

Practical applications to modify and control the development of ametropia

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Abstract

For many individuals, the developmental trend of lessening hyperopia from birth continues past emmetropia towards myopia during childhood. The global pattern for prevalence of refractive errors indicates that the prevalence of hyperopia is low; in contrast, the burden of myopia is on the rise because of rising prevalence and magnitude of myopia. This review highlights the need to lessen the global burden of myopia by intervening with the development and/or slowing the progression of myopia. Further, outcomes from human clinical trials of pharmaceutical, optical, and environmental approaches to control myopia will be summarised. Pharmaceutical treatments are effective in controlling eye growth but are associated with deleterious side effects. Optical strategies that induce myopic defocus at the retina such as peripheral defocus reducing lenses, simultaneous defocus lenses, bifocals, and orthokeratology as well as environmental influences such as increased outdoor activity show promise and provide a substantially risk-free environment in which to control eye growth.

Eye (2014) 28, 134–141; doi:10.1038/eye.2013.255; published online 6 December 2013

Keywords: ametropia; hyperopia; optical intervention; myopia; myopic defocus

Background

The prevalence of ametropia (that is, mostly the refractive errors of myopia, hyperopia, and astigmatism) varies based on age and ethnicity,

and therefore it is difficult to accurately calculate the number of those affected worldwide. However, proceeding with the understanding that those with significant ametropias are likely to have poor vision, it was estimated that in the year 2003, there were more than 2.3 billion people worldwide (37% of world's population) that were suffering from poor vision due to refractive error.¹ Of the ametropias, hyperopia is the routinely observed refractive error in neonates with a trend towards lessening hyperopia in the first few years of life. Table 1 details the prevalence of hyperopia over 2.0 D across various populations from 5 years of age. The global pattern indicates that by age 12–15, the prevalence of the condition has fallen off substantially to low levels.^{2–12} Although moderate-to-high hyperopia may coexist with strabismus⁵ and associated with the risk of developing amblyopia⁵ or angle closure glaucoma in later life, it appears that, given the relatively low prevalence of the condition, there is a paucity of information relating to the condition and its risk factors, and thus strategies to modify and control hyperopia have been limited. There exist claims in the patent literature for modifying or preventing hyperopia with, for example, use of filters, dual focus or diffractive lenses, use of TGF- β activation inhibitor, administration of GABA receptor agonists or antagonists, and by limiting the amount of spherical aberration of the eye to less than +0.50 D; however, there have been no reports or data from human clinical studies that have considered these strategies.^{13–17}

Astigmatism is generally seen to coexist with other refractive errors but the prevalence appears to vary widely in children aged 5–15 years. (Table 2).^{2–4,6–8,10–12,18,19} Although there

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Received: 30 September 2013

Accepted: 10 October 2013

Published online: 6 December 2013

The subject of this article was presented at the 2013 Cambridge Ophthalmological Symposium held at Cambridge 12–13 September 2013.

Table 1 Prevalence of hyperopia ($\geq +2.0$ D)

Authors	Region	Age group (years)	Prevalence of hyperopia
He <i>et al</i> ²	Urban China	5	16.7%
		15	<1%
He <i>et al</i> ¹⁰	Rural China	15	1.5%
Murthy <i>et al</i> ³	Urban India	5	15.6%
		15	10.8%
Dandona <i>et al</i> ¹¹	Rural India	7	0.7%
		15	1.2%
		15	1.2%
Fan <i>et al</i> ⁴	Hong Kong	5–16	4.0%
Ip <i>et al</i> ⁵	Australia	6	13.2%
		12	5.0%
Goh <i>et al</i> ⁶	Malaysia	7	3.8%
		15	1%
Naidoo <i>et al</i> ⁷	South Africa	6	2.4%
		12	3.2%
		15	0.7%
Maul <i>et al</i> ⁸	Chile	5–7	21.6%
		14–15	7.5%
Zadnik <i>et al</i> ⁹ ($\geq +1.25$ D)	USA	10 \pm 2.3	8.6%
Sapkota <i>et al</i> ¹²	Urban Nepal	10	1.0%
		15	0.6%

are suggestions that astigmatism especially ‘against-the-rule’, might have a role in development of myopia,²⁰ studies on this relationship have been equivocal.^{21,22}

Significantly, the evolutionary trend with age towards lessening hyperopia or increasing myopia continues for many during childhood with an increasing number of children becoming myopic with each passing year. As discussed in later sections of the article, there is high prevalence of myopia in many parts of the world and for those affected, myopia generally progresses or increases in magnitude each year during childhood before possibly stabilising in late adolescent years. This increasing magnitude of myopia increases the risk of developing further disorders, some of which are sight threatening.

As it appears that the burden of ametropia is mostly due to myopia, this article explores the need for controlling or modifying the development and progression of myopia and the attempts that have been made to date in controlling childhood.

Why control myopia?

It may be argued that the transition of the human society from an outdoor-oriented, hunter-gatherer-farming society to more indoor-oriented, technology, and desk-based society in the modern world obviates the need for clear distance vision and shifts the focus to more intermediate and near vision. The rural-urban divide in the prevalence of myopia, the intergenerational shift towards increasing prevalence of myopia provides support for this adaptive process.^{2,3,10,11,23} However,

Table 2 Prevalence of astigmatism (≥ 0.75 D, auto refraction values where provided)

Authors	Region	Age group (years)	Prevalence of astigmatism
He <i>et al</i> ²	Urban China	5–15	42.7% (either eye)
He <i>et al</i> ¹⁰	Rural China	13	21.6%
		14	24.8%
		15	25.8%
		16	24.8%
Murthy <i>et al</i> ³	Urban India	5	14.6% (either eye)
		15	14.6% (either eye)
Dandona <i>et al</i> ¹¹	Rural India	7–15	9.7% (either eye)
Fan <i>et al</i> ⁴	Hong Kong	5–16	
Huynh <i>et al</i> ¹⁸	Australia	6	4.8% (right eye)
		12	6.7% (right eye)
Goh <i>et al</i> ⁶	Malaysia	7–15	21.3% (either eye)
Naidoo <i>et al</i> ⁷	South Africa	6–15	14.6% (either eye)
Maul <i>et al</i> ⁸	Chile	5–15	27% (either eye)
Salomão <i>et al</i> ¹⁹	Brazil	11–14	4.6% (right eye)
Sapkota <i>et al</i> ¹²	Nepal	10–15	7.4% (either eye)

alarmingly, this myopic shift appears to be insidious in its development and progression. The prevalence of the condition has reached significant proportions in some East Asian countries, with nearly 80% of those aged 18 years and over myopic.^{2,24–26} The evidence for the rise in prevalence of myopia is compelling and is also evident in the Western population^{27,28} and suggests that in addition to increasing prevalence, there is a shift in recent decades to an earlier onset of myopia and increased prevalence of myopia at any given age comparable to that seen in previous generations resulting in a higher prevalence of highly myopic eyes. In a study of 395 children and their families, it was found that at the age of 11 years, the children’s refractive errors were similar to those of their parents and it was estimated that at 18 years of age, the children would be more myopic by ~ 2.0 D compared with their parent’s refractive error.²⁹ In a study involving randomly selected preschool children (age 4.6 ± 0.9 years), the prevalence of myopia in 1996–1997 was 2.3% but was 6.3% in 2006–2007.³⁰ Five nationwide myopia surveys conducted over a 20-year period in Taiwan showed a significant myopic shift in refraction from 1983 to 2000. In addition, the study also reported that in 1983, the age at which a myopic refraction was first registered was 11 years old and this shifted to 8 years old in 2000.²⁴ This trend towards an earlier onset and a more myopic refraction appears to be associated with a concomitant rise in the prevalence of high myopia (> -6.0 D).²⁴

Each dioptre increase in myopia increases the risk of developing structural changes at the retina and optic disc, and the risk of developing sight-threatening eye disorders and high myopia is now a leading cause of

visual impairment and blindness in many countries across Asia.^{31–33} In addition, these highly myopic eyes are likely to experience reduced visual performance due to spectacle minification and reduced neural sampling density associated with retinal stretching.^{34,35} Cone photoreceptor packing density (cells per square millimetre) was shown to be significantly lower in myopic eyes than in emmetropic eyes.³⁶

Thus, there is an urgent need to intervene with both development and/or progression of myopia to reduce the burden and prevent the pathological consequences associated with high levels of myopia.

Figure 1 provides the annual and estimated progression data for 508 spectacle wearers of mostly Asian ethnicity (data from Guangzhou, China, Hong Kong, and Singapore) aged 6–16 years. These data indicate that the younger the onset of myopia, the greater the annual progression and greater the risk of having high levels of myopia. An intervention that can delay the onset of myopia by 1 or 2 years can significantly delay or prevent the eye from reaching –6.0 D or more of myopia.

Using the estimated progression data, it can be seen that a 6-year old with –1.0 D myopia is likely to reach –6.0 D at 12.9 years of age and –7.0 D at 14.6 years of age (Figure 2). Using these estimates, an intervention that can slow the rate of progress by 30% delays the age at which the eye reaches –6.0 D to past 16 years of age. Assuming that the progression of the eye stabilises after 16 years, this eye is unlikely to become –7.0 D.

Myopia control strategies

Commonly used optical devices such as spectacles and contact lenses employ the use of concave lenses to correct for the refractive error and restore normal

vision but do not counter the mechanism driving the axial length increase that effects the increase in myopia.

Although both genetic and environmental factors appear to have a role in the development and progression of myopia, the overwhelming evidence that ocular growth can be modulated by environmental influences, for example, form deprivation and optical defocus models, has provided avenues for strategies to modify myopia.

In addition, over the years, a number of interventions have been trialled to delay the onset or slowing the progression of myopia in humans. Table 3 lists the results from human clinical trials with interventions mainly aimed at slowing the progress of myopia. Each of the strategies are further explored in the section below.

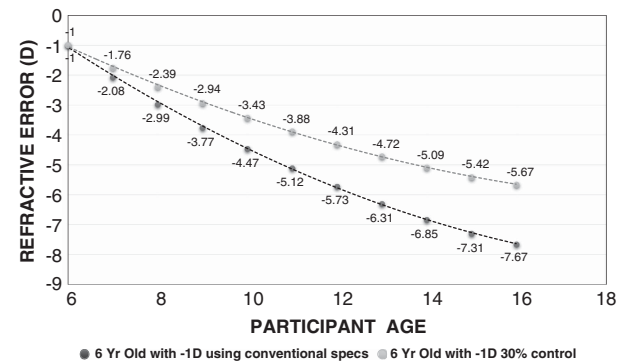


Figure 2 Estimated refractive error progression for a 6-year old with conventional correction and a myopia control strategy with 30% slowing of progression.

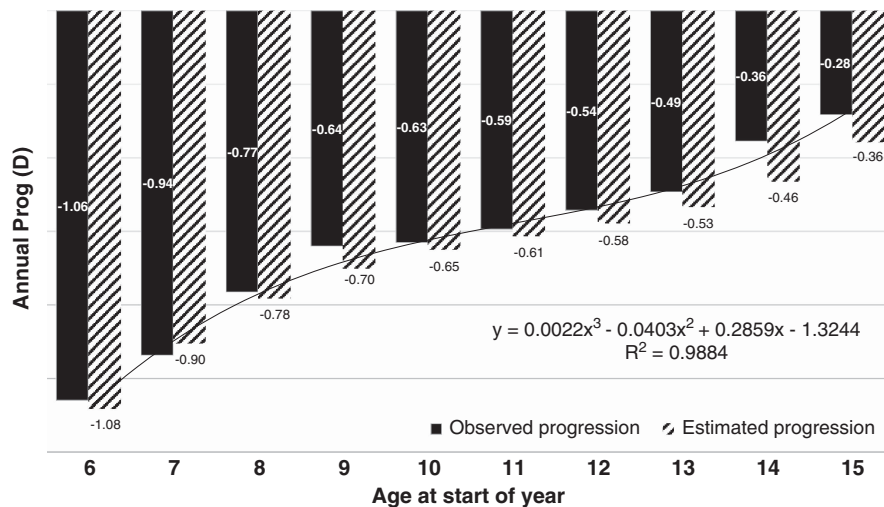


Figure 1 Annual progression data (observed and estimated) for children with myopia aged 6–12 years.

Table 3 Myopia control strategies in human clinical studies (randomised or comparative studies)

Authors	Intervention	Control group	Progression(test vs control D)	% Slowing of myopia progression
Wu <i>et al</i> ⁴⁵	Outdoor activity- 80 min per day	Yes	-0.25 vs -0.38 D	34% (1 year)
Morgan <i>et al</i> ⁴⁶	Outdoor activity- 60 min per day	Yes	-0.75 ± 0.69 vs -0.86 ± 0.77 D	15% (2 years)
Chung <i>et al</i> ⁴⁷	Undercorrection +0.75 D	Fully corrected SPL	-1.00 ± 0.33 vs -0.77 ± 0.33 D	Worsening myopia 29% (1 year)
Adler and Millidot ⁴⁸	Undercorrection +0.50 D	Fully corrected SPL	-0.99 ± 0.35 vs -0.82 ± 0.38 D	Worsening myopia 20% (1 year)
Yang <i>et al</i> ⁵⁵	PAL +1.50 D	Single-vision SPL	-1.24 ± 0.56 vs -1.50 ± 0.67 D	17% (2 years)
COMET 2 ⁵⁸	PAL +2.00 D	Single-vision SPL	-0.87 vs -1.15 D	24% (3 years)
Gwiazda <i>et al</i> ⁵⁴	PAL +2.00 D	Single-vision SPL	-1.28 ± 0.06 vs -1.48 ± 0.06 D	14% (3 years)
Hasebe <i>et al</i> ⁵⁶	PAL +1.50 D	Single-vision SPL	-0.89 ± 0.06 vs -1.20 ± 0.08 D	26% (18 months)
Edwards <i>et al</i> ⁵⁷	PAL +1.50 D	Single-vision SPL	-1.12 ± 0.67 vs -1.26 ± 0.74 D	11% (2 years)
Cheng <i>et al</i> ⁵⁹	Exec bifocal +1.50 D	Single-vision SPL	-0.96 ± 0.09 (B/F) vs	38% (B/F)
	Exec bifocal +1.50 D and 3Δ D		-0.70 ± 0.10 (B/FwithΔ) vs	56% (B/F with Δ) 2 years
Fulk <i>et al</i> ⁵⁰	Base in		-1.55 ± 0.12 D	
	Bifocal spectacles	Single-vision SPL	-0.99 ± 0.68 vs -1.24 ± 0.65 D	20% (2.5 years)
Chua <i>et al</i> ⁷²	1% atropine	Placebo treated	-0.28 ± 0.92 vs	72% (2 years)
			-1.20 ± 0.69 D	
Chia <i>et al</i> ⁷³	0.5, 0.1, 0.01 atropine	No	-0.30 ± 0.60 D (0.5%)	—
			-0.38 ± 0.60 D (0.1%)	
			-0.49 ± 0.63 D (0.01%)	
Tan <i>et al</i> ⁶⁶	2% gel twice daily	Placebo treated	-0.47 D (gel/gel)	44% (1 year)
	2% gel once daily, once		-0.70 D (gel/placebo)	17%
	Placebo; placebo twice daily		-0.84 D (placebo/placebo)	
Siatkowski <i>et al</i> ⁶⁵	Pirenzepine 2%	Placebo treated	-0.58 vs -0.99 D	41% (2 years)
Sankaridurg <i>et al</i> ⁶⁸	Novel designs I, II, III	Single-vision SPL	-0.81 ± 0.43 (I) vs	15% (1 yr, Lens III)
			-0.81 ± 0.46 (II) vs	
			-0.66 ± 0.41 (III) vs	
			-0.78 ± 0.50 D (control)	
Sankaridurg <i>et al</i> ⁶⁹	Novel contact lens design	Single-vision SPL	-0.57 ± 0.33 vs -0.84 ± 0.47 D	34% (1 year)
Anstice and Phillips ⁷¹	Dual focus lens +2.0 D	Single-vision CL	-0.44 ± 0.33 vs -0.69 ± 0.38 D	36% (10 months)

Abbreviations: CL, contact lens; SPL, spectacle.

Outdoor activity

It has been long held that near-work activity is associated with myopia, and recent epidemiological evidence indicates that outdoor activity, rather than indoor activity, appears to be protective for development of myopia.^{37–39} In addition, it appears that progression of myopia might be slower in summer months compared with other months^{40,41} indicating a possible protective role for light, and some preliminary work with animal models has shown that bright light can prevent the development of form deprivation myopia.^{42,43} Although the exact mechanism by which outdoor activity mediates development and progression of refractive errors remains unclear, elevation of retinal dopamine activity, reduced accommodative response, and spectral composition of light have been suggested as possible factors.⁴⁴ Although it is not clear from the above that outdoor activity *per se* influences the progression of myopia, clinical trials have been undertaken to determine whether outdoor activity reduces the progression of myopia.^{45,46} Table 1 summarises the

results from two clinical studies. Although both report a difference in the progression of myopia with improved outdoor activity of as little as 60–80 min, the dioptric difference at the end of the treatment period was <0.25 D and not of clinical relevance. However, of interest is the finding of a decrease in the number of new myopes during the study period. After 1 year, in the study by Wu *et al*,⁴⁵ prevalence of new myopia was 8.4% in the group randomised to outdoor activity compared with 17.7% in the control group. In the other study³⁹ at 2 years, the prevalence of myopia was 25.2% in the group randomised to outdoor activity compared with 20.7% in the control group.

Undercorrection

Undercorrection of myopia is a widely practiced procedure that has been in use for many years. The objective of undercorrection is to achieve (a) the goal of myopic defocus, which in animal models has demonstrated a reduction in progression of myopia and

(b) a reduction of stress on accommodation in near-point environments. However, data from prospective clinical trials suggest that the procedure may, in fact, result in acceleration of the progression of myopia (Table 1). Chung *et al*⁴⁷ showed that undercorrection of myopia by ~ 0.75 D compared with full correction actually worsened myopia by 0.23 D over a period of 2 years.⁴⁷ Similar results were seen in a later study wherein eyes that were undercorrected by 0.50 D showed an increase in myopic progression compared with those who were fully corrected.⁴⁸

Bifocal and progressive addition spectacles

Bifocal spectacles are another of the earliest procedures aimed at controlling the progression of myopia. The rationale of the approach is to reduce accommodative stress at near point. Indeed, myopic eyes are said to have greater lag of accommodation compared with non-myopic eyes with resultant hyperopic defocus at near.⁴⁹ Clinical trials were conducted using bifocal spectacles^{50–52} with an aim to reduce the accommodative demand but the results were equivocal with some studies showing benefit and others reporting no significant difference. It was suggested that poor compliance and/or improper alignment of the spectacles might have confounded results. In 1999, progressive addition spectacles (PALs) were suggested as an alternative, as they allow clear vision at all working distances while maintaining the ability to reduce accommodative demand. Although an initial trial found PALs to slow the progress of myopia significantly in comparison with single-vision spectacles,⁵³ a large, prospective, multicentre trial conducted in the United States (COMET study) found that the difference in terms of dioptric values between eyes wearing PALs and single-vision spectacles was too small to be of any clinical significance.⁵⁴ Other studies found similar results with a small difference between PAL and conventional lenses.^{55–57} Similarly, a more recent trial involving high-risk groups that is, children with high accommodative lags and near-point esophoria also failed to produce any significant benefits.⁵⁸ A more recent trial involving children with myopia randomised to wear single-vision spectacles or executive bifocals with +1.50 D add or +1.50 D add with 3Δ base in prism found that over a period of 24 months, myopia progression was on average -1.55 D for those wearing single-vision spectacles, -0.96 D for those with executive bifocals, and -0.70 D for those with executive bifocals with base in prisms.⁵⁹ Although the spherical equivalent data showed a greater benefit with executive bifocals incorporating prisms, axial length change showed similar changes with and without prisms (0.62 mm increase with single vision *vs* 0.41 mm with

bifocals and 0.41 mm with bifocals and prism). Even after taking into account the differences in efficacy for axial length and spherical equivalent measures, the slowing of progression is substantial and of significance. The reasons for these results remain unclear but could possibly be attributed to factors such as improved effect because of the larger segment size of the bifocal and the plus segment imposing myopic defocus on the peripheral retina. In addition, the use of bifocal contact lenses has also been investigated and found to be effective in slowing the progression of myopia.⁶⁰

Pharmaceutical agents—atropine and pirenzepine

The initial premise for using atropine was its ability to reduce the accommodative effort. In clinical studies, atropine 1% was found to be quite effective in retarding progression of myopia in children⁶¹ but the side effects and inconvenience associated with its long-term use has limited its uptake, especially in Western countries. In addition, rebound of myopia was found to occur upon discontinuation of the drug.⁶² However, in countries such as Taiwan, where the prevalence of myopia is in epidemic proportions with a lack of alternatives to stem the tide, the use of atropine is popular and on the rise.⁶² More recent studies with low-dose atropine of 0.5, 0.1, and 0.01% show mean progression of myopia at 2 years to be -0.30 ± 0.60 , -0.38 ± 0.60 , and -0.49 ± 0.63 D with the above doses compared with -0.28 ± 0.92 with atropine 1% and -1.20 ± 0.69 D with a placebo group.⁶³ Yet, it remains to be seen whether rebound also occurs with low doses. Atropine prevents myopia in a chick model that incorporates a striated ciliary muscle innervated by nicotinic receptors rather than muscarinic receptors. This, therefore, suggests that the mechanism of action is likely to be non-accommodative, possibly affecting the retina and/or sclera.⁶⁴

In addition to atropine, pirenzepine a selective M₁ receptor antagonist was evaluated in clinical trials as it was considered less likely to induce mydriasis and cycloplegia. Pirenzepine was effective in reducing the progression (see Table 1); however, pirenzepine is not yet commercially available.^{65,66}

Peripheral retinal defocus

There is accumulating evidence for the role of the peripheral retina and peripheral vision in the development and progression of refractive errors. Primate studies⁵⁹ indicate that form deprivation at the peripheral retina produced axial myopia despite of clear vision at the fovea and foveal ablation did not disrupt the emmetropization process.⁶⁷ Specifically, human myopic eyes were found to have hyperopic defocus at the

peripheral retina relative to the centre, and the presence of continuing hyperopic retinal defocus at the periphery with conventional corrective devices has been thought to influence progression. Human clinical trials with treatment strategies aimed at reducing the peripheral retinal hyperopic defocus show that it may be possible to slow the progression of myopia. After 12 months of spectacle lens wear, progression of myopia with a rotationally asymmetrical novel spectacle lens was not significant with all myopia. However, for children aged 6–12 years whose parents are myopic, spectacle wear was found to reduce the progression of myopia significantly when higher rates of progression were evident.⁶⁸ Similarly, the rate of progression of myopia was reduced by ~30% in eyes wearing contact lenses designed to reduce hyperopic defocus compared with single-vision spectacles.⁶⁹ Also of interest, orthokeratology has also been found to be effective in reducing progression of myopia, and it has been suggested that the underlying mechanism involves reduction in peripheral hyperopic defocus. One 5 year study found an increase in axial length of 0.99 ± 0.47 and 1.41 ± 0.68 mm for orthokeratology groups and a control group of spectacle lens wearers and indicates a significant slowing of ocular growth with orthokeratology.⁷⁰

Simultaneous defocus

The rationale for simultaneous defocus is that, in addition to having a clear image on the retina, simultaneously having another image in myopic defocus serves as a signal to confuse and stop, or delay, eye growth. In a prospective, contralateral clinical study, one eye of each participant wore a dual focus contact lens with +2.0D of myopic defocus for 10 months, whereas the other eye wore a single-vision contact lens. After 10 months, there was a significant slowing of myopia in the eyes that wore dual focus lenses (average of -0.44 D progression in the dual focus lens-wearing eye *vs* -0.69 D in the control lens-wearing eye).⁷¹

Conclusions

Clearly, there is a need to control the progression of myopia to prevent or limit the morbidity associated with rising myopia. Although a number of approaches have been explored to control myopia, many of these are directed at slowing the progress of myopia rather than delaying the onset of myopia. Although the pharmaceutical agents are able to slow the progress significantly, problems associated with their use have limited their implementation. At the present time, of the optical strategies, contact lenses that induce myopic defocus (peripheral retinal defocus reducing lenses,

simultaneous defocus lenses, and orthokeratology) appear to be superior in slowing the progress compared with spectacles but this might simply be related to close alignment of the contact lens with the eye, thus eliminating the possibility of aberrations with eye movements and also ensuring constant delivery of stimulus for as long as the lens is worn. Although these results need validation and also longer-term data, overall, the optical strategies appear to operate in an environment with minimal to nil risk compared with drugs and thus can be considered for incorporation into day-to-day practice. In addition, although the role of outdoor activity in the onset and progression of myopia needs further exploration, the use of environmental influences is an exciting and promising avenue in the quest to reduce the rate of progression of myopia.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

The work is supported by grants from the Australian Federal Government through the CRC scheme and the Brien Holden Vision Institute.

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