Acta Scientific Ophthalmology (ISSN: 2582-3191)

Volume 6 Issue 12 December 2023

Research Article

Global Myopia: Theories Behind this Epidemic and how to Prevent Progression in Children

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Received: October 20, 2023

Published: November 20, 2023

Abstract

Aim: Myopia, also known as near or short sightedness, is a common refractive defect that generally develops in childhood. This is mainly owing to an elongated eye on axial length, with focusing power of the cornea and/or lens being a less common cause. This leads to the focus of light in front of, instead of, directly on the retina. Uncorrected refractive error is the most common cause for visual impairment and is responsible for the 2nd most common cause of blindness worldwide. Holden., et al. predicted the rise of prevalence in myopia to nearly 50% of the global population by the year 2050 and that a higher proportion of this group would develop moderate to severe myopia. The current alarming trends validate these predictions and has spurred a surge in studies to understand the underlying causes. The process of myopia is still unclear, however there are several hypotheses that describe the development of myopia. There is a varying degree of responsibility that may be attributed to both genetic and environmental variables. There are a variety of treatment options available to treat and manage this condition, but it is apparent that understanding the mechanisms involved in delaying myopia onset and decreasing its advancement will be the key to lowering the rapid growth in global prevalence.

Methods: In this systematic review Medline OVID and Medline Embase are the two databases that were used to search for appropriate material for critical evaluation. The appropriateness of each article and reference was manually assessed before selecting them. Therefore, the important concepts to construct my thesis reflect the global prevalence of myopia, the aetiologias and prevention methods especially in children. The articles must be centered around these concepts and are identified and selected if these search terms were included in the title and abstract.

Results/Discussion: The analysis determines that there are many variables contributing to the myopia epidemic. Theories that have proposed in relation to myopia development has only recently been hypothesized, with no strong conclusions being derived in human trials. However, it is understood that increased near work and reduced day light do allow myopia progression.

Conclusions: The objective of this research is to evaluate the evidence on various therapies and strategies in order to help family doctors deliver the best recommendations to patients and their families. This myopic rise is not only significant enough to warrant investigation, but the frequency of high-grade myopia is linked to a variety of debilitating illnesses.

Keywords: Myopia; Global; Blindness; Pediatrics; Child; Epidemiology

Introduction

Myopia: Definition

Myopia, also known as near or short sightedness, is a common refractive defect that generally develops during childhood [1]. Anatomically, this is mainly owing to an elongated eye on the anteroposterior axis (axial myopia) [2], and/or the focusing power of the cornea and/or lens being a less common cause (refractive myopia). According to the World Health Organization's (WHO) International Classification of Diseases (ICD-10) this anomaly leads to "a refractive error in which rays of light entering the eye parallel to the optic axis are brought to a focus in front of the retina when accommodation (accommodation, ocular) is relaxed" [3], as opposed to focusing directly on the retina. The refractive error is described by the refractive correction that is required by the lens measured in diopters. Diopters (D) is the unit of measurement of the lens power to focus/bend light rays to resolve the refractive error. It is equal to

reciprocal of one meter and reciprocal of the focal length. Sometimes, articles may use spherical equivalent refractive error (SER) to estimate the refractive error in each eye, where it combines the myopia/ hyperopic (spherical component) and astigmatism (cylindrical component).

For example:

1 dioptre = 1 m^{-1}

2 dioptre lens allows parallel rays of light to focus in at 1⁄2 metre.

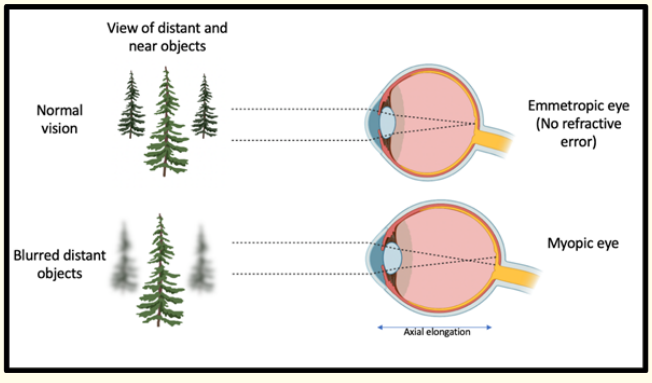


Figure 1a: Axial myopia due to lengthening of the anteroposterior axis of the eye.

Typically, concave lenses, which are described with a negative diopter and used to rectify the myopia blur by diverging the light rays that enters the eye pushing back the focal point on to the retinal plane. (Figure a) The total diopters of the refractive components in a schematic eye that has normal vision (emmetropia) are 60D. However, in axial myopia, despite having normal refractory components, the focal point is brought forward due to the elongated eyeball, with increased mean axial length is the main contributor in most myopes [2,4].

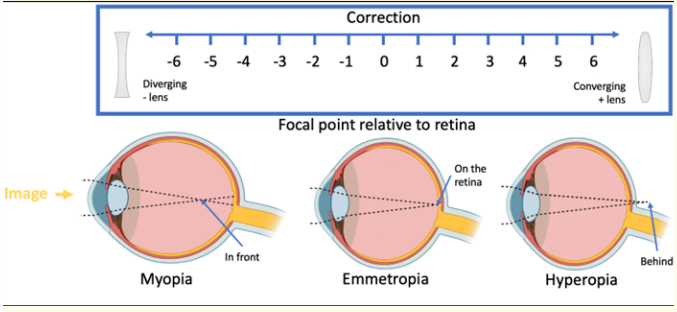


Figure 1b: Illustration demonstrating the image focus relative to the retina in an eye with refractive error compared to an emmetropic eye. Scale component describes the refractive error and which lens required for correction based on refractive error.

Classification

The mechanisms of myopic growth are complicated and variable. Perhaps it is more appropriate to refer to it as "myopias" instead of just a single state of myopia. This complicated pattern masks true myopia categorization and has resulted in various other classifications being proposed [3]. The suggested terms used in various literature has been grouped into Table 1a. One can see the problems with such an arbitrary criterion with further variations within the terms used. For example, degenerative myopia may imply severe myopia or myopia that is associated with degenerative fundus changes but not necessarily pathological [5]. However, dependent on individual article, this term is used interchangeably with "malignant" myopia and "pathological" myopia as explained by Kwok., *et al*. that In Hong Kong the term pathological myopia is used to describe eyes with myopia worse than -8D and other terms, such as simple myopia and school myopia being used interchangeably are further examples that proves this point [6].

Flitcroft., *et al*. sought to emphasize this and postulates quantifying myopia into 2 main diagnostic thresholds: low myopia from -0.5D to -5D, high myopia from <-5D [3]. Other subgroups may also be used to diagnostically quantify severity of myopia and categorize patients based on developing risk of ocular complications. Either way, unanimity among specialists is required for a standardized classification, especially if prevalence data and prospective studies are to be compared and analyzed.

There are several hypotheses that describe a role in the development of myopia. There is varying degree of responsibilities that may be attributed to both genetic and environmental variables. A variety of treatment options available to treat and manage this condition, but it is apparent that understanding the mechanisms involved in delaying myopia onset and decreasing its advancement will be the key to lowering the rapid growth in global prevalence.

Unless otherwise noted, high myopia (HM) shall be referred to in this systematic review as simple or primary myopia of less than -5D. HM that has caused subsequent fundus changes and ocular complications is referred to as pathological high myopia (PHM).

The Myopic spiral

Epidemiology

Approximately 2.2 billion people are affected with refractive errors globally. Additionally, uncorrected refractive errors (URE) is one of the main causes of worldwide visual impairment and vision loss [8]. Ethnic and racial discrepancies in the magnitude and

Classification criteria for Myopia	Terminology
Degree of Myopia	1) Low, 2) moderate, 3) high
Age of onset	Congenital, infantile, juvenile and adult OR Congenital (typically early) vs acquired (typically late onset) OR Late-onset (15 years or older) vs Early-onset myopia (14 years or younger)."
Myopia progression	1) Stable (refractive error changed ≤ -0.25D in > 2 years) 2) Progressive (refractive error changed >-0.25D in 2 years) OR 1) "In 1984, Donders subdivided myopia progression into (1) stationary, (2) temporarily progressive, and (3) chronically progressive (also called malignant or deleterious) myopia."
Fundus changes	1) Physiological/ simple (no changes observed), 2) pathological/ degenerative (fundus changes observed)
Anatomical involvement of the eye Components	(1) Refractive, correlation or combination myopia, and (2) component myopia (e.g., due to corneal curvature myopia, lens myopia, and axial myopia)."
Biological classification	"(1) Physiological or simple myopia as a biological variation of the normal distribution of the eye components, and (2) pathological (progressive or magna) myopia as falling outside the normal distribution."
Clinical forms	1) Nocturnal "drift in the accommodation state that increases the power of the eye under scotopic condition" 2) Pseudomyopia "false myopia due to physiological or pathological increased accommodation state" 3) Myopic refractive shift "Later in life, a myopic refractive shift may result due to crystalline lens changes." 4) Form deprivation 5) Lens defocus
According to presumed aetiology.	Environmental vs Genetic. OR (1) Physiological myopia, (2) school myopia (due to close work), and (3) excessive myopia (i.e. caused by underlying diseases).
Based on treatment	Simple myopia encompasses patients that can be easily corrected with glasses or contact lenses. Pathological myopia is severe short sightedness that is associated with blindness due to increased risk of secondary conditions.

Table 1a: Classification of myopia based on various criteria. Table derived from [3,6,7].

prevalence of myopia have been observed, with both being comparatively higher in Asia than in other regions of the globe [1,9]. Wearing glasses has become the standard in East and Southeast Asian regions as Myopia presently affects 80-90% of late adolescents in these nations, by the end of schooling [10]. Prevalence varies from country to country but is headed towards the same direction globally. Recent trends have shown that there is an 18% increase in just 30 years (1971-2 vs 1999-2004 within a U.S. cohort) [11], with current projections of myopia prevalence predicting to affect 49.8%, (4.7 billion) of global population by 2050, a 95% confidence interval (CI) of 43.4-55.7% [9]. These alarming trends also indicate that there are higher proportions of the population will have moderate to severe myopia [9,11], with high myopia (< - 5D) affecting 1 billion people worldwide (9.8% of global population, 95% CI [5.7% -19.4%]) [9].

Global burden and QoL

This is increasingly a cause for public health concern as higher myopia is associated with ocular complications and blindness which in turn can lead to global financial burden and productivity loss. Uncorrected myopia is estimated to cost around $244 billion in productivity loss [8,12] and can lead to clinical service strain to provide continued care for this cohort [13]. The costs that were

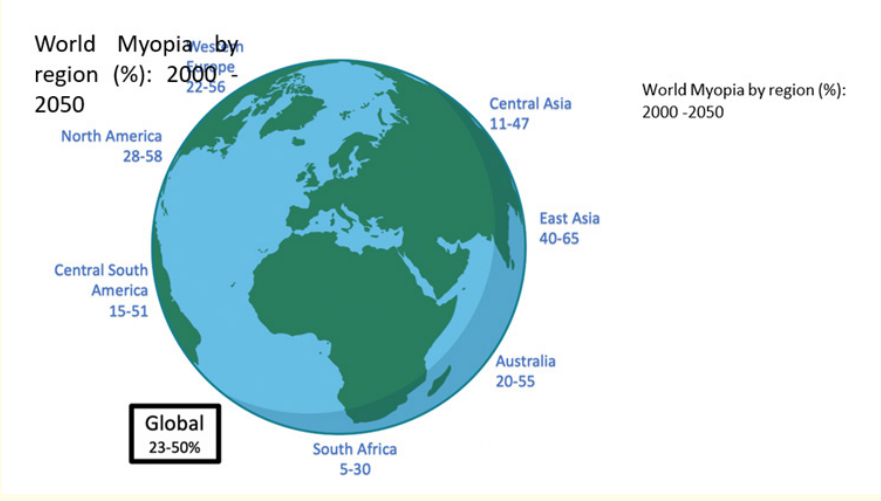


Figure 1c: World Myopia by region (%): 2000 -2050. Lower limit indicates the percentage of population affected by myopia in 2000, and upper limit indicates the projected predictions in 2050 [9].

solely related to either lifetime cost of glasses, contact lenses and/or myopic correction procedures varied from $3.9-7.2 billion/year in the USA. This was not including the treatment of ocular complications from HM [14].

There is significant global cost involved with myopia, and with health care spending becoming a rising issue across many economies it is important to understand the impact of primary prevention on these said costs.

The personal impact of myopia and HM in children is thought to effect their self-esteem and their involvement in school, in particular lower confidence in sports related activities [8]. Not many studies have attempted to ascertain these attitudes so findings are limited. However, Correction of Myopia Evaluation Trial (COMET) did conduct a side study in their relatively large cohort (n = 469) and found that myopia development and spectacles did not affect their level of self-esteem [15,16]. We can surmise that this may be because people's attitudes toward glasses have been normalized. This does not take away from the fact the long-term quality of life (QoL), with the increased risk of life time visual impairment and blindness.

Aetiologies and pathogenesis

The fundamental pubertal eye growth is synchronized with a 1:4 ratio to anterior and posterior eye segments and remains relatively stable during adolescence, mimicking the brain growth trajectory (greatest rise during the first 3-4 years of life, then dropping) [17].

Those with progressive myopia, on the other hand, becomes larger in all diameters but tend to undergo skewed development towards increased axial length (AL) elongation [18] and this reflected with a linear regression with refractive error [17].

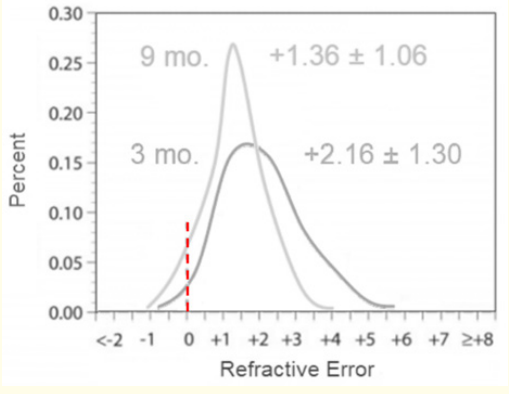
An emmetropic eye is considered to have AL of around 23.6mm however there is considerable overlap between the 3 refractive groups (myopia, emmetropia, hypertropia) [17], but it can be estimated that population with severe myopia (-5 to -7.5 D) is estimated to have at least 25.5 to 26.5mm by one study [19].

In order to comprehend the aetiology of myopia we must understand the stabilisation process that takes place throughout ocular growth.

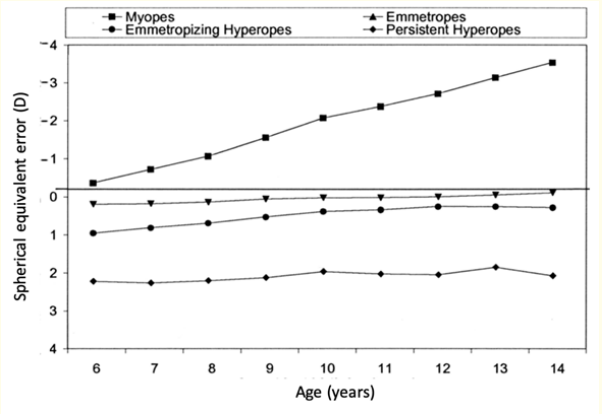
Emmetropisation

Most newborns are somewhat hyperopic at birth and become emmetropic in the first two years of life, thanks to the active process of emmetropisation [7,20]. Emmetropisation is used to describe the physiological process that begins during the postnatal period, where the development of refractive components (lens and cornea total refractive power decreasing) which is counteracted

by increased growth of the eye (that is the increase in vitreous chamber depth) to deviate towards emmetropia [7]. This occurs throughout the young adolescent period [21] and is followed by stabilisation of the cornea. It is suggested that even an emmetropic eye continues this process lifelong to ensure maintenance of emmetropia [20,22].



Graph 1a: The graph shows an increased leptokurtic distribution towards emmetropia in 9-month year olds (pale line) when compared to 3-month infants (dark line), supporting the active emmetropisation process. Adapted from Mutti., et al. [20].



Graph 2: Adapted graph from Jones., et al. that illustrates failed emmetropisation and myopic children diverging away from emmetropia, while other refractive groups remain relatively stable [22].

Eye growth spiral

It is hypothesised that hyperopic children experience refraction changes far more slowly than myopic pupils of the same age [23]. Jones., *et al*. found that while other refractive states remained persistent or underwent a developmental emmetropisation process that shifted the eye towards no refractive error, myopic eyes did not follow the normal growth pattern and spiralled further into myopia [22]. The myopic shift can progress over the next two to three decades [7] but slows with age [24] suggesting that there is a retardation in the stabilisation process [25].

Genetics

Ocular biometrics associated with myopia (axial length, lens thickness, corneal curvature) have been shown to be heritable in their nature.

Landmark studies associating myopia with genetic inheritance are the twin studies, especially the Guangzhou twin eye study (GTES), a 12-year longitudinal study [26] and genes in myopia (GEM) study [27]. These are based on a classical model of a twin study, and is based on the assumptions that monozygotic (MZ) twins share 100% of their genes and environment where dizygotic (DZ) twins would only share 50%. Additionally, both studies included different population subsets. Correlations between the level of refraction and ocular biometrics associated with myopia was higher in MZ twins ($P < 0.05$) [27] - hence providing evidence that genetics does play a role in refractive error [26,27]. However, it must also be considered that exposure to the same myogenic environmental conditions may also lead to sibling similarities and not only rely on the concept of family clustering. Familial clustering is when the condition/disease occurs in some families more frequently than would be predicted based on the occurrence in the general population.

While the heterogeneity in spherical equivalent was primarily explained by additive genetic influences, the heterogeneity in ocular biometrics, notably axial length, was predominantly attributed by dominant genetic variants. Several genes have been mapped to different chromosomal loci that are found to be linked to HM, with variable inheritance. X- linked MYP1 gene [28], autosomal dominant MYP3 and MYP11 genes [28-30] have all been linked to non-syndromic HM. Familial clustering, where the condition/ disease occurs in some families more frequently than would be predicted based on the occurrence in the general population, was also a notable feature in these cases.

However, it must also be considered that in the twin studies, exposure to the same myogenic environmental conditions may also lead to sibling similarities and not only rely on the concept of family clustering. Generally, these studies are in agreement that

myopia develops more rapidly and manifests earlier in children who have myopic parents. It has been hypothesized that parental myopia affects the development of refraction by increasing their risk of lifetime myopia and quickening myopia onset processes [26,27,31,32]. With the addition of environmental factors, HM has become rampant.

Environmental

There are several environmental factors that are thought to have a role, not only in myopia, but also responsible for the myopic epidemic. These are; increased near work, decreased outdoor time and seasonal variations and diet.

Increased near work

The link between education and myopia may be viewed as a causal component, because there are parallel shifts and development occurring internationally, such as dietary variations, pollution, lifestyle including increased technology time that could also be considered. Nonetheless, as previously stated, there is growing data that suggests that near work is the root cause of myopic divergence in school-aged children and very little evidence disputes this [7,21,22,33]. Higher IQ levels seems to also be an independent risk factor for greater myopia degree [34].

More substantial study that noted the cause effect relation between nearwork and the progression of myopia was determined by a 1969 population study, based on the rapidly changing lifestyle of Inuit inhabitants in Alaska [35]. Only 2 of 131 adults who grew up in these secluded regions had myopic eyes but this was not mirrored in the children population, with more than half of their descendant's developing myopia. Even if the populations in question are genetically predisposed, evidence suggests that the myopia epidemic has an environmental cause [36] as genetic evolution occurs too slowly to account for this sudden myopic shift [35,36].

Furthermore, the estimated parent-offspring heritability (h^2) is low but the sib-sib heritability was high which indicates the environmental variables had started to outweigh the genetic role in causing refractive error (parent-offspring $h^2 = 0.10$, sib-sib $h^2 = 0.98$). The biggest culprit was thought to be the implementation of compulsory education in this generation and a "westernised environment" [37].

Outdoors + seasonal variations

There is now convincing evidence that children who spends longer periods outside are less likely to become myopic or undergo myopic progression [38,39] but it is still disputed by others [40]. Still, it is difficult to acquire accurate data of the time spent outdoors as it is frequently collected through questionnaires, which are known to be unreliable and subject to response bias.

In terms of seasonal variation, AL progression which can be measured objectively had halved during summer periods [41]. Other studies find any correlation between time spent outdoors and myopia progression [40].

Through animal testing, bright light (imitation of daylight) had a significant protective factor in at least the form-deprivation myopia (myopia induced by blurred image) [42]. Other studies have hypothesised that retinal dopamine [39] is released in exposure to daylight that acts as a protective mechanism against axial elongation. A dose dependent relation was only recently confirmed with induced experimental myopia with dopamine 2 (D2) receptor inhibitors being injected into the chicks eyes [43].

Diet

There has been very little research into whether diet has any, if any, effect on myopia. A study suggests a diet with wild foods (rich in phytochemicals) and less processed foods in a group of hunter-gatherers to be reason behind low juvenile onset myopia. The outdoor factor was eliminated as the comparison group had similar environmental exposures but had more processed diets [44].

However, the precise aetiology is still unclear despite the recent substantial interest in myopia. Regardless, it is a general consensus that both genetic and environment have an influence in the development and progression of myopia, with perhaps environment playing a bigger role in the myopia epidemic [35].

Ocular complications and imaging

Although near sightedness can be temporarily resolved using simple measures such as lenses, the underlying severity of developing myopia was underestimated. The myopic progression is a major cause for concern as increasingly higher degrees of myopia can directly or indirectly predispose this cohort to many debilitating complications that can lead to blindness [45]. The main ocular complications are myopic macular degenerations, staphylomas, retinal detachment, glaucoma and cataracts.

Structural changes

It is now highly suspected that the thinning of the eyeball wall layers affecting the retina, choroid and scleral layers is associated

with myopic pathology, and is the primary culprit for myopic macular degeneration (MMD). The mechanical lengthening is at fault for the complications behind pathological myopia. It leads to scleral weakening from the elongated eye ball, that can lead to atrophic holes which is slowly progressive [46], with decreased circulatory perfusion [18,19] leading to further MMD findings.

This may be due to mechanical stretching, choroidal ischaemia [47] or hormonal involvement leading to scleral thinning in individual with unknown predisposition [48], however this latter proposition is highly disputed. The choroidal thinning begins at the equator and is the thinnest at the posterior pole [47], similar to the scleral layer to a lesser extent [49].

Myopic macular degeneration

Choroidal thinning (image a) is found to be an independent marker of the progression of myopic maculopathy [50] and directly correlates with high myopes with increased AL [51]. The volume of both layers is preserved in both despite the stretching in the elongated eyeball suggesting that there is a reorganisation of the tissue than new tissue being formed [47,49,52]. Thinning of the choroidal layer can cause blood vessels to be sparser and lead to decreased perfusion. Choroidal ischaemia can result in myopic macular degeneration (MMD) [2,53] and has a high risk of leading to visual loss [47]. A large study (Blue Mountains eye study n = 2335) calculated the risk of MMD was over 50% in severe myopes (<-9D) [54]. MMD includes pathological findings of tessellation, chorio-retinal and macular atrophy with additional lesions such as choroidal neovascularisation, Fuchs's spots and lacquer cracks can be found.

Fundus changes - presence of lacquer cracks are linear breaks in retinal pigment epithelium, bruch's membrane and choriocapillaris complex. Seens as yellowish linear lesions ophthalmoscopically. It represents the mechanical breaks and healing processes posteriorly in high myopia and tends to be progressive. Presence of this features indicates poor prognosis with development of macular pathology, e.g. atrophic holes, retinal haemorrhage and subretinal neovascularisation [55], chorioretinal degeneration [19] which is closely related to fuch's spots.

It can be observed as a pale patch at central retina by an ophthalmoscope and the thinning of the posterior eye layers can be visualised using optical coherence tomography (OCT) as seen below.

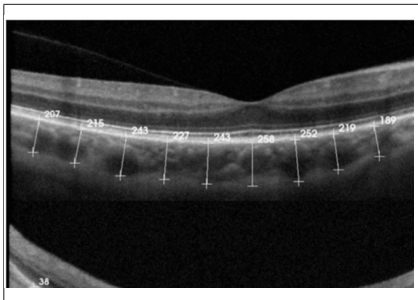
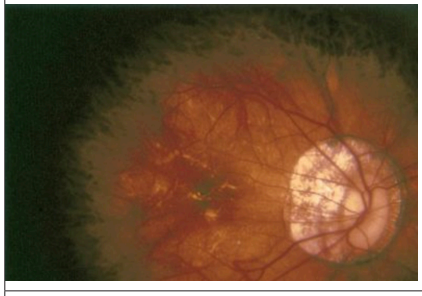
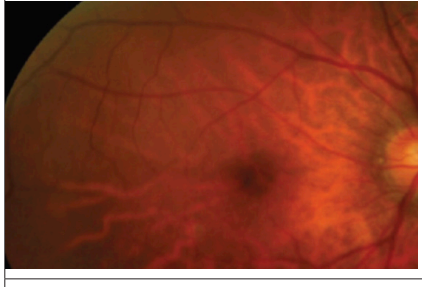
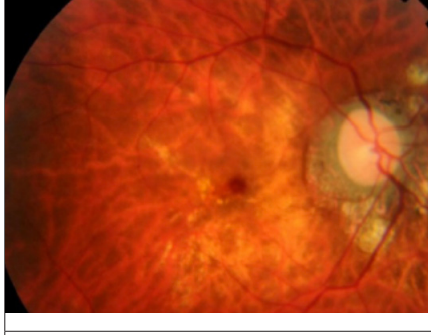
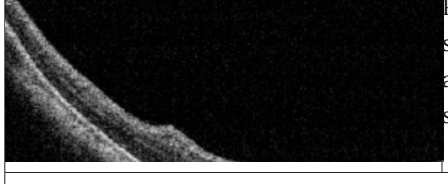
	OCT (Topcon 3D-2000) images of choroidal thickness comparison in control (above) vs myopic patient (below). Significant loss of choroidal thickness seen in myopic eye [56].
	Tilted disc and peripapillary atrophy of RPE and choroid [57].
	Tessellated myopic fundus. Tessellation is an indicator for chorioretinal changes [58]
	Lacquer cracks - crisscrossed yellow lines represent the ruptures in the RPE-Bruch's membrane-choriocapillaris complex [58]
	Posterior staphyloma shown on OCT. Yellow arrow shows retinal schisis. [58]

Image a: High myopia and some of the pathological fundus findings associated with progressive myopia on different imaging modalities (Optical coherence tomography and colour fundus photographs).

Treatments

The main objectives behind the treatment options can be divided into:

- Making the sclera more resistant to elongation and expansion
- Preventing accommodating forces from affecting the sclera and
- Reducing pressure tension on the sclera [62].

The latter objective mainly being accomplished by surgical means e.g. mechanical scleral buckling and scleroplasty. In this thesis, I will explore conservative methods that can be distributed directly from clinics to help cease progressive myopia prophylactically in minors.

Protective factors

Conservative management should consider protective factors. Increasing just 2 hours of outdoor time everyday negated the risk associated with increased near work [39] and also familial risk of progressive myopia [38].

Pharmaceutical treatment

Topical M1 muscarinic antagonist, specifically atropine which has been the most investigated has shown promising results to tackle progressive myopia. Other antimuscarinic drugs e.g. pirenzepine gel have also been tested and results were not as successful as atropine eye drops. Atropine is an anticholinergic drug that has cycloplegic and mydriatic effects. However very little is understood about the mechanism of action, however it is generally hypothesized to inhibit or promote a up regulatory or down regulatory feedback mechanism [63]. Several clinical trials have been conducted in search for the optimal dose and ascertain the long-term efficacy and safety of this medication. There are side effects (SE) associated with atropine including eye stinging, photophobia, headaches, glares, accommodation inhibition [63,64] and systemic SE such as dryness of nose and throat and tachycardia [65].

Intraocular pressure (IOP) lowering medication could also play a role in lowering stress on scleral wall and lower risk of axial elongation. Barraquer and Varas identified that around 68% of myopes had >16mmHg. In hypermetropia, the inverse distribution was seen, showed that of 445 myopes the IOP distribution was: lower than 16 mmHg in 20%, 16 mm in 11%, and higher than 16 mm in 68%. In hypermetropia, the inverse distribution was seen. Lui., *et al*. on the other hand, discovered that accommodation induced a temporary IOP in progressive myopia but otherwise no change in baseline IOP in myopia or emmetropia [66].

Optical

There are several types of lenses that can be prescribed for children to resolve the myopic blur. Single vision lenses (SVLs) are most commonly prescribed and provides long distance correction. However, SVLs don't have any effect in limiting myopic progression. Bifocals works similarly to SVLs but also has a plus addition for near work. There is evidence to suggest that bifocals do provide some benefit in limiting myopia progression.

Progressive additional lenses (PALs) are a type of multifocal lenses that has increase in power to allow smooth transition between the zones. A large randomised clinical trial of 469 children, had taken part in the correction of myopia evaluation trail (COMET), which concluded positive findings in support of PALs especially in lower baseline myopia and baseline accommodative at near [67], based on the experimental animal studies from Smith., *et al*. [68,69]. However, the results are controversial and many trials failing to replicate findings and therefore inconclusive [70]. However, contact lenses with similar effect have proven to be more effective due to the reduced which suggests that PALs have reduced affect as it cannot completely eliminate hyperopic defocus due to the nature of spectacles, due the distance away from lens and eyes in comparison to the contact lenses that sits directly on the eye.

Orthokeratology (OK) is the use of overnight rigid contact lenses to improve myopic blur during the day. It neutralises the stimulus by physical manipulation to flatten the refractive component, cornea. There is evidence of choroidal thickness recovery and reduced myopia progression [71]. However, due to the presence of foreign body in the eye overnight, there is a hypothetical risk of developing keratitis that can lead to corneal opacification causing visual impairment and is the main reason that this option has not been implemented. Moreover, the lens is not comfortable, and children may find it difficult to wear contact lens, individuals may suffer from dry eyes.

Materials and Methods

I have conducted a systematic literature review regarding the theories linked to global myopia and in addition I wanted to explore the different conservative options to limit progression in children. Therefore, the important concepts to construct my thesis reflect the global prevalence of myopia, the aetiologies and preven-

tion methods especially in children. Pathological myopia is rarely attributed to one main cause and its aetiologies are barely understood in children.

Developing a better understanding, can help us target and prevent progression of the disease to a high grade in young patients. This thesis sets to investigate the literature published in both OVID Medline and OVID Embase databases that tackles the understanding behind global myopia or develops techniques to limit progression in children. The literature review will be a qualitative review and the key terms and related search terms that were addressed can be found in the table 1.1 and 1.2 in the appendix.

622 articles and 546 articles were extracted from Medline and Embase databases respectively and exported into Endnote. Duplicate references were removed using a duplicate finder and then manually examined for repeats. Further articles were eliminated since no English translations could be obtained. The articles must be centred around these concepts and are identified and selected if these search terms were included in the title and abstract. The following PRISMA diagram demonstrates the process and follows the collection technique to show you how to arrive at the finalised literature of 198 articles. Other references were handpicked manually through citations.

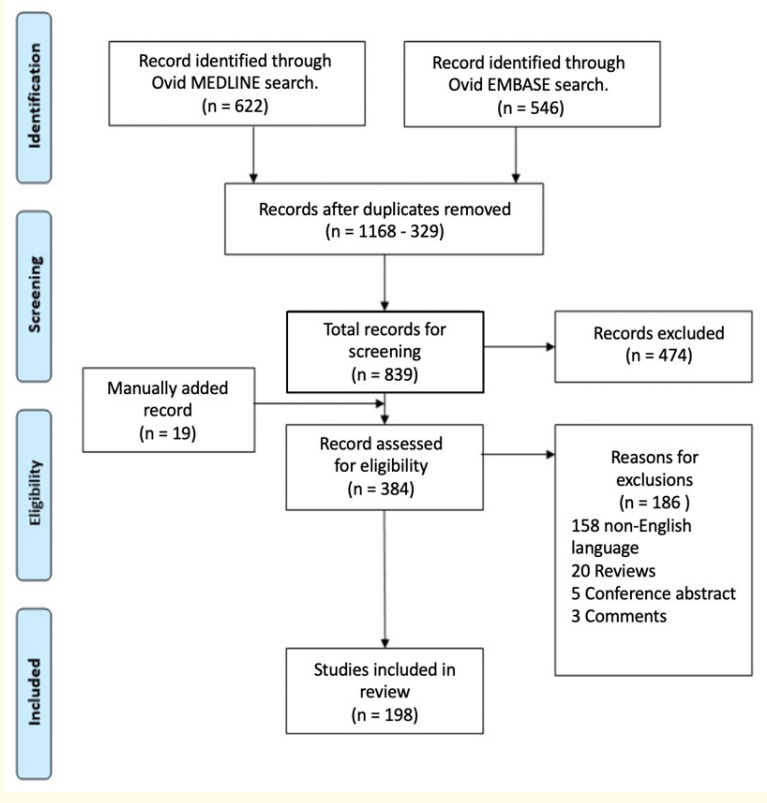


Figure 2: Prisma diagram of demonstrating the steps taken for the search and final selection of studies, followed the PRISMA guidelines [75].

Results and Discussion

Gordon., *et al*. concluded that the eye reaches its adult length +/- 1mm by 6 years of age [76] which could possibly help with the prediction of HM. However, more recent studies show that regardless of the refractive error, children start to actually deviates towards myopia at 6, and correlates this with greater near work and association with school [7,21,22,33]. There is a link between the age of onset and the ultimate refractive status in adulthood; that is, children who become myopic at a younger age (6 vs. 11 years) are more likely to have progressive myopia and have a higher degree of myopia later in life [7]. Therefore, one thing is certain: the earlier the onset and the higher the baseline myopia, the greater the progression; thus, these factors may be used to predict outcomes [31]. As parental refraction is correlated with greater myopia level, family history might also be suggestive of the population at risk [32]. Some studies have shown the hyperopic reserve can limit myopic progression [33].

Defocus theory

A main model for understanding ocular development is defocus theory, which holds that the eye can detect whether light is focused in front or behind the retina and grow in the appropriate direction to reduce blur. This was surprisingly through animal experimentational myopia studies which revealed that peripheral image defocus played a significant role in axial elongation at the expense of central vision. In one group of monkeys, the central fovea was ablated while the peripheral retina was preserved, and in the other, the opposite was administered. Smith., *et al*. found that they had induced myopia only in monkeys with preserved peripheral retinal suggesting that there is feedback mechanism at the peripheral fundus controlling eye growth. This could help explain why astigmatism (multiple focal points) could be predispose progressive myopia in children [77 - n72]. This also explain why certain treatments such as bifocal and PALs have shown results in decreasing myopia progression.

A further extension of the defocus theory depends on the eye's index of refraction (ability to bend light) varies with wavelength. The eye may be able to determine this by recognising chromatic cues: red (long wavelength) light has a lower index of refraction than blue (short wavelength) light. As a result, red wavelengths are focused further back in the eye than blue wavelengths. It is hypothesised that the distinction is detected by retinal cells with different sensitivities to long and short wavelengths, allowing the eye to determine whether it is myopic or hyperopic defocus and adjust its growth accordingly [78 - n73].

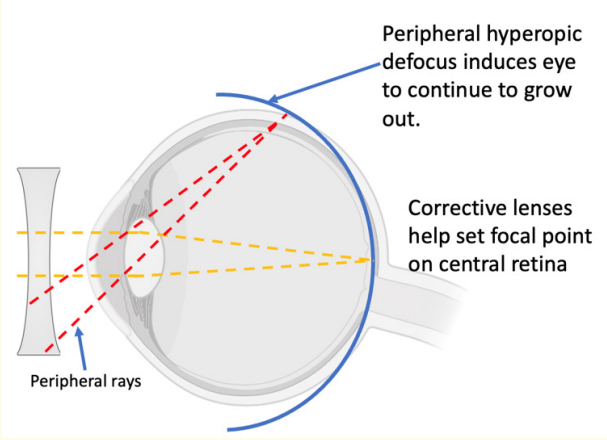


Figure 3

Structural theory

Induced myopia in animal experiments have led to discovery in different factors that affect ocular growth. A low-resolution image can be created through the use of diffuser lens and can lead to form-deprivation myopia (FDM) in the eye that had blurred vision. However, light acted as a protective factor. FDM in children can be caused by retinopathy of prematurity, cataracts or macular dystrophy. This supports the fact that increased outdoor time can reduce risk of myopia. Another form, lens defocus myopia (LDM) can be induced through the use of refractive lens. For example, Smith., *et al*. used -3D lens in one eye inducing hyperopic defocus.

Animal experiments have highlighted the importance of environmental factors in the development of myopia. Raviola and Wiesel., *et al*. experimented suturing eyelids of newborn monkeys with the other eye acting as controls [79 - n74]. Interestingly, the eye that was sutured had increased AL and had developed myopia but the open eye remained emmetropic. However myopia only induced in these primates if kept in a normally lit surroundings, however in dark surrounding the myopia doesn't develop [80 - n75]. This is also observed in human studies where congenital cataracts lead to the development of myopia [48]. This may suggest that there is some synchronicity between the eyes.

Lower plasma cortisol levels were measure in children with unilateral congenital cataract, allowed Balacco-Gabrieli., *et al*. to reach the conclusion of the involvement of the diencephalohypophysial axis, through an unknown mechanism. With poor vision inducing a hormonal imbalance, resulting in scleral collagen weakening in eyes genetically prone to this condition. Interestingly control chil-

dren (emmetropic) had low levels of plasma cortisol levels and was no statistical difference when compared to children with bilateral congenital cataracts [48]. Although dose dependent dopamine role has been identified in experimental myopia in chicks, the chain reaction is not fully understood. There may also be a link between these hormonal components

Conclusion

Clearly the world is changing rapidly and our ours eyes are unable to adapt. Is it coincidental that school work and near work and importance in education is leading cause of myopic spiral? Especially during the years where eye growth and stabilisation is the most vital. There is no denying that there is a genetic component behind myopia, but one would be irrational to believe that is the main reason behind this myopia epidemic. Perhaps the question we should ask ourselves is how are emmetropic able to maintain their eyesight throughout their lifetime? More longitudinal studies and observations need to be carried in order to find way to limit progression. Not only for the sake of the patient but also to limit public strain as clinics will be unable to cope with maintenance and rise of severe ocular complications in this rapidly growing world.

It is now well established that severe myopia is associated with earlier onset in childhood and therefore it is essential to introduce effective myopia management strategies in school-age children, which comprises of preventing the initial onset as well as thwarting progression, in order to tackle global myopia.

Future studies should improve our understanding of the characteristics of pathologic myopia, develop a health management system and predictive index system to track early pathological changes, and encourage early detection and intervention in order to avoid blindness and visual impairment brought on by pathological changes in the myopic fundus. Additionally, the variety of myopic pathologies and the risk of visual impairment and decreased productivity globally emphasise how critical it is to address this phenomenon and curb the myopic surge.

Therefore, effective future planning for the provision of eye care services will be necessary.

Perhaps studies about how emmetropic individuals are able maintain no refractive error should be considered. Also, perhaps we should not wait for a child to progress into myopia before providing prophylactic treatment. Perhaps a risk stratification score can help identify children most at risk and start implementing prophylactic treatment already.

Conflict of Interest

Nil.

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