Supplementary Material

Efficacy and Safety of Low-dose Atropine for Myopia control in Premyopic children: Systematic Review and Meta-Analysis

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Supplement

Table S1. Keywords and search results in different databases

Database	Keyword	Filter	Date	Results
PubMed	(premyopia OR premyopic OR non-myopic OR nonmyopic OR non-myopia OR nonmyopia) AND myopia	NA	December 03, 2023	387
Embase	(premyopia.mp. OR premyopic.mp. OR non-myopic.mp. OR nonmyopic.mp. OR non-myopia.mp. OR nonmyopia.mp.) AND (myopia.mp. or myopia/)	NA	December 03, 2023	409
Cochrane CENTRAL	(premyopia OR premyopic OR non-myopic OR nonmyopic OR non-myopia OR nonmyopia) AND (myopia or myopia [MeSH])	NA	December 03, 2023	38
ClinicalTrials.gov	(premyopia OR premyopic OR non-myopic OR nonmyopic OR non-myopia OR nonmyopia) AND myopia	Condition or disease	December 03, 2023	24

NA: not applied

Table S2. Excluded studies and reasons

Study	Reason for exclusion
Effects of 0.01% atropine eye drops on the prevention of myopia onset among schoolchildren: a randomized, double-blind, controlled trial [57]	Overlapping participants
Prevention of myopia onset and progression with 0.01% atropine solution among school-age children [58]	Myopic participants
The increasing prevalence of myopia in junior high school students in the Haidian District of Beijing, China: a 10-year population-based survey [59]	Insufficient outcome data
Longitudinal changes in corneal curvature and its relationship to axial length in the Correction of Myopia Evaluation Trial (COMET) cohort [60]	Myopic participants
Eye growth pattern of myopic children wearing spectacle lenses with aspherical lenslets compared with non-myopic children [61]	Myopic participants
Characteristics of responders to atropine 0.01% as treatment in Asian myopic children [62]	Myopic participants

Table S3. Detailed quality assessment of included studies using Cochrane risk of bias 2 tool (RoB 2.0)

First Author	Year	Randomization process	Intervention adherence	Missing outcome data	Outcome measurement	Selective reporting	Overall
J. Jethani **[26]**	2022	L	S	L	L	S	S
J.C. Yam **[18]**	2023	L	L	L	L	L	L
W. Wang **[17]**	2023	L	L	L	L	L	L

H, high risk of bias; L, low risk of bias; S, some concern of risk of bias.

Table S4. Detailed quality assessment of included studies using Newcastle-Ottawa Scale (NOS)

First Author	Year	Selection	Comparability	Outcome	Overall
P.C. Fang **[16]**	2010	4/4	2/2	3/3	9/9

Table S5. GRADE Summary of Findings Table

Effect				Certainty
Atropine	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**	
Myopia Incidence - 6m—12m				
51/300 (17.0%)	87/281 (31.0%)	**RR 0.48** (0.22 to 1.01)	**161 fewer per 1,000** (from 241 fewer to 3 more)	⊕⊕⊕◯ Moderate
Myopia Incidence - 12m—24m				
94/262 (36.3%)	136/256 (53.1%)	**RR 0.62** (0.42 to 0.97)	**202 fewer per 1,000** (from 319 fewer to 16 fewer)	⊕◯◯◯ Very low
Fast Myopia Shift - 6m—12m				
117/300 (39.0%)	181/281 (64.4%)	**RR 0.58** (0.39 to 0.86)	**271 fewer per 1,000** (from 393 fewer to 90 fewer)	⊕⊕⊕◯ Moderate
Fast Myopia Shift - 12m—24m				
86/262 (32.8%)	139/256 (54.3%)	**RR 0.50** (0.26 to 0.96)	**271 fewer per 1,000** (from 402 fewer to 22 fewer)	⊕◯◯◯ Very low
Spherical Equivalent - 6m—12m				
331	311	-	MD **0.31 higher** (0.16 higher to 0.47 higher)	⊕⊕◯◯ Low

Effect				Certainty
Atropine	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**	
Spherical Equivalent - 12m—24m				
292	286	-	MD **0.58 higher** (0.18 higher to 0.98 higher)	⨁◯◯◯ Very low
Axial Length - 6m—12m				
328	309	-	MD **0.1 lower** (0.15 lower to 0.06 lower)	⨁⨁◯◯ Low
Axial Length - 12m—24m				
264	260	-	MD **0.19 lower** (0.3 lower to 0.07 lower)	⨁◯◯◯ Very low
Photophobia Incidence - 6m—12m				
66/355 (18.6%)	30/337 (8.9%)	**RR 2.07** (1.39 to 3.10)	**95 more per 1,000** (from 35 more to 187 more)	⨁◯◯◯ Very low
Photophobia Incidence - 12m—24m				
38/268 (14.2%)	28/260 (10.8%)	**RR 1.31** (0.83 to 2.06)	**33 more per 1,000** (from 18 fewer to 114 more)	⨁⨁◯◯ Low

Effect				Certainty
Atropine	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**	
Allergic Conjunctivitis Incidence - 6m—12m				
12/301 (4.0%)	16/281 (5.7%)	**RR 0.70** (0.34 to 1.45)	**17 fewer per 1,000** (from 38 fewer to 26 more)	⊕⊕◯◯ Low
Allergic Conjunctivitis Incidence - 12m—24m				
8/238 (3.4%)	4/230 (1.7%)	**RR 1.92** (0.58 to 6.34)	**16 more per 1,000** (from 7 fewer to 93 more)	⊕⊕◯◯ Low
Pupil Size - 6m—12m				
331	311	-	MD **0.5 higher** (0.27 higher to 0.73 higher)	⊕⊕◯◯ Low
Pupil Size - 12m—24m				
238	230	-	MD **0.46 higher** (0.12 higher to 0.81 higher)	⊕⊕⊕◯ Moderate
Accommodation Amplitude - 6m—12m				
301	281	-	MD **0.6 lower** (1.18 lower to 0.02 lower)	⊕⊕⊕◯ Moderate

Effect				Certainty
Atropine	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**	
Accommodation Amplitude - 12m—24m				
238	230	-	MD **0.82 lower** (1.35 lower to 0.3 lower)	⊕⊕⊕◯ Moderate

Table S6. PRISMA Checklist

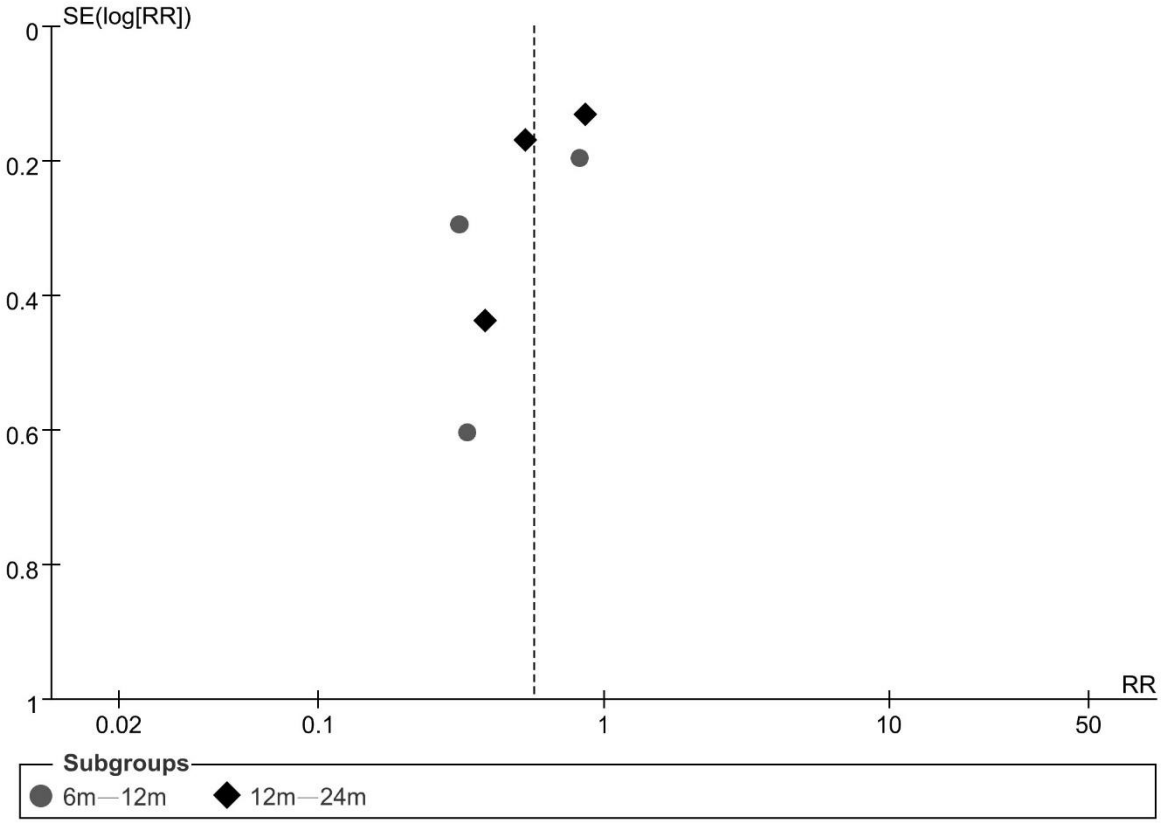
Section and Topic	#	Checklist item	Location
TITLE			
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Method
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Introduction
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Methods
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Methods
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Methods, Table S1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Methods
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Methods
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Methods

	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Methods Table 1
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Methods, TablesS3, S4
Effect measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.	Methods
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Methods, Figure 1,
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Methods
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Methods
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Methods
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression).	Methods
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Methods
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Methods, Tables S3, S4
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Methods, Table S5
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Results, Figure 1

	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Results, Table S2
Study characteristics	17	Cite each included study and present its characteristics.	Results, Table 1
Risk of bias	18	Present assessments of risk of bias for each included study.	Results, Tables S3, S4
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimates and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.	Figures 2-9
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Results, Tables S3, S4
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Results, Figures 2-9
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Results, Figures 2-9
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not appicable
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Results, Figures S1
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Table S5
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion
	23b	Discuss any limitations of the evidence included in the review.	Discussion
	23c	Discuss any limitations of the review processes used.	Discussion
	23d	Discuss implications of the results for practice, policy, and future research.	Discussion

OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Methods
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Methods
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Methods
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Funding
Competing interests	26	Declare any competing interests of review authors.	Conflicts of Interest
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Results, Table 1, Tables S1-S5

Figure S1. Funnel Plot of Myopia Incidence



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