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Real-world Effectiveness of 0.01% Atropine for Primary Prevention of Myopia in Children: A Retrospective Cohort Study

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Key messages

- What is known: The efficacy of 0.01% atropine for preventing myopia onset is controversial, with conflicting evidence from randomized trials.
- What is new: In this real-world cohort of 290 non-myopic and pre-myopic children, 0.01% atropine was not associated with reduced myopia onset or refractive progression, consistent with the LAMP2 trial.
- What is new: Baseline spherical equivalent was the strongest predictor of refractive trajectory; a possible benefit confined to children with baseline SE of −0.50 to 0 D was hypothesis-generating only.

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Statements and Declarations

Competing Interests: The authors have no competing interests to declare that are relevant to the content of this article.

Compliance with Ethical Standards: This study was approved by the Institutional Review Board of the Eye and ENT Hospital of Fudan University (Approval No. 2025067). Because of the retrospective study design, written informed consent for study participation was waived; verbal consent was obtained from parents or legal guardians for telephone follow-up.

Running title: Atropine 0.01% for myopia prevention

Abstract

Purpose: The efficacy of atropine 0.01% for preventing myopia onset remains controversial despite its widespread use. Its effectiveness in preventing incident myopia was evaluated in a real-world clinical setting.

Methods: This retrospective cohort study included 290 non-myopic or pre-myopic children (157 receiving atropine 0.01% and 133 untreated controls) attending a tertiary eye center between January 2018 and October 2024. Longitudinal changes in

spherical equivalent (SE) were analyzed using linear mixed-effects models. Time to myopia onset (SE ≤ −0.50 D) was evaluated using Kaplan–Meier analysis and Cox proportional hazards regression. Multiple imputation and overlap-weighting analyses were performed as sensitivity analyses.
Results: Myopia developed in 96 of 157 children (61.1%) receiving atropine and 98 of 133 controls (73.7%). In the fully adjusted model, the group-by-time interaction was not significant (β = 0.021, 95% CI −0.046 to 0.089; P = 0.536), indicating similar rates of refractive progression. Baseline SE was the strongest predictor (β = 0.888, P < 0.001). Kaplan–Meier analysis showed no significant difference (P = 0.182). Cox regression yielded a hazard ratio of 0.76 (95% CI 0.57–1.00; P = 0.052), while overlap weighting attenuated the association (HR 0.89, 95% CI 0.65–1.20; P = 0.44).
Conclusion: In this real-world cohort, atropine 0.01% was not associated with a significant reduction in myopia onset or refractive progression. These findings do not support routine use of atropine 0.01% solely for preventing myopia onset.
Keywords: atropine; myopia onset; myopia prevention; pre-myopia; real-world evidence

Introduction

Myopia has become one of the leading causes of visual impairment worldwide, particularly in East and Southeast Asia, where both its prevalence and associated vision-threatening complications continue to rise.[1] Because pathological changes associated with progressive axial elongation may begin before clinical myopia develops, increasing attention has shifted from slowing myopia progression to preventing its onset in children at risk.[2]

Low-concentration atropine has emerged as one of the most extensively investigated pharmacological interventions for myopia control.[3, 4] While atropine concentrations of 0.025%–0.05% have consistently demonstrated efficacy in slowing myopia progression, the role of 0.01% atropine in preventing incident myopia remains uncertain.[5-9] The recent Low-concentration Atropine for Myopia Prevention (LAMP2) trial reported that 0.05%, but not 0.01%, significantly reduced the cumulative incidence of myopia and rapid myopic shift in pre-myopic children.[10] In contrast, a prospective randomized double-masked crossover trial from China found that 0.01% atropine reduced myopic shift, axial elongation, and myopia onset over two consecutive 6-month treatment periods in a highly selected cohort of pre-myopic children.[11] Similarly, the Atropine for Myopia Prevention (AMPP) study reported delayed myopia onset with 0.01% in non-myopic schoolchildren.[12] These conflicting findings have generated substantial uncertainty regarding the preventive effectiveness of 0.01% atropine.

Importantly, existing evidence has been derived predominantly from randomized controlled trials conducted under highly controlled conditions with protocol-driven

follow-up. In routine clinical practice, however, treatment decisions are influenced by parental preference, clinician judgement, perceived myopia risk, treatment adherence, and follow-up patterns, all of which may affect treatment effectiveness.[13] Consequently, the effectiveness of atropine observed in real-world clinical settings may differ from the efficacy reported in randomized trials. Real-world evidence therefore provides an important complement to randomized studies by evaluating treatment performance under everyday clinical conditions and informing routine clinical decision-making.[14]

In March 2024, atropine 0.01% was approved by the China National Medical Products Administration for **slowing myopia progression in children with established myopia.**[15, 16] However, this regulatory approval does not extend to primary prevention of myopia onset in non-myopic or pre-myopic children—a distinct clinical objective that may differ substantially in biological mechanisms and therapeutic responsiveness. In routine clinical practice, clinicians and parents may be tempted to use this approved medication for prevention in at-risk children, creating a need for real-world evidence to guide such off-label use. To address this evidence gap, we conducted a retrospective real-world cohort study to evaluate whether low-concentration atropine 0.01% reduces the risk of incident myopia among non-myopic and pre-myopic children receiving routine clinical care.

Materials and Methods

Study Design and Setting

This retrospective observational cohort study was conducted at the Eye and ENT Hospital of Fudan University, Shanghai, China. Consecutive eligible children attending the pediatric ophthalmology clinic between 1 January 2018 and 31 October 2024 were screened through the electronic medical record system. The study was approved by the Institutional Review Board of the Eye and ENT Hospital of Fudan University (Approval No. 2025067). Because of the retrospective study design, written informed consent for study participation was waived; verbal consent was obtained from parents or legal guardians for telephone follow-up.

Participants

Children aged 3–13 years were eligible if they had bilateral spherical equivalent (SE) greater than −0.50 D at baseline, cycloplegic refraction available at baseline, and at least one subsequent cycloplegic examination. Additional eligibility criteria included spherical power between 0 and +1.25 D, cylindrical power between −1.00 and 0 D in both eyes, an interocular SE difference <2.00 D, and no previous or concurrent myopia-control intervention.

Children were excluded if baseline cycloplegic refraction was incomplete, fewer than two visits with analyzable refractive data were available, follow-up was shorter than six months, or another myopia-control treatment was initiated during follow-up. Treatment allocation reflected routine clinical practice. Children prescribed atropine received hospital-compounded atropine sulfate 0.01% eye drops once nightly in both eyes, whereas children in the comparison group received no pharmacological

126 treatment. Treatment decisions were made jointly by ophthalmologists and parents
127 and were independent of study participation.

128 **Ophthalmic Examination and Outcome Measures**

129 Cycloplegic refraction was performed using compound tropicamide according to
130 institutional clinical protocols. The participant was the unit of analysis, and the mean
131 SE of both eyes was used for statistical analyses to account for the high correlation
132 between fellow eyes.

133 The primary outcome was incident myopia, defined as the first visit at which SE was
134 ≤ −0.50 D in either eye or confirmed at the subsequent examination. The secondary
135 outcome was annual change in SE. Rapid myopic progression was defined as an
136 annual change in SE of at least −0.50 D/year.

137 **Covariates**

138 Baseline demographic and clinical variables included age, sex, baseline SE, sphere
139 and cylinder, parental history of myopia, average daily outdoor activity and average
140 daily near-work time. Baseline SE, age and parental myopia were prespecified before
141 statistical modelling.

142 **Statistical Analysis**

143 Baseline characteristics were summarized as mean (standard deviation [SD]) or
144 median (interquartile range [IQR]) for continuous variables and number (percentage)
145 for categorical variables. Between-group comparisons used Student's t test or the
146 Mann–Whitney U test for continuous variables, and the χ^2 test or Fisher's exact test
147 for categorical variables, as appropriate.

Longitudinal refractive change was analyzed using linear mixed-effects models with participant-specific random intercepts to account for repeated measurements. Fixed effects included treatment group, follow-up time, age and sex, with the treatment-by-time interaction prespecified as the principal parameter.

Missing covariate data were addressed using multiple imputation by chained equations under the missing-at-random assumption. Twenty imputed datasets were generated, and parameter estimates and standard errors were combined using Rubin's rules.[17] A fully adjusted mixed-effects model including baseline SE, outdoor activity, near-work time and parental myopia was performed as a sensitivity analysis.

Time to incident myopia was analyzed using Kaplan–Meier estimation and compared with the log-rank test. Multivariable Cox proportional hazards regression estimated hazard ratios (HRs) and 95% confidence intervals (CIs) after adjustment for prespecified confounders. The proportional hazards assumption was assessed using Schoenfeld residuals. Where the assumption was violated, prespecified time-stratified Cox regression models were fitted.

To reduce bias arising from non-random treatment allocation, overlap weighting based on propensity scores was performed as a sensitivity analysis.[18] Propensity scores were estimated using logistic regression. Model 1 included age, sex and baseline refractive variables, whereas Model 2 additionally incorporated parental myopia. Covariate balance was evaluated using standardized mean differences (SMDs), with values <0.10 indicating adequate balance.

All statistical analyses were performed using R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria). All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant unless otherwise specified.

Results

Participant Characteristics

Of 325 children initially identified through the electronic medical record system (172 in the atropine group and 153 in the control group), 290 met the eligibility criteria and were included in the analysis, comprising 157 children in the atropine 0.01% group and 133 untreated controls. Thirty-five children were excluded due to incomplete baseline data, insufficient follow-up, or initiation of other myopia-control treatments during the study period. The mean (SD) age at baseline was 6.94 (1.47) years, and 143 participants (49.3%) were boys.

Baseline refractive status was comparable between groups, with a mean SE of +0.06 ± 0.32 D in the atropine group and +0.03 ± 0.31 D in the control group (standardized mean difference [SMD] = 0.076). Age, sex, outdoor activity and near-work time were also generally balanced (all SMD < 0.25). However, paternal myopia was more common among children receiving atropine than among controls (75.9% vs 49.3%; SMD = 0.568). Baseline characteristics are summarized in Table 1.

Longitudinal Refractive Change

The longitudinal analysis included 763 cycloplegic refraction measurements from 290 participants. In the fully adjusted linear mixed-effects model, SE decreased significantly over time ($\beta = -0.359$ D/year, 95% CI −0.407 to −0.310; $P < 0.001$). The

treatment-by-time interaction was not significant (β = 0.021, 95% CI −0.046 to 0.089; P = 0.536), indicating no differential rate of refractive progression between groups. An unadjusted model yielded consistent findings (β = 0.013, 95% CI −0.058 to 0.085; P = 0.712).

Baseline SE was the strongest independent predictor of follow-up SE (β = 0.888, 95% CI 0.756 to 1.020; P < 0.001). (**Figure 1 and Table 2**).

Time to Myopia Onset

Overall, incident myopia occurred in 194 of 290 children (66.9%) during follow-up, including 96 of 157 (61.1%) in the atropine group and 98 of 133 (73.7%) in the control group. Median time to myopia onset was 1.82 years (95% CI 1.47–2.12) in the atropine group and 1.40 years (95% CI 1.04–1.91) in the control group. Kaplan–Meier analysis showed no significant difference in myopia-free survival between groups (log-rank P = 0.182)(Figure 2). In multivariable Cox regression analysis, atropine treatment was associated with an HR of 0.755 (95% CI 0.568–1.003; P = 0.052). Baseline SE remained an independent predictor of myopia onset (HR 0.221, P < 0.001). Because the proportional hazards assumption was not satisfied, time-stratified Cox models showed no significant association between atropine treatment and incident myopia during any follow-up interval (all P > 0.05).

Sensitivity Analysis

Overlap-weighting analyses achieved satisfactory covariate balance, with all post-weighting SMDs below 0.10. After weighting for demographic and refractive variables (Model 1), the estimated HR for incident myopia was 0.83 (95% CI 0.62–

1.11; P = 0.21). Additional balancing for parental myopia (Model 2) produced an HR of 0.89 (95% CI 0.65–1.20; P = 0.44). Both weighted analyses were consistent with the primary analysis and did not demonstrate a statistically significant association, confirming that the marginal Cox P value (0.052) likely reflected residual confounding rather than a genuine treatment effect.

Exploratory Subgroup Analyses

Among children with baseline SE between −0.50 and 0 D, atropine treatment was associated with a lower risk of incident myopia (HR 0.654, 95% CI 0.465–0.919; P = 0.014). However, the treatment-by-subgroup interaction was not statistically significant (P for interaction = 0.240) (**Table 3**).

Discussion

Principal findings in context

In this real-world cohort of 290 non-myopic and pre-myopic children, nightly administration of 0.01% atropine was not associated with a significant reduction in myopia onset or refractive progression. In the fully adjusted linear mixed-effects model, the treatment effect on refractive progression was minimal (group-by-time interaction 0.021 D/year, 95% CI −0.046 to 0.089; P =0.536), corresponding to a 4-year difference of only 0.09 D. Similarly, survival analyses did not demonstrate a significant preventive effect (Cox regression HR 0.76, 95% CI 0.57 to 1.00; P =0.052). Sensitivity analysis using overlap weighting produced a similar null result (HR 0.89, 95% CI 0.65 to 1.20; P =0.44). Together, these findings suggest that 0.01%

atropine provides limited effectiveness for primary prevention of myopia in routine clinical practice.

Our results are consistent with the LAMP2 randomized trial, in which 0.01% atropine did not significantly reduce myopia incidence in pre-myopic children, whereas higher concentrations demonstrated preventive efficacy.[10] However, they differ from the AMPP study, which reported delayed myopia onset with 0.01% atropine in a selected cohort of non-myopic children.[12] Differences in baseline risk, treatment adherence, and study design may explain these discrepancies: the AMPP cohort may have been at an earlier stage of refractive development, whereas our real-world sample covered a broader spectrum of baseline refractive states. Any preventive effect of low-dose atropine may therefore depend on specific clinical contexts rather than represent a universal treatment effect.

A concentration-dependent response is consistently observed in atropine myopia control studies: the LAMP trial found greater efficacy of 0.05% and 0.025% than 0.01%, [5-8] network meta-analyses rank 0.01% as the least effective studied regimen,[19, 24] and a real-world study reported the weakest and most variable response with 0.01%.[20] It is plausible that 0.01% atropine produces insufficient pharmacological activity at key biological targets to influence the initiation of axial elongation,[21-23] although the relationship between topical concentration, ocular exposure, and clinical efficacy has not been directly established in humans.

Real-world effectiveness and treatment exposure

The discrepancy between clinical trials and routine practice may also reflect differences in treatment exposure. Randomized trials generally achieve high adherence through structured follow-up and monitoring,[8, 12, 25] whereas preventive treatment in asymptomatic children may be affected by variable parental motivation and inconsistent nightly administration.[19] In addition, hospital-compounded preparations may differ from commercial products in stability, pH, and preservative composition.[26-29]

Predictors of myopia development

Baseline spherical equivalent was the strongest predictor of refractive trajectory in our cohort (β=0.888, P<0.001), consistent with previous clinical trials.[10] After adjustment, environmental factors including outdoor time and near-work duration were not independently associated with progression, although incomplete environmental data may have limited statistical power.[2] Exploratory subgroup analysis suggested a possible reduction in myopia onset among children with baseline spherical equivalent between −0.50 D and 0 D (HR 0.654, 95% CI 0.465 to 0.919). However, the treatment-by-subgroup interaction was not statistically significant, and neighboring refractive categories showed inconsistent estimates. Therefore, this observation should be regarded as hypothesis-generating rather than evidence supporting targeted preventive treatment.

Clinical implications

Our findings do not support routine use of 0.01% atropine for prevention of myopia in non-myopic or pre-myopic children. Current evidence supports increased outdoor

277 exposure as the most established preventive strategy.[30-33] **C**onsistent evidence
278 demonstrates reduced incidence of myopia and minimal safety concerns.[34, 35]
279 In contrast, regulatory approval of 0.01% atropine in China applies to slowing
280 progression in children with established myopia rather than preventing onset. Clinical
281 recommendations should therefore distinguish between these two therapeutic
282 objectives and avoid extrapolating evidence from progression control to primary
283 prevention.[15][16]
284 Long-term preventive administration also requires consideration of treatment duration
285 and rebound effects.[7] Previous studies have demonstrated accelerated refractive
286 progression after atropine cessation, with greater rebound observed after lower
287 concentrations.[7, 36] Whether prolonged exposure of low-dose atropine provides
288 meaningful preventive benefit while maintaining long-term safety remains
289 uncertain.[4]

290 **Limitations**

291 Several limitations should be considered. First, axial length measurements were
292 unavailable, preventing evaluation of structural ocular growth. Although cycloplegic
293 spherical equivalent remains the clinical standard for defining incident myopia, axial
294 length provides a more direct marker of ocular elongation and should be incorporated
295 into future prevention studies.
296 Second, treatment allocation was not randomized, resulting in potential confounding
297 by indication. Children receiving atropine had a higher prevalence of paternal myopia,
298 suggesting that clinicians preferentially treated those perceived to be at higher risk.

Although multivariable adjustment, multiple imputation and overlap weighting yielded consistent findings, residual confounding cannot be excluded.

Third, generalizability may be limited because participants were recruited from a tertiary ophthalmic center and predominantly represented Asian children.[10] Finally, subgroup analyses were exploratory and required validation in adequately powered prospective studies.

Conclusion

In this real-world retrospective cohort, 0.01% atropine was not associated with reduced myopia onset or refractive progression in non-myopic and pre-myopic children. These findings are consistent with the concentration-dependent pharmacology of atropine and suggest that the efficacy of 0.01% may be insufficient for primary prevention in routine practice. Future studies should determine whether higher concentrations or risk-stratified treatment strategies can provide effective and safe approaches for preventing myopia onset.

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Author Contributions

T.H. and X.Z.: conception and design. X.L. and S.H.: data collection. X.L. and Z.C.: statistical analysis and data interpretation. X.L., S.H. and Z.C.: drafting the manuscript. X.L. and Z.C.: critical revision. All authors: final approval and accountability.

Data Availability Statement：

The data that support the findings of this study are available from the corresponding author upon reasonable request. Due to the retrospective nature of the study and institutional data protection policies, individual participant data cannot be made publicly available.

Ethics Approval

This study was approved by the Institutional Review Board of the Eye and ENT Hospital of Fudan University (Approval No. 2025067). Written informed consent for study participation was waived due to the retrospective design; verbal consent was obtained from parents or legal guardians for telephone follow-up.

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448 **Tables:**

449 **Table 1. Baseline Characteristics of Study Participants**

Characteristic	Control Group (n = 133)	Atropine Group (n = 157)	SMD
Demographics			
Age, years	6.81 ± 1.56	7.06 ± 1.37	0.172
Male sex, n (%)	70 (52.6)	73 (46.5)	0.123
Baseline refraction, diopter			
Spherical equivalent (SE)	+0.03 ± 0.31	+0.06 ± 0.32	0.076
Sphere, right eye	+0.28 ± 0.32	+0.26 ± 0.34	0.047
Sphere, left eye	+0.22 ± 0.29	+0.24 ± 0.32	0.051
Cylinder, right eye	−0.45 ± 0.32	−0.40 ± 0.30	0.159
Cylinder, left eye	−0.41 ± 0.32	−0.36 ± 0.30	0.146
Environmental factors			
Outdoor time, hours/day	3.41 ± 0.74	3.31 ± 0.89	0.118
Near work time, hours/day	4.03 ± 1.03	4.17 ± 1.37	0.115
Family history of myopia			
Maternal myopia, n (%)	35 (48.6)	30 (55.6)	0.138
Paternal myopia, n (%)	36 (49.3)	41 (75.9)	0.568
Either parent myopic, n (%)	56 (76.7)	48 (88.9)	0.327

450 Values are presented as mean (SD) or n (%). SMD, standardized mean difference.

451

Table 2. Fully Adjusted Linear Mixed-Effects Model: Fixed-Effect Estimates for Spherical Equivalent Trajectory (After Multiple Imputation)

Parameter	Estimate (SE)	95% CI	P value
Intercept	0.103 (0.207)	−0.302 to 0.508	0.618
Group (Atropine)	0.091 (0.050)	−0.008 to 0.190	0.072
Time (years)	**−0.359 (0.025)**	**−0.407 to −0.310**	**<0.001**
Age	−0.022 (0.014)	−0.050 to 0.006	0.119
Sex (Male)	0.047 (0.042)	−0.036 to 0.129	0.265
Baseline SE	**0.888 (0.067)**	**0.756 to 1.020**	**<0.001**
Outdoor time	−0.012 (0.037)	−0.086 to 0.061	0.749
Near-work time	−0.002 (0.021)	−0.043 to 0.040	0.932
Either parent myopic	−0.089 (0.063)	−0.213 to 0.035	0.162
Group × Time	**0.021 (0.035)**	**−0.046 to 0.089**	**0.536**

Model estimates were obtained from 20 multiply imputed datasets using the mice package and combined according to Rubin's rules. The model included a random intercept for participant and fixed effects for treatment group, time, group-by-time interaction, baseline spherical equivalent, age, sex, outdoor time, near-work time, and

459 parental myopia. CI, confidence interval; SE, standard error; REML, restricted

460 maximum likelihood; ICC, intraclass correlation coefficient.

461

462 **Table 3. Exploratory Subgroup Analyses of Atropine Effect**

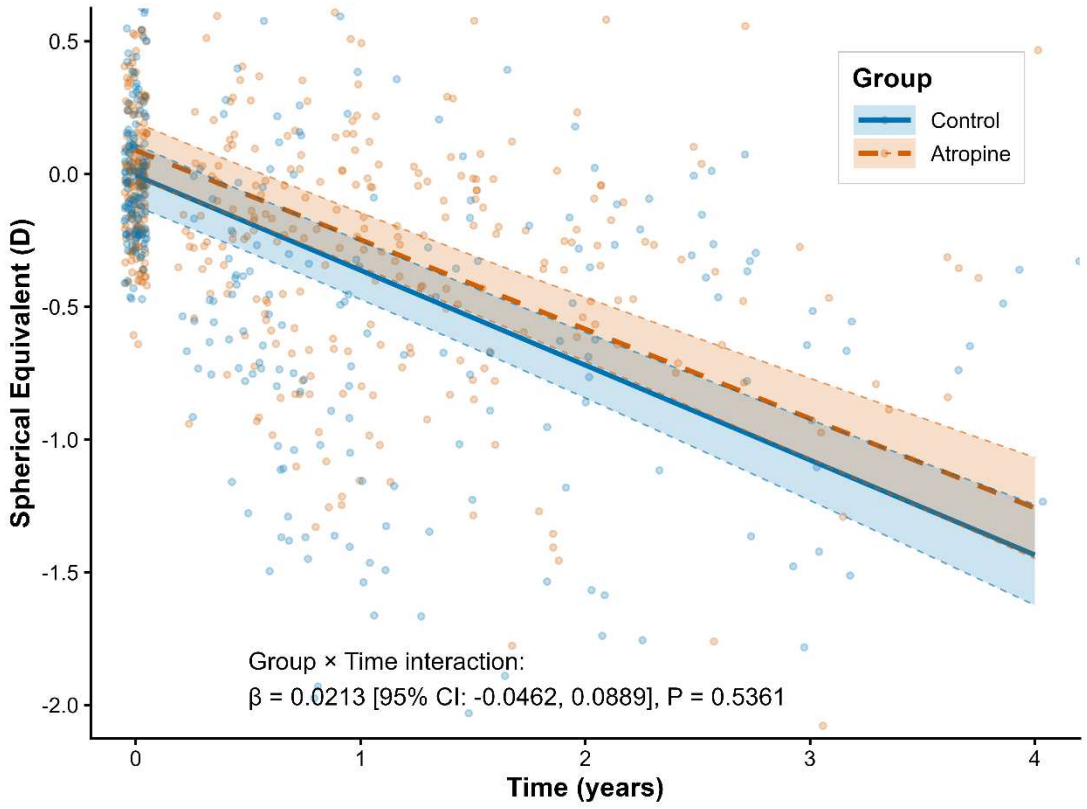
Subgroup	n	Events, n (%)		HR (95% CI)*	P value
		Atropine	Control		
By Baseline SE					
SE > +0.50 D	25	6 (42.9)	8 (72.7)	0.969 (0.330–2.844)	0.954
SE +0.25 to +0.50 D	28	6 (42.9)	11 (78.6)	0.750 (0.275–2.051)	0.576
SE 0 to +0.25 D	56	16 (51.6)	11 (44.0)	1.432 (0.657–3.119)	0.366
SE −0.50 to 0 D	181	68 (69.4)	68 (82.0)	0.654 (0.465–0.919)	0.014
P for interaction					0.240
By Age					
≤6 years	105	—	—	0.997 (0.622–1.598)	0.990
7–8 years	147	—	—	0.751 (0.506–1.114)	0.155
≥9 years	38	—	—	0.522 (0.218–1.253)	0.146
P for interaction					0.381

Joint: SE −0.50 to 0 D by Age					
≤6 years	62	27 (45.0)	20 (55.6)	1.170 (0.648–2.110)	0.604
7–8 years	97	40 (58.8)	35 (81.4)	0.535 (0.333–0.860)	0.010
≥9 years	22	6 (35.3)	8 (72.7)	0.239 (0.071–0.801)	0.020

463 HR, hazard ratio; CI, confidence interval. Hazard ratios were estimated using
464 univariable Cox proportional hazards models. Subgroup analyses were exploratory, not
465 prespecified, and were not adjusted for multiple comparisons

466 **Figure**

467 Figure 1 Predicted longitudinal trajectories of spherical equivalent (SE) in children receiving
468 atropine 0.01% (n=157) and untreated controls (n=133)



469

470

Figure 2 Kaplan–Meier curves showing cumulative myopia-free survival in children receiving atropine 0.01% (n=157) and untreated controls (n=133)

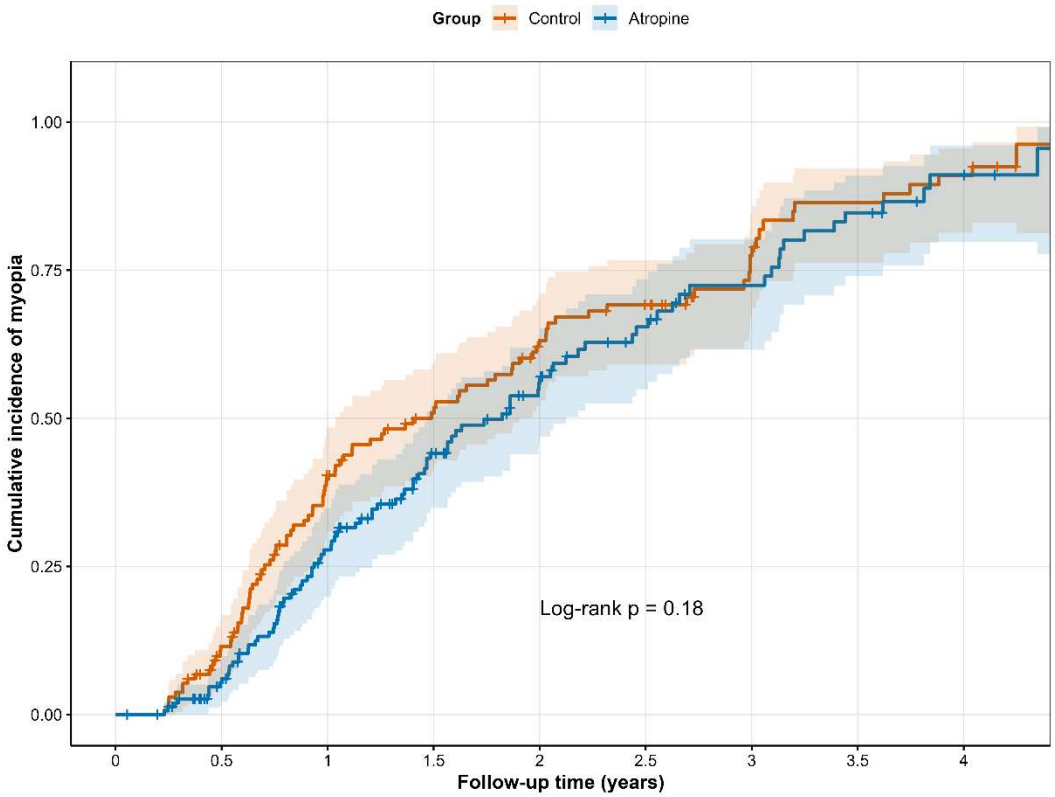


Figure Legends

Figure 1. Predicted longitudinal trajectories of spherical equivalent (SE) in children receiving atropine 0.01% (n=157) and untreated controls (n=133). Solid lines represent fitted values from the fully adjusted linear mixed-effects model, with covariates held at their mean values. Shaded areas indicate 95% confidence intervals. Raw observations are displayed as semi-transparent jittered points. SE, spherical equivalent.

Figure 2. Kaplan–Meier curves showing cumulative myopia-free survival in children receiving atropine 0.01% (n=157) and untreated controls (n=133). Myopia onset was defined as spherical equivalent ≤ −0.50 D. Between-group differences were assessed using the log-rank test.