



## OPEN Repeated low-level red-light therapy vs. conventional treatments for myopic control in children: a systematic review and meta-analysis

Li Ping Liu<sup>1</sup>, Yi Shan Hu<sup>1</sup>, Huai Cheng Chen<sup>1</sup>, Yun Tang<sup>1</sup> & Xiao Min Mao<sup>2</sup>✉

This meta-analysis aimed to evaluate the effectiveness of repeated low-level red-light (RLRL) therapy compared to conventional myopia treatments to guide clinical application. A comprehensive literature search was conducted using PubMed, Embase, Web of Science, and Cochrane Library databases from their inception to December 2024. To quantify changes in axial length (AL), we computed weighted mean differences (WMDs) with 95% confidence intervals (CIs). Meta-regression and subgroup analyses were used to explore heterogeneity based on intervention duration and treatment type, while publication bias and result stability were assessed using Egger's and Begg's tests and sensitivity analysis, respectively. Seven studies, comprising one non-randomized controlled trial, two cohort studies, and four randomized controlled trials, were included, involving 691 pediatric participants (349 in the RLRL group and 342 in the control group receiving orthokeratology and atropine). Overall, AL progression in the RLRL group was significantly lower than in the control group (WMD = -0.24 mm, 95% CI [-0.33, -0.14],  $P < 0.001$ ,  $I^2 = 93.5\%$ ), with benefits increasing over time. At the same time, we also found that the effect of RLRL adjunctive therapy (WMD = -0.35 mm, 95% CI = [-0.46, -0.24]) in controlling axial length growth was better than that of monotherapy (WMD = -0.19 mm, 95% CI = [-0.28, -0.10]). Moreover, RLRL demonstrated a notable enhancement in choroidal thickness, surpassing the effects observed with both orthokeratology (OK) lenses and 0.01% atropine treatments (WMD = 30.79  $\mu\text{m}$ , 95% CI = [17.28, 44.30],  $I^2 = 72.7\%$ ,  $P < 0.05$ ). The reported data from the included studies demonstrated the absence of serious adverse events. RLRL therapy may slow myopia progression more effectively than current standard treatments, but further well-designed trials with longer follow-ups are needed to confirm its clinical value.

**Keywords** Repeated low-level red light, Orthokeratology, Atropine, Axial length, Meta-analysis

The rising prevalence of myopia, particularly high myopia, presents substantial public health challenges and economic repercussions on a global scale, with a pronounced impact on Asia<sup>1,2</sup>. High myopia is associated with serious ocular health issues, including glaucoma, cataracts, myopic choroidal neovascularization (CNV), and retinal detachment, which may result in permanent loss of vision and blindness<sup>3</sup>. In 2020, approximately 30% of the global population was affected by myopia, and projections suggest that this figure could rise to 50% by the year 2050<sup>4</sup>. In China, several studies have reported a high prevalence of myopia among students, with 48.7–55.3% affected and an incidence rate of 85.0% among high school students<sup>5,6</sup>. Consequently, effective strategies for controlling myopia progression are crucial.

Currently, the main interventions for myopia management are orthokeratology (OK), low-concentration atropine, defocus-incorporated multiple-segment (DIMS) spectacles, multifocal soft contact lenses, and a variety of other less frequently utilized methods<sup>7</sup>. Recent literature suggests that pharmacological interventions, including low-concentration atropine, can significantly hinder the advancement of myopia in pediatric

<sup>1</sup>Department of Ophthalmology, the Fourth Affiliated Hospital of School of Medicine, and International School of Medicine, International Institutes of Medicine, Zhejiang University, Yiwu 322000, China. <sup>2</sup>Department of Nursing, the Fourth Affiliated Hospital of School of Medicine, and International School of Medicine, International Institutes of Medicine, Zhejiang University, Yiwu 322000, China. ✉email: mao\_xm@zju.edu.cn

populations, especially in those predisposed to experiencing high myopia<sup>8</sup>. Additionally, optical interventions, including OK, multifocal soft contact lenses, and DIMS glasses, have demonstrated the potential to manage myopia progression without significant adverse effects<sup>9</sup>.

Recently, repeated low-level red light (RLRL) therapy has attracted attention as an emerging intervention to prevent and control myopia. The basic principle of this therapy is to use red light of specific wavelengths to stimulate eye tissues and promote metabolism and cellular function, which may help slow the progression of myopia<sup>10,11</sup>. Although the mechanisms underlying the control of myopia by RLRL remain unclear, numerous studies have confirmed that RLRL exposure can significantly slow the growth of spherical equivalent refraction (SER) and axial length (AL) in children with myopia<sup>12–16</sup>. Furthermore, the noninvasive and painless nature of RLRL therapy makes it a feasible intervention for myopia.

Although recent meta-analyses have compared various intervention methods for myopia control<sup>17,18</sup> few studies have directly compared RLRL with other treatments. Additionally, the evaluation of the curative effects remains relatively limited. This study aimed to better understand the efficacy of RLRL through direct head-to-head comparisons, and provide a more comprehensive analysis of its effects on the choroid and its safety profile.

## Subjects/materials and methods

### Study design

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. All studies incorporated in this analysis complied with the Declaration of Helsinki, and the requirement for individual patient consent or ethical review was not applicable.

### Literature search

We systematically searched relevant articles in PubMed, Embase, Web of Science, and the Cochrane Library from their establishment until December 2024. We also reviewed the references of the identified articles to ensure no relevant articles were overlooked. A literature search used the Medical Subject Headings (MeSH) terminology alongside free-text keywords. These included: “myopia” OR “nearsightedness” OR “myopias” OR “nearsightednesses,” “Repeated Low-Level Red-Light” OR “low-intensity laser” OR “RLRL” OR “Low-Level Red Light,” and “atropine” OR “orthokeratology lenses” OR “OK” OR “soft multifocal contact lens” OR “Defocus Incorporated Multiple Segments glasses” OR “spectacle lenses” OR “DIMS.”

### Inclusion and exclusion criteria

The inclusion criteria encompassed: (1) all clinical studies that assessed the efficacy of RLRL therapy in comparison to conventional methods for controlling myopia; (2) participants were children and adolescents aged below 18 years diagnosed with myopia; (3) the intervention group was administered RLRL therapy, while the control group received conventional myopia control treatments, such as OK, atropine eye drops, DIMS, spectacle lenses or multifocal lenses; (4) studies that reported specific clinical outcomes related to myopia progression, such as changes in SER, AL, or visual acuity; (5) studies that provided follow-up data of at least three months to assess the effects of the interventions.

The exclusion criteria were as follows: (1) studies that were not original, including review articles, abstracts from conferences, expert analyses, and summaries; (2) studies that lacked complete data, making it impossible to extract essential information; (3) studies that did not involve children or adolescents with myopia; (4) studies that compared RLRL therapy with other nontraditional methods not classified as myopia controls; (5) research articles published in languages other than English or Chinese; and (6) research articles for which the full text was not accessible.

### Data extraction and quality assessment

EndNote X9 (Clarivate Analytics, Philadelphia, PA, USA) eliminated duplicate segments identified in the collected articles. Two independent evaluators examined the remaining articles' titles, abstracts, and complete texts based on established inclusion and exclusion criteria. Finally, relevant information, including the first author's name, year of publication, sample size, country of origin, study design, intervention duration, intervention details, baseline SER, and baseline AL, was independently extracted from the included studies. If needed, a third person made the final decision. All extracted data were collected during the treatment period. The articles with the most comprehensive data published by the same research group were selected. Continuous variables are typically summarized as means and standard deviations (SD). Without a directly specified standard deviation (SD), it was calculated using the RevMan calculator based on 95% confidence intervals (CIs) on the Cochrane website. Two reviewers independently assessed the quality of the studies included in the analysis. For randomized controlled trials (RCTs), we applied the “Cochrane Risk of Bias Tool.”<sup>19</sup> while for non-randomized trials and cohort studies, we utilized the “Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I)” framework<sup>20</sup>.

### Data synthesis and analysis

This meta-analysis utilized Stata 15.0 software (Stata Corp LLC, College Station, TX, USA) and Review Manager 5.4 (The Cochrane Collaboration, London, UK). To assess changes in AL, we computed pooled weighted mean differences (WMDs) and 95% confidence intervals (CIs) for pertinent outcomes. A random-effects model was used in the meta-analysis when the  $I^2$  statistic surpassed 50%. Furthermore, a meta-regression analysis was conducted to identify the possible sources of variability in the study findings. Subgroup analyses were performed using different methods (RLRL vs. OK, and RLRL vs. atropine) and therapy durations (1, 3, 6, and 12 months). To ensure robustness, a sensitivity analysis was conducted by methodically omitting each individual study. We generated a funnel plot and used Begg's and Egger's tests to examine possible publication bias.

## Results

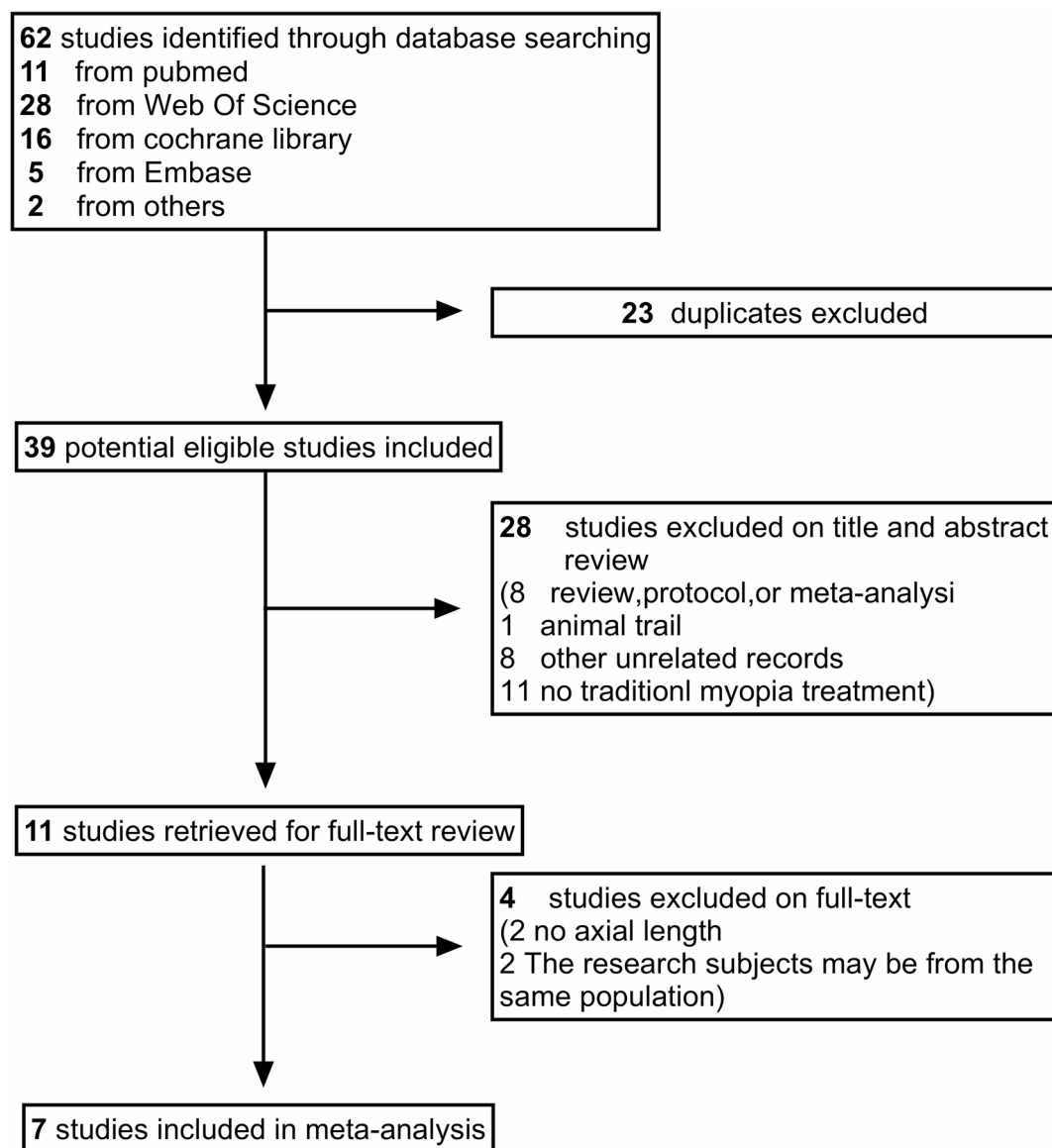
### Search results

Sixty-two studies were identified from multiple databases, comprising 11 studies sourced from PubMed, 28 from Web of Science, 16 from the Cochrane Library, five from Embase, and two from other sources. After the removal of 23 duplicate publications, 39 studies remained. After evaluating the titles and abstracts, irrelevant articles were removed, and 11 full-text articles were assessed. After reading the full text, four studies were excluded (two studies had no AL data, and two may have been from the same population). Ultimately, seven studies (two cohort studies<sup>21,22</sup> four RCTs<sup>23–26</sup> and one non-RCT<sup>27</sup> were included in this meta-analysis (Fig. 1).

### Characteristics of studies included in Meta-analysis

Table 1 presents an overview of the fundamental characteristics of the seven studies included in this analysis. This meta-analysis included 691 patients. All studies included in this review, published between 2021 and 2024, were conducted in China. Five studies focused on the effects of RLRL versus OK lenses or 0.01% atropine (monotherapy group), whereas two studies focused on RLRL combined with OK versus OK alone (adjunctive therapy group). The treatment duration ranged from 3 to 24 months in all seven studies. All studies followed a uniform daily RLRL treatment protocol, which included two 3-min sessions each day, separated by at least 4 h. Four studies administered treatment seven days per week, one applied treatment more than 10 times per week, and one did not specify the treatment frequency.

Figure 2 illustrates the findings regarding the risk of bias from the RCTs included in the analysis. Supplementary Table S1 summarizes the risk of bias outcomes from non-RCTs and cohort studies.



**Fig. 1.** Flow diagram of the literature search process following the PRISMA guidelines.

Studies/ year	Studies design	Age/y	Red-light Parameter	Arm and sample size	Baseline SER(D) Mean (SD)	Baseline AL (mm) Mean (SD)	Follow- up
Sun 2024 <sup>21</sup>	cohort	6–14	635 nm, 0.35mw 2 times/d, 3 min/times, more than 10 times/week	Experimental group: RLRL (67) Control group: OK (71)	NA NA	NA NA	12, 24 month
Xiong 2024 <sup>23</sup>	RCT	8–13	650 ± 10 nm, 0.29mw 2 times/d, 3 min/times, 7 days/week	Experimental group: RLRL + OK (30) Control group: OK (17)	–2.15 (0.84) –2.29 (0.92)	24.41 (0.78) 24.41 (0.78)	1, 3, 6, 12 month
Chen 2022 <sup>24</sup>	RCT	7–15	650 ± 10 nm, 0.29mw 2 times/d, 3 min/times, 7 days/week	Experimental group: RLRL (58) Control group: 0.01% atropine (56)	–2.60 (1.17) –2.59 (1.24)	24.48 (0.79) 24.67 (0.98)	1, 3, 6, 12 month
Yu 2024 <sup>27</sup>	n-RCT	7–15	650 ± 10 nm, 0.29mw 2 times/d, 3 min/times, 7 days/week	Experimental group: RLRL + OK (55) Control group: OK (45)	NA NA	NA NA	12 month
Fu 2024 <sup>25</sup>	RCT	6–12	650 ± 10 nm, 0.29mw 2 times/d, 3 min/time, unknown days/week	Experimental group: RLRL (45) Control group: 0.01% atropine (42)	–2.43(1.13) –2.28(1.04)	24.33(0.81) 24.52(0.82)	3, 6 month
Xiong 2021 <sup>26</sup>	RCT	6–16	650 nm, 2 ± 0.5 mw 2 times/d, 3 min/time, unknown days/week	Experimental group: RLRL (74) Control group: OK (81)	–3.39(2.17) –3.42(1.28)	25.07(1.15) 25.07(0.92)	1, 3, 6 month
Li 2023 <sup>22</sup>	cohort	6–12	650 nm, unknown power 2 times/d, 3 min/times, 7 days/week	Experimental group: RLRL + SVS (30) Control group: OK (30)	–1.99(1.38) –1.80(0.91)	24.25(1.08) 24.35(0.73)	3 month

**Table 1.** Characteristics of the studies included in the meta-analysis. AL: axial length; SER: spherical equivalent refraction; D: diopter; RLRL: repeated low-level red light. OK, orthokeratology lenses; NA, unavailable; n-RCT, non-randomized clinical trial; RCT, randomized clinical trial; SVS, single-vision spectacles; SD, Standard deviation; mw, miliwatt; NA, unavailable. Unknown power, not mentioned in the literature.

### Meta-regression analysis

We conducted a meta-regression analysis to determine how different study characteristics such as study design, treatment approaches, RLRL power, and intervention duration influence the overall findings of the meta-analysis. The results indicated that the intervention duration ( $P=0.024$ ) and RLRL power ( $P=0.01$ ) were the causes of heterogeneity.

### Pooled effects of the efficacy results

#### Changes in AL

To provide larger samples for merged results, we combined RCTs, n-RCTs, and cohort studies because we found that the determination of the conclusions with no changes was performed by sensitivity analysis, excluding non-RCTs one by one (Supplementary Figure S1). Seven studies reported changes in the AL. The aggregated findings indicated that the changes in AL within the RLRL group were notably less pronounced than those seen in the group receiving conventional myopia treatments over the entire duration of treatment, spanning from the initial assessment to the concluding follow-up months of the myopic intervention (WMD =  $-0.24$ , 95% CI =  $[-0.33, -0.14]$ ,  $I^2=93.5%$ ,  $P<0.05$ ) (Fig. 3).

In the subgroup analysis, RLRL adjunctive therapy (WMD= $-0.35$  mm, 95% CI =  $[-0.46, -0.24]$ ,  $P<0.05$ ) better controls axial length growth than monotherapy (WMD= $-0.19$  mm, 95% CI =  $[-0.28, -0.10]$ ,  $P<0.05$ ) (Fig. 3).

In the subgroup analysis comparing different myopia treatments, the aggregated data indicated that the AL changes within the RLRL group were significantly less marked in comparison to both the OK group (WMD =  $-0.15$ , 95% CI =  $[-0.27, -0.04]$ ,  $I^2=90.3%$ ,  $P<0.05$ ) and the group treated with 0.01% atropine (WMD =  $-0.25$ , 95% CI =  $[-0.29, -0.20]$ ,  $I^2=0.0%$ ,  $P<0.05$ ) (Supplementary Figure S2). Therefore, RLRL demonstrated greater efficacy in controlling AL growth than 0.01% atropine and OK lenses.

In the subgroup analysis of RCTs (Xiong et al.<sup>23</sup>Chen et al.<sup>24</sup>Fu et al.<sup>25</sup>and Xiong et al.<sup>26</sup>, the aggregated data demonstrated that AL changes within the RLRL group were significantly diminished compared to those in the control group (WMD =  $-0.22$ , 95% CI =  $[-0.30, -0.14]$ ,  $I^2=84.7%$ ,  $P<0.05$ ) (Supplementary Figure S3).

In the subgroup analysis comparing intervention durations (1, 3, 6, and 12 months), the cumulative effect of RLRL compared to conventional myopia treatments increased with longer treatment durations. The WMDs were recorded as follows: 1 month,  $-0.06$   $[-0.08, -0.05]$ ; 3 months,  $-0.11$   $[-0.15, -0.07]$ ; 6 months,  $-0.18$   $[-0.23, -0.13]$ ; and 12 months, the WMD reached  $-0.32$   $[-0.39, -0.25]$  (Fig. 4).

In the subgroup analysis, based on different RLRL power, upon comparison of the efficacy of RLRL with conventional treatment, the WMDs recorded were as follows: 0.35 mw,  $-0.33$   $[-0.44, -0.22]$ ; 0.29 mw,  $-0.29$   $[-0.36, -0.22]$ ; 2mw,  $-0.12$   $[-0.17, -0.07]$ ; unknown,  $-0.05$   $[-0.10, -0.00]$  (Fig. 5).

Sensitivity analysis was conducted by systematically omitting each included study. The results (Supplementary Figure S4), which aligned with the initial analysis, revealed that individual studies had a minimal impact on the overall results, demonstrating a consistent overall effect size across the studies.

We assessed the existence of publication bias across the seven studies using a funnel plot (Supplementary Figure S5). Both Begg's test ( $z=-1.95$ ,  $P=0.07$ ) and Egger's test ( $t=-2.5$ ,  $P=0.054$ ) indicated an absence of significant publication bias in the seven studies.

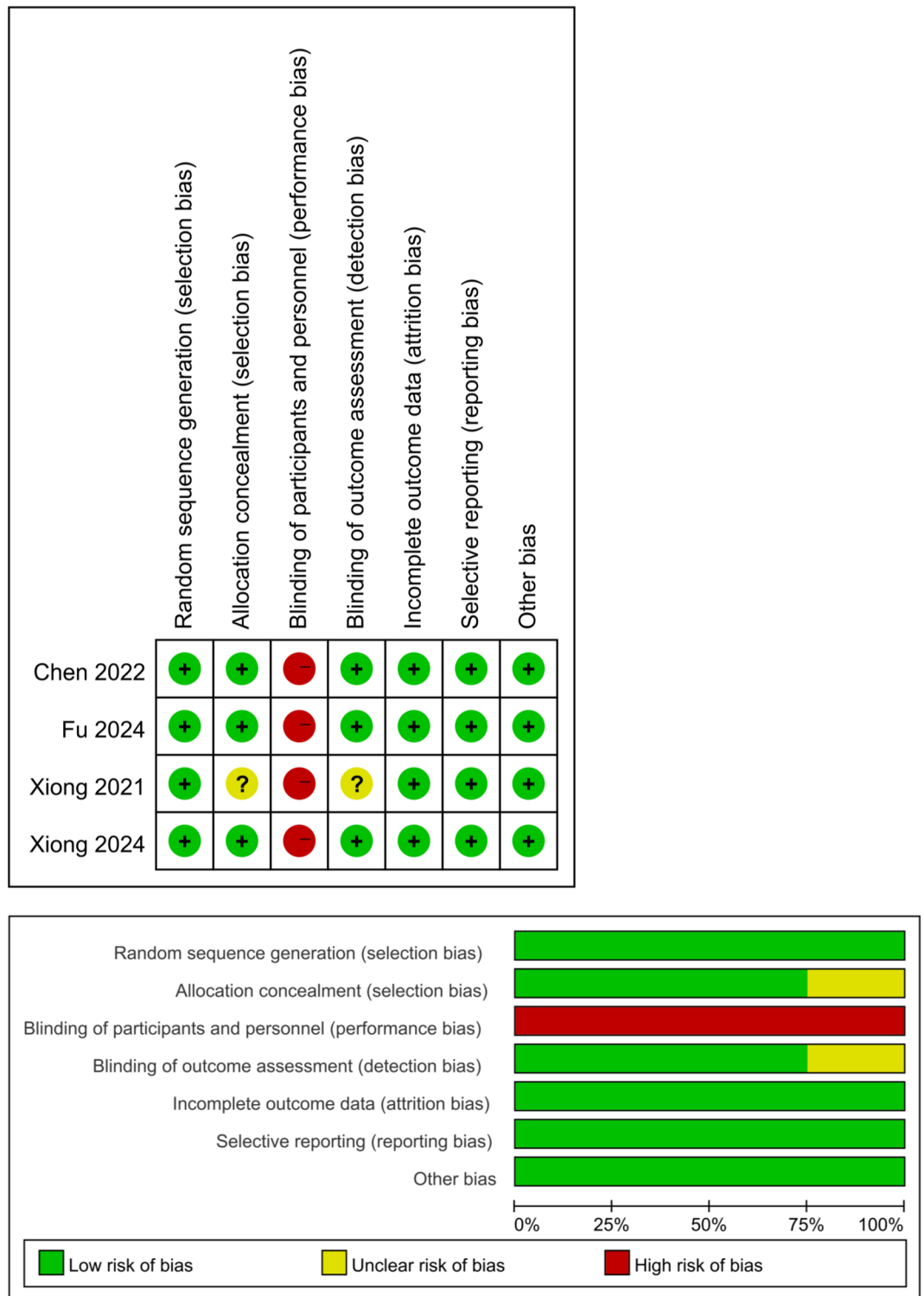
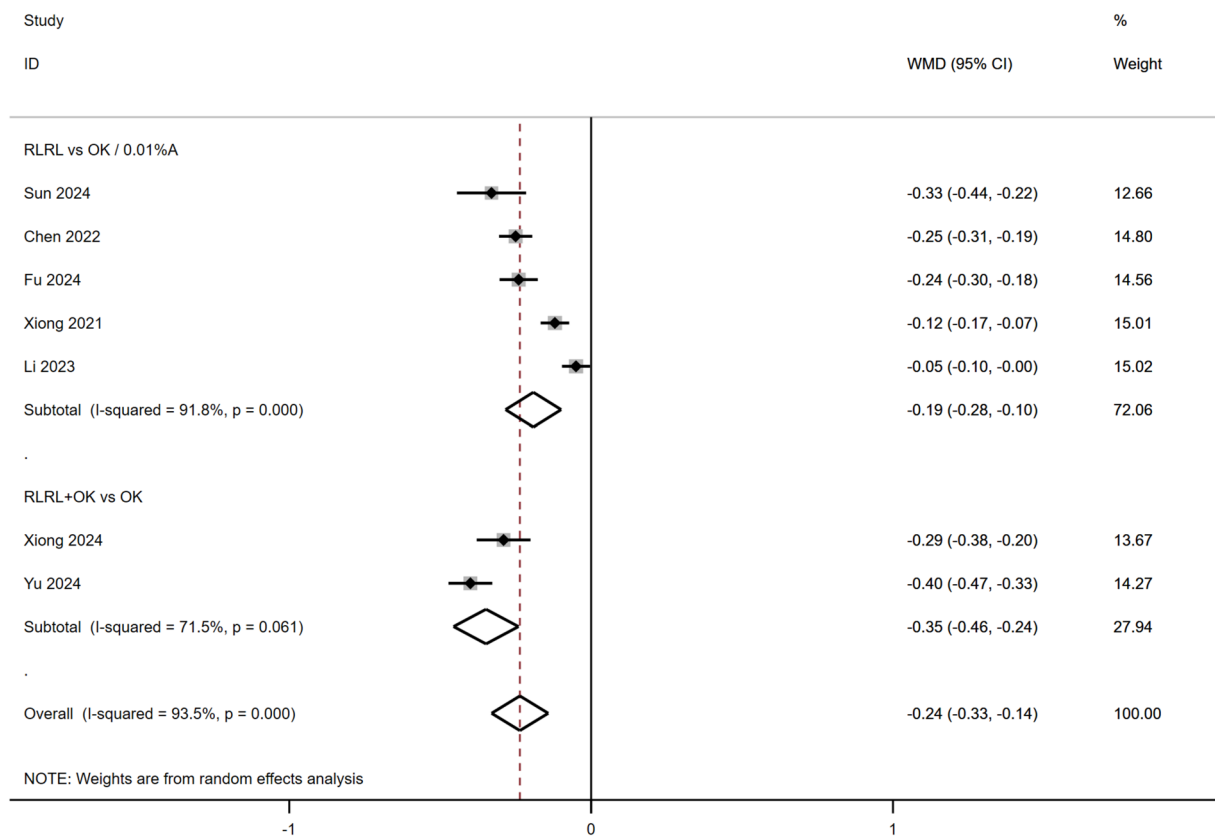


Fig. 2. Assessment of the risk of bias in the included randomized controlled trials (RCTs).

**Effectiveness**

Table 2 outlines the efficacy outcomes observed in participants undergoing RLRL therapy compared with those undergoing conventional myopia treatments. In four of the seven studies, the results of RLRL, both alone and in combination with OK, were compared with those of conventional therapies such as OK or atropine. Most studies found that RLRL outperformed conventional therapies [AL increase of less than 0.10 mm/year: 86.2% vs. 14.3% (Xiong et al.<sup>26</sup>, 53.2% vs. 9.7% (Chen et al.<sup>24</sup>; AL increase of less than 0.30 mm/year: 85% vs. 56% in the first year, and 94% vs. 75% in the second year (Sun et al.<sup>21</sup>). However, Li et al.<sup>22</sup> reported different results,



**Fig. 3.** Forest plots of the changes in AL (mm) between the RLRL and control group and the subgroup analysis. OK = orthokeratology lenses; A = atropine; RLRL = repeated low-level red-light; WMD = weighted mean differences; AL = axial length.

showing that RLRL had a poorer effect [AL increase of less than 0.10 mm (90.0% vs. 93.3%)]. Nevertheless, the conclusions derived from this study were limited by the small sample size and relatively short follow-up period of three months.

### Regression of AL

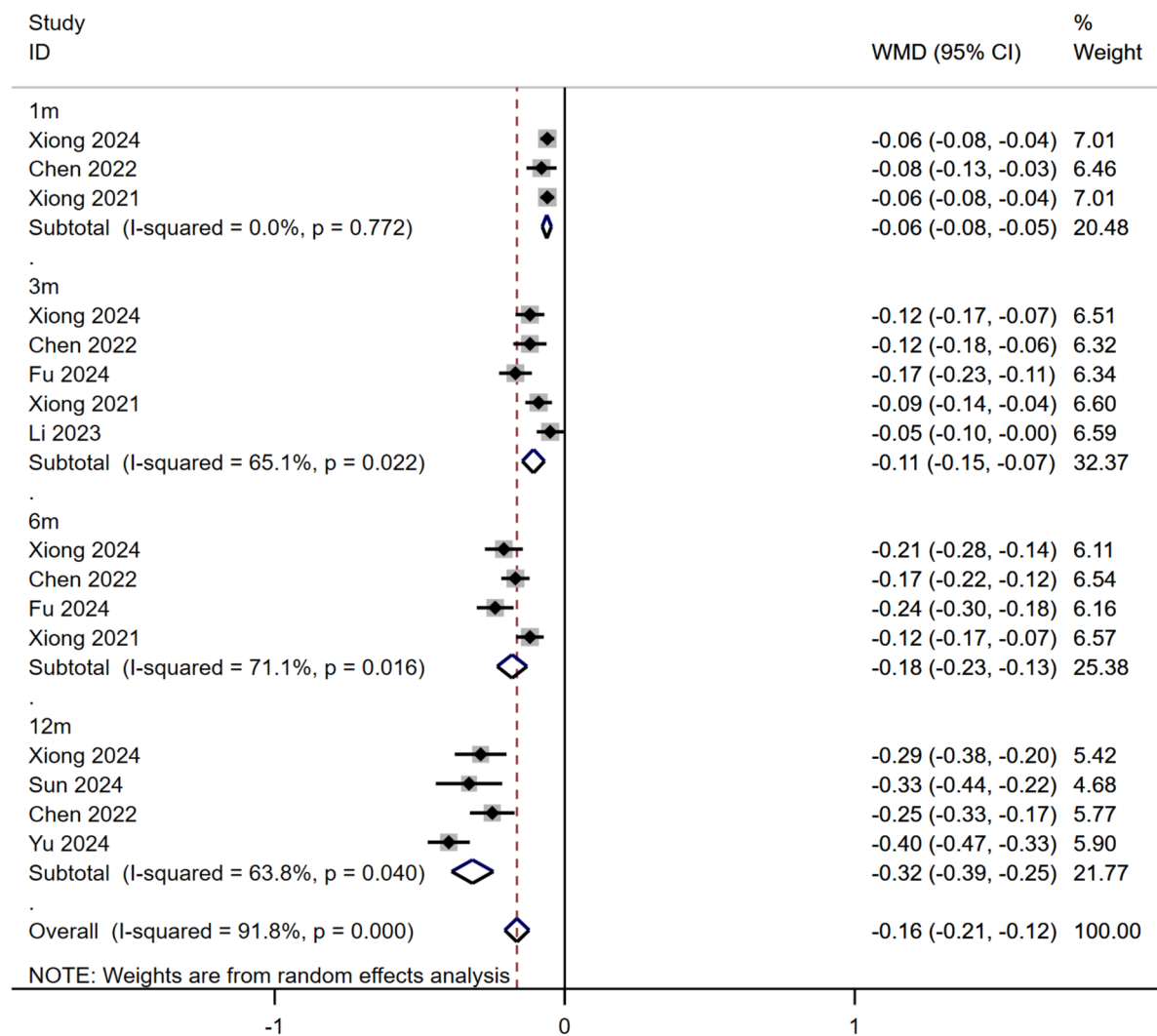
Six studies reported an obvious decrease in AL compared to the baseline AL after RLRL therapy (Table 2). Four studies assessed RLRL against conventional myopia control methods and discovered that RLRL exhibited a greater efficacy in reducing AL [AL shortening  $\geq 0.05$  mm: 55% vs. 3% at 1 month, and 42% vs. 2% at 12 months (Sun et al.<sup>21</sup>; 30.0% vs. 12.5% at 1 month, 42.9% vs. 12.5% at 3 months, 48.3% vs. 13.3% at 6 months, and 44.8% vs. 7.1% at 12 months (Xiong et al.<sup>23</sup>; 42.6% vs. 7.4% at 1 month, 50.0% vs. 10.0% at 3 months, 31.7% vs. 5.2% at 6 months, and 20.6% vs. 3.6% at 12 months (Chen et al.<sup>24</sup>; 62.22% vs. 9.52% at 6 months (Fu et al.<sup>25</sup>; 56.7% vs. 23.3% at 3 months (Li et al.<sup>22</sup>).

### Changes in choroid thickness

Three of the seven studies compared the effects of RLRL therapy, OK lenses, and low-concentration atropine on choroidal thickness after myopia treatment. All three studies reported that RLRL significantly increased choroidal thickness, outperforming both OK lenses and low-concentration atropine (WMD = 30.79  $\mu$ m, 95% CI = [17.28, 44.30],  $I^2 = 72.7%$ ,  $P < 0.05$ ) (Fig. 6).

### Adverse events

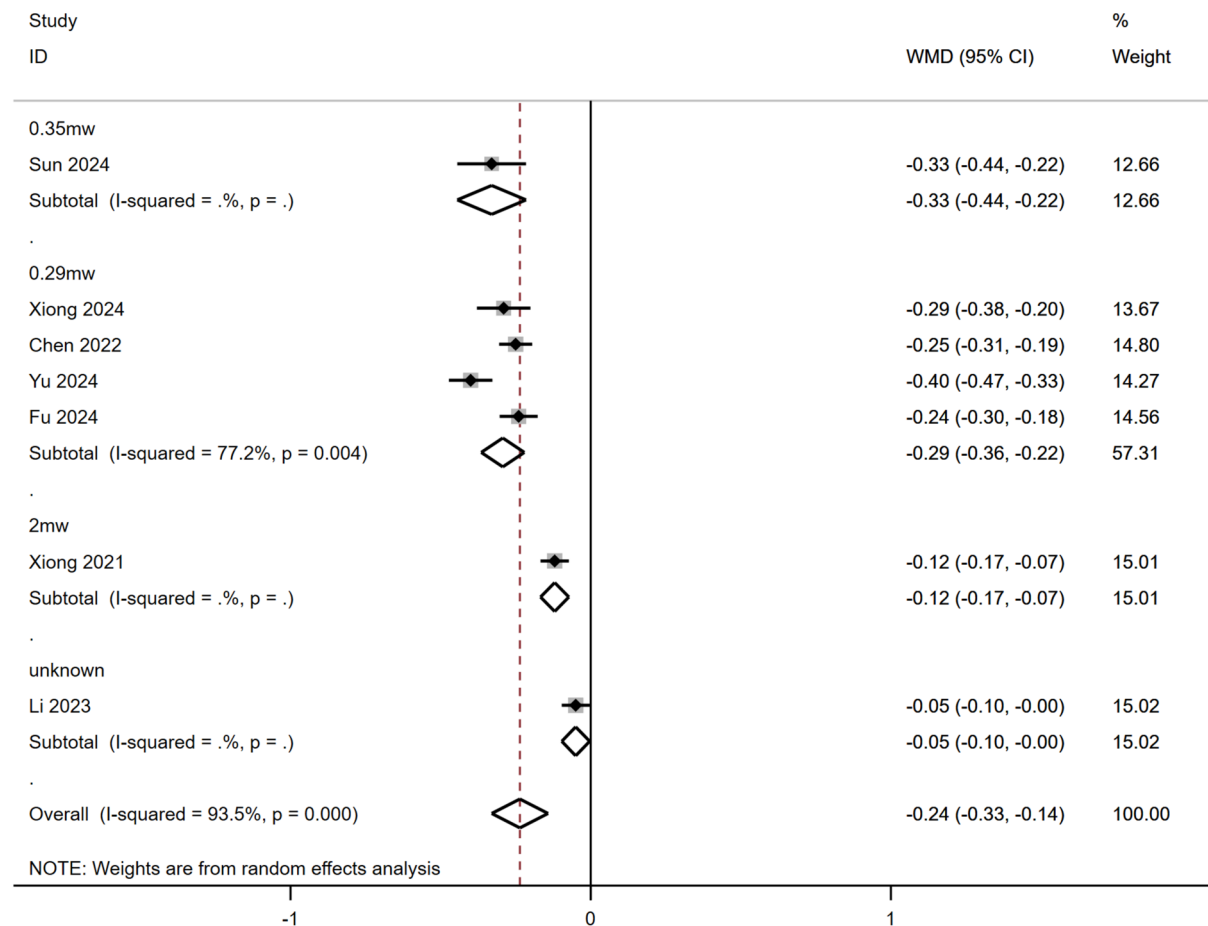
Three studies investigated the adverse events associated with RLRL and conventional therapies: Xiong et al.<sup>23</sup> reported 26 cases, Chen et al.<sup>24</sup> reported four cases, and Fu et al.<sup>25</sup> reported five cases. Sun et al.<sup>21</sup> did not report any adverse events (Table 3). Optical coherence tomography (OCT) revealed no discernible structural injury to the fundus. None of the studies reported significant adverse events.



**Fig. 4.** Forest plots of the changes in AL (mm) between RLRL and the control group according to treatment duration. AL = axial length; WMD = weighted mean differences; RLRL = repeated low-level red-light.

## Discussion

The incidence of myopia in children, particularly in those with high myopia, has increased in recent years. An increase of 1 diopter (D) in myopia significantly increases the likelihood of developing myopic maculopathy by 58%, increases the probability of retinal detachment by 30%, increases the chances of posterior subcapsular cataracts by 21%, and enhances the risk of open-angle glaucoma by 20%<sup>28</sup>. Consequently, research on methods for controlling myopia progression and reducing severe vision decline and its complications<sup>29</sup>. Various techniques have gained attention, including OK, atropine, DIMS, multifocal soft contact lenses, spectacle lenses, and innovative approaches such as RLRL<sup>12,30–33</sup>. A recent meta-analysis assessing the efficacy of 0.01% atropine indicated a weighted mean difference (WMD) of 0.20 D for SER and a reduction of 0.08 mm in AL per annum<sup>34</sup>. Another meta-analysis revealed that OK can decrease axial elongation by 0.15 mm yearly<sup>35</sup>. Contact lenses designed to modify peripheral defocus have been shown to decrease the average axial elongation by roughly 0.11 mm annually, while progressive addition spectacle lenses exhibit modest effects, with a refraction change of approximately 0.14 D and an AL change of  $-0.04$  mm annually<sup>36</sup>. Meanwhile, RLRL effectively controlled the mean SER change by 0.68 D per 6 months and reduced the average axial elongation to 0.35 mm per six months<sup>37</sup>. Despite these promising results, few systematic reviews have directly compared RLRL therapy to conventional myopia treatments. Therefore, this meta-analysis provides valuable insights into future research and clinical practice. Our findings demonstrate that RLRL may be more effective than conventional therapies in slowing myopia progression, with an effect size of WMD  $-0.24$  mm, and RLRL adjunctive therapy (WMD  $-0.35$  mm).



**Fig. 5.** Forest plots of the changes in AL (mm) between RLRL and the control group according to different RLRL power. AL = axial length; WMD = weighted mean differences; RLRL = repeated low-level red-light; mw = miliwatt.

was better than monotherapy (WMD  $-0.19$  mm). This not only indicates that the curative effects of RLRL in controlling axial length growth are better than those of OK lenses and 0.01% atropine but also that the combined auxiliary treatment can achieve an amplifying effect. This also suggests clinicians to consider RLRL for combined use with OK lenses.

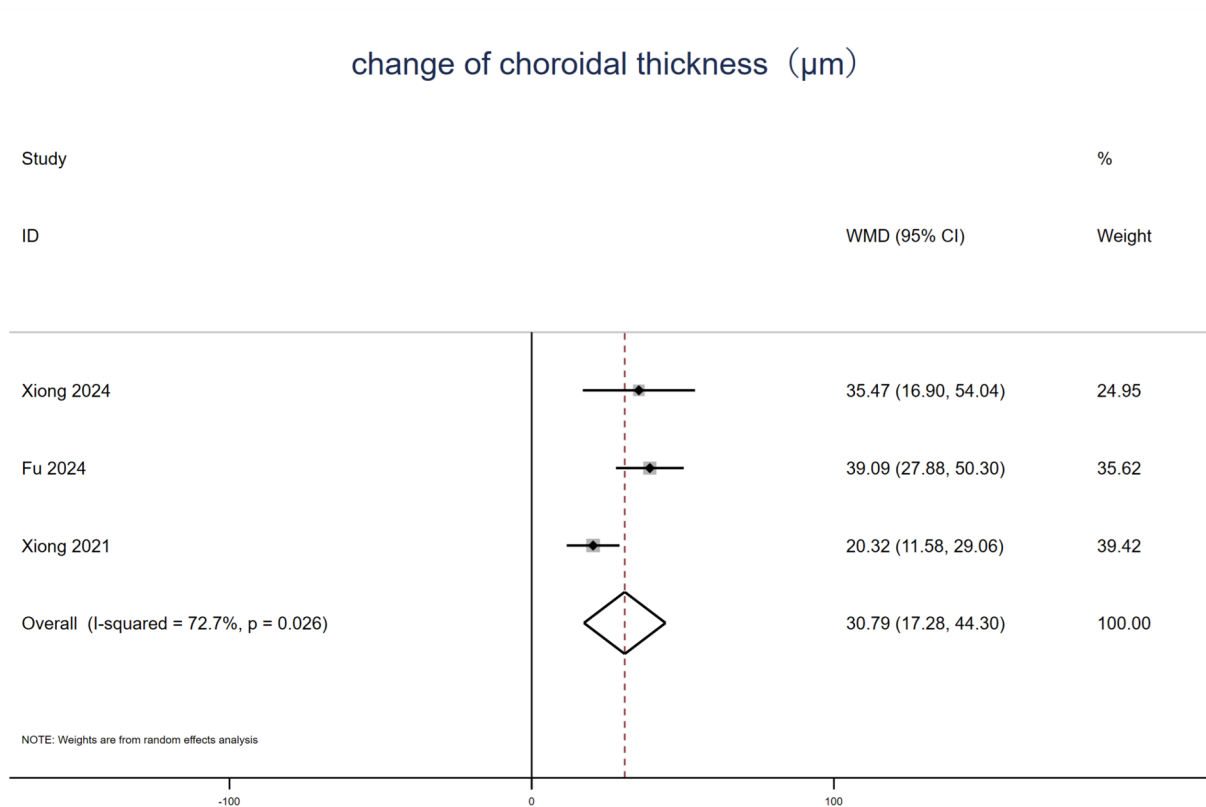
Previous studies have shown that for each 1 mm increase in axial length, there is an approximate corresponding increase of 2.50–3.00 D in refractive progression<sup>38</sup> and AL change of more than 0.20 mm per year is considered a progressive condition<sup>39</sup>. Therefore, the intergroup differences in this study are roughly equivalent to a refractive change of 0.60–0.72 D, which may have clinical significance in the prevention and control of myopia in children and adolescents, particularly in delaying the long-term risk of high myopia and its retinal complications, such as maculopathy.

Furthermore, RLRL demonstrated greater effectiveness in promoting AL regression (AL shortening  $\geq 0.05$  mm) than conventional methods, with annual rates of 20.6–44.8%, compared to just 2–7.1%. However, this evidence has low reliability. In future, it is essential to conduct additional high-quality RCTs with larger sample sizes and longer follow-up durations.

The overall heterogeneity was high ( $I^2 = 93.5\%$ ), and the meta-regression analysis identified intervention duration as the source of heterogeneity. We performed a subgroup analysis based on the duration of therapy. Subtotal heterogeneity declined significantly. The findings showed that longer RLRL treatment durations led to greater cumulative AL (WMD) changes than those in the control group for up to 12 months. However, most of the study durations examined did not surpass the one-year timeframe. While only one study included a 2-year follow-up period, the other had a much shorter follow-up period of only three months. Although subgroup and sensitivity analyses were conducted to minimize heterogeneity, significant differences remained between the two groups. Baseline age and degree of baseline myopia can also affect heterogeneity.

Study	Arm	Effectiveness	The regression of axial length (AL)
Sun 2024	RLRL OK	AL Increase < 0.3 mm: 85% (12 m), 94% (24 m) 56% (12 m), 75% (24 m)	AL shortening ≥ 0.05 mm: 55% (1 m), 42% (12 m) 3% (1 m), 2% (12 m)
Xiong 2024	RLRL + OK OK	AL Increase < 0.10 mm: 86.2% (12 m) 14.3% (12 m)	AL shortening ≥ 0.05 mm: 30.0% (1 m), 42.9% (3 m), 48.3% (6 m), 44.8% (12 m) 12.5% (1 m), 12.5% (3 m), 13.3% (6 m), 7.1% (12 m)
Chen 2022	RLRL 0.01% A	AL Increase ≥ 0.36 mm: 9.7% (12 m) 50.0% (12 m) AL Increase < 0.10 mm: 53.2% (12 m) 9.7% (12 m)	AL shortening ≥ 0.05 mm: 42.6% (1 m), 50.0% (3 m), 31.7% (6 m), 20.6% (12 m) 7.4% (1 m), 10.0% (3 m), 5.2% (6 m), 3.6% (12 m)
Yu 2024	RLRL + OK OK	- -	AL shortening ≥ 0.05 mm: 63.6% (12 m); AL shortening ≥ 0.10 mm: 45.4% (12 m); AL shortening ≥ 0.20 mm: 20% (12 m); AL shortening ≥ 0.30 mm: 10.9% (12 m); AL shortening ≥ 0.40 mm: 5.4% (12 m) -
Fu 2024	RLRL 0.01% A	-	AL shortening ≥ 0.05 mm: 62.22% (6 m) 9.52% (6 m)
Xiong 2021	LILT OK	-	-
Li 2023	RLRL OK	AL Increase < 0.10 mm: 90.0% (3 m) 93.3% (3 m)	AL shortening: 56.7% (3 m) 23.3% (3 m)

**Table 2.** Efficacy outcomes observed in participants undergoing RLRL therapy compared to conventional myopia treatments. AL, axial length; SER, spherical equivalent refraction; D, diopter; RLRL, repeated low-level red light; A, atropine; LILT = Low-Intensity Laser Therapy; OK, orthokeratology lenses; m, month.



**Fig. 6.** Forest plots of the changes in Choroid Thickness between the RLRL and control group. RLRL = repeated low-level red-light; WMD = weighted mean differences.

Study	Arm	Adverse events
Sun 2024	RLRL OK	No adverse events were reported
Xiong 2024	RLRL + OK OK	Eye pain and tearing at the initial 1–2 days after RLRL therapy (1); Eye pain, redness, and tearing after Ortho-k insertion (3); Dry eye (1); Eye itching (2); CLIPC (3); Corneal staining (7) Eye pain, redness, and tearing after Ortho-k insertion (1); Dry eye (1); Eye itching (1); Conjunctival injection (1); CLIPC (1); Corneal staining (4)
Chen 2022	RLRL 0.01% A	uncomfortable (1) dizziness (1) photophobia (1) allergic conjunctivitis (1)
Yu 2024	RLRL + OK OK	NA
Fu 2024	RLRL 0.01% A	No adverse events were reported photophobia (5)
Xiong 2021	LILT OK	NA
Li 2023	RLRL OK	NA

**Table 3.** Adverse events observed in included studies. CLIPC, contact lens-induced papillary conjunctivitis; NA, not available.

Increasing evidence has shown that the choroid is vital for the regulation of eye growth and the progression of myopia. Numerous animal and human studies have demonstrated that choroidal thickness is reduced in myopic eyes<sup>40–43</sup> whereas myopia control methods lead to increased choroidal thickness<sup>44</sup>. The findings indicated that the subfoveal choroidal thickness (SFCT) exhibited a notable increase following orthokeratology (OK) intervention, which was further enhanced when administered in conjunction with 0.01% atropine. The weighted mean differences (WMDs) are 19.47 and 21.81, respectively<sup>44</sup>. Another meta-analysis found that the increase in choroidal thickness after 12 months was markedly more pronounced in the atropine-treated group than in the control group, with a WMD of 15.10  $\mu\text{m}$ <sup>45</sup>. Additionally, He et al. found that the RLRL group experienced positive changes in macular choroidal thickness from baseline over 1 year, achieving a maximum increase of 9.09  $\mu\text{m}$  at 12 months<sup>46</sup>. Studies have shown that choroidal thickness increases with changes in SER and AL after myopia control<sup>37,47</sup>. The specific pathophysiological mechanisms of myopia remain unclear, and the hypothesis that scleral hypoxia leads to scleral remodeling is currently widely accepted<sup>48–50</sup>. Previous studies have indicated that dopamine stimulates the release of nitric oxide (NO) from either the retina or choroid, leading to blood vessel dilation and increased blood flow, which enhances choroidal thickness, alleviates hypoxia, and inhibits ocular growth<sup>51,52</sup>. In our meta-analysis, RLRL significantly increased choroidal thickness, demonstrating a greater effect than OK lenses or low-concentration atropine, with a WMD of 30.79  $\mu\text{m}$ .

Regarding safety, although several cases reported discomfort, the studies included in this meta-analysis did not indicate any vision-threatening occurrences following treatment or any structural damage identified in the photosensory layer through OCT imaging. With the increasing number of clinical studies on RLRL, particularly in China, its safety issues remain controversial. More experts have begun to focus on the safety issues of RLRL. A recent publication presented an atypical instance involving a 12-year-old female patient who exhibited bilateral disruption of the foveal ellipsoid zone and discontinuity of the interdigitation zone, as observed on OCT after five months of exposure to RLRL<sup>53</sup>. Moreover, a cohort study found that cone density in the paracentral fovea declined and other subtle retinal abnormalities occurred in some children after RLRL therapy 1 year later<sup>54</sup>. Although RLRL has a significant myopia control effect, some devices have a photodamaging effect. Clinicians should adopt vigilant, protocol-driven monitoring, especially in children, acknowledging its favorable risk profile in trials and the legitimate concerns arising from retinal imaging studies and photobiological modeling.

This study has some limitations. Robust RCTs that directly compare RLRL with the core alternatives are rare. Most studies have assessed RLRL alone, thus limiting definitive conclusions regarding its relative efficacy. The high heterogeneity observed across studies may reflect variations in study populations, intervention protocols, or outcome assessments. Although subgroup analysis was conducted, the analysis is insufficient due to the small number of studies included. The pooled effect estimates should be interpreted cautiously due to this substantial variability. Moreover, this obscures precise effect estimates and hinders the assessment of long-term sustainability (>12–24 months). All the participants were predominantly Chinese children, severely limiting the generalizability to other ethnicities/regions. These factors increase the uncertainty in the meta-analytic estimates, constrain long-term applicability, and reduce evidence certainty. Future high-quality RCTs with direct comparisons, extended follow-ups, and diverse populations are critical.

In conclusion, our meta-analysis demonstrates that RLRL may be more effective than conventional myopia control methods in slowing axial growth, increasing choroidal thickness, and regressing AL without significant

adverse events. However, evidence remains limited. More robust RCTs with prolonged follow-up durations are needed to enhance the recommendations for clinical practice.

## Data availability

The datasets generated and analyzed in the current study are available from the corresponding author upon reasonable request.

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## Author contributions

L.P.L. designed the study. Y. S. H. and H. C. C. collected and analyzed the data. L.P.L. and Y. T. analyzed the data. L.P.L. wrote the paper. X. M. M. critically revised the manuscript. All the authors reviewed the manuscript.

## Declarations

## Competing interests

The authors declare no competing interests.

## Additional information

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**Correspondence** and requests for materials should be addressed to X.M.M.

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