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Effects of virtual reality on the treatment of amblyopia in children: A systematic review and meta-analysis

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ABSTRACT

Problem: Virtual reality technology has been used to treat amblyopia in children. However, it is unclear how virtual reality technology differs from conventional patching therapy in terms of effectiveness.

Eligibility criteria: Eligible randomized controlled studies were retrieved from PubMed, Embase, Scopus, the Cochrane Library, and Web of Science through February 2023.

Sample: Eight studies included 10 trials with 459 participants were included in the current meta-analysis. Two studies (Herbison et al., 2016; Huang et al., 2022) included two trials each. Thus, a total of ten trials were included in the current meta-analysis.

Results: Overall, virtual reality technology treatment significantly improved visual acuity by 0.07 log MAR (95% confidence interval [CI], −0.11 to −0.02; $P < 0.001$; $I^2 = 94.4\%$) compared with traditional patching therapy. In addition, subgroup analyses also revealed that treatment with virtual reality technology was more effective when the child was younger than seven years old, or when the duration of the intervention was no more than twenty hours.

Conclusions: Virtual reality technology treatment showed significant effects in improving visual acuity in children who were seven years of age or younger with amblyopia.

Implications: Virtual reality technology treatment is effective in treating amblyopia in children. Virtual reality therapy is also entertaining and popular among children and can be applied to the treatment of amblyopia in children in the future.

Introduction

Amblyopia refers to an abnormal development of the visual pathway caused by inconsistent binocular vision during the critical period of visual development (DeSantis & Diana., 2014; Kates & Beal, 2021). It can cause visual impairment in one or both eyes (Roda et al., 2021). The main causes of amblyopia are anisometropia and strabismus, or a combination of the two (Barrett et al., 2004). Amblyopia is the most common visual impairment in preschool children (Levi, 2006). The global prevalence of amblyopia in children was 2%–4% (Hu et al., 2022). Amblyopia could be completely cured if it were diagnosed and treated at the age of seven or younger (K. H. Park et al., 2004). Otherwise, amblyopia could result in irreversible vision loss, reduced contrast sensitivity, impaired stereopsis, and visual crowding (Mostafaie et al., 2020; Ruiying & Xiaoqing, 2021; Yekta et al., 2022). Children with amblyopia typically suffer from impaired daily functioning, poor academic performance and limited career choices (Choong et al., 2004). Therefore, it is necessary to actively treat amblyopia in children seven years of age or younger. Patching and atropine therapy are the two main types of conventional amblyopia treatments (T. Li et al., 2019; Repka et al., 2014). However, some studies have suggested that patching therapy has poor compliance and may reduce vision in the fellow eye (Allen et al., 2010; Jonathan M. Holmes et al., 2008). Atropine therapy also has some disadvantages, such as drug allergy, photophobia, and poor near vision in patients (Gong et al., 2017). Virtual reality (VR)-based therapy has become a new treatment option for amblyopia in

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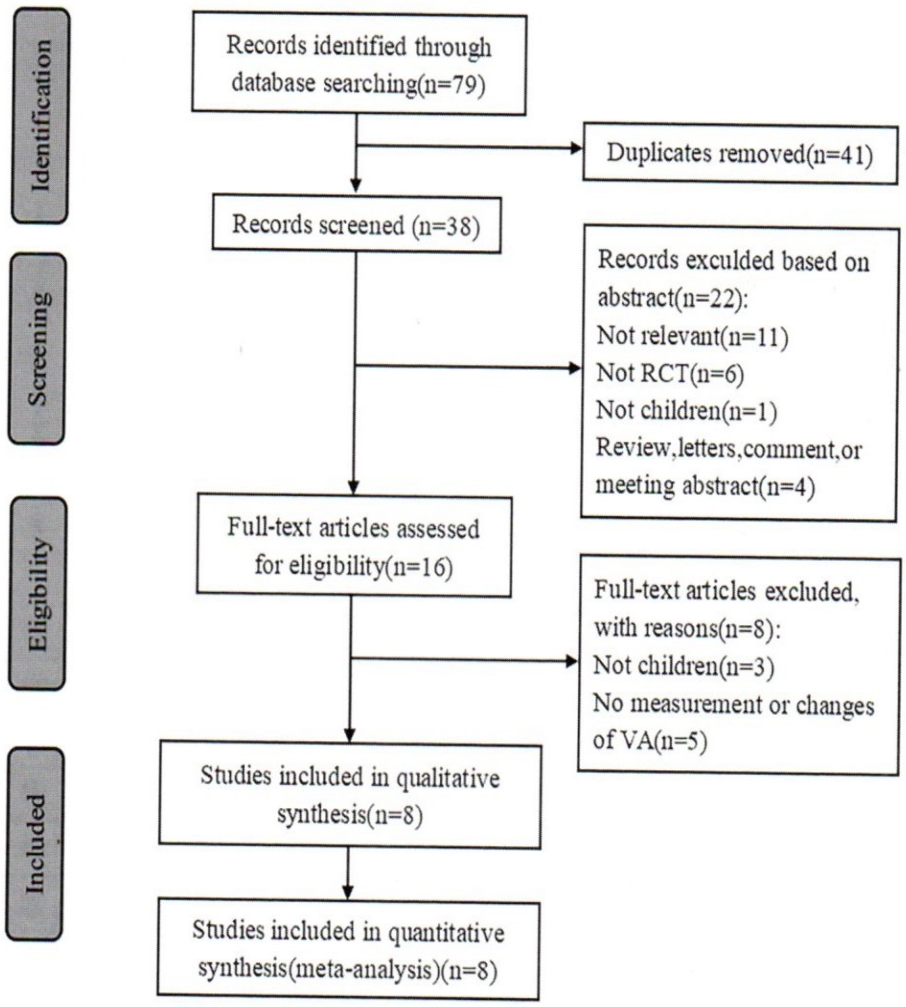

Fig. 1. Flowing diagram of included studies selection process.

recent years. As a binocular amblyopia treatment, this therapy can improve both visual acuity and binocular function in the amblyopic eye (Pineles et al., 2020). In addition, it is more child-friendly, and has fewer side effects than conventional therapies (Kadhum et al., 2021).

In recent years, VR technology has been developed as a potential treatment for amblyopia (Simon-Martinez et al., 2023; Tan et al., 2022). VR technology allows users to experience the virtual world by simulating the real world on the computer (Yang et al., 2019). The VR system provides a stereoscopic image of the 3D virtual environment to each eye separately when it is used to treat amblyopia (Richard Mark Eastgate, 2001). The principle of VR technology in amblyopia treatment is to present two images that are completely different but visually related. An image is presented to each eye independently, and both eyes view the same visual scene simultaneously. The main visual content of the scene is presented to the amblyopic eye (R. M. Eastgate et al., 2006). Eastgate et al. developed the Interactive Binocular Therapy (I-Bit™) system, which used dynamic stimulation to preferentially stimulate the amblyopic eye (R. M. Eastgate et al., 2006). The key feature of the I-Bit™ system was its ability to horizontally, vertically, and torsionally alter the image delivered to each eye to correct for strabismus. Feiyue Qiu et al. proposed the Viston-VR™ system, which allowed children to watch cartoons (Qiu, Wang, Liu, and Yu, 2007). The Viston-VR™ system improved their visual acuity by playing an interactive computer game. The Viston-VR™ system continuously stimulated the amblyopic eye of the patients, improving their visual acuity and stereo vision (Qiu, Wang, Liu, and Yu, 2007).

VR technology has been gradually applied to the treatment of pediatric amblyopia. However, it was unclear how VR technology differed from conventional patching therapy in terms of its effectiveness. Xin Huang et al. introduced asynchronous binocular therapy based on VR technology, which was a more effective treatment than traditional patching therapy and more popular among children (Huang et al., 2022). Moreover, some studies showed that the I-Bit™ system combined with patching therapy had a better effect on amblyopia treatment (Zhale Rajavi et al., 2016; Zhale Rajavi et al., 2019; Z. Rajavi et al., 2021). However, Jost et al. (2022) did not find VR to be superior to traditional therapies. Elhusseiny et al. (2021) found that treatment with VR technology could not significantly improve visual acuity in children. Therefore, this study aims to investigate the effectiveness of VR technology in the treatment of amblyopia in children.

Methods

Search strategy

The present systematic review and meta-analysis followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The study protocol was registered in PROSPERO with the number: CRD42022321241. Eligible studies that assessed the effects of VR on the treatment of amblyopia in children were searched in the Cochrane Library, Scopus, PubMed, Web of Science, and Embase from inception to February 2023.

The search strategy used a combination of the following terms: virtual reality (e.g., virtual reality exposure therapy, educational virtual reality, virtual environment) and amblyopia (e.g., lazy eyes, anisometropic amblyopia, amblyopia, suppression) and random control trial (e.g., random control trial, random clinical trial, controlled clinical trial, control trial, clinical trial, RCT). No restrictions or filters were applied to the search. The full details of the search strategy were reported in the Supplementary Table 1. In addition, other relevant studies were also identified by searching the reference lists of the included studies.

Inclusion and exclusion criteria

Studies were included if they met the following criteria:1) participants were children who were diagnosed with amblyopia; 2) participants in the intervention group were treated with VR devices; 3) the study design was a randomized controlled trial (RCT); 4) the study was published in English.

Studies were excluded if they met the following criteria:1) participants in control groups also used VR devices; 2) animal experiments; 3) abstracts, reviews, letters, duplicate publications, full texts without original data.

Quality assessment

Two reviewers independently assessed the quality of each study using the revised Cochrane Risk of Bias 2.0 (RoB 2.0, released in August 2019) tool for RCTs (Higgins & Green, 2019). The assessed domains were bias arising from the randomization process, deviation from the intended intervention, missing outcome data, measurement of the outcome, and selection of the reported outcome. Data extraction and quality assessment were performed independently by two reviewers, and any disagreements were resolved by consensus or with the involvement of a third researcher.

Data extraction

Two reviewers extracted and assessed the quality of the data independently. Disagreements were arbitrated by the third reviewer. Data extracted from the studies included the first author, year of publication, country, sample size, participant information, topic, study design, intervention duration and outcomes.

Statistical analyses

All analyses were conducted with Stata12.0 software (Stata Corp LP, College Station, TX, USA), the weighted mean difference (WMD; value at the end of the trial minus value at the baseline) and 95% confidence intervals (CI) were defined as the effect sizes of this meta-analysis. The heterogeneity of the pooled results was evaluated by I^2 statistic. The random-effects model was used in this meta-analysis. Subgroup analysis was carried out according to the baseline visual acuity, mean age, sample size and intervention duration to minimize the influence of heterogeneity based on similar characteristics. Sensitivity analyses were conducted to assess whether a single study could have influenced the results. Possible publication bias was detected by testing the funnel plot and Egger's tests. Statistical tests were two-sided, and *P*-values <0.05 were considered as statistically significant.

Results

Study selection

Fig. 1. showed the process of the literature search. A total of 79 studies were searched in the Cochrane Library, Scopus, PubMed, Web of Science, and Embase from inception to February 2023. After removing duplicates, 38 studies were left. There were 16 studies retained after title and abstract screening. Reasons for elimination were as follows: not RCTs ($n = 6$); not children ($n = 1$); reviews, letters, commentaries, meeting abstracts($n = 4$), and not relevant ($n = 11$). After full-text evaluation, eight studies were excluded due to non-English publication ($n = 3$) and no measurements of visual acuity ($n = 5$). Finally, eight studies were included in the final analysis.

Characteristics of the included studies

Eight studies (Elhusseiny et al., 2021; Herbison et al., 2016; Huang et al., 2022; Jost et al., 2022; Zhale Rajavi et al., 2016; Zhale Rajavi et al., 2019; Z. Rajavi et al., 2021; Xiao et al., 2022) with 459 participants were included in this meta-analysis. Two (Herbison et al., 2016; Huang et al., 2022) of these studies included two trials each, making a total of ten trials included in this meta-analysis All the trials were RCTs and published from 2016 to 2023. Participants ranged in age from 3 to 11 years. Baseline visual acuity was >0.3 log MAR (Logarithm of the minimum angle of resolution) in all but one study (Zhale Rajavi et al., 2019). In all included studies, one study (Huang et al., 2022) involved patients with anisometropic amblyopia, seven studies (Elhusseiny et al., 2021; Herbison et al., 2016; Jost et al., 2022; Zhale Rajavi et al., 2016; Zhale Rajavi et al., 2019; Z. Rajavi et al., 2021; Xiao et al., 2022) included patients with unilateral amblyopia due to strabismus, anisometropia or both. Five studies (Elhusseiny et al., 2021; Herbison et al., 2016; Jost et al., 2022; Zhale Rajavi et al., 2019; Z. Rajavi et al., 2021) used VR devices alone, three studies (Huang et al., 2022; Zhale Rajavi et al., 2016; Xiao et al., 2022) combined VR devices with patching as an intervention. The duration of the intervention in all included studies ranged from 2 weeks to 12 weeks. Four studies (Huang et al., 2022; Zhale Rajavi et al., 2019; Z. Rajavi et al., 2021; Xiao et al., 2022) were of high quality, one study (Zhale Rajavi et al., 2016) was of moderate quality and three studies (Elhusseiny et al., 2021; Herbison et al., 2016; Jost et al., 2022) were assessed as low quality according to Cochrane RoB2 (Fig. 2). The specific information of the included studies was shown in Table 1.

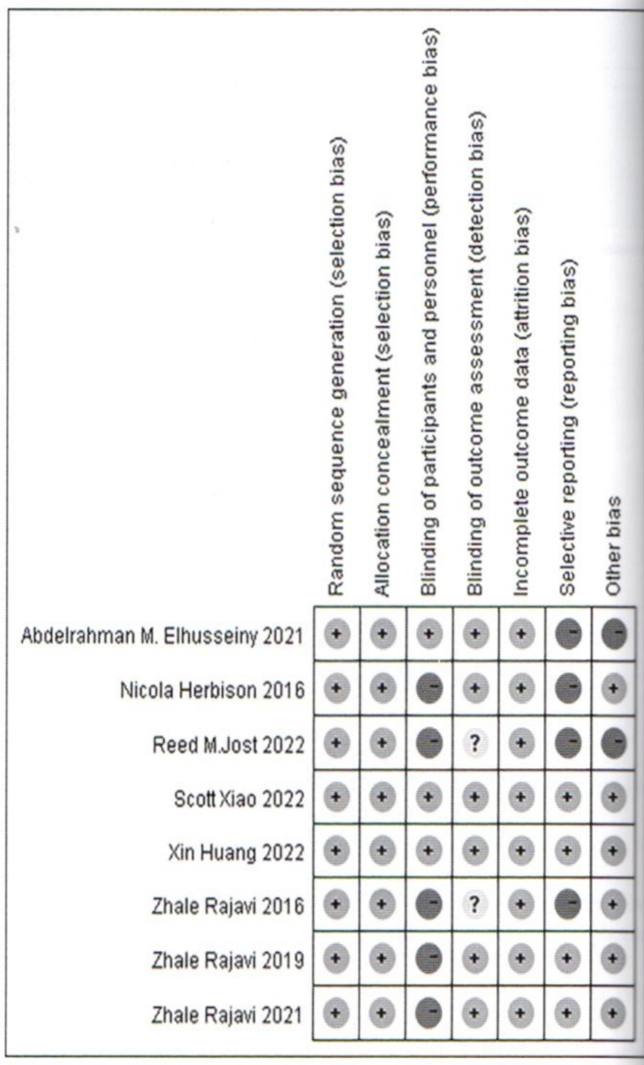

Fig. 2. Quality assessment of included studies using the Cochrane collaboration's tool.

Main outcomes and subgroup analysis

All included trials reported changes in children's visual acuity. The

Table 1
Main information extracted from included studies.

First name	Publication year	Country/ Region	Population	Sample size (I/ C)	Topic	Intervention	Control	Duration	Outcomes
Xin Huang	2022	China	Anisometropia amblyopic pre-school children (5–7 years old), Anisometropia amblyopic children (4–8 years old)	4/4,20/ 20	Treatment based on rules of synaptic plasticity	Asynchronous conditioning + patching	Synchronous conditioning + patching, patching alone	3 weeks,12 weeks	Visual acuity of AE, Visual acuity of FE
Reed M.Jost	2022	USA	Children with anisometropia and/or strabismic (3–7 years old)	32/33	streaming dichoptic movies	contrast-rebalanced dichoptic animated movies	Patching	2 weeks	best corrected visual acuity of AE
Zhale Rajavi	2016	Iran	children with unilateral amblyopia (3–10 years old)	25/25	Interactive Binocular Treatment system	Patching +play I-BiT™ games	Patching	4 weeks	Best corrected visual acuity of AE
Zhale Rajavi	2019	Iran	Children with unilateral amblyopia (3–10 years old)	19/19	interactive binocular treatment in amblyopia	played I-BiT™ games	standard patch therapy and played with placebo I-BiT™ games	4 weeks	Best corrected visual acuity of AE
Zhale Rajavi	2021	Iran	Children with unilateral amblyopia (4–10 years old)	29/29	Virtual Reality Game playing	virtual reality games	Patching	4 weeks	best corrected visual acuity of AE best corrected visual acuity of FE
Abdelrahman M. Elhusseiny	2021	USA	Children with anisometropia and/or strabismic unilateral amblyopia (7–11 years old)	11/9	Virtual reality prototype for binocular therapy	binocular treatment using virtual reality headset	placebo binocular treatment	4 weeks	visual acuity
Nicola Herbison	2016	US	Children with amblyopia (4–8 years old)	26/24/ 25	video clips and interactive games using the I-BiT system	I-BiT game, I-BiT DVD	Non-I-BiT game	6 weeks	visual acuity
Scott Xiao	2022	USA	children with amblyopia (4–7 years old)	51/54	a Dichoptic Digital Therapeutic	dichoptic digital therapeutic +wearing glasses	wearing glasses	12 weeks	visual acuity of AE Best corrected visual acuity of FE

meta-analysis of the change in visual acuity in the 10 trials showed an improvement of 0.07 log MAR (95% CI, −0.11 to −0.02; $P < 0.001$; $I^2 = 94.4\%$) compared with traditional therapy, as shown in Fig. 3. The results of this study were further explored by subgroup analysis (Table 2).

Subgroup analyses were performed according to participants' baseline visual acuity. Six trials including 310 participants with the mean baseline visual acuity greater than or equal to 0.4 log MAR showed an improvement in visual acuity (WMD: -0.07, 95%CI: −0.13 to −0.01; $P = 0.000$) (Elhusseiny et al., 2021; Herbison et al., 2016; Huang et al., 2022 (including two trials); Jost et al., 2022; Xiao et al., 2022). In a further subgroup analysis, the mean age of the individuals was considered, and the results showed that seven trials with 263 participants not older than seven years showed an improvement in visual acuity (WMD: -0.09, 95% CI: −0.14 to −0.04; $P = 0.000$) (Herbison et al., 2016 (including two trials); Huang et al., 2022 (including two trials); Jost et al., 2022; Zhale Rajavi et al., 2016; Xiao et al., 2022). Regarding the duration of treatment, six trials with 246 participants showed that the treatment duration of <20 h resulted in an improvement of visual acuity (WMD: -0.06, 95%CI: −0.11 to −0.01; $P = 0.001$) (Herbison et al., 2016 (including two trials); Huang et al., 2022; Jost et al., 2022; Zhale Rajavi et al., 2016; Zhale Rajavi et al., 2019). The subgroup analysis was also performed according to the sample size, only studies with a sample size of >40 showed an improvement in visual acuity after treatment with VR devices (WMD: -0.05, 95%CI: −0.08 to −0.01; $P = 0.000$) (Herbison et al., 2016; Jost et al., 2022; Zhale Rajavi et al., 2016; Z. Rajavi et al., 2021; Xiao et al., 2022).

Sensitivity analysis and heterogeneity

The effect of the single trial on the overall results was repeatedly analyzed by sequentially removing one trial in each round (Fig. 4). The sensitivity analysis of individual studies did not affect the overall significance of the changes in VR, showing that VR technology significantly improved the level of visual acuity in children. There was high heterogeneity for visual acuity ($I^2 = 94.4\%$) in this meta-analysis model. Subgroup analysis indicated that trials with participants' baseline visual acuity of not <0.4, patients with age of not more than seven years, study duration of not <20 h, and sample size of >40 could be the potential sources of heterogeneity for the results (Table 2).

Publication bias

The funnel plots of this meta-analysis were asymmetric, and Egger's test indicated the potential risk of publication bias ($P = 0.095$) (Supplementary Fig. 1). The trim-and-fill analysis was performed (− 0.065 log MAR, 95% CI: − 0.105 to −0.025, $P < 0.001$), suggesting that the

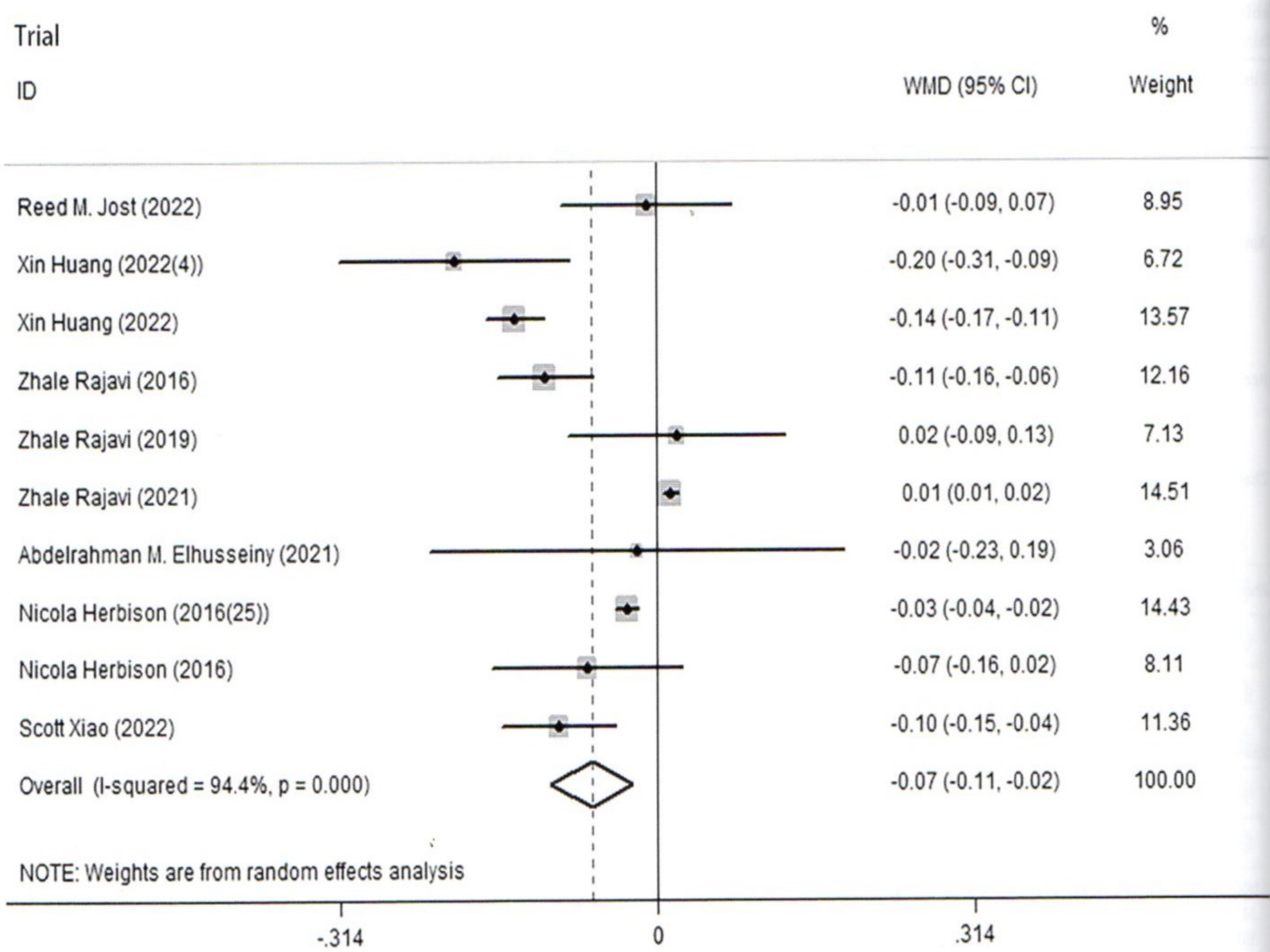

Fig. 3. Forest plot indicating the effect of virtual reality on visual acuity.

Table 2
Result of subgroup analysis of included randomized, controlled trials in meta-analysis.

Groups	n	Visual acuity		
		WMD (95%CI)	*P*-value	I^2 (%)
Baseline of Visual Acuity				
≥0.4	6	-0.07(−0.13, −0.01)	0.000	90.40%
<0.4	4	-0.06(−0.16, 0.03)	0.000	92.30%
Average Age				
>7	3	0.01(0.01, 0.02)	0.943	0.00%
≤7	7	−0.09(−0.14, −0.04)	0.000	90.80%
Duration				
≥20	4	−0.07(−0.17, 0.04)	0.000	97.30%
<20	6	−0.06(−0.11, −0.01)	0.001	75.40%
Sample size				
>40	6	−0.05(−0.08, −0.01)	0.00	93.00%
20–40	2	−0.07(−0.22, 0.09)	0.005	87.30%
<20	2	−0.13(−0.30, 0.04)	0.133	55.70%

result was not altered by the publication bias (Supplementary Fig. 2).

Discussion

This meta-analysis of RCTs was conducted to investigate the effects of VR technology treatment on amblyopia in children. Overall, the results of this study showed that VR technology treatment could improve visual acuity by 0.07 log MAR compared with traditional therapy, which suggesting that VR-based training could improve the visual acuity in amblyopic children.

Amblyopia is caused by a mismatch between the images seen by the two eyes (Birch et al., 2013). Strabismus and anisometropia are the major causes of amblyopia (Kiorpes et al., 1998). Strabismus reduces the number of binocular neurons in the visual cortex, causing neurons in the visual system to connect primarily to one eye rather than both. Anisometropia can lead to a reduction in the neural representation of the eye with chronic blurring and a reduction in binocular driving neurons (Kiorpes et al., 1998). In addition, early abnormal binocular visual experience can lead to a wide range of sensory deficits in children, including spatial integration (Chandna et al., 2001), global motion perception (Meier et al., 2016), and motion-defined form perception (Giaschi et al., 2015). The following are some reasons why VR technology can effectively intervene in amblyopia. Firstly, as a binocular treatment for amblyopia, VR technology can train the coordination of both eyes and binocular function (Jin et al., 2022; Kelly et al., 2016; Pineles et al., 2020). Secondly, the treatment of VR technology is thought to be related to neural plasticity (Bretas & Soriano, 2016; Ziak et al., 2017). Visual stimuli to the amblyopic eye appear to remodel cortical functions. The motivational effects generated during VR treatment may also play an important role in neural plasticity in the central nervous system. Thirdly, VR technology combines visual, somatosensory (haptic), and auditory feedback to provide complex sensory stimulation (Adamovich et al., 2009). VR technology can improve the visual function of amblyopic children through perceptual learning, dichoptic training, gamification, and immersive VR environments (Leal Vega et al., 2022). During treatment with VR, children can maintain their attention and avoid frustration or boredom (Adamovich et al., 2009).

The average age of the amblyopic children and the duration of the intervention varied among the trials included in this meta-analysis. Subgroup analysis showed that participants aged seven years or less had an improvement in visual acuity. The study also showed that children with aged seven years or less are more likely to respond to amblyopia treatment (J. M. Holmes et al., 2011). Since visual development and brain plasticity gradually decreased with age, amblyopia

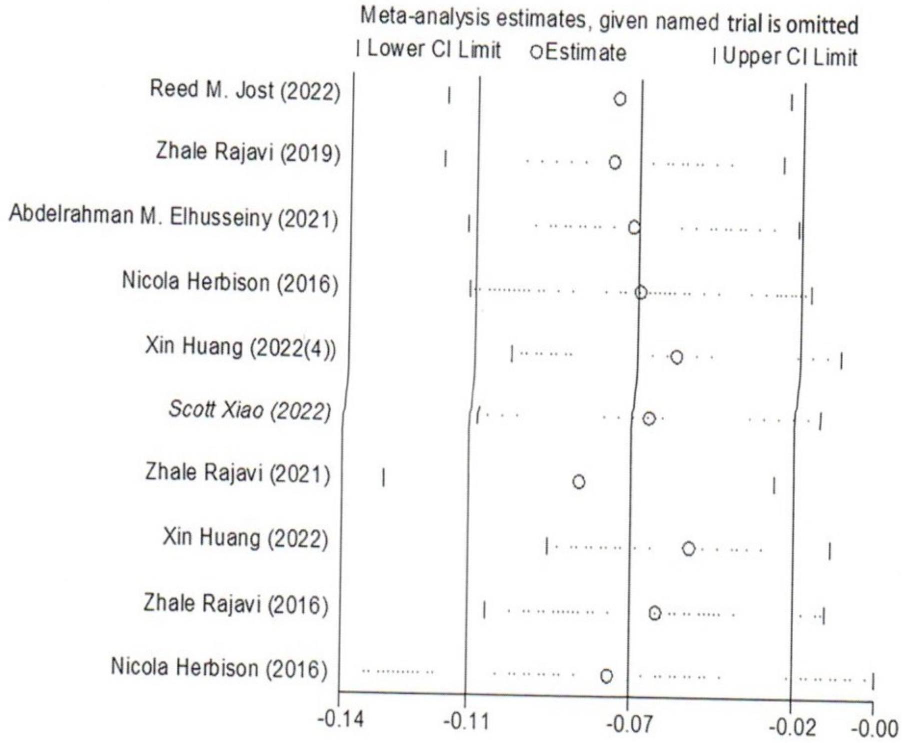

Fig. 4. Sensitivity analysis of included studies in visual acuity.

treatment should be initiated when a patient is less than or equal to seven years of age (Gaier & Hunter, 2017; S. H. Park, 2019). Regarding the duration of treatment, the subgroup analysis showed that the visual acuity with amblyopia was improved when the duration of intervention was <20 h. While the duration of intervention longer than 20 h did not have statistical difference, which might be related to patient compliance. Long duration of treatment decreases patient compliance, which leads to poor treatment outcomes. Compliance is one of the most important factors affecting the effectiveness of amblyopia treatment (Dean et al., 2016). Jonathan M. Holmes et al. found that participants might lose interest in the game after a few days or weeks (Manh et al., 2018). Therefore, we should take active measures to improve children's compliance. According to the study (L. Li et al., 2022), children were more cooperative when they were supervised or supported by their parents. This suggests that as much parental support and supervision as possible should be provided during treatment.

Limitations

The current study also had several limitations. Firstly, this meta-analysis had a high degree of heterogeneity. However, this could not be avoided because the trials included in this meta-analysis had different duration, sample size, and mean age. Secondly, we were unable to analyze the effect of VR technology on stereo acuity because some studies did not report the improvements in stereo acuity. Thirdly, this meta-analysis only included studies published in English.

Implication to practice

Firstly, RCTs with larger sample size and clear protocol are needed to evaluate the effect of VR technology on amblyopia in children. In addition, studies investigating the effects of VR technology on stereoscopic acuity in amblyopic children are recommended. Finally, VR technology may be widely used in the treatment of amblyopic children in the future.

Conclusions

In summary, this meta-analysis showed that treatment with VR technology could significantly improve visual acuity in amblyopic children. Treatment with VR technology was better for children of not older than seven years. In the future, children with amblyopia should be treated as early as possible, preferably before the age of seven. In addition, the effect of VR technology was better when the duration was <20 h and the optimal duration of VR intervention could be explored in the future. VR technology, as an effective treatment with few side-effects, can be further applied to the treatment in amblyopic children.

CRediT authorship contribution statement

Wenxuan Shao: Conceptualization, Investigation, Methodology, Data curation, Writing – original draft, Writing – review & editing. **Yirou Niu:** Writing – original draft. **Saikun Wang:** Investigation. **Jing Mao:** Data curation. **Haiyan Xu:** Investigation. **Jie Wang:** Data curation. **Chengwei Zhang:** Conceptualization, Methodology, Writing – review & editing. **Lirong Guo:** Conceptualization, Methodology, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pedn.2023.07.014.

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