Myopia Control: Are We Ready for an Evidence Based Approach?

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Statements and Declarations

Prior Publication: This review has not been submitted or presented yet.

Supplementary Material

Supplementary Table 1. Summary of number of retrieved articles per intervention.

Search name	**Abbr**	**Number of records incl. duplicates**	**Number of records without duplicates within group**	**Publications, study registrations excluded**	**After manual check**	**Final group**
7-methylxanthine	7-methyl	34	23	20	20	pharma
near work	near	75	37	35	27	behav
sunlight / outdoor	sun	273	157	138	125	behav
Pirenzepine	pirenz	67	30	30	22	pharma
reading distance	dist	53	36	21	17	behav
reading without glasses	noglass	2	3	3	3	noglasses
undercorrection	undercorr	68	25	26	25	noglasses
violet light	violet	15	7	5	5	light
low intensity red light / RLRL	red	30	20	4	9	light
DOT	dot	20	10	7	7	glasses
HAL	hal	50	20	20	20	glasses
DIMS	dims	138	55	39	33	glasses
Atropine	atrop	1050	321	240	192	pharma
near addition	add	49	23	21	16	glasses
orthokeratology	ok	945	423	375	311	contacts
soft contact lenses	scl	355	176	143	134	contacts
		3224	1366	1127	966	
Combination of treatments					52	
Total considered (s. Figure 1)					**1018**	

Supplementary Table 2. RCTs included about interventions increasing outdoor activity or reducing near-work.

	Author, Year	Location	Design; length in months	Sample size (n)	Age (y)	Myopia (D)	Study aim	Intervention	Control	Outcome / Results	Adverse events
1	Liao S., 2023	Chengdu, China	randomized, controlled; 12	201	5 - 7	-0.5 to - 3.0	Exploration of correlations between sports, outdoor lighting, occurrence, and progression of myopia.	100 normal vision, 101 mildly myopic children, randomly assigned to 4 groups: outdoor exercise group, outdoor control group, indoor exercise group and indoor control group. Exercise, i.e. 12 weeks of moderate to high intensity aerobic exercise 3x/week 60min.		Significant difference in D outdoor exercise vs. indoor exercise ($p < 0.05$), outdoor exercise vs. indoor control ($p < 0.006$), outdoor control vs. indoor control ($p < 0.05$). No significant difference between outdoor exercise vs. outdoor control.	None reported
2	He X., 2022	Shanghai, China	cluster-randomized, examiner-masked; 24	6295 enrolled, 5295 analyzed at 24 months	6 - 9	429 (6.8%) myopes at baseline	Efficacy of additional time outdoors per school day on myopia onset and shift.	Stratified and randomized by school in 1:1:1 ratio: control (n = 2037), test I (n = 2329), or test II (n = 1929) group. Test I additional 40min. Test II additional 80 min of outdoor time. Control habitual outdoor time. Objective monitoring of outdoor and indoor time and light intensity with a wrist-worn wearable.		Unadjusted 2-year cumulative incidence of myopia was 24.9%, 20.6%, and 23.8% for control, test I, and II groups. The adjusted incidence decreased by 16% (incidence risk ratio [IRR], 0.84; 95% confidence interval [CI], 0.72–0.99; P = 0.035) in test I and 11% (IRR = 0.89; 95% CI, 0.79–0.99; P = 0.041) in test II, compared with control group. Test groups showed less myopic shift and axial elongation compared to control group (test I: –0.84 D and 0.55 mm, test II: –0.91 D and 0.57 mm, control: –1.04 D and 0.65 mm).	None reported
3	Wu P.-C., 2018	Kaohsiung, Taiwan	cluster-randomized; 12 ROCT 711 Recess Outside Classroom pilot study	693 first grade students	6 - 7	NA	Effectiveness of a school-based program promoting outdoor activities for myopia prevention.	In the intervention group, participants were encouraged to have 11 hours or more weekly of outdoor time. Light meters used for light intensity.		The intervention group showed significantly less myopic shift and axial elongation compared with the control group (0.35 diopter [D] vs. 0.47 D; 0.28 vs. 0.33 mm; P = 0.002 and P = 0.003) and a 54% lower risk of rapid myopia progression (odds ratio, 0.46; 95% CI, 0.28 - 0.77; P = 0.003).	Not reported
4	He M., 2015	Guangzhou, China	randomized, controlled; 24	1903	6 - 7	NA	Efficacy of increasing time spent outdoors at school in preventing incident myopia.	952 (from 6 schools) additional 40 min class of outdoor activities per school day.	951 (from 6 schools) continued their usual pattern of activity.	The cumulative incidence rate of myopia was 30.4% in the intervention group (259 incident cases among 853 eligible participants) and 39.5% (287 incident cases among 726 eligible participants) in the control group (difference of −9.1% [95% CI, −14.1% to −4.1%]; P < .001).	Not reported

5[&]	Wang D., 2023	Yudu, Jiangxi, China	randomized,;12 (one school year)	2032	8 - 10	NA	Effects of additional extracurrricular physical activity on academic performance of schoolchildren.	12 of 24 schools randomly assigned (1012 children) to do 2 hours of after-school physical activity time outdoors on school days.	12 of 24 schools randomly assigned (1020 children) free arrangement of after-school activity.	The mean (SD) mathematics score at the end of 1 academic year was 78.01 (17.56) points in the intervention group and 77.70 (17.29) points in the control group. The adjusted between-group mean difference was 0.65 points (95% CI, −2.85 to 4.15). The adjusted between-group mean difference in physical fitness score was 4.95 points (95% CI, 3.56-6.34; P < .001) and −1.90% (95% CI, −18.72% to 14.91%; P > .99) in myopia incidence.	None reported

[&] this article was included because of relevance, it did not fulfill the predefined inclusion criteria.

Supplementary Table 3. Most recent RCTs retrieved about atropine treatment.

	Author, Year	**Location**	**Design; length in months**	**Sample size (n)**	**Age (y)**	**Myopia (D)**	**Study aim**	**Intervention**	**Control**	**Outcome / Results**	**Adverse events**
6	Chia A., 2023	Singapore	randomized, placebo-controlled, double-masekd; 12	99	6 - 11	-1.0 to -6.0	Analysis of dose-response effects of low-atropine on myopia progression and safety of atropine drops.	Stratified by age group (ages 6–7, 8–9, and 10–11 y), and randomized in a 1:1:1:1 ratio to 0.0025%, 0.005%, or 0.01% of atropine dose or placebo.		Mean ± SD changes in SER in the placebo and atropine 0.0025%, 0.005%, and 0.01% groups were −0.55 ± 0.471, −0.55 ± 0.337, −0.33 ± 0.473, and −0.39 ± 0.519 D, respectively. The LS mean difference estimates (atropine−placebo) for changes in AL from baseline to month 12 in the atropine 0.0025%, 0.005%, and 0.01% groups were – 0.06 mm (p = 0.084; 95% CI: −0.13 mm, 0.01 mm), −0.09 mm (p = 0.012; 95% CI: −0.16 mm, −0.02 mm), and −0.10 mm (p = 0.003;95% CI: −0.17 mm, −0.04 mm).	Glare reported by 3 (3.0%) subjects and eye pain by 2 (2.0%).
7	Hansen N., 2023	Multicenter, Denmark	randomized, placebo-controlled, double-masked; 12, ongoing	97	6 - 12	≤ -1.0 for 6 - 9y olds; ≤ -2 for 9-12y in at least one eye	Investigation of safety and efficacy of one-year treatment with low-dose atropine eye drops for reducing myopia progression.	1:1:1 randomized to 0.01% low-dose atropine eye drops for 24 months (0.01% group) vs. 0.1% loading dose for six months followed by 0.01% for 18 months (0.1% loading dose group) vs. vehicle eye drops for two years (placebo).		At the twelve-month visit, AL had elongated 0.10 mm less (95% CI: 0.17 - 0.02) in the group receiving 0.1% loading dose for the initial six months and 0.07 mm less (95% CI: 0.15 - 0.00) in the 0.01% group, compared to placebo. These effects not statistically significant with multiple comparisons adjustment (adj-p=0.06 and 0.16). At the twelve-month visit, SER had progressed by 0.24 D (95% CI: 0.05; 0.42) and 0.19 D (95% CI: 0.00; 0.38) less in the 0.1% loading dose and 0.01% groups, also not statistically significant after multiple comparisons adjustment (adj-p=0.06 and 0.14, respectively).	14 AE: photopho-bia (n=2), blur during near-work (n=4) and eye redness/ irritation (n=3).

8	Loughman J., 2023	Dublin, Ireland; MOSAIC study	randomized, placebo-controlled, double-masked; 24, ongoing	250	6 - 16	≤ -0.5 in both eyes	0.01% atropine and its efficacy, safety, acceptability and mechanisms of action of low-concentration atropine for myopia control in predominantly Caucasian children.	Randomized 2:1 to receive either preservative-free 0.01% atropine or placebo eye drops. Atropine group n=167; placebo group n=83; completed 24-month n=136 and n=68, respectively.	Not significantly different myopia progression between the two groups at the 24-month visit (p=0.07), but significantly lower in the treatment group at the 18-month visit (p=0.049). Axial elongation was lower in the atropine group at the 18-month (p=0.04) and 24-month visits (p=0.009). No significant difference was observed in the proportion of eyes that progressed by −0.25D, −0.25 to −0.75D and more than −0.75D at 24months (p=0.28).	32 AEs 23/136 (16.9%) in atropine and 9/68 (13.2%) in the placebo groups (p=0.38).
9	Medghal-chi A., 2023	Iran	randomized, placebo-controlled, double-blind; 12	60	6 - 18	-2.0 to -6.0	Effect of two doses (0.1% and 0.01%) of atropine eye drops versus placebo on myopia progression in children and adolescents.	20 subjects per group: 0.1%, 0.01% atropine eye drops, or a placebo. Atropine eye drops applied every night for 6 months, then washout phase for 6 months with discontinued atropine.	In the placebo group, the mean AL was different three, six, and 12 months after the intervention compared to the baseline (p=0.038, p=0.011, and p<0.001, respectively). In the 0.1% atropine group, the mean AL decreased for six months and then increased 12 months after the intervention when compared to the baseline (both p<0.001). In the 0.01% atropine group, the mean AL was different at six months than at the baseline (both p<0.001). At the end of the study (six months after the cessation of the eye drops), rebound effect was observed in most of the studied parameters, including AL and SE.	Headache in 4 (16%) in 0.1%; photo-phobia in 11 (44%) and 4 (20%) in 0.01% and 0.01% atropine (p=0.001); 11 (44%) in 0.1% atropine group with blurred vision.
10	Moriche-Carretero M., 2023	Spain	randomized, controlled; 60	361	5 - 8 at base-line	-1.0 to -4.0	Evaluation of the efficacy and safety of 0.01% atropine eye-drops in controlling myopia progression over 5 years.	Treatment group used 0.01% atropine once daily every night and the control group did not use any treatment or placebo.	The SE increased −0.63±0.42D in children after 5 years of treatment with 0.01% atropine, while in the control group the increase was −0.92±0.56D. AL increased 0.26±0.28 mm in the treatment group compared with 0.49±0.34 mm in the control group. Atropine 0.01% showed an efficacy of 31.5% and 46.9% in the control of the SE and AL increase, respectively.	No side effects after 5 years of 0.01 atropine.
11	Sharma I., 2023	Dehli, India	randomized, placebo-controlled; 12	100	5 - 12	-0.5 to -10.0	Efficacy of low dose atropine (0.01%) eye drops in preventing myopia, mean change in SER and AL.	0.01% atropine daily before bedtime in the treatment group.	The mean change in spherical equivalent refraction and axial length was significantly lower in the treatment group (0.31 ± 0.55 D; 0.11 ± 0.22 mm) than the placebo group (0.80 ± 1.65 D; 0.23 ± 0.44 D) (p-value: 0.003). Less steepening of the corneal curvature was observed in the treatment group (0.16 ± 0.28 D vs 0.29 ± 0.3 D; p < 0.001).	None reported.

12	Wang W., 2023	Zhengzhou, China	randomized, placebo-controlled, double-blind, crossover; 13	60	6 - 12	≤ + 0.50 to > -0.75	To evaluate the efficacy of 0.01% atropine eye drops in preventing myopia shift and myopia onset in premyopic children.	Subjects were randomly assigned in a 1:1 ratio to receive one drop of 0.01% atropine or placebo once nightly for 6 months (period 1), followed by a 1-month recovery period. Then, the 0.01% atropine group was crossed over to the placebo group, and the latter was crossed over to the 0.01% atropine group for another 6 months (period 2).	Data of 50 subjects analysed. Generalized estimating equation (GEE) model performed statistically signicant treatment effect of 0.01% atropine compared with placebo (pSER=0.02, pAL<0.001), with a mean SER and AL difference of 0.20D (-0.15 ± 0.26D vs. -0.34 ± 0.34D) and 0.11mm (0.17 ± 0.11mm vs. 0.28 ± 0.14mm) in period 1, and 0.17D (-0.18 ± 0.24D vs. -0.34 ± 0.31D) and 0.10mm (0.15 ± 0.15mm vs. 0.24 ± 0.11mm) in period 2. GEE model showed that the proportion of myopia onset (p=0.004) and fast myopic shift (p=0.009) were signicantly lower in the 0.01% atropine group than that in the placebo group.	5 (16.6%) in atropine and two (7.8%) in placebo periods with photo-phobia in bright sunlight. No near-vision blur.
13	Yam J., 2023	Hongkong	randomized, placebo-controlled, double-masked, LAMP2; 24	474	4 - 9	+1.0 to 0.0	Efficacy of low-concentration atropine eyedrops at 0.05% and 0.01% concentration for delaying the onset of myopia. Nonmyopic children.	Participants were assigned at random to the 0.05% atropine (n = 160), 0.01% atropine (n = 159), and placebo (n = 155) groups and had eyedrops applied once nightly in both eyes over 2 years.	2-year cumulative incidence of myopia in 0.05% atropine, 0.01% atropine, and placebo groups: 28.4% (33/116), 45.9% (56/122), and 53.0% (61/115); percentages of participants with fast myopic shift at 2 years: 25.0%, 45.1%, and 53.9%. Compared with the placebo group, the 0.05% atropine group had significantly lower 2-year cumulative myopia incidence (difference, 24.6% [95% CI, 12.0%-36.4%]) and percentage of patients with fast myopic shift (difference, 28.9% [95% CI, 16.5%-40.5%]). Compared with the 0.01% atropine group, the 0.05% atropine group had significantly lower 2-year cumulative myopia incidence (difference, 17.5% [95% CI, 5.2%-29.2%]) and percentage of patients with fast myopic shift (difference, 20.1% [95% CI, 8.0%-31.6%]).	Photopho-bia reported by 12.9% of subjects in the 0.05% atropine group, 18.9% in the 0.01% atropine group, and 12.2% in placebo group.

14	Repka, M. et al., 2023	United States, multi-ethnic	Randomized placebo-controlled, double-masked; 24 months treatment, 6 months observation	187	5 - 12	-1.0 to -6.0	To compare atropine 0.01% with placebo for slowing myopia progression in US children.	Randomly assigned 2:1 to atropine 0.01% nightly or 1 drop of placebo. A total of 125 children (67%) received atropine, 0.01%, and 62 children (33%) received a placebo. Follow-up was completed at 24 months by 119 of 125 children (95%) in the atropine group and 58 of 62 children (94%) in the placebo group. At 30 months, follow-up was completed by 118 of 125 children (94%) in the atropine group and 57 of 62 children (92%) in the placebo group.	At the 24-month primary outcome visit, the adjusted mean (95% CI) change in SER from baseline was −0.82 (−0.96 to −0.68) D and −0.80 (−0.98 to −0.62) D in the atropine and placebo groups (adjusted difference =−0.02 D; 95% CI, −0.19 to +0.15 D; p=0.83). Atropine 0.01% eye drops administered nightly did not slow myopia progression or axial elongation when compared with placebo. Also, it did not slow myopia progression or axial elongation.	Ocular AE reported at least once by 87% in atropine group, and in 90% of placebo group. 89% (398 of 445) and 90% (198 of 220) were mild.
15	Zadnik, K. et al., 2023	Multicenter, North America and Europe CHAMP study	Randomized, placebo-controlled, double-masked phase 3 trial; 36	576, 489 modified intention-to-treat	3 - 16	-0.5 to -6.0	Primary outcome: proportion of participants' eyes responding to therapy (<0.50 D myopia progression at 3 years). Secondary efficacy outcomes included mean change from baseline in SER and axial length at month 36 in a modified intention-to-treat population.	Ratio 2:2:3 placebo vs. low-dose atropine, 0.01% and 0.02%. Once-daily placebo, low-dose atropine 0.01%, or low-dose atropine 0.02% eye drops for 36 months.	At month 36, compared with placebo, atropine 0.01%, significantly increased the responder proportion (odds ratio [OR], 4.54; 95% CI, 1.15-17.97; P = .03), slowed mean SER progression (least squares mean [LSM] difference, 0.24 D; 95% CI, 0.11 D-0.37 D; P < .001), and slowed axial elongation (LSM difference, −0.13 mm; 95% CI, −0.19 mm to −0.07 mm; p<0.001). Compared with placebo, atropine 0.02%, showed benefit but did not significantly increase the responder proportion (OR, 1.77; 95% CI, 0.50-6.26; p= 0.37) or slow mean SER progression (LSM difference, 0.10 D; 95% CI, −0.02 D to 0.22 D; p= 0.10) but did slow mean axial elongation (LSM difference, −0.08 mm; 95% CI, −0.13 mm to −0.02 mm; p= 0.005).	No serious ocular AE and few serious nonocular AE; none judged as associated with atropine.
16	Zhu Q., 2023	Yunnan, China	randomized, placebo-controlled; 36	142 (initial 176)	7 - 12	-1.0 to -6.0	To evaluate the effect of 0.05% atropine on the control of myopia for 2y (phase I) and on spherical equivalent refraction (SER) progression for 1y (phase II) after its withdrawal in Chinese myopic children.	Participants in this study were randomized to receive one drop of the atropine or placebo eye drops once nightly in both eyes for continuous medication for 24 months and then withdrawal of atropine or placebo for 12months. To reduce the photophobic response after treatment and to protect the eye tissues from ultraviolet (UV) damage, the atropine and the placebo groups were equipped with UV-sensitive photochromatic single vision lens (SVL).	During phase I, the mean change of SER was -0.46±0.30 D in the atropine group, compared to -1.72±1.12 D in the placebo group (p<0.001). The mean change of AL in the atropine group (0.26±0.30 mm) was significantly shorter than that in the placebo group (0.76±0.62 mm, p=0.002). In phase II (12mo after the withdrawal of atropine), there was no significant difference in AL change from the atropine group, when compared with placebo group (0.31±0.25 mm vs 0.28±0.26 mm, p>0.05). Hence, after cessation of 0.05% atropine, no significant AL rebound found. In the whole 3years,	Main AE: mild photopho-bia, disappear-ing within 7d. No severe allergies, head-aches and rainbow-vision.

									87% of the subjects in the atropine group had myopia progression by less than 1.0 D, compared with 17% in the placebo group.	
17	Lee S., 2022	Australia	randomized, double-masked, placebo-controlled; 24; (WA-)ATOM	153 enrolled	6 - 16	≤ -1.50	Testing hypothesis that nightly instillation of 0.01% atropine eyedrops is a safe and effective myopia-control therapy in a multi-racial cohort of Australian children with myopia.	Of the 153 enrolled participants, 104 (68.0%) and 49 (32.0%) were randomised to receive 0.01% atropine and placebo eyedrops, respectively. Over the 24 months, 22 participants withdrew from the study, including 10 (9.7%) in the atropine group and 12 (24.5%) in the placebo group.	At 12 months, the mean SE and AL change from baseline were 0.31D (95%CI = 0.39 to 0.22) and 0.16 mm (95%CI = 0.13 - 0.20) in the atropine group and 0.53D (95%CI = 0.66 to 0.40) and 0.25 mm (95%CI = 0.20–0.30) in the placebo group (p≤0.01). The mean SE and AL change from baseline was 0.64D (95%CI = 0.73 to 0.56) and 0.34 mm (95%CI = 0.30 - 0.37) in the atropine group, and 0.78D (95%CI = 0.91 to 0.65) and 0.38 mm (95% CI = 0.33–0.43) in the placebo group. Group difference at 24 months was not statistically significant (p=0.10).	9 AE in treatment group, none severe. No difference in incident of AE between groups (p=0.17).
18	Sen S., 2022	Agra, India	randomized, single-blinded, placebo-controlled; 24	145	5 - 15	≤ -2.0	This study was done to determine the effect of atropine 0.01% eye drops on the progression of myopia in children >5 years.	Children who met the eligibility criteria were enrolled and randomized to receive atropine 0.01% once nightly (72 children) or receive placebo drugs (73 children) in an allocation ratio of 1:1.	Mean axial length of group 1 and group 2 was 24.62 mm and 24.85 mm, respectively; mean refraction of group 1 and group 2 was 4.26D and 4.98D. In comparison to the baseline, group 1 exhibits a smaller increase in axial length than group 2, which was 0.115mm and 0.32mm. Similarly, the increase in refraction for group 1 was lower than that for group 2, which was 0.30D and 0.88D (p<0.0001).	No safety concerns with atropine 0.01% were evident in our study.
19	Ye L., 2022	Shanghai, China	randomized, non-masked; 12 ACAMP	207	6 - 12	-0.5 to 6.0	Investigate the efficacy and safety of consecutive use of 1% and 0.01% atropine compared with 0.01% atropine alone over 1 year.	Children randomly assigned to two treatment groups in a ratio of 1:1. Group A received 1% atropine sulfate eye gel (Dishan, Shenyang Xingqi Eye Hospital Co., Ltd. Shenyang, China) once weekly in both eyes for 6 months (starting with 1-week loading dose: 1% atropine once daily in both eyes) and were switched to 0.01% atropine (Myopine, Shenyang Xingqi Eye Hospital Co., Ltd. Shenyang, China) once nightly in both eyes for another 6 months. Group B received 0.01% atropine sulfate eyedrops once nightly in both eyes throughout one year. No placebo group.	91 (87.5%) in group A and 80 participants (77.7%) in group B completed the 1-year treatment. Group A exhibited less refraction progression (- 0.53 ± 0.49 D vs. - 0.74 ± 0.52 D; P = 0.01) and axial elongation (0.26 ± 0.17 mm vs. 0.36 ± 0.21 mm; P <0.001) over 1 year compared with group B. The changes in refraction (- 0.82 ± 0.45 D vs. - 0.46 ± 0.35 D; P <0.001) and axial length (0.29 ± 0.12 mm vs. 0.17 ± 0.11 mm; P <0.001) during the second 6 months in group A were greater than those in group B, with 72.5% of participants presenting refraction rebound.	No serious adverse events were reported.

20	Cui C., 2021	Zhengzhou, China	randomized, double-masked, controlled; 24	400, 300 analyzed at 24	6 - 14	-1.25 to -6.0	Testing long-term use of low-dose atropine efficacy, safety, and dose-dependence in controlling myopia progression. Investigation of difference in efficacies between 0.02 and 0.01% atropine.	Random assignement to atropine 0.02% (n = 138) or 0.01% (n= 142) in both eyes once-nightly for 2 years. 120 subjects, wore only SV spectacles, no placebo treatment. Among the 400 children enrolled, 64 were lost to follow-up within the first year, and 336 (84%) continued to participate in the extended trial. There were 117, 119, and 100 children in the 0.02% and 0.01% atropine and control groups, respectively at 24 months.	After 2 years, the SER changes were −0.80 (0.52) D, −0.93 (0.59) D and −1.33 (0.72) D and the AL changes were 0.62 (0.29) mm, 0.72 (0.31) mm and 0.88 (0.35) mm in the 0.02% and 0.01% atropine groups and control group. There were significant differences between changes in SER and AL in the three groups (all p< 0.001). The changes in SER and AL in the 2nd year were similar to the changes in the 1st year in the three groups (all p > 0.05). 49.5%, 45.2%, and 26.9% of the subjects progressed by less than 1.0 D in the 0.02% and 0.01% atropine and control groups, respectively, whereas 16.2%, 18.8%, and 34.8% subjects progressed by more than 2.0 D in the 0.02% and 0.01% atropine and control groups, respectively.	32 (23%) and 33 (24%) in the 0.02% and 0.01% atropine photopho-bic. No child was allergic to 0.01% or 0.02% atropine or showed any other discomfort associated with drops during 2nd year.
21	Hieda O., 2021	Multicenter, Japan	randomized, double-masked, placebo-controlled; 24	171	6 - 12	-1.0 to -6.0	Evaluation of efficacy and safety of 0.01% atropine eye drops for myopia control in Japanese children.	Subjects were randomized to receive either 0.01% atropine eye drops or atropine-matched placebo eye drops at the ratio of 1:1.	Data from 168 subjects were analyzed. At month 24, compliance was similar in both groups (atropine: 83.3%; placebo: 85.7%). The least squares mean change in SE and AL from baseline were, respectively, −1.26 D (95%CI: −1.35, −1.17) and 0.63 mm (0.59, 0.67) for atropine and −1.48 D (− 1.57, −1.39) and 0.77 mm (0.73, 0.81) for placebo. Inter-group differences were 0.22 D (95% CI: 0.09, 0.35; p < 0.001) for SE and − 0.14 mm (−0.20, −0.08; p< 0.001) for AL.	3 subjects with mild allergic conjunct-ivitis, no inter-group difference (atropine: 2.4%; 2/84 patients; placebo: 1.4%; 1/84 patients).
*	Loughman J., 2023	Dublin, Ireland	Randomized-controlled, double-masked; 24 MOSAIC	250 recruited	6 - 16	≤ -0.5	Exploration of efficacy, safety, acceptability and mechanisms of action of low-concentration atropine for myopia control in predominantly Caucasian, European children.	Participants were randomized 2:1 to receive either preservative-free 0.01% atropine or placebo eye drops, respectively, dispensed as single-use disposable ampoules. In intervention group 136 (of initial 167) completed 24-months; control n=68.	Myopia progression was not significantly different between the atropine and placebo groups at 24 months (p=0.07) but was significantly lower in the treatment group at the 18-month visit (p=0.049). Axial elongation lower in the atropine group at the 18-month (p=0.04) and 24-month visits (p=0.009), compared to the placebo group. No significant difference was observed in the proportion of eyes that progressed by >−0.25 D, −0.25 to −0.75 D and <−0.75 D at 24 months, between placebo and 0.01% atropine groups (p = 0.28).	AE not different between groups. 7 AE related eye dis-comfort, temporary blurred vision at near, temporary pupil dilation

* was added later to the included RCTs.

Supplementary Table 4. RCTs presenting findings on the effect of different myopia control spectacles (PAL, DIMS, DOT, HAL)

	Author, Year	Location	Design; length in months	Sample size (n)	Age (y)	Myopia (D)	Study aim	Intervention	Control	Outcome / Results	Adverse events
22	Hasebe S., 2014	Multicenter, Japan	randomized, masked, cross-over; 24	303	6-12	-1.0 to -4.5	Evaluation of effect of positively aspherized progressive addition lenses (PA-PALs) on the progression of early-onset myopia.	Control 3D base spherical SVLs, PA-PALs with þ1.0D addition, and PA-PALs with þ1.5D addition. Allocation ratio was approximately 1:1:1. The children attended follow-up visits every 6 months for a period of 2 years. One hundred sixty-nine (86%) children completed the follow-up.		Adjusted progression rates showed a mean (SE) progression of -1.39 (0.09) D in the control group wearing SVLs at the 24-month visit. Statistically significant ($p<0.017$) retardation of myopia progression (0.27 vs 0.11 D during 24-month period or reduction ratio of 20%) for PA-PALs relative to the SVLs was found. Nearly all retardation occurred in the first 12 months with no significant efficacy in the second year.	No serious AE reported during the 2-year follow-up.
23	Lam, C. 2020	Hong Kong	randomized, double-masked, controlled; 24	183	8 - 13	-1.0 to - 5.0	To determine if 'Defocus Incorporated Multiple Segments' (DIMS) spectacle lenses slow childhood myopia progression.	Children were randomly assigned to wear DIMS (n=93) or single vision (SV) spectacle lenses (n=90). DIMS with myopic defocus of +3.50 D. 160 children completed the study, n=79 in the DIMS group and n=81 in the SV group.		Average (SE) myopic progressions over 2 years were −0.41±0.06 D in the DIMS group and −0.85±0.08 D in the SV group. Mean (SE) axial elongation was 0.21±0.02 mm and 0.55±0.02 mm in the DIMS and SV groups. Myopia progressed 52% more slowly for children in the DIMS group compared with those in the SV group (mean difference −0.44±0.09 D, 95% CI −0.73 to −0.37, $p<0.0001$). Likewise, children in the DIMS group had less axial elongation by 62% than those in the SV group (mean difference 0.34±0.04 mm, 95% CI 0.22 to 0.37, $p<0.0001$). 21.5% children who wore DIMS lenses had no myopia progression over 2 years, 7.4% for those who wore SV lenses.	No treatment-related AE reported.
24	Rappon J., 2023	14 sites, North America, ongoing (36 planned)	randomized, double-masked, controlled; 12, CYPRESS	265 enrolled, 258 ITT	6 - 10	-0.75 to -4.50	Evaluation of the efficacy and safety of SightGlass Vision DOT spectacle lenses for slowing the progression of juvenile myopia.	Subjects were randomised to one of three study spectacle lenses in a 1:1:1 ratio: For test 1 (called DOT 0.2 commercially), diffusers were applied with 0.365mm spacing. Test 2 had a higher density (ie, closer spacing) of diffusers of 0.240 mm. SV spectacles as control. Test 1, n=88; test 2, n=75; control, n=93.		At 12 months, the least-squared mean change in AL was 0.15mm for Test 1 and 0.20mm for test 2 vs 0.30mm for the control group; the difference between means represented a 50% reduction for test 1 (0.15 mm; 95%CI=0.10to 0.20mm; $p<0.0001$) and 33% reduction for test 2 (0.10 mm; 95% CI 0.04 to 0.17 mm; $p=0.0018$). Observed data (mean±SD) were 0.15±0.15mm for test 1 and 0.18±0.21mm for test 2 vs 0.30±0.17 mm for control.	16 reported ocular AE in 11 subjects, none serious.

25	Li X., 2023 (Bao et al.)	Wenzhou, China	randomized, double-masked, controlled; 24; 36 (last year non blinded)	162	10 - 15 (at 3rd base-line)	-1.75 to -6.0	Investigation of efficacy in children who continued wearing spectacle lenses with highly aspherical lenslets (HAL) or switched from spectacle lenses with slightly aspherical lenslets (SAL) and single-vision spectacle lenses (SVL) to HAL for 1 year after 2-year.	Of 54 children who had worn HAL for 2 years, 52 continued wearing HAL (HAL1 group), and of the 53 and 51 children who had originally worn SAL or SVL, 51 and 48 switched to wearing HAL (HAL2 and HAL3 groups) in year 3, respectively.	A new control group (n=56) was recruited A new SVL (nSVL) group of 56 children was recruited, matched for age, sex, cycloplegic spherical equivalent refraction (SER), and axial length (AL) of the HAL3 .	During year 3, the mean (SE) myopia progression in the nSVL group was −0.56 (0.05) D. Compared with nSVL, the changes in SER were less in HAL1 (−0.38 [0.05] D, p=0.02), HAL2 (−0.36 [0.06] D, p=0.01), and HAL3 (−0.33 [0.06] D, p=0.005). The mean (SE) AL elongation in the nSVL group was 0.28 (0.02) mm. Compared with nSVL, the elongation in AL was less in the HAL1 (0.17 [0.02] mm, p<0.001), HAL2 (0.18 [0.02] mm, p<0.001), and HAL3 (0.14 [0.02] mm, p<0.001) groups. Myopia progression and axial elongation were comparable in all 3 HAL groups (all p> 0.05) in year 3.	No AE reported during the extended study period.
26	Sankari-durg P., 2023	Ho Chi Minh City, Vietnam	randomized, double-blind, cross-over	132	7 - 13	-0.75 to -4.75	Ascertain the efficacy of spectacle lenses with highly aspherical lenslets (HAL) in slowing progression of myopia compared to single vision spectacle lenses.	Enrolled children were randomized to 2 groups: (1) group HSH to spectacle lenses with highly aspherical lenslets (HAL), and (2) group SHH to single vision (SV) spectacle lenses. After 6 months of lens wear in their assigned group (stage 1), participants were switched to the other, remaining lens type (group HSH switched from HAL to SV, and group SHH vice versa) without any washout period for an additional 6 months of lens wear (stage 2).		A total of 132 children were successfully enrolled and randomized to 2 groups. Of these, 119 children were dispensed with lenses. At the end of stage 2, the change in SER (observed mean of −0.05 ± 0.37 D with HAL vs −0.33 ± 0.27 D with SV, 85%) and axial length (adjusted mean of 0.05 ± 0.12 mm with HAL vs 0.17 ± 0.13 mm with SV, 71%) was significantly less in eyes with HAL, and the differences were significant.	During the study pe-riod, there were no lens-related AE. 3 non−lens-related events.
*	Liu X. et al., 2023	Wenzhou, China	Randomized, controlled, 12 months interim analysis	118	8 - 12	-1.0 to -4.0	Assessment of study lenses are efficacy in slowing myopia progression and axial elongation. Primary outcomes were the 1-year change in spheri-cal equivalent cycloplegic autorefraction and axial length.	61 participants randomly assigned to cylindrical annular refractive element (CARE) spectacle lenses. 52 after 12 months.	57 allocated to SV spectacles, 44 completed follow-up at 12 months	Linear mixed model analysis: The model-adjusted 1-year changes in SER were−0.56±0.06 D for the CARE group and −0.71±0.07 D for the SVL group (F = 2.546, p = 0.11). Not significant for SER. The model-adjusted 1-year changes in AL were 0.27±0.02mm and 0.35±0.02mm for the CARE and SVL groups, respectively; there was a significant difference between the two groups (F = 6.692, p=0.011), significant for AL.	No AE reported.
**	Yuval, C., 2024	Israel	Randomized, controlled, double blind; 12 months	126	6 - 13	-0.5 to -6.25	Investigation of effectiveness of Shamir myopia control (SMC) spectacles to slow the progression of myopia in children.	65 participants in the SMC group	61 in the control group wearing SV spectacles.	AL and SER progression were slowed by 0.11 mm (35%, p<0.05) and 0.16 D (25%, p= 0.122), respectively. In subgroup of 6-10y olds, AL and SER progression were slowed by 0.17 mm (41%, p< 0.05) and 0.31 D (43%, p< 0.05). For subgroup of children with 2 myopic parents AL and SER progression were slowed by 0.15 mm (45% p<0.05)	Not reported.

										and 0.36 D (42%, p<0.05), respec-tively.	

* and ** were added later to the included RCTs.

Supplementary Table 5. Recent RCTs about different soft contact lenses (SCL) and OK lenses.

	Author, Year	Location	Design; length in months	Sample size (n)	Age (y)	Myopia (D)	Study aim	Intervention	Control	Outcome / Results	Adverse events
27	Cheng X., 2023	Multicenter, Canada, China, United States	randomized, controlled, double-masked; 6	199	7 - 12	-0.75 to -4.5	Evaluation of efficacy and vision with 2 prototype myopia control soft contact lenses and single-vision (SV) designs.	Two SCLs with noncoaxial ring-focus designs (for enhancing efficacy [EE] and enhancing vision [EV]) compared with dual-focus (DF).	SV soft contact lenses	EE, EV, and DF all had statistically significantly less axial elongation than SV.	No serious ocular AE reported.
28	Weng R., 2022	Guangzhou, China	randomized, contrlateral, cross-over; 12	95	7 - 13	-0.75 to -3.5	To determine the efficacy of two myopia control contact lenses (CL) compared with a single-vision (SV) CL. 1-year.	Eextended depth of focus (EDOF) CL; MiSight® CL.	SV soft contact lenses	Extended depth of focus and MiSight® CL demonstrated similar efficacy in slowing myopia.	None reported.
29	Garcia-del Valle A., 2021	Multicenter, Spain	randomized, parallel, double-masked; 12	70	7 -15	-0.5 to -8.75	Determine the efficacy and safety of the Esencia lens, a new soft contact lens (SCL).	36 subjects Esencia lens (progressive multifocal and reverse geometry SCL).	34 subjects with SV soft contact lenses	A significantly lower increase in axial length was found in the study group (0.13 ± 0.12 mm) compared to control (0.22 ± 0.14 mm) patients (p=0.03).	No serious (ocular) AE reported.
30	Raffa L., 2021	Malaysia	randomized, controlled, double-masked; 18	30	13 - 15	-2.0 to -6.0	Effect of multifocal contact lenses (MFCL) (Multistage + 1.50D and Proclear + 3.00D) on myopia progression and axial length elongation.	multistage MFCL + 1.5D, Proclear + 3.0D	SV soft contact lenses	Myopia progression was controlled by 38.6% and 66.6% in children wearing Multistage + 1.50D, and Proclear +3.00D MFCL, respectively, in comparison to children wearing SVCL over an 18-month period.	None reported.
31	Choi K., 2023	China	randomized, single-blind; 24	71	8 - 12	-1.0 to -4.0	Efficacy and long-term safety of the Breath-O-Correct orthokeratology (OK) lens.	43 OK	28 single vision (SV) lenses	The Breath-O-Correct OK lens significantly reduced AL elongation in schoolchildren without adverse clinical effects or subclinical inflammatory responses.	No AE reported.

32	Guo B., 2023	China	randomized; 24	45	6 - <11	-0.75 to -4.0	Comparison of axial elongation (AE), treatment zone (TZ) characteristics in children wearing 6 mm or 5 mm back optic zone diameter (BOZD) orthokeratology (OK) lens.	Two different OK lens designs.	Smaller BOZD OK lenses resulted in a smaller TZ diameter, which was associated with less AE after 2 years of treatment.	No significant visual AE reported. 15 cases with contact lens-related AE.
33	Liu T., 2023	Sichuan, China	randomized; 12	70	8 - 12	-0.75 to -4.0	Comparison of BCA (aspheric base curve) OK vs BCS (spherical base curve) OK in myopia progression.	Random assignment to BCA or BCS OK lens groups.	1-year results from 31 BCA and 32 BCS subjects: BCA lens produced greater absolut relative peripheral refraction change and axial elongation was slower in the BCA group (0.19 +-0.20mm) than in the BCS group (0.29+-0.14mm, p0.03).	None reported.

Supplementary Table 6. RCTs on red- and violet-light treatment.

	Author, Year	**Location**	**Design; length in months**	**Sample size (n)**	**Age (y)**	**Myopia (D)**	**Study aim**	**Intervention**	**Control**	**Outcome / Results**	**Adverse events**
34	Chen H., 2023	Xuzhou, China	randomized; 12	102	6 - 13	-0.75 to -6.00	Effect of RLRL therapy on myopic control and accommodative function.	51 subjects received RLRL therapy (LONGDA, Jilin Longda Optoelectronics Technology, Jilin, China) twice per day for 3 min each session, with at least a 4-h interval between sessions.	51 subjects. No placebo intervention. All subjects instructed to wear SV spectacles (SVS).	12-month AL elongation and myopic progression were 0.01 mm (95%CI: −0.05 to 0.07 mm) and 0.05 D (95%CI: −0 .08 to 0.19 D) in the RLRL group, which were less than 0.39 mm (95%CI: 0.33 to 0.45 mm) and −0.64 D (95%CI: −0.78 to −0.51 D) in the control group ($p<0.05$).	None reported.
35	Tian L., 2022	Beijing, China	randomized; 6	224	6 - 12	-0.5 to -6.00	Efficacy and safety of the 650 nm RLRL for myopia control in children aged 6–12 years. Primary outcomes included change in AL and change in SER.	112 RLRL treatment 2x/ day, each of 3 min. The light source used was a single-wavelength (650 nm) weak red-light laser, with low intensity (radiation category Class 1). The light source was integrated on	112 subjects . No placebo intervention. All subjects in the study wore SVS.	The median 6-month changes in AL of the RLRL and control groups were - 0.06 mm (IQR - 0.15, 0) and 0.14 mm (IQR 0.07, 0.22). The difference between groups was significant ($Z = 10.021$, $p<0.001$).	No events reported during RLRL treatment.

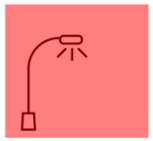
								a head-mounted device.			
36	Xiong R., 2022	Multiple centers, China; post-trial follow-up of Jiang Y., 2022	randomized, 12	264	8 - 13	-1.00 to -5.00	24-month follow-up to investigate the long-term efficacy and safety of continued RLRL therapy as well as the potential rebound effect following RLRL treatment cessation.	69 of the initially included 119. Who had received RLRL with desktop light therapy device (Eyerising) twice daily with an interval of at least 4 hours, each treatment lasting 3 minutes, during weekdays (5 days per week) for total of 12 months.	69 of the initially included 145. No placebo intervention. SVS for all.	A total of 114 (57.3% of the eligible) participants in the final analysis (SVS-SVS: n = 41; SVS-RLRL: n = 10; RLRL-SVS: n = 52; RLRL-RLRL: n = 11). The overall axial elongation was the smallest in the RLRL-RLRL group (0.16 ± 0.37 mm), followed by SVS-RLRL (0.44 ± 0.37 mm), RLRL-SVS (0.50 ± 0.28 mm) and SVS-SVS groups (0.64 ± 0.29 mm; p<0.001).	No side effects or adverse events reported in the follow-up period.
37	Mori K., 2021	Tochigi, Japan	randomized, 24	113	6 - 12	-1.5 to - 4.5	Change in axial length and SER under cycloplegia after 24 months.	56 VL transmitting spectacles	57 conventional spectacles	No significant statistical difference in AL and SER. Subgroup of children wearing spectacles for the first time showed trend (AL in the VL group (difference: −0.206 mm; 95% CI: −0.351, 0.060; p = 0.006.).	No adverse effects associated with VL.

Supplementary Table 7. RCTs on combination of treatments

	Author, Year	**Location**	**Design; length in months**	**Sample size (n)**	**Age (y)**	**Myopia (D)**	**Study aim**	**Intervention**	**Control**	**Outcome / Results**	**Adverse events**
38	Tan Q., 2023	Hong Kong	randomized, 24	96	<11	-1.0 to -4.0	Effect of 0.01% atropine with orthokeratology (AOK) on retarding axial elongation, compared with orthokeratology alone (OK) over two years.	48 subjects in the AOK group one drop of 0.01% atropine 10 min before nightly wear of 4-zone *ortho*-k lenses	48 subjects in control with 4-zone OK lenses, no placebo intervention	AOK subjects had statistically slower axial elongation (adjusted mean [standard error], 0.17 [0.03] mm vs 0.34 [0.03] mm, p<0.001)	None reported.
39	Xu S., 2023	Guangzhou, China	age-stratified, randomized, placebo-controlled; 24	164	8 - 12	-1.0 to -6.0	2-year efficacy of atropine, orthokeratology OK and combined treatment on myopia.	0.01% atropine and SV spectacles, OK and placebo (OK) or combined treatment.	Placebo drops and SV spectacles.	All interventions can significantly reduce axial elongation at all visits (all p<0.05). a significant age-dependent effect in the OK group versus the atropine group (p for interaction=0.035), OK can achieve better efficacy in younger children.	No events reported during 650 nm RLRL treatment.

40	Yu S., 2022	Zhengzhou, China	randomized, placebo-controlled, double-blinded; 12	60	8 - 12	-1.0 to -4.0	Evaluation of additive effects of orthokeratology (OK) lenses and 0.01% atropine on slowing axial elongation in myopic children. 1-year.	30 subjects with OK lenses and atropine 0.01%.	30 subjects with OK lenses and placebo drops.	Axial elongation was 0.10 ± 0.14 mm and 0.20 ± 0.15 mm (p=0.01) for combination vs OK alone at 12 month. Difference in AL change only in the first 4 month.	No side effects or adverse events reported in the follow-up period.
41	Zhao Q., 2021	Dalian, China	randomized, 12	120	8 - 14	<-1.0	Comparison of efficacies of 0.01% atropine vs orthokeratology (OK) in slowing the development of myopia. 1-year.	60 subjects with SA = spectacles and 0.01% atropine; 60 subjects OK = orthokeratology		After one-year, the SE and AL in participants aged ≤10 years were better controlled in the SA in low-myopia group ($p<0.05$), whereas those aged ≥11 years were better controlled in the OK in high-myopia group ($p< 0.05$).	No adverse effects associated with VL.

Supplementary Table 8. Summary of data and information utilized to create Figure 2.

					
Evidence (≈ number per category of the 103 identified RCTs, s. Figure 1)	≈ 10 (= 9 +1), for outdoor and near work together.	≈ 40 (= 41), atropine alone.	≈ 10 (= 11), all spectacles.	≈ 20 (= 10 + 11), for OK lenses and SCL together.	≈ 5 (= 5), red light alone.
	The height of the bar is chosen slightly higher compared to the spectacles' since it represents a more unified group of studies, as well as because the conduction of intervention studies in the field of behavioural changes seems more challenging.				
Effect (based on summarized 41 RCTs, reviews and later added studies, s. Suppl. Tables 2-7)	Cao et al.: pooled RR 0.76 (0.67-0.87); He et al.: IRR 0.84 (0.72-0.99); Wu et al. OR for rapid progression 0.46 (0.28-0.77); He et al.: 9.1% reduction of incidence	Ha et al.: mean differences (MD) for 0.01% atropine of 0.39, 0.21-0.57); Lanca et al. MD of 0.29 (0.22-0.39), LAMP study SER reduction by 27 – 67% depending on dose, LAMP2 study 2-year cumulative incidence of myopia in 0.01% atropine 7.1% lower compared to placebo. Ca. 10% non-responders. Sen et al.; Hieda et al, Cui et al.	Lam et al. 52% reduction of progression, Liu et al. 40% DIMS wearers compared to 19% SVL wearers showed low progression; Bao et al. reduces progression by 67% for SER. Lower estimates from other studies. (Not applicable in children with a higher degree of strabismus.)	30-45% for SCL and 30-60% for OK reduction of myopia progression according to various meta-analyses. Sun et al. 45%, Lanca et. al MD = 0.39 (0.21-0.56). Lam et al. report myopia progression reduction by 60% for DISC. Ca. 10% non- responders.	Chen, Xiong, Tian et al.: 12-month AL elongation 0.01 mm (95%CI: −0.05 to 0.07 mm) in the RLRL group, compared to 0.39 mm (95%CI: 0.33 to 0.45 mm) in the control group. - 0.06 mm (IQR - 0.15, 0) for RLRL and 0.14 mm (IQR 0.07, 0.22) in control. And RLRL-RLRL group (0.16 ± 0.37 mm)., compared to 0.64 ± 0.29 mm in control.
Safety (based on summarized literature, s. Suppl. Tables 2-7)	Safe, appropriate sun protections necessary.	Reversible adverse events (AE), e.g. photophobia, accommodation. No severe AE reported in RCTs.	Generally safe. No mild or severe AE reported in included RCTs.	Potentially irreversible AE occur, e.g. corneal scarring after infection.	Irreversible AE not excluded, e.g. retinal damage.
Cost	Free.	ICER = 220USD/SER reduction*; very much country depending, in East Asian countries ≈ 120 USD/year.	ICER for HALs was 448 USD/ SER reduction; also depending on the country and availablility, ≈ 500 -800 USD/year.	OK lenses was 2376 USD/ SER reduction; costs for SCL and OK range between ≈ 1500 - 3000 USD/year.	Commercialization process ongoing, estimated yearly cost ≈ 1500 USD.
	The yearly costs were approximations from various sources, including the cost-effectiveness analysis by *Agyekum et al. (2023).				