• Review and Commentary •

Who needs myopia control?

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Abstract

● Myopia has become a major visual disorder among school-aged children in East Asia due to its rising prevalence over the past few decades and will continue to be a leading health issue with an annual incidence as high as 20%-30%. Although various interventions have been proposed for myopia control, consensus in treatment strategies has yet to be fully developed. Atropine and orthokeratology stand out for their effectiveness in myopia progression control, but children with rapid progression of myopia require treatment with higher concentrations of atropine that are associated with increased rates of side effects, or with orthokeratology that carries risk of significant complication. Therefore, improved risk assessment for myopia onset and progression in children is critical in clinical decision-making. Besides traditional prediction models based on genetic effects and environmental exposures within populations, individualized prediction using machine learning and data based on age-specific refraction is promising. Although emerging treatments for myopia are promising and some have been incorporated into clinical practice, identifying populations who require and benefit from intervention remains the most important initial step for clinical practice.

● **KEYWORDS:** myopia control; prediction; intervention
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WHY DOES MYOPIA MATTER?

The incidence of myopia is growing at alarming rates with increasingly early onset. Longitudinal data show that the annual incidence of myopia may be as high as 20%-30% amongst school-aged children[1], creating significant public concern for myopia prevention and control. Further, growing rates of early myopia onset and rapid myopia progression may lead to significant increases in the number of people with high myopia. Recent studies predict that nearly half of the world's population may be myopic by 2050, and approximately 10% highly myopic[2].

Uncorrected refractive error is the leading cause of visual impairment and blindness globally[3]. Uncorrected myopia as mild as -1.50 D can result in moderate visual impairment, while refractive error of -4.00 D is sufficient to lead to blindness if based on uncorrected vision. Although optical correction is helpful in most cases, biometric changes in axial length are irreversible. Increases in axial length in myopic eyes, accompanied by thinning of the retinal pigmentary epithelium, choroid, and sclera can result in significant risk of vision-threatening complications including retinal detachment, myopic maculopathy, glaucoma, and cataract[4].

WHAT HAS BEEN DONE TO CONTROL MYOPIA?

Efforts to control myopia have been longstanding. Among numerous interventions proposed in clinical care, animal models, and trials, atropine stands out as an effective medical therapy for myopia progression control, achieving control of 50%-90% of myopic progression in a concentration-dependent response[5-9]. Although low-dose atropine (0.01% and 0.05%) has been identified as effective with minimal side effects, children with the most rapidly progressing myopia require treatment with higher concentrations of atropine that are associated with higher rates of side effects including dry mouth, photophobia, poor near-vision, glare, and allergic conjunctivitis[10-11].

Orthokeratology is another effective treatment with substantial supporting evidence, reducing axial length change by approximately 50% per year[12]. Previous studies have suggested that at least 6mo of wear is required for treatment effect[13], and this effect may diminish over long-term use[14]. Orthokeratology however carries risk of significant complication, including corneal staining[15-17], papillary conjunctivitis[18], and even sight-threatening microbial keratitis[19-20]. The

cost, intensity of follow-up and additional skills required by both practitioners and patients have limited the adoption of orthokeratology in myopic children.

Combined treatment using both low-dose atropine and orthokeratology has recently been proposed to enhance myopia control treatment effects. A study in Japan using combined treatment demonstrated significantly greater treatment effect in reducing axial elongation compared to orthokeratology alone[21]. The overall efficacy and potential side-effects of combined treatment require further investigation.

Other treatments commonly used clinically include progressive, bifocal, and multifocal lenses, soft or rigid contact lenses, and under-corrected glasses. These however do not appear to have strong effects in controlling underlying myopia progression. In addition, spectacles or contact lenses with defocus designs can slow myopia progression with a significant but smaller effect compared to atropine or orthokeratology[22-25], although a recently published single-center clinical trial demonstrated reduced axial elongation by as much as 62% using defocus incorporated multiple segments (DIMS) spectacles[26]. These treatment modalities may represent alternatives for individuals who are unable to tolerate atropine or fail to fit orthokeratology.

Increased time outdoors has been proven through large-scale randomized clinical trials to significantly reduce the onset of myopia in children[27-28], but has not been established to reduce progression of myopia[29].

A meta-analysis evaluating 16 interventions for myopia control demonstrated that atropine and pirenzepine were most effective, with orthokeratology and other specially designed contact lenses of moderate effect, and specially designed spectacles to be minimally effective[12]. Although atropine, pirenzepine, and orthokeratology have been proven to be beneficial in controlling myopia, they should not be applied universally or as prophylaxis due to potential for side effects. Risk assessments of myopic patients should be carried out first to identify those at high risk of developing high myopia later in life, and for improved targeting of intervention.

WHO NEEDS MYOPIA CONTROL?

Given the close relationship between age of onset and severity of myopia in late childhood[30-31], identifying children at high risk of early-onset myopia is of significant importance in enabling delivery of early intervention. The influence of genetics has gained much attention, based on the significant association between parental myopia and onset of childhood myopia[32-33]. Environmental exposures including education[34], near work (*e.g.*, reading, watching television, telephone and computer use)[35], and outdoor activities[29] have been identified as key factors in the development of myopia. Previous studies have attempted to predict myopia onset based on genetic and environmental risk but current models leave room for further improvement.

The Orinda Longitudinal Study of Myopia (OLSM) demonstrated that a cutoff of less than +0.75 D hyperopia in the third grade (age 8y) could predict the onset of juvenile myopia with a sensitivity of 87%, specificity of 73%, and area under the curve (AUC) of 0.88[36]. The Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) Study showed that refractive error in the first grade (age 6y) and number of myopic parents could predict myopia with a decreased sensitivity of 63% and improved specificity of 82%[37]. Zadnik *et al*[38] investigated different sets of risk factors present at different ages to predict myopia, but found that spherical equivalence at baseline was the single best predictor with an AUC of 0.87 to 0.93. The Twins Early Development Study (TEDS) evaluated early developmental factors and found that level of maternal education, fertility treatment, summer birth, and hours spent playing computer games could predict myopia with an AUC of 0.68[39]. Recent advances in machine learning are promising in improving accuracy of myopia development prediction[40], when a large dataset from an optometry service was used.

In addition to genetic background and environmental exposures, changes in ocular and structural variables over time may be more informative when data from longitudinal time points become available. Our previous work revealed that annual change in spherical equivalence and axial length peaked during the year of myopia onset[41], which has been confirmed in other populations[42-43]. Other variables such as peripheral refractive error[42], lens power[43], AC/A ratio, and accommodative lag are also potentially predictive factors[44-45]. Although the IMI Interventions for Controlling Myopia Onset and Progression Report has defined pre-myopia as a refractive state of an eye of ≤+0.75 D and >-0.50 D in children[46], long-term surveillance of refraction, ocular development, and improved multifactorial prediction models are expected to help identify pre-myopia much earlier.

For children who have developed myopia, assessment for risk of progressive myopia is critical. Population studies and control arms in clinical trials have provided important references for the definition of progressive myopia. Zhao *et al*[47] reported the distribution of refraction progression in children living in rural areas, finding an average progression of -0.42 D in 28.5mo, and a 95% confidence interval of -0.37 to -0.47 D, approximating to an upper limit of -0.20 D at one year. Further data on myopia progression can be found within control group data of clinical trials. The COMET (Correction of Myopia Evaluation Trial) study found that the cumulative 3-year progression of myopia in children aged 6-11y within a multiethnic population was -1.42 D, and the upper 95% confidence interval limit for annual progression was -0.50 D[48]. In the ATOM1 (Atropine for the Treatment of Childhood Myopia)

study, an average annual progression of -0.60 D was noted in myopic children aged 6-12y, with a 95% confidence interval limit of -0.67 D[5]. Using these population data, progressive myopia for children aged 6 to 12y has therefore been defined as myopia progressing more than -0.75 D per year.

In most instances of clinical practice however, patients newly diagnosed with myopia have refractive error measurements available only at a single point, and data over time is not present. In addition, a single cut-off of spherical equivalent to define progressive myopia for children aged 5-18y may be accurate. Researchers in Guangzhou, China have attempted to use percentile curves for refraction from the general population as a reference to identify individuals at risk of high myopia at different ages[49]. They found that the 5th percentile curve for refraction had the highest sensitivity, specificity, positive predictive value, and Matthews correlation coefficient in predicting individuals who would develop high myopia at the age of 15. The age-specific cutoff values were -1.20, -1.80, -2.37, -2.94, -3.50, -4.05, -4.59, -5.13 D for children aged 7-14y. Similar percentiles of axial length have been developed for both European and Chinese populations (25th percentiles at 6y: European 21.7-22.1 mm, Chinese 22.0-22.6 mm; at 9y: European 22.2-23.3 mm, Chinese 23.2-23.7 mm; at 15y: European 22.7-23.2 mm, Chinese 23.8-24.4 mm)[50-51]. Due to the low prevalence of myopia in Europe however, the accuracy of refraction references based on European cohorts requires further validation.

For individualized prediction, using data from multiple visits may improve accuracy. Lin *et al*[40] developed a random forest machine learning model based on refraction records collected over time in the real-world (≥3 visits), achieving high accuracy in predicting high myopia development by 18 years of age. Evaluating multiple other risk factors for myopia however may not increase accuracy in prediction. Ghorbani Mojarrad *et al*[52] demonstrated in the Avon Longitudinal Study of Parents and Children birth cohort that the number of myopic patients and genetic risk scores (GRS) were only weakly predictive of future refractive error. Chen *et al*[53] further showed that models incorporating GRS, parental myopia, near work time, or outdoor activity time had limited marginal improvement in predicting future high myopia in children, beyond that based on age-specific refraction data alone. Beyond these findings, the adoption of myopia progression prediction by clinicians and public health officials in routine clinical practice requires the development of websites, phone applications and other accessible tools to assist decision-making.

HOW SHOULD MYOPIA CONTROL BE PRACTICED?

The means in which clinicians should manage individuals identified at high-risk of developing myopia or high myopia remains under investigation. Wu *et al*[54] proposed a strategy that begins with 0.01% atropine, and regular 6-monthly assessments of myopia progression. For individuals with progression greater than 0.50 D per year, increased atropine concentrations, additional time outdoors, and other treatments are suggested. For individuals without access to low-dose atropine eye drops, less frequent use of 1.0% atropine may be considered as an alternative, with once-weekly to thrice-weekly administration comparable in treatment effect to daily low-dose atropine[55]. Progressive and photochromic glasses to manage side effects however are still required for most individuals using part-time 1.0% atropine, although photophobia, allergy, or headache are reported much less frequently compared to full-time use[11]. For children who are unable to tolerate atropine eye drops and are seeking spectacle-free daytimes, orthokeratology can be recommended depending on the age, diopter of refraction, and child tolerability. Close follow-up is required however to reduce risk of complication[56]. Depending on patient specific factors, multifocal soft contact lenses or spectacles may also be recommended. Lastly, new approaches in controlling and even halting the progression of myopia have been under investigation in recent years, including low-level red-light therapy that is currently being tested in a multi-center clinical trial in China (ClinicalTrials.gov Identifier: NCT04073238). Initial analyses demonstrate promising treatment effects (unpublished data). Regardless of the specific intervention used, all patients must be informed of the efficacy and potential side effects of different myopia control strategies, and informed consent obtained where possible.

CONCLUSION

Although emerging treatments for myopia are promising and some have been incorporated into clinical practice, identifying populations who require and benefit from intervention remains the most important initial step for clinical practice. With growing myopia prevalence and associated clinical and economic burden, this need will become increasingly pressing over time. Further, more real-world data are required to identify optimal myopia treatment strategies for individuals, prior to wide population-level adoption. Lastly, further study is required to investigate new treatments that may have improved efficacy and fewer side effects for children who would otherwise respond poorly to currently available options.

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