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Interventions for myopia control in children: a living systematic review and network meta-analysis (Review)

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[Intervention Review]

Interventions for myopia control in children: a living systematic review and network meta-analysis

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ABSTRACT

Rationale

The increasing prevalence of myopia is a growing global public health problem, in terms of rates of uncorrected refractive error and significantly, an increased risk of visual impairment due to myopia-related ocular morbidity. Interventions to slow its progression are needed in childhood, when myopia progression is most rapid. This is a review update, conducted as part of a living systematic review.

Objectives

To assess the comparative efficacy and safety of interventions for slowing myopia progression in children using network meta-analysis (NMA). To generate a relative ranking of interventions according to their efficacy. To produce a brief economic commentary, summarising economic evaluations.

Search methods

We searched CENTRAL, MEDLINE, Embase, and three trial registers. The latest search date was 19 February 2024.

Eligibility criteria

We included randomised controlled trials (RCTs) of optical, pharmacological, light therapy and behavioural interventions for slowing myopia progression in children, up to 18 years old.

Outcomes

Critical outcomes were progression of myopia (mean difference (MD) in the change in spherical equivalent refraction (SER, dioptres (D)), and axial length (AL, mm) in the intervention and control groups at one year or longer), and difference in the change in SER and AL following cessation of treatment (rebound).

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Risk of bias

We assessed the risk of bias (RoB) for SER and AL using the Cochrane RoB 2 tool.

Synthesis methods

We followed standard Cochrane methods. We rated the certainty of evidence using the GRADE approach for change in SER and AL at one and two years. We used the surface under the cumulative ranking curve (SUCRA) to rank the interventions for all available outcomes.

Included studies

We included 104 studies (40 new for this update) that randomised 17,509 children, aged 4 years to 18 years. Most studies were conducted in China or other Asian countries (66.3%), and North America (14.4%). Eighty-four studies (80.8%) compared myopia control interventions against inactive controls. Study durations ranged from 12 months to 48 months.

Synthesis of results

Since most of the networks in the NMA were poorly connected, our estimates are based on direct (pairwise) comparisons, unless stated otherwise.

The median change in SER for controls was −0.65 D (55 studies, 4888 participants; one-year follow-up). These interventions may reduce SER progression compared to controls: repeated low intensity red light (RLRL: MD 0.80 D, 95% confidence interval (CI) 0.71 to 0.89; SUCRA = 93.8%; very low-certainty evidence); high-dose atropine (HDA (≥ 0.5%): MD 0.90 D, 95% CI 0.62 to 1.18; SUCRA = 93.3%; moderate-certainty evidence); medium-dose atropine (MDA (0.1% to < 0.5%): MD 0.55 D, 95% CI 0.17 to 0.93; NMA estimate SUCRA = 75.5%; low-certainty evidence); low dose atropine (LDA (< 0.1%): MD 0.25 D, 95% CI 0.16 to 0.35; SUCRA = 53.2%; very low-certainty evidence); peripheral plus spectacle lenses (PPSL: MD 0.45 D, 95% CI 0.16 to 0.74; SUCRA = 50.2%; very low-certainty evidence); multifocal soft contact lenses (MFSCL: MD 0.27 D, 95% CI 0.18 to 0.35; SUCRA = 49.9%; very low-certainty evidence); and multifocal spectacle lenses (MFSL: MD 0.14 D, 95% CI 0.08 to 0.21; SUCRA = 30.8%; low-certainty evidence).

The median change in AL for controls was 0.33 mm (58 studies, 9085 participants; one-year follow-up). These interventions may reduce axial elongation compared to controls: RLRL (MD −0.33 mm, 95% CI −0.37 to −0.29; SUCRA = 98.6%; very low-certainty evidence); HDA (MD −0.33 mm, 95% CI −0.35 to −0.30; SUCRA = 88.4%; moderate-certainty evidence); MDA (MD −0.24 mm, 95% CI −0.34 to −0.15; NMA estimate SUCRA = 75.8%; low-certainty evidence); LDA (MD −0.10 mm, 95% CI −0.13 to −0.07; SUCRA = 36.1%; very low-certainty evidence); orthokeratology (ortho-K: MD −0.18 mm, 95% CI −0.21 to −0.14; SUCRA = 79%; moderate-certainty evidence); PPSL (MD −0.13 mm, 95% CI −0.21 to −0.05; SUCRA = 52.6%; very low-certainty evidence); MFSCL (MD −0.11 mm, 95% CI −0.13 to −0.09; SUCRA = 45.6%; low-certainty evidence); and MFSL (MD −0.06 mm, 95% CI −0.09 to −0.04; SUCRA = 26.3%; low-certainty evidence). Ortho-K plus LDA probably reduces axial elongation more than ortho-K monotherapy (MD −0.12 mm, 95% CI −0.15 to −0.09; SUCRA = 81.8%; moderate-certainty evidence).

At two-year follow-up, change in SER was reported in 34 studies (3556 participants). The median change in SER for controls was −1.01 D. The ranking of interventions to reduce SER progression was close to that observed at one year; there were insufficient data to draw conclusions on cumulative effects. The highest-ranking interventions were: HAD (SUCRA = 97%); MDA (NMA estimate SUCRA = 69.8%); and PPSL (SUCRA = 69.1%).

At two-year follow-up, change in AL was reported in 33 studies (3334 participants). The median change in AL for controls was 0.56 mm. The ranking of interventions to reduce axial elongation was similar to that observed at one year; there were insufficient data to draw conclusions on cumulative effects. The highest-ranking interventions were: ortho-K plus LDA (SUCRA = 94.2%); HAD (SUCRA = 96.8%); and MDA (NMA estimate SUCRA = 88.4%).

There was limited evidence on whether cessation of myopia control therapy increases progression beyond the expected rate of progression with age. Adverse events and treatment adherence were not consistently reported. Two studies reported quality of life, showing little to no difference between intervention and control groups.

We were unable to draw firm conclusions regarding the relative costs or efficiency of different myopia control strategies in children.

Authors' conclusions

Most studies compared pharmacological and optical treatments to slow the progression of myopia with an inactive comparator. These interventions may slow refractive change and reduce axial elongation, although results were often heterogeneous. Less evidence is available for two years and beyond; uncertainty remains about the sustained effect of these interventions.

Longer term and better quality studies comparing myopia control interventions alone or in combination are needed, with improved methods for monitoring and reporting adverse effects.

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Registration

The previous version of this living systematic review is available at doi: 10.1002/14651858.CD014758.pub2.

PLAIN LANGUAGE SUMMARY

Interventions to slow the progression of short-sightedness in children

Key messages

- Medicines, such as atropine, given as eye drops, can slow the progression of short- or near-sightedness (myopia) in children, and also reduce elongation of the eyeball due to myopia. Higher doses of atropine are most effective. We are uncertain about the effects of lower doses of atropine.
- Several treatments, including special types of lenses in eyeglasses, contact lenses, and a new therapy using low intensity red light, may slow the progression of short-sightedness, but their effect is still uncertain. There is insufficient information on the risk of unwanted side effects associated with strategies to control myopia.
- It is also unclear whether the reported benefit of treatments to slow the progression of myopia is maintained over the years.

What is short-sightedness?

Short-sightedness (or near-sightedness, or myopia) means people struggle to see objects clearly that are far away, while objects that are near remain clear. It is very common worldwide, and affects more than half of the children in China and South-East Asia. Short-sightedness may impair many aspects of life, including educational and occupational activities. Short-sighted people have longer eyes, which means that the retina is stretched. This puts the eye at greater risk of eye diseases, such as glaucoma, maculopathy, and retinal detachment, later in life.

How is short-sightedness treated?

Although conventional eyeglasses or contact lenses can correct short-sightedness, they do not slow its progression. A number of optical treatments (glasses and contact lenses) and medications are available that aim to slow the progression of short-sightedness. But they need to be given in childhood, when short-sightedness progresses most quickly. Medicines, such as atropine eye drops, may be effective, but can increase light sensitivity and cause problems when reading, especially the higher doses. Special eyeglasses are also available that include more than one focus power within the lens (multifocal or peripheral-plus lenses). These can also be provided as soft contact lenses. Other contact lenses, called orthokeratology, aim to temporarily change the shape of the eye surface. They are worn during sleep and removed during the day. Both soft contact lenses and orthokeratology may increase the risk of infections to the eye surface. An emerging treatment involves repeated short-duration exposure to low intensity red light.

What did we want to find out?

We aimed to find out whether medicines used as eye drops, light therapy, and special lenses in eyeglasses or contact lenses, can slow the progression of myopia, and the elongation of the eyeball. We also documented the risk of unwanted effects when using them.

What did we do?

We searched for studies that tested medicines, lenses, and light therapy that aimed to slow the progression of short-sightedness in children, and compared them with a control group, or with other medicines and lenses. Most of the control groups received a placebo (sham) treatment or single vision eyeglasses or contact lenses.

What did we find?

We included 104 studies (40 new for this update) that randomised 17,509 children with myopia.

- Higher doses of atropine may reduce the progression of short-sightedness, but the effect of low-dose atropine could be small and is uncertain.
- Based on short-term studies, orthokeratology is the most effective optical treatment for slowing elongation of the eyeball. However, these lenses were often poorly tolerated, and in some studies, more than half of the children did not complete the treatment.
- Other types of contact lenses, known as multifocal soft contact lenses and myopia-control eyeglasses, may also reduce the progression of short-sightedness, but, again, we remain uncertain about their benefits.
- Although short-term studies in Chinese children suggest that red light therapy may reduce myopia progression, we are very uncertain about these findings.
- Unwanted effects associated with treatments to control myopia were not consistently reported. Eye discomfort in bright light and blurred vision for near objects were the most common treatment-related unwanted effects in studies using atropine. Lower doses of atropine appear to have fewer unwanted effects.

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- Although studies that tested contact lenses did not report any serious unwanted effects, there is limited information on the true rate of unwanted effects in children outside the context of a research study, or when wearing contact lenses for longer periods.

What are the limitations of the evidence?

Most of the evidence came from studies conducted in ways that may have introduced errors into their results, and potential unwanted effects were not well reported. The majority of the studies followed participants for two years or less. Therefore, there is insufficient evidence on whether benefits increase over the years, and whether the effects are sustained.

How up-to-date is the evidence?

This review is up-to-date to February 2024.

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SUMMARY OF FINDINGS

Summary of findings 1. Change in refractive error at 1 year

Interventions for myopia control in children: a living systematic review and network meta-analysis

Population: children with progressive myopia (55 studies, 4888 participants in analyses)

Interventions: optical and pharmacological

Comparator: control (53 studies, 3981 participants). Control arms for optical interventions are either single vision spectacles or contact lenses. Placebo eyedrops were the usual comparator for pharmacological interventions

Outcome: progression of myopia (difference in change in spherical equivalent refraction (SER)) at 1 year (dioptres)

Setting: primary eye care

Assumed control risk: median change in SER in control arms at 1 year −0.65 D

Equivalence criterion: difference in change in spherical equivalent less than 0.25 D

Treatment (versus control)	Number of studies in the treatment arm (participants)	Corresponding intervention risk MD (95% CI) Direct estimates from pairwise MA	Corresponding intervention risk MD (95% CI) Estimates from NMA	Certainty of evidence
High-dose atropine (≥ 0.5%)	3 (512)	0.90 (0.62 to 1.18)	0.84 (0.60 to 1.07)	Moderate[a]
Medium-dose atropine (0.1% to < 0.5%)	2 (254)	No direct estimate	0.55 (0.17 to 0.93)	Low[b]
Low-dose atropine (< 0.1%)	16 (1609)	0.25 (0.16 to 0.35)	0.27 (0.17 to 0.38)	Very low[c]
Repeated low-intensity red light	3 (183)	0.80 (0.71 to 0.89)	0.84 (0.63 to 1.05)	Very low[c]
Multifocal soft contact lenses	12 (815)	0.27 (0.18 to 0.35)	0.25 (0.13 to 0.38)	Very low[c]
Rigid gas-permeable contact lenses	2 (178)	One study showed no difference; the other showed a beneficial effect	0.17 (−0.13 to 0.47)	Very low[c]
Peripheral plus spectacle lenses	6 (536)	0.45 (0.16 to 0.74)	0.25 (0.04 to 0.46)	Very low[c]
Multifocal spectacle lenses	9 (729)	0.14 (0.08 to 0.21)	0.14 (−0.05 to 0.33)	Low[b]
Undercorrected single vision spectacles	2 (72)	−0.15 (−0.29 to 0.00)	−0.15 (−0.46 to 0.16)	Low[b]

GRADE Working Group grades of evidence

High-certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate-certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.

Low-certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low-certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

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Explanation

Negative mean differences for changes in refractive error represent faster progression of myopia in the intervention group compared to progression in the control group.

Measurement of refractive error is not an appropriate outcome in orthokeratology (ortho-K) studies. Overnight wear of ortho-K lenses flattens the central cornea and temporally reduces refractive error. Therefore, it is not possible to assess the true progression of refractive error without ceasing lens wear for a period of time to allow the cornea to return to its pre-treatment state.

CI: confidence interval; **MA:** meta-analysis**; MD:** mean difference; **NMA:** network meta-analysis

Reasons for downgrade

[a]Downgraded one level for risk of bias, not downgraded for inconsistency since all studies show clinically important effects.
[b]Downgraded one level each for risk of bias and imprecision
[c]Downgraded one level each for risk of bias, imprecision, and inconsistence
With the exception of medium-dose atropine, downgrade decisions relate to direct evidence from pairwise MA rather than indirect evidence from the NMA.
In each case, downgrading due to risk of bias was due to concerns arising from the randomisation process and in the selection of the reporting of the results; downgrading for imprecision was due to a confidence interval that included small and clinically unimportant effects or optimal information size not met (using fewer than 400 participants as a 'rule of thumb'); downgrading for inconsistency was due to substantial heterogeneity.

Summary of findings 2. Change in refractive error at 2 years

Interventions for myopia control in children: a living systematic review and network meta-analysis

Population: children with progressive myopia (34 studies, 3556 participants in the analysis)

Interventions: optical and pharmacological

Comparator: control (32 studies, 3056 participants). Control arms for optical interventions are either single vision spectacles or contact lenses. Placebo eyedrops were the usual comparator for pharmacological interventions.

Outcome: progression of myopia (difference in change in spherical equivalent refraction (SER)) at 2 years (dioptres)

Setting: primary eye care

Assumed control risk: median change in SER in control arms at 2 years −1.01 D

Equivalence criterion: difference in change in spherical equivalent less than 0.25 D

Treatment (versus control)	Number of studies in the treatment arm (participants)	Corresponding intervention risk MD (95% CI) Direct estimates from pairwise MA	Corresponding intervention risk MD (95% CI) Estimates from NMA	Certainty of evidence
High-dose atropine (≥ 0.5%)	2 (428)	1.26 (1.17 to 1.36)	0.77 (0.40 to 1.15)	Moderate[a]
Medium-dose atropine (0.1% to < 0.5%)	2 (247)	-	0.48 (0.03 to 0.93)	Low[b]
Low-dose atropine (< 0.1%)	9 (1030)	0.36 (0.32 to 0.40)	0.36 (0.19 to 0.54)	Low[b]
Multifocal soft contact lenses	5 (540)	0.30 (0.19 to 0.41)	0.31 (0.07 to 0.55)	Low[b]
Rigid gas-permeable contact lenses	2 (154)	One study showed no difference; the other showed a beneficial effect	0.23 (−0.16 to 0.62)	Very low[c]

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Peripheral plus spectacle lenses	3 (295)	0.43 (0.13 to 0.73)	0.43 (0.12 to 0.74)	Very low[c]
Multifocal spectacle lenses	9 (740)	0.19 (0.09 to 0.29)	0.20 (0.01 to 0.40)	Low[b]
Undercorrected single vision spectacles	2 (122)	0.02 (−0.05 to 0.09)	−0.08 (−0.46 to 0.30)	Very low[c]

GRADE Working Group grades of evidence

High-certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate-certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.

Low-certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low-certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Explanation

Negative mean differences (MDs) for changes in refractive error represent faster progression of myopia in the intervention group compared to progression in the control group.

Measurement of refractive error is not an appropriate outcome in orthokeratology (ortho-K) studies. Overnight wear of ortho-K lenses flattens the central cornea and temporally reduces refractive error. Therefore, it is not possible to assess the true progression of refractive error without ceasing lens wear for a period of time to allow the cornea to return to its pre-treatment state.

CI: confidence interval; **MA:** meta-analysis**; MD:** mean difference; **NMA:** network meta-analysis

Reasons for downgrade

[a]Downgraded one level for risk of bias, not downgraded for inconsistency since all studies show clinically important effects

[b]Downgraded one level each for risk of bias and imprecision

[c]Downgraded one level each for risk of bias, imprecision, and inconsistency

With the exception of medium-dose atropine, downgrade decisions relate to direct evidence from pairwise MA rather than indirect evidence from the NMA.

In each case, downgrading due to risk of bias was due to concerns arising from the randomisation process and in the selection of the reporting of the results; downgrading for imprecision was due to a confidence interval that included small and clinically unimportant effects or optimal information size not met (using fewer than 400 participants as a 'rule of thumb'); downgrading for inconsistency was due to substantial heterogeneity.

Summary of findings 3. Change in axial length at 1 year

Interventions for myopia control in children: a living systematic review and network meta-analysis

Population: children with progressive myopia (58 studies, 9085 participants) in the analysis

Interventions: optical and pharmacological

Comparator: control (57 studies, 4180 participants). Control arms for optical interventions are either single vision spectacles or contact lenses. Placebo eyedrops were the usual comparator for pharmacological interventions

Setting: primary eye care

Outcome: difference in change in axial length at 1 year (mm)

Assumed control risk: median change in axial length in control arms at 1 year 0.33 mm

Equivalence criterion: difference in change in axial length less than 0.1 mm

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Treatment (vs control)	Number of studies in the treatment arm (participants)	Corresponding intervention risk MD (95%CI) Direct estimates from pairwise MA	Corresponding intervention risk MD (95%CI) Estimates from NMA	Certainty of evidence
High-dose atropine (≥ 0.5%)	3 (512)	−0.33 (−0.35 to −0.30)	−0.30 (−0.36 to −0.24)	Moderate[a]
Medium-dose atropine (0.1% to < 0.5%)	1 (155)	-	−0.24 (−0.34 to −0.15)	Low[b]
Low-dose atropine (< 0.1%)	17 (1646)	−0.10 (−0.13 to −0.07)	−0.09 (−0.12 to −0.06)	Very low[c]
Repeated low intensity red light	2 (183)	−0.33 (−0.37 to −0.29)	−0.35 (−0.41 to −0.29)	Very low[c]
Orthokeratology	12 (710)	−0.18 (−0.21 to −0.14)	−0.27 (−0.34 to −0.21)	Moderate[a]
Multifocal soft contact lenses	12 (815)	−0.11 (−0.13 to −0.09)	−0.11 (−0.14 to −0.08)	Low[b]
Rigid gas-permeable contact lenses	2 (176)	0.02 (−0.05 to 0.10)	0.02 (−0.07 to 0.12)	Low[b]
Peripheral plus spectacle lenses	4 (396)	−0.13 (−0.21 to −0.05)	−0.13 (−0.19 to −0.08)	Very low[c]
Multifocal spectacle lenses	4 (445)	−0.06 (−0.09 to −0.04)	−0.04 (−0.15 to 0.07)	Low[b]
Undercorrected single vision spectacles	1 (47)	0.05 (−0.01 to 0.11)	0.05 (−0.06 to 0.16)	Low[b]

GRADE Working Group grades of evidence

High-certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate-certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.

Low-certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low-certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Explanation

For the measurement of changes in axial length, negative mean differencess for changes in axial length represent faster axial elongation in the control group compared to the intervention group.

CI: confidence interval; **MA:** meta-analysis**; MD:** mean difference; **NMA:** network meta-analysis

Reasons for downgrade

[a]Downgraded one level for risk of bias

[b]Downgraded one level each for risk of bias and imprecision

[c]Downgraded one level each for risk of bias, imprecision and inconsistency

With the exception of medium-dose atropine, downgrade decisions relate to direct evidence from pairwise MA rather than indirect evidence from the NMA.

In each case, downgrading due to risk of bias was due to concerns arising from the randomisation process and in the selection of the reporting of the results; downgrading for imprecision was due to a confidence interval that included small and clinically unimportant effects, or optimal information size not met (using fewer than than 400 participants as a 'rule of thumb'); downgrading for inconsistency was due to substantial heterogeneity

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Summary of findings 4. Change in axial length at 2 years

Interventions for myopia control in children: a living systematic review and network meta-analysis

Population: children with progressive myopia (33 studies, 3334 participants in the analysis)

Interventions: optical and pharmacological

Comparator: control (32 studies, 2800 participants). Control arms for optical interventions are either single vision spectacles or contact lenses. Placebo eyedrops are the usual comparator for pharmacological interventions.

Outcome: median change in axial length in control arms at 2 years

Setting: primary eye care

Assumed control risk: change in axial length at 2 years 0.56 mm

Equivalence criterion: difference in change in axial length less than 0.1 mm

Treatment (vs control)	Number of studies in the treatment arm (participants)	Corresponding intervention risk MD (95%CI) Direct estimates from pairwise MA	Corresponding intervention risk MD (95%CI) Estimates from NMA	Certainty of evidence
High-dose atropine (≥ 0.5%)	2 (428)	−0.47 (−0.61 to −0.34)	−0.35 (−0.48 to −0.22)	Moderate[a]
Medium-dose atropine (0.1% to < 0.5%)	1 (144)	-	−0.32 (−0.49 to −0.15)	Low[b]
Low-dose atropine (< 0.1%)	10 (1070)	−0.16 (−0.21 to −0.11)	−0.16 (−0.22 to −0.11)	Low[b]
Orthokeratology	4 (132)	−0.30 (−0.38 to −0.23)	−0.26 (−0.37 to −0.16)	Moderate[a]
Multifocal soft contact lenses	5 (540)	−0.15 (−0.19 to −0.12)	−0.16 (−0.24 to −0.08)	Moderate[a]
Rigid gas-permeable contact lenses	2 (154)	0.03 (−0.05 to 0.12)	0.03 (−0.11 to 0.17)	Low[b]
Peripheral plus spectacle lenses	3 (296)	−0.23 (−0.35 to −0.10)	−0.23 (−0.34 to −0.13)	Very low[c]
Multifocal spectacle lenses	4 (448)	−0.07 (−0.11 to −0.03)	−0.09 (−0.18 to 0.00)	Low[b]
Undercorrected single vision spectacles	2 (122)	−0.01 (−0.06 to 0.03)	0.01 (−0.11 to 0.13)	Low[b]

GRADE Working Group grades of evidence

High-certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate-certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.

Low-certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low-certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Explanation

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For the measurement of changes in axial length, negative MDs for changes in axial length represent faster axial elongation in the control group compared to the intervention group

CI: confidence interval; **MA:** meta-analysis**; MD:** mean difference; **NMA:** network meta-analysis

Reasons for downgrade

[a]Downgraded one level for risk of bias

[b]Downgraded one level each for risk of bias and imprecision

[c]Downgraded one level each for risk of bias, imprecision and inconsistency

With the exception of medium-dose atropine, downgrade decisions relate to direct evidence from pairwise MA rather than indirect evidence from the NMA.

In each case, downgrading due to risk of bias was due to concerns arising from the randomisation process and in the selection of the reporting of the results; downgrading for imprecision was due to a confidence interval that included small and clinically unimportant effects, or optimal information size not met (using fewer than 400 participants as a 'rule of thumb'); downgrading for inconsistency was due to substantial heterogeneity.

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BACKGROUND

Description of the condition

Myopia, or short- or near-sightedness, is a common refractive anomaly of the eye that occurs when parallel rays of light are brought to a focus in front of the retina with accommodation at rest, causing distant objects to appear blurred and near objects to remain clear [1]. Myopia most often results from the eyeball being too long (i.e. there is excessive axial elongation), but can also occur when the image-forming structures of the eye are too strong [2].

The prevalence of myopia shows significant age, ethnic, and regional variation [3]. Currently, 30% to 50% of adults in the USA and Europe have myopia [4]. Myopia is already reaching 'epidemic' proportions in children and young adults in urban areas of East and South East Asia, with over 80% of children being myopic by the time they complete their high school education [5]. If current trends continue, it is estimated that by 2050, there will be approximately 5 billion (5000 million) people with myopia (i.e. about 50% of the world's population), with around 10% having high myopia (when defined as a spherical equivalent of −5.00 dioptres (D) or worse) [6].

The aetiology of myopia involves a complex interaction between environmental and genetic factors. Although genetic inheritance is a well-established predisposing factor for myopia, genetic factors alone cannot explain the rapidly rising prevalence of the condition [7]. A Mendelian randomisation study, using the UK Biobank cohort, provided strong evidence for the cumulative effect of additional years in education on the development of myopia [8]. Mendelian randomisation is a statistical approach that uses genetics to provide information about the relationship between an exposure and the outcome. This study estimated that for each additional year in education, myopic spherical equivalent increased by −0.27 D. The estimate was reduced by approximately 40% to −0.17 D, when the effects of time outdoors was taken into account, suggesting that a significant proportion of the relationship between myopia and education was mediated by children spending less time outdoors during the school day [9]. Evidence from a number of observational studies further supports the causal association between environmental and social factors and myopia development [10].

Epidemiological studies have shown that myopia is an established risk factor for a number of ocular pathologies, including cataract, glaucoma, and retinal detachment [11]. Although myopia-related complications can occur regardless of age and degree of myopia [12], the excessive axial elongation associated with higher degrees of myopia causes biomechanical stretching of the outer coat of the eye, increasing the risk of sight-threatening pathologies, such as posterior staphyloma and myopic maculopathy [13, 14]. Bullimore and colleagues developed a risk prediction model of visual impairment as a function of degree of myopia and age [15]. The predicted mean years of visual impairment was estimated as 4.4 years for a person with -3.00 D of myopia and 9.5 years for a -8.00 D myope. A meta-analysis of population studies reporting blindness and visual impairment due to myopic maculopathy [16], estimated that in 2015, approximately 10 million people had visual impairment due to myopic macular degeneration, three million of whom were blind. Although the sight-threatening pathologies associated with myopia usually occur later in life, the underlying myopia develops during childhood, and therefore, interventions to reduce the progression of myopia have the potential to reduce future visual impairment.

Description of the intervention and how it might work

Most cases of myopia develop during childhood, and the prevalence of myopia begins to increase noticeably after the age of six years [17]. Progression rates vary significantly, with rates in Asian children being approximately 0.20 D per year faster than their age-matched European counterparts [18]. Since myopia tends to stabilise in late adolescence, interventions to slow myopia progression need to be delivered in childhood.

Interventions to slow the progression of myopia can be grouped into three broad categories: optical, pharmacological, and behavioural [19]. Optical interventions include a variety of spectacle and contact lens designs. Spectacles are the least invasive and most accessible method for potentially slowing myopia progression. Spectacle options include refractive under-correction, bifocal and progressive addition lenses, and more recently, specialised myopia control designs. Soft multifocal and approved myopia control contact lenses are increasingly being used for myopia management in children [20]. Centre-distance soft multifocal lens designs incorporate a central zone that contains the distance refractive correction, with peripheral regions of the lens having relatively increased positive power (myopic defocus). This is achieved by either a gradual increase in power towards the periphery, or by using concentric peripheral zones of alternating myopic defocus and distance correction. An alternative design principle is used in extended depth of focus (EDOF) contact lenses. EDOF lenses are reported to provide competing signals on the retina; one to correct vision centrally, and another to create relative myopic defocus in the periphery [21]. Orthokeratology involves the use of specialised rigid contact lenses that are worn during sleep to change the topography of the cornea to reduce myopic refractive error and manipulate peripheral retinal defocus. Safety remains a concern, because of the greater risk of sight-threatening microbial keratitis with overnight wear compared with daily contact lens wear modalities [22].

The most commonly used topical pharmacological intervention for myopia control is atropine, a non-selective muscarinic antagonist, which has been widely used in clinical trials in concentrations ranging from 0.01% to 1.0%. Although higher atropine concentrations have been shown to be effective in retarding myopia progression in children, the higher incidence of side effects with higher doses, including cycloplegia (inhibition of accommodation) and pupil dilation (which causes blur for near vision and photophobia) limits its use. Furthermore, a rebound effect (involving more rapid myopia progression) after discontinuation of therapy is more pronounced with higher concentrations of atropine [23]. More recent studies have evaluated the efficacy of lower concentrations to reduce side effects and lessen the likelihood of rebound. The results of these studies have led to a renewed interest in the clinical application of low-dose atropine (i.e. 0.01% to 0.05%) for myopia control [24]. Atropine can be used as monotherapy, or in combination with other myopia control interventions [25]. Other pharmacological agents that have been evaluated for myopia control include topical tropicamide, cyclopentolate and pirenzipine (a selective M1 muscarinic antagonist), and the oral adenosine antagonist, 7-methylxanthine.

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Evidence that more time spent on near work activities is associated with higher odds of developing myopia [26], and the observation that increased time spent outdoors is protective against myopia, after adjusting for near work, parental myopia, and ethnicity [27], have raised the possibility that environmental or behavioural interventions could be effective for myopia control. Trials of school-based programmes that promote outdoor activities, conducted in East Asia, have reported a lower incidence of myopia onset, but have limited impact on progression following onset of myopia [28]. The dose-response relationship between time spent outdoors and incident myopia suggests that one to two hours of daily outdoor light exposure could potentially reduce the risk of myopia by 50% [29].

Animal studies have shown that optically-induced changes to the effective refractive status of the eye can regulate eye growth and influence refractive development [30]. Specifically, the observation that imposed relative myopic defocus (image focused in front of the retina) can slow axial elongation has been the impetus for the development of novel multifocal spectacles and contact lenses that provide clear central vision, whilst at the same time presenting myopic defocus over a large proportion of the visual field. The critical area ratio required for these simultaneous, competing defocus signals to dominate eye growth is currently unclear. However, the relative treatment effects reported for different optical treatment regimens suggest that there appears to be an eccentricity-dependent decrease in the efficacy of myopic defocus beyond the near periphery [31, 32].

Orthokeratology involves corneal reshaping lenses that are worn overnight to flatten the central cornea and reduce its dioptric power. The geometry of these lenses also creates a corneal profile that produces relative myopic defocus.

The precise mechanism by which anti-muscarinic agents reduce myopic progression is not fully understood. A non-accommodative mechanism is thought to be the most likely, and alternative targets have been proposed, including eye growth regulatory pathways that arise in the retina and are relayed to the sclera via the retinal pigment epithelium and choroid [33, 34].

The mechanism for the protective effect of increased time outdoors on myopia development is currently unclear. Light levels have been shown to influence refractive development in animal models [35], and higher light intensities stimulate retinal dopamine production, which is thought to inhibit axial elongation [36]. It has been proposed that the spectral composition of ambient light in the natural environment could be a critical factor in the regulation of eye growth [37], and animal studies have demonstrated that exposure to different monochromatic wavelengths of light can influence ocular growth [38]. Repeated low level red light therapy has recently emerged as a new myopia control treatment modality [39]. Several clinical studies using short exposure to long wavelength red light (635 nm to 650 nm), typically for three minutes twice a day, have been published [40], although safety concerns have been raised regarding this therapy [41, 42].

Why it is important to do this review

As a result of its increasing global prevalence and association with sight-threatening pathologies, myopia is emerging as a major public health concern. Myopia is predicted to affect almost half of the world's population by 2050, and the pathologic consequences of high myopia increase the risk of irreversible visual impairment and blindness. There has been considerable interest in the development of strategies to delay the onset of myopia and slow its progression. Myopia control interventions are increasingly being used in routine clinical practice [20, 43]. Evidence from randomised controlled trials (RCTs) indicates that the progression of myopia can be slowed by different interventions, although treatment efficacy is highly variable.

There is a broad consensus that the primary endpoints for judging efficacy in clinical trials of myopia control interventions should include change in axial length, in addition to change in refractive error [44, 45, 46]. Myopia development and progression usually occur due to abnormal axial elongation. Therefore, axial length may be a better predictor of future progression and consequent risk of posterior pole complications [44]. An expert panel reached consensus on the minimal clinically important difference of the key efficacy outcomes in myopia control studies. They concluded that a mean difference between intervention groups of 0.25 D per year would be regarded as clinically significant, i.e. 0.75 D over the course of a three-year study [45]. This would correspond to a difference in axial length of approximately 0.3 mm.

Eye care professionals often find it difficult to assimilate potentially conflicting evidence to inform their clinical decision-making [47]. Therefore, it is important that practitioners can access high-quality and up-to-date evidence to inform practice. Parents of myopic children also need reliable information to help them to understand and interpret research findings. Given the large number of different interventions available for myopia control, and the large number of completed and ongoing RCTs on this topic, there is an urgent need to evaluate the comparative effectiveness of different interventions. A network meta-analysis (NMA) offers an advantage over a standard pairwise meta-analysis, because it provides both direct comparisons of individual trials, and indirect comparisons not directly evaluated in trials across a network of studies, thus generating the comparativeness of all interventions in a coherent manner. An NMA can also provide relative rankings of interventions to inform clinical decision-making.

There are significant resource implications associated with myopia for both individuals and healthcare systems. This includes both corrected and uncorrected myopic refractive error. Lim and colleagues estimated the mean direct costs of managing myopia in school-aged children in Singapore [48]. These costs included optometrist visits, spectacles, contact lenses, and travel costs. The mean cost was estimated as USD 148 (median SGD 83.33) per year in 2006. In 2011, Zheng and colleagues estimated the lifetime costs for a person with myopia would be USD 17,020 over an 80-year lifespan [49]. There are also associated costs and quality-of-life impacts associated with uncorrected refractive error. Tahhan and colleagues found a significant reduction in health state utility (a preference-based quality-of-life measure) associated with uncorrected refractive error [50]. Fricke and colleagues estimated that the direct costs of correcting all cases of uncorrected refractive error globally would be approximately USD 28 billion (USD 28,000 million); the year of the analysis was not stated [51]. Given these cost estimates, understanding the current evidence base for myopia control is key for both individuals and healthcare decision-makers.

We are maintaining this review as a living systematic review. This involves searching the literature annually, and incorporating new

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evidence as it becomes available. This approach is appropriate for this review, since it addresses an important clinical topic and there is currently significant uncertainty as to the most effective intervention. Therefore, it is important that consumers and healthcare providers have access to the most up-to-date evidence to make informed decisions. The review authors are aware of several relevant ongoing trials that will be important to incorporate in a timely manner.

OBJECTIVES

To assess the comparative efficacy and safety of interventions for slowing myopia progression in children using network meta-analysis. To generate a relative ranking of interventions according to their efficacy. To produce a brief economic commentary, summarising economic evaluations.

METHODS

We followed the Methodological Expectations of Cochrane Intervention Reviews (MECIR) when conducting the review, and PRISMA 2020 for the reporting [52].

Since we mainly reported on direct (pairwise) evidence, we used GRADE to assess our confidence in the estimates of effect rather than CINEMA, as planned.

We used the surface under the cumulative ranking (SUCRA) to generate a relative ranking of myopia control interventions, rather than mean rank values.

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) of optical, pharmacological, photobiomodulation (light) therapy, and behavioural modifications used alone or in combination, for slowing the progression of myopia in children.

Types of participants

We considered studies that included children, 18 years old and younger. We excluded studies in which the majority of participants were older than 18 years at the start of the study. We also excluded studies that included participants with spherical equivalent myopia less than −0.50 D at baseline. The spherical equivalent is calculated by the sum of the spherical power plus half the cylindrical power of the refractive error.

We included studies that compared interventions of interest and reported they had measured the relevant outcomes, regardless of whether data for the outcomes were available.

Types of interventions

We included studies that compared any of the interventions listed below with a control group, or with each other.

For this update, we added photobiomodulation as an intervention, since light-based therapy is an emerging intervention for myopia control, with current uncertainty regarding its efficacy and safety [41].

For the purposes of the analysis, we defined a control group as a placebo intervention, single vision spectacles, or contact lenses.

- Undercorrection of myopia with single vision spectacle lenses
- Multifocal (bifocal or progressive addition) spectacle lenses (MFSL), peripheral plus spectacle lenses (PPSL)
- Multifocal soft contact lenses (MFSCL; concentric ring or progressive designs), rigid gas-permeable contact lenses (RGP), or corneal reshaping contact lenses (orthokeratology (ortho-K))
- Atropine (stratified according to dosing regimen as high (≥ 0.5%), medium (0.1% to < 0.5%), and low (< 0.1%)
- Other pharmaceutical agents (e.g. pirenzepine, 7-methylxanthine)
- Photobiomodulation (e.g. repeated low intensity red light (RLRL) therapy
- Behavioural modification (e.g. time spent outdoors, modifications to the performance of near work)

Outcome measures

Critical outcomes

Progression of myopia

Progression of myopia was assessed by:

- mean change in refractive error (spherical equivalent in D) from baseline for each year of follow-up, and measured by any method (e.g. objective or subjective refraction); and
- mean change in axial length for each year of follow-up in millimetres (mm) from baseline for each year of follow-up, and measured by any method (e.g. ultrasound or optical biometry).

Change in refractive error and axial length following cessation of treatment (rebound)

Rebound was evaluated when children in the treatment group were switched to the control treatment and then followed for a minimum period of one year.

Important outcomes

Risk of adverse events

We described adverse events relating to the interventions as reported in the included studies, regardless of severity. These included, but were not limited to blurred vision, photophobia, hypersensitivity reactions, corneal infiltrative events, and infections. In studies that graded clinical signs, using standard anterior eye grading scales from normal to severe, we recorded the number of clinically significant signs (grade 3 or 4) that would usually require clinical action.

Where data were available, we documented withdrawals due to adverse events and the number of serious events.

Quality of life

We documented vision-related or health-related quality of life when reported, measured by any validated questionnaire (e.g. National Eye Institute Visual Function Questionnaire 25 (NEI VFQ-25), or EuroQol questionnaire (EQ-5D)).

Treatment adherence

Studies evaluated adherence to the prescribed treatment regimen using a variety of compliance measures, including daily wearing time with contact lenses and spectacle interventions as reported

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by parents or children, or both, or the proportion of participants in pharmacological studies following the required dosing regimen.

Follow-up

We reported outcomes at one year, two years, and as available for the duration of the study. We imposed no restrictions based on the length of follow-up.

Brief economic commentary

We present evidence regarding relevant economic evaluations, as a brief economic commentary.

Search methods for identification of studies

We did not perform the generic search described in the original review protocol for adverse events [53], instead, we added a filter to the search strategy to identify systematic reviews of adverse events associated with myopia control interventions (see Electronic searches). These are discussed in the Agreements and disagreements with other studies or reviews section of the discussion.

Electronic searches

The Cochrane Eyes and Vision Information Specialist searched the electronic databases below for RCTs and controlled clinical trials. This update includes results from searches conducted up to 19 February 2024.

In addition to these searches, we carried out a MEDLINE and Embase search using economic search filters to specifically identify economic studies, and a search strategy to identify systematic reviews of adverse events associated with myopia control interventions (Supplementary material 1). We compared the findings of the systematic reviews to the adverse events reported in the studies included in the current review.

We developed this review as a living systematic review, and initially ran the searches every six months. This has now been extended to annual searches. Prior to re-running the searches, we will assess the search strategy with an information specialist to incorporate new search terms, if appropriate.

- Cochrane Central Register of Controlled Trials (CENTRAL; which contains the Cochrane Eyes and Vision Trials Register; 2024, Issue 2) in the Cochrane Library (Supplementary material 1)
- MEDLINE Ovid (1946 to 19 February 2024; Supplementary material 1)
- MEDLINE Ovid − economic search (1946 to 19 February 2024; Supplementary material 1)
- MEDLINE Ovid − adverse events (1946 to 19 February 2024; Supplementary material 1)
- Embase Ovid (1980 to 19 February 2024; Supplementary material 1)
- Embase Ovid − economic search (1980 to 19 February 2024; Supplementary material 1)
- Embase Ovid − adverse events (1980 to 19 February 2024; Supplementary material 1)
- ISRCTN registry (www.isrctn.com/editAdvancedSearch; searched 19 February 2024; Supplementary material 1)
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched 19 February 2024; Supplementary material 1)
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp; searched 19 February 2024; Supplementary material 1)

Searching other resources

We searched the reference lists of identified study reports to identify additional studies. We also contacted the principal investigators of included studies for details of other potentially relevant studies not identified by the electronic searches, and of recently completed or ongoing studies. Our comprehensive searches included post-publication amendments. When amendments related to the included studies were identified, we planned to review the status (e.g. retracted) during the full-text screening stage and update relevant sections of the review. However, we did not identify such records in this update.

Data collection and analysis

Selection of studies

The Information Specialist at Cochrane Eyes and Vision downloaded all titles and abstracts retrieved from the electronic searches to EndNote [54], and removed duplicates before uploading to Covidence [55]. Two review authors (from JGL, BH, RD, PV, SN, LED, JW) independently reviewed the titles and abstracts of the search results based on the eligibility criteria stated above. We categorised abstracts for inclusion as yes, maybe, or no. We obtained the full text of articles for the studies categorised as maybe and yes, and reassessed them for final eligibility. After examining the full text, we labelled studies as include or exclude. Studies selected as exclude by both authors were excluded from the review. We documented the reasons for exclusion. We resolved any screening discrepancies through discussion, and if necessary, through consultation with a third review author. One review author (AK) screened the economic search results.

Living systematic review considerations

We plan to screen any new citations retrieved by the annual searches immediately.

Data extraction and management

For eligible studies, two review authors independently extracted the data. We contacted the authors of the original reports to obtain further details if the data reported were unclear or incomplete. We exported the collected data into Review Manager (RevMan [56]). We extracted the following study characteristics.

- Methods: study design, number and location of study centre(s), date of study and total duration
- Participants: inclusion and exclusion criteria, number randomised, number lost to follow-up or withdrawn, number analysed, mean age and standard deviation (SD), age range, gender
- Interventions: description of intervention and comparator
- Outcomes: primary and secondary outcomes specified and collected, and time points reported; unit of analysis
- Notes: funding for study and conflicts of interest of study authors

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Risk of bias assessment in included studies

Pairs of review authors independently assessed the risk of bias in the included studies for all outcomes using Cochrane RoB 2, 22 August 2019 version, described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* [57]. RoB 2 covers five domains of bias:

- bias arising from the randomisation process;
- bias due to deviations from intended interventions;
- bias due to missing outcome data;
- bias in measurement of the outcome; and
- bias in selection of the reported result.

These domain-level judgements provide the basis for an overall risk of bias judgement for the specific outcome being assessed. The response options for an overall risk of bias judgement in RoB 2 are the same as for individual domains (i.e. low risk of bias; some concerns; high risk of bias). The following criteria were adopted:

- Low risk of bias: low risk of bias for all domains;
- Some concerns: some concerns in at least one domain, but not at high risk of bias for any domain;
- High risk of bias: high risk of bias in at least one domain, or the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.

To implement RoB 2 assessments, we used the Excel tool available at https://www.riskofbias.info/welcome/rob-2-0-tool/current-version-of-rob-2.

We included one cluster-randomised trial (Wu 2018 [58]), and used the RoB 2 tool for cluster trials for this study. For cross-over trials, we only used data from the first phase, prior to the cross over, and therefore, used the version of the tool for parallel trials.

For all outcomes, we assessed the effect of assignment to intervention (the intention-to-treat effect).

Assessment of bias in conducting the systematic review

We conducted the review according to the published protocol, and reported any deviations from it in the Methods section of the review.

Measures of treatment effect

We used mean differences (MDs) as the measure of treatment effect for the critical outcome, progression of myopia, that is, difference in mean change in refractive error (SER) and axial length (AL) from baseline, at each year of follow-up.

Unit of analysis issues

When studies randomised only one eye per participant, the unit of analysis was the individual eye (participant). When studies randomised both eyes from the same participant (either to the same or different interventions), we analysed data adjusted for clustering or paired-eye design. In the network meta-analysis (NMA), we accounted for the correlation between the effect sizes derived from the same study.

In multi-arm trials, to overcome a unit-of-analysis error for a study that could contribute multiple, correlated data, we combined groups to create a single pairwise comparison.

In future updates, if we identify cluster-RCTs that are eligible to include in the quantitative synthesis, we will include them in meta-analyses directly when the sample size has been adjusted for clustering. We will combine them with the results from individual studies if there is little heterogeneity between the study designs, and the interaction between the effect of the intervention and the unit of randomisation is considered to be unlikely. If studies present outcomes at an individual level (i.e. a unit of analysis error), we will use established methods to adjust for clustering by calculating an effective sample size by dividing the original sample size by the design effect. This can be calculated from the average cluster size and the intra-class correlation coefficient (ICC). When the ICC is unknown, we will use an estimation from similar trials [59].

Dealing with missing data

We contacted study authors to verify key study characteristics and to obtain missing outcome data. If we did not receive a response within eight weeks, we analysed the studies based on available data. We used the RevMan calculator to calculate missing standard deviations using other data from the study (e.g. confidence intervals), based on methods outlined in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* [60].

Reporting bias assessment

If there are sufficient studies in future updates, e.g. at least 10 studies, we plan to run network meta-regression models to detect associations between study size and effect size.

Synthesis methods

We initially carried out standard pairwise meta-analyses to combine outcome data using random-effects models in RevMan. For comparisons with three or fewer trials, we used a fixed-effect model. We combined change from baseline data in meta-analyses with mean outcome data using the generic-inverse variance (unstandardised) MD method, as outlined in Chapter 10 of the *Cochrane Handbook for Systematic Interventions* [60]. In the case of substantial clinical, methodological, or statistical heterogeneity, we generally did not attempt to combine data from individual trials, but reported study results separately. However, subtotals were included in some analyses when presenting subgroups with varying degrees of heterogeneity.

For cross-over trials, we only extracted data from the first phase prior to cross over.

We conducted an NMA, using the network suite of programs available in STATA, for myopia progression (http://www.stata.com), as defined by the difference in change in SER and AL at 12 and 24 months, using random-effects multivariate models [61, 62, 63]. The STATA code is available at OSF | Cochrane Myopia NMA.

An important concept in NMA is 'transitivity', which implies that the distribution of effect modifiers is similar across all sources of direct evidence. The statistical manifestation of transitivity is consistency, which refers to the statistical agreement between the direct and indirect sources of evidence. We checked for consistency in the network both locally (node-splitting approach) and globally (design by treatment model).

We assumed a common heterogeneity across all comparisons in the network. We used the surface under the cumulative ranking curve (SUCRA) to rank the interventions for all available outcomes. SUCRA

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values range from 0% to 100%. The higher the SUCRA value (i.e. the closer to 100%), the greater the probability of an intervention ranking best [62, 64].

In the primary NMA, we considered MFSCL, ortho-K, and combined ortho-K and atropine as separate nodes. For spectacle lens interventions, there were separate nodes for undercorrected single vision spectacle lenses, MFSL, and PPSL. We considered each pharmacological intervention as a separate node, regardless of the dose. We did not anticipate a strong dose-response effect except for atropine. We grouped atropine according to a dosing regimen, as high-dose (HDA; ≥ 0.5%), medium-dose (MDA; 0.1 % to < 0.5%), and low-dose (LDA; < 0.1%). We grouped all control arms (single vision spectacle lenses (SVL), single vision soft contact lenses (SVSCL), placebo eyedrops, or no treatment) into a single node.

When we were unable to perform a meta-analysis, we undertook a narrative synthesis, following guidance in Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* [65]. Specifically, we presented the effect estimates in structured tables, and provided a descriptive summary of the range and distribution of the observed effects. In particular, we noted the direction of effects and whether these were consistent in the individual studies.

Brief economic commentary

Following the search outlined in the Search methods for identification of studies, we developed a brief economic commentary to summarise the availability and principal findings of the full economic evaluations, assessing interventions for myopia control in children, as outlined in Chapter 20 of the *Cochrane Handbook for Systematic Reviews of Interventions* [66]. This brief economic commentary encompasses full economic evaluations (i.e. cost-effectiveness analyses, cost-utility analyses, and cost-benefit analyses), conducted as part of a single empirical study, such as an RCT, a model based on a single such study or a model based on several such studies.

Living systematic review considerations

Whenever we identify new evidence in future updates (i.e. new studies, data, or other information) that is relevant to the review, we will extract the data and assess the risk of bias, as appropriate. We will wait until the accumulating evidence changes one or more of the following components of the review before incorporating it and re-publishing the review.

- The findings of one or more outcomes (e.g. clinically important change in size or direction of effect)
- Credibility (e.g. change in the overall confidence in the effect estimates for critical outcomes)

We will not use formal sequential meta-analysis approaches for updated meta-analyses.

Methods for future updates

We will review the scope and methods of this review annually, in light of potential changes in the topic area, or in evidence available for inclusion in the review. Each year, we will consider the necessity for the review to be a living systematic review, by assessing the ongoing relevance of the question to decision-makers, and by determining whether uncertainty in the evidence continues, and whether further relevant research is likely.

Assessment of heterogeneity

We assessed clinical and methodological heterogeneity for each pairwise meta-analysis by comparing the characteristics of the included studies and by visual inspection of forest plots. We assessed statistical heterogeneity quantitatively for pairwise comparisons, using the values of the Chi^2 test and the I^2 statistic [67]. We interpreted I^2 statistic values according to Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* [60], as follows:

- 0% to 40% may not be important;
- 30% to 60% may represent moderate heterogeneity;
- 50% to 90% may represent substantial heterogeneity;
- 75% to 100% represents considerable heterogeneity.

For the NMA, we assumed a common estimate for the heterogeneity variance across the different comparisons. The assessment of statistical heterogeneity was based on the magnitude of the heterogeneity variance parameter (Tau^2) estimated from the NMA models.

Assessment of statistical inconsistency

Local approaches for evaluating inconsistency

To evaluate the presence of inconsistency locally, we used the node-splitting approach, which assesses the agreement between direct and indirect evidence for each treatment comparison [68].

Global approaches for evaluating inconsistency

To check the assumption of consistency across the entire network, we used the design by treatment interaction model [63]. This method accounts for different sources of inconsistency that can occur when studies with different designs are incorporated into the network (e.g. two-arm trials versus multi-arm trials), as well as any inconsistency between direct and indirect evidence.

Investigation of heterogeneity and subgroup analysis

We performed predefined subgroup analyses for types of intervention modalities (i.e. spectacle and contact lens designs, and dose of particular pharmaceutical interventions (e.g. low-, medium-, and high-dose atropine)). There were also sufficient data to carry out a predefined subgroup analysis of the effect of ethnicity (comparison of Asian versus non-Asian studies) on the efficacy of low-dose atropine.

Equity-related assessment

We did not consider equity in this review.

Sensitivity analysis

We planned a sensitivity analysis on the exclusion of studies that we judged to be at high risk of bias or that raised some concerns in at least one domain of RoB 2. However, since we judged almost all the included studies at high risk of bias or with some concerns, we did not conduct a sensitivity analysis.

Certainty of the evidence assessment

We planned to follow methods presented in Yepes-Nuñez 2019 to prepare summary of findings tables for the NMA [69]. However, because the network was not well-connected, we primarily based our comparisons on direct evidence from classical pairwise

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meta-analyses, except for moderate-dose atropine. We prepared summary of findings tables for the progression of myopia at one and two years, with separate tables for change in spherical equivalent and change in axial length.

Evaluating confidence in the evidence

Instead of the planned CINeMA framework for evaluating confidence in the domains [70, 71], we summarised four levels of confidence for each relative treatment effect, corresponding to the usual GRADE approach: very low, low, moderate, or high [72]. In fact, because most evidence was direct versus control in the NMAs, we used NMA estimates only when direct evidence was not available.

Consumer involvement

Consumers were not involved in this review.

RESULTS

Description of studies

Results of the search

For this update, our bibliographic database searches identified 1062 non-duplicate records (see Figure 1 for PRISMA flow diagram [73]). We independently screened all records and examined the full text of 162 potentially eligible articles. Thirty-eight new studies were identified for this update (Agarwal 2023 [74]; Chan 2022 [75]; Chen 2022 [76]; Chen 2023 [77]; Chia 2023 [78]; Choi 2023 [79]; Fang 2022 [80]; Hansen 2023 [81]; Hu 2023 [82]; Jiang 2022 [83, 84, 85, 86, 87]; Lau 2023 [88]; Lee 2022 [89, 90]; Lin 2024 [91]; Liu 2023a [92]; Liu 2023b [93]; Liu 2023c [94]; Liu 2024 [95]; MOSAIC Study 2024 [96]; Peng 2023 [97]; Raffa 2022 [98]; CYPRESS Study 2023 [99, 100, 101]; Repka 2023 [102]; Sen 2022 [103]; Sharma 2022 [104]; Shen 2022 [21]; Tang 2022 [105]; Tang 2023 [106]; Xia 2023 [107]; Xu 2023 [108, 109]; Ye 2022 [110]; Yu 2022 [111]; Yuval 2024 [112]; CHAMP 2023 [113]; Zhang 2024 [114]; Zhou 2023 [115]; Zhu 2022 [116]; Zhu 2023a [117]; Zhu 2023b [118]). Following a change in the inclusion criteria to include photobiomodulation as an intervention, two studies that were previously excluded were added (Mori 2021 [119]; Wu 2018). In total, we included 104 studies (40 additional studies from this update and 64 studies from the previous version of the review [120]). Fifty-one new reports linked to studies already in the review were added, together with 38 new references to ongoing studies, and one conference abstract awaiting classification (key features of the included studies are summarised below; see Table 1 and Supplementary material 2 for a full description). We excluded 34 studies in this update and documented the reasons in Supplementary material 3.

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Figure 1. Study flow diagram

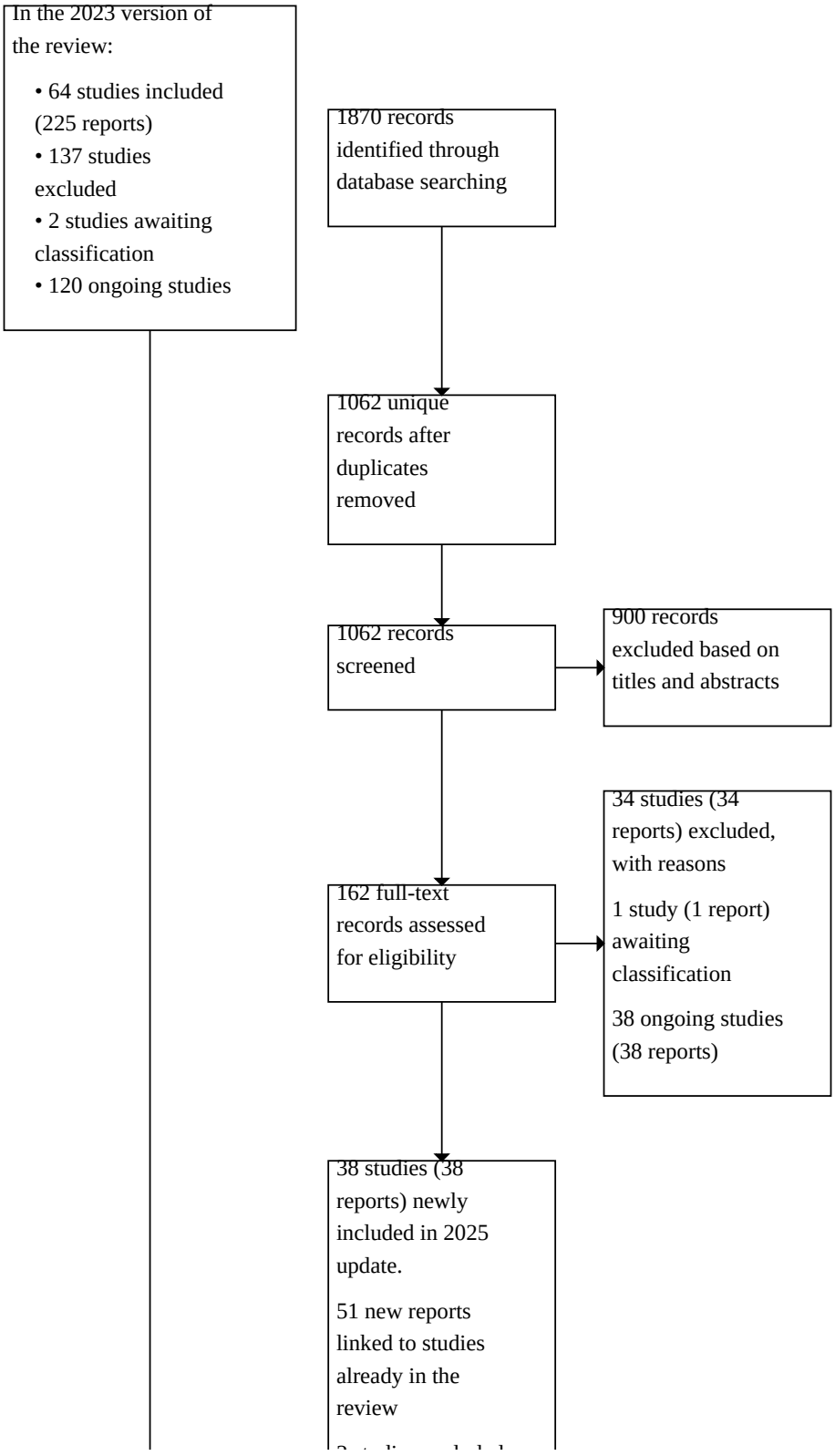

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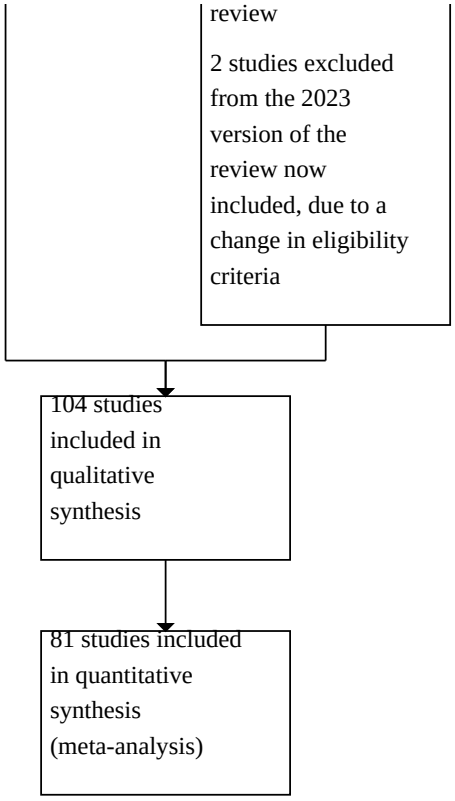
Figure 1. (Continued)



An updated economic search, carried out for this update, identified 36 records. Three of these studies met the inclusion criteria and were included in the brief economic commentary (121, 122, 123; see Supplementary material 9).

An updated search for systematic reviews of adverse events yielded 51 records. Three of these were included in the Agreements and disagreements with other studies or reviews section.

Included studies

Study design

Ninety-six studies used a parallel-group design, five studies used a cross-over design (Anstice 2011 [124]; Fujikado 2014 [125]; Hasebe 2008 [126, 127, 128, 129, 130, 131, 132], Swarbrick 2015 [133, 134]; Wei 2020 [135, 136, 137]), two studies used a paired-eye design (Liu 2023c; Shen 2022), and one study was a cluster-randomised trial (Wu 2018). The median sample size was 127 (range 24 to 660). Most participants were recruited from academic clinic settings, hospitals, and in a few cases, from private optometry or ophthalmology practices. The studies took place in China or other Asian countries (69 studies, 66.3%), North America (15 studies, 14.4%), Europe (nine studies, 8.7%), Australasia (three studies, 2.9%), India (three studies, 2.9%), Israel (two studies, 1.9%), and Ghana (one study, 1.0%); two multicentre studies recruited participants in both Europe and Asia, and Europe and USA (1.9%).

Eighty-four studies (80.8%) compared one or more myopia control interventions against a placebo or other control intervention (generally, single vision spectacles or contact lenses for optical interventions, and placebo or no treatment for pharmacological interventions). Five studies included a combined intervention group compared with control (Han 2019 [138]; MIT Study 2001 [139, 140, 141]; Schwartz 1981 [142, 143, 144, 145]; Xu 2023; Yu 2022), and 15 studies (14.4%) compared single or combined interventions with each other (ATOM 2 Study 2012 [146, 147, 148, 149, 150, 151, 152]; Chen 2022; Cui 2021 [153, 154, 155, 156, 157, 158]; Guo 2021 [159, 160, 161]; Kinoshita 2020 [25, 162]; Lau 2023; Liu 2023b; Liu 2023c; Shih 1999 [163, 164]; Swarbrick 2015; Tan 2023 [165, 166]; Tang 2022; Tang 2023; Ye 2022; Zhao 2021 [167]).

Forty-three (41.3%) studies were of one-year duration, seven studies (6.7%) had a duration of 18 to 20 months, 38 (36.5%) studies were two years long, 15 (14.4%) studies were up to three years long, and only one reported data over three years (Moriche-Carretero 2021 [168, 169]).

Seven studies were conducted before the year 2000 (Fulk 1996 [170]; Houston Study 1987 [171, 172, 173]; Jensen 1991 [174, 175]; Pärssinen 1989 [176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186]; Schwartz 1981; Shih 1999; Yen 1989 [187]). Eighty-four studies declared a source of funding or stated that they were unfunded. Twenty-eight of these studies (33.3%) were funded by the optical or pharmaceutical industry.

Characteristics of the participants

The review included 104 studies that randomised a total of 17,508 children, aged between 4 years and 18 years, with a median age

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of 10.0 years (range 7.3 to 14.2 years); 47.3% of participants were male. In the 65 studies that documented the range of participant myopic refractive error for inclusion, all but 11 studies recruited low to moderate myopes of −6.00 D or less. The remaining studies included participants with higher levels of myopia, up to −10.00 D. Most studies adopted an upper astigmatism limit of 1.00 D or 1.50 D. Four studies specifically recruited myopes with both myopia and near esophoria (Fulk 1996; Fulk 2002 [188, 189, 190, 191, 192, 193, 194, 195, 196]; STAMP Study 2012 [197, 198, 199, 200, 201, 202]; Zhu 2022). One study selectively recruited participants with anisomyopia, with an interocular difference of 1.00 D or greater (Zhang 2023 [203]). Twelve studies restricted recruitment to those demonstrating a minimum myopic progression rate of at least −0.50 D or −0.75 D in the year prior to enrolment (Agarwal 2023; ATOM 2 Study 2012; Anstice 2011; Cheng 2010 [204, 205]; Chia 2023; CONTROL Study 2016 [206, 207, 208]; LAMP Study 2019 [209, 210, 211, 212, 213, 214, 215, 216, 217]; Lu 2015 [218]; Lee 2022; Swarbrick 2015; Zhu 2021 [219]; Zhu 2023a). Participants were sufficiently similar to satisfy the transitivity assumption for the NMA. That is, there were no systematic differences between the available comparisons other than the treatments being compared.

Characteristics of the comparisons

Myopia control intervention versus control or placebo

Optical interventions

Spectacles

- **Undercorrection versus fully corrected single vision spectacle lenses (SVLs):** (3 studies: Adler 2006 [220]; Chung 2002 [221]; Koomson 2016 [222]). These studies, conducted in Israel, China, and Ghana, compared the effect of under correcting myopia by either 0.50 D or 0.75 D versus fully corrected SVL. The follow-up periods were 18 months for Adler 2006, and 24 months for Chung 2002 and Koomson 2016.
- **Multifocal spectacle lenses (MFSLs) versus single vision spectacle lenses (SVLs):** (14 studies: Cheng 2010; COMET Study 2003 [223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269]: COMET 2 Study 2011 [270]; Edwards 2002 [271]; Fulk 1996; Fulk 2002; Hasebe 2008; Houston Study 1987; Jensen 1991; MIT Study 2001; Pärssinen 1989; STAMP Study 2012; Yang 2009 [272, 273]; Zhu 2022). These studies were conducted in North America (seven studies), Asia (five studies), and Europe (two studies). All studies enroled children aged 8 years to 15 years. MFSLs were either bifocal (six studies) or progressive addition lenses (eight studies) with near additions between +1.00 D and +2.50 D. Zhu 2022 used a customised progressive design, and the power of the near addition was calculated individually, based on the near phoria. The study durations were between 18 and 36 months. Nine studies had two arms, and five studies had three arms. Hasebe 2008 compared bifocals with two different near add powers (+1.00 D and +2.00 D) to SVLs. Jensen 1991 randomised children to one of three groups, bifocals, SVLs, or timolol maleate eye drops, and Pärssinen 1989 compared a group wearing bifocals (+1.75 D near add) to a group wearing SVLs for distance vision only, and a reference group wearing SVLs continuously.
- **Peripheral plus spectacle lenses (PPSL) versus single vision spectacle lenses (SVLs):** (7 studies: Bao 2022 [274, 275, 276, 277, 278, 279, 280, 281, 282]; Hasebe 2014 [283]; Han 2018 [284]; Lam 2020 [285, 286, 287, 288, 289, 290, 291, 292, 293]: Lu 2015; Sankaridurg 2010 [294, 295, 296, 297]; Yuval 2024). Novel spectacle lens designs have been developed that aim to reduce peripheral hyperopic defocus. These lenses, designated PPSLs, were compared to SVLs in Chinese, Japanese, and Israeli myopic children aged 6 years to 16 years. Study durations were one to two years. Sankaridurg 2010 tested three lens designs (designated types I, II, and III) that provided different relative peripheral power against SVLs in children aged 6 years to 16 years. Hasebe 2014 compared two positively aspherised progressive addition lens designs, with +1.00 D or +2.00 D near add powers and a relative plus power in the upper portion of the lens, to SVLs. Lu 2015 randomised children to receive either PPSLs with up to a +2.50 D near addition or SVLs. Han 2018 conducted a three-arm study in which children were randomised to PPSLs, SVLs, or ortho-K. Lam 2020 adapted a design that had previously been used in contact lenses (DISC Study 2011 [298, 299]), to develop a spectacle lens with a clear central zone for distance correction, and an annular peripheral zone consisting of a multiple array of segments approximately 1 mm in diameter, providing +3.50 D of myopic defocus. The lens, called the defocus incorporated multiple segments (DIMS) lens, was tested in a two-year study involving Chinese children aged 8 years to 13 years, who were randomised to wear either DIMS lenses or SVLs. Bao 2022 tested a lens design based on the same principle that consisted of concentric rings of aspheric lenslets to provide myopic defocus. Children aged 8 years to 13 years were randomised into a three-arm study to receive either a lens with highly aspherical lenslets, a lens with slightly aspherical lenslets, or SVLs. In Yuval 2024, rather than using a concentric design, the defocus zone was arranged in a U-shape, which created a clear vertical canal correcting distance vision, with progressive defocus towards the periphery. Israeli children, aged 6 years to 12 years, were randomised to wear either the novel myopia control lens design or SVLs.
- **Diffusion optics technology (DOT) spectacle lenses versus single vision spectacle lenses (SVLs):** (1 study: CYPRESS Study 2023). Diffusion optics technology (DOT) lenses are novel spectacle lenses that are proposed to modulate retinal contrast. The biological rationale is that high retinal contrast stimulates axial elongation, and by reducing contrast, axial elongation can be slowed. The Control of Myopia Using Peripheral Diffusion Lenses Efficacy and Safety Study (CYPRESS) is a three-year trial of DOT lenses versus SVLs in myopic children aged 6 years to 10 years. The CYPRESS Study 2023 reported a planned interim analysis at one year.
- **Cylindrical annular refractive element (CARE) spectacle lenses:** (1 study: Liu 2023a). CARE lenses are suggested to generate blur signals on the retina by inducing high-order aberrations. CARE lenses consist of a central clear area with the full correction, and a peripheral area consisting of a microcylinder array arranged in concentric circles. Liu 2023a reported the planned one-year interim results of a two-year RCT in Chinese children aged 8 years to 12 years with myopia, who were randomised to receive CARE lenses or SVLs.
- **Violet light transmitting spectacle lenses versus single vision spectacle lenses (SVLs):** (1 study: Mori 2021). Violet light (360 nm to 400 nm) has been shown to suppress axial elongation in animal models of myopia. Conventional spectacle lenses block violet light, along with short wavelength ultraviolet light.

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Spectacle lenses that selectively transmit violet light have been developed. Mori 2021 conducted an RCT of these lenses versus conventional SVLs in Japanese children, aged 6 years to 12 years, who wore the lenses for two years.

Contact lenses

- **Multifocal soft contact lenses (MFSCL) versus single vision soft contact lenses (SVSCLs) or single vision spectacle lenses (SVLs):** (13 studies: Anstice 2011; BLINK Study 2020 [300, 301, 302, 303, 304, 305, 306, 307, 308, 309]; Chamberlain 2019 [310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320]; CONTROL Study 2016; DISC Study 2011; Fang 2022; Fujikado 2014; Garcia-del Valle 2021 [321]; Liu 2024; Peng 2023; Raffa 2022; MASS Study 2018 [322, 323, 324, 325, 326, 327]; Sankaridurg 2019 [328]). Thirteen studies investigated the efficacy of a variety of MFSCL designs compared to SVSCLs (12 studies) or SVLs (1 study). MFSCLs typically incorporate a central zone to provide clear distance vision with relatively more positive peripheral lens power, which either increases gradually towards the periphery (progressive design) or is presented as discrete peripheral annular zones (concentric ring design). Seven studies followed participants for 12 months, four provided data for 20 months to 24 months, and two had a duration of 36 months (BLINK Study 2020; Chamberlain 2019). Ten studies used a parallel-group design, comparing MFSCLs with SVSCLs, two studies used a cross-over design (Anstice 2011; Fujikado 2014), and one study used a paired-eye RCT design (Liu 2024). Eight studies adopted similar eligibility criteria and randomised children, aged 6 years to 18 years, with low to moderate myopia, up to −6.00 D; Fang 2022 included myopes up to −8.00 D, Garcia-del Valle 2021 up to −8.75 D, and Liu 2024 to −10.00 D. Anstice 2011 and CONTROL Study 2016 only included children with documented myopia progression of −0.50 D or greater in the previous year, and the CONTROL Study 2016 also restricted inclusion to myopic children with near esophoria. Three studies used a similar centre distance dual focus concentric ring design with alternating distance correction zones, and peripheral zones providing +2.00 D of defocus (Anstice 2011; Chamberlain 2019; MASS Study 2018). These studies were conducted in New Zealand (Anstice 2011), Spain (MASS Study 2018), and at sites in Europe, Asia, and Canada (Chamberlain 2019). Garcia-del Valle 2021 tested MFSCL with a progressive design (+2.00 D addition) compared to SVSCL in Spanish schoolchildren, aged 7 years to 15 years. Four studies, conducted in the USA (BLINK Study 2020; CONTROL Study 2016), Malaysia (Raffa 2022), and Taiwan (Liu 2024), used commercially available MFSCLs. The CONTROL Study 2016 evaluated children, aged 8 years to 18 years, with progressive myopia, randomised to wear either a concentric bifocal soft contact lens or SVSCLs. The near add was selected based on the add power to neutralise the associated esophoria. The Bifocal Lenses in Near-sighted Kids (BLINK) study tested the efficacy of bifocal soft contact lenses with a central correcting zone for myopia, and either a medium near add (+1.50 D), or high add (+2.50 D) compared to SVSCLs (BLINK Study 2020). Raffa 2022 randomised children, aged 13 years to 15 years, to wear MFSCLs (+1.50 D or +3.00 D add) or SVSCLs. Five studies, conducted in China and Japan, used novel MFSCL designs (DISC Study 2011; Fang 2022; Fujikado 2014; Peng 2023; Sankaridurg 2019). The DISC Study 2011 tested the defocus incorporated soft contact (DISC) lens, a custom-made bifocal soft contact lens of concentric ring design with a +2.50 D addition alternating with the normal distance correction. The DISC lens was compared to an SVSCL in Chinese school children, aged 8 years to 13 years, who were followed for two years. Peng 2023 also used the DISC lens design in Chinese children, aged 7 years to 12 years, who were followed for one year. Fang 2022 randomised Chinese children, aged 7 years to 15 years, with up to –8.00 D myopia, to wear either a novel aspheric MFSCL design, ortho-K, or a control group wearing SVLs. Fujikado 2014 used a cross-over study design, in which Japanese children, aged 6 years to 16 years, were randomised to wear a progressive MFSCL with a peripheral power of +0.50 D, or SVSCLs in both eyes for one year, and then were switched to the other type of lens for the second year. Sankaridurg 2019 randomised Chinese children, aged 8 years to 13 years, to one of five groups: two groups wore MFSCLs that imposed peripheral myopic defocus of +1.50 D or +2.50 D with a stepped, relative, positive power centrally of up to +1.00 D (test lenses I and II); and two groups wore different extended depth of focus (EDOF) soft lens designs (test lenses III and IV). The control lens was an SVSCL.
- **Spherical aberration soft contact lenses versus single vision soft contact lenses (SVSCLs):** (1 study: Cheng 2016 [329]). This study randomised children, aged 8 years to 11 years, to receive soft contact lenses with or without positive spherical aberration. Although the study was conducted in the USA, it enroled mostly Asian children (91%). The study was planned for two years, but was stopped early, and reported only one-year data.
- **Extended depth of focus (EDOF) soft contact lenses versus single vision soft contact lenses (SVSCLs):** (2 studies: Sankaridurg 2019; Shen 2022). Sankaridurg 2019 tested two EDOF lens designs (test lenses III and IV), designed to optimise focus in front of, and on the retina, and degrade focus behind the retina, in a two-year RCT. The EDOF lenses were compared to SVSCLs. Shen 2022 used a paired-eye RCT design with Taiwanese children, aged 9 years to 14 years. One eye was randomised to receive an EDOF lens and the other an SVSCL. Myopia progression was monitored over one year.
- **Rigid gas-permeable (RGP) contact lenses versus single vision soft contact lenses (SVSCLs) or single vision spectacle lenses (SVLs):** (2 studies: CLAMP Study 2004 [330, 331, 332, 333, 334, 335, 336, 337]; Katz 2003 [338, 339]). Two studies investigated the impact of RGP lenses on myopia progression compared to SVLs. Katz 2003 randomised Singaporean children, aged 6 years to 12 years, to SVLs or RGP lenses. Myopia progression was evaluated at one and two years. The Contact Lens and Myopia Progression (CLAMP) study was conducted in the USA, and randomised children to RGP or soft single vision contact lenses (CLAMP Study 2004). Annual myopia progression was reported based on changes in SER and axial length, for the three-year duration of the study.
- **Orthokeratology (ortho-K) lenses versus single vision spectacle lenses (SVLs) or single vision contact lenses:** (14 studies: Bian 2020 [340]; Charm 2013 [341, 342, 343]; Choi 2023; Fang 2022; Han 2018; Jakobsen 2022 [344, 345]; Lin 2024; Lyu 2020 [346]; Ren 2017 [347]; ROMIO Study 2012 [348, 349, 350, 351, 352, 353]; Tang 2021 [354]; Xu 2023; Zhang 2023; Zhu 2023a). Thirteen parallel-group studies compared overnight ortho-K contact lenses to SVLs, and one study compared them to SVSCLs (Tang 2021). Participants were followed for one to two years. Ten studies enroled children with low to moderate degrees of myopia (up to −6.00 D), and three studies selectively recruited children with higher degrees of myopia (Charm 2013;

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Fang 2022; Lyu 2020). Zhang 2023 included participants with anisomyopia with a difference in myopia between eyes of 1.00 D or greater. Thirteen of the 14 studies were conducted in China, and one in Denmark (Jakobsen 2022). Axial length was the primary outcome in all studies. The Retardation of Myopia in Orthokeratology (ROMIO) study randomised 102 Chinese children, aged 6 years to 12 years, to overnight ortho-K lenses or SVLs. They were followed for two years (ROMIO Study 2012). Charm 2013 randomised 52 highly myopic children, aged 8 years to 11 years, with an SER of at least −5.75 D, to partial reduction ortho-K lenses and daily SVLs for residual myopia, or a control group who were fully corrected with SVLs. Axial length was measured at six-monthly intervals for two years. Lyu 2020 similarly investigated partial reduction ortho-K lenses in participants with myopia up to −8.75 D. They randomised 102 children, aged 8 years to12 years, into three groups: (1) ortho-K lenses with a target myopia reduction of 6.00 D; (2) ortho-K lenses with a 4.00 D target myopia reduction; or (3) SVLs. Axial length was measured at baseline and at 12 months. Jakobsen 2022 randomised 60 Danish children, aged 6 years to 12 years, to ortho-K lenses or SVLs, and followed them for 18 months. Xu 2023 included 164 Chinese children, who were randomly assigned to a control group (placebo eye drops plus SVLs), ortho-K lenses plus placebo eye drops (ortho-k group), 0.01% atropine plus SVLs, or combined treatment with ortho-k and atropine. Seven studies compared ortho-K lenses to SVLs in Chinese children, aged 8 years to 15 years, with low to moderate myopia (Bian 2020; Choi 2023; Han 2018; Lin 2024; Ren 2017; Tang 2021; Zhu 2023a). Ren 2017 also included a group that was treated with 0.01% atropine; Fang 2022 included a group that wore MFSCLs; and Han 2018 included a group that wore PPSLs.

Pharmacological

Anti-muscarinic agents

- **Atropine eye drops versus placebo or untreated control:** (26 studies; Agarwal 2023; ATOM Study 2006 [355, 356, 357, 358, 359, 360, 361, 362, 363, 364]; Chan 2022; Chia 2023; Han 2019; Hansen 2023; Hieda 2021 [365, 366]; Hu 2023; LAMP Study 2019; Lee 2022; Moriche-Carretero 2021; MOSAIC Study 2024; Ren 2017; Repka 2023; Sen 2022; Sharma 2022; Wang 2017 [367]; Wei 2020; Xia 2023; Xu 2023, CHAMP 2023; Yen 1989; Yi 2015 [368]; Zhang 2024; Zhu 2021; Zhu 2023b). These parallel-group studies compared atropine to either placebo or an untreated control, and enroled children with low to high myopia (up to –10.00 D), aged from 4 years to 16 years. Eligibility criteria in Agarwal 2023; Chia 2023; Lee 2022; LAMP Study 2019; Zhu 2021 and Zhu 2023b also included a documented level of myopic progression in the previous year. All studies were conducted in Asia, except for Lee 2022, which was conducted in Australia, Moriche-Carretero 2021 in Spain, Hansen 2023 in Denmark, MOSAIC Study 2024 in Ireland, Repka 2023 in the USA, and CHAMP 2023, which was conducted at multiple sites in the USA and Europe. Participants were followed for periods ranging from one to four years.
  - **High-dose atropine (≥ 0.5%):** six studies compared 1% atropine to placebo or untreated control. The Atropine in the Treatment of Myopia (ATOM) study was conducted in Singapore and involved 400 children, aged 6 years to 12 years, who were randomised to receive either 1% atropine or placebo in one eye, and were followed for two years (ATOM Study 2006). Yi 2015 randomised 140 Chinese children, aged 7 years to 12 years, with low myopia (−0.50 D to −2.00 D) to 1% atropine or placebo eyedrops nightly for 12 months. Zhu 2021 compared 1% atropine to placebo, using a novel dosing regimen, in 660 Chinese children. The study was divided into three phases. In Phase 1, the treatment group received 1% atropine once a month for two years. This was reduced to once every two months for one year in Phase 2, followed by no drops for one year in Phase 3. The placebo group received the same dosing regimen. Wang 2017 compared daily 0.5% atropine with placebo in 126 Chinese children with low myopia, who were followed for one year. Two three-arm studies included a 1% atropine arm. Han 2019 randomised 150 Chinese children, aged 6 years to 12 years, in a 1:2:2 ratio to either an untreated control group, 1% atropine, or a combination of 1% atropine with 0.5% raceanisodamine (a non-selective muscarinic antagonist used as an ingredient of traditional Chinese medicines). Yen 1989 included groups receiving either 1% atropine or 1% cyclopentolate.
  - **Low-dose atropine (< 0.1%):** 20 studies tested lower doses of atropine, ranging from 0.0025% to 0.05%. The Low-concentration Atropine for Myopia Progression (LAMP) study randomised 438 Chinese children, aged 4 years to 12 years, with myopia of at least −1.00 D to four groups (in a 1:1:1:1 ratio): low-concentration atropine eye drops at 0.05%, 0.025%, or 0.01% concentration, or placebo. Participants were followed for one year (LAMP Study 2019). Chia 2023 tested various low atropine doses (0.0025%, 0.005%, and 0.01%) versus placebo in 100 Chinese children, aged 6 years to 11 years. CHAMP 2023 randomised children with low to moderate myopia (N = 576) to placebo, 0.01%, or 0.02% atropine in a 2:2:3 ratio, and followed them for three years. Hansen 2023 conducted a three-arm trial with 97 Danish children, aged 6 years to 12 years, who were randomised into three groups: 0.01% atropine, a group who received a 0.1% atropine loading dose for six months followed by 0.01% for six months, or placebo. Twelve studies used a two-arm design to test the efficacy of 0.01% atropine versus placebo or an untreated control, in participants aged between 5 years and 16 years, with myopia up to –10.00 D (Agarwal 2023; Chan 2022; Hieda 2021; Hu 2023; Lee 2022; MOSAIC Study 2024; Moriche-Carretero 2021; Repka 2023; Sen 2022; Sharma 2022; Wei 2020; Xia 2023). The study duration was up to three years. Agarwal 2023 randomised 70 Indian children, aged 6 years to 16 years; Chan 2022 randomised 71 Chinese children, aged 7 years to 10 years, Hieda 2021 randomised 171 Japanese children, aged 6 years to 12 years; Hu 2023 randomised 295 Chinese children, aged 6 years to 13 years; Lee 2022 randomised 153 Australian children (49% European), aged 6 years to 16 years; MOSAIC Study 2024 randomised 250 Irish children, aged 6 years to 12 years; Moriche-Carretero 2021 randomised 339 Spanish children, aged 5 years to 11 years; Repka 2023 randomised 187 children in the USA (46% Asian), aged 5 years to 12 years; Sen 2022 randomised 150 Indian children, aged 5 years to 15 years; Sharma 2022 randomised 112 Indian children, aged 5 years to 15 years; Xia 2023 randomised 164 Chinese children, aged 6 years to 16 years, and Wei 2020 randomised 220 Chinese children, aged 6 years to 12 years. Two studies tested 0.05% atropine versus placebo in Chinese children, aged 6 years to 12 years, using a parallel group design (Zhang 2024; Zhu 2023b). Two multi-arm trials included additional myopia control interventions. Ren 2017 randomised 150 Chinese children (1:1:1 ratio) to 0.01% atropine, ortho-K, or single vision spectacle lenses. Xu

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2023 conducted a four-arm trial with Chinese children (N = 164), aged 8 years to 12 years. Participants were randomised into groups receiving 0.01% atropine, ortho-K, ortho-K plus 0.01% atropine, or a placebo, and followed for two years.

- **Pirenzepine eye drops versus placebo:** (2 studies: PIR-205 Study 2004 [369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380]; Tan 2005 [381, 382, 383]). These two studies compared 2% pirenzepine gel, a selective M1 muscarinic receptor antagonist, to placebo. The PIR-205 Study 2004 was a two-year, multicentre study conducted in the USA, which randomised 174 myopic children, aged 8 years to 12 years, in a 2:1 ratio, to twice-daily pirenzepine gel or placebo. Tan 2005 was conducted in centres in Singapore, Thailand, and China, and randomised 353 children, aged 6 years to 13 years, to one of three arms: 2% pirenzepine gel twice daily; placebo once daily plus 2% pirenzepine gel once daily; or placebo twice daily.

Anti-muscarinic agent with co-intervention

- **Tropicamide and multifocal spectacles (MFSLs) versus SVLs:** (1 study: Schwartz 1981). This study was conducted in the USA, and randomised 26 monozygous twin pairs, aged 7 years to 14 years, to either MFSLs plus 1% tropicamide, or MFSLs plus SVLs.
- **Atropine and multifocal spectacles (MFSLs) versus placebo:** (2 studies: MIT Study 2001; Yen 1989). The Myopia Intervention Trial (MIT) was conducted in Taiwan, and evaluated SVLs, progressive addition lenses, and progressive addition lenses combined with 0.5% atropine eyedrops (MIT Study 2001). Yen 1989 randomly divided 247 Taiwanese children, aged 6 years to 14 years, into three groups. Group 1 received 1% atropine and bifocal spectacles; group 2 received 1% cyclopentolate; and group 3 received saline eye drops. All groups were followed for 12 months.

Other pharmacological interventions

- **Timolol eye drops versus single vision spectacle lenses (SVLs):** (1 study: Jensen 1991). One arm of Jensen 1991 investigated topical 0.25% timolol maleate, a non-selective beta antagonist. Timolol eye drops were given twice a day for two years, and compared to an MFSL or SVL control.
- **Systemic 7-methylxanthine versus placebo:** (1 study: Trier 2008 [384, 385, 386]). This study investigated the effectiveness of systemic 7-methylxanthine, an adenosine receptor antagonist, in 83 Danish children, aged 8 years to 13 years. Participants were randomised to receive 7-methylxantine or a placebo, once daily.

Photobiomodulation

Repeated low level red light therapy

- **Repeated low level red light (RLRL) therapy versus untreated control:** (3 studies: Chen 2023; Jiang 2022; Zhou 2023). All studies involved children of Chinese ethnicity with myopia. Chen 2023 randomised children, aged 6 years to 12 years, to receive daily, home-based RLRL therapy (twice a day, provided by a laser device that emitted red light of 635 nm for three minutes per session), or no treatment. All children continued to wear SVLs for the one-year duration of the study. Jiang 2022 randomised children, aged 8 years to 13 years, to either RLRL therapy (provided by a desktop device emitting low level red laser light of 650 nm wavelength), or no treatment. RLRL therapy was delivered twice daily, five days a week, at home under parental supervision, for three minutes per session. All participants wore SVLs and were followed for one year. Zhou 2023 also randomised children, aged 8 years to 12 years, to RLRL therapy (650 nm) or SVLs, and followed them for one year.

Behavioural

Outdoor light exposure

- **Increased outdoor light exposure versus control:** (1 study: Wu 2018). We excluded the majority of studies that reported the impact of environmental interventions (e.g. elevated light levels in classrooms or increased outdoor time), since the primary outcome was incident myopia or progression in myopes, and non-myopes were not reported separately. Wu 2018 conducted a cluster-randomised trial, involving children (mean age 6.3 years) in schools in Taiwan. Schools were randomised into an intervention group, in which children were encouraged to go outdoors during recess for up to 11 hours weekly (recess outside classroom program), or a control group. Children were followed for one year. An ongoing study, Shanghai Time Outside to Reduce Myopia (STORM) study (NCT02980445 [387, 388]), is a two-year, school-based, prospective, cluster-randomised study that is investigating the effect of two 'doses' of increased outdoor time (40 minutes and 80 minutes over normal time outdoors). Outcomes include the incidence of myopia in non-myopic children, and the progression of myopia in myopic children.

Myopia control intervention versus myopia control interventions

- **Comparison of atropine doses:** (4 studies: ATOM 2 Study 2012; Cui 2021; Liu 2023c; Ye 2022). The ATOM 2 Study 2012 was conducted in Singapore, and compared the efficacy and safety of three doses of topical atropine: 0.5%, 0.1%, and 0.01%, in 400 children of Chinese ethnicity. Cui 2021 evaluated the safety and efficacy of 0.02% and 0.01% atropine in 400 myopic Chinese children, who were randomly allocated to atropine 0.02% (138 children) or 0.01% (142 children). The study also included a non-randomised control group who wore single-vision spectacle lenses (120 children). All participants were followed for two years. Ye 2022 randomised Chinese children, aged 6 years to 12 years, to receive either the consecutive use of 1% atropine tapering to 0.01% atropine after six months, or 0.01% atropine alone. Participants were followed for one year. Liu 2023c compared two dosing regimens of 0.01% atropine, comparing daily versus alternate daily administration, in 123 Chinese children, aged 6 years to12 years. Efficacy and safety outcomes were reported at one year.
- **Atropine and multifocal spectacle lenses (MFSLs) versus tropicamide:** (1 study: Shih 1999). This study evaluated low-concentration atropine in Taiwanese children, aged 6 years to 13 years. It randomly allocated 200 children to one of three atropine groups (0.5%, 0.25%, or 0.1%), or 1% tropicamide as a control. The 0.5% atropine group was advised to wear MFSLs, and the 0.25% atropine group was advised to wear slightly undercorrected SVLs.
- **Combined orthokeratology (ortho-K) plus atropine versus orthokeratology alone:** (5 studies: Kinoshita 2020; Tan 2023; Xu 2023; Yu 2022; Zhao 2021). Kinoshita 2020 randomly allocated 80 Japanese children with low to moderate myopia, aged 8 years to 12 years, to receive either combined ortho-K and 0.01% atropine, or ortho-K monotherapy. Tan 2023 randomised 72

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Chinese children, aged 6 years to 11 years, to receive combined ortho-K and 0.01% atropine, or ortho-K monotherapy. Xu 2023 randomised 164 Chinese children into 4 groups: 0.01% atropine, ortho-K plus 0.01% atropine, ortho-K alone, or an SVL control group. Yu 2022 randomised 60 Chinese children into an ortho-K group, or a combined 0.01% atropine plus ortho-K group. Zhao 2021 tested combined 0.01% atropine plus ortho-K group versus ortho-K alone. Forty Chinese children, who had been wearing ortho-K lenses for three months, were randomised to receive either ortho-K and 0.01% atropine or ortho-K alone.

- **Comparison of orthokeratology (ortho-K) designs:** (4 studies: Guo 2021; Lau 2023; Liu 2023b; Tang 2023). Guo 2021 compared two designs of ortho-K lenses with different back optic zone diameters in 82 Chinese children, aged 6 years to 11 years, who were randomised to wear lenses with either a 6 mm or 5 mm back optic zone diameter, and followed them for two years. Liu 2023b compared ortho-K lenses with an aspheric or spherical base curve in 70 Chinese children, aged 8 years to 12 years. Lau 2023 and Tang 2023 compared ortho-K lenses with either an increased or conventional compression factor in Chinese children with low to moderate myopia. The compression factor (also known as Jessen factor) refers to the extra power added to the target ortho-K lens power to counteract daytime regression after lens removal.
- **Orthokeratology (ortho-K) versus rigid gas-permeable contact lenses (RGP):** (1 study: Swarbrick 2015). This study conducted a randomised, contralateral-eye cross-over study, over a one-year period. Although the study was conducted in Australia, all 26 children were of East Asian ethnicity. Participants were fitted with an orthokeratology lens in one eye, chosen at random, and a conventional RGP lens, worn daily, in the contralateral eye. Children wore the lenses for six months. After a two-week washout period, the lenses were reversed, and lens wear was continued for a further six months.
- **Orthokeratology (ortho-K) versus atropine:** (2 studies: Ren 2017; Zhao 2021). Both studies compared 0.01% atropine to ortho-K.
- **Repeated low level red light (RLRL) therapy versus atropine:** (1 study: Chen 2022). This study randomised Chinese children, aged 7 years to 15 years, to receive either RLRL therapy (650 nm red light), or 0.01% atropine, and were followed for one year.

Characteristics of the outcomes

All included studies evaluated the progression of myopia, either by measuring the mean change in refractive error, defined as spherical equivalent refraction (SER), mean change in axial length, or both. Eight studies reported SER only (Adler 2006; Hasebe 2008; Jensen 1991, Pärssinen 1989; Schwartz 1981; Shih 1999; Yang 2009; Yen 1989). The 14 studies investigating the efficacy of ortho-K lenses reported change in axial length as the primary efficacy outcome (Bian 2020; Choi 2023; Jakobsen 2022; Kinoshita 2020; Lau 2023; Lin 2024; Liu 2023b; ROMIO Study 2012; Swarbrick 2015; Tang 2021; Tang 2023; Xu 2023; Zhang 2023; Zhu 2023a). Due to the transient changes in corneal curvature and refractive error induced by orthokeratology, most studies presented effectiveness in terms of axial elongation only. The outcomes in Han 2018 were unclear, and the remaining studies provided data on both SER and axial length.

Ten studies investigated the change in refractive error and axial length following cessation of treatment (commonly referred to as rebound). In the STAMP Study 2012, children were randomly assigned to MFSL or SVLs for one year, and all children wore SVLs in the second year. Cheng 2016 invited participants who had been randomised to soft contact lenses with positive spherical aberration or single vision soft lenses for one year, to participate in a withdrawal phase, in which all children wore single vision contact lenses. To assess a potential rebound effect, MASS Study 2018 invited children to participate in an additional year of follow-up. Children were divided into three groups: a group in which children from the original study group continued wearing MFSCLs; a group in which children discontinued MFSCL wear; and an SVL group, in which children from the original control group continued wearing SVLs. Zhu 2023a continued to monitor children for one month after they had worn ortho-K lenses for one year, to evaluate rebound. Five studies investigated the impact of terminating atropine treatment. In the ATOM Study 2006, children received 0.5%, 0.1%, or 0.01% atropine for 12 months, after which treatment was terminated and the children were followed for a further 24 months. In the ATOM 2 Study 2012, children who received topical atropine 0.5%, 0.1%, or 0.01% for 24 months entered Phase 2, the washout phase, during which atropine was discontinued, and SER and axial length were assessed at 26, 32, and 36 months. In Zhu 2021, the frequency of 1% atropine eyedrop instillation was reduced from once a month during the first year, to once every two months in years two and three, and withdrawn completely in year four. Repka 2023 discontinued 0.01% atropine for six months after two years of treatment, and compared myopia progression to the untreated control group. Zhu 2023b similarly withdrew 0.05% atropine for one year following two years of treatment to investigate rebound, compared to an untreated control group. Ye 2022 explored myopia rebound after switching from weekly 1% atropine for six months, to daily 0.01% atropine for the following six months of the trial; this group was compared to a group receiving 0.01% atropine for one year. Two studies investigated rebound with RLRL therapy (Chen 2023; Jiang 2022). Chen 2023 continued to follow participants in the RLRL group for three months after receiving the intervention for one year. In Jiang 2022, participants completing a one-year trial of RLRL therapy were invited to participate in a follow-up study, in which RLRL therapy was terminated in a subgroup for 12 months, and compared to an untreated control subgroup.

Forty studies provided data on safety outcomes, reported as the occurrence of adverse events. These included six studies reporting on adverse events with spectacle lens interventions, 13 reporting on contact lens interventions (including ortho-K), 18 studies reporting on various pharmacological interventions, and three studies reporting on adverse events associated with RLRL therapy.

Two studies reported on quality of life (BLINK Study 2020; LAMP Study 2019). The LAMP Study 2019 investigated the efficacy of low-dose topical atropine, and measured vision-related quality of life at the 12-month follow-up visit. The Chinese version of the 25-Item National Eye Institute Visual Function Questionnaire (NEI VFQ-25) was administered to all participants to determine the impact of different treatment groups on vision-related quality of life. In the BLINK Study 2020, the Pediatric Refractive Error Profile 2 (PREP2) was used to measure vision-related quality of life in children after wearing MFSCLs for two weeks.

Twenty-six studies provided data on treatment adherence. Twelve studies reported on compliance with spectacle lens wear, including

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undercorrection with SVL, bifocal, or progressive addition lenses. Compliance was typically based on parent or child, or both, self-reporting wearing time (hours per day) and overall compliance, expressed as a percentage of participants in each arm. Similarly, six studies using contact lens interventions reported on wearing time and percentage compliance between the intervention and control lenses. Six studies of pharmacological interventions provided data on adherence from self-reported compliance with the study medication, or based on the number of eye drop ampules used. Two studies reported on compliance with RLRL therapy.

Ongoing studies

We identified 158 ongoing studies (see Supplementary material 5). These studies compare contact lenses or spectacle lenses (MFSCL, MFSL, or orthokeratology) or pharmacological interventions to a control, or other myopia control interventions. The majority of the ongoing studies investigate the efficacy of various doses of atropine used alone or in combination with other interventions.

Studies awaiting classification

We classified three studies, published as conference abstracts, as awaiting classification (see Supplementary material 4 (Liu 2023 [389]; Viswanath 2022 [390]; Wang 2005 [391])).

Excluded studies

We excluded a total of 169 studies. The main reasons for exclusion were that the study was not randomised, or the population, intervention, or outcome was ineligible (see Supplementary material 3 for further details).

Risk of bias in included studies

We assessed risk of bias using the RoB 2 [57]. A graphical representation of risk of bias for each comparison for the critical outcome, progression of myopia, can be seen in Analysis 1.1; Analysis 1.2; Analysis 2.1; Analysis 2.2; Analysis 2.3; Analysis 3.1; Analysis 3.2; Analysis 4.1; Analysis 4.2; Analysis 5.1; Analysis 5.2; Analysis 6.1; Analysis 7.1; Analysis 7.2; Analysis 7.3; Analysis 7.4; Analysis 7.9; Analysis 9.1; Analysis 9.2; Analysis 10.1; Analysis 11.1; Analysis 11.2. We present the details of RoB assessments for each analysis in Supplementary material 6.

The overall risk of bias across studies in each analysis reporting this outcome ranged from some concerns to a high risk of bias, depending on the particular intervention used.

For the comparison, undercorrection versus full correction spectacles, we assumed an overall high risk of bias, since all three studies had a high risk of bias in one domain, due to either an inappropriate method used to measure the outcome, or no reasons given for missing data.

Of the 11 studies that reported on progression of myopia in the analysis, multifocal spectacle lenses versus single vision spectacles, we judged one study to be at high risk of bias (Cheng 2010). We had some concerns about the remainder, usually due to insufficient information concerning allocation concealment and lack of an a priori statistical analysis plan. Therefore, we assumed an overall bias of some concerns. For the comparison, peripheral plus spectacle lenses versus single vision spectacles, we had some concerns for four of the seven studies reporting this outcome, and judged three studies at high risk of bias (Han 2018; Hasebe 2014; Lu 2015).

Ten of the 12 studies reporting the progression of myopia in the comparison, multifocal soft contact lenses versus single-vision soft contact lenses, were judged as giving us some concerns, primarily due to a failure to describe the method of allocation concealment, and providing no information on the predetermined analysis plan. One study, Raffa 2022, was judged to be at high risk of bias due to inappropriate methods used to measure the outcome. We gave an overall judgement of some concerns for this outcome.

Only two studies evaluated progression of myopia following RGP wear. We judged one study at high risk (Katz 2003). Therefore, we gave an overall judgement of high risk for this outcome.

We judged seven of the 13 studies reporting change in axial length from baseline after wearing orthokeratology lenses as having some concerns. We judged five studies at high risk of bias (Charm 2013; Lin 2024; Lyu 2020; Ren 2017; ROMIO Study 2012). We gave an overall judgement of some concerns for this outcome.

For progression of myopia in the comparison, anti-muscarinics versus control, we judged seven studies, using different doses of atropine, to be at high risk of bias (Chan 2022; Hu 2023; Lee 2022; Sen 2022; Xia 2023; Zhu 2021; Zhu 2023b), primarily due to missing outcome data or the use of inappropriate methods to measure the outcome. We judged the remainder as having some concerns. We judged the overall risk of bias as having some concerns for this outcome. However, we judged both of the studies reporting on 2% pirenzepine to be at high risk of bias (PIR-205 Study 2004; Tan 2005), which gave an overall judgement of high risk for this outcome.

For the change in axial length, in the comparison between ortho-K lenses plus low dose atropine versus ortho-K alone, we judged one of the five studies to be at high risk of bias (Zhao 2021), and the remainder as having some concerns. We gave an overall judgement of some concerns for this outcome (see risk of bias table for Analysis 9.1).

Only three studies evaluated progression of myopia following RLRL therapy. We judged two studies at high risk of bias (Jiang 2022; Zhou 2023), and one with some concerns (Chen 2022). Therefore, we gave an overall judgement of high risk for this outcome (see risk of bias table for Analysis 11.1, Analysis 11.2).

For the outcome, change in refractive error and axial length following cessation of treatment, five of the seven included studies had some concerns and two were considered to be at high risk of bias (Zhu 2021; Zhu 2023b; see Analysis 2.3; Analysis 4.3; Analysis 4.4; Analysis 7.9; Analysis 7.10).

Detailed risk of bias assessments are available at: OSF | Cochrane Myopia NMA.

Synthesis of results

See the summary of findings tables for the overall treatment effects, the certainty of the evidence, and reasons for downgrading for any myopia control intervention on the progression of myopia compared to placebo (Summary of findings 1; Summary of findings 2; Summary of findings 3; Summary of findings 4).

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We performed standard pairwise and network meta-analyses for optical and pharmacological interventions compared to a control group (consisting of either standard SVLs, contact lenses, or a placebo) for the critical outcome, progression of myopia. We also compared myopia control interventions to each other. In total, we included 81 studies, analysing 12,157 participants, in either the standard or network meta-analysis.

Twenty-three studies did not contribute directly to the quantitative synthesis (Agarwal 2023; Cheng 2016; Cui 2021; CYPRESS Study 2023; Fulk 1996; Guo 2021; Han 2019; Hasebe 2008; Houston Study 1987; Lau 2023; Liu 2023a; Liu 2023b; Liu 2023c; Mori 2021; Schwartz 1981; Shen 2022; Swarbrick 2015; Tang 2022; Tang 2023; Wang 2017; Wu 2018; Ye 2022; Yen 1989). For these studies, we reported study-specific results.

Due to insufficient available data, we were unable to undertake quantitative synthesis for the outcomes, risk of adverse events, quality of life, or treatment adherence. For these outcomes, we provided a descriptive summary of the range and distribution of the observed effects, and summarised the study-level findings in structured tables.

Critical outcomes

Progression of myopia

Myopia control intervention versus control

Pairwise meta-analysis results

Direct treatment estimates from pairwise meta-analysis for optical and pharmacological interventions, and red light therapy versus control/placebo are reported. We assessed progression of myopia as a mean change in refractive error (defined as SER) from baseline for each year of follow-up, or change in axial length (AL) from baseline, or both. To facilitate interpretation of the forest plots, negative mean differences (MDs) for changes in refractive error represent faster progression of myopia in the intervention group compared to the progression in the control group. Thus, point estimates to the left of the null on the forest plots favour the control group. For the measurement of changes in axial length, negative MDs for changes in axial length represent faster axial elongation in the control group compared to the intervention group, and therefore, estimates to the left of the null favour the intervention group.

Optical interventions: spectacles

- Spectacle interventions designed to reduce accommodative demand and lag during near work by undercorrection, or the use of multifocal spectacle lenses (MFSLs) have been common in practice for many years. Three studies, involving 292 participants, compared spectacles that were undercorrected by −0.50 D to −0.75 D to fully corrected SVLs (Analysis 1.1; Analysis 1.2). There was evidence that undercorrection may have little or no effect on myopic progression, based either on change in refractive error (MD at 1 year −0.15 D, 95% CI −0.29 to 0.00); MD at 2 years 0.02 D, 95% CI −0.05 to 0.09), or change in axial length (MD at 1 year 0.05 mm, 95% CI −0.01 to 0.11; MD at 2 years −0.01 mm, 95% CI −0.06 to 0.03).
- Fourteen studies compared bifocal or progressive addition lenses to single vision spectacle lenses (SVLs). We included 11 studies with 1696 participants in a quantitative synthesis (Analysis 2.1; Analysis 2.2). Nine studies provided data for up to two years, and four studies followed participants for up to three years (Cheng 2010; COMET Study 2003; COMET 2 Study 2011; Pärssinen 1989). There was a small reduction in myopia progression at both one- and two-year follow-up (change in refractive error at 1 year, MD 0.14 D, 95% CI 0.08 to 0.21; and at 2 years, MD 0.19 D, 95% CI 0.09 to 0.29). The three-year results showed considerable heterogeneity (I^2 = 86%). The pooled three-year change in refractive error MD was 0.26 D (95% CI −0.07 to 0.59). The three studies not included in the meta-analysis reported inconsistent results (Fulk 1996; Hasebe 2008; Houston Study 1987). In one 18-month study, children wearing bifocals progressed at a rate of −0.39 D per year compared to −0.57 D per year in the SVL group (Fulk 1996). However, these differences were imprecise (P = 0.26). Hasebe 2008 showed evidence of less myopia progression in children wearing progressive addition lenses over the first 18 months of a cross-over study compared to children wearing SVLs, but no difference in the second 18-month period. The Houston Study 1987 found no evidence of an important difference between groups wearing bifocals (+1.00 D and +2.00 D near add) and SVLs. We included five studies with 980 participants that reported changes in axial length with progressive addition lenses in a quantitative analysis (Analysis 2.2). There was a small reduction in axial elongation in progressive addition lens wearers for each year of follow-up (1-year MD −0.06 mm, 95% CI −0.09 to −0.04; 2-year MD −0.07 mm, 95% CI −0.11 to −0.03; 3-year MD −0.12 mm, 95% CI −0.18 to −0.07).
- The rationale for prescribing peripheral plus spectacle lenses (PPSL) is to reduce hyperopic defocus in the peripheral retina. Seven studies compared PPSL to SVLs (Bao 2022; Han 2018; Hasebe 2014; Lam 2020; Lu 2015; Sankaridurg 2010; Yuval 2024). Changes in refractive error from baseline, at one and two years showed considerable heterogeneity (I^2 = 97% and 87%; Analysis 3.1). Mean differences at one year ranged from 0.01 D to 0.97 D. Three studies followed children for two years (Bao 2022; Hasebe 2014; Lam 2020). These studies showed contrasting results. Hasebe 2014 found no difference in myopia progression with positively aspherised progressive addition lenses (MD 0.12 D, 95% CI −0.07 to 0.31). Lam 2020 showed evidence of reduction in progression using the defocus incorporated multiple segments (DIMS) spectacle lens (MD 0.55 D, 95% CI 0.38 to 0.72). Bao 2022 also found evidence of reduced progression using a design with rings of aspheric lenslets (pooled highly aspheric and slightly aspheric designs; MD 0.61 D, 95% CI 0.40 to 0.82). Five studies provided data on changes in axial length from baseline, showing similarly high heterogeneity (Analysis 3.2). The evidence was inconclusive between the combination of all three novel lenses tested by Sankaridurg 2010 and SVLs at one year (MD 0.01 mm, 95% CI −0.15 to 0.17), contrasting with designs used by Yuval 2024, Lam 2020 and Bao 2022, which showed less axial elongation. Three studies provided two-year data for axial length. Hasebe 2014 reported no evidence of difference (MD −0.07 mm, 95% CI −0.20 to 0.06), whereas Lam 2020 showed that the reduced axial elongation shown at one year, continued into the second year (MD −0.32 mm, 95% CI −0.39 to −0.25). This was also the case for Bao 2022 (MD −0.26 mm, 95% CI −0.35 to −0.17).
- Three studies investigated novel spectacle lens designs (CYPRESS Study 2023; Liu 2023a; Mori 2021). Mori 2021 reported no important benefit with violet light transmitting glasses on myopia progression. The CYPRESS Study 2023 found that two designs of diffusion optics technology (DOT) lenses, which claim

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to modulate retinal contrast, were effective in slowing myopia progression at one year, compared to SVLs (DOT lens 1 MD 0.38 D, 95% CI 0.26 to 0.50; and DOT lens 2 MD 0.30 D, 95% CI 0.15 to 0.45). In terms of axial elongation, children with DOT lenses also showed less elongation compared with the control lenses (DOT lens 1 MD –0.15 mm, 95% CI –0.20 to –0.10; DOT lens 2 MD –0.12 mm, 95% CI –0.18 to –0.06). Liu 2023a reported that cylindrical annular refractive element (CARE) lenses slowed axial elongation at one year relative to control lenses (MD –0.09 mm, 95% CI –0.15 to –0.02). However, the difference in refractive error was imprecise (MD 0.14 D, 95% CI –0.04 to 0.32).

Optical interventions: contact lenses

- Studies tested a variety of contact lens designs, including multifocal soft contact lenses (MFSCL), extended depth of focus (EDOF) contact lenses, positive spherical aberration contact lenses, rigid gas-permeable (RGP), and orthokeratology lenses. Conceptually, MFSCLs use a progressive or concentric ring design to create myopic defocus and reduce myopia progression. Thirteen studies compared MFSCLs to single vision soft contact lenses (SVSCL). We excluded Fujikado 2014 from the meta-analysis, since they used a lens design that was distinct from the other lenses in the comparison. Consequently, we included 12 studies, with a total of 1338 participants, in a quantitative synthesis (Analysis 4.1; Analysis 4.2). Five studies provided data on the change in refractive error and axial length up to two years, and two studies followed children for up to three years (BLINK Study 2020; Chamberlain 2019). Over the three-year reporting period, there was a progressive reduction in myopia progression with MFSCL compared to SVCL, although there was a suggestion that the change in refractive error reduced over time (1-year MD 0.27 D, 95% CI 0.18 to 0.35; 2-year MD 0.30 D, 95% CI 0.19 to 0.41; 3-year MD 0.47 D, 95% CI 0.13 to 0.82). There was evidence of reduced axial elongation across all three years (1-year MD −0.11 mm, 95% CI −0.13 to −0.09; 2-year MD −0.15 mm, 95% CI −0.19 to −0.12; 3-year MD −0.22 mm, 95% CI −0.34 to −0.10).
- Cheng 2016 investigated the effect of soft contact lenses with positive spherical aberration. The mean reported difference in SER change from baseline in this study was 0.14 D (95% CI −0.007 to 0.281) for the 52 children in the spherical aberration group, compared with 57 children in the SVSCL group at one-year follow-up. In terms of axial elongation, children in the positive spherical aberration group showed MD 0.14 mm (95% CI −0.19 to −0.10) less elongation compared with the control at one year.
- Sankaridurg 2019 tested two EDOF lens designs compared to SVSCLs, and Shen 2022 randomised one eye to receive an EDOF lens and the other a standard SVSCL. In Sankaridurg 2019, the use of both EDOF designs showed evidence of less myopic progression at two years compared to SVSCLs (EDOF lens III MD 0.31 D, 95% CI 0.07 to 0.55; MD –0.13 mm, 95% CI –0.24 to –0.02) and (EDOF lens IV MD 0.23 D, 95% CI 0.02 to 0.44; MD –0.14 mm, 95% CI –0.24 to –0.04). Myopia progression was monitored over one year by Shen 2022. Although there was less myopic progression in the eye wearing the EDOF lens in terms of change in refractive error (MD 0.18 D, 95% CI 0.01 to 0.35), there was no real difference in axial elongation (MD –0.04 mm, 95% CI –0.10 to 0.02).
- Two studies investigated the use of rigid gas-permeable contact lenses (RGPs) in slowing the progression of myopia compared to single vision contact lenses in one study (CLAMP Study 2004), and SVLs in the other ((Katz 2003) Analysis 5.1; Analysis 5.2). The CLAMP Study 2004 followed participants for three years; Katz 2003 followed participants for two years. We did not pool the data on change in refractive error due to considerable heterogeneity (I^2 > 90%). The two studies reported contrasting results, with the CLAMP Study 2004 showing evidence of less myopia progression over three years with the RGPs compared to participants wearing SVSCLs (1-year MD 0.40 D, 95% CI 0.19 to 0.61; 2-year MD 0.54 D, 95% CI 0.27 to 0.81; 3-year MD 0.63 D, 95% CI 0.30 to 0.96). Katz 2003 observed no real difference in myopia progression over two years (1-year MD −0.02 D, 95% CI −0.14 to 0.10; 2-year MD −0.05 D, 95% CI −0.25 to 0.15). Neither study was able to show any effect on axial elongation over three years (pooled estimate 1-year MD 0.02 mm, 95% CI −0.05 to 0.10; 2-year MD 0.03 mm, 95% CI −0.05 to 0.12; 3-year MD 0.05 mm, 95% CI −0.12 to 0.22).
- Thirteen studies, involving 1373 participants, compared ortho-K lenses to SVLs or SVSCLs. They provided data up to two years for the quantitative synthesis (Analysis 6.1). Overnight wear of ortho-K lenses flattens the central cornea and temporarily reduces refractive error. Since it is not possible to assess the true progression of refractive error without ceasing lens wear for a period of time to allow the cornea to return to its pre-treatment state, the included studies presented change in axial length as the primary efficacy outcome. There was evidence of reduced axial elongation across both years (1-year MD −0.18 mm, 95% CI −0.21 to −0.14; 2-year MD −0.30 mm, 95% CI −0.38 to −0.23).

Pharmacological interventions: antimuscarinics

- **Atropine:** 21 studies comparing topical atropine to control (placebo, no treatment, or SVLs) were included in the meta-analyses. These were grouped according to the dosing regimen, into high-dose (≥ 0.1%) or low-dose (< 0.1%). Nineteen studies reported data at one year, 11 studies reported data at two years (ATOM Study 2006; CHAMP 2023; Hansen 2023; Hieda 2021; Lee 2022; MOSAIC Study 2024; Repka 2023; Sen 2022; Zhang 2024; Zhu 2021; Zhu 2023b), one study reported up to three years (CHAMP 2023), and one up to five years (Moriche-Carretero 2021).
- Several studies tested atropine as either a co-intervention, or in head-to-head dose comparisons.
  - **High-dose atropine:** three studies (1072 participants) compared high-dose atropine (1%) to control (ATOM Study 2006; Yi 2015; Zhu 2021). At one year, effect sizes for the change in refractive error ranged from MD 0.79 D to MD 1.17 D in favour of high-dose atropine (Analysis 7.1). A reduction in axial elongation was also seen with 1% atropine at one year (MD −0.31 mm to MD −0.35 mm; Analysis 7.2). At two years, high-dose atropine also had greater efficacy. The ATOM Study 2006 showed a change in refractive error of MD 0.92 D (95% CI 0.75 to 1.09); and a change in axial length of MD −0.40 mm (95% CI −0.48 to −0.32). Zhu 2021 showed a change in refractive error of MD 1.41 D (95% CI 1.30 to 1.52), and a change in axial length of MD −0.54 mm (95% CI −0.57 to −0.51; Analysis 7.3; Analysis 7.4). Two further studies, not included in the meta-analysis, investigated 1% atropine versus placebo and showed evidence of less myopia progression in children in the atropine group at the end of the follow-up period. However, the data were not presented in a format that could be included in the meta-analysis (Han

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2019; Wang 2017). We also excluded Yen 1989 and MIT Study 2001, since the atropine groups also wore MFSLs.

- **Low-dose atropine:** 18 studies (3027 participants) compared lower atropine doses (0.01% to 0.05%) to control (CHAMP 2023; Chan 2022; Chia 2023; Hansen 2023; Hieda 2021; Hu 2023; LAMP Study 2019; Lee 2022; Moriche-Carretero 2021; MOSAIC Study 2024; Ren 2017; Repka 2023; Sen 2022; Sharma 2022; Wei 2020; Xia 2023; Zhang 2024; Zhu 2023b). Results for these comparisons for each year of follow-up showed considerable heterogeneity ($I^2 \geq 85\%$). However, since all effects were broadly in the same direction, we included subgroup summary effect estimates in the forest plots as the best estimate of the intervention effect. At one year, effect sizes for the change in refractive error were in the range of MD –0.04 D to MD 0.80 D (pooled effect size MD 0.25 D, 95% CI 0.16 to 0.35), and the change in axial length ranged from MD 0.02 mm to MD −0.35 mm (pooled effect size MD –0.10 mm, 95% CI –0.13 to –0.07; Analysis 7.1; Analysis 7.2). Studies reporting at two years also showed a greater efficacy for low-dose atropine; change in refractive error ranged from MD –0.04 D to MD 1.26 D (pooled effect size MD 0.36 D, 95% CI 0.32 to 0.40); change in axial length ranged from MD 0.01 mm to MD -0.50 mm (pooled effect size MD –0.16 mm, 95% CI –0.21 to –0.10; Analysis 7.3; Analysis 7.4). Two studies, monitoring myopia progression over longer periods, reported evidence of reductions in myopia progression, although there was evidence of reduced efficacy over time, with most of the reduction in myopia progression occurring in the first two years of treatment (CHAMP 2023; Moriche-Carretero 2021; Analysis 7.5; Analysis 7.6; Analysis 7.7; Analysis 7.8). A subgroup analysis of the efficacy of low-dose atropine studies in Asian populations compared to six studies with predominantly non-Asian participants, showed lower efficacy in the non-Asians studies (CHAMP 2023; Hansen 2023; Lee 2022; Moriche-Carretero 2021; MOSAIC Study 2024; Repka 2023; Analysis 8.1; Analysis 8.2; Analysis 8.3; Analysis 8.4).

- **Pirenzepine:** two studies investigated 2% pirenzepine eyedrops (PIR-205 Study 2004; Tan 2005; Analysis 7.1; Analysis 7.2 Analysis 7.3). At one-year follow-up, average myopia progression was less for participants treated with pirenzepine compared to placebo (MD 0.27 D, 95% CI 0.11 to 0.43; PIR-205 Study 2004; MD 0.47 D, 95% CI 0.16 to 0.78; Tan 2005). The difference in progression between groups continued at two years (MD 0.41 D, 95% CI 0.13 to 0.69; PIR-205 Study 2004). Data for axial length were only available at one year. Tan 2005 found a slowing of axial elongation (MD −0.13 mm, 95% CI −0.14 to −0.12), whereas the PIR-205 Study 2004 found no important difference in axial length (MD −0.04 mm, 95% CI −0.15 to 0.07).

Other pharmacological interventions

- One arm of Jensen 1991 investigated the non-selective beta-antagonist, timolol maleate, compared to an SVL control. The differences in myopia progression were imprecise at one year (MD −0.05 D, 95% CI −0.21 to 0.11), and at two years (MD −0.04 D, 95% CI −0.30 to 0.22). This study did not measure axial length.
- Trier 2008 compared systemic 7-methylxanthine, an oral adenosine receptor antagonist, versus a placebo tablet for one year. At one-year follow-up, little to no differences were observed in myopia progression (change in refractive error MD 0.07 D, 95% CI −0.09 to 0.24; change in axial length MD −0.03 mm, 95% CI −0.10 to 0.03; Analysis 9.1; Analysis 9.2).

Photobiomodulation interventions

- **Repeated low intensity red light (RLRL) therapy:** three studies, involving 367 participants, investigated RLRL therapy (Chen 2023; Jiang 2022; Zhou 2023). RLRL may reduce myopia progression at one year (refraction change MD 0.80 D, 95% CI 0.71 to 0.89; axial length change MD –0.33 mm, 95% CI –0.37 to –0.29; Analysis 11.1; Analysis 11.2).

Behavioural interventions

- **Outdoor light exposure:** one cluster-randomised study investigated the impact of a school-based programme to promote longer outdoor time in a subset of 73 myopic children (Wu 2018). Over one year, there was evidence of a reduction in myopic progression (refraction change MD 0.22 D, 95% CI 0.04 to 0.40; axial length change MD –0.15 mm, 95% CI –0.26 to –0.04).

Network meta-analysis results

We conducted NMAs for the change in SER and axial length at 12 and 24 months. See Figure 2 for the network maps for each comparison, and Table 2, which presents the number of study arms (participants) for each intervention. There were relatively few direct comparisons between interventions, meaning that most comparisons were indirect. League-tables, presenting all indirect and mixed comparisons for SER and axial length at 12 and 24 months, can be seen at https://osf.io/ms83h/. Figure 3 presents forest plots for NMA comparisons with control.

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Figure 2. Network maps for change in spherical equivalent and change in axial length at 1 and 2 years CONT: control, RLRL: repeated low intensity red light, HDA: high-dose atropine, LDA: low-dose atropine; MDA: medium-dose atropine; MFSCL: multifocal soft contact lenses; MFSL: multifocal spectacle lenses; ORTHOK: orthokeratology; ORTH-A: combined orthokeratology and atropine; PPSL: peripheral plus spectacle lenses ; RGP: rigid gas-permeable contact lenses; UCSL: undercorrected spectacle lenses.

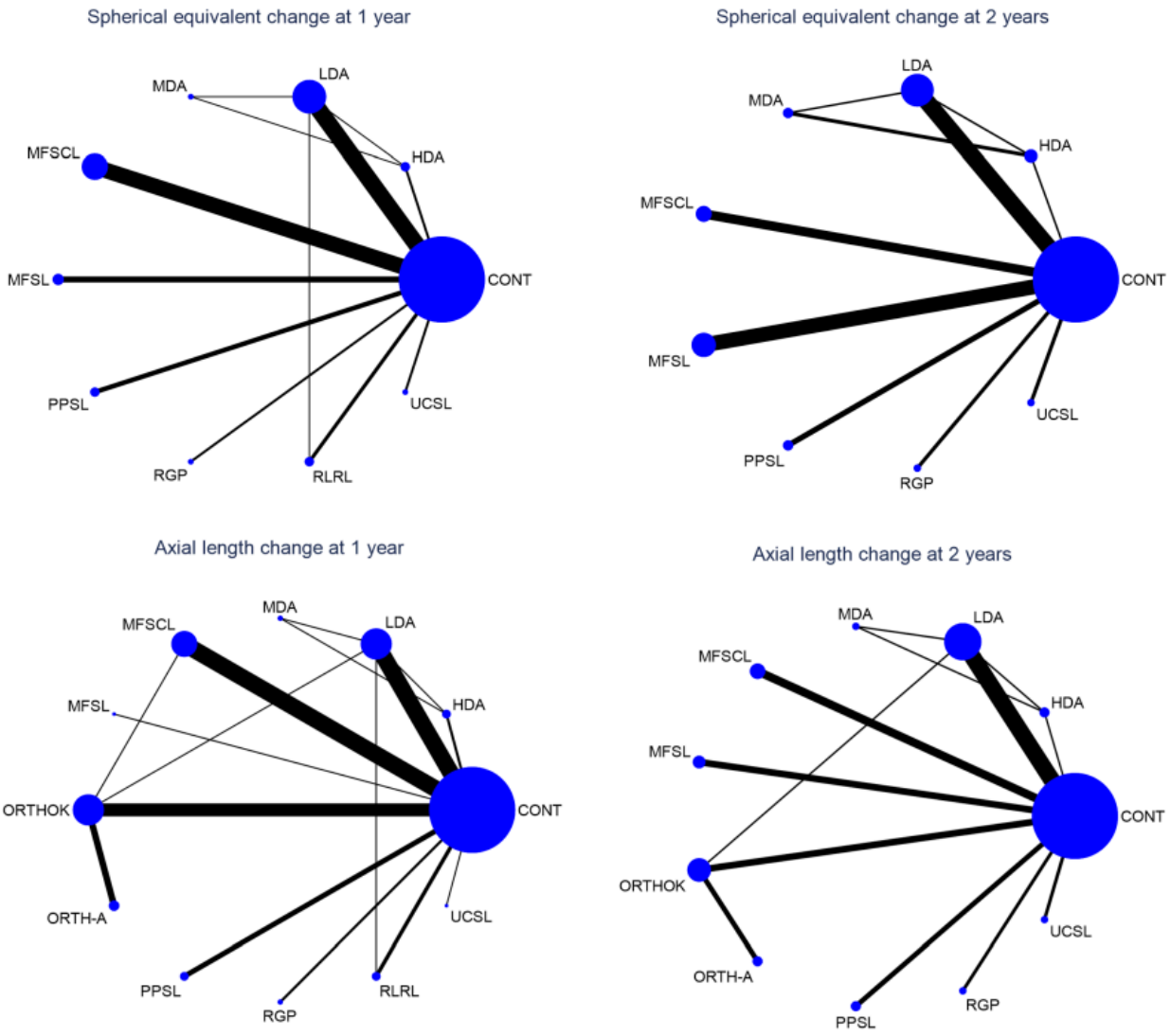

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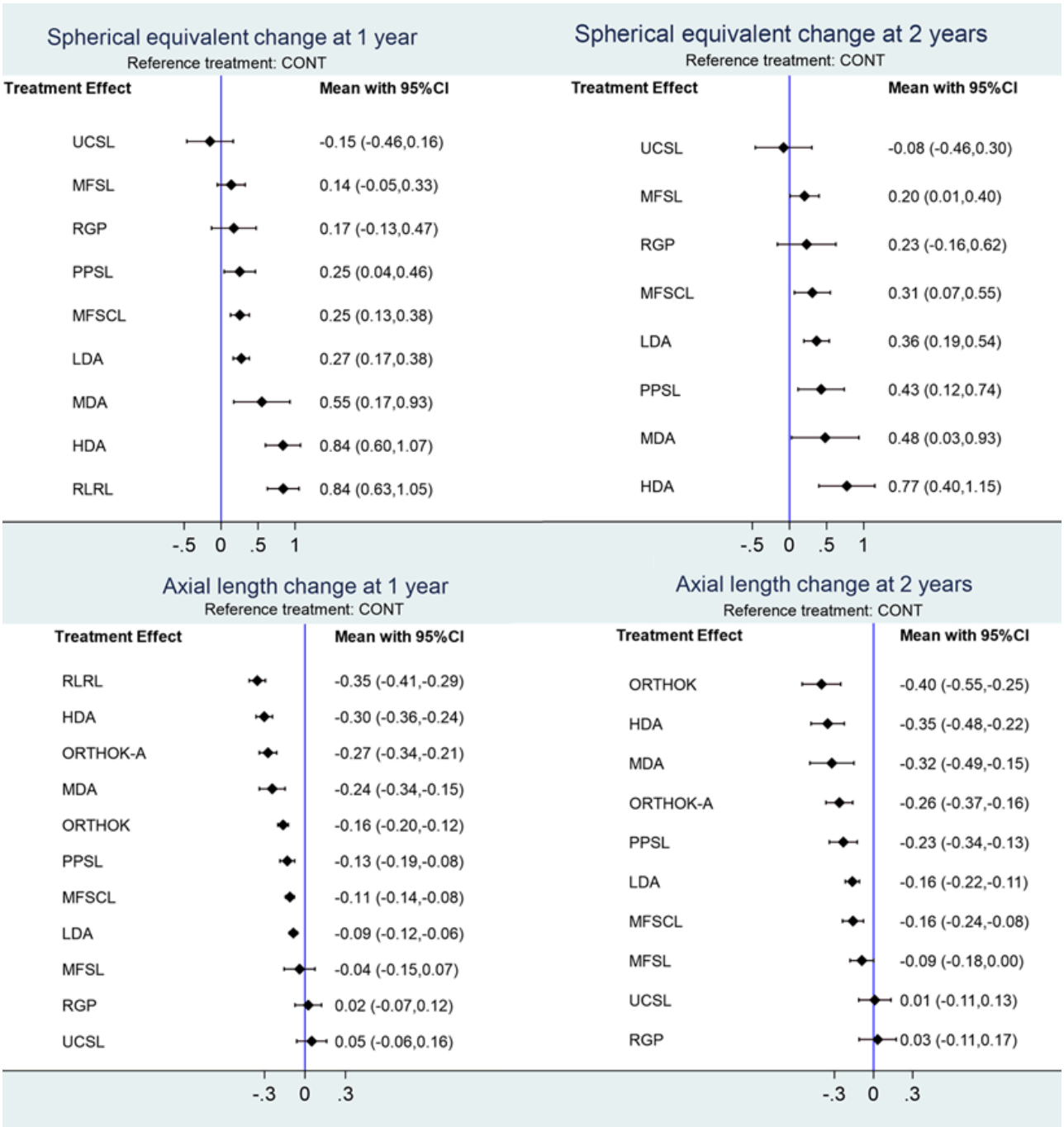
Figure 3. Estimates of eHect from network meta-analyses for all treatments versus control for progression of myopia (based on spherical equivalent and axial length) at 1 and 2 years CONT: control, RLRL: repeated low intensity red light, HDA: high-dose atropine, LDA: low-dose atropine; MDA: medium-dose atropine; MFSCL: multifocal soft contact lenses; MFSL: multifocal spectacle lenses; ORTHOK: orthokeratology; ORTHOK-A: combined orthokeratology and atropine; PPSL: peripheral plus spectacle lenses ; RGP: rigid gas-permeable contact lenses; UCSL: undercorrected spectacle lenses.



- **Change in SER at 1-year follow-up**
  - The NMA included 49 studies (7161 participants) with three connected closed loops, comparing different doses of atropine, different doses of atropine to control, and RLRL to low dose atropine and control. There was no overall inconsistency (P = 0.185). The three closed loops were partly overlapping, and showed no inconsistency.
  - The overall NMA between-study standard deviation (SD) was large (0.19 D), which made most NMA estimates versus control as, or more imprecise than the corresponding direct evidence. For this reason, Summary of findings 1

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presents direct and indirect evidence and its certainty for all comparisons versus control, except for moderate-dose atropine versus control, for which only indirect evidence was available.

- **Change in axial length at 1-year follow-up**
  - The NMA included 59 studies (8359 participants) with five connected closed loops, comparing different doses of atropine or control, RLRL to low dose atropine and control, ortho-K to low dose atropine and control, and ortho-K to multifocal soft contact lenses and control. The closed loops were partly overlapping. Overall, there was evidence of inconsistency (P = 0.022), which was mostly found in the atropine closed loop and the ortho-K versus control loop.
  - The overall NMA between-study SD was large (0.047 mm), which made most NMA estimates versus control as, or more imprecise than the corresponding direct evidence. Summary of findings 3 presents direct and indirect evidence and its certainty for all comparisons versus control, except for moderate-dose atropine versus control, for which only indirect evidence was available.
- **Change in SER and change in axial length at 2-year follow-up**
  - The NMAs of the change in SER at two years included 32 studies (6350 participants); the change in axial length at two years included 34 studies (6294 participants). There was evidence of inconsistency in the axial length network (P = 0.036), principally for the comparisons of atropine doses and ortho-K versus control. Summary of findings 2 and Summary of findings 4 present the evidence and its certainty from direct and indirect comparisons, except for moderate-dose atropine versus control, for which only indirect evidence was available.
- **SUCRAs and mixed comparisons in NMAs**
  - All indirect comparisons are presented for illustrative purposes as league-tables at OSF | Cochrane Myopia NMA.
  - Table 3 presents all SUCRA values for NMAs of change in SER and axial length at one and two years, where the three highest SUCRAs are highlighted in bold print. As can be seen, high-dose atropine and moderate-dose atropine were amongst the three best SUCRAs for all outcomes. Low-dose atropine was third for SER at one year, and PPSLs were third at two years, while ortho-K lenses were amongst the best three for axial length at one and two years.

Antimuscarinics combined with multifocal spectacle co-intervention versus single vision spectacles

Three studies compared antimuscarinics combined with MFSLs to SVLs (MIT Study 2001; Schwartz 1981; Yen 1989). Schwartz 1981 randomised monozygous twin pairs to receive either bifocal spectacles plus 1% tropicamide or SVLs. The paper did not present any numerical results, but the study authors stated that control twins showed more progression of myopia than their co-twins who received tropicamide and bifocals, but the difference was imprecise.

The myopia intervention trial (MIT) evaluated progressive addition spectacle lenses plus 0.5% atropine compared to placebo eyedrops plus SVLs (MIT Study 2001). At the end of the 18-month follow-up period, participants in the atropine plus progressive addition spectacle lenses group showed evidence of less myopia progression in SER (MD 0.98 D, 95% CI 0.76 to 1.20), and in AL (MD −0.47 mm, 95% CI −0.47 to −0.27) than participants in the placebo plus SVL group.

Yen 1989 randomly divided children into three groups. Group 1 received 1% atropine and bifocal spectacles; group 2 received 1% cyclopentolate; and group 3 received placebo eyedrops plus SVLs. At one year, there was less myopia progression in the atropine plus bifocal group compared to the control group (MD 0.70 D, 95% CI 0.43 to 0.97).

Myopia control intervention versus myopia control interventions

Five studies compared different doses of topical atropine to each other (ATOM 2 Study 2012; Cui 2021; Liu 2023c; Shih 1999; Ye 2022). The ATOM 2 Study 2012 compared the efficacy of 0.5%, 0.1%, and 0.01% atropine in children of Chinese ethnicity. The mean changes in refractive error at two years were atropine 0.5% MD −0.30 D (95% CI −0.40 to −0.20); atropine 0.1% MD −0.38 D (95% CI −0.48 to 0.29); and atropine 0.01% MD −0.49 D (95% CI −0.64 to −0.35). Pairwise comparison showed important differences between 0.01% and 0.5% atropine (P = 0.02). Changes in axial length were high-dose MD 0.27 mm (95% CI 0.21 to 0.33); moderate-dose MD 0.28 mm (95% CI 0.24 to 0.33); and low-dose MD 0.41 mm (95% CI 0.36 to 0.46).

Cui 2021 evaluated the efficacy of 0.02% and 0.01% atropine in Chinese children. The mean changes in refractive error at two years were 0.02% concentration MD −0.80 D (95% CI −0.90 to −0.70); and 0.01% concentration MD −0.93 D (95% CI −1.04 to −0.82). The corresponding changes in axial length were 0.02% concentration MD 0.62 mm (95% CI 0.56 to 0.68); and 0.01% concentration MD 0.72 mm (95% CI 0.66 to 0.78).

Liu 2023c compared daily administration of 0.01% atropine eye drops to administration every other day. There was no important difference in either refractive error (MD –0.17 D, 95% CI –2.19 to 1.85); or axial length (MD –0.04 mm, 95% CI –0.30 to 0.22) after one year.

Shih 1999 compared three doses of atropine (0.5%, 0.25%, and 0.15%) with 1% tropicamide control. Participants in the 0.5% group wore bifocal spectacles, those in the 0.25% group were provided with slightly undercorrected SVLs, and the 0.1% group wore fully corrected SVLs. Slowed myopia progression at the end of the two-year follow-up period was evident for each atropine group compared with tropicamide, with the 0.5% atropine dose showing the least progression compared with the tropicamide group (0.1% atropine MD 1.95 D, 95% CI 1.60 to 2.30; 0.25% atropine MD 1.98 D, 95% CI 1.68 to 2.28; and 0.5% atropine MD 2.42 D, 95% CI 2.16 to 2.68).

Ye 2022 adopted a novel dosing regimen, in which one group switched from 1% to 0.01% atropine after six months, continuing to use the lower dose for a further six months. This was compared to a group that used 0.01% atropine for one year. Myopia progression was lower in the combined group at one year follow-up (change in refractive error MD 0.21 D, 95% CI 0.06 to 0.36; change in axial length MD –0.10 mm, 95% CI –0.16 to –0.04).

Five studies evaluated the combination of low-dose atropine (0.01%) plus orthokeratology, compared to orthokeratology alone (Kinoshita 2020; Tan 2023; Xu 2023; Yu 2022; Zhao 2021). These studies were conducted in Japan and China, and followed participants for up to two years. The primary outcome was

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change in axial length (Analysis 10.1). More reduction in axial elongation was found in the combination therapy group than in the monotherapy group at each year of follow-up (1-year MD −0.12 mm, 95% CI −0.15 to −0.09; 2-year MD −0.14 mm, 95% CI −0.19 to −0.08).

Three studies included treatment arms that compared low-dose atropine (0.01%) to orthokeratology. There was little to no difference in axial length between treatments at one year (MD 0.03 mm, 95% CI −0.17 to 0.03; Ren 2017; MD 0.01 mm, 95% CI −0.07 to 0.09; Xu 2023; MD 0.05 mm, 95% CI −0.02 to 0.12; Zhao 2021); or two years (MD −0.01 mm, 95% CI −0.11 to 0.09; Xu 2023)

Chen 2022 compared repeated low intensity red light therapy to 0.01% atropine. Myopia progression was lower in the RLRL therapy group at one-year follow-up (change in refractive error MD 0.57 D, 95% CI 0.48 to 0.66; change in axial length MD −0.25 mm, 95% CI −0.32 to −0.18).

Five studies compared different designs of ortho-K lenses (Guo 2021; Lau 2023; Liu 2023b; Tang 2022; Tang 2023). Guo 2021 and Tang 2022 compared lenses with 6 mm or 5 mm back optic zone diameters. The rationale was that a smaller back optic zone diameter would increase myopia control efficacy by inducing a steeper distribution of the relative corneal refractive power profile within the pupillary diameter and further increase higher order aberrations. Guo 2021 reported that axial elongation was lower in the 5 mm group (MD 0.04 mm, 95% CI −0.005 to 0.08) than the 6 mm group (MD 0.17 mm, 95% CI 0.13 to 0.21) at one year. A lower axial elongation was also reported by Tang 2022 after one year using a 5 mm back optic zone (5 mm group MD 0.05 mm, 95% CI 0.052 to 0.048; 6 mm group MD 0.15 mm, 95% CI 0.152 to 0.148). Lau 2023 and Tang 2023 compared lenses with a conventional compression factor (CCF) to lenses with an increased compression factor (ICF). Lau 2023 reported evidence of reduction in axial elongation in the ICF group compared to the CCF group at 2-years (MD −0.18 mm, 95% CI −0.32 to −0.04). However, Tang 2023 found that the ICF lenses were only more effective for those with moderate myopia (MD −0.07 mm, 95% CI −0.12 to −0.02), but not for those with low myopia.

Swarbrick 2015 conducted a randomised, contralateral-eye cross-over study comparing a regular RGP lens in one eye and an ortho-K lens in the other, conducted over a one-year period. Lenses were worn for six months and then crossed over after a two-week washout period for a further six months. This study did not report data eligible for analysis.

Change in refractive error and axial length following cessation of treatment

Twelve studies investigated changes in refractive error and axial length following cessation of the myopia control intervention (ATOM 2 Study 2012; ATOM Study 2006; Chen 2023; Cheng 2016; Jiang 2022; MASS Study 2018; Repka 2023; STAMP Study 2012; Ye 2022; Zhu 2021; Zhu 2023a; Zhu 2023b). These studies compared the rate of myopia progression in the year after switching to the control intervention or stopping treatment.

In the STAMP Study 2012, children wore MFSLs or SVLs for one year, and all children wore SVLs in the second year. At the end of year two, there was no difference in myopia progression between groups (MD 0.00 D, 95% CI −0.17 to 0.17; Analysis 2.3). This study did not measure progression of axial length.

In the MASS Study 2018, children who wore MFSCLs or single vision spectacles (SVLs) for two years were invited to participate in an additional one-year follow-up study to investigate rebound. One group discontinued MFSCL wear and switched to SVLs. Progression was then compared to the original control group, who continued wearing SVLs. After one year, there was no important difference in progression of refractive error (MD 0.09 D, 95% CI −0.16 to 0.34), or axial length (MD 0.01 mm, 95% CI −0.05 to 0.07; Analysis 4.3; Analysis 4.4).

Cheng 2016 invited participants who had worn either novel soft contact lenses with positive spherical aberration or conventional SVSCLs to participate in a 12-month withdrawal study, in which all children wore single vision lenses. The study authors reported that they found no evidence of a rebound effect at one year.

Zhu 2023a reported that axial length remained relatively stable one month after discontinuing the use of ortho-K lenses, with no important difference compared to that before withdrawal.

Six studies investigated the impact of terminating atropine treatment. The ATOM Study 2006 discontinued atropine treatment after children had received 1% atropine for two years. Children were followed for a further year. At the end of this period, the study compared myopia progression to the placebo-treated group. Progression of refractive error in the original 1% atropine-treated group was greater than the control group at the end of the second year (MD −0.76 D, 95% CI −0.90 to −0.62; Analysis 7.9). The study authors reported axial length data as change from baseline over the entire three-year duration of the study, and therefore, these data were not suitable for evaluating rebound.

In Ye 2022, one group (group A) used 1% atropine for six months followed by 0.01% atropine for a further six months. This was compared to a group using 0.01% atropine for one year (group B). The changes in refraction and axial length during the second six months in group A were greater than those in group B, with 72.5% of participants showing refraction rebound ≥ 0.50 D.

Zhu 2021 used a novel dosing regimen. Participants received 1% atropine eye drops once per month for 24 months, then every other month for 12 months, followed by no drops for 12 months. Progression at the end of the one-year withdrawal period was evaluated and compared to the placebo group. One year after terminating treatment, the atropine group still showed a slowing in the progression of refractive error (MD 0.34 D, 95% CI 0.26 to 0.42; Analysis 7.9), and a reduction of axial elongation (MD −0.21 mm, 95% CI −0.23 to −0.19; Analysis 7.10) compared to the placebo group.

Three studies investigated rebound with low atropine doses. Hieda 2021 and Zhu 2023b discontinued atropine treatment for one year after receiving 0.01% and 0.05% atropine consecutively. Both studies reported minimal rebound effects (<0.25 D and <0.05mm) during the withdrawal period, based on SER and AL compared to placebo (Analysis 7.9; Analysis 7.10).

The ATOM 2 Study 2012 was a dose-comparison study, with participants randomised to receive 0.5%, 0.1%, or 0.01% atropine for 24 months, followed by a 12-month withdrawal phase. During the wishdrawal period, myopic progression was greater in participants treated with 0.5% atropine (MD −0.87 D, 95% CI −0.96 to −0.78) compared to 0.1% (MD −0.68 D, 95% CI −0.76 to −0.61), and

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0.01% atropine (MD −0.28 D, 95% CI −0.36 to −0.20; P < 0.001). Axial elongation was also greater in the 0.5% group (MD 0.35 mm, 95% CI 0.32 to 0.38), compared to the 0.1% (MD 0.33 mm, 95% CI 0.30 to 0.36), and the 0.01% (MD 0.19 mm, 95% CI 0.16 to 0.22) groups.

Two studies investigated the rebound effect after cessation of RLRL therapy (Chen 2023; Jiang 2022). In Chen 2023, participants completing one year of RLRL therapy were monitored for a further three months without treatment. A slight rebound effect was observed during this period. Jiang 2022 conducted a one-year trial of RLRL therapy versus an untreated control group. Following completion of the trial, participants were recruited into a post-trial observational study, in which a subgroup of those originally allocated to RLRL therapy discontinued treatment for one year, and myopia progression was compared to a control subgroup. One year after terminating treatment, the RLRL group showed faster progression of refractive error (MD –0.40 D, 95% CI –0.58 to –0.22; Analysis 11.3) than the control group; and increased axial elongation (MD 0.14 mm, 95% CI 0.07 to 0.21; Analysis 11.4) compared to the control group.

Important outcomes

Risk of adverse events

The risk of adverse events was generally poorly reported. We extracted data on the frequency of adverse events from 40 studies (see Table 4; Table 5; Table 6; Table 7), comprising six studies that reported on the effects of spectacle interventions (Adler 2006; Bao 2022; COMET 2 Study 2011; CYPRESS Study 2023; Hasebe 2008; Sankaridurg 2010), 13 on contact lens interventions, including ortho-K (BLINK Study 2020; Chamberlain 2019; Cheng 2016; CLAMP Study 2004; Garcia-del Valle 2021; Guo 2021; Jakobsen 2022; Kinoshita 2020; Liu 2024; Lyu 2020; MASS Study 2018; Tan 2023; Xu 2023), 18 on topical antimuscarinic agents (ATOM 2 Study 2012; CHAMP 2023; Chia 2023; Cui 2021; Hansen 2023; Hieda 2021; Hu 2023; LAMP Study 2019; Lee 2022; PIR-205 Study 2004; Repka 2023; Shih 1999; Tan 2005; Wei 2020; Xu 2023; Yen 1989; Zhang 2024; Zhu 2021), and three on RLRL (Chen 2023; Jiang 2022; Zhou 2023). Multiple adverse events occurring in the same study participant, including events affecting both eyes, were counted as independent events.

Studies used a variety of methods to record adverse events. Symptoms were usually elicited using questionnaires, telephone interviews, or were self-reported at follow-up appointments by parents or children, or both. Objective clinical signs were usually based on clinical examination at each follow-up visit. However, in some studies, participants were advised to return to the clinic for unscheduled visits should adverse events arise.

Spectacle interventions

Data on adverse events were available from 609 participants wearing spectacle lens (undercorrection, MFSLs, PPSLs, and DOT lenses), and from 395 SVL-wearing controls. The study durations ran from one to three years. Spectacles intended for myopia control were usually well tolerated following a short adaptation period, and the reported adverse events were generally mild. There were 68 events in the active arms and 48 in the control arms. Dizziness and blurred vision were the most commonly reported adverse events (dizziness: active arm 13/609, controls 15/395; blurred vision: active arm 31/609, controls 19/395). See Table 4. Overall, there were three withdrawals due to adverse events in studies using MFSLs.

Contact lens interventions

Thirteen studies provided safety data on 1270 participants receiving contact lens interventions, which included various soft contact lens designs (including MFSCLs and SVSCLs), RGP, and ortho-K. Study durations ran from one to three years. The control arms in ortho-K studies typically wore SVLs. Two studies compared ortho-K monotherapy to combined ortho-K and low-dose atropine. Safety outcomes were monitored by clinical examination of the anterior segment of the eye using the slit lamp biomicroscope, at follow-up appointments. Many studies graded clinical signs using standard grading scales, which used either artist-rendered or photographic images to grade corneal and conjunctival signs on a 0 to 4 scale, from normal to severe. Grades 3 and 4 are considered to be clinically important, and usually require clinical action. For the most part, studies using MFSCLs and SVSCLSs reported adverse events separately for each arm. However, the largest study (294 children) reported safety data for all arms combined (BLINK Study 2020). The most commonly reported adverse events in studies involving soft contact lenses were corneal infiltrative events (17/664 wearers), conjunctival papillary reaction (20/664), and corneal staining (12/664). See Table 5. The number of events were similar for test and control lenses. These events were generally not serious, with only one clinically important (grade 3) event, and one participant in the BLINK Study 2020 who was reported as having a probable microbial keratitis. There were four reported adverse effect-related withdrawals in these studies (incidence: approximately 0.6%).

Adverse events in ortho-K studies (6 studies) were more common: corneal infiltrates (8/386 wearers), and corneal staining (39/386), with four cases of corneal fluorescein staining of grade 3 or higher. There were 12 withdrawals due to adverse events in these studies (incidence: approximately 5%).

Pharmacological interventions

Atropine

Safety data were available for 16 studies, which used various doses of topical atropine. The three most common adverse events were photophobia or glare, blurred vision (particularly for near vision), and hypersensitivity reactions. See Table 6. Atropine studies used high (≥ 0.5%; 564 children), moderate (0.1% to < 0.5%; 251 children), and low (< 0.1%; 2058 children) atropine doses, with study durations ranging from 12 to 48 months. Adverse events were generally dose-dependent, with a greater likelihood of adverse events with higher atropine doses (high-dose 437 events in 564 children; moderate-dose 50 events in 251 children; low-dose 383 events in 2058 children). There were more withdrawals due to adverse events in studies using high-dose atropine (7% over 1 year in the ATOM Study 2006, and 21% over 2 years in Zhu 2021), compared to 2% or fewer in studies using lower atropine doses.

Evaluating the rates of photophobia and difficulties with near vision was confounded by the use of photochromic spectacle lenses or sunglasses to mitigate photophobia, and multifocal lenses for near vision problems in some studies, which may have reduced reporting of symptoms.

Pirenzepine

Two studies (259 children in the active treatment arms) documented ocular and systemic adverse events. The three systemic adverse events most frequently reported were headache,

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common cold, and flu syndrome in the PIR-205 Study 2004, and increased cough, respiratory infection, and rhinitis in Tan 2005. The three ocular adverse events most frequently reported by both studies were symptoms of decreased accommodation, papillae/follicles, and medication residue on the eyelids or eyelashes. Forty-three children in the active treatment arms withdrew due to adverse events.

Repeated low intensity red light

Safety of RLRL therapy was evaluated on 194 treated children, recruited across three studies (Chen 2023; Jiang 2022; Zhou 2023). RLRL therapy was reported to be well tolerated, with no serious side effects (see Table 7). In Jiang 2022, two participants reported that the light was too bright. Zhou 2023 reported that 23/24 participants experienced transient visual disturbance following red light exposure. Optical coherence tomography data were available for 72 participants in Jiang 2022, and no structural damage to the retina was observed.

Quality of life

The LAMP Study 2019 reported on vision-related quality of life, using the Chinese version of the 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25). This validated quality-of-life instrument assesses 11 subscales: general health, general vision, ocular pain, near vision, distance vision, social function, mental health, role limitations, dependency, colour vision, and peripheral vision. Quality of life was evaluated in 438 participants who received one of three doses of atropine (0.05%, 0.02%, or 0.01%) or placebo. The study authors reported no difference between groups in vision-related quality of life, with similar scores across all 11 domains.

The BLINK Study 2020 used the Pediatric Refractive Error Profile 2 (PREP2) to measure vision-specific quality of life in 294 participants who received either SVSCL, or +1.50 D, or +2.50 D add MFSCLs. After two weeks of contact lens wear, scores for the PREP2 vision subscale differed by treatment assignment. Participants with the highest add power reported statistically worse visual functioning than single-vision contact lens wearers (P = 0.03). There was no important difference between MFSCL +1.50 D add and SVSCL, or between the +1.50 D and +2.50 D add powers. There were no important differences amongst treatment groups for the other PREP2 subscale scores.

Treatment adherence

Quantitative data on adherence to myopia control treatment were available in 25 studies, comprising 12 studies investigating spectacle interventions (Bao 2022; COMET 2 Study 2011; COMET Study 2003; CYPRESS Study 2023; Fulk 2002; Hasebe 2008; Koomson 2016; Lam 2020; Pärssinen 1989; STAMP Study 2012; Yang 2009; Yuval 2024), six studies evaluating contact lens interventions (Anstice 2011; BLINK Study 2020; Chamberlain 2019; DISC Study 2011; Fujikado 2014; Katz 2003), six using pharmacological interventions (ATOM 2 Study 2012; CHAMP 2023; Hieda 2021; LAMP Study 2019; PIR-205 Study 2004; Trier 2008), and one using repeated low intensity red light (RLRL) therapy (Jiang 2022). When adherence data were available at multiple time points, we reported the results at the longest time point (see Table 8; Table 9; Table 10).

Studies usually assessed adherence to optical interventions through an estimate by parents or children, or both, of wearing time per day of spectacles or contact lenses, and the number of days per week the optical appliances were worn (6 or 7 days per week was usually judged as being fully adherent). Studies used a variety of methods for data collection, including questionnaires or discussion of adherence at follow-up appointments. These data were available for 1731 participants wearing a variety of spectacle lenses (undercorrection, multifocal, peripheral plus, and single vision). The range of daily wearing times was between 13.1 hours and 15.5 hours per day. The percentage of participants who were judged to be adherent was similar between test and control lenses, although the COMET Study 2003 and Pärssinen 1989 reported that a lower proportion of participants wore MFSL than the SVL controls.

Adherence data were available for 873 participants in contact lens studies, including MFSCL, SVSCL, and RGP. Daily wearing times were between 6.3 hours and 13.7 hours per day, with no statistical differences between multifocal and single vision contact lenses. In Katz 2003, which investigated RGP lenses versus SVLs, the adherence at 24 months in the RGP group was 31.5% compared to 98.4% in the spectacle lens-wearing controls. Adherence was not formally assessed in ortho-K studies, but these studies were often associated with high dropout rates (over 50% in some studies).

For most pharmacological interventions, adherence was monitored by self-reported questionnaires. CHAMP 2023 monitored adherence through ampoule counting, and reported rates of adherence of 86.4% for 0.01% atropine, 88.3% for 0.02% atropine, and 87.1% for the placebo groups. Only the PIR-205 Study 2004 used electronic monitoring. Adherence was defined as using the study medication 75% to 80% of the time. Adherence in 919 participants taking low-dose atropine ranged from 83.3% to 98.8%, with similar levels of adherence between the active and placebo arms. Adherence in the intervention arm of PIR-205 Study 2004 was 79%, and 89% in Trier 2008, which was similar to participants taking the placebo.

Jiang 2022 reported on treatment adherence in the RLRL group. Treatment adherence was calculated based on data from an automated diary function, as a percentage of completed sessions divided by the total number of assigned treatment sessions (2 sessions per day, 5 days per week) during the entire treatment period. Median treatment adherence in the RLRL group was 75% (interquartile range 14.1% to 112.1%).

Equity assessment

We did not examine equity-related characteristics for this review.

DISCUSSION

Summary of main results

This review update included a further 40 studies published since the last version, published in February 2023 [120]. We summarised evidence from 104 studies, randomising a total of 17,509 participants with predominantly low to moderate myopia. Studies investigated optical, pharmacological, and light-based interventions to slow the progression of myopia in children. Participants were girls and boys, aged between 4 years and 18 years, with a median age of 10 years. Eighty-four studies compared one or more myopia control interventions relative to a control or placebo intervention. Five studies included a combined intervention arm compared to control, and 15 studies compared single or combined interventions to each other. Over 65% of studies were conducted

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in China or other Asian countries. Study durations ranged from 12 months to over 36 months: 41% of the studies had a 12-month duration, 43% reported up to 18 months to 24 months, 14% up to 36 months, and only one study measured outcomes over 36 months. We defined the critical outcome, progression of myopia, as both change in refractive error (as SER from baseline) and the more clinically meaningful change in axial length (AL). We judged most of the studies at high risk of bias or having some concerns. We based our comparisons on direct evidence from classical pairwise meta-analyses, because the network was not well-connected, and showed inconsistency between some direct and indirect comparisons (e.g. atropine doses), except for medium-dose atropine.

Myopia progression

At 12-month and 24-month follow-up, all interventions, except for undercorrection with SVLs, RGPs, and the adenosine antagonist 7-methylxanthine, may reduce the change in SER and slow axial elongation better than placebo. The certainty of the body of evidence ranged from very low to moderate, depending on the comparison (see Summary of findings 1; Summary of findings 2; Summary of findings 3; Summary of findings 4). Although there may be evidence of a difference, many of the efficacy estimates and their 95% confidence intervals (CIs) included benefits that were not clinically important. There is limited evidence on the continuing efficacy of myopia control treatment over time, with most of the reduction in progression occurring in the first year.

Overall, high-dose topical atropine (≥ 0.5 %) and ortho-K probably remain the most effective interventions to slow axial elongation at two-year follow-up (approximately 0.5 mm slowing of axial elongation with high dose atropine; 0.3 mm with ortho-K; moderate-certainty evidence). There is some evidence that the efficacy of ortho-K can be enhanced by concomitant use of low-dose topical atropine. The evidence suggests that MFSCLs are similar to low-dose topical atropine (< 0.1%), with a reduction in axial elongation of 0.15 mm with MFSCLs; low-certainty evidence, and 0.16 mm with atropine; moderate-certainty evidence. There is very low-certainty evidence for the effectiveness of PPSL in slowing axial elongation. However, some lens designs with peripheral lenslets showed two-year axial elongation of up to 0.32 mm.

This update included three trials in Chinese children of a new therapy that uses low intensity, long wavelength visible (red) light (RLRL). Although all studies showed reductions in myopia progression at one year, evidence is very uncertain (very low-certainty evidence).

The most commonly studied combination therapy was ortho-K plus low-dose topical atropine. Compared to ortho-K monotherapy, the combination may be associated with a reduction in axial elongation (moderate-certainty evidence).

Studies reporting on the effect of behavioural interventions on childhood myopia progression generally did not present incident myopia data on myopic participants separately from those for whom the intervention was evaluated. One school-based, cluster-trial conducted in China, in which children in the intervention group were encouraged to go outdoors during recess, reported a modest reduction in myopia progression in a myopic subgroup.

Change in refractive error and axial length following cessation of treatment (rebound)

Data on changes to SER and axial length following cessation of treatment (rebound) were available in 12 studies. There was no evidence of rebound in three studies that investigated optical interventions (MASS Study 2018; STAMP Study 2012; Zhu 2023a), and there was inconsistent evidence of the rebound effect for topical atropine. Rebound effects were more pronounced in studies that abruptly terminated higher atropine doses (ATOM 2 Study 2012; ATOM Study 2006; Ye 2022). One study reduced the frequency of 1% atropine instillation over time, and reported that slowing of myopia progression was maintained (Zhu 2021). Rebound was much less pronounced in studies reporting on the termination of low-dose atropine (ATOM 2 Study 2012; Hieda 2021; Zhu 2023b). Two studies reported on the rebound effect after cessation of RLRL therapy; the RLRL group showed more rapid progression of refractive error and increased axial elongation relative to the control group.

Adverse events

Based on limited evidence that was often poorly reported, spectacle interventions were well tolerated, with minimal and mild adverse events, similar to controls. In contact lens studies, the incidence of adverse events for multifocal soft contact lenses was also similar to the single vision soft contact lens controls. Adverse events in these studies generally consisted of expected contact lens-related adverse events that were generally not serious. However, the incidence and severity of corneal staining was higher in studies using ortho-K. The most commonly reported adverse events with topical antimuscarinic agents were photophobia, blurred near vision, and hypersensitivity reactions, which increased with increasing drug concentration. The risk profile of RLRL is based on limited short-term data. Reversible visual disturbance was the most commonly reported short-term adverse effect; longer-term data are currently lacking.

Quality of life

Only two studies provided information on the effect of the interventions on quality of life. In the LAMP Study 2019, three doses of topical atropine were compared to placebo, with no difference in vision-related quality of life observed between groups at 12 months. After two weeks of contact lens wear in the BLINK Study 2020, there was no difference in quality of life between the MFSCL and SVSCL groups, measured with the PREP2,

Treatment adherence

When reported, treatment adherence was generally high; levels of adherence were similar across study arms.

Brief economic commentary

To supplement the main systematic review, we sought to identify economic evaluations on interventions to slow myopia progression in children (see Supplementary material 9 for further details). We did not critically appraise these studies, and they may have used methods that are not consistent with accepted practice. We did not attempt to draw any firm or general conclusions regarding the relative costs or efficiency of myopia control intervention strategies in children. We identified three studies, all of which utilised economic decision models to carry out economic evaluations

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comparing different treatments for slowing myopic progression in children [122], [121], [123]. All three were cohort decision models, utilising a Markov approach, and a hypothetical cohort of children. Differences in the age of the cohorts were noted across studies, which comprised cohorts who were 10 years old [122], 11 years old [121], and at least 6 years old [123].

From these studies, Agyekum and colleagues carried out a cost-effectiveness analysis (CEA [122]), Hong and colleagues carried out a cost utility analysis (CUA [121], and Li and colleagues carried out both a CEA and a CUA [123]. Both Agyekum and colleagues and Hong and colleagues concluded that topical atropine was a potential cost-effective strategy in this population (although Agyekum and colleagues concluded that the 0.05% dose was more cost-effective than the 0.01% dose evaluated by Hong and colleagues). Agyekum and colleagues also concluded that outdoor activity and red-light therapy were potentially cost-effective strategies for myopia prevention in children, with outdoor activity being the most cost-effective. Li and colleagues compared three methods of myopia screening; children who tested positive were sent for treatment. The precise methods used to mitigate myopia were not fully explained. However, two of the strategies used traditional and digital myopia prevention and control strategies. These included education about increased outdoor activities as a form of health education. The traditional delivery method used posters and videos; the digital delivery method used text messages and web chat. Outcomes were expressed as quality-adjusted life years (QALYs), and disability-adjusted life years (DALYs), based on utility values and disability weights from the published literature. The method by which outcomes were calculated from their values in the literature was unclear. Li and colleagues concluded that a digital comprehensive myopia prevention and control strategy was the most cost-effective option compared with traditional school-based myopia control programs.

As we did not critically appraise these studies, and because the studies were conducted at different times and in different geographical locations, we did not attempt to draw any firm or general conclusions about the relative costs or efficiency of different myopia control strategies in children. Future research could include different evaluation approaches, both in terms of alternative modelling approaches, and by including trial-based evaluations to add to the evidence base of myopia prevention in children.

Limitations of the evidence included in the review

The certainty of the evidence for the critical outcome, progression of myopia, at one and two years ranged from very low to moderate, depending on the intervention. The main reasons for downgrading the certainty of evidence were the risk of bias (principally due to lack of reporting details), and unexplained heterogeneity or inconsistency in the results.

We were unable to conduct a quantitative analysis for other outcomes, and we summarised the results for these outcomes at the study level, in summary tables.

Several factors limit the applicability of the evidence in our review. Although we were able to include evidence from 104 randomised controlled trials (RCTs), approximately 85% of the studies followed participants for two years or less. A consensus report produced by the International Myopia Institute (IMI), which provides guiding principles for myopia control clinical study design, recommends three years as the minimum length to assess the efficacy of a treatment for myopia control (at least two years of treatment plus an additional year of no treatment to examine any rebound effect [46]). Therefore, extrapolating efficacy data for outcomes measured at one year is likely to overestimate the effectiveness of treatment.

A number of factors complicated the comparison of studies, including differences in the demographic characteristics of the participants, and variability in the parameters used within similar treatments (e.g. different add powers and lens designs for multifocal spectacles and soft contact lenses, and various doses of atropine). Although most of the studies adopted similar eligibility criteria, recruiting children aged 6 years to 13 years, some studies used a wider age range, including children up to 18 years. This is important, since faster progression occurs in younger myopes and progression slows in older teenagers. Studies were conducted with different ethnic groups, but predominantly, with children from South East Asian countries, who typically have faster progression of myopia [1, 10].

These factors may, at least in part, explain the considerable heterogeneity of treatment effects we identified in some comparisons. Therefore, we should be cautious in our interpretation of the pooled effect estimates. For this update, we were able to perform a predefined subgroup analysis of the effect of ethnicity (Asian versus non-Asian) on the efficacy of low-dose atropine. Although the treatment appeared to be less effective in studies that recruited predominantly non-Asian participants, it is possible that other differences between studies may explain the result, e.g. risk of bias.

It was difficult to compare the incidence of adverse events across studies, because different methods were used to classify and report them. The use of photochromic and multifocal spectacles in pharmacological studies to mitigate potential side effects of higher topical atropine doses (≥ 0.5%) may also have underestimated the true incidence of glare, photophobia, and reading difficulties reported in these studies. Similarly, the evaluation of treatment adherence between studies was complicated by the use of different methods to measure compliance (e.g. retrospective self-report by parents or children, questionnaires, or diaries). Lastly, the short time frame of many studies may have overestimated compliance, since it is possible that compliance may decrease over time.

Limitations of the review processes

We followed the *Cochrane Handbook for Systematic Reviews of Interventions* to conduct this systematic review [392]. We applied a broad search strategy to ensure that all relevant papers were included. Pairs of review authors independently extracted data and assessed the risk of bias; we also followed prespecified methods for classical and network meta-analyses. Therefore, we believe there should be no bias in the study selection process, or analysis of available data.

Whenever possible, we used random-effects pairwise meta-analyses to incorporate heterogeneity amongst studies. Since we were unable to carry out the majority of the planned subgroup and sensitivity analyses to explore heterogeneity, the presence of considerable unexplained heterogeneity for several comparisons reduces our confidence in effect estimates.

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We judged many of the RoB 2 assessments as presenting some concerns across the studies in our review, which often reflected inadequate reporting of information by the study authors, e.g. no information on allocation concealment, and lack of a prespecified analysis plan. Consequently, we may have overestimated the impact of bias on our findings by downgrading the certainty of evidence of the critical and important outcomes due to the risk of bias.

Agreements and disagreements with other studies or reviews

A previous Cochrane systematic review on myopia control interventions in children, reviewed evidence from 41 RCTs and concluded, similar to the current review, that there was moderate-certainty evidence that antimuscarinic drugs reduced myopia progression and axial elongation, with inconclusive evidence for other interventions [393]. By contrast, a network meta-analysis (NMA) of 16 interventions for myopia control in children conducted in 2016, concluded that "a range of interventions can significantly reduce myopia progression when compared with single vision spectacle lenses or placebo" [394]. More recently, a systematic review and NMA comparing the efficacy and safety of different concentrations of topical atropine for myopia control reported that 1%, 0.5%, and 0.05% atropine were the three most efficacious atropine concentrations [395].

Three systematic reviews and an ophthalmic technology assessment by the American Academy of Ophthalmology (AAO) considered safety outcomes of contact lens interventions for reducing myopia progression in children [396, 397, 398, 399]. With respect to daily disposable soft contact lenses, a review of retrospective data of adverse events from six RCTs estimated an incidence of 4.5 adverse events per 100 patient-years, and suggested that soft contact lenses can be safely worn by children [396]. Yu and colleagues analysed data from three studies, and found no difference in adverse events between MFSCLs and control single vision lenses [398]. A review of 45 studies, including RCTs (N = 17) and observational studies (N = 28) concluded that adults and children wearing ortho-Klenses were up to 3.79 times more likely to experience an adverse event compared with conventional contact lenses [399]. An AAO health technology assessment reviewed evidence on ortho-K treatment, and identified a sparsity of evidence in paediatric populations [397]; it noted that ortho-K carries a small but definite risk of sight-threatening keratitis. Bullimore and colleagues estimated the incidence of microbial keratitis associated with ortho-K as 13.9 per 10,000 patient-years (95% CI 1.7 to 50.4), which is similar to the overall incidence of microbial keratitis in overnight soft contact lens wear [400].

In their NMA of efficacy and safety of topical atropine for myopia control, Huang and colleagues considered the safety profiles of different atropine concentrations, based on changes in pupil size and accommodation [394]. The authors found that based on these proxies for photophobia and near vision difficulties, lower atropine concentrations had higher safety ranking probabilities. Two systematic reviews identified for this update, which included data from RCTs and cohort studies, investigated the safety of topical atropine [401, 402]. Both reviews found that the risk of adverse events was dose dependent, with photophobia and blurred near vision the most commonly reported adverse events. One systematic review reported a pooled incidence of photophobia for low-dose atropine of 1.7% (95% CI 0.6% to 3.4%); for medium-dose atropine of 26.6% (95% CI 6.7% to 53.6%); and for high-dose atropine of 65.9% (95% CI 51.0% to 79.4% [402]).

AUTHORS' CONCLUSIONS

Implications for practice

Based on the best available evidence, topical antimuscarinic agents and orthokeratology (ortho-K) currently appear to be the most effective treatments for slowing childhood myopia progression. There is some uncertainty as to the optimal dose of atropine, the most studied antimuscarinic agent. Although higher doses slow overall axial elongation by approximately 0.5 mm over two years, corresponding to an approximate 1.00 D reduction in myopia, higher concentrations are more likely to cause adverse events, and may increase the risk of rebound following cessation of treatment. The current review found limited evidence that rebound could be reduced by tapering the treatment prior to termination. Only one study examined the tapering of higher atropine doses, but that study used an unusual treatment regimen (monthly administration of 1% atropine for two years followed by bi-monthly administration of 1% atropine for one year, followed by one year of no treatment). The results of the study should not be used as evidence for or against tapering with lower concentrations of atropine typically used for myopia control.

There are logistical difficulties in assessing change in refractive error in ortho-K studies, and therefore, evidence of efficacy is based on slowing axial elongation. Ortho-K may also require more specialised knowledge by the eye-care practitioner, and therefore, it may not be as available as some of the other treatment modalities.

Evidence on the efficacy of other treatments for slowing myopia progression in children was limited by short study durations and considerable heterogeneity in treatment response. The finding that treatment efficacy reduces over time would add to the perception of greater efficacy in studies of short duration.

Uncertainty remains regarding the risk-benefit of ortho-K, other contact lens interventions, and repeated low level red light therapy in children. Across the included contact lens studies, adverse events were generally poorly described and lacked standardised reporting. Although none of the included studies reported serious adverse events, the duration of follow-up in trials may have been insufficient to capture long-term or rare adverse events.

Myopia control is a rapidly moving field that emphasises the need for a living systematic review in this area, which is underpinned by continual and active monitoring of new evidence.

Implications for research

There are a number of research priorities in this field. Epidemiological evidence has shown that the age of onset and rate of myopia progression in children vary considerably. There is a need to develop better predictive models to identify children who are most likely to progress rapidly, and will therefore, potentially derive most benefit from treatment. The absence of long-term data provides little evidence as to when myopia control interventions can be stopped or modified during treatment.

Children under six years of age, or those with high or pathological myopia, have generally been excluded from randomised controlled

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trials (RCTs). Therefore, it is unclear whether myopia control interventions are appropriate or effective in these groups.

Although topical atropine shows considerable promise as an intervention to slow the progression of myopia, the optimal dose that suitably balances efficacy, safety, and the tendency for rebound is yet to be established. There are many ongoing trials investigating the efficacy of various doses of atropine, used either as monotherapy or in combination with another intervention, which may provide further data to determine the optimal drug dose or most effective combination therapy for myopia control.

The various multifocal myopia control spectacle and contact lenses that have been tested in trials, incorporate different designs with variable relative amounts of peripheral plus power. This may be a contributing factor to the observed heterogeneity, and may potentially impact efficacy. Further research would provide an opportunity to optimise lens designs to improve efficacy.

This update included studies investigating repeated low intensity red light (RLRL) therapy as an intervention to control myopia in children. These studies provided initial evidence that RLRL may reduce myopia progression in Chinese children at one year of follow-up. However, further long-term studies in more diverse populations are needed to more clearly establish the efficacy and safety of this novel therapy.

The International Myopia Institute developed a consensus set of principles on study design to guide the development of myopia control trial protocols [46]. Many of the trials included in this review did not meet these recommendations, and researchers should be encouraged to adopt these principles to facilitate harmonised reporting of outcomes, including standardised reporting of adverse events. There was also a tendency for authors to report a relative percentage reduction in myopia progression to express treatment effect, which can be misleading.

To address uncertainty in the safety of myopia control interventions, particularly relating to rare and potentially sight-threatening adverse events, it may be necessary to seek evidence from non-randomised studies, since such events are unlikely to be seen in randomised controlled trials due to their small size and relatively short duration. Therefore, future systematic reviews considering safety could also consider evidence from non-randomised studies for a comprehensive evaluation of safety.

Only two of the included studies evaluated the impact of myopia control interventions on quality of life. Therefore, there is a need for further studies, using validated instruments, to measure vision-related and health-related quality of life as outcomes of myopia control studies. There are also a limited number of health economic studies to enable policy-makers and healthcare decision-makers to identify which interventions, policies, or services provide the best value for money.

SUPPLEMENTARY MATERIALS

Supplementary materials are available with the online version of this article: 10.1002/14651858.CD014758.pub2.

Supplementary material 1 Search strategies

Supplementary material 2 Characteristics of included studies

Supplementary material 3 Characteristics of excluded studies

Supplementary material 4 Characteristics of studies awaiting classification

Supplementary material 5 Characteristics of ongoing studies

Supplementary material 6 Risk of bias

Supplementary material 7 Analyses

Supplementary material 8 Data package

Supplementary material 9 Details of economic evaluations identified

ADDITIONAL INFORMATION

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Editorial and peer-reviewer contributions

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The following people conducted the editorial process for this article:
• Sign-off Editor (final editorial decision): Jennifer Evans, London School of Hygiene & Tropical Medicine;
• Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Liz Bickerdike, Cochrane Central Editorial Service;
• Editorial Assistant (conducted editorial policy checks, collated peer-reviewer comments, and supported editorial team): Leticia Rodrigues, Cochrane Central Editorial Service;
• Copy Editor (copy editing and production): Victoria Pennick, Cochrane Central Production Service;
• Peer-reviewers (provided comments and recommended an editorial decision): Nuala Livingstone, Cochrane Evidence Production and Methods Directorate (methods), Jo Platt, Central Editorial Information Specialist (search), and Nicola Logan, Aston University, Birmingham, UK (clinical).

Contributions of authors

JGL conceived the review and drafted the protocol; JGL, BH, RD, SN, PV, LED, and JW selected the studies for inclusion; JGL, BH, RD, SN, PV, LED, JW, and TL extracted data; JGL, RD, BH, and SN, assessed risk of bias; GV and JGL performed the data analysis; AK performed the economic evaluation; JGL drafted the manuscript. All review authors contributed to writing and revising the final report.

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Some authors involved in previous published versions of this review in 2023 are no longer included in the author byline: Rakhee Shah, Dongfeng Li, and Sonia Mavi. Some of the content retained in this review reflects their contributions.

Declarations of interest

JGL: received grant income from the National Institute for Health Research (NIHR) and the UK College of Optometrists for projects outside the submitted review. He is employed by his institution and is an Editor with Cochrane Eyes and Vision, but had no involvement in the editorial process.
BH: had a research grant to work on design optimisation of an orthokeratology lens by Cooper Vision (formerly known as No7 Contact Lenses) outside the submitted review
GV: was Co-ordinating Editor for Cochrane Eyes and Vision until March 2023, and had no involvement in the editorial process for this update. He has no other conflicts to declare.
SN: reports a grant from the National Eye Institute, National Institutes of Health, USA (payment to the institution); serves as a Cochrane Eyes and Vision methodologist but was not involved in the editorial process for this review.
RD: worked as myopia control practitioner at LV Prasad Eye Institute until May 2023. During this time, he prescribed/suggested different myopia control interventions to patients. No other conflicts to declare.
LED: in the past 36 months, received funding to undertake clinical studies on topics relevant to the ocular surface from the Australian Research Council, National Health and Medical Research Council, Alcon Laboratories, Azura Ophthalmics, Iolyx Therapeutics and Coopervision, which was unrelated to this work. Her institution received consultancy funding from Medmont International and Alcon Laboratories for work unrelated to the topic of this review. She received an honorarium from Optometry Australia (2020) to present a lecture on myopia management for a continuing professional development program. She has an unpaid position as an editor for the Cochrane Eyes and Vision Group, but was not involved in the editorial process for this review. She practices as an optometrist, providing patient care, at the University of Melbourne eye care clinic (Melbourne, Victoria, Australia) and Warringal Optometrists (Heidelberg, Victoria, Australia).
PV: received research funding from SEED Pvt Ltd and Nthalmic Pvt Ltd for testing lenses for myopia control. No data from this work was included in this review. Consultant Optometrist at L V Prasad Eye Institute, India.
AK: none known
TL: serves as the Principal Investigator on the National Eye Institute grant that supports the work of Cochrane Eyes and Vision US Project and is Sign-off Editor for Cochrane Eyes and Vision, but was not involved in the editorial process
JW: received research funding related to myopia and/or myopia progression (Principal Investigator on a National Eye Institute-supported grant examining the myopia control effect of soft multifocal contact lenses). He is also a non-compensated member of the Medical Advisory Board for Myoptechs, a medical device company developing a myopia control contact lens. JW was not involved in making eligibility decisions about, extracting data from, or carrying out risk of bias assessment for any included studies in which he had direct involvement.

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Registration and protocol

Protocol (2021) doi: 10.1002/14651858.CD014758 [53]
Previous version of the living systematic review (2023) doi: 10.1002/14651858.CD014758.pub2 [120]

Data, code and other materials

As part of the published Cochrane review, the following are made available for download for users of the Cochrane Library (Supplementary material 8): full search strategies for each database (Supplementary material 1); full citations of each unique report for all studies included (Supplementary material 2); excluded at the full-text screening (Supplementary material 3); awaiting classification (Supplementary material 4); or ongoing (Supplementary material 5) in the final review; study data, including study information, study arms, and study results; consensus risk of bias assessments (Supplementary material 6); and analysis data, including overall estimates and settings, subgroup estimates, and individual data rows (Supplementary material 7). Appropriate permissions have been obtained for such use. Template data extraction forms from Covidence are available from the authors by reasonable request.

What's new

Date	Event	Description
13 February 2025	New citation required but conclusions have not changed	New citation required but conclusions have not changed.

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Date	Event	Description
13 February 2025	New search has been performed	This is a living systematic review. Searches are run and screened yearly. Last search date 19 February 2024. Results of all 40 newly identified studies have been incorporated. Therefore, the conclusions of this Cochrane review are considered up-to-date.

History

Protocol first published: Issue 4, 2021
Review first published: Issue 2, 2023

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ADDITIONAL TABLES

Table 1. Overview of synthesis and included studies table (OSIS)

Study	design	Population	Intervention	Comparison	Outcomes	Method of synthesis
Adler 2006	Parallel group RCT	Children aged 6 to 15 years, myopia range: 0.50 to 6.00 D, astigmatism ≤ 1.50 D	Undercorrection SVL	Full correction SVL	SER (6 m,12 m), AE	MA NMA

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Table 1. Overview of synthesis and included studies table (OSIS) *(Continued)*

Anstice 2011	Paired-eye cross-over RCT	Children aged 11 to 14 years, myopia range 1.25 to 4.50 D, astigmatism < 1.25 D, myopia progression ≥ 0.50 D in the previous year	MFSCL	SVSCL	SER, AL (10 m), adherence	MA NMA
Agarwal 2023	Parallel group RCT	Children aged 6 to 16 years, myopia range 1.00 D to −7.00 D in both eyes, astigmatism ≤ 1.50 D, progression ≥ 0.50 D in the preceding year	0.01% atropine	Placebo	SER, AL (12 m)	Summary
ATOM Study 2006	Parallel group RCT	Children aged 6 to 12 years, myopia range 1.00 to 6.00 D, astigmatism ≤ 1.50D	1% atropine	Placebo	SER, AL (12 m, 24 m), rebound	MA NMA
ATOM 2 Study 2012	Parallel group RCT	Children aged 6 to 12 years, myopia ≥ 2.00 D in both eyes, astigmatism < 1.5 D, myopic progression ≥ 0.5 D in the past year	0.5%, 0.1%, or 0.01% atropine	Head-to-head dose comparison	SER, AL (12 m, 24 m) AE, adherence, rebound	NMA
Bao 2022	Parallel group RCT	Children aged 8 to 13 years, myopia range 0.75 D to 4.75 D, astigmatism ≤ 1.50 D	PPSL (HAL or SAL)	SVL	SER, AL (12 m, 24 m), AE, adherence	MA NMA
Bian 2020	Parallel group RCT	Children aged 8 to 14 years, myopia range 0.75 D to 5.00 D, ≤ 1.50 D astigmatism	Ortho-K	SVL	AL (12 m)	MA NMA
BLINK Study 2020	Parallel group RCT	Boys and girls with myopia aged 7 to 11 years, myopia range 0.75 to 5.00 D, astigmatism < 1.00 D	MFSCL (medium or high add)	SVSCL	SER, AL (12 m, 24 m, 36 m), AE, adherence	MA NMA
Chamberlain 2019	Parallel group RCT	Children aged 8 to 12 years, myopia range 0.75 to 4.00 D, astigmatism < 1.00 D	MFSCL	SVSCL	SER, AL (12 m, 24 m, 36 m), AE, adherence	MA NMA
CHAMP 2023	Parallel group RCT	Children aged 3 to 17 years, myopia range 0.50 to 6.00 D, astigmatism ≤ 1.50 D	0.01% or 0.02% atropine	Placebo	SER, AL (12 m, 24 m, 36 m) AE, adherence	MA NMA
Chan 2022	Parallel group RCT	Children aged 7 to 10 years, myopia range 0.50 to 5.00 D, astigmatism < 1.00 D	0.01% atropine	Placebo	SER, AL (12 m)	MA
Charm 2013	Parallel group RCT	Children with myopia aged 8 to 11 years, myopia ≥ 5.00 D, astigmatism ≤ 1.25 D	Ortho-K	SVL	AL, SER (24 m)	MA NMA
Chen 2022	Parallel group RCT	Children aged 7 to 15 years, myopia ≤ 1.00 D, astigmatism ≤ 2.50 D	RLRL	0.01% atropine	SER, AL (12 m), AE	NMA
Chen 2023	Parallel group RCT	Children aged 6 to 13 years, myopia range 0.75 to 6.00 D, astigmatism ≤ 1.50 D	RLRL	SVL	SER, AL (12 m), AE (rebound)	MA NMA

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Table 1. Overview of synthesis and included studies table (OSIS) *(Continued)*

Cheng 2010	Parallel group RCT	Children aged 8 to 13 years, myopia range 1.00 to 5.50 D, myopia progression ≥ 0.50 in the previous year	MFSL	SVL	SER, AL (12 m, 24 m)	MA NMA
Cheng 2016	Parallel group RCT	Children aged 8 to 11 years, myopia range 0.75 to 4.00 D, astigmatism ≤ 1.00 D	SA-SCL	SVSCL	SER, AL (12 m, 24 m), AE	Summary
Chia 2023	Parallel group RCT	Children aged 6 to 11 years, myopia range 1.00 to 6.00 D in both eyes, myopia progression ≥ 0.5 D in the preceding year, astigmatism ≤ 1.50 D	0.0025%, 0.005%, or 0.01% atropine	Placebo	SER, AL (12 m), AE	MA NMA
Choi 2023	Parallel group RCT	Children aged 8 to 12 years, myopia range 1.00 to 4.00 D in both eyes, astigmatic error half of the spherical error	Ortho-K	SVL	AL (12 m, 24 m)	MA NMA
Chung 2002	Parallel group RCT	Children aged 9 to 14 years, myopia ≥ 0.50 D, astigmatism ≤ 2.00 D	Undercorrection SVL	Full correction SVL	SER, AL (12 m, 24 m)	MA NMA
CLAMP Study 2004	Parallel group RCT	Children aged 8 to 12 years, myopia range 0.75 to 4.00 D, astigmatism ≤ 1.50 D	RGP	SVSCL	SER, AL (12 m, 24 m, 36 m), AE	MA NMA
COMET Study 2003	Parallel group RCT	Children aged 6 to 11 years, myopia range 1.25 to 4.50 D, astigmatism ≤ 1.50 D	MFSL	SVL	SER, AL (12 m, 24 m, 36 m), adherence	MA NMA
COMET 2 Study 2011	Parallel group RCT	Children with myopia aged 8 to 12 years, myopia range 0.50 D to 3.00 D with associated near esophoria, astigmatism ≤ 1.50 D	MFSL	SVL	SER (12 m, 24 m, 36 m), AE, adherence	MA NMA
CONTROL Study 2016	Parallel group RCT	Children aged 8 to 18 years, myopia range 0.50 to 6.00 D with associated near esophoria, myopia progression ≥ 0.50 D since last exam, astigmatism ≤ 1.00 D	MFSCL	SVSCL	SER, AL (12 m)	MA NMA
Cui 2021	Parallel group RCT	Children aged 6 to 14 years, myopia range 1.25 to 6.00 D, astigmatism < 2.00 D,	0.01% or 0.02% atropine	Head-to-head dose comparison	SER, AL (12 m, 24 m), AE	Summary
CYPRESS Study 2023	Parallel group RCT	Children aged 6 to 10 years, myopia range 0.75 to 4.50 D, astigmatism ≤ 1.25 D	Diffusion optics technology (DOT) spectacle lenses (2 designs)	SVL	SER, AL (12 m), AE, adherence	Summary
DISC Study 2011	Parallel group RCT	Children aged 8 to 13 years, myopia range 1.00 to 5.00 D, astigmatism ≤ 1.00 D	MFSCL	SVSCL	SER, AL (12 m, 24 m), adherence	MA NMA
Edwards 2002	Parallel group RCT	Children aged 7 to 10.5 years, myopia range 1.25 to 4.50 D, astigmatism ≤ 1.50 D	MFSL	SVL	SER, AL (12 m, 24 m), AE	MA NMA

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Table 1. Overview of synthesis and included studies table (OSIS) *(Continued)*

Fang 2022	Parallel group RCT	Children aged 7 to 15 years, myopia range 1.00 to 8.00 D, astigmatism ≤ 1.00 D	MFSCL Ortho-K	SVL	SER, AL (12 m)	MA NMA
Fujikado 2014	Randomised cross-over trial	Children aged 6 to 16 years, myopia range 0.75 to 3.50 D, astigmatism ≤ 1.00 D	MFSCL	SVSCL	AL, SER (12 m), adherence	NMA
Fulk 1996	Parallel group RCT	Children aged 6 to 14 years, myopia ≥ 0.50 D and associated near esophoria, astigmatism ≤ 2.00 D	MFSL	SVL	SER, AL (12 m)	Summary
Fulk 2002	Parallel group RCT	Children aged 6 to 12 years, myopia at ≥ 0.50D and associated esophoria at near, astigmatism ≤ 2.00 D	MFSL	SVL	SER (12 m, 24 m), adherence	MA NMA
Garcia-del Valle 2021	Parallel group RCT	Children aged 7 to 15 years, myopia range 0.50 to 8.75 D	MFSCL	SVSCL	SER, AL (12 m), AE	MA NMA
Guo 2021	Parallel group RCT	Children aged 6 to 11 years, myopia range 0.75 to 4.00 D, astigmatism ≤ 2.50 (with the rule)	Ortho-K (6 mm BOZD)	Ortho-K (5 mm BOZR)	AL, SER (12 m), AE	Summary
Han 2018	Parallel group RCT	Children with undefined myopia aged 9 to 14 years	Ortho-K PPSL	SVSCL	SER (12 m)	MA
Han 2019	Parallel group RCT	Children aged 6 to 12 years, myopia range 0.25 to 6.00 D	1% atropine or 0.5% racanisodamine + 1% atropine	Placebo	SER, AL (12 m, 24 m)	Summary
Hansen 2023	Parallel group RCT	Children aged 6 to 12 years; myopia in at least one eye of ≥ 1 D if aged ≥ 6 to < 9 years, or ≥ 2 D if aged ≥ 9 to ≤ 12 years; astigmatism of < 1.5 D	0.01% atropine, or 0.1% atropine loading, then 0.01% atropine	Placebo	SER, AL (12 m), AE	MA NMA
Hasebe 2008	Randomised cross-over trial	Children aged 6 to 12 years, myopia range 1.25 to 6.00 D, astigmatism ≤ 1.50 D	MFSL	SVL	SER (18 m), AE, adherence	Summary
Hasebe 2014	Parallel group RCT	Children aged 6 to 12 years, myopia range 0.50 to 4.50 D, astigmatism ≤ 1.50 D	PPSL	SVL	SER, AL (24 m)	MA NMA
Hieda 2021	Parallel group RCT	Children aged 6 to 12 years, myopia range 1.00 to 6.00 D, astigmatism ≤ 1.50 D	0.01% atropine	Placebo	SER, AL (12 m, 24 m), AE, adherence	MA NMA

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Table 1. Overview of synthesis and included studies table (OSIS) *(Continued)*

Houston Study 1987	Parallel group RCT	Children aged 6 to 15 years, myopia ≥ 0.25 D, astigmatism < 2.00 D	MFSL	SVL	SER, AL (12 m, 24 m, 36 m)	Summary
Hu 2023	Parallel group RCT	Children aged 6 to 13 years; myopia range 0.50 to 6.00 D, astigmatism ≤ 2.00 D	0.01% atropine	Placebo	SER, AL (12 m), AE	MA NMA
Jakobsen 2022	Parallel group RCT	Children aged 6 to 12 years, myopia range 0.50 to 4.75 D, astigmatism ≤ 2.50 D	Ortho-K	SVL	AL (12 m), AE	MA NMA
Jensen 1991	Parallel group RCT	Children with myopia in 2nd to 5th grade, myopia range 1.25 to 6.00 D	MFSL (+ 1.00 or + 2.00 D add) Timolol	SVL	SER (12 m, 24 m)	MA NMA
Jiang 2022	Parallel group RCT	Children aged 8 to 13 years, myopia range 1.00 to 5.00 D, astigmatism ≤ 2.50 D	RLRL	SVL	SER, AL (12 m), AE, adherence, rebound	MA NMA
Katz 2003	Parallel group RCT	Children aged 6 to 12 years, myopia range 1.00 to 4.00 D, astigmatism ≤ 2.00 D	RGP	SVL	SER, AL (12 m, 24 m), adherence	MA NMA
Kinoshita 2020	Parallel group RCT	Children aged 8 to 12 years, myopia range 1.00 to 6.00 D, astigmatism ≤ 1.50 D	Ortho-K + 0.01% atropine	Ortho-K	AL (12 m, 24 m), AE	MA NMA
Koomson 2016	Parallel group RCT	Children aged 10 to 15 years, myopia range 1.25 to 4.50 D, astigmatism ≤ 1.25 D	Undercorrection SVL	Full correction SVL	SER, AL (24 m), adherence	MA NMA
Lam 2020	Parallel group RCT	Children aged 8 to 13 years, myopia range 1.00 to 5.00 D, astigmatism ≤ 1.50 D	PPSL	SVL	SER, AL (12 m, 24 m), adherence	MA NMA
LAMP Study 2019	Parallel group RCT	Children aged 4 to 12 years, myopia ≥ 1.00 D, astigmatism < 2.50 D, documented myopic progression ≥ 0.5 D in the past year	Atropine 0.01%, 0.025%, or 0.05%	Placebo	SER, AL (12 m), AE adherence	MA NMA
Lau 2023	Parallel group RCT	Children aged 6 to 12 years, myopia range 0.50 to 4.00 D in both eyes; astigmatism: < 1.50 D or ≤ 1.25 D for with-the-rule astigmatism (axes 180 ± 30); ≤ 0.50 D for astigmatism of other axes in both eyes	Ortho-K (increased compression factor)	Ortho-K (conventional compression factor)	AL (12 m, 24 m)	Summary
Lee 2022 (WA-ATOM)	Parallel group RCT	Children aged 6 to 16 years, myopia ≥ 1.50 D, astigmatism ≤ 1.50 D, myopia progression ≥ 0.50 D in the last year	0.01% atropine	Placebo	SER, AL (12 m, 24 m) AE	MA NMA
Lin 2024	Parallel group RCT	Children aged 8 to 14 years, myopia range 0.75 to 5.00 D, astigmatism < 1.50 D	Ortho-K	SVL	AL (12 m)	MA NMA

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Table 1. Overview of synthesis and included studies table (OSIS) *(Continued)*

Liu 2023a	Parallel group RCT	Children aged 8 to 12 years, myopia range 1.00 to 4.00 D, astigmatism < 1.50 D	Cyclindrical annular refractive element (CARE) spectacle lenses	SVL	SER, AL (12 m)	Summary
Liu 2023b	Parallel group RCT	Children aged 8 to 12 years, myopia range 0.75 to 4.00 D, astigmatism ≤ 1.00 D	Ortho-K (aspheric base curve)	Ortho-K (spherical base curve)	AL (12 m)	Summary
Liu 2023c	Paired eye RCT	Children aged 6 to 12 years, myopia range 3.00 to 6.00 D, astigmatism < 2.00 D	Different administrated frequencies of LDA (0.01% every day vs every other day)	0.01% atropine once per day	SER, AL (12 m), AE	Summary
Liu 2024	Paired eye RCT	Children aged 6 to 15 years, myopia range 1.00 to 10.00 D, astigmatism ≤ 1.50 D	MFSCL	SVSCL	SER, AL (12 m), AE	MA NMA
Lu 2015	Parallel group RCT	Children aged 9 to 14 years, myopia range1.00 to 5.00 D, astigmatism < 1.50 D with the rule, myopia progression ≥ 0.50 D per year	PPSL	SVL	SER, AL (12 m)	MA
Lyu 2020	Parallel group RCT	Children aged 8 to 12 years, myopia range 6.00 to 8.75 D, astigmatism < 1.50 D	Ortho-K (target myopia reduction 4.00 D or 6.00 D)	SVL	AL (12 m), AE	MA
MASS Study 2018	Parallel group RCT	Children aged 8 to 12 years, myopia range 0.75 to 4.00 D, astigmatism < 1.00 D	MFSCL	SVL	SER, AL (12 m, 24 m), AE, rebound	MA NMA
MIT Study 2001	Parallel group RCT	Children aged 6 to 13 years, with undefined range of myopia (average 3.27 D)	MFSL, MFSL + 0.5% atropine	SVL	SER (12 m)	MA NMA
Mori 2021	Parallel group RCT	Children aged 6 to 12 years, myopia range 1.50 to 4.50 D, astigmatism ≤ 1.50 D	Violet emitting spectacle lenses	SVL	SER, AL (12 m, 24 m)	Summary
Moriche-Carretero 2021	Parallel group RCT	Children aged 5 to 11 years, myopia range 0.50 to 4.50 D, astigmatism ≤ 1.50 D	0.01% atropine	SVL	SER, AL (24 m, 48 m)	MA NMA
MOSAIC Study 2024	Parallel group RCT	Children aged 6 to 16 years, myopia ≥ 0.50 D, astigmatism < 2.50 D	0.01% atropine	Placebo	SER, AL (12 m, 24 m)	MA NMA

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Table 1. Overview of synthesis and included studies table (OSIS) *(Continued)*

Pärssinen 1989	Parallel group RCT	Children with myopia in 3rd to 5th grade (aged 9 to 13 years), myopia range 0.25 D to 3.00 D, astigmatism ≤ 2.00 D	MFSL	SVL	SER (12 m, 24 m, 36 m), adherence	MA NMA
Peng 2023	Parallel group RCT	Children aged 7 to 12 years, myopia range 1.00 to 5.00 D, astigmatism ≤ 1.00 D	MFSCL	SVSCL	SER, AL (12 m)	MA NMA
PIR-205 Study 2004	Parallel group RCT	Children aged 8 to 12 years, myopia range 0.75 to 4.00 D, astigmatism ≤ 1.00 D	2% Pirenzipine gel	Placebo	SER, AL (12 m, 24 m), AE, adherence	MA
Raffa 2022	Parallel group RCT	Children aged 13 to 15 years, myopia range 2.00 to 6.00 D, astigmatism ≤ 1.00 D	MFSCL (low or medium add)	SVSCL	SER, AL (12 m)	MA NMA
Ren 2017	Parallel group RCT	Children aged 8 to 15 years, with myopia (mean 3. 28 D (SD 1.78 D)), astigmatism ≤ 1.75 D	Ortho-K 0.01% atropine	SVL	SER, AL (12 m)	MA NMA
Repka 2023	Parallel group RCT	Children aged 5 to 12 years, myopia range 1.00 to 6.00 D, astigmatism ≤ 1.50D	0.01% atropine	Placebo	SER, AL (24 m), AE, rebound	MA NMA
ROMIO Study 2012	Parallel group RCT	Children aged 6 to 10 years, myopia range 0.50 to 4.00 D, astigmatism ≤ 1.25 D	Ortho-K	SVL	AL (12 m, 24 m)	MA NMA
Sankaridurg 2010	Parallel group RCT	Children aged 6 to 16, myopia range 0.75 to 3.50 D, astigmatism ≤ 1.50 D	PPSL	SVL	SER, AL (12 m), AE	MA NMA
Sankaridurg 2019	Parallel group RCT	Children aged 8 to 13 years, myopia range 0.75 to 3.50 D, astigmatism ≤ 0.75 D	MFSCL EDOF	SVSCL	SER, AL (12 m, 24 m)	MA NMA
Schwartz 1981	Parallel group RCT	Monozygous twins, with undefined myopia aged 7 to 14 years, astigmatism ≤ 1.00 D	MFSL + tropicamide	SVL + placebo	SER (12 m, 24 m, 36 m)	Summary
Sen 2022	Parallel group RCT	Children aged 5 to 15 years, myopia > 2.00 D	0.01% atropine	Placebo	SER, AL (24 m)	MA NMA
Sharma 2022	Parallel group RCT	Children aged 5 to 12 years, myopia range 0.50 to 10.00 D, astigmatism < 1.50 D	0.01% atropine	Placebo	SER, AL (12 m)	MA NMA
Shen 2022	Paired-eye RCT	Children aged 9 to 14 years, myopia 1.00 to 8.00 D, astigmatism ≤ 1.75 D	EDOF	SVSCL	SER, AL (12 m)	Summary
Shih 1999	Parallel group RCT	Children aged 6 to 13 years, myopia range 0.50 to 6.75 D, astigmatism < 2.00 D	MFSL + 0.5% atropine 0.5% atropine	1% tropicamide	SER (12 m, 24 m), AE	NMA

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Table 1. Overview of synthesis and included studies table (OSIS) *(Continued)*

			0.25% atropine 0.1% atropine			
STAMP Study 2012	Parallel group RCT	Children aged 6 to 11 years, myopia ≥ 0.75 D but not more than 4.50 D in each meridian, near esophoria, astigmatism ≤ 2.00 D	MFSL	SVL	SER, AL (12 m, 24 m), adherence, rebound	MA NMA
Swarbrick 2015	Paired-eye cross-over trial	Children aged 8 to 16 years, myopia range 1.00 to 4.00 D, documented myopic progression in past year, astigmatism < 1.50 D	Ortho K	RGP	SER, AL (12 m)	Summary
Tan 2005	Parallel group RCT	Children aged 6 to 13 years, myopia range 0.75 to 4.00 D, astigmatism ≤ 1.00 D	2% Pirenzipine gel	Placebo	SER, AL (12 m), AE	MA
Tan 2023	Parallel group RCT	Children aged 6 to 11 years, myopia range 1.00 to 4.00 D, astigmatism ≤ 2.50 D	Ortho-K + 0.01% atropine	Ortho-K	AL, SER (12 m, 24 m), AE	MA NMA
Tang 2021	Parallel group RCT	Children with myopia range 1.00 to 6.00 D, astigmatism ≤ 1.00 D	Ortho K	SVL	AL (12 m)	MA NMA
Tang 2022	Parallel group RCT	Children aged 8 to 15 years, myopia range 1.00 to 5.00 D	Ortho-K (6 mm BOZR)	Ortho-K (5 mm BOZR).	AL, SER (12 m)	Summary
Tang 2023	Parallel group RCT	Children aged 8 to 16 years, myopia range 1.00 to 5.00 D; astigmatism ≤ 1.50 D	Ortho-K (increased compression factor)	Ortho-K (conventional compression factor)	AL (12 m, 24 m)	Summary
Trier 2008	Parallel group RCT	Children aged 8 to 13 years, ≥ 0.75 D, average axial length growth 0.075 to 0.39 mm over a 6-month period	7-methylxanthine	SVL	SER, AL (12 m), adherence	MA
Wang 2017	Parallel group RCT	Children aged 5 to 10 years, myopia range 0.50 to 2.00 D	0.5% atropine	Placebo	SER, AL (12 m)	Summary
Wei 2020	Randomised cross-over trial	Children aged 6 to 12 years, myopia range 1.00 to 6.00 D, astigmatism ≤ 1.50 D	0.01% atropine	Placebo	SER, AL (12 m), AE	MA NMA
Wu 2018	Cluster-RCT	Grade 1 schoolchildren in 16 schools (aged 6 to 7 years)	Outdoor light (recess outside classroom)	Control (no intervention)	SER, AL (12 m)	Summary
Xia 2023	Parallel group RCT	Children aged 6 to 16 years with binocular myopia	0.01% atropine	SVL	SER, AL (12 m)	MA
Xu 2023	Parallel group RCT	Children aged 8 to 12 years, myopia range 1.00 to 6.00 D, astigmatism ≤ 1.50 D	0.01% atropine,	SVL + placebo	AL (12 m, 24 m) AE	MA NMA

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Table 1. Overview of synthesis and included studies table (OSIS) *(Continued)*

			Ortho-K + placebo, Ortho-K + 0.01% atropine			
Yang 2009	Parallel group RCT	Children aged 7 to 13 years, myopia range 0.50 to 3.00 D, astigmatism ≤ 1.50 D	MFSL	SVL	SER (24 m), adherence	MA NMA
Ye 2022	Parallel group RCT	Children aged 6 to 12 years, myopia ≥ 0.50 D, astigmatism < 2.00 D	Consecutive 1% atropine (6/12) + 0.01% atropine (6/12)	0.01% atropine	SER, AL (12 m), rebound	Summary
Yen 1989	Parallel group RCT	Children aged 6 to 14 years, myopia range 0.50 to 4.00 D, astigmatism ≤ 1.00 D	1% atropine + MFSL, 1% cyclopentolate	Placebo	SER, (12 m), AE	Summary
Yi 2015	Parallel group RCT	Children with myopia between 0.50 and 2.00 D, astigmatism < 1.00D	1% atropine	Placebo	SER, AL (12 m)	MA NMA
Yu 2022	Parallel group RCT	Children aged 8 to 12 years, myopia range 1.00 to 4.00 D, astigmatism < 1.50 D	Ortho K + 0.01% atropine	Ortho K	AL (12 m)	MA NMA
Yuval 2024	Parallel group RCT	Children aged 6 to 13 years, myopia range 0.50 to 6.25 D, astigmatism ≤ 1.50 D	PPSL	SVL	SER, AL (12 m) adherence	MA NMA
Zhang 2023	Parallel group RCT	Children aged 8 to 14 years, myopia range 0.75 to 5.00 D, anisometropia ≥ 1.00D, astigmatism ≤ 1.50 D	Ortho-K	SVL	AL (12 m)	MA NMA
Zhang 2024	Parallel group RCT	Children aged 6 to 12 years, myopia range 1.00 to 6.00 D, astigmatism ≤ 1.50 D	0.05% atropine	Placebo	SER, AL (12 m, 24 m), AE	MA NMA
Zhao 2021	Parallel group RCT	Children with myopia ≥ 1.00 D, myopia range 1.00 to 6.00 D, astigmatism ≤ 1.00 D	0.01% atropine Ortho-K, Ortho-K + 0.01% atropine	SVL	AL (12 m)	MA
Zhou 2023	Parallel group RCT	Children aged 3 to 16 years, myopia range 0.50 to 8.00 D, astigmatism ≤ 2.50 D	RLRL	SVL	SER, AL (12 m), AE	MA NMA

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Table 1. Overview of synthesis and included studies table (OSIS) *(Continued)*

Zhu 2021	Parallel group RCT	Children aged 6 to 12 years with myopia range 2.00 D to 8.00 D, astigmatism ≤ 1.00 D, myopia progression rate > 1.00 D in the last year	1% atropine	Placebo	SER, AL (12 m, 24 m) AE, rebound	MA
Zhu 2022	Parallel group RCT	Children aged 7 to 14 years with myopia range 0.75 to 4.00 D, astigmatism ≤ 1.50 D, esophoria at near ≥ 2 prism dioptres	MFSL	SVL	SER, AL (24 m)	MA NMA
Zhu 2023a	Parallel group RCT	Children aged 8 to 12 years, myopia range 1.00 to 5.00 D, astigmatism < 1.50 D	Ortho-K	SVL	AL (12 m), rebound	MA NMA
Zhu 2023b	Parallel group RCT	Children aged 7 to 12 years, myopia range 1.00 to 6.00 D, myopia progression ≥ 0.75 per year	0.05% atropine	Placebo	SER, AL (12 m, 24 m, 36 m to assess rebound), AE	MA NMA

Overview of synthesis and included studies table
SER: spherical equivalent refraction; **AL:** axial length; **AE:** adverse events; **SVL:** single vision spectacle lenses; **MFSL**: multifocal spectacle lenses; **PPSL**: peripheral plus spectacle lenses: **HAL:** highly aspheric lenslets; **SAL:** slightly aspheric lenslets; **SVSCL:** single vision soft contact lenses; **MFSCL**: multifocal soft contact lenses; **EDOF:** extended depth of focus soft contact lenses; **SA-SCL:** spherical abberation soft contact lenses; **ORTHO-K**: orthokeratology; **RGP**: rigid gas-permeable contact lenses; **RLRL:** repeated low intensity red light;

Table 2. Number of trial arms and participants for each intervention and outcome in all NMAs

	Outcome			
	Spherical equivalent at 1 year	**Spherical equivalent at 2 years**	**Axial length at 1 year**	**Axial length at 2 years**
	Number of treatment arms (participants)	Number of treatment arms (participants)	Number of treatment arms (participants)	Number of treatment arms (participants)
Treatment arm				
Control	46 (2900)	30 (2615)	52 (3271)	30 (2515)
High-dose atropine	3 (411)	3 (346)	3 (411)	2 (305)
Moderate-dose atropine	1 (155)	2 (237)	1 (155)	1 (141)
Low-dose atropine	16 (1744)	10 (1375)	17 (1786)	11 (1417)
Repeated low intensity red light	4 (213)	-	4 (213)	-
Orthokeratology	-	-	15	7

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Table 2. Number of trial arms and participants for each intervention and outcome in all NMAs *(Continued)*

			(699)	(242)
Orthokeratology plus low dose atropine	-	-	5 (161)	3 (114)
Multiifocal soft contact lenses	13 (834)	5 (540)	13 (834)	5 (540)
Peripheral plus spectacle lenses	4 (396)	3 (295)	4 (396)	3 (296)
Rigid gas-permeable contact lenses	2 (178)	2 (154)	2 (176)	2 (154)
Multifocal spectacle lenses	5 (258)	8 (666)	4 (210)	4 (448)
Undercorrected single vision spectacles	2 (72)	2 (122)	1 (47)	2 (122)

Table 3. SUCRAs in all NMAs

Intervention	**SER 1 year**	**SER 2 years**	**AL 1 year**	**AL 2 years**
Repeated low intensity red light	**93.8**	-	**98.6**	-
High-dose atropine	**93.3**	**97.0**	**88.4**	**86.8**
Moderate-dose atropine	**75.5**	**69.8**	75.8	**80.5**
Low-dose atropine	53.2	61.0	36.1	46.2
Peripheral plus spectacle lenses	50.2	**69.1**	52.6	63.7
Multifocal soft contact lenses	49.9	53.0	45.6	45.4
Rigid gas-permeable contact lenses	37.5	43.4	10.4	8.3
Multifocal spectacles	30.8	37.4	26.3	31.1
Control	11.8	10.8	16.0	12.6
Undercorrected single vision spectacles	4.0	8.5	6.3	11.4
Orthokeratology	-	-	79	81.1

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Table 3. SUCRAs in all NMAs *(Continued)*

Orthokeratology plus atropine	-	-	**81.8**	**94.2**

The three highest ranking interventions for each outcome are highlighted in **bold.**

AL: axial length**; NMA:** network meta-analysis; **SER**: refractive error; **SUCRA:** surface under the cumulative ranking curve

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Table 4. Risk of adverse events: spectacle lens interventions

Study	Arm (participants)	Total number of events (participants)	Dizziness	Blurred vision	Distortion	Headache	Difficulty with stairs	Other
Adler 2006	UC (25)	2 (2)	-	2	-	-	-	-
	FC (23)	0 (0)	-	-	-	-	-	-
Bao 2022	PPSL (115)	0 (0)	-	-	-	-	-	-
	SVL (55)	0 (0)	-	-	-	-	-	-
COMET 2 Study 2011	MFSL (59)	3 (3)	1	1	-	-	-	1
	SVL (59)	14 (14)	9	3	-	-	-	2
Hasebe 2008[a]	MFSL (87)	37 (37)	10	19	-	0	8	-
	SVL (91)	24 (24)	6	14	-	0	4	-
CYPRESS Study 2023	DOT (163)	13 (NR)	-	0	-	0	-	13
	SVL (93)	7 (NR)	-	1	-	3	-	3
Sankaridurg 2010	MFSL (160)	13 (13)	2	9	1	1	-	-
	SVL (74)	3 (3)	0	1	2	0	-	-

DOT: diffusion optics technology lenses; **FC:** full correction; **MFSL:** multifocal spectacle lenses; **PPSL:** peripheral plus lenses; **UC:** undercorrection; **SVL:** single vision spectacle lenses

[a]Results of 6/12 questionnaire survey (reported in Suemaru 2008 (secondary reference to to Hasebe 2008).

Table 5. Risk of adverse events: contact lens interventions

Study	Arm (number of participants)	Total number of events (participants)	Grade ≥ 3 slit-lamp findings	Corneal infiltrates	Allergy/ hypersensitivity reactions	Corneal erosions/staining	Corneal neovascularisation	Papillary reaction	Other

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Table 5. Risk of adverse events: contact lens interventions *(Continued)*

Multifocal soft contact lenses									
BLINK Study 2020[a]	Total lens wearers (294)	35 (35)	NR	10	7	4	-	9	5
	MFSCL (196) SVSCL (98)	-	-	-	-	-	-	-	-
Chamberlain 2019	MFSC (70)	8 (6)	1	4	-	-	-	1	2
	SVSCL (74)	7 (5)	0	3	-	-	-	-	4
Cheng 2016	PSASL (64)	2 (1)	0	-	2	-	0	-	0
	SVSCL (63)	3 (2)	0	-	2	-	1	-	0
Garcia-del Valle 2021	MFSCL (32)	10 (8)	NR	-	-	2	3	4	1
	SVSCL (26)	4 (4)	NR	-	-	1	1	2	0
Liu 2024	MFSCL (52)	17 (17)	-	-	4	2	-	-	11
	SVSCL (52)	11 (11)	-	-	3	2	-	-	6
MASS Study 2018[b]	MFSCL (41)	11 (NR)	0	-	-	5	2	4	-
	SVL (33)	3 (NR)	0	-	-	1	0	2	-
Rigid gas-permeable lenses									
CLAMP Study 2004	RGP (59)	0 (0)	NR	-	0	-	-	-	-
	SVSCL (57)	4 (4)	NR	-	1	-	-	-	3
Orthokeratology									
Guo 2021	Ortho-K 6 mm (32)	26 (NR)	0	2	-	11	-	-	13
	Ortho-K 5 mm (26)	16 (NR)	0	3	-	6	-	-	7
Jakobsen 2022	Ortho-K (19)	2 (2)	2	-	-	2	-	-	-
	SVL (28)	0 (0)	0	-	-	0	-	-	-

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Table 5. Risk of adverse events: contact lens interventions *(Continued)*

Kinoshita 2020	Ortho-K + 0.01% atropine (38)	3 (3)	NR	0	-	2	-	-	-
	Ortho-K monotherapy (35)	1 (1)	NR	1	-	1	-	-	-
Lyu 2020	Ortho-K (68)	16 (16)	2	-	-	14	-	-	-
	SVL (34)	3 (3)	0	-	-	3	-	-	-
Tan 2023	Ortho-K + 0.01% atropine (42)	20 (20)	0	1	-	1	-	-	18
	Ortho-K (44)	11 (11)	0	1	-	1	-	-	9
Xu 2023	Ortho-K + 0.01% atropine (42)	2(2)	NR	0	-	1	-	-	1
	Ortho-K (40)	2 (2)	NR	0	-	0	-	-	2
	SVL (40)	0 (0)	NR	0	-	0	-	-	-

MFSCL: multifocal soft contact lenses; **NR**: not reported; **Ortho-K:** orthokeratology; **PSASCL:** positive spherical abberation soft contact lenses; **SVL:** single vision spectacle lenses; **SVSCL:** single vision soft contact lenses

[a]Data combined for intervention and control lenses
[b]Data at final 24-month visit

Table 6. Risk of adverse events: antimuscarinics

Study	Arm (number of participants)	Total number of events (participants)	Photophobia/glare	Blurred vision	Hypersensitivity reactions	Ocular irritation	Systemic complications	Other
High- and medium-dose atropine								
ATOM 2 Study 2012	Atropine 0.5% (161)	43 (23)	1	13	10	-	-	15
	Atropine 0.1% (155)	47 (41)	NR	20	7	-	-	14
Shih 1999	Atropine 0.5% (41)	10 (10)	9	0	1	-	0	-
	Atropine 0.25%, (47)	3 (3)	3	0	0	-	0	-

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Table 6. Risk of adverse events: antimuscarinics *(Continued)*

	Atropine 0.1% (49)	0 (0)	0	0	0	-	9	-
Yen 1989	Atropine 1% (32)	32 (32)	32	0	0	0	0	-
	Cyclopentolate 1% ((32)	0 (0)	0	0	0	0	0	-
	Placebo (32)	0 (0)	0	0	0	0	0	-
Zhu 2021	Atropine 1% (330)	352 (330)	205	65	3	61	-	18
	Placebo (308)	NR	NR	NR	NR	NR	-	NR
Lower-dose atropine								
ATOM 2 Study 2012	Atropine 0.01% (84)	15 (14)	NR	11	0	-	-	3
Chia 2023	Atropine 0.0025% (24)	8 (24)	1	2	-	4	-	1
	Atropine 0.005% (24)	2 (24)	-	1	-	-	-	1
	Atropine 0.01% (25)	7 (25)	2	1	1	2	-	1
	Placebo (26)	0 (26)	-	-	-	-	-	-
Cui 2021	Atropine 0.02% (138)	32 (32)	32	-	0	0	-	-
	Atropine 0.01% (142)	33 (33)	33	-	0	0	-	-
	SVL (120)	3 (3)	3	-	0	0	-	-
Hansen 2023	Atropine 0.1% loading dose (at 6m)(33)	28 (28)	12	12	-	2	-	2
	Atropine 0.01% (at 6 m)(32)	2 (2)	0	1	-	1	-	0
	Placebo (at 6 m)(31)	5 (5)	0	0	-	2	-	3
Hieda 2021	Atropine 0.01% (85)	2 (2)	1	0	-	0	-	1
	Placebo (86)	1 (1)	0	1	-	-	-	0
Hu 2023	Atropine 0.01% (197)	65 (65)	11	2	-	-	-	52

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Table 6. Risk of adverse events: antimuscarinics *(Continued)*

	Placebo (98)	25 (25)	2	0	-	-	-	23
LAMP Study 2019	Atropine 0.05% (93)	17 (17)	8	-	9	-	-	-
	Atropine 0.025% (86)	14 (14))	4	-	10	-	-	-
	Atropine 0.01% (91)	17 (17)	6	-	11	-	-	-
Lee 2022	Atropine 0.01% (104)	9 (9)	-	1	2	3	1	2
	Placebo (49)	1 (1)	-	0	0	0	0	1
Repka 2023	Atropine 0.01% (125)	49 (NR)	32	17	-	-	-	-
	Placebo (62)	27 (NR)	17	10	-	-	-	-
Wei 2020	Atropine 0.01% (110)	8 (8)	5	0	3	-	-	-
	Placebo (110)	2 (2)	1	0	1	-	-	-
Xu 2023	Atropine 0.01% (42)	2 (2)	2	-	-	-	-	-
	SVL (control) (40)	0 (0)	0	-	-	-	-	-
CHAMP 2023	Atropine 0.01% (164)	15 (15)	4	2	3	1	0	5
	Atropine 0.02% (247)	36 (36)	11	4	11	2	2	7
	Placebo (162)	18 (18)	5	0	5	6	1	1
Zhang 2024	Atropine 0.05% (212)	22 (22)	16	-	6	-	-	-
	Placebo (209)	14 (14)	8	-	6	-	-	-
Pirenzepine								
PIR-205 Study 2004	Pirenzepine 2% (117)	163 (NR)	7	91	47	18	-	Several 'other' AEs documented. No significant difference be-
	Placebo (57)	29 (NR)	1	13	10	5	-	

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Table 6. Risk of adverse events: antimuscarinics *(Continued)*

								tween test and placebo
Tan 2005	Pirenzepine 2% (142)	178 (NR)	-	95	83	-	-	Several 'other' AEs documented. No significant difference between test and placebo
	Placebo (171)	16 (NR)	-	6	10	-	-	

AEs: adverse events; **NR**: not reported; **SVL:** single vision spectacles

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Table 7. Risk of adverse effects: repeated low intensity red light therapy

Study	Arm (participants)	Total number of events (participants)	'Light too bright'	**Reversible visual disturbance**
Chen 2023	RLRL (51)	0	0	-
	SVL (51)	0	0	
Jiang 2022	RLRL (119)	2	2	-
	SVL (145)	0	0	
Zhou 2023	RLRL (24)	23	-	23
	SVL (19)	0	-	0

BCVA = best corrected visual acuity

Table 8. Adherence: spectacle interventions

Study	**Arm (number of participants)**	**Wearing time hours per day Mean (SD)**	**% compliant (always or most of the time)**	**P value**
Bao 2022	PPSL HAL (54)	13.4 (2.1)	-	P = 0.34
	PPSL SAL (53)	13.4 (1.8)	-	
	SVL (50)	13.9 (1.7)	-	
COMET Study 2003	MFSL (235)	-	93%	NR
	SVL (234)	-	96%	
COMET 2 Study 2011[a]	MFSL (58)	-	72%	NR
	SVL (58)	-	90%	
Fulk 2002	MFSL (42)	-	90%	NR
	SVL (40)	-	96%	
Hasebe 2008	MFSL (87)	-	96%	Reported as 'not significant'
	SVL (91)	-	94%	
Koomson 2016	UC (75)	-	97%	NR
	FC (75)	-	96%	
Lam 2020	PPSL (79)	15.5 (2.6)	-	Reported as 'not significantly different'
	SVL (81)	15.3 (2.1)	-	

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Table 8. Adherence: spectacle interventions *(Continued)*

Pärssinen 1989	MFSL (79)	-	77%	NR
	SVL (79)	-	82%	
CYPRESS Study 2023	DOT (test lens 1) (78)	12.8 (2.5)	-	NR
	DOT (test lens 2) (56)	12.7 (3.0)	-	
	SVL (91)	13.6 (2.4)	-	
STAMP Study 2012	MFSL (40	-	93%[a]	NR
	SVL (43)	-	91%[a]	
Yang 2009	MFSL (89)	-	87% (combined)	NR
	SVL (89)	-		
Yuval 2024	PPSL (56)	14.0 (1.40)	-	NR
	SVL (43)	13.8 (2.30)	-	

FC: fully corrected single vision spectacles; **HAL:** highly aspheric; **MFSL:** multifocal spectacle lenses; **NR:** not reported; **PPSL:** peripheral plus spectacle lenses; **SD:** standard deviation; **SVL:** single vision spectacle lenses; **SAL:** slightly aspheric; **UC:** undercorrected single vision spectacles

[a]Compliance during school hours.

Table 9. Adherence: contact lens interventions

Study	Arm (number of participants)	Wearing time hours per day Mean (SD)	% compliant (always or most of the time)	P value
Anstice 2011	MFSCL (20)	13.2 (2.8)	100%	P = 0.41
	SVSCL (20)			
BLINK Study 2020	MFSCL (196)	11.0 (4.4)[a]	-	NR
	SVSCL (98)			
Chamberlain 2019	MFSCL (70)	13.7 (1.5)	-	Reported P > 0.05
	SVSCL (74)	13.3 (1.5)		
DISC Study 2011	MFSCL (111)	6.5 (2.2)	-	P = 0.644
	SVCL (110)	6.3 (1.7)		
Fujikado 2014	MFSCL (11)	13.2(1.0)	-	P = 1.00
	SVCL (13)	13.2(1.1)		

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Table 9. Adherence: contact lens interventions *(Continued)*

Katz 2003**	RGP (75)	-	31.5%	NR
	SVL (75)		98.4%	

MFSCL: multifocal soft contact lenses; **NR:** not reported; **RGP**: rigid gas-permeable lenses; **SD:** standard deviation; **SVSCL:** single vision soft contact lenses; **SVL:** single vision spectacle lenses

[a]Both arms combined.

Table 10. Adherence: pharmacological interventions

Study	Arm (number of participants)	Compliance with medication	P value
ATOM 2 Study 2012	Atropine 0.5% (161)	98.7%	NR
	Atropine 0.25% (155)	96.8%	
	Atropine 0.1% (84)	98.8%	
Hieda 2021	Atropine 0.01% (85)	83.3%	NR
	Placebo (86)	85.7%	
LAMP Study 2019	Atropine 0.05% (109)	93.6%	NR
	Atropine 0.025% (108)	95.4%	
	Atropine 0.01% (110)	90.9%	
	Placebo (111)	90.1%	
PIR-205 Study 2004	Pirenzepine 2% (117)	79%	NR
	Placebo (57)	79%	
Trier 2008	7-methylxanthine (35)	89%	NR
	Placebo (42)	92%	
CHAMP 2023	Atropine 0.02% (212)	88.3%	NR
	Atropine 0.01% (141)	86.4%	
	Placebo (143)	87.1%	

NR: not reported

INDEX TERMS

Medical Subject Headings (MeSH)

Atropine [therapeutic use]; *Myopia; Network Meta-Analysis; Refraction, Ocular; *Refractive Errors

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