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

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Research Article

Keywords: myopia control, atropine, children

Posted Date: December 17th, 2020

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

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Title page

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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 tend 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.

1 The rising prevalence of myopia and the growing proportion of the population with high
2 myopia result in significant economic and social impact ^{1,2}. The economic burden of
3 uncorrected distance refractive error, largely caused by myopia, was estimated to be
4 US\$202 billion per annum ³. Myopia brings further vision challenges because high
5 myopia increases the risk of pathologic ocular changes such as cataract, glaucoma,
6 retinal detachment, and myopic macular degeneration, all of which can cause irreversible
7 vision loss ⁴. These factors have generated research and clinical interest in the control
8 of myopia progression.

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

19 In the ATOM2 study ^{5,6}, the change in axial length (AL) and change in spherical
20 equivalent refractive error (SER) were not synchronous, such that in the absence of
21 change in SER, AL changed during use of 0.01% atropine. Conversely, a number of
22 studies, including our previous study found that low concentration atropine reduced
23 myopia progression not only through refractive changes, but also through control of axial
24 elongation ^{10,12-15}. Meanwhile, myopia progression in children varies by race/ethnicity,
25 and East/Southeast Asian children undergo more rapid myopia progression than white
26 children ^{16,17}. The purpose of the current study was to specifically evaluate independent
27 risk factors for rapid AL growth in myopic children using 0.01% and 0.02% atropine in
28 mainland China, which have not previously been explored. Low dose atropine is widely
29 used for myopia control in China but an appropriately powered RCT to explore
30 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 $\pm$ SD change in AL over the 12 months of the study was 0.35 ± 0.24 mm. The mean $\pm$ 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 1mm shorter AL at baseline and 52% for every 1mm 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: $-0.80\sim -0.68$, $P<0.0001$), and this strong relationship was confirmed in multivariate regression analyses after adjusting for potential confounders ($\beta= -0.95$, 95%CI: $-1.02\sim -0.88$, $P < 0.0001$).

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^{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^{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 children¹⁰, 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 children¹⁴, 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% atropine¹³. 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^{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^{11,18}, higher initial myopia⁸, and a family history of high myopia¹⁰. This confirms the importance of conducting

1 appropriately controlled studies to explore independent risk factors associated with rapid
2 AL elongation in myopic children in mainland China treated with low concentration
3 atropine.

4 In the current study, baseline age had a significantly negative correlation with AL
5 increase in myopic children using 0.01% or 0.02% atropine. The younger children were
6 at baseline, the more the AL elongation was evident at the end of the study period. This
7 was consistent with three other studies which explored the same relationship between
8 baseline age and AL increase in myopic children using atropine and whose baseline
9 profiles were similar to the current study. Joachimsen et al ¹¹, Wei et al ¹⁴ and Lee et al
10 ¹⁸ found that younger children in German, mainland China and Taiwan may still progress
11 quickly while using 0.01%, 0.01% and 0.05% atropine, respectively. It is well established
12 that there is slowing of physiological change in AL in older children ¹⁹. Conversely, Moon
13 et al ¹⁰ and Wu et al ⁸ reported no relationship between baseline age and AL change in
14 Taiwanese children using 0.05% atropine and in Korean children using 0.01%, 0.025%
15 or 0.05% atropine. These contrasting results may arise due to different study populations,
16 different baseline characteristics and methodological and analytical differences. For
17 example, myopia progression was faster in East/Southeast Asian than white children
18 aged 4-6 and 8-11 in a large real-world population conducted in United States study ¹⁷.

19 We also found that the children with 0.01% atropine had a more rapid AL elongation
20 and a worse myopic control effect than 0.02% atropine ¹³. Other reports have also found
21 a concentration-dependent response in myopia control with low concentration atropine
22 ^{6,10,12,14}. Side effects and adverse effects are reportedly similar in 0.01% and 0.02%
23 atropine ^{13,20}, suggesting that if children using 0.01% atropine are not achieving adequate
24 myopia control, changing to the 0.02% concentration could be considered. It is important
25 to use an individualized atropine concentration to control myopia development

26 The children with a smaller change in pupil diameter from baseline to 1 year had
27 rapid AL elongation in our study. The underlying reasons why these children did not
28 respond well are unclear. So far, it is unclear how low concentration atropine acts to
29 inhibit myopia progression. One theory ²¹ suggests that increased ultraviolet exposure
30 (secondary to pupil dilation) may increase collagen cross-linking within the sclera,
31 thereby limiting scleral growth during myopia progression and AL elongation. The greater
32 change in pupil diameter, may be due to the better absorption of the drug, greater
33 collagen cross-linking within the sclera and a superior effect on controlling myopia

1 progression. Recently, studies have shown that adding 0.01% atropine eye drops to OK
2 therapy was more effective than OK alone for controlling myopia progression in children
3 ^{22,23}. One of the possible mechanisms may be low concentration atropine's mydriatic
4 effect, as other studies have shown that myopia control effect of OK lens was also
5 affected by pupil diameter ^{24,25}. Children with larger pupil diameter would receive a
6 greater proportion of peripheral myopic defocus associated with OK lens wear, which in
7 turn may be relate to better myopia control ²⁴. This is a possible mechanism that warrants
8 further investigation.

9 We found that a rapid AL elongation related significantly to shorter AL at baseline, but
10 not to initial levels of myopia. In other words, the shorter AL at baseline, the more the AL
11 elongation was found with low concentration atropine, irrespective of baseline refractive
12 error. Lin²⁶ however found that highly myopic children had less increase in AL after using
13 0.125% atropine. Wu et al ⁸ conversely found that higher initial myopia corresponded
14 significantly to a higher chance of myopia progression irrespective of atropine
15 concentration. Moon et al ¹⁰ found that baseline refraction and AL were not associated
16 with the rate of myopia progression irrespective of atropine concentration, however only
17 age, family history and AL were selected for inclusion in the multivariate logistic
18 regression analyses of this study. Several studies ^{27,28} have established a strong
19 association between the eye's AL and its refractive error. Myopia progression usually
20 occurs due to excessive AL elongation of the eye, as evidenced by the strong association
21 between changes in myopia progression and changes in AL growth ^{19,29,30}. There was a
22 strong association between the change in AL and change in SER after 1-year treatment
23 in the present study. Another study ¹⁴ found that 0.01% atropine reduced myopia
24 progression by 34.2% and axial elongation by 22.0% compared with the placebo group.
25 However, in the ATOM2 study ⁶, while the degree of myopia was stable, the AL
26 continued to increase between 8 and 24 months after using 0.01% atropine. For
27 assessing the efficacy of interventions to control the progression of myopia in children,
28 we recommend that the change in AL is not be used interchangeably with the change in
29 refraction.

30 This study did not consider the rate of change in AL using age matched emmetropes,
31 however previous studies ^{31,32} describing the growth curve for AL with age showed that
32 the rate of AL elongation in emmetropes was slower than in myopes, and the AL growth
33 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^{33,34} 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,

1 kept away from the light, 15~25°C room temperature storage, discarded one month after
2 opening the bottle) were made by diluting 1% atropine (Eye & ENT Hospital, Affiliated to
3 Fudan University) with saline under sterile conditions, with the addition of the
4 preservative (0.3mg/ml ethylparaben). Subjects were randomized to either the 0.01% or
5 0.02% concentration based on a double-blinded and randomized selection algorithm.
6 The children were prescribed constant wear of full correction single-vision spectacle
7 lenses (SV) with the highest positive/least negative power consistent with optimum visual
8 acuity and with one drop of 0.01% or 0.02% atropine eye drops administered into both
9 eyes once nightly before bed time.

10 Pupil diameter was measured using an auto refractor (NIDEK, AR-1, Japan) when
11 looking at a distant target without any correction for refractive error under indoor light;
12 the light was constant with an illumination of 300 to 310 lux (TES-1332A Illumination
13 photometer). Children were adapted to the ambient light for 10 minutes in the
14 examination room before taking measurements. On each occasion, three successive
15 measurements were made, and average values were recorded. The right eye was
16 assessed before the left one. Accommodation amplitude (AMP) was measured out
17 monocularly by the push-up technique. The children wore their fully corrected spectacle
18 prescription and focused on the line above the best corrected visual acuity with the right
19 eye while the left one was occluded. The children were instructed to focus on a letter as
20 the chart was moved closer. They were asked to keep the letter as clear as possible until
21 it could no longer be held in clear focus. The inverse of the final distance in meter was
22 recorded as the child's AMP. AMP was recorded 3 times and the average taken. Corneal
23 power, anterior chamber depth (ACD) and AL were evaluated using a non-contact partial
24 coherence interferometer (IOLMaster; Carl Zeiss Meditec AG, Germany). On each
25 occasion, five successive measurements were taken and their mean was used as a
26 representative value. Based on other two similar studies ^{35,36}, rapid AL elongation was
27 defined as >0.36 mm growth per year (i.e., equivalent myopic progression 1.00D per year)
28 and children were categorized as either having rapid or slow AL elongation. Outdoor
29 activity time (hours per day) and nearwork time (hours per day) ¹² were assessed using
30 a paper questionnaire. Cycloplegic autorefraction was performed after the instillation of
31 four drops of compound tropicamide eye drops ^{37,38} (0.5% tropicamide and 0.5% neo-
32 synephrine) (Santen, Japan) administered 10 minutes apart in each of the patients' eyes.
33 Ten minutes after the instillation of the fourth drop, three autorefraction measurements

1 were taken (Topcon RM 8000A, CA) and a mean was obtained. The degree of myopia
2 was expressed as SER.

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

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

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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 $\pm$ SD or n (%).

	Change in AL over 12 months (mm)		
	Rapid change in AL Mean $\pm$ SD, (min-max) 0.50 $\pm$ 0.16, (0.35 to 0.97)	Slower change in AL Mean $\pm$ SD, (min-max) 0.19 $\pm$ 0.12, (-0.18 to 0.34)	P-value
N	132	147	
Age (year)	8.87 $\pm$ 1.69	10.76 $\pm$ 1.72	< 0.001
Body mass index (kg/m ²)	17.33 $\pm$ 3.85	18.78 $\pm$ 3.37	< 0.001
Spherical equivalent refractive error (D)	-2.27 $\pm$ 1.32	-2.98 $\pm$ 1.68	< 0.001
Intraocular pressure (mmHg)	16.98 $\pm$ 2.78	16.58 $\pm$ 2.91	0.22
Pupil diameter (mm)	6.12 $\pm$ 0.76	6.07 $\pm$ 0.67	0.51
Accommodation amplitude (D)	14.87 $\pm$ 4.56	15.74 $\pm$ 5.25	0.22
Corneal astigmatism(D)	-1.21 $\pm$ 0.58	-1.24 $\pm$ 0.57	0.33
Corneal curvature (D)	42.81 $\pm$ 1.37	42.92 $\pm$ 1.45	0.66
Anterior chamber depth (mm)	3.60 $\pm$ 0.21	3.68 $\pm$ 0.27	< 0.001
Axial length (mm)	24.26 $\pm$ 0.81	24.68 $\pm$ 0.93	< 0.001
Outdoor activity (hours per day) ※	2.52 $\pm$ 1.31	2.61 $\pm$ 1.35	0.21
Nearwork (hours per day) #	14.02 $\pm$ 2.82	14.22 $\pm$ 1.52	0.45
Atropine concentration 0.01% 0.02%	71 (53.8%) 61 (46.2%)	70 (47.6%) 77 (52.4%)	0.30
Gender Male Female	73 (55.3%) 59 (44.7%)	72 (49.0%) 75 (51.0%)	0.29
Heredity ++ (both parents myopic) +- (one parent myopic) -- (neither parent myopic)	32 (24.2%) 62 (47.0%) 38 (28.8%)	34 (23.1%) 73 (49.7%) 40 (27.2%)	0.90

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).

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2 **Table 2.** Univariate and multivariate regression analyses showing risk factors associated with rapid
3 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^a
Body mass index (kg/m ²)	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^b
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^c
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 and baseline (mm)	0.56 (0.37~0.75)	0.03	0.48 (0.22~0.74)	0.04^d
Change in accommodation amplitude between 1 year and baseline (D)	0.54 (0.23~0.85)	0.09	0.60 (0.22~0.98)	0.55

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

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

Figure 1. Subject recruitment and randomization flowchart.

Figures

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).

Figure 1

Subject recruitment and randomization flowchart.