Health and Technology (2021) 11:811–833
https://doi.org/10.1007/s12553-021-00561-7

REVIEW PAPER

Effectiveness of immersive virtual reality-supported interventions for patients with disorders or impairments: a systematic review and meta-analysis

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Received: 21 September 2020 / Accepted: 7 May 2021 / Published online: 16 July 2021

Abstract
The study objective was to conduct a systematic review and meta-analysis to assess the effectiveness of immersive virtual reality (VR)-supported interventions for patients with disorders or impairments. Web Science, MEDLINE, CINAHL Plus, and PsycINFO databases were searched from January 1990 to December 2020. We performed random-effects meta-analyses and calculated the standardized mean difference in the health outcomes before and after applying immersive VR-supported interventions. Forty-eight studies representing 52 experiments were meta-analyzed. Six different disorders or impairments were found to be examined in the experiments: anxiety disorders (n=40), psychotic disorders (n=3), poststroke motor impairment (n=3), mild cognitive impairment (MCI) (n=2), amblyopia (n=2), and unilateral vestibular hypofunction (UVH) (n=2). The use of VR interventions resulted in improvement in the following outcomes for the six disorders or impairments: anxiety-related symptoms (e.g., depression, anxiety), psychiatric symptoms, upper extremity function, cognitive function, visual acuity, and confidence in balance during daily activities and vestibulo-ocular reflex. Immersive VR has been mostly studied in individuals with anxiety disorders and can be effective in improving anxiety-related symptoms. Additionally, immersive VR has shown potential in motor rehabilitation after stroke and treating psychotic disorders, MCI, amblyopia, and UVH, and more research is recommended to further validate the current findings.

Keywords Immersive virtual reality · Patients · Treatment · Therapy · Meta-analysis

1 Introduction

Virtual reality (VR), which refers to a computer-generated simulation of reality, has been considered a feasible tool to expand support for the delivery of treatments and therapies for various disorders [1–7], as it offers potentials for delivering treatments and therapies. First, VR can be used to simulate environments that are highly similar to the real world, providing an alternative to deliver treatments and therapies, especially in situations that conducting conventional therapies is impractical. For example, it is less possible to use an actual flight for treating individuals with fear of flying in conventional exposure therapy. Second, variables of the virtual objects can be easily manipulated in virtual environments [8, 9]. Therefore, contents of therapeutic tasks can be more precisely controlled (e.g., time duration, difficulty level). High flexibility in the manipulation of variables also permits the individualization of treatments and therapies. Third, VR can provide real-time feedback in visual, audio, or haptic form on individuals' performance, reflecting the ongoing status of the therapeutic tasks and how well the tasks have been performed [8]. Diverse forms of feedback can help individuals make adjustments in performing the tasks to improve the effectiveness of therapy. Furthermore, therapeutic tasks can be designed as games with VR [10]. Previous studies indicated that VR game-based interventions may help alleviate individuals' non-adherence to treatments and therapies as well as improve motivation in participating in treatments and therapies [11–13].

Although there have been reviews that examined the effects of VR on improving the health of individuals with disorders in treatments and therapies, those reviews did not distinguish between non-immersive VR (e.g.,

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Nintendo Wii) and immersive VR (e.g., head-mounted display [HMD], cave automatic virtual environment [CAVE]) [14–16]. According to previous research, the degree of immersion of a VR system may influence user experience and also the effectiveness of VR interventions [17, 18]. Therefore, the effectiveness of immersive VR for delivering treatments and therapies requires further examination. The purpose of the present review is to examine the effectiveness of immersive VR-supported interventions for patients with disorders or impairments through a systematic review and meta-analysis.

2 Methods

This review followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [19].

2.1 Search strategy

Web of Science, MEDLINE, CINAHL Plus, and PsycINFO databases were searched to identify relevant studies published from January 1, 1990 to December 3, 2020. The following terms were used: ('virtual reality' or 'virtual environment*' or 'cave automatic virtual environment' or 'head mounted display*' or immersive) and (rehabilitat* or treat* or evaluat* or assess* or effect* or therap*) and patient*.

2.2 Inclusion and exclusion criteria

Studies were included for review if they: (1) applied immersive VR-supported interventions for patients with a specific disorder or impairment; (2) quantitatively examined psychological, physical, or physiological health outcomes before and after using immersive VR-supported interventions; (3) were published in peer-reviewed journals; and (4) were written in English. Studies were excluded for review if they: (1) included patients with multiple disorders or impairments, as different disorders or impairments may interact with each other, making it difficult to analyze the independent effect of the intervention on a specific disorder or impairment; (2) used immersive VR in combination with other types of technologies or interventions, as the independent effect of immersive VR could not be determined; (3) did not report mean and standard deviation (SD) values needed for effect size calculation; or (4) were review studies or case reports.

2.3 Study selection

After removing duplicate citations by using Endnote and manual screening, the titles and abstracts were firstly screened by JC, then the full texts of the potentially relevant citations were independently screened by JC and ZX for final inclusion. The reference lists of the identified studies were manually searched to catch missed studies. Disagreements about inclusion were resolved by discussion to achieve a consensus.

2.4 Data extraction

JC and ZX used a standardized form to independently extract data on the studies' characteristics, participants' attributes, the details of the VR-supported interventions, and mean and SD values of the health outcomes.

2.5 Quality assessment

We adapted the Downs and Black Checklist for Quality Assessment [20] to assess the quality of the included studies. The items specifically related to randomized controlled trials (i.e., comparison between groups, blindness, and randomization) were removed, as the present study aimed to compare the difference in health outcomes before and after using immersive VR-supported interventions. The present assessment included 17 items (Appendix 1), assessing the quality of information reporting, external validity, and biases in the measurement of intervention and outcome. The total scale of the assessment ranges from 0 to 17. Studies with a total score less than 9 were considered as poor quality, between 9 and 11 were considered as fair quality, between 12 and 13 was considered as good quality, and between 14 and 17 was considered as very good quality [21]. Scoring was done independently by JC and ZX. Disagreements about scoring were resolved by discussion to achieve a consensus.

2.6 Data analysis

Health outcomes were meta-analyzed if they were reported in at least two experiments. We pooled the data across experiments using random-effects models and calculated the standardized mean difference (SMD) as effect size for each health outcome. Negative values of the effect sizes represent improvements in health outcomes. Heterogeneity across studies was measured by I^2 statistics, with 25%, 50%, and 75% considered as low, moderate, and high levels of heterogeneity, respectively [22]. The possible publication bias was examined by Egger's regression test, with *p* value <0.1 indicating the presence of publication bias [23]. Comprehensive Meta-Analysis software (version 2, Biostat Inc) was used to perform the meta-analysis.

3 Results

3.1 Study selection process

Fig 1 shows the study selection process. Of the 10,643 citations identified in the literature search, 47 studies [1–3, 5, 24–66] were eligible for inclusion. Of the 47 studies, two studies [41, 50] had two groups of participants using VR, with one group of participants using HMD and the other group of participants using CAVE, therefore, these two studies were split into two experiments respectively; one study [54] examined the effects of VR in treating three groups of participants, including a group of participants with fear of flying, a group of participants with social anxiety disorder, and a group of participants with fear of height, therefore, this study was split into three experiments. One additional study [67] was identified by manually search. Therefore, a total of 48 studies, representing 52 experiments, were included in the meta-analysis.

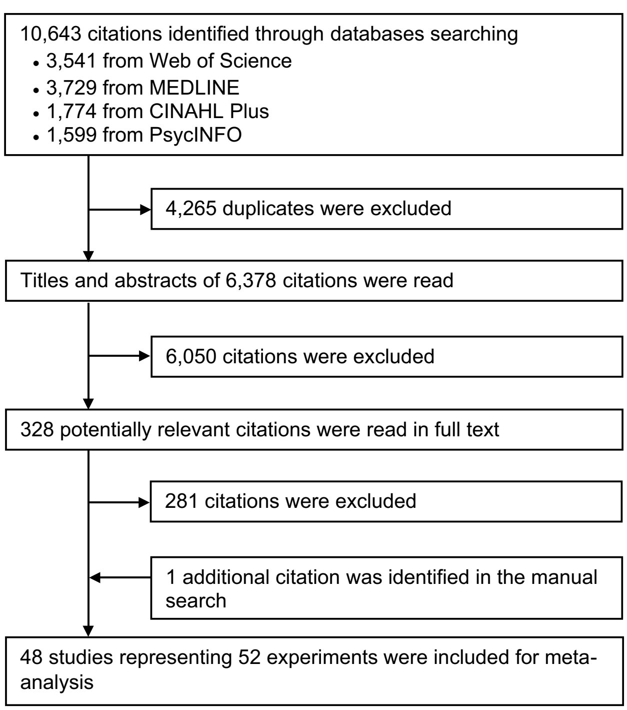

Fig. 1 Study selection process

3.2 Characteristics of the experiments

Table 1 summarizes the characteristics of the 52 experiments, and the study details and the characteristics of the VR-supported intervention of each experiment are presented in Appendix 2.

3.3 Quality assessment

Table 2 presents the results of the quality assessment for the 48 studies. The total scores for quality assessment ranged from 9 to 16 (possible maximum total score is 17), with a median value of 13.5 and a mean value of 13.3 (SD=1.5). Four studies (8.3%) were rated as fair quality, 20 studies (41.7%) were rated as good quality, and 24 studies (50.0%) were rated as very good quality.

3.4 Meta-analysis of the effects of immersive VR-supported interventions

Table 3 shows the results of the meta-analysis, heterogeneity tests, and publication bias tests for the health outcomes for each disorder or impairment type. The corresponding measurement of each health outcome is presented in Appendix 3.

4 Discussion

4.1 Impacts of the development of immersive VR technology on treatments and therapies

Continuous advancement in VR technology has supported the development of immersive VR interventions for targeting a wide range of treatment and therapy. Among the studies included in our review, only one study was published in the 1990s and about one-third of the studies were published in the 2000s. In these two decades, the use of immersive VR mainly focused on treating anxiety disorders, such as PTSD, specific phobias (e.g., fear of height, fear of flying, spider phobia, and claustrophobia), social anxiety disorder, and agoraphobia. A large proportion of the included studies were published in the 2010s, and the use of immersive VR has extended to a wider range of mental disorders, such as psychotic disorders. Moreover, VR has also been used for treating visual system disease, motor rehabilitation, cognitive rehabilitation, and vestibular rehabilitation.

Changes in the amount and scope of VR research in treatments and therapies might be attributed to the prosperity of the VR industry in recent years, so that

Table 1 Summary of the characteristics of the 52 experiments

Characteristics	
Year of publication, n (%)	
1990–1999	1 (1.9) [39]
2000–2009	16 (30.8) [24–27, 29, 31, 32, 34, 38, 40–42, 60, 64, 65]
2010–2020	35 (67.3) [1–3, 5, 28, 30, 33, 35–37, 43–59, 61–63, 66, 67]
Disorder or impairment type examined, n (%)	
Anxiety disorders	
Posttraumatic stress disorder (PTSD)	8 (15.4) [3, 29, 33, 46, 48, 49, 59, 60]
Agoraphobia	7 (13.5) [27, 47, 50, 57, 58, 64]
Fear of height	7 (13.5) [31, 32, 39, 41, 54, 67]
Social anxiety disorder	6 (11.6) [2, 24, 35, 38, 54, 65]
Fear of flying	5 (9.6) [1, 25, 42, 54, 62]
Spider phobia	5 (9.6) [26, 34, 40, 45, 53]
Dental phobia	2 (3.8) [36, 37]
Psychotic disorders	3 (5.8) [5, 30, 63]
Poststroke motor impairment	3 (5.8) [28, 44, 55]
Mild cognitive impairment (MCI)	2 (3.8) [56, 61]
Amblyopia	2 (3.8) [43, 66]
Unilateral vestibular hypofunction (UVH)	2 (3.8) [51, 52]
Study location, n (%)	
Europe	27 (52.0) [1, 5, 25, 28, 31–33, 35, 41, 42, 45, 50–54, 57, 58, 62–64, 66, 67]
North America	14 (26.9) [3, 24, 26, 29, 30, 34, 38–40, 46, 48, 49, 59, 60]
Asia	10 (19.2) [2, 27, 36, 37, 43, 44, 55, 56, 61, 65]
Oceania	1 (1.9) [47]
VR system used, n (%)	
Head-mounted display (HMD)	49 (94.2) [1–3, 5, 24–67]
Cave automatic virtual environment (CAVE)	3 (5.8) [41, 50, 54]
Sample size, median (range)	14 (3–58)
Male ratio in %, median (range)	46.7 (0–100)
Mean age of the participants in years, median (range)	35.7 (8.7–76.9)
Mean duration of disease in years, median (range)	13.3 (0.8–33.5)
Intervention duration in weeks, range	1–16

researchers and healthcare professionals have more available resources when choosing therapy tools. As pointed out by Anthes et al., more VR products that are affordable to the public are emerging and flooding to the consumer market with the start of the second wave of VR technology in 2012 (the first wave was in the late 1980s) [68]. For example, the HMD devices by Oculus VR (Menlo Park, CA) went through quick iterations and the models of development kit 1 (DK1), DK2, Rift CV1, Rift S, and Oculus Quest have been constantly published since 2013.

Advances in immersive VR hardware have also supported the development of more VR therapeutic programs. HMD, as the display device in a VR system, directly affects the presentation of virtual environments and users' visual experience. For example, according to our results, earlier HMD devices usually had a narrow diagonal field of view (FOV) due to the limitations in technology (e.g., complicated optics) and cost [69, 70]. V6 (Virtual Research Systems, Inc.), one of the HMD devices that was commonly used in the included studies in the 2000s, provided a diagonal FOV of 60 degrees. Previous studies indicated that limited FOV might make users see black in their peripheral vision in virtual environments and also influence users' performance on visual search and spatial awareness [69, 70]. In contrast, the recent VR products, such as HTC VIVE Pro and Oculus Rift DK2, have a diagonal FOV of over 100 degrees.

Table 2 The results of quality assessment of the 48 studies

Authors and year of publication	Quality of information reporting	External validity	Biases in the measurement of intervention and outcome	Total score
Anderson et al., 2005 [24]	5	1	4	10
Botella et al., 2004 [25]	7	1	4	12
Bouchard et al., 2006 [26]	6	2	4	12
Choi et al., 2005 [27]	7	1	4	12
Crosbie et al., 2012 [28]	8	2	5	15
Difede et al., 2007 [29]	8	1	4	13
Du Sert et al., 2018 [30]	8	1	4	13
Emmelkamp et al., 2001 [31]	6	1	3	10
Emmelkamp et al., 2002 [32]	8	2	4	14
Freeman et al., 2018 [67]	9	2	5	16
Gamito et al., 2010 [33]	4	1	4	9
Garcia-Palacios et al., 2002 [34]	7	2	5	14
Geraets et al., 2019 [35]	8	1	4	13
Gujjar et al., 2018 [37]	7	2	5	14
Gujjar et al., 2019 [36]	9	2	5	16
Harris et al., 2002 [38]	6	2	4	12
Hodges et al., 1995 [39]	8	2	4	14
Hoffman et al., 2003 [40]	7	2	5	14
Kim et al., 2017 [2]	9	1	4	14
Krijn et al., 2004 [41]	8	1	4	13
Krijn et al., 2007 [42]	8	1	4	13
Lee and Kim, 2018 [43]	8	2	4	14
Lee et al., 2020 [44]	9	1	4	14
Lindner et al., 2020 [45]	9	1	5	15
Loucks et al., 2019 [46]	8	1	4	13
Malbos et al., 2013 [47]	8	1	4	13
McLay et al., 2012 [49]	9	1	4	14
McLay et al., 2014 [48]	8	1	4	13
Meyerbröker et al., 2011 [50]	8	1	3	12
Micarelli et al., 2017 [51]	8	1	5	14
Micarelli et al., 2019 [52]	9	1	4	14
Miloff et al., 2019 [53]	9	2	5	16
Moldovan and David, 2014 [54]	7	1	5	13
Ögün et al., 2019 [55]	7	1	4	12
Park et al., 2020 [56]	9	1	4	14
Pelissolo et al., 2012 [57]	9	2	4	15
Perez-Ara et al., 2010 [58]	5	1	4	10
Pot-Kolder et al., 2018 [5]	9	2	4	15
Reger et al., 2011 [59]	7	1	4	12
Reger et al., 2016 [3]	8	1	5	14
Rothbaum et al., 2001 [60]	8	1	4	13
Rus-Calafell et al., 2013 [1]	8	1	4	13
Thapa et al., 2020 [61]	8	2	5	15
Tortella-Feliu et al., 2011 [62]	9	1	5	15
Vass et al., 2020 [63]	9	1	4	14
Vincelli et al., 2003 [64]	7	2	5	14
Wallach et al., 2009 [65]	7	1	4	12
Ziak et al., 2017 [66]	7	1	5	13

Table 3 Results of the meta-analysis, heterogeneity tests, and publication bias tests of the health outcomes for each disorder or impairment type

Disorder or impairment type and its associated health outcomes	Number of experiments	Sample size	SMD[a] (95% CI[b])	*p* value	I^2	Egger's test	
						t value	*p* value
Posttraumatic stress disorder (PTSD)							
Severity of symptoms	5	124	-0.94 (-1.42 to -0.46)	<0.001	77	0.49	0.33
Anxiety	3	89	-0.62 (-0.85 to -0.40)	<0.001	0	0.07	0.48
Depression	4	77	-0.74 (-0.99 to -0.49)	<0.001	0	0.40	0.36
Distress caused by traumatic events	2	13	-0.32 (-0.87 to 0.24)	0.27	0	NA[c]	NA
Agoraphobia							
Fear of panic attacks	5	69	-1.08 (-1.48 to -0.67)	<0.001	35	0.73	0.26
Depression	3	53	-1.08 (-1.78 to -0.39)	0.002	63	7.69	0.04
State anxiety	3	53	-1.25 (-2.35 to -0.15)	0.03	84	1.27	0.21
Trait anxiety	3	53	-1.41 (-2.41 to -0.41)	0.01	78	1.23	0.22
Severity of panic disorder	4	54	-1.69 (-2.11 to -1.28)	<0.001	0	1.55	0.13
Anxiety sensitivity	3	43	-1.20 (-1.62 to -0.70)	<0.001	25	0.38	0.38
Avoidance, distress, and phobic symptoms	2	33	-0.83 (-1.22 to -0.43)	<0.001	0	NA	NA
Severity of avoidance and panic attacks	3	20	-0.99 (-1.54 to -0.44)	<0.001	1	7.13	0.04
Fear of height							
Anxiety	7	118	-1.18 (-1.67 to -0.68)	<0.001	72	0.52	0.31
Avoidance	6	110	-1.24 (-1.49 to -0.99)	<0.001	0	0.18	0.43
Attitude towards height	5	61	-1.14 (-1.49 to -0.80)	<0.001	9	1.55	0.11
Social anxiety disorder							
Fear and avoidance	4	70	-0.83 (-1.17 to -0.49)	<0.001	30	0.93	0.23
Fearful thoughts experienced during public speaking–positive statement	3	50	-0.97 (-1.31 to -0.63)	<0.001	0	0.21	0.44
Fearful thoughts experienced during public speaking–negative statement	3	50	-0.84 (-1.54 to -0.14)	0.02	74	5.11	0.06
Fear of criticism or negative evaluation	2	40	-1.03 (-1.92 to -0.14)	0.02	80	NA	NA
Social phobia fears	2	21	-0.98 (-1.63 to -0.33)	0.003	33	NA	NA
Fear of public speaking	2	18	-1.73 (-2.46 to -0.99)	<0.001	0	NA	NA
Fear of flying							
Anxiety in flying-related situations	2	38	-0.56 (-0.90 to -0.21)	0.002	0	NA	NA
Symptom modalities of anxiety expression	2	38	-0.60 (-0.95 to -0.25)	0.001	0	NA	NA
Fear in different flying-related situations	3	35	-1.79 (-2.40 to -1.17)	<0.001	21	0.59	0.33
Danger and anxiety expectations	2	16	-1.00 (0.40 to 1.60)	0.001	0	NA	NA
Spider phobia							
Fear and avoidance of spiders	5	92	-1.83 (-2.52 to -1.13)	<0.001	64	8.52	0.002
Behavioral avoidance	4	72	-1.50 (-1.84 to -1.17)	<0.001	0	0.03	0.49
Anxiety	2	15	-1.50 (-2.24 to -0.76)	<0.001	0	NA	NA
Psychotic disorders							
Depression	2	73	-0.28 (-0.71 to 0.14)	0.20	54	NA	NA
Psychiatric symptoms	2	23	-0.49 (-0.92 to -0.05)	0.03	0	NA	NA
Poststroke motor impairment							
Upper extremity function and dexterity	3	54	-0.63 (-1.20 to -0.05)	0.03	69	43.22	0.01
Mild cognitive impairment (MCI)							
Cognitive function	2	43	-0.40 (-0.71 to -0.09)	0.01	0	NA	NA
Dental phobia							
Behavioral avoidance	2	20	-2.84 (-4.38 to -1.30)	<0.001	33	NA	NA
State anxiety	2	20	-1.44 (-2.12 to -0.78)	<0.001	12	NA	NA
Dental trait anxiety	2	20	-1.97 (-2.72 to -1.21)	<0.001	0	NA	NA
Fear of dentistry	2	20	-2.03 (-2.80 to -1.26)	<0.001	0	NA	NA
Amblyopia							

Table 3 (continued)

Disorder or impairment type and its associated health outcomes	Number of experiments	Sample size	SMD[a] (95% CI[b])	*p* value	I^2	Egger's test	
						t value	*p* value
Visual acuity	2	24	-0.42 (-0.84 to 0.00)	0.048	0	NA	NA
Unilateral vestibular hypofunction (UVH)							
Confidence in balance during daily activities	2	34	-2.37 (-3.12 to -1.61)	<0.001	22	NA	NA
Body sway in upright position:							
• The frequency of body oscillations							
-Eye closed (right-left directions)	2	34	-1.40 (-2.03 to -0.77)	<0.001	32	NA	NA
-Eye closed (forward–backward directions)	2	34	-1.95 (-3.24 to -0.66)	0.003	71	NA	NA
-Eye open (right-left directions)	2	34	-3.31 (-7.03 to 0.42)	0.08	90	NA	NA
-Eye open (forward–backward directions)	2	34	-3.52 (-6.63 to -0.41)	0.03	85	NA	NA
• Trace surface (eye closed)	2	34	-1.57 (-2.07 to -1.06)	<0.001	0	NA	NA
• Trace length (eye open)	2	34	-2.74 (-3.49 to -2.00)	<0.001	1	NA	NA
• Trace length (eye closed)	2	34	-2.01 (-2.95 to -1.18)	<0.001	42	NA	NA
Gains of vestibule-ocular reflex	2	34	-2.66 (-3.49 to -1.83)	<0.001	23	NA	NA

[a]SMD: standardized mean difference; [b]CI: confidence interval; [c]NA: not applicable

Wider FOV leads to better visual experience, increasing users' information-processing capabilities, and a higher level of sense of presence and immersion in the virtual environment [69]. Moreover, the improvement of control devices in a VR system also makes the interactions between users and virtual environments more intuitive and natural. Earlier studies conducted in the 2000s commonly used a mouse or joystick for users to interact with virtual objects. In recent years, wireless controllers (e.g., HTC wireless controllers) with buttons, triggers, touchpad, and sensors have been developed, and users can hold one controller in each hand and interact with the virtual objects by natural and simple actions. For example, the controllers can be presented as hand avatars in virtual environments; when users intend to touch a virtual object, they can just reach out their hand avatars to approach the virtual object, which is much like how people do it in the real world. Leap Motion (Leap Motion, Inc.), an optical hand tracker, is another type of control device that has been used in recent studies. Users can place their hands above the device within about 70 cm and their hand movements can be captured and displayed on the screen in real time without touching the device. The more natural way of interactions provided by those innovative control devices makes VR technology feasible in the field of motor rehabilitation, in which the users are usually required to move their body parts in various directions.

Furthermore, more resources of VR software are becoming available to researchers and health professionals in recent years. For example, various software development kits (SDKs) have been released and constantly updated by VR hardware manufacturers such as Oculus and HTC, thus researchers and healthcare professionals can develop therapeutic programs more easily and efficiently [68]. Game engines such as Unity and Unreal Engine provide powerful functions and rich online resources (e.g., tutorials, 3D assets, game effects), with which researchers and healthcare professionals can develop various VR programs for therapeutic purposes.

4.2 The use of immersive VR in treatments and therapies

In the treatment of anxiety disorders, immersive VR has been used to deliver exposure therapy by providing simulated situations that individuals fear. By being exposed to the feared situations with the guide of therapists, individuals would gradually become desensitized to the feared situations, leading to alleviation of anxiety symptoms [9, 71]. Onyesolu and Eze indicated that being exposed to simulated situations is an important step before being exposed to real situations in the treatment of anxiety disorders [72]. Our results further contribute evidence to the literature supporting the use of VR in treating anxiety disorders. However, our conclusions should be interpreted with caution as moderate to high levels of heterogeneity and publication bias were detected in some health outcomes examined (e.g., depression for agoraphobia, severity of symptoms for PTSD).

For the treatment of psychotic disorders, immersive VR has been used to create avatars that reflected the patients' inner thoughts (e.g., an avatar presenting the source of the patients' malevolent voice) [30] or represented surrounding people in social situations in daily life (e.g., a barista in a café, a professor standing in front of a table) [5, 63]. The patients were encouraged to communicate and interact with the avatars to reduce auditory verbal hallucinations [30], alleviate paranoid thoughts [63], and facilitate their social participation [5, 63]. However, the evidence on the use of VR for treating psychotic disorders is still limited, more studies are required.

Immersive VR has also been used in motor rehabilitation among patients following a stroke. The VR-based motor rehabilitation exercise was usually designed as games, which required patients to perform certain movements repetitively, such as reaching to objects, grasping and releasing objects, to achieve the goal of the games. Although the evidence in our review is limited, it is consistent with previous research indicating that immersive VR might be beneficial in improving upper limb motor function [16, 73].

Moreover, immersive VR games have been used for cognitive rehabilitation among patients with MCI. The games were designed based on daily life activities, such as withdrawing money from automated teller machine (ATM), shopping, preparing drink, to improve patients' attention, perceptual space ability, numerical ability, perceptivity, logical ability, and memory [56, 61]. The research into the use of immersive VR in treating cognitive impairment has just started in recent years, and the studies included in our review indicated the feasibility of using immersive VR for assisting cognitive rehabilitation.

In addition, immersive VR has been used for treating UVH. The two included studies were conducted by the same research team, and they developed a car racing game to deliver gaze stabilization exercise. A visual optokinetic stimulation (i.e., a car) kept showing in a virtual car racing scenario, and the patients were able to control the direction of the car by tilting their head to the left or right to improve their coordination of head and eye movements. The results demonstrated the feasibility of using immersive VR in the treatment of vestibular disorders and further studies are encouraged to provide more evidence.

Furthermore, immersive VR was used for dichoptic visual training among patients with amblyopia. One advantage of HMD is that it can provide independent control of the visual stimulation in the right or left eye. In the reviewed studies, HMD provided stronger visual simulation (e.g., increased contrast) to the amblyopic eye while provided weaker visual simulation (e.g., decreased contrast) to the normal eye, aiming at forcing the use of the amblyopic eye [43, 66]. The evidence is limited but promising, and further studies are needed to further examine the effect of immersive VR in treating amblyopia.

4.3 Implications for research

This review provides several implications for research. First, most of the included studies had a small sample size (e.g., approximately half of the included studies had fewer than 14 participants). Future studies are suggested to conduct power analysis and involve a larger sample size, to have adequate power to detect significant changes in health outcomes and reduce the possibility of publication bias [9, 74, 75]. Second, some of the included studies lacked information on characteristics of participants (e.g., disease duration, sex ratio) or characteristics of VR-supported interventions (e.g., specifications of the VR system used in the experiment). The information may include potential factors that influence the effectiveness of VR-supported interventions and can be used as references for future research. Therefore, future studies are recommended to provide detailed and sufficient information related to participants and VR-supported interventions. Third, it was observed that the use of VR-supported interventions was associated with improvements in some of the examined health outcomes. Future studies are suggested to explore the possible reasons for the improvements and identify the features of the VR-supported interventions that are effective for treatments and therapies.

4.4 Implications for practice

This study provides several implications for practice. Our review provided evidence that the use of immersive VR in treating anxiety disorders was associated with improvement in anxiety-related symptoms, such as depression and fear. Using immersive VR can be considered an alternative tool for treating anxiety disorders. Moreover, our results showed that the participant groups vary in different types of disorders. For example, the included studies on the treatment of PTSD had a higher proportion of male (i.e., the male ratio was over 80% in six of the eight studies) while the female ratio was high in the studies on the treatment of spider phobia (i.e., the female ratio was higher than 75% in four of the five studies). According to previous studies [76–80], users of different types may have different perceptions on virtual environments, which may lead to different magnitude of the effectiveness of VR-supported interventions on health outcomes. Therefore, VR programs should be developed based on the characteristics of the target population to improve the usability of the programs, and ultimately improve the effectiveness of VR in treatments and therapies [81–85].

4.5 Limitations

This review has a few limitations. First, moderate to high levels of heterogeneity were observed among the included studies in the meta-analyses. Possible sources of heterogeneity might be clinical or methodological differences, such as diversity in the characteristics of participants (e.g., age, gender, and baseline disease severity), study protocol (e.g., diagnosis code used, participant inclusion/exclusion criteria), study location (e.g., culture, social economy), VR technology used (e.g., HMD or CAVE, HMD used in the 2000s or HMD used in the 2010s), the form of intervention (e.g., using VR program plus conventional therapy or using VR program alone), or the duration of the VR-supported intervention [86–89]. For example, previous studies indicated that there are age and gender differences in perception on virtual environments [76–79]. Elderly users usually have less experience with VR and have more difficulty in navigation in the virtual environments compared to younger users [78]; female users can perceive more shades of colors while male users tend to have a higher sense of presence and better spatial navigation ability in virtual environments [76, 77, 79]. Therefore, VR-supported interventions may impact different groups of participants in different magnitude. However, the small number of studies included for each type of disorder or impairment limits our ability to examine the effect of moderating variables and identify potential causes of heterogeneity. Second, the reported effects of VR-supported interventions should be interpreted cautiously as the participants in some of the included studies received both VR intervention and conventional therapy, for example, VR exposure therapy plus cognitive behavioral therapy for anxiety disorders [31, 50]. The degree of the effects of VR programs on improving health outcomes needs to be further examined. Third, publication biases were detected for some health outcomes (e.g., depression for agoraphobia, anxiety for fear of height), suggesting that our findings may not be conclusive.

5 Conclusions

Immersive VR has emerged as a feasible tool for supporting the delivery of treatments and therapies. This review examined the effectiveness of immersive VR-supported interventions in improving health outcomes among individuals with disorders or impairments. Our results indicated that anxiety disorders have been relatively more studied and the use of immersive VR was associated with improvements in anxiety-related symptoms. Immersive VR has also shown potential in improving psychotic disorders, poststroke motor impairment, MCI, amblyopia, and UVH. More research is required to further validate the current evidence. Well-designed studies with adequate sample sizes are required to provide more supporting evidence for verifying the effects of immersive VR in improving health outcomes in treatments and therapies. VR therapeutic programs that are designed according to the characteristics of the target participant group are highly encouraged to improve the usability of the VR programs and optimize the benefits of VR in treatments and therapies.

Appendix 1. The quality assessment criteria

Quality assessment criteria
Information reporting
1. Is the hypothesis/aim/objective of the study clearly described?
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?
3. Are the characteristics of the patients included in the study clearly described?
4. Are the interventions of interest clearly described?
5. Are the main findings of the study clearly described?
6. Does the study provide estimates of the random variability in the data for the main outcomes?
7. Have all important adverse events that may be a consequence of the intervention been reported?
8. Have the characteristics of patients lost to follow-up been described?
9. Have actual probability values been reported (e.g., 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?
External validity
10. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?
11. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?
12. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?
Biases in the measurement of the intervention and outcome
13. If any of the results of the study were based on “data dredging”, was this made clear?
14. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case–control studies, is the time period between the intervention and outcome the same for cases and controls?
15. Were the statistical tests used to assess the main outcomes appropriate?
16. Was compliance with the intervention/s reliable?
17. Were the main outcome measures used accurate (valid and reliable)?

Appendix 2. Study details and intervention characteristics of the 52 experiments

Author, publication year, and study location	Sample	Details of the virtual reality (VR) system used in the experiment	Virtual environments simulated in the experiment	Frequency and duration of the VR-supported intervention
Posttraumatic stress disorder (PTSD)				
Difede et al., 2007 [29] USA	N=13; Male ratio=84.6%; Mean age=40.9 years; Mean disease duration=not reported (NR)	• VR type: Head-mounted display (HMD) Kaiser XL-50 • Control device: keyboard • Display: Light-emitting diode (LED) • Resolution: 1024×768 pixels • Field of view (FOV): 40° (horizontal)×30°(vertical) • Degree of freedom (DOF): Not reported (NR)	Eleven scenes of the World Trade Center attacks	• Psychoeducation: 2 sessions • Virtual reality (VR) intervention: 75 min/session, 1 session/week for 6 to 13 weeks (mean number of sessions=7.5)
Gamito et al., 2010 [33] Portugal	N=4; Male ratio=100%; Mean age=63.5 years; Mean disease duration=NR	• VR type: HMD eMagin Z800 • Control device: NR • Display: Organic Light-emitting diode (OLED) • Resolution: 800×600 pixels (per eye) • FOV: 40° (diagonal) • DOF: NR	Scenes of a battlefield	• Participants' anamnesis and psychoeducation: 1 session • VR intervention: 11 sessions
Loucks et al., 2019 [46] USA	N=15; Male ratio=26.6%; Mean age=46.0 years; Mean disease duration=NR	• VR type: HMD eMagin Z800 • Control device: Logitech F310 game pad and Ion GoPad thumb mouse • Display: OLED • Resolution: 800×600 pixels (per eye) • FOV: 40° (diagonal) • DOF: NR	Scenes of the Afghanistan-themed forward operating base, and US civilian and military base	• VR intervention: 90 min/session, 6–12 sessions
McLay et al., 2012 [49] USA	N=20; Male ratio=95.0%; Mean age=28.1 years; Mean disease duration=NR	• VR type: HMD • Control device: NR • Display: NR • Resolution: NR • FOV: NR • DOF: NR	Scenes of an Iraq-like city for car driving	• VR intervention: 90–120 min/session, 2 sessions/week, a total of 12–15 sessions over a maximum of 10 weeks
McLay et al., 2014 [48] USA	N=15; Male ratio=93.3%; Mean age=34.1 years; Mean disease duration=NR	• VR type: HMD • Control device: NR • Display: NR • Resolution: NR • FOV: NR • DOF: NR	Scenes of Iraq and Afghanistan	• VR intervention: 90 min/session, 1 or 2 sessions/week. A total of 5, 10, 15, or 20 sessions over 10 weeks
Reger et al., 2011 [59] USA	N=24; Male ratio=NR; Mean age=28.8 years; Mean disease duration=NR	• VR type: HMD eMagin Z800 • Control device: joystick attached to a mock M4 rifle, and Logitech joystick • Display: OLED • Resolution: 800×600 pixels (per eye) • FOV: 40° (diagonal) • DOF: NR	Scenes of a convoy and a patrol in an Iraqi city	• VR intervention: 90 min/session, 3–12 sessions (mean number of sessions=7.4)
Reger et al., 2016 [3] USA	N=54; Male ratio=96.3%; Mean age=29.5 years; Mean disease duration=NR	• VR type: HMD eMagin Z800 • Control device: joystick attached to a mock M4 rifle, and Logitech joystick • Display: OLED • Resolution: 800×600 pixels (per eye) • FOV: 40° (diagonal) • DOF: NR	Scenes of a convoy and a patrol in an Iraqi city	• VR intervention: 90–120 min/session, 1 or 2 sessions/week, 10 sessions

Author, publication year, and study location	Sample	Details of the virtual reality (VR) system used in the experiment	Virtual environments simulated in the experiment	Frequency and duration of the VR-supported intervention
Rothbaum et al., 2001 [60] USA	N=9; Male ratio=100%; Mean age=51.0 years; Mean disease duration=NR	• VR type: HMD Virtual Research V6 • Control device: joystick • Display: Liquid–crystal display (LCD) • Resolution: 640×480 pixels (per eye) • FOV: 60° (diagonal) • DOF: NR	Scenes of a battlefield in the Vietnam jungle	• VR intervention: 90 min/session, 8–16 sessions over 5-7 weeks
Agoraphobia				
Choi et al., 2005 [27] South Korea	N=20; Male ratio=55.0%; Mean age=35.7 years; Mean disease duration=5.2 years	• VR type: HMD Sony Glasstron PLM-A55 • Control device: joystick • Display: LCD • Resolution: 800×225 pixels (per eye) • FOV: NR • DOF: NR	Scenes of an elevator, supermarket, subway, and square	• Each session included 120 min of psychoeducation, cognitive restructuring, diaphragmatic breathing, relaxation techniques, interoceptive exposure, and vivo exposure, plus 30 min of VR intervention, 1 session/week for 4 weeks
Malbos et al., 2013 [47] Australia	N=9; Male ratio=NR; Mean age=44.1 years; Mean disease duration=18.0 years	• VR type: HMD Virtual Realities HMD 42 Pro • Control device: Logitech Momo steering wheel • Display: OLED • Resolution: 800×600 pixels • FOV: 42° (diagonal) • DOF: 3	Scenes of a valley, a town square, a supermarket, bridges, a subway station, an underground car park, a cinema, an airplane with all flight procedures, and a highway with tunnel/traffic jam	• VR intervention: 90 min/session, 1 session/week for 10 weeks
Meyerbröker et al., 2011 [50] Netherlands	N=5; Male ratio=NR; Mean age=NR; Mean disease duration=NR	• VR type: HMD Nvisor sx. Projection • Control device: NR • Display: NR • Resolution: NR • FOV: NR • DOF: NR	Agoraphobic scenes	• Psychoeducation, cognitive restructuring, and interoceptive exposure: 4 sessions • VR intervention: 6 sessions
Meyerbröker et al., 2011 [50] Netherlands	N=6; Male ratio=NR; Mean age=NR; Mean disease duration=NR	• VR type: Cave automatic virtual environment (CAVE) system, including projectors, Crystal Eyes active stereo glasses, and Ascension Technologies Flock of Birds head tracking system • Control device: NR • Number of screens: 4 • Resolution: 1400×1050 pixels • FOV: around 180° • DOF: NR	Agoraphobic scenes	• Psychoeducation, cognitive restructuring, and interoceptive exposure: 4 sessions • VR intervention: 6 sessions
Pelissolo et al., 2012 [57] France	N=29; Male ratio=27.6%; Mean age=37.7 years; Mean disease duration=NR	• VR type: HMD Kaiser Proview 60 • Control device: NR • Display: LCD • Resolution: 640×480 pixels (per eye) • FOV: 48° (horizontal)×36°(vertical) • DOF: NR	Scenes of the subway, tunnels, elevator, supermarket shopping, car-driving, traveling on a plane, movie theatre, traveling by bus, being caught in a conflict, street, and crowded subways	• VR intervention: 60 min/session, 1 session/week for 12 weeks

Author, publication year, and study location	Sample	Details of the virtual reality (VR) system used in the experiment	Virtual environments simulated in the experiment	Frequency and duration of the VR-supported intervention
Perez-Ara et al., 2010 [58] Spain	N=14; Male ratio=20.7%; Mean age=32.8 years; Mean disease duration=NR	• VR type: HMD Virtual Research V6 • Control device: mouse • Display: LCD • Resolution: 640×480 pixels (per eye) • FOV: 60° (diagonal) • DOF: NR	Audio and visual effects, including rapid heartbeat, panting, blurred vision, double vision, and tunnel vision, and also agoraphobic scenes	• Psychoeducation sessions: 2 sessions • VR intervention: a maximum of 6 sessions, each session lasted for approximately 50 min
Vincelli et al., 2003 [64] Italy	N=4; Male ratio=0.0%; Mean age=48.3 years; Mean disease duration=NR	• VR type: HMD Sony Glasstron PLM-A35 • Control device: joystick • Display: LCD • Resolution: 800×225 pixels • FOV: NR • DOF: NR	Scenes of an elevator, supermarket, subway, and square	• VR intervention: 8 sessions
Social anxiety disorder				
Anderson et al., 2005 [24] USA	N=10; Male ratio=20.0%; Mean age=NR; Mean disease duration=NR	• VR type: HMD • Control device: NR • Display: NR • Resolution: NR • FOV: NR • DOF: NR	Scenes a podium for giving speeches and a group of audience	• Anxiety management training: 4 sessions • VR intervention: 4 sessions
Geraets et al., 2019 [35] Netherlands	N=15; Male ratio=46.7%; Mean age=34.9 years; Mean disease duration=9.4 years	• VR type: HMD Sony HMZ-T1 • Control device: joystick • Display: OLED • Resolution: 1280×720 pixels (per eye) • FOV: 51.6° (diagonal) • DOF: NR	Scenes of street, bus, café, and supermarket	• VR intervention: a maximum of 16 60-min sessions, delivered once or twice a week
Harris et al., 2002 [38] USA	N=8; Male ratio=NR; Mean age=NR; Mean disease duration=NR	• VR type: HMD Virtual I/O • Control device: NR • Display: NR • Resolution: 640×480 pixels • FOV: 30° (diagonal) • DOF: NR	Scenes of an empty auditorium for giving speeches and a group audience	• VR intervention: 12–15 min/session, 1 session/week for 4 weeks
Kim et al., 2017 [2] South Korea	N=22; Male ratio=36.4%; Mean age=23.0 years; Mean disease duration=NR	• VR type: HMD Samsung Gear VR • Control device: NR • Display: OLED • Resolution:2560×1440 pixels • FOV: 101° (diagonal) • DOF: 3	Scenes of social situations of school, business, and daily life. There were avatars in those scenes that the participants could interact with	• VR intervention: 8 sessions over 2 weeks
Moldovan and David, 2014 [54] Romania	N=15; Male ratio=40.0%; Mean age=NR; Mean disease duration=NR	• VR type: HMD • Control device: NR • Display: NR • Resolution: NR • FOV: NR • DOF: NR	NR	• Psychoeducation plus VR intervention: 1 session, including 150 min psychoeducation and 90 min VR therapy
Wallach et al., 2009 [65] Israel	N=28; Male ratio=17.9%; Mean age=28.2 years; Mean disease duration=NR	• VR type: HMD Interactive Imaging Systems VFX3D • Control device: NR • Display: LCD • Resolution: 360,000 pixels • FOV: 35° (diagonal) • DOF: NR	Scenes a podium and a large audience	• VR intervention: 60 min/session, a total of 12 sessions

Author, publication year, and study location	Sample	Details of the virtual reality (VR) system used in the experiment	Virtual environments simulated in the experiment	Frequency and duration of the VR-supported intervention
Fear of flying				
Botella et al., 2004 [25] Spain	N=9; Male ratio=NR; Mean age=33.3 years; Mean disease duration=5.7 years	• VR type: HMD Virtual I/O • Control device: mouse • Display: NR • Resolution: 640×480 pixels • FOV: 30° (diagonal) • DOF: NR	Scenes of a bedroom, an airport, and an airplane	• Psychoeducation: 1 session • VR intervention: 45–60 min/session, total 6 sessions
Krijn et al., 2007 [42] Netherlands	N=29; Male ratio=NR; Mean age=35.6 years; Mean disease duration=13.3 years	• VR type: HMD Cybermind Visette Pro • Control device: NR • Display: LCD • Resolution: 640×480 pixels • FOV: 70.5° (diagonal) • DOF: NR	Scenes of an airport and the inside of an airplane	• VR intervention: 60 min/session, 1 session/week for 4 weeks
Moldovan and David, 2014 [54] Romania	N=9; Male ratio=55.6%; Mean age=NR; Mean disease duration=NR	• VR type: HMD • Control device: NR • Display: NR • Resolution: NR • FOV: NR • DOF: NR	NR	• Psychoeducation plus VR intervention: 1 session, including 150 min psychoeducation and 90 min VR therapy
Rus-Calafell et al., 2013 [1] Spain	N=7; Male ratio=12.5%; Mean age=37.1 years; Mean disease duration=NR	• VR type: HMD 5DT model • Control device: mouse • Display: NR • Resolution: NR • FOV: NR • DOF: NR	Scenes of a bedroom, an airport, and the inside of an airplane	• Psychoeducation sessions: 2 sessions • VR intervention: 60–75 min/session, 2 sessions/week for 3 weeks
Tortella-Feliu et al., 2011 [62] Spain	N=19; Male ratio=47.4%; Mean age=36.9 years; Mean disease duration=4.4 years	• VR type: HMD 5DT model 800 • Control device: NR • Display: NR • Resolution: NR • FOV: NR • DOF: NR	The virtual environments were the same as the ones in Botella et al. (2004)	• VR intervention: 60 min/session, 3 sessions/week, a maximum of 6 sessions
Spider phobia				
Bouchard et al., 2006 [26] Canada	N=11; Male ratio=9.0%; Mean age=30.7 years; Disease duration: since childhood	• VR type: HMD I-Glass I/O • Control device: Microsoft joystick • Display: NR • Resolution: 640×480 pixels • FOV: 30° (diagonal) • DOF: 3	Scenes of spiders in different rooms. The size and number of spiders were different in the rooms. The spiders could follow the moves of the participants or walk towards the participants	• Psychoeducation: 1 90-min session • VR intervention: 90 min/session, 1 session/week for 3 weeks
Garcia-Palacios et al., 2002 [34] USA	N=12; Male ratio=9.1%; Mean age=29.3 years; Mean disease duration=21.0 years	• VR type: HMD Virtual Research V8 • Control device: NR • Display: LCD • Resolution: 640×480 pixels • FOV: 60° (diagonal) • DOF: NR	Scenes of a spider in a kitchen. The spiders could be touched or picked up	• VR intervention: average of 4 60-min sessions over 2 or 3 weeks
Hoffman et al., 2003 [40] USA	N=3; Male ratio=NR; Mean age=18.7 years; Mean disease duration=12.0 years	• VR type: HMD Division dVisor • Control device: NR • Display: NR • Resolution: NR • FOV: 105° (horizontal)×40° (vertical) • DOF: NR	Scenes of a spider in a kitchen. The spiders could be touched or picked up	• VR intervention: 60 min/session, 3 sessions/week for 1 week

Author, publication year, and study location	Sample	Details of the virtual reality (VR) system used in the experiment	Virtual environments simulated in the experiment	Frequency and duration of the VR-supported intervention
Miloff et al., 2019 [53] Sweden	N=50; Male ratio=16.0%; Mean age=34.1 years; Mean disease duration=NR	• VR type: HMD Samsung Gear VR • Control device: NR • Display: OLED • Resolution: 2560×1440 pixels • FOV: 101° (diagonal) • DOF: 3	Scenes of a spider. The spider can interact with the participants	• VR intervention: a single session up to 3 h (mean duration of the session=171.52 min)
Lindner et al., 2020 [45] Sweden	N=25; Male ratio=24.0%; Mean age=25.0 years; Mean disease duration=NR	• VR type: HMD Samsung Gear VR • Control device: NR • Display: OLED • Resolution: 2560×1440 pixels • FOV: 101° (diagonal) • DOF: 3	The virtual environments were the same as the ones in Miloff et al. (2019)	• Psychoeducation and VR intervention: a single 3-h session
Fear of height				
Emmelkamp et al., 2001 [31] Netherlands	N=10; Male ratio=30.0%; Mean age=NR; Mean disease duration=NR	• VR type: HMD Virtual I/O • Control device: keyboard and joystick • Display: NR • Resolution: 640×480 pixels • FOV: 30° (diagonal) • DOF: NR	Two scenes, including a diving tower with a swimming pool, and a tower building with a glazed elevator	• Vivo exposure: 60 min/session, 2 sessions for 1 week • VR intervention: 60 min/session, 2 sessions for 1 week
Emmelkamp et al., 2002 [32] Netherlands	N=17; Male ratio=NR; Mean age=44.0 years; Mean disease duration=31.5 years	• VR type: HMD Cybermind Visette Pro. Projection • Control device: joystick • Display: LCD • Resolution: 640×480 pixels • FOV: 70.5° (diagonal) • DOF: NR	Three scenes, including a mall, existing of four floors with escalators and balustrades; a fire escape with approximately 50-feet in height; and a roof garden at top of a building with approximately 65-feet in height	• VR intervention: 60 min/session, 1 session/week for 3 weeks
Freeman et al., 2018 [67] UK	N=49; Male ratio=59.2%; Mean age=30.0 years; Mean disease duration=32.0 years	• VR type: HMD HTC Vive • Control device: wireless controllers • Display: OLED • Resolution: 1080×1200 pixels (per eye) • FOV: 110° (diagonal) • DOF: 6	Scenes of an atrium of a large ten-story office complex. There was an avatar virtual coach that guided participants to drop safety-seeking behaviors (e.g., avoiding heights, closing eyes) when facing high places and to develop memories of safety that counteract fear associations	• VR intervention: 30 min/session, 6 sessions over 2 weeks

Author, publication year, and study location	Sample	Details of the virtual reality (VR) system used in the experiment	Virtual environments simulated in the experiment	Frequency and duration of the VR-supported intervention
Hodges et al., 1995 [39] 1995 USA	N=12; Male ratio=NR; Mean age=20.0 years; Mean disease duration=NR	• VR type: HMD Virtual Research Flight Helmet • Control device: NR • Display: NR • Resolution: NR • FOV: NR • DOF: NR	Three scenes, including an open elevator inside of a 49-story hotel; outside balconies attached to a tall building, and bridges spanning the canyon from one side to the other	• VR intervention: 90 min/session, 1 session/week for 3 weeks
Krijn et al., 2004 [41] Netherlands	N=10; Male ratio=NR; Mean age=50.6 years; Mean disease duration=33.5 years	• VR type: HMD Cybermind Visette Pro. Projection • Control device: NR • Display: LCD • Resolution: 640×480 pixels • FOV: 70.5° (diagonal) • DOF: NR	Four scenes, including a shopping mall with four floors, a fire escape with six floors in open space, a roof garden on a building, and a building with eight floors	• VR intervention: 90 min/session, 1 session/week for 3 weeks
Krijn et al., 2004 [41] Netherlands	N=14; Male ratio=NR; Mean age=50.6 years; Mean disease duration=33.5 years	• VR type: CAVE system, including SGI Onyx2RealityMonster, Crystal Eyes LCD Shutter-glasses, and Ascension Technologies Flock of Birds electromagnetic tracking system • Control device: NR • Number of screens: 4 • Resolution: NR • FOV: NR • DOF: NR	Four scenes, including a shopping mall with four floors, a fire escape with six floors in open space, a roof garden on a building, and a building with eight floors	• VR intervention: 90 min/session, 1 session/week for 3 weeks
Moldovan and David, 2014 [54] Romania	N=8; Male ratio=75%; Mean age=NR; Mean disease duration=NR	• VR type: CAVE system • Number of screens: NR • Resolution: NR • FOV: NR • DOF: NR	NR	• Psychoeducation plus VR intervention: 1 session, including 150 min psychoeducation and 90 min VR intervention
Psychotic disorders				
Du Sert et al., 2018 [30] Canada	N=15; Male ratio=66.7%; Mean age=42.9 years; Mean disease duration=17.8 years	• VR type: HMD Samsung Gear VR • Control device: NR • Display: OLED • Resolution: 2560×1440 pixels • FOV: 101° (diagonal) • DOF: 3	An avatar that that best resembling the most distressing person or entity believed to be the source of participants' malevolent voice. The avatar could have a dialogue with the participants	• VR intervention: 45 min/session, 1 session/week for 7 weeks
Pok-Kolder et al., 2018 [5] Netherlands	N=58; Male ratio=69.0%; Mean age=36.5 years; Mean disease duration=13.3 years	• VR type: HMD Sony HMZ-T1/T2/T3 • Control device: Logitech F310 Gamepad • Display: OLED • Resolution: 1280×720 pixels (per eye) • FOV: 51.6° (diagonal) for HMZ-T1; 45° (diagonal) for HMZ-T2 and HMZ-T3 • DOF: 3	Scenes of social situations, including street, bus, café, and supermarket. There were avatars in those scenes that the participants could interact with	• VR intervention: 60 min/session, 16 sessions over 8–12 weeks

Author, publication year, and study location	Sample	Details of the virtual reality (VR) system used in the experiment	Virtual environments simulated in the experiment	Frequency and duration of the VR-supported intervention
Vass et al., 2020 [63] Hungary	N=9; Male ratio=55.6%; Mean age=38.6 years; Mean disease duration=20.8 years	• VR type: HMD Samsung Gear VR • Control device: Samsung Simple Controller and mouse • Display: OLED • Resolution: 2560×1440 pixels • FOV: 101° (diagonal) • DOF: 3	An avatar that the participants could interact with	• VR intervention: 50 min/session, 1 session/week for 8 weeks
Poststroke motor impairment				
Crosbie et al., 2012 [28] North Ireland	N=9; Male ratio=55.6%; Mean age=56.1 years; Mean disease duration=0.8 years	• VR type: HMD • Control device: NR • Display type: NR • Resolution: NR • FOV: NR • DOF: NR	Scenes of games for upper limb motor training, including reaching to target, grasping-and-releasing target, and wrist extension	• VR intervention: 30–45 min/session, 3 sessions/week for 3 weeks
Lee et al., 2020 [44] South Korea	N=12; Male ratio=58.3%; Mean age=40.2 years; Mean disease duration=3 years	• VR type: HMD HTC VIVE • Control device: wireless controllers • Display: OLED • Resolution: 1080×1200 pixels (per eye) • FOV: 110° (diagonal) • DOF: 6	Scenes of games for upper limb motor training, including hammering, ball catching, cup pouring, bubble touching, and xylophone playing	• VR intervention: 30 min/session, 2–3 sessions/week, total 10 sessions
Ögün et al., 2019 [55] Turkey	N=33; Male ratio=84.9%; Mean age=61.5 years; Mean disease duration=14.7 months	• VR type: HMD • Control device: Leap Motion • Display: NR • Resolution: NR • FOV: NR • DOF: NR	Scenes of games for upper limb motor training, including cube handling, decorating a tree with leaves, picking up vegetables from a bowl, a kitchen experience game, and a drumming game	• VR intervention: 60 min/session, 3 sessions/week for 6 weeks

Author, publication year, and study location	Sample	Details of the virtual reality (VR) system used in the experiment	Virtual environments simulated in the experiment	Frequency and duration of the VR-supported intervention
Mild cognitive impairment (MCI)				
Park et al., 2020 [56] South Korea	N=10; Male ratio=30.0%; Mean age=71.8 years; Mean disease duration=NR	• VR type: HMD HTC VIVE • Control device: wireless controllers • Display: OLED • Resolution: 1080×1200 pixels (per eye) • FOV: 110° (diagonal) • DOF: 6	Scenes of six games for cognitive ability training. The "Crows and Seagulls" game involved shooting crows among seagulls at a bridge; "Seek a Song of Our Own" game involved hitting targets according to the rhythm and drumming; "Automated Teller Machine (ATM)" game involved withdrawing money according to a given amount; "Shopping in the Mart" game involved activities of daily living; "Fireworks Party" game involved decorating a night sky by launching fireworks; "Fruit Cocktail" game involved making a cocktail	• VR intervention: 30 min/session, 2 sessions/week for 12 weeks
Thapa et al., 2020 [61] South Korea	N=34; Male ratio=17.7%; Mean age=72.6 years; Mean disease duration=NR	• VR type: HMD Oculus Quest • Control device: wireless controllers • Display: OLED • Resolution: 1440×1600 pixels (per eye) • FOV: NR • DOF: 6	Scenes of six games for cognitive ability training. The "Juice making" game involved making a juice according to the recipe; "Crow shooting" game involved shooting flying birds; "Fireworks" game involved recalling the firework exploded; "Love house" game involved memorizing the location of objects in a house	• VR intervention: 100 min/session, 3 sessions/week for 8 weeks

Author, publication year, and study location	Sample	Details of the virtual reality (VR) system used in the experiment	Virtual environments simulated in the experiment	Frequency and duration of the VR-supported intervention
Dental phobia				
Gujjar et al., 2018 [37] Malaysia	N=5; Male ratio=NR; Mean age=NR; Mean disease duration=NR	• VR type: HMD Oculus Rift DdK2 • Control device: NR • Display: OLED • Resolution: 960×1080 pixels (per eye) • FOV: 100° (diagonal) • DOF: 6	A scene of a virtual dental operatory, which included a patient avatar and a dentist avatar. The dentist avatar interacted with the patient avatar, including sitting on the dental chair, inspecting the oral cavity, introducing an injection, introducing a drill	• VR intervention: 1 session
Gujjar et al., 2019 [36] Malaysia	N=15; Male ratio=46.7%; Mean age=25.3 years; Mean disease duration=NR	• VR type: HMD Oculus Rift DK2 • Control device: NR • Display: OLED • Resolution: 1920×1080 pixels (per eye) • FOV: 100° (diagonal) • DOF: 6	Five scenes of a dental operatory, including a dentist avatar sitting aside a patient avatar; the dentist avatar approaching to the patient avatar, seemingly to do an oral examination; the dentist avatar holding a dental syringe and moving towards the patient avatar; the dentist avatar holding a drill without sound and moving towards the patient avatar; and the dentist avatar holding a drill with sound and moving towards the patient avatar	• VR intervention: 1 session, mean duration of the session=40.06 min
Amblyopia				
Lee and Kim, 2018 [43] South Korea	N=7; Male ratio=60.0%; Mean age=8.7 years; Mean disease duration=2.6 years	• VR type: HMD • Control device: NR • Display: NR • Resolution: NR • FOV: NR • DOF: NR	Scenes of a game for visual ability training. The game involved throwing ice cream to kids running around	• VR intervention: 30 min per day for at least 2 months
Ziak et al., 2017 [66] Slovakia	N=17; Male ratio=NR; Mean age=31.2 years; Mean disease duration=NR	• VR type: HMD Oculus Rift DK2 • Control device: NR • Display: OLED • Resolution: 960×1080 pixels (per eye) • FOV: 100° (diagonal) • DOF: 6	Scenes of two games for visual ability training. One game was a space game that involved driving a spaceship through rings, the other was a block breaker game	• VR intervention: 40 min/session, 2 sessions/week for 4 weeks

Author, publication year, and study location	Sample	Details of the virtual reality (VR) system used in the experiment	Virtual environments simulated in the experiment	Frequency and duration of the VR-supported intervention
Unilateral vestibular hypofunction (UVH)				
Micarelli et al., 2017 [51] Italy	N=17; Male ratio=NR; Mean age=31.2 years; Mean disease duration=NR	• VR type: HMD Revelation • Control device: NR • Display: NR • Resolution: NR • FOV: 110° (diagonal) • DOF: NR	Scenes of a "Track Speed Racing 3D" game for gaze stabilization exercises. The game involved steering the car by tilting head to the left or right to avoid swerving off the road	• Home exercise: total 30–40 min/day for 4 weeks • VR intervention: 20 min/session, 1 session/day for 4 weeks
Micarelli et al., 2019 [52] Italy	N=11; Male ratio=45.5%; Mean age=76.9 years; Mean disease duration=NR	• VR type: HMD Revelation • Control device: NR • Display: NR • Resolution: NR • FOV: 110° (diagonal) • DOF: NR	The virtual environments were the same as the ones in Micarelli et al. (2017)	• Home exercise: total 30–40 min/day for 4 weeks • VR intervention: 20 min/session, 1 session/day for 4 weeks

Appendix 3. The measurement of the examined health outcomes

Disorder or impairment type and its associated health outcomes	Measurement
Posttraumatic stress disorder (PTSD)	
Severity of symptoms	PTSD checklist (PCL)
Anxiety	Behavioral Anxiety Inventory (BAI)
Depression	Beck Depression Inventory (BDI)
Distress caused by traumatic events	Clinician-Administered Posttraumatic Stress (CAPS)
Agoraphobia	
Fear of panic attacks	Agoraphobic Cognitions Questionnaire (ACQ)
Depression	Beck Depression Inventory (BDI)
State anxiety	State-Trait Anxiety Inventory (STAI)
Trait anxiety	State-Trait Anxiety Inventory (STAI)
Severity of panic disorder	Panic Disorder Severity Scale (PDSS)
Anxiety sensitivity	Anxiety Sensitivity Index (ASI)
Avoidance, distress, and phobic symptoms	Fear Questionnaire (FQ)
Severity of avoidance and panic attacks	Mobility Inventory for Agoraphobia (MI)
Fear of height	
Anxiety	Acrophobia Questionnaire (AQ)
Avoidance	Acrophobia Questionnaire (AQ)
Attitude towards height	Attitude Toward Heights Questionnaire (ATHQ)
Social anxiety disorder	
Fear and avoidance	Liebowitz Social Anxiety Scale (LSAS)
Fearful thoughts experienced during public speaking-positive statement	Self-Statements during Public Speaking (SPSS)
Fearful thoughts experienced during public speaking-negative statement	Self-Statements during Public Speaking (SPSS)
Fear of criticism or negative evaluation	Fear of Negative Evaluation (FNE)
Social phobia fears	Social Interaction Anxiety Scale (SIAS)
Fear of public speaking	Personal Report of Confidence as a Speaker (PRCS)
Fear of flying	
Anxiety in flying-related situations	Flight Anxiety Situation (FAS)
Symptom modalities of anxiety expression	Flight Anxiety Modality (FAM)
Fear in different flying-related situations	Fear of flying questionnaire (FFQ)
Danger and anxiety expectations	Danger expectations and flying anxiety Scale (DEFAS)
Spider phobia	
Fear and avoidance of spiders	Fear of Spiders Questionnaire (FSQ)
Behavioral avoidance	Behavioral Avoidance Test (BAT)
Anxiety	Behavioral Avoidance Test (BAT)
Psychotic disorders	
Depression	Beck Depression Inventory (BDI)

Disorder or impairment type and its associated health outcomes	Measurement
Psychiatric symptoms	Positive and Negative Syndrome Scale (PANSS)
Poststroke motor impairment	
Upper extremity function and dexterity	Action Research Arm Test (ARAT)
Mild cognitive impairment (MCI)	
Cognitive function	Mini-Mental State Examination (MMSE)
Dental phobia	
Behavioral avoidance	Behavioral Avoidance Test (BAT)
State anxiety	Visual Analogue Scale (VAS)
Dental trait anxiety	Modified Dental Anxiety Scale (MDAS)
Fear of dentistry	Dental Fear Scale (DFS)
Amblyopia	
Visual acuity	LogMAR visual acuity
Unilateral vestibular hypofunction (UVH)	
Confidence in balance during daily activities	Activities-specific Balance Confidence (ABC)
Body sway in upright position	Static Posturography Testing (SPT)
Gains of vestibule-ocular reflex	Video Head Impulse Testing (vHIT)

Acknowledgements The study was conducted with the support of the Department of Industrial and Manufacturing Systems Engineering at the University of Hong Kong.

Funding The authors received no specific funding for this work.

Declarations

Conflicts of interest The authors declare that there is no conflict of interest.

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