Ocular and Environmental Factors Associated with Eye Growth in Childhood

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ABSTRACT
Recent advances in measurement technology have improved our ability to quantify a range of ocular components and some environmental exposures that are relevant to myopia. In particular, environmental sensors now allow the dense sampling of personal ambient light exposure data, and advances in ocular imaging, such as developments in optical coherence tomography (OCT), enables high resolution measures of the choroid to be captured in human subjects. The detailed, objective information produced by these noninvasive measurement technologies has the potential to provide important new insights into the complex array of factors underlying eye growth, and myopia development and progression in childhood. Wearable light sensors and enhanced depth imaging OCT were both employed in a recently completed prospective, observational longitudinal study examining factors associated with eye growth in myopic and non-myopic children. Personal light exposure, choroidal thickness, and axial eye growth were quantified in 101 children over an 18-month period. A significant association was found between objectively measured personal daily ambient light exposure and eye growth (independent of refractive status), consistent with greater light exposure protecting against rapid growth of the eye in childhood. Variations in the thickness of the choroid also appeared to be closely linked to the growth of the eye, with choroidal thinning typically being associated with more rapid eye growth, and choroidal thickening with a slowing of eye growth in childhood. The implications of these findings for our understanding of human eye growth regulation, along with their potential importance for our understanding of myopia control interventions, are discussed.

Key Words: eye growth, myopia, choroid, light exposure, optical coherence tomography

The rising global prevalence of myopia and the associated public health implications of this “myopia boom” provide significant impetus for the development of effective interventions to control the development and progression of myopia.1 Because myopia most commonly occurs due to excessive axial eye growth in childhood, a comprehensive understanding of the ocular and environmental factors associated with childhood eye growth is critical for developing, evaluating, and optimizing myopia control interventions. In the past three decades, sophisticated experiments utilizing a range of animal models2 (many involving the pioneering work of Josh Wallman in the 1990s) and large-scale human epidemiological studies3,4 have substantially expanded our understanding of the various factors underlying the growth of the eye and refractive error development. However, many questions still remain regarding the factors involved in the regulation of eye growth in childhood.

In recent years, technological advances have improved our ability to quantify a range of ocular components and environmental exposures relevant to myopia, and have provided the opportunity to further expand our understanding of human eye growth. In particular, recent advances in ocular imaging technology (such as developments in optical coherence tomography (OCT)) now allow ocular structures such as the choroid to be imaged noninvasively with high precision. The development and proliferation of wearable sensor technology also provides a method to densely sample aspects of the individual’s personal visual environment (e.g. ambient light exposure). Our recent work utilizing these technologies has provided evidence supporting the potentially important role of the choroid5,6 and light exposure7,8 in childhood eye growth. This paper will summarize this recent research examining ocular and environmental factors associated with eye growth in childhood, with a particular emphasis on the findings from the recently completed “Role of Outdoor Activity in Myopia Study” (the ROAM study).

The Role of Outdoor Activity in Myopia Study

The ROAM study was an 18-month prospective, observational longitudinal study of childhood eye growth conducted between
2012 and 2014 at the Queensland University of Technology, in Brisbane, Australia. The study aimed to provide new insights into the factors underlying childhood eye growth through objective measures of typical daily environmental exposures (i.e. ambient light exposure and physical activity) and high resolution imaging of the choroid in both myopic and non-myopic children.

Detailed descriptions of the participants, and the experimental and analytical methods used in the study have been published previously.5–8 Briefly, 101 children aged between 10 and 15 years (mean age 13.1 ± 1.4 years) were enrolled in the study and the non-cycloplegic spherical equivalent refractive error (SER) measured at the baseline visit was used to classify the children as myopes (n = 41, mean SER: −2.39 ± 1.51 D) or non-myopes (n = 60, mean SER: +0.35 ± 0.31 D). Subject retention over the course of the study was good, with less than 10% attrition of subjects over the 18-month study period. Fig. 1 provides an overview of the experimental protocol employed in the study. Each child had ocular measurements collected every 6 months over an 18-month period (i.e. four visits over 18 months). The primary measurements performed at each visit were optical biometry to determine axial length (Axl, the axial distance between the anterior cornea and the retinal pigment epithelium (RPE)) using the Lenstar LS 900 instrument (Haag Streit AG, Koeniz, Switzerland), and EDI (enhanced depth imaging) spectral domain OCT imaging using the Heidelberg Spectralis device (Heidelberg Engineering, Heidelberg, Germany) to derive measures of choroidal thickness (ChT, the axial distance between the RPE and the chorio-scleral interface). In addition to the ocular measurements, in the first 12 months of the study, each child also had objective measures of their personal ambient light exposure and physical activity collected using a wrist-worn sensor device (Actiwatch 2; Philips Respironics, USA). These devices were worn for two 14-day periods, separated by approximately 6 months, and provided instantaneous measures of ambient white light illuminance (wavelength range of 400–900 nm and peak sensitivity of 570 nm with a dynamic sensor range from 5 to 100,000 lux) and physical activity (expressed in activity counts per minute (CPM)) every 30 seconds, 24 hours a day (i.e. 2880 samples of light exposure and physical activity per day across the two 14-day measurement periods for each child). Linear mixed model (LMM) analyses were used to examine the longitudinal changes in Axl and ChT, and the factors (e.g. light exposure, physical activity, and demographic factors) potentially associated with these changes.

**Choroidal Thickness and Eye Growth**

Although the major physiological roles of the choroid (primarily supplying oxygen and nutrients to the outer retina)10 have been well understood for many decades, it is only since the 1990s when Josh Wallman and colleagues11,12 demonstrated that the choroid in developing chickens was capable of changing thickness predictably in response to optical defocus, that evidence for an active role of the choroid in eye growth regulation and refractive error development has emerged. Josh Wallman and Chris Wildsoet’s seminal work on the chick choroid demonstrated that exposing young chicks to myopic defocus (that results in a slowing of eye growth in the long term and the development of hyperopic refractive errors) resulted in a rapid thickening of the choroid (effectively pushing the retina forwards towards the defocused image plane to compensate for the myopic blur), and exposure to hyperopic defocus (that results in increased axial eye growth and the development of myopia in the long term) resulted in a rapid choroidal thinning (moving the retina back towards the defocused image plane).

Since this first report of a bi-directional choroidal response to defocus in chicks, similar (although smaller magnitude) choroidal responses have been reported in a wide range of animal species including guinea pigs,13 marmosets,14 and macaques.15 In all of these species, choroidal thickening is found to accompany the development of hyperopia (and a slowing of eye growth) and

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**FIGURE 1.**

A schematic overview of the study procedures performed with each participant in the ROAM study. Each child had ocular measurements (optical biometry and spectral domain OCT images) collected every 6 months over an 18-month period, providing measures of axial length (Axl) and choroidal thickness (ChT) at each visit. Two 14-day periods of wrist-watch light exposure and physical activity measures were also collected for each child, approximately 6 months apart in the first 12 months of the study.

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choroidal thinning accompanies the development of myopia (and an increase in eye growth), with the choroidal changes found to occur rapidly and to precede longer term changes in eye growth. In fact, the choroidal changes to defocus in animals have been shown to occur remarkably quickly, with work from the Wallman laboratory in 2005 showing that measurable changes in the chick choroid in response to myopic defocus occur after only 10 minutes of exposure to blur.16 There is also evidence from work in the chick that exposure to defocus can disrupt the normal timing (phase) of the natural diurnal variations that are known to occur in the thickness of the choroid throughout the day.17 The longer term rate of axial eye growth has also been shown to be significantly associated with the difference in phase observed between the choroidal and axial length diurnal rhythms, which suggests that the synchronization of various diurnal rhythms within the eye is important in the normal regulation of eye growth.17

The evidence of a choroidal response to defocus in a wide variety of animal species and the development of highly precise optical methods for the noninvasive assessment of human ocular biometry18 prompted our research laboratory to examine whether a similar short-term response to defocus also occurred in human eyes. In 2010, we published the first evidence in humans that a 60-minute period of myopic defocus results in a small magnitude increase in choroidal thickness and an associated decrease in axial length (because an increase in choroidal thickness would result in a forward movement of the RPE, thus leading to a reduction in the measured axial length), and that 60 minutes of hyperopic defocus results in a thinning of the choroid and an increase in axial length19 (Fig. 2A).

We expanded upon this initial work using optical biopsy and 60 minutes of defocus by studying the effects of a 12-hour period of hyperopic and myopic defocus using spectral domain OCT (Fig. 2B), which also demonstrated a thinning of the choroid in response to hyperopic defocus, and a thickening in response to myopic defocus, primarily evident in the first 3 hours of exposure to blur.20,21 These changes in choroidal thickness observed in response to defocus throughout the day seem to be modulated by an apparent phase shift occurring in the daily changes in choroidal thickness in the myopic defocus condition and by an increase in the daily amplitude of choroidal thickness change in the hyperopic defocus condition (compared to the normal daily changes observed with no defocus), which is also broadly consistent with previous animal studies.17 Similar short-term bi-directional changes in the human choroid in response to defocus have also recently been reported by Chiang et al.22 using OCT imaging and 60 minutes of defocus exposure. It should be noted though that the magnitude of the choroidal response to defocus in humans is very small (around 10–15 μm, which is equivalent to a refractive change of approximately 0.05 D) and therefore unlikely to affect vision or to substantially compensate for the imposed defocus. The bi-directional nature of the response, however, suggests that these changes may reflect biological signals associated with longer term eye growth. The short-term, transient nature of the changes observed to date though means that the link between short-term choroidal changes and longer term eye growth in humans remains to be established.

A number of recent cross-sectional studies using OCT imaging in humans have also shown that choroidal thickness is associated with axial length23–25 (with a thicker choroid being associated with shorter eyes and hyperopia, and a thinner choroid being associated with longer eyes and myopic refractive errors) and that high myopia is associated with marked choroidal thinning.26 Analysis of the OCT imaging data from the baseline visit in the ROAM study also showed that myopic children have significantly thinner choroids than non-myopic children (Fig. 3), and that the differences in thickness between myopes and non-myopes (on average 56 μm thinner in the myopic children) are greater than would be predicted by a passive choroidal stretch associated with the myopic axial elongation.5 These results are consistent with the choroid having a role in the regulation of human eye growth; however, the cross-sectional nature of these reports means that they do not establish a definitive link between choroidal thickness changes and eye growth.

Longitudinal analyses of the choroidal thickness measures over the 18 months of the ROAM study therefore provide the first assessment of the relationship between the natural changes in choroidal thickness and eye growth occurring in childhood.4 Over the 18-month study period, a significant increase (mean change of 8 μm per year for all children considered together) in choroidal thickness was observed (Fig. 4A), indicating that a thickening of the choroid is a normal feature of the growth of the eye in childhood. Interestingly, studies of nonhuman primates14,15 have also documented developmental increases in choroidal thickness of normally growing adolescent eyes. Although the mechanism underlying these increases in choroidal thickness with age in childhood is not known, it is likely that growth of the choroid’s vascular and connective tissue (and potentially age-related blood flow changes) in childhood are involved.

In Fig. 4A, the myopic children on average show less choroidal thickening compared to the non-myopic children; however, this trend did not reach statistical significance. But interestingly, considering all children, the changes in choroidal thickness were found to be closely linked to the axial growth of the eye, with a significant inverse association found between the changes in choroidal thickness and the rate of axial eye growth (Fig. 4C). Children exhibiting slower axial eye growth tended to show greater thickening of the choroid over time, and children showing faster axial eye growth displayed less thickening and in many cases a thinning of the choroid. When children were categorized according to their rate of axial eye growth (regardless of refractive status, and based upon a tertile split of the axial eye growth data), the children exhibiting the fastest eye growth in this population were also found to show significantly less choroidal thickening (3.0 μm/year) than those children exhibiting medium (8.9 μm/year) and slow (9.1 μm/year) axial eye growth (Fig. 4B). Because the axial length measurement is defined as the distance from the anterior cornea to the RPE, small changes in the position of the RPE as a direct result of increases and decreases in choroidal thickness may have contributed to the observed association between axial length and choroidal thickness. However, further analyses carried out to calculate the ‘total eye length’ of each subject (the sum of the subfoveal choroidal thickness and axial length, which is effectively the axial distance from the anterior cornea to the front surface of the posterior sclera) over the course of the study also showed a similar significant inverse association between the rate of choroidal thickness change and the rate of change in total eye length (p < 0.01), supporting a role of the choroid in the regulation of axial growth.
of overall eye growth. These choroidal thickness changes observed in human children are also broadly consistent with the previous findings in animal studies, where a slowing in eye growth (during the development of hyperopia or recovery from experimental myopia) is also accompanied by choroidal thickening and an increase in eye growth (during experimental myopia development) is accompanied by choroidal thinning.\(^{11-15}\)

The findings from the ROAM study suggest that measures of choroidal thickness are an important biomarker and potentially a novel predictor of the growth of the eye (and hence progression of myopia) in childhood. These findings support an important role for the choroid in the signal cascade involved in the regulation of eye growth in childhood, and provide a catalyst for future research looking at the potential causative link between changes in the choroid and eye growth in childhood. Additional research is required to determine whether the relationship between axial eye growth and choroidal thickness change is due to an active (e.g. the choroid secreting growth factors that act directly on scleral growth) or passive (e.g. the choroid acting as a barrier to the passive diffusion of growth factors) choroidal mechanism. The

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**FIGURE 2.**

Short-term response of the human eye to defocus, illustrating the changes in axial length and choroidal thickness following 60 minutes of exposure to defocus\(^{18}\) (A), and the choroidal thickness variations occurring during a 12-hour period of defocus\(^{19,20}\) (B). Error bars represent the standard error of the mean.
FIGURE 3.
Baseline average choroidal thickness (A) and standard deviation of the average choroidal thickness maps (B) in the myopic (left) and non-myopic (right) children in the ROAM study (white dots indicate the average position of the thickest choroid). Black circles in (A) and (B) indicate the central 1-, 3-, and 6-mm-diameter regions. Example OCT scans from a representative myopic and non-myopic child in the study (matched for age and gender) are shown in (C).
association found between choroidal thickening and slower eye growth also encourages future investigations of interventions (e.g., optical interventions inducing myopic defocus or pharmacological interventions such as dopamine agonists, anticholinergic agents, or agents potentiating the effects of nitric oxide that are known to result in a thickening of the choroid, to also potentially influence myopia development and progression.

Given that it is only in recent years that reliable measures of choroidal thickness in humans have become possible, there is substantial scope for additional future research to further our understanding of the human choroid and its role in myopia development and progression. To date, published findings regarding the short-term response of the choroid to defocus in humans have been restricted to populations of young adults. It will therefore be of interest for future studies to examine these choroidal responses in pediatric populations, to explore any differences in the response associated with age, and the potential impact of more rapid eye growth on the responsiveness of the choroid to defocus stimuli. Evidence from animal studies suggests that the mechanisms underlying bi-directional choroidal thickness changes in response to defocus potentially involve a range of factors such as changes in proteoglycan synthesis or alterations in vascular permeability (that would result in fluid redistribution within the choroid) and/or changes in the tone of nonvascular smooth muscle in the choroid. Further work is required to understand the mechanisms underlying human choroidal thickness changes and to appreciate whether the short-term changes in response to defocus, and the longer term changes occurring during childhood eye growth, share the same mechanisms. The continued evolution of imaging technologies for assessing the human choroid should contribute to new insights into these mechanisms, as imaging much larger regions of the choroid and more detailed characterization of tissue and vascular

FIGURE 4.
Changes in choroidal thickness over time for the children in the ROAM study, stratified according to their baseline refractive error (A) and according to their rate of axial eye growth as exhibiting fast (greater than 67 μm per year), medium (between 25 and 67 μm per year), or slow eye growth (less than 25 μm per year) (B). The correlation between the rate of axial eye growth and the change in choroidal thickness is shown in (C). Error bars represent the standard error of the mean. The change in choroidal thickness over time was not significantly different between the myopic and non-myopic children (A) (p > 0.05); however, the children exhibiting fast axial eye growth showed significantly less choroidal thickening over the 18 months of the study compared to the children exhibiting medium and slow axial eye growth (p < 0.05) (B).
properties (e.g. blood flow and blood vessel architecture) becomes increasingly more possible.

**Light Exposure and Eye Growth**

Although the notion that ambient light exposure may impact upon eye growth and myopia dates back at least 100 years, the recent findings from epidemiological studies that children with myopia spend less time outdoors than non-myopic children have sparked a renewed interest in the potential role of light exposure in the regulation of childhood eye growth. The relatively consistent finding (across a range of epidemiological studies of children in a variety of geographic locations) of an association between greater time outdoors and less prevalence and incidence of myopia in childhood supports a potential role for light exposure in myopia development because light levels outdoors are substantially brighter than those experienced indoors. However, as well as allowing greater ambient light exposure, being outdoors is also typically associated with less near focusing and more physical activity, and although it has been hypothesized that increased light exposure outdoors is the important factor protecting against myopia (potentially through a mechanism involving light induced release of dopamine which is known to slow eye growth in animals), the exact mechanism underlying the protective effects of increased outdoor time on childhood myopia is still not fully understood. One of the reasons for the uncertainty regarding the mechanisms underlying the “outdoor effect” is the fact that the majority of epidemiological studies examining outdoor activity and myopia have relied almost exclusively upon questionnaires to quantify children’s activities. These questionnaires typically involve either a single question or a series of questions about various activities, but regardless of the specific questionnaire used, they all rely on the accuracy of participants’ (or their parents’) memory and perceptions of their previous activities, and additionally do not provide objective, quantitative information regarding the participants actual habitual environment.

A major aim of the ROAM study was therefore to employ objective measures of personal ambient light exposure to examine for the first time the relationship between longitudinal changes in eye growth and light exposure in childhood. Comparisons of the ambient light exposure of the myopic and non-myopic children in the ROAM study (derived from the two 14-day periods of wristwatch light and physical activity measures for each child) revealed that the non-myopic children experienced significantly greater average daily light exposure than the myopic children. Although all children exhibited similar variations in light exposure throughout the day (with the majority of light exposure occurring between 6 am and 6 pm, and peaks in light exposure observed to coincide with times before and after school, and during the typical breaks in the school day), the non-myopic children were observed to exhibit significantly greater daily light exposure, with the greatest differences associated with refractive error observed in the hour before school starts, lunch hour at school, and in the hour after the end of the school day. The non-myopic children were also observed to exhibit greater daily time (on average 104 minutes per day) exposed to bright light (light >1000 lux, which is an estimate of outdoor light exposure, because light levels indoors rarely reach 1000 lux) compared to the myopic children (mean of 80 minutes per day). Interestingly, although the physical activity data exhibited similar trends in terms of the daily pattern of change observed, differences between myopic and non-myopic children’s daily physical activity did not reach statistical significance (Fig. 5). Consistent with previous studies of childhood eye growth, examination of the longitudinal changes in eye growth in the ROAM study revealed significantly faster eye growth in the myopic children compared to the non-myopic children (Fig. 6A) and significantly faster eye growth associated with younger age. A modest but statistically significant inverse association between eye growth and average daily light exposure was also observed, with greater daily light exposure being associated with significantly slower axial eye growth. This analysis also revealed that daily physical activity was not a significant predictor of axial eye growth in childhood. These results provide the first evidence of a significant relationship between objectively measured ambient daily light exposure and axial eye growth in childhood, and support the theory that ambient bright light exposure is the important factor involved in the documented association between outdoor activity and myopia. Because bright light is also known to induce the release of retinal dopamine, these findings of an association between childhood eye growth and light exposure also support the previous hypothesis that the mechanisms underlying the anti-myopiagenic effects of outdoor activity involve dopamine.

Additional analyses were also performed after classifying the children in the study according to their average daily light exposure (based upon a tertile split of the average daily light exposure data, regardless of refractive grouping), as either habitually experiencing low daily light exposure, moderate daily light exposure, or high daily light exposure. Examination of the axial eye growth in these three groups of children revealed statistically significantly faster axial eye growth (0.13 mm/year) in the children habitually exposed to low light levels compared to those children habitually exposed to high (0.065 mm/year) and moderate (0.060 mm/year) light levels (who were not significantly different to each other) (Fig. 6B). Because the low light exposure group on average spent only 56 minutes per day exposed to bright light (>1000 lux), these findings suggest that less than 60 minutes of bright light exposure per day predisposes children to faster axial eye growth/greater myopia progression. When we examine the average magnitude of difference in eye growth between these light exposure groups, the children habitually experiencing low daily light exposure exhibited approximately 0.1 mm greater eye growth over the course of the study, which equates to ~0.3 D greater myopic refractive progression. These analyses include adjustments for potential confounders, including age and refractive grouping, which suggests that the association between light exposure group and eye growth was independent of refractive status.

These findings support the potential for strategies aimed at increasing daily ambient light exposure as potential myopia control interventions, and also provide some insights into the potential strength of the effects and “dosages” required in such interventions. The children in the ROAM study habitually experiencing moderate and high daily light exposure on average experienced 60 more minutes per day exposure to bright light compared to the children habitually experiencing low light exposure, and also exhibited significantly slower eye growth. This suggests therefore that increasing exposure to bright light (>1000 lux) by around 60 minutes...
per day is likely to have an impact on slowing axial eye growth in childhood. Two recent studies\(^{44,45}\) have examined the influence of increasing outdoor time (aiming to increase children’s daily time outdoors by 40 minutes\(^{45}\) and 80 minutes\(^{44}\)) upon childhood refractive development and have noted positive effects of these interventions upon reducing myopia development; however, neither of these studies objectively assessed the light exposure of the participants. The findings from these studies with respect to myopia progression, however, have been less clear cut since Wu et al.\(^{44}\) found a significant effect of their outdoor intervention upon refractive progression only in those children who were non-myopic at the start of the trial (and not in myopic children), and although He et al.\(^{45}\) did find a significant reduction in myopia progression associated with their outdoor intervention, they did not find any statistically significant effects of the intervention upon axial eye growth measures. This highlights the need for further research to better understand the influence of increasing light exposure upon myopia progression and eye growth. The use of wearable light sensors in future interventional studies should help to expand the understanding of these effects by allowing detailed quantification of exposure in treatment and control groups (and providing an objective means of assessing compliance with the intervention). This could also help to clarify if changes in specific light exposure parameters (e.g. intensity and/or duration of daily exposure) have an

![Graphical representation of light exposure and physical activity for myopic and non-myopic children in the ROAM study.](image)

**FIGURE 5.**
Average hourly light exposure (top) and physical activity (bottom) for the myopic and non-myopic children in the ROAM study. Each data point represents the mean of 60 minutes of light and physical activity data recording (sampled every 30 seconds), across all 28 days of measurements (two 14-day periods of data recording were conducted for each subject) for all of the myopic or non-myopic children in the study. Error bars represent the standard error of the mean. Vertical dashed lines indicate the mean timing of the school breaks and gray shading indicates the standard deviation of the break times.
influence upon refractive progression and eye growth. Such an improved understanding may in turn allow the optimization of future interventions to further reduce the development and progression of myopia.

Light Exposure and Choroidal Thickness

The findings from the ROAM study indicate that both ambient light exposure and choroidal thickness\(^6\) are associated with the axial growth of the eye in childhood. There is also evidence from animal studies\(^46\) that exposure to bright light can lead to a small magnitude of choroidal thickening. Human studies also indicate that altering the pattern of light exposure can influence choroidal blood flow.\(^47\) These findings leave open the possibility that the influence of light exposure upon eye growth may involve (at least in part) a choroidal mechanism. To explore this issue further, here we have also examined the potential association between light exposure and choroidal thickening in the children participating in the ROAM study. The choroidal thickness changes over time were examined after categorizing the children based upon their average daily light exposure as habitually experiencing low, moderate, or high light exposure (Fig. 7). This analysis revealed that children habitually experiencing moderate and high daily ambient light exposure exhibited significantly greater choroidal thickening over time compared to children habitually experiencing low light exposure (\(p = 0.001\)). However, it should be noted that the close relationship previously observed between light exposure and eye growth, and between eye growth and choroidal thickness make it difficult to assess, based upon these data alone, whether the changes in the choroid in the different light exposure groups are an independent effect of light on the choroid or an indirect effect related to the association between light and eye growth. This result, however, does suggest that the mechanisms linking light exposure and eye growth could potentially involve the choroid, and encourages future research to examine the effects of light exposure upon choroidal thickness in childhood.

CONCLUSIONS

The work presented in this paper exploits developments in ocular imaging and sensor technology to provide new insights into the ocular and environmental factors involved in childhood eye growth, demonstrating that choroidal thickness changes seem to be providing an ocular biomarker of eye growth in childhood and that ambient light exposure is a modifiable environmental factor associated with eye growth in childhood. These techniques seem to provide robust tools for quantifying ocular changes and environmental effects in myopia research, and the continued use and development of these methodologies in the future will continue to expand our understanding of the factors underlying myopia and should assist in the development and optimization of myopia control interventions.

FIGURE 7.
Average changes in choroidal thickness (ChT) in children stratified according to their average daily light exposure. Error bars represent the standard error of the mean. Vertical black lines indicate the mean timing of the first and second light exposure measurements in the study and gray shading indicates the standard deviation of the timing of the light exposure measures.
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REFERENCES


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The Case for Lens Treatments in the Control of Myopia Progression

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ABSTRACT

Myopia is on the rise in the United States and around the world, and with its progression comes increasing risk of a wide variety of associated vision-threatening conditions. Fortunately, several evidence-based treatments for myopia control are currently available and show promise. Basic research on the visual control of eye growth and the development of refractive state is being successfully translated to clinical studies on lens and drug treatments, and patients are already benefiting. Evidence-based practice is transforming the clinical care for myopia from correction to treatment. In this commentary on the role of lens treatments for myopia control from the 15th International Myopia Conference, the author considers bifocals, progressive addition lenses, multifocal contact lenses, and orthokeratology to make the case that lens treatments, particularly using multifocal contact lenses, are effective for myopia control and should be considered as a first-line treatment. A number of areas for further research and treatment optimization are also identified.

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Key Words: myopia, multifocal contact lenses, lens treatments

These are interesting times in myopia research and for care of myopic children. While myopia is on the rise in the United States1 and around the world,2 research is offering a variety of promising new directions. Basic research on the visual control of eye growth and the development of refractive state is being successfully translated to clinical studies, and patients are already benefiting. Evidence-based practice is transforming the clinical care for myopia from correction to treatment. Several such treatments recently reviewed in a meta-analysis by Huang et al.3 include cycloplegic drugs, orthokeratology, and optical treatments. Together with new insights into environmental factors such as outdoor activity and light,4,5 these treatments may soon provide the means to truly control myopia progression.

At the 15th International Myopia Conference in Wenzhou, China, I was asked to comment on the role of lens treatments in myopia control. In this short paper, I will summarize those comments and make the case that treatment with positive addition lenses, particularly multifocal contact lenses, are effective for myopia control and should be considered as a first-line treatment.

Controlling Visual Experience

It is now widely accepted that both genetic and environmental (visual) factors are involved in the development of myopia. Controlling the visual conditions that affect eye growth offers both noninvasive and economical means to reduce myopia progression. Experimental studies over more than 30 years, using a variety of animal models including nonhuman primates, leave little doubt that retinal defocus carries specific visual information used to regulate the growth and refractive state of the eye.6 Specifically, imposing positive (myopic) retinal defocus from positive lenses provides a potent signal that slows eye growth and reduces refractive shifts toward myopia. Imposing negative (hyperopic) retinal defocus from negative lenses has the opposite effect and may be an important factor in the development of myopia. Furthermore, the signals that regulate eye growth and refractive state are not only processed by the central retina on the visual axis but have been shown to be effective across the entire extent of retina.7–9 Together, these findings support the idea that myopia control should be possible using lens treatments that provide positive retinal defocus while correcting distance vision.

Lens Treatments for Myopia Control

Effective lens treatments to control myopia progression include positive addition lenses (bifocals and progressive addition lenses), multifocal contact lenses, and orthokeratology. I will provide an overview of each in turn.
Positive addition bifocals for myopia control were originally used as a way to reduce accommodation, which was thought to be the cause of myopia but now considered to be indirectly involved, possibly through large hyperopic lags. The use of positive addition in bifocals or progressive addition lenses has shown varying degrees of reduction in myopia progression (for a review see 10). In the COMET study, 11 progressive addition lenses showed a modest but statistically significant reduction in the progression of myopia. More recently, Cheng et al. 12 found that executive bifocals produced approximately 50% reductions in progression rate over 3 years of treatment. The efficacy of positive addition lenses seems to be affected by accommodation vergence interactions. Greater reduction in myopia progression in the COMET study was found in children with near esophoria and large lags of accommodation, and in the Cheng et al. study improved results were found with base-in prism to reduce plus lens induced exophoria at near. Despite the variable results, these studies provide proof of concept that positive addition lenses can be used to reduce myopia progression.

Besides the accommodative vergence interactions, another possible reason for inconsistent results with bifocals and PALs may be in the way the positive additions are used. If the patient uses the add for central near vision (as originally intended), it would not only negate the therapeutic effect of applying positive retinal defocus, it might actually increase hyperopic defocus in the retinal periphery depending on shape of the eye, peripheral refractive state, and the visual environment. 13,14 If the patient does not use the positive add during vision at near (or during distance vision, which may be even more important), a degree of positive defocus will be imposed on a relatively small area of the superior retina (larger in the case of executive bifocals). In fact, Berntsen et al. 15 reported that more positive defocus imposed on the superior retina in this way was related to greater reductions in myopia progression.

Using multifocal contact lenses with positive addition for myopia control eliminates some of these issues. The effect of the positive addition covers a much larger area of retina, and eye movements do not alter the location where it is imposed on the retina as much as they do when viewing through bifocal and PAL spectacles. Experimental studies provide additional evidence that multifocal contact lenses are an effective way to reduce myopia progression while correcting distance vision. Contact lenses are effective in producing changes in eye growth and refractive state in a nonhuman primate model, 16 positive defocus is more effective than negative defocus when imposed simultaneously, 17 and applying defocus more in the retinal periphery than in the central retina is still effective in altering axial growth and refractive state. 18 Results from several recent clinical studies of multifocal contact lenses in myopic children are very encouraging. Some of these used proprietary lens designs 19-21 and others used center distance multifocal designs for presbyopia off-label. 22,23 Taken together, however, these studies show reductions in myopia progression between 25 and 80% over 1 or 2 years of treatment, with associated reduction in axial elongation averaging 44%. There are currently larger, multicenter randomized controlled trials underway, which will provide more data and will show how short-term effects change with time.

Orthokeratology, which reshapes the cornea to correct axial myopia temporarily, has also been shown to reduce axial growth rates significantly in several clinical studies (for a recent review see 24). The reductions in axial length increase reported are between 30 and 55% over trial periods of 2 years and in one study were sustained over 5 years. 25 The reduction in axial elongation mediated by reshaping the cornea is thought to be by producing relative positive peripheral defocus, 26-28 similar to what is produced by the multifocal contact lenses.

Is Peripheral Refractive State Important for Myopia Control?

The role of peripheral refractive state in myopia development has been the subject of considerable interest. It has been known for some time that myopic eyes have relatively more hyperopic peripheral refractions compared to the relative peripheral refractions in emmetropes or hyperopes (for example see 29), but whether this is a cause or an effect of axial myopia is unclear. Several recent studies have not found peripheral refractive state to be a useful predictor for either myopia onset or development, 30-33 suggesting it is not a major factor in myopia development. However, none of these studies looked at refraction beyond 30° off-axis, and they cannot rule out the possibility that integration of the defocus signals off-axis may be involved in the progression of myopia once it has begun (see Atchison in this issue). If the visual signals guiding eye growth are integrated across the retina, as shown in experimental animal models (e.g. 7-9,18), differences in peripheral refraction might help explain why myopia progresses in some individuals but not others.

The apparently weak predictive value of peripheral refraction inside of 30° for myopia development might be explained if the visual eye growth controller is thought of as a center-weighted focusing system. The strongest predictive factors for myopia development are on-axis refraction and axial length, which may normally dominate over peripheral refraction, particularly before myopia onset. This does not exclude, however, a role for peripheral defocus signals in the control of eye growth, which can be exploited as a treatment strategy. Experimental and clinical studies both support this approach. Whether or not peripheral refractive state is a factor in the onset, or progression, of myopia, the fact that imposed defocus in the retinal periphery can affect axial refractive state is useful for myopia control and an important consideration in contact lens designs that optimize central distance vision while providing positive addition.

Future Directions

Although the recent results on contact lens treatments for myopia control are encouraging, there is still much work to be done. Lens designs need to be optimized and treatment programs need to be developed. Many important questions remain unanswered: How much positive defocus is optimal? Where on the retina should it be imposed? What is the best age to start treatment? Does it work on myopia progression in adults or with high myopia? How long should treatment be applied? Answering these questions will help develop fitting guides and monitoring programs.

Another important question is how individual differences should be considered in the decision about whether, when, and how to treat. What is the importance of individual differences in peripheral refraction and astigmatism, spherical aberration, and chromatic aberration? How are the age of myopia onset and the rate...
of progression factor involved? What is the significance of parental refraction, eye size and shape, and binocular function? Finally, understanding the complex nature of the visual stimulus controlling eye growth and how the eye growth controller works to effect changes in growth remain major research challenges. The answers to these questions will provide much needed additional information for understanding the factors involved in the onset and development of myopia and for developing even better lens designs and treatments.

Concluding Remarks

Some consider myopia merely a visual inconvenience, easily correctable with spectacles, contact lenses, or laser refractive surgery. They ask why we should care so much about myopia control. The simple answer is that with the increasing prevalence of myopia and the associated increased risk of vision-threatening complications, myopia is a serious public health concern. Treatments that reduce the axial elongation responsible for myopia progression, or eventually treating to delay the onset of myopia based on reliable indicators of myopia development, will reduce the incidence of vision-threatening complications associated with myopia.

Several treatments are available for progressing myopes. Significant reductions in myopia progression have been reported using atropine, possibly including low-dose formulations (for a review see). Although atropine is a viable treatment option, the mechanisms of action and long-term effects have not been fully established. Recent clinical studies have shown that orthokeratology and multifocal contact lenses that add positive defocus to the peripheral retina are comparably effective and should be seriously considered as treatment options for myopic children. Orthokeratology is an effective treatment but is more complicated to fit and more expensive than multifocal contact lenses. Multifocal contact lens options in the United States are currently limited to off-label distance center lenses for presbyopia. But new designs are under development, and some are available in foreign markets.

The adoption of new treatments and changes in standards of care takes time. There is a natural desire, by researcher and clinician alike, to understand more thoroughly the mechanisms behind new treatments. This is reasonable and acceptable, and is what ultimately drives advances in greater efficacy. But this should not prevent the application of effective evidence-based treatments now. While research and development continues, it is possible to use multifocal lenses off-label, orthokeratology, or atropine, to significantly reduce myopia progression by 30%, or more, right now.

Safety is always a major concern, and some are particularly concerned about contact lens use in children. The best evidence to date shows, however, that contact lens use is safe, and in children is actually safer than in other age groups. In summary, we currently have the means to slow axial elongation and myopia progression in children. If untreated, their myopia will almost certainly progress. Given the increasing prevalence and the known associated complications with increasing myopia, can we continue to justify not to treat?

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REFERENCES


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ABSTRACT
Human studies have provided strong evidence that exposure to time outdoors is protective against the onset of myopia. A causal factor may be that the light levels outdoors (30,000–130,000 lux) are much higher than light levels indoors (typically less than 500 lux). Studies using animal models have found that normal animals exposed to low illuminance levels (50 lux) can develop myopia. The myopia and axial elongation, produced in animals by monocular form deprivation, is reduced by light levels in the 15,000 to 25,000 range. Myopia induced with a negative-power lens seems less affected, perhaps because the lens provides a powerful target for the emmetropization mechanism. Animal studies suggest that raising the light levels may have their effect by increasing retinal dopamine activity, probably via the D2 receptor pathway, altering gene expression in the retina and reducing the signals that produce axial elongation.

Key Words: myopia, animal models, light levels

As described in the previous papers that discussed the question “Do human studies ‘prove’ that (i) outdoor activity is protective, (ii) light is the agent,” human studies1–7 have provided strong evidence that exposure to time outdoors is protective against the onset of myopia and suggest that it is the light levels outdoors that are the causal factor. Animal models are helping us to discover how and why outdoor activity is effective and if, indeed, the causative agent is the higher light levels experienced outdoors. It is important to note that terms like “high” or “bright” or “elevated” light levels refer to the illuminance levels (measured in lux) relative to indoor lighting, which is typically 500 lux or less. Most diurnal terrestrial creatures, including humans, evolved outdoors where light levels are much higher. Illuminance on a sunny day exceeds 100,000 lux. Even on a cloudy day, levels of 10,000 to 20,000 lux are typical. Thus, the “elevated” light levels shown to be protective in animal studies (10,000–40,000 lux) are actually lower than those usually encountered outdoors.

Using animal models, we can examine the effect of illuminance levels both on normal refractive development and on the response to myopiagenic stimuli. During normal refractive development, the illuminance level has a very powerful effect. Cohen et al.,8 showed that chicks raised in cages with 10,000 lux on a 12 hour/12 hour light-dark cycle emmetropize normally. Like most animals and humans, they initially are hyperopic. Then, over the first weeks after hatching, the hyperopia declined toward emmetropia, but stabilized at around 1.1 diopters (D) of hyperopia—a level that is easily cleared with a small amount of accommodation. Chicks raised in 500 lux also emmetropized, but by 90 days of age the mean refraction was 0.03 D and some animals were slightly myopic. Animals raised in 50 lux initially emmetropized, but then all of the animals progressed below emmetropia and became myopic (average at 90 days, –2.4 D).

One can look at this study two ways: on the one hand, it says that “elevated” illuminance (10,000 lux) is protective against spontaneous myopia compared with standard (500 lux) illuminance. On the other hand, it says that low illuminance (50 lux) can produce myopia even without the presence of known myopiagenic stimuli.

At a similar early stage in refractive development, the wavelength of the ambient light also can have a powerful effect. As reported at the 15th International Myopia Conference in Wenzhou, China, tree shrews exposed to steady or flickering long-wavelength (red) light, which only stimulates the long-wavelength sensitive (LWS) cones, slow the rate of axial elongation so that the eyes remain strongly hyperopic.9 Interestingly, this occurs with as little as 2 hours per day of red exposure (the rest of the 14-hour day in fluorescent colony lighting).10 Full-time exposure to red also produces hyperopia in older, adolescent tree shrews that have completed emmetropization.11

Most animals do not develop myopia spontaneously. Myopia is induced by placing a diffuser (form deprivation, FD) or a negative
lens over an eye for a period of days or weeks. Both cause the affected eye to increase its axial length (vitreous chamber depth), moving the retina behind the normal focal plane. Exposure to elevated illumination while animals are in these myopiagentic conditions can reduce the rate at which induced myopia develops compared to the myopia that develops in colony lighting (typically under 500 lux). The myopia in monocularly FD chicks, monkeys, and tree shrews over a limited period of time (days, weeks) is reduced by light levels in the range of 10,000 to 40,000 lux.\textsuperscript{12–14} Interestingly, elevated light (below 40,000 lux) did not reduce the incidence of FDM in chicks and tree shrews— all animals developed some myopia. However, illumination of about 25,000 lux did reduce the incidence (prevent myopia from developing) in some macaque monkeys\textsuperscript{13} and illumination of 40,000 prevented myopia incidence in chicks. In contrast, myopia induced by negative lens wear was not blocked in monkeys, tree shrews, or chicks,\textsuperscript{14–16} although the rate of development was slowed. Given enough time, the lens-wearing eyes fully compensated for the negative lens so that the lens-wearing eye was emmetropic (the refraction, measured with the lens in place, matched the refraction of the control eye). With the lens removed, the treated eyes were myopic.

The difference between the response to FD and negative lens wear may underscore an important difference between these two myopiagentic stimuli. FD removes the possibility of achieving clear images on the retina, placing the emmetropization mechanism in an "open loop" condition where light levels may be better able to affect the generation of retinal GO and STOP signals. In contrast, a negative lens provides a "target." When first applied, it moves the focal plane behind the retina, producing refractive hyperopia. As the eye elongates, the hyperopia lessens and dissipates completely when the eye has elongated to the point where the retina has moved to the shifted focal plane.

Which stimulus is a better model for the environmental conditions that produce human myopia? In most children, there is no form deprivation. However, to the extent that hyperopic defocus, caused by underaccommodation to near targets, is a stimulus for axial elongation (the blur hypothesis\textsuperscript{15}), there is also no fixed "target," similar to the situation with FD. This is because the eye elongates in response to the hyperopic defocus, the underaccommodation continues so that there is continued hyperopic defocus. In that sense (and only in that sense), it is similar to form deprivation. To the extent that the lack of a fixed target is an important factor in the effectiveness of high illumination in slowing myopia, the more consistent effects of high illumination on slowing myopia in response to FD in animals may suggest that additional studies in children exposed to outdoor activity will find at least a small slowing of myopia progression.

Animal models are also helping us to make major inroads into the retinal mechanisms by which light levels can modulate axial elongation and refractive state and the response to myopiagentic stimuli. Many neurotransmitters and peptides in the retina have been implicated in generating the retinal signals that increase axial length ("GO" signals) or retard axial elongation ("STOP" signals).\textsuperscript{18–22} One of these is dopamine, a neurotransmitter used by a class of amacrine cells.\textsuperscript{23–25} Increased release of dopamine may slow elongation and decreased levels may facilitate elongation.\textsuperscript{14,30,31} The interest in dopamine in relationship with illumination is that increasing light levels produce increased dopamine activity. Indeed, if the illumination is increased to 40,000 lux, the progression of myopia in FD chicks is arrested.\textsuperscript{32} Moreover, if the dopamine D2 receptor antagonist spiperone is administered intravitreally in chicks exposed to high illumination, the protective effect of the light is removed.\textsuperscript{16} In conclusion, studies in animal models have provided evidence that "high" illumination facilitates normal emmetropization, that levels of 10,000 lux or more can slow the progression of induced myopia, and that retinal dopamine may play a critical role in these effects.

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REFERENCES

1. Rose KA. Do human studies prove that (i) outdoor activity if protective, (ii) light is the agent? Presentation given at the 15th International Myopia Conference, September 23–27, 2015, Wenzhou, Zhejiang, P.R. China.
2. Flitcroft DI. Discussion: do human studies prove that (i) outdoor activity is protective, (ii) light is the agent? Discussion of the previous presentation given at the 15th International Myopia Conference, September 23–27, 2015, Wenzhou, Zhejiang, P.R. China.


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Animal Studies and the Mechanism of Myopia—Protection by Light?

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ABSTRACT
Epidemiological studies have demonstrated that spending time outdoors during your childhood is protective against the development of myopia. It has been hypothesized that this protective effect is associated with light-induced increases in retinal dopamine levels, a critical neuromodulator that has long been postulated to be involved in the regulation of ocular growth. This paper, along with the paper entitled “What do animal studies tell us about the mechanism of myopia—protection by light?” discusses the evidence provided by animal models for this hypothesis.

Key Words: myopia, animal models, light levels, outdoor activity

It is well established that alterations in the rhythmicity, intensity, or spectral composition of light can affect the emmetropization process in animal models. For instance, extended rearing of chicks under constant light or constant dark leads to excessive vitreal chamber elongation, but, because of severe corneal flattening, an overall hyperopic shift in refraction is seen. Work in chicks has suggested that the abnormal growth patterns observed in response to the removal of diurnal cues are driven by dysregulation of critical retinal circuits, including the retinal dark/light switch, which is formed by inhibitory reciprocal interactions between dopamine, melatonin, and, in chicks, enkephalin. Specifically, within 6 days of constant light exposure, the rhythmic release of dopamine and melatonin is lost, with the absolute levels of both neuromodulators suppressed. This is followed closely by alterations in the normal growth patterns of the eye. Together, animal studies have demonstrated that normal ocular development requires diurnal cues to maintain the retinal pathways underlying eye growth in a normal state.

Changes in luminance levels have also been shown to modulate emmetropization. Rearing chicks under low luminance levels (<50 lux) during the light phase induces axial elongation and a myopic shift in refraction. These results demonstrate that if the absolute luminance levels during the light phase are too low, and/or the dynamic range of diurnal changes in light intensity are too small, abnormal ocular development ensues. This is most likely explained by a lack of appropriate stimulation of the dopaminergic system during the light phase, whose release follows a log-linear pattern to that of light intensity. Based on such results, one could imagine that the move towards a more sedentary indoor lifestyle, in which the absolute light levels we experience during the day are significantly reduced, and with it the dynamic range of diurnal changes, may well explain the increased incidence of myopia. This would also fit with the epidemiological data that time spent outdoors under bright natural light is protective against the development of myopia.

Supporting this hypothesis, Cohen and colleagues have demonstrated that raising chicks diurnally, over a 90-day period, under bright light (10,000 lux) maintains animals in a hyperopic state (~+1.1D) relative to that seen under medium (500 lux, ~+0.03D) or low light intensities (50 lux, ~+2.41D). Importantly, Cohen and colleagues observed a strong correlation between retinal dopamine release, illuminance levels, and mean refraction, supporting the hypothesis that light-induced increases in retinal dopamine levels are inversely correlated with the development of myopia.

In general, changes in ocular growth patterns observed in response to both constant light and low light appear to be associated with dysregulation of the dopaminergic system. In low light, this appears to be associated with inadequate stimulation of the dopaminergic system during the light phase. In constant light, the growth changes may be associated with a loss of dopaminergic rhythmicity and/or a reduction in absolute levels of dopamine.

More recently, elevated light levels have been shown to prevent the development of form-deprivation myopia (FDM) in chicks (40,000 lux), rhesus monkeys (28,000 lux), and tree shrews (15,000 lux). In chicks, a strong negative correlation (logarithmic, \( r^2 = 0.95 \)) is observed between the development of FDM and the intensity of light to which animals are exposed, with greater

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protection provided with higher light intensities. Of note, in chicks, high light not only prevents the onset of FDM but it also halts further progression in already myopic eyes. In both tree shrews and rhesus monkeys, bright light exposure induces a hyperopic shift in contralateral control eyes, and in monkeys, within a significant number of diffuser-treated eyes. Importantly, in all animal models, bright light exposure prevents the excessive axial elongation associated with FDM, a requirement for any candidate treatment for human intervention. In chicks, the protective effects of bright light against the development of FDM can be abolished by the administration of the dopamine D2 receptor antagonist spiperone, again indicating that this process is mediated by light-induced stimulation of the dopaminergic system.

However, there are a number of questions that still remain with regard to the ability of light to modulate ocular growth and its relevance to human myopia. Firstly, why does bright light retard the rate of compensation for negative lenses in chicks and tree shrews, but does not appear to affect lens compensation in rhesus monkeys, although a recent study has reported a possible effect? Further, unlike FDM, bright light does not prevent the development of lens-induced myopia (LIM), but rather hinders the rate of progression, with full compensation still occurring. Although there are a number of similarities in the biological pathways and structural changes observed in response to FDM and LIM, the differential effect of light also illustrates possible dissimilarities in the underlying mechanism. This raises the question as to which model, if any, best represents human myopia. As reviewed in the adjoining paper “What do animal studies tell us about the mechanism of myopia—protection by light?”, the onset of myopia in children is not associated with a fixed refractive endpoint, and in that sense displays characteristics of FDM rather than LIM; however, children are not experiencing a loss of form-vision. We may well see a stronger effect against the development of LIM if the daily duration of bright light exposure is extended. This becomes particularly relevant if negative lens wear is inducing a continuous “GO” growth signal across the entire light phase each day.

The 15th International Myopia Conference has again highlighted a role for spectral composition in the regulation of ocular growth. Work presented in Topic 6 (Wavelength, genes, and refractive development), which builds on a number of earlier studies, illustrates that ocular growth rates can be modified in response to chromatic cues. However, species-to-species differences with respect to the direction of growth observed in response to monochromatic light need to be reconciled. One question that arises from this work is whether intensity and spectral composition are interrelated and whether an even greater protection could be gained through a combination of intense and chromatically adjusted light. The ability of bright light alone to prevent the development of FDM may indicate that modifying the chromatic spectrum is unnecessary; however, as noted above, bright light is unable to induce similar protective effects against the development of LIM, an area in which we may find modulation of chromatic cues to be crucial, as suggested by previous work in chicks. This question becomes of even greater importance if we begin talking about possible interventions involving indoor lighting.

Do light levels underlie the protective effect of time outdoors? Specifically, a number of epidemiological studies have reported that children who spend more time outdoors are less likely to develop myopia, although not all studies have observed this relationship. Supporting this finding, two clinical trials have reported that increasing the time children spend outdoors during the school day produces a small but significant reduction in the onset of new cases of myopia. It is currently unclear if increasing the time a child spends outdoors affects progression rates, although animal studies have suggested that this may be possible. As discussed, animal studies have clearly shown that light levels can alter ocular development, and that this is driven by changes in the activity of the dopaminergic system. Supporting a role for luminance levels, Read et al. recently reported a negative association between higher levels of light exposure and axial elongation in a small longitudinal study. Whether light is the underlying driver requires more epidemiological work. There are a number of other mechanisms that have been hypothesized to underlie the protective effect of time outdoors, including chromatic cues (discussed above), UV exposure, viewing distances, and dioptric space. From the point of animal models, it is difficult to comment on many of these hypothesized mechanisms as they have not been extensively tested. However, both animal studies and human data do not support a role for UV exposure. Specifically, epidemiological analysis has shown that myopia is negatively correlated with time outdoors and, in parallel, vitamin D levels. Survival analysis has indicated that the critical factor for incident myopia is time spent outdoors, rather than vitamin D levels. Furthermore, vitamin D3 supplementation does not affect the development of FDM or LIM in tree shrews. Finally, in animal models, experimental myopia, and normal refractive development, is modifiable by UV-free lighting systems, indicating that UV exposure is not critical for these processes, although this does not preclude UV exposure having a parallel or additive effect. In chicks, no difference in compensation to −10D or −20D lenses is observed under UV-free white light or UV light of matching illuminance. This suggests that optical defocus can be detected and compensated for under UV light, but that the presence or absence of UV light does not modify the emmetropization process.

In summary, the hypothesis that light-induced increases in retinal dopamine levels underlie the protective effects of time outdoors is, for the most part, supported by findings from animal studies. Therefore, the general move towards indoor lifestyles may well be predisposing children to the development of myopia, as animal studies suggest that the light levels experienced inside may be too low, or the dynamic range of diurnal changes too small, to stimulate sufficient levels of dopamine to maintain the eye in a normal state of growth. However, a number of questions still remain. Firstly, why does bright artificial light slow the development of LIM in chicks and tree shrews, but not in rhesus monkeys? Further, why are we able to prevent the development of FDM, but only slow the rate of development of LIM? Does this point to mechanistic differences between these two paradigms? Animal work has shown that spectral composition is also important in normal emmetropization. This raises the question of what the interrelationship is between intensity and spectral composition and whether an even greater protection could be gained through a combination of intense and chromatically adjusted light.
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REFERENCES

25. Mutti DO, Marks AR. Blood levels of vitamin D in teens and young adults with myopia. Optom Vis Sci 2011;88:377–82.

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