A Fresh Look at the Major Cause of Most Myopia

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Background

Myopia, or nearsightedness, causing light to focus in front of the retina, is one of the leading causes of visual impairment in the world. The prevalence of myopia has significantly increased over the past few decades – from 1.5 billion people, or ca. 23% of the world's population, being myopic in 2000 to the estimated 50% of the population, or about 5 billion people to be myopic by 2050, according to the Brien Holden Vision Institute. [1]

Figure 1. Not enough time spent outdoors under natural light could be the major cause of most myopia.

It is known that myopia is caused by both genetic and environmental risk factors. Over 500 genes have been reported to contribute to myopia, but most of them have very small effects. This cannot explain the steep rise in myopia prevalence in recent decades. The data show that in societies where there is little or no formal education, only about 1–2% of any population become myopic and this can be arguably the percentage of myopia that is genetically determined. The genetic background of high myopic cases may mean that people are becoming myopic earlier and may also reach high rates of myopic progression sooner in

life than others, thus magnifying the impact of small initial genetic differences. Therefore, environmental risk factors appear to contribute more to the myopia prevalence than the genetics does [1,2].

Among the ***environmental risk factors***, ***the near-point work, the time spent outdoors, and the visual "diet"***, i.e. the types of visual stimuli the eye receives and affect its growth have been intensively studied [1-10]. The urban lifestyles of children spending more time indoors – a time consisting of excessive engagement in near work of reading and/or using digital devices at close distances, might be responsible for the early onset of myopia and its rapid progression [9,10]. When these close distances are converted into diopters (inverse of the distance in meters), it is obvious that the indoor visual environment shows significantly greater dioptric variations compared to outdoor settings.

Potential mechanism of near work-related risk of myopia is near accommodation, more dominant indoors compared to outdoors, which is associated with long viewing distances, fewer variations in near accommodative demand, and more uniform retinal focus. Indoors, the accommodation demand is high even for basic tasks like reading a book or viewing a computer screen. This variable focus fluctuates by several diopters across the retina (from the fovea to the peripheral retina). When the near accommodation response is considered along with this dioptric variation, outdoor environments have more uniform retinal focus than indoors, which is associated with greater levels of defocus, especially in the peripheral retina. Furthermore, ***near-point accommodative stress*** is produced by the eye's ciliary muscles due to prolonged near work. Prolonged near-point accommodative stress can disturb the retinal dopamine homeostasis by causing a reduction in choroidal blood flow contributing to choroidal thinning and scleral hypoxia, leading to the remodeling of scleral extracellular matrix and eventually to myopia [11].

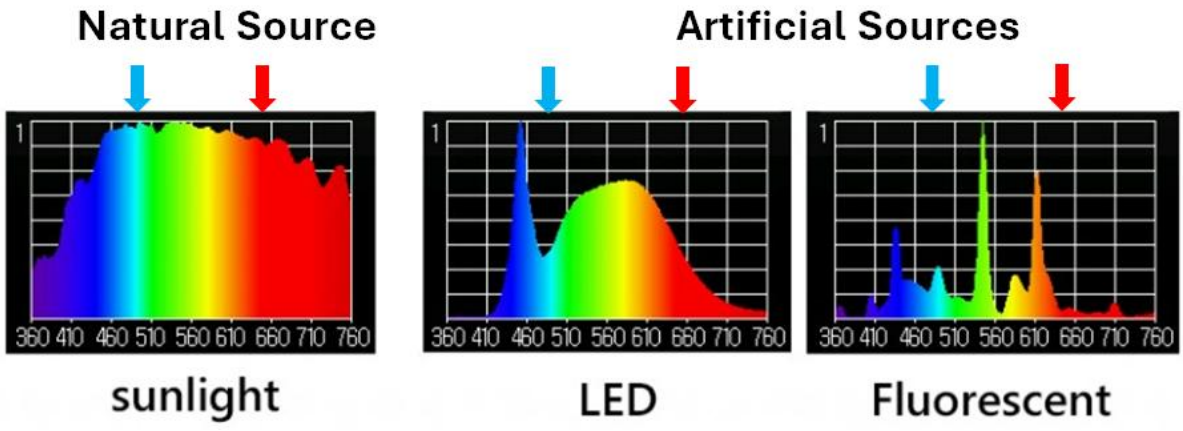


Figure 2. Spectra of sunlight and artificial light sources (LED, fluorescent light).

Our modern lifestyle causes children to spend less time outdoors in sunlight (Figure 1) and approximately 90% of their time indoors under artificial lights. Artificial lights generate very different light intensities, spectral power distributions, and spectral compositions than natural sunlight (Figure 2) [12]. Epidemiological and interventional research has shown a compelling connection between increased outdoor time and a decreased risk of myopia in children [9,10].

The protective effects of natural light are primarily attributed to the much higher light intensity, as well as to exposure to particular wavelengths (blue light and red-light wavelengths) that have an impact on the release of retinal dopamine. The sun emits a broad spectrum of visible (and non-visible) wavelengths. Of particular importance for the health of the eye are sunlight wavelengths within the ranges of 480nm +/-30nm, 650nm +/- 30nm, and 850nm +/- 30nm. This must be contrasted with indoor artificial lighting where 480nm +/- 30nm, and 650nm +/- 30nm are present, but in low irradiance percentages, and where 850nm +/- 30nm is not present at all (Figure 2) [12].

The graph below (Figure 3) shows how time spent indoors at school has expanded over time. While academically beneficial, it has caused children to spend more time indoors doing near point tasks, and therefore, have far less exposure to outdoor sunlight. The authors believe the combination of both factors has contributed to the increase in axial myopia.

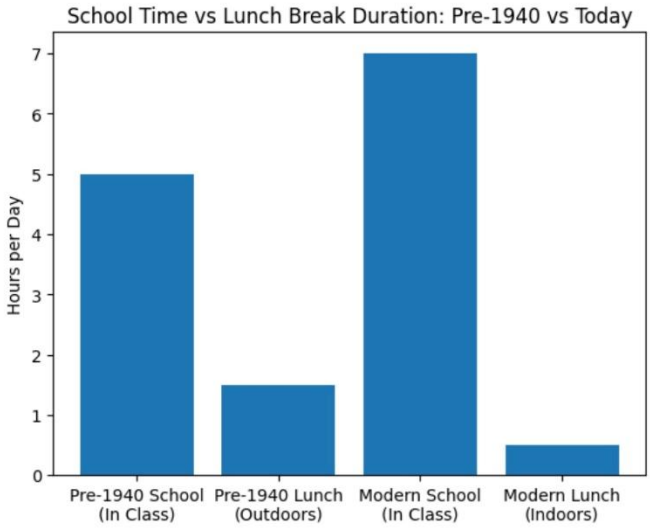


Figure 3. Increased time spent indoors for children while at school today vs. the past.

The wavelength ranges around 480 nm and 650 nm have been found responsible for the direct and indirect ways for release of ***retinal dopamine (DA)*** – a neurotransmitter that mediates diverse functions including visual signaling and refractive development; in fact, DA acts as a "stop" signal in the refractive eye growth [13-35]. 850nm +/-30nm (NIR) is known to increase the activity of mitochondria, thus, increasing the production of ATP in the RPE, choroid and sclera. Therefore, the wavelengths of light in the 480nm +/-30nm, 650nm +/-30nm, and 850nm +/- 30nm ranges contribute to increased blood flow of the choroid, increased choroidal thickness, reduced scleral hypoxia, and ultimately, reduced axial elongation.

For instance, as stated above blue light wavelengths of 480nm +/- 30nm contribute directly to the generation of retinal dopamine, which causes a cascade of physiological events that cause the eyewall to become strengthened, thus resisting the forces of ocular axial elongation. When children spend more time indoors during school hours the retina of the child's eye generates less dopamine. Figure 4 illustrates time indoors at school in 2025 versus outdoor blue light during a 24-hour day.

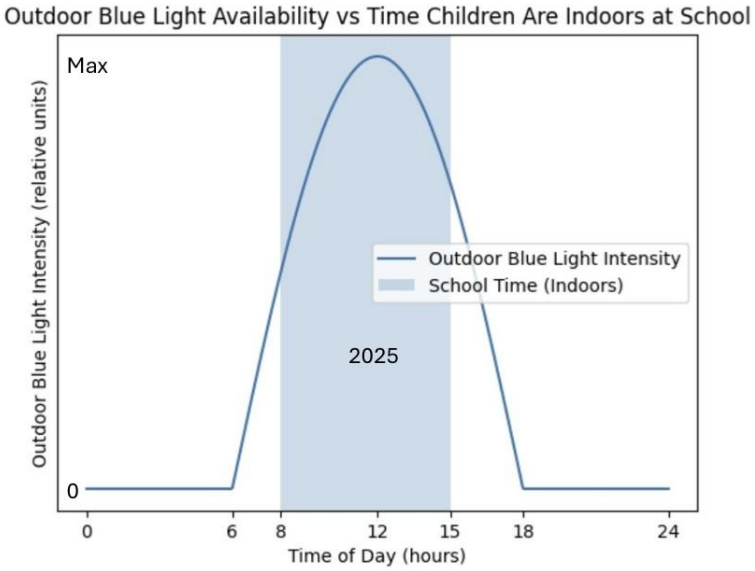


Figure 4. Children spend time indoors at school at the peak of emitted beneficial blue light by the Sun.

It is known that excessive lengthening of the posterior segment of the ocular globe leads to negative refractive error (myopia) due to a mismatch between the axial length and the focal length of the eye. This is the most common structural abnormality associated with myopia. The lack of time outdoors is directly linked to a deficiency of retinal dopamine (DA). This results from a lack of sufficient retinal irradiance of blue light and red-light wavelengths,

which are required for proper DA homeostasis. The authors believe this to be one of the major contributing factors responsible for the current myopia epidemic. Figure 5 is for illustrative purposes only, but directionally correct, and supports the hypothesis - the rise of myopia cases over the past century, has occurred during the reduced time spent outdoors, and the increased use of fluorescent and LED lighting indoors (neither of which can be substituted for the appropriate amount of sunlight exposure outdoors).

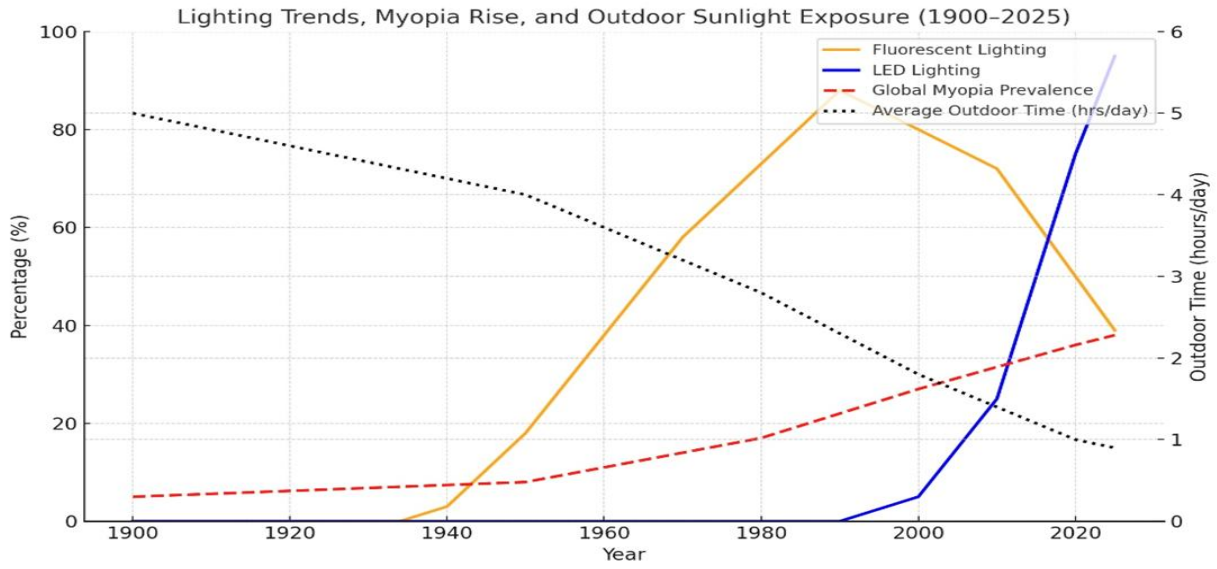


Figure 5. Myopia progression vs artificial lighting vs time spent outdoors.

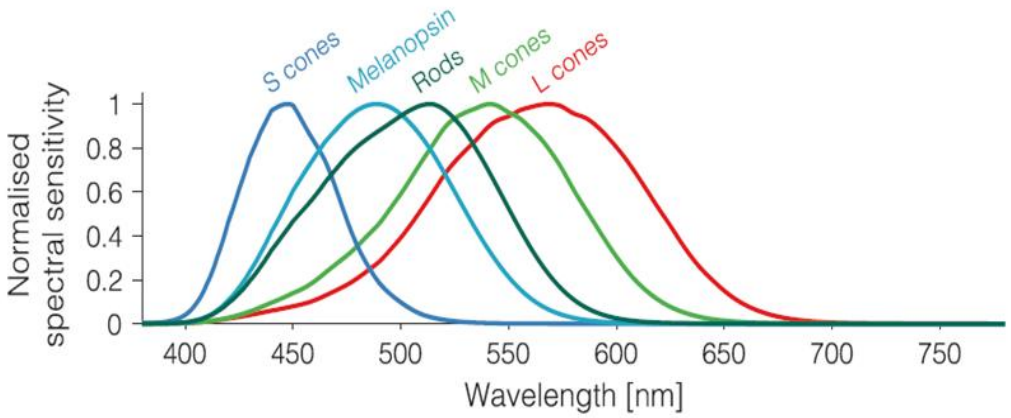
Furthermore, studies have shown that the chromaticity (spectral composition) of light can be an important modulator of eye growth. This can be explained via ***longitudinal chromatic aberration*** (LCA) defined as the chromatic difference of focus between different wavelengths of the spectrum, where short blue wavelengths focus in front of the retina and long red wavelengths focus behind the retina in an emmetropic eye. It is also known that the eye uses visual cues (blur, defocus) to guide its growth. For instance, if the image focuses in front of the retina, then the eye slows its growth, while if the image focuses behind the retina (hyperopic defocus), then the eye elongates. This biological process of using visual cues to guide eye growth, known as emmetropization and is mainly guided by the cone photoreceptors [36-39].

The human eye is composed of about 64% red-light-sensitive cones (long wavelength, L-cones), about 32% green-light-sensitive cones (medium wavelength, M-cones) and about 2–5% blue-light-sensitive cones (short wavelength, S-cones). The highest cone density is in the central retina, in the fovea centralis, where the L- and M- cones dominate the fovea, while the S-cones are much sparser. The spectral sensitivity of the cones, along with the sensitivity

of the other two photoreceptors found in the human eye, is shown in Figure 6A. It is worth mentioning that roughly 120 million rods are present in the human peripheral retina compared to 5-6 million cones in the central retina, while the 4,000-7,000 ipRGCs are spread across the central and peripheral retina (Figure 6B) [40].

Due to the much higher number of red L-cones, their higher resolution, and their faster and stronger response than the S-cones, the retina receives ~ 20–30 times more L-cone information than S-cone information**.** The blue light, focused in front of the retina, is more blurred, while the red light is much better focused behind the retina.

(A)



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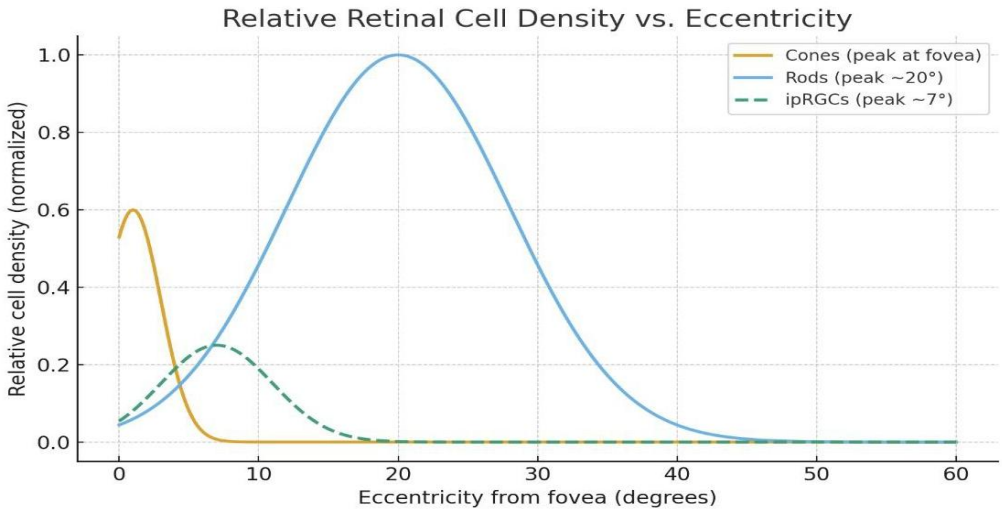

Figure 6. (A) Normalized spectral sensitivity of human photoreceptors. (B) Distribution of photoreceptors in human retina.

Therefore, the human eye visual system is strongly “affected” by the red L-cone pathway while the influence of the blue S-cone pathway is very weak. Because of this, the eye visual

system perceives that the polychromatic light that is mainly focused behind the retina (hyperopic focus) and, consequently, gives signal that the eye should elongate.

The L-cones are the most plentiful of the cone-types with most located within the center or the fovea and decreasing in number towards the periphery of the fovea. The L-cones have a stronger and faster response than the M and S cone populations. When this is coupled with, the red wavelength fraction being more present in the indoor lighting sources than the blue wavelengths, this further contributes to the elongation of the eye when children spend more time indoors [36-40].

The authors believe myopia progression "may" be further influenced by ***high-refractive-index lenses.*** *High index lenses have been* intensively used over the past several decades. These lenses are prescribed and utilized by eye care professionals to provide the patient with thinner and lighter weight lenses for providing improved aesthetics and comfort. The human eye normally has ~ 2.00D of longitudinal chromatic aberration (LCA). High index lenses generate additional LCE and therefore increase the LCA which the eye must handle. An increase in the amplitude of LCA widens the red–blue focus gap. LCA is detected by both the S-cones and the L-cones of the eye. However, the detection by the larger number of L-cones leads to a stronger L-cone signal. The eye interprets this as a hyperopic defocus. The net result is a signal from the L-cones to cause the eye to grow in length and cause the red light to focus on the retina. Thus, it is believed that high index lenses may also contribute to myopia progression. This has been most difficult to prove as presented in Figure 7; as it is difficult to interpret which came first the chicken (myopia) or the egg (high index lenses).

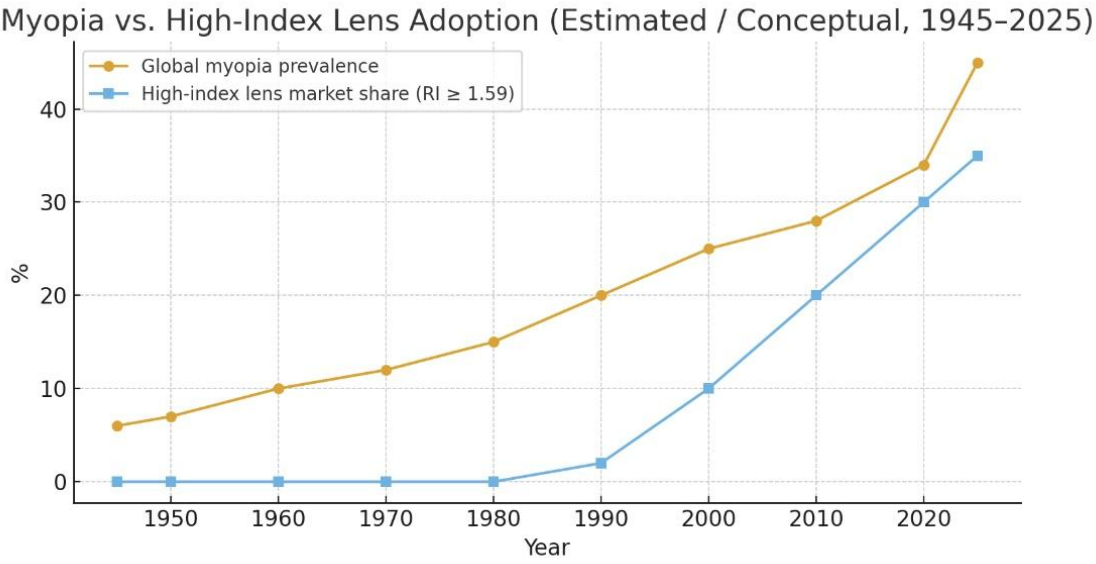

Figure 7. Increased penetration of high index lenses vs. the increased incidence of myopia.

Other potential environmental factors, like the spatial frequency of the visual environment, circadian rhythm, sleep, nutrition, physical activity, pollution, smoking, inflammation, socio-economic status, and education have shown debatable effects on myopia onset and its development [3-8, 41].

Retinal Dopamine

Retinal dopamine (DA) has been found to influence eye growth and the emmetropization process. In fact, ***DA is considered to be protective against myopia*** - it acts as a "stop signal" for excessive eye growth. DA in the eye is produced and released by a subset of dopaminergic amacrine cells (DACs) that are sparsely distributed in the retina. From there it diffuses through the extracellular space of the retina and interacts with two receptor families (D1-like and D2-like receptors) that regulate biochemical pathways controlling the scleral and choroidal tissues, collectively called here as "***eye wall***" which is responsible for maintaining the eye shape (Figure 8) [13-20, 42-45].

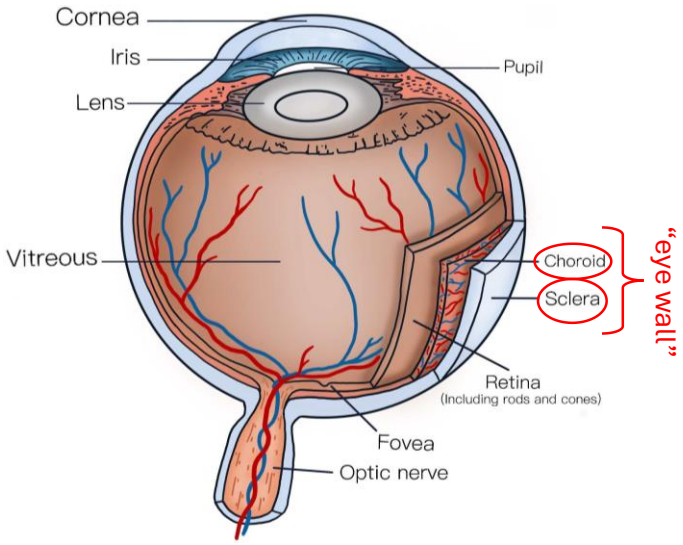

Figure 8. Schematic presentation of eye anatomy.

The released DA triggers the release of another neurotransmitter, ***nitric oxide (NO),*** which is known to modulate the retinal perfusion, choroidal thickness, choroidal blood flow, and inhibits the scleral remodeling and axial growth. The relationship between retinal DA and NO is complex, with both neurotransmitters modulating the function of each other in the retina. For instance, NO can facilitate DA-release, but with improper light intensity and exposure may also block the re-uptake of DA, thus prolonging its effects. NO, as a vasodilator, increases the choroid blood flow, and thus improves choroidal health and thickness. Better choroidal blood perfusion is a vital process for delivering oxygen and nutrients that nourish

the sclera which improves the scleral health and stops its remodeling and thinning. Improved choroid and scleral health and thickness (reinforced "eye wall", Figure 8) means better control over the ocular elongation. Moreover, DA enhances light-driven circadian rhythms as-DA release is known to follow the daily pattern linked to daylight exposure. A stable circadian signaling in the retina protects against uncontrolled eye growth. Disrupted circadian and DA rhythms are associated with higher myopia progression, which could be explained by the disrupted melatonin production [13-20, 42-45].

The Eye Wall: Choroid and Sclera

Choroidal thinning, reduced choroidal blood flow, and hypoxia are considered the key contributors to scleral remodeling and thus, to weakening the eye wall (Figure 6), which then allows the eye axial elongation to happen. It is worth mentioning that hyperopic defocus and LCA, mentioned in the previous sections, are not sufficient to explain the significant rise in myopia cases. Therefore, the authors believe the absence of the appropriate amount of outdoor sunlight (not enough irradiance of 480nm +/- 30nm, 650nm +/- 30nm and 850nm +/- 30nm) leads to not sufficient retinal DA, which results in ***scleral hypoxia*****.** The lack of the appropriate amount of retinal DA causes a cascade of these local processes in the choroid and sclera. The scleral hypoxia theory proposes that thinning of the choroid and the reduced choroidal blood flow causes oxygen deprivation ~~to~~ the sclera. This in turn triggers changes in the scleral extracellular matrix (so-called scleral remodeling), potentially enabling further elongation of myopic eye. [46, 47].

The ***choroid*** layer is a dynamic structure where thickness both directly and indirectly is subjected to modulation by a variety of physiological and visual stimuli. The choroid has a major role in the eye growth regulation and emmetropization – it "adjusts" the position of the retina by changes in its thickness. Another major function of the choroid is to supply oxygen and nourishment to the outer retina, as it is located between the sclera and the retinal pigment epithelium (Figure 9). Being a complex multifunctional tissue the choroid has a variety of other functions, in addition to the provision of nutrients to nearby tissues. These include the release of growth factors involved in modulation of vascularization, removal of waste, regulation of ocular temperature, as well as modulation of intraocular pressure through the regulation of choroidal blood flow as well as providing a pathway for egress of aqueous humor from the anterior chamber. It also serves as a conduit for vessels and nerves entering and leaving the eye [48-58].

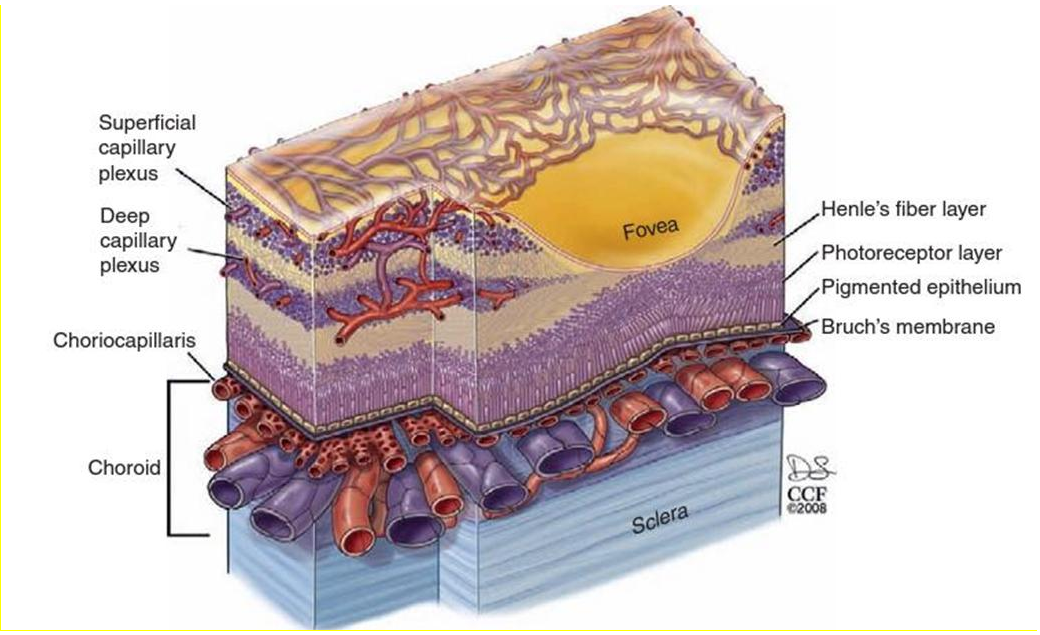

Figure 9. Schematic presentation of the vasculature of the retina and choroid [57].

The choroid is composed of blood vessels, melanocytes, fibroblasts, resident immunocompetent cells, and supporting collagenous and elastic connective tissue. To meet the nutritional demands of the retina and sclera, ***the choroid has the highest rate of blood flow of any tissue in the human body***, reflecting its important role as a source of nutrients for the outer retina - one of the most metabolically demanding tissues of the body. The outermost layer of the choroid, the suprachoroidal, is composed of loose connective tissue and represents a choroid-to-sclera transition layer. The bulk of the choroid is otherwise dominated by blood vessels, organized loosely into three layers of progressively smaller-diameter blood vessels; Haller's layer being the outermost layer, with the largest vessels, the middle Sattler's layer containing medium diameter blood vessels, and the inner choriocapillaris comprised of fenestrated capillaries, adjacent to Bruch's membrane. ***The choroid regulates about 85% of outer retinal blood flow***. Having a highly vascular structure, the choroid can rapidly change the blood flow in the eye. Choroidal blood perfusion is actually the carrier of optical signals into biochemical signals during the homeostatic development of the eye.

Choroidal thinning is a structural feature of myopia showing a strong correlation with the eye axial length. This suggests that the change in choroidal thickness can be a predictive biomarker for changes in ocular elongation during myopia. As is known, the most common structural abnormality associated with myopia is excessive lengthening of the posterior segment of the ocular globe which leads to negative refractive error (myopia) due to a mismatch between the axial length and the focal length of the eye.

Choroidal blood flow is the main source of oxygen and nourishment supply for the underlying outer retina and the overlying sclera. The reduced choroidal blood flow can lead to a relatively hypoxic environment, which could induce a series of changes in sclera. It is known that oxygen is essential for cellular metabolism and biochemical reactions. Hypoxia occurs when there is not sufficient oxygen supply to the tissue; in this case, the reduced choroidal blood flow does not supply sufficient amount of oxygen and nutrients to the sclera. While physiological hypoxia is sometimes beneficial to maintain normal functional homeostasis, pathological hypoxia is harmful as it aggravates inflammatory response and tissue dysfunction.

Choroidal thickness can be reliably quantified with, by way of example, a Heidelberg Spectralis device. Blood flow through the choroid is not currently quantifiable in what is believed to be a reliable manner. It is understood that if there is greater blood flow in the choroid the choroid thickness will increase, since as the flow of blood increases, the aggregated volume of the vessels in the choroid will increase. Because the choroid is present in a space that can dynamically expand and contract with variations of blood flow, the measurement of changes in the choroidal thickness are a reasonable reflection of the choroidal perfusion at the time the measurements are made.

The choroidal blood flow and thickness dynamically change diurnally over 24 hours, with the choroid being thicker in the morning and thinner in the late afternoon and evening. Fluctuations of choroidal blood flow can also be multifactorial and are related to local influences within the eye and systemic influences from the cardiovascular status of the animal. Choroidal thickness and blood flow therefore have a baseline character that is maintained by homeostasis within the eye. ***Choroidal thinning and the reduced choroidal blood flow have been correlated with the onset and development of myopia***.

There is the potential to shift the entire choroidal blood flow baseline to a new level or impart shorter term transients in choroidal thickness and blood flow through interventions and treatments. Even intermittent interventions that can quickly increase choroidal blood flow and choroidal thickness can have long lasting impacts on blood flow and choroidal thickness hours later.

The ***sclera*** is the outermost layer of the eye wall, which is thin, yet tough and normally relatively inelastic. Along with the choroid layer, it directly controls the shape of the eyeball and the eye axial length (Figure 8). Most cells in the sclera are fibroblasts, which secrete collagen and other extracellular matrix (ECM) components. The scleral ECM is mainly composed of collagen type I, which supports fibroblasts and dictates the biomechanical properties of the sclera. When myopia starts, the reduced choroidal blood flow deprives the sclera from oxygen and nutrients leading to its remodeling – the sclera becomes thinner and

with altered biomechanical properties. In fact, in myopic human eyes, the tensile strength of the sclera was found to be lower, while the elasticity of the sclera was found to be increased, allowing the eye to elongate. The structural changes of the scleral ECM are associated with a reduced synthesis and accelerated degradation of ECM components. This is known as ***scleral remodeling.*** When the ECM weakens the scleral structural this results in eye elongation. A reduction in collagen type I weakens the scleral structural framework. Collagen Type I is a major component of the scleral ECM. During myopia development, the metabolism of type I collagen increases due to the downregulation of its synthesis, but also due to its increased degradation [47, 48, 59, 60].

Effects of Light on Retinal DA Homeostasis and Eye Growth

Strong scientific evidence confirms that retinal DA is released in the retina in response to light exposure; the release has been found to be light- and dose-dependent. Bright outdoor light exposure (10,000–100,000 lux, which greatly exceeds typical indoor light levels of 100–500 lux) is very efficient in retinal DA release. DA release is nonlinear - it increases dramatically over a certain light threshold. Even intermittent, short, but bright light exposure, was found to be more effective than continuous light in stimulating DA release. Short periods of sunlight can produce hours of elevated dopamine. In addition, particular light wavelengths from artificial sources, such as long-wavelength beneficial blue light (~480 nm) and red light (~ 650 nm) have been shown to support the homeostasis of retinal DA. Higher DA levels signal the eye to slow down its growth via a cascade of physiological processes; therefore, ***DA inhibits the axial elongation of the eye*** [12, 15-17, 22-35].

In the text below, the mechanisms behind the blue and red-light wavelengths in regulation of retinal DA are briefly explained.

Blue light, in a narrow band that centers around 480 nm stimulates the melanopsin pigment present in the axons of intrinsically photosensitive retinal ganglion cells (ipRGCs). These cells have synaptic connections with DACs (dopaminergic amacrine cells) that are responsible for the release of DA-neurotransmitter [23-25, 32, 42, 44, 45]. As shown in Figure 4A, besides the melanopsin-containing ipRGCs, the rhodopsin contained within rod photoreceptors strongly absorbs blue light (480-510 nm) and have also been implicated in the synthesis of retinal DA [43]. Rods are faster and more sensitive to light photons than ipRGCs; they respond within milliseconds and are activated by scotopic (dim) light conditions. The ipRGCs are less light-sensitive and only respond to bright light and longer light durations. They have a slower onset to become activated but show more sustained activity (hundreds or milliseconds to seconds), once they are activated. Moreover, ipRGCs

receive rods' input through the retinal circuitry. Consequently, ipRGCs integrate these signals with their own intrinsic melanopsin-driven signals. Rod activity is initiated first with a fast signal in response to blue light 480nm +/- 30nm activation. This then activates the ipRGCs, which provide a "steady state" activity for a prolonged time. These blue wavelengths enhance DA-release and thus contribute to choroidal expansion and its blood flow via DA- and NO-signaling. The blue S-cones also compete for the blue light, although to a lesser extent (Figure 6A).

Red light around 650 nm acts on the eye health via different mechanisms than the blue light. It indirectly increases DA release through ***photo biomodulation of mitochondrial function*** in the retinal cells, including the photoreceptors. Dopaminergic amacrine cells (DACs), which are known to release retinal DA, have a very high mitochondrial density [33,34, 61-73].

Red light activates the mitochondrial enzyme cytochrome-c oxidase (CCO) in DACs. When CCO absorbs red light, the retinal cell metabolism and energy are improved by increasing the adenosine triphosphate (ATP) production and releasing NO by its dissociation from CCO. Increased ATP in DACs increases DA synthesis and release, while the release of NO bound to the mitochondrial CCO improves the retinal blood flow. Red light also reduces the retinal inflammation and oxidative cell stress by reducing the reactive oxygen species (ROS). Hypoxia and inflammation are conditions that suppress DA production (and many other physiological functions) in the retina. As stated before, myopic stressed retinas show choroidal thinning, decreased oxygen diffusion, and reduced dopamine expression, among other abnormalities. Red light releases the bound NO from the CCO in mitochondria, which not only helps DA homeostasis, but also promotes the synthesis of collagen I proteins important for the strength of the sclera, and downregulation of hypoxia-inducible factors in the scleral fibroblasts (Figure 10). The released NO has biological effects. It acts as vasodilator, which increases the blood flow in the choroid, which in turn improves oxygen delivery and results in improved mitochondrial efficiency. NO also acts as a neuromodulator by enhancing DA-neurotransmitter release by interacting with DAC pathways.

Simply, the red-light exposure yields a more energetic, less stressed mitochondrial state, which better supports the retinal functions, like DA-production by DACs. In other words, ***red light exposure acts as a metabolic stimulant of DA pathways rather than a photoreceptor-driven stimulant of DA which is the case with the blue light exposure.*** However, there are antagonistic effects of the red light as it is absorbed by the red L-cones. As discussed before, L-cones with their strong L-weighted effect on the blur cues, send signals for to the visual system for the eye to elongate. Thus, red light actually causes a ***physiological tension*** in the retina due to L-cone activation. This physiological tension can be best explained by the CCO-activation pathway which supports DA signaling and acts as

a stop pathway for eye elongation versus the L-cone activation pathway which gives the signal for the eye to elongate.

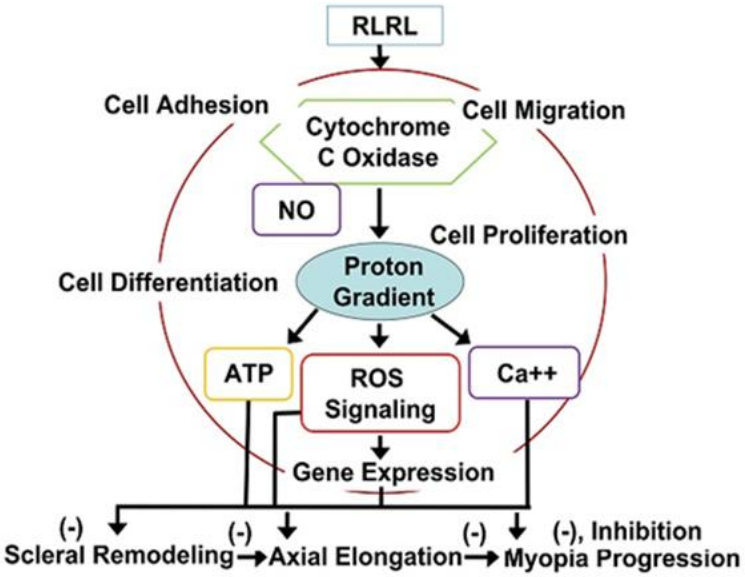

Figure 10. Activation of COO with red light and its mechanisms to inhibit myopia.

The Major Cause of Axial Myopia

Taking into consideration the above presented scientific findings on the effects of retinal DA on the choroid, sclera and eye growth, a plausible hypothesis for the myopia onset and its progression is briefly described below and schematically presented in Figures 11 and 12. As the children spend more time indoors, the lack of sunlight, and particularly the lack of beneficial blue light wavelengths (around 480 nm) and red-light wavelengths (around 650 nm) indoors, leads to retinal DA deficiency. Abnormal DA homeostasis eventually causes thinning of the choroid and reduces choroidal blood flow. Decreased blood flow to the adjacent sclera means insufficient oxygen and nutrients reach the sclera. This causes scleral hypoxia, scleral remodeling, and this results in scleral thinning. Consequently, in concert with the prolonged near-point stress (near point accommodation) of the eye ciliary muscles, the weakened sclera and choroid eye wall to foster elongation of the eye– one of the hallmarks of myopia. Thus, the sclera, the white outer covering of the eye, becomes more elastic like a balloon and is not tough like that of a basketball (Figure 11).

Figure 11. The scleral remodeling and thinning make the sclera more elastic, which allows the eye to elongate and become myopic. The authors use the term elastic broadly to cover also that of scleral remodeling.

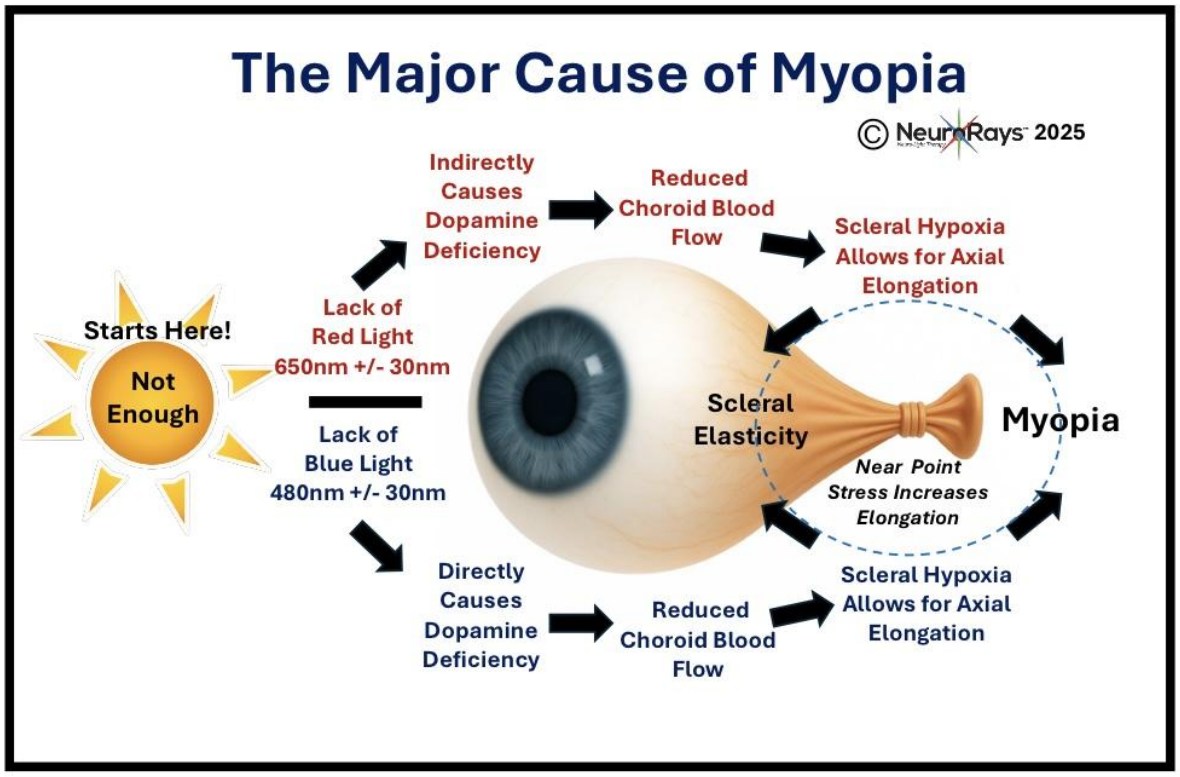

Figure 12. Retinal dopamine deficiency is a major cause of axial myopia. The authors use this diagram broadly to also cover that of scleral remodeling.

In summary, Figure 12 shows what occurs when the retina of the eye does not get enough outdoor sunlight irradiance. This is confirmed by the global lens manufacturers of myopia control lenses advising eye care professionals to tell their myopic child patients, who purchase myopia control lenses, to spend 2 hours in the sun each day while wearing their myopia control spectacle lenses. The fact that this is happening raises an important unanswered scientific question: *Do myopia control lenses work, as advertised - by peripheral defocus, or is their mode of action due to the spreading defocused blue 480 nm +/-30 nm, red 650 nm +/- 30 nm, and NIR 850 nm +/-30nm light wavelengths onto and around the peripheral retina when the children wearing these glasses are outside?*

Novel Light Therapy for Treatment of Myopia while Protecting the Macula

It was discussed above that beneficial ***blue light (480 nm +/-30nm)*** increases retinal DA release via melanopsin-containing ipRGCs and rod photoreceptor pathways. To a smaller extent, blue absorbing S-cones located in the fovea, absorb ~480 nm light (Figure 6A). Their number is much lower than the number of rods, which are located in the peripheral retina (Figure 6B). Moreover, the S-cones are not as sensitive as the rods to lower intensity blue light.

Unlike the blue light 480nm +/- 30nm, which acts directly on photoreceptors to stimulate retinal DA, ***red light (650 nm +/- 30nm)*** acts as a metabolic stimulant - it increases the retinal DA release via mitochondrial CCO-activation. Exposure to both light wavelengths enhances the DA signaling pathways which results in increased choroidal thickness and choroidal blood perfusion, reduced hypoxia, inhibition of scleral remodeling, strengthened eye wall, and thus, signals to retard eye growth that leads to reduced or arrested myopia progression.

However, exposure with red light 650 nm +/- 30nm activates the red L-cones found in the central retina. As discussed before, the human eye visual system “favors” the red L-cones due to multiple biological reasons, which also sends a strong signal for the eye to elongate. This antagonistic effect implies physiological stress in the eye.

An overview of the blue- and red-light effects on the retina and DA release is provided in the table below.

Table. Mechanisms of actions of blue and red wavelengths in the retina

Wavelength	Primary absorbers	Mechanisms	Dopamine (DA) release
480+/-30 nm	• Rods (rhodopsin) • ipRGC (melanopsin) • S-cones	• DACs activation: DA & NO release • Circadian activation	• Strong
650+/-30 nm	• Mitochondria (CCO) • L-cones	• ATP increase • NO release • ROS reduction • Inflammation reduction	• Moderate-strong

Given the preceding content it appears that ocular light therapy will be a great non-pharmacological way to control myopia progression [74-80]. In fact, recent reviews have reported that the light therapy and combination of light therapy with myopia control lenses have the highest efficacy in the treatment for slowing or stopping myopia progression [79-81]. However, the main concerns related to ocular light therapy have been related to safety due to its repeated daily use. Reduced cone density has been reported after repeated light therapy is utilized over time [82]. Safety concerns also have been reported with the current commercial ocular LLRL light sources which utilize laser LLRL light sources [83].

Therefore, a safer and more effective way to apply ocular light therapy to the eye is needed. A potential way to safely deliver the ocular light therapy to the retina in a daily repeatable manner is to mask or protect the macula and thus protect the cone photoreceptors. By protecting or blocking the macula from seeing light during an ocular light therapy session ocular therapy light can be safely delivered to the peripheral retina – especially where the rods reach the highest density (Figure 4B). Recent studies have confirmed that the peripheral retina, and a perifoveal area of the macula outside the fovea, have the most effect in myopia control [84, 85]. At the same time, by protecting the cones in the fovea from light exposure, the L-cone physiological antagonistic effects are suppressed. Thus, the blue 480nm +/-30nm and red 650 +/-30nm light wavelengths stimulate only the rods and ipRGCs causing a release of retinal DA, which in turn contributes to a healthier and thicker eye wall needed to stop axial elongation in myopic eyes.

Protecting the macula during ocular light therapy allows for the safe delivery of the light to the intended photoreceptors in the retinal periphery without damaging the macula and also removes the physiological antagonistic effects of ocular light therapy. This avoids the eventual physiological ~~tenson~~ tension caused by the different mechanisms

when the ocular light therapy is delivered, such as removing the negative L-cone drag on slowing or stopping myopia. This should increase the efficacy of ocular light therapy in slowing or completely stopping myopia progression. While this sounds compelling, this hypothesis needs to be proven by way of additional quality clinical research.

Disclaimer:

This white paper is not to be confused with that of a peer reviewed paper. It represents the most up to date visionary thinking at NeuroRays™ (www.NeuroRays.com). It is intended to provide a forward looking, educated, hypothesis and path forward. NeuroRays is presenting this white paper with the hope it will be a catalyst for additional research that is focused on "Ocular Light Therapy with Macula Protection" that may prove most helpful in the effort to completely "Stop" myopia progression. As expected, NeuroRays has filed multiple patent applications and anticipates being granted global protection. Research Companies, Universities or other such Organizations who desire to research the effects of slowing or stopping myopia progression by way of protecting all, or part of, the macula while stimulating the peripheral retina are encouraged to contact either; Anita T. Broach, PhD at (Anita@NeuroRays.com) or Ronald D. Blum, OD, DOS at (RBlum@EggFactory.com). Such research is being solicited and encouraged.

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