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Comparative Effectiveness of Feasible Myopia Control Interventions for Children in Indonesia: A Systematic Review and Network Meta-Analysis

Sabrina Brigitta Valerie Setiono[*1], Richella Miranda Wynne Setiono[1]
[1]*Faculty of Medicine, University of Sam Ratulangi, Manado, Indonesia, 95115*
[*]Corresponding Author: sabrinasetiono011@student.unsrat.ac.id

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ABSTRACT

Background: **:** Myopia in children is a growing public health concern in Indonesia, leading to long-term visual impairment and economic burden. Early intervention is crucial, yet no study has comprehensively compared axial length (AL) changes among feasible interventions for Indonesian children. **Objectives:** This study aims to evaluate and compare the efficacy of feasible myopia control strategies for children in Indonesia using a systematic review and network meta-analysis (NMA), focusing on AL changes. **Methods:** Following the PRISMA-NMA guideline, systematic searches up to 8 April 2025 were carried out in four online databases, including Europe PMC, PubMed, Sage Journals, and Wiley. Randomized studies measuring the AL of different myopia control interventions to placebo or each other were included. A total of 1266 titles and abstracts were screened, and 18 studies were included in the analysis. A Bayesian NMA was conducted using the "gemtc" package in RStudio, with mean difference (MD) and 95% credible interval (CrI) as summary measures. **Results:** Eighteen randomized studies involving 2145 children were included. The combination of low-dose atropine 0.01% and orthokeratology (ACO) showed the most effective reduction in axial elongation (SUCRA: 0.078). SVS alone ranked lowest in effectiveness (SUCRA: 0.9986). ACO consistently outperformed monotherapies and control interventions in slowing myopia progression. **Conclusion:** ACO is the most effective intervention for controlling myopia progression in children and holds promising applicability in Indonesia. These findings support its recommendation in clinical and public health settings, though further research involving Indonesian populations and safety outcomes is warranted.
Keyword: Axial length, control interventions, efficacy, myopia progression, network meta-analysis

ABSTRAK

Latar Belakang: Miopia pada anak-anak merupakan masalah kesehatan masyarakat yang terus berkembang dan semakin mengkhawatirkan di Indonesia, karena menyebabkan gangguan penglihatan jangka panjang dan beban ekonomi bagi penderitanya. Intervensi dini menjadi sangat penting, namun belum ada penelitian yang secara komprehensif membandingkan perubahan *axial length* (AL) di antara intervensi yang layak digunakan oleh anak-anak di Indonesia. **Tujuan:** Penelitian ini bertujuan untuk mengevaluasi dan membandingkan efektivitas strategi pengendalian miopia yang layak untuk anak-anak di Indonesia menggunakan tinjauan sistematis dan *network meta-analysis* (NMA), dengan fokus utama pada perubahan AL. **Metode:** Mengikuti pedoman PRISMA-NMA, pencarian sistematis hingga 8 April 2025 dilakukan di empat basis data daring, termasuk Europe PMC, PubMed, Sage Journals, dan Wiley. Penelitian acak yang mengukur AL dari berbagai intervensi pengendalian miopia terhadap plasebo atau satu sama lain disertakan. Sebanyak 1266 judul dan abstrak disaring, dan 18 penelitian disertakan dalam analisis. NMA Bayesian dilakukan menggunakan paket "gemtc" di RStudio, dengan *mean difference* (MD) dan 95% *credible interval* (CrI) sebagai ukuran ringkasan. **Hasil:** Delapan belas studi acak yang melibatkan 2145 anak-anak disertakan. Kombinasi atropin dosis rendah 0,01% dan

orthokeratology (ACO) menunjukkan pengurangan paling efektif dalam pemanjangan aksial (SUCRA: 0,078). SVS sendiri memiliki peringkat terendah dalam efektivitas (SUCRA: 0,9986). ACO secara konsisten mengungguli monoterapi dan intervensi kontrol dalam memperlambat perkembangan miopia. **Kesimpulan:** ACO adalah intervensi paling efektif untuk mengendalikan perkembangan miopia pada anak-anak dan memiliki peranan yang menjanjikan di Indonesia. Temuan ini mendukung rekomendasinya dalam pengaturan klinis dan kesehatan masyarakat, meskipun penelitian lebih lanjut yang melibatkan populasi Indonesia dan hasil keamanan diperlukan.

Kata Kunci: hiperplasia prostat jinak, LUTS, tamsulosin, tadalafil, terapi kombinasi Axial length, control interventions, efficacy, myopia progression, network meta-analysis

1. Introduction

Myopia, also known as shortsightedness or nearsightedness, is the most common ocular disorder worldwide that develops primarily during childhood.[1] The prevalence of myopia starts to rise significantly after the age of six and generally stabilizes in late adolescence.[2] Approximately 50% of the global population, is affected by this condition, making it a major public health concern.[3] In Asian countries, 60–90% of young adults report having myopia compared to Europe (45%). In addition, the prevalence of myopia is escalating rapidly in numerous countries. The prevalence of myopia among school-age children (ages 6–19 years) in Indonesia is reported to be 32.68%, while in individuals aged over 21 years, it reaches 48.1%. A particularly worrisome trend is that individuals diagnosed at an earlier age are at greater risk of developing more severe myopia-related complications later in life, such as retinal detachment, macular degeneration, and glaucoma, which can contribute to loss of vision and, ultimately, blindness.[4,5] This disorder is typically characterized by a refractive anomaly of the eye in which parallel light rays focus in front of the retina when the eye is in a relaxed state, leading to blurred vision for distant objects while nearby objects remain clear.[6] It most commonly occurs due to an elongated eyeball (excessive axial length), but can also result from overly powerful image-forming components of the eye.[7] Therefore, the increased value of axial length is associated with the risk of its complications.[4]

Donovan *et al.* in 2012 showed that the rate of myopia progression differs widely, with Asian children experiencing progression about 0.20 diopters per year faster than European children of the same age.[8] Progressive myopia is a form of nearsightedness that gradually worsens over time, potentially leading to high myopia, defined as –5 or –6 diopters or greater and associated with excessive eyeball growth, which significantly increases the risk of serious vision-threatening conditions such as presenile cataract, myopic maculopathy, macular hemorrhage, choroidal neovascularization, glaucoma, and retinal detachment.[1,9] Myopia in children also has a negative impact on children's cognitive development, social interactions, academic achievement, and psychological well-being.[10,11] Therefore, myopic children require prompt and accurate treatment to restore visual acuity and prevent consequences related to improper correction.[12,13]

Myopia also imposes a considerable socioeconomic burden. In the United States alone, annual costs for eye care and vision correction are estimated at $4.6 billion. Moreover, complications stemming from high myopia tend to affect individuals during their most economically productive years. Since myopia represents a significant public health issue, placing a substantial health and economic burden on society. Identifying and implementing a safe and effective way during childhood to slow its progression is crucial to reduce this impact.[12,14]

Strategies to slow myopia progression can be broadly classified into three main types, including optical, pharmacological, and environmental (behavioral) approaches. Optical approaches involve the use of various designs of spectacles and contact lenses. Spectacles are the least invasive choice that are easy to fit, generally well-accepted and tolerated, also reasonably affordable for most people. Spectacle options include single-vision (SV) lens designs with or without undercorrection, SV peripheral defocus-correcting lenses, bifocal, peripheral defocus modifying spectacle lenses, and progressive addition spectacle lenses.[15] However, five of these six lenses, except the SV spectacle lens without undercorrection, faced several shortcomings related to small and nonsignificant effects in controlling myopia in children in some clinical trial studies which led to their exclusion from this review. Apart from being widely used in Indonesia, corrected spectacle lenses offer several advantages over other optical interventions for slowing myopia progression in children, as they are simple to fit, generally well accepted and tolerated, affordable for most families, and minimally invasive. For contact lenses, orthokeratology (Ortho-k) is included in this review due to its usage relevance.[16] A meta-

analysis reported that ortho-k is effective, reducing myopia progression by approximately 50% over two years.[17,18]

Topical pharmacological interventions, which are included in this review, for myopia control is atropine. Atropine eye drop is a nonselective muscarinic receptors (located in the ciliary muscle, retina, and sclera) antagonist that has been used for myopia control for some years.[19-21] It is thought to slow myopia progression by preventing the retina and sclera from thinning and stretching. This statement is supported by the Atropine for the Treatment of Myopia (ATOM) 1 study which found that nightly 1% atropine eye drops in one eye over two years significantly inhibited myopia progression by 77%, and unlike the control group (0.39 mm), prevented any axial lengthening of the eyeball. However, many parents are hesitant to use traditional atropine treatment due to side effects like blurred near vision, light sensitivity (photophobia), and increased UV exposure.[16,20,21] Recent studies, like the ATOM 2 trial, show that LDA eyedrops (0.01%) effectively slow myopia progression with fewer side effects and less rebound effect after stopping treatment, making it a more favorable option.[22-24]

Myopia, particularly in its progressive form, has emerged as a global public health challenge with significant visual, social, and economic consequences. In Indonesia, the prevalence of myopia among children and young adults continues to rise, yet optimal preventive and control strategies remain underutilized. Therefore, synthesizing existing data is necessary to determine the most effective myopia progression control interventions to provide more apparent control strategies for managing myopia. This network meta-analysis (NMA) aims to critically evaluate and identify myopia control strategies from randomized studies that present superior results in axial length (AL) change. This NMA also seeks to highlight the efficacy of these approaches that have potential applications in Indonesia to support evidence-based recommendations for clinical practice and public health policy. A NMA allows for comparing many myopia control strategies, including their combinations. It provides a quantitative comparison between these groups, thus synthesizing the optimal myopia progression control interventions.

2. Method

This systematic review and NMA discussing the impact of various myopia progression control interventions were conducted based on the Preferred Reporting Items for Systematic Review and Meta Analysis Network Meta-Analyses (PRISMA NMA) checklist of items and guided by the Cochrane Handbook for Systematic Reviews of Interventions.

2.1 Search Strategy

Literature search was performed across multiple databases including Europe PMC, PubMed, SAGE Journals, and Wiley. The search focused on studies related to myopia control strategies, with data up to April 8th, 2025. The primary keyword searches used in searching for this study were "atropine", "orthokeratology", and "myopia". Medical Subject Headings (MeSH) terms linked to the main search keywords with Boolean operators (AND, OR, NOT) were also employed to expand and specify the intended study. The detailed keywords for each database are attached in **Appendix 1**. Suitable advanced search techniques were applied whenever appropriate. Restriction on study findings by year of publication and study language was not carried out during the literature search.

2.2 Data Sources and Search Strategy

When collecting articles, the author adheres to specific inclusion and exclusion criteria based on the Population, Intervention, Comparison, Outcome, Study Design (PICOS) framework, as outlined in **Table 1**. From this framework, inclusion and exclusion criteria were developed and implemented in studies' screening. Studies to be included fulfill the requirements: (1) studies that used the myopia control strategies which are possible to be applied in Indonesia, listed in **Table 1**, as a treatment for children diagnosed with myopia; (2) Randomized Controlled Trials (RCTs) studies; (3) RCTs reporting ophthalmic parameter of myopia progression outcome, such as AL; and (4) studies that included an active comparator or placebo. In terms of exclusion criteria, the following conditions are applied: (1) studies lacking a control group; (2) studies mentioning outcomes without providing estimates; (3) review articles, editor's letters, case reports, case studies, and posters; (4) articles available only in abstracts and keyword form or full-text is not retrievable; (5) inappropriate or irrelevant title and abstract; (6) articles originating from unreliable sources; (7) patient with story or presence of strabismus, ocular trauma, other ocular diseases, systemic diseases, or had received other myopia control treatment; and (8) non-human clinical trials.

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Table 1. PICOS framework

Components of PICOS	Description
Population	Children aged ≤18 years with myopia
Intervention	Different types of myopia progression control interventions, such as: - Pharmacological approach (PA): LDA 0.01% - Optical approach (OA): Ortho-K, SVS - Combination: PA-OA (ACO, etc.)
Comparison	Different types of myopia progression control interventions, including head-to-head comparisons with a control group, and placebo
Outcome	AL (mm)
Study Design	RCT

ACO, low-dose atropine 0.01% combine with orthokeratology; *AL*, axial length; *D*, dioptre; *LDA 0.01%*, low-dose atropine 0.01%; *mm*, millimeter; *OA*, optical; *Ortho-K*, orthokeratology; *PA*, pharmacological; *PICOS*, population, intervention, comparison, outcome, study design; *RCT*, randomized controlled trial; *SVS*, single-vision spectacle lens.

The study population comprises children aged less than or 18 years who were diagnosed with myopia and express a willingness to participate in the research. Various methods of myopia interventions are considered. In terms of outcomes, articles were included if they addressed ophthalmic parameters of myopia progression outcomes as part of their primary or secondary focus.

The collection of study search results from databases was compiled into Rayyan AI (https://www.rayyan.ai/), which has been tested for use in study selection. Duplication detection was carried out both automatically and manually by excluding studies with more than 90% similarity. Prior to screening, a "blind-on" mode was enabled to minimize subjective bias during the selection process. Studies were excluded if their titles and abstracts did not meet the predefined eligibility criteria. Additionally, non-full-text articles and conference abstracts were also removed. The PRISMA flow diagram will present the reasons for the exclusion and the number of studies obtained from the selection process. All investigators (SBVS, RMWS) conducted the literature search and screening overall to completion. Conflicts of screening judgment and disagreement were resolved together in the discussion.

2.3 Outcome

The primary outcome of this study is the change AL expressed in millimeter (mm) expressed in diopters (D) at 12-month compared to baseline. Axial length or axial elongation is defined as the length of the eyeball from the front (cornea) to the back (retina, specifically the fovea), measured via the optical biometry before cycloplegia use. In this study, an increase in AL at the 12th month compared to baseline means that at the 12th month, there was an elongation of the eyeball which indicates myopia progression. Meanwhile, a slowdown in AL indicates an inhibition in the growth of the eyeball length which is an indication of successful myopia control or good therapeutic effects

2.4 Data Extraction

In conducting this systematic review and NMA, we employed a structured data extraction approach. Data extraction on studies was conducted to arrange the characteristics of the included studies and perform statistical analysis. A predefined tabular data extraction sheet was utilized to systematically capture all pertinent details from the included studies. The following items were extracted from each study to structure the characteristics of included studies: (1) author and year of publication; (2) study characteristics, including location study design, and study duration; (3) population demographics, featuring sample size, participant's characteristics, participant's age (mean and standard deviation (SD) for normal distribution data, while median and interquartile range (IQR) for non-normal data distribution), participant's body mass index (BMI), participant's sex, and also participant's baseline AL; (4) detailed intervention and control (treatment arms) group's description, outlining the nature of intervention and control group, as well as the intervention methods/types

and dose, and (5) primary and secondary outcomes measures, with a specific emphasis on AL change at 12-month, including baseline and post-treatment scores. The mean and standard deviation (SD) of the AL from all of the treatment arms were extracted. In cases where studies reported standard error (SE) instead of standard deviation, the SD was calculated by multiplying the SE with the square root of the sample size, as recommended by the Cochrane Handbook for Meta-Analysis.

2.5 Quality Asssessment

The quality assessment of all included studies was done using the version 2 of the Cochrane Collaboration's risk-of-bias tool for randomized trials (RoB 2.0), which has five domains (plus domain S for crossover trials) and three rates for studies. All reviewers evaluated the study quality separately, and any discrepancies that arose were resolved through consensus discussions among the reviewers. The overall quality checks are compiled in the domain file "bias (.xlsx)" and subsequently uploaded to the ROBVIS website for risk of bias visualization.

2.6 Statistical Analysis

Statistical analyses were conducted using RStudio version 4.3.3. A pairwise random-effect model meta-analysis comparing the treatment arms using direct evidence or head-to-head comparisons available in inclusion literatures (**Table 2** for AL change at 12-month) was conducted using the summary measure of mean difference (MD) with a 95% CI via the "meta" package in R version 4.3.3 on Rstudio. We also assessed the heterogeneity with the I^2 statistic, with I^2 values greater than 50% indicating substantial heterogeneity. Meta-regression was performed with publication year, intervention sample size, intervention duration, continent, treatment arms, and/or risk of bias as moderator variables.

Table 2. Available direct evidence of treatment arms comparisons for AL change

Direct Evidence for AL Change	
LDA 0.01% + SVS	Placebo + SVS
ACO	Placebo + Ortho-K
LDA 0.01% + SVS	Ortho-K
Ortho-K	SVS
ACO	Ortho-K
ACO	SVS
LDA 0.01% + SVS	SVS
LDA 0.01% + SVS	ACO

ACO, low-dose atropine 0.01% combined with orthokeratology; *AL*, axial length; *LDA 0.01%*, low-dose atropine 0.01%; *LDA 0.01% + SVS*, low-dose atropine 0.01% combined with single-vision spectacle lens; *Ortho-K*, orthokeratology; *Placebo + Ortho-K*, placebo in combination with orthokeratology; *Placebo + SVS*, placebo in combination with single-vision spectacle lens; *SVS*, single-vision spectacle lens.

A random-effect model, Bayesian network meta-analysis, comparing the AL change at 12-month of different myopia progression intervention methods was performed using the "gemtc" package in R version 4.3.3 on Rstudio with arm-based approach. Analysis was performed with the summary measure of mean difference (MD) and a 95% credible interval (CrI). A network graph was generated to analyze the network's geometry. A surface under the cumulative ranking (SUCRA) curve was generated for each analysis. The node-splitting method assessed local inconsistency by separating direct and indirect evidence.

3. Result

3.1 Study Selection

Out of the 313 studies that passed the eligibility test, 30 studies aligned with the author's inclusion and exclusion criteria. Among these, 157 studies have intervention methods those are not listed in **Table 1**; 36 studies did not meet the participants criteria (both in terms of age, diagnosis, and other participant provisions

that have been mentioned previously); eight studies have no outcomes regarding the change in AL at 12-month; 32 studies while mentioning outcomes, did not present estimations or missing data; eight studies lacked or did not provide a control group; 42 studies have a different study or intervention duration that furthermore causing the outcome at the 12th month to be unavailable; and and 18 studies involve interventions that do not form indirect comparisons. As a result, these latter 295 studies were excluded from the analysis.

Therefore, out of the 313 eligible studies selected for the final screening, 18 RCT studies consisting of Cho *et al.* (2012),[25] Fang *et al.* (2022),[26] Guo *et al.* (2024),[27] Hao *et al.* (2021),[28] Hiraoka *et al.* (2012),[4] Jakobsen *et al.* (2022),[29] Kinoshita *et al.* (2018),[30] Lee *et al.* (2025),[31] Lin *et al.* (2023),[32] Sharma *et al.* (2023),[33] Tan *et al.* (2020),[34] Tan *et al.* (2023),[35] Xu *et al.* (2022),[36] Yam *et al.* (2019),[9] Yu *et al.* (2022),[37] Zhang *et al.* (2021),[38] Zhao *et al.* (2021),[39] and Zhu *et al.* (2023)[40] involving 2,145 children were included in this study. Seven of the 18 included studies had a multi-arm design and among 18 studies contributing to the analysis, two main types, optical and pharmacological, approaches and the combination of myopia progression control strategies were involved. There are some studies comparing interventions outside the main network that must be excluded for NMA because they form disconnected subnetworks, which do not allow modeling of indirect relationships between all interventions in the network analysis. Also, comparisons that are only discussed by one study will not be made into forest plots for pairwise meta-analysis. The PRISMA diagram flow details the study selection process (**Figure 1**).

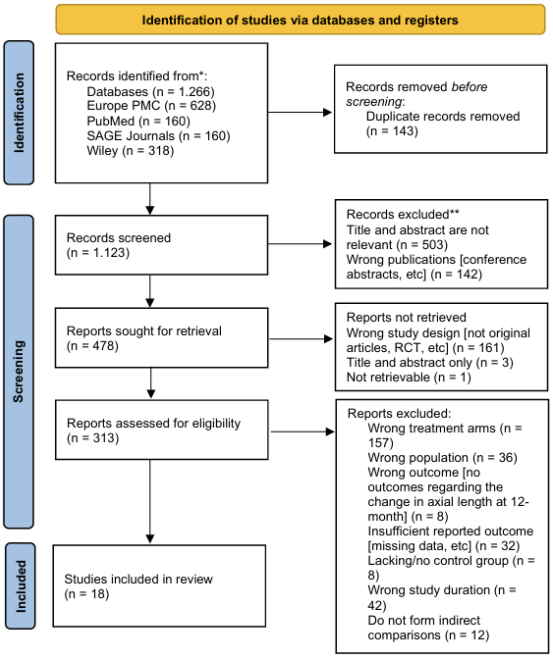


Figure 1. PRISMA diagram flow of the study selection

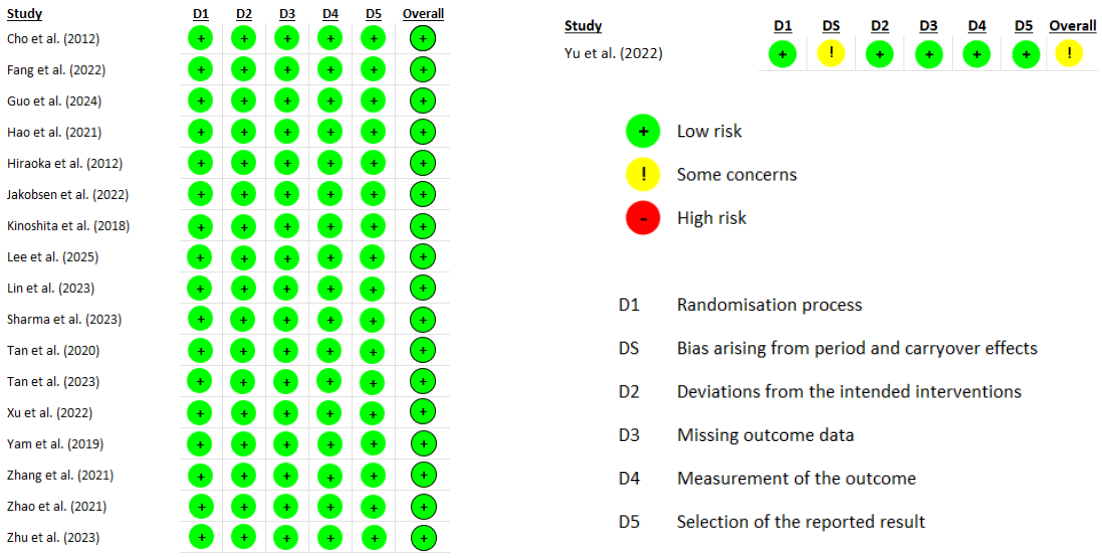
3.2 Quality Assessment of Included Studies

The quality of the 30 RCTs included in this study was assessed using the Cochrane risk-of-bias tool for randomized trials version 2 (RoB 2), which focuses on five domains: (1) bias due to the randomization process, (2) deviation from intended intervention, (3) missing outcome data, (4) measurement of outcomes, (5) selection of the reported result, and "overall risk of bias" judgement. For crossover trials, domain S exists to assess possible bias arising from period effects and carryover effects. These domain-level assessments form the foundation for determining the overall risk of bias for the specific outcome under evaluation. The "overall risk of bias" judgement in RoB 2 uses the same categories as those applied to individual domains: 'low risk of bias', 'some concerns', and 'high risk of bias'. The criteria used are as follows:

- Low risk of bias: all domains are rated as low risk;
- Some concerns: at least one domain raises some concerns, but none are rated as high risk;
- High risk of bias: at least one domain is rated as high risk, or multiple domains raise concerns that significantly reduce confidence in the outcome.

The assessment results are presented in the traffic light plot and the summary plot. The assessment results, represented in a Risk of Bias graph (**Figure 2**), indicate that the majority of the studies show a low risk across most domains. Yu *et al.* (2022)[37] demonstrated a low risk in all domains except for an unclear risk in the domain S due to insufficient information related to the carryover effect and washout period. However, we still

include this study because in a crossover trial, we only use data from the first period before the crossover occurs. The other 17 RCT studies maintained a low risk across all evaluated domains.



(A) **(B)**

Figure 2. (a) risk of bias assessment graph of the included randomized studies on RoB 2.0; (b) risk of bias assessment graph of the included crossover randomized study on crossover RoB 2.0.

3.3 Demography and Clinical Characteristics of the Included Studies

This systematic review and NMA used thirty RCTs and randomized crossover trials as its source of data and information. For crossover trials (Yu *et al.*, 2022), we included only the data from the first phase before the crossover occurred and, as a result, applied the version of the tool designed for parallel trials. Published between 2004 and 2025, these studies compare various methods of myopia interventions for children with myopia, focusing on the AL change at the 12th month of each intervention group as the outcome. The complete study characteristics can be seen in **Appendix 2.**

3.4 Pairwise Efficacy Comparison between the Treatment Arms on the AL Outcome

Direct treatment estimates from pairwise meta-analyses comparing optical, pharmacological, and combination to control or placebo are presented below. We evaluated myopia progression by measuring the mean change in AL from baseline to 12th month. To aid in interpreting the forest plots, negative MDs in AL measurements indicate greater axial elongation in the control group, so estimates to the left of the null line favor the experimental.

3.4.1 Pairwise Efficacy Comparison between the Combination of Low-Dose Atropine 0.01% and Single-Vision Spectacle Lens (LDA 0.01% + SVS) and Placebo + SVS

The myopia progression, depicted by an ascension in AL value at 12th month, among participants who receive placebo + SVS is greater and statistically significant compared to the LDA 0.01% + SVS participants (MD: -0.14; 95% CI: -0.27 – -0.01; **Figure 3**). Significant considerable heterogeneity was present (I^2: 79.3%; $p < 0.01$; **Figure 3**).

The meta-regression results showed that the publication year variable was not a significant predictor of the difference in effects between studies ($R^2 = 0\%$; $p > 0.05$; **Table 3**), so this moderator did not explain the observed heterogeneity. Also, the results in **Table 3.** showed that sample size and treatment arms were not significant sources of heterogeneity (95% CI:-0.0002 – 0.0027; p-value > 0.05 and 95% CI:-0.2095 – 0.1755 p-value > 0.05, respectively). However, there was still high and moderate heterogeneity not accounted for by publication year and sample size, with 76.33%, 47.36%, and 89.58%, respectively. Intervention durations among studies was a significant source of heterogeneity (95% CI:-0.0285 – -0.0059; p-value: 0.0029; **Table 3**). For every 1 month increase in intervention/study duration, there was a reduction of 0.0172 MD. Study location/continent was not further analyzed by meta-regression because it did not show any differences according to those listed in the demographic and clinical characteristics table (**Appendix 2**). Bubble plot of publication year, sample size, intervention duration, and treatment arms meta-regression can be seen in **Figure 4.**

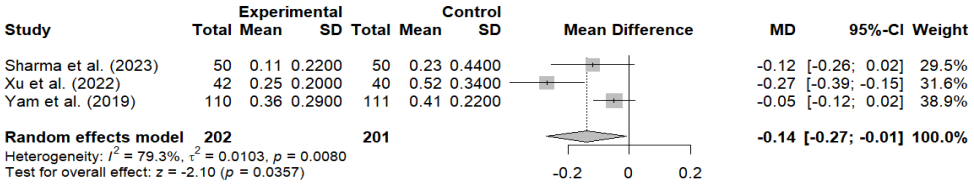
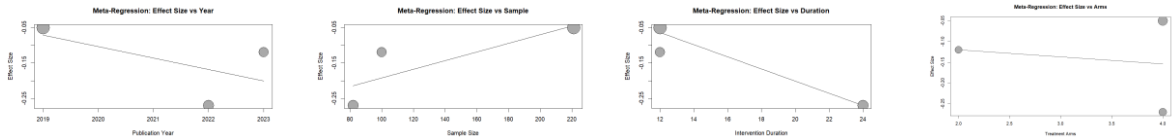


Figure 3. Forest plot for the comparison between LDA 0.01% + SVS and placebo + SVS.

Table 3. Result of meta-regression with publication year, intervention sample size, intervention duration, treatment arms, and risk of bias as moderator variables.

Moderator	Estimate	Lower CI	Upper CI	SE	P-value	R-square	I-square
Publication year	-0.0323	-0.1156	0.0510	0.0425	0.4471	0.00%	76.33%
Intervention sample size	0.0012	-0.0002	0.0027	0.0007	0.0960	61.67%	47.36%
Intervention duration	-0.0172	-0.0285	-0.0059	0.0058	0.0029	100.00%	0.00%
Treatment arms	-0.0170	-0.2095	0.1755	0.0982	0.8626	0.00%	89.58%

CI, confidence interval; *SE*, standard error; *R-square*, accounted heterogeneity; *I-square*, residual heterogeneity.



(A) **(B)** **(C)** **(D)**

Figure 4. Bubble plot of meta-regression with publication year (A), intervention sample size (B), intervention duration (C), and treatment arms (D).

3.4.2 Pairwise Efficacy Comparison between the Combination of Low-Dose Atropine 0.01% and Orthokeratology (ACO) and Placebo + Ortho-K

The results from this pairwise meta-analysis showed that the progression of myopia is greater and statistically significant in the ACO group compared to the placebo + Ortho-K group (MD: -0.07; 95% CI: -0.13 – -0.01; **Figure 5**). There was no significant heterogeneity between studies (I^2 = 0.7%, p = 0.3155), indicating consistency in the treatment effects across studies (**Figure 5**).

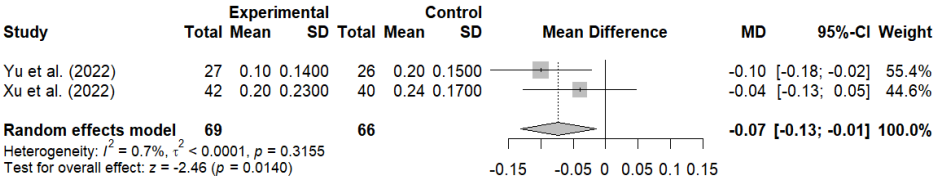


Figure 5. Forest plot for the comparison between ACO and placebo + Ortho-K.

3.4.3 Pairwise Efficacy Comparison between LDA 0.01% + SVS and Ortho-K

Pairwise meta-analysis comparing LDA 0.01% + SVS to Ortho-K showed that the use of LDA 0.01% + SVS provides a statistically significant slower progression of axial lengthening compared to Ortho-K at 12th month (MD: -0.12; 95% CI: -0.18 – -0.06; **Figure 6**), meaning that the Ortho-K group experienced a higher myopia progression compared to the LDA 0.01% + SVS group. Significant substantial heterogeneity was present (I^2: 64.0%; p < 0.05; **Figure 6**).

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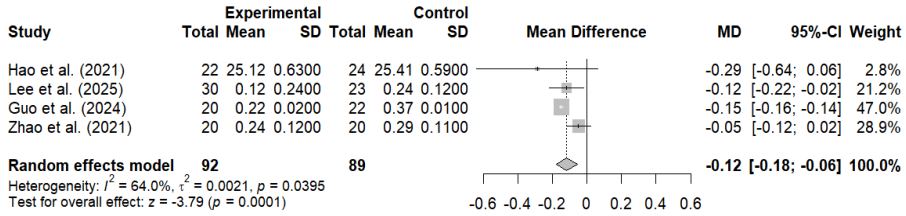


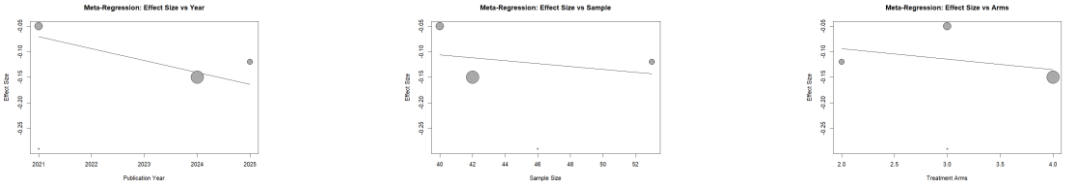
Figure 6. Forest plot for the comparison between LDA 0.01% + SVS and Ortho-K.

The meta-regression results showed that sample size and treatment arms variables were not significant predictors of the difference in effects between studies (R^2 = 0%; p > 0.05; **Table 4**), so these moderators did not explain the observed heterogeneity. However, there was still high and moderate heterogeneity not accounted for by sample size and treatment arms, with 75.93% and 57.81%, respectively. Also, publication year was not a significant source of heterogeneity (95% CI: -0.0512 – 0.0046; p-value > 0.05; **Table 4**). Intervention duration and study location/continent were not further analyzed by meta-regression because it did not show any differences according to those listed in the demographic and clinical characteristics table (**Appendix 2**). Bubble plot of publication year, sample size, and treatment arms meta-regression can be seen in **Figure 7**.

Table 4. Result of meta-regression with publication year, intervention sample size, treatment arms, and risk of bias as moderator variables.

Moderator	Estimate	Lower CI	Upper CI	SE	P-value	R-square	I-square
Publication year	-0.0233	-0.0512	0.0046	0.0142	0.1015	77.38%	20.57%
Intervention sample size	-0.0028	-0.0177	0.0120	0.0076	0.7069	0.00%	75.93%
Treatment arms	-0.0205	-0.1143	0.0733	0.0478	0.6682	0.00%	57.81%

CI, confidence interval; *SE*, standard error; *R-square*, accounted heterogeneity; *I-square*, residual heterogeneity.



(A) **(B)** **(C)**

Figure 7. Bubble plot of meta-regression with publication year (A), intervention sample size (B), and treatment arms (C).

3.4.4 Pairwise Efficacy Comparison between Ortho-K and SVS

Pairwise meta-analysis comparing Ortho-K to SVS showed that the use of Ortho-K provides a statistically significant slower progression of axial lengthening compared to SVS at 12th month (MD: -0.20; 95% CI: -0.27 – -0.14; **Figure 8**), meaning that SVS group experienced a higher myopia progression compared to the Ortho-K group. Significant considerable heterogeneity was present (I^2: 98.3%; p < 0.0001; **Figure 8**).

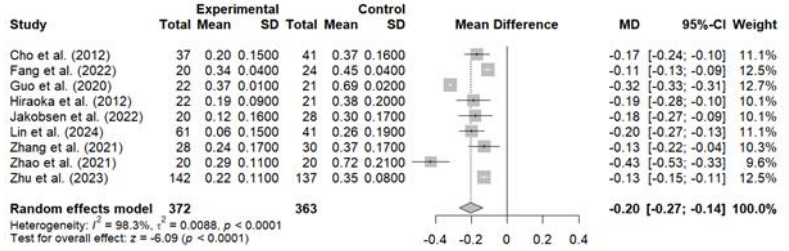


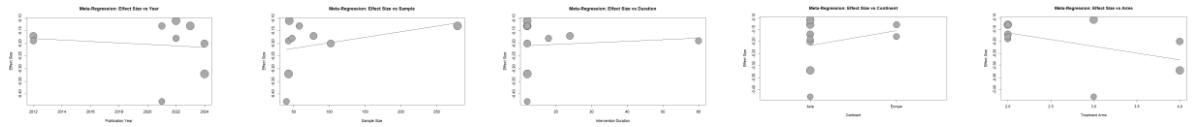
Figure 8. Forest plot for the comparison between Ortho-K and SVS

The meta-regression results showed that the moderator variables (publication year, sample size, intervention/study duration, and continent) were not a significant predictor of the difference in effects between studies (R^2 = 0%; p > 0.05; **Table 5**), so this moderator did not explain the observed heterogeneity. **Table 5.** also showed that treatment arms were not significant sources of heterogeneity (95% CI:-0.1288 – 0.0161; p-value > 0.05, respectively). However, there was still high heterogeneity not accounted for by moderator variables, with 97.13%, 95.61%, 97.55%, 97.40%, and 93.38%, respectively (**Table 5**). Bubble plot of publication year, sample size, intervention duration, continent, and treatment arms meta-regression can be seen in **Figure 9.**

Table 5. Result of meta-regression with publication year, intervention sample size, intervention duration, continent, treatment arms, and risk of bias as moderator variables.

Moderator	Estimate	Lower CI	Upper CI	SE	P-value	R-square	I-square
Publication year	-0.0029	-0.0186	0.0128	0.0080	0.7177	0.00%	97.13%
Intervention sample size	0.0004	-0.0004	0.0013	0.0004	0.3212	0.00%	95.61%
Intervention duration	0.0006	-0.0042	0.0055	0.0025	0.8016	0.00%	97.55%
Continent Europe	0.0620	-0.1061	0.2300	0.0857	0.4699	0.00%	97.40%
Treatment arms	-0.0564	-0.1288	0.0161	0.0370	0.1275	17.61%	93.38%

CI, confidence interval; *SE*, standard error; *R-square*, accounted heterogeneity; *I-square*, residual heterogeneity.



(A) **(B)** **(C)** **(D)** **(E)**

Figure 9. Bubble plot of meta-regression with publication year (A), intervention sample size (B), intervention duration (C), continent (D), and treatment arms (E).

3.4.5 Pairwise Efficacy Comparison between ACO and Ortho-K

Pairwise meta-analysis comparing ACO to Ortho-K showed that the use of ACO provides a statistically significant slower progression of axial lengthening compared to Ortho-K at 12th month (MD: -0.14; 95% CI: -0.21 – -0.07; **Figure 10**), meaning that Ortho-K group experienced a higher myopia progression compared to the ACO group. Significant considerable heterogeneity was present (I^2: 92.5%; p < 0.0001; **Figure 10**).

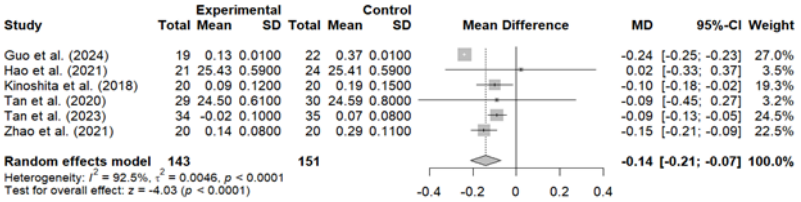


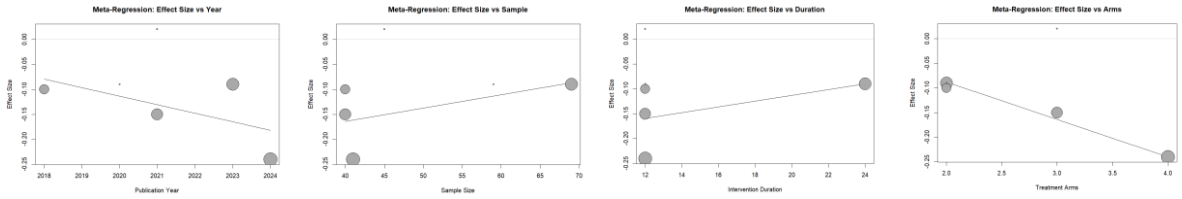
Figure 10. Forest plot for the comparison between ACO and Ortho-K.

Meta-regression showed that treatment arms were a significant source of heterogeneity. For every 1 unit increase in the treatment arm, there was a reduction of 0.0759 MD (95% CI: -0.0943 – -0.0575; **Table 6**). However, publication year, sample size, and intervention duration were not significant sources of heterogeneity (95% CI: -0.0480 – 0.0139; p-value > 0.05, 95% CI: -0.0029 – 0.0082; p-value > 0.05, and 95% CI: -0.0075 – 0.0190; p-value > 0.05, respectively (**Table 6**)). Study location/continent was not further analyzed by meta-regression because it did not show any differences according to those listed in the demographic and clinical characteristics table (**Appendix 2**). Bubble plot of publication year, sample size, intervention duration, and treatment arms meta-regression can be seen in **Figure 11.**

Table 6. Result of meta-regression with publication year, intervention sample size, intervention duration, treatment arms, and risk of bias as moderator variables.

Moderator	Estimate	Lower CI	Upper CI	SE	P-value	R-square	I-square
Publication year	-0.0170	-0.0480	0.0139	0.0158	0.2816	6.89%	82.16%
Intervention sample size	0.0027	-0.0029	0.0082	0.0028	0.3439	3.46%	79.12%
Intervention duration	0.0058	-0.0075	0.0190	0.0068	0.3924	2.36%	78.86%
Treatment arms	-0.0759	-0.0943	-0.0575	0.0094	<0.0001	100.00%	0.00%

CI, confidence interval; *SE*, standard error; *R-square*, accounted heterogeneity; *I-square*, residual heterogeneity.



(A) **(B)** **(C)** **(D)**

Figure 11. Bubble plot of meta-regression with publication year (A), intervention sample size (B), intervention duration (C), and treatment arms (D).

3.4.6 Pairwise Efficacy Comparison between ACO and SVS

The results from this pairwise meta-analysis showed that the progression of myopia is greater and statistically significant in the SVS group compared to the ACO group (MD: -0.56; 95% CI: -0.57 – -0.55; **Figure 12**). There was no significant heterogeneity between studies (I^2 = 0.0%; p = 0.6920), indicating consistency in the treatment effects across studies (**Figure 12**).

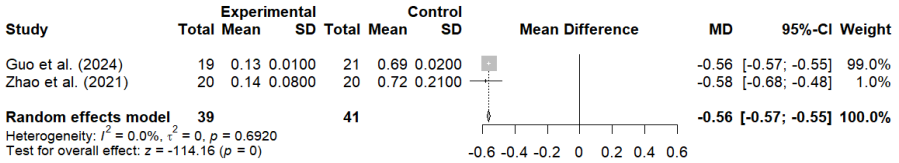


Figure 12. Forest plot for the comparison between ACO and SVS

3.4.7 Pairwise Efficacy Comparison between LDA 0.01% + SVS and SVS

Pairwise meta-analysis comparing LDA 0.01% + SVS to SVS showed that the use of LDA 0.01% + SVS provides a statistically significant slower progression of axial lengthening compared to SVS at 12th month (MD: -0.47; 95% CI: -0.48 – -0.46; **Figure 13**), meaning that the SVS group experienced a higher myopia progression compared to the LDA 0.01% + SVS group. There was no significant heterogeneity between studies (I^2 = 0.0%; p = 0.8543), indicating consistency in the treatment effects across studies (**Figure 13**).

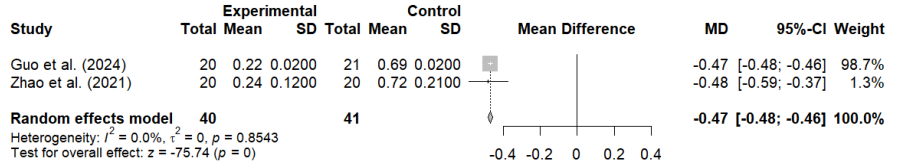


Figure 13. Forest plot for the comparison between LDA 0.01% + SVS and SVS.

3.4.8 Pairwise Efficacy Comparison between LDA 0.01% + SVS and ACO

The results from this pairwise meta-analysis showed that the progression of myopia is greater and statistically significant in the ACO group compared to the LDA 0.01% + SVS group (MD: 0.09; 95% CI: 0.08 – 0.10; **Figure 14**). There was no statistically significant heterogeneity between studies (I^2 = 44.8%, p = 0.1428), suggesting that the observed variability could be due to chance rather than true differences in treatment effects (**Figure 14**).

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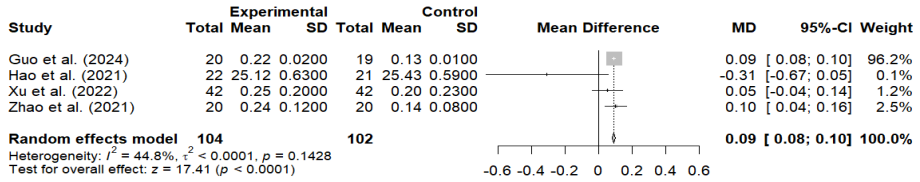
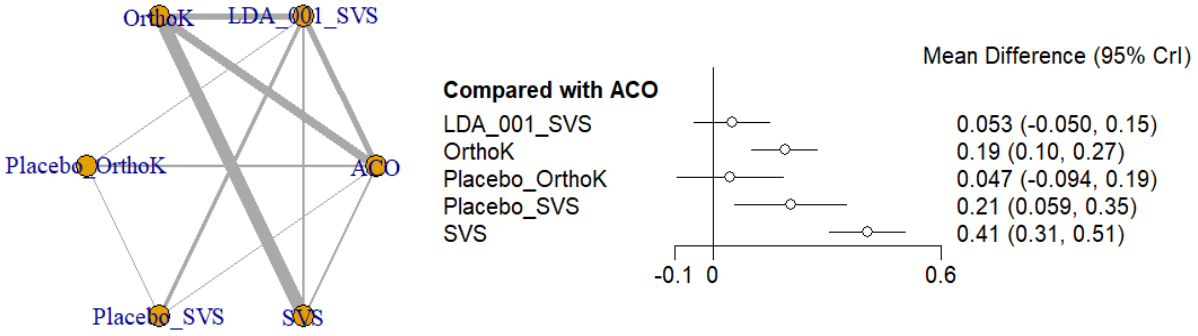


Figure 14. Forest plot for the comparison between LDA 0.01% + SVS and ACO.

3.5 Comparison of Various Myopia Progression Control Interventions on the AL Outcome

The first network for the interventions of myopia was shown in **Figure 15a**. This network graph visualizes the connections from head-to-head trials (direct comparisons) between groups. The network had a low global heterogeneity (I^2: 4%; 95% CrI: 0.06334 – 0.1436). A random effects NMA combining the direct and indirect evidence to compare different myopia progression control interventions with ACO (**Figure 15b**) and with each other via the league table (**Table 7**).



(A) **(B)**

Figure 15. (A) Connected network graph of direct comparisons of the first analysis for change in AL at 12-month and (B) forest plot of network estimates comparing LDA 0.01% + SVS, Ortho-K, placebo + Ortho-K, placebo + SVS, and SVS to ACO as referent intervention.

Each node represents one treatment. The edges represent direct comparisons, and the width of the edge is proportional to the number of trials. *ACO*, low-dose atropine combined with orthokeratology; *CrI*, credible interval; *LDA_001_SVS*, low-dose atropine 0.01% combined with single-vision spectacle lens; *OrthoK*, orthokeratology; *Placebo_OrthoK*, placebo combined with orthokeratology; *Placebo_SVS*, placebo combined with single-vision spectacle lens; *SVS*, single-vision spectacle lens.

Network meta-analysis showed that the LDA 0.01% + SVS (95% CrI: -0.050 – 0.15) and placebo + ortho-K intervention (95% CrI: -0.094 – 0.19) did not show any significant difference compared to ACO, meanwhile the ortho-K (MD: 0.19; 95% CrI: 0.10 – 0.27), placebo + SVS (MD: 0.21; 95% CrI: 0.059 – 0.35), and SVS intervention (MD: 0.41; 95% CrI: 0.31 – 0.51) had a significantly higher AL value at 12-month than ACO (**Figure 15b**). Comparison between the ortho-K and the SVS intervention (MD: -0.2163; 95% CrI: -0.2163 – -0.1499) showed that participants in the SVS significantly experienced a higher myopia progression compared to the ortho-K group (**Table 7**).

Table 7. Network meta-analysis comparing all myopia progression control interventions via the league table.

Mean Difference (95% CrI)

ACO	0.0517 (-0.04864, 0.1464)	**0.1902 (0.1022, 0.2726)**	0.04632 (-0.09402, 0.1825)	**0.2055 (0.06056, 0.3482)**	**0.4065 (0.3065, 0.5023)**
-0.0517 (-0.1464, 0.04864)	LDA_001_SVS	**0.1383 (0.04436, 0.234)**	-0.005088 (-0.1519, 0.1433)	**0.154 (0.03287, 0.2802)**	**0.3544 (0.2511, 0.4617)**
-0.1902	**-0.1383**	OrthoK	-0.1435	0.01581	**0.2163**

(-0.2726, -0.1022)	**(-0.234, -0.04436)**		(-0.2971, 0.009294)	(-0.1311, 0.1647)	**(0.1499, 0.2839)**
-0.04632 (-0.1825, 0.09402)	0.005088 (-0.1433, 0.1519)	0.1435 (-0.009294, 0.2971)	Placebo_OrthoK	0.159 (-0.01011, 0.3331)	**0.3597 (0.2015, 0.5198)**
-0.2055 (-0.3482, -0.06056)	**-0.154 (-0.2802, -0.03287)**	-0.01581 (-0.1647, 0.1311)	-0.159 (-0.3331, 0.01011)	Placebo_SVS	**0.2007 (0.04562, 0.3546)**
-0.4065 (-0.5023, -0.3065)	**-0.3544 (-0.4617, -0.2511)**	**-0.2163 (-0.2839, -0.1499)**	**-0.3597 (-0.5198, -0.2015)**	**-0.2007 (-0.3546, -0.04562)**	SVS

Significant results are bolded. The league table contained a network estimate (lower triangle; read as column vs row) and direct estimate (upper triangle; read as row vs column). *ACO*, low-dose atropine combined with orthokeratology; *CrI*, credible interval; *LDA_001_SVS*, low-dose atropine 0.01% combined with single-vision spectacle lens; *OrthoK*, orthokeratology; *Placebo_OrthoK*, placebo combined with orthokeratology; *Placebo_SVS*, placebo combined with single-vision spectacle lens; *SVS*, single-vision spectacle lens.

Based on the rank probability table, SUCRA curve ranking, and rankogram (**Table 8**; **Figure 16**), SVS provides the highest possibility of causing an increase in AL values (SUCRA: 0.998609) and thus has the greatest probability of leading patients to increase myopia, followed by the combination of placebo and SVS (SUCRA: 0.708760), ortho-K (SUCRA: 0.676414), the combination of LDA 0.01% and SVS (SUCRA: 0.280026), and the combination of placebo and ortho-K (SUCRA: 0.257761). The combination of LDA 0.01% and ortho-K (ACO) ranked as the worst group in increasing axial lengthening (SUCRA: 0.078430), thus making ACO the best intervention method for slowing the myopia progression as measured by the AL parameter.

Table 8. Rank probability table combined with SUCRA values that were used for comparing how the different myopia progression control interventions rank against each other in myopia progression (depicted as greater axial lengthening at 12-month)

% Probability	**ACO**	**LDA_001_SVS**	**OrthoK**	**Placebo_OrthoK**	**Placebo_SVS**	**SVS**
j = 1	0.0000000	0.0000000	0.0000000	0.0001000	0.0079625	0.9919375
j = 2	0.0000125	0.0000875	0.4133625	0.0098500	0.5686500	0.0080375
j = 3	0.0022750	0.0081375	0.5556625	0.0475250	0.3863750	0.0000250
j = 4	0.0574500	0.4883625	0.0297500	0.3925125	0.0319250	0.0000000
j = 5	0.2715125	0.3978250	0.0012125	0.3254625	0.0039875	0.0000000
j = 6	0.6687500	0.1055875	0.0000125	0.2245500	0.0011000	0.0000000
SUCRA Values	0.078430	0.280026	0.676414	0.257761	0.708760	0.998609

ACO, low-dose atropine combined with orthokeratology; *LDA_001_SVS*, low-dose atropine 0.01% combined with single-vision spectacle lens; *OrthoK*, orthokeratology; *Placebo_OrthoK*, placebo combined with orthokeratology; *Placebo_SVS*, placebo combined with single-vision spectacle lens; *SUCRA*, surface under the cumulative ranking curve; *SVS*, single-vision spectacle lens.

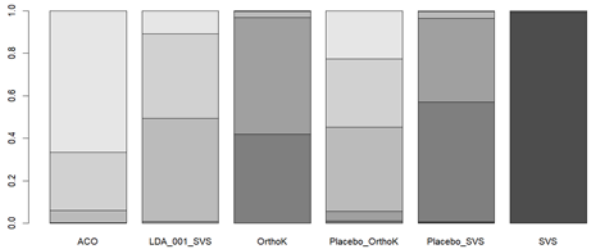


Figure 16. Bar chart of the SUCRA curve (rankogram) of each intervention.

Tests for local inconsistency showed no significant inconsistency (p-value > 0.05) between direct and indirect estimates in almost all comparisons where direct and indirect estimates are available, except for comparisons of ACO to ortho-K, ACO to SVS, and LDA 0.01% + SVS to SVS (p-value < 0.05; **Table 9**).

Table 9. Test for local inconsistency in the first network model by separating direct and indirect evidence.

Comparison	Network	Direct	Indirect	Difference	p-value
ACO:LDA 0.01% + SVS	0.052	0.056	0.090	-0.034	0.757800
ACO:Ortho-K	**0.19**	**0.14**	**0.37**	**-0.23**	**0.018650**
ACO:Placebo + SVS	0.21	0.32	0.12	0.20	0.163725
ACO:SVS	**0.41**	**0.57**	**0.27**	**0.30**	**0.000075**
LDA 0.01% + SVS:Ortho-K	0.14	0.12	0.11	0.01	0.881675
LDA 0.01% + SVS:Placebo + Ortho-K	-0.0058	-0.011	0.046	-0.057	0.719150
LDA 0.01% + SVS:SVS	**0.35**	**0.47**	**0.25**	**0.22**	**0.006550**
Placebo + Ortho-K:Placebo + SVS	0.16	0.28	0.0096	0.2704	0.123225

Significant results are bolded. *ACO*, low-dose atropine combined with orthokeratology; *LDA 0.01%*, low-dose atropine 0.01%; *OrthoK*, orthokeratology; *SVS*, single-vision spectacle lens.

4. Discussion

This study is the first NMA that quantitatively compares children's myopia control interventions that are the most possible intervention methods to be implemented in Indonesia. The interventions include LDA 0.01%, SVS, ACO, and ortho-k. Atropine, a non-selective muscarinic receptor antagonist, has demonstrated effectiveness in slowing the progression of myopia.[41-43] Various studies have explored a range of concentrations, from very low (0.01%) to moderate (0.01%–0.5%) and high (1%), to control myopia progression.[9,20,22,44] However, earlier research has indicated that higher concentrations may lead to side effects such as blurred vision, impaired accommodation, and increased sensitivity to light. While, LDA has minimal effect on pupil size, accommodation, and near vision.[22] Atropine eye drops exert a direct effect by inhibiting axial elongation, influencing scleral remodeling, and limiting the growth of the vitreous chamber, thereby helping to prevent myopia progression. Additionally, they have an indirect effect by relaxing the ocular muscles.[45] Although LDA has been suggested as a promising option for controlling myopia progression, its overall effectiveness remains insufficiently studied. Single vision spectacles are commonly used to slow down the progression of myopia in a safe, cost-effective, and non-invasive manner. However, SVS does not provide beneficial efficacy for myopia control. Therefore, SVS is generally used as a backup option in most of myopia control strategies.[8,46,47] Ortho-k is an optical intervention method that involves the use of specially designed rigid contact lenses worn overnight to reshape the cornea and correct refractive errors, allowing patients to see clearly during the day without the need for glasses or contact lenses.[48] Research has demonstrated that ortho-k can effectively slow axial eye growth and the progression of myopia.[49] The results of this NMA provide evidence of the comparative efficacy between various myopia progression control strategies and may be

beneficial in the decision-making of determining the most effective strategy in conjunction with the needs and demands of the patient.

The main findings of our analysis are as follows: (1) the combination between LDA 0.01% and SVS, ortho-k, and ACO showed clear effects in myopia control (all were effective as myopia control strategies) and (2) ACO was the best strategy for controlling the progression of myopia in children, followed by the combination between placebo and ortho-k, the combination between LDA 0.01% and SVS, ortho-k, the combination between placebo and SVS, and SVS. This study's findings confirm previous research, showing that LDA effectively slows the progression of myopia.[22,50-52] While the exact mechanism of atropine's action is still unknown, it's thought to work through a non-accommodative pathway in the retina or sclera possibly through a nicotinic pathway, rather than by affecting lens accommodation. Atropine might also have biochemical effects on the retina or sclera, influencing scleral remodeling.[22,50-56] One theory is that LDA acts through a neurochemical process starting at M1/4 receptors in the retina, likely in amacrine cells. Another suggests it inhibits glycosaminoglycan synthesis in scleral fibroblasts through a non-muscarinic mechanism.[57,58] Other ideas propose that pupillary dilation could increase ultraviolet exposure, potentially limiting eye elongation.[59] Additionally, atropine might reduce chronic inflammation in the eye, which could be linked to myopia.[60] Also, compared to commercial or high-dose atropine (HDA) 1%, a much lower atropine concentration (1/100th of the commercial dose) in LDA didn't affect pupil size or near vision, consistent with some past research. Commercial atropine causes bothersome pupil dilation that blurs near vision and creates glare.[9,50,51] Fortunately, lower doses of atropine (0.01%) show a dose-dependent effect, proving to be one of the most effective treatments with minimal side effects.[22,61] This lower dose also avoids the rebound effect seen with higher doses, making it a promising candidate for myopia control.[22] Not only that, since it's a once-daily bedtime dose, it's less of a hassle and can lead to better adherence. This bedtime timing also helps prevent potential side effects from pupil dilation.[33]

Ortho-k, a contact lens-based treatment, effectively controls myopia progression by reshaping the cornea to alter how light focuses on the retina, potentially slowing eye elongation.[4,62-64] Our discovery is in line with the research results put forward by Wildsoet *et al.* (2019)[15] and Huang *et al.* (2016)[61] which found that ortho-k and LDA are considered the most effective and safest interventions for controlling myopia even though their effectiveness differs widely among individuals.[25,65-67] Xu *et al.* (2022) shows that age was found to be the most significant factor impacting the annual increase in AL and the ortho-k as a monotherapy intervention can achieve better efficacy compared to LDA alone at a younger age, which was in accord with previous studies.[25,36,65-67] Meanwhile, LDA in older children shows a better efficacy compared to ortho-k in older children, which was consistent with previous studies.[23,36,67] Also, this age-stratified RCT comparing atropine, ortho-k, and ACO treatments over two years reconfirmed the long-term effectiveness of 0.01% atropine drops and ortho-k. Overall, the study found that ACO treatment achieved better 2-year efficacy compared to either monotherapy alone. Minimal side effects were observed in both the combined and single-treatment groups.[36] Our study provides several clinical implications that are useful for healthcare professionals in Indonesia to guide treatment decisions for childhood myopia. Specifically, our findings suggest that a combination of LDA 0.01% with SVS, ortho-k, or ACO can effectively manage myopia progression. Secondly, for clinicians considering which strategy is the most appropriate choice for their patients, our study provides a rank of efficacy that would help them identify the most efficacious myopia progression control strategy while still accounting for the patient's desires and contraindications. ACO appears to be the most effective strategy among those evaluated, offering a strong option for clinical practice. Thus, the results of this study could help guide clinical decisions.

We identified several knowledge gaps that could benefit this field of research by being investigated in future studies. First, of all the included studies, none involved an Indonesian population and further studies might be needed to confirm if the efficacy of these drugs still holds to the Indonesian population. Secondly, we were unable to make a safety analysis as studies were inconsistent in the reporting of adverse events. Further studies assessing adverse events from these strategies would provide beneficial insights.

Despite the analytical and statistical results we have applied in this review, there are some inherent limitations in this analysis that need to be highlighted. First, not all intervention methods for myopia progression control in the included studies could be analyzed statistically comparatively because not all intervention groups could be connected to other groups due to the absence of available studies or data that could bridge. Therefore, in order for the NMA results to be valid, we were forced to exclude studies with disconnected interventions. Second, studies had various participants' characteristics. For example, the age intervals and the baseline

myopic degree might differ across studies. The wide variation in subject ages in this review could not be further analyzed to determine how treatment varied with age because included studies only reported the age range or mean age of participants. Third, many studies were concerned about bias, majorly because of unmasked participants in most studies due to the physical nature of a treatment (e.g., contact lenses versus spectacles). In addition, although our study has provided information on efficacy, it cannot provide information regarding the safety of the various treatment options due to the lack of data in the included studies.

5. Conclusion

In conclusion, some of the control strategies can significantly slow the progression of myopia in children. Our findings provide valuable insights into the best myopia control strategy through the use of ACO. Although this method is beneficial as a first-line control intervention, consultation with a healthcare professional is still recommended to reduce the possibility of complications and find the most suitable control strategy for the patient based on individual observations. It is essential to recognize that clinical decisions regarding any intervention must be based on data about its effectiveness, potential benefits in both the short and long term, and the risk of side effects, making further evaluation of the intervention's safety a critical step.

Moving forward, we hope that more trials in the future will aim to confirm the results of indirect comparisons of intervention strategies. We also hope that future trials will involve larger sample sizes, which are needed to provide better quality data to help establish the effects of different interventions in controlling myopia.

6. Conflict of Interest

The authors declare that there is no conflict of interest.

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