• Review Article •

# A review of mechanism of action of outdoor exposure in preventing myopia incidence and progression

*Chikezie Grand Ihesiulor[1], Khaled Alzahrani[2], Hema Rhadhakrishnan[1]*

[1]Division of Pharmacy & Optometry, School of Health Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester M139PL, United Kingdom

[2]Department of Ophthalmology, King Fahad Armed Forces Hospital, Jeddah 23311, Saudi Arabia

**Correspondence to:** Khaled Alzahrani. Department of Ophthalmology, King Fahad Armed Forces Hospital, Jeddah 23311, Saudi Arabia. khaledod@gmail.com

Received: 2023-03-10 Accepted: 2024-01-30

## Abstract

● Various studies have suggested several environmental, pharmacological, medical, and optical interventions and some are in use but their efficacy in myopia control may be transient, and the cellular, molecular, and biochemical mechanisms involved unclear. Daylight exposure is currently regarded as an effective and enduring strategy in the control of myopia development and progression. However, the mechanism behind the effect of outdoor exposure and its association with genetic predisposition and other relatively more significant environmental factors on myopia is still a conundrum. This review focuses on survey-based and intervention-based studies carried out to propose a mechanism that accounts for myopia development and important for its control.

● **KEYWORDS:** outdoor exposure; daylight exposure; myopia control; myopia

**DOI:10.18240/ijo.2024.06.21**

**Citation:** Ihesiulor CG, Alzahrani K, Radhakrishnan H. A review of mechanism of action of outdoor exposure in preventing myopia incidence and progression. *Int J Ophthalmol* 2024;17(6):1144-1155

## INTRODUCTION

The protective role of daylight on myopia development has been highlighted by several studies over the last 2 decades. Nowadays, research is focused on understanding underlying mechanisms of myopia development and controlling the epidemic[1-4]. This will be discussed subsequently.

In 2016, myopia was reported to be a public health challenge because it increases the risk of having irreversible blindness from pre-senile cataract, glaucoma, retinal detachment, and macular atrophy[5-6]. Also, myopia complications significantly affect the socioeconomic well-being of its sufferers reducing their quality of life substantially[6]. The increasing prevalence of myopia is a major issue with global economic impact[5-8]. Holden *et al*[5] reports that 1.046 billion people were myopic in 2000 worldwide, and 1.89 billion (27%) in 2010, and myopia will affect 2.56 billion individuals in 2020. In the next three decades, the affected people worldwide will double if current trends continue, making myopia an epidemic and a leading cause of blindness. Currently, it has been estimated that the worldwide annual potential lost productivity due to visual impairment from uncorrected myopia is almost US$250 billion[9]. High or pathological myopia (myopia beyond -5.00 D) which affects one-fifth of the myopic population, mostly working age patients, is a major cause of visual impairment and blindness[5-6].

Furthermore, myopia prevalence has risen dramatically over the past 50y especially in South and East Asia in schoolchildren and young adults (80%–90%) including China, the Republic of Korea, Singapore and other areas with significant economic transition. The prevalence rate is lower in Australia (~4%–30%)[10-11], Europe (10%–23%)[12-13], the USA (15%–41%)[14], and Africa (4%–6%)[15]. However, myopia is responsible for preventable blindness in many developing countries including urban regions of India and Africa[5,16-19]. Based on these studies, higher rate of urbanization and education are responsible for the rural-urban differences, but the explanation is not clear or conclusive[5]. This rapid increase in prevalence has been linked to a combination of genetic predisposition and stronger environmental influence[20-25]. Although heredity plays a key role in early myopia development, with children of two myopic parents being 6.4 times more likely to have juvenile myopia[26-27], controllable environmental factors are a major focus of epidemiological studies as the dramatic rise in myopia prevalence cannot be explained by genetics alone[20-25]. This has been further highlighted by findings from animal model research. Animal model studies has also helped reveal the more

**Table 1 Demographic, behavioural, and optical risk factors of myopia prevalence and progression**

| S/n | Risk factors | Component | References | Summary of results and interpretation |
|---|---|---|---|---|
| 1 | Time spent outdoors | Environmental | [1-6,25,31-37] | Causal role to incident myopia; stronger evidence than near work |
| 2 | AL | Ocular and optical | [38-39] | Causal role for early onset myopia |
| 3 | Close work | Environmental | [29,38] | Additive role, with parental myopia |
| 4 | Urbanization | Environmental | [5,20-22,39-40] | Additive role; near work |
| 5 | Age | Demographic | [41-45] | Additive role; highest progression was at 6–7y. Decreased with increasing age. Prevalence rate was higher in 12–13 year-olds; depending on region |
| 6 | Diet | Environmental | [46-49] | Additive role; vitamin D supplements improve accommodation accuracy/dopamine levels in myopia. Others are refined sugar. Inconsistent evidence |
| 7 | Ethnicity | Genetic | [16,20-22,39-40] | Causal role; genetic predisposition to myopia |
| 8 | Family history (parental and sibling myopia) | Genetic | [5,27,36] | Causal role; responsible for early onset myopia (at 3y) |
| 9 | Gender | Demographic | [39,40,50-52] | Additive role; no statistically significant role in certain studies |
| 10 | Genes/heredity | Genetic | [5,16,36,53] | Causal role; predisposition; but not a major cause of increased myopia prevalence rate. Accounts for small percentage of total myopia |
| 11 | Nearpoint esophoria and bifocal lens | Optical | [32,51,54] | Causal role; convergence has stronger link to myopia development than accommodation |
| 12 | Peripheral defocus (hyperopic) | Optical | [28,35,55-58] | Causal role in some studies/additive role combined with bright illumination |
| 13 | Seasons | Environmental | [59-60] | Additive role; myopia progression rates and AL elongation was lower in summer than winter |
| 14 | Intraocular pressure | Ocular | [61-62] | Additive role; thin corneas have low resistance to normal IOP. Evidence not conclusive |
| 15 | Birth weight | Demographic | [36,63] | Additive role; birth weight increased with AL. Inconsistent evidence |

AL: Axial length; IOP: Intraocular pressure.

developed cues that guide emmetropization, vision-dependent nature of eye growth and the biochemical signal cascade occurring in the retina, choroid and sclera[28].

Finding the best control method for abnormal eye growth through environmental manipulation is more plausible as environmental factors are modifiable sometimes with very little effort. For instance, increasing the lighting levels in child's classroom with more fluorescent tubes or increasing the number of windows in the class or spending optimal level of time outdoors is easier than gene therapy[5,8,27-29].

An interplay of certain risks factors accounts for myopia onset and progression. Some play more significant roles than others[26-27,30] (Table 1)[1-6,16,20-22,25,27-29,31-63].

**Ambient Illuminance Levels** Time outdoor means the amount of time spent out-of-door, outside or in the open air. In the UK, recently a survey revealed that 74% of UK children spent less than an hour daily outside[64]. The normal outdoor light level is between 30 000–50 000 lx[33,64]. The illuminance levels outside vary with factors such as topography, geographical location and season. For instance, the brightness level in Singapore and Sydney where most of the questionnaire-based surveys were conducted have outdoor illuminance of almost 100 times higher than the indoor levels due to plane dioptric topographies outdoor[2-3,25,65]. The fluorescent tubes indoor produces levels of up to 630 lx. During summer in Houston, Texas, the outdoor lighting levels can be beyond 130 000 lx and almost 20 000 lx under tree shades[25].

**Animal Models for Lighting Level and Myopia** The first animal model for environmentally induced myopia was described by Wiesel and Raviola in 1977, using monkeys. They reported that visual deprivation is the chief cause of axial length (AL) elongation and myopia[66-67]. Recently, ambient lighting levels has been put forward as another important factor[33]. Several underlying mechanisms have also been proposed by various researchers using different species. We will focus on a few that are linked to lighting levels[28]. In 1996, Kröger and Wagner[68] discovered that the eye size of blue acara was dependent upon the wavelength of light used to rear them during development. In the same year ultrastructural alterations, after myopia was induced in chicks following two weeks of translucent occlusion, were observed using electron micrographs. The 60% thinning of the choroid, 20% thinning of the retina, lengthening of the photoreceptor mainly the rods outer segment closely adjacent to the retinal pigment epithelium (RPE) basement membrane were reported[55,69]. Rada *et al*[70] in 2002 then proposed that axial elongation due to form-deprivation is the outcome of proteoglycan (PG) production and accumulation in the chick's sclera. In 2003, Wiechmann and Rada[71] suggested that refractive errors mainly myopia are linked to melatonin and melatonin receptors

localized in cornea and sclera of *Xenopus laevis*. They further proposed that these nonneural ocular tissues exhibit circadian rhythms in cellular proliferation, extracellular matrix (ECM) turnover and wound healing[71]. In 2007, after inducing myopia in 2-day old chicks with translucent plastic googles for 10d, suprachoroidal fluid showed an upregulation of the glucosaminoglycan (GAG) synthesis. During recovery, GAG synthesis declines as the choroidal permeability increases[72]. Although the mechanism is still vague, alterations in retinal and choroidal retinoic acid production may cause a drop in scleral GAG synthesis rate that accompanies increase in AL extension rate using the eyes of common juvenile marmosets and *in vivo* and *in vitro* analyses[73]. In 2008, researchers postulated a biological link between abnormal eye growth in myopia and less time spent outdoors or less light intensity[2-3] or the spectral components of light[74-75]. This link is not clear, but using chick's eye, it was concluded that retinal neurotransmitter (NT) dopamine released in response to increased lighting conditions may inhibit eye elongation[76]. Dopamine is an important neuromodulator that acts *via* two major groups D1-like (D1 & D5) and D2-like (D2, D3 and D4) receptors. These receptors are found in various ocular tissues[76-77]. In 2013, Park *et al*[78] stated that low levels of dopamine in mice caused increase susceptibility to form-deprivation myopia (FDM). The following year, Jiang *et al*[77] using 2 weeks old albino guinea pigs, reported that apomorphine, a dopamine antagonist, inhibited myopia development at a higher dose (250 ng per injection) *via* lower affinity D1-like receptors and promoted myopia progression at a lower dose (25 ng per injection) stimulating the higher affinity D2-like receptors. Later in 2015, Smith *et al*[75] proposed that exposing infant rhesus monkeys to long wavelength lighting (red filters) under certain conditions, may promote a hyperopic shift.

Earlier, Mertz and Wallman[79] proposed that retinal signals including dopamine, glucagon, acetylcholine, *etc*., can stimulate the RPE to releases a biologically active modulator that regulates retinoic acid secretion from the adjacent choroid which in turn guides scleral growth/reduced PG synthesis and axial myopia. Studies have been carried out using the sclera of tree shrews because their sclera is similar to the human sclera more than that of the chick[80]. Other factors identified in studies responsible for a weak and thin myopic sclera include disorganized collagen fibrils, decrease in fibril diameter, altered expression of the sclera genes including genes for collagen type 1 and matrix metalloproteinase (MMPs)[80-81].

Some of the methodologies of these studies are invasive and lack accuracy to show the difference *in vivo* between an emmetropic and a myopic sclera. For instance ocular biometry is not accurate and sensitive to AL changes[21]. Also, most studies on the emmetropization and myopigenic mechanisms have used FDM models although FDM and lens-induced myopia (LIM) have different mechanisms[21]. In 2009, Smith *et al*[57] reported the existence of an independent, vision-related mechanism in the retina of infant rhesus monkeys that contributes to eye growth in response to restricted retinal form deprivation. They proposed a similarity in mechanism in the human eye. This is in tandem with previous reports by McBrien *et al*[56] who using tree shrews showed that the recovery from induced axial myopia is driven by an active scleral adjustment process sensitive to retinal image feedback.

Although the mechanisms in these animal studies using chicks, tree shrews, macaque monkeys, rhesus monkeys, marmosets and guinea pigs are similar, extrapolation into human findings may be difficult and unreasonable as the mechanisms operate differently. However, they have helped clarify reports from epidemiological studies and reveal potential myopia treatment strategies[28,55-57,69].

In 2006, Cohen *et al*[31] reported that bright light (10 000 lx) hampered myopia development in chicks while dim ambient light (50 lx) promoted myopia progression. Six years later, Cohen *et al*[31] using the same chick model proposed an underlying mechanism by showing a link between exposure to light-dark cycles and continuous light, and vitreal dihydroxyphenylacetic acid (DOPAC) and dopamine concentrations. Low vitreal DOPAC concentrations, flat cornea, eye elongation and myopia development were associated with light-dark cycles[33]. In the same year, Siegwart *et al*[82] reported that juvenile tree shrews with FDM and LIM had statistically significant reduction in FDM by 44% and LIM by 39% after an approximately 8h/d exposure to ~16 000 lx light.

Recently, Torii *et al*[83] using animal models and human subjects discovered that violet light (VL) may have a preventive influence on adult myopia. VL (with wavelength 360 to 400 nm: shorter than blue light) is at the upper end of ultraviolet (UV) A. Animal models were male white leghorn chicks of FDM and LIM. Using special biotechniques (real time-polymerase chain reaction, RT-PCR), it was discovered that the myopia protective gene (*EGR*1) expression was amplified in the chorioretina of the 6–13d old chicks following 7d exposure to VL than blue light. Furthermore, the VL-exposed chicks developed -4.59 D myopia compared to the VL-covered chicks (-15.2 D of myopia). In the second part, Japanese myopic students (10–15 years of age) were followed up for a year with VL-blocking glasses and VL-transmitting contact lenses (CL) and another group (13–18y) wore partially VL-blocking CL and VL-transmitting CL, followed for 1y as well. Using ultrasound techniques, AL elongation occurred in the younger males wearing VL-blocking glasses and CL (0.25 mm) compared to the VL-transmitting glasses or CL (0.17 mm).

Those wearing partially VL-blocking glasses (0.19 mm) had higher AL elongation compared to those wearing the VL-transmitting lenses (0.14 mm). The ocular biometry technique used is not accurate and sensitive to AL changes[83].

Using various animal models and human participants, researchers have established that emmetropization is governed by a retina-centred visual control and certain nonvisual cues rather than the brain or simple retinal blur (Figure 1)[28]. The nonvisual cues include a biochemical cascade involving molecules in the retina, choroid and sclera. Some of these modulators such as dopamine are linked to light levels rather than near work and time spent outdoors rather than sporting activities[25]. Zhou *et al*[22] proposed that emmetropization-guided homeostatic eye growth functions through activation of dopamine D1-like and D2-like receptors in specific cell types distributed throughout the retina. Dopamine found in the inner plexiform layer of the human retina is produced by the amacrine cells after light stimulation[76]. Although these light-related factors show a stronger link to myopia than air pollution or diet, a greater insight on the link between dopamine and myopia is still explored[21].

In conclusion, the myopia epidemic is a growing public health concern. Methods to prevent its onset or control its progression has been in the front burner in recent epidemiological studies. Genetic susceptibility, near work, outdoor time and other environmental factors are currently explored. Although time spent outdoors has more evidence presently, the underlying mechanisms are neither clear nor independent. The fact that myopia prevention/control is dependent on outdoor time or near work time or a combination of both is also inconclusive.

**Survey-Based Studies for Time Outdoor and Myopia**

Evidence from surveys reveal a strong association between school children's time spent outdoor and myopia development. Myopia prevalence has been reported to be highest between 4 and 15y while 9–12y is a common time of onset[41-43]. There are marked variations in prevalence based on ethnicity and urbanization with higher myopia prevalence in East Asian population[16,84-86]. In 2000, Mutti *et al*[87] in the Orinda Longitudinal Study of Myopia (OLSM), studied eighth grade participants who had one or both parents myopic. They established that the effect of near work was not as significant as heredity let alone time spent outdoors in accounting for myopia development in the future[29,87-88]. A recent survey using the data from OLSM followed up school children from 1989 to 2001 and 21% (111 children) of the 514 subjects became myopic. This proportion had myopic parents and spent less time outdoors[37]. Furthermore, it was deduced after the study that the myopic subjects spent around 8h outdoors/week compared time spent by the non-myopes (about 12h outdoors/week). They proposed that outdoor activity acted independently

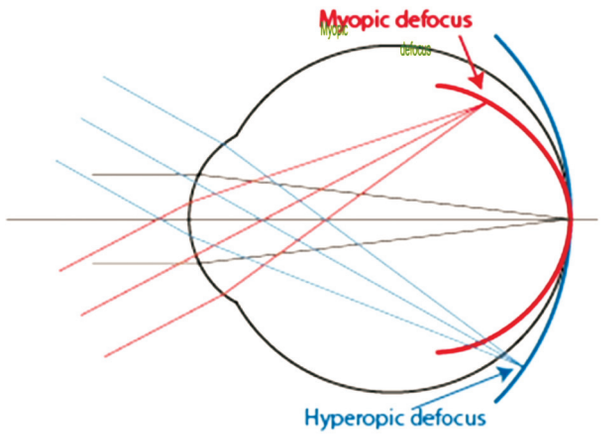


**Figure 1 Myopic and hyperopic defocus adapted from https://contactlensupdate.com/2011/11/16/use-of-contact-lenses-in-myopia-control-a-case-study.**

of near work[37,42]. The incomplete follow-up (till 8th grade) data affected the reliability of this survey. Jones-Jordan *et al*[50] in 2012 followed up myopic children in a Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) survey from 1989 to 2009. They reported that near work (mainly reading) with other co-variables controlled, was responsible for the slightly significant annual myopic progression (0.08 D/y) in boys[89]. The results are not consistent with Pärssinen and Lyyra's[51] report in 1993 which stated that near work was associated with juvenile myopia development in girls. Although CLEERE study pointed that the role of outdoor activity may be important for myopia onset than for its progression in children. This is however inconclusive[50]. Sydney Myopia Study (SMS) in 2008 showed the association between myopia prevalence and near work, indoor and outdoor activities through a population-based survey for year 1 and year 7 school children in Sydney. Data were obtained from questionnaires filled by children's parents and adjustments were made for parental history of myopia, ethnicity and gender. Refractive errors were determined by cycloplegic autorefraction. With proper details given and a large sample size (over 4000 children), time spent outdoors was found to be associated with more hyperopic refractions[2].

In 2009, the Sydney Adolescent Vascular and Eye Study (SAVES) revealed that time spent outdoors had a protective role against juvenile myopia development mostly between ages 6 and 12y, with other covariables such as near work and parental myopia complementing the effect. Also, having two myopic parents increased the odds ratio of incident myopia in the younger participants of the study[1]. French *et al*[24] revealed reports from the SAVES and SMS that East Asian younger (6–12y) and older (12–17y) children spent less time outdoors than their Caucasian counterparts. Furthermore, boys spent more time outdoors than the girls while the girls did more near work than boys. As the children get older, their myopigenic

activities increase which may account for myopia progression in this young population.

In 2009, Dirani *et al*[65] reported data from the Singapore Cohort Study of Risk factors for Myopia (SCORM) for individuals from 11–20y of age during a 2006 visit. It was shown that teenagers and children who spent less time outdoors (3.09h/d and 2.38h/d respectively) were myopic compared to their nonmyopic counterparts (3.59h/d and 2.74h/d). Moreover, outdoor sports helped reduce myopia prevalence rate according to the study[65], while parental and sibling myopia where significant risk factors of myopia in the UK[90-93]. A follow-up study conducted in 2014 in Finland revealed that myopia progression from childhood into adulthood is dependent on heredity and outdoor time[42]. It combined questionnaires and intervention. The 240 myopic school children (with mean age of 10.9y) were recruited into a randomized clinical trial and followed up for 23y. Myopia progression was higher at a younger age, with myopic parent(s); odd ratio of 1.42 for children with one myopic parent and 3.39 for two parents[26] and in females 0.093 D annually[50,89]. Also, more reading time and less time outdoors and sports (<3h daily) was significantly associated with myopia progression. After 3y, it was observed further that myopia progression was not reduced by reading with bifocals or without single vision correction. However, near work at childhood was not a strong predictor of adult myopia[42].

Some of these questionnaire-based studies, longitudinal or cross-sectional with large sample sizes, covariates controlled and cycloplegic refraction techniques adopted, may be however unreliable. They have focused on a particular schooling grade and may be beset with recall bias (underestimation of time spent outdoors by children) or participation bias (significantly more participants than nonparticipants) therefore may require more research[2-3,25]. Also, it is important for ethnicity to be considered in these studies. This will help reveal the extent or mechanism (genetic or environmental) by which it affects myopia development and outdoor time influence on incident myopia or progression. For instance, out of all the survey-dependent studies, the CLEERE study was the most ethnically mixed survey including Asians, Caucasians, Native Americans, African-Americans, Hispanics and Native Americans[16,85-88].

In Europe, formal education has been reported to be associated with the increased myopia prevalence. For instance, myopia prevalence among cohorts in the European Eye Epidemiology ($E^3$) Consortium study who attained higher educational levels increased from 26% between 1920 and 1929 to 40% between 1960 and 1969[94]. This Meta-analysis cross-sectional study reported that myopia prevalence across Europe has amplified significantly (mostly across western and northern Europe); similar to the level reported in North America but lower than the proportion in Southeast Asian regions in which time outdoor was seen to be a more consistent causal factor[16,94]. In the UK, findings from the Aston Eye Study reveal that myopia prevalence, which was discovered to be 29.4% in the 12–13 year-olds and 9.9% in the 6–7 year-olds, is mostly linked to parental and sibling myopia. Genetic factors such as parental myopia according to the study account for only a small percentage of myopia cases[93]. Higher educational level plays stronger additive role rather than a causal role[94]. Recent studies including subjects of age ranges 12–54y showed that prevalence rate increased from 25% to 41%, which agrees with the additive role rather than causal role of education, even in young adulthood[39-40]. In Japan, a 6-year longitudinal study of same high school students showed heightened myopia prevalence from 35.5% in 1985 to 58.1% in 1991[95-97]. Other factors involved were gender and race; prevalence is lower in males than females, higher in white than black Americans[39-41]. Several studies conducted across the globe over a century suggests that urbanization, outdoor activity, and more formal education accounts for the increase in myopia prevalence[4,94,97]. The prevalence in schoolchildren in Taiwan is up to 70%, and 62% in Hong Kong, China[4,97]. In 1999 as well as in 2012, Hong Kong schoolchildren showed earlier myopia onset and higher myopia progression and prevalence compared to their European counterparts. Although non-cycloplegic refraction was used, it was suggested that it was because environmental factors may have reached a maximum and stable level[4,97].

Outdoor time remains a more consistent environmental factor which may also have a direct effect on human AL[16,94]. For instance, in 2004, Stone *et al*[97] using partial coherence interferometry to measure the distance from the cornea to the RPE revealed that daily fluctuation in the eye's AL of human participants occurs. The highest AL is present at midday.

**Interventional Studies for Time Outdoor and Myopia** In 2013, Wu *et al*[6] studied 7–11y old Chinese myopic and non-myopic children of years 1 to 5 from two elementary schools. One group of the participants were administered 80min/d or 6.7h/wk Recess Outside Class room (ROC) program, other groups had low-concentration atropine eye drops instilled and a control group. After a one-year follow up, it was discovered that outdoor activities within class recess (ROC) regulated myopia onset (8.4% new myopes in ROC group compared to 17.7% in control group) and transition (-0.25 D in ROC group compared to -0.38 D in control) towards myopia in non-myopes. No significant effect occurred in myopes. However, a combination of atropine treatment and the ROC slightly inhibited slowly progressing myopia in myopic children. It was concluded that outdoor light levels inhibit myopia development through pupil constriction and reduction of visual blur in myopes or through dopamine release stimulation with

inhibits AL elongation[6]. The limitation of this pilot study was contamination between the control and intervention group during the study and lack of ensuring a specific number of hours was spent outdoors by a particular group[6]. Another study (called ROCT711: 11h outdoor for 7d) compensated for these limitations by following up children in Taiwan, China from 16 different schools for a year[7]. They were exposed for 11h a week to light at low (1000 lx) and high levels (3000 lx) and AL measurements were carried out with a noncontact technique. It was concluded that less myopia shift occurred with longer time spent (200min) under relatively lower light levels (1000 lx). Between the intervention and control groups, shift in the myopic direction in both dioptres and AL were -0.35 *vs* -0.47 D and 0.28 *vs* 0.33 mm increases from baseline amount. Also, new cases of myopia reduced from 17.4% to 14.5%[7]. Earlier, in 2015, similar results were reported in a 3-year randomized trial in Guangzhou, China in which the "cumulative incidence rate of myopia in the intervention and control groups" was assessed[85]. Refractive and biometric measurements were taken from participants (mostly 6y of age). The intervention included introducing 40min of outdoor time after school hours in school days and ensuring the same time was spent outdoors during weekends and holidays. With 952 children in intervention group and 951 in the control groups, the incidence rate of myopia was approximately 30% in intervention group and 40% in control group after 3-years amounting to an overall 23% reduction in new cases of myopia. The myopic shift or cumulative spherical equivalent refraction (SER) was found to be -1.42 D and -1.59 D in the intervention and control groups respectively. No statistically significant difference in AL was found in both groups[20]. Although the 23% was smaller than expected, they concluded that it is in tandem with the study by Wu *et al*[6] which showed a 50% reduction after 80min of outdoor time. This reveals a dose-response association between outdoor time and myopia. Also, the findings show the positive protection of time spent outdoors against pathological myopia development common in early juvenile myopia sufferers[16,20,32,63]. Although these intervention studies and randomized trials have limitations such as observational bias due to incomplete masking of the examiners, their data are consistent with existing epidemiological findings and animal studies[20].

## PROPOSED HUMAN MYOPIA DEVELOPMENT MECHANISMS

Several theories have been proposed to explain the process of emmetropization, refractive error development and myopia control in animal models and human subjects. In 2004, Wallman and Winawer[98] concluded that genetic, environmental or a combination of both factors can cause a failure of the emmetropization process and result in refractive error. The different mechanisms researchers have used to explain myopia onset and progression may be grouped into blur, biochemical signal and the "BINGE" (blur, illumination, near-work, genetics, education) theories.

**Blur Hypothesis** Optical blur or retinal defocus is an important factor of the visual environment. It could be sustained or intermittent, myopic or hyperopic, induced or disease-related. Induced blur could have a short, as in progressive addition lenses (PAL)[99-100] or long-lasting effect, as in dual-focus CL[58]. Defocus of retinal imagery governs refractive development and is the basis for certain myopia treatment strategies[101-105]. For instance, a sustained optically imposed peripheral myopia has been found to produce central hyperopia and hamper axial elongation (Figure 1)[58]. The blur hypothesis was first postulated by Thorn *et al*[106]. It states that blurred vision or the inability to appropriately use blur cues initiates myopic progression. These researchers believed that children who develop myopia or who have progressive myopia inherited an abnormal sensitivity to retinal image blur. This is also compounded by a compensating adjustment to accommodative gain, neural deblurring and processing[106-107].

In 2003, Gwiazda *et al*[99] showed that myopic defocus controls myopia progression if induced by multifocal lenses (mostly bifocal soft CL due to the reduction in accommodative demand during near work[100-101]. Adler and Millodot[91] revealed that defocus is myopiagenic. It was concluded by Smith *et al*[75] that peripheral myopic defocus must be of a large degree and cover wider retinal area to cause a long term, beneficial and significant myopic control. Moreover, refractive error development in response to visual stimuli is governed by homeostatic nonvisual signals and visually-modulated control signals in the retina[99,103].

To minimize retinal blur, emmetropization and accommodation are two important postnatal visually-mediated control mechanisms utilized by the eye. Accommodation responds to a more sudden onset of blur than emmetropization[99]. While emmetropization occurs locally in the retina and is directly associated with eye growth, accommodation has an indirect and less significant effect on refractive development. There is limited evidence of its link with blur-induced myopia[108]. Convergence (near heterophoria) compared to accommodation, may be have a stronger link to myopia[42]. Emmetropization is a process maintained throughout childhood into early adult life in which the optical (cornea and lens) and the ocular (retina, choroid and sclera) components combine to prevent refractive error[67,109]. FDM induced with minus lens or translucent diffuser can be reversed by an emmetropization-based recovery revealed in several animal model experiments[110]. In conclusion, blur is the stimulus, the retina is the centre of

origination of signals. Emmetropization, accommodation and convergence are the mechanisms to respond but their mechanisms differ in operation. Myopia occurs/progresses if the compensating mechanisms are unable to counter the stimulus effect (Figure 2). This theory is incomplete[101,111].

**Biochemical Signal Hypothesis** Hung and Cuiffreda (1999)[103] postulated another theory called the Incremental Retinal-Defocus theory (IRD) which states that environmentally induced alteration in the retinal defocus magnitude during an increment of normally occurring "genetically" programmed AL elongation will result in modulation of the normal genetically-programmed NT release rate[103-105]. In other words, defocus mediates release of NT from "visual feedback". The NT is dopamine present in human retinal inner plexiform layer and distal photoreceptor tips of clawed frog retina[112-113]. Retinal dopamine controls vitreous chamber depth by influencing the PG and GAG synthesis in the scleral ECM, and altering choroidal thickness, based on animal model experiments[56,110,114-115]. However, in 1991 evidence with optic-nerve-sectioned eyes that grew beyond emmetropia showed that it was not clear whether feedback from the retinal ganglion cells or the central nervous system was responsible[116]. Melatonin, glucagon, acetylcholine and retinoic acid have also been proposed to be linked with eye growth[71,79,101,117-118]. Recent studies have postulated that ambient illumination and VL, rather than blur, may affect retinal dopamine release rate and AL elongation[25,33,84].

**"BINGE" Hypothesis** The next theory states that the retinal feedback ensues through a proposed sustained non-decayed Near-Work Induced Transient Myopia (NITM). NITM combines with the near accommodative response and correlated steady-state error to cause permanent myopia, especially in school children with myopic parents[37,90-91]. They support earlier findings that under-correction or undetected myopic defocus promotes myopia progression in developing eyes of children[91-92].

However, the evidence for the role of near work is deficient and inconsistent[52]. The researchers have stated that the high illuminance levels theory operates by increasing the blood concentration of hydrolysed vitamin D molecule (25(OH)D) and dopamine release rate which regulates the AL elongation and myopia development[1,24,34] (Figure 3). In conclusion, all mechanisms are not separate, therefore the best treatment method should factor in all these possible mechanisms[119].

"Ideal myopia control would likely include modification to all purported mechanisms+may include low dose atropine+modification to indoor lighting+even biometric feedback on working distance & time outdoors"[119].

**"The Myopic Cycle"—Summary** The "myopic cycle"

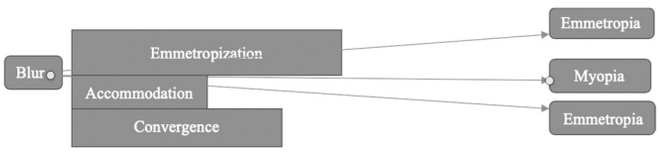


**Figure 2 Relationship between blur, accommodation, convergence, and myopia** Emmetropization and convergence (larger rectangles) may play a stronger (larger blue boxes) and long-term role in eliminating blur effect compared to accommodation.

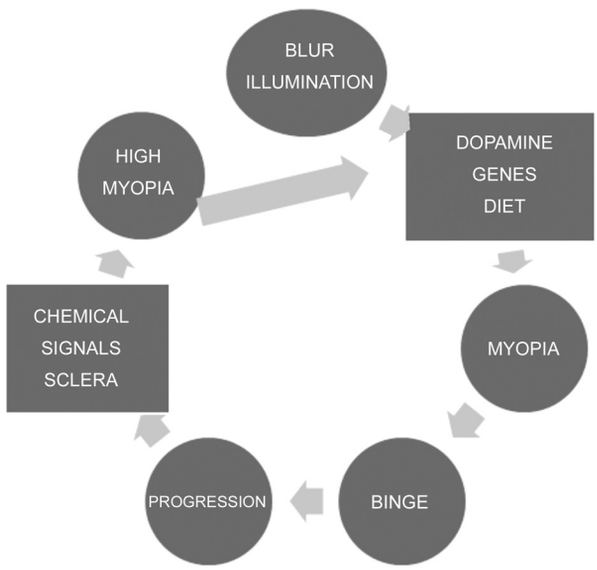


**Figure 3 Combination of major myopia risk factors** BINGE: Blur, illumination, near-work/nutrition, genetics, education.

is a model summarizing the combination of causal and additive factors in the genesis and progression of human myopia based on human-based studies and animal model experiments[1,23-25,30,36]. Juvenile myopia results from the interplay of genetic susceptibility and visual environment (blur, illumination)[27]. Outdoor time of 2h daily may protect the growing eyes and early adults from developing myopia[2,120-124]. Moderate progression of myopia occurs as some other factors such as near work and education contribute their effects[94]. Further progression into sight-threatening high myopia in young adulthood and beyond, occurs at a more molecular level as the scleral biomechanical properties are altered abnormally and significantly by several factors including diet, regardless of the race[5,110-111,120-136].

## ACKNOWLEDGEMENTS

**Conflicts of Interest: Ihesiulor CG,** None; **Alzahrani K,** None; **Radhakrishnan H,** None.

## REFERENCES

1 French AN, Morgan IG, Mitchell P, Rose KA. Risk factors for incident myopia in Australian schoolchildren: the Sydney adolescent vascular and eye study. *Ophthalmology* 2013;120(10):2100-2108.

2 Rose KA, Morgan IG, Ip J, Kifley A, Huynh S, Smith W, Mitchell P. Outdoor activity reduces the prevalence of myopia in children. *Ophthalmology* 2008;115(8):1279-1285.

3 Rose KA, Morgan IG, Smith W, Burlutsky G, Mitchell P, Saw SM. Myopia, lifestyle, and schooling in students of Chinese ethnicity in Singapore and Sydney. *Arch Ophthalmol* 2008;126(4):527-530.

4 Zhu MH, Lin TN, Lin JH, Wen Q. Myopia among children and adolescents: an epidemiological study in Fuzhou City. *Front Pediatr* 2023;11:1161329.

5 Holden BA, Fricke TR, Wilson DA, *et al*. Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. *Ophthalmology* 2016;123(5):1036-1042.

6 Wu PC, Tsai CL, Wu HL, Yang YH, Kuo HK. Outdoor activity during class recess reduces myopia onset and progression in school children. *Ophthalmology* 2013;120(5):1080-1085.

7 Wu PC, Chen CT, Lin KK, *et al*. Myopia prevention and outdoor light intensity in a school-based cluster randomized trial. *Ophthalmology* 2018;125(8):1239-1250.

8 Landis EG, Park HN, Chrenek M, *et al*. Ambient light regulates retinal dopamine signaling and myopia susceptibility. *Invest Ophthalmol Vis Sci* 2021;62(1):28.

9 Naidoo KS, Fricke TR, Frick KD, Jong M, Naduvilath TJ, Resnikoff S, Sankaridurg P. Potential lost productivity resulting from the global burden of myopia: systematic review, meta-analysis, and modeling. *Ophthalmology* 2019;126(3):338-346.

10 MacKey DA, Lingham G, *et al*. Change in the prevalence of myopia in Australian middle-aged adults across 20 years. *Clin Exp Ophthalmol* 2021;49(9):1039-1047.

11 Fu AC, Watt K, Junghans BM, Delaveris A, Stapleton F. Prevalence of myopia among disadvantaged Australian schoolchildren: a 5-year cross-sectional study. *PLoS One* 2020;15(8):e0238122.

12 Hammond CJ. European Eye Epidemiology (E3) Consortium; Myopia prevalence in Europe: cohort effect of increasing prevalence not fully explained by higher educational levels. *Invest Ophthalmol Vis Sci* 2014;55(13):1268.

13 Czepita M, Czepita D, Safranow K. Role of gender in the prevalence of myopia among Polish schoolchildren. *J Ophthalmol* 2019;2019:9748576.

14 Fortin P, Kwan J. The myopia management opportunity in the United States using the 2020 census. *Invest Ophthalmol Vis Sci* 2022;63(7):244-A0098.

15 Ovenseri-Ogbomo G, Osuagwu UL, Ekpenyong BN, *et al*. Systematic review and meta-analysis of myopia prevalence in African school children. *PLoS One* 2022;17(2):e0263335.

16 Rudnicka AR, Kapetanakis VV, Wathern AK, *et al*. Global variations and time trends in the prevalence of childhood myopia, a systematic review and quantitative meta-analysis: implications for aetiology and early prevention. *Br J Ophthalmol* 2016;100(7):882-890.

17 Prakash WD, Marmamula S, Mettla AL, Keeffe J, Khanna RC. Visual impairment and refractive errors in school children in Andhra Pradesh, India. *Indian J Ophthalmol* 2022;70(6):2131-2139.

18 Okoye O, Ogbonnaya C, Ogbonnaya L, Ezeanosike E. Prevalence of refractive errors in primary school children in a Rural Community in Ebonyi State of Nigeria. *Int J Med Health Dev* 2013;18(2):23.

19 Opubiri I, Adio A, Emmanuel M. Refractive error pattern of children in South-South Nigeria: a tertiary hospital study. *Sky Journal of Medicine and Medical Sciences* 2013;1(3):10-14.

20 Yam JC, Tang SM, Kam KW, *et al*. High prevalence of myopia in children and their parents in Hong Kong Chinese Population: the Hong Kong Children Eye Study. *Acta Ophthalmol* 2020;98(5):e639-e648.

21 Wolffsohn JS, Kollbaum PS, Berntsen DA, *et al*. IMI - clinical myopia control trials and instrumentation report. *Invest Ophthalmol Vis Sci* 2019;60(3):M132-M160.

22 Zhou XT, Pardue MT, Iuvone PM, Qu J. Dopamine signaling and myopia development: what are the key challenges. *Prog Retin Eye Res* 2017;61:60-71.

23 Grzybowski A, Kanclerz P, Tsubota K, Lanca C, Saw SM. A review on the epidemiology of myopia in school children worldwide. *BMC Ophthalmol* 2020;20(1):27.

24 French AN, Morgan IG, Mitchell P, Rose KA. Patterns of myopigenic activities with age, gender and ethnicity in Sydney schoolchildren. *Ophthalmic Physiol Opt* 2013;33(3):318-328.

25 Smith EL 3rd, Hung LF, Huang J. Protective effects of high ambient lighting on the development of form-deprivation myopia in rhesus monkeys. *Invest Ophthalmol Vis Sci* 2012;53(1):421-428.

26 Jiang XJ, Tarczy-Hornoch K, Cotter SA, Matsumura S, Mitchell P, Rose KA, Katz J, Saw SM, Varma R, Consortium POPEEE. Association of parental myopia with higher risk of myopia among multiethnic children before school age. *JAMA Ophthalmol* 2020;138(5):501-509.

27 Demir P, Baskaran K, Theagarayan B, Gierow P, Sankaridurg P, Macedo AF. Refractive error, axial length, environmental and hereditary factors associated with myopia in Swedish children. *Clin Exp Optom* 2021;104(5):595-601.

28 Schaeffel F, Feldkaemper M. Animal models in myopia research. *Clin Exp Optom* 2015;98(6):507-517.

29 Pärssinen O, Kauppinen M. Associations of near work time, watching TV, outdoors time, and parents' myopia with myopia among school children based on 38-year-old historical data. *Acta Ophthalmol* 2022;100(2):e430-e438.

30 Wang YL, Liu YJ, Zhu XX, Zhou XT, He JC, Qu XM. Corneal and lenticular biometry in Chinese children with myopia. *Clin Exp Optom* 2023;106(8):836-844.

31 Cohen Y, Belkin M, Avni I, Polat U. Dependency between light intensity and chick's refractive development under light dark cycle. *Invest Ophthalmol Vis Sci* 2006;47(13):3325-3325.

32 Russo A, Boldini A, Romano D, Mazza G, Bignotti S, Morescalchi F, Semeraro F. Myopia: mechanisms and strategies to slow down its progression. *J Ophthalmol* 2022;2022:1004977.

33 Lingham G, Yazar S, Lucas RM, *et al*. Time spent outdoors in childhood is associated with reduced risk of myopia as an adult. *Sci Rep* 2021;11(1):6337.

34 Philipp D, Vogel M, Brandt M, Rauscher FG, Hiemisch A, Wahl S, Kiess W, Poulain T. The relationship between myopia and near work, time outdoors and socioeconomic status in children and adolescents. *BMC Public Health* 2022;22(1):2058.

35 Zhang LJ, Wang WD, Dong XY, Zhao L, Peng J, Wang RH. Association between time spent outdoors and myopia among junior high school students: a 3-wave panel study in China. *Medicine (Baltimore)* 2020;99(50):e23462.

36 Jiang DD, Lin HS, Li CC, Liu LJ, Xiao HS, Lin YY, Huang XQ, Chen YY. Longitudinal association between myopia and parental myopia and outdoor time among students in Wenzhou: a 2.5-year longitudinal cohort study. *BMC Ophthalmol* 2021;21(1):11.

37 Tang SM, Kam KW, French AN, Yu M, Chen LJ, Young AL, Rose KA, Tham CC, Pang CP, Yam JC. Independent influence of parental myopia on childhood myopia in a dose-related manner in 2,055 Trios: The Hong Kong Children Eye Study. *Am J Ophthalmol* 2020;218: 199-207.

38 Tasneem AF, Nayak IV, Shwetha BA. A comparative study in axial length of eye and radius of curvature of cornea between myopes and emmetropes in Indian population. *J Evol Med Dent Sci* 2015;4(70):12097-12111.

39 Banashefski B, Rhee MK, Lema GMC. High myopia prevalence across racial groups in the United States: a systematic scoping review. *J Clin Med* 2023;12(8):3045.

40 Lee SSY, Lingham G, Sanfilippo PG, Hammond CJ, Saw SM, Guggenheim JA, Yazar S, MacKey DA. Incidence and progression of myopia in early adulthood. *JAMA Ophthalmol* 2022;140(2):162-169.

41 Verkicharla PK, Kammari P, Das AV. Myopia progression varies with age and severity of myopia. *PLoS One* 2020;15(11):e0241759.

42 Wong K, Dahlmann-Noor A. Myopia and its progression in children in London, UK: a retrospective evaluation. *J Optom* 2020;13(3):146-154.

43 Tricard D, Marillet S, Ingrand P, Bullimore MA, Bourne RRA, Leveziel N. Progression of myopia in children and teenagers: a nationwide longitudinal study. *Br J Ophthalmol* 2022;106(8):1104-1109.

44 Harrington SC, Stack J, Saunders K, O'Dwyer V. Refractive error and visual impairment in Ireland schoolchildren. *Br J Ophthalmol* 2019;103(8):1112-1118.

45 Logan NS, Shah P, Rudnicka AR, Gilmartin B, Owen CG. Childhood ethnic differences in ametropia and ocular biometry: the Aston Eye Study. *Ophthalmic Physiol Opt* 2011;31(5):550-558.

46 Muralidharan AR, Lança C, Biswas S, Barathi VA, Wan Yu Shermaine L, Seang-Mei S, Milea D, Najjar RP. Light and myopia: from epidemiological studies to neurobiological mechanisms. *Ther Adv Ophthalmol* 2021;13:25158414211059246.

47 Chamarty S, Gupta SK, Dhakal R, Verkicharla PK. Is there any association between nutrition and myopia? A systematic review. *Optom Vis Sci* 2023;100(7):475-485.

48 Tang SM, Lau T, Rong SS, Yazar S, Chen LJ, MacKey DA, Lucas RM, Pang CP, Yam JC. Vitamin D and its pathway genes in myopia: systematic review and meta-analysis. *Br J Ophthalmol* 2019;103(1):8-17.

49 Zi YX, Deng Y, Zhao JR, Ji MQ, Qin YL, Deng TT, Jin M. Morphologic and biochemical changes in the retina and sclera induced by form deprivation high myopia in guinea pigs. *BMC Ophthalmol* 2020;20(1):105.

50 Jones-Jordan LA, Sinnott LT, Cotter SA, Kleinstein RN, Manny RE, Mutti DO, Twelker JD, Zadnik K. Time outdoors, visual activity, and myopia progression in juvenile-onset myopes. *Invest Ophthalmol Vis Sci* 2012;53(11):7169.

51 Pärssinen O, Lyyra AL. Myopia and myopic progression among schoolchildren: a three-year follow-up study. *Invest Ophthalmol Vis Sci* 1993;34(9):2794-2802.

52 Lanca C, Yam JC, Jiang WJ, *et al*, The Asian Eye Epidemiology Consortium (AEEC). Near work, screen time, outdoor time and myopia in schoolchildren in the Sunflower Myopia AEEC Consortium. *Acta Ophthalmol* 2022;100(3):302-311.

53 Tedja MS, Haarman AEG, Meester-Smoor MA, *et al*, Consortium CREAM. IMI—myopia genetics report. *Invest Ophthalmol Vis Sci* 2019;60(3):M89-M105.

54 Chamberlain P, Bradley A, Arumugam B, *et al*. Long-term effect of dual-focus contact lenses on myopia progression in children: a 6-year multicenter clinical trial. *Optom Vis Sci* 2022;99(3):204-212.

55 Liang H, Crewther SG, Crewther DP, Pirie B. Morphology of the recovery from form deprivation myopia in the chick. *Aust N Z J Ophthalmol* 1996;24(2 Suppl):41-44.

56 McBrien NA, Gentle A, Cottriall C. Optical correction of induced axial myopia in the tree shrew: implications for emmetropization. *Optom Vis Sci* 1999;76(6):419-427.

57 Smith EL 3rd, Huang J, Hung LF, Blasdel TL, Humbird TL, Bockhorst KH. Hemiretinal form deprivation: evidence for local control of eye growth and refractive development in infant monkeys. *Invest Ophthalmol Vis Sci* 2009;50(11):5057-5069.

58 Lam CSY, Tang WC, Tse DYY, Lee RPK, Chun RKM, Hasegawa K, Qi H, Hatanaka T, To CH. Defocus Incorporated Multiple Segments (DIMS) spectacle lenses slow myopia progression: a 2-year randomised clinical trial. *Br J Ophthalmol* 2020;104(3):363-368.

59 Gwiazda J, Deng L, Manny R, Norton TT, Study Group COMET. Seasonal variations in the progression of myopia in children enrolled in the correction of myopia evaluation trial. *Invest Ophthalmol Vis Sci* 2014;55(2):752-758.

60 Dhakal R, Huntjens B, Shah R, Lawrenson JG, Verkicharla PK. Influence of location, season and time of day on the spectral composition of ambient light: investigation for application in myopia. *Ophthalmic Physiol Opt* 2023;43(2):220-230.

61 Wan K, Cheung SW, Wolffsohn JS, Orr JB, Cho P. Role of corneal biomechanical properties in predicting of speed of myopic progression in children wearing orthokeratology lenses or single-vision spectacles. *BMJ Open Ophthalmol* 2018;3(1):e000204.

62 Chang PY, Chang SW, Wang JY. Assessment of corneal biomechanical properties and intraocular pressure with the Ocular Response Analyzer in childhood myopia. *Br J Ophthalmol* 2010;94(7):877-881.

63 Arora P, Arora K, Utaal SKD, Bansal N. Refractive error profile of preterm infants at 1-year follow-up in a tertiary care hospital. *J Pediatr Ophthalmol Strabismus* 2022;59(3):151-155.

64 Carrington D. 2016 Three-quarters of UK children spend less time outdoors than prison inmates–survey. TheGuardian. Accessed on 11th July, 2019. https://www.theguardian.com/environment/2016/mar/25/three-quarters-of-uk-children-spend-less-time-outdoors-than-prison-inmates-survey

65 Dirani M, Tong L, Gazzard G, *et al*. Outdoor activity and myopia in Singapore teenage children. *Br J Ophthalmol* 2009;93(8):997-1000.

66 Raviola E, Wiesel TN. 2007, September. Neural control of eye growth and experimental myopia in primates. In Ciba Foundation Symposium 155-Myopia and the Control of Eye Growth: Myopia and the Control of Eye Growth: Ciba Foundation Symposium 155 (pp. 22-44). Chichester, UK: John Wiley & Sons, Ltd.

67 Norton TT. Animal models of myopia: learning how vision controls the size of the eye. *ILAR J* 1999;40(2):59-77.

68 Kröger RH, Wagner HJ. The eye of the blue acara (Aequidens pulcher, Cichlidae) grows to compensate for defocus due to chromatic aberration. *J Comp Physiol A* 1996;179(6):837-842.

69 Muralidharan AR, Low SWY, Lee YC, Barathi VA, Saw SM, Milea D, Najjar RP. Recovery from form-deprivation myopia in chicks is dependent upon the fullness and correlated color temperature of the light spectrum. *Invest Ophthalmol Vis Sci* 2022;63(2):16.

70 Rada JA, Johnson JM, Achen VR, Rada KG. Inhibition of scleral proteoglycan synthesis blocks deprivation-induced axial elongation in chicks. *Exp Eye Res* 2002;74(2):205-215.

71 Wiechmann AF, Rada JA. Melatonin receptor expression in the cornea and sclera. *Exp Eye Res* 2003;77(2):219-225.

72 Rada JA, Palmer L. Choroidal regulation of scleral glycosaminoglycan synthesis during recovery from induced myopia. *Invest Ophthalmol Vis Sci* 2007;48(7):2957-2966.

73 Troilo D, Quinn N, Baker K. Accommodation and induced myopia in marmosets. *Vision Res* 2007;47(9):1228-1244.

74 Wen L, Cao Y, Cheng Q, Li X, Pan L, Li L, Zhu H, Lan W, Yang Z. Objectively measured near work, outdoor exposure and myopia in children. *Br J Ophthalmol* 2020;104(11):1542-1547.

75 Smith EL 3rd, Hung LF, Arumugam B, Holden BA, Neitz M, Neitz J. Effects of long-wavelength lighting on refractive development in infant rhesus monkeys. *Invest Ophthalmol Vis Sci* 2015;56(11):6490-6500.

76 Thomson K, Morgan I, Karouta C, Ashby R. Levodopa inhibits the development of lens-induced myopia in chicks. *Sci Rep* 2020;10(1):13242.

77 Jiang LQ, Long KL, Schaeffel F, Zhou XT, Zheng YB, Ying HF, Lu F, Stell WK, Qu J. Effects of dopaminergic agents on progression of naturally occurring myopia in albino guinea pigs (Cavia porcellus). *Invest Ophthalmol Vis Sci* 2014;55(11):7508-7519.

78 Park H, Tan CC, Faulkner A, Jabbar SB, Schmid G, Abey J, Iuvone PM, Pardue MT. Retinal degeneration increases susceptibility to myopia in mice. *Mol Vis* 2013;19:2068-2079.

79 Mertz JR, Wallman J. Choroidal retinoic acid synthesis: a possible mediator between refractive error and compensatory eye growth. *Exp Eye Res* 2000;70(4):519-527.

80 Metlapally R, Wildsoet CF. Scleral mechanisms underlying ocular growth and myopia. *Prog Mol Biol Transl Sci* 2015;134:241-248.

81 Yu Q, Zhou JB. Scleral remodeling in myopia development. *Int J Ophthalmol* 2022;15(3):510-514.

82 Siegwart JT, Ward AH, Norton TT. Moderately elevated fluorescent light levels slow form deprivation and minus lens-induced myopia development in tree shrews. *Invest Ophthalmol Vis Sci* 2012;53(14):3457.

83 Torii H, Kurihara T, Seko Y, *et al*. Violet light exposure can be a preventive strategy against myopia progression. *EBioMedicine* 2017;15:210-219.

84 Wang JY, Ying GS, Fu XJ, Zhang RH, Meng J, Gu F, Li JJ. Prevalence of myopia and vision impairment in school students in Eastern China. *BMC Ophthalmol* 2020;20(1):2.

85 He MG, Xiang F, Zeng YF, Mai JC, Chen QY, Zhang J, Smith W, Rose K, Morgan IG. Effect of time spent outdoors at school on the development of myopia among children in China: a randomized clinical trial. *JAMA* 2015;314(11):1142-1148.

86 Rudnicka AR, Owen CG, Nightingale CM, Cook DG, Whincup PH. Ethnic differences in the prevalence of myopia and ocular biometry in 10- and 11-year-old children: the Child Heart and Health Study in England (CHASE). *Invest Ophthalmol Vis Sci* 2010;51(12):6270-6276.

87 Mutti DO, Zadnik K. Age-related decreases in the prevalence of myopia: longitudinal change or cohort effect? *Invest Ophthalmol Vis Sci* 2000;41(8):2103-2107.

88 Jones-Jordan LA, Sinnott LT, Chu RH, *et al*, Study Group CLEEEE. Myopia progression as a function of sex, age, and ethnicity. *Invest Ophthalmol Vis Sci* 2021;62(10):36.

89 Swiatczak B, Schaeffel F. Emmetropic, but not myopic human eyes distinguish positive defocus from calculated blur. *Invest Ophthalmol Vis Sci* 2021;62(3):14.

90 Lingham G, Yazar S, Lucas RM, *et al*. Time spent outdoors in childhood is associated with reduced risk of myopia as an adult. *Sci Rep* 2021;11(1):6337.

91 Adler D, Millodot M. The possible effect of undercorrection on myopic progression in children. *Clin Exp Optom* 2006;89(5):315-321.

92 Cumberland PM, Bountziouka V, Hammond CJ, Hysi PG, Rahi JS, Biobank Eye and Vision Consortium UK. Temporal trends in frequency, type and severity of myopia and associations with key environmental risk factors in the UK: findings from the UK Biobank Study. *PLoS One* 2022;17(1):e0260993.

93 Grzybowski A, Kanclerz P, Tsubota K, Lanca C, Saw SM. A review on the epidemiology of myopia in school children worldwide. *BMC Ophthalmol* 2020;20(1):27.

94 Thorn F, Chen J, Li CC, Jiang DD, Chen WH, Lin YY, Chang X, Deng RZ, Chen YY. Refractive status and prevalence of myopia among

Chinese primary school students. *Clin Exp Optom* 2020;103(2):177-183.

95 Xiang ZY, Zou HD. Recent epidemiology study data of myopia. *J Ophthalmol* 2020;2020:4395278.

96 Lam CSY, Edwards M, Millodot M, Goh WSH. A 2-year longitudinal study of myopia progression and optical component changes among Hong Kong schoolchildren. *Optom Vis Sci* 1999;76(6):370-380.

97 Stone RA, Quinn GE, Francis EL, Ying GS, Flitcroft DI, Parekh P, Brown J, Orlow J, Schmid G. Diurnal axial length fluctuations in human eyes. *Invest Ophthalmol Vis Sci* 2004;45(1):63-70.

98 Wallman J, Winawer J. Homeostasis of eye growth and the question of myopia. *Neuron* 2004;43(4):447-468.

99 Gwiazda J, Hyman L, Hussein M, *et al*. A randomized clinical trial of progressive addition lenses versus single vision lenses on the progression of myopia in children. *Invest Ophthalmol Vis Sci* 2003;44(4):1492-1500.

100 Thakur S, Dhakal R, Verkicharla PK. Short-term exposure to blue light shows an inhibitory effect on axial elongation in human eyes independent of defocus. *Invest Ophthalmol Vis Sci* 2021;62(15):22.

101 Delshad S, Collins MJ, Read SA, Vincent SJ. The human axial length and choroidal thickness responses to continuous and alternating episodes of myopic and hyperopic blur. *PLoS One* 2020;15(12):e0243076.

102 Harb EN, Wildsoet CF. Origins of refractive errors: environmental and genetic factors. *Annu Rev Vis Sci* 2019;5:47-72.

103 Hung GK, Ciuffreda KJ. Model of human refractive error development. *Curr Eye Res* 1999;19(1):41-52.

104 Chakraborty R, Ostrin LA, Benavente-Perez A, Verkicharla PK. Optical mechanisms regulating emmetropisation and refractive errors: evidence from animal models. *Clin Exp Optom* 2020;103(1):55-67.

105 Zhu XY, Kang P, Troilo D, Benavente-Perez A. Temporal properties of positive and negative defocus on emmetropization. *Sci Rep* 2022;12(1):3582.

106 Thorn F, Grice K, Held R, Gwiazda J. 2000. Myopia: Nature, Nurture, and the Blur Hypothesis. In: Lin LLK, Shih YF, Hung PT. (eds). *Myopia Updates II*. Springer, Tokyo.

107 Swiatczak B, Schaeffel F. Emmetropic, but not myopic human eyes distinguish positive defocus from calculated blur. *Invest Ophthalmol Vis Sci* 2021;62(3):14.

108 Jos R, Sebastian D, Rafael I. Emmetropization and non-myopic eye growth. *Surv Ophthalmol* 2023;68(4):759-783.

109 Rada JA, Shelton S, Norton TT. The sclera and myopia. *Exp Eye Res* 2006;82(2):185-200.

110 Troilo D, Smith EL 3rd, Nickla DL, *et al*. IMI—report on experimental models of emmetropization and myopia. *Invest Ophthalmol Vis Sci* 2019;60(3):M31-M88.

111 Forrester JV, Dick AD, McMenamin P, Roberts F, Pearlman, E. *The eye: basic sciences in practice*. (4th ed.) Elsevier. 2016.

112 Popova E. Role of Dopamine in Retinal Function. 2020 May 28. In: Kolb H, Fernandez E, Nelson R, editors. *Webvision: the Organization of the Retina and Visual System*. Salt Lake City (UT): University of Utah Health Sciences Center; 1995.

113 Rada JA, McFarland AL, Cornuet PK, Hassell JR. Proteoglycan synthesis by scleral chondrocytes is modulated by a vision dependent mechanism. *Curr Eye Res* 1992;11(8):767-782.

114 Jia X, Yu J, Liao SH, Duan XC. Biomechanics of the sclera and effects on intraocular pressure. *Int J Ophthalmol* 2016;9(12):1824-1831.

115 Brown DM, Mazade R, Clarkson-Townsend D, Hogan K, Datta Roy PM, Pardue MT. Candidate pathways for retina to scleral signaling in refractive eye growth. *Exp Eye Res* 2022;219:109071.

116 Summers JA. (2021). The Sclera and Its Role in Regulation of the Refractive State. In: Spaide RF, Ohno-Matsui K, Yannuzzi LA: (eds). *Pathologic Myopia*. Springer, Cham.

117 Gifford KL, Richdale K, Kang P, *et al*. IMI—clinical management guidelines report. *Invest Ophthalmol Vis Sci* 2019;60(3):M184-M203.

118 Zhang XY, Zhou YL, Yang J, Wang Y, Yang WY, Gao LW, Xiang Y, Zhang FY. The distribution of refraction by age and gender in a non-myopic Chinese children population aged 6-12 years. *BMC Ophthalmol* 2020;20(1):439.

119 Gentle A, McBrien NA. Retinoscleral control of scleral remodelling in refractive development: a role for endogenous FGF-2? *Cytokine* 2002;18(6):344-348.

120 Gentle A, Liu YY, Martin JE, Conti GL, McBrien NA. Collagen gene expression and the altered accumulation of scleral collagen during the development of high myopia. *J Biol Chem* 2003;278(19):16587-16594.

121 Chiang SY, Weng TH, Lin CM, Lin SM. Ethnic disparity in prevalence and associated risk factors of myopia in adolescents. *J Formos Med Assoc* 2020;119(1 Pt 1):134-143.

122 Abdul M, Madhusudhan, Shankarappa, Bhanuprakash. A comparative study in axial length of eye and radius of curvature of cornea between myopes and emmetropes in Indian population. *J Evid Based Med Healthc* 2015;2(26):3870-3874.

123 Xiang ZY, Zou HD. Recent epidemiology study data of myopia. *J Ophthalmol* 2020;2020:4395278.

124 Lee SSY, Lingham G, Sanfilippo PG, Hammond CJ, Saw SM, Guggenheim JA, Yazar S, MacKey DA. Incidence and progression of myopia in early adulthood. *JAMA Ophthalmol* 2022;140(2):162-169.

125 Brennan NA, Toubouti YM, Cheng X, Bullimore MA. Efficacy in myopia control. *Prog Retin Eye Res* 2021;83:100923.

126 Logan NS, Radhakrishnan H, Cruickshank FE, *et al*. IMI accommodation and binocular vision in myopia development and progression. *Invest Ophthalmol Vis Sci* 2021;62(5):4.

127 Zhang PB, Zhu H. Light signaling and myopia development: a review. *Ophthalmol Ther* 2022;11(3):939-957.

128 Medina A. The cause of myopia development and progression: theory, evidence, and treatment. *Surv Ophthalmol* 2022;67(2):488-509.

129 Bullimore MA, Brennan NA. Efficacy in myopia control: does race matter? *Optom Vis Sci* 2023;100(1):5-8.

130 Brennan NA, Toubouti YM, Cheng X, Bullimore MA. Efficacy in myopia control. *Prog Retin Eye Res* 2021;83:100923.

131 Nouraeinejad A. Urban inequality: a hypothetic risk factor for myopia. *Med Hypothesis Discov Innov Optom* 2021;2(4):146-149.

132 Chande PK, Dave NT, Qazi M, Vora PB. Myopia progression in children before and after the coronavirus disease lockdown. *Med Hypothesis Discov Innov Optom* 2022;3(4):136-141.

133 Sallam MA, Mohammed MA, Karrar MM, Ghoneim EM. Stay-at-home myopia among school children during the COVID-19 pandemic. *Med Hypothesis Discov Innov Optom* 2022;3(2):48-54.

134 Harb EN, Wildsoet CF. Nutritional factors and myopia: an analysis of national health and nutrition examination survey data. *Optom Vis Sci* 2021;98(5):458-468.

135 Anshel J. The role of nutrition in myopia control. 2023. https://www.optometrytimes.com/view/the-role-of-nutrition-in-myopia-control

136 Li FF, Zhu MC, Shao YL, Lu F, Yi QY, Huang XF. Causal relationships between glycemic traits and myopia. *Invest Ophthalmol Vis Sci* 2023;64(3):7.