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REVIEW ARTICLE

Myopia control strategies: A systematic review and meta-meta-analysis

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Abstract

Purpose: To summarise pooled estimates of the efficacies of various myopia control interventions, as drawn from published meta-analyses.

Method: PubMed, SCOPUS and Web of Science were searched from inception to February 2024 for systematic reviews and meta-analyses reporting treatment effects of various myopia control strategies. The qualities of the included meta-analyses were assessed using the 16-item *A MeaSurement Tool to Assess systematic Reviews* (*AMSTAR*) 2. An intervention was defined as having a clinically significant effect if it resulted in a change in spherical equivalent refraction (SER) of ≥0.50 D/year or axial length (AL) change of ≤−0.18 mm/year.

Results: A total of 38 studies were identified. The overall respective changes in SER and AL, mean difference (95% CI) were high-concentration (≥0.5%) atropine 0.67 D (0.58–0.77) and −0.24 mm (−0.36 to −0.11); moderate-concentration (>0.05% to <0.5%) atropine 0.48 D (0.34–0.62) and −0.23 mm (−0.27 to −0.19); low-concentration (0.01%, 0.025%, 0.05%) atropine 0.33 D (0.23–0.43) and −0.14 mm (−0.19 to −0.09); orthokeratology −0.47 mm (−0.66 to −0.28); peripheral plus soft contact lenses 0.30 D (0.18–0.42) and −0.35 mm (−0.62 to −0.08); peripheral plus spectacles 0.77 D (0.40–1.14) and −0.43 mm (−0.78 to −0.08); multifocal spectacles 0.21 D (0.11–0.31); repeated low-level red light therapy 0.55 D (0.46–0.65) and −0.25 mm (−0.29 to −0.20); outdoor time 0.17 D (0.16–0.18) and −0.04 mm (−0.06 to −0.01).

Conclusion: High and moderate concentrations of atropine, orthokeratology, peripheral plus spectacles and repeated low-level red light demonstrated clinically significant effects on slowing AL elongation, while high and moderate concentrations of atropine, peripheral plus spectacles and repeated low-level red light demonstrated clinically significant effects on slowing SER progression.

KEYWORDS
axial length, efficacy, myopia control, myopia progression, spherical equivalent refraction

INTRODUCTION

Myopia is a common eye condition where the eye focuses parallel light in front of the retina, rather than directly on it, thereby making distant objects blurry.[1] It is now recognised as one of the leading causes of preventable blindness globally and has been reported to have reached epidemic proportions in parts of the world.[2] The condition has rapidly evolved into a public health burden worldwide, posing substantial challenges for healthcare systems and individuals alike. The prevalence of myopia has surged at an alarming rate in recent years, and it seems inevitable that the proportion of the population affected by this burgeoning public health challenge will further rise in the decades ahead.[3–7]

The causes of myopia have been the subject of extensive research. While many questions persist, the existing evidence points to several key contributing factors, including excessive near-work activities, diminished outdoor time, intensive educational demands and to a lesser but still significant degree, genetic predispositions.[8–10] It is becoming clear that the early onset and rapid progression of myopia

could lead to a significant increase in the number of people with high myopia.[5,6] Myopia can be associated with progressive abnormal axial elongation and resultant mechanical stretching of the outer coats of the eye, increasing the risks of ocular complications such as cataracts, glaucoma, macular degeneration and even blindness.[11–13] There is currently no safe degree of myopia when it comes to the risk of developing complications. Individuals with relatively low degrees of myopia also have increased risk of developing these blinding conditions, although for those who progress to high myopia, the risks become significantly higher.[2,14] While sight-threatening myopia-related pathologies are classically observed in later life, the underlying refractive condition is believed to develop during childhood. In fact, complications such as myopic maculopathy and retinal detachment may also occur in children.[11,15,16]

Although myopia can be corrected, simply correcting the refractive error with single vision spectacles or contact lenses does not halt or reverse the progressive axial elongation that drives the condition. This has sparked significant research in developing effective interventions to slow myopia progression and potentially delay its onset. Multiple individual clinical trials and pooled analyses have demonstrated the beneficial effects of various myopia control strategies, some of which have now been adopted into mainstream clinical practice in various parts of the world. There is limited evidence as to whether these interventions will eventually prevent the occurrence of myopia-associated complications. However, it seems logical and plausible that they might. Since the complications appear to be fundamentally associated with the progressive elongation of the globe, interventions capable of slowing axial length elongation may, by extension, also avert the downstream complications. Faced with an array of competing myopia control strategies, clinicians often experience difficulty making a choice that will not delay the implementation of an effective intervention to ameliorate the burden of future vision loss. Furthermore, while the available meta-analyses of the relative effectiveness of myopia control interventions have provided precise quantitative estimates drawn from numerous individual clinical trials, the proliferation of these meta-analytic studies has introduced an additional layer of complexity—variability in results due to differences in methods and study selection, necessitating a meta-synthesis of these meta-analyses. Hence, this study aimed to provide a comprehensive synthesis of the current evidence derived from published meta-analyses of myopia control interventions to inform clinical practice.

Key points

- This meta-meta-analysis provides more robust evidence by combining research from published meta-analyses to show how well different myopia control strategies work.
- High and moderate concentrations of atropine, orthokeratology, peripheral plus spectacles and low-level red light are highly efficient in slowing myopia progression.
- It is imperative that the early adoption of an ideal myopia control strategy is encouraged, especially for children with myopia.

MATERIALS AND METHODS

The meta-meta-analysis has been registered on PROSPERO (registration number CRD42023417258) and was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines. The PRISMA checklist has been provided as Data S1. The PubMed, SCOPUS and Web of Science databases were searched from inception to February 2024 for systematic reviews and meta-analyses reporting treatment effects of various myopia control strategies (Data S2). All identified records were imported into the systematic review management platform, Covidence (Veritas Health Innovation, covidence.org), for title and abstract screening.

Eligibility criteria

The inclusion criteria employed in this study were based on methodological and clinical factors which included study population, intervention, control, outcomes and study design.[17]

Population

The following criteria were used to include meta-analyses: (1) Examined myopia control strategies in juvenile populations (<18 years of age) with a baseline spherical equivalent refraction (SER) of ≤−0.50 D and without ocular comorbidities such as strabismus and amblyopia; (2) Included randomised control trials and non-randomised comparative studies (clinical trials and cohort studies); (3) Reported quantitative data on the efficacy of myopia control strategies published in a peer-reviewed journal; (4) Provided distinct, intervention-specific efficacy estimates. Meta-analyses that focused on adult populations, non-myopic patients or patients with myopia and strabismus or amblyopia were excluded. Furthermore, correlational studies, as well as investigations related to surgical interventions for myopia correction were excluded.

Interventions and comparators

Meta-analyses that compared the following myopia control interventions against single vision spectacle lenses,

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single vision soft contact lenses, placebo treatment or with each other were included: high (≥0.5%), moderate (>0.05% to <0.5%) and low (0.01%, 0.025%, 0.05%) concentrations of atropine; orthokeratology (ortho-*k*); peripheral plus soft contact lenses; peripheral plus spectacles, multifocal spectacles; repeated low-level red light; outdoor time and combined treatments.

Outcome

Meta-analyses were included that reported mean differences (MD) in cycloplegic SER and axial length (AL) between the intervention and control groups. Meta-analyses with critically low quality were excluded. Studies were also excluded if they were published in a language other than English or were not published in a peer-reviewed scientific journal (e.g., book chapters and dissertation theses).

Selection process

Two reviewers (co-authors SK and RA) independently screened the meta-analyses. The screening process involved an initial evaluation of titles and abstracts, followed by a subsequent evaluation of the full text. Discrepancies that arose during this phase were resolved through a process of consensus. Relevant information was extracted from included articles using a data extraction sheet. Two reviewers (SK, RA) checked the extracted data, and disagreements were resolved by consulting the articles and by discussion. In instances where information regarding sample and effect size was not explicitly stated in the text, estimates were derived from tables and forest plots, with the objective of achieving the greatest possible accuracy. In exceptional cases, primary studies were consulted in order to clarify ambiguous information present in meta-analyses. Additionally, if relevant information was lacking, requests for further information were made to the authors of the meta-analyses. SER progression and AL elongation were estimated at a follow-up period of 1 year. Data from studies with less than or >1-year follow-up periods were standardised to 1 year.[18] Data were further standardised to 6 month intervals.[18]

Data collection process

Relevant information on the inclusion criteria and outcomes of myopia control strategies was gathered from meta-analyses. Meta-meta-analyses of effect sizes from the meta-analyses of myopia control strategies were conducted in R (version 4.3.3, r-project.org/).[19] The weighted estimate of heterogeneity across meta-analyses was quantified as I^2, which represented the percentage of total variation between studies that was due to heterogeneity as opposed to chance. Estimates of heterogeneity of 25%, 50% and 75% were used to represent low, moderate and high heterogeneity, respectively.[20,21] For meta-analyses that reported heterogeneity using Cochran's Q,[22] heterogeneity scores were recalculated in order to ease comparison across reviews.[21] Large values of I^2 signified greater heterogeneity between studies, and $p < 0.05$ was used to indicate that the heterogeneity was significantly different from zero. An intervention was defined as having a clinically significant efficacy if it resulted in a change in SER of ≥0.50 D/year or AL change of ≤−0.18 mm/year.[23]

Publication bias

Funnel plots were generated to examine the risk of publication bias, while Egger's test for asymmetry was used to detect and quantify asymmetry for interventions with >10 eligible effect sizes.[24,25] Summary effects adjusted for publication bias were provided by Duval and Tweedie's trim and fill method.[26]

Quality assessment

Two reviewers (RA, SK) independently evaluated the quality of the meta-analyses using the 16-item AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews, revised instrument 2).[27] The quality classifications were as follows: critically low, low, moderate and high quality. In the event of a discrepancy in grading, the reviewers discussed the differences and reached a consensus.

Overlap

The overlap of included studies was assessed using the corrected covered area (CCA). The CCA calculations were conducted in accordance with the protocol proposed by Pieper et al.[28]: $\mathrm{CCA} = \frac{N-r}{rc-r}$, where N is the number of included publications (including double counting), r is the number of primary publications and c is the number of reviews. The interpretation of overlap was based on predetermined overlap thresholds, which were categorised as: 0%–5% (slight), 6%–10% (moderate), 11%–15% (high) and >15% (very high).[28]

RESULTS

The process of selecting studies for inclusion is outlined in Figure 1 in accordance with the PRISMA 2020 statement.[29] Database searches yielded 272 potentially relevant entries. After removing duplicated publications using Covidence,[30] 199 articles remained for title and abstract screening. These 199 abstracts were initially screened, with 81 sought

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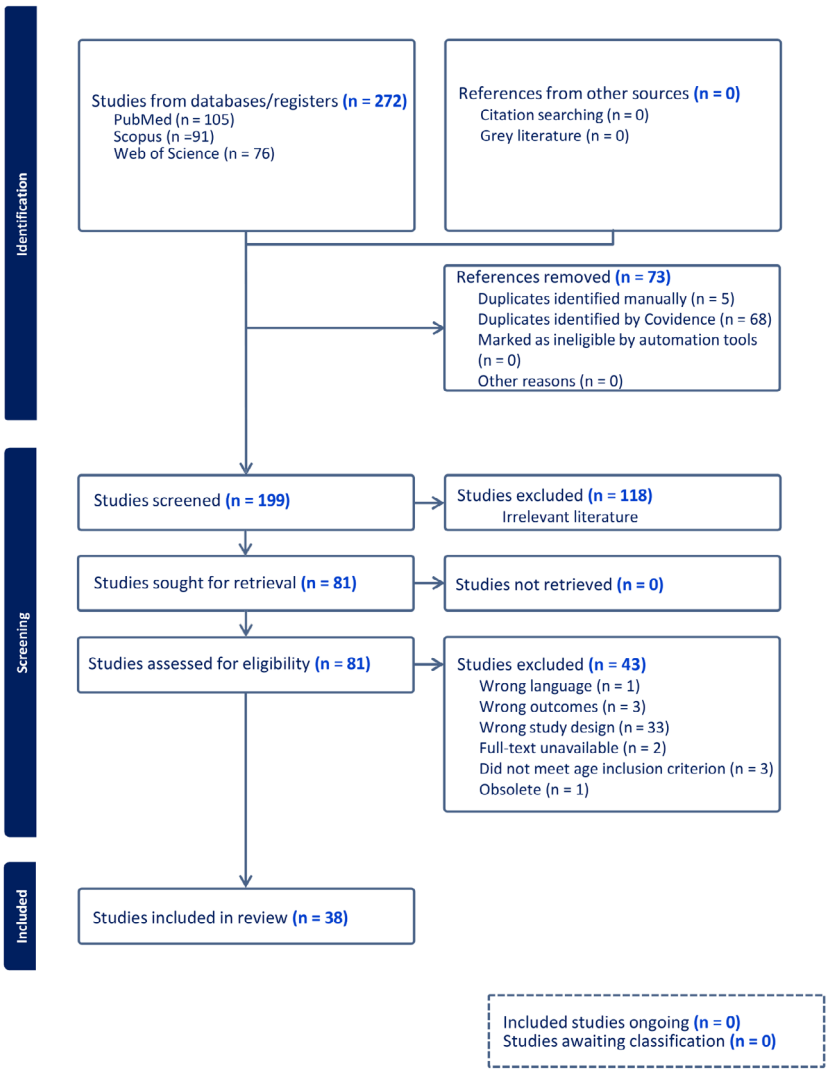

FIGURE 1 PRISMA flowchart.

for full-text retrieval. Following this process, 43 abstracts were excluded for various reasons, including not being written in English, irrelevant study outcomes, incorrect study design or unavailability of the full text. Ultimately, 38 studies met the inclusion criteria and were included in the systematic review and meta-meta-analysis, with 24 studies qualifying for standardisation.

A total of 107 (97,359 individuals, as reported by 29 of the studies) effect sizes were extracted from the meta-analyses. These effect sizes informed the outcomes of change in SER (52 effect sizes) and AL (55 effect sizes). Table 1 provides a summary of the key characteristics of the included studies.

Overlap

The 38 systematic reviews and meta-analyses comprised 153 overlapping index publications, of which 69 were unique. Index publications that were represented in more than one eligible review were recognised in the citation matrix. To avoid potential double counting of outcomes, the degree of actual overlap was calculated by estimating the CCA, where N is the number of included publications (including double counting), r is the number of primary publications, c is the number of reviews and rc is the product of r and c.

$$\mathrm{CCA} = \frac{N - r}{rc - r} = \frac{153 - 69}{69 \times 38 - 69} = \sim 3.3\,\%$$

The pairwise overlap assessment between the individual systematic reviews and meta-analyses revealed an overall estimated degree of overlap (CCA) of 3.3%. This reflects limited overlap and a slight risk of skewed reporting in the systematic reviews and meta-analyses.[28] A matrix heatmap of the calculated CCA between pairs of included meta-analyses is presented in Figure 2. The estimated degree of overlap was obtained with no consideration of the specific outcomes.

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TABLE 1 Characteristics of the included studies.

Study ID	Country/Area/Ethnicity (*n*)	Study designs (*n*)	Sample size	Baseline characteristics (years of age)
Li (2011)[78]	USA (2), Hong Kong (2), Mainland China (1), Taiwan (1), Japan (1), Canada (1), Finland (1)	Randomised controlled trial (9)	1464	6–13
Sun (2015)[79]	Hong Kong (4), USA (1), Japan (1), Spain (1)	Randomised controlled trial (2), Clinical trial (5)	546	6–16
Si (2015)[80]	Hong Kong (4), Japan (1), Spain (1), USA (1)	Randomised controlled trial (2), non-randomised controlled trial (5)	435	6–16
Huang (2016)[23]	Asian (16), White (11)	Randomised controlled trial (30)	5387 (5422 eyes)	<18
Li (2016)[54]	Hong Kong (5), Japan (2), Spain (1), China (1)	Randomised controlled trial (3), Cohort (6)	–	6–17
Gong (2017)[81]	Taiwan (10), USA (3), Singapore (3), Mainland China (2), Hong Kong (1)	Randomised controlled trial (9), Cohort (10)	3137	<18
Li (2017)[82]	USA (3), Mainland China (1), Hong Kong (1), New Zealand (1), Japan (1), Spain (1)	Randomised controlled trial (5), Cohort (3)	587	6–18
Deng (2019)[83]	Chinese (5)	Clinical trial (5)		6–18
Ho (2019)[84]	China, Taiwan, Australia, UK, USA	Comparative study (CS) (4), Cohort (CH) (3), Intervention studies (IS) (6)	15,081 (CS 5745, CH 4622, IS 4714)	4–14
Guan (2020)[43]	Spain (2), China (7), Japan (2), Korea (1), East Asia (1)	Prospective Comparative study (5), retrospective study (4), others (4)	804 (408 children received orthokeratology treatment and 396 children as control)	<18
Cao (2020)[85]	China (4), Singapore (1)	Randomised controlled trial (5)	3014	6–12
Wang (2021)[86]	Japan (1), Mainland China (2), Hong Kong China (1)	Randomised controlled trial (4)	267	6–16
Tsai (2021)[87]	China (2), USA (2), Japan (1), Hong Kong (1), India (1), Italy (1)	Randomised controlled trial (5), retrospective case–control (3)	1178	<18
Gao (2021)[88]	Japan (1), China (2), Hong Kong (1), Taiwan (1)	Randomised controlled trial (3), non-randomised controlled trial (2)	-	<18
Chen (2021)[89]	Singapore (3), Spain (1), Japan (1), India (1), Taiwan (3), Hong Kong (3), China (5)	Randomised controlled trial (17)	2955	<18
Yu (2022)[90]	–	Randomised controlled trials, cohort and case–control (total: 9)	387	<18
Ha (2022)[91]	–	Randomised controlled trial (16)	3272	
Gan (2022)[92]	Mainland China (7), Taiwan (8), USA (4), Singapore (2), Hong Kong (2), Europe (2), Japan (1), India (10)	Randomised controlled trial (12), cohort (15)	–	6–15
Yang (2022)[93]	China (6), Japan (2)	Randomised controlled trial (6), cohort (2)	461	<18
Yang (2022)[44]	Japan (1), China (5), Korea (1)	Cohort (5), Randomised controlled trial (2)	682	<18
Yu (2022)[55]	New Zealand (1), Hong Kong (1), Japan (1), Spain (2), China (1), USA (1)	Randomised controlled trial (7)	–	6–18
Zhao (2022)[45]	China (5)	Randomised controlled trial (2), case–control (2), cohort studies (1)	360 patients (182 in the experimental group and 178 in the control group)	<18
Tsai (2022)[94]	China (7), Hong Kong (3), India (1), Japan (2), Singapore (2), Taiwan (4)	Randomised controlled trial (19)	3435	<18
Zheng (2022)[95]	Japan (2), Hong Kong (2), Taiwan (1), China (10)	Non-randomised controlled trial (1), retrospective cohort studies (3), randomised controlled trial (11)	969	<18
Wang (2023)[96]	Japan (2), Mainland China (12)	Randomised controlled trial (8), non-randomised controlled trial (3)	1230	<18

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TABLE 1 (Continued)

Study ID	Country/Area/Ethnicity (*n*)	Study designs (*n*)	Sample size	Baseline characteristics (years of age)
Wei (2023)[97]	China (6), Hong Kong (4), Taiwan (1)	Randomised controlled trial (15)	2268	<18
Lanca (2023)[47]	Japan (1), China (5), India (1), Hong Kong (1), Spain (1), Denmark (1), Portugal (1), United Kingdom (1), Singapore (1), Canada (1)	Randomised controlled trial (12)	–	<18
Wang (2023)[98]	China (7)	Randomised controlled trial (7)	1031	6–16
Zhang (2023)[52]	–	Randomised controlled trial (80)	27,103 667; Randomised controlled trial (156), Cohort (511)	6–18
Tang (2023)[61]	China (8)	Non-randomised controlled trial (1), randomised controlled trial (5), cohort (2)	934	<18
Tang (2023)[48]	Chinese (5), Scandinavian (1), East Asian (1)	Randomised controlled trial (7)	655 eyes	6–16
Zaabaar (2023)[99]	China (9), Japan (3), Taiwan (2), USA (1)	Prospective comparative study (1), comparative interventional study (3), randomised controlled trial (8)	–	<18
Sarkar (2023)[46]	Asian, Caucasian, Hispanic or Latino, Black or African American and Native Hawaiian ethnic backgrounds	Randomised controlled trial, historical controls, prospective and longitudinal studies	4687 (2688 and 1999 myopic participants in the intervention and control groups, respectively)	6–18
Li (2023)[100]	–	Clinical controlled trials (8)	–	<18
Li (2023)[42]	South Korea (1), USA (1), China (12)	Randomised controlled trial (14)	2058	6–18
Hou (2023)[101]	–	Cohort (17), Randomised controlled trial (27)		<18
Lawrenson (2023)[49]	China/Other Asian countries (39), North America, (13)	Randomised controlled trial (64)	11,617	<18
Deng (2024)[102]	China (6)	Randomised controlled trial (6)	820	7–15

Assessment of methodological quality

According to AMSTAR 2 scoring, one meta-analysis was of moderate quality and three meta-analyses were of high quality (Data S3). The remaining meta-analyses were considered to be of low quality, typically due to the lack of explicit statements that review methods were determined before the review was conducted and an inadequate explanation of the design of the included studies (Data S4).

Effects of interventions

The interventions were evaluated in comparison with control treatments, including single-vision spectacle, single-vision soft contact lenses or placebo, to ascertain which treatments were effective in slowing SER progression and AL elongation. For myopia progression, assessed as the mean change in SER from baseline, negative MDs represented faster progression of myopia in the treatment group compared to the control group (Figure 3). Thus, estimates to the left of the null effect line on the forest plots favour the control group. For axial length, negative MDs represent less axial elongation for the treatment group compared with the control group—estimates to the left of the line of null effect on the forest plots favour the treatment group (Figure 4).

Mean differences in SER progression and AL elongation relative to control

High to low concentrations of atropine

The overall average MDs in SER progression were 0.67 D (95% CI 0.58–0.77, $I^2 = 0\%$), 0.48 D (95% CI 0.34–0.62, $I^2 = 0\%$) and 0.33 D (95% CI 0.23–0.43, $I^2 = 91\%$) for high, moderate and low concentrations of atropine, respectively (Figure 3a). The corresponding respective mean differences in AL elongation were −0.24 mm (95% CI −0.36 to −0.11, $I^2 = 87\%$), −0.23 mm (95% CI −0.27 to −0.19, $I^2 = 0\%$) and −0.14 mm (95% CI −0.19 to −0.09, $I^2 = 83\%$) (Figure 4a).

Standardisation of the effect sizes after 6 months revealed mean differences in SER progression of 0.41 D (95% CI 0.35–0.47, $I^2 = 0\%$), 0.29 D (95% CI 0.21–0.38, $I^2 = 0\%$) and 0.20 D (95% CI 0.17–0.23, $I^2 = 9\%$) for high, moderate and low concentrations of atropine, respectively. The corresponding mean differences in AL elongation were −0.15 mm (95%

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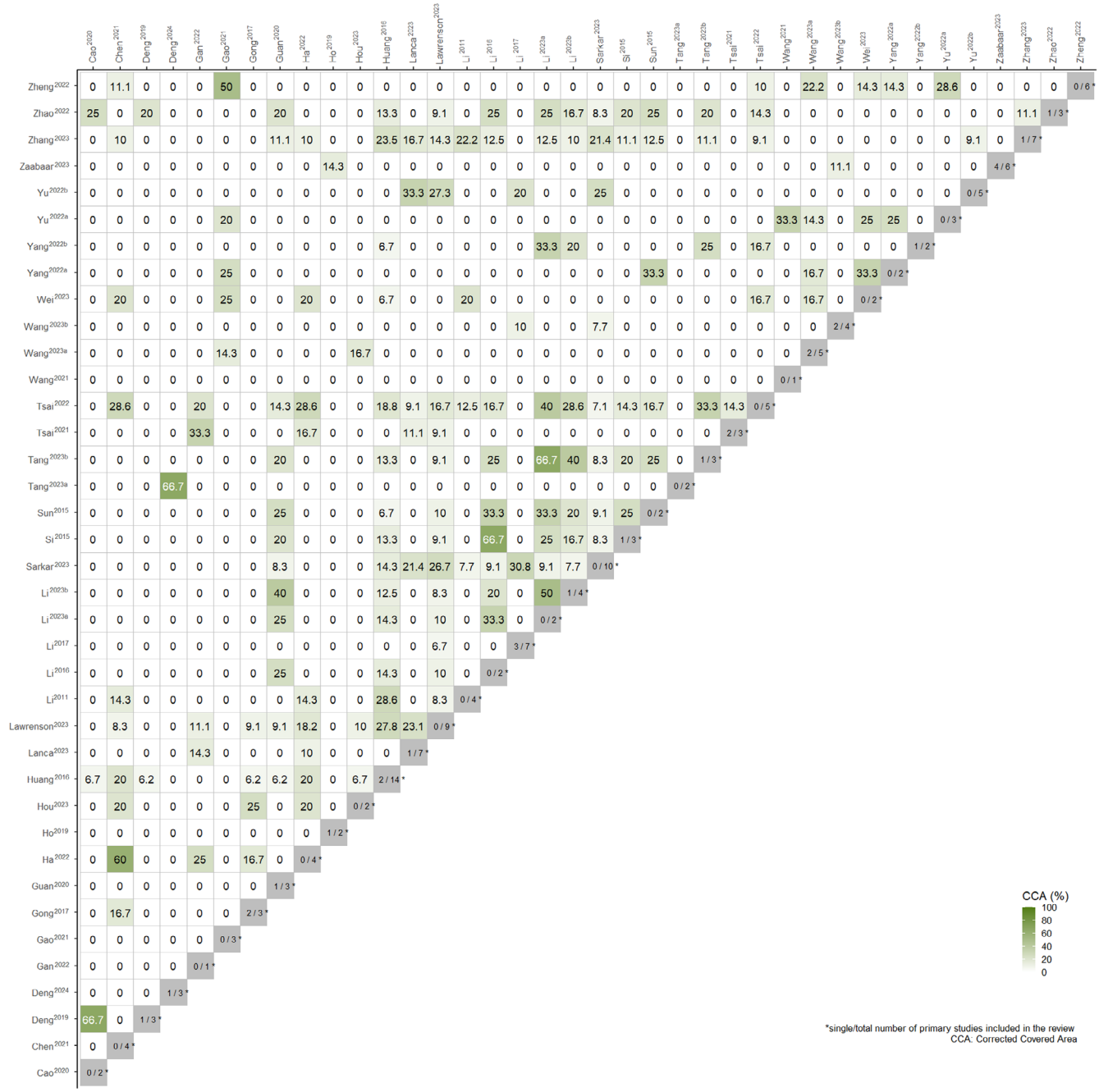

FIGURE 2 A matrix heatmap of the calculated corrected covered area (CCA) between pairs of the included meta-analyses.

CI −0.22 to −0.07, $I^2 = 87\%$), −0.14 mm (95% CI −0.16 to −012, $I^2 = 0\%$) and −0.09 mm (95% CI −0.13 to −0.04, $I^2 = 86\%$) (Data S4).

Standardisation of the effect sizes by 1 year revealed mean differences in SER progression of 0.67 D (95% CI 0.58–0.77, $I^2 = 0\%$), 0.48 D (95% CI 0.34–0.63, $I^2 = 0\%$) and 0.33 D (95% CI 0.28–0.38, $I^2 = 9\%$) for high, moderate and low concentrations of atropine, respectively. The corresponding mean differences in AL elongation were −0.24 mm (95% CI −0.36 to −0.11, $I^2 = 87\%$), −0.23 mm (95% CI −0.27 to −0.19, $I^2 = 0\%$) and −0.15 mm (95% CI −0.22 to −0.07, $I^2 = 86\%$) (Data S5).

Contact lenses

Ortho-*k* demonstrated statistically significant myopia control effects, slowing AL elongation by −0.47 mm (95% CI −0.66 to −0.28, $I^2 = 94\%$) compared to the control condition (Figure 4b). Peripheral plus soft contact lenses also yielded statistically significant myopia control effects on SER progression, 0.30 D (95% CI 0.18–0.42, $I^2 = 74\%$) (Figure 3b) and AL elongation, −0.35 mm (95% CI −0.62 to −0.08, $I^2 = 95\%$) (Figure 4b), versus the control. Concerning the peripheral plus soft contact lenses, the individual meta-analyses merged the concentric ring

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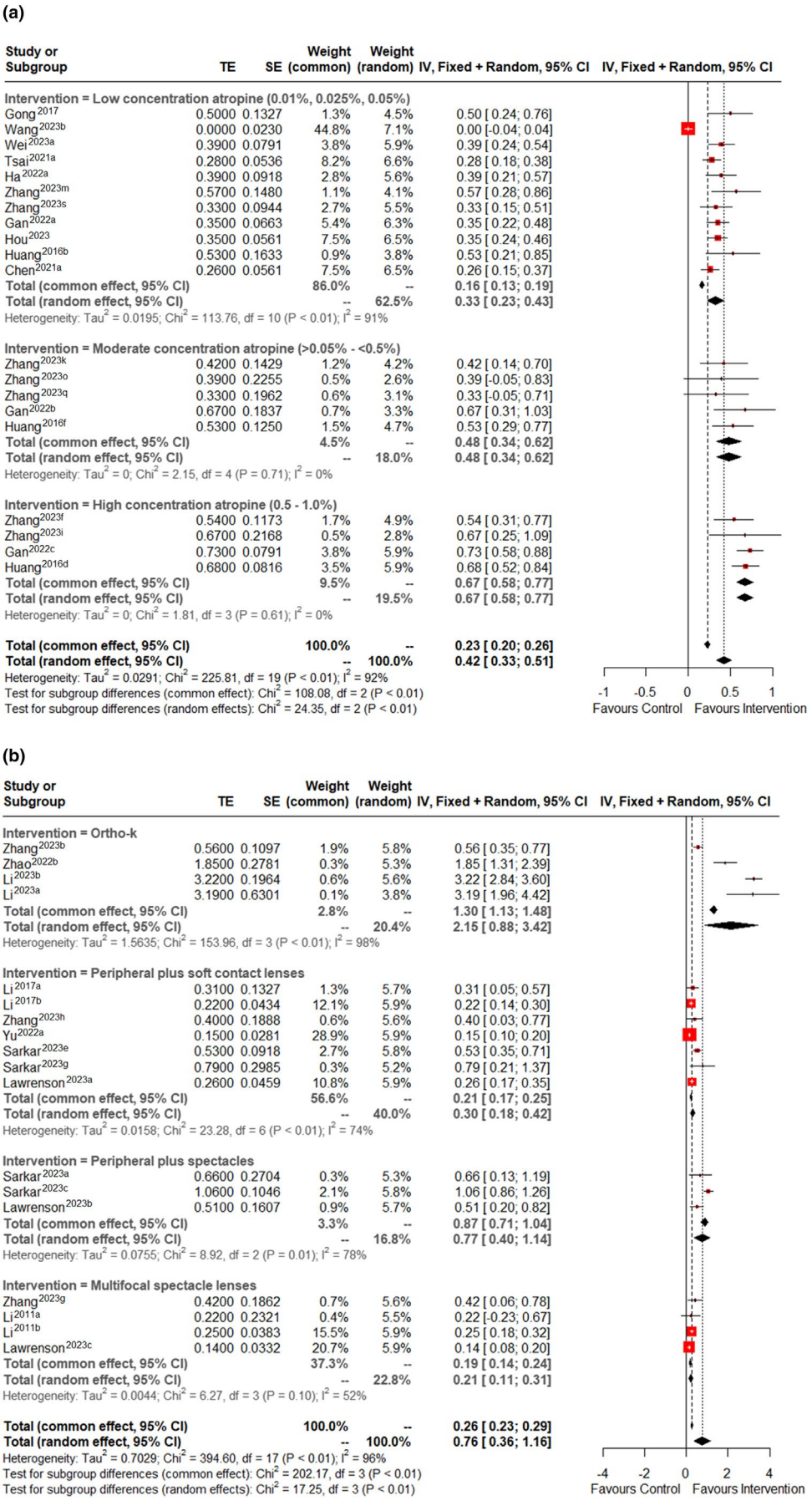

FIGURE 3 Forest plot presenting effect sizes of interventions based on change in refractive error (SER). (a) Pharmacological interventions; (b) optical interventions; (c) outdoor time and repeated low-level red light; (d) combinations of interventions.

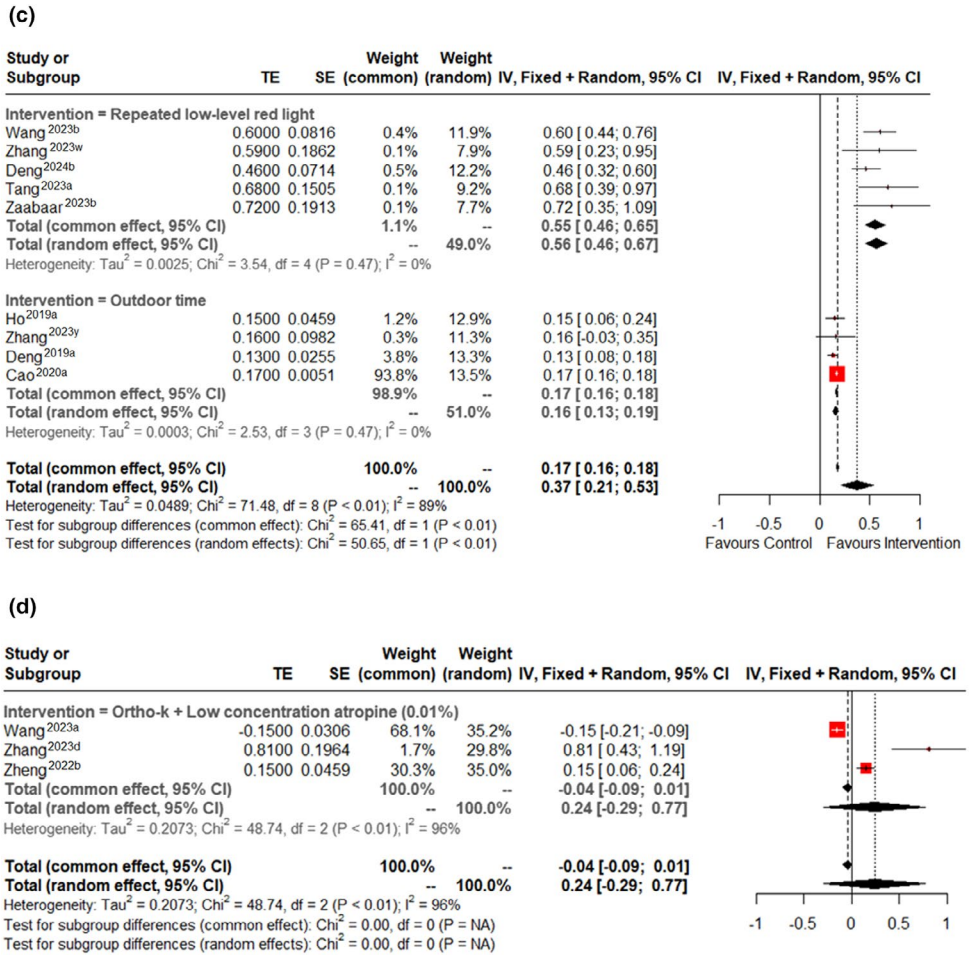

FIGURE 3 (Continued)

dual focus designs, which included MiSight contact lenses (misight.com), with the progressive peripheral add designs.

Standardisation of the myopia control effects of ortho-*k* by 6 months revealed retardation of AL elongation by −0.21 mm (95% CI −0.32 to −0.11, $I^2 = 94\%$), compared to the control condition. Peripheral plus soft contact lenses produced statistically significant myopia control effects on SER progression, 0.19 D (95% CI 0.11–0.26, $I^2 = 74\%$) and AL elongation, −0.26 mm (95% CI −0.49 to −0.04, $I^2 = 97\%$) (Data S4).

Upon annualisation of the myopia control effects of ortho-*k*, AL elongation was slowed by −0.35 mm (95% CI −0.52 to −0.17, $I^2 = 94\%$), compared to the control. Peripheral plus soft contact lenses produced statistically significant myopia control effects on SER progression, 0.30 D (95% CI 0.18–0.42, $I^2 = 74\%$) and AL elongation, −0.35 mm (95% CI −0.52 to −0.17, $I^2 = 94\%$) (Data S5).

Spectacles

The peripheral plus spectacles included peripheral addition and simultaneous defocus designs. The simultaneous defocus designs comprised the Defocus Incorporated Multiple Segments (DIMS) spectacle lenses and the spectacle lenses with Slightly/Highly Aspherical Lenslets (SALs and HALs). The individual meta-analyses pooled the estimates across both designs. Overall, the peripheral plus spectacles delayed SER progression and AL elongation by 0.77 D (95% CI 0.40–1.14; $I^2 = 78\%$) (Figure 3b) and −0.43 mm (95% CI −0.78 to −0.08, $I^2 = 88\%$) (Figure 4b), respectively, compared to the control.

Standardisation of the myopia control effects of peripheral plus spectacles after 6 months revealed retardation of SER progression and AL elongation by 0.13 D (95% CI −0.02 to 0.29; $I^2 = 54\%$) and −0.31 mm (95% CI −0.64 to 0.03, $I^2 = 89\%$), respectively (Data S4). Annualisation of the myopia control effects of peripheral plus spectacles revealed retardation of SER progression and AL elongation by 0.77 D (95% CI 0.40–1.14; $I^2 = 78\%$) and −0.50 mm (95% CI −1.05 to −0.05, $I^2 = 89\%$), respectively (Data S5).

Multifocal spectacles consisted of bifocals and progressive addition lenses with near additions of +1.00 to +2.00 D. Overall, the average SER progression was 0.21 D (95% CI 0.11–0.31, $I^2 = 52\%$) (Figure 3b), i.e., slower for multifocal spectacle wearers than for controls. Among the studies that investigated the myopia control effects

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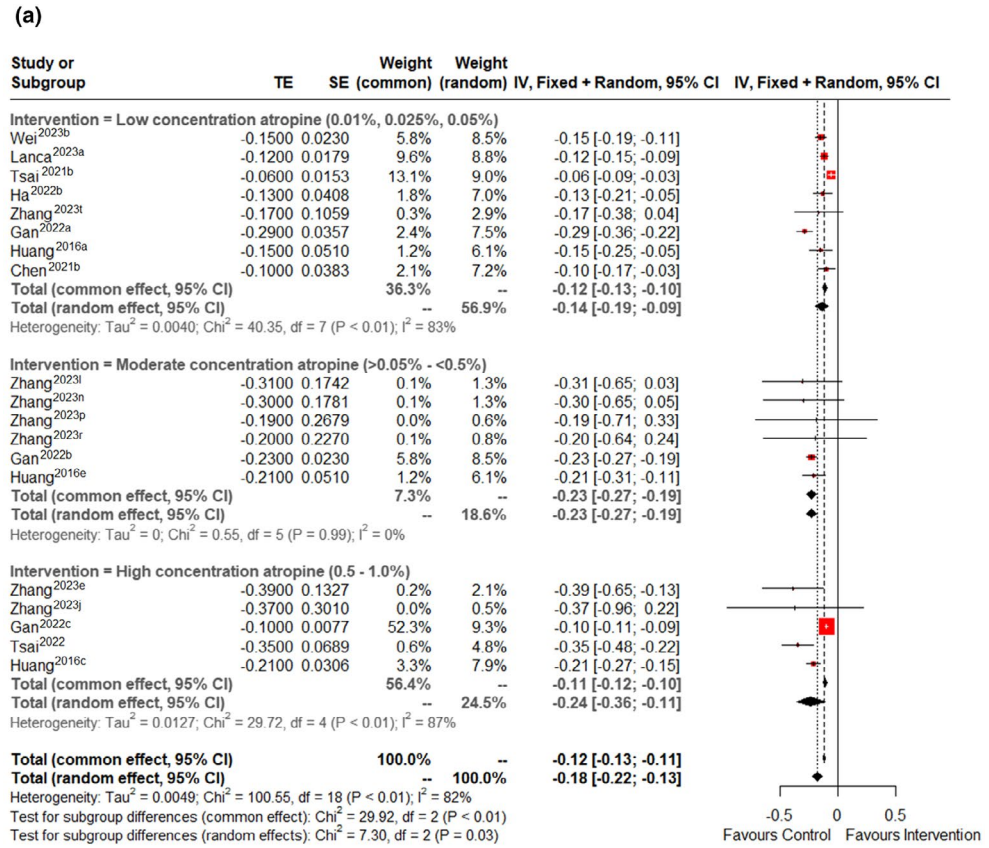

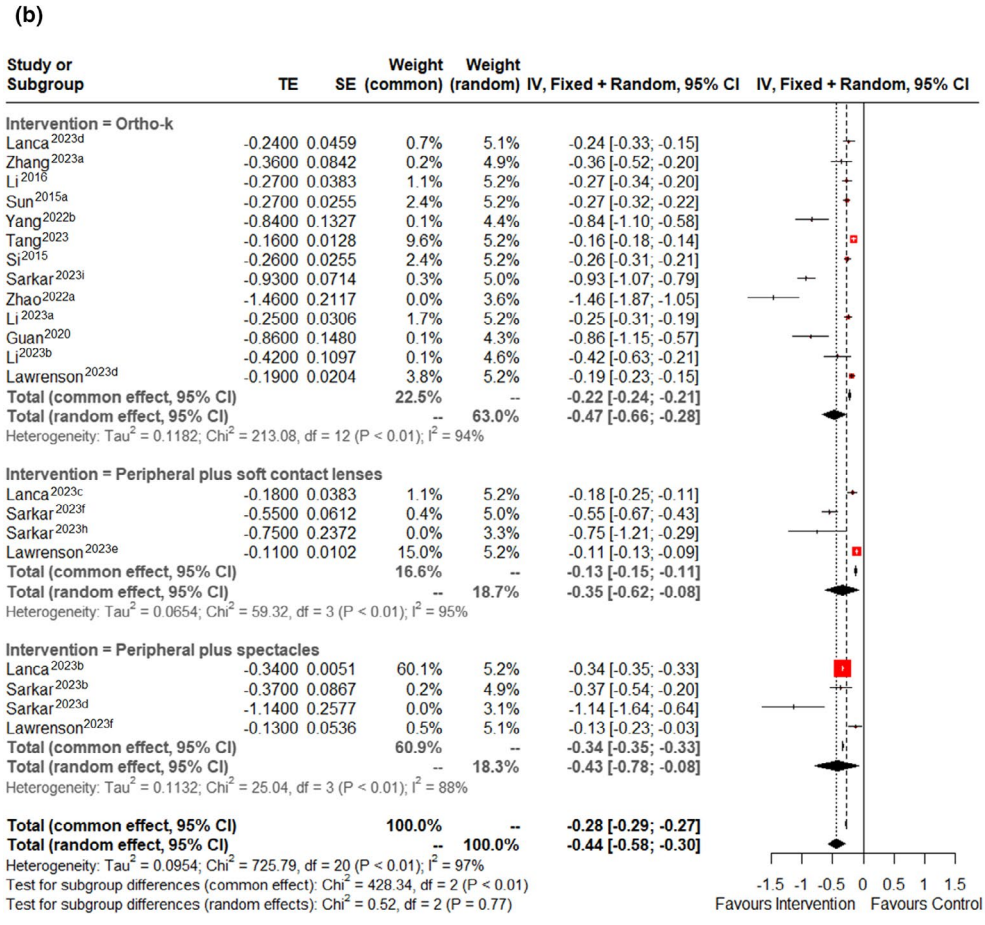

FIGURE 4 Forest plot presenting effect sizes of interventions based on change in axial length (AL). (a) Pharmacological interventions; (b) optical interventions; (c) outdoor time and repeated low-level red light; (d) combinations of interventions.

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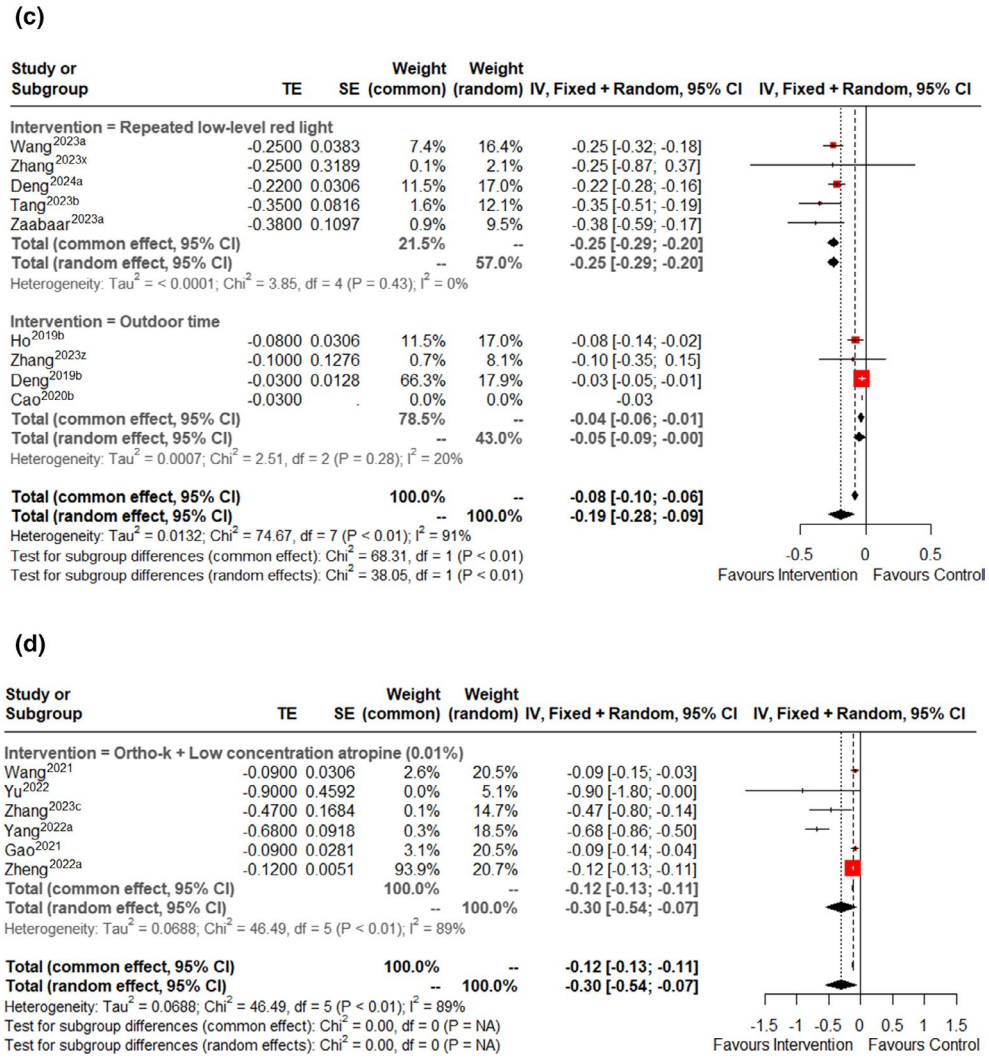

FIGURE 4 (Continued)

of multifocal spectacles, only one estimated the specific effect of these lenses on AL elongation reliably. The remaining studies pooled estimates across different spectacle lens designs, making it difficult to ascertain the specific effects of multifocal spectacles. Hence, pooled estimates for AL elongation are not reported for multifocal spectacles in this review.

Standardisation by 6 months showed retardation of SER progression by 0.13 D (95% CI −0.02 to 0.29, $I^2 = 54\%$) for multifocal spectacle wearers compared with controls (Data S4). Upon standardisation by 1 year, average SER progression was 0.22 D (95% CI −0.03 to 0.47, $I^2 = 54\%$) slower for the multifocal spectacle wearers than controls (Data S5).

Repeated low-level red light

Overall, the myopia control effects of repeated low-level red light on SER progression and AL elongation were 0.55 D (95% CI 0.46–0.65, $I^2 = 0\%$) (Figure 3c) and −0.25 mm (95% CI −0.29 to −0.20, $I^2 = 22\%$) (Figure 4c), respectively, compared to the control. Standardisation of the myopia control effects of repeated low-level red light yielded retardation of SER progression and AL elongation by 0.47 D (95% CI 0.31–0.63, $I^2 = 31\%$) and −0.27 mm (95% CI −0.37 to −0.17, $I^2 = 0\%$), respectively, after 6 months of follow-up (Data S4) and 0.77 D (95% CI 0.50–1.04, $I^2 = 31\%$) and −0.44 mm (95% CI −0.31 to −0.28, $I^2 = 0\%$), respectively, after a year of follow-up (Data S5).

Outdoor time

Increased outdoor time impeded SER progression and AL elongation by 0.17 D (95% CI 0.16–0.18, $I^2 = 0\%$) (Figure 3c) and −0.04 mm (95% CI −0.06 to −0.01, $I^2 = 20\%$) (Figure 4c), respectively, when compared to the control. Standardisation of the myopia control effects of outdoor time yielded retardation of SER progression and AL elongation by 0.08 D (95% CI 0.06–0.11, $I^2 = 0\%$) and −0.03 mm (95% CI −0.06 to −0.00, $I^2 = 20\%$), respectively,

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after 6 months of follow-up (Data S4) and 0.14 D (95% CI 0.09–0.18, $I^2 = 31\%$) and −0.05 mm (95% CI −0.09 to −0.00, $I^2 = 20\%$), respectively, after 1 year of follow-up, compared to the control (Data S5).

Combined therapy

Combining ortho-*k* with low-concentration atropine slowed SER and AL progression by 0.24 D (95% CI −0.29 to 0.77, $I^2 = 96\%$) (Figure 3d) and −0.30 mm (95% CI −0.54 to −0.07, $I^2 = 89\%$) (Figure 4d), respectively, versus the control.

All interventions were statistically significant in controlling SER progression and AL elongation. However, not all had clinically significant effects. High and moderate concentrations of atropine, peripheral plus spectacles and repeated low-level red light demonstrated clinically significant effects on slowing both AL elongation and SER progression. Peripheral plus soft contact lenses and ortho-*k*/low-concentration atropine combined therapy had clinically significant effects on controlling AL elongation but not on SER progression.

Publication bias

Publication bias assessment for interventions with >10 eligible effect sizes was carried out using Egger's test and by visual inspection of funnel plots. The interventions considered were low-concentration atropine (0.01%, 0.025% and 0.05%) on the change in refraction and ortho-k on the change in axial length. The results indicated potential publication bias for the studies included for both interventions.

Visual inspection revealed significant asymmetry in the funnel plots of low-concentration atropine (0.01%, 0.025% and 0.05%) (Figure 5a) and ortho-*k* (Figure 5b), and these were consistent with the results of the Egger's test (low-concentration atropine (0.01%, 0.025% and 0.05%) $Z = 6.42$, $p < 0.001$; ortho-*k* $^*Z = -5.21$, $p < 0.001$. In order to assess the impact of publication bias on the meta-analysis results, a trim and fill analysis was conducted. The analysis revealed that after imputing six studies for the low-concentration atropine (0.01%, 0.025% and 0.05%) intervention and seven studies for ortho-*k*, the adjusted pooled effect estimate did not remain statistically significant (low-concentration atropine (0.01%, 0.025% and 0.05%) $p = 0.13$; ortho-*k* $p = 0.09$) suggesting that the results were sensitive to the imputation.

DISCUSSION

This study presents a meta-synthesis of the existing systematic reviews and meta-analyses on the efficacy of various interventions for slowing myopia progression in juvenile populations. All relevant and methodologically robust systematic reviews and meta-analyses were identified and included in a meta-meta-analysis. Outcomes were defined as changes in SER and AL. All interventions demonstrated statistically significant myopia control effects. Among them, high-concentration atropine, moderate concentration atropine, ortho-*k*, peripheral plus spectacles and repeated low-level red light yielded clinically significant effects on controlling AL elongation. High-concentration atropine, moderate concentration atropine, peripheral plus spectacles and repeated low-level red light yielded clinically significant effects for controlling SER progression. Further, peripheral plus power soft contact lenses and ortho-*k*/low-concentration atropine combined therapy also achieved significant clinical effects in controlling AL elongation but not for controlling SER progression.

Consistent with the findings of the Low-Concentration Atropine for Myopia Progression (LAMP) study,[31] the use of atropine eye drops demonstrated a concentration-dependent efficacy. Moderate and high concentrations of atropine showed clinically significant AL and SER progression control efficacy, which was not seen for low-concentration atropine. While high concentrations of atropine produced clinically significant efficacy in slowing myopia progression, they were associated with a significant rebound in myopia progression and/or side

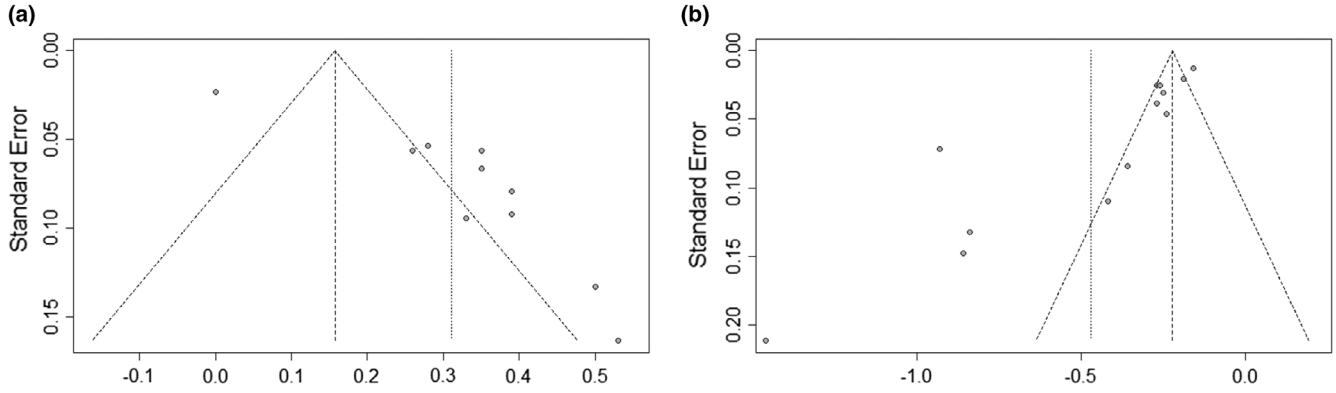

FIGURE 5 Funnel plot of included meta-analyses that reported outcomes based on (a) the low-concentration atropine and (b) orthokeratology interventions.

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effects such as pupil dilation, glare and loss of accommodation.[32–34] Although not maximally effective, the use of low-concentration atropine (0.01%, 0.025% and 0.05%) has grown in popularity, and it is commonly prescribed and recommended for myopia control in many parts of the world.[35] However, there have been suggestions to transition to the use of concentrations >0.01%, with some specifically advocating for a shift to 0.025% and 0.05% atropine to ensure implementation of an effective treatment, particularly for younger children and those at higher risk of myopia-associated complications.[35–39] While future studies on 0.025% and 0.05% atropine are needed in other populations, the progression of myopia to sight-threatening levels will not pause for this evidence to emerge. Therefore, a prudent approach may involve implementing a personalised strategy that includes collaborating closely with patients and their families to identify the most effective and acceptable atropine concentration, considering factors such as efficacy, safety, tolerability and individual preferences.

Ortho-*k* produced greater AL elongation control than the other interventions, yielding a −0.35 mm annual change compared to the control. AL elongation was the only parameter reported for ortho-*k*, as it is difficult to assess myopia progression with refractive measurement when managing with ortho-*k*.[40,41] In a meta-analysis of randomised controlled trials, Li et al.[42] found a comparable AL change of −0.42 mm after 1 year of ortho-*k* lens wear. Some meta-syntheses yielded higher mean differences ranging from −0.84 to −1.46 mm,[43–46] while others demonstrated lower efficacy.[47–49] The myopia control effect of ortho-*k* lenses may vary with their design. Findings from previous studies indicated that lenses with smaller back optic zone diameters may be more advantageous for reducing axial elongation.[50,51] We were unable to stratify the analyses by the different lens designs since such specifications were not made in the individual meta-analyses. The inconsistent findings across various meta-analyses could also be due to variations in the inclusion criteria. Some focused on high-quality randomised controlled trials,[47,52] while others included observational studies or trials with less rigorous designs.[43,45] A common concern with the use of ortho-*k* has been the risk of corneal infections. In their review, Kam et al.[53] reported that the majority of ortho-*k*-related infections resulted in the formation of corneal scars and almost 10% of eyes needed surgical treatment. However, all of the studies they reviewed were case series and case reports, with no level 1 evidence or randomised controlled trial. Meta-syntheses of results from randomised controlled trials, case–control and cohort studies on the use of ortho-*k* for myopia control reported no serious adverse events.[45,54] In any event, appropriate instruction and advice on safe handling, proper maintenance and storage of these lenses, along with hand hygiene, are necessary to mitigate the risk of complications.

Peripheral plus soft contact lenses demonstrated a clinically meaningful effect in controlling AL elongation. However, their effect on slowing SER progression was not as substantial. The peripheral plus soft contact lenses appear to exhibit greater efficacy in controlling myopia as the level of peripheral plus power increased.[40,55] Yet, many of the meta-analyses pooled the results across the various designs and magnitudes of addition power. This may have led to a dilution of the effect, as the lower additions potentially offset a portion of the effect seen with the medium and higher additions. Consequently, the overall SER progression control effect observed in the current study may not have fully captured the potential of the higher peripheral plus power designs. Another plausible reason is the precise measurement of the effect sizes. AL measurements offer greater precision and are less susceptible to errors compared with cycloplegic assessments of refraction.[40] Future meta-synthesis should consider examining the specific impact of different designs and addition powers.

The peripheral plus spectacles achieved meaningful clinical effects on AL elongation and SER progression, with the AL elongation control being closer to that observed with ortho-*k*. Similar to the peripheral plus soft contact lenses, it appears that the efficacy of this spectacle lens design also depends on the magnitude of the peripheral plus power and zones of correction, with the simultaneous defocus designs (DIMS, SALs and HALs) yielding higher efficacy than the peripheral addition designs.[55] The powers of the lenslets in DIMS and HAL lenses were measured as +3.50 and 4.00 D, respectively,[56] and these lenses produce broadly similar results.[57] These powers are higher than the maximum plus power of +2.50 D reported for the peripheral addition designs.[58] Other spectacle lens designs not captured in previous meta-analyses have demonstrated effectivity in controlling myopia progression. These include Diffusion Optics Technology (DOT) lenses, which work by reducing retinal contrast and have been shown to slow AL elongation by 50% and SER progression by 74% after 12 months.[59] Another design, the Cylindrical Annular Refractive Element (CARE) lens, is based on higher-order aberration theory and has resulted in a 23% reduction in AL elongation and a 21% reduction in SER progression over 12 months.[60] Multifocal spectacle lenses (i.e., conventional bifocals and progressive addition lenses) did not yield clinically significant effects on controlling SER progression and AL elongation.

Repeated low-level red light therapy (RLRL) demonstrated significant clinical effects on SER and AL at both the 6- and 12-month follow-up periods, in comparison with the control group. The efficacy of RLRL was reported to be considerably higher in the meta-analysis by Tang et al.,[48] while other meta-analyses indicated a lower efficacy.[46,61] The efficacy of RLRL in slowing SER progression and AL elongation was clinically significant and similar to that of moderate concentrations of atropine, probably because they have overlapping effects on their target tissues. RLRL and 0.05% atropine have both been shown to increase choroidal thickness by approximately 20 μm

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over 2 years.[62,63] More recently, RLRL therapy has demonstrated efficacy for controlling high myopia and enhancing treatment outcomes in children who do not respond well to ortho-*k*.[64,65] The primary clinical trials suggest that RLRL is a low-risk therapy,[63,66] although there is a lack of long-term safety data beyond 2 years. Ostrin and Schill[67] reported that 3 min of continuous viewing of RLRL (the usual treatment duration per session) surpasses the maximum permissible exposure and puts the retina at risk of photochemical and thermal damage. Additionally, a recent case report described an incident in a 12-year-old girl who experienced a temporary decrease in best-corrected visual acuity following 5 months of regular RLRL exposure for myopia management.[68] Fundus photographs revealed darkening of the foveae and macular hypoautofluorescence, and there were disruptions in the foveal ellipsoid zone and interdigitation zone on optical coherence tomography scans. After discontinuing RLRL therapy for 3 months, the outer retinal damage showed signs of recovery and the patient's visual acuity improved. While this case may represent an atypical or isolated event, potentially related to individual sensitivity to the phototoxic effects of red light, it underscores the importance of maintaining vigilance through thorough clinical assessments. Ongoing monitoring of visual acuity, colour sensitivity and comprehensive retinal health evaluations are crucial for patients undergoing long-term RLRL therapy.

The efficacy of outdoor time for myopia control was the lowest found here. While outdoor time demonstrated good efficacy in delaying myopia onset,[69,70] limited evidence exists regarding its efficacy for controlling myopia progression in already myopic children. There has been little or no clinically beneficial effect shown across studies. This could be because the sensitivity of the myopic eye to spending time outdoors diminishes. Longitudinal chromatic aberration (LCA) provides a signed signal under white light viewing conditions,[71,72] and it has been demonstrated that the ability of the retina to use the difference in focus between blue and red light to determine the sign of defocus for emmetropisation is lost in myopes.[71,73,74] Outdoor time can still be considered as an adjunct therapy along with other clinical interventions for myopia control. Promoting increased outdoor time is a simple and low-cost strategy that can be easily implemented by schools, communities and families, and seamlessly integrated with other interventions to synergistically slow the progression of myopia once it develops.

Combining ortho-*k* with 0.01% atropine was better at slowing AL elongation than using 0.01% atropine alone, but not better than ortho-*k* monotherapy. A greater proportion of the synergistic effect may have resulted from the ortho-*k* lenses due to the lower efficacy of 0.01% atropine. Future studies can explore combining relatively higher concentrations of atropine with ortho-*k*. Combining ortho-*k* with RLRL has been reported to achieve a better additive effect, even in children who do not respond well to ortho-*k*.[64]

Interventions that were clinically beneficial for controlling AL elongation but not SER progression can still be employed for the clinical management of myopia. This is because measurements of AL are more precise than those of SER, and can reliably detect smaller changes in eye growth.[75,76] Besides, it is recommended that AL be considered the primary outcome for determining progression in myopia management.[75,77]

Strengths and limitations

Several meta-analyses on myopia control interventions have been conducted. To the best of our knowledge, this will be the first meta-meta-analysis of myopia control interventions. A meta-meta-analysis, by combining multiple meta-analyses, enhances statistical power. This increased power can lead to more precise effect size estimates and more robust conclusions.

A comprehensive search was conducted across three databases in accordance with a pre-specified protocol. The methodological quality and statistical evidence of the included reviews were carefully evaluated to gauge the robustness of the available evidence. However, there was some overlap between the meta-analyses, which may present a minor risk of skewed reporting. Additionally, the search strategy was limited to reviews published in the English language; hence, the possibility exists of omission of relevant studies published in other languages. There was also substantial heterogeneity in terms of study populations among the primary studies included within each systematic review and meta-analysis. Moreover, some meta-analyses pooled effect sizes across various subcategories of particular interventions. As a result, the specific effects of some individual strategies could not be assessed. The limitations of the underlying evidence are acknowledged and the findings should be interpreted with appropriate caution.

In conclusion, high-concentration atropine, moderate-concentration atropine, ortho-*k*, peripheral plus power spectacle lenses and RLRL therapy yielded clinically significant effects in retarding AL elongation and SER progression. Given that the primary rationale for myopia control is to mitigate the future risks of sight-threatening ocular complications, it is crucial to ensure the timely implementation of the most effective interventions. This is especially critical for younger children and those at greater risk of rapid myopia progression, as they face an elevated likelihood of developing serious eye problems and vision loss over time. Factors such as the patient's age, degree of myopia, speed at which their myopia progresses, family history and race should guide clinicians in making the appropriate choice.

AUTHOR CONTRIBUTIONS

Ebenezer Zaabaar: Conceptualization (lead); methodology (equal); supervision (equal); writing – review and editing (equal). **Randy Asiamah:** Data curation (equal); formal

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analysis (equal); investigation (equal); methodology (equal); software (equal); visualization (equal); writing – original draft (lead); writing – review and editing (equal). **Samuel Kyei:** Investigation (equal); methodology (equal); project administration (equal); resources (equal); supervision (equal); writing – review and editing (equal). **Samuel Ankamah:** Data curation (equal); investigation (equal).

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CONFLICT OF INTEREST STATEMENT

All authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data used for this study are available from the corresponding author upon reasonable request.

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