering the statistical power for the selection of the true effect.<sup>45</sup>

Our meta-analysis showed that rehabilitation training based on virtual reality could significantly improve the balance function of patients with Parkinson's disease. This finding is in line with that of recent reviews.<sup>7,10,11</sup> One possible reason for this finding is that training based on virtual reality can promote sensory input, central integration, and information coordination, and such enhancements are linked to subsequent improvements in muscle control and coordination.<sup>8,46</sup> The integration of virtual reality in rehabilitation training has positive effects on both static and dynamic balance function.<sup>36</sup> Furthermore, training can be set to multiple difficulty levels such that patients can receive the most appropriate intensity of training.<sup>35</sup> Another possible reason is that this type of training has the characteristics of immersion, interaction, and imagination that play an important role in improving the vestibular and visual perception<sup>47</sup> of the patients, and consequently in improved balance function of the patients.

Subgroup analysis suggested that training should use video game consoles. Video game consoles are especially designed for virtual reality that can provide authentic and motivational feedback such as bonuses, music, and encouraging commentaries that can facilitate training<sup>47</sup> by providing feedback on their performance, enabling individualized repetitive practice of motor functions, and opportunities to learn new motor activities.<sup>7</sup> Random effects meta-regression revealed that rehabilitation training was more effective in younger patients than in older patients. This may be

linked to the progressive degeneration in power, endurance, and muscle strength in the aging process, which could result in balance difficulties.<sup>9</sup> Another possibility is that older patients may have memory and familiarity issues with learning new technology.<sup>7,47</sup> Nevertheless, high intensity long sessions can provide enough effect of training to patients with Parkinson's disease.<sup>8,36</sup> Such repetitive and intense training in motivating environments allows patients to get used to similar tasks over a long period of time in order to regain their balance function.<sup>47,48</sup>

Similar to a previous review,<sup>10</sup> this study found that rehabilitation training based on virtual reality had beneficial effects on improving activities of daily living of persons with Parkinson's disease. Virtual reality based training can provide a virtual environment that is similar to the real world, allowing patients to practice skills by simulating real daily life activities in a virtual environment.<sup>7,8,36</sup> Virtual reality provides greater potential for transfer to functional activities of daily living.<sup>8,36</sup> As a sense of control, challenges, and success are essential features of virtual reality training, patients may receive visual, auditory, and tactile feedback that can help them establish normal motor patterns and recapture functioning in their daily life.<sup>8,36</sup>

In line with previous reviews,<sup>7,10,11</sup> our study revealed that rehabilitation training based on virtual reality facilitated enhancing the quality of life of patients. In simulating real activities, virtual reality allows the brain to perceive physical movements, thereby improving neuroplasticity in the deficient areas of the brain, and enhancing motor functioning.<sup>49</sup> When patients with Parkinson's disease experience a significant increase in motor function during the training period, it can improve their perceived quality of life.<sup>8</sup> Notably, our meta-analysis adds to the literature by demonstrating that rehabilitation training based on virtual reality causes significant improvements in depressive symptoms. This could be explained by the possibility that integrating virtual reality into rehabilitation training provides an enjoyable experience in terms of a high level of motivation and immersion that have a positive impact on patients' emotional well-being.<sup>30,46</sup> Another possibility is that being in rehabilitation training with peers may improve social interaction,

decrease loneliness, enhance a sense of accomplishment, and mitigate depressive symptoms.<sup>9</sup>

Our study has several strengths. First, it strictly adhered to the PRISMA statement, and our review protocol was registered. Second, a three-step search strategy was adopted for 12 databases, trial registries, reference lists, specialized journals, and gray literature. Only the randomized controlled trial design was selected because of its credibility. We used Hedges' *g* to provide an accurate estimation of the overall effect size when the included trials had small sample sizes. We adopted a random-effects meta-regression model to examine the effect of covariates on the effect size of trials. Additionally, we used the Grading of recommendations, assessment, development, and evaluation criteria to examine the outcomes' evidence grade. Finally, both English and Chinese articles were selected to improve the comprehensiveness of the evidence.

However, our study also has certain limitations. First, the small sample size in all the selected trials might have caused small effects. Second, given that most included trials were conducted in Asian countries, the generalizability of the results might be restricted. Third, given that the overall evidence ranged from very low to low, the internal validity of the findings might be diminished. Fourth, some selected trials did not provide comprehensive intervention descriptions. Fifth, none of the selected randomized controlled trials reported the adverse effects or economic outcomes of training. Lastly, ecological fallacy and/or Simpson's paradox (there is no *a priori* reason to expect that the results of group-level analyses and individual participant data analyses should be similar in either magnitude or direction) might have affected the results.<sup>50</sup>

To ensure robustness, future trials should disclose information regarding allocation concealment, and register and publish research protocols in order to facilitate proper research implementation and reporting. intention-to-treat analysis and missing data management should be used in future randomized controlled trials. Further, larger trials are needed to strengthen evidence. Future studies should also investigate the safety issues and cost-effectiveness of training. Finally, upcoming research can evaluate the long-term impact of reha-

bilitation training based on virtual reality to confirm its sustainability.

### Clinical messages

- Rehabilitation training based on virtual reality may be considered a potential solution for patients with Parkinson's disease.
- Balance, quality of life, activities of daily living, and depression symptoms improved significantly after training.
- Training is favorable to young patients with long and intense sessions in improving balance function.

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### Author contributions

RZL was involved in generating search strategies and performing the literature search, screening articles, extracting and analyzing data, and writing the manuscript. YL was involved in developing the research question, planning the search, guiding the article screening and selection process, providing help in the interpretation of data, and revising the manuscript. YRZ was involved in the article screening and selection process. MYW was involved in the Chinese literature search and screening. YXJ was involved in the article investigation. WHDA was involved in writing, quality appraisal, editing, and submission of the manuscript. All authors approved of the last version of manuscript.

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## Supplemental material

Supplemental material for this article is available online.

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