Risk factors for rapid axial length elongation with low concentration atropine for myopia control

Aicun Fu
the First Affiliated Hospital of Zhengzhou University

Fiona Stapleton
School of Optometry and Vision Science, UNSW, Sydney

Li Wei
the First Affiliated Hospital of Zhengzhou University

Weiqun Wang
the First Affiliated Hospital of Zhengzhou University

Bingxin Zhao
the First Affiliated Hospital of Zhengzhou University

Kathleen Watt
School of Optometry and Vision Science, UNSW, Sydney

Shiao Yu
the First Affiliated Hospital of Zhengzhou University

Can Cui
the First Affiliated Hospital of Zhengzhou University

Yong Lyu (lyong@zzu.edu.cn)
the First Affiliated Hospital of Zhengzhou University

Research Article

Keywords: myopia control, atropine, children

Posted Date: December 17th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-119151/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Title page

**Title:** Risk factors for rapid axial length elongation with low concentration atropine for myopia control

**Authors:**
Aicun Fu 1, a, Fiona Stapleton 2, a, Li Wei 1, Weiqun Wang 1, Bingxin Zhao 1, Kathleen Watt 2, Shiao Yu 1, Can Cui 1 & Yong Lyu 1

1The First Affiliated Hospital of Zhengzhou University, No. 1 Jianshe road, Zhengzhou, 450000, China
2School of Optometry and Vision Science, UNSW, Sydney, 2052, Australia

aThese authors contributed equally to this work

* Corresponding Author: Yong Lyu
E-mail address and phone number:
lyong@zzu.edu.cn, +8613607693109

**Word count:** title: 19 words; abstract: 199 words; main body: 2216 words; methods: 898 words.
Abstract

Three hundred and twenty-eight myopic children, randomized to use either 0.01% (N=166) or 0.02% (N=162) atropine were enrolled in this study. Gender, age, body mass index (BMI), parental myopia status, atropine concentration used, pupil diameter, amplitude of accommodation, spherical equivalent refractive error (SER), anterior chamber depth (ACD) and axial length (AL) were collected at baseline and 1 year after using atropine. Rapid AL elongation was defined as >0.36 mm growth per year. Univariate analyses showed that children with rapid AL elongation tended to be younger, have a smaller BMI, use of 0.01% atropine, narrow ACD, lower SER, shorter AL, smaller change in pupil diameter between 1 year and baseline (all \( P < 0.05 \)). Multivariate regression analyses confirmed that rapid AL elongation was associated with children that were younger at baseline (\( P < 0.0001 \)), use of 0.01% atropine (\( P = 0.04 \)), a shorter baseline AL (\( P = 0.03 \)) and a smaller change in pupil diameter between 1 year and baseline (\( P = 0.04 \)). Younger children with shorter AL at baseline, less change in their pupil diameter with atropine treatment and using the lower of the two atropine concentrations may undergo rapid AL elongation over a 12 months myopia control treatment period.
The rising prevalence of myopia and the growing proportion of the population with high myopia result in significant economic and social impact 1,2. The economic burden of uncorrected distance refractive error, largely caused by myopia, was estimated to be US$202 billion per annum 3. Myopia brings further vision challenges because high myopia increases the risk of pathologic ocular changes such as cataract, glaucoma, retinal detachment, and myopic macular degeneration, all of which can cause irreversible vision loss 4. These factors have generated research and clinical interest in the control of myopia progression.

Many studies have shown that low concentrations of atropine can control the progression of myopia in children with good efficacy, minimal side effects, convenient use, and slight rebound effects after discontinuation 5-7. Conversely, it has been observed that low concentration atropine has not effectively controlled myopia in all children 5-15. Children with highly myopic parents were more likely to show rapid myopia progression with low concentration (0.01-0.05%) atropine 10. Less initial myopia but not age, sex, and initial astigmatism was associated with less myopia progression in 0.05% atropine 8. Younger age children showed faster myopic progression in 0.01% atropine. Studies have found a concentration-dependent response in myopia control with low concentration atropine 6,10,12,13.

In the ATOM2 study 5,6, the change in axial length (AL) and change in spherical equivalent refractive error (SER) were not synchronous, such that in the absence of change in SER, AL changed during use of 0.01% atropine. Conversely, a number of studies, including our previous study found that low concentration atropine reduced myopia progression not only through refractive changes, but also through control of axial elongation 10,12-15. Meanwhile, myopia progression in children varies by race/ethnicity, and East/Southeast Asian children undergo more rapid myopia progression than white children 16,17. The purpose of the current study was to specifically evaluate independent risk factors for rapid AL growth in myopic children using 0.01% and 0.02% atropine in mainland China, which have not previously been explored. Low dose atropine is widely used for myopia control in China but an appropriately powered RCT to explore independent risk factors has not been conducted.
Results

Among the 328 children who were enrolled initially, 279 children successfully completed the 1 year follow-up examinations. Forty-nine children (14.9%) dropped out of the study after attending the baseline visits, including 25 (15.1%) and 24 (14.8%) in the 0.01% atropine and 0.02% atropine, respectively (Figure 1). There were no significant differences in baseline parameters between the children who dropped out of the study and those who completed the study (unpaired t-test, all P > 0.05). Table 1 showed a summary of the baseline data of the children grouped by their rate of AL change over the 12 months of the study.

The mean ± SD change in AL over the 12 months of the study was 0.35 ± 0.24 mm. The mean ± SD (min-max) change AL in rapid growth group and slower growth group was 0.50 ± 0.16 mm (0.35 to 0.97) and 0.19 ± 0.12 mm (-0.18 to 0.34), respectively. AL change was 0.30 ± 0.22 mm and 0.36 ± 0.19 mm in the 0.02% and 0.01% atropine, respectively (P = 0.02). One hundred twenty eight (90.8%) and 124 children (89.9%) in the two corresponding atropine groups who completed the 1-year follow-up had good compliance. Based on the univariate analysis (Table 2), we found that younger age, smaller BMI, using lower concentration atropine, narrow ACD, lower SER, shorter AL, a smaller change pupil diameter from baseline were the risk factors for a rapid change in AL (all P< 0.05). There were, however, no statistically significant associations with gender, parental myopia status, baseline IOP, pupil diameter and AMP, corneal curvature, corneal astigmatism and change in AMP between 1 year and baseline.

Multivariate regression analyses after adjusting for potential confounders showed that the factors associated with rapid AL elongation children were younger age (HR= 0.58, 95%CI: 0.48~0.68, P < 0.0001), using lower concentration atropine (HR=0.66, 95%CI: 0.34~0.98, P=0.04) and shorter AL at baseline (HR= 0.45, 95%CI: 0.20~0.70, P=0.03), lower change pupil diameter between 1 year and baseline (HR= 0.48, 95%CI: 0.22~0.74, P=0.04) (Table 2). There was a 42% higher risk of rapid AL elongation with every year of decreasing age at baseline. Meanwhile, the risk of rapid AL elongation using 0.01% atropine increased by 34% in comparison with 0.02% atropine. Similarly, the risk of rapid AL elongation increased by 55% for every 1 mm shorter AL at baseline and 52% for every 1 mm lower change in pupil diameter over the 12 months of the study.

Based on univariate analysis, there was a strong association between the change in
AL and change in SER after 1-year treatment ($r=0.74$, 95%CI: -0.80–0.68, $P<0.0001$), and this strong relationship was confirmed in multivariate regression analyses after adjusting for potential confounders ($\beta=0.95$, 95%CI: -1.02–0.88, $P<0.0001$).

**Discussion**

In this prospective study, the axial length of the younger children, using lower concentration atropine, with shorter axial length at baseline and smaller change in pupil diameter may still increase rapidly while receiving atropine treatment in mainland China. These factors seem to suggest that these children may be less responsive to the effects of low concentration atropine.

Rapid AL elongation despite the use of low concentration atropine treatment has been described in other different atropine concentrations and populations studies. In the ATOM2 study\textsuperscript{5,6}, where children were randomized to atropine concentrations of 0.01%, 0.1% and 0.5%, the AL change after twelve months was $0.24 \pm 0.19\text{mm}$, $0.13 \pm 0.18\text{mm}$ and $0.11 \pm 0.17\text{mm}$, respectively. In a study of 0.01%, 0.025% and 0.05% atropine concentrations, Yam et al\textsuperscript{12,15} found that the AL change after one year was $0.36 \pm 0.29\text{mm}$, $0.29 \pm 0.20\text{mm}$ and $0.20 \pm 0.25\text{mm}$, after two years was $0.59 \pm 0.38\text{mm}$, $0.50 \pm 0.33\text{mm}$, and $0.39 \pm 0.35\text{mm}$, respectively. In a one year study of Korean myopic children\textsuperscript{10}, the AL elongation was about $0.44 \pm 0.32\text{mm}$, $0.30 \pm 0.24\text{mm}$ and $0.23 \pm 0.25\text{mm}$ in 0.01%, 0.025% and 0.05% atropine, respectively. In a study of Chinese myopic children\textsuperscript{14}, the AL elongation after one year was about $0.32 \pm 0.19\text{mm}$ and $0.41 \pm 0.09\text{mm}$ in 0.01% atropine and placebo, respectively. By comparison, in the present study the AL elongation was $0.36 \pm 0.19\text{mm}$ with 0.01% and $0.30 \pm 0.22\text{mm}$ with 0.02% atropine, 0.02% atropine had a better effect on myopia control than 0.01% atropine\textsuperscript{13}. There seems to be considerable variation in the range of AL change results with some children changing very little and others increasing very quickly. Other reports of low concentration atropine for controlling myopia progression in children measured refraction and not AL\textsuperscript{8,9,11,18}. They defined myopia progression of more than 0.50D or 1.0D at 1 year as rapid myopic progression. Again rates of refractive progression varied considerably between studies, risk factors for faster myopic progression in low concentration atropine studies include younger age at baseline\textsuperscript{11,18,}, higher initial myopia\textsuperscript{8}, and a family history of high myopia\textsuperscript{10}. This confirms the importance of conducting...
appropriately controlled studies to explore independent risk factors associated with rapid
AL elongation in myopic children in mainland China treated with low concentration
atropine.

In the current study, baseline age had a significantly negative correlation with AL
increase in myopic children using 0.01% or 0.02% atropine. The younger children were
at baseline, the more the AL elongation was evident at the end of the study period. This
was consistent with three other studies which explored the same relationship between
baseline age and AL increase in myopic children using atropine and whose baseline
profiles were similar to the current study. Joachimsen et al, Wei et al and Lee et al
found that younger children in German, mainland China and Taiwan may still progress
quickly while using 0.01%, 0.01% and 0.05% atropine, respectively. It is well established
that there is slowing of physiological change in AL in older children. Conversely, Moon
et al and Wu et al reported no relationship between baseline age and AL change in
Taiwanese children using 0.05% atropine and in Korean children using 0.01%, 0.025%
or 0.05% atropine. These contrasting results may arise due to different study populations,
different baseline characteristics and methodological and analytical differences. For
example, myopia progression was faster in East/Southeast Asian than white children
aged 4-6 and 8-11 in a large real-world population conducted in United States study.

We also found that the children with 0.01% atropine had a more rapid AL elongation
and a worse myopic control effect than 0.02% atropine. Other reports have also found
a concentration-dependent response in myopia control with low concentration atropine
6,10,12,14. Side effects and adverse effects are reportedly similar in 0.01% and 0.02%
atropine, suggesting that if children using 0.01% atropine are not achieving adequate
myopia control, changing to the 0.02% concentration could be considered. It is important
to use an individualized atropine concentration to control myopia development

The children with a smaller change in pupil diameter from baseline to 1 year had
rapid AL elongation in our study. The underlying reasons why these children did not
respond well are unclear. So far, it is unclear how low concentration atropine acts to
inhibit myopia progression. One theory suggests that increased ultraviolet exposure
(secondary to pupil dilation) may increase collagen cross-linking within the sclera,
thereby limiting scleral growth during myopia progression and AL elongation. The greater
change in pupil diameter, may be due to the better absorption of the drug, greater
collagen cross-linking within the sclera and a superior effect on controlling myopia
progression. Recently, studies have shown that adding 0.01% atropine eye drops to OK therapy was more effective than OK alone for controlling myopia progression in children. One of the possible mechanisms may be low concentration atropine’s mydriatic effect, as other studies have shown that myopia control effect of OK lens was also affected by pupil diameter. Children with larger pupil diameter would receive a greater proportion of peripheral myopic defocus associated with OK lens wear, which in turn may be relate to better myopia control. This is a possible mechanism that warrants further investigation.

We found that a rapid AL elongation related significantly to shorter AL at baseline, but not to initial levels of myopia. In other words, the shorter AL at baseline, the more the AL elongation was found with low concentration atropine, irrespective of baseline refractive error. Lin however found that highly myopic children had less increase in AL after using 0.125% atropine. Wu et al conversely found that higher initial myopia corresponded significantly to a higher chance of myopia progression irrespective of atropine concentration. Moon et al found that baseline refraction and AL were not associated with the rate of myopia progression irrespective of atropine concentration, however only age, family history and AL were selected for inclusion in the multivariate logistic regression analyses of this study. Several studies have established a strong association between the eye’s AL and its refractive error. Myopia progression usually occurs due to excessive AL elongation of the eye, as evidenced by the strong association between changes in myopia progression and changes in AL growth. There was a strong association between the change in AL and change in SER after 1-year treatment in the present study. Another study found that 0.01% atropine reduced myopia progression by 34.2% and axial elongation by 22.0% compared with the placebo group. However, in the ATOM2 study, while the degree of myopia was stable, the AL continued to increase between 8 and 24 months after using 0.01% atropine. For assessing the efficacy of interventions to control the progression of myopia in children, we recommend that the change in AL is not be used interchangeably with the change in refraction.

This study did not consider the rate of change in AL using age matched emmetropes, however previous studies describing the growth curve for AL with age showed that the rate of AL elongation in emmetropes was slower than in myopes, and the AL growth slowed down in emmetropes as the children became older, but little or no decrease in
the rate of change of AL in myopic children is observed. Another limitation is that the study measured axial elongation over a 1 year period only. Further investigations including age matched emmetropes and using a study design with a longer follow-up time are required to confirm the present findings. An additional limitation of the present study, is that the age at onset of myopia was not available. Previous studies have identified that age at onset of myopia is a risk factor for myopia progression and this factor should included in future studies.

In conclusion, our study showed that the axial length in young children, using lower concentration of atropine, having a shorter axial length at baseline and smaller change in pupil diameter may still increase rapidly while receiving low concentration atropine treatment in mainland China. If the axial length of these children with these characteristics continues to grow at a rate similar to that before the start of atropine treatment, then a change in atropine concentration or combining with other myopia control therapies to control the progression of axial length may be considered.

Methods

We report a prospective doubled blinded randomized controlled trial of 0.01% and 0.02% atropine in myopic children recruited from the First Affiliated Hospital of Zhengzhou University. This study was part of a larger series of clinical studies which also evaluated a further three non-contemporaneous non randomized patient groups, not reported here, including subjects wearing single-vision spectacles, subjects with low myopia using 0.005% atropine, and a subsequent group evaluating 0.02% atropine used every other day.

In this prospective study, three hundred and twenty-eight Chinese myopic children (right eyes, Han nationality) who presented between July 2016 and October 2017 and met the inclusion criteria (Table 3) were recruited. This study was approved by the Medical Ethics committee of the First Affiliated Hospital of Zhengzhou University and registered in the Chinese Clinical Trial Registry (registration number: ChiCTR-IPD-16008844, first registration in 14/07/2016). This study conformed to the tenets of the Declaration of Helsinki. Written informed consent was obtained from parents before the procedures, and possible risks were fully explained before treatment initiation.

The 0.01% and 0.02% atropine eye drops (pH value of 5.4~5.6, 3-mL sealed bottle,
kept away from the light, 15~25°C room temperature storage, discarded one month after opening the bottle) were made by diluting 1% atropine (Eye & ENT Hospital, Affiliated to Fudan University) with saline under sterile conditions, with the addition of the preservative (0.3mg/ml ethylparaben). Subjects were randomized to either the 0.01% or 0.02% concentration based on a double-blinded and randomized selection algorithm. The children were prescribed constant wear of full correction single-vision spectacle lenses (SV) with the highest positive/least negative power consistent with optimum visual acuity and with one drop of 0.01% or 0.02% atropine eye drops administered into both eyes once nightly before bed time.

Pupil diameter was measured using an auto refractor (NIDEK, AR-1, Japan) when looking at a distant target without any correction for refractive error under indoor light; the light was constant with an illumination of 300 to 310 lux (TES-1332A Illumination photometer). Children were adapted to the ambient light for 10 minutes in the examination room before taking measurements. On each occasion, three successive measurements were made, and average values were recorded. The right eye was assessed before the left one. Accommodation amplitude (AMP) was measured out monocularly by the push-up technique. The children wore their fully corrected spectacle prescription and focused on the line above the best corrected visual acuity with the right eye while the left one was occluded. The children were instructed to focus on a letter as the chart was moved closer. They were asked to keep the letter as clear as possible until it could no longer be held in clear focus. The inverse of the final distance in meter was recorded as the child’s AMP. AMP was recorded 3 times and the average taken. Corneal power, anterior chamber depth (ACD) and AL were evaluated using a non-contact partial coherence interferometer (IOLMaster; Carl Zeiss Meditec AG, Germany). On each occasion, five successive measurements were taken and their mean was used as a representative value. Based on other two similar studies, rapid AL elongation was defined as >0.36 mm growth per year (i.e., equivalent myopic progression 1.00D per year) and children were categorized as either having rapid or slow AL elongation. Outdoor activity time (hours per day) and nearwork time (hours per day) were assessed using a paper questionnaire. Cycloplegic autorefraction was performed after the instillation of four drops of compound tropicamide eye drops (0.5% tropicamide and 0.5% neo-synephrine) (Santen, Japan) administered 10 minutes apart in each of the patients’ eyes. Ten minutes after the instillation of the fourth drop, three autorefraction measurements
were taken (Topcon RM 8000A, CA) and a mean was obtained. The degree of myopia
was expressed as SER.

Children were provided with four bottles of eye drops after the first examination and
subsequent each follow-up. When the child was reexamined, they were asked to return
all four bottles and compliance was assessed according to the remaining amount of eye
drops. One-drop of eye drops is about 0.04ml, one child will use more than 2.4ml each
month. If a child's remaining eye drops in any bottle exceeded 10% (about 1ml) of the
total amount of each bottle, then his compliance was not good. In order to improve
compliance, we have also adopted two methods: 1. we explained to children and their
parents the importance of using eye drops correctly every day for myopia control after
they entered the research group. 2. The WeChat group was set up for all the children’s
parents in the research group, there were two colleagues of the research group answered
all kinds of questions encountered by the children in the medication process.

Continuous baseline variables were expressed as mean ± standard deviation (SD)
and evaluated by one-way ANOVA. Categorical variables, such as gender, atropine
concentration and parental myopia status, were expressed as percentage (%) and
evaluated by the Chi-squared test. Univariate analysis and multivariate regression
analyses after adjusting for confounding factors were used to determine risk factors for
rapid AL elongation, whether or not the covariance was adjusted was determined by the
following principle; when a factor was added to this model, the matched odds ratio
changed by at least 10%. A value of P < 0.05 was considered statistically significant. All
analyses were performed using Empower (R) (www.empowerstats.com, X & Y solutions
Inc., Boston, MA) and R (http://www.R-project.org).
References

1. Lim, M.C.C., Gazzard, G., Sim, E.L., Tong, L. & Saw, S. M. Direct costs of myopia in Singapore. *Eye.* 23,1086-1089(2009).

2. Holden, B. A. *et al.* Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. *Ophthalmol.* 123,1036-1042(2016).

3. Smith, T.S.T. *et al.* Potential lost productivity resulting from the global burden of uncorrected refractive error. *Bull World Health Org.* 87,431-473(2009).

4. Wong, T. Y. *et al.* Epidemiology and disease burden of pathologic myopia and myopic choroidal neovascularization: an evidence-based systematic review. *Am J Ophthalmol.* 157, 9-25.e12(2014).

5. Chia, A. *et al.* Atropine for the treatment of childhood myopia: changes after stopping atropine 0.01%, 0.1% and 0.5%. *Am J Ophthalmol.* 157,451-457(2014).

6. Chia, A., Lu, Q.S. & Tan, D. Five-year clinical trial on atropine for the treatment of myopia 2: myopia control with atropine 0.01% eye drops. *Ophthalmol.* 123,391-399(2016).

7. Sacchi, M. *et al.* Efficacy of atropine 0.01% for the treatment of childhood myopia in European patients. *Acta Ophthalmol.* 97,e1136-e1140(2019).

8. Wu, P. C., Yang, Y. H. & Fang, P. C. The long-term results of using low-concentration atropine eye drops for controlling myopia progression in schoolchildren. *J Ocul Pharmacol Ther.* 27,461-466(2011).

9. Clark, T. Y. & Clark, R. A. Atropine 0.01% Eye drops significantly reduce the progression of childhood myopia. *J Ocul Pharmacol Ther.* 31,541-545(2015).

10. Moon, J. S. & Shin, S. Y. The diluted atropine for inhibition of myopia progression in Korean children. *Int J Ophthalmol.* 11,1657-1662(2018).

11. Joachimsen, L. *et al.* A pilot study on the efficacy and safety of 0.01% atropine in German schoolchildren with progressive myopia. *Ophthalmol Ther.* 8,427-433(2019).

12. Yam, J. C. *et al.* Low concentration atropine for myopia progression (LAMP) study: A randomized, double-blinded, placebo controlled trial of 0.05%, 0.025%, and 0.01% atropine eye drops in myopia control. *Ophthalmol.* 26,113-124(2019).

13. Fu, A. C. *et al.* Effect of low-dose atropine on myopia progression, pupil diameter and accommodative amplitude: low-dose atropine and myopia progression. *Br J Ophthalmol.* 0,1-7(2020).
14. Wei, S. F. et al. Safety and Efficacy of Low-Dose Atropine Eyedrops for the Treatment of Myopia Progression in Chinese Children: A Randomized Clinical Trial. *JAMA Ophthalmol.* 1, e203820 (2020).

15. Yam, J. C. et al. Two-Year Clinical Trial of the Low-Concentration Atropine for Myopia Progression (LAMP) Study: Phase 2 Report. *Ophthalmol.* 127, 910-919 (2020).

16. Donovan, L. et al. Myopia progression rates in urban children wearing single-vision. *Optom Vis Sci.* 89, 27-32 (2012).

17. Luong, T. Q. et al. Racial and ethnic differences in myopia progression in a large, diverse cohort of pediatric patients. *Invest Ophthalmol Vis Sci.* 61, 20 (2020).

18. Lee, J. J. et al. Prevention of myopia progression with 0.05% atropine solution. *J Ocul Pharmacol Ther.* 22, 41-46 (2006).

19. Diez, P. S. et al. Growth curves of myopia-related parameters to clinically monitor the refractive development in Chinese schoolchildren. *Graefes Arch Clin Exp Ophthalmol.* 257, 1045-1053 (2019).

20. Cooper, J., Eisenberg, N., Schulman, E. & Wang, F. M. Maximum atropine dose without clinical signs or symptoms. *Optom Vis Sci.* 90, 1467-1472 (2013).

21. Prepas, S. B. Light, literacy and the absence of ultraviolet radiation in the development of myopia. *Med Hypotheses.* 70, 635-637 (2008).

22. Kinoshita, N. et al. Additive effects of orthokeratology and atropine 0.01% ophthalmic solution in slowing axial elongation in children with myopia: first year results. *Jpn J Ophthalmol.* 62, 544-553 (2018).

23. Kinoshita, N. et al. Efficacy of combined orthokeratology and 0.01% atropine solution for slowing axial elongation in children with myopia: a 2-year randomized trial. *Sci Rep.* 10, 12750 (2020).

24. Chen, Z. et al. Impact of pupil diameter on axial growth in orthokeratology. *Optom Vis Sci.* 89, 1636-1640 (2012).

25. Santodomingo-Rubido, J., Villa-Collar, C., Gilmartin, B. & Gutiérrez-Ortega, R. Factors preventing myopia progression with orthokeratology correction. *Optom Vis Sci.* 90, 1225-1236 (2013).

26. Lin, H. J. et al. Overnight orthokeratology is comparable with atropine in controlling myopia. *BMC Ophthalmol.* 14, 40-48 (2014).

27. Richter, G. M. et al. Ocular determinants of refractive error and its age and sex-related variations in the Chinese American eye study. *JAMA Ophthalmol.* 135, 724-732 (2017).
28. Hou, W. et al. Axial elongation in myopic children and its association with myopia progression in the correction of myopia evaluation Trial. *Eye Contact Lens.* **44**, 248-259 (2018).

29. Gwiazda, J. et al. A randomized clinical trial of progressive addition lenses versus single vision lenses on the progression of myopia in children. *Invest Ophthalmol Vis Sci.* **44**, 1492-1500 (2003).

30. Saw, S. M. et al. Eye growth changes in myopic children in Singapore. *Br J Ophthalmol.* **89**, 1489-1494 (2005).

31. Jones, L. A. et al. Comparison of ocular component growth curves among refractive error groups in children. *Invest Ophthalmol Vis Sci.* **46**, 2317-2327 (2005).

32. Wong, H.B., Machin, D., Tan, S.B., Wong, T.Y. & Saw, S. M. Ocular component growth curves among Singaporean children with different refractive error status. *Invest Ophthalmol Vis Sci.* **51**, 1341-1347 (2010).

33. Chua, S. Y. L. et al. Age of onset of myopia predicts risk of high myopia in later childhood in myopic Singapore children. *Ophthalmic and Physiological Optics.* **36**, 388-394 (2016).

34. Saw, S. M. et al. Incidence and Progression of Myopia in Singaporean School Children. *Invest Ophthalmol Vis Sci.* **46**, 51-57 (2005).

35. Cho, P. & Cheung, S. W. Retardation of myopia in Orthokeratology (ROMIO) study: a 2-year randomized clinical trial. *Invest Ophthalmol Vis Sci.* **53**, 7077-7085 (2012).

36. Cho, P. & Cheung, S. W. Protective role of orthokeratology in reducing risk of rapid axial elongation: a reanalysis of data from the ROMIO and TO-SEE studies. *Invest Ophthalmol Vis Sci.* **58**, 1411-1416 (2017).

37. Lin, L. L. et al. The cycloplegic effects of cyclopentolate and tropicamide on myopic children. *J Ocul Pharmacol Ther.* **14**, 331-335 (1998).

38. Yazdani, N., Sadeghi, R., Momeni-Moghaddam, H., Zarifmahmoudi, L. & Ehsaei, A. Comparison of cyclopentolate versus tropicamide cycloplegia: A systematic review and meta-analysis. *J Optom.* **11**, 135-143 (2018).
Author Contributions
AC.F. and Y.L. designed the study. AC.F, L.W., BX.Z., SA.Y. and C.C. collected all data. AC.F, F.S., K.W., WQ.W. and Y.L. analyzed and interpreted the data. AC.F. and F.S. wrote the first draft of the paper, and all authors revised the work and approved the final version of the manuscript. AC.F. had full access to all data and takes responsibility for data integrity and the accuracy of the data analysis.

Competing interests: None declared.

Table 1. Baseline characteristics of participants mean ± SD or n (%).

| Change in AL over 12 months (mm) | Rapid change in AL | Slower change in AL | P-value |
|---------------------------------|--------------------|---------------------|---------|
|                                 | Mean ± SD, (min-max)| Mean ± SD, (min-max)|         |
| N                               | 132                | 147                 |         |
| Age (year)                      | 8.87 ± 1.69        | 10.76 ± 1.72        | < 0.001 |
| Body mass index (kg/m²)         | 17.33 ± 3.85       | 18.78 ± 3.37        | < 0.001 |
| Spherical equivalent refractive error (D) | -2.27 ± 1.32    | -2.98 ± 1.68        | < 0.001 |
| Intraocular pressure (mmHg)     | 16.98 ± 2.78       | 16.58 ± 2.91        | 0.22    |
| Pupil diameter (mm)             | 6.12 ± 0.76        | 6.07 ± 0.67         | 0.51    |
| Accommodation amplitude (D)     | 14.87 ± 4.56       | 15.74 ± 5.25        | 0.22    |
| Corneal astigmatism (D)         | -1.21 ± 0.58       | -1.24 ± 0.57        | 0.33    |
| Corneal curvature (D)           | 42.81 ± 1.37       | 42.92 ± 1.45        | 0.66    |
| Anterior chamber depth (mm)     | 3.60 ± 0.21        | 3.68 ± 0.27         | < 0.001 |
| Axial length (mm)               | 24.26 ± 0.81       | 24.68 ± 0.93        | < 0.001 |
| Outdoor activity (hours per day) | 2.52 ± 1.31        | 2.61 ± 1.35         | 0.21    |
| Nearwork (hours per day) #      | 14.02 ± 2.82       | 14.22 ± 1.52        | 0.45    |
| Atropine concentration 0.01%    | 71 (53.8%)         | 70 (47.6%)          | 0.30    |
| Atropine concentration 0.02%    | 61 (46.2%)         | 77 (52.4%)          |         |
| Gender                          |                    |                     |         |
| Male                            | 73 (55.3%)         | 72 (49.0%)          | 0.29    |
| Female                          | 59 (44.7%)         | 75 (51.0%)          |         |
| Heredity                        |                    |                     |         |
| + + (both parents myopic)       | 32 (24.2%)         | 34 (23.1%)          | 0.90    |
| + - (one parent myopic)         | 62 (47.0%)         | 73 (49.7%)          |         |
| - - (neither parent myopic)     | 38 (28.8%)         | 40 (27.2%)          |         |

Note: Rapid change in AL defined as > 0.36 mm/year.
※ Outdoor activity = outdoor exercise + outdoor leisure activity.
# Nearwork = 3* (homework + reading + playing on cell phone) + 2* (using computer + playing video game) + 1* (watching TV).
Table 2. Univariate and multivariate regression analyses showing risk factors associated with rapid axial length elongation over 12 months.

| Risk factors                              | Non-adjusted HR, (95% CI) | P value | Adjust HR, (95% CI) | P value |
|-------------------------------------------|---------------------------|---------|---------------------|---------|
| Gender                                    |                           |         |                     |         |
| Male                                      | Reference                 |         | Reference           |         |
| Female                                    | 0.78 (0.48~1.08)          | 0.22    | 0.78 (0.42~1.14)    | 0.62    |
| Age (years)                               | 0.54 (0.44~0.64)          | < 0.0001 | 0.58 (0.48~0.68)    | < 0.0001 |
| Body mass index (kg/m2)                   | 0.87 (0.82~0.92)          | 0.0006  | 0.95 (0.88~1.02)    | 0.58    |
| Heredity                                  |                           |         |                     |         |
| - - (neither parent myopic)               | Reference                 |         | Reference           |         |
| + - (one parent myopic)                   | 0.44 (0.29~0.59)          | 0.08    | 0.39 (0.18~0.60)    | 0.18    |
| + + (both parents myopic)                 | 0.51 (0.16~0.86)          | 0.12    | 0.58 (0.19~0.97)    | 0.10    |
| Atropine concentration                    |                           |         |                     |         |
| 0.01%                                     | Reference                 |         | Reference           |         |
| 0.02%                                     | 0.76 (0.22~1.30)          | 0.046   | 0.66 (0.34~0.98)    | 0.04    |
| Intraocular pressure (mmHg)               | 1.06 (0.96~1.16)          | 0.22    | 1.02 (0.95~1.09)    | 0.75    |
| Pupil diameter (mm)                       | 1.07 (0.72~1.42)          | 0.86    | 0.88 (0.56~1.20)    | 0.58    |
| Accommodation amplitude (D)               | 0.95 (0.88~1.02)          | 0.08    | 0.95 (0.87~1.03)    | 0.09    |
| Corneal curvature (D)                     | 0.86 (0.70~1.02)          | 0.16    | 0.88 (0.68~1.08)    | 0.33    |
| Corneal astigmatism (D)                   | 0.58 (0.28~0.88)          | 0.16    | 0.55 (0.21~0.83)    | 0.19    |
| Anterior chamber depth (mm)               | 3.88 (1.34~6.42)          | 0.01    | 1.25 (0.35~2.15)    | 0.98    |
| Spherical equivalent refractive error (D) | 1.34 (1.13~1.55)          | 0.0003  | 1.09 (0.81~1.37)    | 0.69    |
| AL baseline (mm)                          | 0.60 (0.44~0.76)          | 0.0001  | 0.45 (0.20~0.70)    | 0.03    |
| Outdoor activity (hours per day)          | 0.85 (0.80~0.91)          | 0.09    | 0.92 (0.84~1.00)    | 0.15    |
| Nearwork (hours per day)                  | 0.73 (0.52~0.94)          | 0.12    | 0.81 (0.62~1.01)    | 0.08    |
| Change in pupil diameter between 1 year   | 0.56 (0.37~0.75)          | 0.03    | 0.48 (0.22~0.74)    | 0.04    |
| and baseline (mm)                         |                           |         |                     |         |
| Change in accommodation amplitude between  | 0.54 (0.23~0.85)          | 0.09    | 0.60 (0.22~0.98)    | 0.55    |
| 1 year and baseline (D)                   |                           |         |                     |         |

Note: HR: hazard ratio; CI: confidence interval. *Adjusted: body mass index (BMI), spherical equivalent refractive error (SER), accommodation amplitude (AMP), anterior chamber depth (ACD), outdoor activity and nearwork. b Adjusted: age, parental myopia status, SER, AMP, corneal curvature, ACD and nearwork.  c Adjusted: gender, age, BMI, SER, AMP, corneal curvature, ACD, outdoor activity and nearwork.  d Adjusted: age, BMI, SER, AMP, pupil diameter, corneal curvature, ACD and nearwork. *Outdoor activity = outdoor exercise + outdoor leisure activity. # Nearwork = 3* (homework + reading + playing on cell phone) + 2* (using computer + playing video game) + 1* (watching TV).
Table 3. Inclusion criteria.

|   |                                                                                           |
|---|--------------------------------------------------------------------------------------------|
| 1 | 6 ~ 14 years of age                                                                       |
| 2 | Cycloplegic autorefraction (spherical equivalent refractive error) from -6.00 D to -1.25 D for both eyes |
| 3 | Astigmatism of less than 2.0 D                                                            |
| 4 | Anisometropia of less than 1.0 D                                                           |
| 5 | Monocular best corrected visual acuity of 16/20 or better                                  |
| 6 | 10 ~ 21 mmHg of intraocular pressure                                                       |
| 7 | No other eye diseases and surgery                                                          |
| 8 | No ocular and systemic conditions that might affect vision or vision development            |
| 9 | No history of using atropine, pirenzepine, rigid gas permeable, soft contact lenses and orthokeratology contact lens to control myopia progression |
Figure 1. Subject recruitment and randomization flowchart.

Note: # due to: Spherical equivalent refractive error > -1.25D (N = 8) or < - 6.0D (N = 2), astigmatism ≤ - 2.0D (N = 3), intraocular pressure >21mmHg (N = 2), had cataract surgery (N = 1).
Figures

Figure 1

Subject recruitment and randomization flowchart.

354 Subjects assessed for eligibility

26 Excluded
16 Did not meet inclusion criterion #
5 Declined to participate
3 History of using atropine
2 History of using orthokeratology

328 Subjects double-blind randomly assigned

166 received 0.01% atropine
25 Lost to follow-up
10 Loss of contact
8 Concerned about side-effects
4 Busy/inconvenient
3 Difficulty in applying eyedrop
141 Analyzed

162 received 0.02% atropine
24 Lost to follow-up
10 Loss of contact
8 Concerned about side-effects
4 Busy/inconvenient
2 Difficulty in applying eyedrop
138 Analyzed

Note: # due to: Spherical equivalent refractive error > -1.25D (N = 8) or < - 6.0D (N = 2), astigmatism ≤ - 2.0D (N = 3), intraocular pressure >21mmHg (N = 2), had cataract surgery (N = 1).