

The Effectiveness of Virtual Reality for Rehabilitation of Parkinson Disease: An Overview of Systematic Reviews and Meta-Analyses

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Abstract

Background: An increasing number of systematic reviews (SRs) and meta-analyses (MAs) of clinical trials have begun to investigate the effects of virtual reality (VR) in patients with Parkinson disease (PD). The aim of this overview was to systematically summarize the current best evidence for the effectiveness of VR therapy for the rehabilitation of people with PD.

Methods: We searched SRs/MAs based on randomized controlled trials (RCTs) for relevant literature in PubMed, Embase and Cochrane library databases from inception to December 5, 2020. The methodological quality of included SRs/MAs was evaluated with the Assessing the Methodological Quality of Systematic Reviews 2 (AMSTAR-2), and the evidence quality of outcome measures with the Grading of Recommendations, Assessment, Development and Evaluation (GRADE).

Results: A total of nine SRs/MAs were included. The evaluation with AMSTAR-2 showed that all included SRs/MAs but one were rated as low or critically low quality studies. The GRADE criteria revealed 19 studies with very-low-quality evidences, 20 with low-quality evidences, 8 with moderate-quality evidences, and 1 with high-quality evidence. Effectiveness evaluation showed that VR therapy had greater improvement of stride length compared with control groups. However, there were inconsistent results (better or similar effects) regarding to gait speed, gait ability, balance, global motor function, activities of daily living, quality of life, postural control, cognitive function, and neuropsychiatric symptoms.

Conclusions: VR therapy appears to be a promising and effective treatment for PD, but there is still a lack of high-quality evidence. In the future, rigorous-designed, high-quality RCTs with larger sample sizes are needed to further verify the effectiveness of VR therapy in the treatment of PD.

Background

Parkinson disease (PD) is the most common progressive neurodegenerative disease worldwide. PD prevalence is increasing with age and PD affects 1% of the population above 60 years[1]. It is estimated that by around 2030, the number of PD patients in China will reach 5 million, accounting for about 50% of the total number of PD patients in the world[2]. PD is characterized by motor symptoms such as rest tremor, bradykinesia, rigidity and postural instability, which affect gait, balance and movement quality, leading to difficulty in performing basic daily activities and quality of life and placing a heavy burden on families and society[3]. Multidisciplinary input is increasingly recognized as important in the treatment and management of PD[4]. Currently, drugs and surgical approaches were main treatments of PD. Clinically approved drug treatments for PD mainly include levodopa, dopaminergic receptor agonists, and monoamine oxidase-B inhibitors. Levodopa is considered as “first line” drug, but the long-term use of it leads to many complications[5]. Deep brain stimulation may be an effective treatment in PD patients; however, clinical trials have shown that it may have cognitive and psychiatric side effects[6]. Rehabilitation treatment is considered as an adjuvant to pharmacological and surgical treatments for PD to improve many dysfunctions and self-care ability, even delay the progression of the disease.

Virtual reality (VR) has emerged as a promising technology for researching complex impairments in people with PD and for providing personalized rehabilitation[7]. This technology typically combines real-time motion detection within a virtual environment in the context of a (video)game. The user can perceive, feel and interact with virtual environments, viewing an avatar (a character or graphical representation of the user) that mimics the user's movements[8] by multiple sensory channels such as sight, sound and touch[9]. Immediate feedback about performance and success is provided both concurrently (during game play) and terminally (at the end of the game). VR therapy attempt to promote activity-dependent neuroplasticity and motor learning[10, 11]. Recently, numerous systematic reviews (SRs) and meta-analyses (MAs) based on randomized controlled trials (RCTs) regarding the clinical effectiveness of VR therapy in the treatment of PD have been published. However, the overall results have remained mixed or inconclusive and their quality is uneven. An overview of SRs/MAs is a relatively new method that aims to support clinical decision-making by synthesizing the findings, critically appraising the quality and attempting to resolve discordant outcomes.

Therefore, we conducted an overview of SRs/MAs to identify and summarize the existing evidence and to systematically determine the clinical effectiveness of using VR therapy to treat PD.

Methods

The overview was completed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[12] and the guidelines recommended by the Cochrane Collaboration[13]. The PRISMA checklist can be found in Additional file 1. The protocol was not prospectively registered.

Search Strategy

We systematically searched PubMed, Embase and Cochrane library databases from inception to December 5, 2020. We used a combination of Medical Subject Headings with Entry Terms, or Emtree with keywords as follows: *Parkinson Disease, virtual reality exposure therapy, systematic review, and meta-analysis*. In addition, to ensure a comprehensive data collection, references of relevant reviews were searched manually to identify additional eligible studies. The search strategy for the PubMed database is shown in Additional file 2.

Eligibility Criteria

Types of studies: The overview included reviews, which had to be clearly identified by the authors as a ‘systematic review’ or ‘meta-analysis’ in either the title or abstract of the review. SRs/MAs having a systematic search strategy, covering RCTs and published in English were included.

Types of participants: Participants involved in reviews were clinically definite diagnosis of PD and were defined by the UK Parkinson's Disease Society Brain Bank or other diagnostic criteria. We had no restrictions on gender, age, drug dosage, duration and severity of PD. We included reviews reporting an intervention carried out in a mixed sample of participants if data for participants with PD were provided separately.

Types of interventions: Intervention groups were VR therapy alone or in combination with active interventions (AT) or passive interventions (PT). AT involved conventional exercise therapy, sensory integration balance training, neurodevelopment treatment, functional electrical stimulation, stationary cycling, maintenance of usual activities, cognitive training or usual care. PT included either health education or no intervention.

Types of controls: Control groups was defined as either AT or PT without a VR component.

Types of outcome measures: reviews that assessed the motor and non-motor symptoms of PD as the outcome indicators were considered eligible.

The exclusion criteria included: (1) studies which had mixed samples (PD, stroke, multiple sclerosis, cerebral palsy or other neurological disorders) cannot extract data separately; (2) studies where PD patients all used VR without control group or control group was healthy individuals; (3) studies where PD patients with different symptoms (freezers vs. non-freezers) underwent the same VR therapy; (4) reviews, guidelines, conference abstracts, surveys, commentaries, editorials, letters, and notes.

Study Selection

All titles and abstracts were initially screened by two independent investigators (L.Y.Q and G.Y.G) after automatically removing duplicate results to identify potentially relevant studies for inclusion. At this stage, we excluded studies that were not focused on effects of VR therapy on PD patients or not described as SRs/MAs. Further, full-text articles were reviewed and selected according to eligibility criteria. We excluded reviews that did not present summary statistics for outcomes (effect size with 95% CIs). Final relevant studies were shortlisted. In case of discrepancies, consensus was achieved by discussion. If consensus could not be reached, a third reviewer (Y.Y.S) was consulted.

Data Extraction

Two investigators (L.Y.Q and G.Y.G) extracted the following basic characteristics from each eligible review: the first author, publication year, country, the number of included studies, sample size, interventions (experiment interventions and control interventions), outcomes, quality assessment tools, main conclusions. Differences between the review authors were settled by discussion, and a third reviewer (Y.Y.S) was consulted if differences persisted. The study authors were contacted with the aim of acquiring additional information on the data presented.

Quality assessment

Quality of methodology of the each included review was evaluated using the Assessing the Methodological Quality of Systematic Reviews 2 (AMSTAR-2) tool[14]. AMSTAR-2 is a comprehensive critical appraisal tool for SRs/MAs of randomized and non-randomized studies that focuses on weaknesses in critical domains but not an overall score. The tool assesses 16 items, among which 7 are critical domains (item 2, 4, 7, 9, 11, 13 & 15). The evaluation is reduced to three options, "Yes", "Partial Yes" and "No". AMSTAR-2 classifies the overall confidence on the results of the review into four levels: high, moderate, low, and critically low.

The quality of the evidence was rated by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guideline according to five items (inconsistency, imprecision, indirectness, quality, and publication bias)[15]. Results are divided into four levels: high, moderate, low and very low.

Two independent investigators (L.Y.Q and G.Y.G) conducted the assessment process of methodology quality and evidence quality. Discrepancies between investigators were resolved by discussion or by a third reviewer (Y.Y.S) in cases when a consensus was not reached.

Statistical Analysis

We carried out descriptive analyses of the methodology quality and evidence quality of the included SRs/MAs. We further described the summary measures (standard mean difference (SMD) or weighted mean difference (WMD), both with 95% CI, number of RCTs and patients) of the effectiveness of VR therapy for PD for different outcome indicators or comparison modes. We created a bubble plot to present evidence base using Microsoft office Excel 2016 software (Microsoft Corp., Redmond, WA, www.microsoft.com). Each bubble plot displayed information in 4 dimensions: (a) the x-axis represented the outcome indicators in included SRs/MAs; (b) the y-axis represented number of studies for each clinical outcome included in each SRs/MAs; (c) the bubble size provided a very broad indication of the clinical effectiveness estimate of each outcome indicator; (d) different colors represented different GRADE evidence strengths: red bubble indicates high-quality evidence, yellow bubbles indicate moderate-quality evidences, green bubbles indicate low-quality evidences, blue bubbles indicate very low-quality evidences.

Results

Search Results

A flow diagram of study screening and selection procedures is illustrated in Fig. 1. Our electronic search yielded 92 potentially relevant publications. After automatic removal of duplicates, 54 records were screened on the basis of the title or abstract. Of the remaining 37 reviews, 28 reviews were excluded: participants were not PD (n = 6), intervention was not VR (n = 1), SRs/MAs were not based on RCTs (n = 8), conference abstracts lacked full text (n = 3),

necessary data were not extracted (n = 9), and SRs/MAs were not English language (n = 1) after reading the full text. Finally, nine SRs/MAs[16–24] met the inclusion criteria and were included in this overview.

Study Characteristics

The characteristics of the nine SRs/MAs included in our final analysis are summarized in Table 1. All studies were published between 2015 and 2020, including four articles from China[18–20, 22], and one from UK[16], Italy[17], Brasil[21], Belgium[23], Japan[24] each. The number of apposite studies included in each review ranged from 2 to 16, and the sample sizes ranged from 74 to 574. The interventions in the experiment groups were mainly VR therapy alone or VR therapy plus AT, and the control groups were either AT or PT. The methodological quality assessment scales varied across the included SRs/MAs: five SRs/MAs used the Cochrane Collaboration's tool, and four SRs/MAs used the PEDro scale. The conclusions from these SRs/MAs differed, but at least showed that VR therapy can achieve similar even better performance in some outcomes in patients with PD.

Table 1
Characteristics of the included reviews.

Author (Year)	Country	Trials (Sample size)	Intervention		Outcomes	Quality assessment tool	Main conclusions
			Experiment intervention	Control intervention			
Triegaardt J (2020)	UK	10(343)	VR	AT; PT	gait, balance, global motor function, quality of life, activities of daily living, cognitive function, mental health	Cochrane Collaboration's tool	Compared with AT, VR led to greater improvement of stride length, gait speed, balance and co-ordination, cognitive function and mental health, quality of life and activities of daily living. Compared with PT, VR had greater effects on balance.
Marotta N (2020)	Italy	7(236)	VR	AT; PT	functional locomotion; gait quality	Cochrane Collaboration's tool	Wii show immediate positive effects on functional locomotion in people with PD.
Lina C (2020)	China	12(360)	VR; VR + AT	AT; PT	motor function, balance during gait, and the ability to perform activities of daily living	Cochrane Collaboration's tool	VR rehabilitation may be valuable in improving the balance, motor function, gait and ability to perform activities of daily living in patients with PD.
Chen Y (2020)	China	14(574)	VR; VR + AT	AT	balance	PEDro scale	Existing moderate evidence of the effectiveness of VR with the Berg Balance Scale, Dynamic Gait Index, and Functional Gait Assessment for individuals with PD was promising.
Wang B (2019)	China	12(419)	VR; VR + AT	AT	balance, gait ability	PEDro scale	VR enhanced the balance of patients with PD.
Santos P (2019)	Brasil	5(152)	VR + AT	AT	balance, quality of life	PEDro scale	Combination VR and traditional physiotherapy was more effective on balance rehabilitation and quality of life of patients with PD,
Lei C (2019)	China	16(555)	VR	AT; PT	gait, balance function, mobility, global motor function, activities of daily living, quality of life, perceived confidence in balance, neuropsychiatric symptoms, cognitive function, adverse events	Cochrane Collaboration's tool	VR performed better than AT: step and stride length, balance function, mobility, quality of life, level of confidence and neuropsychiatric symptoms.
Dockx K (2016)	Belgium	8(263)	VR	AT; PT	gait, balance, global motor function, activities of daily living, quality of life, cognitive function, adverse events, exercise adherence	Cochrane Collaboration's tool	Results presented a positive effect of short-term VR exercise on step and stride length. VR and physiotherapy may have similar effects on gait, balance, and quality of life.
Harris DM (2015)	Japan	2(74)	VR; VR + AT	AT; PT	balance, activities of daily living, postural control	PEDro scale	Two PD studies showed an improvement in static balance and postural control

VR, virtual reality; AT, active intervention; PT, passive intervention; PD, Parkinson Disease; PEDro, Physiotherapy Evidence Database; BBS, Berg balance scale; TUG, Timed Up and Go test.

Methodological Quality of SRs/MAs

Detailed information on the methodological quality of included SRs/MAs was provided in Table 2. AMSTAR-2 score showed that one (11.1%) review[22] was of moderate quality, three (33.3%)[19, 20] were low, and that of all the others[16–18, 21, 24] (55.6%) were critically low. The key factors affecting the quality of the literature included item 2 (only two reviews[22, 23] had registered and had a protocol before performing the review.), item 4 (five reviews[16, 19, 20, 23, 24] used a comprehensive literature search strategy with searching references of relevant reviews or searching relevant gray literature), item 7 (only one review[23] provided a list of excluded studies and justified the exclusions), item 9 (all reviews[16–24] reported risk of bias use a satisfactory technique), item 11 (all reviews [16–22, 24] conducted statistical combination of results using appropriate methods), item 13 (all reviews[16–24] accounted for risk of bias in the primary studies when interpreting the results of the reviews), and item 15 (three reviews[19, 20, 22] carried out an adequate investigation of publication bias study and discuss its impact on the review).

Table 2
Result of the AMSTAR-2 assessments.

study	AMSTAR-2																Quality
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	
Triegaardt J (2020)	Y	N	Y	Y	N	N	PY	PY	Y	N	Y	Y	Y	Y	N	Y	CL
Marotta N (2020)	Y	N	N	PY	Y	Y	PY	PY	Y	N	Y	N	Y	N	N	Y	CL
Lina C (2020)	Y	N	Y	PY	Y	Y	PY	PY	Y	N	Y	Y	Y	Y	N	N	CL
Chen Y (2020)	Y	N	Y	Y	Y	Y	PY	Y	Y	N	Y	Y	Y	Y	Y	N	L
Wang B (2019)	Y	N	Y	Y	Y	Y	PY	Y	Y	N	Y	N	Y	Y	Y	Y	L
Santos P (2019)	Y	N	Y	PY	Y	Y	PY	Y	Y	N	Y	N	Y	Y	N	N	CL
Lei C (2019)	Y	Y	Y	PY	Y	Y	PY	Y	Y	N	Y	N	Y	Y	Y	Y	M
Dockx K (2016)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	L
Harris DM (2015)	Y	N	Y	Y	Y	N	N	Y	Y	N	Y	Y	Y	N	N	Y	CL
Y: Yes; PY: partial Yes; N: No; CL: Critically low; L: Low; M, Moderate; H: High.																	
Q1: Did the research questions and inclusion criteria for the review include the components of PICO?																	
Q2: Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?																	
Q3: Did the review authors explain their selection of the study designs for inclusion in the review?																	
Q4: Did the review authors use a comprehensive literature search strategy?																	
Q5: Did the review authors perform study selection in duplicate?																	
Q6: Did the review authors perform data extraction in duplicate?																	
Q7: Did the review authors provide a list of excluded studies and justify the exclusions?																	
Q8: Did the review authors describe the included studies in adequate detail?																	
Q9: Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?																	
Q10: Did the review authors report on the sources of funding for the studies included in the review?																	
Q11: If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?																	
Q12: If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?																	
Q13: Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?																	
Q14: Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?																	
Q15: If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?																	
Q16: Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?																	

Evidence Quality of Outcomes

The results of the GRADE assessment were summarized below in Table 3. Figure 2 provided a graphic representation of the evidence base. Among these 48 outcome indicators, there were one (2.1%) high-quality evidence, eight (16.7%) moderate-quality evidences, 20 (41.7%) low-quality evidences, and 19 (39.6%) very low-quality evidences. Reasons for downgrading the quality of evidence to moderate or low even very low included poor methodological quality as a large

bias in random, distributive findings or blind, heterogeneity between study results, the inclusion of trials with a high publication bias, and low numbers of participants pooled.

Table 3
Result of the GRADE assessments.

study	Intervention	Control	Outcomes	Effect estimate 95 % CI	Studies (participants)	Limitations	Inconsistency	Indirectness	Imprecision	
Triegaardt J (2020)	VR	AT	Stride length	SMD 0.70 (0.32,1.08)	4(116)	0	0	0	-1 [⊕]	
			Gait speed	SMD 0.08 (-0.27,0.44)	6(209)	0	0	0	-1 [⊕]	
			Balance (BBS)	SMD 0.26 (-1.02,0.62)	5(166)	0	-1 [⊕]	0	-1 [⊕]	
			Motor function (UPDRS)	SMD - 0.38 (-1.45,0.69)	3(75)	0	-1 [⊕]	0	-1 [⊕]	
			Quality of life (PDQ39/PDQ8)	SMD 0.20 (-0.16,0.57)	5(176)	0	0	0	-1 [⊕]	
			Activities of daily living (UPDRS-II)	SMD - 0.13 (-0.82,0.57)	1(32)	0	0	0	-1 [⊕]	
		VR	PT	Cognitive function (MoCA)	SMD 0.08 (-0.61,0.78)	1(32)	0	0	0	-1 [⊕]
	Stride length			SMD 1.27 (0.38,2.16)	1(24)	0	0	0	-1 [⊕]	
	Gait speed			SMD 1.43 (0.51,2.34)	1(24)	0	0	0	-1 [⊕]	
	Balance (BBS)			SMD 1.02 (0.38,1.65)	2(44)	-1 [⊕]	0	0	-1 [⊕]	
			Activities of daily living (MBI)	SMD 0.96 (0.02,1.89)	1(20)	-1 [⊕]	0	0	-1 [⊕]	
Marotta N (2020)	VR (Nintendo Wii™)	AT; PT	Functional locomotion	SMD 2.44 (0.48,4.38)	4(125)	0	-1 [⊕]	0	-1 [⊕]	
	VR (Xbox™ Kinect)	AT; PT	Functional locomotion	SMD - 0.32 (-0.98,0.35)	3(111)	0	-1 [⊕]	0	-1 [⊕]	
Lina C (2020)	VR; VR + AT	AT	Balance (BBS)	WMD 2.28(1.39,3.16)	9(281)	-1 [⊕]	0	0	-1 [⊕]	
	VR	AT; PT	Motor function (TUG)	WMD - 1.66(-2.74,0.58)	7(190)	-1 [⊕]	0	0	-1 [⊕]	
	VR	AT; PT	Gait ability (10-MWT)	WMD 0.13(0.02,0.24)	4(174)	-1 [⊕]	0	0	-1 [⊕]	
	VR; VR + AT	AT	Activities of daily living (MBI)	WMD 2.93(0.80,5.06)	2(51)	-1 [⊕]	0	0	-1 [⊕]	
Chen Y (2020)	VR; VR + AT	AT	Balance (BBS)	WMD 1.23(0.15,2.31)	8(266)	0	-1 [⊕]	0	-1 [⊕]	
	VR	AT	Balance (ABC)	WMD 1.69 (-2.62,6.01)	2(115)	0	0	0	-1 [⊕]	
	VR	AT	Dynamic balance (TUG)	WMD - 0.18 (-1.37,1.00)	4(120)	0	-1 [⊕]	0	-1 [⊕]	
	VR	AT	Dynamic balance (DGI/FGA)	WMD 0.31 (-0.56,1.19)	5(220)	0	-1 [⊕]	0	-1 [⊕]	
Wang B (2019)	VR	AT	Gait velocity	WMD - 0.00 (-0.06, -0.06)	5(203)	-1 [⊕]	0	0	-1 [⊕]	
	VR	AT	Walk distance (6-MWT)	WMD 8.91 (-43.43,61.13)	2(45)	-1 [⊕]	0	0	-1 [⊕]	

VR, virtual reality; AT, active intervention; PT, passive intervention; BBS, Berg balance scale; TUG, Timed Up and Go test; PDQ-39, 39-Item Parkinson's Disease Questionnaire; 10-MWT, 10-Meter Walk Test; MBI, modified Barthel Index; ABC, Activities-Specific Balance Confidence; DGI, Dynamic Functional Gait Assessment; 6-MWT, 6-Minute Walk Test; UPDRS, Unified Parkinson's Disease Rating Scale. ⊕, Very low; L, Low; M, Moderate; H, High. ⊕: The had a large bias in random, distributive findings or was blind. ⊕: The confidence intervals overlapped less, the P-value for the heterogeneity test was very sma ⊕: The confidence interval was not narrow enough. ⊕: Fewer studies were included, and publication bias cannot be carried out.

study	Intervention	Control	Outcomes	Effect estimate 95 % CI	Studies (participants)	Limitations	Inconsistency	Indirectness	Imprecision
	VR	AT	Stride length	WMD 9.65 (4.31,14.98)	2(79)	-1 [⊖]	0	0	-1 [⊖]
	VR; VR + AT	AT	Balance (BBS)	WMD 2.69 (1.37,4.02)	9(299)	-1 [⊖]	-1 [⊖]	0	0
	VR	AT	Dynamic balance (TUG)	WMD - 2.86 (-5.60, -0.12)	5(144)	-1 [⊖]	-1 [⊖]	0	-1 [⊖]
Santos P (2019)	VR + AT	AT	Balance (BBS)	WMD 1.24 (0.24, 2.25)	3(72)	-1 [⊖]	0	0	-1 [⊖]
			Quality of life (PDQ39)	WMD - 8.90 (-15.22, -2.58)	2(56)	-1 [⊖]	0	0	-1 [⊖]
Lei C (2019)	VR	AT	Gait (DGI)	SMD - 0.15 (-0.50,0.19)	3(130)	-1 [⊖]	0	0	-1 [⊖]
	VR	AT; PT	Gait speed	SMD 0.19 (-0.03,0.40)	7(347)	0	0	0	0
	VR	AT; PT	Stride length	SMD 0.72 (0.40,1.04)	4(166)	-1 [⊖]	0	0	-1 [⊖]
	VR	AT	Balance	SMD 0.22 (0.01,0.42)	11(360)	0	0	0	0
	VR	AT; PT	Mobility (TUG)	SMD - 1.95 (-2.81, -1.08)	7(237)	-1 [⊖]	-1 [⊖]	0	-1 [⊖]
	VR	AT	Global motor function (UPDRS-III)	SMD - 0.50 (-1.48,0.48)	5(164)	0	-1 [⊖]	0	-1 [⊖]
	VR	AT	Activities of daily living (UPDRS-II)	SMD 0.25 (-0.14,0.64)	4(103)	0	0	0	-1 [⊖]
	VR	AT; PT	Quality of life (PDQ-39 / WHOQOL-OLD)	SMD - 0.47(-0.73, -0.22)	6(248)	-1 [⊖]	0	0	-1 [⊖]
	VR	AT; PT	Perceived confidence in balance	SMD - 0.73(-1.43, -0.02)	3(104)	0	-1 [⊖]	0	-1 [⊖]
	VR	AT	Neuropsychiatric symptoms	SMD - 0.96(-1.27, -0.65)	4(184)	-1 [⊖]	0	0	-1 [⊖]
	VR	AT	Cognitive function (DSF/MoCA)	SMD 0.21(-0.28, 0.69)	2(68)	-1 [⊖]	0	0	-1 [⊖]
Dockx K (2016)	VR	AT	Gait (composite measure)	SMD 0.20 (-0.14, 0.55)	4(129)	0	0	0	-1 [⊖]
			Gait speed	SMD 0.18 (-0.20, 0.57)	3(106)	0	0	0	-1 [⊖]
			Stride length	SMD 0.69 (0.30, 1.08)	3(106)	0	0	0	-1 [⊖]
			Balance (composite measure)	SMD 0.34 (-0.04, 0.71)	5(155)	0	0	0	-1 [⊖]
			Balance (BBS)	WMD 0.55 (-0.48,1.58)	3(86)	0	0	0	-1 [⊖]
			Quality of life (PDQ-39)	WMD 3.73 (-2.16, 9.61)	6(106)	0	0	0	-1 [⊖]
	VR	PT	Balance (composite measure)	SMD 1.02 (0.38, 1.65)	2(44)	-1 [⊖]	0	0	-1 [⊖]

VR, virtual reality; AT, active intervention; PT, passive intervention; BBS, Berg balance scale; TUG, Timed Up and Go test; PDQ-39, 39-Item Parkinson's Disease Questionnaire; 10-WMT, 10-Meter Walk Test; MBI, modified Barthel Index; ABC, Activities-Specific Balance Confidence; DGI, Dynamic Functional Gait Assessment; 6-WMT, 6-Minute Walk Test; UPDRS, Unified Parkinson's Disease Rating Scale. VL, Very low; L, Low; M, Moderate; H, High. ⊖: The study had a large bias in random, distributive findings or was blind. ⊖: The confidence intervals overlapped less, the P-value for the heterogeneity test was very small. ⊖: The confidence interval was not narrow enough. ⊖: Fewer studies were included, and publication bias cannot be carried out.

study	Intervention	Control	Outcomes	Effect estimate 95% CI	Studies (participants)	Limitations	Inconsistency	Indirectness	Imprecision
Harris DM (2015)	VR + AT	AT	Balance (BBS)	SMD 0.12(-0.58, 0.83)	1(32)	-1 [⊖]	0	0	-1 [⊖]
	VR	PT	Postural Control	SMD 2.58(1.53,3.60)	1(28)	-1 [⊖]	0	0	-1 [⊖]

VR, virtual reality; AT, active intervention; PT, passive intervention; BBS, Berg balance scale; TUG, Timed Up and Go test; PDQ-39, 39-Item Parkinson's Disease Questionnaire; 10-WMT, 10-Meter Walk Test; MBI, modified Barthel Index; ABC, Activities-Specific Balance Confidence; DGI, Dynamic Functional Gait Assessment; 6-WMT, 6-Minute Walk Test; UPDRS, Unified Parkinson's Disease Rating Scale. VL, Very low; L, Low; M, Moderate; H, High. ⊖: The had a large bias in random, distributive findings or was blind. ⊖: The confidence intervals overlapped less, the P-value for the heterogeneity test was very small. ⊖: The confidence interval was not narrow enough. ⊖: Fewer studies were included, and publication bias cannot be carried out.

Effectiveness Evaluation

Gait

Gait (composite measure). Only one SR/MA[23] involving four RCTs with a total of 129 participants with PD found no significant difference between VR therapy and AT (SMD = 0.20, 95%CI = -0.14 to 0.55) in gait as a composite measure.

Stride length. Four SRs/MAs[16, 20, 22, 23] reported the stride length and concluded that VR therapy had greater improvement of stride length compared with AT (SMD = 0.70, 95%CI = 0.32 to 1.08, 4 RCTs, 116 patients[16]; WMD = 9.65, 95% CI = 4.31 to 14.98, 2 RCTs, 79 patients[20]; SMD = 0.69, 95% CI = 0.30 to 1.08, 3 RCTs, 106 patients[23]), or compared with PT (SMD = 1.27, 95%CI = 0.38 to 2.16, 1 RCT, 24 patients[16]), or AT or PT (SMD = 0.72, 95%CI = 0.40 to 1.04, 4 RCTs, 166 patients[22]).

Gait speed. Four SRs/MAs[16, 20, 22, 23] focused on the gait speed, but only one of them[16] revealed that VR therapy was significantly better than PT on gait speed (SMD = 1.43, 95%CI = 0.51 to 2.34, 1 RCT, 24 patients). The others concluded that there was no statistically significant difference between VR therapy and AT (SMD = 0.08, 95%CI = -0.27 to 0.44, 6 RCTs, 209 patients[16]; WMD = -0.00, 95% CI = -0.06 to 0.06, 5 RCTs, 203 patients[20]; SMD = 0.18, 95% CI = -0.20 to 0.57, 3 RCTs, 106 patients[23]), and between VR therapy and AT or PT (SMD = 0.19, 95%CI = -0.03 to 0.40, 7 RCTs, 347 patients[22]).

Gait ability. Four SRs/MAs[18-20, 22] reported Timed Up and Go (TUG), as a useful test for evaluating gait ability and balance function, two of which[18, 22] compared VR therapy with AT or PT, their results were inconsistent (WMD = -1.66, 95% CI = -2.74 to 0.58, 7 RCTs, 190 patients[18]; SMD = -1.95, 95% CI = -2.81 to -1.08, 7 RCTs, 237 patients[22]). The other two SRs/MAs[19, 20] also reported conflicting results when VR therapy compared with AT (WMD = -0.18, 95% CI = -1.37 to 1.00, 4 RCTs, 120 patients[19]; WMD = -2.86, 95% CI = -5.60 to -0.12, 5 RCTs, 144 patients[20]). Only one SR/MA[18] found that VR therapy was superior than AT or PT in the gait ability using 10-Meter Walk Test (10-WMT) (WMD = 0.13, 95%CI = 0.02 to 0.24, 4 RCTs, 174 patients). One SR/MA[20] showed no significantly greater increases in walk distance using 6-Minute Walk Test (6-WMT) when VR therapy compared with AT (WMD = 8.91, 95% CI = -43.32 to 61.13, 2 RCTs, 45 patients). Moreover, one SR/MA[17] indicated that Nintendo Wii (SMD = 2.44, 95% CI = 0.48 to 4.38, 4 RCTs, 125 patients) had immediate positive effects on functional locomotion (measured by gait speed and the time that a person takes to complete certain locomotion tasks: TUG and 10-WMT), but Xbox Kinect (SMD = -0.32, 95% CI = -0.98 to 0.35, 3 RCTs, 111 patients) didn't observe this phenomenon.

Balance Function

Balance (composite measure). Two SRs/MAs[22, 23] reported the balance as a composite measure. One SR/MA[22] with the largest sample size included 11 RCTs with 360 patients found that VR therapy was superior to AT on balance function (nine RCTs used Berg Balance Scale (BBS) and one RCT used Activities-Specific Balance Confidence (ABC)) (SMD = 0.22, 95%CI = 0.01 to 0.42). The other SR/MA[23] assessed balance as a composite measure, and found no significant difference between VR therapy and AT (SMD = 0.34, 95% CI = -0.04 to 0.71, 5 RCTs, 155 patients), while VR therapy was superior than PT (SMD = 1.02, 95% CI = 0.38 to 1.65, 2 RCTs, 44 patients).

BBS. Seven SRs/MAs[16, 18-21, 23, 24] focused on the balance function using BBS. Two SRs/MAs demonstrated that there was no difference between VR therapy and AT (SMD = 0.26, 95%CI = -1.02 to 0.62, 5 RCTs, 166 patients[16]; WMD = 0.55, 95%CI = -0.48 to 1.58, 3 RCTs, 86 patients[23]). Two SRs/MAs[21, 24] compared VR therapy plus AT with AT alone, their results were inconsistent. One SR/MA[21] showed a favorable improvement in BBS score (WMD = 1.24, 95%CI = 0.24 to 2.25, 3 RCTs, 72 patients). The other SR/MA[24] showed a non-favorable effect (SMD = 0.12, 95%CI = -0.58 to 0.83, 1 RCT, 32 patients). Three SRs/MAs concluded that VR therapy alone or VR plus AT could help improve the BBS score than AT alone (WMD = 2.28, 95%CI = 1.39 to 3.16, 9 RCTs, 281 patients[18]; WMD = 1.23, 95%CI = 0.15 to 2.31, 8 RCTs, 266 patients[19]; WMD = 2.69, 95%CI = 1.37 to 4.02, 9 RCTs, 299 patients[20]). Only one SR/MA indicated that VR therapy was superior than PT in the improvement of BBS score (SMD = 1.02, 95%CI = 0.38 to 1.65, 2 RCTs, 44 patients).

Dynamic Gait Index (DGI)/ Functional Gait Assessment (FGA). There were two SRs/MAs[19, 22] focused on the dynamic balance during gait using DGI[25] and FGA[26] tools. The FGA is a modified version of the DGI. The results were consistent and revealed no significant difference between the VR therapy and the AT (WMD = 0.31, 95%CI = -0.56 to 1.19, 5 RCTs, 220 patients[19]; SMD = -0.15, 95% CI = -0.50 to 0.19, 3 RCTs, 130 patients[22]).

Perceived confidence in balance. Two SRs/MAs[19, 22] reported the perceived confidence in balance, of which one SR/MA[19] reported ABC scale changes and illustrated that VR resulted in no significant difference when VR was compared with AT (WMD = 1.69; 95% CI = -2.62 to 6.01, 2 RCTs, 115 patients). The other SR/MA[22] included three RCTs with 104 patients compared VR with AT or PT indicated that VR had a significant effect on perceived confidence in balance than AT or PT (SMD = -0.73, 95%CI = -1.43 to -0.03).

Global Motor Function

Two SRs/MAs[16, 22] reported the global motor function, they indicated that there was no significant effect on global motor function assessed by Section III of Unified Parkinson Disease Rating Scale (UPDRS-III) between VR therapy and AT (SMD = -0.38, 95%CI = - 1.45 to 0.69, 3 RCTs, 75 patients[16]; SMD = -0.50, 95%CI = -1.48 to 0.48, 5 RCTs, 164 patients[22]).

Activities of Daily Living

Three SRs/MAs[16, 18, 22] reported on activities of daily living, two of which concluded that there was no statistically significant difference between VR therapy and AT in activities of daily living, assessed by Section II of the Unified Parkinson Disease Rating Scale (UPDRS-II) (SMD = - 0.13, 95%CI = - 0.82 to 0.57, 1 RCT, 32 patients[16]; SMD = 0.25, 95%CI = -0.14 to 0.64, 4 RCTs, 103 patients[22]). One SR/MA[18] compared VR or VR plus AT with AT alone indicated that VR therapy had beneficial effects on activities of daily living according to the modified Barthel Index (MBI) (WMD = -2.93, 95% CI = 0.8 to 5.06, 2 RCTs, 51 patients). One[16] demonstrated that VR therapy led to greater improvement in MBI than PT (SMD = 0.96, 95%CI =0.02 to 1.89, 1 RCT, 20 patients).

Quality of Life

Three SRs/MAs[16, 21, 22] focused on quality of life at the end of treatment. one of them[21] compared VR plus AT with AT alone indicated that VR therapy showed a significant improvement in quality of life assessed by Parkinson's Disease Questionnaire (PDQ39) (WMD= -8.90, 95% CI=-15.22 to - 2.58, 2 RCTs, 56 patients). Another one[22] concluded that VR therapy was better in improving the quality of life compared with AT or PT in quality of life (five RCTs used PDQ39 and one RCT used World Health Organization Quality of Life-Old (WHOQOL-OLD)) (SMD = -0.47, 95%CI =-0.73 to - 0.22, 6 RCTs, 248 patients). The other SR/MA[16] showed no difference was found between VR therapy and AT (four RCTs used PDQ39 and one RCT used PDQ8) (SMD = 0.20, 95%CI = - 0.16 to 0.57, 5 RCTs, 176 patients).

Postural Control

Only one SR/MA[24] investigated postural control between VR therapy and PT, and found a significant improvement in postural control for people with VR therapy (SMD = 2.58, 95% CI = 1.538 to 3.60, 1 RCT, 28 patients).

Cognitive Function

Only two SRs/MAs provided complete data on cognitive function changes, and there was no significant difference between VR therapy and AT in cognitive function assessed by Montreal Cognitive Assessment (MoCA)(SMD = 0.08, 95%CI = - 0.61 to 0.78, 1 RCT, 32 patients[16]), assessed by MoCA and Digit Span forward (DSF) (SMD = 0.21, 95%CI = -0.28 to 0.69, 2 RCTs, 68 patients[22]).

Neuropsychiatric Symptoms

Only one SR/MA[22] reported the effect of VR on neuropsychiatric symptoms which were recorded by Beck Anxiety Index (BAI), Beck Depression Index (BDI) and Hamilton Depression Scale (HAMD), and found VR therapy had a significant positive effect than AT (SMD = -0.96, 95%CI = -1.27, -0.65, 4 RCTs, 184 patients)

Discussion

Summary of Main Findings

With this overview, the findings regarding the effectiveness of VR therapy for treating PD were as follows: (1) We identified nine SRs/MAs summarized the clinical evidence on the effectiveness of VR therapy for PD rehabilitation in this overview, and all studies were published in the last five years, illustrating that VR augmented therapy is a relatively new technology applied to the field of clinical medical. (2) The current evidence indicated that VR therapy presented better benefits on stride length in PD patients when compared with other therapies. (3) Of the included SRs/MAs, there were no unanimous conclusions on gait speed, gait ability, balance, global motor function, activities of daily living, quality of life, postural control, cognitive function, and neuropsychiatric symptoms, but VR therapy presented at least similar effects with other therapies. Therefore, we explained cautiously that VR therapy can be regarded as a complementary and alternative therapy for PD.

The possible mechanism of therapeutic effect of VR therapy for PD in stride length are as follows: (1) A decrease in stride length is an example of deterioration of motor automaticity in PD patients. PD patients have to rely on attentional control helping to perform motor skills to bypass automatic control mechanisms[27]. VR therapy provided more accurate and complete motor feedback and therefore enabled better stride amplitude correction than traditional physiotherapy[7]. (2) PD patients revealed the typical gait asymmetry with a significant difference between stride lengths of both legs. Dissociation of the visual and proprioceptive inputs can be manipulated in VR so that people with PD step to a target that is visually perceived to be of a smaller range of motion than is actually achieved, thereby training their motor systems to produce larger movements during subsequent trials[28].

In addition, we investigated potential causes of inconsistent results for outcome as follows: (1) PD patients had different tremor amplitude and rhythm patterns in different clinical stages (Hoehn-Yahr stage), which may affect the effects of the intervention to a certain extent. (2) The confounding influence of intervention type and dose is a key shortcoming of included SRs/MAs. VR systems differed across primary studies, the majority of trials used recreational systems, a few researches used commercialized rehabilitation- specific systems or customized systems. Different studies applied VR therapy in conventional exercise, gait training, balance training, cognitive training and other rehabilitation training. The duration of the session varied from 30 to 60 minutes, the training frequency varied from 2 to 5 times per week, and the training time varied from 4 weeks to 12 weeks. (3) The measurement of functional outcomes

lacked a unified standard, for instance, balance performance was measured using BBS, DGI, FGA, ABC, etc. While BBS is considered to be a robust measure of balance performance[29], it is also characterized by substantial floor and ceiling effects[30].

From this overview, we found that the methodological quality and evidence quality of included SRs/MAs were unsatisfactory. According to AMSTAR-2, the methodological quality of all included SRs/MAs but one[22] were low or critically low. Only two SRs/MAs[22, 23] had been registered protocols. The lack of registration may result in a great adjustment of the study process than expected, increasing the risk of bias and affecting the rigor of the SRs/MAs. Four SRs/MAs[17, 18, 21, 22] didn't take into account the gray literatures or the references of included studies in the retrieval process, which may cause publication bias and language bias. All included SRs/MAs but one[23] did not provide a list of excluded trials with reasons for exclusions, which may undermine the transparency of the SRs/MAs and affect the reliability of their results. The sources of funding are not reported in all included SRs/MAs except for one[23], which may reduce the credibility of the research results due to potential conflicts of interest. Six SRs/MAs[16–18, 21, 23, 24] didn't carry out an adequate investigation of publication bias and discuss its likely impact on the results of the review, which may affect the judgment of the validity of the analysis results. Future studies could avoid these obvious deficiencies to improve methodological quality. According to GRADE, evidence quality of each outcome measurement was between moderate and very low. Most SRs/MAs (81.3%) were with low or very low-quality evidence. The most common among the downgrading factors in the included SRs/MAs was imprecision, which was reflected in the wide confidence interval and the small sample size. Next was publication bias, limitations and inconsistency, which was reflected in insufficient search strategy, large defects in the method design of random, blinding and allocation concealment, larger heterogeneity, etc. Based on this, there may be a certain degree of difference between the conclusions of the included MAs and the true results.

Strengths And Limitation Of The Overview

To the best of our knowledge, our study is the first overview of MAs to explore the effect of VR therapy on PD rehabilitation, which may have certain reference value for the clinical practice. In addition, the findings of this overview were based on relatively recent evidence, as all studies were published in the last five years. Moreover, this overview included MAs of RCTs using strict inclusion standards, and excluded non-RCTs, observational cohort studies or MAs without extracting data in order to reduce the risk of bias. However, this study has several limitations. First, the methodological quality and evidence quality of the included MAs were generally low; thus, results based on primary studies should be interpreted with caution. Furthermore, we only searched English databases, so MAs published in other languages that met the inclusion criteria may have been missed.

Conclusion

The current evidence based on nine SRs/MAs suggests that VR therapy may be a promising complementary treatment for PD patients. This conclusion must be interpreted cautiously, given the generally low methodological quality and low evidence quality of the included SRs/MAs. Rigorous-designed, high-quality RCTs with larger sample sizes are needed to further verify the effectiveness of VR therapy in the treatment of PD.

Abbreviations

AMSTAR-2 = Assessment of Multiple Systematic Reviews 2, AT = active interventions, GRADE = Grading of Recommendations, Assessment, Development and Evaluation, MAs = meta-analyses, PD = Parkinson disease, PRISMA= Preferred Reporting Items for Systematic Reviews and Meta-Analyses, PT = passive interventions, RCT = randomized controlled trials, SRs = systematic reviews. VR = virtual reality.

Declarations

Ethics approval and consent to participate

Ethical approval and patient consent are not required since this is an overview based on published studies.

Consent for publication

All authors approved the final publication of the manuscript.

Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing interests

The authors declare that there is no conflict of interest.

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None.

Authors' contributions

Y.Y.S and L.Y.Q developed the initial idea for the study; G.Y.G conducted the database searches; Y.Y.S, G.Y.G and L.Y.Q screened studies, extracted information and data from the studies and conducted quality assessment; X.W.T drew a bubble plot of the evidence base; Y.Y.S, G.Y.G, C.W.Q, W.L.S, and Z.C.X drafted

the manuscript. L.Y.Q revised the manuscript. All authors read, critically reviewed, and approved the final manuscript as submitted.

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Figures

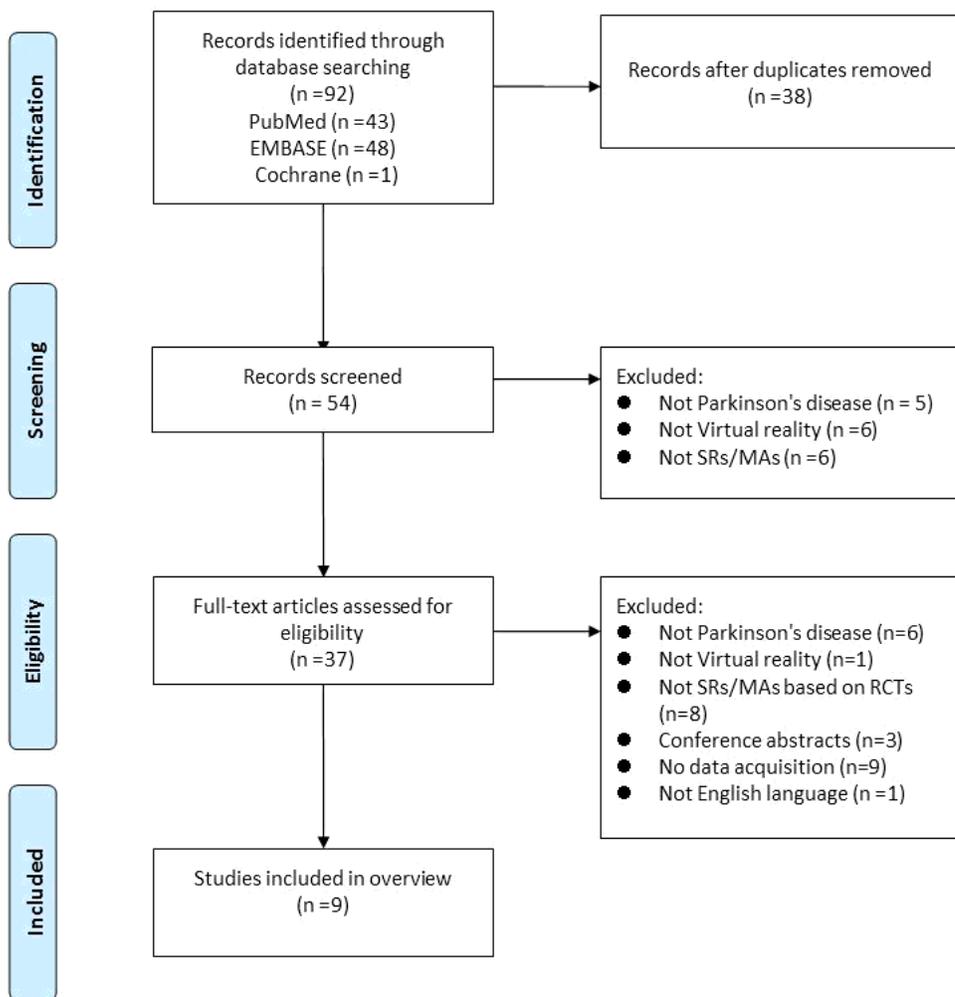


Figure 1

A flow diagram of study screening and selection procedures.

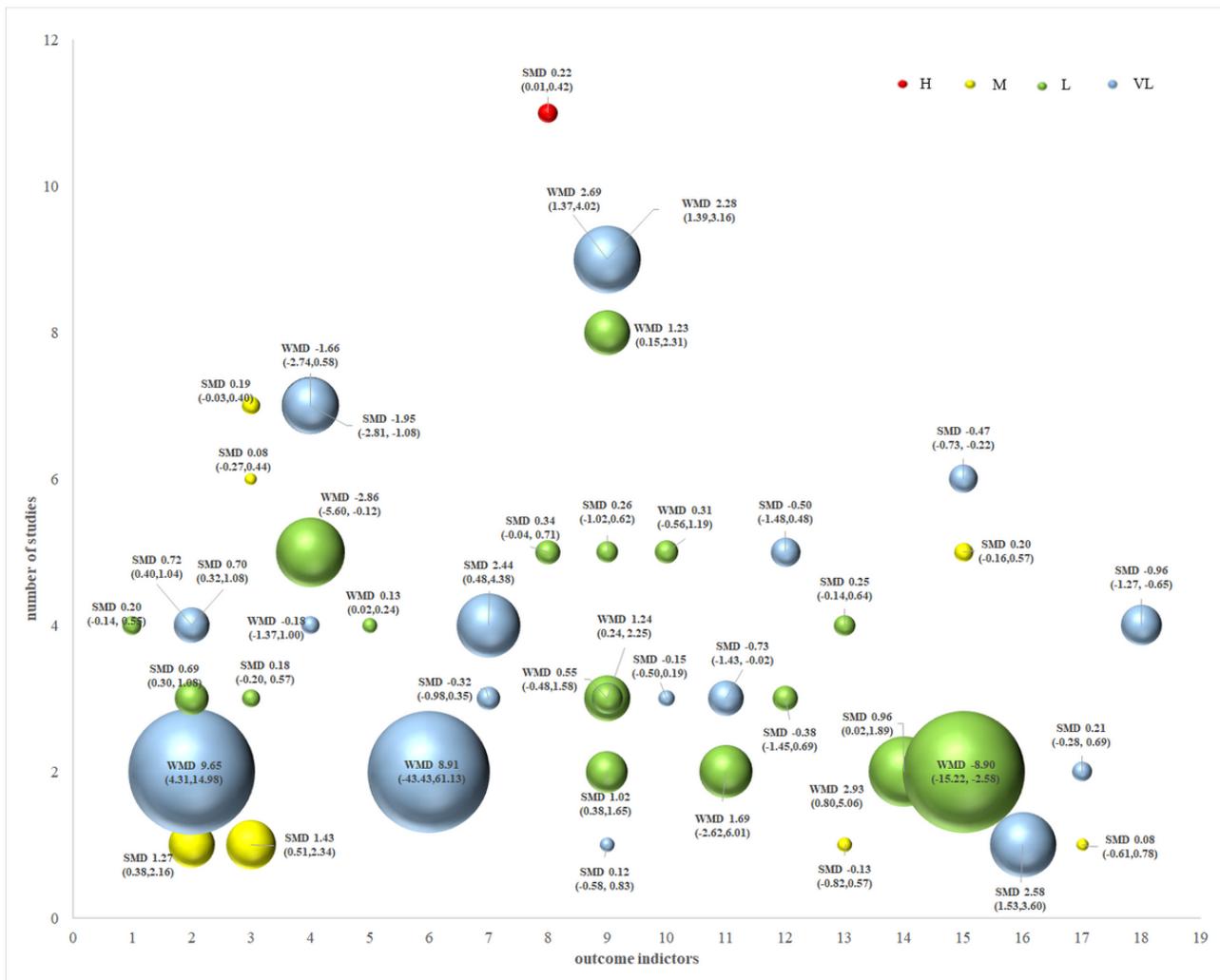


Figure 2

Evidence map of Virtual Reality therapy. x-axis represented clinical outcome indicators (1: Gait as composite measure, 2: Stride length, 3: Gait speed, 4: TUG, 5: 10-MWT, 6: 6-MWT, 7: Functional locomotion, 8: Balance as composite measure, 9: BBS, 10: DGI/FGA, 11: Perceived confidence in balance, 12: UPDRS-III, 13: UPDRS-II, 14: MBI, 15: Quality of Life, 16: Postural Control, 17: Cognitive Function, 18: Neuropsychiatric Symptoms).

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