Prevention and Management of Myopia and Myopic Pathology

Seang-Mei Saw,[1–3] Saiko Matsumura,[1] and Quan V. Hoang[1,3–5]

[1]Singapore Eye Research Insitute, Singapore
[2]Saw Swee Hock School of Public Health, National University of Singapore, Singapore, Singapore
[3]Duke-NUS Medical School, Singapore
[4]Singapore National Eye Centre, Singapore
[5]Department of Ophthalmology, Columbia University Medical Center, New York, New York, United States

Correspondence: Seang-Mei Saw, Singapore Eye Research Institute, The Academia, 20 College Road, Discovery Tower Level 6, Singapore 169856, Singapore; ephssm@nus.edu.sg.

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Myopia is fast becoming a global public health burden with its increasing prevalence, particularly in developed countries. Globally, the prevalence of myopia and high myopia (HM) is 28.3% and 4.0%, respectively, and these numbers are estimated to increase to 49.8% for myopia and 9.8% for HM by 2050 (myopia defined as −0.50 diopter [D] or less, and HM defined as −5.00 D or less). The burden of myopia is tremendous, as adults with HM are more likely to develop pathologic myopia (PM) changes that can lead to blindness. Accordingly, preventive measures are necessary for each step of myopia progression toward vision loss. Approaches to prevent myopia-related blindness should therefore attempt to prevent or delay the onset of myopia among children by increased outdoor time; retard progression from low/mild myopia to HM, through optical (e.g., defocus incorporated soft contact lens, orthokeratology, and progressive-additional lenses) and pharmacological (e.g., low dose of atropine) interventions; and/or retard progression from HM to PM through medical/surgical treatments (e.g., anti-VEGF therapies, macula buckling, and scleral crosslinking). Recent clinical trials aiming for retarding myopia progression have shown encouraging results. In this article, we highlight recent findings on preventive and early interventional measures to retard myopia, and current and novel treatments for PM.

Keywords: myopia, pathologic myopia, prevention

Myopia is one of the most prevalent eye diseases and a worldwide public health burden.[1–4] Globally, there are approximately 1950 million (28.3% of the global population) with myopia (defined as −0.50 diopters [D] or less) and 277 million (4.0% of the global population) with high myopia (HM) (defined as −5.00 D or less).[1] Refractive Error Study in Children surveys of 12-year-old children have shown that the prevalence of myopia is higher in urban Asian cities, such as Singapore (62.0%), Hong Kong (53.1%),[5] and Guangzhou, China (49.7%)[6] than in the United States (20.0%),[7] Australia (11.9%),[8] urban India (9.7%),[9] Nepal (16.5%),[10] and Cambodia (6.0%).[11]

Both environmental and genetic factors play a role in the development of myopia. Environmental factors have recently contributed to the increase in myopia over the past few decades in populations with a stable genetic pool and thus are the main contributors to myopia. The major environmental risk factors are less outdoor time and more near-work, including reading, writing, and screen time.[12–18] With regard to genetic factors, a consistent finding is that children with myopic parents have a higher prevalence of myopia.[19–21] In addition, some genetic loci associated with myopia and HM have been identified previously.[22–25]

There may be a future epidemic of myopia, especially in urban Asian cities such as Singapore, whereby the prevalence of myopia, HM, and pathologic myopia (PM) are likely to increase drastically in older adults (older than 45 years) over the next few decades. This is largely contributed by the generational effect. The prevalence of myopia in young adults (83%) is much higher than middle-aged and elderly adults (approximately 30%). The present young generation with the highest myopia rate will become older in the next few decades, resulting in higher myopia prevalence (83%) in all the age groups in the near future (Fig. 1). The pattern of HM and subsequent development of PM may differ between young adults and older adults due to generational differences, or changes in lifestyle factors, such as the education system, increased near-work, and reduced outdoor time exposure in rapidly developing urban Asian countries. As young adults grow older in the next few decades, the prevalence of myopia in middle-aged adults will be expectedly higher. In addition, urban Asian cities such as Singapore have populations that are recently shifting, with Singapore's population aging rapidly in the next few decades. Thus, the combination of the generational effect and rapidly aging populations will result in an epidemic of HM and PM in Singapore and other Asian cities.

There are two possible origins of HM. The recent development of a large proportion of HM in young adults may be due to lack of time outdoors, and excessive near-work encouraged by recent intensive schooling systems, whereas HM and PM in our current older generation of adults may be linked to the earlier onset of myopia and be largely genetic in origin. The older generation in urban Asian countries may not have undergone a rigorous schooling system during their childhood compared with the present young generation.[26,27] According to our previous paper, the prevalence of myopia increased rapidly during the past few decades, especially in those who went to

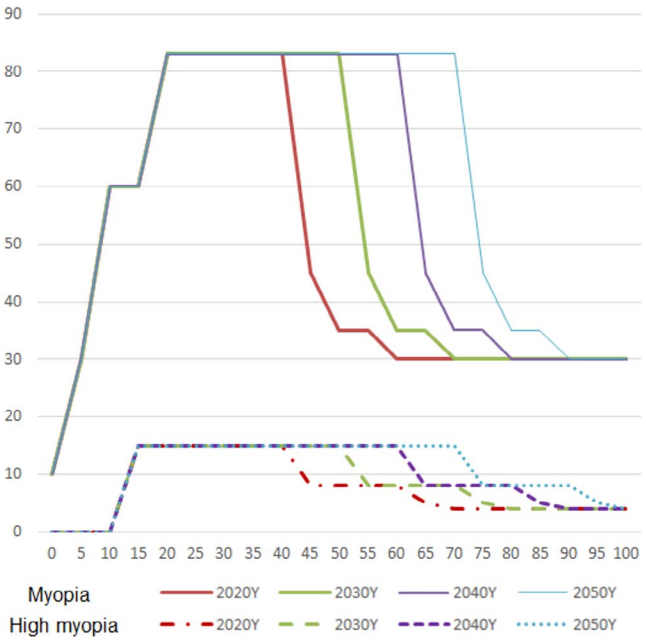

FIGURE 1. Future epidemic of myopia and high myopia in Singapore (in 2050).

elementary school in the 1980s (born after 1970).[26] The education system was expanded after Singapore's independence in 1965, and the new education system was introduced in 1978. These changes, together with increasingly intensive schooling, may have contributed to the increase in myopia prevalence, whereas the genetic contribution to the pandemic myopia is likely to be less in this younger generation.

In HM, not only would there be marked scleral thinning in these extremely elongated eyes,[28,29] but some eyes may also thin to the extent that local outpouchings, called staphylomas, form. A greater grade of staphyloma is associated with further eye elongation,[30] as well as more severe and progressive myopic macular degeneration (MMD).[31–33] Staphyloma formation or development of MMD signifies the transition from HM to PM.

The burden of myopia is tremendous, as adults with HM are more likely to develop PM changes. With regard to Singapore, population-based studies have shown a higher prevalence of HM in adults in Singapore (10%) compared with other East Asian (2%–4%) or Western countries (2%–3%).[34] In the same vein, the rates of HM are linked to the prevalence of myopia.[35] Thus, in countries such as Singapore where the prevalence rate of myopia is high, the rates of HM and PM will be expectedly higher.[36]

PM is more common in eyes with HM worse than −5.0 D or axial length (AL) >26 mm, although moderate myopia or shorter ALs do not always exclude the possibility of PM lesions. PM is classified in order of increasing severity: no macula degenerative lesion (category 0); tessellated fundus only (category 1); diffuse chorioretinal atrophy (category 2); patchy chorioretinal atrophy (category 3); and macular atrophy (category 4) based on the International META-PM classification in recent studies (Fig. 2). Two population-based studies in China, the Beijing Eye Study[37] and the Handan Eye Study,[38] have shown that the prevalence of PM increased from 1% and 19% in moderate myopia, respectively, to approximately 70% in HM (< − 9.0 D).[39] In Singaporean adults aged 40 to 80 years, Chang et al.[40] reported higher prevalence rates of peripapillary atrophy (81.2%) and optic disc tilt (57.4%), as well as macular changes, such as staphyloma and chorio-retinal atrophy, which increased from 11% to 13% in adults (aged <50 years) to 40% in older adults (>60 years).

In the Rotterdam Study of adults older than 55 years, the major cause of visual impairment in highly myopic adults was MMD.[41] In the Beijing Eye Study, of 4439 adults older than 40 years, the most frequent cause of low vision/blindness was cataract followed by degenerative myopia.[42] Similar results were reported in a population-based study of 3870 adults conducted in Tajimi, Japan.[43] Other studies have also consistently reported that PM is the major cause of low vision or blindness in European[44,45] and Asian populations.[46–48] In contrast to uncorrected myopia, the visual impairment caused by PM is not correctable and can lead to irreversible vision loss. Thus, PM has a great adverse impact on visual function, quality of life, and emotional well-being. A previous cross-sectional study carried out in Japan on 200 adults with PM using a self-rated 52-item health-related quality-of-life questionnaire confirmed that PM reduces the functional status in daily life.[49] It is hence of great importance to identify myopic patients with high risk of future PM development, toward whom preventive and early interventional measures can then be targeted.

Approaches to prevent myopic pathology should therefore attempt to prevent or delay myopia onset, retard progression from low/mild myopia to HM, and/or retard progression from HM to PM.

Solution 1: Early-Stage Interventions: Outdoor Time to Prevent Early-Onset Myopia

In the past decade, the relationship between time outdoors and myopia onset has been documented in several epidemiologic studies.[50–54] The prevalence of myopia in Chinese children aged 6 years was significantly lower in Sydney (3.3%) than in Singapore (29.1%).[55,56] The outdoor time was 13.8 hours per week in Sydney compared with 3 hours per week in Singapore. Several cross-sectional[20,56–59] and cohort studies[53,60–64] have addressed the protective role increased outdoor time has on the prevention of myopia onset. Randomized controlled trials for myopia control with outdoor light interventions are summarized in Table 1. A randomized trial of 952 schoolchildren in China showed that a 40 minutes per day outdoor intervention decreased myopia onset by 9% after 3 years.[61] Another intervention study in Taiwan showed that 80 minutes per day of intermittent outdoor time during recess decreased myopia onset by up to 9% in only 1 year.[62]

There are several possible mechanisms by which time spent outdoors may protect against myopia onset.[50–54] In animal studies, experiments in chicken and nonhuman primate animal models have shown that high illuminance levels of light (>15,000 Lux) can slow or even stop the development of experimentally induced myopia.[65–68] Another hypothesis is that the pupillary miosis that occurs while viewing distant objects outdoors results in less image blur and peripheral hyperopic defocus.[69]

Evidence from both animal and human studies has shown that ambient light exposure plays an important role in controlling eye growth. Portable light exposure measurement devices were used to track the light level. A recent longitudinal observational study using Actiwatch revealed that greater daily light exposure was associated with less axial eye growth over the 18-month period among 101 children aged 10 to 15 years.[70] A novel fitness tracker (FitSight) was developed by S.M. Saw (Taiwan patent application No.104110280) to record light levels and encourage children to increase time spent outdoors; and has been evaluated in the FitSight study of 23 children,[71] and other Singapore myopia studies. The children were also given a 1-week outdoor activity diary to complete.

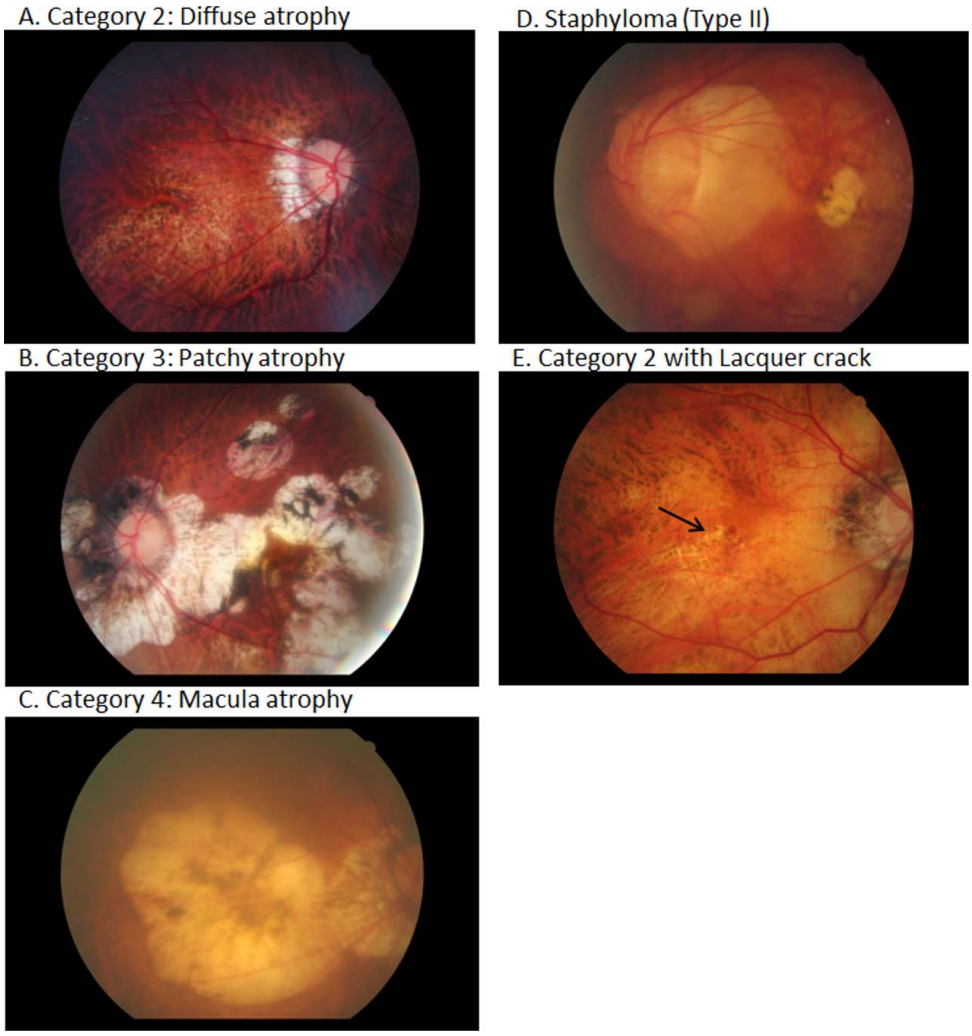

Figure 2. Examples of fundus photographs based on the International Classification of Myopia Maculopathy. (**A**) Diffuse atrophy (Category 2). (**B**) Patchy atrophy (Category 3). (**C**) Macula atrophy (Category 4). (**D**) Left fundus of a 61-year-old Malaysian man with SE −18.25 D and an AL 31.73 mm presenting staphyloma (Type II). (**E**) Right fundus of a 55-year-old Malaysian woman with SE −13.75 D and an AL 28.24 mm presenting category 2 with lacquer crack (*black arrow*).

The daily and weekly pattern and regularity of light levels from the watch provide insight on outdoor behavior patterns. Results have shown that children spend more time outdoors on weekends compared with weekdays. Interestingly, children in Singapore go outdoors in episodes or spurts of approximately 20 minutes 6 to 8 times per day. The top outdoor activities from the diaries were walking, playing at the park, and running in younger children; as well as walking, running, and ballgames in teenage children.

More detailed evaluation of outdoor activity patterns in further studies will inform government, schools, and health policy makers on appropriate nationwide outdoor programs. In urbanized Asian countries with more indoor-centric lifestyles, the increase in outdoor time will provide public health benefits. Children are encouraged to engage in outdoor activities for at least 2 hours per day and at least 14 hours per week.[60] Outdoor programs in schools may encompass the adoption of outdoor activities within the school, such as science classes conducted outdoors, school assemblies in an outdoor setting, or time during recess for outdoor play. Community-based outdoor sports classes for children and the construction of age-relevant playgrounds may be rolled out. Furthermore, spending more time outdoors has other benefits. Children may exercise more, as most outdoor time is often spent at play or sports. The increased physical activity will prevent obesity and decrease the risks of chronic diseases, such as diabetes, hypertension, heart disease, and cancer later in life. In addition, children will have better emotional health with lower levels of depression, anxiety, and stress. In encouraging children to increase time spent outdoors, the engagement and support from governments in establishing community-wide outdoor programs is essential.

As for another environmental risk factor for myopia, excessive near-work is also considered important. The Sydney myopia study evaluated 2103 children with myopia onset at ages 6 and 12 years and reported myopic children performed significantly more near-work (19.4 vs. 17.6 hours per week, respectively; $P = 0.02$) in the younger cohort.[53] It suggests that less time spent on near-work may prevent or delay the onset of myopia, particularly in younger children. However, as an interventional measure, decreasing study time may not be entirely practical because educational success is heavily stressed, especially in East Asian countries, in which there is a belief that effort rather than innate ability is the key to success.

Table 1. Summary of Evidence From Randomized Controlled Trials for Myopia Control With Outdoor Light Interventions

Study: Authors, Year	Study Design	Participants: Number, Age y, Location	Duration, y	Intervention, Control	Refraction Method	Study Outcomes
He et al. 2015 (Ref. 61)	Randomized clinical trial, school-based	$N = 1848$, 6–7, China	3	I: Additional 40-minute class of outdoor activities on each school day C: No program	Cycloplegic autorefraction	Cumulative incidence rate: I: 30.4%, C: 39.5% ($P < 0.001$) Myopia progression rates: I: −1.42 D (95% CI −1.58 D to −1.27 D), C: −1.59 D (95% CI −1.76 D to −1.43D) ($P = 0.04$) Change in AL: I: 0.95 mm, C: 0.98 mm ($P = 0.07$)
Wu et al. 2018 (Ref. 132)	Cluster-randomized intervention-controlled trial	$N = 693$, 6–7, Taiwan	1	I: School-based recess outside classroom to encourage outdoor time (>1000 lux) up to 11 hours weekly C: No program	Cycloplegic autorefraction	Incidence rate: I: 14.47%, C: 17:40% ($P = 0.05$) Myopia progression rate: I: −0.35 D ± 0.58 D, C: −0.47 D ± 0.74 D ($P = 0.002$) Change in AL: I: 0.28 mm ± 0.22 mm, C: 0.33 mm ± 0.35 mm ($P = 0.003$)
Jin et al. 2015 (Ref. 63)	Randomized intervention trial, school-based	$N = 3051$, 6–14, China	1	I: Two additional 20-minute recess programs outside the classroom during school days C: No program	Cycloplegic refraction	Incidence rate: I: 3.70%, C: 8:50% ($P = 0.048$) Myopia progression rates: I: −0.10 D ± 0.65 D, C: −0.27 D ± 0.52 D ($P = 0.005$) Change in AL: I: 0.16 ± 0.30 mm, C: 0.21 ± 0.21 mm ($P = 0.034$)
Wu et al. 2013 (Ref. 62)	Randomized intervention trial, school-based	$N = 571$, 7–11, Taiwan	1	I: Two additional 40-minute outdoor time in the recess C: No program	Cycloplegic autorefraction	Incidence rate: I: 8.41%, C: 17.65% ($P < 0.001$) Myopia progression rates: I: −0.25 ± 0.68 D, C: −0.38 ± 0.69 D ($P = 0.029$)

C, control group; I, Intervention group; D, diopter.

Nowadays children have been exposed to extensive screen time, particularly with computers and mobile phones. The Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) study of 1329 children aged 6–14 years showed that hours for activities such as computer/playing video games were significantly greater in myopes than in emmetropes at onset by 0.7 hours per week.[72] Saxena et al.[73] evaluated the association between the progression of myopia and behavior risk factors among 629 children aged 5 to 15 years over 1 year in the North India Myopia study and found that use of computers and video games was a significant risk factor for progression of myopia ($P < 0.001$). However, we must take into consideration that the high prevalence of myopia due to the intensive education system was reported before the widespread use of smart phones or electronic devices.[26] In summary, near-work can be a major modifiable risk factor for myopia, although the contribution of recent increase of screen time may be small.

Early Age of Onset of Myopia Is Linked to HM and Blindness Later in Life

Another interesting aspect is the link between age of onset of myopia and permanent vision loss later in life. Children who develop myopia at an earlier age are more likely to have HM as an adult.[74] Our study has shown that children with an earlier age of onset of myopia (3 to 6 years old) or longer duration of myopia progression (over 5 years), are likely to have more myopic refractive errors, longer AL, and a higher risk of HM at 11 years of age. Although late-onset myopia in adolescents progresses to only mild to moderate myopia in adults, early-onset myopia can result in more severe myopia that is associated with visually disabling PM in adulthood. Thus, measures including outdoor interventions to prevent early-onset myopia are a crucial part of a preventive strategy.

Solution 2: Retard Myopia Progression From Low/Mild Myopia to HM in Children

To date, the use of atropine eye drops is the most effective intervention in slowing myopia progression, whereby low-dose atropine (0.01%) in particular showed high efficacy for clinical use.[75–78] A recent network meta-analysis indicated that a range of interventions can reduce myopia progression when compared with single-vision spectacle lenses or placebo. High-dose atropine (1% and 0.5%) showed a significant effect compared with other interventions, except for moderate-dose atropine (0.1%), and low-dose of atropine (0.01%).[79] However, high-dose atropine induced clinical symptoms of cycloplegia and photophobia, and displayed a rapid rebound effect in

Table 2. Summary of Evidence From Randomized Controlled Trials for Slow Myopia Progression With CLs

Study (Authors, Year)	Study Design	Participants: Number, Age y, Location	Duration	Intervention, Control	Study Outcomes
Walline et al. 2008 (Ref. 133)	Randomized clinical trial	$N = 484$, 8–11, USA	3 y	I: SVSCLs	SE, I: −1.29 D, C: −1.10 D (over 3 y) (95% CI −0.46 to 0.02)
				C: Spectacle	AL, I: 0.63 mm, C: 0.59 mm (over 3 y) ($P = 0.37$)
Walline et al. 2004 (Ref. 134)	Single masked-randomized clinical trial	$N = 116$, 8–11, USA	3 y	I: RGPs	SE, I: −1.56 D, C: −2.19 D (over 3 y) ($P < 0.001$)
				C: SVSCLs	AL, I: 0.81 mm, C: 0.76 mm (over 3 y) ($P = 0.57$)
Katz et al. 2003 (Ref. 135)	Randomized clinical trial	$N = 428$, 6–12, Singapore	2 y	I: RGPs	SE, I: −1.33 D, C: −1.28 D (over 2 y) ($P = 0.64$) AL, I: 0.84 mm, C: 0.79 mm (over 2 y) ($P = 0.38$)
				C: SVSCLs	(Completion rate, I: 37.5%, C: 67.8%)
Lam et al. 2014 (Ref. 81)	Double-blind randomized controlled trial	$N = 221$, 8–13, Hong Kong	2 y	I: DISCLs	SE, L: −0.59 D, C: − 0.79 D (over 2 y) ($P = 0.031$) AL, L: 0.25 mm, C: 0.37 mm (over 2 y) ($P = 0.009$)
				C: SVSCLs	(Dropout rate: 42%)
Cheng et al. 2016 (Ref. 136)	Double-blind randomized control trial	$N = 127$, 8–11, USA	2 y	I: Custom design CLs	Differences in AL and SE change from baseline between two groups: SE, 0.14 D (over 1 y) ($P = 0.068$)
				C: SVSCLs	AL, 0.14 mm (over 1 y) ($P < 0.05$)
Ruiz-Pomeda et al. 2018 (Ref. 137)	Randomized clinical trial	$N = 89$, 8–12, Spain	2 y	I: Concentric CLs	SE, I: −0.45 D, C: −0.74 D (over 2 y) ($P < 0.001$)
				C: Spectacle	AL, I: 0.28 mm, C: 0.44 mm (over 2 y) ($P < 0.001$)
Aller et al. 2016 (Ref. 138)	Double-blind randomized clinical trial	$N = 86$, 8–18, USA	1 y	I: BFSCLs	SE, I: −0.22 D, C: −0.79 D (over 1 y) ($P < 0.001$)
				C: SVSCLs	AL, I: 0.05 mm, C: 0.24 mm (over 1 y) ($P < 0.001$)
Sankaridurg et al. 2011 (Ref. 139)	Randomized clinical trial	$N = 100$, 7–14, China	1 y	I: Multifocal SCLs	SE, I: −0.54 D, C: −0.84 D (over 1 y) ($P = 0.002$)
				C: Spectacle	AL, I: 0.24 mm, C: 0.39 mm (over 1 y) ($P = 0.001$)
Fujikado et al. 2014 (Ref. 140)	Randomized clinical trial	$N = 24$, 10–16, Japan	1 y	I: Low-addition SCLs	SE, I: −0.8 4 D, C: −0.62 D (over 1 y) (No difference)
				C: SVSCLs	AL, I: 0.15 mm, C: 0.20 mm (over 1 y) (No difference)
Anstice et al. 2011 (Ref. 141)	Randomized, paired-eye control, investigator-masked trial with crossover	$N = 80$, 11–14, New Zealand	10 mo	I: DF SCLs	SE, I: −0.44 D, C: −0.69 D (over 10 mo) ($P < 0.001$)
				C: SVSCLs	AL, I: 0.11 mm, C: 0.22 mm (over 10 mo) ($P < 0.001$)

BFSCLs, bifocal soft CLs; C, control group; DF SCLs, dual-focus soft CLs; DISCLs, defocus incorporated soft CLs; I, intervention group; RGPs, rigid GP CLs; SVSCLs, single-vision soft CLs; D, diopter.

myopia when the treatment was stopped.[76–78] On the other hand, low-dose atropine (0.01%) does not show the same rebound effect seen in higher doses and has fewer visual side effects. A recent clinical trial in Singapore demonstrated that the low-dose atropine group had the lowest myopia progression (−1.38 ± 0.98 D) over 5 years compared with the moderate-dose atropine (0.1%) (−1.83 ± 1.16 D, $P = 0.003$) and high-dose atropine (0.5%) groups (−1.98 ± 1.10 D, $P < 0.001$). The mean change in AL was smaller in the 0.01% group (0.19 + 0.18 mm) compared with the 0.1% atropine (0.24 + 0.21 mm, $P = 0.042$) and 0.5% atropine (0.26 + 0.23 mm, $P = 0.013$) groups by the end of phase 3. However, compared with the outcome for spherical equivalent (SE), the myopia progression in AL showed a relatively smaller effect. Furthermore, it resulted in minimal pupil dilation (0.8 mm) and no clinical loss in accommodation (2–3 D).[80]

Recent trials of contact lenses (CLs) with added myopic defocus are promising (Table 2). Defocus incorporated soft contact (DISC) lenses are refractive concentric bifocal CLs with 10 to 12 rings of alternating power over the optic zone, with

successful results reported in recent studies. Lam et al.[81] conducted a 2-year double-blind randomized controlled trial in 128 children aged 8 to 13 years with myopia between −1.00 D and −5.00 D and astigmatism less than −1.00 D. Children who wore DISC lenses had myopia that progressed 25% more slowly than those who wore single-vision soft CLs.[81] MiSight CLs (Cooper Vision, Lake Forest, CA, USA) are bifocal concentric lenses with a large central correction area of 3.36 mm surrounded by concentric zones of alternating distance and near powers.[82] Although these data have not yet been published, a prospective multicenter double-masked randomized study assessed the 3-year effect of MiSight CLs on 144 myopic children aged 8 to 12 years in Singapore, Canada, England, and Portugal. Dual-focus CLs achieved greater control in myopia progression (59%) and axial elongation (52%) than single-vision 1-day CLs.[83] Although these CLs designed for myopia control show promising effects against myopia progression, the quality of vision offered by these lenses may be decreased due to their greater myopic defocus to improve myopia control. This may result in poorer compliance.[84]

Orthokeratology (OK) is an established clinical technique to flatten the central cornea moderately while steepening the peripheral cornea using CLs worn overnight. A single-masked, randomized clinical trial by Cho and Cheung[85] of 78 children aged 6 to 10 years demonstrated that the subjects who wore OK lenses had a 43% slower increase in axial elongation than those who wore single-vision glasses at the end of 2 years. Swarbrick et al.[86] performed a randomized, contralateral-eye crossover study of 26 children aged 10 to 17 years to investigate myopia progression in OK compared with conventional rigid gas-permeable (GP) lenses. They revealed that after the first 6 months of lens wear, AL increased by 0.04 ± 0.06 mm ($P = 0.011$) in the eyes of subjects who wore GP lenses, but had no change (–0.02 ± 0.05 mm; $P = 0.888$) in the eyes of those who wore OK lenses. In the subsequent 6 months of lens wear, there was still no change (–0.04 ± 0.88 mm; $P = 0.218$) from baseline in the AL of the eyes of the OK group, while significant increase in AL (0.09 ± 0.09 mm; $P < 0.001$) was shown in the eyes of the GP group.[86] According to a network meta-analysis comparing OK with other myopia interventions, OK showed moderate effects on the change in AL compared with single-vision spectacle lenses/placebo over a year (AL change: –0.15 mm over a year, 95% confidence interval [CI], –0.22 to –0.08 over a year).[79] However, there has been slow adoption of this intervention, mostly due to possible complications, such as the risk of infective keratitis and the discomfort with overnight wearing.[87–89] In addition, questions remain regarding the treatment period required to attain stabilization and avoid rebound effects.

The therapeutic effect of spectacles on myopia progression has been evaluated in several trials, unfortunately few have shown clinical efficacy. The Correction of Myopia Evaluation Trial (COMET) 2 is a double-masked multicenter randomized trial to compare progressive-additional lenses (PAL) and single-vision lenses among 180 children aged 8 to 12 years with high accommodative lag and near esophoria. It showed that PALs slowed down myopia progression by 0.28 D (95% CI, 0.01–0.55 D) over 3 years. However, no clinically significant effect was proved in children with high accommodative lag and near esophoria.[90] Cheng et al.[91] performed a 3-year randomized clinical trial and reported that bifocal spectacle treatment with and without near prism retarded myopia progression among 135 Chinese-Canadian children aged 8 to 13 years. Myopia progression over 3 years was –0.81 D ($P < 0.001$) and –1.05 D ($P < 0.001$) less in the bifocal lens and prismatic lens groups compared with the single-vision lens group. Both bifocal groups had less axial elongation (0.25 mm and 0.28 mm, respectively) than the control group ($P < 0.001$). The beneficial effect was 39% and 51% for bifocals with and without prism, respectively.[91] More recently, Lam et al. evaluated the effect of a novel designed "multi-segment myopic defocus" (MSMD) spectacle lens with a 50/50 ratio between distance correction and +3.50 lenslet add power across the surface. Their 2-year randomized study among 160 Hong Kong children aged 8 to 12 years demonstrated that children who wore MSMD lenses had 59% less myopic progression (–0.55 ± 0.09 D, $P < 0.0001$) and 60% reduction in axial elongation (0.31 ± 0.04 mm, $P < 0.0001$) compared with those who wore the single-vision lenses.[92]

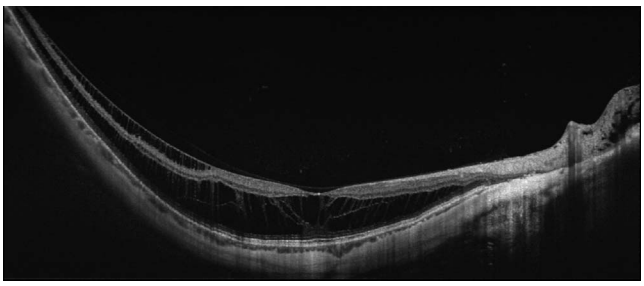

Figure 3. Figure depicting MTM. Horizontal optical coherence tomography image showing macular retinoschisis.

The effectiveness and safety of combination therapies on myopia control in children could be explored. Combinations such as novel CLs with atropine, CLs with outdoor time, and OK with atropine are expected to be beneficial with additive efficacy. The mechanisms underlying myopia control through OK and atropine have not been fully understood. However, it is believed that they act via different mechanisms. Hence, it is possible that by combining these methods, additional retardation of myopia progression could be achieved. Sequential treatment, such as low-dose atropine for the first few years followed by CL for the next few years is another possibility. In the early years after the onset of myopia, the progression of myopia is faster and an effective treatment such as atropine eye drops could be applied. In the teenage years, CLs are more acceptable with higher likely compliance. Such a combined approach may result in an overall lengthening of the treatment duration, which is especially important in Asian children in whom the duration of myopia progression is particularly long due to the early onset of myopia. By combining various treatment strategies, we may achieve additional retardation of myopia progression more effectively than with single-therapy approaches.

Solution 3: Advanced Stage Disease Interventions: Current and Novel Treatments for PM

Various vision-threatening complications can develop in patients with PM, including posterior staphyloma, chorioretinal atrophy, retinal pigment epithelium atrophy, lacquer cracks, choroidal neovascularization (CNV), myopic foveoschisis, and myopic macular hole (MH). Among these, myopic CNV (mCNV) is one of the most severe vision-threatening conditions, occurring in 5% to 10% of highly myopic eyes. The main myopic macular complications of pathologic myopia and possible treatments are summarized in Table 3. Several efficient treatment options are available for mCNV, with the visual loss due to mCNV reversible. Anti-VEGF therapies using ranibizumab or aflibercept are currently used as the first line.

Another vision-threatening complication is myopic traction maculopathy (MTM) (Fig. 3), for which suggested pathogenesis

Table 3. Common Forms of Myopic Macular Complications of Pathologic Myopia and Possible Treatments

Complication	Type of Intervention
Myopic CNV	Anti-VEGF, PDT (less common in select cases: focal laser)
MTM	PPV with membrane peel (less common: macular buckle alone or in conjunction with PPV)
MMD (atrophy)	None (experimental: retinal prosthesis, intraocular telescope, stem cells)
Myopic glaucomatous optic neuropathy	None (controlled with IOP-lowering interventions)
Staphyloma	None (experimental: collagen crosslinking, macular buckle)

MTM includes foveoschisis, lamellar and full-thickness macula hole, foveal retinal detachment, vitreomacular traction. CNV, choroidal neovascularization; PDT, photodynamic therapy; MTM, myopic traction maculopathy; PPV, pars plana vitrectomy; MMD, myopic macular degeneration; IOP, intra ocular pressure.

includes tangential traction in the inner retina exerted by an epiretinal membrane or residual vitreous cortex, rigidity of internal limiting membrane (ILM), thinning of the retina, stiffness of retinal vessels, and scleral curvature changes within the posterior staphyloma.[93–100] MTM progresses to foveal detachment and full-thickness MH range from 3.4% to 37.5%, and from 0.9% to 33%, respectively.[101] Vitrectomy with ILM peeling has been used to treat MH and macula hole retinal detachment with successful macula closure rates ranging from 87% to 100%, in particular with variations including foveal-sparing ILM peeling[102] and the use of ILM flaps.[103]

Macular buckling (MB) is another surgical approach that has been suggested to have the additional benefit (over vitrectomy) of counteracting the posteriorly directed tractional effects of posterior staphyloma by altering the posterior shape of the eye from a concave to a flatter form. Several approaches are used for MB surgery,[104–106] with similar anatomical and functional results.[107] Concomitant resolution of foveoschisis, retinal reattachment, and MH closure has been suggested to be achieved more frequently with MB than pars plana vitrectomy (PPV), particularly so in those with eyes of greater AL.

The anatomic changes underlying global eye elongation and local staphyloma formation likely occur in the component structural elements of the sclera, namely collagen. Novel treatments that are developed in an attempt to arrest progression of PM, or progression of HM to PM, thus focus on the sclera and collagen. In mammalian models, there is scleral thinning and tissue loss during myopia development,[108] with a net decrease in scleral collagen (with decreased collagen synthesis and increased degradation) as evidenced by reduced dry weight and hydroxyproline content.[109,110] Decreased collagen fiber diameter and decreased collagen crosslinking (CXL) are seen in both mammalian models and HM patients.[29,111] Specifically, in the guinea pig myopia model, there is scleral remodeling, possibly from greater slippage between collagen bundles from fibroblast deactivation, with decreased expression of type I collagen, and alpha2 and beta1 integrin.[112,113] In the tree shrew mammalian myopia model, blockage of CXL with β-aminopropionitrile resulted in an increased degree of myopia-induced vitreous elongation and scleral thinning at the posterior pole.[114]

Recent evidence has revealed that scleral CXL is a promising treatment for treating PM. Artificial crosslinking mediated by photo-oxidation between UV-A and riboflavin has been shown effective in stabilizing progressive keratoconus.[115,116] This "CXL technique" has been applied to the sclera to change scleral viscoelastic behavior, to prevent deformity under constant pressure over time in HM.[108] Animal studies have shown that scleral CXL with riboflavin and blue light (of intensity below a defined damage threshold) induced a long-lasting growth inhibitory effect.[117] In the near future, newer scleral CXL techniques using chemicals activated by visible light or non–light-activated chemicals may be introduced as possible treatments to increase scleral tissue stiffness, and to inhibit excessive axial elongation of highly myopic eyes. In addition to the risks inherent with UV-A, it is ergonomically challenging to irradiate the posterior sclera with light.[118] Specifically, UV-A/riboflavin treatment of the cornea has been associated with cortical cataracts and keratocyte death.[119,120] UV-A use with scleral CXL has been associated with decreased dark-adapted ERG amplitudes up to 3 months posttreatment, with apoptotic cells and ultrastructural changes in retina layers also found.[121] Scleral CXL remains in the experimental stage with no human trials as of yet. Alternatives include CXL with visible light (McFadden SA, et al. *IOVS* 2010;51:ARVO E-Abstract 1192) and CXL without light (i.e., glutaraldehyde, glyceraldehyde, nitroalcohols, genipin), which have been suggested to provide stabilization of scleral shape in progressive myopia (Hoang Q, et al. *IOVS* 2013;ARVO E-Abstract 5169).[111,118,119,122–130] Glyceraldehyde is a non–light-activated chemical shown to increase scleral rigidity, but has ill effects on the neighboring cornea and muscles.[120]

Alternatively, topical beta-nitroalcohols (or "BNAs," commonly found in antibiotics and shampoos) and formaldehyde releasers (or "FARs," which are preservatives found in cosmetics, body wash, and ophthalmic solutions; e.g., BLU Gel A multidose artificial tears, SOOFT italia [Montegiorgio FM, Italy]) effectively crosslink corneal and scleral collagen in vitro, and have very good safety profiles (Hoang Q, et al. *IOVS* 2013;54:ARVO E-Abstract 136).[122–127] Specifically, in a comparative toxicity study of nine topical crosslinking agents in four different cell lines with a semiquantitative analysis using five categories of toxicity/fixation (Hoang Q, et al. *IOVS* 2013;54:ARVO E-Abstract 136), the toxicity levels varied by a factor of 10^3, with the least toxic being mononitroalcohol BNAs, and genipin among the most relatively toxic.[122] Ultimately, regardless of the scleral reinforcement approach used, it is paramount to detect scleral weakness before staphyloma formation, to determine which highly myopic eyes are headed down the path toward staphyloma and MMD formation. We have used both quantitative ultrasound (Mamou J, et al. *IOVS* 2018;59:ARVO E-Abstract 712) and super-resolution three-dimensional magnetic resonance imaging[123] to localize areas of scleral weakness in both guinea pigs ex vivo and human in vivo.

Conclusions

Approaches to prevent myopic pathology must use both early interventions directed at early-stage myopia in children, as well as preventive and rescue treatments for advanced disease states (HM and PM) in adults directed toward vision-threatening changes (Fig. 4). The most important modifiable environmental factor for myopia is outdoor time during early childhood. The mechanisms of myopia onset and progression have not been fully proven, and the onset and progression may be mediated

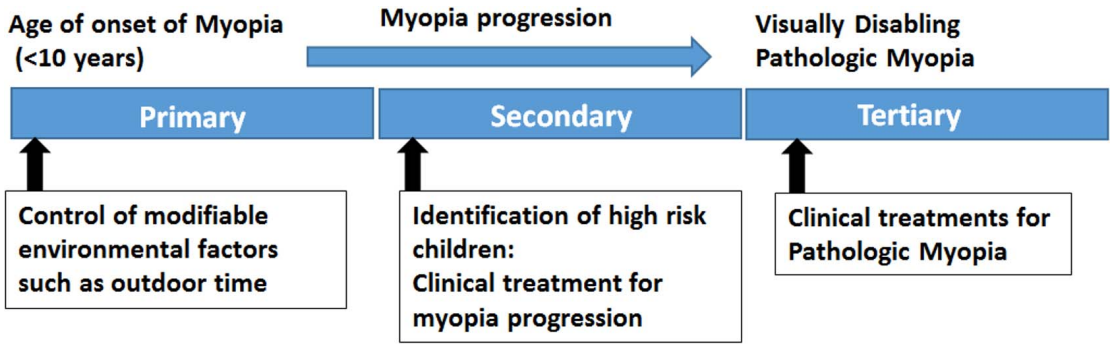

FIGURE 4. Diagram on prevention (primary, secondary, tertiary).

by different mechanisms. Encouraging children to spend more time outdoors is an excellent strategy to prevent or delay myopia onset. On the other hand, current treatment options that include low doses of atropine (0.01%) are known to contribute to a favorable outcome on myopia progression. These strategies may act via different mechanisms. Thus, we proposed that the best way to stop the epidemic of HM is a multi-pronged approach to tackle both myopia onset and progression. A combination of increased outdoor time and medical treatments such as atropine can lower the prevalence of myopia and HM in young adults and decrease the risk of developing PM. This is also significant from an economic standpoint, in which the mean annual costs of myopia in Singapore (due to annual visits, optical purchases, and LASIK surgery) are estimated to be US$148 per child in teenagers and US$709 in adults.[131] Reducing the prevalence of myopia from 83% (5 million) to 70% (4.2 million) across all age groups in the next few decades can thereby potentially save $1000 per adult per year.

Although new treatment strategies against PM, such as anti-VEGF and surgical treatment have shown favorable outcomes, considerable challenge remains in the management of vision-threatening changes caused by PM. Therefore, well-timed interventional measures are needed to retard myopia progression.

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Investigative Ophthalmology & Visual Science

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