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Efficacy of Interventions for Premyopia: A Protocol for a Systematic Review and Network Meta-Analysis of Randomized Clinical Trials

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 14 February 2026 and was last updated on 14 February 2026.

INTRODUCTION

Review question / Objective The objective of this systematic review is to evaluate and rank the relative effectiveness and treatment dropout risk of pharmacologic, optical, physical, and behavioral interventions for preventing myopia onset or reducing refractive shift in children with premyopia. To this end, the proposed systematic review will address the following question: Which intervention provides the greatest reduction in refractive progression and demonstrates acceptable tolerability in premyopic children?

Participants (P): Children with premyopia (defined as baseline refraction ≤ +1.00 D and > −0.75 D).
Intervention (I): Pharmacologic (e.g., low-concentration atropine), optical (e.g., defocus spectacles or contact lenses), physical (e.g., repeated low-level red-light therapy), and behavioral (e.g., outdoor activity) strategies.
Comparator (C): Control conditions (placebo, no intervention, or single-vision lenses) or other active interventions.
Outcome (O): The primary outcome will be the mean annualized change in spherical equivalent refraction (SER). The secondary outcome will be the mean annualized change in axial length and treatment dropout, as an indicator of acceptability in a preventive setting.
Study Design (S): Randomized clinical trials (RCTs).

Rationale The prevalence of myopia in children and adolescents is rising rapidly worldwide, presenting a public health challenge (1). The age at onset of myopia is a key predictor of future refractive outcomes; earlier onset is associated with a longer period of myopic progression, resulting in a substantially increased risk of high myopia and vision-threatening complications such as myopic maculopathy, retinal detachment, and glaucoma (2). Therefore, delaying or preventing the onset of myopia has become a critical objective for

reducing the long-term burden of visual impairment (3).

To facilitate the identification of children at high risk of developing myopia, the International Myopia Institute (IMI) introduced the concept of premyopia in 2019 (4). Premyopia is defined as a refractive status of > −0.50 D and ≤ +0.75 D in children, in whom a combination of age and other quantifiable risk factors is associated with an increased future risk of myopia development. Premyopia is increasingly recognized as a "window of opportunity" for therapeutic intervention. Early preventive strategies have primarily focused on behavioral modifications, particularly increased outdoor time, and pharmacological treatments such as low-dose atropine, both of which are supported by a growing body of clinical evidence. More recently, novel intervention modalities have emerged, including optical interventions such as peripheral defocus lenses and device-based therapies such as low-level red-light therapy (RLRL) (5,6). However, despite the growing number of available interventions, the existing clinical evidence remains fragmented and has not been comprehensively evaluated.

Most existing studies compare a single intervention with a control group, resulting in limited head-to-head evidence and restricting the ability of conventional pairwise meta-analyses to establish a relative hierarchy of preventive efficacy (7). Furthermore, heterogeneity in intervention types and control conditions complicates clinical decision-making, and the relative effectiveness and treatment dropout risk of these strategies have not been comprehensively evaluated in premyopic populations. Importantly, because premyopic children typically maintain good uncorrected visual acuity, preventive treatments may be perceived as less immediately necessary, making long-term adherence a central determinant of real-world effectiveness; thus, dropout risk is a clinically meaningful indicator of acceptability in this preventive setting.

To address this evidence gap, we will conduct a network meta-analysis integrating both direct and indirect evidence. The primary objective of this review will be to evaluate the relative effectiveness of different premyopia interventions on the annualized change in spherical equivalent refraction (SER). The annualized change in axial length will be examined as a secondary outcome. Treatment dropout risk will also be assessed as an indicator of acceptability. By constructing a comparative network of interventions, this study will aim to inform clinical decision-making for myopia prevention.

Condition being studied The condition being studied is premyopia in children, a transitional refractive state between normal emmetropization and the onset of clinical myopia. In this systematic review, premyopia is pragmatically defined as a baseline spherical equivalent refraction (SER) of ≤ +1.00 D and > −0.75 D, capturing children with reduced hyperopic reserve who are at increased risk of future myopia onset. Although the International Myopia Institute (IMI) consensus proposes slightly different thresholds (4), this broader refractive range is adopted to include clinically relevant at-risk populations and pivotal trials conducted before widespread implementation of IMI criteria.

The review will evaluate preventive interventions applied at the premyopia stage and examine their effects on: 1. annualized change in SER, 2. annualized change in axial length, and 3. treatment discontinuation as a measure of intervention acceptability in a preventive setting.

METHODS

Search strategy A comprehensive electronic search will be conducted in the following sources: PubMed (MEDLINE via PubMed interface), Cochrane Library, Web of Science, and ClinicalTrials.gov.

Searches will be designed for high sensitivity using free-text terms and standardized subject terms when applicable (e.g., MeSH in MEDLINE). Search strategies will be reported separately for each source because search interfaces, controlled vocabulary, and field structures differ across databases. Boolean operators will be applied as follows: synonyms within each concept domain will be combined using OR, and the major concept domains will be combined using AND. No language or publication date restrictions will be applied.

1. PubMed (MEDLINE via PubMed interface)

The PubMed search will combine population, premyopia/at-risk status, interventions, outcomes, and randomized-trial terms using AND/OR as shown below. No additional filters will be applied.

Search string:

((child* OR pediatric* OR paediatric* OR schoolchild* OR preschool*) AND ("premyopia" OR "pre-myopia" OR "pre myopia" OR non-myopic OR emmetropi* OR "at risk of myopia" OR "risk of myopia" OR "low hyperopia" OR "borderline refraction")) AND ("outdoor time" OR "time outdoors" OR daylight OR "near work" OR "screen time" OR "digital device*" OR lifestyle OR behavior* OR atropine OR "low-dose atropine" OR "defocus lens*" OR DIMS OR H.A.L. OR "peripheral defocus" OR orthokeratology OR

ortho-k OR "multifocal contact lens*") AND ("incident myopia" OR "myopia onset" OR "spherical equivalent" OR "refractive error" OR "axial length" OR "axial elongation") AND ("random" OR "randomized" OR "randomised")
Filters: None (NA).
2. Cochrane Library
The Cochrane Library search will be performed using the Title/Abstract/Keyword fields. The same core keyword framework and Boolean structure (OR within concept domains; AND across domains) will be implemented using the platform's syntax.
Search fields/interface: Title/Abstract/Keyword.
Filters: None (NA).
3. Web of Science
Web of Science will be searched using free-text keywords mapped to the same concept domains (population; premyopia/at-risk status; interventions; outcomes) and combined using OR/AND as described above, adapted to the database-specific search syntax.
Search interface: Web of Science-All databases.
Filters: None (NA).
4. ClinicalTrials.gov
ClinicalTrials.gov will be searched using structured fields, primarily the "Condition or disease" field, applying equivalent terms for premyopia/at-risk refractive status and myopia prevention interventions.
Search fields/interface: Condition or disease.
Filters: None (NA).
5. Additional search methods
Reference lists of relevant reviews and included studies will be manually screened to identify additional eligible trials.

Participant or population The review will include children with premyopia, pragmatically defined as a baseline spherical equivalent refraction (SER) of ≤ +1.00 D and > −0.75 D in at least one eye. This refractive range is selected to capture a clinically relevant at-risk pediatric population while allowing inclusion of pivotal trials conducted before widespread implementation of the International Myopia Institute (IMI) criteria. Eligible participants will be pediatric populations enrolled in randomized clinical trials; studies enrolling adults will be excluded. No restrictions will be applied based on sex, ethnicity, country, or setting (clinical, community, or school), provided that eligibility criteria are met and relevant outcomes are extractable. Studies including mixed non-myopic populations will be eligible only if outcome data for participants meeting the prespecified refractive range are reported separately or can be extracted for the eligible subgroup; otherwise, such studies will be excluded from quantitative synthesis. Participants with baseline SER outside the prespecified range will not be included in the analysis. At the study level, trials without extractable SER data or with follow-up shorter than 6 months will be excluded.

Intervention The interventions of interest are preventive strategies for children with premyopia, including pharmacologic, optical, physical, and behavioral interventions, as well as combination strategies. Pharmacologic interventions will include low-concentration atropine administered as topical eye drops, and eligible variations will include different low-dose concentrations (e.g., 0.01%–0.05%) when trials meet the population criteria and report extractable outcomes. Optical interventions will include defocus spectacle lenses and defocus contact lens designs intended to modify peripheral defocus, with eligible variations including different lens technologies and wearing schedules as specified in individual trials. Physical interventions will include repeated low-level red-light therapy (RLRL), and eligible variations will include device wavelength and session regimens consistent with pediatric clinical trials, with all key parameters extracted to ensure interventions can be distinguished across studies. Behavioral interventions will include strategies designed to increase outdoor exposure; where feasible, outdoor exposure definitions will be harmonized across trials using a prespecified operational threshold (e.g., 120 minutes/day), and studies reporting outdoor time in other formats will be mapped to this definition when possible.
Combination interventions will be eligible when they represent a prespecified concurrent strategy (e.g., low-concentration atropine plus an optical intervention) compared with control or other active interventions. Trials will remain eligible if co-interventions (e.g., standard refractive correction or general lifestyle advice) are balanced across arms such that between-group differences primarily reflect the intervention(s) of interest. Detailed intervention characteristics (e.g., atropine concentration and dosing frequency; lens design and wearing schedule; RLRL parameters and session regimen; and outdoor exposure definitions) will be extracted to allow consistent node classification in the subsequent network meta-analysis.

Comparator Comparators will include control conditions and active comparators. Control conditions will consist of placebo, no intervention/usual care, or single-vision correction (single-vision spectacles or single-vision contact lenses) where these are used as the reference condition in preventive trials. Active comparators will include

any other eligible preventive interventions (pharmacologic, optical, physical, behavioral, or combination strategies) evaluated within randomized clinical trials of children with premyopia.
To ensure clear distinction between intervention and comparator nodes in the network meta-analysis, comparator details will be extracted and reported for each study, including (when applicable) whether the comparator involved placebo eye drops, single-vision lenses, standard refractive correction only, general lifestyle advice, or another active preventive modality. Trials will be considered eligible when co-interventions (e.g., refractive correction or general counseling) are balanced across arms, such that the between-group contrast primarily reflects the intervention(s) under evaluation.

Study designs to be included We will include randomized clinical trials (RCTs) in children with premyopia. Eligible designs include parallel-group, cluster-randomized, and multi-arm RCTs with extractable data for eligible participants.

Eligibility criteria Studies will be eligible if they meet the following prespecified criteria based on the PICOS framework. Participants: pediatric participants (children/adolescents) with premyopia, defined pragmatically as baseline spherical equivalent refraction (SER) of ≤ +1.00 D and > -0.75 D in at least one eye. Interventions: pharmacologic (e.g., low-concentration atropine), optical (e.g., defocus spectacles or contact lenses), physical (e.g., repeated low-level red-light therapy), behavioral (e.g., increased outdoor activity), or combination preventive strategies. Comparators: placebo, no intervention/usual care, single-vision correction, or other active preventive interventions. Outcomes: studies must report extractable data for the primary outcome (annualized change in SER) and/or at least one secondary outcome (annualized change in axial length or treatment discontinuation). Study design: randomized clinical trials (parallel-group, cluster-randomized, or multi-arm).
Additional eligibility criteria will include a minimum follow-up duration of 6 months to allow meaningful assessment of refractive change over time, and sufficient reporting to permit outcome extraction for eligible participants. Studies enrolling mixed refractive populations will be included only if data for participants meeting the prespecified premyopia range are reported separately or can be extracted for the eligible subgroup.
No restrictions will be applied based on language, country, setting, or publication date. When multiple reports describe the same study population, the most complete dataset will be used to avoid double counting. All eligibility criteria will be applied as prespecified and will not be modified based on study findings; if unexpected issues necessitate protocol deviations, the rationale will be documented and sensitivity analyses will be conducted where appropriate.

Information sources The following information sources will be searched from inception to the final search date: PubMed (MEDLINE via PubMed interface), Cochrane Library (including Reviews and CENTRAL), Web of Science (All databases), and ClinicalTrials.gov. In addition, we will screen the reference lists of relevant reviews and all included studies, and we will search trial registry records for completed or ongoing eligible randomized trials. When necessary, study authors will be contacted to clarify eligibility or obtain missing outcome data. No restrictions will be applied based on language, country, publication date, or publication status.

Main outcome(s) The primary outcome of this review is the mean annualized change in spherical equivalent refraction (SER), measured in diopters (D). To maintain comparability across studies with varying follow-up durations, all results will be standardized to a 12-month time frame. For trials reporting data at a 6-month follow-up, the mean change in SER will be annualized by multiplying the observed values by 2 for integration into the meta-analysis. The analysis will employ a random-effects network meta-analysis model to compare these outcomes. The treatment effect will be expressed as mean differences (MDs) with corresponding 95% confidence intervals (CIs).

Additional outcome(s) The secondary outcomes will be the annualized change in axial length and treatment discontinuation (dropout). Treatment discontinuation will be measured as the risk of dropout during follow-up in each study arm and summarized as a comparative effect (e.g., risk difference) between interventions. This outcome is included to assess acceptability in a preventive setting, where long-term adherence may influence real-world implementation. When dropout is reported at multiple time points, we will use the time point closest to 12 months; if only shorter follow-up is available, dropout will be converted to a 12-month equivalent using a method based on a constant hazard assumption, when appropriate, to improve comparability across trials. Axial length change will be annualized to a 12-month equivalent when follow-up durations vary, and will be synthesized using the same comparative

framework as the primary outcome when data are extractable.

Data management Data extraction and management will be conducted independently by two reviewers (T.T. Lin and Y.C. Yang) using a standardized electronic form. Disagreements during study selection or data extraction will be resolved through consensus or consultation with a third reviewer (D.C. Tsai). Extracted data will include study characteristics, participant demographics, intervention details, and primary and secondary outcomes. To ensure consistency within a 12-month analytic framework, 6-month spherical equivalent refraction (SER) and axial length data will be annualized under the assumption of approximately linear change over time by multiplying observed values by two. Dropout rates will be standardized to a 12-month equivalent using a conversion method based on a constant hazard assumption when follow-up durations differ. Missing means or standard deviations will be derived using established statistical methods, assuming a pre/post correlation coefficient of 0.8 for change scores when unavailable. Statistical synthesis and network meta-analysis will be performed using MetaInsight (version 4.6.0) (8), which implements the netmeta package in R. Publication bias assessments, including Egger's test, will be conducted using Google Colaboratory.

Quality assessment / Risk of bias analysis The methodological quality of the included randomized clinical trials will be assessed using the Cochrane Risk of Bias tool (RoB 2). Two reviewers will independently evaluate the five domains: the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Each study will be categorized as having a "low risk," "some concerns," or "high risk" of bias. Discrepancies between reviewers will be resolved through discussion or consultation with a third reviewer.

For the network meta-analysis, inconsistency between direct and indirect evidence will be evaluated using both global inconsistency models and local node-splitting approaches. Statistical heterogeneity will be examined using between-study variance estimates. Publication bias and small-study effects will be assessed by visual inspection of comparison-adjusted funnel plots and Egger's regression test.

The certainty of evidence for each network comparison will be evaluated using the Confidence in Network Meta-Analysis (CINeMA) framework, which operationalizes the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for network meta-analysis (9,10). The assessment will consider six domains: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence. The overall certainty of evidence will be rated as high, moderate, low, or very low.

Strategy of data synthesis Quantitative synthesis will be performed. For the primary outcome (annualized change in spherical equivalent refraction [SER]), treatment effects will be summarized as mean differences (MDs) with 95% confidence intervals. For secondary outcomes, axial length effects will be summarized as MDs and dropout effects as risk differences (RDs), each with 95% confidence intervals.

A frequentist random-effects network meta-analysis (NMA) will be conducted to compare multiple interventions by integrating direct and indirect evidence. Pairwise meta-analyses (when applicable) will use an inverse-variance random-effects approach. Heterogeneity will be assessed using τ^2 and I^2 statistics.

Intervention ranking will be estimated using P-scores. Network consistency will be evaluated using design-by-treatment interaction and/or node-splitting approaches where feasible. Missing variance data will be handled using standard transformations (e.g., deriving SDs from SEs or confidence intervals). When follow-up durations vary, outcomes will be standardized to a 12-month equivalent.

Small-study effects and potential publication bias will be explored using comparison-adjusted funnel plots and regression-based tests adapted for NMA.

Subgroup analysis No subgroup analyses are prespecified. The primary objective of this review is to compare intervention modalities at the network node level using a transitivity-based framework. Prespecifying multiple subgroup analyses may increase the risk of spurious findings and compromise network connectivity, particularly when indirect comparisons are required. Therefore, to preserve the coherence and interpretability of the network structure, subgroup analyses will not be routinely conducted. Any exploratory analyses, if performed, will be clearly reported as post hoc.

Sensitivity analysis Prespecified sensitivity analyses will be performed to assess the robustness of findings. These will include:

1. repeating analyses using alternative assumptions for within-group pre–post correlation when deriving variance for change scores (e.g., r = 0.8 vs r = 0.5)

2. excluding studies judged to be at higher risk of bias based on the Cochrane RoB tool (11)
3. leave-one-out analyses to evaluate the influence of any single study on the network estimates.
Where applicable, results will be compared across sensitivity analyses to assess stability of treatment rankings and effect estimates.

Language restriction No language restrictions will be applied.

Country(ies) involved Taiwan.

Other relevant information This protocol is reported in accordance with PRISMA-P recommendations (12). Any important amendments to this protocol will be documented with reference to the date of the change and the rationale. These changes will be tracked in the trial registry (INPLASY) and reported in the final systematic review. The review is supported by the National Science and Technology Council, Taiwan (Grant number: NSTC 114-2314-B-A49-049). The funder (National Science and Technology Council, Taiwan) had no role in the design of the study, the collection, analysis, and interpretation of data, or the writing of the protocol.

Contributorship: Tzu-Tang Lin and Yu-Chieh Yang contributed equally to this work.

Keywords Premyopia; myopia prevention; atropine; defocus lenses; repeated low-level red-light therapy; outdoor activity; network meta-analysis; randomized clinical trials.

Dissemination plans The findings of this systematic review and network meta-analysis will be disseminated through submission to a peer-reviewed journal and presentation at relevant ophthalmology or vision science conferences.

Contributions of each author

Author 1 - Tzu-Tang Lin - Conceptualized the review question; drafted the protocol and manuscript; coordinated study selection and data extraction; contributed to interpretation of findings.
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Author 2 - Yu-Chieh Yang - Co-led protocol development; performed literature screening and data extraction; contributed to manuscript drafting and critical revision.
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Author 3 - Hsin-Yu Yang - Provided clinical domain expertise in pediatric refractive development and myopia prevention; refined eligibility criteria and intervention taxonomy; critically revised the protocol for clinical relevance.
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Author 4 - Chiao-Yu Wang - Managed data organization and cleaning; supported verification of extracted outcomes and follow-up harmonization.
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Author 5 - Chia-Wei Lee - Advised on intervention classification and feasibility in real-world settings; contributed to interpretation of results and manuscript revision.
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Author 6 - Mong-Ping Shyong - Reviewed and revised the protocol/manuscript for intellectual content.
Email: mpshyong@gmail.com
Author 7 - Nai-Wei Hsu - Provided methodological oversight on evidence synthesis planning and reporting; reviewed the protocol/manuscript and advised on presentation of outcomes and interpretation.
Email: davidnwh@ms28.hinet.net
Author 8 - Shih-Hwa Chiou - Provided expert guidance on study design considerations and reporting standards; critically revised the protocol/manuscript and approved the final content.
Email: 10010@hosp.nycu.edu.tw
Author 9 - Der-Chong Tsai - Supervised the project; provided overall methodological and clinical oversight; adjudicated disagreements during study selection/data extraction; critically revised the protocol/manuscript and approved the final version.
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