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# Myopia Development and Control: An Integrative Review of Genetic, Optical, and Environmental Mechanisms With Implications for Personalized Intervention

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## ABSTRACT

Myopia is a rapidly growing global health challenge, affecting 1.9 billion people and projected to reach 4.9 billion by 2050, with high myopia and its sight-threatening complications such as maculopathy, retinal detachment, and glaucoma increasing disproportionately. The condition imposes an annual socioeconomic burden exceeding $250 billion. This review synthesizes mechanistic, genetic, and environmental evidence within a framework linking near work (NW) and reduced outdoor time to optical defocus, dopamine-mediated retinal signaling, and scleral remodeling, moderated by gene-environment (GxE) interactions. Interventions are classified as corrective (spectacles, surgery), dual-function optical strategies (orthokeratology, DIMS, HALT, DOT, CARE lenses), pharmacological approaches (low-dose atropine), and behavioral measures (outdoor exposure). Three principles guide management: each diopter increases complication risk, effective interventions act through validated biological mechanisms, and individual variability necessitates personalized care. Optimal control requires tailored and combined strategies, informing clinical practice, public health policy, and future research to address the global myopia epidemic.

## 1 | Introduction

### 1.1 | Global Epidemiology and Societal Impact of Myopia

Myopia has emerged as one of the most significant and rapidly escalating threats to global eye health. It is currently the most prevalent refractive condition across both developed and developing regions, and its rapidly rising incidence demands urgent public health intervention [1]. Prevalence varies significantly across regions and age groups. In East and Southeast Asia, childhood myopia rates are exceptionally high—reaching 60%–80% by mid-teens, with some populations (e.g., Singaporean Chinese) exceeding 85% by age 15 [2]. In contrast, prevalence among similarly aged children in Europe, Africa, and the Eastern Mediterranean remains below 30%, with pooled estimates of about 3.9% in children aged 5–10 and about 7.5% in adolescents aged 11–17 [3].

Globally, myopia prevalence in children and adolescents rose from about 24.3% (95% CI: 15.2–33.4) in 1990–2000 to 35.8% (95% CI: 31.7–39.9) in 2020–2023, with projections reaching 39.8% by 2050 [2]. Urban environments and East Asian populations show particularly high rates, and females tend to have slightly higher prevalence than males [4].

In adults, approximately 27% (1.9 billion) had myopia and 2.8% (170 million) had high myopia in 2010. By 2050, these figures are projected to rise to 52% (4.9 billion) and 10% (0.9–1.0 billion), respectively [5]. High myopia is clinically significant

[Correction added on 14 April 2026, after first online publication: Figures 4 and 5a were deleted, with related figures and citations adjusted accordingly.]

due to its association with irreversible complications such as myopic macular degeneration (MMD), retinal detachment, and choroidal neovascularization. A 2015 meta-analysis estimated 10 million people had vision impairment from myopic macular degeneration, with 3.3 million blind; these numbers may rise to 55.7 million impaired and 18.5 million blind by 2050 [6].

Age of onset is a key factor. Myopia prevalence is lower in children under 10 but increases sharply in adolescence. For example, in Europe, prevalence rises from 5.5% in children (6–11 years) to 25.2% in adolescents (12–17 years), and 24.3% in young adults (18–39 years) [7]. Females generally show higher prevalence from around age 9, potentially due to earlier puberty, behavioral factors (e.g., less outdoor time), and socio-environmental influences [3].

Myopia has significant societal and economic consequences, affecting education, work performance, and quality of life [2]. The 2015 WHO–Brien Holden Vision Institute meeting estimated global productivity losses from uncorrected refractive error at more than $250 billion annually, with additional costs from high myopia complications [5]. These include direct healthcare costs such as optical correction, clinical care, and surgery, as well as indirect costs from reduced productivity [5, 8]. The burden is expected to rise sharply: by 2050, 55.7 million people may have vision impairment from myopic macular degeneration, with 18.5 million blind [6]. Uncorrected refractive error remains a leading cause of avoidable visual impairment globally, central to WHO's Vision 2020 initiative [9, 10]. Irreversible complications of high myopia such as maculopathy, glaucoma, cataract, and retinal detachment pose a growing threat that optical correction alone cannot resolve [8, 11, 12]. These trends highlight the need to understand myopia progression and develop effective interventions.

While the global epidemiology of myopia highlights its growing prevalence and societal burden, these figures only tell part of the story. Beyond the challenges posed by uncorrected refractive error, the progression to high myopia introduces a distinct set of clinical risks that extend far beyond simple optical correction. Understanding why myopia evolves from a manageable refractive condition to a sight-threatening pathology is critical for addressing its long-term impact. The next section examines this transition, emphasizing the complications associated with high myopia and the biological processes underlying its progression.

### 1.2 | From Refractive Error to Pathology: Why High Myopia Matters

Uncorrected refractive error remains one of the leading causes of avoidable visual impairment globally and has been a central focus of WHO's Vision 2020: the right to sight global initiative [9, 10]. Despite its substantial global burden affecting billions, it is largely preventable through timely and accessible optical correction [13]. It is crucial, however, to distinguish uncorrected refractive error from pathological forms. High myopia, for instance, is associated with serious complications such as myopic maculopathy, glaucoma, cataract, and retinal detachment, all of which can result in irreversible vision loss and are emerging as significant causes of permanent blindness [8, 11, 12].

At the core of normal visual development is a tightly regulated process known as emmetropization, which ensures that the eye grows in a way that allows light to focus accurately on the retina. This vision-dependent feedback mechanism modulates ocular growth during early life, typically guiding the eye from a hyperopic state at birth toward emmetropia—an absence of refractive error by early childhood [13]. Disruption of this process can lead to progressive axial elongation, resulting in myopia. When unchecked, this elongation may continue into adolescence and adulthood, increasing the risk of pathological changes and irreversible visual impairment associated with high myopia.

The structural dynamics of myopia development are driven by changes in ocular biometric parameters and mechanical forces acting on the eye. These factors influence both normal growth and the pathological remodeling seen in progressive myopia. Understanding the temporal sequence of refractive development—from a Gaussian distribution in infancy to a leptokurtic pattern in early childhood—and the relative contributions of axial length and refractive power is essential for identifying deviations that signal the onset of myopia [11].

Despite advances in understanding the optical and developmental basis of myopia, significant gaps remain in our ability to predict, prevent, and manage its progression. The increasing global burden of high myopia and its associated complications underscores the need for further research into the mechanisms of emmetropization, the biomechanical forces driving axial elongation, and the development of effective interventions to mitigate long-term visual impairment. Understanding why myopia progresses from a benign refractive state to a sight-threatening condition requires a detailed examination of the biological processes that regulate ocular growth. The following section synthesizes current knowledge of these pathogenic pathways into a unified mechanistic framework.

## 2 | Integrated Pathogenic Pathways of Myopia Progression

### 2.1 | Vision-Guided Eye Growth and the Failure of Emmetropization

Normal refractive development depends on a tightly regulated, vision-dependent feedback system known as emmetropization, which coordinates ocular growth to align axial length with optical power. Thus, emmetropization is the vision-guided developmental process that coordinates ocular growth to minimize refractive error, typically achieving emmetropia by early childhood [14]. This homeostatic system relies on visual feedback to balance axial length with optical power. Disruption of the emmetropization process lies at the core of myopia development. Rather than arising from a single defect, myopia reflects the convergence of optical, neural, biomechanical, and molecular pathways that collectively promote axial elongation. In this section, we integrate these mechanisms into a coherent causal chain linking environmental inputs to structural remodeling of the eye.

## 2.2 | A Unified Causal Framework for Myopia Development

Myopia development reflects the failure of vision-guided emmetropization in response to persistent environmental and optical cues, resulting in maladaptive ocular growth [14]. A wide range of exposures including sustained near work (NW), reduced outdoor light exposure, form-deprivation (FD), and urbanized visual environments alter retinal image quality by introducing central and peripheral hyperopic defocus, reducing contrast, or degrading optical signals. These optical perturbations are transduced by the retina into neurochemical and molecular growth signals, notably involving dopaminergic and growth-factor–mediated pathways, whose effects are modulated by genetic susceptibility. Sustained pro-growth signaling promotes axial elongation through choroidal thinning, scleral remodeling, and vitreous chamber expansion, with accommodative and biomechanical forces further biasing growth along the axial axis. This cascade: environmental cues, optical defocus, retinal signaling, structural remodeling provides a unifying framework explaining how diverse experimental paradigms and real-world risk factors converge on a common anatomical outcome and underpins the mechanistic rationale for contemporary myopia control strategies.

## 2.3 | Ocular Biometry and Biomechanical Forces in Axial Elongation

The axial length of the eye, primarily determined by vitreous chamber depth, is the dominant factor influencing refractive state across the lifespan [15]. While the cornea and lens contribute to refraction through their curvatures and dimensions, their role in myopia development is more modest. Myopic eyes typically exhibit thinner choroids than emmetropic eyes, with thinning increasing in proportion to axial elongation [16]. Importantly, the ratio of axial length to corneal radius has been shown to predict refractive status more accurately than axial length alone [15].

During childhood myopia onset, lens thickness decreases more rapidly than in emmetropic eyes, suggesting that myopia progression reflects not only axial elongation but also disproportional growth between ocular components [17]. With progression, the anterior chamber deepens and the crystalline lens becomes thinner; however, posterior segment changes—vitreous chamber elongation, scleral thinning, and choroidal remodeling are the principal drivers of refractive error [18].

Mechanical forces may also contribute to elongation. Sustained accommodation generates ciliary muscle tension that transmits to the choroid and sclera, potentially restricting equatorial growth while promoting axial elongation (Figure 1) [19]. This hypothesis is supported by clinical evidence of choroidal thinning in progressing myopes. Beyond biomechanics, light exposure has emerged as a key environmental factor. Animal models show that even brief, low-intensity light exposures can accelerate axial growth [20], underscoring how both biomechanical strain and environmental cues interact during critical developmental windows to shape refractive trajectories. While biomechanical changes define the structural phenotype of myopia, the signals initiating these changes originate from visually driven feedback mechanisms.

## 2.4 | Experimental Disruption of Visual Feedback: Form-Deprivation

Experimental models have been pivotal in revealing the mechanisms of visually guided eye growth. FD, achieved using lid sutures or diffusers, induces rapid axial elongation and high myopia in animals ranging from chicks to primates [21–24]. Translucent diffusers have emerged as the preferred experimental method, avoiding the confounding corneal

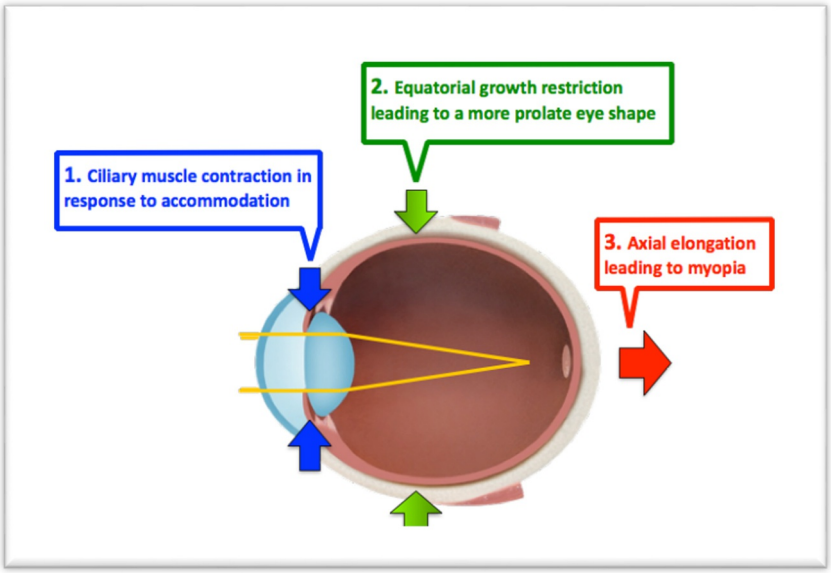


**FIGURE 1** | Accommodation involves contraction of the ciliary process which exerts a bi-directional axial pulling on the eyeball. This pressure tends to hinder growth in the opposite direction resulting in a prolongation of the eyeball to cause myopia [14].

curvature changes associated with lid sutures. FD creates an open-loop condition in ocular development, disrupting the coordinated growth patterns necessary for normal refractive development (Figure 2) [11]. For instance, chicks can develop up to −9 D of myopia within 5 days, while macaques develop approximately −5 D after 17 weeks of deprivation [23]. Despite species differences, consistent anatomical features are observed: vitreous chamber elongation, scleral thinning, and choroidal atrophy.

The clinical relevance is evident in pediatric patients with congenital cataracts, ptosis, or corneal opacities, who frequently develop deprivation-induced myopia. Younger children display heightened vulnerability, reflecting greater ocular plasticity [22]. These findings highlight both the critical period for emmetropization and the lifelong consequences of its disruption. In contrast to non-directional blur induced by FD, the emmetropization system also responds selectively to the sign and location of optical defocus.

### 2.5 | Peripheral Retinal Defocus and Open-Loop Growth Control

Peripheral retinal defocus also modulates eye growth. Minus-lens–induced peripheral hyperopic defocus accelerates axial elongation, whereas plus-lens–induced peripheral myopic defocus slows growth [26]. This regulatory process, fundamental to emmetropization, enables the visual system to achieve optimal refractive state. These adaptive changes involve either rapid overall eye growth accompanied by ciliary process thinning (in hyperopic defocus) or growth deceleration with ciliary process thickening (in myopic defocus) (Figure 3). This bidirectional feedback represents a core mechanism of emmetropization. Birds exhibit broad compensation ranges (−10 D to +15 D in chicks), whereas mammals including humans have narrower ranges (e.g., −2 D to +8 D in rhesus monkeys) [11, 23].

In humans, evidence suggests that persistent hyperopic defocus at the peripheral retina may drive progressive myopia [25]. Importantly, while the emmetropization system normally allows for recovery when defocus stimuli are removed, in children exposed chronically to NW or inappropriate optical correction, compensatory growth becomes maladaptive. Clinical trials have shown that full correction with minus lenses may inadvertently exacerbate axial elongation, whereas strategies employing peripheral myopic defocus (e.g., orthokeratology, multifocal contact lenses) can slow progression [27, 28].

Emmetropization functions as an open feedback loop, modulating eye growth in response to refractive error. Even in cases of minimal refractive error, such as −1.0 D myopia, the emmetropization system actively stimulates corresponding axial growth. This compensatory mechanism can become problematic when full myopic correction is prescribed, creating a continuous feedback loop of axial elongation in response to the corrective lens [27]. This phenomenon has been likened to “a donkey chasing a carrot it carries on an extended rod from its body”, where the correction itself perpetuates further myopic progression.

This theory gains support from clinical observations showing myopia progression rates approximately tripling in children following optical correction with minus lenses, a phenomenon

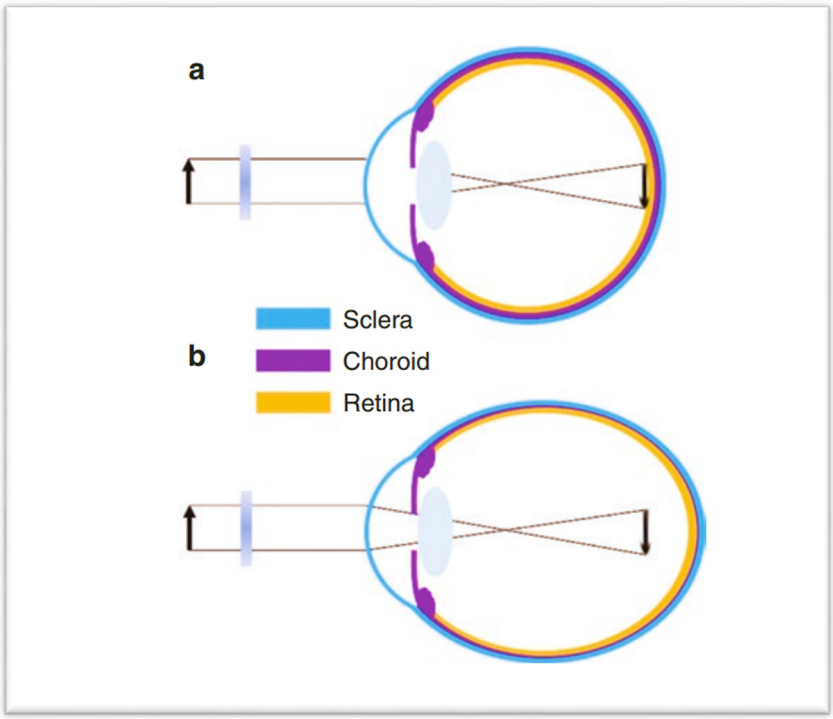


**FIGURE 2** | How the visual system compensates for form-deprivation (FD). (a) Semi-transparent diffuser placed before the eye results in a non-directional blur that decreases retinal image contrast. (b) Myopia develops when no visual feedback is present about the state of refraction due to choroidal thinning and elongation of the eyeball [11, 25].

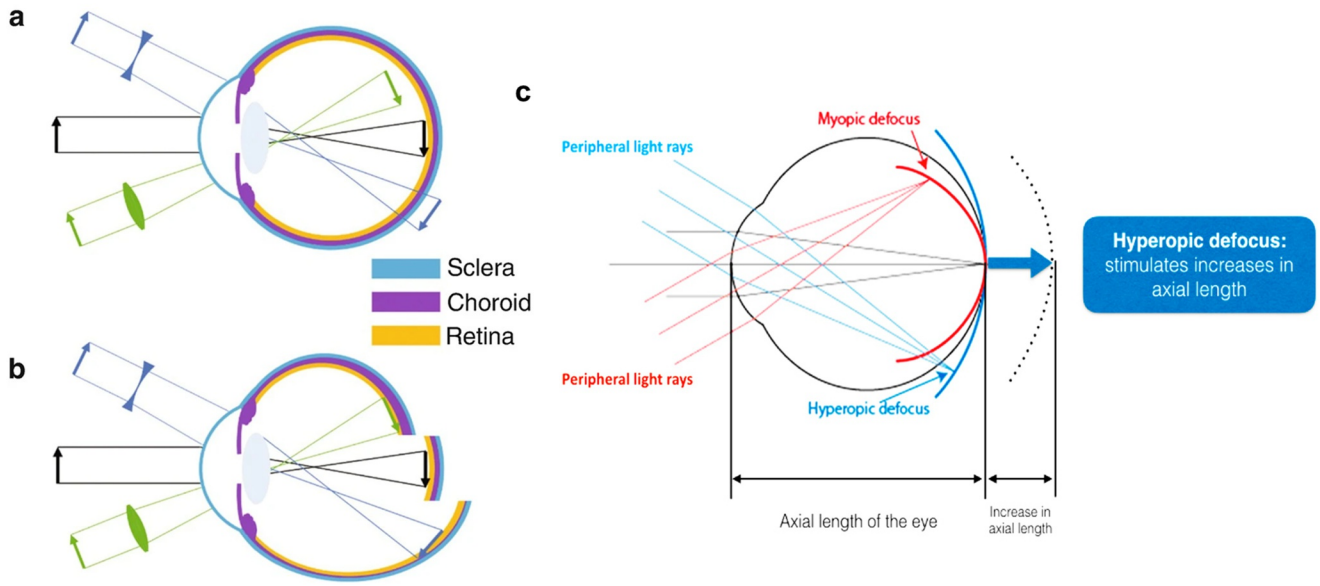


**FIGURE 3** | Peripheral retinal defocus modulates eye growth. (a) Induced lens defocus illustration. The black arrow indicates the normal circumstance with light rays from infinity incident on the retina without any external lens. A green convex lens results in forming a myopic-defocus peripheral retinal image (green arrow). A blue concave lens causes hyperopic-defocus (HD) peripheral retinal image (blue arrow). (b) The black arrow represents how an emmetrope with no induced defocus grows in length and choroidal thickness. Plus lenses (green) induce myopic defocus that causes choroidal thickening and reduces the total development of the eye which eventually causes far-sightedness. Also, minus lenses (blue) induce hyperopic defocus resulting in the thinning of the choroid, elongating the eyeball to cause myopia. (c) Combined changes to the length of the eyeball to compensate for peripheral defocus [11, 14, 25].

termed "myopia depression" [27]. A significant study of 605 young participants (ages 6–14) documented this effect, showing marked myopic acceleration following minus lens correction in the fifth year of follow-up [28]. The study revealed that while emmetropes maintained stable refraction under identical environmental conditions, myopic subjects experienced dramatic progression post-correction, with intergroup differences expanding from 0.5 D pre-correction to significantly larger disparities afterward.

The open loop feedback model further suggests that myopia progression accelerates with over-correction or inappropriate minus lens prescription but stabilizes with partial or under-correction. This understanding has practical implications for myopia management, suggesting strategic approaches such as limiting corrective lens use during certain activities. The established correlation between full minus lens correction and accelerated myopia progression provides compelling evidence for the causal relationship between minus lenses and myopia progression. Together, these experimental paradigms demonstrate that persistent hyperopic defocus, whether induced optically or behaviorally, can drive maladaptive axial growth.

### 2.6 | Retinal, Neurochemical and Genetic Signaling Pathways

Visual signals arising from optical defocus and light exposure are transduced by the retina into neurochemical and molecular pathways that regulate ocular growth, providing the biological link between environmental inputs and structural remodeling. Among these, retinal dopamine has emerged as a key inhibitory modulator of axial elongation, with higher light intensity, particularly outdoor daylight—stimulating dopamine release and suppressing excessive eye growth [29]. Dopamine signaling interacts with downstream molecular pathways governing extracellular matrix turnover, scleral biomechanics, and choroidal thickness, including growth factor– and matrix metalloproteinase–mediated processes that ultimately shape axial length. Genetic susceptibility further modulates these signaling cascades, with variants in genes related to retinal development, light-responsive pathways, and scleral remodeling influencing individual sensitivity to optical and environmental stimuli. Importantly, these gene-environment (GxE) interactions help explain the marked interindividual variability in myopia onset and progression under similar visual conditions. Together, retinal neurochemical signaling and genetic modulation form a convergent biological substrate through which behavioral and environmental risk factors exert their effects, providing a mechanistic foundation for the risk-based and translational analyses developed in the subsequent sections. These insights provide a biological framework through which environmental and behavioral risk factors exert their effects on myopia development and progression.

## 3 | Environmental and Individual Risk Factors Through a Mechanistic Lens

### 3.1 | Mechanism-Informed Risk Factors for Myopia Progression

Building on the integrated pathogenic framework outlined above, this section examines major environmental and

individual risk factors for myopia through a mechanistic lens. Rather than treating these factors as isolated associations, we evaluate how each interferes with vision-guided growth regulation, optical signaling, and structural remodeling pathways. This approach clarifies why certain exposures consistently increase risk and informs the development of targeted strategies for myopia control.

### 3.2 | Near Work and Sustained Hyperopic Defocus

Epidemiological evidence increasingly highlights lifestyle and behavioral factors as key contributors to the rising prevalence of myopia worldwide. Among these, NW has received particular attention due to its strong association with both myopia onset and progression in children. Understanding how NW interacts with underlying biological mechanisms of refractive development is therefore essential for linking experimental findings to real-world risk factors.

While experimental models have demonstrated how optical defocus influences refractive development, understanding environmental factors, particularly NW, is crucial for comprehending myopia development in real-world contexts. Activities at near sight, which have increased dramatically in modern societies, represent a significant environmental factor that may interact with these basic mechanisms of refractive development to influence myopic progression. NW's contribution to myopia development demonstrates a causal relationship similar to that observed with lens-induced defocus. During close-range activities, myopic individuals typically exhibit increased accommodative lag, resulting in hyperopic retinal blur that can trigger abnormal axial elongation [30]. This mechanism is supported by observations of reduced accommodative responses in myopic versus emmetropic individuals, indicating an impaired ability to respond effectively to blur. As illustrated in Figure 4, this decreased accommodative response creates a hyperopic retinal blur pattern that activates the eye's emmetropization mechanism, subsequently promoting compensatory axial growth and myopia progression. This mechanistic understanding has important clinical implications: when children with myopia use plus lenses for near activities such as reading, the accommodative lag decreases, reducing hyperopic blur at the fovea. Consequently, this intervention may prevent abnormal axial elongation and potentially halt myopia progression [31].

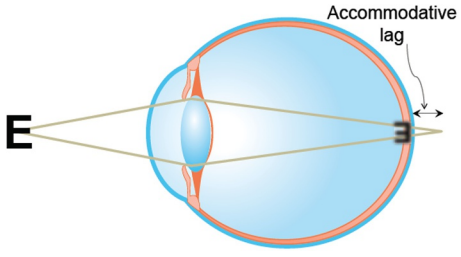


**FIGURE 4** | Myopic individuals typically exhibit increased accommodative lag, resulting in hyperopic retinal blur that can trigger abnormal axial elongation. Accommodative lag forms hyperopic blur on the retina during reading due to inadequate response to accommodation [14, 30].

The open-loop feedback model establishes a fundamental equivalence between close activities and negative lens use. The innate axial elongation response triggered by minus lens correction parallels the effects of NW. This principle demonstrates that viewing a target through a minus lens of power 1/f is optically equivalent to directly viewing the same target at distance f, maintaining identical visual angles. For instance, viewing an object at 2 m produces the same optical effect as viewing it through a −0.5 D lens [27, 32]. Both scenarios generate identical retinal images and trigger similar physiological responses, including ciliary body accommodation and pupillary miosis. This optical equivalence suggests that negative lens use and close activities may contribute equally to myopia development and progression.

The relationship between NW, particularly computer use, and myopia development has been extensively documented. Research demonstrates significant correlations between myopia development and the intensity of NW and close working distances. Conversely, increased outdoor time appears protective against myopia development [33–35]. Recent studies measuring light intensity and working distance revealed that children without refractive errors experience significantly higher light exposure levels and maintain greater working distances compared to their myopic counterparts [33]. Enthoven et al.'s research on axial elongation established significant correlations between computer use and outdoor exposure, noting that increased outdoor activity diminished the impact of NW on myopia development [36]. Notably, traditional reading activities, typically involving shorter working distances than computer use, may pose a greater risk for myopia development.

The relationship between close activities and myopic progression was further highlighted by Woodman et al. [37] who demonstrated increased axial elongation following prolonged near tasks in both early-onset myopia (EOM) and progressive myopia (PM) groups compared to emmetropes. Environmental factors, including urban versus rural dwelling and school type, significantly influence children's indoor-outdoor activity patterns and, consequently, their myopia risk. Guo et al. [38] confirmed this association, finding significant correlations between myopia development and reduced outdoor time combined with increased indoor activities, particularly reading. Additional evidence suggests that sustained reading periods exceeding 30 min and close working distances under 30 cm, as reported by parents, correlate with myopia incidence and development [39].

The mechanisms underlying the relationship between NW and myopia development, while complex, have been investigated through various theoretical frameworks and experimental studies. A pivotal animal study using guinea pigs demonstrated the comparative effects of different myopia-inducing conditions: NW, FD, and hyperopic-defocus (HD) [40]. In this study, animals exposed to shorter viewing distances over 14 days showed significantly greater myopic shifts in refraction and axial parameters compared to those with medium or long viewing distances. Notably, the NW mechanism closely paralleled HD-induced myopia, suggesting that animals struggled to compensate for close-viewing-induced defocus [40].

The high prevalence of myopia among individuals engaged in prolonged near activities supports the hypothesis that chronic hyperopic defocus, resulting from accommodative lag, significantly influences myopia development in young populations [41, 42]. Recent investigations into electronic display use have revealed potential contributions to myopia development through two pathways: reduced outdoor exposure (diminishing the protective effects of daylight) and induced hyperopic defocus [35, 41, 43, 44]. This defocus may arise from either elevated accommodative lag during device use or extended exposure to NW [41]. Interestingly, studies have shown that children experience mild hyperopic defocus during electronic device use, with non-myopes showing slightly greater defocus than myopes [41]. This challenges earlier hypotheses about the role of accommodative lag's role in myopia development, though age-related differences between study groups may have influenced these results. Current evidence suggests that modern electronic devices may not be more detrimental than traditional near tasks, as they induce comparatively lower levels of hyperopic defocus [41].

Near work-induced transient myopia (NITM) represents another potential mechanism linking NW to myopia progression. Research by Vera-Díaz and colleagues revealed that progressing myopes exhibited shallower accommodation response gradients and greater accommodation inaccuracies compared to emmetropes and stable myopes, resulting in enhanced retinal defocus and potential eye growth [45]. The study demonstrated higher NITM levels in both early and late-onset myopes compared to emmetropes, suggesting that even small defocus levels (approximately 0.3 D) may contribute to myopia development and progression [45, 46]. Supporting this hypothesis, Ciuffreda et al. [47] observed significant myopic refractive changes in both myopic and emmetropic individuals following 1 h of NW. These findings collectively suggest that NITM-induced axial length changes may contribute to permanent myopic development.

### 3.3 | Urbanization, Educational Pressure and Lifestyle Intensification

The global rise in myopia has been strongly associated with rapid urbanization, underscoring the critical role of environmental and lifestyle factors in refractive development. Urban living is typically characterized by heightened educational demands, pervasive use of digital devices, and limited exposure to natural outdoor light. These elements interact with biological mechanisms that regulate eye growth, contributing to the increasing prevalence of myopia. As urbanization continues to expand globally, particularly affecting younger populations, understanding these associations becomes increasingly important for early intervention and prevention strategies.

One key environmental factor linked to urbanization is NW activity, which is considered a modifiable risk factor for myopia development. Although numerous studies have reported correlations between higher educational attainment and increased myopia prevalence, the underlying mechanisms remain speculative [48, 49]. In contrast to rural settings, which often feature lower educational demands and limited access to digital infrastructure, urban environments tend to offer better socioeconomic conditions, more rigorous academic expectations, and greater access to internet and digital technologies. These factors contribute to a lifestyle in which children and young adults spend more time indoors engaged in educational and screen-based activities, and less time outdoors exposed to ambient light. This reduction in outdoor activity has been consistently associated with a higher risk of both myopia onset and progression.

### 3.4 | Outdoor Light Exposure as a Protective Biological Signal

Among environmental risk factors, outdoor light exposure has emerged as one of the most consistent protective influences against myopia onset and progression. Unlike NW and urbanization, which increase risk through behavioral and lifestyle pressures, time outdoors provides a biological counterbalance by modulating ocular growth through multiple light-dependent mechanisms. These include dopamine-mediated signaling in the retina, the regulation of circadian rhythms, and the influence of spectral composition, particularly short-wavelength light. Understanding these mechanisms is essential to designing effective public health interventions that leverage outdoor exposure as a practical, modifiable strategy for myopia prevention.

Recent studies have consistently reported that greater exposure to outdoor light is associated with lower risk of myopia development, with increased time outdoors corresponding to reduced prevalence [50, 51]. Children who spend less time outdoors likely experience insufficient exposure to ambient light, increasing their risk of developing myopia. For example, one large-scale study found that allowing children an additional hour outdoors daily was associated with an approximate 2% reduction in incident myopia [43]. Similarly, longitudinal data demonstrated that children who engaged in outdoor activity for $\geq$ 14 h per week had the lowest risk of developing myopia [50]. Meta-analyses confirm that even 40–80 min of daily outdoor exposure significantly lowers myopia onset [52, 53]. These findings emphasize that habitual outdoor light exposure modulates axial elongation, with children exposed to moderate-to-high levels of daylight showing slower eye growth compared to those with limited exposure.

Mechanistically, outdoor light is thought to protect against myopia through several interrelated pathways. The most widely studied is the dopamine hypothesis, which posits that high light intensity stimulates dopamine release from the retina, acting as a “stop” signal for axial elongation and thereby slowing myopia progression [29]. However, dopamine is unlikely to act in isolation. Emerging evidence highlights the importance of spectral composition—the balance of different light wavelengths in regulating eye growth. Experimental studies suggest that short-wavelength (violet/blue) light (400–500 nm) may provide additional protection by inducing a hyperopic shift and inhibiting abnormal elongation [54, 55]. Exposure to natural blue light from sunlight also helps regulate circadian rhythms, which may indirectly influence ocular growth and

emmetropization. By contrast, excessive exposure to artificial blue light sources such as LED lighting and digital screens does not replicate these protective effects and may instead disrupt circadian regulation, contributing to visual fatigue and potentially exacerbating myopia risk [56].

Together, these findings suggest that both quantity (duration/intensity) and quality (spectral balance) of light exposure are critical in shaping ocular development. The protective role of outdoor light highlights a unique and modifiable pathway for myopia prevention, underscoring the need for interventions that increase safe daylight exposure in children. Unlike NW and urbanization, outdoor exposure represents a modifiable protective factor that directly counteracts axial elongation through light-dependent retinal signaling.

### 3.5 | Accommodation: Initiator or Progression Modifier?

Accommodation, the process by which the eye adjusts its optical power to maintain clear vision at near distances, has long been implicated in theories of myopia development. The interplay between accommodative function, retinal image quality, and axial eye growth has drawn attention to mechanisms such as accommodative lag and associated hyperopic defocus during NW. While these factors have been proposed as contributors to the onset of myopia, accumulating evidence suggests their role may be more nuanced, particularly in distinguishing between initiation and progression. Understanding this temporal relationship is essential, as it directly informs the design of optical interventions, such as multifocal lenses and contact lenses, aimed at altering accommodative demands to slow myopia progression.

The relationship between accommodative response and myopia presents a complex picture, particularly regarding the role of accommodative lag in myopia onset versus progression. Mutti et al.'s research revealed that accommodative lag was not significantly elevated in pre-myopic individuals compared to emmetropes, regardless of refractive correction [29]. However, they observed increased accommodative lag, accompanied by hyperopic defocus and axial elongation, after myopia onset, suggesting its role in progression rather than initiation. This temporal relationship is further supported by studies showing that the highest accommodative lag appears in individuals with established, stable myopia, indicating that altered accommodative response may be a consequence rather than a cause of myopia [54].

Contact lens studies have provided additional insights into this relationship. Cheng et al. demonstrated that soft contact lenses with positive spherical aberration reduced accommodative response and induced exophoric shifts. They noted that the efficacy of relative plus lenses in myopia control might be compromised in children with decreased accommodative response, as these individuals may still experience hyperopic defocus during near tasks [55].

However, contradictory evidence exists. Chen et al. found no significant correlation between myopia progression and various accommodative parameters, including lag area, accommodative stimulus-response curves (ASRC) slope, and distance accommodative facility [56]. This discrepancy has led to several hypotheses: first, that myopia onset and progression may involve distinct mechanisms; second, that accommodative lag might be a consequence rather than a cause of myopia [29, 56]; and third, that myopia development represents a complex, multifactorial process extending beyond accommodation alone [56].

Supporting these alternative perspectives, additional research has failed to establish a significant relationship between near accommodative lag and myopia progression in children with mild, progressive myopia [57]. Weizhong et al.'s findings that myopia progression rates were not necessarily higher in subjects with high near accommodative lag suggest that near accommodative lag may not be a primary driver of myopia progression post-onset [57]. This implies that interventions targeting near lag reduction might have limited clinical significance in preventing myopia progression.

The inconsistencies in research findings may be attributed to methodological variations across studies. Different experimental conditions, participant characteristics, and measurement techniques could account for the conflicting results regarding the relationship between accommodative lag and myopia progression. These discrepancies highlight the need for further research to elucidate the precise nature of the accommodation-myopia relationship, particularly through standardized, longitudinal studies that can better control for confounding variables.

### 3.6 | Higher-Order Aberrations and Optical Quality Signals

Beyond refractive error and accommodation, subtle optical imperfections in the eye known as higher-order aberrations (HOAs) have emerged as an important area of investigation in myopia research. These aberrations influence retinal image quality in ways that extend beyond simple defocus and astigmatism, potentially providing cues that regulate ocular growth. While HOAs are often viewed as detrimental to visual performance, their relationship with myopia development is complex, with evidence suggesting both risk-enhancing and protective roles. Understanding these mechanisms is particularly significant, as they provide the foundation for novel optical interventions, such as orthokeratology and specially designed contact lenses, that aim to harness or manipulate aberrations to slow myopia progression.

HOAs demonstrate complex relationships with refractive error development and axial elongation. These optical defects, which degrade image quality, are influenced by multiple factors including pupil diameter, age, and accommodation [58]. Research has particularly focused on the role of spherical aberrations in accommodation and refractive development [59–61].

Studies have demonstrated that manipulating spherical aberrations through contact lens wear can significantly impact retinal image quality. Specifically, transitions from positive to negative spherical aberrations have been shown to improve retinal image quality [60]. The relationship between spherical aberrations and

accommodation reveals a distinctive pattern: positive spherical aberrations tend to induce accommodative lag, while negative spherical aberrations reduce it [59, 61]. This finding has important implications for myopia development, as positive spherical aberration-induced accommodative lag may promote hyperopic defocus, potentially stimulating axial elongation.

While some research has associated HOAs with increased myopic refractive error and compromised visual performance under low luminance and contrast conditions, longitudinal studies have revealed unexpected protective effects. A 2-year study of young Chinese Hong Kong children demonstrated that HOAs might slow axial length growth [62]. Specifically, the root mean squares of HOAs, spherical aberrations, vertical trefoil, and oblique trefoil showed positive correlations with reduced axial growth. This finding supports the hypothesis that HOAs may provide optical signals that inhibit myopia progression, contrasting with the effects of peripheral hyperopic defocus. This principle has been successfully applied in orthokeratology treatment for myopia control [63].

The distinct patterns of HOAs observed between emmetropic and ametropic eyes have significant clinical implications. Understanding these differences not only helps predict ametropia progression but also informs the development of control measures, including the optimization of laser-assisted in situ keratomileusis (LASIK) procedures [58]. These findings underscore the complex role of optical quality in refractive error development and the potential for manipulating HOAs in myopia management strategies.

### 3.7 | Gene-Environment Interaction and Individual Susceptibility

The development of myopia cannot be attributed to either genetic or environmental influences alone; instead, it arises from a complex interaction between inherited susceptibility and lifestyle-related exposures. Genome-wide association studies (GWAS) have identified hundreds of genetic variants linked to ocular growth and refractive error, yet their penetrance is strongly modulated by environmental factors such as NW and time spent outdoors. Understanding these GxE interactions is crucial, as they explain why some individuals develop high myopia under identical exposures that leave others unaffected. This framework not only enhances our understanding of disease mechanisms but also opens pathways for tailored prevention strategies that integrate both genetic risk profiling and lifestyle modification.

A complex interplay between genetic susceptibility and environmental risk factors influences the development and progression of myopia. The synergistic effect in this interaction suggests that genetically predisposed individuals are more likely to develop the condition when exposed to specific environmental factors.

GWAS strategies have revealed the complexity of the myopic trait, presenting many genetic variants. Research has identified numerous loci that contribute to myopia, particularly *MYOC*, *PAX6*, *COL2A1*, and *ZC3H11B*, which are associated with eye growth, refractive development, and retinal signaling [64, 65]. In a GWAS review of meta-analysis, candidate genes such as *PAX6* and *TGFB1* showed inconsistent associations with myopia, highlighting the ambiguity of its genetic architecture. It is anticipated that future genetic risk score prediction models will broaden clinical applicability by improving individualized risk assessment and enabling early intervention.

Evidence from GxE studies further illustrates the modifying role of environmental exposures. In North America, interaction analyses showed that single-nucleotide polymorphisms (SNPs) in matrix metalloproteinase genes (*MMP1–MMP10*) were associated with refractive error only in individuals with lower levels of education [66]. In Singapore, variants in *DNAH9*, *GJD2*, and *ZMAT4* were associated with a stronger myopic effect among individuals with higher education levels [67]. Similarly, other studies in children suggest that genetic interactions with NW and time outdoors involve up to 39 SNPs, though the strength of evidence remains limited.

Importantly, recent work has highlighted the role of the vasoactive intestinal peptide receptor 2 (*VIPR2*) gene in modulating ocular growth in interaction with outdoor activity. He et al. demonstrated that the *VIPR2* polymorphism rs2071623 interacts with time outdoors to regulate axial length in Han Chinese children, with those carrying risk alleles showing greater axial elongation when outdoor exposure was insufficient [68]. This finding underscores the importance of light-related signaling pathways in mediating GxE effects and suggests that outdoor activity may mitigate genetic susceptibility in some populations.

Altogether, these findings highlight that individuals with high-risk genetic variants exhibit greater myopia progression under conditions of prolonged NW or reduced outdoor exposure. The higher prevalence of myopia in urban environments can therefore be understood as the amplification of genetic predisposition by modern lifestyle factors such as intensive education, screen use, and limited outdoor activity [66–68]. Understanding these synergistic interactions will be essential for designing personalized prevention strategies, integrating genetic profiling with targeted lifestyle modifications and early clinical interventions for at-risk children.

## 4 | Clinical Management and Intervention Strategies

### 4.1 | Management Classification and Intervention Strategies

Advances in the understanding of myopia pathogenesis have transformed clinical management from simple refractive correction to biologically informed strategies aimed at modifying disease progression. Contemporary interventions differ not only in efficacy, but also in their primary therapeutic goal—whether to restore visual acuity, to modulate ocular growth, or to achieve both simultaneously. In this section, we classify current myopia interventions according to their functional role and underlying mechanisms, thereby linking basic optical and biological principles to clinical decision-making.

We examine the current landscape of myopia interventions across three primary domains: optical treatments, environmental modifications, and pharmacological approaches. Interventions for myopia can be categorized into two groups, geared towards myopia correction and control/prevention. Interventions for myopia correction focus on improving vision by compensating for refractive error but do not show or prevent myopia progression. On the other hand, strategies for myopia control and prevention aim to prevent myopia onset and slow myopia progression. We evaluate the efficacy, safety profiles, and appropriate target populations for each intervention strategy, providing clinicians with a comprehensive framework for developing personalized myopia management plans based on patient-specific factors, including age, progression rate, and risk profile. Figure 5 presents the flowchart of current clinical intervention strategies for myopia management.

### 4.2 | Purely Corrective Interventions: Vision Restoration Without Growth Modulation

These interventions improve retinal image focus by compensating for refractive error but do not alter the biological mechanisms driving axial elongation. Various optical interventions, such as single vision spectacles, standard or progressive soft contact lenses, and refractive surgeries, have emerged as effective strategies for myopia correction. Single vision and progressive contact lenses have shown varying degrees of success (Figure 5). The correction of myopia evaluation trial (COMET), a landmark 3-year study by Gwiazda et al. [69] demonstrated that progressive addition lenses (PAL) were more effective than single vision lenses (SVL) in controlling myopia progression, particularly in patients with lower degrees of myopia. The treatment effect was most pronounced in subjects with larger accommodative lag, closer reading distances, and extended near activities, suggesting that PALs may be particularly beneficial for children with these characteristics by minimizing retinal defocus.

Refractive surgeries such as laser-assisted in situ keratomileusis (LASIK), photorefractive keratectomy (PRK), and small incision lenticule extraction (SMILE) primarily serve corrective rather than control functions. These procedures reshape the corneal curvature to correct refractive error but do not influence axial elongation mechanisms. LASIK, introduced in the early 1990s, ablates corneal stroma beneath a flap and is recommended for up to −10.00 D of myopia to minimize ectasia risk [70, 71]. SMILE, a minimally invasive alternative, offers faster recovery and reduced postoperative dryness with comparable refractive outcomes [72].

Despite their efficacy, 96% of LASIK patients achieve visual acuity of 20/40 or better and over 67% reach 20/20 or better—these procedures are restricted to adults with stable refraction and primarily address visual correction, not myopia progression [70, 71]. While single-vision spectacles, standard contact lenses, and refractive surgical procedures remain highly effective for restoring visual acuity, they do not address the biological mechanisms driving axial elongation. As such, their role in pediatric myopia management is inherently limited, underscoring the need for interventions that extend beyond optical correction to actively influence disease progression.

### 4.3 | Dual-Function Interventions: Simultaneous Correction and Myopia Control

A defining advance in myopia management has been the emergence of interventions that combine refractive correction with active modulation of eye growth. These dual-function

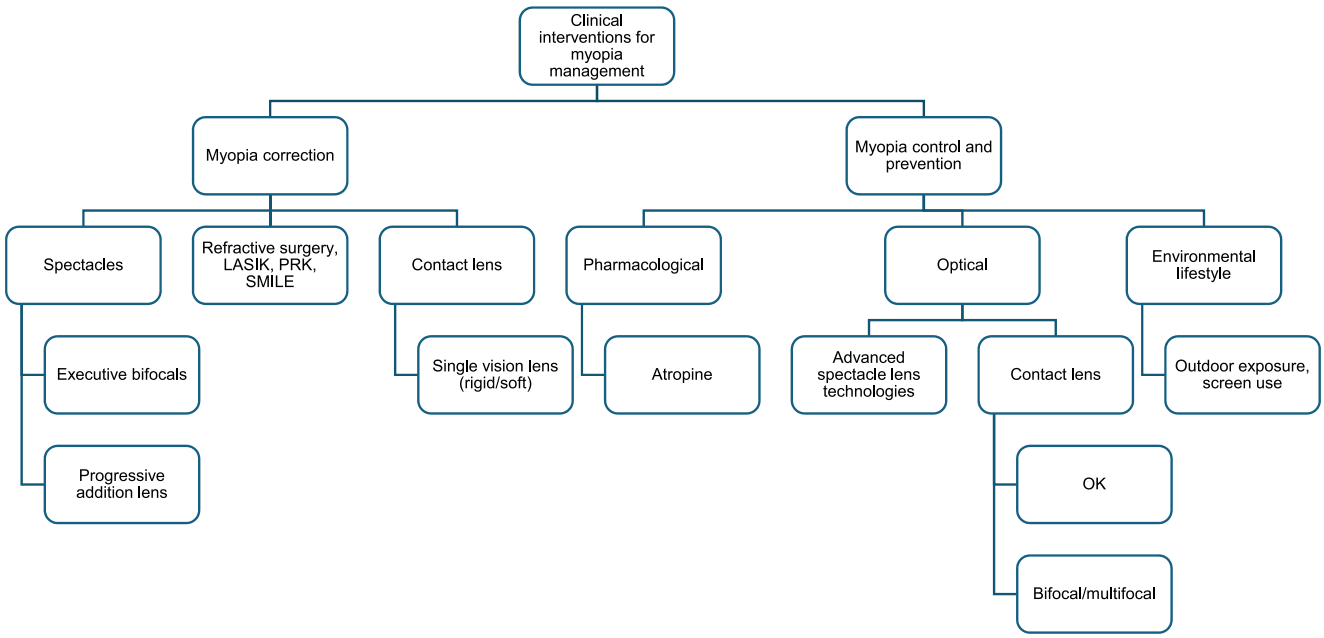


**FIGURE 5** | A flowchart of current clinical intervention strategies for myopia management.

strategies exploit the eye's sensitivity to peripheral defocus, retinal contrast, and choroidal signaling to slow axial elongation while maintaining functional vision. Their effectiveness directly reflects the mechanistic pathways outlined in Parts II and III. We outline a clinically oriented framework for myopia control and prevention, integrating evidence-based interventions that span optical correction, pharmacological treatment, and behavioral modification. By categorizing strategies according to their mechanisms and clinical utility, this section aims to guide eye care professionals, researchers, and educators in selecting and optimizing interventions tailored to individual patient profiles and population-level needs.

Myopia control and prevention strategies have evolved from traditional optical correction to an integrated framework that combines optical, surgical, pharmacological, and behavioral approaches. This evolution reflects the growing understanding that myopia is a multifactorial condition involving visual experience, ocular biomechanics, and genetic susceptibility. Efforts to control or prevent myopia have traditionally focused on optical interventions that correct refractive error or slow axial elongation. However, emerging evidence suggests that many modern approaches, particularly orthokeratology and specialized spectacle lenses, serve dual functions. These approaches simultaneously correct vision and modulate the biological processes that drive myopia progression.

To clarify this framework, interventions can be grouped into three categories. First, corrective interventions, which restore refractive focus without altering eye growth mechanisms (e.g., LASIK, PRK, SMILE); second, control interventions, which directly modulate ocular growth through optical or biomechanical cues (e.g., orthokeratology, DIMS, HALT, CARE lenses), and third, dual-function interventions, which combine refractive correction with active control mechanisms (e.g., orthokeratology, customized multifocal designs, and emerging lens technologies that manipulate HOAs or choroidal signaling). Understanding these overlapping mechanisms is critical, as several interventions achieve their effects not merely by correcting refractive error, but by modifying peripheral image defocus, retinal contrast, and choroidal perfusion, pathways known to influence scleral remodeling and axial elongation [71, 73–76]. Dual-function interventions represent a paradigm shift in myopia management by integrating refractive correction with biologically informed control mechanisms. By modifying peripheral defocus, retinal contrast, and choroidal signaling, these approaches directly target the pathways responsible for axial elongation, positioning them as cornerstone therapies in contemporary clinical practice.

#### 4.3.1 | Orthokeratology

Among optical strategies, overnight orthokeratology (OK) has emerged as one of the most effective dual-function interventions. It employs rigid gas-permeable lenses worn overnight to reshape the corneal curvature, temporarily correcting myopia and inducing peripheral myopic defocus that slows eye growth. Long-term studies confirm its clinical utility: Hiraoka et al. [77] reported sustained reductions in myopia progression over 5 years compared to spectacles, although the effect plateaued after the third year. Similarly, Santodomingo-Rubido et al. [78] found a 33% reduction in axial elongation rate over 7 years of OK wear relative to single-vision correction. Lee et al. [79] extended this evidence with a 12-year follow-up showing lower annual refractive change (0.2–0.3 D/year) compared to 0.4–0.5 D/year with spectacles.

Mechanistically, OK lenses reshape the anterior cornea to generate peripheral myopic defocus, reducing the hyperopic peripheral blur that triggers axial elongation. Li et al. [73] reported that OK-induced choroidal thickening correlated with reduced axial elongation after 3 weeks, supporting the hypothesis that OK stabilizes refractive development via choroidal and retinal signaling. However, its long-term safety requires ongoing surveillance. Complications include hypoxia, infection, and endothelial cell density reduction, which can compromise corneal clarity and cause refractive regression after discontinuation [80].

OK exemplifies a mechanism-driven dual-function intervention, combining effective refractive correction with robust modulation of peripheral defocus and choroidal thickness. Despite safety considerations that necessitate careful patient selection and monitoring, its sustained efficacy highlights the therapeutic potential of optical strategies that directly engage growth-regulatory pathways.

#### 4.3.2 | Advanced Spectacle Lens Technologies

Myopia control spectacle lenses represent the most rapidly evolving category, utilizing advanced optics to manipulate retinal image quality. Designs such as defocus incorporated multiple segments (DIMS), highly aspherical lenslet target (HALT), diffusion optics technology (DOT), and cylindrical annular refractive element (CARE) lenses use distinct mechanisms to achieve control or dual-function outcomes.

- DIMS lenses create simultaneous clear and defocused retinal images, using +3.50 D peripheral defocus segments to reduce axial elongation [26, 81].
- HALT lenses extend this concept by producing a volume of myopic defocus—distributed in three-dimensional space—rather than two fixed planes [82].
- DOT lenses apply diffusers to reduce retinal contrast signaling, based on evidence that high-contrast retinal stimulation accelerates ocular growth [75].
- CARE lenses utilize micro-cylinder arrays to induce HOAs in the peripheral retina, introducing controlled blur thought to regulate emmetropization and restrain axial elongation [76].

Clinical trial results in children have been reported for myopia control spectacles, showing promising results (Table 1). Collectively, these designs blur the traditional boundary between correction and control by providing functional vision while simultaneously manipulating the optical environment to suppress myopia progression biologically. Their diverse optical strategies, ranging from myopic defocus induction to contrast diffusion and aberration manipulation, demonstrate that

**TABLE 1** | Summary of clinical trials involving the use of myopic control spectacles.

| | DIMS trial [81] Aged 8–13 years | | HALT trial [74] Aged 8–13 years | | DOT trial [75] Aged 6–10 years | | CARE trial [83] Aged 8–12 years | |
|---|---|---|---|---|---|---|---|---|
| **Clinical trials** | **DIMS ($n$ = 79)** | **Control SV (81)** | **HALT ($n$ = 54)** | **Control SV ($n$ = 52)** | **DOT ($n$ = 83)** | **Control SV ($n$ = 93)** | **CARE ($n$ = 61)** | **Control SV ($n$ = 57)** |
| Refractive progression (cycloplegic spherical equivalent refraction, D) | | | | | | | | |
| 6 months | −0.13 ± 0.03 | −0.37 ± 0.04 | −0.10 ± 0.04 | −0.34 ± 0.04 | NA | NA | −0.38 ± 0.35 | −0.47 ± 0.37 |
| 12 months | −0.17 ± 0.05 | −0.55 ± 0.04 | −0.27 ± 0.06 | −0.81 ± 0.06 | −0.14 ± 0.05 | −0.54 ± 0.05 | −0.56 ± 0.46 | 0.71 ± 0.39 |
| Axial length progression (interferometric measurement, mm) | | | | | | | | |
| 6 months | 0.03 ± 0.01 | 0.20 ± 0.01 | 0.08 ± 0.01 | 0.20 ± 0.01 | NA | NA | 0.19 ± 0.12 | 0.23 ± 0.12 |
| 12 months | 0.11 ± 0.02 | 0.32 ± 0.02 | 0.13 ± 0.02 | 0.36 ± 0.02 | 0.15 ± 0.02 | 0.30 ± 0.02 | 0.26 ± 0.18 | 0.36 ± 0.16 |

Abbreviations: CARE, cylindrical annular refractive element; DIMS, defocus incorporated multiple segments; DOT, diffusion optics technology; HALT, highly aspherical lenslet target; SV, single vision.

spectacle-based interventions can serve as active biological modulators rather than passive corrective devices.

#### 4.3.3 | Multifocal and Bifocal Soft Contact Lenses

Multifocal and bifocal soft contact lenses represent a flexible dual-function approach to myopia control that integrates refractive correction with optical modulation of retinal image formation. By creating simultaneous focal planes on the retina, these lenses reduce central and peripheral hyperopic defocus particularly during NW thereby engaging the same vision-dependent growth-regulatory mechanisms implicated in experimental models of myopia. Their clinical efficacy highlights the importance of accommodative behavior and visual task demands in shaping individual treatment response.

Soft multifocal contact lenses have shown promising results. Studies report approximately a 29% reduction in axial elongation and a 50% decrease in myopia progression rate compared to single-vision controls over 2 years [84]. Both corneal reshaping and soft multifocal contact lenses have demonstrated significant efficacy, reducing myopia progression by 36%–79% [77, 84–90]. The mechanism is thought to involve either induced myopic blur or reduced accommodative demand. The multifocal lens design creates dual focal points—one on the retina and another anterior to it during distance viewing, with the anterior myopic blur potentially serving as a signal to inhibit eye growth, as demonstrated in animal studies [84, 91–93].

Bifocal soft contact lenses (BFSCL) have demonstrated superior efficacy compared to bifocal or PAL spectacles [94]. This advantage may be attributed to practical considerations: while multifocal spectacles require specific head and eye positions for optimal near vision, potentially reducing compliance in children compared to presbyopic adults, contact lenses function independently of gaze direction. Furthermore, traditional multifocal spectacle designs may be impractical for contemporary lifestyles involving extensive computer use [94].

Multifocal and bifocal soft contact lenses provide a flexible dual-function option that leverages simultaneous retinal imaging to reduce hyperopic defocus during near tasks. Their efficacy, particularly in children with accommodative lag or high NW demands, reinforces the principle that optical control strategies must be tailored to individual visual behavior and lifestyle.

#### 4.3.4 | Pharmacological Modulation: Low-Dose Atropine

Pharmacological intervention with low-dose atropine offers a non-optical strategy for myopia control, acting directly on neurochemical pathways that regulate ocular growth. Unlike optical approaches that modify retinal image quality, atropine influences muscarinic signaling and downstream choroidal and scleral responses, providing complementary biological modulation of axial elongation. Its dose-dependent efficacy and side-effect profile have positioned low-concentration atropine (0.01%–0.05%) as a key component of contemporary, mechanism-based myopia management. This has consistently demonstrated a 30%–60% reduction in myopia progression by modulating muscarinic receptor activity and promoting choroidal thickening [95, 96].

The use of atropine has been shown to provide some level of efficacy in slowing down myopia progression among children in Asian population-based studies [95]. However, this intervention is not too popular perhaps due to the side effects associated with the use of atropine in children such as prolonged pupil dilation resulting in glare, photophobia, blurry vision due to loss of accommodation, allergic reactions, hallucination, and risk of increased intraocular pressure, etc. [95]. Moreover, in the course of management especially those involving high doses in younger children, the magnitude of the condition deteriorated when the children discontinued the use of atropine [96]. For its safety profile, some practitioners prefer low-dose atropine (0.01%–0.05%). For these reasons, it is crucial to find the optimal balance between the treatment efficacy and side effects to achieve desirable results. Hence, this treatment option is often not attractive to practitioners but remains a subject of investigation by researchers.

Low-dose atropine offers a non-optical means of modulating ocular growth through neurochemical and choroidal pathways, achieving clinically meaningful reductions in myopia progression. However, variability in response, rebound effects, and tolerability considerations highlight its optimal role as part of a

broader, individualized control strategy rather than a standalone solution.

### 4.4 | Behavioral and Public Health Interventions

In contrast to device-based and pharmacological therapies, behavioral interventions target upstream environmental drivers of myopia, offering scalable, population-level impact. These strategies act primarily by modifying retinal light exposure and neurochemical signaling, thereby complementing clinical interventions. Behavioral interventions especially increased outdoor activity have shown robust protective effects by increasing retinal dopamine release and inhibiting axial elongation. Importantly, He et al. [68] identified a GxE interaction between outdoor activity and the *VIPR2* polymorphism rs2071623, demonstrating that greater outdoor time modulates genetically driven axial growth in children. This finding reinforces the rationale for personalized myopia prevention frameworks that integrate genetic risk with lifestyle modification. Also, lifestyle and behavioral approaches such as increased outdoor time, where more daylight exposure is linked to lower myopia risk and reduced NW and screen time, have been shown to slow myopia by limiting prolonged close-up activities [97, 98]. School authorities and parents can deliberately increase the amount of time children spend outdoors in school and at home to delay myopia onset among children significantly. This intervention has been implemented in Australia through increasing outdoor activities and exposure to high light intensity for school children [12].

Behavioral interventions, particularly increased outdoor exposure, target upstream environmental drivers of myopia by enhancing light-mediated retinal signaling and interacting with genetic susceptibility. Their low cost, scalability, and preventive potential make them indispensable components of both individual-level management and population-based myopia control programs.

### 4.5 | Combination and Personalized Intervention Strategies

Interventions should be targeted at improving the balance between academic achievement and strategies to slow down myopia onset. Combining optical correction (e.g., DIMS or OK) with low-dose atropine or outdoor activity may yield additive or synergistic benefits through converging mechanisms that target both retinal signaling and ocular structural remodeling. Future clinical trials should systematically evaluate multimodal regimens to optimize long-term outcomes.

Given the multifactorial nature of myopia pathogenesis, combination therapies that integrate optical, pharmacological, and behavioral approaches offer the greatest potential for sustained disease control. Aligning intervention selection with individual risk profiles, visual habits, and genetic susceptibility represents a critical step toward personalized, mechanism-based myopia management. A summary of myopia control interventions by function, mechanism, age suitability, and effectiveness, is presented in Table 2.

## 5 | Conclusion and Future Perspectives

### 5.1 | Synthesizing the Evidence: From Mechanisms to Management

The escalating global burden of myopia reflects a convergence of biological susceptibility and modern visual environments that

**TABLE 2** | Summary of myopia control interventions by function, mechanism, age suitability, and effectiveness.

| Intervention type | Example(s) | Primary mechanism | Age suitability | Reported effectiveness | Key references |
|---|---|---|---|---|---|
| Optical—corneal reshaping | Orthokeratology (OK) | Induces peripheral myopic defocus; increases choroidal thickness; slows axial elongation | Children, adolescents | 33%–50% reduction in axial elongation; strongest effect in first 3–5 years | [74, 75, 85, 89–91] |
| Optical—spectacle lens technologies | DIMS, HALT, DOT, CARE | Induce myopic defocus, reduce retinal contrast, or increase peripheral aberrations | Children | 25%–60% reduction in progression depending on design and duration | [26, 86–88, 92–94] |
| Optical—surgical | LASIK, PRK, SMILE | Reshapes cornea for refractive correction; no effect on axial growth | Adults with stable myopia | 67%–96% achieve ≥ 20/40 VA; not preventive for progression | [82, 84] |
| Pharmacological | Low-dose atropine (0.01%–0.05%) | Muscarinic receptor blockade; choroidal thickening; scleral remodeling | Children (≥ 6 years) | 30%–60% reduction in myopia progression and axial elongation | [95, 96] |
| Behavioral/ environmental | Increased outdoor time | Light-induced dopamine release inhibits axial elongation; interacts with *VIPR2* polymorphism rs2071623 | Children, school-aged | Reduces myopia onset risk by about 50%; GxE interaction enhances benefit | [68] |
| Multimodal (dual-function) | OK + atropine; DIMS + outdoor activity | Combined optical and physiological mechanisms (defocus + neurochemical) | Children, adolescents | Additive or synergistic control; up to 60%–70% slower progression | [68, 75, 95] |

Abbreviations: CARE, cylindrical annular refractive element; DIMS, defocus incorporated multiple segments; DOT, diffusion optics technology; HALT, highly aspherical lenslet target; LASIK, laser-assisted in situ keratomileusis; PRK, photorefractive keratectomy; SMILE, small incision lenticule extraction.

has transformed a once-benign refractive condition into one of the most pressing public health challenges of the 21st century. This review has traced myopia from its epidemiological dimensions, affecting 1.9 billion people in 2020 and projected to reach nearly 4.9 billion by 2050, through its mechanistic underpinnings to contemporary intervention strategies, establishing a coherent framework linking environmental inputs to structural outcomes [1, 5].

## 5.2 | Core Arguments and Mechanistic Integration

The central thesis emerging from this synthesis is that myopia development reflects a failure of vision-guided emmetropization in the face of persistent environmental and optical challenges. Environmental factors such as prolonged NW and limited outdoor exposure disrupt normal visual feedback, leading to central and peripheral hyperopic defocus. This optical imbalance triggers biological responses, including retinal dopamine dysregulation and activation of growth factor cascades, which in turn drive structural changes such as choroidal thinning, scleral weakening, and progressive axial elongation. Together, these processes form a causal chain that explains how diverse risk factors converge on a common anatomical outcome and why interventions grounded in these mechanisms can effectively interrupt disease progression [11, 14].

Three principles emerge as foundational for clinical practice: First, there is no safe threshold for myopia. Each additional diopter of myopia incrementally increases the lifetime risk of sight-threatening complications, including myopic maculopathy, retinal detachment, glaucoma, and cataract [6, 8]. This dose-response relationship mandates that myopia control efforts target all affected children, not merely those with high refractive error.

Second, optical and pharmacological interventions achieve their effects through biologically plausible mechanisms. Orthokeratology, DIMS, HALT, DOT, and CARE spectacle lenses, and multifocal contact lenses induce peripheral myopic defocus or modulate retinal image quality, engaging the same growth-regulatory pathways identified in experimental models [26, 73–76]. Low-dose atropine acts through neurochemical modulation of muscarinic signaling, promoting choroidal thickening and restraining scleral remodeling [95, 96]. The convergence of experimental evidence and clinical trial outcomes validates the translational approach underlying contemporary myopia management.

Third, GxE interactions modulate individual susceptibility and treatment response. The *VIPR2*–outdoor activity interaction exemplifies how genetic variants influence the protective effects of environmental exposures, suggesting that uniform public health recommendations may be insufficient for high-risk individuals [68]. This heterogeneity provides the biological rationale for personalized intervention strategies.

## 5.3 | Toward Personalized and Combination Therapy

The evidence synthesized in this review points toward two complementary directions for optimizing myopia management: personalized therapy and combination strategies.

### 5.3.1 | Personalized Therapy

Treatment selection for myopia control must extend beyond comparative efficacy data to incorporate individual patient characteristics. Factors warranting consideration include:

- Age and progression rate: Younger children and rapid progressors may benefit from more aggressive intervention, potentially including combination approaches, whereas older adolescents with stable refraction may require less intensive management.
- Genetic risk profile: As polygenic risk scores and specific GxE interactions (e.g., *VIPR2*, *MMP* genes) become clinically accessible, they may guide both the intensity of intervention and the selection of mechanistically appropriate therapies [66–68].
- Lifestyle and visual demands: Athletes and individuals engaged in water sports may find orthokeratology advantageous, while children with low compliance potential may benefit from spectacle-based solutions such as DIMS or HALT lenses. Pharmacological interventions offer modality-independent control that can complement any optical correction.
- Tolerability and adherence: The success of any intervention depends on sustained compliance. Low-dose atropine's favorable side-effect profile at 0.01%–0.05% concentrations makes it suitable for combination therapy, whereas orthokeratology requires rigorous lens hygiene and monitoring [80, 95].

Eye care practitioners must engage patients and families in shared decision-making, weighing efficacy, safety, practicality, and individual values to optimize both outcomes and adherence.

### 5.3.2 | Combination Strategies

Given the multifactorial pathogenesis of myopia, monotherapy may be insufficient for high-risk or rapidly progressing cases. Emerging evidence supports the rationale for multimodal approaches that engage complementary mechanistic pathways:

- Optical + Pharmacological: Combining orthokeratology or defocus spectacles with low-dose atropine may yield additive or synergistic effects by simultaneously modulating peripheral defocus signaling and neurochemical growth regulation [68, 75, 95].

- Optical + Behavioral: Augmenting optical interventions with structured outdoor time recommendations leverages the protective effects of light-induced dopamine release, particularly in genetically susceptible individuals [68].
- Pharmacological + Behavioral: For children unable to tolerate optical interventions, atropine combined with increased outdoor exposure offers an alternative strategy grounded in complementary biological mechanisms.

Future clinical trials must systematically evaluate these combinations to establish optimal protocols, identify responder phenotypes, and quantify long-term benefits.

## 5.4 | Future Research Priorities

Future research on myopia should prioritize innovations in optical and device design, including optimized defocus-based lenses, spectral composition studies, and smart contact lenses capable of dynamic interventions. Pharmacological strategies require refinement of atropine dosing, exploration of novel agents such as dopaminergic agonists and scleral cross-linking compounds, and evaluation of combination therapies. Mechanistic studies should focus on retinal signaling pathways, scleral extracellular matrix remodeling, and genetic risk stratification through polygenic scores. Finally, technology-driven approaches, including machine learning for predictive modeling, wearable devices for behavioral monitoring, and implementation science to enhance uptake of evidence-based interventions, will be critical to translating research into practice.

## 5.5 | Concluding Remarks

Myopia has evolved from a minor refractive condition to a global epidemic with profound implications for visual health, quality of life, and socioeconomic productivity. The mechanistic framework outlined in this review, which links environmental exposures to optical and neurochemical signaling and structural remodeling, provides a foundation for current interventions and future innovation. Addressing this challenge requires coordinated efforts across public health, clinical practice, education, and research, including promotion of healthy visual behaviors, implementation of evidence-based therapies, and sustained investment in novel strategies. Advances in personalized care, combination treatments, and translational research position the field at a critical juncture. By leveraging these opportunities, the trajectory of the myopia epidemic can be altered to safeguard vision for future generations.

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### Author Contributions

**Victor Opoku-Yamoah:** conceptualization (lead), data curation (lead), investigation (lead), methodology (lead), validation (lead), visualization (lead), writing – original draft (lead), writing – review and editing (equal). **Sahar Khakneshin:** conceptualization (supporting), formal analysis (supporting), investigation (supporting), methodology (supporting), validation (supporting), visualization (supporting), writing – original draft (supporting), writing – review and editing (supporting). **Ebenezer Afrifa-Yamoah:** investigation (supporting), resources (equal), supervision (lead), validation (equal), writing – review and editing (lead).


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