



Neuro-ophthalmic review on pediatric myopia: Advancing from refraction to a brain-centric model of axial growth

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Abstract

Pediatric myopia is conventionally characterized as a refractive anomaly influenced by optical defocus and environmental factors. Emerging evidence suggests that axial elongation during childhood may be usefully reframed through a

neuro-ophthalmic perspective, integrating retinal signaling, visual cortex maturation, and neuroplasticity. This minireview examines myopia within an eye-brain axis framework, emphasizing the roles of retinal neurotransmitters, dopaminergic pathways, and visual processing networks in regulating eye growth. Here, “brain-centric” denotes a clinically integrative model in which neurodevelopmental state and brain-governed behaviors (e.g., sleep/circadian timing, viewing habits, outdoor exposure) shape the visual inputs that engage established intraocular growth pathways, rather than implying that post-retinal processing is required for emmetropization. Advances in high-resolution imaging, electrophysiology, and functional neuroimaging have reported structural and functional differences in the retina and central visual pathways that may be detectable early during myopia development; however, evidence that such alterations consistently precede refractive error remains limited, and causal direction is not fully established. We examine how early visual experiences, sleep, digital viewing behaviors, and neurodevelopmental factors may influence these pathways in children. Reconceptualizing pediatric myopia within an eye-brain axis framework may support targeted prevention, individualized monitoring, and treatment selection, as well as hypothesis-driven predictive work to identify higher-risk trajectories, while avoiding causal overinterpretation when evidence remains primarily associative.

Key Words: Myopia; Child; Axial length; Eye; Visual pathways; Retina; Neuroplasticity; Dopamine

Core Tip: Pediatric myopia is not simply a refractive state, but a disorder of visually driven axial elongation shaped by neuroretinal signaling and developmental visual experience. Evidence supports prioritizing axial length as a core endpoint and integrating intermediate biomarkers (e.g., choroid and optical coherence tomography angiography or optical coherence tomography angiography metrics) to refine risk phenotyping and monitor response. A brain-informed “eye-brain axis” model can guide earlier prevention and individualized escalation, while avoiding overclaiming when central mechanisms remain only partially causal.

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INTRODUCTION

Pediatric myopia is increasingly recognized as a major global public health concern. A comprehensive systematic review and meta-analysis in children and adolescents indicates that approximately one in three is already affected, with projections suggesting a continued rise in prevalence and an expanding absolute number of cases by mid-century[1]. While much epidemiologic attention has focused on East and Southeast Asia, Europe carries a measurable, highly heterogeneous pediatric burden; a dedicated European systematic review and meta-analysis report substantial between-study and between-country variability and support the need for region-specific epidemiologic surveillance based on cycloplegic, population-level data[2].

Consensus work from the international myopia institute (IMI) has clarified that “risk factors” should not be treated as a flat list of associations but should be interpreted in light of the strength of the evidence, confounding, and causal plausibility[3]. In particular, the IMI report identifies educational pressure and reduced time outdoors as the most consistently supported modifiable exposures, while noting that associations between near work and myopia are generally weaker and less consistent (although backed by meta-analyses), and emphasizing the importance of causal inference and mechanistic plausibility when translating epidemiology into prevention-oriented interventions[3]. Building on this, the IMI 2025 digest emphasizes earlier identification and targeted intervention during the pre-myopic phase by refining concepts such as pre-myopia and “hyperopic reserve”, and by noting that methodological and population differences (including thresholds and measurement approaches) can limit comparability across studies and influence clinical translation[4].

IMI’s 2025 white paper on interventions reviews peer-reviewed evidence through the end of 2024 and describes multiple effective approaches across optical, pharmacological, and environmental/behavioral categories, consistent with the view that childhood myopia progression is closely linked to axial elongation and that delaying onset can materially reduce later myopia burden[5]. The IMI Myopia Genetics Report (2025) summarizes that over 1000 common variants have been associated with refractive error and myopia, and that polygenic risk scores show improved predictive power when combined with environmental and demographic factors; it also highlights growing evidence on gene-environment interactions, including educational attainment and screen time/physical activity[6].

Among potentially modifiable exposures, greater time spent outdoors is consistently associated with lower odds of myopia in children and adolescents. In a systematic review and meta-analysis, each additional hour of outdoor time per week was associated with a 2% reduction in the adjusted odds of myopia. The same review also summarized prospective and randomized evidence suggesting that increased outdoor time is associated with a lower risk of incident myopia and reduced myopic progression in pediatric populations[7]. More recent randomized evidence supports outdoor time as an

intervention: A systematic review and meta-analysis reported improvements in spherical equivalent refraction (SER), and lower myopia incidence following outdoor interventions; however, these trials were all conducted in China, and the optimal “dose” and implementation strategy remain unclear, with sunlight/UV-related risks needing consideration[8].

At the same time, digital screen exposure has been examined as a potential risk factor for myopia. A systematic review and dose-response meta-analysis found that each additional hour of daily digital screen time was associated with higher odds of myopia. In nonlinear dose-response analyses, odds increased from 1 hour/day, with the steepest increase between 1 and 4 hours and a more gradual rise thereafter; the authors also reported substantial heterogeneity and rated the overall certainty of evidence as low[9]. Classic near work remains relevant, but the evidence base is mixed across outcomes and study designs. In a systematic review and meta-analysis, greater near work exposure was associated with higher odds of prevalent myopia, and in a subgroup analysis, the odds of myopia increased by 2% for each additional diopter-hour per week of near work. However, in a meta-analysis of three cohort studies, increasing near work (diopter-hours) was not associated with an increased incidence of myopia, and findings on progression were too heterogeneous for quantitative pooling[10].

Sleep has also been examined as a potentially modifiable exposure, but conclusions should be cautious because the literature is methodologically heterogeneous and not consistently supportive. A systematic review (16 included studies) concluded that only six studies reported a significant relationship between shorter sleep duration and myopia development, with substantial variation across studies in how sleep was measured (mostly questionnaires; few used validated sleep instruments or actigraphy), how myopia was assessed (cycloplegic *vs* non-cycloplegic refraction *vs* self-report), and overall study methods-limiting comparability and preventing meta-analysis in that review[11]. In a separate systematic review and meta-analysis of insufficient sleep in children, insufficient sleep was associated with higher myopia prevalence and higher prevalence of high myopia. In contrast, pooled longitudinal evidence did not show a significant association with myopia incidence, and several refractive/biometric outcomes were not consistently associated; shorter sleep duration was linked to faster axial length (AL) change in continuous-variable analyses. Overall, the very high heterogeneity for prevalence outcomes and the observational nature of much of the evidence support interpreting sleep as a correlated lifestyle factor rather than a single proven causal driver[12].

Meta-analytic pooling of observational studies suggests that both short and long sleep duration are associated with myopia in children and adolescents (short sleep: Higher odds; long sleep: Lower odds), whereas Mendelian randomization analyses using genetic instruments for chronotype and sleep-duration traits do not show significant evidence of a causal effect of these sleep traits on myopia. Taken together, these findings indicate that sleep may not be an independent predictor of myopia risk, while leaving open the possibility that sleep-related behaviors could still be indirectly linked to myopia through correlated exposures or habits[13].

More broadly, contemporary evidence frames myopia as dysregulated ocular growth shaped by the visual environment. In their synthesis on the “epidemics of myopia”, Morgan and colleagues argue that the sharp rise in myopia and high myopia-particularly in East and Southeast Asia-is best explained by modifiable environmental drivers, especially intensive education and reduced time outdoors. They emphasize that earlier onset combined with higher progression rates contributes to the burden of high myopia, and they discuss biologically plausible pathways linking visual experience and light exposure to ocular growth, including a proposed role for light-related retinal dopamine signaling [14].

In parallel, the IMI white paper highlighted animal and human evidence that greater time spent outdoors is consistently associated with delayed myopia onset, and that this has been incorporated into prevention programs. At the same time, it underscores that the mechanisms remain under investigation and that evidence is currently insufficient to define which specific properties of light exposure in humans (*e.g.*, intensity thresholds, exposure duration, spectral composition, temporal patterns) drive protection, limiting evidence-based guidance beyond general outdoor-time recommendations and motivating further standardized randomized trials and objective exposure measurement using wearable technologies[15].

A neuro-ophthalmic “eye-brain axis” framing is most persuasive when it is anchored in the established local biology linking visual experience to ocular growth. Classical emmetropization is widely described as a largely intraocular homeostatic process in which retinal-derived cues can regulate axial elongation without requiring higher visual processing. In this context, our ‘brain-centric’ emphasis is clinically motivated: Central development and brain-governed behaviors modulate the timing and quality of visual experience (light exposure, near-viewing patterns, sleep/circadian factors), which, in turn, alter the retinal signals entering the retinoscleral cascade. Within this retina- retinal pigment epithelium (RPE)-choroid-sclera (“retinoscleral”) cascade, candidate chemical mediators receiving major attention include dopamine, retinoic acid, and adenosine, alongside retina-to-choroid transduction routes and downstream extracellular-matrix remodeling in the sclera (including collagen reorganization and altered synthesis/degradation of collagen and proteoglycans/glycosaminoglycans)[16].

Consistent with this, retina-focused syntheses emphasize that myopia-relevant mechanisms are not purely optical: The retina is a fine-layered sensory neural tissue that processes visual signals through multiple cell types and molecular pathways. These reviews discuss how abnormal visual experience can be associated with altered retinal signaling-prominently dopaminergic mechanisms, together with contributions from rod and cone pathways, ON/OFF signaling considerations, and structural changes involving the RPE and neuro-retinal layers, framing “retinal dysfunction” as abnormal signaling induced by aberrant visual input rather than an intrinsically faulty retina[17].

Evidence implicating central visual pathways has also expanded, but it warrants methodological caution. A 2024 review summarizes clinical neuroimaging findings (largely in high myopia) reporting altered brain activity and connectivity, as well as structural differences, and it also reviews animal studies suggesting involvement of specific central nuclei (including the visual cortex and circadian-related pathways). At the same time, it highlights that experimental myopia can still occur when eye-brain communication is disrupted, and that the mechanisms, brain-region

specificity, interactions with intraocular pathways, and causal direction (cause *vs* consequence *vs* compensation) remain incompletely resolved[18].

Recent neuroimaging syntheses of high myopia report widespread neuroanatomical and functional brain alterations, including cortical thickness changes, white-matter microstructural abnormalities, and disrupted functional connectivity, alongside reported cognitive-emotional associations. However, the summarized evidence is largely observational; notably, a large United Kingdom Biobank analysis found associations between myopia and reduced total brain and white-matter volumes, whereas Mendelian randomization did not support a causal relationship. In line with the mechanistic framing of the review, these findings are therefore most defensibly interpreted as correlates of high myopia and experience-dependent neural plasticity, rather than definitive proof of causality[19].

Electrophysiology offers a complementary, clinically grounded window on retinal and post-retinal function. In a systematic review of 11 studies (340 myopic participants) assessing multifocal electroretinography (ERG), pattern ERG, flash ERG, and visual evoked potentials (VEP), most ERG studies reported reduced amplitudes in myopic eyes compared with controls; several also reported delayed latencies, and the single included VEP study found both reduced amplitude and delayed latency in myopic eyes. Overall, the review concluded that myopia is associated with functional neurovisual impairment detectable with ERG and VEP, supporting their value as complementary tools for assessing retinal and visual pathway function in myopic individuals[20].

Taken together, this body of evidence motivates an “eye-brain axis” perspective, particularly in high myopia, that integrates ocular changes with measurable alterations in visual-pathway function and central structure/function within a neuro-ophthalmic framework[19,20]. This mini-review proposes a neuro-ophthalmic framing of pediatric myopia as an eye-brain axis condition in a clinical and developmental sense, while recognizing that intraocular mechanisms can operate independently of post-retinal processing and that the direction of central nervous system (CNS) associations often remains unresolved. Accordingly, we aim to: (1) Synthesize high-level evidence on epidemiological burden and modifiable exposures; (2) Connect exposures to retinal and neurobiological signaling pathways; and (3) Identify clinically actionable opportunities for earlier prediction, individualized prevention, and mechanistically informed monitoring. **Figure 1** summarizes the proposed eye-brain axis framework for pediatric myopia and highlights the main modifiable exposures, retinal pathways, and measurable biomarkers.

PATIENTS AND METHODS

This narrative minireview integrates epidemiologic evidence and mechanistic insights to frame pediatric myopia as a disorder of visually guided axial growth within an eye-brain axis perspective. The aims were to summarize higher-level evidence on pediatric burden and modifiable exposures (outdoor/light exposure, near work/digital viewing, sleep-related factors), link these exposures to candidate retinal and retina-to-sclera signaling pathways implicated in axial elongation, and critically appraise the rationale and limitations of central visual pathway findings (neuroimaging and electrophysiology) for risk phenotyping.

A structured literature search was performed in PubMed/MEDLINE, EMBASE, Web of Science Core Collection, and the Cochrane Library from inception to 31 December 2025 (last search date), complemented by targeted searches in Google Scholar and ClinicalTrials.gov and by hand-searching reference lists of key consensus papers and major evidence syntheses. Study selection was purposive and pediatric-focused, prioritizing the evidentiary hierarchy over exhaustiveness; therefore, no PRISMA-style study flow was constructed, and no new meta-analysis was performed. Priority was given to peer-reviewed English-language systematic reviews/meta-analyses, consensus statements, and high-quality reviews. Primary studies were included selectively when providing pediatric-specific quantitative outcomes (incident myopia, progression, AL) or objective neurovisual/biomarker endpoints [ERG; VEP; optical coherence tomography (OCT); OCT angiography (OCTA) measures, neuroimaging] relevant to the eye-brain axis. Adult-only studies without pediatric relevance, non-original items lacking methodological detail, and refractive surgery-focused reports were excluded. Experimental animal studies were included selectively when they provided mechanistic insights. The search strategy was developed, executed and, approved by authors Capobianco M and Zeppieri M, who independently screened titles and abstracts for relevance.

Data extraction and synthesis were qualitative. Evidence was weighted by level (meta-analytic/consensus > interventional > mechanistic/translation), and CNS-related interpretations were explicitly bounded by common limitations (*e.g.*, cross-sectional designs, enrichment for high myopia, and uncertainty about causality). This review used only published literature; no new patient recruitment or identifiable data were collected, so ethics approval and informed consent were not required.

ANALYSIS OF SEARCH RESULTS FOR PEDIATRIC MYOPIA

Overview of the evidence base

The structured search retrieved a set of high-level evidence syntheses (systematic reviews, meta-analyses, and network meta-analyses) addressing: (1) Prediction of myopia onset/progression in children; (2) Comparative efficacy of established and emerging myopia-control interventions; and (3) Objective structural biomarkers that extend beyond refraction, particularly choroidal thickness (ChT) and OCTA microvascular metrics. The findings below are presented as thematic results, consistent with the narrative and mechanistic scope of this minireview.

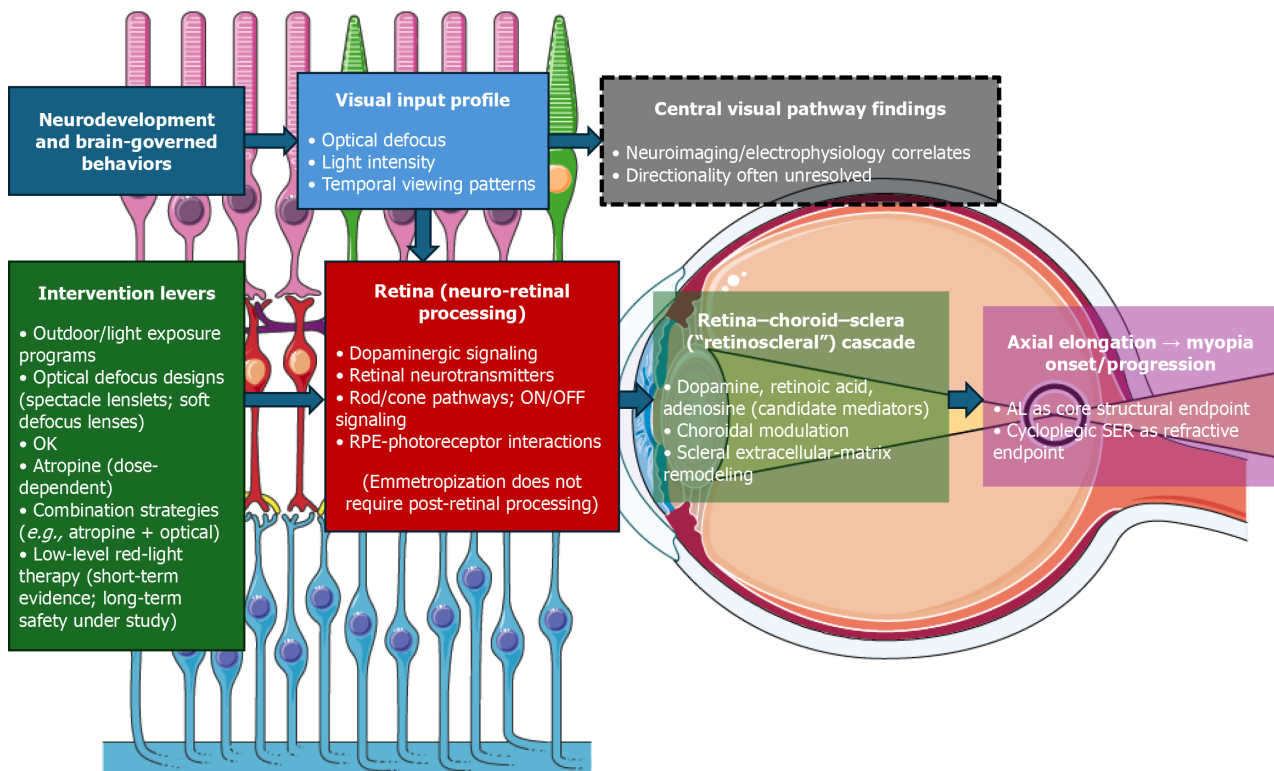


Figure 1 Eye-brain axis framework for pediatric myopia. Brain-governed behaviors shape the visual input profile, driving retinal signaling and the retina-choroid-sclera ("retinoscleral") cascade that promotes axial elongation and myopia progression. Central visual pathway findings are included as correlates, although directionality remains uncertain, and emmetropization can occur without post-retinal processing. Biomarkers/endpoints (axial length, cycloplegic spherical equivalent refraction, choroidal thickness, optical coherence tomography angiography, electrorretinography/visual evoked potentials, neuroimaging) support risk phenotyping and monitoring. AL: Axial length; RPE: Retinal pigment epithelium; SER: Spherical equivalent refraction; OK: Orthokeratology.

Risk prediction and early identification beyond refraction

A systematic review of myopia prediction models summarized research published between 1990 and February 2021 and reported that existing approaches have been developed using baseline refraction and ocular biometry, lifestyle/environmental factors, genetic data, or integrated data sources. Across studies, there is substantial variability in myopia/high-myopia definitions, predictor sets, statistical or machine-learning methods, and prediction targets (e.g., onset, progression, or future spherical equivalent), and the review concludes that no model can currently be considered for wide clinical application. A recurring limitation is the lack of robust evaluation in independent external datasets; accordingly, the review emphasizes the need for standardized methods for data collection and myopia definition and for successful validation in independent populations (preferably multi-ethnic) with stable performance before real-world deployment in clinical practice[21].

Comparative effectiveness of interventions targeting progression and axial elongation

A Cochrane living systematic review with network meta-analysis assessed randomized trials of myopia-control interventions in children (≤ 18 years), using change in SER and AL at ≥ 1 year as the critical outcomes and rating certainty of evidence with GRADE (overall ranging from very low to moderate across comparisons). However, environmental interventions were within scope; no eligible studies of environmental interventions reported myopia progression outcomes in children with myopia[22]. In a network meta-analysis of 80 randomized controlled trial (RCT) (27103 eyes) that directly and indirectly compared 37 interventions for childhood myopia control, combined measures were ranked as the most effective for slowing both AL elongation and refractive progression, with atropine-based and orthokeratology-based strategies also demonstrating significant benefits *vs* control in the available comparisons[23].

When optical approaches are considered together, a systematic review and meta-analysis (35 studies; 34 in the meta-analysis) found that myopia-control spectacles, soft contact lenses (SCL), and orthokeratology produced larger treatment effect sizes for both SER change and AL change than single-vision (SV) controls; the effects were largest during the first 6-12 months and tended to reduce toward 24-36 months, with orthokeratology showing a significantly larger impact on AL than peripheral add design spectacles[24]. Focusing on orthokeratology, a systematic review and meta-analysis of seven randomized controlled trials (655 eyes) found that orthokeratology significantly reduced AL elongation *vs* control at multiple follow-up points [weighted mean difference (WMD) -0.11 mm at 6 months, -0.16 mm at 12 months, -0.23 mm at 18 months, and -0.28 mm at 24 months], while reporting that the myopia control rate declined over time (64%, 53%, 50%, 47% at 6, 12, 18, and 24 months, respectively) and that adverse events did not differ significantly between groups [odds ratio (OR) = 2.63, 95%CI: 0.72-9.61][25]. A systematic review and meta-meta-analysis of 38 meta-analyses defined "clinically significant" control as SER ≥ 0.50 D/year or AL ≤ -0.18 mm/year, and reported pooled mean differences (MD)

showing that high- and moderate-concentration atropine, orthokeratology, peripheral-plus spectacles, and repeated low-level red-light (LLRL) therapy met the AL threshold, while high- and moderate-concentration atropine, peripheral-plus spectacles, and repeated LLRL therapy met the SER threshold in the summarized evidence base[26].

Objective biomarkers: Choroid and OCTA microvasculature

Beyond refractive outcomes, a meta-analysis and systematic review in children found that subfoveal ChT (SFCT) is significantly thinner in myopic than non-myopic eyes (WMD: $-40.06\ \mu\text{m}$, 95%CI: -59.36 to -20.75), and reported that SFCT increases after orthokeratology (WMD: $19.47\ \mu\text{m}$, 95%CI: 15.96 - 22.98) and after orthokeratology combined with 0.01% atropine (WMD: $21.81\ \mu\text{m}$, 95%CI: 12.92 - 29.70), whereas 0.01% atropine alone showed little change (no significant difference) in the included pediatric studies[27]. Complementing this, a meta-analysis of randomized controlled trials evaluating atropine monotherapy reported that SFCT was thicker with atropine than with control (placebo or spectacles) across the trial periods (WMD: $11.83\ \mu\text{m}$, 95%CI: 0.88 - $22.79\ \mu\text{m}$), and subgroup results suggested dose-related differences, with 0.01% atropine not reaching statistical significance (WMD: $9.53\ \mu\text{m}$, 95%CI: -4.01 to 23.07) while 0.025%, 0.05%, and 0.1% showed statistically significant thickening; 0.05% atropine showed the largest pooled SFCT increase (WMD: $25.70\ \mu\text{m}$, 95%CI: 17.46 - $33.94\ \mu\text{m}$)[28].

Emerging light-based approaches

A systematic review and random-effects meta-analysis of LLRL therapy in myopic children (5 studies: 4 RCTs and one observational; 685 patients) found better mean change in cycloplegic SER *vs* control (MD: 0.58, 95%CI: 0.33-0.83) and less axial elongation *vs* control (MD: -0.33 , 95%CI: -0.52 to -0.13), with no significant between-group difference in adverse effects (OR = 5.76, 95%CI: 0.66-50.14); the authors conclude LLRL is a non-invasive, effective, and safe short-term option, but emphasize the need for additional long-term evaluation, comparisons with other therapies, and confirmation of safety standards, noting that safety concerns have been raised regarding exposure limits in recent work[29].

Mechanistically, the IMI consensus review concludes that animal studies support effects of light characteristics (*e.g.*, intensity, chromaticity, photoperiod) on refractive development-often discussed in relation to dopaminergic pathway modulation-but that translation to humans is challenging, evidence is insufficient to specify evidence-based light “dose” characteristics, and interest in light-based therapies is growing while most remain early-stage, with no current clinical recommendations due to limited efficacy data and/or unresolved safety concerns; therefore, LLRL clinical evidence should be interpreted cautiously within this broader light-refractive development literature rather than as definitive proof of a single dominant upstream driver of pediatric axial growth[15,29].

At the retinal microvascular level, a PRISMA-based OCTA meta-analysis (12 studies; 2302 eyes) that compared mild, moderate, and high myopia found that retinal vessel density (VD) decreases with increasing myopia severity, with a clear reduction in the superficial capillary plexus (SCP) as severity increases; high myopia was associated with lower VD, particularly in the foveal and parafoveal regions [reported in both SCP and deep capillary plexus where assessed], while FAZ size remained relatively stable across groups (approximately 0.30 - $0.32\ \text{mm}^2$) rather than showing consistent enlargement. Taken together, these pooled OCTA results support that worsening myopia severity is accompanied by measurable microvascular changes, especially in the SCP, and-given that the included studies assessed different regions (macular and/or peripapillary) and used pooling approaches contingent on heterogeneity-underSCORE the value of incorporating OCTA-derived vascular metrics as objective tissue-level readouts alongside other structural measures in broader myopia phenotyping approaches[30].

DISCUSSION ABOUT CHILDHOOD MYOPIA

Our narrative synthesis is consistent with the idea that childhood myopia is closely linked to elongation of the eyeball, and that treatment monitoring should therefore consider biometric changes in AL alongside refractive changes in SER. Recent evidence syntheses operationalize this approach by defining key outcomes as the between-group differences in changes in SER (diopters) and AL (mm) at follow-up of at least one year. At the same time, these reviews highlight barriers to straightforward clinical translation: Results can be heterogeneous across trials, comparative network models may be poorly connected (with consequent imprecision for some estimates), and both the certainty and the apparent durability of effects are less secure when evidence is limited to longer follow-up (*e.g.*, two to three years) or when treatment effects diminish over 24-36 months[22-24]. In this setting, adopting AL as a core endpoint is not simply a methodological preference; it aligns outcome assessment with structural progression and long-term risk, while reducing the temptation to overinterpret short-term refractive changes in isolation[22-26].

Within optical strategies, orthokeratology shows consistent RCT-only evidence of reduced AL elongation *vs* control through 24 months, with larger pooled between-group differences reported at later follow-up points. In the same RCT synthesis, the reported myopia control rate decreases with longer follow-up, suggesting that the proportion of children meeting the study-defined “control” criterion may decline over time and reinforcing the need for ongoing monitoring rather than assuming uniform durability. Safety/acceptability outcomes did not show a statistically significant difference in adverse events between the treatment and control groups, but the confidence interval was wide; therefore, the most defensible interpretation is that no clear difference was demonstrated in these trials, rather than that risk is excluded[25].

A complementary lens comes from a meta-analysis that predefines clinical significance thresholds (SER $\geq 0.50\ \text{D/year}$ or AL $\leq -0.18\ \text{mm/year}$) and then summarizes pooled effects across published meta-analyses. In that synthesis (38 included studies), the interventions highlighted as meeting the authors’ criteria for clinically significant AL slowing were high- and moderate-concentration atropine, orthokeratology, peripheral-plus spectacles, and repeated LLRL therapy; for

SER, high/moderate atropine, peripheral-plus spectacles, and repeated low-level red light met the prespecified threshold. By contrast, outdoor time showed smaller pooled average effects (SER = 0.17 D; AL = -0.04 mm). This type of threshold-based summary is useful for assessing whether statistically pooled effects plausibly clear a “clinically meaningful” bar, while keeping in mind that it is a synthesis of meta-analyses rather than a single uniform trial framework[26].

If you use an eye-brain axis framing to justify earlier risk phenotyping and multimodal follow-up, the rationale is stronger when it is tied to measurable ocular intermediates. One candidate is ChT, which has been positioned as part of the signaling pathway linking retina and sclera. In pediatric data pooled across observational designs, myopic eyes show a thinner subfoveal choroid than non-myopic eyes (SFCT WMD: -40.06 μ m), and topographic variation is reported, with thickness decreasing from the temporal to the nasal sectors. In the same pediatric synthesis, myopia-control interventions showed different ChT responses: SFCT increased after orthokeratology (WMD: 19.47 μ m) and after orthokeratology combined with 0.01% orthokeratology atropine (WMD: 21.81 μ m), whereas 0.01% atropine alone did not show a statistically significant change in SFCT in pooled analyses. The comparison analyses also suggested that orthokeratology produced a larger SFCT increase than 0.01% atropine (WMD: 9.86 μ m) while orthokeratology atropine was not clearly superior to orthokeratology alone for SFCT thickening[27].

Evidence restricted to randomized trials and focused on atropine monotherapy also points to a potential ChT thickening signal relative to control, but with substantial between-study inconsistency. In an RCT-only meta-analysis, SFCT was thicker in atropine-treated eyes than in placebo/spectacle controls overall (WMD: 11.83 μ m), alongside very high heterogeneity ($I^2 = 98.8\%$). Subgroup analyses indicated that the effect varied by concentration: 0.01% atropine did not show a statistically significant SFCT increase *vs* control (WMD: 9.53 μ m; 95%CI: -4.01 to 23.07), whereas 0.025%, 0.05%, and 0.1% showed statistically significant thickening, with the largest pooled SFCT increase reported for 0.05% (WMD: 25.70 μ m). Meta-regression identified atropine dose as a contributor to heterogeneity, reinforcing the conclusion that any “thickening” should be interpreted as dose- and study-dependent rather than uniform[28].

Taken together, these syntheses position ChT as a plausible intermediate readout that can move with certain interventions (notably orthokeratology/orthokeratology atropine and higher-dose atropine in RCT-only pooling), but the signal is not yet definitive because it is sensitive to measurement context and study-level variability (*e.g.*, inter-device differences and inconsistent examination timing), and because heterogeneity remains a dominant feature of the atropine RCT literature[27,28].

Overall, the additional evidence incorporated here strengthens two linked clinical messages. First, AL should be prioritized as a core endpoint for progression monitoring and treatment response assessment, with RCT-based support for orthokeratology as an AL-targeted strategy, and a clear need for sustained follow-up beyond the initial year of treatment[25]. Second, ChT may function as a candidate biomarker that helps bridge exposure-driven retinal signaling with downstream growth regulation, potentially refining risk phenotyping and early response assessment—especially when integrated with other objective readouts (*e.g.*, electrophysiology and OCTA metrics) in settings where these tools are available[20,27-30]. Importantly, an eye-brain axis model remains clinically useful when it drives earlier prevention and individualized escalation, while avoiding causal overclaim when central mechanisms remain incompletely resolved and much of the evidence remains correlational[19,20].

Treatment durability and the rebound problem

A key translational gap is durability: While many pediatric myopia trials quantify effects during active treatment, fewer studies characterize outcomes after cessation using prespecified washout periods and comparable endpoints (SER and/or AL)[31,32]. In atropine-specific evidence, a systematic review and meta-analysis of children treated for ≥ 6 months and followed after stopping atropine (13 studies; 2060 children) found time-dependent rebound: The rebound effect was larger at 6 months than at 12 months after discontinuation for both spherical equivalent (WMD: 0.926 day/year at 6 months *vs* 0.268 day/year at 12 months) and AL (WMD: 0.328 mm/year at 6 months *vs* 0.121 mm/year at 12 months). A more pronounced rebound was associated with shorter treatment duration, younger age, and higher baseline SER, and a dose-dependent trend was reported. Rebound could still be observed when transitioning to a lower dose or when using stepwise cessation. In contrast, the limited available studies combining atropine with optical methods reported no rebound relative to progression during treatment[31].

Beyond atropine, a systematic review across different myopia-control treatments (11 studies) reported that rebound can occur after stopping multiple modalities. When effects were unified across treatments, mean rebound estimates after an average washout of about 10 months were 0.10 ± 0.07 mm for AL and -0.27 ± 0.2 D for SER. Optical approaches [highly aspherical lenslet (HAL)/defocus incorporated multiple segments (DIMS)] spectacles, soft multifocal contact lenses, and orthokeratology—though evidence on orthokeratology was limited) yielded lower rebound estimates than atropine and low-level light therapy, and the authors emphasized that more and better-standardized studies are needed to confirm comparative conclusions[32].

Atropine: Dose-response, safety, and prevention

Dose selection is clinically consequential. In a meta-analysis of 18 randomized controlled trials (3002 eyes), atropine slowed myopia progression (SER) and axial elongation over 6-36 months, with greater effects at higher concentrations (*i.e.*, a dose-dependent pattern for both SER and AL). In the same pooled analyses, low-dose atropine (0.01%) showed no significant differences relative to control in accommodation amplitude or photopic pupil size. The reported rates of photophobia, allergy, blurred vision, and other side effects were similar between low-dose atropine and control, leading the authors to conclude that 0.01% appears safer from a tolerability perspective[33].

Complementing this, a network meta-analysis of 16 RCTs (3272 participants) comparing eight atropine concentrations (1% to 0.01%) generated a ranking across outcomes: 1%, 0.5%, and 0.05% were ranked as the three most beneficial for both mean annual refraction change and axial elongation, while 0.05% ranked as most helpful for the relative risk of overall

myopia progression. The analysis also found that adverse effects tended to increase with higher concentrations, particularly for pupil size and accommodation amplitude, supporting a pragmatic dose selection that weighs efficacy outcomes against dose-related safety effects[34].

From a prevention standpoint, evidence in premyopia is emerging but still limited. A systematic review and meta-analysis comprising four studies (644 children, ages 4-12; atropine 0.01%-0.05%) found lower myopia incidence and reduced rapid myopic shift (≥ 0.5 D/1 year) over 12-24 months, along with attenuated SE progression and AL elongation in atropine-treated children. No major adverse events were reported; photophobia and allergic conjunctivitis did not differ between groups over 12-24 months, although photophobia was higher with atropine over 6-12 months. The authors note that further research is warranted given the small number of studies and heterogeneity in the available evidence base[35].

Combination therapy and escalation logic

Combination strategies have been explored in pediatric myopia control, particularly where adding a second modality may enhance effects on structural progression. In a meta-analysis including five studies (341 participants < 18 years), atropine combined with orthokeratology was associated with less axial elongation than orthokeratology alone (reported mean axial elongation 0.25 *vs* 0.35; WMD: -0.09 mm, 95%CI: -0.15 to -0.04). The authors frame this as a preliminary estimate intended to inform further research[36].

Controlled evidence also exists for combining atropine with myopia-control spectacle optics. The ASPECT randomized controlled trial compared 0.025% atropine + SV spectacles *vs* 0.025% atropine + DIMS spectacles in children aged 4-16 years (SER -1.00 D to -6.00 D; astigmatism ≤ 2.00 D), with cycloplegic SER and AL assessed at baseline, 6, and 12 months. At 12 months, axial elongation was 0.18 ± 0.16 mm in the atropine + SV group *vs* 0.07 ± 0.16 mm in the atropine + DIMS group (MD = 0.11 mm; 95%CI 0.05 to 0.17; $P \leq 0.001$), and 39.6% of children in the atropine + DIMS group had no axial elongation *vs* 12.2% in the atropine + SV. SER progression differed numerically (-0.19 ± 0.42 D *vs* -0.09 ± 0.35 D) but was not statistically significant. These results support a potential additive effect that is clearer for AL than for refraction over 12 months[37].

Taken together, these studies support the plausibility of combination approaches. Still, they also underline evidence gaps: The orthokeratology meta-analysis pools a small number of heterogeneous studies, and ASPECT reports 12-month outcomes from a longer (24-month) RCT. Future head-to-head trials will still be needed to define when and how to escalate treatment, with consistent reporting of safety and adherence[36,37].

Optical interventions: Spectacle lenslets, orthokeratology, and SCL

Evidence syntheses of myopia-control spectacles now provide a clearer quantitative signal, while also showing that “spectacles” is not a single intervention category. In a meta-analysis restricted to RCTs (23 trials; 13315 participants) comparing myopia-control spectacle designs with standard SV lenses, the pooled effects favored the myopia-control lenses for both structural and refractive outcomes (AL MD of about -0.15 mm; SER progression of about -0.31 D *vs* SV). The same analysis reports that effects are design-dependent. For example, HAL lenses show larger pooled reductions. In contrast, DIMS lenses show a significant pooled SER benefit but have limited pooled AL evidence because only one eligible RCT contributed complete AL data for that design[38]. A separate systematic review/meta-analysis focused on spectacle lenses “specifically designed” for myopia control (21 studies; 17 in meta-analysis; 6175 participants) likewise supports short-term benefit: Significant reductions in both SER and AL at 12 months, but no statistically significant differences at 24 months for SER or AL in the pooled analyses, with peripheral-refraction findings summarized qualitatively and noted to vary across lens models. This framing matters clinically: It supports effectiveness in the first year while keeping longer-term certainty more cautious, rather than assuming the 12-month average automatically generalizes forward[39].

For orthokeratology, a systematic review/meta-analysis explicitly weighing benefits and risks (45 papers; mixed RCT and non-randomized evidence) reports slower axial elongation in children at 1 year *vs* non-orthokeratology comparators (MD around -0.16 mm), but also flags key safety limitations: Overall certainty is variable/moderate, selection bias may inflate apparent benefit, and adverse-event reporting is inconsistent. In the available comparative data, orthokeratology wearers were more likely to experience an adverse event than conventional contact-lens comparators (OR about 3.79), and the review also reports rebound axial growth after orthokeratology discontinuation *vs* continuing orthokeratology (MD about +0.10 mm). Taken together, the review’s bottom line is that orthokeratology can control progression while in use, but optimal duration, discontinuation effects, and longer-term adverse-event risk remain incompletely resolved in the current evidence base[40].

SCL: Peripheral defocus and peripheral-add multifocal designs

Within SCL-based myopia control, pooled evidence supports clinically relevant slowing of progression, with some important nuances. A meta-analysis of peripheral defocus SCL (PDSCs) in children and adolescents (21 studies: 13 RCTs and 8 cohort studies) found that, *vs* SV lenses, PDSCs were associated with less refractive progression (MD = +0.23 D) and less axial elongation (MD = -0.11 mm) in pooled analyses. When compared with orthokeratology, pooled effects were statistically similar for both refractive change (MD = 0.01 D) and AL change (MD = -0.01 mm), suggesting comparable efficacy across the included datasets[41].

Complementing this, a separate meta-analysis restricted to peripheral-add multifocal SCL (excluding bifocal SCL; 11 studies, 787 participants) also reported reduced refractive progression (MD = +0.20 D) and reduced axial elongation (MD = -0.08 mm) *vs* controls (SV contact lenses or spectacles). Visual performance outcomes were not uniform: High-contrast distance acuity did not differ meaningfully between groups, whereas low-contrast distance acuity favored SV lenses (MD

= 0.06 LogMAR). The same analysis quantified contact lens-related adverse events with a pooled incidence estimate of 0.065 (95%CI: 0.048-0.083) and did not find a significant difference in overall adverse-event incidence between defocus/multifocal and SV SCL groups (OR = 1.11), reinforcing the value of consistent, prespecified safety and visual-quality endpoints (including low-contrast acuity) in future trials and follow-up systems[42].

Positioning newer modalities within a comparative evidence hierarchy

Because clinicians often have several active options to choose from and may also consider combination strategies, comparative evidence syntheses are especially useful for placing newer modalities in context. A large systematic review of 74 RCTs (12154 children aged 6-18 years) used network meta-analysis to compare many optical, pharmacological, and device-based approaches and to rank 1-year effects on axial elongation, while also reporting how key constraints in the evidence base (*e.g.*, uneven population representation, variability in study designs, and limited network-ready data beyond 1 year) affect interpretation and long-term comparability across treatments[43].

A more focused Bayesian network meta-analysis (41 RCTs; 6434 eyes) directly compared repeated LLRL therapy, 0.01% atropine, orthokeratology, and atropine + orthokeratology at 6 and 12 months; it found all were effective *vs* control and ranked repeated red-light highest for slowing AL at 12 months, but also documented substantial heterogeneity across comparisons and emphasized the need for stronger long-term safety and rebound data-particularly for the red-light approach[44]. Finally, efficacy “on paper” is only part of the story: A systematic review of RCTs published between 2019 and 2021 highlights that differential dropout/discontinuation and protocol adherence (including wear-time effects reported for some optical designs) can materially shape observed benefits, reinforcing that implementation factors can modulate how trial-level effects translate into routine care[45].

Future directions

Future work in pediatric myopia should move beyond a refraction-only approach by aligning the measurements and their methods across cohorts and trials. Alongside cycloplegic SER, studies should routinely quantify AL and report both endpoints in parallel, given the central role of axial elongation in evaluating treatment effects and its frequent co-reporting with choroidal outcomes[27,28]. In addition, intermediate structural and vascular markers should be captured using harmonized protocols: ChT (measured with OCT) is influenced by factors such as device type and examination timing, which can contribute substantially to between-study heterogeneity, while OCTA-derived metrics (*e.g.*, retinal vascular density across macular regions) add complementary information on microvascular changes across myopia severities[27,28,30]. Standardizing acquisition settings, segmentation frameworks (including consistent regional definitions), and reporting conventions, including controlling or documenting examination time to mitigate diurnal effects, would improve comparability, strengthen interpretation of treatment-related changes, and support more reliable evidence synthesis across settings[27,28].

The field needs trials designed to quantify what happens after treatment ends, because evidence syntheses show a measurable rebound following cessation across myopia-control modalities, and atropine discontinuation in particular is associated with time- and dose-dependent post-treatment acceleration. In a meta-analysis focused on atropine, rebound in both spherical equivalent and AL was larger in the first 6 months after stopping than at later time points, and was more pronounced with higher doses, shorter treatment duration, younger age, and higher baseline myopia; importantly, rebound was still observed even when switching to a lower dose or using stepwise tapering, whereas combining atropine with optical strategies appeared to mitigate rebound in the limited available data[31].

A broader systematic review across treatments likewise concluded that rebound can be detected after cessation, with optical approaches (*e.g.*, DIMS/HAL spectacles, soft multifocal contact lenses, orthokeratology) showing lower average rebound than pharmacologic (atropine) or light-based therapies, and it highlighted that most studies only assess rebound at the end of washout rather than tracking trajectories during the washout period[32]. Accordingly, future trials should predefine discontinuation plans (*e.g.*, stepwise reduction *vs* abrupt stopping), treat rebound as a prespecified endpoint, and report longitudinal post-cessation outcomes (AL and cycloplegic SER) at multiple washout time points to enable clinically usable stopping rules and comparisons across modalities[31,32].

Prevention efforts should increasingly target children with premyopia, but this requires consistent and operational definitions. Current meta-analytic evidence indicates that low-dose atropine can lower the risk of incident myopia and reduce rapid myopic shift, while also attenuating spherical equivalent and AL progression over 12-24 months in premyopic children, with no major adverse events reported; photophobia may be more frequent early on, whereas longer follow-up shows no clear between-group differences for photophobia or allergic conjunctivitis. However, the available evidence base remains small heterogeneous, especially regarding how “premyopia” is defined across studies (with differing spherical equivalent ranges and age bands)-which limits comparability and generalizability and highlights the need for further well-designed studies to clarify optimal dosing and treatment duration and to standardize entry criteria for premyopia[35].

Combination strategies warrant structured evaluation because the evidence suggests additive benefits in specific pairings, but long-term evidence remains limited. In children with myopia, pooled data indicate that adding atropine to orthokeratology results in less axial elongation than orthokeratology alone. In addition, a randomized controlled trial comparing 0.025% atropine plus DIMS spectacle lenses *vs* 0.025% atropine plus SV lenses found significantly smaller axial-length increase over 12 months with the DIMS combination and a higher proportion of children with no axial elongation, while the between-group difference in spherical equivalent change did not reach statistical significance. Taken together, these findings support the potential for enhanced axial-length control with combined optical-pharmacologic approaches, but they also underscore the need for longer follow-up to better define sustained efficacy and overall safety beyond the first year and, and to understand how best to deploy combinations in practice[36,37].

Future evidence must embed safety and acceptability as co-primary priorities, not secondary footnotes. This is especially important for interventions with modality-specific risks (*e.g.*, orthokeratology) and for those requiring sustained wear and follow-up (*e.g.*, SCL). Trials and registries should use harmonized adverse-event taxonomies, objective adherence measures, and patient-reported outcomes to support personalized selection and reduce preventable discontinuation or complications[40-42].

Comparative syntheses-especially network meta-analyses-are valuable for quantifying and ranking short-term effects across multiple myopia-control options, but those rankings should be interpreted as decision aids rather than definitive “winners.” In Schmidt *et al*[43], 74 RCTs (12154 participants) were synthesized and a 1-year network meta-analysis compared 45 interventions, showing statistically significant slowing of axial elongation for several modalities (including LLRL approaches, orthokeratology variants, atropine at higher concentrations, and selected spectacle designs), while also documenting outcome-relevant trade-offs such as photophobia with low-dose atropine concentrations and lower adherence for atropine 1.0%; importantly, most trials were conducted in Asian populations and comparative ranking beyond 1 year was limited by insufficient long-term network data and uncertainty in some estimates (*e.g.*, wide confidence intervals for combination therapy)[43]. Similarly, Zheng *et al*[44] focused on 0.01% atropine, orthokeratology, repeated LLRL therapy (RLRL), and their combination: All were effective *vs* control at 12 months, with RLRL ranking highest for axial-length slowing, but the authors also highlighted substantial heterogeneity and the need to clarify longer-term safety and rebound effects, particularly for RLRL[44].

Evidence of efficacy should be weighed against feasibility and adherence in practice. In their review of recent RCTs, Lanca *et al*[45] emphasized that follow-up duration is often limited, heterogeneity across regimens is high, and discontinuation/loss-to-follow-up can be substantial in some trials (*e.g.*, notable drop-out in orthokeratology and early discontinuation in some contact-lens studies), all of which can attenuate real-world effectiveness and constrain conclusions about sustained benefit and optimal treatment duration or cessation strategies[45].

CONCLUSION

Pediatric myopia should be approached as a developmental disorder of visually guided axial growth, in which refraction represents an endpoint rather than the underlying substrate. Across contemporary evidence syntheses, treatment benefit is most meaningfully captured by AL alongside refractive outcomes, and emerging intermediate biomarkers-particularly ChT and OCTA microvascular metrics-support a broader, neuroretinal interpretation of progression and response. Integrating these objective measures with established modifiable exposures (light/outdoor time, near work/digital viewing, and sleep-related traits) aligns with an eye-brain axis framework. It may enable earlier, more individualized risk stratification. However, important gaps remain, including limited long-term durability data, rebound mitigation strategies after discontinuation, and the need for standardized pediatric phenotyping and safety reporting across modalities. Future work should prioritize harmonized endpoints, mechanism-informed monitoring, and pragmatic pathways that translate comparative evidence into scalable, precision-oriented care.

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