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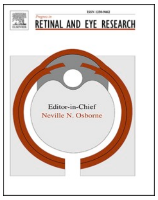

Global perspectives on myopia and pathologic myopia: From environmental drivers to precision medicine

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ABSTRACT

The global prevalence of myopia and pathologic myopia (PM) has dramatically increased, raising significant public health concerns due to associated vision-threatening complications, such as myopic maculopathy (MM). This comprehensive review integrates the latest evidence regarding the environmental, genetic, and epigenetic factors contributing to myopia, as well as recent advances in precision medicine and therapeutic approaches aimed at mitigating the disease's impact. We examine how environmental factors interact with polygenic risk factors and epigenetic changes to influence disease progression. The application of artificial intelligence (AI) enhances the integration of genomic, environmental, and clinical data, thereby improving risk assessment and personalizing treatment options. Therapeutic strategies, including the use of low-dose atropine, orthokeratology, and repeated low-level red-light therapy, have shown promise in controlling myopia. Furthermore, emerging gene-editing techniques are being developed, although they are unlikely to be implemented as treatments for myopia and PM in the near future. Despite these advancements, disparities in resource availability and the implementation of interventions continue to hinder global equity, underscoring the need for scalable solutions such as mobile health applications and community-based preventive programs. This review emphasizes the importance of interdisciplinary collaboration to merge precision medicine with public health strategies, ensuring that scientific breakthroughs are equitably translated into clinical care. By aligning environmental preventive measures, genetic discoveries, and AI-powered innovations, this review outlines a strategic plan for reducing the global burden of myopia and its complications.

1. Overview of myopia

1.1. The global myopia epidemic: trends and projections

Myopia is now considered a public health problem due to the burden induced by high myopia and the risk of visual impairment posed by myopia complications (K. K. W. Li et al., 2023). Although lower levels of myopia have been implicated in the development of vision-threatening conditions (Haarman et al., 2020), higher levels of myopia are most concerning due to higher risk of development of low vision and

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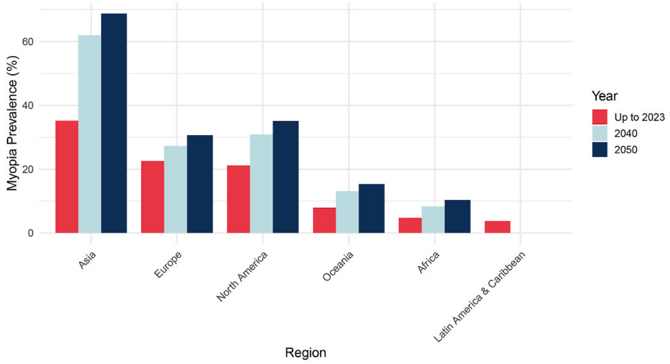
blindness (Cotter et al., 2006; Hsu et al., 2004; Iwase et al., 2006). Furthermore, the consequences of vision loss may impact several other health aspects, such as mental health, as vision loss has been identified as a risk factor for dementia (Livingston et al., 2024). Health expenditure associated with the cost of myopia correction varies between $4 and $755 million US dollars in the United States and Singapore, with significant increases in costs associated with comorbidities such as visual impairment and blindness due to myopic choroidal neovascularization (CNV) or loss of productivity (Lim et al., 2009; Naidoo et al., 2019; Zheng et al., 2013). Thus, myopia prevention should be a global health priority.

In the past decades, myopia rates have risen in several countries, such as China, Singapore and other parts of East Asia (B. Y. Ding et al., 2017; W. Pan et al., 2025a). This rising trend has led to a myopia epidemic, with a noticeable boom over the past three decades (Dolgin, 2015). This trend is quantitatively underscored by a recent comprehensive systematic review, which reported a global prevalence increase from 24.32 % (1990–2000) to 35.81 % (2020–2023) among children and adolescents (J. Liang et al., 2025). Approximately 9 years ago, a systematic review predicted a global increase in myopia by 2050, affecting approximately half of the world's population (Holden et al., 2016). While recent projections are more conservative, estimating a global prevalence of 39.80 % by 2050, the figure still represents a substantial public health concern (J. Liang et al., 2025). The highest prevalence was reported in Asia (35.22 %; Fig. 1), particularly East Asia, where rates exceeded 80 % in some countries, such as Japan (85.95 %). Furthermore, significant regional disparities are anticipated, with Asia projected to have a prevalence of 68.78 % by 2050, compared to 30.69 % in Europe and 35.09 % in North America. Other regions, such as Oceania, Africa and Latin America and the Caribbean, appear to remain with low prevalence, although projections point towards an increases in the near future.

Recently, the prevalence of myopia with cycloplegic refraction in Chinese children under 20 years of age was reported to be 36.6 %, whereas the prevalence of high myopia was 5.3 % (W. Pan et al., 2025a). Notably, a lower prevalence of myopia was found in children aged 0–4 years (2.6 %) than in children aged 15–19 years (67.2 %). In addition, the prevalence of myopia is relatively low in those aged 0–4 years (0.1 %), increasing to 9.5 % in adolescents (15–19 years). In the same study, the highest forecast for the year 2050 was 71.9 %. By contrast, the prevalence of myopia among school-age children in the Eastern Mediterranean region remains low at 5.23 % (Alrasheed and Alghamdi, 2024). Other regions of the world, such as the Middle East, remain underexplored, but research studies published in the last 2 years have reported a prevalence of myopia of 27.4 % in Emirates from Dubai, United Arab Emirates, contrasting with 19.5 % in non-Emirates aged 40 years or older from the Dubai Eye Health Survey (Rabiu et al., 2023).



Data from Liang et al. (2025).

Fig. 1. Prevalence of myopia up to 2023 and projections for 2040 and 2050 among children and adolescents by world region. Data were from J. Liang et al. (2025).

Understanding prevalence data from different regions of the world is essential for evidence-based policymaking, as it allows for strategic planning and equitable allocation of medical resources. By accounting for regional variations in eye health, healthcare systems can tailor interventions, optimize service delivery, and address the specific needs of diverse populations more effectively.

Myopic maculopathy (MM), also known as myopic macular degeneration (MMD), is a hallmark of pathologic myopia (PM). The prevalence of PM increases with higher degrees of myopia, with a 1-diopter increase being associated with an increase in the prevalence of PM by 67 % (Bullimore and Brennan, 2019). A meta-analysis of 12 studies involving 58,558 subjects reported the pooled global prevalence of MM (defined as META-PM category 2, 3, 4, or any "plus" lesion) at 2.1 % (95 % CI: 1.3 %–3.3 %) in 2020 (M. Zou et al., 2020). Another meta-analysis of 16 studies with 71,052 participants further highlighted that the pooled prevalence of MM in high myopia patients reached 49.0 % (95 % CI: 31.5 %–66.7 %) (H. Shi et al., 2024; Vongphanit et al., 2002). However, variations between countries were observed. These regional differences in MM may reflect corresponding variations in global myopia and high myopia rates. However, recent studies have highlighted potential thresholds in this association, noting that the relationship between myopia severity and MM risk may not be perfectly linear (Bullimore and Brennan, 2019) (Fig. 2A). For example, the prevalence of MM was only 0.9 % in rural Chinese individuals aged 30 years or older from the Handan Eye Study (L. Q. Gao et al., 2011). A higher prevalence of 1.2 % was reported in Australian individuals aged 49 years or older from the Blue Mountains Eye Study (Vongphanit et al., 2002). Fig. 2 B shows that the prevalence of MM in adults (30 years and over) was low in Russia (Bikbov et al., 2024), Southern China (Z. Li et al., 2019), Northwestern China (X. L. Zhang et al., 2007), Sydney Australia (Vongphanit et al., 2002), Northern China (L. Q. Gao et al., 2011), Germany (Hopf et al., 2020) and India (Jonas et al., 2017b). By contrast, higher prevalence estimates have been reported in Eastern China (M. Zou et al., 2020), Shihpai, Taiwan (S. J. Chen et al., 2012), Beijing, China (H. H. Liu et al., 2010), Hisayama, Southern Japan (Ueda et al., 2019), Singapore (Y. L. Wong et al., 2018) and Chinese Americans from the USA (Choudhury et al., 2018). Importantly, although Western China seems to have a lower prevalence, the age of the participants is much younger, ranging from 6 to 15 years old (Pi et al., 2012). The incidence of visual impairment due to myopia in this cohort of children was found to be 1.27 %.

A rising trend in the prevalence of MM was observed in the Hisayama Eye Study in Japan, a longitudinal study that tracked the same population over three surveys conducted in 2005, 2012, and 2017. The prevalence of MM increased from 1.6 % in 2005 to 3.6 % in 2017, with a particular rise in the incidence of diffuse chorioretinal atrophy and patchy chorioretinal atrophy (Ueda et al., 2019). The prevalence of MM triples among Singaporean high myopic individuals compared with low- and moderate myopic individuals, increasing with age and spherical equivalent (Y. L. Wong et al., 2018). In addition, best corrected visual acuity decreases in the presence of Meta-PM categories 3 and 4. In individuals of European ancestry with high myopia, the prevalence of MM is 25.9 % (Haarman et al., 2022). In addition to increased rates with older age and a lower spherical equivalent, greater axial length (AL) was also found to be an important risk factor for MM, with risk profiles similar to those of individuals of Asian ancestry.

The global burden of MM is increasing alongside high myopia trends. Individuals with high myopia have an increased lifetime risk of visual impairment up to 22 times when considering myopia of 10D or higher (Verhoeven et al., 2015). A systematic review estimated 10 million cases of MM-related visual impairment (visual acuity worse than 6/18) and 3.3 million cases of blindness (visual acuity worse than 3/60) in 2015, which are projected to surge to 55.7 million and 18.5 million, respectively, by 2050 (Fricke et al., 2018). Specific projections for the US estimate that 27–43 % of individuals may have visual impairment due to myopia by 2050 (Bullimore and Brennan, 2019).

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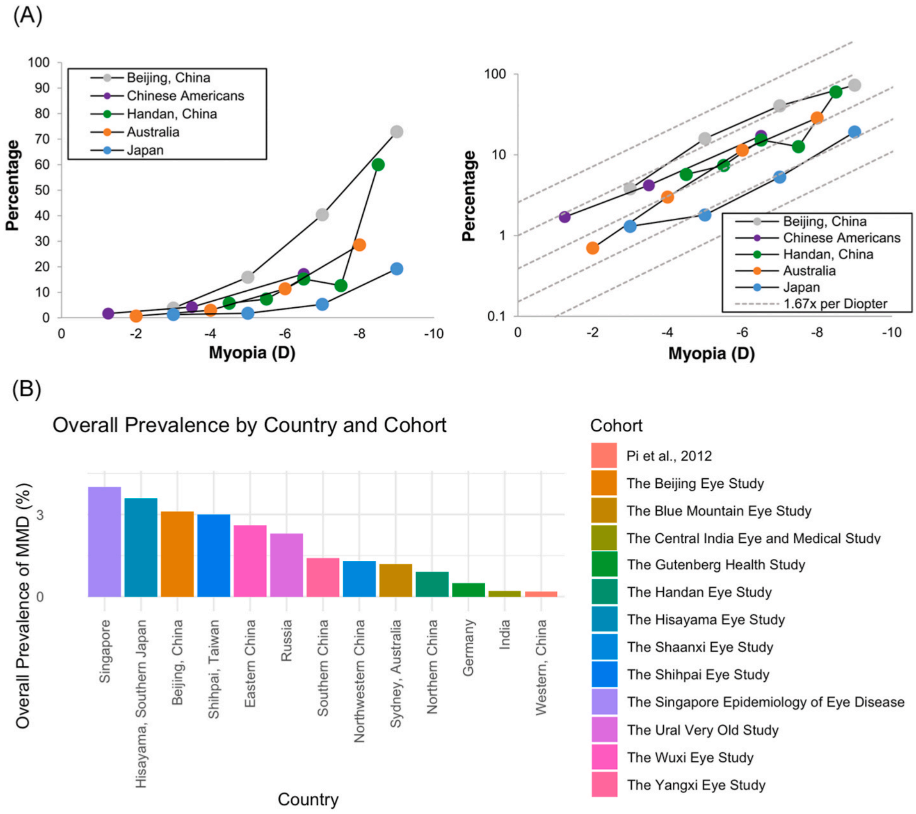


Fig. 2. Prevalence of myopic maculopathy. A displays MM prevalence data plotted via linear (left panel) and logarithmic (right panel) scales (from Bullimore et al.). B presents the overall MM prevalence across different countries and study cohorts.

Limited data on MM and visual impairment are available in other regions, such as South America, Africa and the Middle East. Although country-specific estimates of the prevalence of PM and trends in high myopia prevalence and incidence are available for several countries, a comprehensive and consistent set of estimates, combining historical trends and the most up-to-date data with projections of the future burden of myopia, is needed for as many countries as possible. Countries projected to retain a high prevalence of myopia in 2050, need effective implementation of measures for myopia prevention and control. Urgent and sustained control of myopia should be an urgent priority as well as preventive action against risk factors for visual impairment.

1.2. Environmental paradigms in myopia pathogenesis

Genetic variation explains from 12 % to 30 % of the variance in the mean spherical equivalent in populations of European ancestry (Guggenheim et al., 2015; Hysi et al., 2020). The pronounced geographical and ethnic disparities in the prevalence of myopia, particularly the notably higher rates in East Asia compared to regions such as Africa and the Eastern Mediterranean, cannot be solely attributed to genetic susceptibility. Previous multiracial epidemiological studies have indicated that Chinese populations exhibit a significantly higher prevalence of myopia relative to other ethnic groups (Pan et al., 2013a; Pan et al., 2013b). Furthermore, substantial differences in lifestyle practices across various ethnicities are likely the primary contributors to the varying risks of myopia among these groups. Additionally, the rapid and significant increase in myopia prevalence over the past few decades, which cannot be explained by genetic changes within populations, further underscores the importance of environmental factors in shaping the myopia epidemic.

Near work, including education and outdoor light exposure, has long been identified as a major environmental driver of myopia development in school children. A landmark study conducted in Australian children (1665 children aged 6 and 2367 children aged 12) revealed that students with higher levels of outdoor activity exhibit less myopia compared to those with less outdoor exposure (Rose et al., 2008). In addition, students with combined high levels of near work and low levels of outdoor activity tended to have a higher prevalence of myopia. These findings highlight the importance of encouraging outdoor activities to mitigate the risk of myopia in school-aged children. A previous study assessed the direction of causality of education and myopia via Mendelian randomization and revealed that prolonged exposure to education contributes to the increasing prevalence of myopia, suggesting that extended time spent in education may increase the risk of myopia (Mountjoy et al., 2018). More recently, a review of 5 studies of birth months at school enrollment from China revealed that the schooling environment rather than age seems to be a key element driving myopia development (Brennan et al., 2025). Every additional year at school has been associated with a decrease in the spherical equivalent of −0.17 diopters per year (C. Zhang et al., 2022). More evidence has been provided by the findings of the “raising of the school-leaving age (ROSLA) 1972 reform” study (Plotnikov et al., 2020). The authors reported a more negative refractive error after the implementation of the reform, providing further support for a causal relationship between education and myopia. The prevalence of myopia in East Asian countries, including China, Japan, Korea, and Singapore, is strongly associated with educational systems characterized by intense academic competition, prolonged school hours, and substantial homework assignments (Dirani et al., 2010; Lam et al., 2012; Morgan et al., 2012). These factors significantly reduce opportunities for outdoor activities. In contrast, regions in Africa typically exhibit lower literacy rates and a later onset of formal education, with most children beginning school between the ages of 6 and 8 (Anera et al., 2006; Jiménez et al., 2012). These factors may contribute to a reduced prevalence of myopia. Additionally, the disproportionate distribution of near-work activities has further contributed to the uneven global distribution of myopia prevalence.

Concerns related to the rise of myopia increased due to the COVID-19 pandemic, as there were increases in near work, including screen time and reduced outdoor activities. While some studies have reported that the prevalence of myopia has decreased to pre-pandemic levels (W. Wang et al., 2023), others have concluded that lifestyles have not returned to pre-COVID-19 levels, impacting myopia prevalence (X. J. Zhang et al., 2023). Most importantly, younger children (aged 6–8 years) and children from low-income families have been identified as utmost vulnerable to environmental changes (J. Wang et al., 2023; X. J. Zhang et al., 2023). Of note, the COVID-19 pandemic further highlighted this influence of near work on myopia, as varying intensities and durations of lockdowns across regions differentially affected outdoor access and the burden of near work. China's dynamic zero-COVID-19 policy, designed to safeguard public health, significantly restricted individual mobility, leading to a marked increase in the prevalence of myopia (Y. Hu et al., 2021; M. Ma et al., 2021; J. Wang et al., 2021).

While genetics, outdoor time and near-work activities remain the primary drivers of myopia, secondary factors such as spatial frequency exposure (Flitcroft et al., 2020; D. L. Li et al., 2025a; D. L. Li et al., 2025b), air pollution (Kai et al., 2025; Z. Wang et al., 2025), sleep (X. X. Dong et al., 2024b; Jin et al., 2024) and diet (Chamarty et al., 2023; Massoudi et al., 2024) have been described as potential risk factors. The evidence for these secondary factors varies from weak to moderate, with weaker associations compared to primary drivers. While some studies suggest potential links, the mechanisms remain unclear, and confounding variables make it difficult to establish causation. Most of these perceived risk factors are surrogates of the two main environmental risk factors, either near-work or lack of outdoor activities. More longitudinal and interventional studies are needed to evaluate the role of these secondary factors in myopia development and progression. Addressing primary factors, such as promoting outdoor time and reducing nearness, should be a priority to prevent myopia incidence (Dhakal et al., 2022; M. He et al., 2015; X. He et al., 2022). Crucially, recognizing the significant variability in the influence of environmental factors based on region, ethnicity, culture, and socioeconomic status is essential for the transition to precision medicine. Tailoring interventions necessitates a comprehensive understanding of the specific environmental risk profiles across diverse regions. This environmental heterogeneity, combined with individual genetic susceptibility, forms the critical foundation for AI-driven precision approaches, which can effectively stratify risk and personalize prevention and management strategies, thereby reducing the disproportionate burden on high-risk populations identified by their unique environmental exposures.

1.3. Precision medicine revolution

The traditional one-size-fits-all approach, especially in genetics and environmental sciences, has been increasingly criticized for failing to account for the inherent heterogeneity in biological and environmental systems (Agustina et al., 2019; Sisodiya, 2021). This criticism is rooted in the recognition of gene-environment interaction (G × E), where genetic predispositions and environmental exposures do not act in isolation but dynamically interact to drive heterogeneous outcomes (X. Zhang et al., 2022). A previous study demonstrated that single-nucleotide polymorphisms (SNPs) exert their strongest effects on extreme myopic phenotypes and weaker effects on emmetropes, which implies that G × E or gene-gene interactions are prevalent in the development of myopia (Pozarickij et al., 2019). The one-size-fits-all approach frequently overlooks the intricate interactions that are key drivers of the heterogeneity observed in population health and individual responses (Agustina et al., 2019), not only in myopia but also across complex diseases. The heterogeneity of genetic and epigenetic factors plays a crucial role in disease progression and treatment response. For example, in cancer research, genetic and epigenetic heterogeneity are pivotal drivers of disease progression and therapeutic resistance, shaping the diversity of tumor cell populations. This biological heterogeneity endows tumor cells with dynamic evolutionary capabilities, enabling adaptive survival strategies under therapeutic pressure (Heng et al., 2009). Similarly, in the study of complex diseases such as type 2 diabetes, genetic and environmental heterogeneity significantly influence disease manifestation and progression. Stratified genome-wide association studies (GWAS) have revealed subgroups within individuals with type 2 diabetes that exhibit distinct genetic and environmental profiles, underscoring the need for tailored intervention strategies that consider these differences (Christiansen et al., 2023).

Within the precision medicine paradigm, a spectrum of intervention strategies has emerged, each with its own advantages and limitations. Targeted therapies, which are tailored to specific molecular alterations, demonstrate high efficacy and minimal side effects in biomarker-selected patient populations, however, this approach faces challenges such as the development of acquired resistance and limited applicability across diverse genetic backgrounds (Aldea et al., 2021). Genetic testing technologies can accurately identify genetic variants to reveal potential drug targets and calculate polygenic risk scores (PRSs) for the stratification of complex disease risk, thereby informing personalized medical interventions. Nevertheless, the accuracy of these technologies is currently limited when applied to different ethnic groups (Konuma and Okada, 2021). AI-assisted healthcare has the potential to enhance diagnostic accuracy and efficiency, while simultaneously reducing the incidence of human error. However, its accuracy is constrained by the quality of training data and algorithms, necessitating clinical validation before practical application (Bhinder et al., 2021; Ng Yin Ling et al, 2024).

In addition, numerous studies have revealed a G × E framework for myopia, including environmental factors interacting with GWAS, PRS, and other forms of statistical interactions (environmental and genetic index) (X. He and Li, 2023). Unraveling the molecular mechanisms that drive the formation of heterogeneity will establish a crucial scientific foundation for advancing precision therapeutic paradigms (Heng et al., 2009). In the context of myopia prevention and control, precision approaches may include personalized optical interventions (e.g., those tailored to AL and progression risk), targeted medication regimens (e.g., low-dose atropine and light therapy based on individual responses), and customized environmental and behavioral modifications informed by genetic and environmental heterogeneity (Chang et al., 2024; L. Jiang et al., 2023). Despite these advancements, the practical application of precision medicine for myopia faces several challenges. To develop an effective myopia risk assessment model, the integration of multisource data is essential, incorporating ocular physiological parameters, genetic information, eye usage habits, and environmental factors. However, due to variations in data quality and significant regional and population differences, the generalizability of current models is inadequate (Ng Yin Ling et al., 2024). Consequently, large-scale, multicenter studies are imperative for the optimization and validation of these models. Therefore, it is crucial to consider the pathogenesis of myopia, the efficacy and safety of intervention methods, and to establish scientifically sound and practical risk thresholds. It is important to emphasize that precision medicine of myopia is a closed-loop system founded on "scientific stratification, dynamic management, and individualized intervention".

Environmental heterogeneity also plays a key role in maintaining genetic variation and facilitating adaptation to novel selection pressures. Research on *Drosophila melanogaster* populations has demonstrated that environmental heterogeneity can enhance adaptive potential, thereby influencing conservation priorities and strategies without necessitating detailed genetic studies (Y. Huang et al., 2016). Moreover, the field of translational bioinformatics highlights the importance of data heterogeneity in improving the generalizability and applicability of research findings. Limited by the scarcity of information that encompasses ample genetic diversity, comprehensive environmental factors, and detailed eye-related parameter records for myopia, research on G × E interactions in myopia has faced challenges in attaining sufficient statistical power (X. He and Li, 2023). The lack of adequate heterogeneity in datasets often results in non-representative models that fail to capture the heterogeneity observed in real-world patient populations. Emphasizing data heterogeneity can lead to more accurate and effective models for disease prediction and treatment (Cahan and Khatri, 2020). In the context of public health and policy, the one-size-fits-all approach has been shown to exacerbate existing disparities and fail to address the unique needs of diverse populations. Policy interventions that target the social determinants of health and apply a health equity lens are more likely to reduce health disparities and improve outcomes across different demographic groups (Hall et al., 2016). The integration of precision public health concepts, which leverage data to tailor interventions for specific subgroups or communities with unique risks, presents significant potential for improving the efficiency and effectiveness of public health initiatives. However, this approach requires careful consideration of equitable resource allocation, the ethical implications of targeting specific subgroups, and the necessity to ensure that it reinforces, rather than undermines, the principles of universal health coverage.

1.4. The “Environment-Gene-AI triad”

The “Environment-Gene-AI triad” offers a transformative framework for risk stratification and personalized interventions by integrating environmental factors, genetic information, and AI technologies to understand and manage complex diseases (Fig. 3). This triad is particularly significant in the context of precision medicine, where the goal is to tailor healthcare interventions to individual patients based on their unique genetic makeup, environmental exposures, and lifestyle factors. G × E interactions are pivotal in the development of numerous complex diseases, and a deeper understanding of these interactions can significantly enhance the development of effective prevention and treatment strategies. Previous studies have shown that integrating PRSs with modifiable risk factors significantly improves the accuracy of disease risk prediction, highlighting the necessity of incorporating both genetic and environmental elements into risk assessment frameworks (Jacobs et al., 2020; Kachuri et al., 2020; Machlitt-Northen et al., 2022). In contrast to models that incorporate only genetic risk scores (GRS) and environmental risk scores (ERS), models that account for the G × E multiplicative interactions substantially increase the explained variance of myopia (by 2.4 %–2.9 %) and improve the predictive accuracy by 0.04–0.06 (Enthoven et al., 2019). Similarly, the intricate interplay between genetic predispositions and environmental exposures plays a critical role in the etiology of various diseases, emphasizing the importance of understanding these complex interactions to optimize prevention strategies (Crea, 2020; Y. Huang et al., 2021; Wu et al., 2024). Although traditional statistical methods have significantly contributed to our understanding of G × E interactions, they often struggle to manage the complexity and scale of modern omics and environmental exposure data.

AI technologies hold significant potential for transforming the analytical frameworks and interpretative paradigms employed in processing multi-dimensional datasets, particularly those encompassing G × E interactions (C. Li et al., 2019; Tate et al., 2022; D. Zhao et al., 2023). These advanced computational approaches are capable of improving the accuracy of genetic risk assessments and facilitating the integration of genetic data with clinical and environmental information. For example, AI-driven models have been used to integrate omics datasets and conventional clinical biomarkers for the identification of

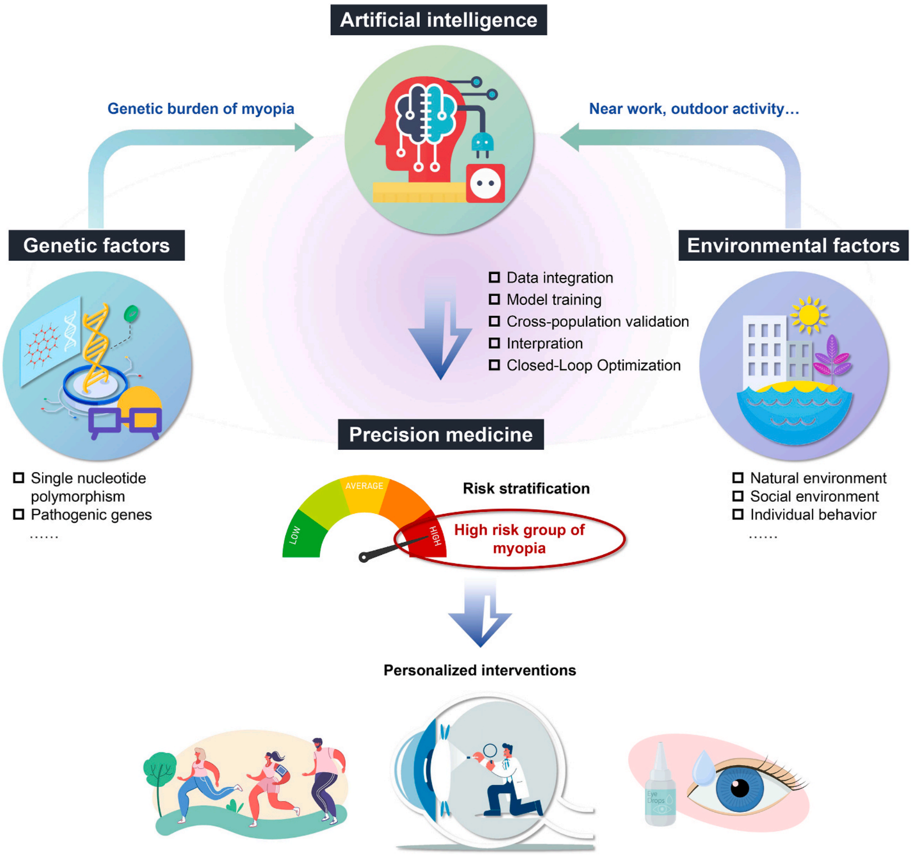


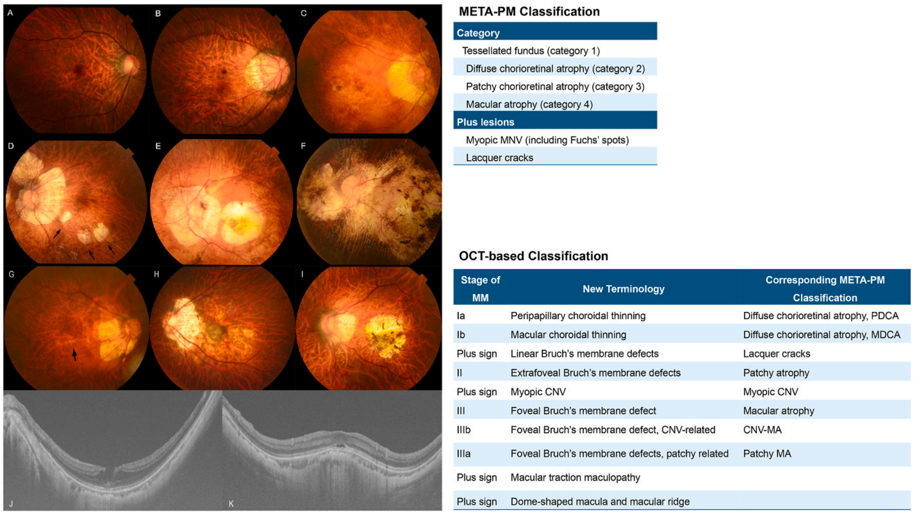
Fig. 3. Schematic workflow of the multi-modal AI framework integrating genomic and environmental determinants for precision **medicine.** A multi-modal AI framework integrates genetic burden (polygenic risk scores) and environmental exposure data (e.g., pollutants, lifestyle). A cross-scale interaction model is trained, validated across populations, and interpreted with the SHapley Additive exPlanations value. Combined with real-world medical data for closed-loop optimization, it enables dynamic risk stratification and generates evidence-based, personalized intervention plans.

myopic retinopathy in children and adolescents, demonstrating the potential of AI to personalize medicine by identifying high-risk patients and predicting disease progression (Hou et al., 2023). Moreover, the use of AI in genomic medicine is expanding, with applications ranging from the identification of genetic interactions in genome-wide association studies to the development of personalized RNA therapeutics. These advancements underscore the transformative potential of AI in enhancing the accuracy and efficiency of genetic analyses, ultimately leading to better targeted interventions (Enthoven et al., 2019). The integration of AI with genetic and environmental data is also being explored in the context of myopia, where G × E interactions are being investigated as a path to precision medicine. By combining genetic, environmental, and lifestyle risk factors, researchers aim to develop personalized therapeutic approaches that can modify or even reverse the course of the disease (Eid et al., 2019). In summary, the "Environment-Gene-AI triad" offers a comprehensive framework for advancing precision medicine. By leveraging the strengths of genetic and environmental data alongside AI technologies, this approach holds the promise of transforming risk stratification and enabling personalized interventions that are more effective and tailored to individual patient needs. This triad not only enhances our understanding of disease mechanisms but also paves the way for innovative strategies in disease prevention and management (J. Li et al., 2019; Zeggini et al., 2019).

1.5. Myopic maculopathy: the end-stage burden of PM

In 2015, an international panel of experts on high myopia developed a simplified, systematic classification system based on a meta-analysis of PM (META-PM). In this system, MM is classified into five categories according to the degree of atrophic change, from no myopic retinal lesions (category 0), tessellated fundus only (category 1), diffuse choroidal atrophy (category 2), patchy choroidal atrophy (category 3), and macular atrophy (category 4). Additionally, the META-PM classification includes three "plus" features: lacquer cracks, myopic macular neovascularization (MNV), and Fuchs spot (Ohno-Matsui et al., 2015). According to this classification, PM is defined as myopic eyes exhibiting MM that is equal to or more severe than diffuse atrophy, or those presenting with a plus lesion, or eyes characterized by the presence of a posterior staphyloma (Ohno-Matsui et al., 2016b; Ohno-Matsui et al., 2021). Although the META-PM system has proven useful for standardized grading and large-scale epidemiological studies, it also has certain limitations. The appearance of fundus color can vary depending on the degree of pigmentation among different racial and ethnic groups, which may affect the consistent and accurate detection and classification of atrophic lesions. Furthermore, conventional color fundus photographs lack the capability to visualize fine retinal and choroidal structures, making it challenging to detect certain lesions associated with PM. To address these limitations, an optical coherence tomography (OCT)--based classification system has been developed (Y. Fang et al., 2019). Several key features, such as extreme choroidal thinning, Bruch's membrane (BM) defects, myopic traction maculopathy (MTM), and dome-shaped macula, can only be identified through OCT imaging and are considered critical in determining the severity of PM. The comparison and typical lesions of the META-PM classification and the OCT-based classification of MM was shown in Fig. 4. Additionally, a newly proposed ATN classification system for MM comprising three components: atrophic (A), tractional (T), and neovascular (N) was also been developed. This ATN system does not modify the existing atrophy classification. It adds a new tractional component, which includes five stages: inner and/or outer foveoschisis, foveal detachment, macular hole, and retinal detachment (Ruiz-Medrano et al., 2019).

Highly myopic patients with longer ALs and more severe myopia are at higher risk of developing MM (da Silva et al., 2024; Deng et al., 2024; Foo et al., 2023; F. Jiang et al., 2025; M. Zou et al., 2020). However, specific cut-off values for refractive error and AL have not been established in the definition of PM, as posterior staphyloma has been reported in eyes with normal AL or in eyes with AL less than 26.5 mm (Moriyama et al., 2011; N. K. Wang et al., 2016). In addition, many studies have



META-PM Classification

Category
Tessellated fundus (category 1)
Diffuse chorioretinal atrophy (category 2)
Patchy chorioretinal atrophy (category 3)
Macular atrophy (category 4)
Plus lesions
Myopic MNV (including Fuchs' spots)
Lacquer cracks

OCT-based Classification

Stage of MM	New Terminology	Corresponding META-PM Classification
Ia	Peripapillary choroidal thinning	Diffuse chorioretinal atrophy, PDCA
Ib	Macular choroidal thinning	Diffuse chorioretinal atrophy, MDCA
Plus sign	Linear Bruch's membrane defects	Lacquer cracks
II	Extrafoveal Bruch's membrane defects	Patchy atrophy
Plus sign	Myopic CNV	Myopic CNV
III	Foveal Bruch's membrane defect	Macular atrophy
IIIb	Foveal Bruch's membrane defect, CNV-related	CNV-MA
IIIa	Foveal Bruch's membrane defects, patchy related	Patchy MA
Plus sign	Macular traction maculopathy	
Plus sign	Dome-shaped macula and macular ridge	

Fig. 4. Different lesions of myopic maculopathy on META-PM Classification and OCT-based Classi**fication.** META-PM Classification Category 1, tessellated fundus (A) is defined by the increased visibility of large choroid vessels owing to axial elongation. Category 2, diffuse chorioretinal atrophy, is observed as an ill-defined yellowish lesion in the posterior fundus, which is subclassified to peripapillary diffuse choroidal atrophy (B) and macular diffuse choroidal atrophy (C). Category 3, patchy chorioretinal atrophy (D, arrows) can be seen as a grayish-white, well-defined atrophy. Category 4, macular atrophy is a well-demarcated, grayish-white or whitish, atrophic lesion centered on the fovea. It is subclassified into MNV-related macular atrophy (E) and patchy atrophy-related macular atrophy (F). META-PM Classification also included plus lesions. Lacquer cracks (G, arrows) can be detected as fine, irregular, yellow lines in and around the macula. Myopic MNV included three phases: the active phase with proliferation of a fibrovascular membrane including MNV, exudation, and hemorrhage (H); the scar phase with pigmentation exemplified by a Fuchs spot (I); and the atrophic phase represented by MNV-related macular atrophy. OCT-based Classification included two plus signs that cannot be observed in fundus, which are macular traction maculopathy (J) and dome-shaped macula (K). Figure A–E reproduced from: Ohno-Matsui et al. (2021). OCT, optical coherence tomography; MNV, myopic macular neovascularization; MM, myopic maculopathy; CNV, choroidal neovascularization; PDCA, peripapillary diffuse choroidal atrophy; MDCA, macular diffuse choroidal atrophy; MA, macular atrophy. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

demonstrated that progressive choroidal thinning and the formation of BM defects in the macular region are key phenomena associated with MM (Deng et al., 2024; Midorikawa et al., 2024; Ueda et al., 2023). Xie et al. found that choroidal thinning was more prominent in the center and parafoveal regions as AL increased (Xie et al., 2022). Fang et al. reported that the cut-off value of choroidal thickness can be used to diagnose peripapillary diffuse choroidal atrophy (PDCA) and macular diffuse choroidal atrophy (MDCA) (Y. Fang et al., 2019). Furthermore, choroidal thickness has been reported to be an independent predictor of MM progression (Z. Li et al., 2021; U. C. Park et al., 2022) and is associated with a decrease in retinal sensitivity (da Silva et al., 2024).

Among various MM lesions, tessellated fundus and diffuse chorioretinal atrophy generally do not cause significant vision loss (Y. Fang et al., 2018; Yan et al., 2018). Although patchy atrophy typically occurs outside the fovea and does not directly affect central vision, further development of MNV in the foveal area can significantly impair central vision (Du et al., 2020). Consequently, myopic MNV, MNV-related macular atrophy (Y. Fang et al., 2018; Yoshida et al., 2003), MTM (Cheong et al., 2022; Parolini et al., 2021), and optic nerve (ON) damage (Jonas et al., 2017a; X. Zhang et al., 2024) are important contributors to vision loss in patients with PM.

Intravitreal anti-vascular endothelial growth factor (VEGF) therapy has replaced verteporfin photodynamic therapy (vPDT) as the standard treatment for myopic MNV(Ohno-Matsui et al., 2018). Agents such as ranibizumab (Y. Chen et al., 2019; Hamilton et al., 2020; Wolf et al., 2014), aflibercept (Ikuno et al., 2015) and conbercept (L. Gao et al., 2024) demonstrated short-term visual improvements after treatment. However, additional studies are needed to assess their long-term benefits, as the development of myopic MNV-related macular atrophy may lead to a gradual loss of initially gained visual acuity. Vitreoretinal surgeries have improved anatomical and visual outcomes in some cases of MTM. Nevertheless, the surgical indications for MTM remain controversial, and a consensus is needed (Parolini et al., 2021). Furthermore, current therapeutic approaches remain insufficient for managing other complications of MM, such as choroidal atrophy and serous macular detachment associated with dome-shaped macula (DSM). Therefore, early detection of MM is crucial for preserving central vision. Fang et al. reported the development of macular atrophy starting immediately after vitrectomy, which manifests as BM defect at the fovea followed by enlargement over time. This vitrectomy-induced macular atrophy is different from the progression of pre-existing MM(Y. Fang et al., 2020).

Glaucoma or ON damage is often overlooked and underdiagnosed in patients with high myopia and PM, sometimes until advanced stages. Unlike MM, ON damage in PM may begin at a younger age than that in non-myopic individuals, and it is not uncommon for affected patients to lose their sight during their productive years (L. Xu et al., 2007). A dose-response meta-analysis reported that for each unit (1-diopter) increase in myopia, the risk of glaucoma increases by approximately 20 % (Ha et al., 2022). In PM, the exact prevalence of ON damage remains uncertain due to diagnostic challenges. Some lesions associated with ON damage are unique to the PM, such as acquired conus pits and full-thickness retinal defects along the edges of the intrachoroidal cavitation (ICC). Other lesions, such as lamina cribrosa (LC) defects, resemble those observed in glaucoma (Jonas et al., 2020; X. Zhang et al., 2024). For macular lesions, patients often notice symptoms, leading to diagnosis and treatment after symptom onset. However, in the case of ON damage, initiating therapy only after symptoms appear is often too late. Therefore, early detection and treatment are especially crucial for ON damage.

2. Environmental mechanisms in myopia development

2.1. Near work, screen time, and accommodative dysfunction

In 1812, Ware observed that students at Colleges in Oxford and Cambridge, who frequently engaged in near-work activities such as reading and writing, were more likely to suffer from myopia compared to soldiers (Ware, 1813). However, previous studies have reported inconsistent associations between near work and myopia, with several investigations showing weak or non-significant relationships (Jones-Jordan et al., 2011; Z. Lin et al., 2014; Loman et al., 2002; B. Lu et al., 2009; Saw et al., 2005). Inconsistencies may be attributed to study limitations, particularly the reliance on self-reported data on near work from questionnaires, which are prone to recall and parental bias. These limitations can lead to discrepancies in measuring near-work duration and intensity, potentially underestimating or overestimating its impact on myopia development. More objective measurement methods, such as wearable devices or digital tracking, could help improve the accuracy of near-work exposure assessment in future studies. Nevertheless, a previous meta-analysis revealed an association between more time spent on near-work and higher odds of myopia by 1.14 (H. M. Huang et al., 2015). In addition, the odds of myopia increased by 2 % for every one diopter-hour more of near work per week. Similarly, the evidence on the association between increased screen time and myopia remains weak and inconsistent in earlier studies (Morgan et al., 2021). However, the latest meta-analyses have revealed a positive pooled effect, indicating that screen time, a modern form of near-work activity, is significantly related to myopia (Foreman et al., 2021; Ha et al., 2025). A clear dose-response relationship was observed, with each additional hour of daily screen time associated with 21 % greater odds of myopia (Ha et al., 2025), a key finding from the latest evidence.

The potential mechanisms linking near work to myopia development are associated primarily with visual blur phenomena, particularly through accommodative lag and peripheral defocus, which are central to understanding axial elongation (Gajjar and Ostrin, 2022). Other investigated hypotheses involve ciliary body anatomy and biomechanics, temporal viewing patterns, and the contrast polarity of reading material (Gajjar and Ostrin, 2022). Regarding accommodative function, previous studies reported that sustained accommodation during near work was associated with greater accommodative lag in myopic patients, leading to hyperopic defocus on the retina, which may drive myopic progression (Abbott et al., 1998; Gwiazda et al., 1995). However, mixed evidence has supported a new theory that accommodative lag may be a consequence rather than a cause of myopia (Berntsen et al., 2011; Y. Chen et al., 2020; Mutti et al., 2006). While higher accommodative convergence/accommodation (AC/A) ratios have been observed in myopic patients, their role in progression remains unclear (Mutti et al., 2017). Additionally, myopic individuals often exhibit larger and stiffer ciliary muscles, which could influence eye growth through biomechanical forces, although their precise impact is still uncertain (Gwiazda et al., 1995; Thakur and Verkicharla, 2021). Another widely studied mechanism is peripheral defocus, where hyperopic defocus in the retinal periphery may signal continued eye growth, forming the basis for myopia control strategies such as orthokeratology (Ortho-k) lenses, multi-focal lenses and new spectacle/contact lenses designs (Berntsen et al., 2013; Berntsen and Kramer, 2013; Erdinest et al., 2023; Queirós et al., 2025). However, some researchers contend that peripheral defocus is a consequence of axial elongation rather than a causative factor (Rotolo et al., 2017). More recently, a new discussion emerged on whether all lenslet-based spectacles operate via peripheral defocus or mid-peripheral contrast reduction (Guggenheim and Terry, 2025), such as diffusion optics technology (Rappon et al., 2023). This raises new questions about whether myopia control lenses operate primarily via contrast modulation rather than peripheral defocus, with further research needed to determine their precise mechanism.

Furthermore, research has explored the role of temporal viewing patterns and contrast polarity. Some studies have shown that temporal viewing properties, such as taking regular breaks from near work and briefly shifting focus to distant objects, may help mitigate myopia progression by regulating eye growth (P. C. Huang et al., 2020; Ip et al., 2008). Additionally, the contrast polarity of reading material has been investigated, with findings suggesting that white text on a black background may stimulate ON retinal pathways, potentially inhibiting myopia, whereas black text on a white background could overstimulate OFF pathways, encouraging axial elongation (Aleman et al., 2018; Wagner and Strasser, 2023). While these mechanisms provide valuable information, the evidence remains inconclusive, and further longitudinal and interventional studies using objective near-work measures are needed to establish causality.

2.2. Outdoor light exposure: biological mechanisms and innovations

Light exposure is a behavioral determinant of health, particularly in the context of modern lifestyles that limit outdoor exposure, leading to an increased prevalence of myopia. Inadequate light exposure, especially insufficient time spent outdoors in natural daylight, has been implicated in the development and progression of myopia (Clark et al., 2023a; French et al., 2013; X. He et al., 2022; Sherwin et al., 2012). The strong evidence suggests that brighter light exposure is a key protective factor, as higher outdoor light levels inhibit myopia development (Lingham et al., 2020). Bright daylight exposure seems to be critical in the regulation of eye growth, contributing to reducing the risk of myopia (P. C. Wu et al., 2018). Current recommendations for healthy light exposure are largely based on laboratory-controlled settings and fail to consider real-world behavioral factors that influence light exposure, such as location, urban living, meteorological conditions, home/school environments (presence or absence of windows), personal habits/hobbies, age and gender (Biller et al., 2024). Thus, myopia prevention requires not only technological solutions but also lifestyle and behavioral interventions that encourage intentional and sustainable outdoor exposure. This aligns with strategies that promote outdoor play and daylight engagement as key components of myopia control.

The association between increased time spent outdoors and reduced myopia risk is strong and has been consistently reported across studies, including findings from meta-analyses (Dhakal et al., 2022; Martinez-Perez et al., 2025). Furthermore, the protective effects of interventions aimed at increasing outdoor time have been supported by several randomized clinical trials (M. He et al., 2015; X. He et al., 2022). A meta-analysis that included 15 randomized controlled trials and observational studies ($n = 16,597$ participants) revealed that increased outdoor exposure significantly reduced or delayed the onset of myopia by −0.08 mm per year and 0.16 diopters per year, respectively, with effects sustained for up to three years (Martinez-Perez et al., 2025). These findings emphasize the importance of increasing outdoor time as a preventive strategy against myopia. Nevertheless, further research to refine exposure duration recommendations and understand regional variations in effectiveness is necessary. Light exposure plays a crucial role in myopia development, with key parameters such as timing, duration, temporal pattern, intensity, and spectrum influencing its effects on eye growth regulation. Previous studies suggest that exposure to natural light, particularly for at least 2 h per day, can significantly reduce the risk of myopia (S. Xiong et al., 2017; Y. C. Yang et al., 2022). More recently, the role of intermittent exposure has been explored in animal and human studies (Arumugam Ramachandran et al., 2022; Dhakal et al., 2024; Lan et al., 2014; Najjar et al., 2023). These results suggest that intermittent exposure is more effective than infrequent but prolonged outdoor activities, as continuous light stimulation helps regulate dopamine release, which inhibits axial elongation. However, further studies are necessary to confirm these findings.

The intensity of outdoor light, which often exceeds 10,000 lux, contrasts sharply with typical indoor lighting levels below 200 lux in some indoor regions of the world, contributing to its protective effect (Lanca et al., 2019). Additionally, the light spectrum may play a role. However, emerging evidence suggests that even moderate outdoor light levels (1000–5000 lux), achievable under shaded or overcast conditions, can provide protective effects when sustained over time (J. Chen et al., 2024b; Read et al., 2015; P. C. Wu et al., 2018). These findings emphasize that the duration of cumulative light exposure, rather than only extreme brightness, plays a central role in myopia prevention. Violet light (360–450 nm) has been linked to choroidal thickness through opsin signaling associated with the circadian rhythm, although the results of two previous trials provide limited evidence supporting a significant effect of violet/UV light therapy on myopia prevention and control (Mori et al., 2021; Torii et al., 2022). While the benefits of outdoor light exposure are well-documented, future strategies may explore new light therapies or modifications to indoor lighting conditions, such as increasing light intensity (Cohen et al., 2022), adjusting spectral composition, or introducing outdoor scenes to mimic outdoor conditions (Pan et al., 2025b; Yi et al., 2023), to replicate the protective effects and help mitigate myopia development and progression.

Higher outdoor light intensity likely plays a key role in preventing myopia, probably because of its influence on dopamine release, which can regulate eye growth (Landis et al., 2021). Dopamine is a key neurotransmitter in the retina that is stimulated by bright outdoor light, which inhibits retinal metabolism, potentially reducing oxidative stress and retinal degeneration. Reduced dopamine levels, often observed in myopic eyes, contribute to scleral remodeling and elongation, with D1 and D2 receptors playing distinct roles in growth inhibition and choroidal modulation (F. Huang et al., 2022; X. Zhou et al., 2017). Increased choroidal blood flow associated with outdoor light exposure may increase the oxygen and nutrient supply to the macula, providing a defense against ischemia-induced atrophic changes. In addition to retinal dopamine signaling, epigenetic regulation also plays a crucial role in myopia development and progression. Epigenetic mechanisms, particularly methylation of specific genes (*PAX6*, *PEX1338*, *NNT*, *COL1A1* and *PCDHA10*), have been implicated in the development of myopia (X. X. Dong et al., 2024a; Seow et al., 2019; Swierkowska et al., 2022; Vishweswaraiah et al., 2019; Zhou et al., 2012), influencing oxidative stress and collagen synthesis processes that impact the structure and biomechanics of the sclera. Thus, it seems plausible that environmental factors such as low light exposure, increased near work, and circadian disruptions may be involved in triggering these epigenetic modifications, linking lifestyle behaviors to genetic predisposition. These findings also highlight the complex interplay between dopaminergic signaling, epigenetic regulation, and environmental influences, suggesting that targeted interventions, such as enhancing retinal dopamine activity or modulating gene expression, could be promising strategies for myopia control (Landis et al., 2020). However, further research is needed to fully understand these mechanisms, particularly how epigenetic modifications interact with dopamine pathways and environmental factors to influence eye growth. Expanding our knowledge with further research could lead to more effective and personalized medicine approaches for myopia prevention and treatment.

Outdoor light exposure is well known for its protective role against myopia onset, and emerging evidence suggests that it may also help mitigate the risk of macular atrophy in highly myopic individuals (S. S. Lee et al., 2022; Lingham et al., 2021). Macular atrophy, a severe complication of high myopia, involves chorioretinal thinning, retinal pigment epithelium atrophy, and photoreceptor degeneration, leading to central vision loss. Outdoor light may help reduce oxidative stress and inflammation, delaying degenerative changes in myopic eyes. By slowing myopia progression from low or mild myopia to high myopia through increased outdoor time, the prevention of macular atrophy due to myopia may be possible (Saw et al., 2019). However, while these mechanisms suggest a potential protective effect of outdoor light against myopic macular atrophy, further longitudinal studies and clinical trials are needed to confirm these effects and explore whether optimizing light exposure parameters could be a viable strategy for preventing MM.

3. Genetic and epigenetic markers

3.1. Advantages of the polygenic risk scores

PRS serve as a pivotal tool in myopia genetics, offering significant advantages in understanding and managing myopia. PRS effectively quantifies an individual's genetic susceptibility to myopia by aggregating the effects of numerous genetic variants, thus providing a comprehensive measure of genetic risk (Ghorbani Mojarrad et al, 2020; Kassam et al., 2022; Lanca et al., 2021). Multiple genetic susceptibility studies have identified *ZC3H11B*(Fan et al., 2012; F. F. Li et al., 2021; J. Liu et al., 2021), *MTOR* (X. Li et al., 2022; X. L. Yuan et al., 2021), *WNT7B* (S. Y. Lu et al., 2020; Miyake et al., 2015), *PAX6* (Hammond et al., 2004; Han et al., 2009; B. Jiang et al., 2011; C. L. Liang et al., 2011), *SNTB1*(Khor et al., 2013; F. F. Li et al., 2021; Y. Shi et al., 2013; S. M. Tang et al., 2020), and other genes as candidate genes associated with myopia, high myopia, and PM. In this way, PRS aids in understanding the genetic architecture of myopia, identifying key genes and pathways involved in its development.

A core strength of PRS lies in their ability to capture the polygenic architecture of refractive error, a trait with high heritability where GWAS have identified hundreds of loci linked to myopia risk (Clark et al., 2023b; Ghorbani Mojarrad et al., 2020; Kassam et al., 2022; Verhoeven et al., 2013b). This multi-variant approach surpasses traditional single-gene analysis, providing a more comprehensive and nuanced assessment of genetic liability. PRS models for high myopia have demonstrated robust predictive utility across diverse populations. A previous study revealed that the area under the receiver operating characteristic curve (AUROC) of the PRS for high myopia was 0.78, 0.58, 0.71, and 0.67 in independent samples of European, African, South Asian, and East Asian ancestry, respectively (Clark et al., 2023b). These results indicate that the PRS can effectively predict myopia risk across diverse populations, albeit with varying degrees of accuracy.

Furthermore, PRS are instrumental in advancing precision medicine for myopia management. The integration of PRS with environmental factors demonstrates significant potential for advancing precision medicine in myopia management. Emerging evidence highlights the synergistic value of combining genetic predispositions with modifiable risk factors. Enthoven et al. revealed enhanced predictive power through gene-environment interaction analysis in Dutch children: while parental myopia alone explained 4.8 % of the variance (R^2) and PRS accounted for 2.6 %, their combination with ERS explained 7 % of the variance with statistical significance (Enthoven et al., 2019). This G × E interaction was further validated in a model combining PRS with age, outdoor time and parental myopia, achieving superior predictive performance ($AUC = 0.77$), suggesting that parental influence operates through both genetic transmission and environmental shaping (Lanca et al., 2021). A previous study indicated that the interactive effects of genetic susceptibility and educational level on myopia development are significantly greater than the simple sum of their individual influences (synergy index: 4.2). Specifically, a GRS constructed from 26 myopia-associated SNPs, in conjunction with educational level, markedly increases the risk for myopia (Verhoeven et al., 2013a). These findings provide empirical support for the development of multidimensional risk stratification systems. Therefore, PRS hold promise as a strategy for translating genetic insights into potential tools that could connect genomic discoveries with precision ophthalmology in the management of myopia. However, their full clinical applicability has yet to be established, given the complexity of the condition.

3.2. Limitations of polygenic risk scores

The limitations of PRS are multifaceted. PRS captures only a fraction of heritability due to the limited variance explained by common genetic variants. For instance, in a study of ~500,000 individuals, PRS accounted for 19 %, 2 %, 8 %, and 6 % of spherical equivalent refraction (SER) variation in European, African, South Asian, and East Asian populations, respectively (Clark et al., 2023b). This leaves a large portion of the genetic landscape unaccounted for, and the lack of inclusion of rare variants in PRS models limits their effectiveness in predicting myopia. Moreover, the reliance on SNP numbers and GWAS populations may limit the predictive power of PRS (Schwarzerova et al., 2024). In addition, PRS oversimplifies genetic architecture by relying predominantly on SNP numbers and additive genetic models from GWAS, while ignoring critical biological processes (transcription, translation, metabolism) and G × E interactions (Kachuri et al., 2024; Schwarzerova et al., 2024). Recent whole-exome sequencing (WES) studies suggest that rare variants disproportionately contribute to extreme myopia risk, yet their integration into PRS remains challenging due to data scarcity and computational demands (Musolf et al., 2023; J. Yuan et al., 2024).

Moreover, epigenetic mechanisms may complement PRS limitations. As discussed in Section 3.3, environmental exposures dynamically regulate gene expression through DNA methylation and chromatin remodeling processes that are absent in static PRS models. Therefore, integrating epigenetic data with PRS could bridge the gap between genetic predisposition and phenotypic expression. This is particularly important for myopia, where environmental factors such as education, near-work, and outdoor activity duration interact dynamically with genetic risk (Lanca et al., 2021; Morgan et al., 2021; Schwarzerova et al., 2024). Notably, current PRS frameworks directly link genetic variants to phenotypes without accounting for these intermediate layers, limiting their predictive power (Schwarzerova et al., 2024). Finally, methodological advancements reveal opportunities for improvement. A recent GWAS meta-analysis demonstrated enhanced PRS performance by incorporating both SNP main effects and SNP-education interaction terms, identifying novel loci (Fan et al., 2016). However, racial disparities persist: PRS exhibit population-specific effects due to divergent genetic backgrounds and G × E patterns across ethnic groups, risking biased predictions (Schwarzerova et al., 2024).

3.3. Non-additive genetic effects

While additive genetic models have been dominant in myopia genetics, recent studies have focused on non-additive genetic effects, including dominance and epistasis (Pozarickij et al., 2020). Sufficient evidence has shown that non-additive genetic effects are widespread in various diseases (Lenz et al., 2015; Plotnikov et al., 2019; Wood et al., 2016). The neglect of non-additive effects in PRS construction is a critical limitation. For example, dominance effects-where the phenotypic impact of a heterozygous genotype deviates from the additive expectation-could mask true genetic contributions in GWAS datasets (Pozarickij et al., 2020). Similarly, epistatic interactions (gene-gene or G × E interdependencies) may generate non-linear phenotypic outcomes that additive models fail to capture. These non-additive phenomena likely contribute to the "missing heritability" observed in PRS-based predictions, underscoring the need to integrate interaction terms into genetic risk models.

Pozarickij et al. conducted a study on 146 GWAS variants associated with refractive error and found that only a small number exhibited evidence of non-additive effects, particularly dominance (Pozarickij et al., 2020). While these non-additive effects did not substantially improve the accuracy of polygenic risk scores, the study underscores the importance of considering non-additive interactions in myopia genetics. This finding suggests that even subtle dominance or epistasis may cumulatively account for residual variance in myopia risk, particularly in extreme phenotypes where PRS performance is weakest. This is especially relevant when examining rare variants or loci with larger effect sizes, where the presence of dominance or epistasis might influence the phenotypic outcome. Moreover, non-additive genetic effects could help explain the variability in myopia severity observed across different populations, further complicating the implementation of universal PRS.

The implications for PRS refinement are clear. If non-additive effects are pervasive, current additive models may systematically underestimate genetic risk in subgroups with specific allele combinations or environmental exposures. For example, a recessive variant influencing scleral remodeling might manifest its effect only in homozygous carriers, a scenario invisible to additive PRS. Similarly, epistatic interactions between collagen genes (e.g., COL1A1 and COL5A1) could amplify myopia risk in ways that additive scores cannot capture. Future PRS models could address these limitations by incorporating interaction terms or machine learning algorithms capable of detecting non-linear genetic effects, as discussed in Section 4 (AI-Powered Prediction).

3.4. *Epigenetic influences*

Epigenetics, the study of changes in gene expression without altering the underlying DNA sequence, is emerging as a critical component in understanding myopia (Joustra et al., 2023) (Table 1; Fig. 5). Although genetics form the foundation of myopia susceptibility, exogenous environmental stimuli, such as education-related near work, may leave marks on the genome, inducing epigenetic regulation and mediating myopia development and progression. Notably, this epigenetic regulation is reversible, unlike irreversible gene mutations, offering a novel molecular basis for developing targeted therapies based on epigenetic reprogramming.

Numerous studies have established a significant association between myopia-related factors, such as physical activity, diet, and night-shift work, and epigenetic modifications, suggesting that environmental exposure may influence myopia through epigenetic mechanisms (Bhatti et al., 2015; Kadayifci et al., 2018; Świątowy et al., 2021). A previous review reported that epigenetics could mediate myopia development via oxidative stress, protein kinase A signaling, growth factor signaling, and cell differentiation (Desmettre et al., 2022). The role of DNA methylation and histone modifications in the regulation of genes related to myopia has been investigated in animal models (X. Ding et al., 2020; Thomson et al., 2022) and there is growing evidence that these epigenetic changes may play a role in myopia development (Hsi et al., 2019; Liao et al., 2017; Swierkowska et al., 2022; Wen et al., 2021). Zhou et al. reported in a murine deprivation myopia model that elevated DNA methylation levels in the *COL1A1* promoter are associated with inhibited scleral collagen synthesis and myopia progression (Zhou et al., 2012). In population-based studies, Vishweswariah et al. conducted a paired study involving 18 high myopia patients and 18 controls, identifying differential methylation in myopia-related genes such as *PAX6* and *ZNRF3(*Vishweswaraiah et al., 2019*)*. Additionally, miRNAs exhibit differential expression in the sclera and retina of humans and animals. Tkatchenko induced myopia in C57BL/6J mice through unilateral form deprivation and identified 53 differentially expressed miRNAs in the myopic retina via miRNA-mRNA interaction network analysis (Tkatchenko et al., 2016). In the choroid, transfer RNA-derived fragment 22 binds to *METTL3* mRNA to suppress its expression, further inhibiting the choroidal neovascular system by downregulating Wnt signaling molecules (C. Liu et al., 2023). Histone acetylation has also been shown to affect the expression of extracellular matrix (ECM) components, such as elastin and fibrillin, indicating its potential role in myopia development (H. L. Park et al., 2017; Watanabe and Murakami, 2016). Therefore, the interplay between genetic predispositions and environmental factors may lead to epigenetic modifications that increase or decrease myopia risk. This highlights the necessity for a more comprehensive approach to myopia research that integrates both genetic and epigenetic factors. For instance, myopia-related epigenetic changes could help explain the differences in myopia prevalence between individuals with similar genetic risk but different levels of environmental exposure, such as those with varying levels of educational attainment.

3.5. *Integrating epigenetics and genetics for precision medicine*

As research into myopia continues to evolve, the integration of genetic, epigenetic, and environmental data will be crucial in developing precision medicine approaches for myopia prevention and treatment. While PRSs have been effective in identifying individuals at high genetic risk, their utility in clinical settings remains limited due to the complex G × E interactions and the modest variance explained by common genetic variants (Schwarzerova et al., 2024). Previous studies have demonstrated the potential of epigenetics in predicting disease-related phenotypes (Sánchez-Cruz and Medina-Franco, 2021; Q. Zou et al., 2021; Zuccato et al., 2025). Notably, in myopia research, the methylation of certain genes, such as *PAX6*, *LRRC8C*, and *MICAL3*, has been proven to accurately predict myopia in children and adolescents (D. Jiang et al., 2024; Vishweswaraiah et al., 2019). Therefore, epigenetic modifications may serve as biomarkers for the early detection of myopia risk, particularly in children, and may even offer targets for therapeutic intervention (W. Dai et al., 2024). Current myopia research lacks a systematic integration of differential epigenetic data with genomic variations and environmental exposures. Cancer research has demonstrated the efficacy of multi-omics integration. For instance, Zuccato et al. utilized whole-genome methylation sequencing, ChIP-seq, RNA-seq, and proteomics, combined with clinical data, to develop a prediction model that enhanced the accuracy of colorectal brain metastasis prediction to 80 %, representing a 15 % improvement over traditional models (Zuccato et al., 2025). These findings provide valuable insights for myopia research. Establishing a multi-dimensional prediction framework that incorporates genetic susceptibility, epigenetic regulation, and environmental exposure could address the limitations of current models, which explain less than 20 % of myopia development. By incorporating epigenetic markers related to these environmental exposures, precision medicine approaches could offer individualized strategies for preventing myopia and its associated complications. Given the success of AI in disease prediction via epigenetics (Murphy et al., 2024; Toneyan et al., 2022), it may hold the key to integrating these cross-scale data.

4. AI-Powered Prediction and monitoring

4.1. *Current advancements of AI in myopia management*

The integration of AI into myopia management represents a paradigm shift in addressing the global burden of refractive errors and PM. AI-driven tools, particularly those leveraging deep learning and machine learning, have demonstrated transformative potential in early detection, risk stratification, and personalized intervention. Recent advancements highlight the ability of AI to predict myopia progression via multi-modal data. For instance, Lin et al. developed a machine learning model trained on electronic medical records to forecast high myopia development in children over a decade, achieving an AUC of 0.94–0.99 at three years and 0.80–0.84 at eight years (H. Lin et al., 2018). Similarly, retinal fundus imaging coupled with convolutional neural networks (CNNs) has enabled refractive error prediction with a mean absolute error of 0.56–0.91 diopters, demonstrating clinical-grade precision (Varadarajan et al., 2018). These models capitalize on features such as AL dynamics, corneal curvature, and environmental factors (e.g., near-work duration, outdoor exposure) to generate individualized risk profiles. Such tools could theoretically optimize the timing of interventions such as Ortho-k or low-dose atropine, which are most effective when initiated early. In PM, AI applications extend beyond prediction to diagnostic precision. Algorithms trained on OCT images can detect vision-threatening complications, including retinoschisis, macular holes, retinal detachment and pathologic myopic choroidal neovascularization, with sensitivities exceeding 90 % and specificities above 94 % (Y. Li et al., 2022). Li et al. developed a CNN model using swept-source OCT to identify macular lesions, achieving an AUC of 0.97

Table 1

Key studies linking epigenetic modifiers with myopia and pathologic myopia.

First author (year)	Nation	Types of modification	Study design	Types of myopia	Biomarker
Zhou et al. (2012)	China	DNA methylation	Animal experiments	FDM	*COL1A1* (↑)
Seow et al. (2019)	Singapore	DNA methylation	Case-control study and animal experiments	Early-onset myopia; LIM	*8p23* (↓),*12q23.2* (↓),*FGR* (↓), *PQLC1* (↓) and *KRT12*(↓)
Liang et al. (2019)	Singapore	DNA methylation	Case-control study, animal and cellular experiments	Early-onset myopia; LIM	*HOXA9* (↑)
Jiang et al. (2024)	China	DNA methylation	Case-control study	Myopia	*PAX6* (↓)
Vishweswaraiah et al. (2019)	Poland	DNA methylation	Case-control study	High myopia	Top 10 hypermethylated targets based on fold change: *LINGO1*↑ (cg26526312), *PTPN11*↑ (cg27541540), *ZNRD1*↑ (*cg00609363*), *PEX13*↑ *&* *PUS10*↑(cg24877391), *KIF20A*↑*&* *BRD8*↑ (cg21790796), *TRAPPC1*↑ *&* *CNTROB*↑ (cg14282407), *ERLIN2*↑ (cg18191664), *KIAA0528*↑ (cg08048517), *ZNF224*↑ (cg10646633) and *TCEA1*↑ (cg14694176)
Dong et al. (2024)	Europe	DNA methylation	Summary-databased Mendelian randomization	Myopia	*PRMT6* (cg00944433 and cg15468180), *SH3YL1* (cg03299269, cg11361895, and cg13354988), *ZKSCAN4* (cg01192291), *GATS* (cg17830204), *NPAT*(cg04826772), and *UBE2I* (cg03545757 and cg08025960).
Ding et al. (2020)	China	DNA methylation	Animal experiments	FDM	*IGF-1* (↑), *MMP-2* (↑)
Swierkowska et al. (2023)	Poland	miRNA modification	Case-control study	High myopia	*MIR3621* (↑), *MIR34C* (↑), *MIR423* (↑), *MIR1178* (↓), *MIRLET7A2* (↓), *MIR885* (↓), *MIR548I3* (↓), *MIR6854* (↓), *MIR675* (↓), *MIRLET7C* (↓) *and MIR99A* (↓)
Swierkowska et al. (2022)	Poland	DNA methylation	Case-control study	High myopia	*PCDHA10* (↓), *ADAM20* (↓), *PAG1*(↓), *ZFAND6* (↓), *ETS1* (↓), *ABHD13* (↓), *LIG4* (↓), *SBSPON*(↓), *SORBS2*(↓), *SLC25A3P1* (↓), *TANC1*(↓), *LMOD3* (↓), *ATXN1* (↓), *FARP2* (↓), *and OR6B3* (↓)
Thomson et al. (2022)	Australia	DNA methylation	Animal experiments	Myopia	*EGR1*, *FOS*, and *NAB2*
Hsi et al. (2019)	China	DNA methylation	Case-control study and animal experiments	High myopia and FDM	*LINE-1* (↑)
Liao et al. (2017)	China	Histone modification	Case-control study	High myopia	H3K4me1 and H3K27ac
Wen et al. (2021)	China	mRNA methylation (m6A)	Case-control study	High myopia	*C11orf96* (↑), *CSF1*(↑), *TMEM176B* (↑), *PTP4A3* (↑), *CHL1* (↑), *COL6A3* (↑), *CHI3L1* (↑), *PXDN* (↑), *IGFBP4*(↑), *RIMS1*(↓), *PTCHD4* (↓), *CABP7* (↓), *OCLN* (↓), *PTCHD4* (↓), *ANKRD24* (↓), *ALS2CL*(↓), *HEY2* (↓), *FGF10* (↓), *HEY2* (↓)
Xi et al. (2017)	China	mRNA modification	Animal experiments	Highly myopic-astigmatic	MMP2、TIMP2 and TGFB2
Tkatchenko et al. (2016)	USA	miRNA modification	Animal experiments	FDM	mmu-miR-18b-5p, mmu-miR-1306-3p, mmu-miR-291a-3p, mmu-miR-429-3p, mmu-miR-539-5p, mmu-miR-449c-5p, mmu-miR-206-3p, mmu-miR-1903, mmu-miR-500-3p, mmu-miR-122-5p, mmu-miR-143-3p, mmu-miR-496-3p, mmu-miR-431-5p, mmu-miR-671-5p, mmu-miR-216b-5p, mmu-miR-223-3p, mmu-miR-199a-5p, mmu-miR-146a-5p, mmu-miR-142-3p, mmu-miR-125a-3p, mmu-miR145-5p
Metlapally et al. (2016)	USA	miRNA modification	Animal experiments	Myopia	miRNAs: Let-7a, miR16-2, Let-7b mRNAs: Smok4a, Pepb2, Gnat1
Mei et al. (2017)	China	miRNA modification	Animal experiments	FDM	miR-468 (↑), miR-16-1*(↑), miR-466h-5p (↑), miR-466j (↑), miR-669e (↑), miR-15a*(↑), miR-466c-5p_v15.0 (↑), miR-294 (↑)
Huang et al. (2025)	China	miRNA modification	Case-control study	High myopia	Characterized miRNAs in high myopia: hsa-miR-490-3p (↓), hsa-miR-4423-3p (↓), hsa-miR-4485-3p (↑)
Guo et al. (2020)	China	miRNA modification	Animal experiments	LIM	cavPor3-miR-novel-chrscaffold_107_36268 (↑), cavPor3-miR-novel-chrscaffold_111_36350 (↑), cavPor3-miR-novel-chrscaffold_4_5889 (↑), cavPor3-miR-novel-chrscaffold_7_7504 (↑), cavPor3-miR-novel-chrscaffold_111_36469 (↑), cavPor3-miR-novel-chrscaffold_76_32980 (↑), cavPor3-miR-novel-chrscaffold_11_11041 (↑), cavPor3-miR-novel-chrscaffold_111_36611 (↑), cavPor3-miR-novel-chrscaffold_132_37863 (↑), cavPor3-miR-novel-chrscaffold_128_37706 (↑), cavPor3-miR-novel-chrscaffold_10_11197 (↓), cavPor3-miR-novel-chrscaffold_111_36353 (↓), cavPor3-miR-novel-chrscaffold_111_36441 (↓), cavPor3-miR-novel-chrscaffold_15_15154 (↓), cavPor3-miR-novel-chrscaffold_12_12421 (↓), cavPor3-miR-novel-chrscaffold_2_2212 (↓), cavPor3-miR-novel-chrscaffold_119_37316 (↓), cavPor3-miR-novel-chrscaffold_111_36472 (↓), cavPor3-miR-novel-chrscaffold_68_31730 (↓), cavPor3-miR-novel-chrscaffold_84_33871 (↓), cavPor3-miR-novel-chrscaffold_128_37724 (↓), cavPor3-miR-novel-chrscaffold_120_37436 (↓), cavPor3-miR-novel-chrscaffold_46_27908 (↓), cavPor3-miR-novel-chrscaffold_27_20777 (↓), cavPor3-miR-novel-chrscaffold_13_13335 (↓), cavPor3-miR-novel-chrscaffold_84_33870 (↓), cavPor3-miR-novel-chrscaffold_26_19738 (↓)
Tanaka et al. (2019)	USA	miRNA modification	Animal experiments	LIM	Upregulated miRNAs (56 in cornea tissue, 13 in iris tissue, 6 in lens tissue, 0 in retina tissue, 29 in RPE/choroid tissue, and 30 in sclera tissue); Downregulated miRNAs (7 in cornea tissue, 28 in iris tissue, 17 in lens

(*continued on next page*)

Table 1 (*continued*)

First author (year)	Nation	Types of modification	Study design	Types of myopia	Biomarker
					tissue, 9 in retina tissue, 7 in RPE/choroid tissue, and 40 in sclera tissue)
Liu et al. (2022)	China	miRNA modification	Animal experiments	FDM	mmu-miR-1936 (↑), mmu-miR-338-5p (↑), mmu-miR-673-3p (↑)
Zhu et al. (2020)	China	miRNA modification	Case-control study	High myopia	249 differentially expressed miRNAs
Ren et al. (2022)	China	miRNA modification	Animal experiments, case-control study and cellular study	Pathologic myopia	miR-150-5p (↓)
Chen et al. (2019)	China	miRNA modification	Case-control study	Myopia	Myopia-specific miRNAs: hsa-miR-125b-3p, hsa-miR-1274a, hsa-miR-1274b, hsa-miR-133a-3p, hsa-miR-152-3p, hsa-miR-17-5p, hsa-miR-19b-3p, hsa-miR-203a-3p, hsa-miR-24-3p, hsa-miR-450b-5p, hsa-miR-518d-3p, hsa-miR-521, hsa-miR-570-3p, hsa-miR-582-3p, hsa-miR-885-3p Myopia-absent miRNAs: hsa-miR-586, hsa-miR-378a-5p, hsa-miR-367-3p, hsa-miR-338-5p
Ando et al. (2022)	Japan	miRNA modification	Case-control study	MH and high myopic MH	let-7c (↑), miR-200a (↓)
Kunceviciene et al. (2019)	Lithuania	miRNA modification	Case-control study	Myopia	miR-328
Li et al. (2022)	China	lncRNA modification	Animal experiments	FDM	655 differentially expressed miRNAs
Geng et al. (2020)	China	lncRNA modification	Animal experiments	FDM and LIM	Ref: normal counterparts FDM groups: 372 differentially expressed lnRNAs LIM groups: 247 differentially expressed lnRNAs
Wu et al. (2024)	China	lncRNA modification	Case-control study	LIM	*Ctnnb1*(↑), *Pik3r1*(↑)and *Itgb1* (↑)
Zhang et al. (2024)	China	circRNAs modification	Case-control study and animal experiments	High myopia	CircPank1/miR-145-5p/NRAS and circNbea/miR-204-5p/ITPR1

Table 2
Comparative analysis of myopia control interventions: Mechanisms, efficacy, and clinical considerations.

Therapies	Low-Concentration Atropine	Ortho-K	Soft Multifocal Contact Lenses	Posterior Scleral Reinforcement
Type	Pharmaceutical	Optical	Optical	Surgical
Primary Mechanism	Cholinergic antagonism, inhibits excessive ocular growth (dose-dependent)	Nightly rigid lens wear induces corneal reshaping, creating peripheral myopic defocus	Peripheral myopic defocus (center-distance design)	Biomechanical stabilization of posterior sclera
Key Advantages	• Non-invasive administration • Easy daily use • Minimal adverse events (low doses) • First-line recommendation (LAMP trials)	• Daytime optical freedom • Reversible • High compliance in active children	• No nocturnal wear required • Reversible • Familiar lens modality • Low infection risk	• Halts structural degeneration • Benefits for high myopia with staphyloma • Prevents vision-threatening complications
Major Limitations	• Rebound effect (high doses) • Photophobia (high doses)	• Microbial keratitis risk • Nightly wear required • High cost • Visual adaptation issues	• High discontinuation rate (25–43 %) • Subjective visual disturbances (ghosting, glare) • Variable efficacy (pupil-dependent)	• Invasive surgery • Surgical morbidity (retinal detachment, CNV) • Technically demanding procedure • Limited to pathological myopia
Optimal Candidates	Children with progressive myopia	Active children with low-to-moderate myopia, aversion to daytime correction	Children/adolescents tolerant of soft lenses, unsuitable for Ortho-K	Progressive high myopia with posterior staphyloma or macular pathology

Orthokeratology, Ortho-K; LAMP, low-concentration atropine for myopia progression; CNV, choroidal neovascularization.

(Y. Li et al., 2022). These systems reduce reliance on subjective clinician interpretation, particularly in regions with limited specialist access. Telehealth platforms such as Cybersight AI further amplify this impact by enabling real-time, automated grading in low-resource settings, as evidenced by improved referral adherence in Rwanda compared with traditional human grading. However, the transition from theoretical promise to real-world clinical utility remains fraught with technical, ethical, and systemic challenges that demand critical scrutiny.

4.2. *Challenges in AI-driven prediction and diagnostic precision*

Despite these strides, critical limitations persist. A foremost concern is the heterogeneity and representativeness of training datasets (Aung et al., 2021). Most AI models are derived from homogeneous populations, often excluding underrepresented ethnic groups or individuals with comorbid ocular conditions. The Open Fundus Photograph Dataset with Pathologic Myopia Recognition and Anatomical Structure Annotation (PALM) dataset used for PM classification predominantly features East Asian cohorts, raising questions about its generalizability to African or European populations (H. Fang et al., 2024). This homogeneity risks algorithmic bias, as evidenced by performance drops when models trained on high-quality fundus images encounter low-resolution or artifact-laden data from real-world settings. Varadarajan et al. deep learning model for refractive error prediction, while groundbreaking, was validated on retrospective data from select clinics, neglecting socioenvironmental variables such as educational disparities or healthcare access that influence myopia development (Varadarajan et al., 2018). Technical reproducibility further complicates clinical translation. Studies frequently omit details on image preprocessing, model architecture, or threshold calibration, undermining cross-study

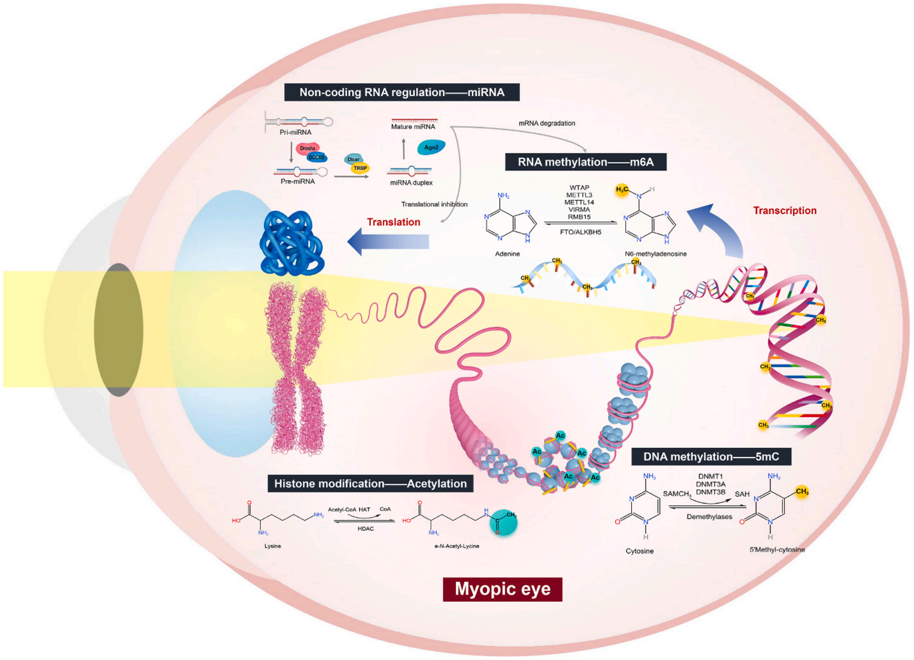


Fig. 5. Epigenetic events in myopia. m6A, N6-methyladenosine; 5 mC, 5-methylcytosine; mRNA, messenger RNA; miRNA, microRNA.

comparability. For example, Yang et al. developed a support vector machine (SVM)-based prediction model for adolescent myopia, which reported 93 % accuracy. However, the model's feature selection process lacked transparency, thereby precluding independent validation (X. Yang et al., 2020). Similarly, inconsistencies in disease definitions, including varying criteria for PM across studies, hinder the aggregation of datasets needed for robust AI training. The absence of standardized reporting frameworks, as critiqued by Wang et al., exacerbates this issue, leaving clinicians unable to assess whether a model's sensitivity of 95 % in a research setting translates to actionable insights in daily practice (Y. Wang et al., 2021).

The infrastructure gap in low- and middle-income countries (LMICs) presents another barrier. While smartphone-based screening tools such as Peek Acuity and AI-enabled portable fundus cameras (e.g., Singapore's DeepUWF system) democratize access, their deployment stumbles over erratic internet connectivity, power shortages, and inadequate technician training (Bastawrous et al., 2015; Cleland et al., 2024; W. Zhang et al., 2021; L. Zhao et al., 2019). In the automated algorithm for screening diabetic retinopathy trial, the use of non-mydriatic retinal photographs resulted in many images being ungradable (John et al., 2023). This challenge is also observed in India's telemedicine initiatives. Moreover, cost-effectiveness analyses remain sparse. Nguyen et al.'s Singaporean study found semi-automated AI-human hybrid models are more economical than fully automated systems are; however, similar evaluations in LMICs are rare, leaving policymakers without evidence to justify investments in AI infrastructure (H. V. Nguyen et al., 2016).

Ethical dilemmas loom large, particularly regarding data privacy and algorithmic accountability (Lopez et al., 2020; Ting et al., 2017). Federated learning and blockchain-based platforms, such as Tan et al.'s proof-of-concept for myopia detection, offer partial solutions by enabling multi-institutional collaboration without raw data exchange (T. E. Tan et al., 2021). However, these frameworks require computational resources and expertise, which are often absent in underfunded public health systems. Furthermore, the "black-box" nature of deep learning models erodes clinician trust (Kahn, 2017; F. Wang and Preininger, 2019). While explainable AI (XAI) techniques such as attention mapping or layer-wise relevance propagation are emerging, their integration into ophthalmic AI remains nascent (Abgrall et al., 2024; Ikram and Imran, 2025; Rong et al., 2024). A clinician cannot confidently act on an AI-generated referral for MM if the model's decision-making logic, which may be influenced by spurious correlations in the training data, is unclear.

4.3. *Strategic pathways for scalable implementation*

To bridge the data-action gap, a multi-dimensional strategy is imperative. First, diverse, longitudinal datasets must be prioritized (Fig. 6). Initiatives like the Beijing Myopia Cohort Study, which tracks genetic, biometric, and environmental factors, exemplify the potential of rich, multi-ethnic data pools. Second, standardized reporting guidelines, such as the CONSORT-AI and SPIRIT-AI extensions, should be mandated to increase reproducibility. Third, models for human-AI collaboration require refinement. In diabetic retinopathy screening, hybrid systems in which AI manages initial triage while clinicians review borderline cases have reduced workloads without compromising accuracy. This framework can be adapted for myopia management (X. Huang et al., 2022; Rajesh et al., 2023). Finally, policy-driven investments in digital literacy and infrastructure are essential. South Korea's national myopia prevention program, which integrates school-based AI screening with parent-facing mobile apps, demonstrates how systemic alignment can amplify AI's public health impact (Y. Lee et al., 2024).

AI holds unprecedented potential to reshape the clinical management of myopia, yet its current trajectory risks exacerbating inequities if deployed uncritically. By confronting data biases, fostering transparency, and embedding AI within strengthened health systems, the field can transition from fragmented pilot studies to scalable, ethical solutions. As Ting et al. caution, the democratization of AI in eye health demands not only technological innovation but also a commitment to equity, ensuring that the benefits of precision medicine extend beyond high-income clinics to the communities most burdened by preventable vision loss (Ting et al., 2019).

5. Therapeutic innovations

5.1. *The present status of various therapeutic procedures towards myopia*

5.1.1. *Atropine eye drops*

Bedrossian (1971) first reported that 1 % topical atropine could

Fig. 6. Bridging AI limitations to future research pathways in myopia management.

prevent the progression of low myopia (Bedrossian, 1971). A subsequent investigation by Hu et al. revealed a dose-dependent pattern in the efficacy of atropine treatment for myopia. The 1 % atropine concentration completely halted myopia progression (with a mean progression in control eyes of −0.42 D), but this high dose was accompanied by significant adverse effects, including 80 % light sensitivity and 13 % allergic conjunctivitis (D. N. Hu, 1998). In contrast, a 0.1 % concentration achieved 60 % efficacy with fewer side effects, and a 0.01 % concentration exhibited minimal efficacy but was free of adverse events. These findings suggest a trade-off between risk and benefit, with high-dose atropine being more suitable for rapid progression and low-dose atropine being preferred for long-term safety.

Subsequent trials confirmed a dose-dependent effect for atropine concentrations ranging from 0.01 % to 1.0 %, with concentrations greater than 0.1 % strongly associated with mydriasis-induced photophobia, near-vision blur, and myopia rebound upon discontinuation (Chia et al., 2016; C. Zhao et al., 2020). The clinical adoption of atropine was solidified by the Singapore National Eye Center's landmark trials. The Atropine for the Treatment of Myopia (ATOM)1 trial (2006, placebo-controlled) demonstrated the efficacy of 1 % atropine but also revealed severe refractive rebound after discontinuation (Chua et al., 2006). Its follow-up, ATOM2 (2012, open-label), shifted focus to lower concentrations, showing that 0.01 % atropine provided sustained control with minimal rebound, leading to its global acceptance as a first-line therapy (Chia et al., 2012). Subsequent studies across diverse populations revealed a 0.01 % atropine safety profile, with no clinically significant photophobia or near-vision blur despite modest efficacy (measurable reduction in axial elongation and myopia progression). Notably, both the low-concentration atropine for myopia progression (LAMP)1 and LAMP2 studies reported that 0.05 % atropine was the most effective concentration for controlling both SE progression and AL elongation but had no adverse effects on vision-related quality of life (Yam et al., 2019, 2023). These findings spurred the global adoption of low-dose atropine, which was supported by subsequent studies in diverse populations. Clinically, low-dose atropine reduces myopia progression and axial elongation via measurable margins, with no clinically significant visual side effects such as photophobia or near-vision blur. Its safety and efficacy profile have cemented its role as a first-line option for long-term myopia management in children.

5.1.2. Orthokeratology

The worldwide increase in the incidence of myopia among children and adolescents has prompted investigations into methods to slow its progression. Ortho-K, a non-invasive and reversible treatment option, has become a prominent clinical intervention, especially in East Asia, which has the highest prevalence of myopia. By utilizing reverse-geometry rigid gas-permeable contact lenses worn nocturnally, Ortho-K induces transient corneal reshaping through central epithelial thinning and mid-peripheral thickening (Swarbrick et al, 1998). This defocus is hypothesized to modulate retinal and choroidal signaling, inhibiting axial elongation, a primary driver of myopic progression. As these corneal modifications are reversible, consistent nightly lens wear is critical to sustain therapeutic effects; vision correction and axial elongation control diminish progressively upon treatment discontinuation.

Robust clinical evidence supports the efficacy of Ortho-K as a treatment for myopia (Si et al., 2015; Sun et al., 2015; Walline et al., 2008). The Longitudinal Ortho-K Research in Children (LORIC) study demonstrated a 43 % reduction in myopia progression over a two-year period compared with the use of spectacles (Cho et al., 2005). A comprehensive meta-analysis encompassing 38 randomized and observational studies further demonstrated 0.47 mm less annual AL elongation in Ortho-K users than in controls (Zaabaar et al., 2025).

Ortho-K presents several unique advantages, making it a desirable choice for numerous patients, especially children and adolescents. First, it is a non-invasive and reversible treatment option, unlike refractive surgery, which avoids permanent changes in the eye's structure. The reshaping of the cornea is temporary, and the cornea gradually reverts to its original shape without long-term effects if the treatment is discontinued. Second, it offers the freedom of wearing corrective lenses during the day, enabling users to maintain clear vision without glasses or contact lenses. This is particularly beneficial for individuals involved in sports, outdoor activities, or environments where glasses may be inconvenient or hazardous. Third, it has demonstrated efficacy in controlling myopia progression, with studies showing a substantial decrease in axial elongation rates in children compared with conventional corrective methods (Charm and Cho, 2013). This can reduce the frequency of prescription changes and potentially lower the risk of developing severe complications such as retinal detachment, glaucoma, and MM. Fourth, it can enhance self-esteem and quality of life for children by improving their self-image and facilitating more natural social interactions, which may positively affect their psychosocial development.

Despite these advantages, Ortho-K also presents several limitations and challenges. First, strict adherence to nightly lens wear is necessary; inconsistent use can lead to suboptimal vision the following day. Second, it involves higher upfront and maintenance costs than traditional spectacle or soft contact lens correction does, including the expense of custom lenses, frequent follow-up visits, and potential lens replacements, which are often not covered by insurance. Third, while rare, there is a risk of infection, including the rare occurrence of microbial keratitis, which requires careful hygiene practices and regular monitoring to prevent infection (Bullimore et al., 2013). The incidence of microbial keratitis is approximately 13.9 cases per 10,000 patient-years in children (Bullimore and Johnson, 2020). Adherence to strict hygiene practices, proper lens handling, and regular follow-up appointments are essential to minimize the risk of infection. Fourth, it may not be suitable for all patients, as specific corneal shapes, high levels of astigmatism, or certain ocular surface conditions can make some individuals less suitable for treatment. Fifth, during the initial period of lens wear, patients may experience temporary changes in visual acuity or contrast sensitivity, particularly under low-light conditions, which can affect daily activities until the eyes adapt to the lenses.

In conclusion, Ortho-K represents a validated therapeutic strategy for concurrent myopia correction and progression management in pediatric populations. Optimal outcomes require meticulous lens care, parental oversight of compliance, and individualized clinical management guided by AL monitoring and corneal integrity assessments. If properly applied, Ortho-K plays a crucial role in combating the increasing global issue of progressive myopia.

5.1.3. *Soft multifocal contact lenses*

Soft multifocal contact lenses, which were originally developed for presbyopia, have been repurposed as a therapeutic intervention for managing myopia by tackling peripheral hyperopic blur, a factor that can contribute to axial elongation (Pérez-Prados et al., 2017). These lenses utilize a distance-center design, which features a central zone optimized for clear distance vision and concentric peripheral zones with additional positive power. This design induces myopic defocus on the peripheral retina while preserving central visual acuity, suggesting that these defocus signals may suppress excessive ocular growth (Ruiz-Pomeda et al., 2018). Unlike single-vision corrections, which can exacerbate peripheral hyperopia, multifocal lenses aim to reshape the retinal image profile to mitigate the stimuli that promote elongation. Clinical efficacy is supported by the Bifocal Lenses In Nearsighted Kids (BLINK) study, a three-year randomized controlled trial showing that high-level (+2.50 D) multifocal lenses significantly slowed myopia progression and axial elongation compared with single vision (Walline et al., 2020). Recent meta-analyses corroborate these findings, demonstrating statistically significant reductions in SER and AL elongation with soft multifocal lenses (Cavuoto et al., 2025; J. Huang et al., 2016; Zaabaar et al., 2025).

Soft multifocal contact lenses provide non-invasive, reversible myopia control alongside vision correction, eliminating the need for nighttime wear and offering daytime visual freedom. They grant visual freedom during the day without the need for nighttime wear and maintain a good safety record when used with appropriate hygiene and regular monitoring. The design is similar to that of conventional contact lenses, which increases patient acceptance and eases the transition to this form of therapy. However, limitations exist. While generally well-tolerated, some patients may experience initial adaptation challenges, including transient ghosting, reduced contrast sensitivity, or discomfort in dry environments. Certain users may also report issues with glare, reduced night vision or lens-related complications (Song et al., 2024). Patient adherence is a notable concern, with existing studies reporting dropout rates of 25 %–43 %, primarily due to lens-related discomfort (Chamberlain et al., 2019; Lam et al., 2014; Pauné et al., 2015; Sankaridurg et al., 2011; Walline et al., 2013). Cost barriers may also arise, as multifocal lenses are typically pricier than single-vision options and are often excluded from health insurance coverage. Efficacy variability linked to individual factors such as pupil size or accommodative responses underscores the need for personalized fitting. Additionally, clinicians may require extended follow-up periods to address fitting complexities and ensure optimal outcomes.

In conclusion, soft multifocal contact lenses, particularly those with a center-distance configuration, offer an effective and well-tolerated option for managing childhood myopia. When prescribed and monitored appropriately, these lenses provide a safe and practical solution for children and adolescents at risk of high myopia. Future research should focus on optimizing lens design and individualizing treatment protocols to maximize efficacy.

5.1.4. *Surgical procedure*

While traditional treatments typically focus on managing symptoms, posterior scleral reinforcement (PSR) stands out for its ability to target the biomechanical roots of progressive scleral ectasia. Initially, proposed in the 1950s, PSR seeks to stabilize deformation of the posterior pole via exogenous scaffold implantation, thereby mitigating axial elongation and reducing the incidence of secondary retinal pathologies. The traditional ab-externo technique was employed to reinforce the ocular surface and maintain the integrity of the scleral interface or wall, providing protection for ocular tissues against the erosive effects of implantable devices (Freedman, 1987; Q. D. Nguyen and Foster, 1999; Wigton et al., 2014).

Several studies have examined the long-term efficacy of PSR surgery. A three-year study revealed the efficacy of PSR in 59 eyes of 40 patients with high myopia. The PSR-treated group exhibited a significant reduction in axial elongation (0.14 ± 0.09 mm/year compared with 0.30 ± 0.11 mm/year in the control group), as well as a decrease in the progression of MM and stable or improved best-corrected visual acuity (BCVA) in 72 % of the treated eyes (Peng et al., 2019). Posterior staphyloma, a characteristic feature of pathological myopia, is characterized by localized scleral ectasia that results in retinal stretching and subsequent visual impairment. Ohno-Matsui et al. (2018) highlighted the crucial role of biomechanical scleral support in preventing progressive staphylomatous changes. PSR helps flatten the posterior pole, thereby decreasing retinal tension and the risk of foveoschisis or macular holes (Ohno-Matsui and Jonas, 2019). Similarly, (He et al., 2022) investigated PSR in patients with MTM and reported significant resolution of macular retinoschisis and improved foveal contour in 93.75 % of eyes without any significant adverse events (Q. He et al., 2022).

Recent innovations have introduced minimally invasive ab-interno techniques enabling intraocular scleral tissue application. Through minimal modifications to precise geometries and delivery via ab-interno micro-interventional instrumentation, scleral bio-tissue can provide durable and non-resorbable structural reinforcement for surgical applications (De Francesco et al., 2024). When minimally modified to obtain precise geometries and delivered with ab-interno micro-interventional instrumentation, scleral bio-tissue can provide durable and non-resorbable structural reinforcement for glaucoma and retina surgical applications. The biomaterial properties of the scleral graft can enable a new frontier of clinical utility for both conductive and/or occlusive scaffolding with intraocular implantation.

Graft material selection remains a critical determinant of surgical success, influencing both procedural feasibility and long-term biomechanical outcomes. Ma et al. conducted a comparative study of the elasticity, tensile strength, and biocompatibility of lyophilized dura mater, processed human sclera, and synthetic materials (J. Ma et al., 2022). The processed human sclera exhibited excellent conformability and integration with the host tissue, whereas synthetic meshes provided benefits in terms of uniformity and sterilization but raised concerns about potential inflammatory responses. Therefore, the optimal graft material should strike a balance between flexibility and strength to adjust the curvature of the sclera without compromising choroidal circulation.

PSR is a promising structural intervention for controlling progressive myopia, particularly in eyes with posterior staphyloma and associated macular pathology. Integration with early diagnostic tools and adjunct therapies may further optimize its role in modern ophthalmic practice.

However, PSR has several limitations. Despite its benefits, PSR is associated with postoperative complications, including ocular hypertension, conjunctival edema, subconjunctival hemorrhage, choroidal atrophy, choroidal neovascularization, diplopia or eye movement disorder, retinal detachment, optic atrophy and graft rejection (Cao et al., 2020; Curtin and Whitmore, 1987). However, most studies indicate a favorable safety record when using biocompatible grafts and minimally invasive surgical techniques (Q. He et al., 2022; Széll et al., 2022). The current evidence has limitations, such as variability in surgical methods, relatively short follow-up durations, and a lack of standardized criteria for patient selection. Future research should focus on multicenter, randomized controlled trials with longer-term follow-up to establish standardized protocols and assess long-term anatomical and functional outcomes.

5.1.5. *Comparison of various procedures*

Several studies have systematically assessed various interventions designed to slow the progression of myopia in children, with reported efficacy varying depending on the approach taken. A comprehensive network meta-analysis conducted by Huang et al. (covering the period from the inception of studies to August 2014) analyzed 30 randomized controlled trials involving 5,422 eyes and reported that atropine eye drops were the most effective intervention (J. Huang et al., 2016). Compared with placebo or single-vision spectacles, high, moderate, and low doses of atropine significantly reduced myopia progression, with the efficacy decreasing progressively with decreasing concentrations (SER from high to low: 0.68, 0.53 and 0.53 D/year; AL from high to low: 0.21, −0.21, and −0.15 mm/year, respectively). These results are consistent with those of subsequent meta-analyses and clinical trials, including those discussed by Lagrèze and Schaeffel, who noted that low-concentration atropine treatments (aimed at minimizing side effects) could decrease myopia progression by as much as 0.71 diopters over a two-year period (Lagrèze and Schaeffel, 2017). Mak et al. and Weiss et al. further corroborated these conclusions in literature reviews, emphasizing that atropine eye drops are the most effective treatment, followed by Ortho-K, in slowing axial elongation (Mak et al., 2018; Weiss and Park, 2019). Huang et al. reported that Ortho-K lenses were linked to a reduction in AL of −0.15 mm/year, and that peripheral defocus-modifying contact lenses also exhibited a significant, although smaller, effect with an AL reduction of −0.11 mm/year (J. Huang et al., 2016).

Overall, the evidence collectively identifies atropine eye drops as the most effective intervention for halting the progression of myopia in children, whereas Ortho-K and peripheral defocus-modifying contact lenses demonstrate moderate levels of efficacy. Specially designed spectacle lenses, such as multifocals, offer less pronounced benefits. These findings highlight the importance of employing targeted interventions to address the growing prevalence of pediatric myopia. A consolidated cross-sectional comparison of all interventions reviewed in this section, including their mechanisms, relative efficacy, and practical clinical considerations, is presented in Table 2.

5.2. *Repeated low-level red-light therapy*

Repeated low-level red-light (RLRL) therapy has emerged as a promising approach for the management of myopia, drawing significant attention from both clinical and academic settings. Therapy involves the use of low-intensity red light and has shown potential for halting or even reversing some of the processes underlying myopia progression, particularly in children and adolescents. While RLRL therapy is a noninvasive intervention, its long-term safety, especially regarding repeated exposure, remains uncertain. A recent study has indicated the potential for cone photoreceptor damage associated with RLRL, raising concerns about its safety for the retina (Liao et al., 2025). Therefore, caution is warranted when considering RLRL as an alternative to traditional myopia control methods, such as atropine eye drops or Ortho-k, which also have their own associated side effects or complications (J. Huang et al., 2016).

The potential mechanism of RLRL in controlling myopia is still under investigation, as indicated by the following research clues (Fig. 7). First, oxidative stress and inflammatory responses are believed to play significant roles in the onset and progression of myopia. Studies suggest that hypoxia-induced oxidative damage may disrupt the neuromodulatory patterns of nitric oxide (NO) and dopamine, which are critical for eye development (L. Dai et al., 2019; Francisco et al., 2015). RLRL intervention appears to have a pronounced effect on the NO system, leading to a reduction in oxidative stress and levels of specific inflammatory factors, such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor-α (TNF-α) (Ojaghi et al., 2014; Rubis, 2013; F. Xiong et al., 2021). Previous research has demonstrated that 670 nm red light can interact with the mitochondria in retinal cells, resulting in increased energy production by activating cytochrome *c* oxidase (Begum et al., 2013). Following exposure to 670 nm light, cytochrome *c* oxidase (COX) was significantly upregulated, thereby enhancing the efficiency of oxidative phosphorylation. This increase in energy metabolism resulted in elevated ATP production and a reduction in reactive oxygen species (ROS) levels, consequently mitigating oxidative stress and inflammatory responses within the outer retina. Second, dopamine is thought to act as a 'stop signal' in refractive development. It has been shown that bright light stimulation can enhance retinal dopamine synthesis and release (Cohen et al., 2012). Red light at 650 nm may activate this pathway, subsequently influencing choroidal vessels by stimulating the NO system (e.g., dilating blood vessels and enhancing blood flow), which may promote choroidal thickening (Cao et al., 2024; J. Dong et al., 2023; X. He et al., 2023; Y. Jiang et al., 2022; Nickla et al., 2009; Nickla and Wildsoet, 2004; Sekaran et al., 2005; Tang et al., 2023; Xiang et al., 2025; R. Xiong et al., 2023; Zhu et al., 2023). Third, the choroid, a critical structure for supplying nutrition to the retina, is thought to regulate eye growth by influencing the metabolism of the scleral extracellular matrix (Cicinelli et al., 2017; Nickla and Wallman, 2010; Queirós et al., 2018; Summers, 2013; Wallman et al., 1995). Clinical studies have observed a significant correlation between the shortening of AL of the eye after RLRL intervention and the increase in subfoveal choroidal thickness (SFChT) (H. Chen et al., 2023; J. Dong et al., 2023; Y. Jiang et al., 2022; Tian et al., 2022; W. Wang et al., 2023). Based on these findings, we propose a hypothesis that RLRL may inhibit excessive axial eye growth by enhancing choroidal oxygenation and optimizing the scleral hypoxic microenvironment (Fu et al., 2020; H. Wu et al., 2018). NO may exert a range of downstream anti-hypoxic effects, contributing to the alleviation of scleral hypoxia. Activation of the TGF-β/Smad pathway, which increases the production of *COL1A1*, may promote scleral remodeling. Furthermore, this activation, in conjunction with NO, may help reverse the transdifferentiation of scleral fibroblasts (P. Zhang and Zhu, 2022). We propose a hypothetical model: oxidative stress inhibition as the initiating link, the dopamine-NO system as the signaling hub, and choroidal function optimization as the effector terminal (Fig. 7). However, the quantitative relationships between these links and individual differences in responses require further verification through prospective studies. It is particularly important to clarify the intervention thresholds for different age groups and degrees of myopia, as well as to establish long-term safety parameters. A systematic review and meta-analysis by Youssef et al. (2024) underscored the efficacy of RLRL therapy, reporting significant improvements in both AL and spherical equivalent refraction (SER) after treatment (Youssef et al., 2024). These findings are consistent with those of Zhu et al., who provided scientific evidence supporting RLRL therapy as a unique paradigm for myopia control and highlighted its potential benefits (Zhu et al., 2023).

However, while the promise of this approach is clear, several issues surrounding its efficacy, mechanisms, and long-term safety still warrant critical examination. Some studies have noted a rebound effect upon cessation of therapy, where myopia progression accelerates after

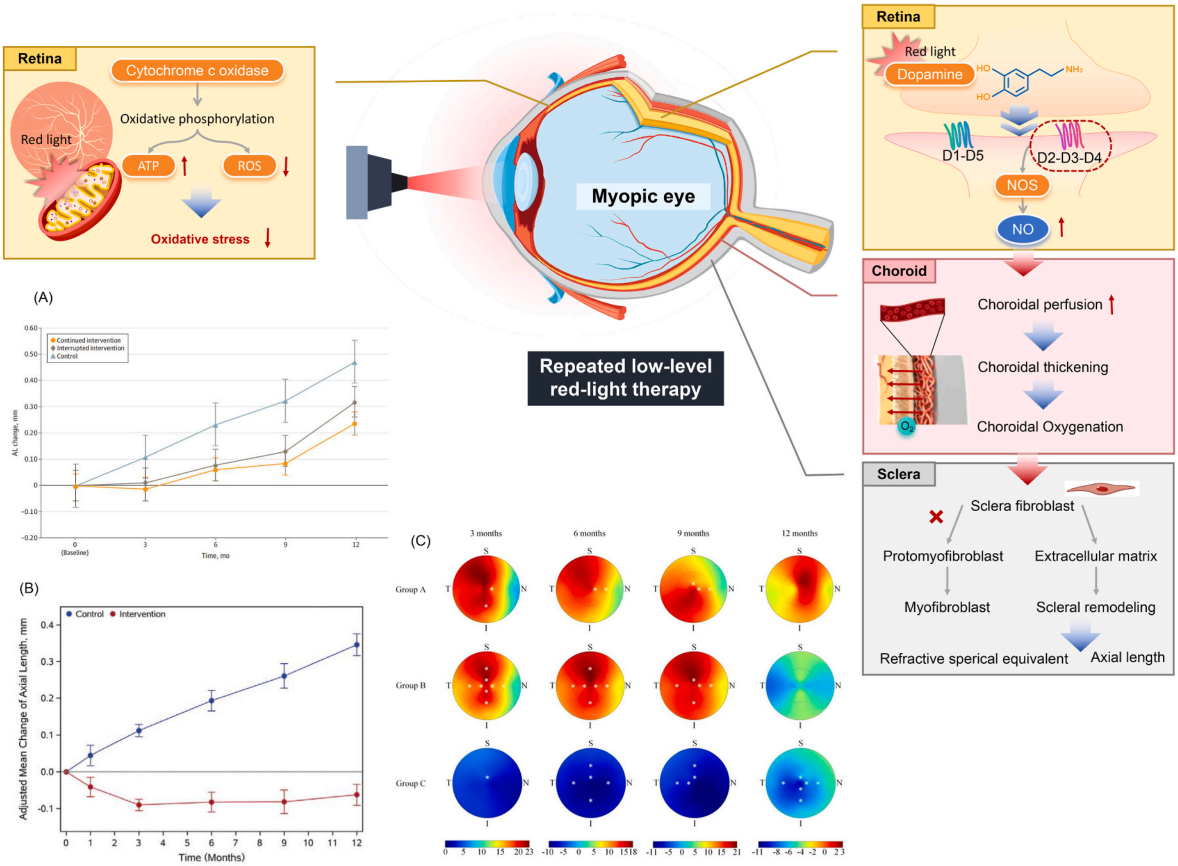


Fig. 7. Potential Mechanisms of Low-Level Red-Light Therapy in Myopi**a Control.** (A) and (B), sourced from studies by He et al. and Xu et al., respectively, both demonstrate axial length growth. (C), from research by Xiang et al., shows the changes in choroidal thickness following red-light therapy. In (C), Group A represents the continued intervention group, Group B represents the interrupted intervention group, and Group C represents the control group. The labels T, S, N, and I denote the temporal, superior, nasal, and inferior regions of the macula, respectively. The asterisk (*) indicates a statistically significant difference (P < 0.05) when adjacent Sections are compared. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

treatment stops (H. Chen et al., 2023; F. Xiong et al., 2021). This phenomenon raises concerns about whether RLRL can offer a permanent solution or if its effects are merely transient. Additionally, the safety profile of RLRL, although generally favorable, has been questioned in light of reports indicating potential short-term side effects such as temporary afterimages (X. He et al., 2023; Z. H. Lin et al., 2023; H. Liu et al., 2023; Tian and Xiao, 2023). These findings point to the necessity of further research to ascertain the long-term safety of the treatment, particularly with respect to retinal health and the potential for cumulative damage with repeated exposure. Critics of RLRL therapy also argue that the optimal parameters for treatment, such as light intensity, exposure duration, and frequency, are still not well established (Zhu et al., 2023). Different studies have used varying protocols, which complicates the generalizability of the results. The studies included in the meta-analysis by Youssef et al. (2024) varied in terms of the exact dosage and regimen, which could account for some of the discrepancies observed in clinical outcomes (Youssef et al., 2024). Moreover, while short-term results are promising, there is a lack of large-scale, long-term trials to confirm whether the benefits are sustained over years of treatment. Furthermore, the impact of RLRL therapy on the broader spectrum of myopia-related complications remains to be fully understood. High myopia is associated with an increased risk of conditions such as maculopathy, glaucoma, and retinal detachment. While RLRL therapy may slow axial elongation, it is unclear whether it also reduces the risks associated with these severe complications. Some studies suggest that RLRL could protect against retinal damage through its neuroprotective effects, but this remains speculative without solid evidence from long-term studies (Beirne et al., 2017; Clarke et al., 2001; Sommer et al., 2001). The cost-effectiveness of RLRL therapy also warrants attention. Treatment requires access to specialized devices, which may not be readily available in all clinical settings. This could limit its widespread implementation, particularly in lower-resource environments. Furthermore, the affordability of RLRL devices, compared with more established methods such as spectacle lenses or atropine, remains a key consideration for both clinicians and patients.

While these findings support the potential of red-light therapy as a promising intervention for myopia control, the long-term safety and optimal dosage of red-light therapy remain areas for further research (Chang et al., 2024; H. Liu et al., 2023; Ostrin and Schill, 2024). The evidence supporting its efficacy is robust in the short term, but the long-term safety, optimal treatment protocols, and cost-effectiveness of RLRL therapy need further investigation. Until these aspects are fully explored, RLRL should be viewed as a promising but still experimental treatment option for myopia. Future research, particularly large-scale, long-duration studies, will be crucial in determining whether RLRL can fulfill its potential as a mainstream therapeutic approach for myopia control.

5.3. Combination therapies

Recent randomized trials highlight the potential of combined interventions to enhance myopia control beyond monotherapy. Compared with the Ortho-k group, the combined Atropine with the Ortho-k (AOK) group demonstrated a slower axial elongation rate (mean (SD), 0.07 (0.16) mm vs. 0.16 (0.15) mm; $P = 0.03$) (Q. Tan et al., 2020). Similarly, trials integrating low-dose atropine (0.01–0.25 %) with auricular acupoint stimulation (AAS) reported additive effects, achieving myopia progression reductions comparable to those associated with higher atropine concentrations (0.5 %) while minimizing photophobia (Cheng and Hsieh, 2014; X. Kong et al., 2023; X. H. Kong et al., 2021; C. K. Liang et al., 2008). These findings suggest that hybrid approaches may address the multi-factorial nature of myopia progression via synergistic mechanisms: atropine may modulate choroidal thickening and pupil dynamics, Ortho-K redistributes peripheral retinal defocus, and AAS (acupoint-assisted stimulation) activates visual-related acupoints to enhance ocular microcirculation, collectively reducing myopia progression (Bai et al., 2023; Oleson, 2003; H. Xu et al., 2023). Critically, such combinations mitigate the rebound effects observed after high-dose atropine cessation, as lower concentrations paired with optical methods sustain efficacy with fewer side effects. However, heterogeneity in study designs-variable atropine concentrations and inconsistent AAS protocols-limits cross-trial comparability. Standardized protocols are urgently needed to validate these synergies. AI holds transformative potential for personalizing hybrid interventions. Machine learning models can integrate multimodal data, including GRS, biometric parameters (such as choroidal thickness and AL velocity), and environmental factors (such as near-work hours and outdoor exposure), to predict individual responses (Atehortúa et al., 2023; Jabbour et al., 2024; Kovacheva et al., 2024; Tao et al., 2023). For example, one study found that children with baseline SE ≤ -2.25 D or younger age derived greater benefits from 0.01 % atropine + AAS, suggesting that AI could stratify patients for tailored combinations (X. Kong et al., 2023). Reinforcement learning algorithms might dynamically adjust intervention intensity (e.g., atropine dosing frequency, AAS duration) based on real-time OCT biomarkers or wearable device metrics (Nath et al., 2022). While promising, hybrid strategies face unresolved issues. First, long-term safety profiles remain unclear: 0.01 % atropine + Ortho-K trials reported transient choroidal thickening but lacked 5-year follow-up data for complications such as microbial keratitis (X. Kong et al., 2023). Second, the mechanisms of AAS are poorly understood; robust mechanistic studies on the effects of the former on intraocular pressure (IOP) and anterior chamber depth are lacking. Third, the implementation of AI necessitates large-scale, diverse datasets to mitigate algorithmic bias, which is a significant gap in current myopia research that is predominantly focused on East Asian cohorts. Hybrid interventions represent a paradigm shift in myopia management, leveraging complementary mechanisms to maximize efficacy and tolerability. AI-driven precision medicine could revolutionize this field by enabling real-time, adaptive treatment protocols. However, rigorous validation through multi-center trials and mechanistic studies is essential to translate these innovations into clinical practice. Future research must prioritize equity in AI model training and address long-term safety to ensure global applicability.

5.4. Gene editing

Gene editing technologies, particularly clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9, base editors, and prime editors, hold potential for addressing needs in the treatment of various eye diseases, such as macular degeneration, glaucoma and retinitis pigmentosa (Giannelli et al., 2018; Gumerson et al., 2022; Jain et al., 2017; Mandai et al., 2017; Rayana et al., 2021). This underscores the extensive potential of gene editing in ophthalmology. However, the multifactorial nature of myopia and PM, which involves genetic, environmental, and biomechanical mechanisms, poses significantly greater therapeutic challenges compared to monogenic ocular disorders.

Genetic studies have identified associations between rare variants in genes such as *ARR3*, *BSG*, *CTSH*, *CCDC111*, *LEPREL1*, *LOXL3*, *LRPAP1*, *NDUFAF7*, *P4HA2*, *SCO2*, *SLC39A5*, *UNC5D*, and *ZNF644* and high myopia (Tedja et al., 2019). Intraretinal neovascularization is a common pathogenic change in several ocular diseases associated with retinal and choroidal circulation, including MM, proliferative diabetic retinopathy (PDR), age-related macular degeneration (AMD), and retinopathy of prematurity (ROP) (Bressler, 2009; Dreyfuss et al., 2015). VEGF is a key therapeutic target shared by these diseases (Ferrara and Davis-Smyth, 1997). Current first-line therapies, primarily intravitreal anti-VEGF agents such as ranibizumab and bevacizumab, demonstrate efficacy in stabilizing vision by reducing CNV activity. However, these treatments require repeated injections, impose significant economic burdens, and fail to address the underlying pathophysiology driving disease progression (Toutounchian et al., 2022). Although photodynamic therapy (PDT), though occasionally used in refractory cases, shows inconsistent long-term benefits and risks exacerbating chorioretinal atrophy (Parravano et al., 2014). The limitations of these temporary measures underscore the urgent need for therapies that specifically target the molecular drivers of MM and myopia pathogenesis, providing durable solutions rather than merely symptomatic relief. Although these genetic and molecular insights are only partially validated in animal models of pathological myopia, they represent potential targets for advanced therapeutic modalities, such as gene editing, pending definitive mechanistic clarification. However, given the multifactorial nature of myopia and PM, targeting individual genes or pathways through gene editing is unlikely to fully address the complexity of the disease, thereby limiting its feasibility as a standalone therapeutic approach.

Potential targets under investigation include pathways involved in angiogenesis (e.g., VEGF), scleral extracellular matrix remodeling (e.g., collagen-related genes, TGF-β signaling), and inflammation (e.g., complement factors) (J. Chen et al., 2024a; Harper and Summers, 2015; X. Wang et al., 2022; Zeng et al., 2023). While anti-VEGF agents neutralize excess VEGF protein, CRISPR-based approaches can suppress VEGF gene expression at the transcriptional level. For example, engineered Cas9 systems targeting VEGF promoters or enhancers might achieve sustained downregulation, reducing dependency on recurrent injections. Animal models, while still in the exploratory phase and necessitating further mechanistic clarification, have prompted investigations into the application of gene editing for the regulation of ocular growth. A recent study in mice revealed that the use of CRISPR-Cas9 technology to knockout the ATF6 gene in scleral cells or the simultaneous deletion of both PERK and ATF6 effectively suppressed AL elongation and thereby inhibited the onset of lens-induced myopia (LIM) (Ikeda et al., 2022). Similarly, associations between complement factor genes (*C2*, *C3* and *C4*) and MM suggest potential targets for modulating inflammatory pathways, though causal roles and therapeutic potential require rigorous validation (Zeng et al., 2023). Base editors might modulate these loci to restore regulatory balance, mitigating inflammation-driven retinal damage (Tran et al., 2019).

Recent studies have highlighted the feasibility of ocular gene editing. In mouse models of Leber congenital amaurosis, subretinal delivery of dual vector adeno-associated virus (AAV) vectors encoding adenine base editors achieved up to 40 % correction of RPE65 mutations with minimal off-target effects, restoring retinal function (Choi et al., 2022). Similarly, CRISPR-Cas9 disruption of Aquaporin 1 in the ciliary epithelium reduces intraocular pressure in glaucoma models, a strategy adaptable to MM-associated scleral remodeling (Wu et al., 2020). For CNV, optogenetic approaches using AAV-delivered light-sensitive opsins have restored light perception in retinitis pigmentosa, suggesting analogous applications for reactivating degenerating photoreceptors in MM (Poboży et al., 2025). Notably, a major limitation of AAV is its small packaging capacity, which is restricted to approximately 5 kb (Trapani, 2018). The therapeutic genes for many hereditary retinal degenerations are too large to be packaged into a single AAV capsid. ABCA4, the ideal target for Stargardt disease gene therapy, has a size of 6.8 kb (R. Li et al., 2023). To overcome the limitations of AAV vector capacity, researchers have developed dual-vector strategies for ultra-large transgenes by leveraging the ability of the AAV genome to be tandemly linked (Dyka et al., 2019; McClements et al., 2020; Riedmayr et al., 2023). The large transgene cassette is divided into two separate vectors, which may allow for efficient integration of large therapeutic constructs, addressing mutations common in MM-associated atrophy. Direct in vivo reprogramming of Müller glia into photoreceptors via CRISPR-activated neurogenic factors offers a novel avenue to replace lost cells in advanced MM (R. Wong et al., 2020). However, the inflammatory milieu of degenerative retinas may impede transdifferentiation efficiency. Light-inducible Cas9 systems or tissue-specific promoters (e.g., VMD2 for RPE) could increase precision, minimizing off-target effects in non-diseased regions (J. Park et al., 2023).

Despite the aforementioned advantages, several barriers hinder its clinical translation in the field of ophthalmology. Efficient and safe targeting of specific retinal or choroidal cell types remains a significant challenge. Subretinal delivery can lead to transient retinal detachment, which may exacerbate damage to the fragile, degenerating retina (Prosseda et al., 2022). Safety concerns, including potential off-target effects and immune responses to vectors or editors, necessitate the continuous refinement of gene editing tools, including the development of tissue-specific promoters and engineered capsids, as well as rigorous long-term monitoring.

Gene editing holds significant potential for the management of myopia and related ocular diseases, however, its transition to clinical practice faces several scientific and technical challenges. The advancement of this field critically depends on three key components: first, enhancing our understanding of the molecular pathogenesis of myopia and establishing precise disease modeling systems; second, overcoming biological barriers in gene delivery systems to ensure stable expression within target tissues; and third, developing robust long-term safety evaluation frameworks to minimize off-target effects. Although gene editing offers conceptual intervention strategies, its clinical application is limited by the multifactorial etiology of myopia. Current evidence suggests that gene editing may primarily serve to elucidate disease mechanisms and identify novel therapeutic targets, rather than acting as an immediate clinical intervention.

5.5. *Myopic maculopathy: pathogenesis to therapy*

5.5.1. *Pathogenic mechanisms*

Among MM lesions, diffuse atrophy (category 2 according to the META-PM classification) is characterized by extreme choroidal thinning (Deng et al., 2024; Y. Fang et al., 2019). Even in highly myopic patients without MM, reduced choroidal thickness was independently associated with worse BCVA (Y. Wang et al., 2024). In eyes with PM, extreme choroidal thinning can begin in childhood (Deng et al., 2024; Yokoi et al., 2016, 2017). This thinning starts abruptly temporal to the ON, whereas the choroidal thickness is relatively preserved in the fovea and temporal to the fovea (Z. Jiang et al., 2023; Jonas et al., 2023a; Yokoi et al., 2017). These findings suggest that choroidal thinning may not result from circulatory disturbances but rather from mechanical compression between the BM and the sclera.

Patchy atrophy (category 3 according to the META-PM classification) is characterized by defects in the BM and the retinal pigment epithelium (RPE) (Du et al., 2020; Ohno-Matsui et al., 2012; Ohno-Matsui et al., 2016a). The inner retina subsequently comes into direct contact with the sclera. The area of patchy atrophy typically does not involve the fovea. Therefore, even as it enlarges, the fovea and central vision are usually preserved. A recent study revealed that 11 % of eyes with patchy atrophy presented OCT features characteristic of active multi-focal choroiditis/punctate inner choroidopathy (MFC/PIC) lesions (Hady et al., 2022). These findings suggest that inflammation may play a significant role in the development of patchy atrophy.

Other lesions, such as lacquer cracks (C. F. Liu et al., 2014; Neelam et al., 2024), MNV- and MNV-related macular atrophy (Ohno-Matsui et al., 2018; T. Y. Wong et al., 2015), and dome-shaped macula (García-Zamora et al., 2023; Jonas et al., 2025), are characterized by BM defects. The histology of macular BM defects lacking RPE cells and photoreceptors implies that they correspond to an absolute scotoma in the visual field (Jonas et al., 2023a). A recent histomorphometric study also suggested an association between BM defects and the stretching of the adjacent retinal nerve fiber layer. Furthermore, axial elongation-induced stretching of the BM may be a key factor in the development of BM defects (Panda-Jonas et al., 2023).

Most cases of macular atrophy (category 4 according to the META-PM classification) represent the atrophic stage of MNV, with only a small percentage resulting from secondary foveal involvement due to the enlargement of patchy atrophy. Among them, the development of MNV, MNV-related macular atrophy, and enlargement of MNV-related macular atrophy are major causes of central vision loss (Y. Fang et al., 2018). Wang et al. demonstrated that MNV- and MNV-related macular atrophy were significant predictive factors for long-term visual outcomes in patients with PM (Y. Wang et al., 2023).

To better understand the structural basis of these lesions, OCT-based classification systems have provided valuable insights into the pathogenic mechanisms underlying MM progression. Fang et al. proposed progression patterns of MM based on the corresponding characteristics of the OCT findings. The earliest detectable change is a significant thinning of the choroid, which coincides with the appearance of fundus tessellation and is considered the initial clinical sign of MM development. With aging and axial elongation, choroidal thinning initially develops nasal to the fovea, and is recognized as PDCA on fundus examination. Over time, the thinning extends across the entire posterior pole, evolving into MDCA. In more advanced stages, atrophic lesions, such as patchy atrophy and macular atrophy (both CNV-related and patchy-related) come from the formation and subsequent enlargement of defects in BM (Y. Fang et al., 2019).

5.5.2. *Pathogenesis of myopic MNV*

The pathogenesis of myopic MNV is not yet fully understood. However, structural changes in eyes with PM are believed to contribute to its development. MNV has been reported to occur along the edges of the peripapillary conus (Nagaoka et al., 2011), lacquering cracks and patchy atrophy (Ohno-Matsui et al., 2003). The peripapillary gamma zone is also characterized by BM defects (Jonas et al., 2023b; Jonas et al., 2012). These findings suggest that BM defects located very close to the fovea may serve as precursors to MNVs. In this context, myopic MNVs may share similarities with MNVs that occur secondary to traumatic choroidal rupture.

MNV is a common complication of MFCs/PICs(Cunningham et al., 2020; Servillo et al., 2025). Hady et al. reported that in patients with patchy atrophy that initially presented as MFC/PIC, 81.8 % of the eyes developed MNV(Hady et al., 2022). Gallego-Pinazo et al. reported that the overlap between myopic atrophy and MFC is more frequent in patients after the fifth decade of life, suggesting that chorioretinal atrophic changes may develop in association with previously healed MFC lesions (Gallego-Pinazo et al., 2021). In such cases, anti-inflammatory therapies may be beneficial in reducing the risk of MNV development.

Neovascularization of the macula is a common complication of both AMD and PM. A recent genome-wide meta-analysis including 608 cases and 2175 controls identified rs56257842 at TEX29-LINC02337 as a novel susceptibility SNP for myopic MNV and suggested shared genetic susceptibility between myopic MNV and AMD (Morino et al., 2025).

5.5.3. *Current therapies*

Prior to the availability of anti-angiogenesis therapy, verteporfin photodynamic therapy (vPDT) was the standard treatment for patients with myopic MNV (Ng et al., 2023). However, its long-term visual outcomes remain controversial. A randomized clinical trial reported that compared with a placebo, PDT did not have better visual outcomes after two years (Blinder et al., 2003). Additionally, standard-fluence PDT may contribute to chorioretinal atrophy in the long term (Giansanti et al., 2012; Rishi et al., 2016). Given these limitations, the current standard of care for MNVs is treatment with anti-VEGF agents. The efficacy and safety of intravitreal anti-VEGF therapy for the treatment of myopic MNV have been evaluated in numerous clinical trials. The results have conclusively demonstrated that intravitreal ranibizumab, aflibercept, and conbercept lead to significant mean visual acuity gains in patients with myopic MNV at their primary endpoints, with excellent safety profiles.

In a phase III, randomized, double-masked, multi-center study (RADIANCE), the efficacy and safety of two regimens of intravitreal 0.5 mg ranibizumab (guided by visual stabilization or disease activity) for MNV were compared against those of vPDT (Wolf et al., 2014). These findings suggest that although eyes previously treated with vPDT may still experience vision gains after switching to ranibizumab, the improvement may not be as pronounced as that in eyes treated initially with ranibizumab. The BRILLIANCE study further assessed the efficacy and safety of ranibizumab for regulatory approval in China, confirming the results of the RADIANCE study (Y. Chen et al., 2019). While the RADIANCE study included both Asian and white populations, the BRILLIANCE study focused on a purely Asian (predominantly Chinese) cohort. Overall, the BRILLIANCE study corroborated the efficacy of ranibizumab in treating myopic MNV, regardless of the retreatment criteria. Additionally, the LUMINOUS study evaluated the safety and effectiveness of ranibizumab in real-world settings across all its indications, including myopic MNV (Ikuno et al., 2015). The efficacy and safety of aflibercept were evaluated in a 48-week, phase III, multi-center, randomized, double-masked, sham-controlled trial (MYRROR) (Ikuno et al., 2015). The efficacy and safety of intravitreal conbercept for treating myopic MNV were assessed in the phase III, randomized, multi-center, double-masked, sham-controlled (SHINY) trial (L. Gao et al., 2024). The off-label use of intravitreal bevacizumab (Kasahara et al., 2017; Ruiz-Moreno et al., 2013; Ruiz-Moreno et al., 2015; Sarao et al., 2016) and ziv-aflibercept (Braimah et al., 2017; Nawar and Shafik, 2020; Singh et al., 2019), which were originally developed for the treatment of systemic neoplasia, has also been evaluated for myopic MNV, with both agents demonstrating favorable visual acuity gains after treatment.

6. Global health equity

6.1. Low-resource solutions

To address the challenges of myopia prevention and control in low-resource settings, innovative and accessible solutions are critical for reducing the burden of this growing public health issue. As global prevalence rates for myopia, especially in children, continue to rise, especially in LMICs, finding sustainable and scalable strategies is paramount. One promising solution lies in the use of technology, particularly mobile health (mHealth) applications, to enable widespread access to myopia care (Holden et al., 2016; J. Liang et al., 2025). Previous studies have shown that smartphone-based screening tools can be used effectively in resource-limited areas, where traditional eye care infrastructure is sparse (S. Ma et al., 2020; G. J. Wang et al., 2021). A smartphone-based photoscreening system, developed for schoolchildren in rural China, employs image processing and artificial intelligence algorithms to measure interpupillary distance, relative visual axis alignment, and refractive error ranges (S. Ma et al., 2020). This system has shown high diagnostic precision in identifying myopia, strabismus, and anisometropia, achieving sensitivity and specificity rates of 0.83 and 1.00 for myopia, 0.80 and 0.98 for strabismus, and 0.80 and 1.00 for anisometropia, respectively. This system, which uses image processing and artificial intelligence, can be operated by low-skilled health workers and provides an affordable, quick, and non-invasive solution for screening. Such initiatives not only offer an immediate solution for vision screening but also pave the way for integrating long-term monitoring with digital patient records, ensuring continuity of care. In addition to mHealth, educational programs play a significant role in increasing awareness of myopia prevention. A previous study conducted in Brazil highlighted the effectiveness of school-based visual health screenings, with follow-up treatments and donated corrective lenses making a tangible difference in preventing visual impairment (Costa et al., 2021). However, challenges remain in ensuring that these programs reach the most underserved populations, particularly in rural areas where access to trained eye care professionals is limited. Thus, initiatives that train teachers or community health workers to identify vision issues in students constitute a cost-effective strategy that should be scaled up. The “Vision for the Future” project in São Paulo serves as an example of how such community-based screening and intervention programs can be integrated into the educational system to address myopia at an early stage (Costa et al., 2021). Another critical component of low-resource solutions is the promotion of outdoor activities to mitigate the onset and progression of myopia. Epidemiological evidence and randomized clinical trials have consistently shown that increased time spent outdoors reduces the risk of myopia in children and adolescents (Clark et al., 2023a; Dhakal et al., 2022; M. He et al., 2015; Kido et al., 2024; M. Li et al., 2023). Simple interventions, such as encouraging outdoor play during school hours or integrating outdoor activities into after-school programs, can be a low-cost way to address the environmental risk factors associated with myopia. Governments and schools must prioritize these environmental modifications alongside medical and technological interventions to create a multi-faceted approach to myopia prevention.

However, while these strategies are promising, several challenges need to be addressed. One of the main barriers to successful implementation is the lack of awareness and understanding among parents and caregivers about the long-term implications of myopia (A. Q. He et al., 2022; Q. Li et al., 2021; S. Zhou et al., 2017). Many parents view myopia as a benign condition; therefore, vision care often takes backseat to educational demands where education about myopia is scarce, and public health campaigns targeting parents are essential. These campaigns should emphasize not only the physical consequences of myopia but also the potential socioeconomic impacts of uncorrected visual impairments. Furthermore, the use of mHealth tools and school-based screening programs must be accompanied by a robust system for follow-up care. While the detection of vision problems is a critical first step, the lack of access to corrective measures or treatments in rural or impoverished areas can undermine these efforts. Previous studies have demonstrated that populations with high SES exhibit an earlier onset and higher incidence of myopia, particularly in East Asia, where rapid economic growth has coincided with a surge in myopia prevalence (Jan et al., 2019). Conversely, the lower incidence of myopia in high-income Western societies implies that the intensity of the education system may be a more consistent determinant (Morgan et al., 2018; Morgan and Rose, 2013). Therefore, integrating low-cost corrective solutions, such as subsidized or donated eyeglasses, into these programs is essential for ensuring that children receive the treatment they need after screening.

While myopia prevention and management in low-resource settings is complex, the integration of technology, educational initiatives, and public awareness campaigns offers a promising path forward. By leveraging mobile health tools, enhancing community-based screenings, and encouraging outdoor activities, it is possible to create a sustainable model for myopia care that is both effective and scalable. However, continued investment in infrastructure, training, and follow-up care is needed to ensure that these solutions can reach the populations most in need.

6.2. Ethical and policy challenges

As the global prevalence of myopia continues to rise, particularly in children and adolescents, the ethical and policy challenges surrounding myopia prevention and control have become increasingly prominent (Holden et al., 2016; J. Liang et al., 2025). While myopia has long been considered a manageable condition, the increasing rates of myopia onset and progression necessitate a reevaluation of both ethical considerations and policy approaches, raising questions about the balance between public health goals and individual freedoms, the accessibility of treatments, and the role of cultural values in shaping public health interventions.

One of the most significant ethical dilemmas in the management of myopia is the tension between individual autonomy and public health priorities. In many regions, particularly East Asia and Southeast Asia, where myopia has reached epidemic proportions, public health measures aimed at preventing or slowing myopia progression often require mandates that intervene in children's daily routines, such as restrictions on screen time, enforced outdoor activities, and, in some cases, pharmacological treatments such as atropine eye drops (L. Dong et al., 2020; Holden et al., 2016; Morgan et al., 2012). While these measures are grounded in sound scientific evidence and have demonstrated effectiveness in slowing myopia progression, they can raise concerns about parental rights and the autonomy of families. In societies where parental authority is highly valued, interventions that are perceived as infringing upon parental decision-making, such as mandatory outdoor play or restrictions on study hours, may be met with resistance (Leung et al., 2024). The ethical question, then, revolves around the appropriateness of such interventions when the benefits, although significant for public health, may not be universally accepted or desired by parents.

Moreover, there are ethical concerns regarding the stigmatization of children who develop myopia. In many cultures, visual impairment is often associated with social disadvantage, and children who wear corrective lenses may face bullying or exclusion, particularly in school environments (Horwood et al., 2005). Thus, public health policies that focus on early intervention may inadvertently contribute to social stigma, further exacerbating the psychological and social challenges that myopic children may face. These considerations highlight the need for sensitive and inclusive approaches that not only promote myopia prevention but also protect the well-being of children, ensuring that interventions do not result in unintended negative consequences, such as increased anxiety or social exclusion.

From a policy perspective, the challenges of resource allocation in LMICs are significant (X. He et al., 2021; Morgan & Jan 2022). Myopia prevention and control strategies often involve significant financial investment, particularly for treatments such as low-dose atropine, Ortho-k, and specialized spectacle lenses. In these settings, the availability of resources is often limited, and the cost of these interventions can be prohibitive for many families. While outdoor activities and environmental modifications are low-cost solutions that can be widely implemented, more specialized treatments require access to trained healthcare professionals, infrastructure, and financial resources that are often lacking in underserved areas. This creates a significant ethical dilemma: how can policies be designed to ensure equitable access to myopia prevention and treatment, particularly when financial constraints limit the availability of care? Furthermore, the lack of trained optometrists and ophthalmologists in many rural and underserved regions exacerbates this challenge, leaving large portions of the population without access to even basic eye care.

The increasing reliance on technology to address these challenges, such as the use of AI and telemedicine, offers both promise and ethical considerations (S. M. Li et al., 2022; H. Lin et al., 2018; T. Tang et al., 2020; X. Yang et al., 2020). AI-driven diagnostic tools and teleophthalmology can help bridge the gap in healthcare access by enabling remote screenings and consultations, making eye care more accessible and cost-effective. However, this technology is not without its own set of ethical challenges. Issues of data privacy, the potential for over-reliance on technology, and the unequal distribution of technological resources can exacerbate existing inequalities (Lopez et al., 2020; Ting et al., 2017). In regions with limited access to the internet or digital devices, the benefits of these technologies may not be realized, leaving certain populations behind. Additionally, there are concerns about the ethical implications of relying on AI for diagnosing and managing myopia, particularly when the technology is still developing and may not always be accurate. Ensuring that these technological solutions are implemented in a way that promotes equity and does not exacerbate existing disparities is critical to their success in low-resource settings.

Cultural factors also play a significant role in shaping the effectiveness of myopia prevention policies. In many Asian countries, the emphasis on academic success is intense, and children are often under significant pressure to perform well in school (X. He et al., 2021). This cultural emphasis on education can create a paradox when trying to implement interventions that encourage outdoor activities and limit screen time. The promotion of such interventions may be seen as a threat to children's academic achievement, with parents and schools potentially resisting policies that they perceive as undermining their children's future prospects. Moreover, the idea of reducing academic pressure to mitigate myopia may clash with deeply held cultural values, making it more difficult to implement comprehensive prevention strategies. The ethical challenge here is ensuring that myopia prevention measures do not come at the expense of educational opportunities, especially when interventions such as reducing study hours or increasing play time may be seen as conflicting with academic goals. The challenge is to design policies that respect both public health needs and cultural values, finding a balance between preventing myopia and supporting educational achievement.

The global nature of the myopia epidemic also presents a challenge in terms of policy coordination. While countries and areas such as Singapore and Taiwan have implemented successful nationwide programs to control myopia, the application of these strategies in other parts of the world is often hindered by differences in healthcare infrastructure, cultural norms, and economic capacity (Ang et al., 2020). A lack of coordinated global policy on myopia prevention may lead to disparities in how interventions are implemented across different regions. Furthermore, the implementation of these strategies may not always align with local priorities or be feasible given the existing healthcare systems. Ethical concerns arise when interventions that work in one context are imposed in another without sufficient consideration of local conditions, potentially leading to ineffective or even harmful outcomes. Global policy frameworks must be flexible enough to account for local realities while promoting best practices based on evidence.

While myopia prevention and control are critical public health goals, the ethical and policy challenges associated with these efforts are complex. Balancing public health benefits with individual rights, ensuring equitable access to treatment, and respecting cultural values are critical considerations in the development of effective myopia control policies. The growing reliance on technology and the increasing emphasis on early intervention further complicate these issues, requiring careful consideration of both the benefits and risks of such approaches. Policymakers must navigate these challenges with sensitivity and foresight, ensuring that myopia prevention strategies are not only scientifically sound but also ethically responsible and culturally appropriate.

7. Conclusion

The global rise in myopia and PM presents a pressing public health challenge, driven by complex interactions of environmental factors, particularly prolonged near work and reduced outdoor light exposure, alongside genetic susceptibility and epigenetic regulation. Advances in precision medicine, powered by AI-driven integration of multi-modal data (genetic, environmental, and clinical biomarkers), are revolutionizing risk prediction and personalized interventions. Although advancements in therapeutic and diagnostic tools hold great promise, the uneven access to and implementation of these innovations highlight the necessity for equitable and scalable solutions. Integrating environmental preventive measures, genetic insights, and AI-enhanced precision strategies will be essential for controlling myopia epidemics and alleviating their sight-threatening complications on a global scale, ensuring that interventions are scientifically sound and universally accessible.

CRediT authorship contribution statement

Chen-Wei Pan: Writing – review & editing, Writing – original draft, Supervision, Project administration, Funding acquisition, Conceptualization. **Xing-Xuan Dong:** Writing – original draft, Investigation, Data curation. **Carla Lanca:** Writing – original draft, Formal analysis. **Yining Wang:** Visualization, Methodology. **Seang-Mei Saw:** Writing – review & editing, Validation. **Xiangui He:** Resources, Data curation. **Dan-Ning Hu:** Writing – review & editing, Writing – original draft, Investigation. **Qiao Fan:** Writing – original draft, Methodology, Formal analysis. **Andrzej Grzybowski:** Writing – review & editing, Validation. **Kyoko Ohno-Matsui:** Writing – review & editing, Supervision.

Conflict of interest

All authors declare that they have no conflict of interest.

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