REVIEW

Current approaches to myopia control

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Purpose of review
Myopia is a global problem, being particularly prevalent in the urban areas of east and southeast Asia. In addition to the direct economic and social burdens, associated ocular complications may lead to substantial vision loss. With prevalence of myopia above 80% and high myopia over 20%, it is crucial to control myopia. The aim of this review to is provide an update on the interventions to slow the onset of myopia and retard its progression.

Recent findings
The epidemic of myopia is characterized by increasingly early onset, combined with high myopia progression rates. There are two pathways for myopia control: firstly to slow the onset of myopia and secondly to reduce or prevent progression. Increased time outdoors can reduce the onset of myopia. Atropine 0.01% dose offers an appropriate risk-benefit ratio, with no clinically significant visual side effects balanced against a significant 50% reduction in myopia progression. Orthokeratology contact lenses can slow axial length elongation, but infective keratitis is a risk. Peripheral defocussing lenses may both have a role in slowing myopic progression in a subset of children and further help our understanding of the physiologic control of ocular growth.

Summary
Myopia control can be achieved by slowing the onset of myopia, which now appears to be possible through increasing time outdoors and slowing the progression of myopia with interventions like atropine and orthokeratology.

Keywords
atropine eye drops, myopia, orthokeratology, outdoor

INTRODUCTION

Myopia is the most common human eye disorder in the world, affecting 85–90% of young adults in some Asian countries like Singapore and Taiwan, and 25–50% of older adults in the United States and Europe. Unlike Western populations, where the prevalence of myopia is low (<5%) in children, in Taiwan and Singapore, the prevalence is 20–30% among 6–7-year-olds and as high as 84% in high school students [1▪]. In 12-year-old children, the prevalence is 62.0% in Singapore and 49.7% in Guangzhou, China, compared with 20.0% in the United States, 11.9% in Australia, 9.7% in urban India, and 16.5% in Nepal [2–9]. With its increasing prevalence and earlier age of onset in recent birth cohorts, myopia now affects 33% of adults in the United States. Between 1999 and 2004, the prevalence of myopia was two-thirds higher than between 1971 and 1972 [10]. Its prevalence is increasing alarmingly in East Asia's developing economies and will affect 2.5 billion by 2020. The myopia progression rate in East Asian children is high [nearly − 1 diopter (D) per year], and approximately 24% of the myopic population become high myopes as adults [1▪].

PROBLEMS

Apart from the obvious socio-economic burden estimated at annual US$268 billion worldwide, myopia is a global public health concern [11]. Severe or high-grade myopia is a leading cause of blindness because of its associated comorbidities of retinal detachment, macular choroidal degeneration, premature cataract, and glaucoma [12–17]. The

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KEY POINTS

- The epidemic of myopia is characterized by increasingly early onset, combined with high myopia progression rates.
- There are two pathways for myopia control: firstly to slow the onset of myopia and secondly to reduce or prevent progression.
- Increased time outdoors can reduce the onset of myopia.
- Atropine 0.01% dose offers an appropriate risk-benefit ratio, with no clinically significant visual side effects balanced against a significant 50% reduction in myopia progression.
- Orthokeratology contact lenses can slow axial length elongation, but infective keratitis is a risk.

yearly incidence of retinal detachments had been estimated as 0.015% in patients with less than 4.74 D myopia, and increases to 0.07% in patients with myopia greater than or equal to 5 D and 3.2% in patients with myopia greater than or equal to 6 D [12,13]. Myopes also have increased risks of developing macular choroidal neovascularization, ranging from two times for patients with 1–2 D of myopia, four times with 3–4 D of myopia, and nine times for −5 to 6 D [14–16]. The Blue Mountains Eye Study showed that glaucoma was present in 4.2% of eyes with low myopia and 4.4% of eyes with moderate to high myopia [17]. Pathologic myopia is estimated to have a global prevalence of 0.9–3.1% and to be the cause of low vision in 5.8–7.8% in Europeans and 12.2–31.3% in East Asians [18]. Given the increasing prevalence of myopia in East Asia, where the prevalence of myopia in young adults now approaches 80% and high myopia rates exceed 20%, the disease burden and cost of pathologic myopia will continue to increase over time [19]. There are significant odds ratios (ORs) for myopic maculopathy, retinal detachment, cataracts, and glaucoma, even for low and moderate levels of myopia, and these ORs increase further with higher levels of myopia [20]. The epidemic of myopia is characterized by increasingly early onset, combined with high myopia progression rates. Early onset of myopia leaves more time for progression at higher rates and inevitably to higher myopia. It is therefore crucial to control myopia in children to prevent them from developing high myopia and associated visual impairment [21▪]. The aim of this review to is provide an update on the interventions to slow the onset of myopia and retard myopia progression.

GENETICS

Myopia is etiologically heterogeneous, with a low level of myopia of clearly genetic origins that appears without exposure to risk factors [22▪]. Ample evidence supports heritability of the non-syndromic forms of myopia, especially for high-grade myopia commonly referred to as myopic spherical refractive power of 5–6 D or higher [23]. Recent large genome-wide association studies (GWAS) have identified more than 20 associated loci for myopia [24]. However, the rise in prevalence of high myopia currently has an unusual pattern of development, with increases in prevalence first appearing at approximately age 11. This pattern suggests that the increasing prevalence of high myopia is because of progression of myopia in children who became myopic at approximately age 6 or 7, and age-specific progression rates typical of East Asia will take these children to the threshold for high myopia in 5–6 years. This high myopia seems to be acquired, whereas high myopia in previous generations tended to be genetic in origin [22▪].

OUTDOOR TIME

Recent epidemiological data have identified outdoor time as a key environmental determinant of myopia. In both Singaporean and Australian children, total time spent outdoors was associated with less myopia, independent of indoor activity, reading, and engagement in sports [25,26]. A comparative study of Chinese children in Singapore and Sydney also revealed a protective effect of outdoor activity [27,28]. The pooled OR for myopia indicated a 2% reduced odds of myopia per additional hour of time spent outdoors per week, after adjustment for covariates [29]. The Orinda study showed that higher levels of time outdoors/sports reduced the additional risk of myopia associated with having myopic parents, whereas Sydney Myopia Study showed that higher levels of time outdoors reduced the effects of increased amounts of near work [30,31]. Both studies provided evidence of threshold and saturation effects, and suggested that 2–3 h a day outdoors, outside of school hours, would provide considerable protection. Importantly, three clinical trials in East Asia concluded that increasing the amount of time that children spend outdoors is able to reduce the onset of myopia [32▪,33▪,34]. The mechanism of the protective effect is still uncertain. It has been proposed that bright light exposures outdoors during daylight hours (which easily reaches 10 000–100 000 lux or more) compared with typical low light intensities indoors (generally less than 1000 lux) might be the important factor, based

on two phenomena well documented in animal studies, namely, light stimulation of dopamine release from the retina and inhibition of axial elongation by dopamine agonists [35,36]. Ultraviolet exposure is also not important in protection against myopia onset. This means that increased time outdoors can be combined with skin and eye protection measures [22▪]. Although time outdoors slows the onset of myopia, it paradoxically does not seem to affect the progression of myopia, that is, the myopic shift in refraction seen in established myopes [30,37]. Both onset and progression depend on axial elongation, and it is not clear how axial elongation could be differentially regulated before and after onset.

NEAR WORK

Near work was found to be associated with myopia among American children in the Orinda Longitudinal Study of Myopia and Australian children the Sydney Myopia Study, but was not significantly associated with incident myopia in Singaporean children [38▪,39,40]. Even the results from more recent studies have been equivocal, with some studies showing positive findings, whereas others reported no relationship [3,41–48]. A recent meta-analysis found that more time spent on near work activities was associated with higher odds of myopia [OR 1.14, 95% confidence interval (CI) 1.08–1.20] and that the odds of myopia increased by 2% (OR 1.02, 95% CI 1.01–1.03) for every 1-diopter-h more of near work per week [49▪]. Increasing evidence suggests that the intensity of near work, that is, sustained reading at closer distance (less than 30 cm) with fewer breaks, may be more important than the total hours of near work [44–47]. It is important to note that the precise quantification of near work is difficult.

Interventions to retard the progression of myopia

Many interventions aimed at slowing myopia progression have been proposed. In the latest network meta-analysis by Huang *et al.* [50▪▪] that involved 30 RCTs to determine the effectiveness of different interventions in slowing down the progression of myopia in children, the authors found that the most effective intervention that showed a marked reduction in myopia progression was atropine, followed by pirenzepine, orthokeratology. Peripheral defocus–modifying contact lenses showed moderate effects and progressive addition spectacle lenses showed minimal effects [50▪▪].

Atropine eye drops

Atropine is a nonselective muscarinic antagonist. It was first used for myopia treatment by Wells in nineteenth century. Subsequent studies by various authors showed some clinical effect in slowing myopia progression in children [51–62]. Atropine inhibits myopia in tree shrew and monkey myopia models, and blocks from deprivation myopia or lens-induced myopia in chicks [63–65]. In contrast to the mammalian eye, the avian eye contains striated intraocular muscle and hence this indicates a nonaccommodative mechanism for antimyopia activity of atropine and via nicotinic pathway instead [65–69]. There are currently two theories to explain this: atropine functions at a relatively low dose via a neurochemical cascade, which begins at M1/4 receptors in the retina (possibly in amacrine cells); atropine has a direct effect on scleral fibroblasts by inhibiting glycosaminoglycans synthesis via a nonmuscarinic mechanism [70▪]. The Atropine for the Treatment of Myopia studies (ATOM1 and 2) were randomized, double-masked, placebo-controlled trials involving 400 Singapore children [71]. ATOM1 showed that 1% atropine eye drops instilled nightly in one eye over a 2-year period reduces myopic progression significantly by 77% (0.28 D in the control group versus 1.2 D in the atropine group) and reduced the axial length elongation (mean axial length increase of 0.39 mm in controls versus no growth in atropine group). The topical atropine was well tolerated. Multifocal electroretinogram testing at 2 or 3 months after cessation of treatment revealed no significant effect on retinal function [72]. Side effects of atropine 1% include photophobia due to mydriasis and decreased near vision due to cycloplegia. As a result, if atropine 1% is used in both eyes, the patient needs photochromatic, progressive additional lenses. The ATOM1 study reported no systemic side effects, although possibilities include dry eye, dry mouth, dry throat, flushed skin, constipation, and difficulty with micturition. Like the Amblyopia Treatment Studies (ATS), the ATOM1 study found that the paralysis of accommodation and the associated near vision blur secondary to atropine treatment was temporary and was reversible upon cessation of treatment [73,74]. ATOM1 established the clinical safety and efficacy of atropine 1%. ATOM2 studies were subsequently performed to evaluate lower concentrations of atropine. Phase 1 of ATOM2 established that atropine 0.01% was almost as effective in reducing myopia progression as higher concentrations. There seemed to be a dose-related response to atropine, with higher doses inhibiting myopia progression to a slightly greater degree than lower doses, although

the myopia progression of −0.49, −0.38, and −0.30 D in the atropine 0.01, 0.1, and 0.5% groups, respectively, were not significantly different at 24 months [75]. However, when atropine was stopped for 12 months after 24 months of treatment (phase 2 of ATOM2), there was a rapid increase in myopia in children originally treated with higher concentrations of atropine, whereas those receiving the lowest concentration of 0.01% showed minimal change [76]. This resulted in myopia progression being significantly lower in children previously assigned to the 0.01% group (−0.72 D) at 36 months compared with that in the 0.1% (−1.04 D) and 0.5% (−1.15 D) groups. In addition, the lowest dose also caused less photopic pupil dilation (0.74 mm, compared with 2.25 and 3.11 mm in the 0.1 and 0.5% groups, respectively) and no clinically significant loss in accommodation or near visual acuity (4.6 D, compared with 10.1 and 11.8 D in the 0.1 and 0.5% groups, respectively).Overall, there was a dose-related response in phase 1, with a greater effect in higher doses, but an inverse dose-related increase in myopia during phase 2 (washout), resulting in atropine 0.01% being most effective in reducing myopia progression at 3 years. In the final phase (phase 3), spanning the fourth and fifth years of the ATOM2 study, children who continued to progress (>0.5 D/year) during phase 2 (the washout year) were re-treated with atropine 0.01% [77▪]. Some 24, 59, and 68% of children originally in the atropine 0.01, 0.1, and 0.5% groups, respectively, who progressed in phase 2, were restarted on atropine 0.01%. Younger children and those with greater myopic progression in year 1 were more likely to require re-treatment. The lower myopia progression in the 0.01% group persisted during phase 3, with overall myopia progression and change in axial elongation at the end of 5 years being lowest in this group (−1.38D; 0.75 mm) compared with the 0.1% (−1..83 D, $P = 0.003$; 0.85 mm, $P = 0.144$) and 0.5% (−1.98 D, $P < 0.001$; 0.87 mm, $P = 0.075$) groups. Atropine 0.01% also caused minimal pupil dilation (0.8 mm), minimal loss of accommodation (2–3 D), and no near visual loss compared with higher doses. Children on atropine 0.01% did not need progressive additional lenses. Over 5 years, atropine 0.01% eye drops were more effective in slowing myopia progression by 50% with less visual side effects compared with higher doses of atropine. The efficacy of lower dose atropine is corroborated by Taiwanese cohort studies concluding that doses of 0.025–0.05% could be effective [78]. In a recent retrospective case-controlled study conducted in the United States, the authors similarly found that atropine 0.01% significantly reduced the rate of myopic progression with minimal adverse effects in a mostly white population [79]. However, there may be children who are poor responders to atropine. In ATOM1, 12.1% of children (younger, with higher myopia, and greater tendency of myopic progression) had myopia progression of by more than 0.5 D after 1 year of treatment with atropine 1% [80▪]. In phase1 of ATOM2, 9.3% of children in the 0.01% group, 6.4% of children in the 0.1% group, and 4.3% of children in the 0.5% group had myopia progression more than 1.5 D over 24 months. Further studies with a longer period of follow-up should be considered to evaluate the use of low-dose atropine in myopia control.

Pirenzepine

Topical pirenzepine 2% ophthalmic gel is a selective antimuscarinic (M1) agent that was used in two randomized controlled trials, which showed approximately 40% reduction in myopia progression with a corresponding reduction in axial length after 12 months of follow-up in patients who used pirenzepine gel twice a day [81,82]. Although it was thought that a more selective antimuscarinic agent would result in less cycloplegia, the authors noted that children receiving pirenzepine still encountered difficulties with accommodation and mild mydriasis. Further trials and registration of this drug were not pursued, and pirenzepine gel is no longer available.

Bifocals

Reports in animal studies suggest that increased retinal defocus is a factor in the pathogenesis of myopia [83–86]. In humans, high accommodative lag has been associated with myopia [86]. It was postulated that bifocals or multifocals could provide clear vision over a range of viewing distances, reduce retinal defocus, and slow the progression of myopia. However, randomized clinical trials in the United States, Finland, and Denmark showed no significant slowing of myopia [87–90]. The only promising results were reported by Cheng *et al.* [90–92] in a group of Chinese Canadian children, which found a 39% slowing of myopia progression for bifocal-only spectacles and 50% effect for bifocal spectacles with base-in prism, although there was not a significant difference in progression between the bifocal-only and bifocal and prism groups [93▪]

Progressive additional lenses

The use of progressive addition lenses (PALs) has produced relatively small treatment effects [94–96]. In particular, the correction of myopia evaluation

trial (COMET, a multicenter, randomized, double-masked clinical trial) concluded that the overall adjusted 3-year treatment effect of 0.20 ± 0.08 D was statistically significant ($P = 0.004$), but not clinically meaningful [94]. All the treatment effects occurred in the first year. Additional analyses showed that there were more significant treatment effects in children with larger lags of accommodation in combination with near esophoria (0.64 ± 0.21 D), shorter reading distances (0.44 ± 0.20 D), or lower baseline myopia (0.48 ± 0.15 D) [94,97]. Though statistically significant, these differences over a 3-year period are not clinically meaningful. The 3-year treatment effects decreased even further after 5 years [98].

Contact lenses

Randomized clinic trials showed that soft contact lenses and rigid gas permeable (RGP) lenses were not effective in retarding myopia progression [99–102]. In the Contact Lens and Myopia Progression (CLAMP) study, there was a statistically significant difference in myopia progression in the RGP lens versus soft lens group (-1.56 ± 0.95 D for RGP lens wearers versus -2.19 ± 0.89 D for the soft lens group; $P < 0.001$), with most of the treatment effects found in the first year. Corneal curvature steepened significantly less in the RGP lens group (0.62 ± 0.60 D) compared to the soft lens group (0.88 ± 0.57 D; $P = 0.01$) [103].Three-year axial elongation was not significantly different between treatment groups. These results suggest that the slowed myopia progression was mainly due to corneal flattening and not true slowing of myopia, which may be reversible with discontinuation of RGP lens wear.

Orthokeratology

In overnight orthokeratology – also known as OOK, OK, ortho-k, and corneal reshaping – the patient wears reverse geometry lenses overnight to temporarily flatten the cornea and provide clear vision during the day without any glasses or contact lenses [104]. Reduction in the myopia (up to -6 D) is achieved by central corneal epithelial thinning, midperipheral epithelial, and stromal thickening. More than one hundred cases of severe microbial keratitis related to orthokeratology have been reported since 2001[105]. Orthokeratology lenses slow axial length growth compared to single vision gas permeable contact lenses, single vision soft contact lenses, and single vision spectacles [106–115]. The first randomized clinical trial of orthokeratology myopia control demonstrated significantly slower mean axial elongation in children wearing orthokeratology lenses (0.36 ± 0.24 mm) than children wearing single vision spectacles (0.63 ± 0.26 mm; $P = 0.01$) [110]. These results were similar to other randomized clinical trials [108] Orthokeratology contact lenses correct central refractive error while leaving peripheral myopic blur, which may act as a putative cue to slow the progression of myopia [115]. A recent meta-analysis showed that of the seven eligible studies, myopic progression was reduced by approximately 45% after 2 years [116▪]. The latest study involving 14 participants concluded that a trend toward a reduction in the rate of axial elongation of the order of 33% was found in the orthokeratology group following 7 years of lens wear [117▪]. In summary, ortho-k results in an approximately 40% reduction in the progression of myopia. It has the advantage of eliminating the need for daytime of contact lenses wear. Its disadvantages include cost, risk of infection, discomfort, problems with insertion and removal, and reduced visual acuity as compared to glasses or daily wear contact lenses as the day progresses. There is no good, controlled, long-term study demonstrating sustained myopia control effect and there is no washout data.

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 studies 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 [113]. Although initial human studies involving mainly Caucasians found an association with relative peripheral hyperopia, defined as a more hyperopic peripheral refraction compared to the central refraction and central myopia, the Peripheral Refraction in Preschool Children (PREP) Study of Singaporean Chinese children and Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) study showed that relative peripheral hyperopia had little consistent influence on the risk of myopia onset, myopia progression, or axial elongation [118–123]. It is thought that relative peripheral hyperopia did not precede the onset of myopia, but rather occurred in parallel with axial elongation as the ocular shape changed from oblate to relatively more prolate. Among human clinical trials with treatment strategies aimed at reducing the peripheral retinal hyperopic defocus, there was no statistically significant differences in the rates of myopia progression between children who wore one of three novel spectacle lenses that decreased

relative peripheral hyperopia and those who wore the conventional single-vision spectacle lenses. However, for children aged 6–12 years, whose parents are myopic, one of the three spectacle lenses was found to reduce the progression of myopia significantly when higher rates of progression were evident [124]. Similarly, the rate of progression of myopia was reduced by approximately 30% in eyes wearing contact lenses designed to reduce hyperopic defocus compared with single-vision spectacles [125]. Interestingly, the underlying mechanism of orthokeratology for retardation of myopia progression involves reduction in peripheral hyperopic defocus [113].

Undercorrection

The objectives of undercorrection were to achieve myopic defocus, which demonstrated a reduction in progression of myopia in animal models, and to reduce the stress on accommodation in near-point environments. However, data from prospective clinical trials suggest that undercorrection of myopia in humans either increases or has no effect on myopia progression [126,127]. Undercorrection should not be advocated.

Part-time lens wear

Preliminary data of 43 patients suggest that there is no effect of the pattern of lens wear on the progression of myopia. Three-year refractive shifts were not significantly different among the four groups: fulltime wearers; myopes who switched from distance to full-time wear; distance wearers; and non-wearers [128]. A randomized clinical trial using a large sample of children randomly assigned to a lens wear regimen is warranted.

CONCLUSION

The current studies demonstrate the importance of environmental influences (particularly increased outdoor time), which may be important precipitant of myopia onset, and the advice to parents is to increase their children's outdoor time. Atropine 0.01% dose appears to have a good risk-benefit ratio, with no clinically significant visual side effects balanced against a reasonable and clinically significant 50% reduction in myopia progression. Further studies could explore if there is still a role for high-dose atropine (e.g. for rapid progressors) and the additive effect of combining atropine with other emerging myopia therapies (e.g. orthokeratology, peripheral defocus lenses) and environmental interventions (e.g. increased outdoor time). Orthokeratology contact lenses also appear to slow axial length elongation by approximately 40%, but care needs to be taken to ensure there is minimal risk of corneal-related problems. In both interventions, longer-term studies may help demonstrate how and when the intervention can be stopped, and ensure there are no long-term adverse effects.

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- ■ of special interest
- ■■ of outstanding interest

1. Wu PC, Huang HM, Yu HJ, *et al.* Epidemiology of myopia. Asia Pac J ■ Ophthalmol 2016; 5:386–393.

This article gives an update of the epidemiology of myopia.

2. Saw SM, Shankar A, Tan SB, *et al.* A cohort study of incident myopia in Singaporean children. Invest Ophthalmol Vis Sci 2006; 47:1839–1844.
3. Saw SM, Tong L, Chua WH, *et al.* Incidence and progression of myopia in Singaporean school children. Invest Ophthalmol Vis Sci 2005; 46:51–57.
4. He M, Huang W, Zheng Y, *et al.* Refractive error and visual impairment in school children in rural southern China. Am J Ophthalmol 2000; 129:427–435.
5. Zadnik K. The Glenn A. Fry award lecture. Myopia development in childhood. Optom Vis Sci 1997; 74:603–608.
6. Ip JM, Huynh SC, Robaei D, *et al.* Ethnic differences in refraction and ocular biometry in population-based sample of 11-15 year old Australian children. Eye 2008; 22:649–656.
7. Dandona R, Dandona L, Srinivas M, *et al.* Refractive error in children in a rural population in India. Invest Ophthalmol Vis Sci 2002; 43:615–622.
8. Murthy GV, Gupta SK, Ellwein LB, *et al.* Refractive error in children in an urban population in New Delhi. Invest Ophthalmol Vis Sci 2002; 43:623–631.
9. Pokharel GP, Negrel AD, Munoz SR, *et al.* Refractive error study in children: results from Mechi Zone, Nepal. Am J Ophthalmol 2000; 129:436–444.
10. Vitale S, Ellwein L, Cotch MF, *et al.* Prevalence of refractive error in the United States, 1999-2004. Arch Ophthalmol 2008; 126:1111–1119.
11. Kempen JH, Mitchell P, Lee KE, *et al.* The prevalence of refractive errors among adults in the United States, Western Europe, and Australia. Arch Ophthalmol 2004; 122:495–505.
12. Arevalo JF, Ramirez E, Suarez E, *et al.* Rhegmatogenous retinal detachment after laser-assisted in situ keratomileusis (LASIK) for the correction of myopia. Retina 2000; 20:338–341.
13. Arevalo JF, Azar-Arevalo O. Retinal detachment in myopic eyes after laser in situ keratomileusis. Am J Ophthalmol 2000; 129:825–826.
14. Avila MP, Weiter JJ, Jalkh AE, *et al.* Natural history of choroidal neovascularization in degenerative myopia. Ophthalmology 1984; 91:1573–1581.
15. Steidl SM, Pruett RC. Macular complications associated with posterior staphyloma. Am J Ophthalmol 1997; 123:181–187.

16. Vongphanit J, Mitchell P, Wang JJ. Prevalence and progression of myopic retinopathy in an older population. Ophthalmology 2002; 109:704–711.
17. Mitchell P, Hourihan F, Sandbach J, *et al.* The relationship between glaucoma and myopia: the Blue Mountains Eye Study. Ophthalmology 1999; 106:2010–2015.
18. Hayashi K, Ohno-Matsui K, Shimada N, *et al.* Long-term pattern of progression of myopic maculopathy: a natural history study. Ophthalmology 2010; 117:1595–1611.
19. Wong TY, Ferreira A, Hughes R, *et al.* Epidemiology and disease burden of pathological myopia and myopic choroidal neovascularization: an evidence-based systemic review. Am J Ophthalmol 2014; 157:9–25.
20. Flitcroft DI. The complex interactions of retinal, optical and environmental factors in myopia aetiology. Prog Retin Eye Res 2012; 31:622–660.
21. ■ Morgan IG, He M, Rose KA. Epidemic of pathologic myopia: what can laboratory studies and epidemiology tell us? Retina 2016. [Epub ahead of print]

This article is a systematic review of epidemiologic and laboratory studies on the cause of high myopia and its links to pathologic myopia.

22. ■ Rose KA, French AN, Morgan IG. Environmental factors and myopia: paradoxes and prospects for prevention. Asia Pac J Ophthalmol 2016; 5:403–410.

This is a review of the environmental factors that can be modified to reduce the onset of myopia.

23. Young TL, Metlapally R, Shay A. Complex trait genetics of refractive error. Arch Ophthalmol 2007; 125:38–48.
24. Cooke Bailey JN, Sobrin L, Pericak-Vance MA, *et al.* Advances in the genomics of common eye diseases. Hum Mol Genet 2013; 22 (R1):R59–R65.
25. Saw SM, Chua WH, Hong CY, *et al.* Near-work in early-onset myopia. Invest Ophthalmol Vis Sci 2002; 43:332–339.
26. Rose KA, Morgan IG, Ip J, *et al.* Outdoor activity reduces the prevalence of myopia in children. Ophthalmology 2008; 115:1279–1285.
27. Rose KA, Morgan IG, Smith W, *et al.* Myopia, lifestyle, and schooling in students of Chinese ethnicity in Singapore and Sydney. Arch Ophthalmol 2008; 126:527–530.
28. Dirani M, Tong L, Gazzard G, *et al.* Outdoor activity and myopia in Singapore teenage children. Br J Ophthalmol 2009; 93:997–1000.
29. Sherwin JC, Reacher MH, Keogh RH, *et al.* The association between time spent outdoors and myopia in children and adolescents: a systematic review and meta-analysis. Ophthalmol 2012; 119:2141–2151.
30. Jones-Jordan LA, Sinnott LT, Cotter SA, *et al.* Time outdoors, visual activity, and myopia progression in juvenile onset myopes. Invest Ophthalmol Vis Sci 2012; 53:7169–7175.
31. French AN, Morgan IG, Mitchell P, *et al.* Risk factors for incident myopia in Australian schoolchildren: the Sydney adolescent vascular and eye study. Ophthalmology 2013; 120:2100–2108.
32. ■ He M, Xiang F, Zeng Y, *et al.* Effect of time spent outdoors at school on the development of myopia among children in China: a randomized clinical trial. J Am Med Assoc 2015; 314:1142–1148.

This article assessed the efficacy of increasing time spent outdoors at school in preventing incident myopia. It showed that among 6-year-old children in Guangzhou, China, the addition of 40 min of outdoor activity at school compared with usual activity resulted in a reduced incidence rate of myopia over the next 3 years.

33. ■ Jin JX, Hua WJ, Jiang X, *et al.* Effect of outdoor activity on myopia onset and progression in school-aged children in northeast China: the Sujiatun Eye Care Study. BMC Ophthalmol 2015; 15:73.

This study looked at the impact on myopia development of a school-based intervention program aimed at increasing the time student spent outdoors in 3051 students in a year. It concluded that increasing outdoor activities prevented myopia onset and development, as well as axial growth and elevated IOP in children.

34. Wu PC, Tsai CL, Wu HL, *et al.* Outdoor activity during class recess reduces myopia onset and progression in school children. Ophthalmology 2013; 120:1080–1085.
35. Feldkaemper M, Schaeffel F. An updated view on the role of dopamine in myopia. Exp Eye Res 2013; 114:106–119.
36. Witkovsky P. Dopamine and retinal function. Doc Ophthalmol 2004; 108:17–40.
37. French AN, Morgan IG, Burlutsky G, *et al.* Prevalence and 5- to 6-year incidence and progression of myopia and hyperopia in Australian schoolchildren. Ophthalmology 2013; 120:1482–1491.
38. ■ Ramamurthy D, Lin Chua SY, Saw SM. A review of environmental risk factors for myopia during early life, childhood and adolescence. Clin Exp Optom 2015; 98:497–506.

This review summarizes the possible underlying biological mechanisms for the protective association between time outdoors and myopia, including the potential role of nicotinic acetylcholine receptors in refractive error development.

39. Mutti DO, Mitchell GL, Moeschberger ML, *et al.* Parental myopia, near work, school achievement and children's refractive error. Invest Ophthalmol Vis Sci 2002; 43:3633–3640.
40. Saw SM, Shankar A, Tan SB, *et al.* A cohort study of incident myopia in Singaporean children. Invest Ophthalmol Vis Sci 2006; 47:1839–1844.
41. Jones-Jordan LA, Mitchell GL, Cotter SA, *et al.* Visual activity before and after the onset of juvenile myopia. Invest Ophthalmol Vis Sci 2011; 52:1841–1850.
42. Guo Y, Liu LJ, Xu L, *et al.* Outdoor activity and myopia among primary students in rural and urban regions of Beijing. Ophthalmology 2013; 120:277–283.
43. 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:e75260.
44. You QS, Wu LJ, Duan JL, *et al.* Factors associated with myopia in children in China: the Beijing childhood Eye Study. PLoS One 2012; 7:e52668.
45. Lee YY, Lo CT, Sheu SJ, *et al.* What factors are associated with myopia in young adults? A survey study in Taiwan military conscripts. Invest Ophthalmol Vis Sci 2013; 54:1026–1033.
46. Gong Y, Zhang X, Tian D, *et al.* Parental myopia, nearwork, hours of sleep and myopia in Chinese children. Health 2014; 6:64–70.
47. Wallman J, Gottlieb MD, Rajaram NV, *et al.* Local retinal regions control local eye growth and myopia. Science 1987; 237:73–77.
48. 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.
49. ■ Huang HM, Chang DS, Wu PC. The association between near work activities and myopia in children: a systematic review and meta-analysis. PLoS One 2015; 10:e0140419.

This study is a systematic review to quantify the effect of near work activities on myopia in children.

50. ■■ Huang J, Wen D, Wang Q, *et al.* Efficacy comparison of 16 interventions for myopia control in children: a network meta-analysis. Ophthalmology 2016; 123:697–708.

This article provides a network meta-analysis of interventions proposed to retard myopia progression. A network meta-analysis integrates relevant data without losing the strength of randomization in individual randomized controlled trials (RCTs).

51. Bedrossian RH. The effect of atropine on myopia. Ann Ophthalmol 1971; 3:891–897.
52. Bedrossian RH. The effect of atropine on myopia. Ophthalmology 1979; 86:713–719.
53. Bedrossian RH. The treatment of myopia with atropine and bifocals: a long-term prospective study. Ophthalmology 1985; 92:716.
54. Gimbel HV. The control of myopia with atropine. Can J Ophthalmol 1973; 8:527–532.
55. Dyer JA. Role of cyclopegics in progressive myopia. Ophthalmology 1979; 86:692–694.
56. Sampson WG. Role of cycloplegia in the management of functional myopia. Ophthalmology 1979; 86:695–697.
57. Gruber E. Treatment of myopia with atropine and bifocals. Ophthalmology 1985; 92:985.
58. Brodstein RS, Brodstein DE, Olson RJ, *et al.* The treatment of myopia with atropine and bifocals. A long-term prospective study. Ophthalmology 1984; 91:1373–1379.
59. Brenner RL. Further observations on use of atropine in the treatment of myopia. Ann Ophthalmol 1985; 17:137–140.
60. Yen MY, Liu JH, Kao SC, *et al.* Comparison of the effect of atropine and cyclopentolate on myopia. Ann Ophthalmol 1989; 21:180–182.
61. Shih YF, Chen CH, Chou AC, *et al.* Effects of different concentrations of atropine on controlling myopia in myopic children. J Ocul Pharmacol Ther 1999; 15:85–90.
62. Shih YF, Hsiao CK, Chen CJ, *et al.* An intervention trial on efficacy of atropine and multifocal glasses in controlling myopic progression. Acta Ophthalmol Scand 2001; 79:233–236.
63. McKanna JA, Casagrande VA. Atropine affects lid-suture myopia development: Experimental studies of chronic atropinization in tree shrews. Doc Ophthal Proc Series 1981; 28:187–192.
64. Raviola E, Wiesel TN. An animal model of myopia. N Engl J Med 1985; 312:1609–1615.
65. Tigges M, Juvone PM, Fernandes A, *et al.* Effects of muscarinic cholinergic receptor antagonists on postnatal growth of rhesus monkeys. Optom Vis Sci 1999; 76:398–407.
66. Stone RA, Lin T, Laties AM. Muscarinic antagonist effects on experimental chick myopia. Exp Eye Res 1991; 52:755–758.
67. Schmid KL, Wildsoet CF. Inhibitory effects of apomorphine and atropine and their combination in chicks. Optom Vis Sci 2004; 81:137–147.
68. Glasser A, Howland HC. A history of studies of visual accommodation in birds. Q Rev Biol 1996; 71:475–509.
69. McBrien NA, Moghaddam HO, Reeder AP. Atropine reduces experimental myopia and eye enlargement via a nonaccommodative mechanism. Invest Ophthalmol Vis Sci 1993; 34:205–215.
70. ■ Tan D, Tay SA, Loh KL, Chia A. Topical atropine in the control of myopia. Asia Pac J Ophthalmol 2016; 5:424–428.

This study reviewed the use of topical atropine eye drops in the retardation of myopia progression in children, and discussed the efficacy and safety profiles when used at different concentrations (1.0, 0.5, 0.1, and 0.01%). Atropine 0.01% has the best therapeutic index, with clinically insignificant amounts of pupil dilation, near vision, and accommodation loss but remains as effective as higher doses.

71. Chua WH, Balakrishnan V, Chan YH, *et al.* Atropine for the treatment of childhood myopia. Ophthalmology 2006; 113:2285–2291.
72. Luu CD, Lau AM, Koh AH, Tan D. Multifocal electroretinogram in children on atropine treatment for myopia. Br J Ophthalmol 2005; 89:151–153.
73. Scheiman MM, Hertle RW, Beck RW, *et al.,* Pediatric Eye Disease Investigator Group. Randomized trial of treatment of amblyopia in children aged 7 to 17 years. Arch Ophthalmol 2005; 123:437–447.
74. Tong L, Huang XL, Koh AL, *et al.* Atropine for the treatment of childhood myopia: effect on myopia progression after cessation of atropine. Ophthalmology 2009; 116:572–579.
75. 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 (ATOM2). Ophthalmology 2012; 119:347–354.
76. Chia A, Chua WH, Li W, *et al.* Atropine for the treatment of childhood myopia: changes after stopping atropine 0.01%, 0.1% and 0. 5% (ATOM2). Am J Ophthalmol 2014; 157:451–457.
77. ■ Chia A, Lu QS, Tan D. Five-year clinical trial on atropine for the treatment of myopia 2: myopia control with atropine 0.01% eye drops. Ophthalmology 2016; 123:391–399.

This study compared the safety and efficacy of different concentrations of atropine eye drops in controlling myopia progression over 5 years, and concluded that atropine 0.01% eye drops were more effective in slowing myopia progression with less visual side effects compared with higher doses of atropine.

78. Wu PC, Yang YH, Fang PC. The long-term results of using low-concentration atropine eye drops for controlling myopia progression in schoolchildren. J Ocul Pharmacol Ther 2011; 27:461–466.
79. Clark TY, Clark RA. Atropine 0.01% eyedrops significantly reduce the progression of childhood myopia. J Ocul Pharmacol Ther 2015; 31:541–545.
80. ■ Loh KL, Lu Q, Tan D, Chia A. Risk factors for progressive myopia in the atropine therapy for myopia study. Am J Ophthalmol 2015; 159:945–949.

This study reported on a small group of children (younger, with higher myopia, and greater tendency of myopic progression) who still progressed while receiving atropine treatment.

81. Tan DT, Lam DS, Chua WH, *et al.* One-year multicenter, double-masked, placebo-controlled, parallel safety and efficacy study of 2% pirenzepine ophthalmic gel in children with myopia. Ophthalmology 2005; 112:84–91.
82. Siatkowski RM, Cotter SA, Crockett RS, *et al.* Two-year multicenter, randomized double-masked, placebo-controlled, parallel safety and efficacy study of 2% pirenzepine ophthalmic gel in children with myopia. JAAPOS 2008; 12:332–339.
83. Norton T. Animal models of myopia: learning how vision controls the size of the eye. Inst Lab Anim Res J 1999; 40:59–77.
84. Wildsoet CF. Active emmetropization: evidence for its existence and ramifications for clinical practice. Ophthalmic Physiol Opt 1997; 17:279–290.
85. Gwiazda J, Thorn F, Bauer J, Held R. Myopic children show insufficient accommodative response to blur. Invest Ophthalmol Vis Sci 1993; 34:690–694.
86. Grosvenor T, Perrigin DM, Perrigin J, *et al.* Houston Myopia Control Study: a randomized clinical trial. Part II. Final report by the patient care team. Am J Optom Physiol Opt 1987; 64:482–498.
87. Pärssinen O, Hemminki E, Klemetti A. Effect of spectacle use and accommodation on myopic progression: final results of a three-year randomised clinical trial among schoolchildren. Br J Ophthalmol 1989; 73:547–551.
88. Jensen H. Myopia progression in young school children: a prospective study of myopia progression and the effect of a trial with bifocal lenses and beta blocker eye drops. Acta Ophthalmol Suppl 1991; 200:1–79.
89. Fulk GW, Cyert LA, Parker DE. A randomized trial of the effect of single-vision vs. bifocal lenses on myopia progression in children with esophoria. Optom Vis Sci 2000; 77:395–401.
90. Cheng D, Woo GC, Drobe B, Schmid KL. Effect of bifocal and prismatic bifocal spectacles on myopia progression in children: three-year results of a randomized clinical trial. J Am Med Assoc Ophthalmol 2014; 132:258–264.
91. Cheng D, Schmid KL, Woo GC, Drobe B. Randomized trial of effect of bifocal and prismatic bifocal spectacles on myopic progression: two-year results. Arch Ophthalmol 2010; 128:12–19.
92. Cheng D, Woo GC, Schmid KL. Bifocal lens control of myopic progression in children. Clin Exp Optom 2011; 94:24–32.
93. ■ Walline JJ. Myopia control: a review. Eye Contact Lens 2016; 42:3–8.

This article reviews the peer-reviewed literature regarding several modalities attempting to control myopia progression.

94. Gwiazda J, Hyman L, Hussein M, *et al.* A randomized clinical trial of progressive addition lenses versus single vision lenses on the progression of myopia in children. Invest OphthalmolVis Sci 2003; 44:1492–1500.
95. Leung JT, Brown B. Progression of myopia in Hong Kong Chinese schoolchildren is slowed by wearing progressive lenses. Optom Vis Sci 1999; 76:346–354.
96. Edwards MH, Li RW, Lam CS, *et al.* The Hong Kong progressive lens myopia control study: study design and main findings. Invest Ophthalmol Vis Sci 2002; 43:2852–2858.
97. Correction of Myopia Evaluation Trial 2 Study Group for the Pediatric Eye Disease Investigator Group. Progressive-addition lenses versus single-vision lenses for slowing progression of myopia in children withhigh accommodative lag and near esophoria. Invest Ophthalmol Vis Sci 2011; 52:2749–2757.
98. Gwiazda JE, Hyman L, Everett D, *et al.* Five-year results from the correction of myopia evaluation trial (COMET). Investig Ophthalmol Vis Sci 2006; 47: E-abstract 1166.
99. Fulk GW, Cyert LA, Parker DE, *et al.* The effect of changing from glasses to soft contact lenses on myopia progression in adolescents. Ophthalmic Physiol Opt 2003; 23:71–77.
100. Horner DG, Soni PS, Salmon TO, Swartz TS. Myopia progression in adolescent wearers of soft contact lenses and spectacles. Optom Vis Sci 1999; 76:474–479.
101. Walline JJ, Jones LA, Sinnott L, *et al.* A randomized trial of the effect of soft contact lenses on myopia progression in children. Invest Ophthalmol Vis Sci 2008; 49:4702–4706.
102. Katz J, Schein OD, Levy B, *et al.* A randomized trial of rigid gas permeable contact lenses to reduce progression of children's myopia. Am J Ophthalmol 2003; 136:82–90.
103. Walline JJ, Jones LA, Mutti DO, *et al.* A randomized trial of the effects of rigid contact lenses on myopia progression. Arch Ophthalmol 2004; 122:1760–1766.
104. Swarbrick HA. Orthokeratology review and update. Clin Exp Optom 2006; 89:124–143.
105. Van Meter WS, Musch DC, Jacobs DS, *et al.* Safety of overnight orthokeratology for myopia: a report by the American Academy of Ophthalmology. Ophthalmology 2008; 115:2301–2313.
106. Swarbrick HA, Alharbi A, Watt K, *et al.* Myopia control during orthokeratology lens wear in children using a novel study design. Ophthalmology 2015; 122:620–630.
107. Walline JJ, Jones LA, Sinnott LT. Corneal reshaping and myopia progression. Br J Ophthalmol 2009; 93:1181–1185.
108. Charm J, Cho P. High myopia-partial reduction ortho-k: a 2-year randomized study. Optom Vis Sci 2013; 90:530–539.
109. Chen C, Cheung SW, Cho P. Myopia control using toric orthokeratology (TO-SEE study). Invest Ophthalmol Vis Sci 2013; 54:6510–6517.
110. Cho P, Cheung SW. Retardation of myopia in Orthokeratology (ROMIO) study: a 2-year randomized clinical trial. Invest Ophthalmol Vis Sci 2012; 53:7077–7085.
111. Cho P, Cheung SW, Edwards M. The longitudinal orthokeratology research in children (LORIC) in Hong Kong: a pilot study on refractive changes and myopic control. Curr Eye Res 2005; 30:71–80.
112. Santodomingo-Rubido J, Villa-Collar C, Gilmartin B, *et al.* Myopia control with orthokeratology contact lenses in Spain (MCOS): refractive and biometric changes. Invest Ophthalmol Vis Sci 2012; 53:5060–5065.
113. Hiraoka T, Kakita T, Okamoto F, *et al.* Long-term effect of overnight orthokeratology on axial length elongation in childhood myopia: a 5-year follow-up study. Invest Ophthalmol Vis Sci 2012; 53:3913–3919.
114. Kakita T, Hiraoka T, Oshika T. Influence of overnight orthokeratology on axial elongation in childhood myopia. Invest Ophthalmol Vis Sci 2011; 52:2170–2174.
115. Santodomingo-Rubido J, Villa-Collar C, Gilmartin B, *et al.* Myopia control with orthokeratology contact lenses in Spain: refractive and biometric changes. Invest Ophthalmol Vis Sci 2012; 53:5060–5065.
116. ■ Sun Y, Xu F, Zhang T, *et al.* orthokeratology to control myopia progression: a meta-analysis. PLoS One 2015; 10:e0124535.

This is a meta-analysis of seven well designed controlled studies investigating the effects of orthokeratology in school-aged children.

117. ■ Santodomingo-Rubido J, Villa-Collar C, Gilmartin B, *et al.* Long-term efficacy of orthokeratology contact lens wear in controlling the progression of childhood myopia. Curr Eye Res 2016; 21:1–8.

This study compared the axial length growth of white European myopic children wearing orthokeratology contact lenses to a control group over a 7-year period.

118. Smith MJ, Walline JJ. Controlling myopia progression in children and adolescents. Adolesc Health Med Therapeut 2015; 6:133–140.
119. Smith 3rd EL, Ramamirtham R, Qiao-Grider Y, *et al.* Effects of foveal ablation on emmetropization and form-deprivation myopia. Invest Ophthalmol Vis Sci 2007; 48:3914–3922.
120. Hoogerheide J, Rempt F, Hoogenboom W. Acquired myopia in young pilots. Ophthalmologica 1971; 163:209–215.
121. Mutti D, Hayes J, Mitchell G, *et al.* Refractive error, axial length, and relative peripheral refractive error before and after the onset of myopia. Invest Ophthalmol Vis Sci 2007; 48:2510–2519.
122. Sng CC, Lin XY, Gazzard G, *et al.* Change in peripheral refraction over time in Singapore Chinese children. Invest Ophthalmol Vis Sci 2011; 52:7880–7887.
123. Mutti D, Sinnott L, Mitchell G, *et al.* Relative peripheral refractive error and the risk of onset and progression of myopia in children. Invest Ophthalmol Vis Sci 2011; 52:199–205.

124. Sankaridurg P, Donoval L, Varnas S, *et al.* Spectacle lenses designed to reduce progression ofmyopia:12 month results. Optom Vis Sci 2010; 87:631–641.
125. Sankaridurg P, Holden B, Smith 3rd E, *et al.* Decrease in rate of myopia progression with a contact lens designed to reduce relative peripheral hyperopia: one year results. Invest Ophthalmol Vis Sci 2011; 52:9362–9367.
126. Adler D, Millodot M. The possible effect of undercorrection on myopic progression in children. Clin Exp Optom 2006; 89:315–321.
127. Chung K, Mohidin N, O'Leary DJ. Undercorrection of myopia enhances rather than inhibits myopia progression. Vision Res 2002; 42:2555–2559.
128. Ong E, Grice K, Held R, *et al.* Effects of spectacle intervention on the progression of myopia in children. Optom Vis Sci 1999; 76:363–369.