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Myopia and orthokeratology for myopia control

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The prevalence of myopia in children is increasing worldwide and is viewed as a major public health concern. This increase has driven interest in research into myopia prevention and control in children. Although there is still uncertainty in the risk factors underlying differences in myopia prevalence between ethnic groups, rates in children of East Asian descent are typically higher regardless of where they live. Mounting evidence also suggests that myopia prevalence in children increases with age. Earlier commencement and more rigorous education systems in these countries, resulting in more time spent on near-work activities and less time on outdoor activities, may be responsible for the earlier age of myopia onset. However, to date, the mechanisms regulating myopia onset and progression are still poorly understood. Findings from several studies have shown orthokeratology to be effective in slowing axial elongation and it is a well-accepted treatment, particularly in East Asian regions. While our understanding of this treatment has increased in the last decade, more work is required to answer questions, including: How long should the treatment be continued? Is there a rebound effect? Should the amount of myopia control be increased? To whom and when should the treatment be offered? Practitioners are now faced with the need to carefully guide and advise parents on whether and when to undertake a long somewhat complex intervention, which is costly, both in time and money. In the near future, a greater demand for effective prophylaxis against childhood myopia is envisaged. Other than orthokeratology, atropine therapy has been shown to be effective in slowing myopia progression. While its mechanism of control is also not fully understood, it is likely that it acts via a different mechanism from orthokeratology. Thus, a combined treatment of orthokeratology and atropine may have great potential to maximise the effectiveness of myopia control interventions.

Key words: myopia control, myopia prevalence, orthokeratology, review

Myopia is caused by excessive refractive power of the cornea or lens or a longer than normal axial length, with the latter accounting for over 95 per cent of human myopia.[1] To date, there is no universally accepted threshold for myopia in terms of refractive error or axial length. With respect to refractive error, myopia is most commonly defined in epidemiological studies as a spherical equivalent refraction (SER) of at least −0.50 or −0.75 or −1.00 dioptres (D),[2–6] but other studies have defined myopia as SER more than −0.25 D.[7] There is also no uniform definition of high myopia: different studies have defined high myopia as a refractive error of at least −5.00 D, −6.00 D, or −8.00 D; or axial length greater than 25.5 mm,[8] 26 mm, or 26.5 mm.[9–14]

Prevalence of myopia in children

The prevalence of myopia in children as reported in cross-sectional studies varies worldwide, attributable to several factors, which include the targeted study population (population-based or school-based), methods of measurement (cycloplegic or non-cycloplegic), ethnicity, the definition of myopia, as well as the cut-off age for recruitment (Table 1). Although this makes it difficult to provide straightforward comparisons of myopia prevalence worldwide, a general comparison strongly suggests that childhood myopia has reached unprecedented levels in certain areas (Eastern Asia), justifying the necessity for interventions to slow the progression of myopia in children.

Studies on the prevalence of myopia performed in the last two decades revealed that myopia was present in less than five per cent of children at age five, irrespective of ethnicity, or whether the children were living in urban or rural areas (Table 1). However, in Chinese children, an upward trend in myopia prevalence commenced around age seven and increased exponentially throughout the older age groups. For instance, in the early 2000s, in metropolitan Guangzhou, myopia prevalence was only 3.3 per cent and 6.8 per cent in children aged five and seven, respectively, but increased rapidly to 13.7 per cent, 25.3 per cent, 55.8 per cent, and 73.1 per cent in children aged eight, 10, 13, and 15, respectively.[15]

A similar trend was observed in rural Shunyi, China[16] and also more recently in

Author	Sites/year conducted/ sample size	Methodology and myopia definition (D)	Age, years	Prevalence, %	High myopia (D)/prevalence
Sun et al.[3]	China (Qingdao)/2015–2016/3,753	Cycloplegic autorefraction SER < –0.50	10	22.6	SER ≤ –6.00/1.3%
			11	32.7	1.5%
			12	45.7	3.9%
			13	56.9	6.9%
			14	66.3	8.2%
			15	69.3	9.1%
			Overall	52.0	5.7%
Rim et al.[2]	South Korea/2008–2012/7,486	Non-cycloplegic autorefraction SER ≤ –0.75	5–6	20.4	SER < –6.00/0.1%
			7–11	58.4	2.1%
			12–18	80.2	9.3%
Li et al.[28]	China (Heilongjiang)/––/1,675	Cycloplegic autorefraction SER ≤ –0.75	5–18	5.0	––/––
French et al.[20]	Australia/2004–2005/4,118 (6 years: 1,765; 12 years: 2,353)	Cycloplegic autorefraction SER ≤ –0.50	6	1.4	––/––
				European Caucasian: 0.7	–
				East Asian: 2.4	–
			12	11.5	–
				European Caucasian: 4.4	–
				East Asian: 38.5	–
	Australia/2008/2,059 (12 years: 863; 17 years: 1,196)		12	18.9	–
				European Caucasian: 8.6	–
				East Asian: 52.5	–
			17	30.8	–
				European Caucasian: 17.7	–
				East Asian: 59.1	–
Wen et al.[5]	USA/2002–2008/3,008 (Asian: 1,507; non-Hispanic White: 1,501)	Cycloplegic autorefraction and retinoscopy SER ≤ –1.00	6–72 months	Non-Hispanic White: 1.2	––/––
				Asian: 3.98	–
Wu et al.[35]	China (Shandong)/––/6,026	Cycloplegic autorefraction SER ≤ –0.50	4	1.7	SER ≤ –6.00/0
			5	0.8	0
			6	4.1	0.5%
			12	54.5	1.8%
			15	72.8	7.3%
			18	80.4	2.8%
			Overall	36.9	2.0%
Lam et al.[6]	Hong Kong/2005–2010/2,651	Non-cycloplegic autorefraction SER < –0.50	6	18.3	SER < –6.00/0.7%
			7	26.4	0
			8	46.4	1.4%
			9	51.4	1.6%
			10	59.3	1.7%
			11	63.9	3.8%
			12	61.5	3.8%
			Overall	47.5	1.8%

Table 1. Prevalence of myopia in children

Author	Sites/year conducted/ sample size	Methodology and myopia definition (D)	Age, years	Prevalence, %	High myopia (D)/prevalence
Logan et al.[19]	England/––/596 (6–7 years: 327; 12–13 years: 269)	Cycloplegic autorefraction SER ≤ −0.50	6–7	9.4	––/––
				South Asian: 10.8	–
				Black African Caribbean: 11.4	–
				White European: 5.7	–
			12–13	29.4	–
				South Asian: 36.8	–
				Black African Caribbean: 27.5	–
				White European: 18.6	–
Dirani et al.[36]	Singapore/2006–2008/2,639	≥ 1 year cycloplegic autorefraction If autorefraction failed or < 1 year cycloplegic retinoscopy SER ≤ −0.50	6–11 months	15.8	SER ≤ −6.00/0
			12–23 months	14.9	0
			24–35 months	20.2	0
			36–47 months	8.6	0.6%
			48–59 months	7.6	0.4%
			60–72 months	6.4	0.2%
			Overall	11.4	0.2%
MEPEDS Group[24]	USA/––/6,024 (Hispanic: 3,030; African American: 2,994)	Cycloplegic autorefraction and retinoscopy SER ≤ −1.00	6–72 months	African American: 6.6	––/––
				Hispanic 3.7	–
Pi et al.[27]	China (Yongchuan), rural/2006/3,070	Cycloplegic retinoscopy SER ≤ −0.50	6	0.4	––/––
			7	1.9	–
			8	5.0	–
			9	8.6	–
			10	9.4	–
			11	16.9	–
			12	19.3	–
			13	21.0	–
			14	28.8	–
			15	27.1	–
			Overall	13.8	–
Plainis et al.[22]	Greece and Bulgaria/ 2006–2007/898 (0–15 years; Bulgarian: 310; Greek: 588)	Non-cycloplegic autorefraction SER ≤ −0.75	10–15	Bulgarian: 13.5	––/––
				Greek: 37.2	–
					–
					–
					–
Vitale et al.[23]	USA/1971–1972; 1999–2004/––	Lensometry on spectacles	12–17	1971–1972	
				Black and White: 24	SER ≤ −7.90/0.4%
				Black: 12	–
				White: 25.8	–
			12–17	1999–2004	
				Black and White: 33.9	0.3%
				Black: 31.2	–
				White: 34.5	–
Robaei et al.[34]	Australia/2003–2004/1,740	Cycloplegic autorefraction SER ≤ −0.50	6	1.4	–
					–

Table 1. Continued

Author	Sites/year conducted/ sample size	Methodology and myopia definition (D)	Age, years	Prevalence, %	High myopia (D)/prevalence
Goh et al.[25]	Malaysia (Gombak District)/2003/4,634	Cycloplegic retinoscopy/ cycloplegic autorefraction	7	9.8/10	−−/−−
			8	13.6/14	–
		SER ≤ −0.50	9	16.3/16.3	–
			10	14.3/16.2	–
			11	20.4/22.6	–
			12	23/24.8	–
			13	23/25.3	–
			14	30.6/32.5	–
			15	34.4/32.5	–
			Overall	19.3/20.7	–
Saw et al.[18]	Singapore/1999–2002/273 (Chinese: 231; non-Chinese: 42)	Cycloplegic autorefraction	7	42.7	−−/−−
		SER ≤ −0.50	8	38.4	–
		Incident myopia over 3 years	9	32.4	–
Lin et al.[7]	Taiwan/1983–2000/4,125 (1983), 10,878 (2000)	Cycloplegic autorefraction	7	1983: 5.8	SER < −6.00/−−
		SER ≤ −0.25		2000: 21	–
			12	1983: 36.7	–
				2000: 61	–
			15	1983: 64.2	–
				2000: 81	–
			16–18	1983: 74	–
				2000: 84	–
			18	–	1983: 10.9%
				–	2000: 21%
He et al.[15]	China (Guangzhou)/ 2002–2003/4,364	Cycloplegic retinoscopy/ cycloplegic autorefraction	5	3.3/5.7	SER ≤ −6.00/−−
			6	2.7/5.9	–
		SER ≤ −0.50	7	6.8/7.7	–
			10	25.3/30.1	–
			13	55.8/57.4	–
			15	73.1/78.4	4.8%/−−
			Overall	35.1/38.1	–
Naidoo et al.[33]	South Africa (Durban area)/ 2002/4,890	Cycloplegic retinoscopy/ cycloplegic autorefraction	5	1.9/3.2	−−/−−
			6	1.6/4.6	
		SER ≤ −0.50	15	9/9.6	
			Overall	2.9/4.0	
Dandona et al.[32]	India (Mahabubnagar District)/2000–2001/4,074	Cycloplegic retinoscopy	7	2.8	SER ≤ −2.00/−−
		SER ≤ −0.50	8	2.83	–
			15	6.72	–
			Overall	4.1	1.3%/−−
Mruthy et al.[26]	India (New Delhi), urban/2000/5,696	Cycloplegic retinoscopy	5	4.7	SER ≤ −2.00/−−
		SER ≤ −0.50	6	5.9	–
			7	3.1	–
			8	5.7	–
			9	5.3	–
			10	7.0	–
			11	9.9	–
			12	9.7	–
			13	10.6	–
			14	10.2	–
			15	10.8	–
			Overall	7.4	1.8%

Table 1. Continued

Author	Sites/year conducted/ sample size	Methodology and myopia definition (D)	Age, years	Prevalence, %	High myopia (D)/prevalence
Saw et al.[17]	Singapore/1999, 2001/––	Cycloplegic autorefraction SER ≤ −0.50	7	29.0	–
			8	34.7	–
			9	53.1	–
Villarreal et al.[21]	Sweden/1997–1998/ 1,045	Cycloplegic retinoscopy SER ≤ −0.50	12–13	49.7	SER ≤ −5.00/2.5%
Maul et al.[30]	Chile (La Florida, Santiago)/1998/5,303	Cycloplegic retinoscopy SER ≤ −0.50	5	3.4	––/––
			5–7	3.5	–
			14–15	12.5	–
			15	Male: 19.4	–
				Female: 14.7	–
			Overall	7.3	–
Zhao et al.[16]	China (Shunyi)/1998/ 5,884 (5–15 years)	Cycloplegic retinoscopy/ cycloplegic autorefraction SER ≤ −0.50	15	Male: 36.7	–
				Female: 55	
			Overall	16.2/21.6	
Pokharel et al.[31]	Nepal/1998/5,067	Cycloplegic retinoscopy SER ≤ −0.50	5–15	1.2	–

SER: spherical equivalent refraction.

Table 1. Continued

the Economic and Technological Development Zone of Qingdao (Eastern China).[3] These results contrasted strongly with those reported in non-Eastern ethnicities (Table 1). It is apparent that a comparatively early and rapid increase underlies the high prevalence of myopia in Chinese children.

A cross-sectional study conducted in Hong Kong between late 2005 and early 2010 determined that myopia prevalence was 18.3 per cent in six-year-old preschool children and increased to 61.5 per cent by age 12. The magnitude of myopia also increased with age, with a mean of 0.06 D at age six and −1.67 D at age 12. High myopia (SER > 6.00 D), increased from 0.7 per cent at age six to 3.8 per cent at age 12, representing a four-fold increase.[6]

In Taiwan, pooled results from five nationwide surveys of ocular refraction, dating back to 1983 and ending in 2000, revealed that the prevalence of myopia, which was 5.8 per cent in children aged seven and 36.7 per cent in those aged 12 in 1983, increased to 21 per cent and 61 per cent respectively by 2000.[7] The prevalence of high myopia in young adults aged 18 rose from 10.9 per cent in 1983 to 21 per cent by 2000. This paralleled an increase in the average magnitude of myopia with age from 0.52 D at age seven and −0.48 D at age 12 in 1983 to 0.17 D and −1.45 D by 2000.[7] Overall, more children became myopic and tended to be more myopic in 2000, compared with the same age group in 1983.

The Singapore Cohort Study of Risk Factors for Myopia (SCORM), a cross-sectional, school-based study (1999–2002) of children aged seven to nine years, reported that the age-specific prevalence of myopia was 29.0 per cent in seven-year-olds, 34.7 per cent in eight-year-olds, and 53.1 per cent in nine-year-olds.[17] The three-year cumulative incidence rates were 47.7 per cent, 38.4 per cent, and 32.4 per cent for seven-, eight-, and nine-year-old children, respectively.[18] These results indicated a high level of myopia prevalence and progression in children in Singapore.

The most recent report of The Korean National Health and Nutrition Examination Survey (KNHANES), involving children aged five to 18 years from 2008 to 2012, demonstrated that myopia prevalence increased from 20.4 per cent in the 5–6 age group to 58.4 per cent and 80.2 per cent in the 7–11 and 12–18 age groups, respectively.[2] The rate of high myopia in this study reached 9.3 per cent in children over 12 years. However, there is no longitudinal data to determine if there is a rising trend in prevalence of childhood myopia in South Korea.

With respect to ethnic differences, a study conducted in England found that children of Asian origin demonstrated higher myopia prevalence rates of 36.8 per cent compared to 18.6 per cent in white European children aged 12–13 years.[19] A study, conducted between 2009–2011 in Australia revealed differences in myopia prevalence with respect to ethnicity, with 52.5 per cent and 59.1 per cent in 12-year-old and 17-year-old school-aged children of East Asian ethnicity, respectively, in contrast to 8.6 per cent and 17.7 per cent in Caucasian children.[20] The prevalence of myopia in Swedish children aged 12–13 years (1997–1998) was 49.7 per cent[21] and those of Greek and Bulgarian children aged 10–15 years were 37.2 per cent and 13.5 per cent, respectively.[22]

In the UK, myopia prevalence in children aged six to seven years and 12–13 years was 9.4 per cent and 29.4 per cent, respectively.[19] In the USA, Vitale et al. reported that myopia prevalence had increased in children aged 12–17, from 12.0 per cent to 31.2 per cent in Blacks and from 25.8 per cent to 34.5 per cent in Whites over the preceding 30 years.[23] In pre-school children (six months to six years old) (between 2002 and 2008), it was reported to be 1.2 per cent in non-Hispanic Whites, 3.7 per cent in Hispanics, 4.0 per cent in Asians, and 6.6 per

cent in African Americans.[5,24] However, with no longitudinal data available, it is unclear if myopia prevalence is increasing in this age group.

Trend of myopia prevalence

The effect of ethnicity on myopia prevalence is seen in children of Asian descent, who typically have higher prevalence rates regardless of whether they live in Asia or elsewhere. This was noted in California[5] and in Singapore, where the myopia prevalence in children of Chinese origin was almost two-fold greater than children of Malay origin.[25] However, the risk factors underlying differences in myopia prevalence between ethnic groups is still uncertain. Both genetic and environmental factors, and their interaction, may contribute to the difference.

There is a trend that myopia prevalence in children increases with age. This trend is more obvious in Asia. For example, myopia prevalence increased from 21 per cent in seven-year-olds to 61 per cent in those aged 12 in Taiwan,[7] from 57.4 per cent at age 13 to 78.4 per cent at age 15 in southern China,[15] and from 18.3 per cent in preschool children aged six to 61.5 per cent in those aged 12 in Hong Kong.[6] Elsewhere, rates also increased with age, albeit not as dramatically due to a lower overall prevalence: only 4.7 per cent of children were myopic at age five, which increased to 10.8 per cent by age 15 in India.[26] In Australia, 8.6 per cent of children aged 12 were myopic, compared to 17.7 per cent of those aged 17.[20]

Studies conducted in rural and urban areas in China suggest that myopia prevalence has dramatically increased in some urbanised regions. Results have shown overall myopia prevalence of 21.6 per cent in a semi-rural community near Beijing versus 38.1 per cent in Guangzhou, reported in 2000 and 2004, respectively.[15,16] Other cross-sectional studies provide less comparable results due to the different survey methods used. However, they do suggest that the prevalence in mainland China differs by areas and regions, and the figure is comparatively lower in less developed regions.

A survey in an urban area of western China, where socio-economic development is lower than that in southern China, revealed that the overall myopia prevalence was 13.7 per cent in schoolchildren aged between six and 15.[27] In northern China, a survey conducted in a rural area of Heilongjiang Province in children aged between five and 18, reported an overall myopia prevalence of five per cent.[28] In a more recent study, conducted from December 2015 to January 2016, in the Economic and Technological Development Zone of Qingdao (Eastern China), Sun et al.[3] reported an overall prevalence of 52 per cent in 10–15-year-old children.

In theory, the difference in the genetic makeup of Chinese children would not cause such an obvious difference among rural and urbanised regions, so it is likely that different environmental exposures lead to differences between rural and urban areas.

Age of myopia onset in children

Chua et al.[29] demonstrated that children in Singapore who had a younger onset age were more likely to develop severe myopic refractive error, indicating that the age of onset of myopia plays an important role in myopia progression. Globally, myopia has been reported to commence at around age six, the age at which children enter primary school. Studies conducted at different sites have shown that myopia was uniformly less than five per cent at age five, indicating that myopia at this age is almost absent in various ethnic groups, regardless of living in urban or rural areas.[15,16,25,26,30–33]

Myopia prevalence was comparatively low in children under the age of six in the USA, with only 1.2 per cent in non-Hispanic Whites, 3.7 per cent in Hispanics, and four per cent in Asians.[5,24] It was reported that only 1.4 per cent of six-year-old children were myopic in Australia.[34] However, the prevalence in children aged six in East Asia is in stark contrast to those elsewhere: 4.1 per cent in China,[35] 6.4 per cent in Singapore,[36] 18.3 per cent in Hong Kong,[6] and 20.4 per cent in South Korea,[2] implying a younger age of myopia onset may occur in these areas. It was suggested that the early commencement and more rigorous education systems in East Asian countries and families of East Asian origin may lead to more time spent on near-work activities and less on outdoor activities, and could be responsible for the earlier age of myopia onset.[29]

Progression rate of myopia in children

Although several longitudinal observational studies of myopia among children have been conducted in East Asia, the USA, and Australia, the reported progression rate varied by regions and ethnicity, making it difficult to make comparisons.[37] Based on data from previously mentioned studies, it appears that the myopia progression rate is faster in younger children and in those of Asian ethnicity.

In the USA, an annual progression rate of −0.38 D was reported in children with a mean age of nine.[38] However, this annual progression rate is not ethnicity-specific. In Australia, annual progression rates of −0.28 D in seven-year-olds and −0.21 D in 12-year-olds were found in children of East Asian ethnicity, compared to only −0.13 D in seven-year-olds and −0.11 D in 12-year-old Caucasian children,[20] suggesting that children of East Asian ethnicity tend to have higher progression rates than their Caucasian counterparts.

In China, an annual incidence of myopia of 7.8 per cent and an annual rate of myopia progression of −0.17 D in children aged 5–13 years were observed.[39] A later study[40] reported an annual incidence of 10.6 per cent and an annual progression of −0.43 D in children aged 6–15 years. However, there is a lack of age-related myopia progression rates in these studies. In contrast, in Singapore, three-year cumulative mean myopia progression rates of −2.40 D in seven-year-olds, −1.97 D in eight-year-olds, and −1.71 D in nine-year-olds (respective annual progression rates of −0.80 D, −0.66 D, and −0.57 D) were reported, indicating that myopia progression slows down with age.[18]

In Hong Kong, the average rate of myopic progression was reported to be −0.40 D per year in Chinese children aged 5–16 years.[41] The average annual change in SER for myopic children was −0.63 D, compared with −0.29 D for those who were not myopic at the beginning of the study, suggesting that the progression rate was faster in children who were already myopic than in those who were not myopic at the commencement of the study. A similar trend was reported in Japan where the annual progression rate of 12-year-olds ranged from −0.14 D (for the +1.00 D group) to −0.40 D (for the −2.00 D group) when data were stratified according to baseline refractive error.[42]

Associated ocular disease and goal of myopia control

There is a documented dose-related relationship between myopia and sight-threatening

ocular diseases, such as myopic maculopathy,[43–45] glaucoma,[46,47] cataract,[48–50] and retinal detachment.[51–53] Although retinal problems are associated with increased axial length, the old division of myopia into 'physiological' and 'pathological' myopia by a simple cut-off value of refractive error of –5.00 D or –6.00 D is arbitrary and imprecise, because ocular pathologies also occur in 'physiological' myopia.[54] Therefore, even physiological myopes have additional risks compared with emmetropes.

Given the high prevalence of myopia in children in Eastern Asia, in conjunction with its strong association with sight-threatening ocular diseases, myopia has become a major public health concern. Furthermore, there is a tendency of childhood myopia to progress until adulthood, rendering children with early onset or fast progression of myopia at greater risk of suffering from sight-threatening ocular diseases when they reach adulthood.

In addition to elevated risks of complications of myopia with increased refractive error, myopia correction imposes an increased financial burden on families with myopic children. Although limited information is available regarding the overall cost/benefits of myopia correction in children, it is reasonable to conclude that the cost of myopia tends to escalate with increasing myopia incidence and prevalence.[55] Taken together, the high prevalence of childhood myopia with the elevated risk of sight-threatening ocular complications in myopic eyes in later life, makes the aim of myopia control clear: to reduce such risks and prevent sight-threatening complications later in life by retardation of myopia progression as early as possible in childhood.

Mechanism of myopia progression

Currently, the mechanisms regulating myopia onset and progression remain poorly understood. Various hypotheses for its development have been proposed. However, to date, no single theory can fully explain the aetiology of myopia.

The presence of optical defocus is a result of the mismatch between the retina and the retinal image plane; hyperopic defocus is induced when the retinal image is focused behind the retina, while myopic defocus is present when the retinal image is focused in front of the retina. The presence of optical defocus, especially hyperopic defocus, has been suggested as one of the potential aetiologies of myopia onset and progression.[56,57] However, to date, no consensus has been achieved for this and it remains an active area of research. The evidence supporting optical defocus as a major predisposing factor for myopia is mainly extrapolated from animal studies, principally based on lens compensation experiments, which involve the fixing of negative and positive lenses on neonatal animals to investigate how corresponding optical defocus influences refractive error development.[58]

The measurement of relative peripheral refraction, defined as the refractive error difference between the central and peripheral retina, was pioneered by Rempt et al., who examined horizontal peripheral refraction profiles in adult emmetropes, hyperopes, and myopes using retinoscopy.[57] Several studies have reported consistent results concerning relative peripheral refraction in children with hyperopic or myopic status, determining that opposing relative peripheral refraction is present in myopic and hyperopic children – hyperopic unaided eyes tend to have myopic relative peripheral refraction, whereas myopic unaided eyes tend to show hyperopic relative peripheral refraction in the horizontal meridian.[59–61] However, there is controversy over the generality of this finding with respect to other meridians.[62–64]

For emmetropic children, the results obtained are inconsistent, as it was reported that peripheral refraction within 30° was relatively myopic, but beyond 30°, relative peripheral refraction was relatively hyperopic in emmetropes,[60] and relative peripheral refraction was found to be almost zero in emmetropic children with no difference between central and peripheral refraction.[61] Taken together, these studies demonstrate that myopic and hyperopic children experience opposing relative peripheral refraction, at least in the horizontal meridian.

With respect to emmetropic eyes, inconsistent results make it impossible to draw any conclusion. Mutti et al. showed that emmetropes who eventually became myopic started to exhibit hyperopic relative peripheral refraction two years before its onset.[65] However, their subsequent study showed that, although relative peripheral refraction varied with ethnicity, there was no significant association between the amount of hyperopic relative peripheral refraction and either the onset or progression of childhood myopia, suggesting that peripheral refraction does not predict future myopic progression.[38]

An insignificant association between relative peripheral refraction and myopia progression was also found in studies conducted solely in Asian children.[60,66] Therefore, there is no direct evidence to support that hyperopic peripheral defocus is the determinant of myopia development. More recent longitudinal studies[38,60,66,67] suggest that hyperopic relative peripheral refraction is a result, rather than the cause, of the development of myopia. Rosen et al.[68] suggested that the belief in the association arose from a misunderstanding of the findings reported by Hoogerheide et al.,[56] who actually reported relative peripheral refraction after, rather than before, myopia development in their subjects. It was proposed that the eye stops growing when relative peripheral emmetropia has been achieved.[69]

It is possible that peripheral refraction in the myopic eye may be magnified, maintained, reduced, neutralised, or even inverted by corrective lenses. In addition, various treatment lenses, including spectacles and contact lenses, have been designed, based on the hypothesis that, by modifying peripheral defocus, myopia progression in children may be slowed.

Orthokeratology for myopia control

First introduced in the early 1960s, orthokeratology lenses originally used conventional bicurve hard polymethylmethacrylate contact lenses, fitted significantly flatter than K. They suffered from poor centration and unpredictable myopia reduction[70] and their use was discontinued. In the late 1980s, reverse geometry lenses, which included a steeper reverse curve were introduced. These three-zone orthokeratology lenses allowed better centration, as well as more predictable and faster myopia reduction, thus being termed accelerated orthokeratology.[71,72]

Modern orthokeratology lenses are designed with four to five curves, achieved by adding peripheral alignment curves to further improve lens centration. In addition to the improved design of orthokeratology lenses, the application of corneal topography allows further optimisation of the lens fit and more accurate monitoring of the corneal response during follow-up. Furthermore, the

introduction of highly oxygen-permeable lens materials allows for safer overnight wear and good unaided visual acuity in the daytime after stabilisation of the treatment.

Based on these considerable technical improvements, orthokeratology is currently regarded as a safe approach for myopia correction up to 6.00 D.[73] More importantly, orthokeratology is a major intervention for myopia retardation in children, as its effectiveness has been demonstrated in various studies, although the mechanism behind the control effect is still unclear.[74–80] While it is well-documented that orthokeratology lenses convert relative peripheral defocus of the eye from being hyperopic pre-treatment to being myopic post-treatment, regardless of the wearing time,[81–83] the causal relationship between the reduction in relative peripheral refraction defocus with myopia retardation by orthokeratology has not been established. It is therefore difficult to conclude that the modified peripheral defocus underlies the retardation effect of this treatment.

In Hong Kong, a two-year pilot study involved 35 children aged 7–12 years in a treatment group of orthokeratology and 35 children in an historical single-vision spectacle lenses control group. The mean increase in axial length of 0.29 mm in the orthokeratology group was significantly lower than that of 0.54 mm in the control group, indicating a reduction rate of 46 per cent induced by orthokeratology.[80] A similar result was obtained when only the vitreous chamber depth was considered. This was the first clinical trial that demonstrated that orthokeratology is effective for the retardation of myopia progression in children.

To confirm the results obtained in Hong Kong, a two-year study was conducted in the USA, involving 40 children aged 8–11 years in an orthokeratology group.[76] A group of subjects who were randomly assigned to wear soft contact lenses in a previous study were used as an historical control group. The axial length increase over two years in the orthokeratology group was 0.32 mm less than those wearing soft contact lenses (0.25 mm versus 0.57 mm), indicating a significant control effect of orthokeratology in comparison to subjects wearing single-vision soft contact lenses.

Two cohort studies were also conducted in Japan. The first two-year study recruited children aged 8–16 years; 45 children and 60 children were enrolled in the orthokeratology treatment group and the single-vision spectacle lenses group, respectively.[75] The increase in axial length over two years was significantly different between groups: 0.39 mm and 0.61 mm in the orthokeratology and the single-vision spectacle lenses groups, respectively, giving a myopia control effect of 36 per cent. However, it is important to note that the baseline axial length for the orthokeratology group was measured after three months of treatment, whereas the control group were measured at the commencement of the study. This difference in measurement time of baseline axial length may lead to an underestimation of axial length changes in the treatment group, thus possibly underestimating the reduction in the rate of myopia progression induced by orthokeratology.

As most studies examining the effectiveness of orthokeratology have been limited to 24 months, the treatment duration of a further study in Japan was extended to five years with the aim to elucidate the long-term effectiveness of orthokeratology.[84] A total of 59 children aged 8–12 years were enrolled, including 22 (12 orthokeratology, 10 controls) from Kakita's study,[75] and the treatment was self-selected rather than randomised (29 in the orthokeratology group and 30 children in the single-vision spectacle lenses group). It demonstrated that the 0.99 mm increase in axial length over five years for the orthokeratology group was significantly lower than 1.41 mm for the control group, indicating an overall 30 per cent reduction rate in orthokeratology wearers over five years. Further analysis revealed that the treatment effect of orthokeratology was greater in the first year, as the reduction rate in axial growth of the orthokeratology group decreased from 50 per cent in the first year to 30 per cent in the fifth year. The differences in axial length between the orthokeratology and single-vision spectacle lenses groups were significant for the first, second, and third years, but not for the remaining two years, suggesting the treatment effect of orthokeratology was limited to the first three years of treatment, when children were experiencing active eye growth. Again, this study took the baseline axial length measurement after three months of treatment, possibly underestimating the axial length changes in the treatment group.

In Spain, a two-year study involving children aged 6–12 years revealed that the increase in axial length over two years of 29 children fitted with orthokeratology was significantly lower than that of 24 children wearing single-vision spectacle lenses (0.47 mm versus 0.69 mm).[77] This study was not randomised and the treatment was allocated by self-selection. The reduction of 32 per cent in axial growth in children receiving orthokeratology treatment was comparable to those obtained in Japan (36 per cent), but lower than that in Hong Kong (46 per cent). Fourteen children who continued wearing orthokeratology lenses returned five years later[85] and their axial elongation was 33 per cent slower than that in the control group, which consisted of four single-vision spectacle lenses and 12 subjects who switched from single-vision spectacle lenses to single-vision soft contact lenses.

In mainland China, an analysis based on medical records of 65 orthokeratology treated children and 63 children corrected with single-vision spectacle lenses, showed that orthokeratology effectively slowed myopia progression in children, with a reduction rate of 59 per cent (0.16 mm versus 0.39 mm) and 50 per cent (0.34 mm versus 0.70 mm) for the first and second year, respectively.[86] Unlike previously mentioned studies, which only involved children with low to moderate myopia, a major strength of this study was that children with high myopia up to −10.00 D were included. Myopia reduction up to 6.00 D was induced by orthokeratology in these highly myopic eyes and residual myopia was corrected by spectacles, when the orthokeratology treatment stabilised. Further analysis revealed that reduction rates were 49 per cent, 59 per cent, and 46 per cent for the low (> −3.00 D), moderate (> −6.00 D) and high myopia subgroups (≤ −6.00 D), respectively, indicating the myopia control effect of orthokeratology is comparable for children with low to high myopia.

However, the retardation effect demonstrated in previous studies was achieved by the use of orthokeratology lenses with spherical design,[75–77,80,84–86] which are mainly used in children with lower corneal astigmatism less than 1.50 D. Toric orthokeratology, which may demonstrate different control effects in comparison to spherical designs, is recommended for myopic eyes with corneal astigmatism over 1.50 D to provide better centration and unaided vision in the daytime.[87] To investigate the effectiveness of toric orthokeratology in the retardation of myopia progression in children with moderate-to-high corneal astigmatism, a non-randomised clinical study, Toric

Orthokeratology – Slowing Eyeball Elongation (TO-SEE) study, was conducted in Hong Kong, involving myopic children with 1.25 D to 3.50 D astigmatism that was mainly corneal-derived.[78]

In the TO-SEE study, 35 children were treated with orthokeratology and 23 corrected with single-vision spectacle lenses. The mean increase of 0.30 mm in axial length over two years in the orthokeratology group was significantly lower than the 0.64 mm observed in the control group, that is, axial elongation was reduced by 52 per cent in the orthokeratology subjects compared to the control group. Moreover, myopia progression in children was not associated with baseline astigmatism and initial corneal toricity, suggesting that corrected moderate-to-high astigmatism is not a stimulator of myopia progression.

In summary, several cohort studies have shown that orthokeratology is effective in retardation of myopia progression in children with a two-year reduction rate ranging from 30 per cent to 59 per cent and a five-year reduction rate of 30 per cent.

The effectiveness of orthokeratology was also successfully demonstrated by a randomised controlled trial, the Retardation of Myopia in Orthokeratology (ROMIO) study, in which 102 children aged 6–10 years, with myopia between −0.50 D and −4.00 D, were randomised into orthokeratology and single-vision spectacle lenses group.[74] Axial elongation of 0.36 mm in axial length observed in the orthokeratology group was significantly lower than the 0.63 mm in the control group, reflecting a reduction rate of 43 per cent after a two-year treatment with orthokeratology.

Further analysis showed that axial elongation in children was associated with initial age and treatment, rather than the initial degree of myopia.[74] In addition, the percentage of children younger than nine years with fast myopic progression was 20 per cent in the orthokeratology group, which was significantly lower than 65 per cent of those in the control group. In contrast, the percentages of older subjects with fast myopic progression in the orthokeratology and control groups were comparable (nine per cent versus 13 per cent), suggesting a slower progression rate in children aged over nine, regardless of treatment. Based on these results, the authors concluded that the effectiveness of myopia control from orthokeratology is better in younger children than older ones.

More recently, the combined data from ROMIO and TO-SEE studies were re-analysed[88] and it was observed that the percentage of subjects with rapid progression (that is axial elongation > 0.36 mm/year) was reduced from 67 per cent at the age of six to 28 per cent at the age of eight years, and less than 15 per cent of the older subjects (9–12 years). At the end of two years, younger (6–8 years) subjects wearing single-vision spectacle lenses showed the greatest and most rapid axial elongation, and orthokeratology lens wear significantly reduced the risk of rapid progression by 89 per cent. The 'number needed to treat' for the younger orthokeratology subjects was 1.8, which suggested that treating just two 6–8-year-old subjects with orthokeratology, instead of prescribing single-vision spectacles, could prevent one subject from rapid myopia progression over a two-year period of treatment.

Although studies have demonstrated that use of orthokeratology lenses can improve visual acuity and obviate the need for daytime visual aids, there is an actual limit of myopia reduction that can be induced by overnight wear of orthokeratology. Because high myopic reduction with commercially available orthokeratology lenses (for correction of low-moderate myopia) can lead to corneal staining, heavy lens binding, and lens decentration, which potentially compromises corneal health, full correction of highly myopic eyes using such lenses is not recommended for children.[89] Partial correction, for example up to −4.00 D, may be considered for highly myopic children, but it is necessary for them to wear additional single-vision spectacle lenses to correct residual refractive errors to maintain clear vision in the daytime. However, such an arrangement raises the question of whether partial reduction by orthokeratology in eyes with high myopia is still as effective as full reduction.

To investigate whether orthokeratology combined with single-vision spectacle lenses is effective in retarding myopia progression in highly myopic children, a two-year randomised controlled study in Hong Kong involving children aged 8–11 years was conducted.[79] Highly myopic children with a spherical equivalent refraction of at least 5.75 D were randomised into a single-vision spectacle lenses group and a treatment group, which involved partial reduction by orthokeratology combined with single-vision spectacle lenses correction in the daytime. The mean increase in axial length of the treatment group was 0.19 mm, which was 63 per cent lower than the 0.51 mm observed in the control group, indicating that partial reduction orthokeratology was effective in retarding myopia progression in highly myopic children by 63 per cent.

Safety of orthokeratology

All treatments carry risks, especially if not used properly, and orthokeratology is no exception. There are concerns about the safety of this treatment as overnight wear by children is involved. Prospective cohort studies published between 2011 and 2014 have reported only non-significant adverse effects, ranging from mild corneal staining,[74,78,79,86,90] mild conjunctival hyperemia,[74] mild corneal erosions,[75,84,90] to papillary conjunctivitis.[90] These problems, which can occur in association with any contact lens wear modality or lens type, were resolved satisfactorily, without any effects on vision.

Microbial keratitis, a serious sight-threatening condition, is associated with a number of factors, one of which is the use of contact lenses. Many studies have determined the incidence of microbial keratitis in contact lens and non-contact lens wearers,[91,92] but the incidence of microbial keratitis associated with overnight orthokeratology in children cannot be determined because of its short history of use. However, an attempt was made by Bullimore et al.,[93] who acknowledged the limitations of their study in view of the small number of cases reported. They investigated voluntary reports from practitioners on 1,317 orthokeratology wearers, about half of whom were children. The average orthokeratology treatment duration was two years and the only two incidents of microbial keratitis identified were in children. They estimated the risk of microbial keratitis to be 13.9 per 10,000 patient-years in children compared to 7.7 per 10,000 patient-years in all patients.

Watt and Swarbrick[94] identified 123 cases of microbial keratitis reported between 2001 to 2007, 64 of which had been reported in an earlier review in 2005.[95] These 64 cases originated from China (73.4 per cent), Taiwan (17.2 per cent), and Hong Kong (9.4 per cent) and involved infection with *Acanthamoeba* and *Pseudomonas*, which suggested use of tap water and poor hand hygiene. The incidence was reduced after

2001, which was likely to be due to the intervention of the Chinese government which tightened the regulation of orthokeratology practice in China.

In 2016, Liu and Xie[96] reviewed the safety of orthokeratology based on 170 papers, most of which were published in Chinese. They reported comparable risk of microbial keratitis in orthokeratology lens wearers and other overnight modalities and concluded that the treatment was safe, if good compliance from patients and practitioners was employed. In their meta-analysis, Li et al.[97] reported an odds ratio of 8.87 for encountering an adverse event in orthokeratology subjects compared to spectacle-wearing subjects. However, none of the adverse events observed were significant, with all subjects recovering quickly after clinical action was taken.

Microbial keratitis in orthokeratology is generally associated with poor practice, use, or compliance with care routines. A guideline on good clinical practice in orthokeratology was proposed,[98] which covered various areas such as the requirement for proper education on orthokeratology fitting, proper equipment, and a strict follow up schedule. Such guidelines aim to promote orthokeratology practice at the highest professional standard, thus minimising complications and other associated problems.

Axial elongation after discontinuation of orthokeratology

Most cohort studies and randomised controlled trials investigating the effectiveness of orthokeratology have focused on its retardation effect during the treatment period. Limited information is available regarding axial elongation after discontinuation of orthokeratology. As it is well-documented that there is a rebound effect in atropine treatment for myopia control in children,[99,100] it is highly likely that a rebound effect may also exist after discontinuation of orthokeratology.

Despite the above concern, currently, only one study has provided relevant information on axial elongation after discontinuation of orthokeratology. A 14-month study in Hong Kong, involving children aged 8–14 years from the previous ROMIO[74] and TO-SEE studies,[78] investigated the effects of discontinuation and resumption of orthokeratology lens wear in children.[101] The study consisted of two periods, each lasting seven months. Fifteen children wearing orthokeratology lenses in the preceding study discontinued orthokeratology wear in the first period, and lens wear was resumed in the second period. Thirteen and 16 children wearing single-vision spectacle lenses and orthokeratology, respectively, continued the previous treatment allocated in the ROMIO or TO-SEE studies for the whole study duration of 14 months.

The results showed that, in the first period of seven months, the children who discontinued orthokeratology demonstrated significantly faster axial elongation (0.153 mm) compared to those who continued wearing orthokeratology lenses (0.087 mm) and single-vision spectacle lenses (0.082 mm), respectively. However, the faster progression rate seen in period one in those who discontinued orthokeratology was comparable to that of children wearing single-vision spectacle lenses during the preceding two-year trial (TO-SEE and ROMIO studies). In other words, it appears that children who discontinued orthokeratology treatment resumed the progression rate of myopia that they would likely have demonstrated if they did not receive orthokeratology treatment.

Taking into account that this re-emergence of myopia progression was not worse than the rate in children wearing single-vision spectacle lenses during the preceding two-year trial, it cannot be defined as an actual rebound effect after discontinuation of the orthokeratology lens wear. In period two, when orthokeratology lens wear was resumed, the faster axial elongation demonstrated in period one in those who discontinued orthokeratology treatment slowed down, and the corresponding progression rate was comparable to that in those who continued orthokeratology lens wear without stopping (0.059 mm versus 0.068 mm) and those who wore single-vision spectacle lenses (0.059 mm versus 0.064 mm).

Based on these results, the authors concluded that faster axial elongation was present after discontinuation of orthokeratology in children (aged less than and equal to 14 years) who received two-year orthokeratology treatment, and the treatment should be resumed if myopia progression is observed during the first six months after discontinuation.

Orthokeratology and relative peripheral refraction

Orthokeratology leads to a steepening of the mid-peripheral cornea, correspondingly changing the status of peripheral defocus in orthokeratology-treated eyes. In addition, as the central refraction is fully or slightly over-corrected after orthokeratology treatment, the relative peripheral refraction would certainly become myopic after orthokeratology treatment. Several studies have characterised the alteration in periphery defocus after orthokeratology treatment, and yielded similar results, indicating that orthokeratology lenses reform relative peripheral refraction from a hyperopic pre-treatment state to being myopic post-treatment, regardless of the wearing time.[81–83]

Despite consensus on the ability of orthokeratology to reform relative peripheral refraction, controversy still exists over whether or not symmetrical relative peripheral refraction can be induced. Queiros et al.[81] demonstrated symmetrical myopic defocus induced beyond 25° of both the nasal and temporal visual fields one month after commencement of orthokeratology lens wear, when myopia was fully corrected. In contrast, asymmetrical myopic relative peripheral refraction has also been reported.

A study recruiting 16 adolescents and comparing their peripheral refraction before and after three months of orthokeratology treatment, found that significant myopic relative peripheral refraction was only present in the nasal visual field when the horizontal meridian was assessed.[82] Despite inconsistent findings in the temporal visual field, the observation that orthokeratology can lead to significant myopic relative peripheral refraction was further confirmed in a study which compared ten-day orthokeratology lens wear with multi-focal soft contact lenses to determine if a comparable magnitude of myopic defocus could be induced.[83]

However, it is important to note that the change of relative peripheral refraction induced by orthokeratology is highly likely to be driven by the amount of myopia reduction in the central field, rather than a cumulative effect of myopia reduction in the central field and the induction of myopic defocus in the periphery. Charman et al.[102] reported that refraction in the peripheral field of four adult wearers with low to

moderate myopia, was almost unchanged, while their central myopia had been 0.50 D over-corrected, thus rendering the relative peripheral refraction myopic in the periphery. Furthermore, it was demonstrated that the ratio of the highest myopic relative peripheral refraction induced in the periphery by orthokeratology to baseline central myopia was one to one,[81] implying that induced myopic relative peripheral refraction is inherently determined by the amount of myopia that has been centrally corrected.

With respect to the magnitude of myopic relative peripheral refraction induced, a meta-analysis has shown that orthokeratology induced the greatest myopic shift in the periphery, followed by peripheral gradient rigid gas permeable lenses, gradient soft contact lenses, and multi-focal soft contact lenses with +3.00 D added.[103] Traditional optical approaches for myopia correction, such as single-vision spectacle lenses, standard rigid gas permeable lenses, and soft contact lenses, have demonstrated little influence on peripheral defocus[103] and these correction methods were unable to retard myopia progression.[104–107]

With respect to novel spectacles, they fail to achieve their intention to modify peripheral defocus profile or to retard myopia progression in children.[108] However, there is no evidence to support a causal relationship between the limited influence of these approaches on peripheral defocus and their inability to retard myopia progression. It is quite possible that the relative hyperopic peripheral defocus experienced by myopic eyes under correction by these approaches are a by-product rather than a cause of failure to retard myopia progression. Likewise, no causal relationship can be established between induced myopic defocus and myopia progression rate in strategies that demonstrated retardation effect on myopia progression.

It is well-attested that orthokeratology can induce myopic relative peripheral refraction and the magnitude is dependent on centrally corrected myopia.[81,83] Despite consistent reports on myopic relative peripheral refraction in orthokeratology-treated eyes, no study has yet explored the relationship between the magnitude of myopic relative peripheral refraction induced and the myopia retardation rate in orthokeratology-treated eyes. Therefore, there is no direct evidence to support myopic relative peripheral refraction having an influence on myopia progression and retardation in orthokeratology treatment. Similarly, although experimental rigid gas permeable lenses and soft contact lenses, as well as commercially available centre-distance multi-focal soft contact lenses, demonstrated capability of inducing myopic relative peripheral refraction in the periphery,[109–113] no single study has investigated the association between induced myopic relative peripheral refraction or reduced hyperopic relative peripheral refraction with myopia retardation effect.

In short, further studies are warranted to determine the association between the peripheral defocus changes induced by various strategies and corresponding myopia retardation or progression rate. However, it is important to note that hyperopic defocus may fluctuate in the presence of an accommodative lag. This factor has been suggested to be one of the aetiologies of myopia onset and progression, when performing near reading tasks. Therefore, such confounding effects should be ruled out or clarified when investigating any associations between peripheral defocus changes and myopia retardation.

Role of the choroid in myopia control

By extrapolating findings from animal studies, it has been proposed that the choroid plays an important role in childhood eye growth via a dramatic change in thickness and choroidal secretion of growth factors.[114] Choroidal thickening was observed as a response to interventions for myopia control in humans. A study which examined choroidal thickness before and after one-week use of one per cent atropine found there was a significant increase in thickness after application, suggesting the choroid may mediate eye growth through a thickness-dependent mechanism.[115]

Similar responses were observed in children wearing orthokeratology lenses for three weeks,[116] or six months,[117] although Gardner et al.[118] failed to detect choroidal changes in their subjects. Given that these optical and pharmaceutical interventions affecting choroidal thickening also affect axial elongation, it may be suggested that there is a causal relationship between choroidal thickness changes in response to treatment and ultimate eye growth. The most apparent limitation of these studies monitoring choroidal thickness changes is the short duration of observation, which make the investigation of the relationship between long-term axial changes and choroidal thickness alteration impracticable.

In conclusion, further long-term surveys are warranted to investigate the relationship between choroidal thickening and inhibition of ocular elongation during optical and pharmaceutical treatments proven to be effective in myopia control.

Future directions for myopia control in children

Management of myopia

Avoiding the development of high myopia in children can lead to reduced risk of serious, sight-threatening disorders in later life and this is a major goal of myopia control. Making decisions and giving evidence-based advice on how to manage at-risk children has therefore become an important and essential role of eyecare practitioners, failure of which may even be considered unethical.[119]

On the other hand, practitioners need to be prudent and not recommend myopia control therapy to all myopic children without due consideration, as not all myopes will demonstrate fast progression[88] and only about 10 per cent of myopic children will progress to high myopia.[11] Hence, a decision to undertake a long somewhat complex intervention at considerable costs, both in time and money, needs to be carefully made. Monitoring children and gaining an understanding of their progression rate before offering therapy would be prudent.

Combined treatment for myopia control

There is a great need for effective prophylaxis against childhood myopia. Despite various strategies having been explored to arrest or slow myopia progression in children, there are no proven effective interventions against childhood myopia other than atropine and contact lenses, such as orthokeratology and peripheral defocus modified soft contact lenses. However, the adverse side effects make higher concentration atropine unsuitable as a mainstream treatment. Lower concentration atropine, including 0.01 per cent concentration, which has clinically negligible side effects on pupil dilatation and loss of accommodation, may not be potent enough to inhibit myopia progression in children, compared to higher concentrations, if a single treatment is used,

because the treatment effect is concentration-related.[120–123]

The mechanisms of optical and pharmaceutical interventions in myopia control are not fully understood.[117,124] It is believed that optical and pharmaceutical strategies act via different mechanisms. Thus, a combined treatment approach may have great potential to maximize the treatment effect of current interventions for myopia control. However, when optical interventions are applied, there are limited opportunities to combine these two interventions, because different optical correction approaches cannot be simultaneously used.

By the same token, overlapping of pharmaceutical treatment may lead to greater side effects, rendering combined treatments non-viable. Based on this reasoning, the combination of optical and pharmaceutical strategies, such as combination of orthokeratology and 0.01 per cent atropine, may produce better treatment effects while maintaining their own benefits as single treatments. A study conducted in Japan has recently reported that the combined treatment of orthokeratology and 0.01 per cent atropine was more effective in slowing axial elongation in myopic children compared to orthokeratology alone (0.09 mm versus 0.19 mm).[125] But more studies are warranted to provide further evidence.

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REFERENCES

1. McBrien NA, Gentle A. Role of the sclera in the development and pathological complications of myopia. *Prog Retin Eye Res* 2003; 22: 307–338.
2. Rim TH, Kim SH, Lim KH et al. Refractive errors in Koreans: the Korea National Health and nutrition examination survey 2008-2012. *Korean J Ophthalmol* 2016; 30: 214–224.
3. Sun JT, An M, Yan XB et al. Prevalence and related factors for myopia in school-aged children in Qingdao. *J Ophthalmol* 2018; 2018: 9781987.
4. 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.
5. Wen G, Tarczy-Hornoch K, McKean-Cowdin R et al. Multi-Ethnic Pediatric Eye Disease Study Group; Prevalence of myopia, hyperopia, and astigmatism in non-Hispanic white and Asian children: multi-ethnic pediatric eye disease study. *Ophthalmology* 2013; 120: 2109–2116.
6. Lam CS, Lam CH, Cheng SC et al. Prevalence of myopia among Hong Kong Chinese schoolchildren: changes over two decades. *Ophthalmic Physiol Opt* 2012; 32: 17–24.
7. Lin LL, Shih YF, Hsiao CK et al. Prevalence of myopia in Taiwanese schoolchildren: 1983 to 2000. *Ann Acad Med Singapore* 2004; 33: 27–33.
8. Tabandeh H, Flynn HW Jr, Scott IU et al. Visual acuity outcomes of patients 50 years of age and older with high myopia and untreated choroidal neovascularization. *Ophthalmology* 1999; 106: 2063–2067.
9. Miki A, Ikuno Y, Asai T et al. Defects of the lamina Cribrosa in high myopia and glaucoma. *PLoS ONE* 2015; 10: e0137909.
10. Chen SJ, Cheng CY, Li AF et al. Prevalence and associated risk factors of myopic maculopathy in elderly Chinese: the Shihpai eye study. *Invest Ophthalmol Vis Sci* 2012; 53: 4868–4873.
11. Holden BA, Fricke TR, Wilson DA et al. Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. *Ophthalmology* 2016; 123: 1036–1042.
12. 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, 1611.e1591–1594.
13. Xu L, Wang YX, Wang S et al. Definition of high myopia by parapapillary atrophy. The Beijing Eye Study. *Acta Ophthalmol* 2010; 88: e350–e351.
14. Ohsugi H, Ikuno Y, Shoujou T et al. Axial length changes in highly myopic eyes and influence of myopic macular complications in Japanese adults. *PLoS ONE* 2017; 12: e0180851.
15. He M, Zeng J, Liu Y et al. Refractive error and visual impairment in urban children in southern China. *Invest Ophthalmol Vis Sci* 2004; 45: 793–799.
16. Zhao J, Pan X, Sui R et al. Refractive error study in children: results from Shunyi District, China. *Am J Ophthalmol* 2000; 129: 427–435.
17. Saw SM, Carkeet A, Chia KS et al. Component dependent risk factors for ocular parameters in Singapore Chinese children. *Ophthalmology* 2002; 109: 2065–2071.
18. 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.
19. Logan NS, Shah P, Rudnicka AR et al. Childhood ethnic differences in ametropia and ocular biometry: the Aston Eye Study. *Ophthalmic Physiol Opt* 2011; 31: 550–558.
20. 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.
21. Villarreal MG, Ohlsson J, Abrahamsson M et al. Myopisation: the refractive tendency in teenagers. Prevalence of myopia among young teenagers in Sweden. *Acta Ophthalmol Scand* 2000; 78: 177–181.
22. Plainis S, Moschandreas J, Nikolitsa P et al. Myopia and visual acuity impairment: a comparative study of Greek and Bulgarian school children. *Ophthalmic Physiol Opt* 2009; 29: 312–320.
23. Vitale S, Sperduto RD, Ferris FL 3rd. Increased prevalence of myopia in the United States between 1971-1972 and 1999-2004. *Arch Ophthalmol* 2009; 127: 1632–1639.
24. Multi-Ethnic Pediatric Eye Disease Study Group. Prevalence of myopia and hyperopia in 6- to 72-month-old African American and Hispanic children: the multi-ethnic pediatric eye disease study. *Ophthalmology* 2010; 117: 140–147.e143.
25. Goh PP, Abqariyah Y, Pokharel GP et al. Refractive error and visual impairment in school-age children in Gombak District, Malaysia. *Ophthalmology* 2005; 112: 678–685.
26. 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.
27. Pi LH, Chen L, Liu Q et al. Refractive status and prevalence of refractive errors in suburban school-age children. *Int J Med Sci* 2010; 7: 342–353.
28. Li Z, Xu K, Wu S et al. Population-based survey of refractive error among school-aged children in rural northern China: the Heilongjiang eye study. *Clin Experiment Ophthalmol* 2014; 42: 379–384.
29. Chua SY, Sabanayagam C, Cheung YB et al. Age of onset of myopia predicts risk of high myopia in later childhood in myopic Singapore children. *Ophthalmic Physiol Opt* 2016; 36: 388–394.
30. Maul E, Barroso S, Munoz SR et al. Refractive error study in children: results from La Florida, Chile. *Am J Ophthalmol* 2000; 129: 445–454.
31. 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.
32. 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.
33. Naidoo KS, Raghunandan A, Mashige KP et al. Refractive error and visual impairment in African children in South Africa. *Invest Ophthalmol Vis Sci* 2003; 44: 3764–3770.
34. Robaei D, Rose K, Ojaimi E et al. Visual acuity and the causes of visual loss in a population-based sample of 6-year-old Australian children. *Ophthalmology* 2005; 112: 1275–1282.
35. Wu JF, Bi HS, Wang SM et al. Refractive error, visual acuity and causes of vision loss in children in Shandong, China The Shandong Children Eye Study. *PLoS ONE* 2013; 8: e82763.
36. Dirani M, Chan YH, Gazzard G et al. Prevalence of refractive error in Singaporean Chinese children: the strabismus, amblyopia, and refractive error in young Singaporean children (STARS) study. *Invest Ophthalmol Vis Sci* 2010; 51: 1348–1355.
37. Donovan L, Sankaridurg P, Ho A et al. Myopia progression rates in urban children wearing single-vision spectacles. *Optom Vis Sci* 2012; 89: 27–32.
38. Mutti DO, Sinnott LT, Mitchell GL 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.
39. Zhao J, Mao J, Luo R et al. The progression of refractive error in school-age children: Shunyi district, China. *Am J Ophthalmol* 2002; 134: 735–743.
40. Zhou WJ, Zhang YY, Li H et al. Five-year progression of refractive errors and incidence of myopia in school-aged children in Western China. *J Epidemiol* 2016; 26: 386–395.
41. Fan DS, Lam DS, Lam RF et al. Prevalence, incidence, and progression of myopia of school children in Hong Kong. *Invest Ophthalmol Vis Sci* 2004; 45: 1071–1075.
42. Matsumura H, Hirai H. Prevalence of myopia and refractive changes in students from 3 to 17 years of age. *Surv Ophthalmol* 1999; 44: S109–S115.
43. Gao LQ, Liu W, Liang YB et al. Prevalence and characteristics of myopic retinopathy in a rural Chinese adult population: the Handan Eye Study. *Arch Ophthalmol* 2011; 129: 1199–1204.
44. Asakuma T, Yasuda M, Ninomiya T et al. Prevalence and risk factors for myopic retinopathy in a Japanese population: the Hisayama study. *Ophthalmology* 2012; 119: 1760–1765.
45. Koh VT, Nah GK, Chang L et al. Pathologic changes in highly myopic eyes of young males in Singapore. *Ann Acad Med Singapore* 2013; 42: 216–224.
46. Marcus MW, de Vries MM, Junoy Montolio FG et al. Myopia as a risk factor for open-angle glaucoma: a systematic review and meta-analysis. *Ophthalmology* 2011; 118: 1989–1994.e1982.
47. Shen L, Melles RB, Metlapally R et al. The Association of Refractive Error with glaucoma in a multiethnic population. *Ophthalmology* 2016; 123: 92–101.
48. Chang MA, Congdon NG, Bykhovskaya I et al. The association between myopia and various subtypes of lens opacity: SEE (Salisbury eye evaluation) project. *Ophthalmology* 2005; 112: 1395–1401.
49. Mukesh BN, Le A, Dimitrov PN et al. Development of cataract and associated risk factors: the Visual Impairment Project. *Arch Ophthalmol* 2006; 124: 79–85.

50. Pan CW, Boey PY, Cheng CY et al. Myopia, axial length, and age-related cataract: the Singapore Malay eye study. *Invest Ophthalmol Vis Sci* 2013; 54: 4498–4502.
51. The Eye Disease Case-Control Study Group. Risk factors for idiopathic rhegmatogenous retinal detachment. *Am J Epidemiol* 1993; 137: 749–757.
52. Tsai ASH, Wong CW, Lim L et al. Pediatric retinal detachment in an Asian population with high prevalence of myopia: clinical characteristics, surgical outcomes, and prognostic factors. *Retina* 2018; https://doi.org/10.1097/IAE.0000000000002238.
53. Huang YC, Chu YC, Wang NK et al. Impact of etiology on the outcome of pediatric rhegmatogenous retinal detachment. *Retina* 2017; https://doi.org/10.1097/IAE.0000000000001908.
54. Flitcroft DI. The complex interactions of retinal, optical and environmental factors in myopia aetiology. *Prog Retin Eye Res* 2012; 31: 622–660.
55. Wolffsohn JS, Calossi A, Cho P et al. Global trends in myopia management attitudes and strategies in clinical practice. *Cont Lens Anterior Eye* 2016; 39: 106–116.
56. Hoogerheide J, Rempt F, Hoogenboom WP. Acquired myopia in young pilots. *Ophthalmologica* 1971; 163: 209–215.
57. Rempt F, Hoogerheide J, Hoogenboom WP. Peripheral retinoscopy and the skiagram. *Ophthalmologica* 1971; 162: 1–10.
58. Smith EL 3rd. Prentice award lecture 2010: a case for peripheral optical treatment strategies for myopia. *Optom Vis Sci* 2011; 88: 1029–1044.
59. Mutti DO, Sholtz RI, Friedman NE et al. Peripheral refraction and ocular shape in children. *Invest Ophthalmol Vis Sci* 2000; 41: 1022–1030.
60. Lee TT, Cho P. Relative peripheral refraction in children: twelve-month changes in eyes with different ametropias. *Ophthalmic Physiol Opt* 2013; 33: 283–293.
61. Chen X, Sankaridurg P, Donovan L et al. Characteristics of peripheral refractive errors of myopic and non-myopic Chinese eyes. *Vision Res* 2010; 50: 31–35.
62. Seidemann A, Schaeffel F, Guirao A et al. Peripheral refractive errors in myopic, emmetropic, and hyperopic young subjects. *J Opt Soc Am A Opt Image Sci Vis* 2002; 19: 2363–2373.
63. Atchison DA, Pritchard N, Schmid KL. Peripheral refraction along the horizontal and vertical visual fields in myopia. *Vision Res* 2006; 46: 1450–1458.
64. Schmid GF. Variability of retinal steepness at the posterior pole in children 7-15 years of age. *Curr Eye Res* 2003; 27: 61–68.
65. Mutti DO, Hayes JR, Mitchell GL 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.
66. 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.
67. Atchison DA, Li SM, Li H et al. Relative peripheral hyperopia does not predict development and progression of myopia in children. *Invest Ophthalmol Vis Sci* 2015; 56: 6162–6170.
68. Rosen R, Lundstrom L, Unsbo P et al. Have we misinterpreted the study of Hoogerheide et al. (1971)? *Optom Vis Sci* 2012; 89: 1235–1237.
69. Atchison DA, Rosen R. The possible role of peripheral refraction in development of myopia. *Optom Vis Sci* 2016; 93: 1042–1044.
70. Jessen GN. World wide summary of contact lens techniques. *Am J Optom Arch Am Acad Optom* 1962; 39: 680–682.
71. Wlodyga R, Bryla C. Corneal molding: the easy way. *Contact Lens Spectrum* 1989; 4: 58–65.
72. Winkler TD. Accelerated orthokeratology: a case report. *Clin Exp Optom* 1995; 78: 11–13.
73. Swarbrick HA. Orthokeratology review and update. *Clin Exp Optom* 2006; 89: 124–143.
74. 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.
75. Kakita T, Hiraoka T, Oshika T. Influence of overnight orthokeratology on axial elongation in childhood myopia. *Invest Ophthalmol Vis Sci* 2011; 52: 2170–2174.
76. Walline JJ, Jones LA, Sinnott LT. Corneal reshaping and myopia progression. *Br J Ophthalmol* 2009; 93: 1181–1185.
77. 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.
78. Chen C, Cheung SW, Cho P. Myopia control using toric orthokeratology (TO-SEE study). *Invest Ophthalmol Vis Sci* 2013; 54: 6510–6517.
79. Charm J, Cho P. High myopia-partial reduction orthokeratology: a 2-year randomized study. *Optom Vis Sci* 2013; 90: 530–539.
80. 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.
81. Queiros A, Gonzalez-Meijome JM, Jorge J et al. Peripheral refraction in myopic patients after orthokeratology. *Optom Vis Sci* 2010; 87: 323–329.
82. Kang P, Swarbrick H. Peripheral refraction in myopic children wearing orthokeratology and gas-permeable lenses. *Optom Vis Sci* 2011; 88: 476–482.
83. Ticak A, Walline JJ. Peripheral optics with bifocal soft and corneal reshaping contact lenses. *Optom Vis Sci* 2013; 90: 3–8.
84. 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.
85. 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* 2017; 42: 713–720.
86. Zhu MJ, Feng HY, He XG et al. The control effect of orthokeratology on axial length elongation in Chinese children with myopia. *BMC Ophthalmol* 2014; 14: 141.
87. Chen CC, Cheung SW, Cho P. Toric orthokeratology for highly astigmatic children. *Optom Vis Sci* 2012; 89: 849–855.
88. Cho P, Cheung SW. Protective role of orthokeratology in reducing risk of rapid axial elongation: a reanalysis of data from the ROMIO and TO-SEE studies. *Invest Ophthalmol Vis Sci* 2017; 58: 1411–1416.
89. Charm J, Cho P. High myopia-partial reduction orthokeratology (HM-PRO): study design. *Cont Lens Anterior Eye* 2013; 36: 164–170.
90. Santodomingo-Rubido J, Villa-Collar C, Gilmartin B et al. Orthokeratology vs. spectacles: adverse events and discontinuations. *Optom Vis Sci* 2012; 89: 1133–1139.
91. Stapleton F, Carnt N. Contact lens-related microbial keratitis: how have epidemiology and genetics helped us with pathogenesis and prophylaxis. *Eye (Lond)* 2012; 26: 185–193.
92. Young AL, Leung KS, Tsim N et al. Risk factors, microbiological profile, and treatment outcomes of pediatric microbial keratitis in a tertiary care hospital in Hong Kong. *Am J Ophthalmol* 2013; 156: 1040–1044.e1042.
93. Bullimore MA, Sinnott LT, Jones-Jordan LA. The risk of microbial keratitis with overnight corneal reshaping lenses. *Optom Vis Sci* 2013; 90: 937–944.
94. Watt KG, Swarbrick HA. Trends in microbial keratitis associated with orthokeratology. *Eye Contact Lens* 2007; 33: 373–377.
95. Watt K, Swarbrick HA. Microbial keratitis in overnight orthokeratology: review of the first 50 cases. *Eye Contact Lens* 2005; 31: 201–208.
96. Liu YM, Xie P. The safety of orthokeratology-a systematic review. *Eye Contact Lens* 2016; 42: 35–42.
97. Li SM, Kang MT, Wu SS et al. Efficacy, safety and acceptability of orthokeratology on slowing axial elongation in myopic children by meta-analysis. *Curr Eye Res* 2016; 41: 600–608.
98. Cho P, Cheung SW, Mountford J et al. Good clinical practice in orthokeratology. *Cont Lens Anterior Eye* 2008; 31: 17–28.
99. Chia A, Chua WH, Wen L et al. Atropine for the treatment of childhood myopia: changes after stopping atropine 0.01%, 0.1% and 0.5%. *Am J Ophthalmol* 2014; 157: 451–457.e451.
100. 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.
101. Cho P, Cheung SW. Discontinuation of orthokeratology on eyeball elongation (DOEE). *Cont Lens Anterior Eye* 2017; 40: 82–87.
102. Charman WN, Mountford J, Atchison DA et al. Peripheral refraction in orthokeratology patients. *Optom Vis Sci* 2006; 83: 641–648.
103. Queiros A, Lopes-Ferreira D, Gonzalez-Meijome JM. Astigmatic peripheral defocus with different contact lenses: review and meta-analysis. *Curr Eye Res* 2016; 41: 1005–1015.
104. Adler D, Millodot M. The possible effect of undercorrection on myopic progression in children. *Clin Exp Optom* 2006; 89: 315–321.
105. Chung K, Mohidin N, O'Leary DJ. Undercorrection of myopia enhances rather than inhibits myopia progression. *Vision Res* 2002; 42: 2555–2559.
106. 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.
107. 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.
108. Sankaridurg P, Donovan L, Varnas S et al. Spectacle lenses designed to reduce progression of myopia: 12-month results. *Optom Vis Sci* 2010; 87: 631–641.
109. Paune J, Thivent S, Armengol J et al. Changes in peripheral refraction, higher-order aberrations, and accommodative lag with a radial refractive gradient contact lens in young myopes. *Eye Contact Lens* 2016; 42: 380–387.
110. Paune J, Queiros A, Quevedo L et al. Peripheral myopization and visual performance with experimental rigid gas permeable and soft contact lens design. *Cont Lens Anterior Eye* 2014; 37: 455–460.
111. Lopes-Ferreira D, Ribeiro C, Neves H et al. Peripheral refraction with dominant design multifocal contact lenses in young myopes. *J Optom* 2013; 6: 85–94.
112. Kang P, Fan Y, Oh K et al. The effect of multifocal soft contact lenses on peripheral refraction. *Optom Vis Sci* 2013; 90: 658–666.
113. Rosen R, Jaeken B, Lindskoog Petterson A et al. Evaluating the peripheral optical effect of multifocal contact lenses. *Ophthalmic Physiol Opt* 2012; 32: 527–534.
114. Nickla DL, Wallman J. The multifunctional choroid. *Prog Retin Eye Res* 2010; 29: 144–168.
115. Zhang Z, Zhou Y, Xie Z et al. The effect of topical atropine on the choroidal thickness of healthy children. *Sci Rep* 2016; 6: 34936.
116. Chen Z, Xue F, Zhou J et al. Effects of orthokeratology on choroidal thickness and axial length. *Optom Vis Sci* 2016; 93: 1064–1071.
117. Li Z, Cui D, Hu Y et al. Choroidal thickness and axial length changes in myopic children treated with orthokeratology. *Cont Lens Anterior Eye* 2017; 40: 417–423.
118. Gardner DJ, Walline JJ, Mutti DO. Choroidal thickness and peripheral myopic defocus during orthokeratology. *Optom Vis Sci* 2015; 92: 579–588.
119. Cho P, Boost MV. Blanket therapy, one size fits all, or personal tailoring for myopia control? *Cont Lens Anterior Eye* 2018; 41: 403–404.

120. Loh KL, Lu Q, Tan D et al. Risk factors for progressive myopia in the atropine therapy for myopia study. *Am J Ophthalmol* 2015; 159: 945–949.
121. Chia A, Chua WH, Cheung YB et al. Atropine for the treatment of childhood myopia: safety and efficacy of 0.5%, 0.1%, and 0.01% doses (atropine for the treatment of myopia 2). *Ophthalmology* 2012; 119: 347–354.
122. Shih YF, Hsiao CK, Chen CJ et al. An intervention trial on efficacy of atropine and multi-focal glasses in controlling myopic progression. *Acta Ophthalmol Scand* 2001; 79: 233–236.
123. Yam JC, Jiang Y, Tang SM et al. Low-Concentration Atropine for Myopia Progression (LAMP) Study: A randomized, double-blinded, placebo-controlled trial of 0.05%, 0.025%, and 0.01% atropine eye drops in Myopia control. *Ophthalmology* 2018; https://doi.org/10.1016/j.ophtha.2018.05.029.
124. Galvis V, Tello A, Parra MM et al. Topical atropine in the control of myopia. *Med Hypothesis Discov Innov Ophthalmol* 2016; 5: 78–88.
125. Kinoshita N, Konno Y, Hamada N et al. Additive effects of orthokeratology and atropine 0.01% ophthalmic solution in slowing axial elongation in children with myopia: first year results. *Jpn J Ophthalmol* 2018; 62: 544–553.