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Interventions to reduce incidence and progression of myopia in children and adults

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ABSTRACT

The alarming increase in childhood myopia has emerged as a significant public health concern. Due to its long-term consequences, there is also an expanding interest in adult-onset myopia. This review provides a comprehensive summary of interventions for slowing the onset and progression of myopia and discusses factors influencing their efficacy. Outdoor time is an effective intervention for at-risk pre-myopes, which can reduce myopia onset by up to 50 % and has been implemented on a large scale in some countries through school reforms. 0.05 % atropine and repeated low-level red light (RLRL) have also shown the potential to prevent myopia onset by approximately 50 %, though the cost-benefit of implementing them on a large scale warrants more research. Low-concentration atropine, various designs of peripheral defocus spectacles, contact lenses, and RLRL

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effectively slow myopia progression by at least 50 %. A history of higher baseline myopia status, faster baseline progression, parental myopia, high-risk lifestyle, and less outdoor time requires rigorous interventions. When combined with RLRL or atropine concentrations higher than 0.025 %, orthokeratology significantly improves myopia control in fast progressors and/or high myopes. Combining low-concentration atropine with peripheral defocus glasses or dual-focus contact lenses also yields better efficacy than monotherapy. There is limited research on adult myopia control, but offering comprehensive lifestyle and visual environment recommendations remains essential. Consistent use of these interventions and thorough safety monitoring are crucial for building clinical confidence. The success of myopia control hinges on personalization, given the diverse factors influencing efficacy and the challenges of large-scale implementation.

1. Introduction

Myopia is a growing public health threat, with its prevalence rising sharply in recent decades (Dolgin, 2015; Morgan et al., 2012; Yam et al., 2020b). Although the most pronounced increases have been observed in Asia, this trend is a worldwide concern (Matsumura et al., 2020). It has been predicted that around half of the global population will be myopic by 2050, with about one-tenth of them having high myopia [Spherical equivalent (SE) $\leq$ -6.00 D] (Holden et al., 2016). The condition generally starts in childhood and progresses over time. The age at which myopia develops is becoming younger (McCullough et al., 2016), implying that children will experience progression over extended periods of time, resulting in more severe myopia later in life. The development and progression of myopia is marked by increased axial elongation or growth and a high risk of sight-threatening complications that can lead to vision impairment and even blindness, particularly in cases of high myopia (Flitcroft, 2012; Haarman et al., 2020). It has become a social health and economic burden, and unless the current trend of its increasing prevalence changes, the associated costs will continue to grow (Sankaridurg et al., 2021). From 2018 to 2050, global blindness caused by myopia is projected to increase threefold, with the total estimated myopia-related costs expected to hit $1.7 trillion (Holy et al., 2019). There has been wide research interest in developing effective methods to control myopia by preventing its onset or slowing its progression. Numerous clinical trials have demonstrated the beneficial effects of various myopia control strategies, some of which have been adopted in mainstream clinical practice in recent years.

In this review, we aim to provide a comprehensive update of the literature on the current and evolving trends in these therapeutic approaches for myopia control and prevention. We will highlight the key clinical trials that have effectively investigated the efficacy and safety of myopia control interventions in children and young adults. Furthermore, we will address unresolved questions and challenges, outlining future directions to inform evidence-based practice and improve decision-making in myopia management.

2. Epidemiology of myopia

The global prevalence of myopia among children and adolescents has shown a steady increase, rising from 24.32 % in 1990 to 35.81 % in 2023, and projections indicate that it could reach 39.80 % by 2050 (Liang et al., 2024). The prevalence of myopia is higher in East and Southeast Asian regions, with rates ranging from 49.7 % to 62.0 % among 12-year-olds, compared to other countries where the rates are much lower, between 6.0 % and 20 % (Matsumura et al., 2020). Similarly, among teenagers and young adults, East Asian regions report a higher prevalence of myopia, ranging from 65.5 % to 96.5 %, in contrast to other countries, where the prevalence falls between 12.8 % and 35.0 % (Matsumura et al., 2020). These variations are thought to be attributable to intense education, increased near-work, and reduced outdoor time, which are key contributors to the higher myopia prevalence rates reported in Asia (Morgan et al., 2020). Studies have shown that Chinese children spend less time outdoors (Chen et al., 2024a) compared to similarly aged children in the UK and Australia (Ostrin et al., 2018; Read et al., 2015b). Even so, trends indicate that there is also a rising prevalence of myopia among children in non-Asian regions. In the UK, the prevalence of myopia in children aged 10 to 16 more than doubled over 50 years, and children are developing myopia at increasingly younger ages (McCullough et al., 2016). In Australia, the prevalence of myopia among children aged 6 to 15 had doubled when it was compared to the rate in similarly aged children 40 years prior (Fu et al., 2020b). Comparably, the prevalence in Americans increased from 25 % to 42 % over 30 years (Vitale et al., 2009). In the Sydney Myopia Study, the prevalence rose substantially over approximately 5–6 years, increasing from 1.4 % to 14.4 % in younger children (mean $\pm$ SD age: 6.7 $\pm$ 0.4 years) and from 13.0 % to 29.6 % in older children (mean $\pm$ SD age: 12.7 $\pm$ 0.4) (French et al., 2013). These suggest a possible influence of community development or urbanization over time. Notable differences in myopia prevalence have been reported between urban and rural areas (Rudnicka et al., 2016). In East and Southeast Asia, the prevalence of myopia is higher in urbanized societies like Singapore and Hong Kong, while it is lower in countries such as Cambodia, Nepal, and Laos (Lanca et al., 2021). Other regions in Asia and Australia have also reported higher prevalence rates of myopia in urbanites than in rural dwellers (Fu et al., 2020b; Hashemi et al., 2004; Ip et al., 2008a; Lee and Mackey, 2021; Matsumura et al., 2020). The association of an urbanized environment with myopia development could be mediated by intensive education and greater levels of near-work and less outdoor time.

In adults, the prevalence of myopia is approximately 25 %–40 % in urban East Asian countries, 20 %–35 % in Western Europe and the United States, and 15 %–20 % in developing Asian countries and some Western countries like Australia (Matsumura et al., 2020). While Asian adult populations may be more susceptible to myopia than their Western counterparts, essentially a reflection of a much higher incidence and prevalence of myopia that begins in childhood, the geographic differences in myopia prevalence among older individuals are less pronounced than those observed in younger populations (Matsumura et al., 2020). The alarming increasing trend of myopia worldwide calls for effective preventive measures.

3. Interventions for myopia prevention and control in children

3.1. Time outdoors for myopia prevention and control

3.1.1. Biological mechanisms

The mechanisms linking increased outdoor time to a lower incidence of myopia have been extensively studied, particularly highlighting the role of natural light exposure. The initial hypothesis was founded on evidence from animal studies demonstrating that brighter and flickering lights trigger dopamine (a light-driven neurohormone) release, and the capacity of dopamine agonists to block axial elongation (Boelen et al., 1998; Iuvone et al., 1978, 1991; McCarthy et al., 2007). This has received support from experimental studies conducted on various species, showing that exposure to bright light suppresses deprivation myopia (FDM) (Ashby et al., 2009; Chen et al., 2017; JTS et al., 2012; Smith et al., 2012; Zhang and Qu, 2019). Similar findings have been found for lens-induced myopia (LIM) in chicks, guinea pigs, and tree shrews but not in monkeys (Smith et al., 2013), which are considered a

more reflective model for human myopia. One explanation for the differing responses of FDM and LIM is the existence of two separate control systems at work (Karouta et al., 2025). The first mechanism involves regulating the release of dopamine based on light intensity and contrast – the introduction of a lens or diffuser reduces contrast, leading to lower dopamine levels (Karouta et al., 2025). This decrease in dopamine in both LIM and FDM serves as a growth signal but lacks a defined endpoint (Karouta et al., 2025). The second mechanism is triggered by detecting a shifted focal plane from a change in optical power. This is a dopamine-independent defocus cue with a clear endpoint (compensation) (Karouta et al., 2025). Consequently, bright light stimulation of dopamine release can abolish FDM development (Karouta and Ashby, 2014), but in LIM, it serves as a growth inhibitor that cannot override the stronger focal cue driving the eye toward compensation (Ashby and Schaeffel, 2010). The dopaminergic activity mechanism may also be valid for humans (Gurlevik et al., 2021).

Another hypothesis also suggested that Vitamin D plays a role, with correlations observed between myopia and low Vitamin D levels (Choi et al., 2014; Yazar et al., 2014); however, detailed analyses have indicated that this association is not causal (Cuellar-Partida et al., 2017; Guggenheim et al., 2014). An additional proposed mechanism is that outdoor environments typically provide uniform dioptric spaces, minimizing peripheral hypermetropic defocus, which is associated with myopia progression (Bowrey et al., 2017; Charman, 2011; Flitcroft, 2012). The varying spatial frequency compositions of indoor and outdoor environments may also be contributing factors (Flitcroft, 2012; Flitcroft et al., 2020). Investigations suggest that mid-to high spatial frequencies play an important role in the success of the emmetropization process, whereas low spatial frequencies can increase the risk of myopia incidence (Li et al., 2025a). Studies have also demonstrated that the spatial content of viewed scenes regulates retinal dopamine release (Feldkaemper et al., 1999; Feldkaemper and Schaeffel, 2013).

3.1.2. The protective role of time outdoors

Early research provided limited evidence indicating that time spent outdoors or engaging in physical activity might offer some protection against myopia. This conclusion was largely drawn from the lower prevalence of myopia observed in rural areas and among outdoor workers (Goldschmidt, 2003; Pärssinen, 1987). Subsequent studies found that about 2 h a day outdoors eliminated the additional risk associated with parental myopia (Jones et al., 2007) and more near work (Rose et al., 2008). Randomized clinical trials (RCT) have also demonstrated the efficacy of outdoor time interventions in reducing myopia incidence (Table 1). One trial in Guangzhou found a 23 % (30.4 % vs 39.5 %) reduction in myopia incidence over three years with 40 min of outdoor time daily (He et al., 2015). In Taiwan, an annual 52 % (8.41 % vs 17.65 %) reduction in myopia incidence was observed after 80 min of outdoor time per day (Wu et al., 2013). Another trial showed that continuous outdoor exposure for at least 15 min, coupled with a minimum sunlight intensity of 2000 lux, significantly reduced myopic shift in children after a year, compared to fragmented exposure or lower light intensity (Chen et al., 2024a). Such moderate light levels of at least 2000 lux are typically achievable in most outdoor environments during daylight hours, even in shaded areas beneath trees (Lanca et al., 2019). The varying designs of the clinical studies on the amount of time spent outdoors complicate comparisons. Nevertheless, a meta-analysis of these studies estimated that an increase of 76 min per day of outdoor time is necessary to achieve a 50 % reduction in the incidence of myopia and that increasing outdoor time by 1 h per day or 7 h per week could lead to a 45 % reduction in incident myopia compared to controls (Xiong et al., 2017). A protective effect of outdoor time was found for incident myopia with a risk ratio of 0.54 (Xiong et al., 2017). A recent review also reported that more time spent outdoors helped in slowing down axial eye growth, thereby reducing the risk of myopia onset (Cao et al., 2020). A limitation of the reported studies is that they did not consider how much time each child habitually spent outdoors. As a result, the level of outdoor exposure among children may have varied considerably. Besides, the studies lacked objective measures to track whether children adhered to the recommendations for increased outdoor time. Nevertheless, the findings suggest that additional outdoor time may be slowing the onset of myopia.

There has been controversy regarding whether increased outdoor time can slow the progression of myopia in already myopic children. Initial epidemiological data yielded negative findings (Jones-Jordan et al., 2012), and meta-syntheses also showed that outdoor time was not effective in slowing progression in already myopic eyes (Li et al., 2024a; Xiong et al., 2017). However, a study that used objective, quantitative measures of outdoor time and sunlight intensity found that myopic children who spent more time outdoors experienced approximately 30 % (-0.57 ± 0.40 D vs -0.79 ± 0.38 D) less progression after a year compared with the control group (Wu et al., 2018c), an effect somewhat less than that typically achieved with other myopia control interventions. In a 23-year follow-up study, Parssinen et al. reported less time spent on sports and outdoor activities during childhood as a major factor associated with high adulthood myopia (Pärssinen et al., 2014). Moreover, results of some reports from China and Japan indicated accelerated myopia progression and axial elongation during COVID-19 lockdowns and school closures compared to pre-pandemic levels (Najafzadeh et al., 2023), a trend associated with a significant decrease in outdoor time during the COVID-19 period. A myopia screening survey of children and teenagers in primary and junior high schools in Hangzhou, China, revealed that accelerated myopia progression observed during COVID-19 was partially reversed when lockdown restrictions were lifted (Chang et al., 2021).

Lighting conditions are likely the key contributors to the protective role of outdoor time. Animal studies have indicated that significant inhibitory effects on eye growth require high light intensities of at least 10,000 to 20,000 lux, but evidence suggests that lower light intensities (2000–5000 lux) may also be effective in humans (Chen et al., 2024a; Read et al., 2015b; Wu et al., 2018c). Bright light inhibits lens-induced and form deprivation experimental myopia in an intensity-dependent manner (Karouta and Ashby, 2014; Karouta et al., 2025), and in humans, sunlight intensity is linearly associated with myopic shift (Chen et al., 2024a). Additionally, He et al. indicated that there may be a cumulative effect of bright light exposure against myopia (He et al., 2022). The intensity-dependent effect of bright light likely occurs through an intensity-dependent retinal dopamine release (Brainard and Morgan, 1987; Cohen et al., 2012; Karouta et al., 2025). Supporting the protective role of light, prior investigations have shown slower progression of myopic refraction and axial elongation during summer compared to winter months (Donovan et al., 2012a; Donovan et al., 2012b; FULK et al., 2002; Gwiazda et al., 2014; Rusnak et al., 2018). In Inuit and Yupik populations residing in the circumpolar/arctic regions, myopia prevalence has been reported to be at epidemic levels (Morgan et al., 2021; Rozema et al., 2021). This has been partly attributed to the unique lighting conditions in the Arctic, characterized by fewer hours of sunshine during waking periods and lower illuminance. Moreover, the long, harsh, and icy winters in these regions, resulting from their extreme latitudes, necessitated the use of heavy curtains to retain classroom heat, which covered small windows that allowed minimal natural light (Rozema et al., 2021). Inadequate indoor electric lighting further diminished illumination levels (Rozema et al., 2021). Besides, to manage glare from light reflected from the snow, goggles were commonly used (Rozema et al., 2021), which may have further contributed to reduced light exposure. High myopia prevalence among the Inuit correlates with latitude, with the most northern regions showing the highest rates (Rozema et al., 2021). Consistently, there was also a trend towards a higher prevalence of myopia among Finnish military conscripts living above the Arctic Circle (Vannas et al., 2003). This may be associated with spending more time indoors since it gets colder and darker further North. Comparably, lower global horizontal illuminance is associated with elevated myopia prevalence rates among

Table 1
Randomized controlled trials for outdoor activities in myopia control.

Year	Author	Area	Level	Sample size	Age, year	Method	Follow up time, month	Baseline SE (SD), D	Change of SE (SD/95 % CI), D	Baseline AL (SD), mm	Change of AL (SD/95 % CI), mm	Prevalence (SD), %	Remarks
2011	Yi JH (Yi and Li, 2011)	China	Individual	37 vs. 29	7–11	Outdoor activity >14–15 h/ week	24	1.12 (0.42) vs. 1.02 (0.30)	0.38 (0.15) vs. 0.52 (0.19)	NA	NA	NA	Myopia progression in school children may be slowed down by more outdoor activities
2015	He M (He et al., 2015)	China	Cluster	853 vs. 726	6.61 (0.33) vs. 6.57 (0.32)	Intervention group: added a 40-min outdoor time to each schoolday. Control group: usual class activities	36	1.30 (0.97) vs. 1.26 (0.81)	−1.42 (−1.58 to −1.27) vs. −1.59 (−1.76 to −1.43)	22.60 (0.71) vs. 22.66 (0.70)	0.95 (0.91–1.00) vs. 0.98 (0.94–1.03)	30.4 vs. 39.5	Added 40 min of outdoor activity reduced the incidence rate of myopia over the following 3 years
2015	Jin JX (Jin et al., 2015)	China	Cluster	214 vs. 177	10.77 (2.14) vs. 10.42 (2.72)	added a 20-min recess outside classrooms	12	−0.83 (1.54) vs. −0.87 (1.68)	−0.10 (0.65) vs. −0.27 (0.52)	23.85 (0.98) vs. 23.68 (0.91)	0.16 (0.30) vs. 0.21 (0.21)	3.70 vs. 8.50	Increased outdoor activities prevented myopia onset
2018	Wu PC (Wu et al., 2018c)	Taiwan	Cluster	267 vs. 426	6.34 (0.48)	Intervention group: A school-based "Recess Outside Classroom Trial" up to 11 h/ week	12	0.36 (1.14) vs. 0.30 (0.99)	0.35 (0.58) vs. 0.47 (0.74)	22.78 (0.77) vs. 22.81 (0.76)	0.28 (0.22) vs. 0.33 (0.35)	54 % lower risk of rapid myopia progression	Outdoor activities had a significant protective effect in both non-myopic and myopic children compared to the control group.
2022	Li SM (Li et al., 2022)	China	Cluster	132 vs. 129	8.38 (0.34) vs. 8.35 (0.30)	Messaging parents twice daily for 1 year to take their children outdoors. All children wore portable light meters to record light exposure on 3 randomly selected days (2 weekdays and 1 weekend day) before and after the intervention	12	0.66 (1.05) vs. 0.37 (1.34)	0.42 (0.34–0.50) vs. 0.51 (0.43–0.59)	23.06 (0.69) vs. 23.16 (0.84)	0.27 (0.24–0.30) vs 0.31 (0.29–0.34)	33 (24.8) vs. 38 (28.6)	Texting messages to parents could help with reducing myopia, possibly through increased outdoor time and light exposure.
2022	He X (He et al., 2019, 2022)	China	Cluster	853 vs. 726	6–9	Stratified and randomized by school in a 1:1:1 ratio to control (n = 2037), test I (n = 2329), or test II (n = 1929) group. Added 40 or 80 min outdoor time was allocated to test I and II groups.	24	0.98 (1.02), 1.02 (1.02) and 1.00 (0.99) for control, test I, and II groups, respectively	−1.04, −0.84, −0.91 for control, test I, and II groups, respectively	22.89 (0.76), 22.89 (0.77) and 22.86 (0.74) for control, test I, and II groups, respectively	0.65, 0.55, 0.57 for control, test I, and II groups, respectively	24.9, 20.6, and 23.8 for control, test I, and II groups, respectively	Sufficient outdoor time necessary for dose-response effect
2023	Wang D (Wang et al., 2023a)	China	Cluster	1012 vs.1020	9.21 (0.62) vs. 9.23 (0.62)	1 year study Intervention group: added 2-h extracurricular physical activity after school Control group: free use of time after school.	12	0.63 (1.05) vs. 0.55 (1.13)	−0.28 (0.37) vs. −0.32 (0.47)	23.10 (0.77) vs. 23.11 (0.75)	0.17 (0.14) vs. 0.20 (0.14)	8.3 vs. 10.2	Adding 2 h of extracurricular physical activity outdoors after school was noninferior in academic performance

All comparisons are intervention vs. control, unless otherwise stated; changes presented are for the entire treatment period; h/week, hours per week; SD, standard deviation; 95 % CI, 95 % confidence interval; D, dioptre; mm, millimetre; SE, spherical equivalent; AL, axial length.

the Inuit (Rozema et al., 2021). Other studies conducted in Singapore and Japan found no evidence of a seasonal effect (Fujiwara et al., 2012; Tan et al., 2000). This could be due to the fairly uniform weather and relatively constant light exposure around the year in Singapore. The trend is also plausibly driven by a strong emphasis on intensive and competitive education, as children are likely to continue their studies even during summer breaks. Amid recent global disruptions that led to declining student performance in many countries, Japan and Singapore were among the regions that maintained or even improved learning outcomes and were among the top performers in the Programme for International Student Assessment (PISA) 2022 results (OECD, 2023). Singapore outperformed all other participating countries/economies in mathematics, reading, and science (OECD, 2023).

There have been questions about how light intensity and exposure duration may interact to influence therapeutic outcomes. Animal studies suggest that intermittent bright light exposure may offer superior benefits compared to continuous exposure (Lan et al., 2014; Najjar et al., 2025). This benefit may stem from the transient surge in retinal dopamine release triggered by the onset of the light exposure, which levels off with continuous exposure. Repeated brief exposures may thus yield greater cumulative protective effects from these acute neurochemical responses. Translating these findings to humans requires further research to determine optimal dosing regimens for intermittent outdoor light exposure in real-world settings.

The protective effect of bright light may also depend on its spectral composition. In a previous study, red, blue, and UV lighting all triggered the release of retinal dopamine, exhibiting wavelength-dependent differences in dopamine release and metabolism (Wang et al., 2018b). There are interspecies variations in the effect of the spectral content of light on eye growth (Muralidharan et al., 2021). However, in tree shrews, which are closely related to primates, long-wavelength light induced hyperopic shift (Gawne et al., 2017b; Ward et al., 2018), whereas short-wavelength light produced myopia (Gawne et al., 2018; Khanal et al., 2023). This pattern appears conserved in monkeys, where long-wavelength light promotes hyperopic shifts in refractive error and protects against myopia development (Hung et al., 2018b; Smith et al., 2015). In humans, exposure to violet and blue light slowed myopia progression, but further research is needed to explore this potential relationship (Akagun and Altiparmak, 2025; Lorenz et al., 2025; Torii et al., 2017a, 2017b). A meta-analysis of 12 clinical studies revealed that myopia control efficacy varied across different wavelengths of light, with red light being the only wavelength that significantly slowed axial elongation and myopia progression compared to violet and white light (Zaabaar et al., 2023).

The relationship between reduced outdoor time and increased myopia progression may have been mediated by increased screen time or near work in general. Screen time among children surged during the COVID-19 pandemic and has remained elevated even after the relaxation of many public health measures (Hedderson et al., 2023), with primary-aged children reporting the highest increase in both total and leisure screen time during the pandemic (Trott et al., 2022). Yotsukura et al. found that three months of school closure after the onset of COVID-19 resulted in increased time spent on near work, reduced outdoor time, and increased axial elongation among elementary school children (Yotsukura et al., 2024). Myopia prevalence in the Inuit and Yupik communities was very low (below 3 %) before the resettlement of the populations and the introduction of mandatory schooling (Morgan et al., 2021; Rozema et al., 2021). Following these changes, the prevalence of myopia surged to over 50 % among younger people within a single generation (Morgan et al., 2021; Rozema et al., 2021). In Singapore, a consistent upward trend in myopia prevalence was observed among Chinese adults who began elementary school between 1928 and 1995 (those born from 1922 to 1989) (Sensaki et al., 2017). Notably, there was an exponential increase in prevalence among individuals who started school after the 1980s (born after 1970). This trend was likely due to the rising educational demands following independence, particularly due to the heightened competition introduced by the New Educational System in 1978.

In summary, there is considerable evidence to support the idea that increased time outdoors perhaps slows the onset and progression of myopia. Initiatives to promote time outdoors, along with the reduction of excessive near work, could play a crucial role in myopia management.

3.1.3. Family and clinical recommendations for increasing outdoor time

Family engagement plays a vital role in encouraging children to spend more time outdoors. Children's lifestyle, including outdoor time, is influenced by family support and parenting style (Fan et al., 2025). A study found that sending SMS text messages to parents to increase time outdoors in school children resulted in lower axial elongation and slower myopia progression over 3 years (Li et al., 2022). Outdoor play together with family also enhances relationships. The World Health Organization (WHO) has created the myopia messaging library, a template aimed at promoting behavior change by consistently sending targeted messages to recipients through an app or SMS (Keel et al., 2022). An intervention like this can be very useful for families, but it needs to be empirically validated.

Clinicians can also play an active role by simply encouraging increased outdoor time. Research indicates that eye care practitioners significantly influence parents' adoption of myopia control interventions (Yang et al., 2022). Educating children and their families about the benefits of outdoor activities helps. Outdoor time is a simple and cost-effective intervention, although the optimal duration for myopia prevention remains elusive. At least 2 h per day of outdoor time has been recommended (Rose et al., 2008). Extended or frequent outdoor sessions could be more beneficial, but adequate UV protection is needed in regions with high ultraviolet light exposure. Sun-protective measures, including tree shade, wide-brimmed hats, and UV-blocking sunglasses, still permit sufficient ambient light exposure for myopia prevention while mitigating harmful UV radiation (Lanca et al., 2019). Outdoor time can complement other clinical myopia control interventions. A study found that decreased time outdoors during COVID-19 confinement reduced the treatment efficacy of Defocus Incorporated Multiple Segment (DIMS) spectacle lenses (Choi et al., 2022). Similarly, COVID-19-related restrictions accelerated myopia progression in children treated with low concentration atropine (0.01 %–0.05 %) (Erdinest et al., 2022b; Flitcroft et al., 2023; Yum et al., 2021). Clinicians can advise on lifestyle and the visual environment, especially to individuals whose parents or siblings are myopic, or with high-risk ancestry (Farbrother et al., 2004; Jiang et al., 2020). A minimum of 2 h/day of outdoor time (Lanca et al., 2022; Rose et al., 2008), less than 2 h/day of leisure near work (Rose et al., 2008), increasing viewing distance, and having frequent breaks during near work should be recommended (Huang et al., 2020; Ramamurthy et al., 2015; Wen et al., 2020). More education is also needed to stimulate practitioners' engagement in preventive practices. Surveys have revealed that although practitioners' concern about myopia has increased, the majority of them continue to prescribe single vision lenses for young myopes (Wolffsohn et al., 2020, 2023) and demonstrate low preventive practices (Osuagwu et al., 2023).

3.1.4. Recommendation to increase time outdoors at the policy level

Promoting outdoor time presents a viable policy-level intervention, especially in educational settings. Taiwan, Singapore, and mainland China implemented school outdoor programs that had significant effects on myopia (Karuppiah et al., 2021; Morgan and Jan 2022; Wu and Chang, 2019; Wu et al., 2020). To amplify these proven efforts, we propose the following recommendations, which are informed by the current evidence on myopia and principles of public health implementation, though their specific efficacy in myopia prevention campaigns requires further validation: (1) Public health campaigns should be used to raise awareness of the sight-threatening complications of myopia and the need to spend more time outdoors. This initiative can

employ a diverse range of strategies, including mass media campaigns, television and radio broadcasts, newspaper articles, podcasts, social media outreach, localized media engagements, interviews, and advertisements in community outlets. (2) Sufficient window-to-floor and window-to-wall ratios should be mandated in new school constructions to allow for adequate classroom lighting. (3) Shaded outdoor study areas should be created near schools. Outdoor light remains strong enough to reduce myopic shift, even in the shade (Chen et al., 2024a; Lanca et al., 2019). (4) Children should be taught to self-monitor light intake, like dietary macros. This can be aided by implementing wearable light sensors that track cumulative lux exposure, allowing students to make up missed outdoor time. (5) There should be professional development on outdoor pedagogy and UV protection strategies for teachers. (6) Experts armed with compelling evidence on increased outdoor time for myopia prevention could collaborate with government entities to advocate for changes in public policy. Convincing arguments regarding the future costs of controlling myopia progression, purchasing high-powered glasses, and managing complications, supported by economic analyses, can be used to prompt policymakers that myopia represents a significant and costly issue, both economically and socially, and that the impact transcends the costs of optical correction and treatment, including lost productivity, morbidity, and mortality associated with visual impairment later in life.

Implementing these policies also requires tackling cultural attitudes, as community perceptions may take time to shift. A study evaluating parental attitudes toward myopia development and control revealed a generally nonchalant stance regarding the health risks associated with myopia (McCrann et al., 2018). Li et al. also reported that about half of parents with myopic children considered myopia as posing no significant health threat, believing it could be effectively corrected, while most also had outdated and insufficient knowledge about myopia prevention and control (Li et al., 2024b). A Spanish study found that nearly 40 % of parents were not aware of the existence of myopia control methods (Ortiz-Peregrina et al., 2023). Some studies have reported adequate knowledge of myopia prevention and control, but among highly educated parents (Li et al., 2024b; Qian and Lu, 2024). These imply the urgent need for societal sensitisation to the public health importance of myopia.

Increased outdoor time raises concerns about lowering educational standards, though it may rather positively impact academic performance. The Shanghai Time Outside to Reduce Myopia (STORM) study found that increased outdoor time may play a positive role in increasing academic performance (Wang et al., 2023b), consistent with the 2018 PISA rankings of the Organization for Economic Co-operation and Development (OECD), which indicated that many European countries achieved reading performance levels similar to those of Hong Kong without a myopia epidemic (OECD, 2019). This also parallels the Finnish educational system, which is renowned for its "less is more" approach. Students in Finland enjoy fewer school days each year, fewer lessons per day, reduced hours at school, and significantly less homework compared to their peers in most other OECD countries, yet they achieve impressive results, thanks to substantial investments in developing and empowering highly qualified teachers. Of note, throughout the 20th century, the prevalence of myopia among 7- to 8-year-old schoolchildren in Finland did not increase, varying between 0.5 % and 1.9 % (Pärssinen, 2012).

3.1.5. Challenges in practical implementation

Increasing the time spent outdoors may encounter challenges in practical implementation. In a clinical trial in Shanghai, the intervention groups were prescribed an additional 40 or 80 min of outdoor time daily. However, the objective monitor showed that none of the study participants met the intended targets, highlighting the difficulties in effectively implementing such measures (He et al., 2022). The availability of physical space (Fan et al., 2025), cultural attitudes toward sun exposure and academic performance (Morita et al., 2024; Wang et al., 2023b), changing climate (Wang et al., 2025), as well as air quality (Guo et al., 2022), may all influence the implementation of increased outdoor time. Moreover, the competitive educational pressures in some regions, as well as the increasing digitalization of learning environments, significantly limit children's outdoor activities (Fan et al., 2022). These challenges, along with weather extremes and occasional pandemic-related restrictions, create significant barriers to increasing outdoor time and underscore the urgent need to develop alternative indoor interventions capable of replicating the photoprotective benefits of natural outdoor light exposure. Evidence suggests that incentives may help improve outdoor exposure. In one study, children in the intervention group received cash prizes and outdoor excursions if they met their monthly pedometer step goals and attended at least two outdoor sessions each month (Ngo et al., 2014). Compared to the control group, there was an increase in outdoor time for children in the incentive-based physical activity outdoor program after 6 months. Policies like China's educational reform that eased the burden of excessive homework and off-campus tuition for students undergoing compulsory education can help achieve the goal of getting children to go outside. Community-engaged approaches leveraging parental influence could enhance intervention uptake through family-based behavioral modification (Fan et al., 2025).

3.1.6. Measurement of time outdoors

The most common method for measuring outdoor time in children is through a parent questionnaire, where parents estimate the amount of time their children spend outside. Most studies that used questionnaires have yielded similar results, supporting the protective effect of time spent outdoors against myopia (Wang et al., 2018a). Using questionnaires offers some advantages (Gajjar and Ostrin, 2022; Wang et al., 2018a). They are both cost-effective and easy to distribute widely, making them ideal for large population-based and long-term studies. Additionally, they can gather basic information such as parental refractive error, myopia history, and other factors of interest to researchers. E-questionnaires are gaining traction thanks to the rapid growth of the Internet, offering flexibility, improved interaction with participants, and reduced data entry errors. Questionnaires come with certain limitations that should also be considered, though ongoing improvements may help address the challenges (Gajjar and Ostrin, 2022; Wang et al., 2018a). They are subject to recall and parental biases, and it appears impractical to assess light intensity through questionnaires. Diaries, akin to questionnaires, have also been used (Dharani et al., 2012; Wu et al., 2018b). While they can help minimize recall bias in assessing outdoor time, their success may be constrained by participants' adherence to the recording process.

Conjunctival ultraviolet autofluorescence (UVAF) is another method that has been used to monitor outdoor exposure. It was initially developed to identify preclinical UV damage to the ocular surface caused by sunlight (Lucas et al., 2008). Cellular changes from UV radiation are recorded and analyzed to determine the level of outdoor exposure (Wang et al., 2018a). Conjunctival UVAF has high intra- and inter-observer reliability (Sherwin et al., 2012a, 2012b) and significantly correlates with questionnaire-based outdoor activity level (Sherwin et al., 2012b). However, the uncertainty surrounding the rate of UVAF accumulation and decay hampers its success since it can lead to inaccurate estimates of outdoor time. Additionally, it may be unsuitable for large-scale studies due to potential noncompliance from children during the examination.

Recent innovative approaches for outdoor data collection in myopia research involve using wearable electronic monitoring devices to objectively measure light intensity and outdoor time. One such device is the HOBO Pendant Temperature/Light Data Logger, a device featuring a light sensor that records time and white light luminance (Alvarez and Wildsoet, 2013; Dharani et al., 2012; Wu et al., 2018b). Other wearable devices for outdoor time and light intensity include the Actiwatch Spectrum (Philips Respironics) and FitSight, which are wrist-worn

devices that combine a light sensor and accelerometer (Li et al., 2023; Ostrin, 2017; Ostrin et al., 2018; Read et al., 2015a; Verkicharla et al., 2017), as well as the "Mumu" smartwatch, which is also a wrist-worn device that features a light sensor, an accelerometer, and a GPS receiver (Chen et al., 2024a; He et al., 2022; Ye et al., 2019). The accuracy of the "Mumu" smartwatch in measuring time spent outdoors and indoors, as well as during sunny and cloudy conditions, was assessed against subjective records, achieving an accuracy rate of 92.4 % (Ye et al., 2019). In addition to measuring light intensity and duration of light exposure, the accelerometer function of the watches records and monitors physical activity (Ostrin et al., 2018; Verkicharla et al., 2017; Ye et al., 2019), whereas the GPS receiver receives satellite signals and collects data on longitude and latitude of the location (Ye et al., 2019). A limitation of these devices is that they are positioned at distances away from the eyes, potentially leading to inaccuracies in capturing the light exposure that directly affects myopia development or progression. More recent devices, including the Clouclip, the Visual Environment Evaluation Tool (VEET), and the Vivior monitor, are spectacle-mounted and may address this limitation (Bhandari et al., 2022; Mrochen et al., 2020; Sah et al., 2025; Sarkar et al., 2025; Wen et al., 2021). The Clouclip, Vivior, VEET, and a helmet-mounted device developed by Gibaldi et al. measure viewing distances in addition to the illumination characteristics (Gibaldi et al., 2024; Mrochen et al., 2020; Sah et al., 2025; Wen et al., 2021). Among them, the VEET and the helmet-mounted device by Gibaldi and colleagues also measure the spectral content of illumination (Gibaldi et al., 2024; Sah et al., 2025). Though these recent devices offer the advantages of being objective, relatively accurate, and providing comprehensive data, questionnaires are still valuable to assess aspects of behavior and family histories that cannot be captured objectively.

3.1.7. The range of refractive errors for which outdoor time is effective

Studies have suggested that the natural endpoint of early refractive development is mild hyperopia, clustering around +1.00 D in young children, rather than emmetropia (0 D), which poses a risk for subsequent progression to myopia (Han et al., 2024; Ma et al., 2021; Morgan et al., 2010). This reserve is crucial, as it provides a buffer against the axial elongation that characterizes childhood growth. However, the appropriate, protective endpoint may be age-dependent. This age-dependency is reflected in the varying hyperopic reserve cut-offs used to predict myopia risk across studies. In the multi-ethnic Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) Study, a hyperopic reserve of at least +0.75 D was cited as the cut-off for myopia risk in children aged 6 years, with lower hyperopic reserve for older children (Zadnik et al., 2015). Comparably, French et al. indicated that Australian children with a baseline refraction of $\leq$ +1.0 D at age 6 had a greater risk of developing myopia than children with a more hyperopic refraction, whereas the cutoff for 12-year-olds was $\leq$ +0.50 D (French et al., 2013). Ma et al. also found that among grade one Chinese students, the best cut-off for prediction of 4-year incident myopia was $\leq$ +0.75 D (Ma et al., 2018). In a secondary analysis of the Shanghai Time Outside to Reduce Myopia (STORM) study, myopic shift accelerated at SE below +1.0 D and remained stable when SE was above +1.0 D among children aged 6–9 years old (Chen et al., 2025b). Recent evidence suggests that a child's hyperopic reserve may help define a window of maximal therapeutic opportunity. In the STORM study, a substantial and dose-dependent protective effect of daily time outdoors on myopic SE shift and AL increase was observed in 6 to 9-year-old hyperopes (SE > +0.75 D) after a year, plateauing at 120 min/day of outdoor time (Chen et al., 2025a). However, there was limited protection in premyopes ($\leq$+0.75 D), who demonstrated a J-shaped relationship between time outdoors and myopic SE shift, and only showed significantly reduced axial growth at outdoor time exposure of >120 min/day (Chen et al., 2025a). Only 0.3 % of the hyperopes became myopic, while 31.0 % of those with baseline premyopia became myopic. In the Recess Outside Classroom (ROC) program, which included relatively older children (7- to 11-year-olds), increasing outdoor time over one year reduced myopia onset and shift by half in premyopes ($\leq$+0.75 D), and 19.6 % of the premyopes developed myopia (Wu et al., 2025), a proportion lower than that reported in the STORM study (Chen et al., 2025a). The impact of outdoor time in hyperopes was not reported in the ROC program since premyopes constituted the majority of the ROC program, and hyperopes a small fraction (5 % per arm).

In already myopic children, the specific range of refractive errors for which an increase in outdoor time is most effective is unclear. Studies have indicated that longitudinal chromatic aberration (LCA) is the basis for defocus detection in human vision (Swiatczak and Schaeffel, 2021; Zhang and Zhu, 2022). LCA provides a signed signal under white light viewing conditions (Swiatczak and Schaeffel, 2021; Zhang and Zhu, 2022). The phenomenon is based on matching the focal plane of the dominant wavelength by increasing the eye growth when the dominant wavelength is long and decreasing the eye growth when the dominant wavelength is short. In human vision, chromatic aberration typically spans up to 2.5 D (Swiatczak and Schaeffel, 2022). Thus, if an eye becomes more myopic, the images provided by both the blue and red wavelengths may be out of focus and outside the range where the comparison of sharpness between blue and red light can provide a useful signal. Consequently, the sensitivity of the myopic eye to outdoor light may be lost (Schaeffel and Swiatczak, 2024; Swiatczak and Schaeffel, 2021, 2022). Ho et al. reported that myopic children exhibit a reduction in central macular high-contrast multifocal ERG responses (Ho et al., 2012). While this may clarify why myopia tends to progress when it falls outside the regulated range, it does not account for why optical correction fails to restore this mechanism or why refractions initially deviate from the regulated range in the first place. Maybe the sensitivity only reduces and probably does not entirely disappear in corrected myopes. Future studies are warranted to provide a better understanding.

In conclusion, the range of refractive errors for which outdoor time can effectively prevent myopia onset is not a fixed set of numbers but a moving target inextricably linked to age. Public health policy must reflect this: the greatest population-level benefit will be achieved by promoting increased outdoor time and reduced near work aggressively in the earliest years of primary school, effectively increasing the number of children who maintain a protective hyperopic reserve. Once that reserve is depleted in the early years, the battle becomes significantly more challenging. Children below the protective hyperopic reserve for their age may benefit from prolonged, high-intensity light exposure regimens. For children who are already myopic, while more evidence is needed, encouraging more time spent outdoors remains crucial since greater outdoor time enhances the effectiveness of other myopia control interventions.

3.1.8. Summary

Putting it all together, there is evidence indicating that increased time outdoors may delay the onset and slow the progression of myopia. The mechanism may involve stimulation of retinal dopamine release by brighter light outdoors, although other postulated mechanisms require further investigation. Programs increasing time spent outdoors have been successfully implemented through large-scale public health initiatives and school reforms in some regions, mostly in Asia, yielding promising results. Pairing this initiative with efforts to educate families about the importance of outdoor time may enhance its effectiveness and ensure successful implementation. The appropriate indoor light intensity to match outdoor scenes, exposure time, and refractive error ranges for treatment needs further exploration.

3.2. Near work

For over 410 years, near work has been a key focus among lifestyle factors associated with myopia. As far back as 1611, Kepler asserted in the *Dioptrics* that "Those who do much close work in their youth become myopic (Mark, 1971)." However, extensive investigations into near work as a risk factor have shown an inconsistent relationship with

myopia (Gajjar and Ostrin, 2022). Even so, a pooled analysis showed that more time spent on near work activities was associated with higher odds of myopia, with every diopter more of near work increasing the odds of myopia by 2 % (Huang et al., 2015). It appears that the influence of near work on the onset and progression of myopia is based on the characteristics of the near work activity, including absolute working distances and temporal properties. In the Sydney Myopia Study, a short reading distance (<30 cm) and continuous reading (>30 min) independently raised the likelihood of myopia in children, even though the total time spent on near work activities was not associated with myopia (Ip et al., 2008b). Consistently, the Myopia Investigation study in Taipei found that near work distance >30 cm, discontinuing near work every 30 min, and more time outdoors in recess from parent self-report yielded less myopia progression in 9-to-11-year-old children (Huang et al., 2020). Similar findings have been reported in China (Guo et al., 2016; Huang et al., 2019). Frequent, continuous, and longer periods of reading or writing, as well as shorter reading or writing distances, also increased the risk of incident myopia (Yao et al., 2019). These findings suggest that increasing viewing distance and taking regular breaks during near work may help reduce myopia incidence and progression. A common clinical guideline, likely based on the foregoing studies, is the rule of keeping working distances greater than 30 cm and taking 30-s breaks after every 30 min of near work. The other is the 20/20/20 rule, although initially targeted to reduce computer-related visual fatigue. The rule suggests taking 20-s breaks to view objects 20 feet away after 20 min of digital device use (Anshel, 2007). It became associated with myopia prevention by extension because the 20/20/20 rule is all about breaking up sustained near work. Spending more time outdoors may also help reduce near work and/or its associated effects. The Sydney Myopia Study and the Sydney Adolescent Vascular and Eye Study showed that children who engaged in significant amounts of near work but also spent considerable time outdoors were still protected from developing myopia (French et al., 2013; Rose et al., 2008). Research using objective measures of near work duration and viewing distance is necessary, as the existing scientific evidence largely depends on subjective surveys. Lately, rangefinding devices have been developed. Instruments like the Clouclip, VEET, Vivior, and RangeLife are spectacle-mounted rangefinders that measure viewing distances (Wen et al., 2019; Williams et al., 2019). A study using the Clouclip found that myopic children spent more time daily on activities less than 20 cm away compared to non-myopic children (Wen et al., 2020). In China, the Clouclip and similar devices are promoted as tools to prevent myopic behaviors in children (Gajjar and Ostrin, 2022). The Clouclip alerts the child with vibrations and notifies parents through an app when the child's viewing habits are considered unhealthy. Applications are also being developed for handheld devices to measure face-to-screen distance (Salmerón-Campillo et al., 2019). Validation studies are necessary to verify the accuracy, reliability, and usefulness of the data obtained from these instruments.

The connection between near work and myopia is also thought to operate through an increased amount of screen time, but studies have reported inconsistent associations between screen time and the occurrence of myopia (Gajjar and Ostrin, 2022). A significant confounding factor is the variable definition of screen time across studies, which often combines activities with vastly different working distances and visual demands (Gajjar and Ostrin, 2022). Nevertheless, a recent meta-analysis found that smart device screen time alone or in combination with computer use increased the risk of myopia (Foreman et al., 2021). It has been suggested that objective measurement of screen time is necessary for comprehensive evaluations of the relationship between screen time and myopia, since people tend to underestimate their own digital screen time (Foreman et al., 2021; Lanca and Saw, 2020). A study providing objective data on smartphone use found a significant association between smartphone data consumption and myopia, with myopic individuals using twice as much data (1130.71 MB) compared to non-myopic individuals (613.63 MB) (McCrann et al., 2021). In another study that investigated how different learning modes influenced myopia progression in Chinese schoolchildren, visual behaviour was objectively measured in real time with Akeso eyeglasses, which incorporated a light-sensing strip and a proximity sensor (Fan et al., 2022). The children had attended school as usual before having to access lessons remotely online due to the COVID-19 pandemic. Objective measurement of visual behaviour spanned from November 2019 to November 2020, and participants took online classes from mid-February to early May 2020. The children spent more time on near work and less time outdoors during the online learning time than during normal school attendance, and these behaviour changes resulted in more myopia progression. Beyond being another form of near work, the use of digital devices, particularly smartphones, fundamentally alter viewing habits in ways that may intensify myopiagenic stimuli. The engaging, flickering nature of screen content and the portability of devices often lead to significantly closer working distances and more sustained, uninterrupted periods of accommodation and convergence compared to traditional activities like book reading. This combination of extremely close proximity and prolonged duration creates a stimulus for axial elongation, potentially making digital screen time a more potent risk factor for myopia onset and progression than other forms of near work. It is worth noting that the myopia epidemic had already reached a critical point prior to the widespread adoption of computers and smartphones, making a simple return to books an ineffective solution. Nevertheless, the current high usage of smartphones, tablets, and computers among both children and adults may be further exacerbating the pre-existing myopia epidemic. Besides, considering the pervasive use of digital devices and the fact that most activities are now conducted in virtual environments, digital device use can serve as a modifiable risk factor.

The association between educational pressure and myopia risk is also likely a component of the near-work hypothesis. Higher school grades (Ding et al., 2023; Saw et al., 2007; Yu et al., 2025), years of education (Mountjoy et al., 2018; Zhang et al., 2022a), and the school environment (Brennan et al., 2025) have been associated with a greater prevalence, risk, or shift in myopia. This relationship is not merely correlational but mechanistic. Intensive schooling systems, often characterized by prolonged reading, homework, and a competitive academic environment, may lead to an increase in the total cumulative dose of sustained near work during a child's critical developmental years. Completing more than 3 h of homework each day, participating in 36–40 core subjects a week, and going to bed late were associated with increased risk of myopia in middle school students (Peng et al., 2022). A significant positive correlation between higher PISA scores and increased myopia prevalence was observed, with the strongest correlation found for maths, followed by science and reading (Jong et al., 2023). These same educational demands often concurrently reduce opportunities for time outdoors, a known protective factor. In summary, the pressure to succeed in school increases myopia risk by requiring children to spend more hours on near work, such as reading and homework, which directly stimulates eye elongation.

3.3. Pharmacological interventions

3.3.1. Atropine for myopia control

3.3.1.1. Mechanism of action

3.3.1.1.1. Cellular receptors. Acetylcholine (ACh) is a neurotransmitter that plays a role in postnatal ocular development and eye growth. Muscarinic antagonists, which block the action of acetylcholine, inhibit form-deprivation-induced myopia (FDM) (Thomson et al., 2021a). Atropine mainly acts as a reversible competitive antagonist with an affinity for all the five subtypes of acetylcholine muscarinic receptors 1 to 5 (MR1–MR5), a superfamily of G protein–coupled receptors (GPCRs). In mammals, they are widely distributed in the cornea, iris, ciliary body, and ciliary muscles (Gil et al., 1997), epithelium of crystalline lens (Collison et al., 2000), retina (in amacrine cells), retinal pigment

epithelium (RPE) (Friedman et al., 1988), choroid, and sclera (in scleral fibroblasts). Atropine also interacts with non-MRs such as a2A-adrenergic receptors (aAR) (Carr et al., 2018), ɣ-aminobutyric acid receptors (GABA-R) (Barathi et al., 2014), and receptor tyrosine kinases (RTKs) in ocular tissues (Barathi et al., 2009). The first two are also members of the GPCR family. Epidermal growth factor receptor (EGFR), a family member of RTKs, is also a target of atropine (Barathi et al., 2009).

3.3.1.1.2. Pharmacological action and affinity. The link between myopia and near work led some to propose that prolonged convergence and accommodation during activities such as reading or other close-up tasks contributed to its development (Horn et al., 2025b). Convergence was believed to cause the eye muscles (lateral rectus and obliques) to exert pressure on the globe, leading to an increase in intraocular pressure (IOP) and stretching of the sclera (Horn et al., 2025b). This, in turn, was thought to increase axial length (AL) and result in myopia (Horn et al., 2025b). Similarly, accommodation was thought to elevate IOP and contribute to axial elongation (Horn et al., 2025b). Thus, it appeared probable that atropine, which inhibits accommodation and dilates the pupil, could help slow the progression of myopia. However, later studies found that atropine does not act through the accommodative pathway. Atropine and pirenzepine, another muscarinic antagonist, effectively inhibited myopia in chicks that do not possess muscarinic receptors in the ciliary muscle (Leech et al., 1995; McBrien et al., 1993). Furthermore, in chick eyes that could not accommodate due to lesions in the Edinger-Westphal nuclei, functional hyperopia induced with negative spectacle lenses led to myopia and eye elongation (Schaeffel et al., 1990). This prompted a shift from concentrating on accommodative pathways to exploring mechanisms within the retina, choroid, and sclera. In most mammalian species, muscarinic receptors (M1 to M5) are present in the retina, choroid, and sclera (Upadhyay and Beuerman, 2020). Studies have suggested that the sclera is not a site of action for atropine in myopia control (Lind et al., 1998; McBrien et al., 2013; Morgan et al., 2005). The direct effects of muscarinic antagonists on scleral glycosaminoglycan synthesis did not account for the inhibition of axial elongation *in vivo* (Morgan et al., 2005). Besides, atropine inhibited cellular proliferation and extracellular matrix production in whole sclera, as well as in its cartilaginous layer (Lind et al., 1998). Atropine may rather exert its effects by altering retinal neurotransmission. The retinal peptide *ZENK* is a candidate molecule that has been implicated in the regulation of eye growth (Ashby et al., 2010). *ZENK* is part of the immediate early gene (IEG) family of transcriptional regulators and serves as the avian and mouse ortholog of the IEG *Egr-1* (Ashby et al., 2010; Schippert et al., 2007; Yan et al., 2000). In the retina, *ZENK* expression is regulated by two distinct programs. One is light-driven, which either upregulates *ZENK* in ganglion and amacrine cells or downregulates it in photoreceptor cells, depending on the type of neuronal cell (Caputto and Guido, 2000). The other program involves a spontaneous rhythm in *ZENK* expression under constant illumination, regulated by the circadian pacemaker (Caputto and Guido, 2000). There was a rapid and sustained suppression of the *ZENK* peptide and RNA transcript in lens-induced and form deprivation myopia (Ashby et al., 2010). On the other hand, *ZENK* synthesis was enhanced when axial eye growth was inhibited by plus defocus or termination of form deprivation (Bitzer and Schaeffel, 2002; Fischer et al., 1999). In the central nervous system, *ZENK* expression is increased by both muscarinic cholinergic antagonists and dopamine agonists (Wang et al., 2021). In chicks, both form deprivation and lens-induced myopia significantly reduced retinal *ZENK* mRNA levels, while atropine administration reversed this down-regulation caused by both conditions (Ashby et al., 2007, 2010). It is still uncertain whether ZENK contributes to the prevention of myopia pathogenesis or merely acts as a marker of cellular activity following treatment. The choroid has also been investigated as a potential site of action, given its role as a dynamic buffer layer whose thickness is inversely correlated with axial elongation and degree of myopia (Muhiddin et al., 2022). Atropine has been shown to prevent choroidal thinning caused by hyperopic defocus (Chiang and Phillips, 2018; Nickla et al., 2013) and increase choroidal thickness in myopic subjects (Yam et al., 2022a). Overall, the existing evidence indicates that atropine may influence multiple pathways.

3.3.1.2. Clinical trials on atropine for myopia progression in Asian populations. Atropine eye drops have been used for myopia control for decades. Beginning in the 1960s, studies by Bedrossian and others started reporting the efficacy of 1 % atropine for myopia control in non-randomized comparative studies (Horn et al., 2025a). The efficacy of 1 % atropine in controlling myopia has also been demonstrated in the Atropine for the Treatment of Myopia (ATOM) 1 study, a randomized controlled trial in children aged 6 to 12 (Chua et al., 2006). In the ATOM 1 study, one eye of each participant was randomly assigned to receive either 1 % atropine eye drop or a placebo. After two years, myopia progression and axial elongation in the 1 % atropine group (-0.28 ± 0.92 D and -0.02 ± 0.35 mm) were less than those of the placebo group (-1.20 ± 0.69 D and 0.38 ± 0.38 mm) (Chua et al., 2006). While 1 % atropine produced substantially higher efficacy, it was associated with allergic reactions to discomfort, glare, blurred near vision, and significant rebound after one year of treatment cessation, with formerly atropine-treated eyes demonstrating a faster myopia progression compared with placebo-treated eyes (-1.14 ± 0.80 D vs. -0.38 ± 0.39 D) (Chua et al., 2006; Tong et al., 2009). A 20-year follow-up of these participants, who did not continue treatment after the initial two-year study period, found no long-term differences in SE, AL, or the incidence of cataract/lens opacities, glaucoma suspect status, myopic macular degeneration (MMD), parapapillary atrophy (β/γ zone), and optic disc tilt between the 1 % atropine-treated group and the placebo group (Li et al., 2024c).

ATOM 2 compared the effects of three relatively low atropine concentrations of 0.5 %, 0.1 %, and 0.01 % in 6 to 12-year-old children (Chia et al., 2012), and after two years, myopia progression was -0.30 ± 0.60 D, -0.38 ± 0.60 D, and -0.49 ± 0.63 D, with axial elongation of 0.27 ± 0.25 mm, 0.28 ± 0.28 mm, and 0.41 ± 0.32 mm in the 0.5 %, 0.1 %, and 0.01 % atropine groups, respectively. Compared to the 0.5 % and 0.1 % concentrations, 0.01 % atropine had minimal effect on accommodation, pupil size, and visual acuity (Chia et al., 2012). The most common adverse events, including allergic conjunctivitis and dermatitis, were reported in the 0.5 % and 0.1 % but not in the 0.01 % atropine group (Chia et al., 2012). Treatment was ceased for one year, after which any child progressing by ≥ 0.50 D in at least one eye was reinitiated on 0.01 % atropine for 24 months (Chia et al., 2014). Over 12 months of treatment cessation, myopia progression was -0.87 ± 0.52 D, -0.68 ± 0.45 D, and -0.28 ± 0.33 D for 0.5 %, 0.1 %, and 0.01 % atropine, respectively, and the corresponding AL changes were 0.35 ± 0.20 mm, 0.33 ± 0.18 mm, and 0.19 ± 0.13 mm. The significant rebound obliterated the initial advantage of atropine at higher concentrations, making the three-year myopia progression lower in the 0.01 % atropine group compared to the 0.1 % and 0.5 % atropine groups. 24 %, 59 % and 68 % of the 0.01 %, 0.1 %, and 0.5 % groups needed to restart treatment. The lower progression in the 0.01 % atropine group persisted after five years, with the overall myopia progression and axial elongation being -1.38 ± 0.98 D and 0.75 ± 0.48 mm, compared to the -1.98 ± 1.10 D and 0.87 ± 0.49 mm for 0.5 % atropine, as well as -1.83 ± 1.16 D and 0.85 ± 0.53 mm for 0.1 % atropine (Chia et al., 2016). Long-term follow-up of the ATOM 2 study cohort revealed that 2 years of treatment with 0.5 % or 0.1 % and 2–4 years with 0.01 % resulted in no difference in efficacy among the three concentrations after 10 years (Li et al., 2024c). The Ten-year incidence of MMD increased with higher atropine concentrations, showing rates of 19.6 %, 28.7 %, and 38.1 % for 0.01 %, 0.1 %, and 0.5 % concentrations, respectively. A significant odds ratio of 2.60 (95 % CI: 1.15–5.89) for increased MMD was observed when comparing 0.5 % atropine to 0.01 % atropine in a multivariable analysis. While this may suggest greater rebound effects at higher concentrations, the

absence of significant MMD among subjects using 1 % atropine in ATOM 1, contrasting with those using 0.5 % and 0.1 % in ATOM 2, necessitates further investigation.

Initially, the 0.01 % concentration was intended to serve as the placebo group; however, a historical control from ATOM 1 was used instead since 0.01 % atropine demonstrated significant efficacy. Compared to the historical control, 0.01 % atropine showed no effect on axial elongation (0.01 % atropine: 0.41 ± 0.32 mm; control: 0.38 ± 0.38 mm over 2 years), despite its significant effect on SE progression (0.01 % atropine: 0.49 ± 0.63 D; control: 1.20 ± 0.69 D over 2 years). AL measurements offer superior precision and reduced susceptibility to errors compared to cycloplegic refraction assessments. Consequently, the unexpected disparity—where 0.01 % atropine reduced SE progression yet failed to mitigate axial elongation—elicited concerns regarding the use of a historical control and the validity of comparing outcomes among disparate patient cohorts. However, similar results were found in the I-ATOM study in India, which had a concurrent placebo group (Saxena et al., 2021). The study found that 0.01 % atropine slowed SE progression by 54 % (−0.16 ± 0.40 D vs −0.35 ± 0.40 D) over a year but had no significant effect on axial elongation (Saxena et al., 2021). In the two-year ATOM-J study in Japan, there was only a modest effect of 0.01 % atropine, compared to placebo, on SE progression,−1.26 D (95 % CI: −1.35, −1.17) vs −1.48 D (95 % CI: −1.57, −1.39) and AL elongation, 0.63 mm (95 % CI: 0.59, 0.67) vs 0.77 mm (95 % CI: 0.73, 0.81) (Hieda et al., 2021). Similar modest efficacies of 0.01 % atropine have been reported in Chinese studies (Fu et al., 2020a; Wei et al., 2020).

Comparing 0.05 %, 0.025 %, and 0.01 % concentrations of atropine with placebo, the low-concentration atropine for myopia progression (LAMP) study sought to identify a concentration-dependent response and determine an optimal concentration that balances good efficacy and safety for myopia management in 4-12-year-olds (Yam et al., 2019). Compared with the placebo, 0.05 %, 0.025 %, and 0.01 % atropine reduced myopia progression by 67 % (−0.27 ± 0.61 D vs −0.81 ± 0.53 D), 43 % (−0.46 ± 0.45 D vs −0.81 ± 0.53 D), and 27 % (−0.59 ± 0.61 D vs −0.81 ± 0.53 D), respectively after a year. The corresponding reductions in axial elongation were 51 % (0.20 ± 0.25 mm vs 0.41 ± 0.22 mm), 29 % (0.29 ± 0.20 mm vs 0.41 ± 0.22 mm), and 12 % (0.36 ± 0.29 vs 0.41 ± 0.22 mm). There was no significant difference in axial elongation between 0.01 % atropine and the placebo. All concentrations were well tolerated without any adverse effects on vision-related quality of life. In the second year, the children in the placebo group were switched to 0.05 % atropine, whereas the children in the other atropine groups remained unchanged. Over the 2 years, the mean change in refractive error was −0.55 ± 0.86 D for 0.05 % atropine, −0.85 ± 0.73 D for 0.025 % atropine, and −1.12 ± 0.85 D for 0.01 % atropine, with corresponding mean AL changes of 0.39 ± 0.35 mm, 0.50 ± 0.33 mm, and 0.59 ± 0.38 mm (Yam et al., 2020a). In the switch group, myopia progression was significantly reduced following one year of treatment with 0.05 % atropine: changes in refraction and AL were −0.18 D and 0.15 mm in the second year, compared to −0.82 D and 0.43 mm in the first year.

In the third year, pairwise comparisons revealed that after a year of washout, the previously treated 0.05 % group had a slightly faster AL elongation, by approximately 0.04 mm, than the 0.01 % group, but 0.05 % atropine remained more effective than 0.01 % over 3 years (Yam et al., 2022b). Across all concentrations, continuous treatment was more effective in slowing SE progression compared to washout. Additionally, it significantly reduced axial elongation compared to washout, but only for 0.05 % and 0.025 % concentrations (Yam et al., 2022b). During years four and five, all continued treatment subgroups were switched to 0.05 % atropine for continued treatment, while all treatment cessation subgroups followed a *pro re nata* (*PRN*) retreatment protocol to resume 0.05 % atropine for children with myopic progressions of 0.50 D or more over one year. Over five years, SE progressions were −1.34 ± 1.40D for the initial 0.05 % atropine group, −1.97 ± 1.03D for the initial 0.025 % atropine group, and −2.34 ± 1.71D for the initial 0.01 % atropine group. AL elongation over the five years demonstrated a similar trend among groups: 0.79 ± 0.54 mm, 1.11 ± 0.46 mm, and 1.24 ± 0.72 mm for the initial 0.05 %, 0.025 %, and 0.01 % atropine subgroups, respectively. Among the *PRN* retreatment group, 87.9 % of children needed retreatment, and the proportion of retreatment across all studied concentrations was similar. For the children who restarted treatment, 0.05 % atropine achieved similar efficacy as continued treatment.

Considering that the efficacy of atropine is concentration-dependent, treatment schedules and dosing strategies that can mitigate rebound and adverse events associated with higher concentrations will be essential for ensuring effective myopia control. In one trial, subjects received 1 % atropine drops once every month for 24 months, then once every 2 months for 12 months, followed by no drops for 12 months (Zhu et al., 2020). Atropine was administered alternately between the two eyes, with one eye treated on day 1 and the other on day 16. During the washout phase, no significant rebound effect was observed. The atropine group demonstrated reduced SE and AL progression compared to the placebo group (−0.41 ± 0.23 D/year vs. −0.75 ± 0.64 D/year and 0.19 ± 0.13 mm/year vs. 0.40 ± 0.16 mm/year, respectively), with no serious adverse events related to atropine reported. The progression in the 1 % atropine group was lower when compared to the progression observed in the 1 %, 0.5 %, and 0.1 % atropine groups following treatment cessation in the ATOM 1 and ATOM 2 studies, where atropine was used daily (Chia et al., 2014; Tong et al., 2009). In a retrospective analysis, Du et al. found that weekly use of 1 % atropine could achieve nearly the same level of myopia control as daily use, with manageable side effects and sustained efficacy over 4 years (Du et al., 2025). In another retrospective study, the 15-month change in SE was similar among children who used 1 % atropine once, twice, or three times per week (Foo et al., 2020). Side effects were comparable among the groups, with the once-per-week group recording 0 % side effects (Foo et al., 2020). Overall, this part-time regimen (maximum thrice a week) resulted in discomfort in 1.2 % and blurred near vision in 0.6 % of participants (Foo et al., 2020), lower than the 4.5 % discomfort and 1 % blurred near vision cases in the ATOM 1 study (Chua et al., 2006). Lowering the frequency of 0.01 % atropine has also been associated with fewer side effects (Loughman et al., 2025), and the World Health Organization has recommended tapering the frequency before stopping treatment with 0.01 % atropine (World Health Organization, 2015). In terms of tapering atropine concentration, consecutive treatment with weekly 1 % atropine followed by daily 0.01 % after 6 months was found to demonstrate better efficacy in controlling SE progression and axial elongation than continued treatment with 0.01 % alone after a year, and both regimens were well tolerated (Ye et al., 2022). Polling et al. also reported that ongoing treatment with 0.5 % atropine provided comparable control over SE and AL progression to a stepwise dosing regimen, which included 0.5 % followed by 0.25 % and 0.1 % at six-month intervals (Polling et al., 2020). In a more recent trial, children were randomised to receive either 0.01 % atropine for 24 months, 0.1 % loading dose (6 months of 0.1 % followed by 18 months of 0.01 %), or placebo, followed by a 1-year washout (Hansen et al., 2025). Compared to placebo, the continued 0.01 % atropine group significantly slowed SE, 0.26 D (95 % CI: 0.04 to 0.48) and AL, −0.10 mm (95 % CI: 0.19 to −0.01) after two years, while the 6 months 0.1 % loading dose + 18 months 0.01 % atropine treatment showed no significant effect (Hansen et al., 2024), possibly due to the rebound after ceasing the 0.1 % atropine (Hansen et al., 2025). There was no difference in myopia progression between groups following washout (Hansen et al., 2025). The step-down from 0.1 % to 0.01 % atropine may have been too abrupt. A more gradual tapering strategy—for instance, transitioning through intermediate concentrations such as 0.05 % and 0.025 % before reaching 0.01 %—could have allowed the ocular growth mechanisms to adjust more smoothly and better preserved the initial therapeutic gains achieved during the high-dose phase. Li et al. demonstrated that myopia progression in 6-year-old children administered 0.05 % atropine was comparable to that of 8-year-olds receiving 0.025 % atropine and

10-year-olds receiving 0.01 % atropine after two years (Li et al., 2021a), implying that tapering off atropine concentration as a child grows may not only reduce rebound and adverse events but may also maintain efficacy, since physiological eye growth slows with age (Yam et al., 2025). More robust evidence on tapering the frequency and concentration of atropine is warranted.

In summary, the efficacy of atropine is concentration-dependent. While high to moderate concentrations (1 %–0.1 %) of atropine were effective for slowing myopia progression, they were associated with significant rebound and unwanted adverse events. Tapering off frequency and concentration of atropine may alleviate these drawbacks. The relatively low concentration of 0.05 % demonstrated good myopia control efficacy over five years while maintaining an acceptable safety profile. 0.01 % atropine had modest to no effect on axial eye growth. Short-term treatment with atropine may not reflect sustained effects on axial eye growth over a longer period. This is especially important due to the association between AL and the future development of myopia-associated pathologies. Ongoing treatment is essential, especially for those at higher risk of fast progression. A summary of the treatment outcomes of the various concentrations is shown in Table 2.

3.3.1.3. Clinical trials on atropine for myopia progression in non-Asian populations. Randomized controlled trials have also been conducted to explore the efficacy of atropine in non-Asian populations (Table 2). The Western Australia Atropine for the Treatment of Myopia (WA-ATOM) Study investigated the effectiveness of 0.01 % atropine in a multi-racial cohort of 6- to 16-year-old Australian children with myopia for 24 months (Lee et al., 2022a). The mean change in SE for the 0.01 % atropine group was −0.64 D (95 % CI: 0.73, −0.56) while the AL change was 0.34 mm (95 % CI: 0.30, 0.37). Respective changes in the placebo group were −0.78 D (95 % CI: 0.91, −0.65D) and 0.38 mm (95 % CI: 0.33, 0.43 mm). The difference between the groups at 24 months was not significant. In subgroup analyses, children of East Asian or South Asian descent showed no significant differences in SE or AL changes between the placebo and 0.01 % atropine groups. However, in European children, 0.01 % atropine significantly slowed myopia progression and AL elongation up to 18 months, but this effect was not maintained at 24 months. The atropine group showed reduced accommodative amplitude and pupillary light response compared to placebo, with few reports of sore eyes or blurred near vision. However, 0.01 % atropine was well-tolerated and did not impact near work, outdoor activities, or learning in most children.

In the placebo-controlled Childhood Atropine for Myopia Progression (CHAMP) trial, the myopia control efficacy and safety of 0.01 % and 0.02 % atropine were assessed in American and European children over 36 months (Zadnik et al., 2023). 0.01 % atropine significantly increased responder proportion (proportion with <0.50 D progression), as well as reduced SE progression [−1.04 D (95 % CI: 1.14 to −0.94) vs −1.28 D (95 % CI: 1.37 to −1.19)] and axial elongation [0.68 mm (95 % CI: 0.63 to 0.72) vs 0.81 mm (95 % CI: 0.76 to 0.85)]. 0.02 % atropine was effective in slowing AL growth [0.73 mm (95 % CI: 0.69 to 0.76) vs 0.81 mm (95 % CI: 0.76 to 0.85)] but did not demonstrate significant SE progression control or responder proportion increase. There were no serious ocular adverse events and only a few serious non-ocular events, none of which were linked to atropine. Both low-dose atropine concentrations were well tolerated. The higher efficacy of 0.01 % atropine for myopia control than 0.02 % in the CHAMP study was likely due to improved compliance in the 0.01 % atropine group. The 0.01 % atropine group had the highest median compliance of 93.3 %. It is also plausible that the small difference in concentration between the 0.01 % and 0.02 % atropine may have caused the lack of a concentration-dependent effect, compared to the LAMP study. The LAMP study used a wider range of concentrations (0.01 %, 0.025 %, and 0.05 %) (Yam et al., 2019, 2020a). A similar trial involving 5 to 12-year-old children in the United States reported inconsistent findings (Repka et al., 2023). At 24 months, there were no significant differences in the adjusted mean changes in SE and AL between the 0.01 % atropine and the placebo groups. The 0.01 % atropine group of this trial had a higher proportion of Asian children compared to the placebo group. The uneven ethnic composition may have skewed the overall treatment effect since the effect of 0.01 % atropine is less pronounced in Asian children (Yam et al., 2019).

The Atropine for the Prevention of Myopia Progression (APP) study was a 36-month randomized controlled trial that aimed to investigate the efficacy of low-concentration eye drops in slowing myopia progression in Danish children aged 6–12 years (Hansen et al., 2024; Hvid-Hansen et al., 2023b). The participants were randomized to one of three treatment groups: a loading dose of 0.1 % atropine for six months followed by 0.01 % atropine for 18 months, 0.01 % atropine for 24 months, or a placebo for 24 months. Compared to placebo, there were significant mean two-year reductions in SE, 0.26 D (95 % CI: 0.04 to 0.48) and AL, −0.10 mm (95 % CI: 0.19 to −0.01) in the 0.01 % group, with the 6 months 0.1 % loading dose + 18 months 0.01 % atropine group showing no significant effect (Hansen et al., 2024), possibly due to the rebound after ceasing the 0.1 % atropine (Hansen et al., 2025). At the two-year visit, distance and near best-corrected visual acuity, accommodation amplitude, and pupil diameter were comparable across all groups, with no serious adverse events or reactions reported (Hansen et al., 2024).

In the Myopia Outcome Study of Atropine in Children (MOSAIC), myopia progression did not differ between the 0.01 % atropine and placebo groups at 24 months, but AL elongation was lower in the 0.01 % atropine (0.33 ± 0.27 mm) compared to the placebo group (0.40 ± 0.31 mm) (Loughman et al., 2024; McCrann et al., 2019). In a subgroup analysis, there were significant treatment effects on SE at 18 months and AL at 18 and 24 months among Whites, but not non-Whites. This is consistent with the WA-ATOM study (Lee et al., 2022a). This could be related to variations in iris pigmentation. Individuals with darker irises, common in Asian and Black/African populations, may have greater absorption of the atropine drug due to the melanin pigment. Higher melanin content in the iris could result in a greater sequestering of the administered atropine by the pigment, resulting in less active drug available to bind to the muscarinic receptors.

The third year of the MOSAIC trial (MOSAIC2) consisted of two groups. Group one comprised the placebo group from the MOSAIC trial assigned to receive 0.05 % atropine eye drops for a year (placebo then 0.05 % atropine group). Group two was the 0.01 % atropine group from the MOSAIC trial assigned to use placebo nightly (atropine then nightly placebo group), tapering placebo (atropine then tapering placebo group), or tapering 0.01 % atropine eye drops (0.01 % atropine then tapering 0.01 % atropine group). The atropine then nightly placebo and atropine then tapering placebo groups were merged and labeled atropine then placebo. Over the third year, the atropine then placebo group had faster myopia progression (atropine then placebo group: 0.23 ± 0.34 D; placebo then 0.05 % atropine group: 0.11 ± 0.30 D) and axial elongation (atropine then placebo group: 0.14 ± 0.17 mm; placebo then 0.05 % atropine group: 0.09 ± 0.14 mm) compared to the placebo then 0.05 % atropine group. The placebo then 0.05 % atropine group also significantly slowed axial elongation better than the 0.01 % atropine then tapering 0.01 % group (0.01 % atropine then tapering 0.01 % atropine group: 0.10 ± 0.11 mm; placebo then 0.05 % atropine group: 0.09 ± 0.14 mm). In the first year results of the LAMP study, there was a 67 % (−0.27 ± 0.61 D vs −0.81 ± 0.53 D) reduction in myopia progression and a 51 % (0.20 ± 0.25 mm vs 0.41 ± 0.22 mm) reduction in axial elongation with 0.05 % atropine eye drops, but the MOSAIC2 trial found reductions of approximately 52 % (−0.11 ± 0.30 D vs −0.23 ± 0.34 D) and 36 % (0.09 ± 0.14 mm vs 0.14 ± 0.17 mm), respectively, over a year (the third year). This difference may be attributed to the placebo group in the MOSAIC2 trial having previously received 0.01 % atropine for 24 months, which did not result in a significant rebound effect in the third year. Despite experiencing more adverse events, participants using 0.05 % atropine during year 3 showed no differences

Table 2
Summary of Trials on Atropine for Myopia Control in Asian and non-Asian populations.

Author (s), Year	Region	Follow-up (month)	Sample Size	Age (years)	Treatment	Baseline SE (SD), D	Baseline AL (SD) mm	Refraction Control (treatment/ control)	AL Control (treatment/ control)
1 % Concentration of Atropine									
Yen, MY. et al., 1989; Yen et al. (1989)	Taiwan	12	96	6 to 14		−0.5 to −4.0 D			
			32	10.5	1 % Atropine	−1.52 (0.96)	NA	−0.22D/-0.91D	NA
			32	10.0	1 % Cyclopentolate	−1.45 (0.85)	NA	−0.58D/-0.91D	NA
			32	10.4	Placebo	−1.59 (0.92)	NA		
Chua, WH. et al., 2006 (ATOM1 study) (Chua et al., 2006)	Singapore	24	400	6 to12		−1.0 D to −6.0 D			
			200	9.2	1 % Atropine	−3.36 (1.38)	24.80 (0.83)	77 %	−0.02mm/0.38 mm
			200	9.2	Placebo	−3.58 (1.17)	24.80 (0.84)		
Fan, DS. et al., 2007; Fan et al. (2007)	Hong Kong	12	46	5 to 10		−3.0 or less			
			23	7.4 (1.6)	1 % Atropine	−5.18 (2.05)	25.06 (1.03)	+0.06 D/−1.19	0.09mm/0.70 mm
			23	7.4 (1.6)	Control	−5.12 (2.33)	24.85 (0.78)		
Yi, S. et al., 2015; Yi et al. (2015)	China	12	132	7 to 12		−0.5 to −2.0 D			
			68	9.91 (1.36)	1 % Atropine	−1.23 (0.32)	23.75 (0.10)	0.32D/-0.85D	−0.03mm/0.32 mm
			64	9.72 (1.40)	Placebo	−1.15 (0.30)	23.72 (0.12)		
0.5 %, 0.25 %, and 0.1 % Concentrations of Atropine									
Shih, YF. et al., 1999; Shih et al. (1999)	Taiwan	24	200	6 to 13		−0.5 to −7.0 D			
			41	9.8	0.5 % Atropine	−4.89 (2.06)	NA	−0.04D/-1.06D	NA
			47	9.7	0.25 % Atropine	−4.24 (1.74)	NA	−0.45D/-1.06D	NA
			49	8.9	0.1 % Atropine	−4.41 (1.47)	NA	−0.47D/-1.06D	NA
			49	8.3	0.5 % Tropicamide	−4.50 (1.86)	NA		
Chia, A. et al., 2012 (ATOM2 study) (Chia et al., 2012)	Singapore	24	400	6 to 12		−2.0 or less			
			161	9.70 (1.5)	0.5 % Atropine	−4.7 (1.8)	25.2 (0.9)	−0.30D/-0.49D	0.27mm/0.41 mm
			155	9.70 (1.6)	0.1 % Atropine	−4.8 (1.5)	25.2 (0.8)	−0.38D/-0.49D	0.28mm/0.41 mm
			84	9.50 (1.5)	0.01 % Atropine	−4.5 (1.5)	25.1 (1.0)		
Wang, YR. et al., 2017; Wang et al. (2017)	China	12	126	5 to 10		−0.5 to −2			
			63	9.1	0.5 % Atropine	−1.3 (0.4)	24.1 (1.0)	−0.8D/-2.0D	23.0 mm at 1 year/24.3 mm at 1 year
			63	8.7	Placebo	−1.2 (0.3)	23.8 (0.9)		
0.05 %, 0.025 % and 0.01 % Concentrations of Atropine									
Lee et al	Taiwan	20	57	6 to 12		−0.5 to −5.5			
		19.95	21	8.38	0.05 % Atropine	−1.58 (1.37)	NA	−0.28D/-0.75D	NA
		21.47	36	8.11	Control	−1.41 (0.86)	NA		NA
Moon JS. et al., 2018; Moon and Shin (2018)	South Korea	12	285	5 to 14		−6 or less			
			133	8.1	0.05 % Atropine	−3.94 (2.76)	24.91 (1.43)	−0.019 D/mo	0.019 mm/mo
			63	8.4	0.025 % Atropine	−3.97 (1.65)	24.66 (0.93)	−0.047 D/mo	0.025 mm/mo
			89	8.0	0.01 % Atropine	−3.97 (1.65)	24.86 (1.22)	−0.070 D/mo	0.037 mm/mo
Yam, JC. et al., 2019 (LAMP study) (Yam et al., 2019)	Hong Kong	12	438	4 to 12		−1.0 or less			
			109	8.45 (1.81)	0.05 % Atropine	−3.98 (1.69)	24.85 (0.90)	67 %	51 %
			108	8.54 (1.71)	0.025 % Atropine	−3.71 (1.85)	24.86 (0.95)	43 %	29 %
			110	8.23 (1.83)	0.01 % Atropine	−3.77 (1.85)	24.70 (0.99)	27 %	12 %

(*continued on next page*)

Table 2 (*continued*)

Author (s), Year	Region	Follow-up (month)	Sample Size	Age (years)	Treatment	Baseline SE (SD), D	Baseline AL (SD) mm	Refraction Control (treatment/ control)	AL Control (treatment/ control)
			111	8.42 (1.72)	Placebo	−3.85 (1.95)	24.82 (0.97)		
0.02 % and 0.01 % Concentrations of Atropine									
Fu, A. et al., 2020; Fu et al. (2020a)	China	12	336	6–14		−1.25 to −6.00			
			117	9.40 (1.80)	0.02 % Atropine	−2.76 (1.47)	24.60 (0.72)	−0.38D/-0.70D	0.30mm/0.46 mm
			119	9.30 (1.90)	0.01 % Atropine	−2.70 (1.64)	24.58 (0.74)	−0.47D/-0.70D	0.37mm/0.46 mm
			100	9.50 (1.40)	Control	−2.68 (1.42)	24.55 (0.71)		
Zadnik, K. et al., 2023 (CHAMP study) (Zadnik et al., 2023)	USA	36	576	3–16		−0.50 to −6.0			
			164	9.0 (2.1)	0.01 %Atropine	−2.41 (1.17)	24.37 (0.81)	−1.04D/-1.28D	0.68mm/0.81 mm
			247	9.0 (2.1)	0.02 %Atropine	−2.42 (1.17)	24.30 (0.87)	−1.18D/-1.28D	0.73mm/0.81 mm
			165	8.8 (1.8)	Placebo	−2.45 (1.13)	24.33 (0.84)		
0.01 % Concentration of Atropine									
Wei, S.et al., 2020 (Wei et al., 2020)	China	12	220	6–12		−1.0 D to −6.0			
			110	9.44 (1.80)	0.01 % Atropine	−2.52 (1.33)	24.50 (0.76)	34.2 %	22 %
			110	9.84 (1.53)	Placebo	−2.64 (1.46)	24.69 (0.97)		
Hieda, O.et al., 2021 (Hieda et al., 2021)	Japan	24	168	6–12		−1.0 to −6.0			
			84	8.99 (1.44)	0.01 % Atropine	−2.91	24.43	−1.26D/-1.48D	0.63mm/0.77 mm
			84	8.98 (1.50)	Placebo	−2.98	24.51		
Moriche-Carretero, Ma et al., 2021 (Moriche-Carretero et al., 2021)	Spain	24	339	5–11		−1.0 D to −4.0			
			171	7.37 (1.54)	0.01 % Atropine	−2.13 (0.63)	24.22 (0.66)	32 %	0.20mm/0.37 mm
			168	7.24 (1.77)	Control	−2.16 (0.62)	24.26 (0.91)		
			45	10.8 (2.2)	Placebo	−3.68 (1.3)	24.70 (0.74)		
Saxena, R.et al., 2021 (Saxena et al., 2021)	India	12	102	6–14		−0.5D to −6.0			
			47	10.6 (2.2)	0.01 % Atropine	−3.45 (1.3)	24.62 (0.98)	54 %	21 %
			45	10.8 (2.2)	Placebo	−3.68 (1.3)	24.70 (0.74)		
Chan, HHL.et al., 2022 (Chan et al., 2022)	Hong Kong	18	61	7–10		−0.5 D to −5.0			
					0.01 % Atropine	−1.88 (1.08)	24.17 (0.79)	−0.70D/-0.66D	0.32mm/0.30 mm
					Placebo	−1.74 (0.71)	24.09 (0.74)		
Lee, SS.et al., 2022 (WA-ATOM study) (Lee et al., 2022a)	Australia	24	153	9–14		Less than −1.50			
			104	11.2 (2.7)	Atropine 0.01 %	−3.13	24.6	−0.64D/-0.78D	0.34mm/0.38 mm
			49	12.2 (2.5)	Placebo	−3.56	24.7		
Sen, S.et al., 2022 (Sen et al., 2022)	India	24	145	5–15		More than −2.0			
			72		Atropine 0.01 %	−4.26	24.61	0.33D/0.89D	0.12mm/0.31 mm
			73		Placebo	−4.98	24.86		
Repka, MX. et al., 2023; Repka et al. (2023)	USA	30	187	5 to 12		−1.00 to −6.00			
			125	10.1	0.01 % Atropine	−2.83 (1.17)	24.4 (0.8)	−0.94D/-0.88D	0.51mm/0.49 mm
			62	10.1	Placebo	−2.83 (0.97)	24.7 (0.8)		
Loughman J.et al., 2024 (MOSAIC study) (McCrann et al., 2019)	Ireland	24	204	6–16					
			136	11.84 (2.47)	0.01 % Atropine	−3.21	24.85	−0.53D/−0.63D	0.33mm/0.40 mm
			68	11.78 (2.17)	Placebo	−3.38	24.93		

Changes presented are for the entire treatment period; Refraction Control: represented as actual progression in treatment/control groups; AL Control: represented as actual elongation in treatment/control groups; NA: not available; SD, standard deviation; 95 % CI, 95 % confidence interval; D, dioptre; mm, millimetre; SE, spherical equivalent; AL, axial length.

in treatment completion rates. Moreover, 92.8 % of parents and 76.8 % of participants expressed a willingness to continue using their assigned eye drops.

In summary, the myopia control efficacy of 0.01 % atropine in non-Asian children is inconclusive. A higher concentration, such as 0.05 % atropine, may be more effective, but more studies are needed to substantiate the findings in the MOSAIC2 trial. Low-concentration atropine is generally well tolerated in non-Asian populations.

3.3.1.4. Low-concentration atropine for myopia prevention. The LAMP-2 trial was the first large-scale, 2-year randomized, placebo-controlled, double-masked study to evaluate the impact of low-concentration atropine eye drops, specifically at concentrations of 0.05 % and 0.01 %, on the incidence of myopia in children (Yam et al., 2023). The study recruited 474 healthy children aged 4–9 years who did not have myopia (SE between 0 D to 1.0D) but had a history of parental myopia. The participants were randomly assigned to receive either 0.05 % atropine, 0.01 % atropine, or saline placebo eyedrops, and were instructed to use the assigned eye drops every night for a duration of two years. Nightly use of 0.05 % atropine eye drops led to a lower 2-year cumulative myopia incidence, a relative reduction of 46.4 % (28.4 % vs 53.0 %), and a lower percentage of subjects with fast myopic shift when compared to the placebo group, while the 0.01 % atropine and placebo groups produced similar effects. Only 28.4 % of the 0.05 % atropine group became myopic, compared with 53 % of children randomized to the placebo group. Similarly, 25 % of children in the 0.05 % atropine group and 53.9 % of children in the placebo group experienced fast myopic shift. The 0.05 % atropine group experienced a refractive shift of −0.46 D and eye growth of 0.48 mm, compared with a refractive shift of −1.01 D and eye growth of 0.70 mm in the placebo group. Consistent with previous studies, photophobia was the most common adverse event and was reported by 20.6 %, 20.9 %, and 10.2 % in 0.05 % atropine group, 0.01 % atropine group and placebo group in the first year and 12.9 %, 18.9 % and 12.2 % in the respective groups in the second year (Yam et al., 2023). None of the severe adverse events that required hospitalization were related to atropine treatment. No significant differences were observed among groups in vision-related quality of life (Yam et al., 2023).

The LAMP-2 study has revealed the ability of low-concentration atropine to delay myopia onset. However, it is unknown whether delaying myopia onset will reduce the final degree of myopia in adulthood or whether it simply postpones the typical myopia progression to later years and thus does not decrease the long-term risk associated with higher degrees of myopia. It is also unknown whether decreasing the myopic shift in refractive error and eye growth by initiating treatment prior to myopia onset amplifies the benefit, or whether a similar reduction can be achieved by initiating treatment early after onset. Answering these questions will require a longer follow-up.

A prospective, randomized, double-masked, placebo-controlled, and crossover trial was recently conducted over 13 months to investigate the use of low-concentration atropine drops in pre-myopic children aged 6–12 years (Wang et al., 2023e). Sixty Chinese children were randomly assigned to receive one drop of either 0.01 % atropine or placebo once nightly for 6 months, followed by a 1-month recovery period. After this, the 0.01 % atropine group was crossed over to the placebo group, while the placebo group was crossed over to the 0.01 % atropine group for another 6 months. The results showed that the use of 0.01 % atropine drops resulted in lower rates of myopia onset and fast myopic shift, compared to the placebo. During the first and second periods of the study, the proportion of myopia onset was found to be 12 % and 13 %, respectively, in the 0.01 % atropine group, compared to 36 % and 41 % in the placebo group. Similarly, the proportion of fast myopic shift was 40 % and 40 % in the atropine group, compared to 76 % and 72 % in the placebo group. These findings show a better performance of 0.01 % atropine in preventing myopia onset than reported in the LAMP 2 study. However, the LAMP had a larger sample size and a longer follow-up period, which might be able to account for the difference. There are planned studies of atropine for premyopic children in other populations.

3.3.1.5. Factors of treatment efficacy. Several factors may affect the efficacy of atropine, including age, concentration of atropine, duration of treatment, and myopia progression rate.

(a) Effects of age and baseline progression

There is a natural growth of the eyeball and a corresponding rapid shift in refractive state during childhood (Wallman and Winawer, 2004). Thus, when myopia develops at a younger age, the inherent eye growth combined with extra eye growth triggered by extrinsic factors exacerbates axial elongation and myopia progression (Naduvilath et al., 2023, 2025), increasing the risk of high myopia (Pärssinen and Kauppinen, 2019). Due to this accelerated physiological progression in younger children, myopia may continue to progress at a faster rate despite treatment with atropine, particularly with lower concentrations. On the other hand, in older children, where physiological eye growth may have stabilized or slowed down, atropine treatment may seem to be more effective, although the efficacy of atropine is invariant across ages (Brennan et al., 2024; Li et al., 2021a; Wang, 2021). In the LAMP study, younger children required a higher concentration of 0.05 % atropine to achieve a similar efficacy as that for older children receiving lower concentrations of 0.01 % atropine (Li et al., 2021a). Myopia progression of 10-year-olds in the 0.01 % group was similar to the 8-year-olds in the 0.025 % group and 6-year-olds in the 0.05 % group over two years (Li et al., 2021a). Myopia control efficacies of 0.5 % atropine and 0.01 % atropine have also been reported to be lower in younger children compared to older children (Joachimsen et al., 2019; Polling et al., 2016, 2020). In a study in Australia, 0.01 % atropine did not slow down axial elongation in children with fast initial myopia progression, who were younger than those with slow progression (Myles et al., 2021). Since myopia stabilization typically occurs around the age of 16 years (Group, 2013), it is plausible to assume that older participants might have experienced a natural reduction of myopia progression without any intervention. In a study in Singapore, non-progressing children (refractive error change <0.50 D/year) had less myopia progression in the 1 % atropine-treated eye as compared with the untreated fellow eye (+0.16 ± 0.37 D vs −0.73 ± 0.48 D); however, progression was more similar between eyes in progressors (−0.92 ± 0.31 D vs −1.06 ± 0.44 D; P = 0.363) (Loh et al., 2015).

(b) Myopic status at baseline and parental myopia

In ATOM 1, 22/182 (12.1 %) children after one year of atropine treatment were classified as progressors (SE change >0.50 D/year in the atropine-treated eye). Compared with non-progressors, they were younger (8.5 ± 1.4 years vs 9.3 ± 1.5 years), had higher baseline SE (−3.6 ± 1.3 D vs −2.8 ± 1.4 D), and had 2 myopic parents (77.3 % vs 48.1 %) (Loh et al., 2015). A more myopic status at baseline, rather than a younger age, was associated with poor response in 117 school children receiving low low-concentration atropine eye drop regimen (0.05 %–0.1 %) (Wu et al., 2011). Another study showed that for mothers with moderate myopia (less than 6.0 D), birth by cesarean section and lower baseline myopia were risk factors for poor response (Zhang et al., 2020). Non-Asian children with low initial myopia had the most significant clinical improvement following treatment with 0.01 % atropine,

compared to those with moderate and high initial myopia (Clark and Clark, 2015). Higher myopia is primarily associated with a higher degree of axial elongation (Verkicharla et al., 2020), likely related to the stretching and lengthening of the eyeball.

(c) Other factors

An uncontrolled variable that could potentially affect the outcomes of different studies is the formulation of atropine dilutions. Although sourced from pharmacies, their exact composition, pH values, and the specific conditions of use are often unknown. One study found a wide range of formulation methods, storage practices, and beyond-use recommendations for atropine in the USA (Richdale et al., 2022). These factors could potentially impact the stability and efficacy of atropine.

3.3.1.6. Effects of atropine on ocular Traits

3.3.1.6.1. Effects on ocular biometrics. In 2001, a study reported less lens thickening and axial elongation in a 0.5 % atropine group compared to a spectacle lens group (Shih et al., 2001). In 2015, a re-evaluation of the biometric parameters of the ATOM-1 study cohort showed the associations of hyperopic shift and myopic rebound with changes in the vitreous chamber depth, and thereby the AL (Kumaran et al., 2015). Both the ATOM 2 and LAMP studies confirmed that the effect of atropine is primarily by slowing axial elongation (Chia et al., 2012; Yam et al., 2019). In the ATOM 2 study, following a one-year washout period, a significant rebound effect (resurgence in myopia after discontinuation of treatment, resulting in a more rapid progression than what would be expected in an untreated myope) was observed, resulting in greater axial elongation in the higher atropine concentrations (0.5 % and 0.1 %). This led to the 0.01 % atropine group emerging as the most effective in mitigating axial eye growth after five years (Chia et al., 2016). Similarly, the LAMP study's washout phase revealed a slight rebound in axial elongation in the 0.05 % group compared to the 0.01 % group; however, this did not diminish the overall superior efficacy of 0.05 % atropine (Yam et al., 2022b). Corneal power changes were minimal across atropine concentrations in the LAMP study, with lens power and anterior chamber depth remaining similar as well (Li et al., 2020). The findings from Wang et al. support these results, demonstrating that 0.02 % and 0.01 % atropine had no significant clinical impact on corneal power, lens power, or anterior chamber depth (Wang et al., 2023c). However, Hvid-Hansen observed concentration-dependent changes in these parameters in Danish children, with higher concentrations yielding a greater increase in anterior chamber depth, lesser increase in vitreous chamber depth and AL, as well as thinner lens thickness (Hvid-Hansen et al., 2023a). An Indian cohort also showed less corneal curvature steepening in the 0.01 % atropine group, indicating a possible indirect effect of atropine through reduced axial elongation (Sharma et al., 2023). The direct mechanism of atropine's effect on the cornea is not available. While atropine controls myopia by inhibiting axial elongation, as demonstrated in most studies, whether it acts in conjunction with other ocular biometric factors remains to be investigated.

3.3.1.6.2. Effects on choroidal thickness. Findings from animal models and clinical research suggest that choroidal thickness may play an active role in regulating ocular growth and changes in the refractive state of the eye (Hung et al., 2000; Prousali et al., 2021). Supporting this mechanistic link, a clinical trial demonstrated that administration of 1 % atropine gel twice daily for a week increased choroidal thickness (Zhang et al., 2016). A 6-month study showed that a 1-week loading dose of 1 % atropine increased choroidal thickness, which remained stable with weekly treatment (Ye et al., 2020). In contrast, treatment with 0.01 % atropine resulted in decreased choroidal thickness and greater eye elongation after 6 months. These comparative findings are limited by the study's lack of a placebo group (Ye et al., 2020). In the LAMP study, subjects were examined for the effects of varying concentrations of atropine on sub-foveal choroidal thickness (SFChT) over two years (Yam et al., 2022a). The two-year changes in SFChT from baseline were significant across the different atropine groups: 21.15 ± 32.99 μm for 0.05 %, 3.34 ± 25.30 μm for 0.025 %, and −0.30 ± 27.15 μm for 0.01 %. A concentration-dependent response was noted, with thicker choroids linked to higher atropine concentrations. Of note, significant increases in SFChT were observed at 4 months for the 0.025 % and 0.05 % groups, which were stabilized thereafter. Over two years, increased SFChT correlated with slower myopia progression and decreased axial elongation, with 18.45 % of the effect of atropine 0.05 % on myopia progression observed to be mediated through choroidal thickening. The choroidal response to atropine may be best understood not as absolute thickening, but as the prevention of the thinning that accompanies childhood myopia progression. This suggests that no thickening may not necessarily indicate no treatment effect and indicates that monitoring choroidal thickness should be for assessing whether a given atropine concentration is effectively countering choroidal thinning linked to myopia. Thus, choroidal response may serve as a biomarker for assessing treatment outcomes and guiding atropine concentration adjustments.

3.3.1.7. Clinical implementations. Low-concentration atropine 0.01 %–0.05 % showed a balance between therapeutic effects and side effects (Yam et al., 2019). The recent 5-year reports of LAMP-1 study showed that atropine 0.05 % had a satisfactory treatment efficacy with no servere adverse events during the 5 years, indicating the potential of 0.05 % atropine in clinical administration (Zhang et al., 2024). Before starting the treatment, it is crucial to discuss the treatment objective, procedure, potential side effects, success criteria, and success rate with the parents and children. It is important for parents to understand that atropine treatment works to slow down myopia progression but does not improve vision. In addition, although the side effects of atropine therapy are low, they still need to be closely monitored. Factors that help with the prediction of progression include the child's age, myopia progression, baseline SE, and refractive error of parents. The duration of atropine usage has not been confirmed. However, a recent study showed that more than 80 % of children needed re-treatment after two years of intial treatment and two years of cessation in all atropine concentration groups (0.05 %, 0.025 %, and 0.01 %) (Zhang et al., 2024). Thus, long-term treatment with low-concentration atropine may be necessary until adolescence.

3.3.1.8. Unsolved questions and future direction. Despite the promising results in using low-concentration atropine for myopia control, several challenges and unsolved questions remain. First, there is substantial individual variability in response to atropine treatment, with some children experiencing greater myopia control than others. There is a need to predict treatment outcomes and optimize personalized management of myopia. Second, the long-term data from the ATOM 1 and ATOM 2 studies lay a foundation for exploring key questions about the optimal duration of atropine treatment for achieving sustained outcomes. In particular, it raises important considerations about the appropriate time for treatment cessation and whether tapering the concentration or continuing treatment into adolescence is the more effective approach. Future studies will need to address these issues. Third, while the efficacies of some concentrations are known (e.g., 0.01 %, 0.025 %, and 0.05 %), the ideal concentration and the frequency of administration have yet to be clarified. Fourth, current understanding of the precise underlying mechanisms of atropine remains incomplete. The specific molecular pathways and signaling cascades affected by atropine are still to be elucidated. Lastly, while most studies have been focused on children so far, some future investigations may also include adult highly myopic patients with progressive axial elongation, with or without coincident myopic macular degeneration.

3.3.2. Other pharmacological interventions

3.3.2.1. Levodopa. Levodopa is thought to have a protective role in myopia through increasing dopamine synthesis and release from the retina, and this effect can be inhibited by D2-like receptor antagonist spiperone (Thomson et al., 2021b). In clinical practice, the administration often combines levodopa with carbidopa which can prevent levodopa from being converted to dopamine before reaching the desired tissue. The efficacy of such coadministration has been demonstrated in FDM and LIM (Thomson et al., 2019, 2020). There is a dose-dependent inhibitory effect of levodopa/carbidopa, with higher concentrations providing complete protection (Thomson et al., 2019, 2020), and increased treatment efficacy when applied topically as compared to using levodopa alone (Thomson et al., 2021b). The first RCT to evaluate the safety of levodopa/carbidopa involved healthy adult males aged from 18 to 30 years randomly assigned to receive either a low (1.4 levodopa: 0.34 carbidopa [μmoles/day], n = 14) or standard dose (2.7 levodopa:0.68 carbidopa [μmoles/day], n = 15) of levodopa/carbidopa eye drops in one eye and placebo in the fellow eye once daily for 4 weeks (28 days). Consistent with preclinical studies, there was no effect on ocular tolerability, anterior surface integrity, visual function, ocular health, and refraction/ocular biometry, and no non-ocular adverse events were induced after a 4-month follow-up visit (Thomson et al., 2022). The results lay the groundwork for subsequent studies exploring the potential of levodopa/carbidopa eye-drops as a viable treatment for human myopia.

3.3.2.2. 7-Methylxanthine. 7-methylxanthine (7-MX), an adenosine antagonist, has demonstrated potential in slowing myopia progression through animal studies. It increased posterior sclera collagen concentration and fibril diameter in rabbits (Trier et al., 1999) and reduced myopia and axial eye growth while preventing scleral thinning in guinea pigs (Cui et al., 2011). In FDM pigmented rabbits and LIM rhesus monkeys, it also inhibited myopia and eye growth without adverse effects (Hung et al., 2018a; Nie et al., 2012). However, it exerted limited or no impact on FDM in chickens and tree shrews (Khanal et al., 2020; Wang et al., 2014; Liu et al., 2020). The variability of 7-MX's effects across species warrant further investigation.

In a clinical trial conducted in Denmark, 68 myopic children received orally either 400 mg of 7-MX once daily or a placebo (Trier et al., 2008). 7-MX effectively reduced eye elongation and the progression of myopia, with a 24-month treatment period leading to greater reductions in axial growth than a 12-month treatment. No side effects were detected (Trier et al., 2008). In 2009, the Danish Medicines Agency approved 7-MX for myopia control. Data from a retrospective study analyzing the longitudinal records of 711 treated children revealed a cumulative reduction in myopia progression of 0.68 D over three years and 0.84 D over six years, achieved with an average daily oral dose of 1000 mg (Trier et al., 2023). Based on observational studies, the one-year efficacy of 1000 mg per day of 7-MX in slowing axial growth (−0.07 mm) was comparable to that of 0.01 % atropine eyedrops and multifocal soft contact lenses, which demonstrated reductions ranging from −0.06 to −0.11 mm (Sun and Hasebe, 2022). Notably, the absolute effect size achieved by 7-MX appears to be independent of age, contrasting with atropine eyedrops (Li et al., 2021a), which are less effective in younger children, and orthokeratology (Ortho-K), which works better in younger children (Xu et al., 2023). It remains to be determined whether 7-MX can enhance the effects of other myopia control methods, such as optical devices or atropine eyedrops. Further clinical trials are warranted.

3.3.2.3. Pirenzepine. In a multi-center clinical trial conducted by the US Pirenzepine Study Group, 2 % pirenzepine, an M1-muscarinic antagonist, was administered as an eye gel to 117 children aged 8–12 years, effectively slowing myopia progression (-0.26 ± 0.36 D) compared to a placebo group of 57 children (-0.53 ± 0.50 D) (Siatkowski et al., 2004). In another study involving 282 schoolchildren aged 6–12 years across multiple centers in Asia, pirenzepine demonstrated a lower mean increase in myopia at 12 months compared to placebo (0.47 D vs 0.84 D, P < 0.001) (Tan et al., 2005). Both studies reported no adverse effects, and a meta-analysis of the combined data (N = 326) indicated moderate effects on changing SE by 0.31 D (95 % CI: 0.17 to 0.44) and AL by −0.13 mm (95 % CI: 0.14 to −0.12) (Walline et al., 2020a). Pirenzepine has not been further studied due to its twice-a-day dosing.

3.3.2.4. Oral crocetin. Crocetin, an apocarotenoid dicarboxylic acid extracted from the crocus flower, is known for its multiple beneficial biomedical properties as a diet (Guo et al., 2021). It was found to exert dose-dependent activation of the early growth response 1 (*Egr-1*) gene (Mori et al., 2019a). *Egr-1* is referred to as an immediate-early response protein due to its quick induction kinetics, occurring within minutes of a stimulus, and its rapid decline, typically within hours (Yan et al., 2000). Knocking out *Egr-1* in mice resulted in longer eyes and a relative myopic shift in refraction (Schippert et al., 2007). Moreover, lens-induced and form deprivation myopia led to a rapid and sustained suppression of the *ZENK* peptide and its RNA transcript in chicken (*ZENK* is the chicken and mice ortholog of *Egr-1*) (Ashby et al., 2010). On the other hand, *ZENK* was upregulated when axial eye growth was inhibited (Bitzer and Schaeffel, 2002; Fischer et al., 1999). In a murine model, 0.001 % of crocetin suppressed both refractive and AL changes ($P < 0.001$) (Mori et al., 2020). An RCT which included 69 myopic participants aged 6–12 years evaluated the effects of 7.5 mg of oral crocetin taken daily for 24 weeks and found less change in SE in the crocetin group (−0.33 ± 0.05 D) than the placebo group (−0.41 ± 0.05 D). Axial elongation was also reduced in the crocetin group at 0.18 ± 0.02 mm vs 0.21 ± 0.02 mm in the placebo group (Mori et al., 2019b). Dietary natural compounds should be safe and convenient for myopia prevention. Further and large-scale studies are warranted.

3.3.2.5. ω-3 PUFAs. Emerging evidence positions ω-3 polyunsaturated fatty acids (PUFAs) as promising candidates for myopia control (Pan et al., 2021). This study demonstrated that daily intake of ω-3 PUFA or peribulbar injection of docosahexaenoic acid (DHA) could significantly impede the progression of experimental myopia in animal models. This correlated with the inhibition of the cascade of decreases in choroidal blood perfusion (ChBP)–scleral hypoxia (Ostrin et al., 2023; Wu et al., 2018a). Notably, DHA exerted a more favorable protective effect on the declines in ChBP and myopia development than 0.1 % atropine. ω-3 PUFAs are conveniently available in the form of oral supplements and are even safe for pregnant women and infants. Oral administration of ω-3 PUFAs partially suppressed the near-work–induced declines of ChBP in human young adults. Genetic epidemiological validation via two-sample Mendelian randomization (MR) analysis further supported the protective effect of omega-3 and DHA on myopia, potentially through modulation of ChBP (Xue et al., 2024).

The American Heart Association recommends regular intake of either ω-PUFAs-rich foods or oral supplements (upon consultation with a physician) for the improvement of cardiovascular health (Rimm et al., 2018). While the American Heart Association endorses ω-3 PUFA supplementation for cardiovascular health, current dosage guidelines—optimized for neurodevelopmental safety—lack ocular-specific pharmacokinetic/pharmacodynamic validation. To bridge these translational challenges, multicenter randomized controlled trials (RCTs) must address two pivotal questions: (1) Whether ω-3 PUFA supplementation demonstrates clinically meaningful myopia suppression in humans; (2) The optimal therapeutic window (dose-duration relationship) balancing ocular efficacy with systemic safety. Furthermore, in comparison with oral administration, the delivery of ω-3 PUFAs via eye drops may offer a more preferable option for human myopia control in the future.

3.3.2.6. Oral Difrarel. The efficacy of oral Difrarel for slowing the progression of myopia and high myopia has been investigated. Difrarel E is made from anthocyanosidic extracts of *Vaccinium myrtillus* (bilberry extract) and α-tocopherol acetate (vitamin E) (Omar, 2018). Bilberry is high in anthocyanins, which are part of the broader class of bioflavonoids (Tsuda, 2012). In rabbits, administration of blackcurrant anthocyanins resulted in the distribution of anthocyanins in several ocular tissues, including the sclera, choroid, and retina (Matsumoto et al., 2006). A retrospective analysis found that short-term (6 months) oral delivery of Difrarel in children could control the progression of mild and high myopia (Zhou et al., 2016). In a prospective case-control study, highly myopic children received 50 mg tablets of Difrarel E twice daily for 20 days each month, with the control group receiving no treatment (Omar, 2018). After one year, oral Difrarel E significantly slowed myopia progression, showing SE and AL progressions of -0.12 ± 0.08 D and 0.26 ± 0.17 mm compared to -0.39 ± 0.16 D and 1.03 ± 0.3 in the control group. In another study, fermented bilberry extract (400 mg/day) increased subjective accommodation and mesopic contrast sensitivity in myopic eyes after a month of treatment (Kamiya et al., 2013). The marked differences in the outcomes between the control and treated groups are promising for the management of the progression of high myopia.

3.3.2.7. Dietary glucose restriction. Epidemiological evidence suggests a potential association between excessive dietary glucose intake and myopia progression, possibly mediated through postprandial insulin response amplification (Cordain et al., 2002; Reiser et al., 1979). Using a guinea pig myopia model, Lin et al. showed that a high sugar diet (HSD) exposure did not only induce myopia but also aggravated experimental myopia development by activating the scleral insulin signaling and glycolysis pathways (Lin et al., 2024). Clinical corroboration identifies poor glycemic control as an independent risk factor for axial elongation (Lin et al., 2024). Additional *in vivo* studies are needed to discriminate whether insulin pathway activation directly drives scleral remodeling or merely correlates with myopic changes. Human studies lack dose-response characterization of sugar intake thresholds and temporal insulin fluctuations relevant to ocular pathophysiology. If these indications are confirmed, dietary glucose restriction could emerge as a viable myopia control strategy. In addition, the synergistic potentiation of near-work and HSD effects on promoting glycolysis suggests temporal behavior modification—delaying near tasks during postprandial hyperinsulinemic windows—might be an effective strategy for myopia control.

3.4. Optical interventions

3.4.1. Novel spectacle lenses

An early study in chicks showed that wearing a minus lens during development created a hyperopic defocus, which induced compensatory axial elongation and ultimately led to myopia (Schaeffel et al., 1988). Subsequent research in rhesus monkeys revealed that laser ablation of the fovea did not hinder the development of myopia in response to optically induced relative hyperopic defocus or form deprivation (Smith et al., 2007). Cross-sectional studies in humans reinforced these findings by reporting greater relative peripheral hyperopia in myopic children compared to relative peripheral myopia in emmetropes and hyperopes (Chen et al., 2010; Mutti et al., 2000; Sng et al., 2011). However, it was unclear whether relative peripheral hyperopic defocus was the cause or the consequence of myopia (Sng et al., 2011). While these findings suggested that foveal visual signals are not essential for regulating AL growth, they did not prove that central defocus has no impact on refractive error development. Thus, the simultaneous competing defocus theory became a probable mechanism for defocus myopia control spectacle and contact lenses (Arumugam et al., 2016; Smith Iii et al., 2020a; Tse et al., 2007). The effects of simultaneous competing defocus signals on emmetropization have been studied by rearing chicks (Tse et al., 2007), guinea pigs (McFadden et al., 2014), marmosets (Benavente-Perez et al., 2012), and rhesus monkeys (Arumugam et al., 2014, 2016) with lenses that have concentric annular zones of alternating refractive powers. In chicks and guinea pigs, the dual-focus lenses guided refractive development toward either the average imposed defocus or a slightly more hyperopic state than the average (McFadden et al., 2014; Tse et al., 2007). In marmosets raised with dual-focus contact lenses (±5 D power zones), the treated eyes developed a level of hyperopia similar to that produced by +5 D single-vision lenses (Benavente-Perez et al., 2012). When infant macaques were exposed to two approximately equally distinct focal planes, refractive development shifted toward the more myopic/less hyperopic focal plane, fully compensating for the more anterior foci (Arumugam et al., 2014). Currently, most optical interventions employ this principle, achieving clear central vision with myopic correction while simultaneously inducing relative myopic defocus across a significant portion of the peripheral retina with plus power.

3.4.1.1. MyoVision lenses: reducing relative peripheral hyperopic defocus. The first trial on defocus spectacle lenses tested three highly aspherized designs intended to reduce relative peripheral hyperopic defocus. The lenses differed in the size of the central optic zone and the magnitude of the relative positive power in the periphery (Sankaridurg et al., 2010). The only successful lens type, later commercialized and named MyoVision by Zeiss, had an asymmetric design, a clear central aperture of approximately 10 mm, and a peripheral zone with +1.9 D Add power. In a 12-month trial in 6 to 16-year-old children, the lens significantly slowed SE progression by 30 % (-0.68 ± 0.47 D vs -0.97 ± 0.48 D) only in a subgroup of 6-12-year-old children with parental history of myopia, but had no significant effect on axial elongation. A multicentre clinical trial in Japanese children with a family history of myopia found no significant difference in myopia progression between MyoVision lenses and monofocal glasses (Kanda et al., 2018). The modest clinical impact is likely because the reduction of relative peripheral hyperopia was insufficient to control myopia progression.

3.4.1.2. Multiple segments spectacle lenses: inducing myopic defocus in the mid-periphery of the retina. In this type of lens design, multiple small, circular (approximately 1 mm in diameter), positively powered lens elements are molded across all or part of the peripheral region on the front surface of a distance correction lens (single vision lens), which serves as the "carrier" lens. The lenses are designed to create a relative myopic focus in the peripheral retina. Peripheral myopic defocus is critical for these lenses to manage and slow myopia progression.

The defocus-incorporated multiple segments (DIMS) spectacle lens features a collection of miniature lenslets arranged in a triangular, honeycomb-like pattern across the front surface of the carrier lens. These lenslets are situated within a hexagonal annular ring, while the central area surrounding the optical center of the carrier lens is left unobstructed and clear. Light rays originating from a distant point object and passing through the lenslet-covered portion of the lens as they enter the eye's pupil are nominally brought to a dual focus. The first focus results from the lens' basic distance correction, while the second, more myopic focus is created by the combined refractive power of the distance correction and each of the embedded lenslets. The DIMS lenses were designed to have a central zone (diameter 9 mm) of myopic refractive correction, giving clear vision and a surrounding zone of lenslets that create myopic defocus across the mid-periphery of the retina (Lam et al., 2020). In a 2-year randomized controlled trial, 8-13-year-old Chinese children who wore DIMS spectacle lenses had myopia progression retarded by 52 % (-0.41 ± 0.06 D vs -0.85 ± 0.08 D) and axial elongation by 62 % (0.21 ± 0.02 mm vs 0.55 ± 0.02 mm) compared to those wearing single vision spectacles (Lam et al., 2020). Approximately 21 % of the children who wore the DIMS had no myopia progression,

compared to just 7.4 % in the single vision group. Participants who completed the two-year trial were followed for six years and divided into four groups: Group 1 wore DIMS spectacles for six years; Group 2 wore DIMS for 3.5 years before switching to single vision spectacles; Group 3 started with single vision spectacles for two years and then switched to DIMS; and Group 4 wore single vision spectacles for two years, switched to DIMS for 1.5 years, and then returned to single vision spectacles (Lam et al., 2023). Group 1 showed the least SE progression and axial elongation, which were −0.92 ± 1.15 D and 0.60 ± 0.49 mm. Group 1 showed no differences in SE progression (−0.52 ± 0.66 D vs −0.40 ± 0.72 D) or axial elongation (0.32 ± 0.26 mm vs 0.28 ± 0.28 mm) between the first three years and the later three years. Over the final 2.5 years, the DIMS lens groups (Groups 1 and 3) had less SE progression and axial elongation than the single vision groups (Groups 2 and 4). There was no evidence of rebound after stopping treatment. Best corrected visual acuity, phoria, stereopsis, and accommodation amplitude through DIMS have been reported to be within normal ranges (Lam et al., 2023); however, acuity with DIMS diminished when looking mid-peripherally, nasally, or temporally (Kaymak et al., 2022; Lu et al., 2020). The DIMS lenses are marketed as MiYOSMART spectacle lenses.

There is also a spectacle lens design that uses multiple concentric rings of lenslets of varying myopic defocus, described as aspherical lenslets (Bao et al., 2022; Li et al., 2021c). The lenslets are arranged in a series of concentric circular patterns surrounding the central clear area, rather than being distributed in a triangular lattice configuration as seen in the DIMS design. The central clear zone is intended for correcting distance refractive error. The aspheric shaping of the lenslets is argued to extend the myopic focal region produced by the lenslets, creating a "volume of myopic focus" rather than a single plane of myopic defocus (Bao et al., 2022). In a 2-year trial, lenses with highly aspherical lenslets target (HALT) and slightly aspherical lenslet target (SALT) were more effective than single vision lenses in slowing myopia progression in Chinese children aged 8–13 years, reducing SE progression by −0.66 ± 0.09 D, −1.04 ± 0.06 D, and −1.46 ± 0.09 D, respectively, and axial elongation by 0.34 ± 0.03 mm, 0.51 ± 0.04 mm, and 0.69 ± 0.04 mm, respectively (Bao et al., 2022). The efficacy of HALT lenses in slowing myopia progression over a 5-year term was later evaluated, and the changes in SE were −1.27 ± 0.14 D and −3.03 ± 0.18 D for HALT and the control, respectively (Li et al., 2025b). The corresponding AL changes were 0.67 ± 0.06 mm and 1.40 ± 0.07 mm. The incidence of high myopia after 5 years (>-6.00D) was 9 % in the HALT group, and 38 % in the control group, with no significant treatment-related complications reported during this period. Sankaridurg et al. demonstrated that children who wore HALT for six months showed no signs of rebound effects after discontinuing treatment for the following six months (Sankaridurg et al., 2023). While the size of the functional zone responsible for generating mid-peripheral myopic defocus is greater, the HALT does not result in a better efficacy than the DIMS lens. The two designs may have broadly similar effects on retinal imagery and myopia control (Radhakrishnan et al., 2023a, 2023b). This is supported by findings from a retrospective study by Lembo et al., which found that the efficacies of DIMS and HALT in slowing SE progression (−0.50 ± 0.64 D vs. −0.63 ± 0.56 D, respectively) and axial elongation (0.29 ± 0.63 mm vs. 0.32 ± 0.72 mm, respectively) over two years were statistically and clinically similar in European children (Lembo et al., 2024). Similar comparable effects have been reported by a one-year trial in South Asian children (Gupta et al., 2025). However, a retrospective study in Chinese children observed that subjects who wore HALT showed less SE progression (−0.34 ± 0.04 D) and axial elongation (0.17 ± 0.02 mm) than those who wore DIMS (−0.63 ± 0.07 D and 0.28 ± 0.04 mm, respectively) (Guo et al., 2023b). This study's conclusions may be limited, as the analysis included only 102 of 296 HALT wearers and 33 of 107 DIMS wearers due to missing data (Guo et al., 2023b). Further limitations included necessary data adjustments for varying examination intervals and the potential for overestimated myopia progression due to the use of non-cycloplegic refraction in some follow-ups.

The Cylindrical Annular Refractive Elements (CARE) spectacle lens was developed to investigate whether a smaller central zone, sufficiently small to create an effective functional area that projects myopic defocus onto the near periphery close to the fovea, as well as a higher degree of defocus, could enhance treatment effects (Chen et al., 2025c). Animal research has indicated that the influence of myopic defocus on refractive development diminishes with increasing eccentricity, being most effective in the near periphery near the fovea (Smith Iii et al., 2020b). The design aims to achieve an optimal balance by maximizing the size of the functional zone to enhance simultaneous competing defocus across a broad area of the retina, while minimizing the central clear zone enough to guarantee that children maintain sharp and clear vision for their daily activities. The CARE lens features a central zone for myopia correction, encircled by a treatment zone made up of multiple micro-cylinders arranged in concentric rings (Alvarez-Peregrina et al., 2025; Chen et al., 2024b). The lens has two design variants, commercialized by Zeiss as MyoCare and MyoCare S. The MyoCare has a central zone measuring 7 mm, with a nominal power of the cylindrical elements along the power meridian set at +9.2 D, whereas the MyoCare S features a larger central zone of 9 mm, and the nominal power of its cylindrical elements is lower at +7.6 D (Alvarez-Peregrina et al., 2025; Chen et al., 2024b). Over two years, MyoCare and MyoCare S effectively controlled myopia in Chinese children compared to single vision lenses, slowing SE progression by −0.75 D (95 % CI: 0.89 to −0.61) and −0.78 D (95 % CI: 0.92 to −0.65) compared to −1.19 D (95 % CI: 1.33 to −1.05), respectively (Chen et al., 2025c). The corresponding AL changes were 0.41 mm (95 % CI: 0.35 to 0.47) and 0.44 mm (95 % CI: 0.38 to 0.50) compared to 0.61 mm (95 % CI: 0.55 to 0.67). Efficacy did not vary significantly between the two treatment lenses. However, it seems there may be a connection between the lens features and their effectiveness. Compliance with the treatment lenses was high, with a mean wearing time of 14 h per day compared to 13.9 h in the single vision group (Chen et al., 2025c). The first-year results of a 2-year trial in European children also showed that MyoCare spectacles significantly slowed SE progression (−0.20 ± 0.41 D) and AL elongation (0.09 ± 0.14 mm) compared to single vision spectacles (−0.41 ± 0.41 D and 0.23 ± 0.15 mm, respectively) (Alvarez-Peregrina et al., 2025). Central visual acuity did not decrease with MyoCare lenses, but peripheral visual acuity decreased in the nasal and temporal zones (Alvarez-Peregrina et al., 2025). 16.7 % of the treated group had not adapted to the MyoCare lenses after one week, compared to 0.9 % of the control group (Alvarez-Peregrina et al., 2025). Direct comparisons among DIMS, HALT and CARE lenses revealed that DIMS and HALT showed comparable and significantly better efficacy than CARE spectacles at 1 year follow-up (Gupta et al., 2025).

3.4.2. Novel spectacle lenses with other optical mechanisms

Alongside peripheral myopic defocus, other optical mechanisms may also affect axial elongation in children with myopia. Contrast modulation was adopted in the Diffusion Optics Technology (DOT) spectacle lenses (Rappon et al., 2022a). The design is based on the principle that low contrast visual experience, like that from a natural outdoor environment, weakly stimulates the visual system and elicits low-level, more natural bipolar cell activity that does not appear to disrupt normal eye growth (SightGlass Vision, 2023), whereas elevated contrast signaling in the retina, whether from genetic predisposition (Neitz et al., 2022; Rappon et al., 2022a) or the modern urban visual environment, may overstimulate bipolar cells and signal axial elongation and myopia progression (SightGlass Vision, 2023). Studies indicate that high-contrast images from close-up activities (like black text on a white background) can overstimulate peripheral midget bipolar cells (retinal cells that detect contrast), leading to signals that promote eye elongation (Wolffsohn and Gifford, 2025). DOT spectacle lenses are designed to minimize this overstimulation by scattering light in a way that simulates more natural contrast. Similar to DIMS and HALT, it has a clear distance zone in the center and a background of single vision correction throughout the periphery. However, the DOT lens does not have lenslets

but diffusers (diffusion microlenses) to slightly reduce contrast by scattering light in the peripheral retina. In a two-year clinical trial, DOT lenses were more effective compared to control lenses, delaying myopia progression by 59 % (−0.36 ± 0.54 D vs −0.88 ± 0.77 D) and axial elongation by 38 % (0.33 ± 0.23 mm vs 0.53 ± 0.33 mm) (Rappon et al., 2022b). After 4 years, the lenses remained safe and more effective compared to standard single-vision control lenses (Chalberg et al., 2023). The DOT lenses maintain visual function and performance similar to single vision lenses and better than DIMS and HALT (Rani et al., 2024; Wolffsohn et al., 2024).

The novel Lenslet-ARray-Integrated (LARI) spectacle lenses with negative power lenslets (NLARI) control myopia by inducing peripheral hyperopic defocus (Su et al., 2024), contrary to the popular concept that peripheral hyperopic defocus induced by negative lenses promotes axial elongation (Smith et al., 2009). The rationale was to understand how wavefront modulation and retinal contrast alteration may influence myopia progression (Guggenheim and Terry, 2025; Jiang et al., 2025; Su et al., 2024). It was found that phase modulation induced by the micro-structures of the lenslet array contributes to an increase in root mean square wavefront aberrations, leading to image blur or decrease in image contrast, which may play a role in controlling myopia (Jiang et al., 2025). In a one-year RCT, children who wore NLARI had their myopia progression slowed by 68 % (−0.21 ± 0.35 D vs −0.66 ± 0.40 D) and axial elongation by 50 % (0.17 ± 0.14 mm vs 0.34 ± 0.18 mm) (Su et al., 2024), even higher than children who wore LARI lenses with positive power lenslets (PLARI) which impeded myopia progression by 55 % (−0.30 ± 0.48 D vs −0.66 ± 0.40 D) and axial elongation by 44 % (0.19 ± 0.20 mm vs 0.34 ± 0.18 mm) (Su et al., 2024). These results prompt further investigation into the underlying mechanisms of myopia progression and highlight the potential for developing new optical interventions that leverage peripheral defocus effects more effectively.

3.4.3. Novel spectacle lenses for myopia prevention

Few studies have investigated the effect of peripheral defocus spectacles for preventing myopic shift in non-myopes. Among 6- to 9-year-old children with baseline SE of 0.0 to +2.0 D, Zhang et al. found no significant difference in the effect of HALT spectacles and single vision lenses on myopic shift and axial eye growth after a year (Zhang et al., 2025). A Clouclip device recorded an average lens wear time of 35.09 h per week for the single vision lens group and 38.60 h per week for the HALT group, with no intergroup difference. Subjects who wore their HALT lenses for more than 30 h per week had significantly slower axial elongation [0.11 mm (95 % CI: 0.05 to 0.17)] compared to their single vision lens counterparts [0.27 mm (95 % CI: 0.21 to 0.33)]. In another study, wearing the Optical Technical Of Guiding Emmetropization (O.T.O.G.E.) lens for at least 10 h a day significantly slowed myopic shift and AL growth in 5- to 8-year-old children with baseline SE of −0.25 D to +2.0 D over a year (Zhao et al., 2025). Compared to control (no lens worn), SE changes were 0.26 ± 0.26 D vs 0.55 ± 0.59 D, and AL changes were 0.21 ± 0.09 mm vs 0.44 ± 0.20 mm. Overall, while peripheral defocus spectacle may reduce myopic shift in nonmyopes, adherence to more hours of lens wear may be necessary to achieve the desired results.

3.4.4. Bifocal and progressive addition spectacle lenses

Bifocals and progressive addition lenses were initially considered for myopia management because they reduce accommodative lag and near-point esophoria, which have been associated with myopia progression. Studies have also reported that multifocal spectacles cause a myopic shift in peripheral defocus, and this was associated with less central myopia progression (Berntsen et al., 2013; Sun et al., 2012). Fulk et al. reported that flat-top bifocals with +1.50 D Addition slowed SE progression to a slight degree compared to single vision glasses in children with near-point esophoria (0.99 ± 0.68 D vs 1.24 ± 0.65 D) but did not affect axial elongation (Fulk et al., 2000). Later, Cheng et al. investigated an executive bifocal with a +1.50 Addition, and the same Addition with a 3-base-in prism in each eye (Cheng et al., 2014). Over three years, SE progression averaged −2.06 ± 0.13 D for the single-vision lens group, −1.25 ± 0.10 D for the bifocal group, and −1.01 ± 0.13 D for the prismatic bifocal group (Cheng et al., 2014). The corresponding changes in AL were 0.82 ± 0.05 mm, 0.57 ± 0.07 mm, and 0.54 ± 0.06 mm (Cheng et al., 2014). For children with high lags of accommodation (≥1.01 D), both bifocals and prismatic bifocals had a similar treatment effect of 1.1 D. In contrast, for those with low lags (<1.01 D), prismatic bifocals showed a greater effect (0.99 D) compared to bifocals (0.50 D). The treatment effects were independent of near phoria status. Progressive addition lenses with additions of +1.50 D to +2.0 D demonstrate minimal myopia control effects; however, their effectiveness improves when used for children with near esophoria and accommodative lag (Correction of Myopia Evaluation Trial 2 Study Group for the Pediatric Eye Disease Investigator G, 2011; Edwards et al., 2002; Gwiazda et al., 2004; Hasebe et al., 2014; Yang et al., 2009; Zhu et al., 2022).

To conclude, earlier studies of traditional bifocals and progressive addition lenses have demonstrated overall modest effects, and more recent research has focused on novel designs. The reported outcomes suggest the novel spectacle lenses are effective and essentially non-invasive with significant clinical benefits (Table 3). However, some of these spectacle-based interventions may reduce high contrast visual acuity and contrast sensitivity at higher spatial frequencies when viewed off-axis through the myopia control elements (Table 3) (Alvarez-Peregrina et al., 2025; Bullimore et al., 2021b; Li et al., 2021b; Lu et al., 2020).

3.4.5. Orthokeratology lenses

Ortho-K lenses were first developed in the early 1960s using conventional bicurve PMMA hard contact lenses fitted substantially flatter than the flat corneal curvature reading (Jessen, 1962). The lens designs used at this time were worn during the day. The early designs of Ortho-K demonstrated poor lens centration and inconsistent myopia control effects, leading to their eventual discontinuation. In the late 1980s, reverse geometry lenses featuring a steeper reverse curve were introduced (Wlodyga, 1989). These three-zone Ortho-K lenses improved centration and enabled more predictable myopia control. Ortho-K was recommended for daytime wear well into the 1990s, when Stuart Grant pioneered an overnight wear method (Grant, 1995). He proposed that wearing lenses during sleep would provide daytime visual freedom, offering greater convenience and potentially enhanced efficacy from eyelid pressure, which might also slow myopic progression. Modern Ortho-K lenses, worn overnight, are designed with four to five curves, incorporating peripheral alignment curves to enhance lens centration even further (Cho and Tan, 2019). The lenses have a flat central curve (base curve/back optic zone radius) and an adjacent reverse curve, which is steeper than its neighbouring curves. The reverse curve joins the base curve to the alignment and other peripheral zones, which align with the midperipheral cornea and allow for comfortable fitting. The central curve flattens the central cornea to correct the myopic refractive error, while the reverse zone steepens the paracentral cornea to induce myopic defocus in the peripheral retina (Kang and Swarbrick, 2011a; Zhou et al., 2024), likely through changes in wavefront aberrations (Hiraoka et al., 2015; Mathur and Atchison, 2009b). The central flattened region is called the treatment zone (TZ) (Carracedo et al., 2019; Gifford et al., 2020b).

In 2005, a pilot study suggested that Ortho-K might reduce myopia progression over two years (Cho et al., 2005). Studies in Asia have reported significant AL control efficacies of 36 % (0.39 ± 0.27 mm vs 0.61 ± 0.24 mm) to 46 % (0.29 ± 0.27 mm vs 0.54 ± 0.27 mm) over 2 years (Cho and Cheung, 2012; Cho et al., 2005; Choi et al., 2023; Kakita et al., 2011). There are similar findings in 2-year studies conducted in Spain, 32 % (0.47 mm vs 0.69 mm); Denmark, 59 % (0.17 mm vs 0.41 mm); and the United States, 56 % (0.25 mm vs 0.57 mm) (Jakobsen and Moller, 2022; Santodomingo-Rubido et al., 2012; Walline et al., 2009). The efficacy of Ortho-K is notable during the first and second years of treatment, especially when it is initiated at an early age of 6–8 years

Table 3
Efficacy, benefits, and limitations of the interventions for myopia control in children.

	Refraction Control	Axial Length Control	Benefits	Limitations
Outdoor Time				
	30 % over 1 year (Wu et al., 2018c) up to over 50 % (prevention of myopia onset) (Wu et al., 2013)	0.45mm/0.60 mm over 1 year (Wu et al., 2018c)	1. Simple and cost-effective 2. Safe and less invasive 3. Promotes physical activity, exposure to sunlight, and social interaction 4. Less in-office time	1. Optimal duration for myopia control is still uncertain. 2. Requires protection against potential UV Damage 3. Optical correction still needed
1 % to 0.1 % Concentrations of Atropine				
1 % Atropine (Chua et al., 2006)	77 % over 2 years	−0.02/0.38 mm over 2 years	1. Greater myopia control efficacy compared to lower concentrations 2. Yields consistent responses across individuals 3. Less in-office time 4. Parental oversight	1. Greater rebound and adverse events 2. Low compliance 3. Optical correction still needed
0.5 %, 0.25 %, 0.1 % Atropine (Chia et al., 2012; Shih et al., 1999)	0.5 %: 0.30D/-0.49D over 2 years 0.25 %: 0.45D over 2 years 0.1 %: 0.38D/-0.49D over 2 years	0.5 % atropine: 0.27/0.41 mm over 2 years 0.1 % atropine: 0.28/0.41 mm over 2 years		
Lower Concentrations of Atropine				
0.05 % Atropine (Yam et al., 2019, 2023)	67 % over 1 year 46.4 % over 2 years (prevention of myopia onset)	51 % over 1 year	1. Reduced side effects 2. Lower risk of rebound of myopia. 3. More cost-effective compared to higher concentrations 4. Less in-office time 5. Parental oversight	1. Limited evidence of efficacy and safety in some populations. 2. Optical correction still needed
0.025 % Atropine (Fang et al., 2010; Yam et al., 2019)	43 % over 1 year 61 % over 1 year (prevention of myopia onset)	29 % over 1 year		
0.02 % Atropine (Cui et al., 2021; Fu et al., 2020a; Zadnik et al., 2023)	Mixed Results	Mixed Results		
0.01 % Atropine (Chia et al., 2012; Repka et al., 2023; Yam et al., 2019; Zadnik et al., 2023)	Mixed Results	Mixed Results		
Myopia Control Spectacle Lenses				
MyoVision Lenses (Sankaridurg et al., 2010)	No significant effect to 30 % (in a subset of 6-12-year-old children)	No significant effect	1. Safe and less invasive 2. Minimal adjustments to visual habits 3. Correct distance vision while controlling myopia 4. Do not require daily maintenance	1. Visual disturbance during adaptation (Li et al., 2021b; Lu et al., 2020) 2. Hyperactive children may be more prone to misplacing or breaking their glasses 3. Not available in all prescriptions 4. Limited options for high astigmatism 5. May reduce off-axis visual acuity, contrast sensitivity, and reading speed
Defocus-incorporated multiple segments (DIMS) spectacle lens (Lam et al., 2020)	52 % over 2 years	62 % over 2 years		
Highly Aspherical Lenslets Target (HALT) Spectacle Lenses (Bao et al., 2022)	67 % over 2 years (Full-time wearers)	60 % over 2 years (Full-time wearers)		
Diffusion optics spectacle lenses (Diffusion Optics Technology-DOT) (Rappon et al., 2022b)	59 % over 2 years	38 % over 2 years		
Bifocal and Progressive Addition Spectacle Lenses (Cheng et al., 2014; Correction of Myopia Evaluation Trial 2 Study Group for the Pediatric Eye Disease Investigator, 2011; Edwards et al., 2002; Fulk et al., 2000)	Not clinically effective	Not clinically effective		
Orthokeratology Lenses				
		32 %–59 % over 2 years (Cho and Cheung, 2012; Cho et al., 2005; Choi et al., 2023; Jakobsen and Moller, 2022; Kakita et al., 2011; Santodomingo-Rubido et al., 2012; Walline et al., 2009)	1. No glasses or contact lenses during the day 2. Suitable for active children 3. Corrects distance vision and controls myopia 4. Can correct higher levels of astigmatism 5. Parental oversight	1. Require advanced imaging techniques and expertise 2. Supplementary duration of consultation in the clinic 3. Risk of microbial keratitis, corneal scarring, and vision loss 4. Reduced contrast sensitivity from corneal irregular astigmatism and higher-order aberrations 5. Not available in all prescriptions
Peripheral Addition Multifocal Soft Contact Lenses				
Add +2.00D (Walline et al., 2013)	50 % over 2 years	29 % over 2 years	1. They are daily disposable 2. Corrects distance vision and controls myopia	1. Visual disturbances during adaptation to treatment zones 2. Dryness of eyes
Add +2.50D (Walline et al., 2020b)	43 % over 3 years	36 % over 3 years		
Add +3.00D (Raffa et al., 2021)	66.6 % over 1.5 years	63.2 % over 1.5 years		

(*continued on next page*)

Table 3 (*continued*)

	Refraction Control	Axial Length Control	Benefits	Limitations
			3. Children reluctant to wear glasses full time 4. Physically active children	3. Risk of microbial keratitis, corneal scarring, and vision loss 4. Not available in all prescriptions 5. Limited options for high astigmatism
Concentric Ring Bifocal Soft Contact Lenses				
Acuvue Bifocal by Vistakon (Aller et al., 2016)	72 % over 1 year (subjects with esotropic fixation disparity)	80 % over 1 year (subjects with esotropic fixation disparity)	1. Correct distance vision while controlling myopia 2. Children reluctant to wear glasses full time 3. Physically active children 4. They are daily disposable (MiSight and RingBoost technology)	1. Visual disturbances during adaptation to treatment zones 2. Dryness of eyes 3. Risk of microbial keratitis, corneal scarring, and vision loss 4. Not available in all prescriptions 5. Limited options for high astigmatism
MiSight Lenses (Chamberlain et al., 2019)	59 % over 3 years	52 % over 3 years		
Defocus-incorporated Soft Contact Lenses (DISC) (Lam et al., 2014)	25 % over 2 years	32.4 % over 2 years		
Enhancing efficacy (EE) prototype of the RingBoost technology (Cheng et al., 2023)		0.11 mm compared to control over 6 months		
Repeated Low-level Red-Light Therapy				
	75 % over 2 years (Xiong et al., 2022)	75 % over 2 years (Xiong et al., 2022)	1. Potential to shorten axial length. 2. Short duration of therapy 3. Minimal interference with daily life 4. Less in-office time 5. Parental oversight	1. Less portable. 2. Long-term safety needs to be validated

(Cho and Cheung, 2017; VanderVeen et al., 2019).

Studies have reported that Orth-K lenses with a smaller back optic zone diameter (BOZD) may enhance treatment efficacy. Using Ortho-K lens designs with smaller BOZD results in reduced TZ areas (Carracedo et al., 2019; Gifford et al., 2020b). This approach is intended to increase the extent of the peripheral retina exposed to myopic defocus from the steeper corneal periphery, thereby improving the treatment effect. However, Gifford et al. reported that reducing the TZ diameter in Ortho-K did not alter relative peripheral refraction (Gifford et al., 2020b). Even so, a retrospective study by Pauné et al. found that AL elongation was less in children fitted with small BOZD Ortho-K lenses for 12 months than in those wearing Ortho-K with large BOZD (0.08 ± 0.12 mm vs 0.16 ± 0.11 mm) (Pauné et al., 2021). Additionally, the Variation of Orthokeratology Lens Treatment Zone (VOLTZ) study randomly assigned children aged between 6 and 11 years to be fitted with either 5 mm BOZD or 6 mm BOZD Ortho-K lenses, and found that the smaller BOZD Ortho-K lenses yielded less axial elongation after 2 years compared to the larger BOZD lenses (0.15 ± 0.21 mm vs 0.35 ± 0.23 mm) (Guo et al., 2023a). Interactions between pupil diameter and the Ortho-K plus power ring (PPR), the mid-peripheral annular ring of corneal steepening, may have contributed to the enhanced efficacy of the smaller BOZD lenses. In the study by Pauné et al., children with pupil diameters larger than the Ortho-K PPR diameter experienced slower axial eye growth, while those with pupil diameters within the PPR diameter showed greater axial elongation (Pauné et al., 2021). Thus, merely reducing the BOZD may not suffice; ensuring that the PPR diameter falls more within the pupil diameter will likely yield a more beneficial myopia control effect.

Orth-K provides clear daytime vision without the need for glasses or contact lenses and has the advantage of maintaining relative stability on the cornea and constant treatment, regardless of eye movements. However, a common concern is the potential side effects associated with its use. Even successful Ortho-K fitting, which requires advanced imaging and practitioner expertise, may increase corneal irregular astigmatism and higher-order aberrations, sometimes reducing contrast sensitivity (Hiraoka et al., 2006, 2007). An earlier study found that the risk of microbial keratitis (MK) in children wearing Ortho-K lenses was approximately 13.9 per 10,000 patient-years, based on data from 677 children over 1435 patient-years of wear (Bullimore et al., 2013). The study surveyed nearly 200 eye care practitioners in the United States, with clinical care conducted between 2004 and 2006. Subsequently, data were collected from a group of ophthalmology and optometry practices, along with a local Children's Hospital in Moscow, Russia (Bullimore et al., 2021a). More than 23,000 Ortho-K fits were conducted between 2010 and 2018, and slightly over 1000 records were reviewed. The incidence of MK was estimated to range from 4.9 to 5.3 per 10,000 patient-years of wear. Recently, a retrospective multicenter study investigated the onset of MK among 1438 Japanese patients who had been prescribed Ortho-K lenses and had worn them for at least 3 months. Four cases of MK were identified, yielding an overall incidence of 5.4 per 10,000 patient-years. While these findings suggest that Ortho-K safety and compliance may have improved over time, it could also imply that Ortho-K is perhaps safer than originally indicated, and is not riskier than other contact lens types, which was the original thought due to overnight wear of lenses. Notwithstanding, appropriate instruction and advice on the safe handling, proper maintenance, and proper storage of these lenses, along with the importance of hand hygiene, are essential to mitigate the risk of complications.

3.4.6. *Soft contact lenses*

Like other optical methods, soft contact lenses offer the dual benefit of correcting as well as controlling myopia. One of the biggest transformations we have seen is the variety of options now available in the optics of these lenses. Efficacy appears to vary between designs, and full-time wear is recommended for optimum myopia control outcomes. In this section, we discuss the concentric ring (bifocal) soft contact lenses [alternating bifocal design], progressive peripheral add (multifocal) contact lenses, extended depth of focus (EDOF) soft contact lenses, and the aspheric single-vision design (Table 3).

3.4.6.1. Concentric ring bifocal soft contact lenses (alternating bifocal design). The Dual-Focus contact lens was the first design and was first studied in a clinical trial by Antice and Philips (Anstice and Phillips, 2011). The optical zone comprises three correction zones designed to correct the myopic refractive error, alongside two treatment zones with an additional power of 2.00 D (Li and Fang, 2019). Light passing

through the correction zones falls on the fovea, while light passing through the treatment zones is focused in front of the retina (Li and Fang, 2019). In theory, this arrangement results in a sharp image point on the retina, surrounded by concentric rings of blur. The concentric five-ring pattern in the Dual-Focus design is employed to accommodate the variability of human pupil size under different lighting conditions (Li and Fang, 2019). The diameters of the correction and treatment zones are selected to ensure that both zones occupy roughly half of the pupil diameter in both photopic (small pupil) and mesopic (large pupil) environments (Li and Fang, 2019). Additionally, the diameter of the outermost correction zone (11.66 mm) is specifically designed to ensure optimal visual performance during nighttime viewing (Li and Fang, 2019). Given that the pupil expands in low light, a larger correction zone helps to minimize the risks of ghost imaging and glare (Li and Fang, 2019). The Dual-Focus contact lens was subsequently commercialized and marketed by CooperVision as MiSight daily disposable soft contact lenses. The power profile of MiSight contact lenses features an add power of 2.00 D. In a three-year RCT of 8–12 – year – old children, unadjusted myopia progression was −0.73 D less in children who wore MiSight contact lenses than in the control group (−0.51 ± 0.64 D vs −1.24 ± 0.61 D), and axial elongation was 0.32 mm less (0.30 ± 0.27 mm vs 0.62 ± 0.30 mm) (Chamberlain et al., 2019). In the six-year report, the reduction in myopia progression observed during the first three years was sustained in the following three years (−0.52 ± 0.076 D vs −0.51 ± 0.076 D), with comparable findings noted for axial elongation (0.28 ± 0.033 mm vs 0.23 ± 0.033 mm) (Chamberlain et al., 2022). Treatment was discontinued during the seventh year, and during this post-treatment year, axial elongation and myopia progression rates were similar to those expected of untreated myopic children of the same age (Chamberlain et al., 2025), implying that prior treatment gains were retained. However, the post-treatment year progression was greater in younger adolescents (ages 14–16 at cessation), suggesting that extending treatment into older teenage years may help preserve treatment gains achieved.

The Defocus Incorporated Soft Contact lens (DISC) also employs an alternating bifocal lens design (Lam et al., 2014). It features a central correction zone surrounded by a series of alternating defocusing and correction zones that extend toward the periphery in a 50:50 ratio. The correction zones match the distance prescription, while the defocusing zones incorporate a treatment add power of 2.50 D. In a 2-year clinical trial of 8–13 – year – old children, the mean myopia progressions following the use of DISC and control lenses were −0.59 ± 0.49 D and −0.79 ± 0.56 D, respectively, whereas the increase in AL was 0.25 ± 0.23 mm in the DISC group and 0.37 ± 0.24 mm in the control group (Lam et al., 2014).

Increasing the add power in the treatment zone of myopia control soft lenses has been demonstrated to enhance treatment efficacy (Walline et al., 2020b). However, higher add powers adversely affect visual quality in simultaneous vision coaxial designs (Bickle et al., 2021; Kang et al., 2017; Schulle et al., 2018). Consequently, there is usually a trade-off between vision quality and myopia control efficacy when adjusting the magnitude of add power or the dimensions and placement of the treatment zone. In an effort to reduce the compromise associated with the efficacy-vision trade-off, the non-coaxial ring focus contact lens was introduced. It incorporates non-coaxial optics in its add annuli, along with additional coaxial plus power at the center of the lens (Cheng et al., 2023). The non-coaxial optics reduce the resultant blur levels of added plus power, aiming to minimize its impact on vision (Cheng et al., 2023). The lens was designed to enhance myopia control efficacy through the introduction of a greater amount of plus power than conventional multifocal or Dual-Focus lens designs while maintaining comparable visual performance (Cheng et al., 2023). It has two concentric, annular treatment zones of +7.00D non-coaxial plus power and an additional +10 D coaxial treatment zone for greater efficacy without compromising visual acuity, due to the dispersal of light rays. Commercialized as ACUVUE® Abiliti™ 1-Day, a daily disposable contact lens with novel ring focus technology. In a six-month multicenter trial, the ACUVUE Abiliti lens had significantly less axial elongation than single-vision lens (0.079 ± 0.125 mm vs 0.189 ± 0.121 mm), as well as less myopia progression (−0.12 ± 0.27 D vs −0.35 ± 0.33 D) (Cheng et al., 2023). It also had significantly less axial elongation than the Dual-Focus lens (least square mean difference: −0.049, 95 % CI −0.093 to −0.004 mm).

The Acuvue Bifocal (Vistakon, Inc., Jacksonville, FL, USA) is a multiring bifocal soft contact lens (BFSCL) initially developed for managing presbyopia and later adapted for myopia control (Aller et al., 2016; Madrid-Costa et al., 2015). This repurposing was partly substantiated by retrospective data from the practice of Thomas Aller, which indicated that BFSCLs, prescribed as alternatives to bifocal spectacles to address compliance challenges, demonstrated significant promise (Aller et al., 2016). Additional motivation came from animal studies that confirmed imposed myopic defocus as an inhibitor of eye growth, as well as from reports that bifocal spectacles, often used to correct near esophoria and eso fixation disparity, could slow myopia progression in those with this specific binocular vision condition (Aller et al., 2016). It has a ring bifocal design with five alternating distance and near zones. The lens was employed in an RCT involving myopes with near eso fixation disparities, drawing on earlier studies that suggested bifocal spectacles were more effective in mitigating myopia progression in this population (Aller et al., 2016). After 12 months, myopia progressed by −0.22 ± 0.34 D in the BFSCL group and −0.79 ± 0.43 D in the control group. The corresponding AL changes were 0.05 ± 0.14 mm and 0.24 ± 0.17 mm, respectively. The ACUVUE bifocal has been discontinued.

3.4.6.2. Progressive peripheral add soft contact lenses: multifocal. The first progressive multifocal design for myopia control was reported by Sankaridurg et al., in 2011 (Sankaridurg et al., 2011). It featured a 3.0 mm clear central correction zone surrounded by a 9.0 mm annular treatment zone, with power increasing from +1.00 D at 4 mm (diameter) to +2.00 D at 9 mm, for reduction of relative peripheral hyperopia (Sankaridurg et al., 2011). This lens has a smaller central zone than the Dual-Focus design (3 mm vs. 3.36 mm), which may induce myopic defocus in central vision under photopic conditions (Li and Fang, 2019). The smaller optical zone may also affect night vision with larger pupils (Li and Fang, 2019). In a study conducted in children aged 7–14 years, the lens significantly slowed myopia progression (Sankaridurg et al., 2011). SE change after 12 months was −0.57 D (95 % CI, −0.45 to −0.69 D) in the contact lens group and −0.86 D (95 % CI, −0.74 to −0.99 D) in the single-vision spectacle group. The corresponding AL changes were 0.27 mm (95 % CI, 0.22–0.32 mm) and 0.40 mm (95 % CI, 0.35–0.45 mm), respectively.

The Proclear Multifocal Distance (D) design by CooperVision is also one of the popular options for myopia control. It offers add powers ranging from +1.00 D to +4.00 D (Li and Fang, 2019). The 8.5 mm optical zone features a spherical central correction zone with a diameter of 2.3 mm, surrounded by both a progressive treatment zone and a spherical treatment zone (Li and Fang, 2019). This design is also employed in the Biofinity Multifocal “D”. In 2013, CooperVision’s "D" centred multifocal contact lens design was investigated (Walline et al., 2013). A Proclear material and a +2.00 add were used, and compared to single-vision contact lenses (historical control). After 2 years, the adjusted myopia progression was −0.51 ± 0.06 D for the soft multifocal contact lens wearers and −1.03 ± 0.06 D for the single-vision contact lens wearers. The corresponding axial elongations were 0.29 ± 0.03 mm and 0.41 ± 0.03 mm. Subsequently, the three-year Bifocal Lenses in Nearsighted Kids (BLINK) study compared +1.50 (Medium Add) and +2.50 (High Add) Add CooperVision "D" centred multifocal contact lenses, this time in the Biofinity material, and found only the +2.50 Add had a significant effect on slowing myopia progression and axial elongation (Walline et al., 2020b). Adjusted 3-year myopia progression was −0.60 D (95 % CI -0.72 to −0.47 D) for High Add power, −0.89 D (95 %

CI -1.01 to −0.77 D) for Medium Add power, and −1.05 D (95 % CI -1.17 to −0.93 D) for single-vision contact lenses. The adjusted AL changes were 0.42 mm (95 % CI: 0.38–0.47 mm), 0.58 mm (95 % CI: 0.54–0.63 mm), and 0.66 mm (95 % CI: 0.61–0.71 mm) for High Add, Medium Add, and single-vision lenses, respectively. The results suggested a dose-dependent effect, with greater peripheral myopic defocus resulting in greater myopia control. The Proclear and Biofinity multifocal lenses were originally designed for presbyopia but are now considered effective off-label options for myopia control due to their centre-distance design.

Most multifocal soft contact lenses feature a rotationally symmetric optical zone centred at the lens's geometric center (Li and Fang, 2019). However, the pupil's center often does not align with the corneal apex. To address this, Fujikado et al. developed Low-addition soft contact lenses with an optical zone, comprising a distance correction zone surrounded by a progressive treatment zone, decentered 0.5 mm nasally from the lens's geometric center (Fujikado et al., 2014). This design aims to align the optical center of the lens with the center of the pupil, ensuring that the optical effects of the treatment zone are evenly distributed across the visual field. However, the Add power of +0.50 D in the treatment zone is too low to produce significant changes in peripheral refraction. In their crossover pilot study, the change in AL over 11 months was significantly smaller in the test lens group (0.09 ± 0.08 mm) than in the control lens group (0.17 ± 0.08 mm) (Fujikado et al., 2014). During the same period, the change in refractive error in the test lens group was not significantly different from that in the control group. Neither the change in AL nor SE in the test lens group was significantly different from those in the control lens group in the second phase, after cross-over.

3.4.6.3. Extended depth of focus contact lenses (EDOF). Depth of focus (DOF) is the tolerable amount of variation in the image distance of a lens or optical system that still produces a perceptually sharp image (Wang and Ciuffreda, 2006). EDOF lenses produce a wider DOF along the visual axis (area of focus is extended to give clear uninterrupted vision at all distances) compared to zonal multifocal lenses (lenses with two focal points which the wearer needs to translate between to change focus, and each has a short DOF) and single vision lenses (lenses with one focal point and a short DOF) (Thompson, 2023). Currently, the market features two primary EDOF designs, including NaturalVue Multifocal 1-Day (a proprietary design from Visioneering Technologies, Inc., Alpharetta, Georgia, USA) and the Brien Holden Vision Institute (BHVI) design lenses [SEED 1dayPure EDOF (SEED Co., Ltd A, Tokyo, Japan) and MYLO (Mark'ennovy; Euclid Vision Group)]. The mechanisms behind the EDOF functionality differ between the two designs: the NaturalVue lens is based on catenary curves, while the BHVI design is non-monotonic and aperiodic. The catenary curve power profile (Neurofocus Optics) of the Naturalvue lens is highly aspheric and mimics the shape of a free-hanging chain, such as a chain necklace. The optical center of the lens corresponds to the lowest point on the curve and contains the distance prescription (Cooper et al., 2018, 2022). Building in 5 μm steps from the center of the lens design, it generates up to 8.0 D of relative plus power at the edge of the pupil (Cooper et al., 2018, 2022). The plus power induces a large amount of myopic defocus (Smith, 2011), and by suppressing the peripheral stimulus, this design generates a 'virtual pinhole' effect that extends the depth of focus without restricting the patient's peripheral perception. The BHVI EDOF lenses use selective higher-order aberrations to enhance global retinal image quality, optimizing it for points at and in front of the retina while degrading it for points behind (Sankaridurg et al., 2019). The refractive power profile across the optic zone is non-monotonic (varying above and below the average mean power) and aperiodic (lacking distinct power zones) (Sankaridurg et al., 2019). These lenses were designed to provide an extended depth of focus of up to +1.75D and +1.25D (Sankaridurg et al., 2019). It was hypothesized that the degraded image quality behind the retina inhibits axial elongation (Sankaridurg et al., 2019).

In a retrospective cohort analysis, Cooper et al. found that in patients who showed at least −0.50D of myopic progression before treatment, wearing NaturalVue multifocal contact lenses for 6–72 months significantly slowed myopia progression by 0.84 D at all time points, compared to baseline (Cooper et al., 2022). The average change in AL in a subset of the population over 47 months of follow-up was about 0.10 mm/year (Cooper et al., 2022). In a 2-year RCT, Sankaridurg et al. evaluated the efficacy of two contact lens designs for myopia control (Sankaridurg et al., 2019). The first design (lenses I and II) aimed to reduce hyperopic defocus and induce myopic defocus across a large portion of the retina. The second design (lenses III and IV) featured an EDOF. After two years, the mean myopia progression for design 2 (lenses III and IV) was significantly lower than the control group. The SE changes were −0.78 D (95 % CI -0.62 to −0.94 D), −0.85 D (95 % CI -0.85 to −1.00 D), and −1.15 D (95 % CI -0.99 to −1.30 D) for lens III, lens IV, and control, respectively. A significant reduction in axial elongation was noted for all lens types compared to control, with AL changes of 0.41 mm (95 % CI 0.34–0.48 mm), 0.46 mm (95 % CI 0.39–0.53 mm), 0.45 mm (95 % CI 0.38–0.52 mm), 0.43 mm (95 % CI 0.36–0.50 mm), and 0.60 mm (95 % CI 0.53–0.66 mm) for lens I, lens II, lens III, lens IV, and control lens, respectively. Thus, while all the test lenses significantly reduced elongation of AL, only the EDOF design (lenses III and IV) significantly reduced SE progression. The effect of the test lenses did not vary from one another. This EDOF technology is used in the SEED 1dayPure and Mylo (Mark'ennovy) EDOF lenses. In 7-15-year–old Indian children, the SEED lenses significantly slowed myopia progression compared to control, with SE and AL changes of −0.20 ± 0.08 D vs −0.48 ± 0.07 D/year and 0.11 ± 0.03 mm vs 0.22 ± 0.03 mm/year, respectively (Manoharan and Verkicharla, 2024). Similarly, a recent study of progressing (at least −0.75 D/year) 6–13-year–olds found that 3 years of MYLO contact lens wear resulted in significantly slower myopia progression compared with control (Díaz-Gómez et al., 2025). The SE and AL changes were −0.90 ± 0.36 D vs −1.64 ± 0.26 D and 0.55 ± 0.05 mm vs 0.97 ± 0.03 mm, respectively.

3.4.6.4. Aspheric single-vision design. Aspheric single-vision contact lenses have been shown to be effective in slowing the progression of myopia. Cheng et al. examined the effects of soft contact lenses with positive spherical aberration on myopia progression in children aged 8 to 11(Cheng et al., 2016). Approximately 0.175 μm of spherical aberration was induced through the aspheric front surface of the lens for a 5 mm pupil diameter. The aim was to counteract the negative spherical aberration of the eye during accommodation. Since aspheric lenses with positive spherical aberration function similarly to progressive multifocal designs, it was thought that these lenses could decrease hyperopic defocus in both central and peripheral vision. The test lens significantly slowed axial elongation by −0.143 D (95 % CI -0.188 to −0.098 D) compared to control but had no significant effect on myopia progression after a year (Cheng et al., 2016). After a 1.5-year treatment cessation period, neither axial elongation nor SE progression was significantly different between the initial two cohorts. In a separate study, custom-made contact lenses were designed to adjust the spherical aberration of the human eye to −0.1 μm (for a 5 mm pupil diameter) (Allen et al., 2013). This value was selected as it was thought to be optimal for reducing the lag in accommodation and, consequently, minimizing hyperopic defocus during near work. However, the lenses did not demonstrate a significant treatment effect on myopia progression after two years.

Overall, the alternating bifocal soft contact lenses, progressive peripheral Add soft contact lenses, and the EDOF lenses significantly slowed myopia progression. Soft contact lenses can be an alternative for patients who are not indicated for or are unsuccessful in Ortho-K treatment or who may not wish to wear spectacles. Compared to spectacle lenses, soft contact lenses offer the advantage of maintaining

relative stability on the cornea. This ensures that the intended retinal image patterns are consistently presented, with minimal fluctuations, regardless of eye movement. Unlike Ortho-K, soft contact lenses can be prescribed for individuals with higher levels of myopia. (Table 3). Additionally, soft contact lenses for myopia control have been shown to have good safety profiles in children, with no serious contact lens-related adverse events, even after long-term use (Cheng et al., 2023; Walline et al., 2020b; Woods et al., 2021). They pose a lower risk of infection due to their daily wear and frequent disposability. Nevertheless, they require strict adherence to treatment regimen and lens care. Multifocal soft contact lenses have lower rebound compared to Ortho-K, atropine, and low-level red light (Chiu et al., 2023; Sánchez-Tena et al., 2024).

3.4.7. Unsolved questions and future directions

There is an ongoing need for innovation in materials that enhance comfort to improve wearability and reduce the risk of complications associated with contact lenses. Long-term follow-up results (≥5 years) for children using MiSight contact lenses, DIMS, and HALT for myopia management are now available. Further long-term studies on other optical methods will facilitate valuable comparisons, though clarity will still be needed on when to cease treatment with optical methods.

3.5. Repeated low-level red-light therapy

3.5.1. Mechanisms

The spectral composition of light plays a crucial role in regulating eye growth and refractive state (Biswas et al., 2023; Gawne et al., 2021; Liu et al., 2011; Rucker, 2019; Rucker and Wallman, 2009; Troilo et al., 2019). Short-wavelength (blue or violet) light, compared to medium or long-wavelength (green or red) light, caused less myopia in fish, chicks, and guinea pigs (Foulds et al., 2013; Jiang et al., 2014; Kröger and Wagner, 1996; Liu et al., 2011). In contrast, in non-human primates, narrowband red light yielded slower eye growth and hyperopic shifts. It also inhibited form deprivation-induced and minus lens-induced myopia (Gawne et al., 2017b; Hung et al., 2018b; She et al., 2023). In humans, recent studies suggest the protective effect of blue light in children (Akagun and Altiparmak, 2025; Lorenz et al., 2025), but additional studies are required. The most extensively investigated spectral component in humans is red light (Tang et al., 2023; Zaabaar et al., 2024). A pooled analysis found red light to be the only component that significantly slowed axial elongation and SE progression in children, compared to violet and white light (Zaabaar et al., 2024). The mechanism of red light therapy in myopia remains unknown. Current hypotheses suggest that it may involve enhanced retinal mitochondrial function through the direct stimulation of mitochondria, which have an absorbance peak around 650 nm (Hamblin, 2018). Cytochrome *c* oxidase, a component of the mitochondrial electron transport chain, is thought to absorb red light (Karu et al., 1995, 2005) and may facilitate nitric oxide (NO) production by promoting the reduction of nitrite to NO (Quirk and Whelan, 2020). Intraocular NO has been shown to inhibit myopia in a dose-dependent manner and is essential for atropine's anti-myopia effect (Carr and Stell, 2016). Other proposed mechanisms include increased choroidal blood flow, reduced retinal inflammation and oxidative stress, and effects on the sclera such as promoting collagen synthesis and fibroblast proliferation (Wu et al., 2018a; Zhang et al., 2023). It has also been speculated that emmetropization may use long-wavelength image contrast as a signal of excessive axial elongation, triggering "STOP" growth cues (Gawne and Norton, 2020; Gawne et al., 2017a; Salzano et al., 2023). These mechanisms remain hypothetical and require further validation.

3.5.2. Efficacy

Several randomized controlled trials have demonstrated the efficacy of repeated low-level red light (RLRL) for myopia control (Chen et al., 2022a, 2023; Dong et al., 2023; Jiang et al., 2022; Lin et al., 2023; Tian et al., 2022; Wang et al., 2023f; Xiong et al., 2021, 2022; Zhao et al., 2023; Zhou et al., 2022b, 2023). In these trials, the participants completed two sessions of a 3-min-long treatment per day at home for 5–7 days a week, with the daily treatment sessions done 4 h apart. The red light is emitted from a desktop device and commonly has a peak wavelength of 650 ± 10 nm (Chen et al., 2022a; Dong et al., 2023; Jiang et al., 2022; Lin et al., 2023; Tian et al., 2022; Wang et al., 2023f; Xiong et al., 2021, 2022; Xu et al., 2024; Zhao et al., 2023), although some studies used 635 nm (Chen et al., 2023; Zhou et al., 2022b). The commonest instrument has been reported to emit red light with an illuminance level of 1600lux (Chen et al., 2022a; Dong et al., 2023; Jiang et al., 2022; Tian et al., 2022; Xiong et al., 2022; Xu et al., 2024) and 0.29 mW of power going through a pupil size of 4 mm (Dong et al., 2023; Jiang et al., 2022; Wang et al., 2023d; Xu et al., 2024). Other studies have reported powers ranging from 0.35 mW to 2 mW (Chen et al., 2023; Lin et al., 2023; Wang et al., 2023f; Xiong et al., 2021; Zhao et al., 2023; Zhou et al., 2022b). The red laser employed in the device has significantly lower energy levels than any laser modalities used in ophthalmic clinical practice. For comparison, conventional ophthalmic lasers such as photocoagulation or capsulotomy typically operate in the range of several hundred milliwatts to multiple watts, delivering energy densities sufficient to induce photothermal or photodisruptive effects on ocular tissues. In contrast, the output power of the low-level red light device is in the milliwatt range with energy densities several orders of magnitude lower, insufficient to cause tissue damage. Accordingly, the treatment is referred to as low-level red light therapy, low-intensity red light therapy, or low-intensity laser therapy.

A large RCT of 117 myopic children in the intervention group found that RLRL slowed SE progression by 76.6 % (−0.20 D vs −0.79 D) and axial elongation by 69.4 % (0.13 mm vs 0.38 mm) after one year (Jiang et al., 2022). Increasing compliance from <50 % to over 75 % enhanced efficacy from 41.7 % [−0.459 ± 0.674 D vs −0.79 D (95 % CI: 0.88 to −0.69)] to 87.7 % [−0.097 ± 0.517 D vs −0.79 D (95 % CI: 0.88 to −0.69)] in slowing SE progression and from 44.6 % [0.210 ± 0.252 mm vs 0.38 mm (95 % CI: 0.34 to 0.42)] to 76.8 % [0.088 ± 0.215 mm vs 0.38 mm (95 % CI: 0.34 to 0.42)] in controlling axial elongation (Jiang et al., 2022), suggesting a potential dose-dependent effect with RLRL therapy. A similar dose-response relationship has been observed in preclinical findings from tree shrews, where even modest increases in the duration of daily treatment with narrow-band long-wavelength light rapidly resulted in hyperopic shifts (Ward et al., 2018). The benefits of RLRL extend to high myopes. In a 12-month trial involving high myopia subjects (−4.00 D or higher in at least one eye), the mean SE change was 0.11 D (95 % CI: 0.02 to 0.19) and −0.75 D (95 % CI: 0.88 to −0.62) in the RLRL and control groups, respectively, whereas the mean change in AL was −0.06 mm (95 % CI: 0.10 to −0.02) in the RLRL group and 0.34 mm (95 % CI: 0.30 to o.39) in the control group (Xu et al., 2024). These results corroborate those from the study by Jiang et al. (2022) but suggest even stronger effects, possibly due to the higher compliance rate in the latter study (84 % vs 75 %). The power used in the RLRL device also seems to demonstrate a dose-dependent effect. A sham treatment using RLRL at 10 % of the power applied in the intervention group resulted in less progression in myopic SE and AL after 6 months, but the efficacy was lower than that of the intervention group (Dong et al., 2023).

Remarkably, RLRL therapy has been associated with axial shortening—a phenomenon counterintuitive to normal ocular growth. In a post hoc analysis of an RCT, 21.85 % of RLRL-treated eyes vs 1.38 % of controls showed significant axial shortening >0.05 mm after 12 months (Wang et al., 2023d). For AL shortening >0.10 mm, the rates were 15.13 % (RLRL) vs 0 % (control), and for >0.20 mm, 5.88 % vs 0 %. Mean shortening was −0.156 mm (RLRL) vs −0.06 mm (control). In another study, Liu et al. reported a greater proportion of AL shortening of >0.05 mm in high myopes (≤-6.0 D) treated with RLRL after 12 months (59 % vs 0 %) (Liu et al., 2025). AL and SE changes were −0.11 ± 0.25 mm and 0.18 ± 0.63 D for the RLRL group and 0.32 ± 0.09 mm and −0.80 ±

0.42 D for the control group, respectively (Liu et al., 2025). The study by Xu et al. also reported that after a year of treatment with RLRL, 50.3 % of high myopia subjects (−4.00 D or higher in at least one eye) who underwent RLRL therapy still had AL shortening of >0.05 mm compared to 1.2 % of those in the control group (Xu et al., 2024). Even subtherapeutic RLRL power (10 % of the treatment dose) yielded AL shortening after six months (Dong et al., 2023). Studies suggest that while choroidal thickening may contribute to the AL shortening by physically displacing the retinal pigment epithelium forward, it does not fully explain the observed shortening (Liu et al., 2022, 2025; Wang et al., 2023d), implying a possible true scleral remodeling (Wang et al., 2023d). Proposed mechanisms include RLRL-driven improved blood flow and fundus metabolism, alleviating scleral hypoxia and restoring collagen homeostasis (Jiang et al., 2022; Jonas et al., 2016; Metlapally and Wildsoet, 2015).

Compared to the daily use of 0.01 % atropine over one year, RLRL demonstrated significantly better results (Chen et al., 2022a). The changes in SE were −0.03 D (95 % CI: 0.01 to −0.08) in the RLRL group and −0.60 D (95 % CI: 0.70 to −0.48) in the atropine group, with corresponding AL changes of 0.08 mm (95 % CI: 0.03 to 0.14) and 0.33 mm (95 % CI: 0.27 to 0.38). RLRL therapy also outperformed Ortho-K lenses in a 3-arm study (Xiong et al., 2021), showing axial elongation of −0.06 ± 0.15 mm after 6 months, compared to 0.06 ± 0.15 mm for Ortho-K and 0.23 ± 0.06 mm for the control group.

Low-level red light has also been found to be effective in delaying the onset of myopia in premyopic children. In a 12-month school-based RCT, RLRL therapy yielded 54.1 % (28.1 % vs 61.3 %) uninterrupted treatment efficacy in preventing myopia incidence in premyopic children (He et al., 2023). The uninterrupted intervention group demonstrated 76.3 % (−0.18 ± 0.61 vs −0.76 ± 0.60) efficacy in slowing shifts in SE and 48.9 % (0.24 ± 0.23 vs 0.47 ± 0.25) efficacy in reducing AL changes. Of note, significantly better efficacy was noted in children with SE of 0.01–0.50 D compared to those with SE of −0.50 to 0.00 D, with relative incidence reductions of 64.0 % (17.7 % vs 49.1 %) compared to 14.0 % (71.5 % vs 83.1 %), respectively. For the children with SE of −0.50 to 0.00 D, the control group had an incidence rate of up to 83.1 %, suggesting that it may already be too late to prevent the onset of myopia in individuals with an SE between −0.50 and 0.00 D, as their likelihood of developing myopia within a year could be as high as 83.1 %. Thus, low-level red light therapy for myopia prevention may be most effective for SE in the range of 0.01–0.50 D, or even higher, to effectively mitigate the risk of developing myopia. Consistent results on the efficacy of low-level red light for myopia prevention have been reported in subsequent independent trials (Cao et al., 2024; Liu et al., 2024).

3.5.3. Safety

While there are evidence of efficacy and short term safety of RLRL in children and adolescents, more long-term studies are needed to determine the long term safety. An initial—albeit indirect—signal of safety comes from over a decade of clinical use of red-light therapy for amblyopia in children and adolescents in China, and its more recent use for myopia management, during which no serious adverse events have been reported (Chen et al., 2023; Dong et al., 2023; Xiong et al., 2022; Zhang et al., 2022b). Most studies on the use of RLRL for amblyopia reported that children in the intervention group received red light irradiation at the macula for 3 min per day and up to 20 days per treatment course (Chen et al., 2020; Zhang et al., 2022b). The power of the laser ranged from 0.3 to 1.0 mW, and the treatment was effective. Though the regimen for myopia control (3 min at a time, twice a day) is more rigorous than that for amblyopia (3 min per day), there is no clinical evidence indicating that myopia control with RLRL harms children's visual health, but further investigations into the optimal safety thresholds for myopia management are encouraged. The RLRL devices are classified as Group 1 (no light hazard)under ANSI Z80.36–2021 standards (American National Standards Institute, 2016; Battersby, 2024). Evaluation of retinal structure and function with optical coherence tomography and multifocal electroretinography showed no damaging effects after the use of low-level red light for 12 months (Zhu et al., 2024).

Despite these findings on safety, isolated adverse effects have been reported. A 12-year-old girl experienced a temporary decrease in best-corrected visual acuity following 5 months of regular low-level red light exposure, with darkening of the foveae, macular hypoautofluorescence, and disruptions in the foveal ellipsoid and interdigitation zones on OCT changes (Liu et al., 2023). After discontinuing the therapy for 4 months, the retinal structure remained intact, the integrity and continuity of the ellipsoid zone in the macula were restored in both eyes, and the best corrected visual acuity improved to 0.8 (decimal equivalent) in both eyes (Yu and Zhigang, 2023). Another study suggested that 3 min of continuous red-light exposure may exceed maximum permissible exposure limits, posing photochemical or thermal risks, though the devices tested were uncertified and unstandardized (Ostrin and Schill, 2024).

A recent study by Liao et al. (2025) examined the retinal effects of RLRL therapy and found reduced cone density within 0.5 mm of the fovea (particularly temporally) in the treatment group compared to controls, along with hyperreflective signals in some children and a single small cystoid OCT change (Liao et al., 2025). However, these findings should be interpreted cautiously due to the study's limitations, such as the absence of baseline measurements, its retrospective design, and inadequate statistical adjustments—all of which undermine the reliability of the results. More robust evidence on the effects of RLRL on cone density is needed.

Overall, there is still inadequate long-term safety evidence (Jiang et al., 2022; Zhu et al., 2024), therefore, clinical use should follow approved indications and device labeling. Baseline assessment and scheduled follow-up should monitor safety and effectiveness across key parameters, including best-corrected visual acuity, color/contrast vision, intraocular pressure, axial length, and retinal structure/function (e.g., OCT/OCTA).

3.5.4. Rebound effect

Rebound effects can negate the accumulated benefits achieved during the active treatment phase. In a study by Chen et al., treatment with RLRL was ceased after a year, and outcomes were monitored over a 3-month washout period (Chen et al., 2023). SE increased by −0.20 D (95 % CI: 0.26 to −0.14), and AL increased by 0.16 mm (95 % CI: 0.11 to 0.22) (Chen et al., 2023). Similarly, switching from RLRL to single-vision spectacles after a year of initial treatment led to an increase of −0.91 ± 0.48 D in SE and 0.42 ± 0.20 mm in AL, after 12 months (Xiong et al., 2022), whereas the group that continued wearing single-vision spectacles had smaller progressions of −0.54 ± 0.39 D and 0.28 ± 0.14 mm, respectively. These findings indicate that stopping RLRL is associated with a measurable rebound effect. Therefore, abrupt cessation should be avoided; where appropriate, consider a tapering (step-down) protocol or transition to another evidence-based myopia control modality. Further, more definitive studies are needed to characterize rebound and optimize discontinuation strategies—ideally randomized controlled trials with predefined tapering arms and adequate follow-up.

3.5.5. Unsolved questions and future work

There is a need for portable devices to enhance accessibility and convenience in daily routines without requiring specialized equipment or dedicated treatment sessions. Second, the efficacy of RLRL appears dose-dependent. It is important to determine the optimal dosage that maximizes benefits and minimizes risks. Third, to avoid the risks associated with the highly focused, coherent laser light used in red light devices, alternatives like non-coherent red light-emitting diodes (LEDs) should be investigated. Fourth, further studies are warranted to understand whether stimulating the more peripheral regions of the retina or whether foveal stimulation improves therapeutic efficacy. Fifth, the

protocol to minimize rebound effects after treatment cessation has to be established. Specifically, it is uncertain whether a longer duration of treatment would lead to a brief rebound period, or if the rebound would continue until there is a complete loss of accumulated benefits. It is possible that gradually tapering red light therapy could mitigate the rebound effects.

3.6. Combined treatments

In cases of intractable, rapidly progressing myopia, monotherapy may be insufficient to control progression. In such instances, combined treatment, targeting multiple pathways, may be advantageous to consider.

3.6.1. Low-concentration atropine combined with orthokeratology

Atropine is believed to work by blocking the muscarinic receptors in the retina and sclera, which are involved in the elongation of the eyeball (Gallego et al., 2012; McBrien et al., 2011) while Ortho-K is thought to improve defocus on the peripheral retina and increase higher-order aberrations (Kang and Swarbrick, 2011b; Mathur and Atchison, 2009a, 2009c; Smith et al., 2009). This effect is achieved through corneal epithelial redistribution, where the central cornea is thinned, and the mid-periphery is thickened (Alharbi and Swarbrick, 2003). Thus, atropine and Ortho-K may slow the progression of myopia through different mechanisms, both of which contribute to myopia inhibition in the combined therapy.

A retrospective study conducted in Taiwan categorized eyes into low (≥-6.00D) or high (<-6.00D) myopia, and then divided them into subgroups to receive Ortho-K monotherapy or a combination therapy involving either 0.125 % or 0.025 % atropine (Wan et al., 2018). For both low and high myopia, the combined treatment with 0.125 % atropine and Ortho-K led to a slower progression of AL and SE compared to Ortho-K monotherapy over two years. However, combining 0.025 % atropine with Ortho-K could only slow axial elongation for the low myopia group but not for those with high myopia. Slowing axial elongation in children with high myopia may require higher concentrations of atropine even when combined with Ortho-K. In a separate retrospective study in China, all participants were treated with Ortho-K in the first year, followed by the addition of 0.01 % atropine in the second year to those with fast axial elongation (AL change >0.25 mm) (Chen et al., 2019). There was a significant reduction in axial elongation in the combination therapy group during the second year, compared to a historical control group that exhibited fast progression. In a similar retrospective study, the addition of 0.01 % nightly atropine to Ortho-K did not change the three-year axial elongation outcome compared to Ortho-K monotherapy in individuals who experienced fast myopia progression or poor response to Ortho-K (Chen et al., 2022b). A recent retrospective study assessed the effects of adding 0.05 % atropine to Ortho-K treatment for children with rapidly progressing myopia (Wen et al., 2025). The participants had myopia ranging from 1.00D to 6.00D and were classified as fast progressors, based on axial elongation exceeding 0.15 mm in six months or 0.30 mm in a year despite using Ortho-K monotherapy. They were divided into two groups: one continued with Ortho-K alone, while the other combined it with 0.05 % atropine. Axial elongation was 0.14 ± 0.13 mm in the combined treatment group and 0.27 ± 0.12 mm in the Ortho-K monotherapy group after 12 months.

RCTs have also shown that combining 0.01 % atropine with Ortho-K is more effective in slowing axial elongation than using Ortho-K alone over two years (Kinoshita et al., 2020; Tan et al., 2023). Similarly, combining 0.01 % atropine with Ortho-K was more effective than using only atropine over two years, particularly in younger children with shorter AL (Xu et al., 2022; Zhou et al., 2022a).

3.6.2. Low-concentration atropine combined with myopia control spectacle lenses

The mechanism of the additive effect of atropine and myopia control spectacles is unclear. It is plausible that the use of atropine could result in a larger pupil diameter, leading to increased retinal illumination and positive spherical aberration, thereby enhancing the myopic defocus effects of spectacles. Additional studies are necessary to clarify the underlying mechanisms.

An early RCT in a children's cohort aged 6–13 years showed that the combination of 0.5 % atropine with multifocal glasses reduced myopia progression compared to multifocal glasses after 18 months, with no significant difference found between the multifocal glasses group and the control group (Shih et al., 2001). A more recent retrospective cohort study conducted in Hangzhou in 7-year to-12-year-old Chinese found that children who received a combination of 0.01 % atropine and DIMS had lower myopia progression and axial elongation than those who received either DIMS alone or single vision lenses (Huang et al., 2022), suggesting an additive effect in the combined treatment. The combination therapy reduced myopia progression by 54 % (−0.49 ± 0.66 D vs −1.07 ± 0.64 D) and axial elongation by 46 % (0.28 ± 0.24 mm vs 0.52 ± 0.22 mm) over one year compared to the single-vision lenses group. The corresponding reductions by DIMS alone were 26 % (−0.79 ± 0.47 D vs −1.07 ± 0.64 D) and 21 % (0.41 ± 0.22 mm vs 0.52 ± 0.22 mm). The efficacy levels of the DIMS monotherapy group are less than the first-year results of the initial study conducted on DIMS, which showed 69 % (−0.17 ± 0.05 D vs −0.55 ± 0.04 D) reduction in SE and 66 % (0.11 ± 0.02 vs 0.32 ± 0.02) reduction in AL, compared to single vision lenses (Lam et al., 2020, 2022). The differences in findings may be due to variations in study design or lifestyle. In a prospective controlled study on children and adolescents in Italy, the participants were assigned to one of four groups: (1) 0.01 % atropine eye drops, (2) DIMS spectacles, (3) a combination of atropine and DIMS spectacles, or (4) single vision spectacle lenses. After 12 months, the combined therapy slowed SE progression by 70 % and axial elongation by 77 % compared to the control group, while 0.01 % atropine and DIMS achieved 62 %/57 % and 57 %/57 %, respectively (Hejtmancik et al., 2023). In the Atropine and Spectacle lens Combination Treatment (ASPECT) study, the myopia control efficacies of 0.025 % atropine + DIMS spetacles, 0.025 % atropine, and single vision spectacles were compared in a RCT (Guemes-Villahoz et al., 2025). Children were randomly assigned to two groups: Group A, receiving 0.025 % atropine with single-vision spectacle lenses, and Group B, receiving 0.025 % atropine with DIMS spectacle lenses. At 12 months, the mean change in AL was 0.18 ± 0.16 mm in group A and 0.07 ± 0.16 mm in group B, but mean SE progression did not differ between the two groups.

A retrospective cohort study compared HALT +0.01 % atropine, HALT monotherapy, and single-vision lenses and found SE changes were −0.13 D (95 % CI: 0.25 to 0.00), −0.25 D (95 % CI: 0.63 to −0.25), and −0.63 D (95 % CI: 1.00 to −0.25), respectively, with corresponding AL changes of 0.09 ± 0.11 mm, 0.19 ± 0.16 mm, and 0.34 ± 0.16 mm after 12 months (Zhao et al., 2024). The combined treatment yielded significantly slower SE and AL progressions than HALT and single vision spectacles. In a prospective cohort study, Sim et al. evaluated the effect of combining low-concentration atropine (0.01 % and 0.025 %) with HALT lenses in children who continued to progress (axial elongation: 0.24 mm/6 months; SE progression: 0.60 D/6 months) despite treatment with low-concentration atropine monotherapy (Sim et al., 2025). After adding HALT lenses, progression (SE/AL) slowed to −0.06 D/0.06 mm at 6 months and −0.15 D/0.14 mm at 12 months.

3.6.3. Low-concentration atropine combined with myopia control soft contact lenses

Contrary to the findings reported for combining other optical interventions with low-concentration atropine, the Bifocal and Atropine in Myopia (BAM) study, an ancillary study of the BLINK study, found that combining 0.01 % atropine and soft multifocal contact lenses (SMCLs;

add: +2.50-D) did not improve myopia control compared with SMCLs alone after three years (Jones et al., 2022). A retrospective study investigated the myopia control effect of combining 0.01 % atropine and MiSight soft contact lenses in 85 Caucasian children for 3 years (Erdinest et al., 2022a). SE ranged from −1.25 to −10.87 D at the beginning of the treatments, and all subjects had a minimal increase in myopia of 1.00 D during the year prior to treatment. After treatment, progressions of myopia were −1.13 ± 0.36 D, −0.24 ± 0.35 D, and −0.18 ± 0.34 D for single vision spectacles, 0.01 % atropine monotherapy, and 0.01 % atropine + MiSight soft contact lenses. The combination therapy did not prove to be more effective than atropine monotherapy. The absence of AL data and the use of subjective refraction may explain the similarity in the outcomes of the treatment groups. However, it is plausible that the 0.01 % atropine concentration was too low to help address the rapid baseline progression of 1.00 D or more/year, as well as the progression in the included high myopia cases. In a subsequent retrospective analysis, the efficacy of combining MiSight contact lenses with a higher atropine concentration of 0.05 % was evaluated (Yum et al., 2025). The children included in the study had a baseline SE ranging from −1.00 D to −9.00 D. They received the combined treatment if their SE or AL progressed by more than 0.75 D or 0.25 mm/year (fast progressors), respectively, despite treatment with 0.05 % atropine monotherapy. 0.05 % atropine + MiSight contact lens slowed SE/AL progression from −0.70 ± 0.58 D/0.35 ± 0.27 mm per year with atropine alone to −0.43 ± 0.46 D/0.22 ± 0.32 mm per year. The combined treatment slowed myopia progression and axial elongation in fast progressors, similarly to 0.05 % monotherapy in slow progressors. The additive effect was greater in children with low/moderate myopia than in those with high myopia.

3.6.4. Repeated low-level red light combined with orthokeratology

Suboptimal myopia control with Ortho-K monotherapy may also be enhanced with the addition of low-level red light therapy (Xiong et al., 2024; Yu et al., 2024). In children poorly responding to Ortho-K monotherapy treatment (AL progressed by > 0.50 mm/year), those who received the combined therapy showed less axial elongation, −0.02 mm (95 % CI: 0.08 to 0.03) compared to those who continued with Ortho-K monotherapy, 0.27 mm (95 % CI: 0.19 to 0.34). The adjusted mean difference between the groups was −0.29 mm (95 % CI: 0.44 to −0.14 mm) after 12 months (Xiong et al., 2024), with 44.8 % of the combined therapy group demonstrating AL shortening of >0.05 mm. In another study involving Chinese children, a 12-month treatment combining Ortho-K with repeated low-level red light yielded AL shortening, compared with Ortho-K monotherapy (−0.10 ± 0.16 mm vs 0.30 ± 0.19 mm), with 63.6 % of the combined therapy group demonstrating AL shortening of >0.05 mm/year (Yu et al., 2024). Further research is needed to explore the effectiveness of combining low-level red light therapy with other myopia control interventions, particularly for individuals who do not respond to standard treatments and those identified as high-risk groups.

3.6.5. Safety and complications

There is concern about increased side effects from combination therapy. In four studies on the combined effects of 0.01 % atropine and Ortho-K, infiltrative keratitis was more frequent in the Ortho-K monotherapy group compared to the combined treatment group (Kinoshita et al., 2020; Tan et al., 2020, 2023; Yu et al., 2022). Less corneal infiltration could be due to the extra lubrication provided by the atropine eye drops. Photophobia was higher in the combined 0.01 % atropine-Ortho-K groups but did not lead to dropouts (Tan et al., 2020, 2023; Yu et al., 2022). In one study, two subjects in the combined 0.01 % atropine-Ortho-K group and one subject in the Ortho-K monotherapy group had mild superficial punctate keratitis, which worsened later and led to their withdrawal from the study (Kinoshita et al., 2020). There was no complaint of glare, near, or peripheral blur in children after starting treatment with HALT + low-concentration atropine (0.01 % and 0.025 %) (Sim et al., 2025), and a low rebound was reported following cessation of treatment with MiSight soft contact lenses + 0.01 % atropine (Erdinest et al., 2022a).

3.6.6. Summary and future direction

Combination therapy for myopia management is still emerging and presents opportunities to improve treatment outcomes beyond those achieved with monotherapy. While Ortho-K + atropine is backed by stronger evidence of its effectiveness, newer combinations such as DIMS + low-concentration atropine, HALT + low-concentration atropine, dual-focus soft contact lenses (MiSight) + low-concentration atropine, and RLRL + Ortho-K show promise but require additional studies. A combination of an effective optical method with repeated low-level red light or a relatively strong but safe concentration of atropine may be necessary to effectively slow progression in high myopes, fast progressors, or poor responders to monotherapy. Additional data is needed to confirm whether such relatively strong combinations can also provide additional benefits in individuals who are already achieving good control. As research progresses, determining the best combination for other high-risk patient profiles will be essential in optimizing myopia control strategies. Future studies are necessary to understand the mechanisms of synergistic effects and to establish whether there is a threshold for each treatment that would make it effective in combination therapy, such as the minimum atropine concentration or the required wearing time for spectacles or contact lenses. A major limitation of most of the combination treatment studies is the insufficient number of treatment arms, as they typically lack both monotherapy groups. This complicates the assessment of whether these combinations truly exhibit a synergistic effect or merely reflect a more pronounced treatment effect attributable to untested monotherapies.

The efficacy, benefits, and limitations of the interventions for myopia control in children are shown on Table 3.

3.7. Meta-synthesis of interventions for controlling myopia progression in children

We pooled data from 43 meta-analyses conducted on high (≥0.5 %), moderate (>0.05 % to <0.5 %), and low (≤0.05 %) concentrations of atropine; Ortho-K; peripheral plus soft contact lenses (concentric ring bifocal soft contact lenses and progressive peripheral add soft contact lenses); peripheral plus spectacles (multiple segments spectacle lenses and spectacle lenses that reduce relative peripheral hyperopic defocus), multifocal spectacle lenses (bifocal and progressive addition spectacle lenses); repeated low-level red light; outdoor time; and combined treatments (Table A.1. in appendix A). A detailed description of the methods is presented in Appendix A. An intervention was deemed clinically significant if it led to a change in refraction of ≥0.50 D/year or a reduction in axial length of ≤ −0.18 mm/year (Huang et al., 2016; Zaabaar et al., 2025).

Using the AMSTAR 2 scoring, we determined that 7 meta-analyses had low quality, and 36 had critically low quality. This suggests a need for more high-quality primary studies and meta-analyses to better assess the interventional effects of myopia control strategies. Fig. 1 is a pairwise intersection heatmap visualizing the degree of overlap among the included meta-analyses. The extent of overlap of primary studies between pairs of reviews is represented by the corrected covered area (CCA) values displayed in the color-coded cells of the triangular matrix. A CCA of 0 % indicates no overlap of primary studies (shown in white), while a CCA of 100 % signifies complete overlap between the systematic reviews (depicted in deep green). Furthermore, the diagonal tiles of the plot show the single/total number of primary studies included in each review. A single primary study is unique to a single systematic review, meaning it appears in only one review. The 43 systematic reviews and meta-analyses comprised 725 overlapping index publications, of which 302 were unique. To avoid potential double counting of outcomes, the degree of actual overlap was calculated by estimating the CCA:

$$CCA = \frac{N-r}{rc-r} = \frac{725-302}{302\times 43-302} = \sim 3.3\%$$

The pairwise overlap assessment between the individual systematic reviews and meta-analyses revealed an overall estimated degree of overlap (CCA) of 3.3 %. This reflects limited overlap and a slight risk of skewed reporting in the systematic reviews and meta-analyses.

Annual changes in SE after treatment were 0.80 D (95 % CI 0.38 to 1.22), 0.64 D (95 % CI 0.57 to 0.71), 0.64 D (95 % CI 0.47 to 0.82), 0.45 D (95 % CI 0.37 to 0.53), 0.40 D (95 % CI 0.17 to 0.64), 0.33 D (95 % CI 0.28 to 0.37), 0.26 D (95 % CI 0.17 to 0.34), 0.13 D (95 % CI 0.09 to 0.17), 0.11 D (95 % CI -0.01 to 0.23), for high concentration atropine + multifocal spectacles, RLRL, high concentration atropine, moderate concentration atropine, peripheral plus spectacles, low concentration atropine, multifocal soft contact lenses, outdoor time, and multifocal spectacles, respectively (Figs. 2–6). On the other hand, annual AL changes were −0.45 mm (95 % CI -0.85 to −0.05), −0.32 mm (95 % CI -0.36 to −0.27), −0.28 mm (95 % CI -0.39 to −0.16), −0.24 mm (95 % CI -0.30 to −0.18), −0.22 mm (−0.38 to −0.06), −0.16 mm (95 % CI -0.22 to −0.10), −0.15 mm (95 % CI -0.24 to −0.06), −0.13 mm (95 % CI -0.15 to −0.11), −0.12 mm (95 % CI -0.13 to −0.11), −0.06 mm (95 % CI -0.07 to −0.04), and −0.05 mm (95 % CI -0.07 to −0.02) for high concentration atropine + multifocal spectacles, RLRL, Ortho-K, high concentration atropine, multifocal soft contact lenses, moderate concentration atropine, peripheral plus spectacles, low concentration

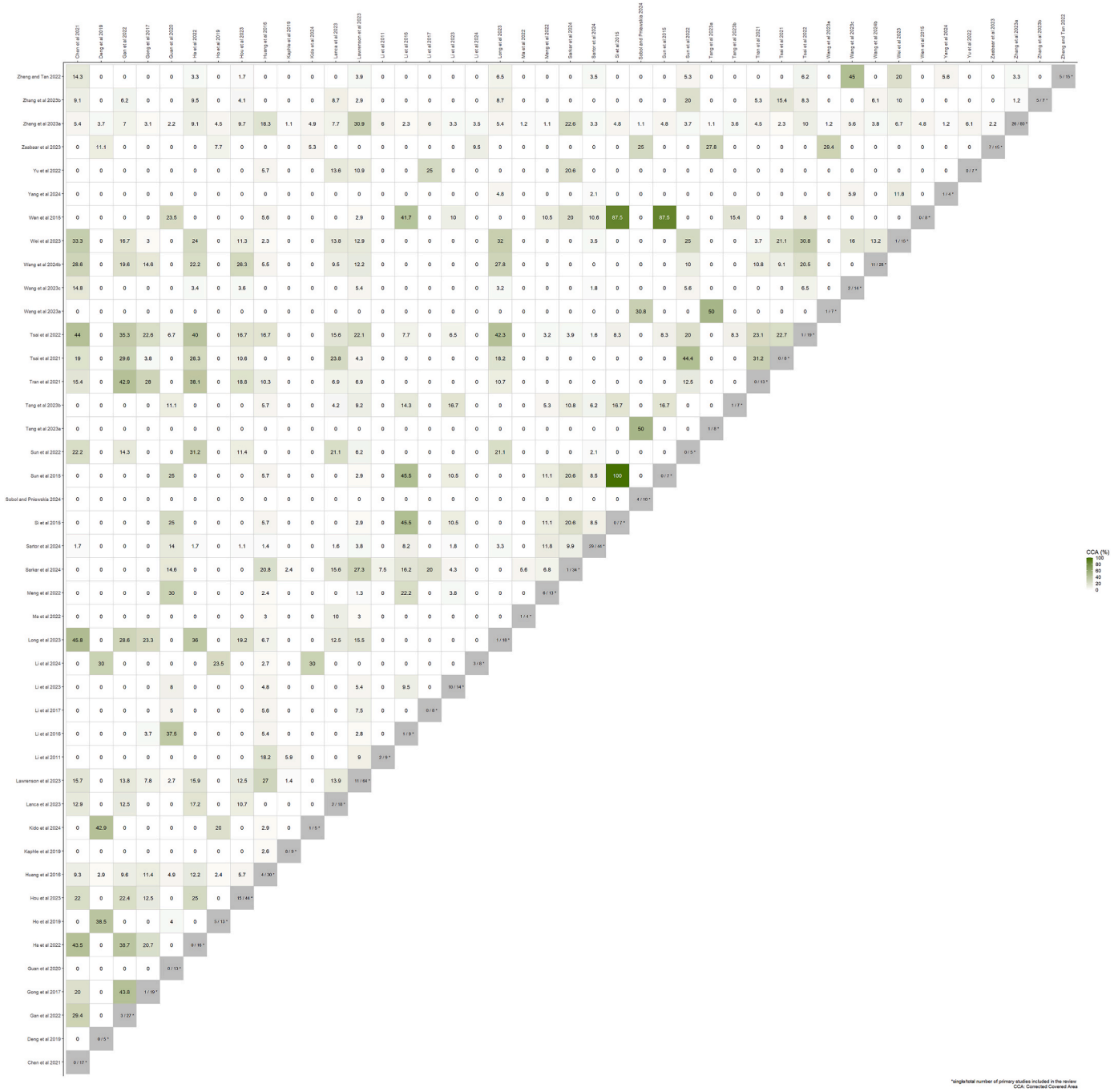


Fig. 1. A pairwise intersection heatmap illustrating the degree of overlap among the included reviews. The triangular matrix features color-coded cells that represent the percentage of corrected covered area (CCA) for each pair of reviews, with darker colors indicating a higher CCA percentage. The grey diagonal cells reflect the total number of primary studies included in each review.

atropine, low concentration atropine + Ortho-K, multifocal spectacles, and outdoor time, respectively (Figs. 2–6).

Combining multifocal spectacle lenses with high-concentration atropine resulted in a substantial reduction in axial elongation. A larger share of this synergistic effect is likely driven by the high-concentration atropine, given the lower efficacy of the multifocal spectacle lens monotherapy. RLRL, Ortho-K, high-concentration atropine, and multifocal soft contact lens monotherapies yielded clinically significant effects in slowing AL. Despite its clinically significant efficacy, high-concentration atropine has been reported to be associated with significant rebound of myopia progression and/or side effects such as pupil dilation, glare, and loss of accommodation (Chia et al., 2012, 2016; Tong et al., 2009). Accordingly, RLRL, Ortho-K, and multifocal soft contact lenses could be effective alternatives since they are

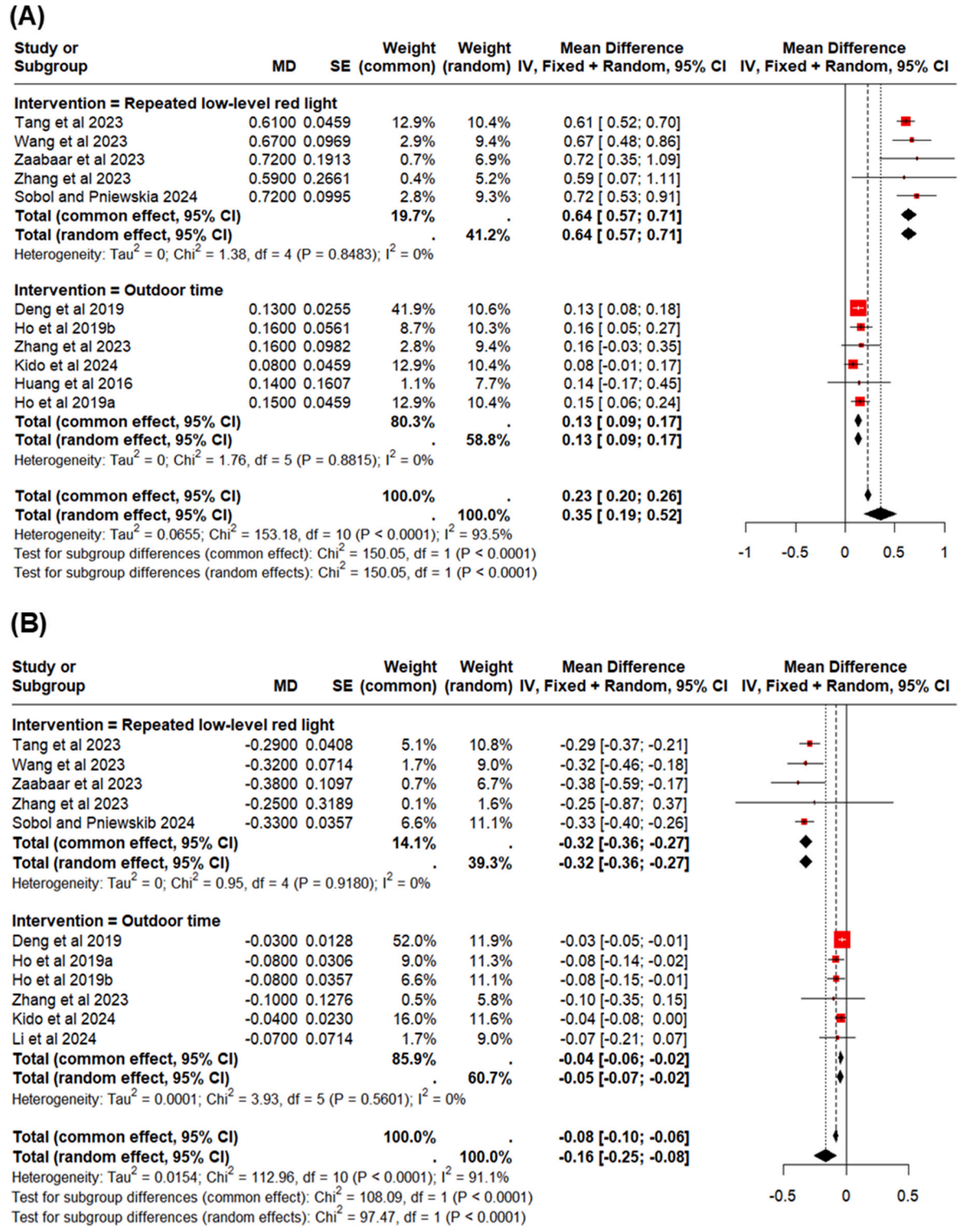


Fig. 2. Forest plot of treatment effect sizes for repeated low-level red light therapy and outdoor time based on changes in (A) spherical equivalent refraction and (B) axial length.

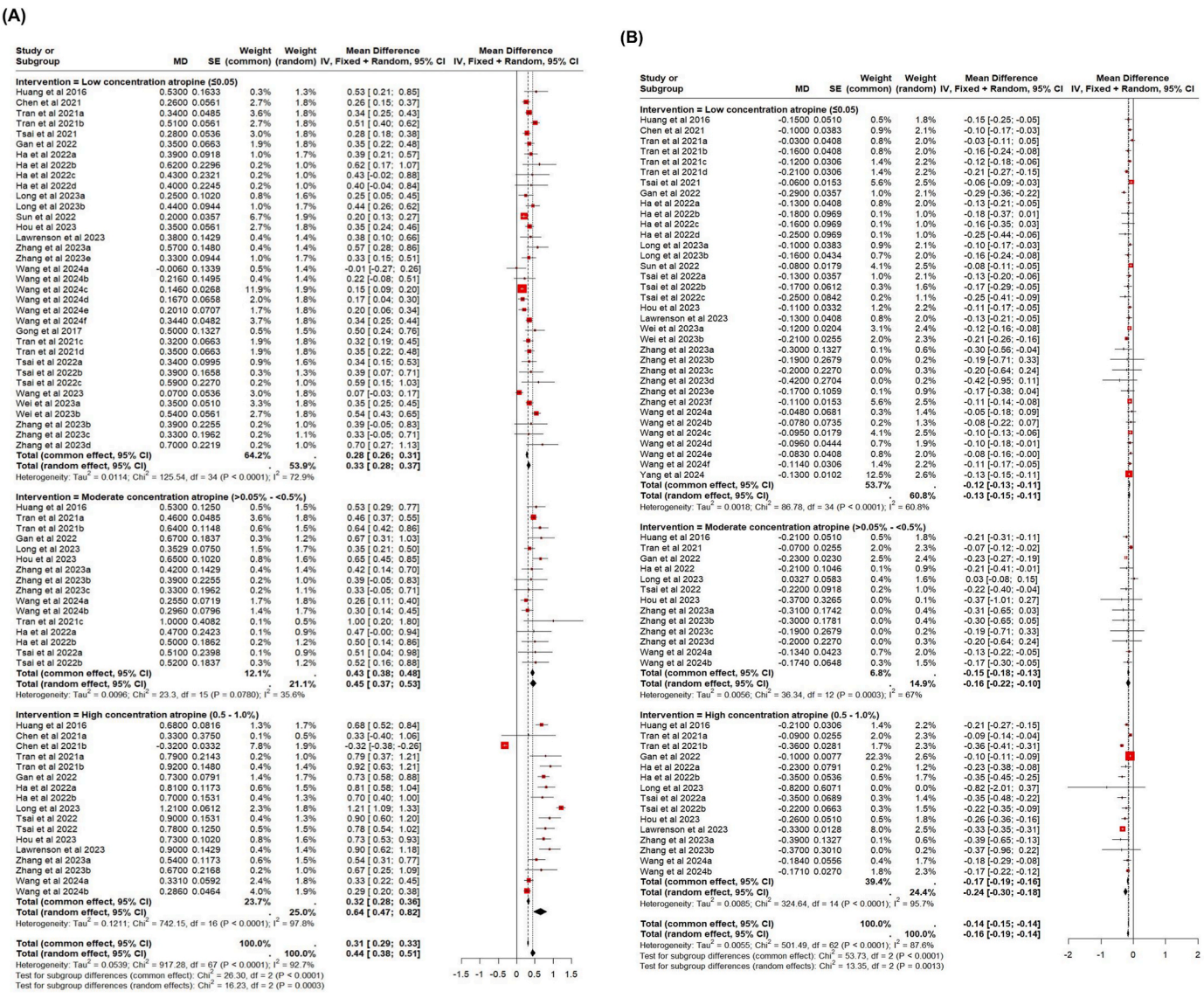


Fig. 3. Forest plot of treatment effect sizes for high, moderate, and low concentrations of atropine based on changes in (A) spherical equivalent refraction and (B) axial length.

comparatively more tolerable.

4. Myopia control in adults

4.1. Myopia onset in adults and its associations

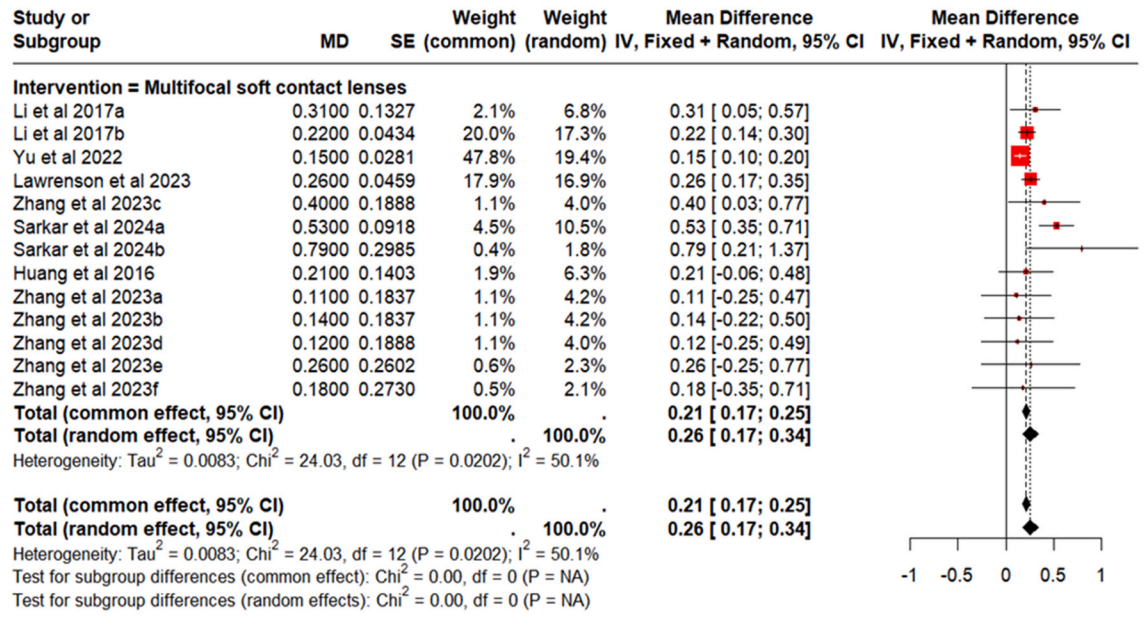
Childhood myopia begins when the human eye is still growing (Flitcroft et al., 2019), whereas adult-onset myopia and progression can occur even when normal eye growth is expected to have stopped or stabilized (Bullimore et al., 2023b). There are significant individual variabilities in the age of stabilization, ranging from 14 to 22 years (Bullimore et al., 2023b; Foo et al., 2024). According to the Correction of Myopia Evaluation Trial (COMET), which is a prospective study that collected longitudinal refractive data over 11 years from a large, ethnically diverse cohort in the United States (COMET Group, 2013), the mean age at which myopia stabilized (defined as the age at which the estimated spherical refractive error was within 0.50 D of the asymptote) was15.6 ± 4.2 years, and the mean refractive error at this point was −4.87 ± 2.01 D. In this cohort, myopia had stabilized in 48 % of participants by age 15, 77 % by age 18, and 90 % by age 21, implying that the condition persists into early adulthood.

Adult-onset myopia is usually low to moderate (Fledelius, 1995). The annual incidence of myopia observed across various prospective studies ranged from 2 % to 24 %, with the majority between 5 % and 14 %. There are more studies reported in populations outside of East Asia (Fesharaki et al., 2006; Jacobsen et al., 2008; Jorge et al., 2007; Kinge and Midelfart, 1999; Lee et al., 2022b; McBrien and Adams, 1997; O'Neal and Connon, 1987), where the incidence of juvenile myopia is higher than in other regions. The available studies in Asia reported an annual incidence of 5 %–14 % for adult-onset myopia (Duan et al., 2023; LIN et al., 1996; Lv and Zhang, 2013). Adult-onset myopia is associated with female sex, Asian ethnicity, less outdoor time, and parental myopia (Lee et al., 2022b). The Genes in Myopia (GEM) twin study has provided evidence of a genetic component underlying the development of adult-onset myopia (Dirani et al., 2008).

4.2. Myopia progression in adults and its associations

An early study suggested that by the age of 13, AL reaches values typical of emmetropic adults (Larsen, 1971). However, subsequent studies have documented progression of myopia in adult populations, and the rate is slower than in childhood myopia (Adams and McBrien,

(A)



(B)

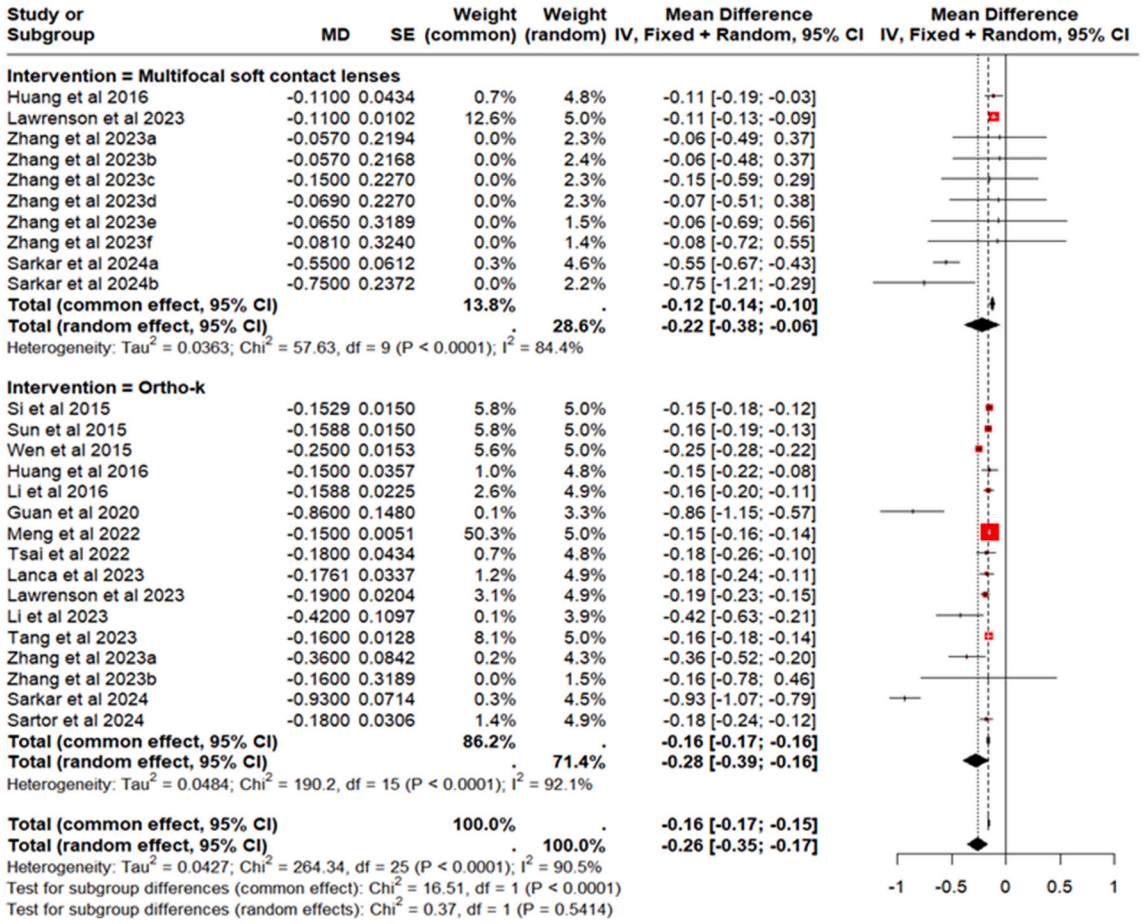
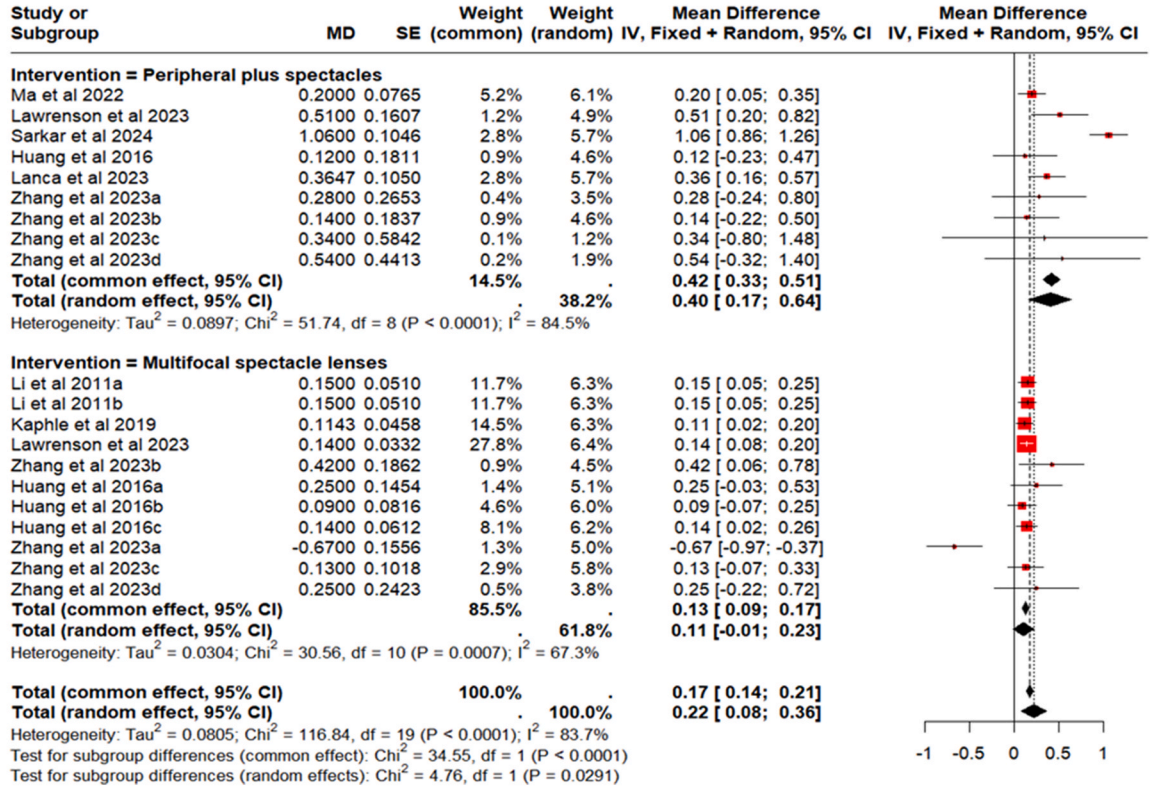


Fig. 4. Forest plot of treatment effect sizes for multifocal contact lenses based on changes in (A) spherical equivalent refraction and (B) axial length.

(A)



(B)

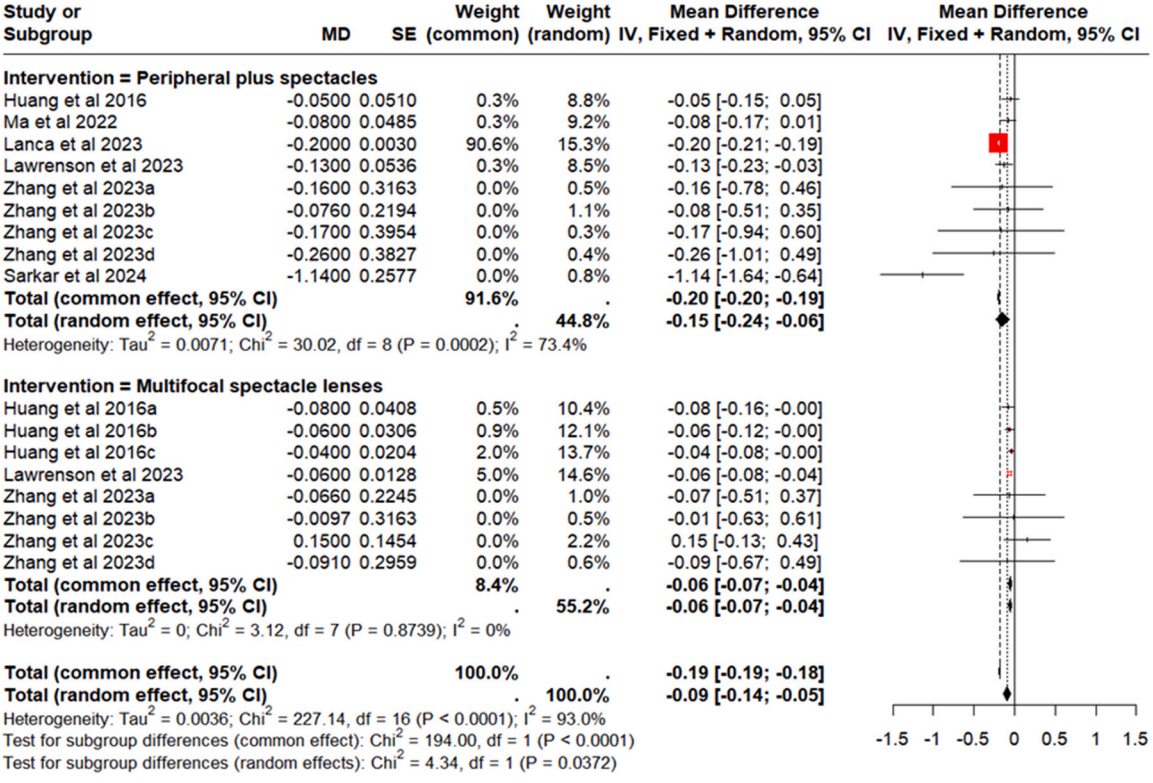


Fig. 5. Forest plot of treatment effect sizes for peripheral plus and multifocal spectacle lenses based on changes in (A) spherical equivalent refraction and (B) axial length.

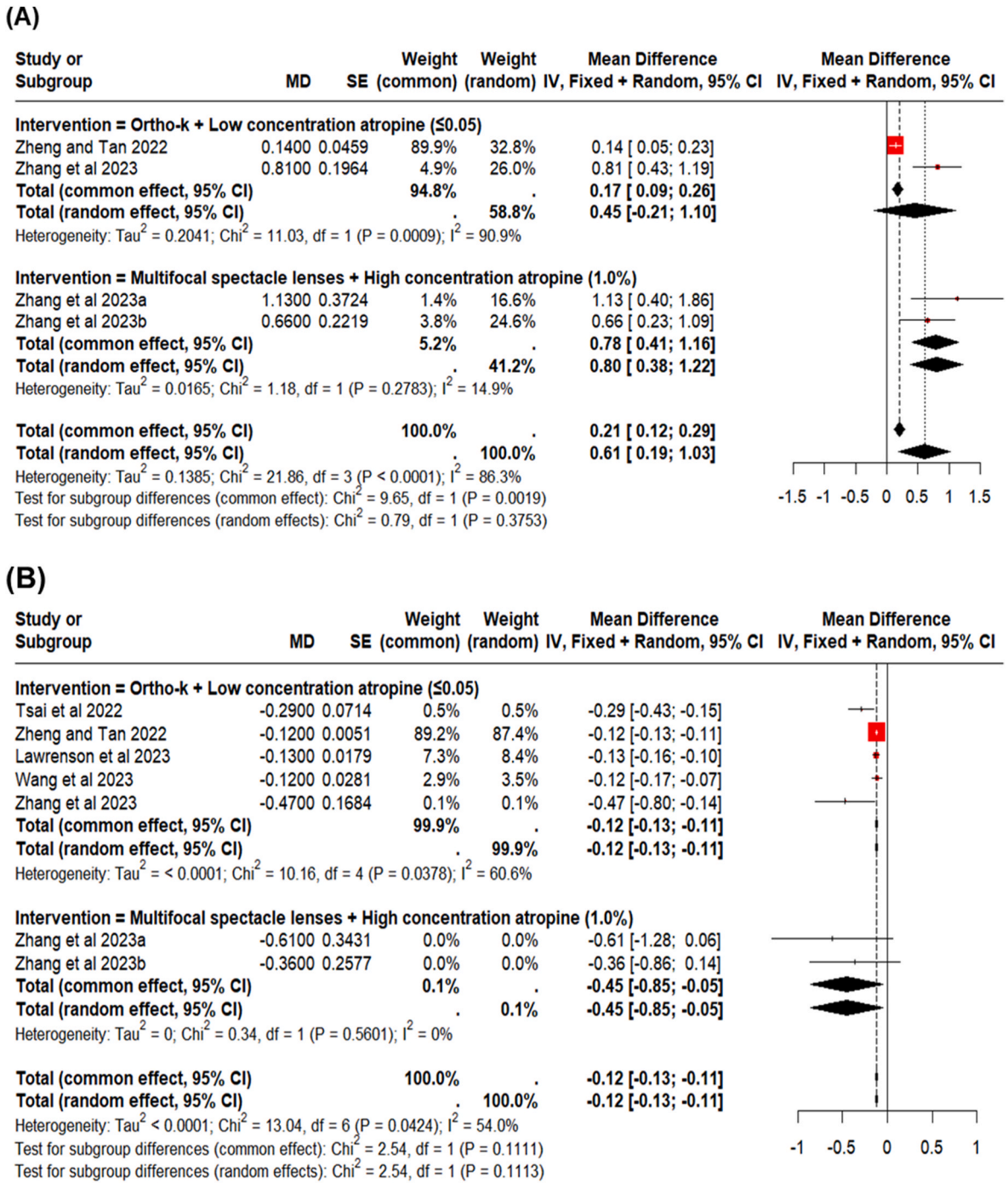


Fig. 6. Forest plot of treatment effect sizes for low-concentration atropine combined with orthokeratology and high-concentration atropine combined with multifocal spectacle lens based on changes in (A) spherical equivalent refraction and (B) axial length.

1992; Bullimore et al., 2002; Grosvenor and Scott, 1993; Khan et al., 2023; Lee et al., 2022b; McBrien and Adams, 1997). For myopic adults between 18 and 25 years of age, the average annual rate of myopia progression ranges from −0.08 to −0.23 D/year, with an average rate of approximately −0.13D/year (Bullimore et al., 2023b; Khan et al., 2023). For myopic adults between the ages of 25 and 40 years, the annual rate of myopia progression is generally lower than −0.1D/year (Bullimore et al., 2023b). Among myopic adults between 18 and 25 years old, the annual average axial length growth is approximately 0.1 mm/year, based on two studies in Caucasian populations (Grosvenor and Scott, 1993; Kinge and Midelfart, 1999). The Study of Progression of Adult Nearsightedness (SPAN) reported a mean increase in axial length of 0.27 mm over 5 years (~0.05 mm/year) in adults 25 years and older (Bullimore et al., 2008). Thus, similar to children, age affects myopia progression in adults. However, these estimates in adults are notably lower than the increases in spherical equivalent refraction and axial eye growth reported for children and adolescents (Donovan et al., 2012c; Naduvilath et al., 2023).

In adults who have undergone corneal refractive surgery to correct their myopia, AL and myopia may continue to progress after the surgical procedure. A retrospective study examined the long-term refractive outcomes for young adult patients who had undergone laser vision correction procedures (Sasaki et al., 2020). After epithelial laser-assisted in situ keratomileusis (LASIK), there was significant myopic shifts over 4

years, with average refractive changes of −0.44D for those aged 20–39 and −0.26D for those aged 30–39. The corresponding increases in AL were 0.12 mm and 0.09 mm, respectively. High preoperative myopic refraction and axial length >26 mm have been reported to increase the risk of post-LASIK myopia progression in adults (Gab-Alla, 2021). In a study involving 1219 patients (2316 eyes) in Egypt, among those whose myopia continued to progress after full LASIK correction, 52.6 % had pre-operative high myopia, 34 % had moderate myopia, and 13.4 % had low myopia. The mean AL for patients with myopic progression was 26.6 ± 0.44 mm (range: 26.0–27.86 mm), while for those with stable refraction, it was 24.38 ± 0.73 mm (range: 22.9–25.9 mm) ($P < 0.001$) (Gab-Alla, 2021). Myopic shifts have also been reported after photorefractive keratectomy (PRK) (Koshimizu et al., 2010; O'Brart et al., 2014; O'Connor et al., 2006; Vestergaard et al., 2012). The effect of refractive surgery on peripheral refractive error remains unclear, and it is unknown whether this effect is similar to or distinct from that of Ortho-K or other optical methods.

In addition to age (Bullimore et al., 2002; Khan et al., 2023), other factors have been identified to be associated with myopia progression in adults. Rates of myopia progression and axial elongation have been found to be faster in females than in males in a study in Australia (Lee et al., 2022b), although the reverse has been reported among medical students in Taiwan (LIN et al., 1996). Parental myopia (Lee et al., 2022b), excessive near-work (Kinge et al., 2000), and less outdoor time (Jacobsen et al., 2008) also increase the risk of adult myopia progression. Among college/university students and individuals employed as microscopists, a larger proportion of myopic individuals were found to become increasingly myopic over time (Loman et al., 2002; McBrien and Adams, 1997). Further, adult myopes working or studying in a higher learning/academic environment had higher odds of progression than those in non-academic environments (Khan et al., 2023). According to one study, myopia progression was similar between Asians and Europeans (Tricard et al., 2022). Evidence from cross-sectional and longitudinal studies suggests that adult myopia progression results from axial elongation and corneal steepening, with a greater contribution from axial elongation (Grosvenor and Goss, 1998; Grosvenor and Scott, 1993; Khan et al., 2023). Large-scale and multi-ethnic studies in adult myopia are needed to document its epidemiology and risk factors.

4.3. Interventions for adulthood myopia

There are limited studies on the efficacy and safety of myopia control interventions in adults. Considering that amplitude of accommodation diminishes with age, a valid concern regarding the use of atropine in adults is that the side effect profile may be more severe. This risk may be particularly pronounced in lightly pigmented Caucasian eyes, as race and iris color are known factors that influence cycloplegia (Manny et al., 2001). Loughman and Flitcroft investigated the acceptability and visual impact of low-concentration (0.01 %) atropine as a treatment for myopia in 14 university students (18–27 years) with lightly pigmented irides, who received a drop of atropine daily in each eye for 5 days (Loughman and Flitcroft, 2016). It was found that 0.01 % atropine did not significantly reduce amplitude of accommodation, visual acuity (distance and near), and reading speed (Loughman and Flitcroft, 2016). Though the significant effect of atropine on pupil size slightly increased symptoms such as glare, the treatment did not affect overall quality of life. In contrast, Kaymak et al. evaluated the short-term effects of low-concentration atropine on pupil size and accommodation and found that a single dose of 0.01 % atropine caused pupil dilation and reduced near point of accommodation for at least 24 h in a study of 20 eyes of Caucasian young adults aged 21 to 40 (Kaymak et al., 2018). These studies had very short durations and did not report actual treatment outcomes, which limits our understanding of the treatment effects and long-term safety of atropine in adults. However, the results imply that the potential for more pronounced long-term side effects, especially in lightly pigmented individuals and with relatively high concentrations, warrants caution. Further investigations with longer treatment durations are essential to assess the overall impact and effectiveness of atropine for myopia management in adult populations.

Some studies have reported effective treatment of adult-onset myopia with Ortho-K. In an investigation of the zone of clear single binocular vision (ZCSBV) in eight young adult myopes (18–29 years) who wore Ortho-K, AL was stable over 12 months, while the ZCSBV expanded towards a more divergent, increased accommodation response compared to single vision soft contact lens wear (Gifford et al., 2020a). Similarly, in three Caucasian early adult-onset progressing myopic subjects who were fitted with Ortho-K lenses, there was slower or no progression of refractive error, while AL remained stable over three years (González-Méijome et al., 2016). In another study, Ortho-K had no significant adverse impact on visual acuity, contrast sensitivity, or visual performance in young Caucasian adults (Johnson et al., 2007). The absence of control groups in these studies raises concerns about the validity of the findings. Since the precise timeframe for when myopia stabilizes is uncertain, the myopia control efficacy of Ortho-K reported in these studies could be 'natural plateauing' due to globe stabilization rather than treatment effect. Even so, the results indicate that Ortho-K may slow myopia progression in young adults and warrant further investigations. In a study that evaluated the effects of multifocal soft contact lenses used for myopia control on quality of vision, the lenses seemed undesirable as they adversely affected low-contrast visual acuity and quality of vision in young adults (Kang et al., 2017).

Thakur et al. exposed young adults to red, green, and blue light for 1 h across four sessions, inducing hyperopic defocus (3D) in one eye (Thakur et al., 2021). Red light exposure caused significant AL increases in both eyes (11.2 ± 2 μm for defocused; 6.4 ± 2.3 μm for non-defocused), along with reduced choroidal thickness. Green light also increased AL (9.2 ± 3 μm and 7.0 ± 2.5 μm) with decreased choroidal thickness. In contrast, blue light exposure reduced AL in the defocused eye (−8.0 ± 3 μm) without affecting the non-defocused eye or choroidal thickness. While this shows some promise for blue light, the duration of treatment was very short, and further studies are warranted.

Liu et al. explored the impact of a four-week RLRL regimen in myopic adults aged 18-35, measuring changes in AL, subfoveal choroidal thickness, choroidal vascularity index, and anterior segment components (Liu et al., 2022). AL decreased by an average of 0.06 mm (from 24.63 ± 1.04 mm to 24.57 ± 1.04 mm, range: 0–0.13 mm), with 69.23 % of subjects achieving clinically significant shortening (>0.05 mm) - a more pronounced effect than typically seen in children (Jiang et al., 2022; Xu et al., 2024), likely due to the confounding influence of ongoing ocular growth in younger populations (Wallman and Winawer, 2004). In the control group, AL had no significant changes during the follow-up. Concurrently, treated eyes showed subfoveal choroidal thickening (+18.34 μm) and subtle but significant improvements in choroidal vascularity within the 0–6 zone, while all anterior segment parameters did not change significantly. This pattern of posterior segment changes (choroidal thickening and vascular enhancement) without anterior segment alterations suggests that the RLRL-induced axial shortening likely stemed from structural remodeling in the posterior segment, to a larger extent.

Current research on myopia control interventions in adults remains limited, with existing studies typically constrained by short follow-up periods. This gap in evidence is particularly concerning given that myopia continues to progress in adults, along with potentially severe clinical consequences. Rigorous, large-scale, long-term studies evaluating myopia control in adult populations are crucial to establishing evidence-based management strategies for this understudied demographic.

4.4. Challenges, clinical Significance, and Unmet questions

Myopia progression in adults appears comparable across different ethnic groups. Refractive surgeons have to carefully evaluate baseline

AL and refractive error when counseling patients on the long-term refractive outcomes they can expect after laser vision correction. Surgery in patients in their early twenties may result in a re-emergence of myopia later in adulthood. Large population-based studies with long-term follow-up to explore incidence and risk factors in young adults are warranted.

Evaluating the effectiveness of myopia control interventions in adults can be difficult, primarily due to the slower progression of myopia compared to children and adolescents. Measuring the impact of treatments may take a much longer time. Consequently, clinical studies investigating myopia control in adults must be designed with longer durations to capture subtle changes in myopia. Another major challenge in evaluating myopia control interventions in adults is the uncertainty of the stabilization of myopia. While myopia progression in children and adolescents is essentially predictable, there are large variations among adults. This unpredictability complicates the management strategies and necessitates a flexible and personalized approach to treatment.

5. Global studies to optimize myopia interventions

A significant gap in current myopia research is the limited data on the efficacy of interventions across different ethnic groups. Most studies on atropine eye drops, Ortho-K, and other interventions are reported in East Asian populations, where myopia prevalence is high. Variations in ethnicity and age have to be considered to extrapolate results and directly compare the effectiveness of different treatment methods. There has not been widespread clinical uptake of some potentially efficacious interventions like red light and atropine 0.05 % eye drops. However, myopia is increasing in prevalence worldwide, including populations in various regions like Europe and North America. Large-scale, global studies are essential to gather comprehensive data on how various interventions perform across diverse populations. Global studies would help establish standardized treatment guidelines that take into account varying lifestyle factors, environmental influences, and healthcare access in different regions. The challenge lies in the availability of several effective myopia control interventions for patients, making it ethically complex to conduct placebo-controlled randomized trials (Bullimore et al., 2023a). This situation may also hinder recruitment, result in participants accessing other treatments alongside the trial intervention, inflate the number of slow progressors if fast progressors withdraw from the control group, and lead to participant dropout if masking is unsuccessful (Bullimore et al., 2023a). There have been suggestions to use an approved drug or device as the control in non-inferiority trials, create predictive models for long-term efficacy outcomes of new interventions, use virtual control from historical data, extrapolate short-term control data to future years, and employ time-to-treatment failure trials (Bullimore et al., 2023a). Properly implementing these strategies may enhance the quality of research while ensuring that patient care remains uninterrupted.

6. Novel environmental and lifestyle interventions

In addition to pharmacological and optical treatments, environmental and lifestyle factors play a significant role in myopia progression. Children who spend more time outdoors tend to have slower myopia progression, likely due to increased exposure to natural light. Other factors, such as living in urban environments or limited access to green spaces, have also been associated with onset and progression of myopia. More research is needed to obtain data on specific environmental factors, such as urban planning, school lighting, and access to green spaces, on myopia progression. Additionally, there is potential for nutritional interventions, as diet may influence eye health and myopia risk. By incorporating environmental and lifestyle factors into myopia treatment protocols, researchers may uncover new, non-invasive strategies to slow myopia progression, particularly in populations with limited access to medical interventions.

7. Conclusions

The global rise in myopia among children, adolescents, and adults has led to significant advancements in the development of myopia control methods in recent years, with some approaches showing a satisfactory balance between effectiveness and safety. Increased outdoor time remains the simplest and most effective lifestyle intervention for at-risk pre-myopes, potentially reducing myopia onset by up to 50 %. Treatments such as 0.05 % atropine and RLRL also showed promise in reducing myopia onset. The efficacy of low-concentration atropine in slowing myopia progression is concentration-dependent, achieving up to 67 % control at 0.05 %. Other interventions, including RLRL, novel spectacle lenses (HALT, DIMS, DOT, PLARI, and NLARI), dual-focus soft contact lenses, and Ortho-K, show at least 50 % efficacy in slowing progression. Combination therapy is an emerging field in myopia management, presenting opportunities to improve treatment outcomes beyond monotherapy. Ortho-K combined with 0.01 % atropine has the most robust evidence of effectiveness; however, it is less effective for fast progressors and high myopes. Dual focus contact lenses combined with 0.05 % atropine, as well as Ortho-K paired with RLRL or atropine concentrations of at least 0.05 %, yield better efficacy in fast progressors. Additionally, combining peripheral defocus spectacles with 0.01 % and 0.025 % atropine also shows promising results. Since there is an inherent growth of the eyeball and associated shift in refractive state that occurs in childhood, even in non-myopic children, myopia control interventions are not to completely halt these natural changes but to reduce the risk of developing high myopia and subsequent sight-threatening complications. Therefore, the level of myopia control that can be deemed effective and protective is when an intervention reduces eye growth to a rate experienced by an emmetrope. Patient-centric and intervention-specific factors that affect efficacy and safety are essential for tailoring interventions to meet individual patient needs. As the prevalence of myopia continues to rise globally, improvements in myopia control require new technologies and novel approaches aimed at enhancing effectiveness, accessibility, and individualization of treatment.

CRediT authorship contribution statement

Jason C. Yam: Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Conceptualization. **Xiu Juan Zhang:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization. **Ebenezer Zaabaar:** Writing – review & editing, Writing – original draft, Visualization, Investigation, Formal analysis. **Yuyao Wang:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation. **Yuelan Gao:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Yuzhou Zhang:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Xiaotong Li:** Writing – review & editing, Writing – original draft. **Ka Wai Kam:** Writing – review & editing, Supervision. **Fangyao Tang:** Writing – review & editing, Investigation. **Wai Kit Chu:** Writing – review & editing, Writing – original draft. **Xiangtian Zhou:** Writing – review & editing, Writing – original draft. **Wei Zhang:** Writing – review & editing. **Xiangui He:** Writing – review & editing. **Pei-Chang Wu:** Writing – review & editing, Writing – original draft, Validation. **Kathryn A. Rose:** Writing – review & editing, Validation. **Ian Morgan:** Writing – review & editing, Writing – original draft, Validation. **Mingguang He:** Writing – review & editing. **Kyoko Ohno-Matsui:** Writing – review & editing. **Jost B. Jonas:** Writing – review & editing, Writing – original draft, Validation. **Mingzhi Zhang:** Writing – review & editing. **Clement C. Tham:** Writing – review & editing, Supervision. **Li Jia Chen:** Writing – review & editing, Writing – original draft, Validation, Supervision. **Chi Pui Pang:** Writing – review & editing, Writing – original draft, Validation, Supervision.

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Declaration of interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Jason C. Yam: OCUS Innovation (HK) Limited.

Xiaotong Li: Pending patent.

Wei Zhang: Pending patent.

Mingguang He: Eyerising Ltd, Eyerising International Pty Ltd, patent - "A method to increase retinal blood flow and metabolism" (CN201910490186.6) - pending to Suzhou Xuanjia Optoelectronics Technology Co Ltd, Zhongshan Ophthalmic Center.

All other authors have no conflicts of interest.

Appendix A. Supplementary data

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