The difference between cycloplegic and non-cycloplegic autorefraction and its association with progression of refractive error in Beijing urban children

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Abstract

*Purpose***:** To investigate the difference between cycloplegic and non-cycloplegic autorefraction and its association with the progression of refractive error in Beijing urban children.

*Methods***:** A total of 386 children aged 6-17 years were enrolled in the baseline investigation of Beijing Myopia Progression Study in 2010. They were invited for follow-up vision examinations in the years 2011, 2012, and 2013, including cycloplegic (cyclopentolate 1%, 3 times) autorefraction. We investigated the difference between the cycloplegic spherical equivalent (SE) and the non-cycloplegic SE (DSE) provided by autorefraction and its association with refractive error progression. The progression of refractive error was defined as the difference between the cycloplegic SE at follow-up and at baseline.

Results: Two hundred and nineteen children (57%) with completed refractive data (mean ± standard deviation: -1.36 ± 2.44 D at baseline) were ultimately enrolled. The DSE reduced from 0.51 ± 0.72 D at baseline to 0.19 ± 0.43 D in the third year of follow-up (p=0.01). The baseline DSE was positively associated with the children's baseline cycloplegic refraction (β=0.193 dioptre/dioptre, p<0.001). After further divided by refractive status, the DSE was consistently higher in the hyperopic group than in eitherthe emmetropic or myopic groups at each follow-up (all p<0.001). In the multivariate regression analysis, the myopic children with larger baseline DSE (β=-0.404 dioptre/dioptre, p=0.01) exhibited more myopic refractive change. However, baseline DSE was not found to be a significant risk factor (relative risk, 95% confidence interval: 1.06, 0.79-1.41) for those with newly developed myopia.

*Conclusion***:** In this sample, the children's DSE was found to be increased as the hyperopic refraction increased. Furthermore, greater the DSE was associated with the progression of refractive error among the myopic children, but not with the onset of myopia.

Introduction

Pseudomyopia and latent hyperopia refer to a typically intermittent and temporary shift of refraction towards myopia (or less hyperopia) due to a transient spasm of the ciliary muscle and resultant inability to rapidly and accurately relax the ciliary muscle and alter shape of the crystalline lens, thus causing an increase in refractive power of the eye. It can be reduced or eliminated with cycloplegia. Spasms of

accommodation are found in children and young adults who have over-active accommodation, and it typically occurs after a period of sustained near work. For example, in the Tehran Eye Study, Fotouhi *et al.* reported the difference between cycloplegic and non-cycloplegic refraction (DSE) of up to 0.71D and 0.40D in 5-10 year old children and in 16-20 year old teenagers and young adults, respectively.[1] Recently, Mimouni *et al.* reported that this difference was 0.68D in 18-21 year old young adults, and furthermore that hyperopic young adults had a greater difference than myopic ones (1.30D vs. 0.46D).[2]

According to the Chinese Medical Association of Ophthalmology, Division of Refraction, myopia can be classified into three subgroups after atropine-induced cycloplegia is performed: (1) pseudomyopia: the "apparent" myopia that disappears with atropine-induced cycloplegia, and with the eyes now exhibiting either emmetropia or hyperopia; (2) mixed myopia: the "apparent myopia" that does not disappear but is reduced with atropine-induced cycloplegia by 0.50D or more; and (3) true myopia: the myopia that does not disappear with atropine-induced cycloplegia, and thus is reduced by less than -0.50D.[3] Hu summarised the myopia surveys on Chinese children and found that pseudomyopia and mixed myopia presented in approximately 10% and 50% of the myopic school children, which when combined suggested accommodative factors present in approximately 60% of the sample.[4] Lastly, in a longitudinal study, Mei and Rong reported that 59.4% of the recent-onset myopia had true myopia, followed by pseudomyopia (36%).[5]

The exact mechanism between excessive accommodation and myopia progression is not clear, and some controversy abounds. Myopia progression by some has been speculated to be caused by spasm of the ciliary muscle and inability to accurately relax the ciliary muscle and alter the crystalline lens, with subsequent myopic defocus occurring at the retina.[6, 7] The possible link between myopic retinal defocus and myopia progression has been supported by several studies showing the association between refractive undercorrection and myopia progression in myopic children.[8-12] Furthermore, treatment is directed at preventing or retarding the myopic progression. Several randomised controlled trials (RCTs) have found that the use of atropine had a positive effect in controlling myopic progression,[13-16] and related axial length growth[15, 16] as compared to the control group; and, the higher the concentration of atropine, the stronger the effect.[13-16] However, higher concentrations of atropine produce a larger rebound effect for both myopic progression and axial length growth.[17, 18] Hence,

3

excessive accommodation, which would cause increased myopic retinal defocus, is thought by some to be associated with myopia and/or its progression. However, studies on excessive accommodation are rare, especially dealing with the longitudinal observation of its effect on myopia progression.[5] Hence, the present study reports the natural change of excessive accommodation (as measured by the difference between cycloplegic and non-cycloplegic autorefraction), and its association with progression of refractive error, in school children derived from the Beijing Myopia Progression Study (BMPS).

Methods

Subjects

The study design, procedures, and baseline characteristics of BMPS have been reported elsewhere.[7] Briefly, children (aged 6-17 years old) from primary (8.4 ± 1.1 years) and secondary (14.2 ± 1.6 years) schools in Beijing were recruited from July to September 2010. The inclusion criteria were: (1) best-corrected visual acuity (with children's own spectacles when worn) of 0.1 LogMAR or better; and (2) willingness to cooperate and return for scheduled annual visits. The exclusion criteria were: (1) presence of amblyopia and/or strabismus; (2) history of intraocular surgery or penetrating ocular trauma; and (3) serious medical/ocular health problems. The enrolled children were invited to be re-examined at the clinic centre at a similar time of the year in 2011, 2012, and 2013. The vision examinations of the children included visual acuity, ocular biometry, cycloplegic refraction, and a detailed myopia-related questionnaire. The parents of these children were also invited to have a similar vision examination and respond to a questionnaire regarding their children at baseline.

The study followed the tenets of the Declaration of Helsinki and was approved by the Beijing Tongren Hospital Ethics Committee. All participants (children and their parents) signed written informed assent/consent.

A total of 386 children with a completed vision examination and myopia questionnaire at baseline in the year 2010 were requested to be re-examined in the years 2011, 2012, and 2013. Of the original children, 241 (62%) were re-examined at the final follow-up in 2013. Twenty-two of these children were excluded, as there was either lack of refractive data at the follow-up, or they had received

4

orthokeratology after the baseline vision examination. Hence, 219 children (57%), including 107 boys (49%) and 115 (51%) girls, were enrolled in the present study and used in the related analyses.

Refractive error

All children received a non-cycloplegic and cycloplegic autorefraction (*Accuref-K9001, Shin Nippon,* www.shin-nippon.jp/products/ack9001/index.html) at each vision examination, whereas the parents received a non-cycloplegic autorefraction (*Accuref-K9001*) only at the baseline vision examination. Three drops of cyclopentolate 1% (Cyclogyl, Alcon) were instilled in each eye approximately 10-minutes apart. Cycloplegic autorefraction was performed 30 minutes after the last drop was instilled. Three readings were obtained in each eye and averaged in all participants. At the end of the each examination, for children whose habitual best-corrected visual acuity was worse than 0.1 LogMAR, they were prescribed spectacles initially based on the cycloplegic autorefraction, with subsequent subjective refinement (maximum plus to maximum visual acuity including Jackson cross-cylinder).

Daily activity

A detailed questionnaire to obtain information regarding the children's daily activity, living environment, parental education, et cetera, was surveyed by children and their parents at baseline. The average hours spent on near work activity were summarised from the questionnaire regarding drawing, homework, reading, and handheld computer use. Time spent on outdoor activities (including outdoor sports and outdoor leisure) was based on questions about playing outdoors, family picnics and barbeques, bicycle riding, hiking, and outdoor sports.[19]

Definitions

The spherical equivalent (SE) of the right and left eyes was highly correlated (Pearson correlation coefficient of the SE was 0.95, 0.96, and 0.93 for children, fathers, and mothers at baseline, respectively). Therefore, for simplicity, only data from the right eyes were used. The difference between cycloplegic and non-cycloplegic autorefraction SE (DSE) was analysed as a continuous variable and as a discrete classified variable. The refractive change was defined as the cycloplegic SE at the final follow-up minus the cycloplegic SE at baseline. The mean annual refractive change

was defined as the total refraction change divided by three (averaged over the three-year period of 2010 to 2013). Myopia, emmetropia, and hyperopia were defined as SE < -0.5 dioptres (D), -0.5D ≤ SE ≤0.5D, and SE > 0.5D, respectively.[20] Low myopia, moderate myopia, and high myopia were defined as -3.0D ≤ SE < -0.5 D, -5.0D ≤ SE <-3.0D, and SE <-5.0D, respectively.[20]

Data analysis

The normally distributed parameters were presented as the mean ± standard deviation. Student t-tests and chi-square tests were performed for comparison of the normally continuous data and the discrete categorised data, respectively. General linear models (GLMs) were used to assess the relationship between the excessive accommodation and its putative factors, as well as the relationship between refractive change and the DSE. Variance inflation factors of the putative factors in the linear models were also presented. Furthermore, logistic regressions were performed using GLMs to explore the associations between myopic onset and the putative risk factors. The relative risk (RR) and 95% confidence interval (CI) were presented. The baseline parameters of the children's age, children's cycloplegic SE, and parental non-cycloplegic SE were used in the statistical analysis. All statistical analyses were performed with Statistical Analysis System for Windows version 9.1.3 (SAS Inc., Cary, NC).A *P*-value of <0.05was considered statistically significant.

Results

The mean baseline age of the enrolled 219 children was 10.8 ± 3.2 years. There were 135 myopic (-2.86 ± 1.69 D), 35 emmetropic (0.12 ± 0.34 D), and 49 hyperopic (1.72 ± 1.27 D) children at baseline. Detailed baseline characteristics are presented in *Table 1*. The mean follow-up time and the mean annual refractive change were 35.6 ± 1.0 months and -0.48 ± 0.34 D/year, respectively, in these 219 children. The mean annual refractive change was -0.51 ± 0.34 D/year and -0.45 ± 0.34 D/year (p=0.20) in the boys and girls, respectively. The mean annual refractive change was -0.47 ± 0.35 D/year, -0.58 ± 0.38 D/year, and -0.43 ± 0.28 D/year (p=0.12) in the myopic, emmetropic, and hyperopic children, respectively.

According to the definition of myopia from the Chinese Medical Association of Ophthalmology, Division of Refraction, there were 18 with pseudomyopia and 29 with mixed myopia at baseline. These accounted for 8% and 13% of all children, and 12% and 19% of the myopic children (pseudo, mixed, and true myopia). The pseudomyopia and mixed myopia tended to decrease, while the true myopia tended to increase, from baseline to the last follow-up examination (*Figure1a*). Since both the mixed myopia and true myopia were similar (both non-cycloplegic and cycloplegic refraction were myopic), these children were combined and presented in *Figure 1b*.

Putative factors associated with DSE

The overall DSE reduced from 0.51 ± 0.72 D at baseline to 0.19 ± 0.43 D in the third year follow-up (p=0.01). In the multivariate regression analysis with the children's baseline DSE as the dependent variable, and the children's age, gender, baseline refraction, paternal refraction, maternal refraction, near work time, and time outdoors as the independent variables, only the parameter of baseline cycloplegic refraction (β=0.193, p<0.001) was significantly related to the DSE (*Table 2*).The DSE was then further divided as a function of refractive status into hyperopia (n=40), emmetropia (n=35), low myopia (n=87), moderate myopia (n=33), and high myopia (n=15). See *Table 3*. The DSE was consistently and significantly higher among the hyperopic children as compared to either the emmetropic or myopic children at baseline and in the follow-up assessments (all p<0.001). Furthermore, except for the high myopia group, the DSE consistently and significantly decreased from baseline at the follow-up assessments among the different refractive groups (all p<0.05).

DSE and progression of refractive error

In another multivariate regression analysis performed on all of the children, with the children's three-year refractive change (from baseline to the third year follow-up) as the dependent variable, and the children's age, gender, baseline DSE, baseline refraction, paternal refraction, maternal refraction, time spent on near work, and outdoors as the independent variables, children who were younger (β= 0.220 D/year, p<0.001), and spent more time on near work (β= -0.077 D/hour, p=0.049)

exhibited more myopic refractive change. Children who had more myopic paternal refraction ($\beta=$ 0.045 D/D, p=0.07) had borderline more myopic refractive change. However, the children's gender ($\beta=$ -0.10, p=0.93), baseline DSE ($\beta=$0.085D/D, p=0.37), baseline refraction ($\beta=$0.049D/D, p=0.19), maternal refraction ($\beta=$-0.004D/D, p=0.87), and time spent on outdoor activities ($\beta=$0.062D/hours, p=0.20) were not found to be significantly associated with their refraction change.

Similar multivariate regression analysis was then performed for the myopic children at baseline (n=135), i.e., with the children's three-year refractive change (from baseline to the third year follow-up) as the dependent variable, and the children's age, gender, baseline DSE, baseline refraction, paternal refraction, maternal refraction, time spent on near work, and time spent outdoors as the independent variables. Children who were younger ($\beta=$ 0.251 D/year, p<0.001), and had larger baseline DSE ($\beta=$ -0.404 D/D, p=0.01), exhibited more myopic refractive change. However, baseline refraction ($\beta=$-0.042D/D, p=0.35), paternal refraction ($\beta=$-0.030D/D, p=0.21), and time spent on near work ($\beta=$-0.051D/hours, p=0.21) were not found to be significantly associated with the children's refractive change (*Table 4*).

For these myopic children, when the dependent variables were now changed to their two-year refractive change (from first-year follow-up to third-year follow-up), and when the independent variables were changed to the children's age at the first-year follow-up, and the dependent variable were gender, DSE at first year follow-up, refraction at first year follow-up, paternal refraction, maternal refraction, time spent on near work and outdoors at first year follow-up, only children who were younger ($\beta=$ 0.165 D/year, p<0.001) exhibited more myopic refractive change. No significant association between the children's refractive change and the DSE was found ($\beta=$ -0.194 D/year, p=0.21).

For these myopic children, when the dependent variable was again changed to the children's one-year refractive change (from second-year follow-up to third-year follow-up), and the independent variables were changed to the parameters used at the second-year follow-up accordingly, children who were younger ($\beta=$ 0.073 D/year, p<0.001), with larger DSE ($\beta=$ -0.549 D/D, p<0.001), and with more myopic refraction($\beta=$ 0.052 D/D, p=0.008) had more myopic refractive change.

When a similar multivariate regression analysis was performed for only the emmetropic and hyperopic children at baseline (n=84), i.e., with the children's three-year refractive change as the dependent variable, and the children's age, gender, baseline DSE, baseline refraction, paternal refraction, maternal refraction, time spent on near work, and outdoors as the independent variables, only children who were younger (β= 0.182 D/year, p<0.001) exhibited more refractive change towards myopia. No significant association between the DSE and myopic progression was found (β= 0.08 D/D, p=0.57).

There were 37 children (37/84, 44%) who developed myopia at the final follow-up vision examination. In a multivariate logistic regression for their newly-developed myopia, with the children's age, gender, baseline DSE, baseline refraction, paternal refraction, maternal refraction, and time spent on near work and outdoor as the independent variables, only children who were older (RR, 95% CI: 0.87, 0.77-0.98), and with a more hyperopic baseline refraction (RR, 95% CI: 0.31, 0.21-0.47) had less risk to develop myopia. No significant association between the DSE and the newly developed myopia was found (*Table 5*).

Discussion

Pseudomyopia has been defined as the "apparent" myopic disappearance following cycloplegia.[3, 5] Mei and Rong suggested that pseudomyopia was a transient first stage towards permanent myopia.[5] However, this transient situation is not easily observed clinically. According to this definition, pseudomyopia accounted for less than10% in all children, and less than 20% in the myopic students in this study.

In the present study, there are two interesting and important findings. First, the DSE was associated with the children's refraction, i.e., the more hyperopic refraction, the more the DSE. Furthermore, after divided into different refractive groups, the hyperopic children consistently exhibited greater DSE than either the emmetropic or myopic children at each vision examination. This is consistent with previous findings in Chinese children. For example, Rao reported that 93% and 2% of the pseudomyopes were hyperopes and emmetropes in Chinese preschool children, respectively.[21] Hu reported that accommodative factors were present in 81%, 54%, and 32% of

school children with myopic refraction of-0.50D ~ -1.50D, -1.75D ~ -2.75D, and more than -3.0D, respectively.[4] Mimouni *et al*. also reported the difference between cycloplegic and non-cycloplegic refraction was greater in hyperopic young adults than myopic ones (1.30D vs. 0.46D).[2] Although refractive correction was prescribed at the end of the each vision examination, most of the hyperopic children had not worn the prescription, since there were only four children with hyperopic refraction more than 3 dioptres at baseline. Hence, the current finding is expected, since uncorrected hyperopes require more accommodation when focusing at both distant and near targets as compared to either emmetropes or myopes. Although the present data show that the DSE decreased as the child's age increased, this could be due to a decrease of the hyperopic refraction rather than be directly associated with the children's age *per se*.

Pseudomyopia is due to an intermittent spasm of the ciliary muscle,[22] classically thought to be due to an overactive or excessive accommodative response that primarily occurs after sustained near work in children and young adults. Several longitudinal studies have supported the role of near work and myopic progression.[23-29] In the present sample, it was also found that children who spent more time performing near work were associated with greater myopic progression.[29] However, and somewhat unexpectedly, the DSE was not found to be associated with the amount of near work time in this sample. However, we believe this may not necessarily exclude the association between near work and excessive accommodation. First, this may be due to recall bias on activity hours, since a questionnaire was used to collect the data, and help was sought from the children's parent(s) for very young children who could not read or understand the questionnaire very well. Second, the activity hours in this study were only the average daily hours, and more detailed information, such as the distribution and intervals of the activity, was not obtained. Third, the individual susceptibility to near work may be different. After a period of sustained near work, the refractive state of most human eyes will exhibit a transient myopic shift, i.e., near work induced transient myopia (NITM).[6, 7] NITM was found to be larger and required more time to dissipate in myopes than in either emmetropes or hyperopes in Chinese school children.[7] Furthermore, NITM is additive, i.e., there is increased magnitude and dissipation time as near work time increases without interruption.[30, 31] Hence, NITM, a transient reaction of the ciliary muscle to near work (average 0.16D and 50 seconds in myopes)[7]

could show differential susceptibility to near work. Lastly, the lack of variation with amount of near work time may reflect a saturation phenomenon. Hence, we conclude that the DSE may also have differential sensitivity to near work.

Second, the most important finding was that greater DSE was associated with myopia progression among myopic school children. In this sample, after considering the possible effects of the putative risk factors for myopic progression, for each dioptre increase in the DSE, the myopia progression increased by approximately 0.135D/year among these myopic children. The mechanism for larger DSE being associated with more myopic progression in myopic children remains unclear. Excessive accommodation would cause myopic retinal defocus. The association between myopic retinal defocus and myopia progression has been supported by several clinical studies and also systematic review on refractive undercorrection in myopic children.[8-12] For example, Chung *et al.* conducted a two-year, randomised controlled clinical trial in Hong Kong myopic children aged 9-14 years having the same mean initial refraction. Half were prescribed the full cycloplegic distance refraction, whereas the others were purposely undercorrected by -0.75 D, which would produce increased *myopic* defocus at far. At the end of the trial, both myopic progression and axial length were significantly greater in the *under*corrected group as compared with those who were fully corrected (approximately0.50vs. 0.38 D/year, and approximately 0.34 vs. 0.30mm/year).[8] These results were confirmed by studies using a similar clinical trial paradigm (full correction vs. undercorrection of 0.25-0.50D) in myopic children.[9, 10] In a retrospective study, Yu *et al.* reported that the spherical equivalent progression in Chinese children aged 9-16 years with undercorrection was -0.63 ± 0.31 D/year, which was significantly greater than found in those with full correction (-0.21 ± 0.12 D/year).[9] In a cohort study with mostly Jewish children aged 6-15 years, Adler and Millodot also reported a greater myopic progression with modest undercorrection (0.66 vs. 0.55 D/year).[10] Recently, a retrospective study by Vasudevan *et al.* found that myopic progression consistently increased with undercorrection magnitude among children and young adults in the United States. For example, myopic progression was -0.20D/year, -0.29D/year, and -0.45D/year for full correction, undercorrection of -0.25D, and undercorrection of -0.50D, respectively.[12] However, there were three recent studies that did not support this view.[32-34] Phillips reported that the myopic progression was

greater in the eyes with full correction than eyes with undercorrection (0.73 ± 0.32 vs. 0.32 ± 0.30 D/year).[32] In the Anyang Childhood Eye Study (ACES), it was reported that there was no significant difference in myopia progression (0.64 ± 0.44 vs. 0.68 ± 0.46 D/year) and axial length elongation (0.31 ± 0.11 vs. 0.31 ± 0.12mm/year) between undercorrection and full correction, although the eyes with undercorrection had more baseline myopia (-3.75 ± 1.23 vs. -3.12 ± 1.29) and longer axial length (25.04 ± 0.77 vs. 24.81 ± 0.81 mm).[33] Also in ACES, it was reported that children without correctionhad slower myopia progression (0.38 vs.0.52 D/year) and less axial elongation (0.24vs. 0.26 mm/year) than children with fullcorrection.[34] Thus, the findings are equivocal, and warrant a further large-scale investigation.

Other evidence for the association of excessive accommodation and myopic progression involves the topical use of atropine for control of the myopic progression in myopia children.[14-16] Several randomised, controlled trials have demonstrated that the use of atropine significantly reduced myopia progression and retarded axial length growth. Furthermore, this effect of atropine was dose-related.[14, 16] Unfortunately, it also exhibits abound effect after its cessation.[17, 18] Although a biochemical effect on the retina and sclera is thought to be involved in controlling myopic progression using atropine,[35-37] one must exercise caution translating the animal studies into the human context. Even if it does, the adverse and long-term effect on accommodation remains to be determined.

There were some limitations in the present study. First, a relatively large proportion of children was unavailable in the final follow-up, and the children enrolled for the final analysis tended to be less myopic than those lost to follow-up. In addition, due to a relatively small sample size of the non-myopic children, this may account for the lack of association found regarding the DSE in these children. Hence, further studies with a larger sample, especially non-myopic children, are warranted. Second, this hospital-based study tended to enrol children with more myopic refraction at baseline, as their parents presumably paid more attention to their child's visual and ocular health. As a result, extrapolation/generalisation of the conclusion is limited at a certain extent. Hence, school-based and population-based longitudinal studies with a larger sample size are warranted. Third, the amount of DSE may be underestimated, since cyclopentolate was reported to result in a cycloplegic refraction approximately 0.77D more myopic than atropine in Japanese children older than seven years.[38]

Finally, the amount of the DSE may be dependent on the autorefractor used and linked to proximal accommodation.

In summary, in this sample, Chinese school children with larger hyperopic refraction exhibited greater DSE. Most importantly, myopic children with a greater DSE exhibited more myopic progression.

Disclosure

The authors report no conflicts of interest and have no proprietary interest in any of the materials mentioned in this article.

References

1. Fotouhi A, Morgan IG, Iribarren R, Khabazkhoob M, Hashemi H. Validity of noncycloplegic refraction in the assessment of refractive errors: the Tehran Eye Study. *Acta Ophthalmol.* 2012;90:380-386.
2. Mimouni M, Zoller L, Horowitz J, Wygnanski-Jaffe T, Morad Y, Mezer E. Cycloplegic autorefraction in young adults: is it mandatory? *Graefes Arch Clin Exp Ophthalmol.* 2016;254:395-398.
3. Chinese Medical Association of Ophthalmology DoR. Definition and classic criterion for distinguishing between true myopia and pseudo-myopia. *Chinese Journal of Ophthalmology.* 1986;22:184-185.
4. Hu DN. Pseudo-myopia: is it common and treatable? *Ophthalmol CHN.* 2006;15:10-12.
5. Mei Q, Rong Z. Early signs of myopia in Chinese schoolchildren. *Optom Vis Sci.* 1994;71:14-16.
6. Ciuffreda KJ, Vasudevan B. Nearwork-induced transient myopia (NITM) and permanent myopia--is there a link? *Ophthalmic Physiol Opt.* 2008;28:103-114.
7. Lin Z, Vasudevan B, Liang YB, *et al.* Baseline characteristics of nearwork-induced transient myopia. *Optom Vis Sci.* 2012;89:1725-1733.
8. Chung K, Mohidin N, O'Leary DJ. Undercorrection of myopia enhances rather than inhibits myopia progression. *Vision Res.* 2002;42:2555-2559
9. Yu AY, Wang QM, Lv F, Wu GB, Yu XD. Relation between the rate of childhood myopia progression and spectacle prescription types included single vision lenses with under correction. *Rec AdvOphthalmol.* 2003;23:429-431.
10. Adler D, Millodot M. The possible effect of undercorrection on myopic progression in children. *Clin ExpOptom.* 2006;89:315-321.
11. Li SY, Li SM, Wu SS, *et al.* Effects of under correction and full correction of myopia on slowing the progression of myopia in school-aged children: a systematic review. *Chin JOptom Ophthalmol Vis Sci.* 2011;13:223-226.
12. Vasudevan B, Esposito C, Peterson C, Coronado C, Ciuffreda KJ. Under-correction of human myopia--is it myopigenic?: a retrospective analysis of clinical refraction data. *J Optom* 2014;7:147-152.
13. Yen MY, Liu JH, Kao SC, Shiao CH. Comparison of the effect of atropine and cyclopentolate on myopia. *Ann Ophthalmol.* 1989;21(5):180-182.
14. Shih YF, Chen CH, Chou AC, Ho TC, Lin LL, Hung PT. Effects of different concentrations of atropine on controlling myopia in myopic children. *J Ocul Pharmacol Ther.* 1999;15:85-90.
15. Chua WH, Balakrishnan V, Chan YH, et al. Atropine for the treatment of childhood myopia. *Ophthalmology.* 2006;113:2285-2291.
16. Chia A, Chua WH, Cheung YB, et al. Atropine for the treatment of childhood myopia: safety and efficacy of 0.5%, 0.1%, and 0.01% doses (Atropine for the Treatment of Myopia 2). *Ophthalmology.* 2012;119:347-354.
17. Tong L, Huang XL, Koh AL, Zhang X, Tan DT, Chua WH. Atropine for the treatment of childhood myopia: effect on myopia progression after cessation of atropine. *Ophthalmology.* 2009;116:572-579.
18. Chia A, Chua WH, Wen L, Fong A, Goon YY, Tan D. Atropine for the treatment of childhood myopia: changes after stopping atropine 0.01%, 0.1% and 0.5%. *Am J Ophthalmol.* 2014;157:451-457
19. Lin Z, Vasudevan B, Jhanji V, *et al.* Near work, outdoor activity, and their association with refractive error. *Optom Vis Sci.* 2014;91:376-382.

20. Liang YB, Wong TY, Sun LP, *et al.* Refractive errors in a rural Chinese adult population the Handan eye study. *Ophthalmology.* 2009;116:2119-2127.

21. Rao Y. Analysis of 292 cases of preschoolers with pseudomyopia. *Chinese Journal of Strabismus &Pediatric Ophthalmology.* 2009;17:15-16.

22. Ong E, Ciuffreda KJ. *Accommodation, Nearwork, and Myopia.* Santa Ana, CA: Optometric Extension Program Foundation Press. 1997.

23. Parssinen O, Lyyra AL. Myopia and myopic progression among schoolchildren: a three-year follow-up study. *Invest Ophthalmol Vis Sci.* 1993;34:2794-2802.

24. Kinge B, Midelfart A, Jacobsen G, Rystad J. The influence of near-work on development of myopia among university students. A three-year longitudinal study among engineering students in Norway. *ActaOphthalmol Scand.* 2000;78:26-29.

25. Hepsen IF, Evereklioglu C, Bayramlar H. The effect of reading and near-work on the development of myopia in emmetropic boys: a prospective, controlled, three-year follow-up study. *Vision Res.* 2001;41:2511-2520.

26. Jacobsen N, Jensen H, Goldschmidt E. Does the level of physical activity in university students influence development and progression of myopia?--a 2-year prospective cohort study. *Invest Ophthalmol Vis Sci.* 2008;49:1322-1327.

27. Guo Y, Liu LJ, Xu L, *et al.* Myopic shift and outdoor activity among primary school children: one-year follow-up study in Beijing. PLoS One. 2013;8(9):e75260.

28. French AN, Morgan IG, Mitchell P, Rose KA. Risk factors for incident myopia in Australian schoolchildren: the Sydney adolescent vascular and eye study. *Ophthalmology.* 2013;120:2100-2108.

29. Lin Z, Vasudevan B, Mao GY, *et al.* The influence of near work on myopic refractive change in urban students in Beijing: a three-year follow-up report. *Graefes Arch ClinExp Ophthalmol.* 2016; 254:2247-2255.

30. Vasudevan B, Ciuffreda KJ. Additivity of near work-induced transient myopia and its decay characteristics in different refractive groups. *Invest Ophthalmol Vis Sci.* 2008;49:836-841.

31. Arunthavaraja M, Vasudevan B, Ciuffreda KJ. Nearwork-induced transient myopia (NITM) following marked and sustained, but interrupted, accommodation at near. *Ophthalmic Physiol Opt* 2011;30:766-775.

32. Phillips JR. Monovision slows juvenile myopia progression unilaterally. *Br J Ophthalmol.* 2005;89:1196-1200.

33. Li SY, Li SM, Zhou YH, *et al.* Effect of undercorrection on myopia progression in 12-year-old children. *Graefes Arch Clin Exp Ophthalmol.* 2015;253:1363-1368.

34. Sun YY, Li SM, Li SY, *et al.* Effect of uncorrection versus full correction on myopia progression in 12-year-old children. *Graefes Arch Clin Exp Ophthalmol.* 2017;255:189-195.

35. Barathi VA, Weon SR, Beuerman RW. Expression of muscarinic receptors in human and mouse sclera and their role in the regulation of scleral fibroblasts proliferation. *Mol Vis.* 2009;15:1277-1293.

36. McBrien NA, Arumugam B, Gentle A, Chow A, Sahebjada S. The M4 muscarinic antagonist MT-3 inhibits myopia in chick: evidence for site of action. *Ophthalmic Physiol Opt.* 2011;31:529-539.

37. Barathi VA, Beuerman RW. Molecular mechanisms of muscarinic receptors in mouse scleral fibroblasts: Prior to and after induction of experimental myopia with atropine treatment. *Mol Vis.* 2011;17:680-692.

38. Kawamoto K, Hayasaka S. Cycloplegic refractions in Japanese children: a comparison of atropine and cyclopentolate. *Ophthalmologica.* 1997;211:57-60.

Table 1 Baseline characteristics of the children in the presentstudy

Parameters	
Age (year)	10.8 ± 3.2
Gender (male/female)	107/112
Myopia/Emmetropia/Hyperopia	135/35/49
Myopia (n=135)	
Cycloplegic sphere (dioptre)	-2.63 ± 1.73
Cycloplegic cylinder (dioptre)	-0.44 ± 0.72
DSE (dioptre)	0.23 ± 0.40
Emmetropia (n=35)	
Cycloplegic sphere (dioptre)	0.33 ± 0.44
Cycloplegic cylinder (dioptre)	-0.45 ± 0.41
DSE (dioptre)	0.55 ± 0.61
Hyperopia (n=49)	
Cycloplegic sphere (dioptre)	1.81 ± 1.38
Cycloplegic cylinder (dioptre)	-0.19 ± 0.96
DSE (dioptre)	1.26 ± 0.93

DSE: difference between cycloplegic and non-cycloplegic autorefraction spherical equivalent.

Table 2 Putative risk factors for baseline difference between cycloplegic and non-cycloplegic autorefraction

spherical equivalent

	Regression coefficient β	95% CI	Standardised coefficient β	P*	VIF
Age (year)	0.027	-0.010, 0.06	0.115	0.15	1.811
Gender (M/F)	0.070	-0.108, 0.25	0.047	0.44	1.036
Baseline cycloplegic refraction (dioptre)	0.193	0.145, 0.24	0.649	**<0.001**	1.912
Paternal refraction (dioptre)	-0.009	-0.046, 0.03	-0.031	0.63	1.190
Maternal refraction (dioptre)	-0.020	-0.059, 0.02	-0.068	0.32	1.318
Near work time (hour/day)	-0.020	-0.079, 0.04	-0.045	0.49	1.196
Outdoor time (hour/day)	-0.006	-0.079, 0.07	-0.011	0.87	1.103

P*: tested by multivariate regression analysis;

CI: confidence interval; VIF: variance inflation factor

BOLD: significant factor

Table 3 The difference between cycloplegic and non-cycloplegic autorefraction spherical equivalent (dioptres) at each follow up assessment for the different refractive states

	Baseline	One-year follow-up	Two-year follow-up	Three-year follow-up	$P^{\dagger}$
Total (n=219)	0.51 ± 0.72	0.43 ± 0.57	0.30 ± 0.50	0.19 ± 0.43	**0.01**
Hyperopia (n=49)	1.26 ± 0.93	0.99 ± 0.78	0.71 ± 0.69	0.48 ± 0.64	**<0.001**
Emmetropia (n=35)	0.55 ± 0.61	0.43 ± 0.52	0.35 ± 0.42	0.23 ± 0.32	**0.01**
Low myopia (n=87)	0.27 ± 0.41	0.21 ± 0.25	0.13 ± 0.29	0.10 ± 0.32	**0.002**
Moderate myopia (n=33)	0.18 ± 0.41	0.27 ± 0.39	0.14 ± 0.43	-0.02 ± 0.20	**0.03**
High myopia (n=15)	0.09 ± 0.22	0.29 ± 0.28	0.19 ± 0.24	0.06 ± 0.16	0.09
P^{*}	<0.001	<0.001	<0.001	<0.001	

P^{*}: tested by analysis of variance; $P^{\dagger}$: tested by repeated-measures analysis of variance; BOLD: significant factor

Table 4 Multivariate analysis of the associations with the children's three-year refractive change among myopic children (n=135)

	Regression coefficient β	95% CI	Standardised coefficient β	P	VIF
Age (years)	0.251	0.198, 0.304	0.760	**<0.001**	1.809
Gender (M/F)	-0.030	-0.286, 0.225	-0.015	0.81	1.053
Baseline DSE (dioptre)	-0.404	-0.722, -0.086	-0.157	**0.01**	1.082
Baseline cycloplegic refraction (dioptre)	-0.042	-0.132, 0.047	-0.070	0.35	1.548
Paternal refraction (dioptre)	0.030	-0.017, 0.078	0.083	0.21	1.182
Maternal refraction (dioptre)	-0.030	-0.083, 0.023	-0.081	0.26	1.423
Near work time (hour/day)	-0.051	-0.131, 0.029	-0.086	0.21	1.269
Outdoor time (hour/day)	0.020	-0.092, 0.133	0.024	0.72	1.227

CI: confidence interval; VIF: variance inflation factor; DSE: difference between cycloplegic and non-cycloplegic autorefraction spherical equivalent.

BOLD: significant factor

Table 5 Relative risk (RR) and 95% confidence interval (CI) for the children with newly developed myopia (n=84)

	Univariate		Multivariate	
	RR	**95% CI**	**RR**	**95% CI**
Age (years)	0.93	0.82, 1.05	**0.87**	**0.77, 0.98**
Gender (M/F)	0.89	0.55, 1.45	0.92	0.59, 1.46
Baseline DSE (dioptre)	0.54	0.35, 0.85	1.06	0.79, 1.41
Baseline cycloplegic refraction (dioptre)	0.34	0.26, 0.44	**0.31**	**0.21, 0.47**
Paternal refraction (dioptre)	0.9	0.81, 1.00	1.06	0.95, 1.18
Maternal refraction (dioptre)	0.95	0.84, 1.07	0.99	0.88, 1.13
Near work time (hour/day)	1.11	0.93, 1.33	1.05	0.83, 1.33
Outdoor time (hour/day)	0.97	0.80, 1.18	1.01	0.86, 1.19

DSE: difference between cycloplegic and non-cycloplegic autorefraction spherical equivalent
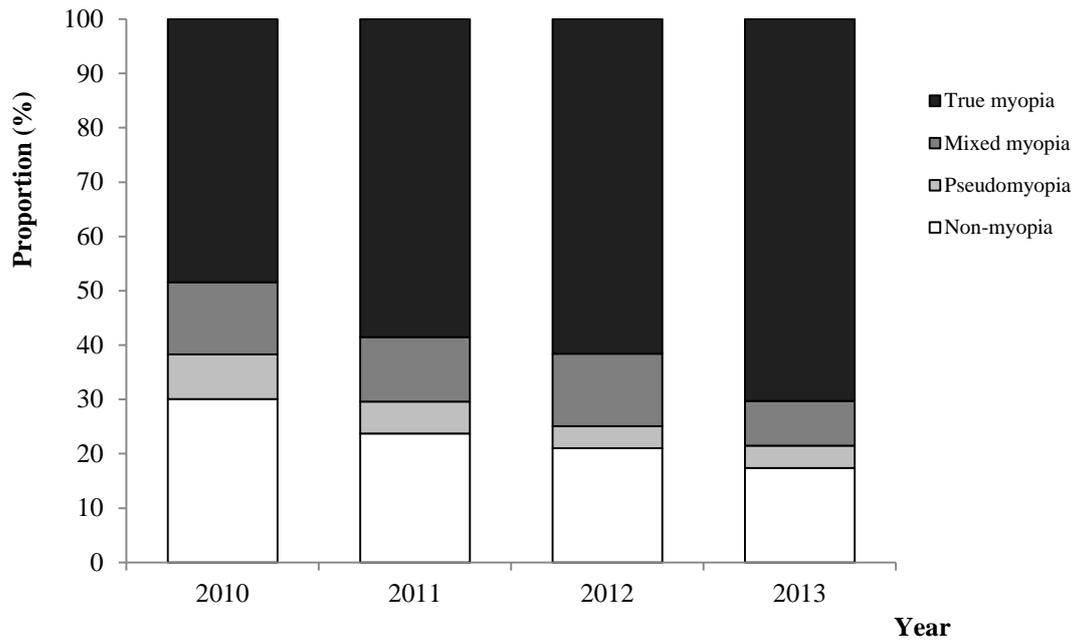
BOLD: significant factor

Figure 1a Distribution (proportion, %) of refractive status as a function of myopia (according to the Chinese Medical Association of Ophthalmology, Division of Refraction) at each examination year.

Non-myopia: i.e. emmetropia or hyperopia, both non-cycloplegic refraction and cycloplegic refraction ≥-0.50D; pseudomyopia: non-cycloplegic refraction < -0.50D and cycloplegic refraction ≥-0.50D; mixed myopia: cycloplegic refraction <-0.50D and excessive accommodation≥0.50D; true myopia: cycloplegic refraction <-0.50D and excessive accommodation<0.50D.
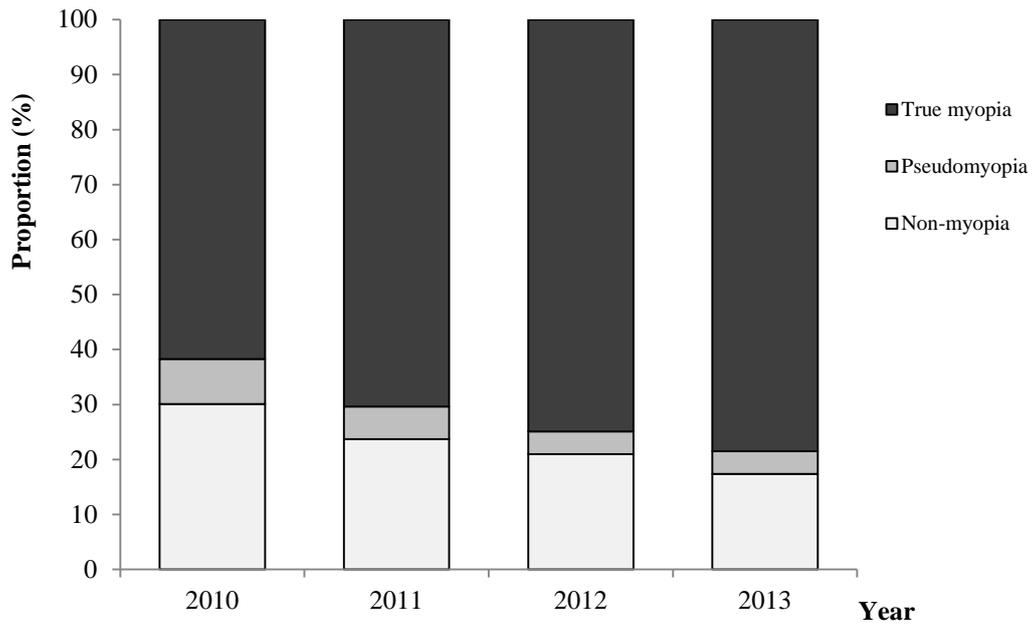
Figure 1b Distribution (proportion, %) of refractive status as a function of myopia at each examination year. Non-myopia: i.g. emmetropia or hyperopia, both non-cycloplegic refraction and cycloplegic refraction ≥-0.50D; pseudomyopia: non-cycloplegic refraction < -0.50D and cycloplegic refraction ≥-0.50D; true myopia: both non-cycloplegic refraction and cycloplegic refraction <-0.50D.