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ORIGINAL RESEARCH

Relationship of Atropine in Controlling Myopia Progression Among Pediatric Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Purpose: Myopia is a refractive error where light focuses in front of the retina, causing blurred distance vision. It is linked to complications such as macular degeneration, retinal detachment, glaucoma, and cataracts, potentially resulting in irreversible vision loss. Controlling myopia progression is critical to reduce long-term impairment. This systematic review evaluate and compare different atropine concentrations for slowing myopia progression in pediatric patients.

Patients and Methods: A comprehensive electronic search was conducted in PubMed, Google Scholar, Embase, and the Cochrane Central Register of Controlled Trials for studies published between June 1, 2006, and September 1, 2024. Included studies enrolled participants aged <18 years, used a randomized placebo-controlled design, and evaluated atropine effects on myopia progression in individuals with spherical equivalent ≤ 0.25 D. Primary outcomes, spherical equivalent refractive error (SER) and axial length (AL), were analyzed via meta-analysis using mean differences (MDs) with 95% confidence intervals (CIs).

Results: This meta-analysis included 10 studies (2006–2024) evaluating atropine effects on myopia progression. Atropine significantly slowed progression versus placebo. At 6 and 12 months, MD in SER was 0.26 (95% CI, 0.17–0.34) and 0.54 (95% CI, 0.26–0.82), respectively, ($p < 0.001$). Atropine also significantly reduced AL growth at 6 months (MD −0.09, 95% CI, −0.14 to −0.04).

Conclusion: Atropine effectively reduced AL growth and myopia progression. Heterogeneity across studies suggests variability. Further research is essential to clarify its mechanism.

Plain Language Summary: Myopia, or nearsightedness, is a common eye problem in children that makes distant objects appear blurry. If it worsens quickly, it can lead to serious eye problems later in life, such as retinal damage, glaucoma, or cataracts. Slowing down the progression of myopia is important to protect children's vision in the long term.

This study reviewed and combined results from multiple high-quality clinical trials to find the best dose of atropine eye drops for controlling myopia in children. We looked at how atropine affected vision clarity and eye growth, as well as its side effects.

We found that atropine eye drops effectively slowed myopia progression and reduced eye growth. Lower doses were generally safer and caused fewer side effects, while higher doses worked more strongly but sometimes caused blurred near vision or sensitivity to light.

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These results help doctors and parents make informed decisions about using atropine to protect children's eyesight. They also highlight the need for more research to understand how atropine works and to identify the safest and most effective dosing strategies.

Keywords: low-concentration therapy, refractive error control, photophobia, mydriasis

Introduction

Myopia (nearsightedness) is a refractive error that causes blurred distance vision by focusing light in front of the retina.[1] This condition commonly results from excess axial elongation of the eyeballs.[2] Although vision can be corrected through various methods,[3] myopia is associated with certain complications, including macular degeneration, retinal detachment, glaucoma, and cataracts.[4] Such complications can lead to irreversible visual impairment,[5] emphasizing the critical importance of preventing the progression of myopia.

Myopia usually develops in early childhood. Genetic and environmental factors, including near-work activities and lack of outdoor activities, appear to play a role in its development.[6,7] Myopia is a major health problem worldwide. In 2000, it was estimated that >28.8% of the global population had myopia. By 2050, 48.9% of the global population is predicted to have myopia.[8] The high incidence and its associated complications make myopia a high priority for early detection, management, and progression control.

To prevent myopia progression, various interventions have been used,[9,10] including optical methods such as spectacle lenses, contact lenses, and orthokeratology (Ortho-K); environmental methods such as encouraging outdoor activities; and pharmaceutical agents. Among pharmacological agents, atropine, a non-selective muscarinic antagonist, is the most widely used medication for slowing the progression of childhood myopia.[10,11] While the exact mechanism by which atropine slows the progression of myopia remains unclear, it is believed to inhibit eyeball elongation, thereby slowing the progression of myopia.[12,13]

Various doses of atropine have been investigated for their effectiveness in controlling myopia progression.[14] The safety profile of atropine is crucial because higher doses are linked to a greater risk of adverse effects, including photophobia, reduced near-visual acuity, and allergic reactions.[15] Lower doses provide a better safety profile; however, they may be less effective than higher doses in slowing myopia progression.[16]

Despite clear evidence regarding the effectiveness of various doses of atropine in controlling the progression of myopia, the optimal dosage remains uncertain. Based on the latest randomized controlled trials (RCTs), this systematic review aimed to evaluate and compare different atropine concentrations for slowing myopia progression in pediatric patients.

Materials and Methods

Literature Search Strategy

This systematic review was prospectively registered in PROSPERO (CRD42024543633) and adhered to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. A comprehensive electronic search was conducted using PubMed, Google Scholar, Embase, and the Cochrane Central Register of Controlled Trials for studies published between 2006 and 2024. The search strategy was designed independently by one author (H.M.) and approved by the study team. Medical Subject Headings and keywords, including "Atropine," "Atropinol," "Atropine Sulfate," "AtroPe," "Myopia," "Nearsightedness," "Ocular elongation," "Vision loss prevention," "Paediatric myopia control," "Low-dose atropine," and "High-dose atropine," were used to identify all relevant studies. References of selected studies were also reviewed.

Inclusion/Exclusion Criteria

This review included clinical studies with participants aged <18 years that were randomized placebo-controlled trials, evaluated atropine for myopia progression, enrolled participants with spherical equivalent ≤ −0.25 D, had ≥1-year treatment, reported annual myopia progression, and were published in English. Studies were excluded if they were non-

English, were non-randomized or non-placebo-controlled, did not use atropine as the primary intervention, involved participants aged >18 years or unspecified age, were short-term (<1 year), or lacked specific myopia-related outcomes.

Choice of Article and Data Extraction

Two reviewers independently screened titles and abstracts, followed by a full-text review. Study characteristics, participant demographics, interventions, and outcomes were extracted using a standardized form. Disagreements were resolved by discussion or a third reviewer.

Statistical Analysis

Median values and interquartile ranges were converted to means and standard deviations (SDs), as previously described.[1] Within-group differences and their respective SDs between the baseline and follow-up time points were estimated using a standardized method, as previously published.[2] Between-group differences and SD values were derived based on the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions.[3]

The outcomes investigated were the spherical equivalent refractive error (SER) and axial length (AL). These numerical outcomes were incorporated into the meta-analysis models by calculating the mean differences (MDs) and their respective 95% confidence intervals (CIs). An inverse variance method was used. Heterogeneity was assessed using I^2, with significant heterogeneity set at $I^2 > 50\%$. Random-effects models were constructed for instances of significant heterogeneity. Subgroup analysis was performed based on the year of publication and sample size. The risk of publication bias was assessed using funnel plots and Egger's test.

Results

Characteristics of the Included Studies

The results of 10 studies were included in this meta-analysis.[13,17–25] Studies were published between 2006 and 2024, with three being published before 2020.[20–22,24] The sample sizes ranged from 126 to 570, and four studies had a sample size of <150 patients.[5,9,26] Overall, 2325 patients were enrolled across the included studies. In studies with available data on the frequencies of males and females (n = 2027), 1020 females and 1007 males were included (representing 50.3% and 49.7%, respectively). The baseline values of the SER and AL outcomes are presented in Table 1.

The results of the meta-analysis of SER indicated that atropine slowed the progression of myopia, as measured using SER, across all time points compared with placebo (Figure 1). At 6 months, the overall MD in SER between the atropine and placebo groups was 0.26 (95% CI, 0.17–0.34; $p < 0.001$). Heterogeneity was moderate, with an I^2 value of 64%. At 12 months, the MD was 0.54 (95% CI, 0.26–0.82), again indicating a statistically significant effect ($p < 0.001$) with high heterogeneity ($I^2 = 98\%$). The trend continued at 18 months, where the MD was 0.65 (95% CI, 0.12–1.18, $p = 0.017$),

Table 1 Baseline Characteristics of the Included Studies

Authors	Sample Size		Gender (Male/Female)	Intervention Dose	Fixed Dose	Baseline SER (Mean ± SD)		Baseline AL (Mean ± SD)	
	Overall	Atropine/ Placebo				Atropine	Placebo	Atropine	Placebo
Chua et al[13]	400	200/200	220/180	1	No	−3.36 ± 1.38	−3.58 ± 1.17	24.80 ± 0.83	24.80 ± 0.84
Lee et al[25]	153	104/49	NA	0.01	Yes	−3.23 ± 1.20	−3.62 ± 1.38	24.67 ± 0.75	24.83 ± 0.76
Loughman et al[18]	250	167/83	95/155	0.1	Yes	−3.28 ± 1.79	−3.22 ± 1.80	24.85 ± 1.02	24.93 ± 1.09
Repka et al[19]	187	125/62	86/101	0.01	No	−2.83 ± 1.17	−2.83 ± 0.97	24.40 ± 0.80	24.40 ± 0.80
Sen et al[20]	145	72/73	NA	0.01	No	−3.92 ± 1.01	−4.05 ± 1.25	24.65 ± 0.62	24.85 ± 0.74
Wang et al[21]	126	63/63	67/59	0.5	Yes	−1.30 ± 0.40	−1.20 ± 0.30	24.10 ± 1.00	23.80 ± 0.90
Wei et al[17]	220	110/110	117/103	0.01	Yes	−2.52 ± 1.33	−2.64 ± 1.46	24.50 ± 0.76	24.69 ± 0.94
Yi et al[22]	132	68/64	65/67	1	No	−1.23 ± 0.32	−1.15 ± 0.30	23.75 ± 0.12	23.72 ± 0.12
Zhu et al[23]	570	262/308	286/284	1	No	−3.82 ± 0.44	−3.74 ± 0.51	24.93 ± 0.21	24.91 ± 0.18
Zhu et al[24]	142	72/70	71/71	0.05	No	−3.26 ± 0.20	−3.27 ± 0.32	23.71 ± 0.23	23.69 ± 0.19

Abbreviations: SD, standard deviation; SER, spherical equivalent refractive error.

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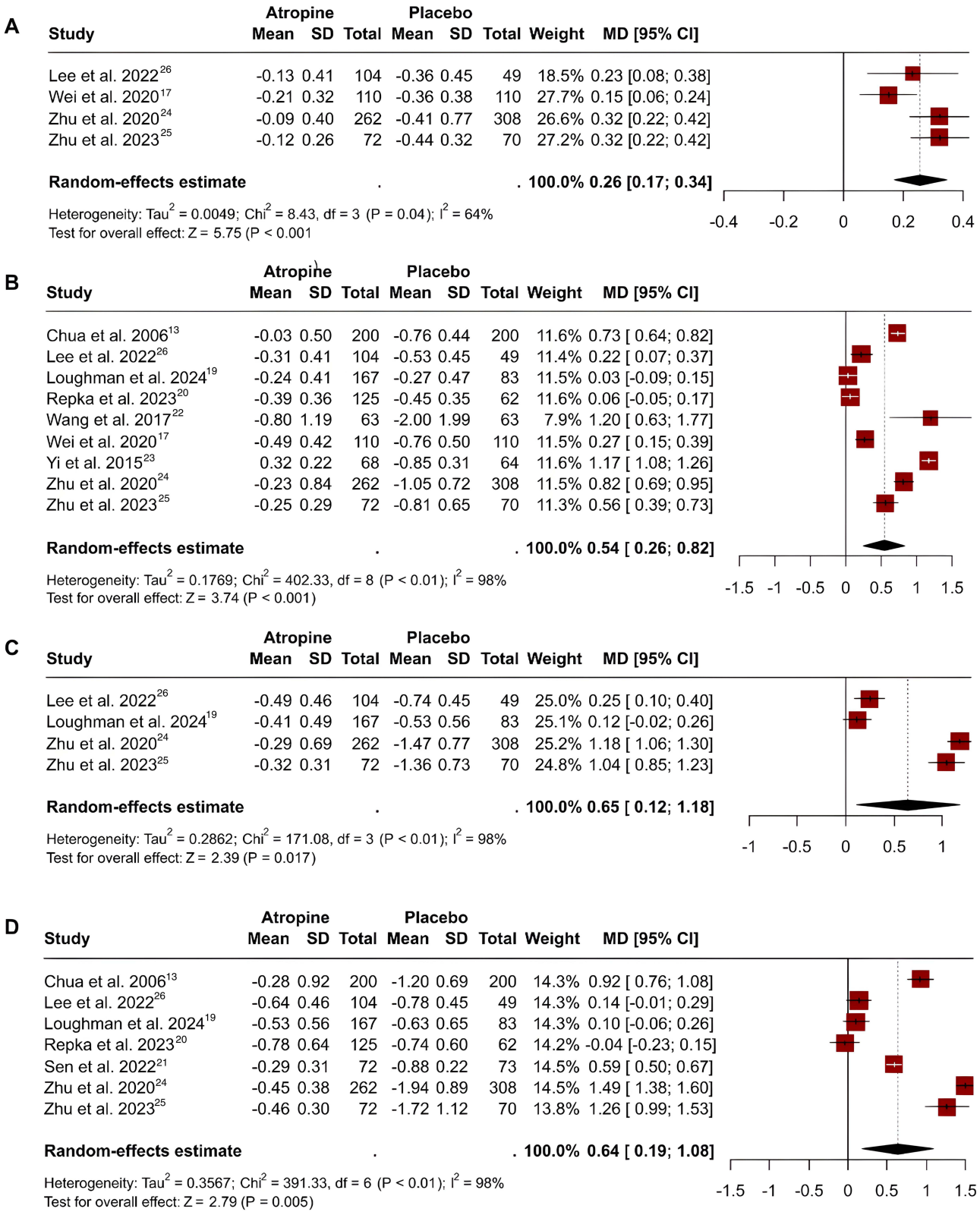

Figure 1 Forest plots depicting the mean differences in spherical equivalent refractive error between the atropine and placebo groups at (**A**) 6 months, (**B**) 12 months, (**C**) 18 months, and (**D**) 24 months.
Abbreviations: CI, confidence intervals; SD, standard deviation; MD, mean difference.

with substantial heterogeneity (I^2 = 98%). At 24 months, the MD was 0.64 (95% CI, 0.19–1.08, p = 0.005), and heterogeneity remained high (I^2 = 98%, Figure 1).

Atropine effectively reduced the AL growth compared with placebo at 6, 18, and 24 months. The MD between atropine and placebo at 6 months was −0.09 (95% CI, −0.14 to −0.04; p < 0.001). The heterogeneity was substantial at this time point (I^2 = 86%). At 12 months, the MD was −0.07 (95% CI, −0.31 to 0.18), which was not statistically significant (p = 0.587) and had high heterogeneity (I^2 = 97%). However, at 18 months, a significant reduction in axial elongation was observed, with an MD of −0.24 (95% CI, −0.45 to −0.04; p = 0.017) and relatively high heterogeneity (I^2 = 99%). At 24 months, the MD was −0.25 (95% CI, −0.42 to −0.07; p = 0.005), with similarly high heterogeneity (I^2 = 99%, Figure 2).

Subgroup Analysis for SER

In the subgroup analysis based on sample size (Table 2), heterogeneity remained high in both smaller (<150 participants) and larger (≥150 participants) studies across all time points for SER outcomes. For studies with a sample size of <150, I^2 values were not calculated in cases with only one study; however, where multiple studies were present, heterogeneity was significant, such as at 12 (I^2 = 95%, Q p < 0.001) and 24 (I^2 = 95.3%, Q p < 0.001) months. In studies with ≥150 participants, heterogeneity remained high, with I^2 values of 66.7% and 98.7% at 6 (Q p = 0.049) and 18 (Q p < 0.001) months, respectively. In the subgroup analysis based on publication date (Table 3), studies published before 2020 generally showed high heterogeneity, with an I^2 of 95.5% at 12 months (Q p < 0.001). Studies published in 2020 or later also exhibited significant heterogeneity, with I^2 values reaching 64.4% and 98.9% at 6 (Q p = 0.038) and 24 (Q p < 0.001) months, respectively.

Subgroup Analysis for AL

In the subgroup analysis based on sample size, heterogeneity for AL outcomes was substantial across all time points in both smaller (<150 participants) and larger (≥150 participants) studies. For studies with <150 participants, heterogeneity was not assessed when only one study was available; however, when multiple studies were available, heterogeneity was high, such as at 24 months (I^2 = 92.7%, Q p < 0.001). In studies with ≥150 participants, high heterogeneity was observed consistently, with I^2 values of 90.6% and 99.2% at 6 (Q p < 0.001) and 18 (Q p < 0.001) months, respectively. In the subgroup analysis based on publication date, studies published before 2020 demonstrated high heterogeneity at 12 months (I^2 = 94.7%, Q p < 0.001). Studies published in 2020 or later also demonstrated substantial heterogeneity, with I^2 values reaching 86.3% and 99.9% at 6 (Q p < 0.001) and 24 (Q p < 0.001) months, respectively.

Assessment of Publication Bias

Egger's test and the results of funnel plots for SER and AL outcomes suggested a low risk of publication bias across most time points (Figure 3). For SER at each time point (6, 12, 18, and 24 months), the funnel plots appeared relatively symmetrical, indicating minimal evidence of publication bias. This was further supported by the results of Egger's test, where the p-values were all above the significance threshold (p = 0.996, 0.707, 0.742, and 0.639 for 6, 12, 18, and 24 months, respectively). Similarly, for AL outcomes at 6, 12, 18, and 24 months (Figure 4), the funnel plots appeared symmetrical, with no extreme outliers suggestive of publication bias. The Egger's test p-values for AL at these time points were also above the significance level, with p-values of 0.817, 0.083, 0.303, and 0.371 for 6, 12, 18, and 24 months, respectively.

Discussion

The results of the systematic review and meta-analysis indicate that atropine is effective in slowing myopia progression in children. Higher concentrations generally demonstrated greater efficacy across the included studies. Among the evaluated concentrations, 0.05% atropine appeared to show the most consistent effect in controlling myopia progression. Additionally, longer treatment durations were associated with greater reductions in myopia progression.

Among the various interventions available for myopia, atropine, a well-known non-selective antimuscarinic agent, has emerged as an effective agent for controlling the progression of myopia in children, offering a viable option for

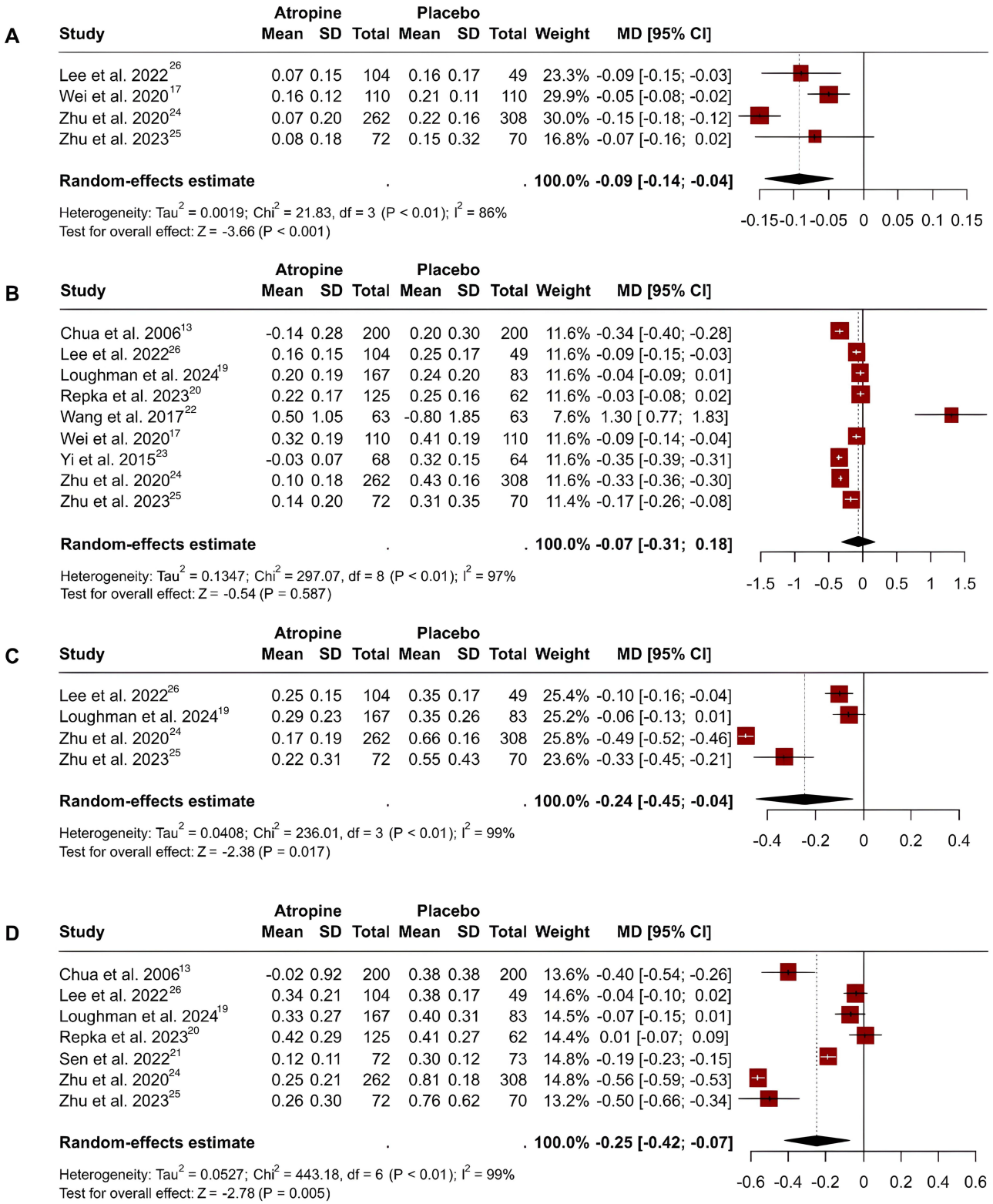

Figure 2 Forest plots depicting the mean differences in axial length between the atropine and placebo groups at different time points: (**A**) 6 months. (**B**) 12 months. (**C**) 18 months. (**D**) 24 months.

Abbreviations: CI, confidence intervals; SD, standard deviation; MD, mean difference.

Table 2 Results of the Overall and Subgroup Analyses of Study Outcomes Based on the Sample Size

Outcome	Parameter	N of Studies	MD (95% CI)	p-value	I^2	Q p-Value	Model
SER at 6 m	Overall	4	0.26 (0.17–0.34)	<0.001	64.4	0.038	R
Sample size	<150	1	0.32 (0.22–0.42)	<0.001	NA	NA	R
	150 or more	3	0.23 (0.13–0.34)	<0.001	66.7	0.049	R
SER at 12 m	Overall	9	0.54 (0.26–0.82)	<0.001	98	<0.001	R
Sample size	<150	3	0.95 (0.51–1.38)	<0.001	95	<0.001	R
	150 or more	6	0.36 (0.08–0.63)	0.01	97.1	<0.001	R
SER at 18 m	Overall	4	0.65 (0.12–1.18)	0.017	98.2	<0.001	R
Sample size	<150	1	1.04 (0.85–1.23)	<0.001	NA	NA	R
	150 or more	3	0.52 (−0.14 to 1.17)	0.122	98.7	<0.001	R
SER at 24 m	Overall	7	0.64 (0.19–1.08)	0.005	98.5	<0.001	R
Sample size	<150	2	0.91 (0.25–1.57)	0.007	95.3	<0.001	R
	150 or more	5	0.52 (−0.05 to 1.10)	0.076	98.9	<0.001	R
AL at 6 m	Overall	4	−0.09 (−0.14 to −0.04)	<0.001	86.3	<0.001	R
Sample size	<150	1	−0.07 (−0.16 to 0.02)	0.109	NA	NA	R
	150 or more	3	−0.10 (−0.16 to −0.04)	0.002	90.6	<0.001	R
AL at 12 m	Overall	9	−0.07 (−0.31 to 0.18)	0.587	97.3	<0.001	R
Sample size	<150	3	0.23 (−0.76 to 1.22)	0.651	95.9	<0.001	R
	150 or more	6	−0.15 (−0.27 to −0.04)	0.009	97.7	<0.001	R
AL at 18 m	Overall	4	−0.24 (−0.45 to −0.04)	0.017	98.7	<0.001	R
Sample size	<150	1	−0.33 (−0.45 to −0.21)	<0.001	NA	NA	R
	150 or more	3	−0.22 (−0.49 to 0.05)	0.114	99.2	<0.001	R
AL at 24 m	Overall	7	−0.25 (−0.42 to −0.07)	0.005	98.6	<0.001	R
Sample size	<150	2	−0.33 (−0.64 to −0.03)	0.032	92.7	<0.001	R
	150 or more	5	−0.21 (−0.43 to 0.01)	0.064	98.9	<0.001	R

Abbreviations: N, number; NA, not applicable; SER, spherical equivalent refractive error; AL, axial length; MD, mean difference; CI, confidence interval.

Table 3 Results of Subgroup Analysis Based on the Date of Publication

Outcome	Parameter	N of Studies	MD (95% CI)	p-value	I^2	Q p-Value	Model
SER at 6 m	< 2020	0	NA	NA	NA	NA	NA
	2020 or more	4	0.26 (0.17–0.34)	<0.001	64.4	0.038	R
SER at 12 m	< 2020	3	1.00 (0.67–1.33)	<0.001	95.5	<0.001	R
	2020 or more	6	0.32 (0.08–0.57)	0.01	95.5	<0.001	R
SER at 18 m	< 2020	0	NA	NA	NA	NA	NA
	2020 or more	4	0.65 (0.12–1.18)	0.017	98.2	<0.001	R
SER at 24 m	< 2020	1	0.92 (0.76–1.08)	<0.001	NA	NA	R
	2020 or more	6	0.59 (0.07–1.11)	0.026	98.7	<0.001	R
AL at 6 m	< 2020	0	NA	NA	NA	NA	NA
	2020 or more	4	−0.09 (−0.14 to −0.04)	<0.001	86.3	<0.001	R
AL at 12 m	< 2020	3	0.17 (−0.87 to 1.22)	0.745	94.7	<0.001	R
	2020 or more	6	−0.13 (−0.22 to −0.03)	0.008	97.4	<0.001	R
AL at 18 m	< 2020	0	NA	NA	NA	NA	NA
	2020 or more	4	−0.24 (−0.45 to −0.04)	0.017	98.7	<0.001	R
AL at 24 m	< 2020	1	−0.40 (−0.54 to −0.26)	<0.001	NA	NA	R
	2020 or more	6	−0.22 (−0.42 to −0.03)	0.026	98.9	<0.001	R

Abbreviations: N, number; NA, not applicable; SER, spherical equivalent refractive error; AL, axial length; MD, mean difference; CI, confidence interval.

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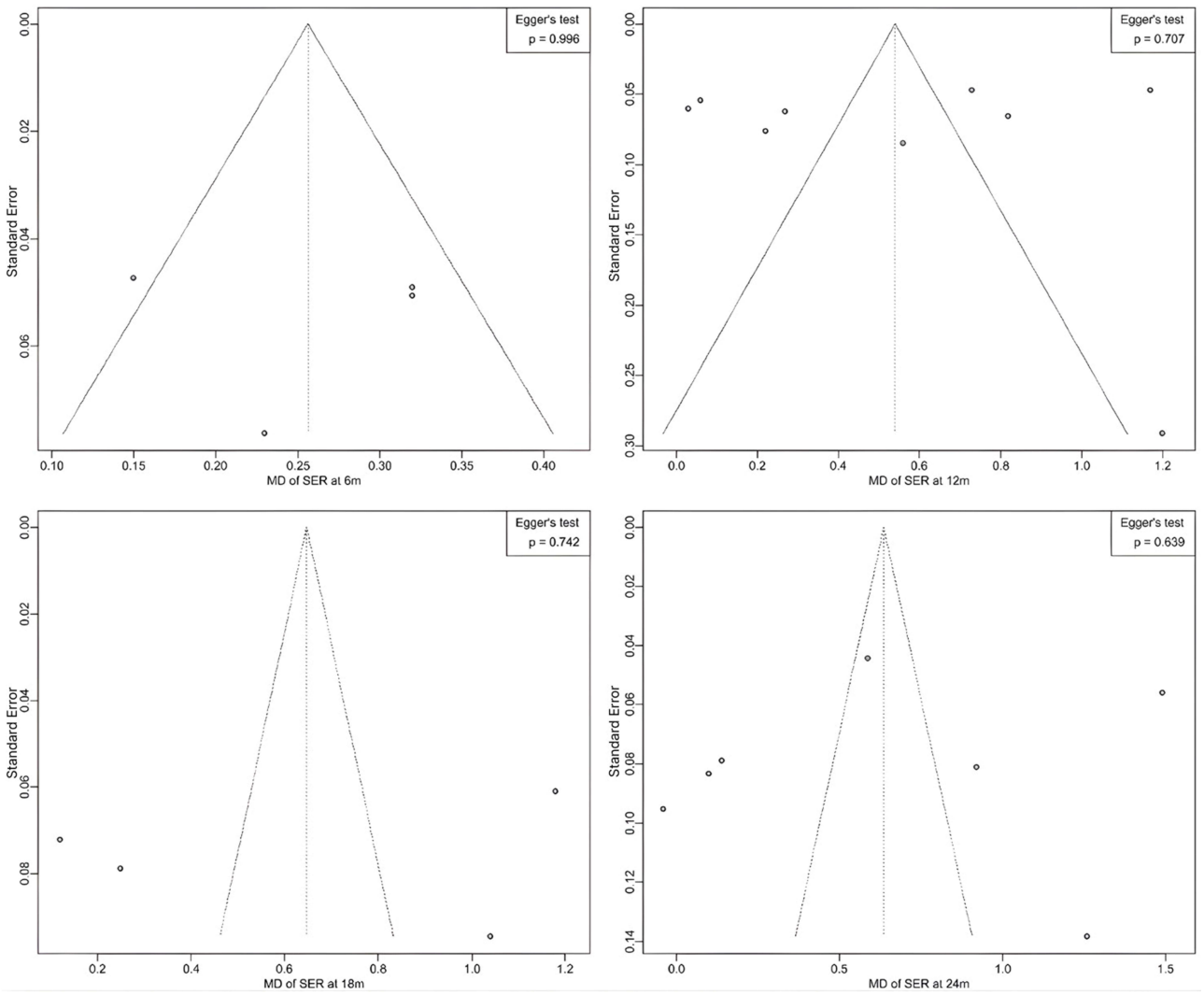

Figure 3 Funnel plots depicting the risk of publication bias assessment for SER outcomes at different time points.
Abbreviations: MD, mean difference; SER, spherical equivalent refractive error.

addressing the global burden of myopia. This meta-analysis of 10 RCTs comprising 2325 pediatric patients evaluated the dose-response effect of atropine on myopia progression, as measured via SER and AL. The analysis revealed that atropine at various doses—high (0.5–1%), moderate (0.1%), and low (0.05–0.01%)—greatly reduced the progression of myopia in the treatment group compared with that in the control group across all time points (6, 12, 18, and 24 months).

A significant reduction was observed in SER at 12 months with an MD of 0.54 (95% CI, 0.26–0.82). This effect persisted over time, with MD of 0.65 (95% CI, 0.12–1.18; p = 0.017) and 0.64 (95% CI, 0.19–1.08; p = 0.005) at 18 and 24 months, respectively. Similarly, AL showed a significant reduction at 18 (MD = −0.24; 95% CI, −0.45 to −0.04; p = 0.017) and 24 (MD = −0.25; 95% CI, −0.42 to −0.07; p = 0.005) months. However, the reduction in AL was negligible at 12 months (MD = −0.07; 95% CI, −0.31 to 0.18; p = 0.587). This can be attributed to the high heterogeneity at this time point, a trend that persisted at 18- and 24-month time points for both SER and AL.

Notably, prominent reductions in both the SER and AL were observed at later time points, suggesting that a longer treatment duration is required for optimal efficacy. This finding is supported by the Atropine for the Treatment of Myopia 2 study,[14] which also found that longer treatment durations, particularly with low-dose atropine, provided more effective myopia control.

A dose-dependent response was observed in the analysis, with higher doses of atropine (1%) demonstrating superior efficacy in controlling myopia progression compared with lower doses (eg, 001%). Increasing the dose of atropine was

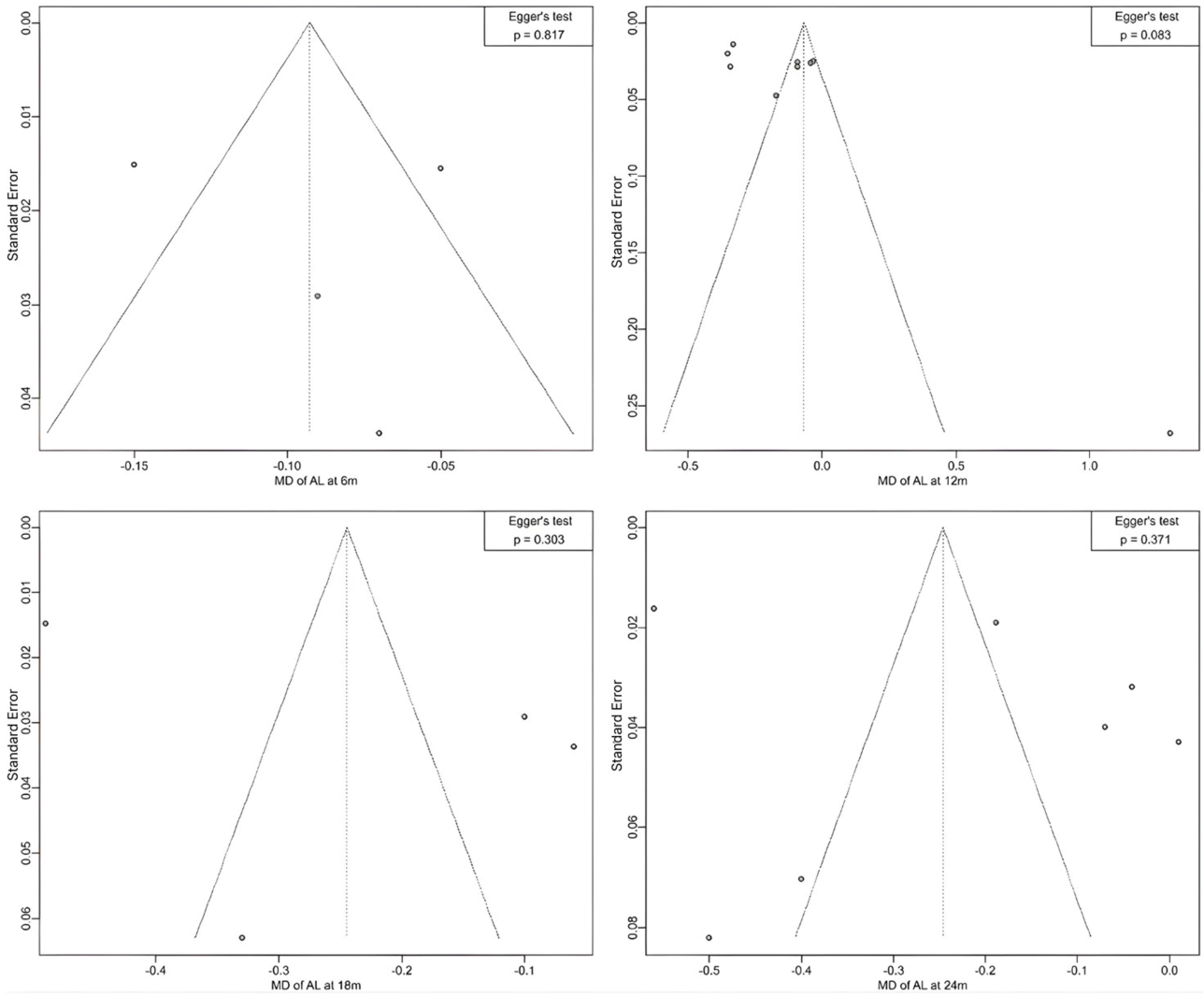

Figure 4 Funnel plots depicting the risk of publication bias assessment for AL outcomes at different time points.
Abbreviations: MD, mean difference; AL, axial length.

also associated with a higher incidence of adverse effects, particularly photophobia and reduced near visual acuity, as reported in a meta-analysis by Gong et al[15] However, this research included cohort studies, which may have introduced methodological limitations and resulted in insufficient evidence to establish a definitive causal relationship.

Among the lower doses, 0.05% atropine demonstrated efficacy comparable to that of higher doses across all time points. This evidence is supported by the third phase of the low-concentration atropine for myopia progression study, which showed that atropine was more than two times as effective at 0.05% as at 0.01%.[16] Although 0.05% atropine remains the optimal concentration, 0.01% atropine is a valuable alternative, particularly for combination therapies. For instance, Tsai et al[26] found that combining 0.01% atropine with Ortho-K significantly reduced myopia progression, achieving effects comparable to those of higher doses. However, this research included only one study that explored 0.05% atropine synergy with Ortho-K. Therefore, further research is warranted to investigate the potential of 0.05% atropine in combination therapies to offer greater benefits for myopia control.

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Limitations

Although this meta-analysis provides valuable insights into atropine for controlling myopia progression, some limitations should be noted to contextualize findings and guide future research. First, heterogeneity was substantial across studies using SER and AL as primary outcomes. Second, several studies had few participants (<150), likely contributing to variability and increased heterogeneity. Third, follow-up times were mostly short (≤24 months), illustrating only short-to-intermediate-term benefits, while long-term effects remain uncertain. Funnel plots and Egger's tests indicated low publication bias, but it cannot be excluded. Subgroup analyses considered sample size and publication year, while other variables were not analyzed. Many studies were limited to specific ethnic or geographic populations, reducing generalizability. Research methods introduced potential bias, including single-center designs, imbalanced group sizes, and insufficient randomization or masking. Finally, limited data exist on withdrawal protocols and their effect on myopia progression.

Conclusion

This systematic review of randomized controlled trials evaluated the effectiveness of atropine in slowing myopia progression in children across different concentrations. Ten studies (2006–2024) showed that atropine significantly slowed myopia progression compared with placebo at 6, 12, 18, and 24 months, with improvements in spherical equivalent refraction (SER). Atropine also reduced axial length (AL) growth at 6, 18, and 24 months. Although heterogeneity among studies was high, publication bias appeared minimal. Among the evaluated concentrations, 0.05% atropine demonstrated consistent efficacy across studies and may represent an effective option for controlling myopia progression in pediatric patients. Further well-designed studies are needed to better clarify the comparative effectiveness of different atropine concentrations and the mechanisms underlying atropine's effect on myopia progression.

Abbreviations

SER, spherical equivalent refractive error; AL, axial length; MD, mean differences; CI, confidence interval; RCT, randomized controlled trial; SD, standard deviation; Ortho-K, orthokeratology.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

Ethics Approval and Informed Consent

Not applicable. This study is a systematic review and meta-analysis and does not involve direct data collection from human participants.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests in this work.

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