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Origins of Refractive Errors: Environmental and Genetic Factors

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Abstract

Refractive errors are the product of a mismatch between the axial length of the eye and its optical power, creating blurred vision. Uncorrected refractive errors are the second leading cause of worldwide blindness. One refractive error currently attracting significant scientific interest is myopia, mostly owing to the recent rise in its prevalence worldwide and associated ocular disease burden. This increase in myopia prevalence has also been rapid, suggesting environmental influences in addition to any genetic influences on eye growth. This review defines refractive errors, describes their prevalence, and presents evidence for the influence of genetic and environmental factors related to refractive error development.

Keywords

refractive error; hyperopia; myopia; astigmatism; axial length; emmetropization

OVERVIEW OF REFRACTIVE ERRORS AND EMMETROPIZATION

The World Health Organization ranks uncorrected refractive errors as one of the top causes of vision impairment worldwide (44%) and estimated that in 2010 285 million people were visually impaired, of which 39 million were blind. More recently, Naidoo et al. (2016) reported that in 2010 uncorrected refractive errors were responsible for moderate or severe visual impairment in 101.2 million people worldwide, with blindness (visual acuity worse than 3/60) affecting 6.8 million people.

Almost every human eye has some level of refractive error, regardless of whether it is optically corrected with spectacles or contact lenses. This review aims to summarize identified genetic and environmental influences on the development of refractive errors, with particular emphasis on those linked to myopia.

Etiology and Symptoms of Refractive Errors

Refractive errors reflect a mismatch between the axial length of the eye and its optical power, resulting in blurred retinal images (Figure 1). This mismatch is commonly

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encountered in new-born infants, who frequently exhibit significant refractive errors. However, in most cases, these errors decline during early development, i.e., the eye emmetropizes, as the powers of the optical components, namely the cornea and intraocular crystalline lens, decrease and the eye elongates (Mutti et al. 1998, 2005). To achieve emmetropia, a visually mediated active process supplements the latter passive process to eliminate residual refractive errors; its failure results in residual or new refractive errors (Wildsoet 1998) (also discussed further below).

There are three main types of refractive errors: hyperopia and myopia, which represent so-called spherical errors, and astigmatism, which involves an optical asymmetry. Although considered as an independent category, astigmatism may be a feature of both hyperopic and myopic eyes.

Hyperopia.—Also known as farsightedness, hyperopia is the product of the axial length of an eye being too short for its optical power. Hyperopic eyes are relatively underpowered, and near objects, as well as distant objects to a lesser extent, appear blurred unless corrected by accommodation or optical devices. Hyperopia may have its origin in one or more ocular components, such as a shorter than normal axial length, a relatively flat cornea, or insufficient crystalline lens power (Harb 2010, Mutti 2007). Individuals with uncorrected hyperopia may experience a range of visual symptoms, including blurred vision, asthenopia, binocular dysfunction, amblyopia, and/or strabismus. The nature and severity of such symptoms depend on the magnitude of hyperopia; the demands placed on the visual system (i.e., distance versus near viewing); accommodative amplitude, which shows an age-related decline; and the functional status of the accommodative-convergence control system.

Myopia.—By contrast, myopia (or nearsightedness) is the product of the axial length of an eye being too long for its optical power. Myopic eyes are relatively overpowered, resulting in maximally blurred vision of objects at far viewing distances and less blur at nearer viewing distances. Sharp vision at some near distance corresponds to the natural plane of focus, the so-called far point. Myopia may occur as part of a systemic congenital syndrome involving several bodily tissues, so-called syndromic myopia. However, most myopia falls outside this category and is typically classified according to its age of onset, i.e., congenital (present at infancy, often at high levels, especially in premature infants), preschool, juvenile-onset or school (the most common form), and adult-onset. Juvenile- and adult-onset myopias are mostly axial in nature, the products of dysregulated eye growth. Myopia carries a significant risk of visual impairment linked to retinal detachments, myopic maculopathy, glaucoma, and cataracts, even when present only in low to moderate levels, although the risks of such pathological complications are much greater in high myopia [typically defined as worse than −6.00 diopters (D)] (reviewed in Flitcroft 2012, Saw et al. 2005).

Astigmatism.—Most commonly occurring as a product of rotational asymmetries, astigmatism involves one or both of the corneal surfaces (corneal astigmatism) and/or those of the crystalline lens (internal astigmatism) and/or a tilt of the latter. Owing to the neutralizing effect of internal astigmatism on corneal astigmatism, the overall magnitude of regular astigmatism is generally limited, even though spherical symmetry is rare for these ocular surfaces. Astigmatism gives rise to two planes of focus that may lie in front of, lie

behind, or straddle the retinal plane, depending on whether it occurs alone or in combination with hyperopia or myopia. Indeed, astigmatism is a common feature of higher levels of hyperopia or myopia (Dobson et al. 2007, Heidary et al. 2005, Rezvan et al. 2011). In all cases, blurred and/or distorted vision will be encountered at both far and near viewing distances. Astigmatism may also be classified as with-the-rule, against-the-rule, or oblique to reflect the orientation of the most powerful optical meridian, i.e., vertical, horizontal, or oblique, respectively. Similar to hyperopia, high levels of astigmatism are often present in infancy, quickly declining during early development. Significant residual astigmatism is considered an amblyogenic risk factor, owing to the associated blurred distance and near vision when left uncorrected. Regular astigmatism is typically correctible with optical treatment. However, irregular astigmatism, which can occur as a product of corneal disease, e.g., keratoconus, or surgical intervention involving the anterior ocular segment, is more difficult to correct (for a review on the diagnosis and treatment of irregular astigmatism, see Wang 2008).

Emmetropization

Emmetropization describes the reduction in refractive errors from their neonatal starting point toward emmetropia. Ocular development alone contributes to this process through a scaling effect linked to eye elongation and a reduction in the optical (dioptric) power of the eye (Sorsby et al. 1961). This process is reflected in the change in refractive error distributions, which is near normal for neonatal infants, with a peak (average) of approximately +2.00 D hyperopia. This distribution quickly narrows, and the peak shifts toward emmetropia over the first 2 years of life (Mayer et al. 2001) (Figure 2). Whereas passive emmetropization can account for many of these early changes, an active, visually mediated process is responsible for refining the balance between an eye’s optical power and its axial length to achieve emmetropia.

Several animal models showed that eye growth could be altered by visual manipulations such as spatial form deprivation, thus providing the first evidence for the existence of the emmetropization process (for a review, see Wildsoet 1997). Clinical parallels include eyes deprived of form vision, e.g., owing to congenital cataract or ptosis, where the emmetropization process also appears to fail (Kiorpes & Wallman 1995, Rabin et al. 1981). Animal studies also point to a local, defocus-sensitive active emmetropization process, implying that the retina is responsible for both detecting and decoding focusing errors and generating growth-modulating signals to guide compensatory eye growth (for a review, see Wallman & Winawer 2004). Although the latter studies typically involve refractive errors artificially induced with defocusing lenses, the same mechanism(s) likely underlie normal emmetropization. Related studies have also provided important insights into the probable environmental factors underlying the development and progression of human myopia (discussed below).

Prevalence of Refractive Errors: Effects of Age and Ethnicity

A recent meta-analysis by Hashemi et al. (2018) estimated global and regional prevalence figures for the three main categories of refractive errors. For children across regions defined by the World Health Organization, the estimated pooled prevalence of astigmatism (>0.50

D) was higher than that of hyperopia (≥+2.0 D) and myopia (≤−0.50 D); mean percentages with 95% confidence interval were 14.9% (12.7–17.1), 4.6% (3.9–5.2), and 11.7% (10.5–13.0), respectively. It was also comparatively higher in adults: 40.4% (34.3–46.6), 30.9% (26.2–35.6), and 26.5% (23.4–29.6), respectively. However, this study also found the prevalence of refractive errors varied greatly between countries, suggesting genetic and/or environmental influences on their development. Notably, prevalence estimates for myopia have been trending upward, climbing from 10.4% in 1993 to 34.2% in 2016 (Hashemi et al. 2018). However, this meta-analysis is limited by the fact that some included studies did not perform refraction measurements under cycloplegia.

As noted above, hyperopia tends to decrease with age, rapidly during infancy then more slowly, as seen in school-aged children. Whether partially or fully correcting hyperopic refractive errors impedes the emmetropization process remains the subject of debate. Specifically, Atkinson et al. (2000) followed for 36 months infants who were either partially corrected with spectacles or not corrected for their hyperopia and found no effect of partial correction on emmetropization. Nonetheless, infants who more consistently wore their spectacles and thus experienced less defocus (which drives active emmetropization) were more hyperopic at 36 months of age. The prevalence of clinically significant hyperopia increases again in the aging population, reflecting the diminishing ability to compensate for such errors via accommodation, which undergoes age-related decline (presbyopia).

Unlike the natural history of hyperopia and astigmatism, myopia may first appear around 6–8 years of age. Myopes typically exhibit early, fast progression, followed by slowing and eventual stabilization of their refractive error in late adolescence, e.g., 15–21 years of age (Hyman 2013). However, there is significant variability between individuals and ethnic groups in the age of onset of myopia and its subsequent evolution. Thus, several reports described myopia development and/or progression in young adults following a period of stabilization, typically in university students, suggesting that eyes remain susceptible to environmental influences, even when encountered later in life (Gilmartin 1998, Kinge et al. 2000, Wildsoet 1998). Other reports, mostly from East Asian countries, described myopia developing in preschool years (Fan et al. 2004a).

The prevalence of myopia worldwide has rapidly increased, and it is now projected to affect more than 50% of the world's population by 2050 (Holden et al. 2016). One US-based study reported the prevalence of myopia increased in both men and women by 66.4% between 1971 and 2004 (Vitale et al. 2009), and another study involving a large, ethnically diverse population of school-aged children reported average prevalence rates ranging from 4.4% to 18.5%, depending on ethnicity (Asians had the highest rates) (Kleinstein et al. 2003). Prevalence rates have risen even more dramatically in East Asia, according to the results of several large-scale population-based studies. In a recent meta-analysis of 50 population-based studies across Asia, Pan et al. (2012) reported a pooled prevalence of 47% in those aged 20–29 years compared with only 26% in those aged 50–59 years. Within the rural China cohort of their large-scale study involving 5–15-year-old children, Zhao et al. (2000) found myopia was largely absent in 5-year-olds, but present in 36.7% of males and 55% of females by 15 years of age. These trends mirror those of a US-based multiethnic pediatric eye disease study of much younger children (6–72 months): Wen et al. (2013)

found that Asian children had both a slightly higher prevalence of myopia and lower severity of hyperopia compared with non-Hispanic white children. Interestingly, the prevalence of myopia in Scandinavian countries has remained low. Hagen et al. (2018) reported myopia in only 13% of Norwegian adolescents, aged 16–19 years.

Compared with older children and adults, infants are typically born with relatively steep (more curved) corneas and relatively high astigmatism, generally against-the-rule. Astigmatism then decreases until approximately 18 years of age, rapidly in earlier years, and with-the-rule astigmatism is the more typical pattern (Mutti et al. 2005, Read et al. 2007). However, after the age of 40 years, a trend toward against-the-rule astigmatism reemerges, corresponding to a relative steepening of the horizontal corneal meridian (for a more in-depth review, see Read et al. 2007).

Numerous studies have documented ethnic-related differences in the prevalence and magnitude of astigmatism in children, noting the prevalence of high astigmatism is greater in Native American (Dobson et al. 2007, Goss 1989, Mohindra & Nagaraj 1977), East Asian (Fan et al. 2004b), and Hispanic (Kleinstein et al. 2003, Thorn et al. 2005) populations. After adjusting for age and gender, Wen et al. (2013) showed similar trends in the prevalence of high astigmatism (>1.5 D): Hispanics 6.8%, Asians 8.29%, African-Americans 6.6%, and non-Hispanic whites 6.33%. Genetic factors and/or eyelid pressure may explain the increased prevalence of astigmatism in these populations (Read et al. 2007).

In summary, both age- and ethnic-related differences in the prevalence of different types of refractive errors have been described. Genetic factors may contribute to ethnic differences. However, it is important to recognize the potential role of shared environments, which may also vary with ethnicity (discussed below).

ROLE OF GENES

It is often observed that parents who wear glasses beget children who wear glasses. Apropos, two large population-based, longitudinal studies found that the risk of being myopic was increased, albeit marginally, for children with two versus one or no myopic parents (Jones-Jordan et al. 2010, Lam et al. 2008), and Lam et al. (2008) also reported slightly greater eye growth and associated myopic shift over 1 year in children with two myopic parents versus those with none (mean axial length/spherical equivalent refraction change: 0.37 mm/−0.22 D versus 0.20 mm/−0.02 D). Although such trends have been commonly attributed to genetic influences, other contributing factors are likely involved. Classical twin studies, genome-wide association studies (GWAS), and more recent epigenetic studies are among the various approaches used to investigate the roles of genes in myopia development (and more generally, refractive error). Syndromic myopia has also been the specific focus of attention in a recent investigation into the biological pathways involved in ocular growth regulation (Flitcroft et al. 2018).

Twin Studies

The earliest attempts to identify genes linked to myopia development involved classical twin studies, which assume a 100% match in the genetic profiles of monozygotic twins and an

approximate 50% match for dizygotic twins. The first such study found that the refractive errors of monozygotic twins were more similar than those of dizygotic twins (Jablonksi 1922). However, likely owing to differences in sampling and analytic methods, there is wide variability in the reported rates of heritability of refractive error in twin studies (Dirani et al. 2006), e.g., 30.6% (Tsai et al. 2009), 8–14% (Angi et al. 1993), and 90% (Hammond et al. 2001). Dirani et al. (2006) further noted a need for objective longitudinal measures of eye length to better understand the role of genes in eye growth. It must also be recognized that heritability estimates represent indicators of both environmental and genetic influences on the phenotypic variation in a population rather than on an individual's phenotype (Chen et al. 2016). As a final cautionary note, it is important to consider that classical twin studies assume a 100% match of environmental influences for all twins, potentially leading to an overestimation of heritability (Boomsma et al. 2002).

Genome-Wide Association Studies

Recent advances in genome mapping have allowed for a better understanding of how variations in genetic and refractive error profiles correlate among individuals. Nucleotides represent the DNA building blocks, and GWAS probe the entire genome to identify single-nucleotide polymorphisms and their possible relationship to the refractive error of an individual. Findings from two large GWAS data sets generated by the Consortium for Refractive Error and Myopia (CREAM) and 23andMe have contributed significantly to our understanding of the role of genes in myopia and are briefly summarized below.

Using a sample of 45,771 European participants, the DNA testing company 23andMe identified 22 significant loci associated with myopia, of which 20 were novel (Kiefer et al. 2013). Identified loci of single-nucleotide polymorphisms suggest that a variety of ocular functions may contribute to myopia development; related genes were variously linked to extracellular matrix formation (*LAMA2*), regeneration of 11-*cis*-retinal (*RGR*, *RDH5*), growth and guidance of retinal ganglion cells (*ZIC2*, *SFRP1*), and neuronal signaling or development (*KCNMA1*, *RBFOX1*, *LRRC4C*, *DLG2*, *TJP2*) (Kiefer et al. 2013). However, an important limitation of this study is the reliance on questionnaires in determining the refractive error status of participants. Thus, significant refractive error misclassification may have occurred.

In contrast, CREAM used objective measures of refractive error to classify participants. Analysis of data from 37,382 individuals of European descent and 12,332 of Southeast Asian ancestry (Verhoeven et al. 2013) linked 24 chromosomal loci to the presence of refractive error. Significant overlap between the two cohorts suggested shared genetic determinants for myopia development across these populations. Identified gene loci corresponded to a variety of functions, including neurotransmission (*GRIA4*), ion channels (*KCNQ5*), retinoic acid metabolism (*RDH5*), extracellular matrix remodeling (*LAMA2*, *BMP2*), and eye development (*SIX6*, *PRSS56*).

To date, GWAS have identified approximately 30 distinct susceptibility loci associated with myopia and/or refractive error. The conclusion from these studies and other recent meta-analyses of such data is that overall genetic variations account for less than 12% of variations in refractive error (Fan et al. 2016, Kiefer et al. 2013, Verhoeven et al.

2013, Wojciechowski & Hysi 2013). Interestingly, Flitcroft et al. (2018) recently studied syndromic myopia using the Online Mendelian Inheritance in Man database and identified several novel genes and biological pathways linked to myopia development in addition to those previously linked to myopia in GWAS of non-syndromic myopia.

Epigenetics

Epigenetic influences encompass altered gene expression and thus phenotypes that do not reflect an individual's DNA sequence (genotype). Instead, phenotypes arise from post-translational modifications (e.g., through DNA methylation) (Holliday 2006). Such modifications may be the product of environmental influences on the genome (Jirtle & Skinner 2007). Attention has only recently been paid to the role of epigenetics in the development of myopia, with the hope of shedding new light on myopiagenic risk factors.

As an example of the power of focusing on epigenetics, CREAM investigators recently performed a gene–environment-wide association analysis that considered the role of education (Fan et al. 2016). They found that the effect of education was more strongly associated with the severity of myopia in Asian participants, compared with European participants, and accounted for approximately −0.60 D more myopia in the former group. The gene loci *AREG*, *GABRR1*, and *PDE10A* significantly interacted with education level. To rule out the possibility that education level represented a surrogate for near-work activity, the interacting effects of near work were also analyzed, and only one significant association involving the *PDE10A* gene was identified (Fan et al. 2016). However, the applied indexes of near-work activity in these findings were subjective in nature, a point further discussed below.

Beyond Genetics

Juvenile myopia is the most common form of non-syndromic myopia and is considered a complex eye disorder. It is also very likely multifactorial, involving interacting genetic and environmental influences. As summarized above, although genetic factors appear to play a role in the development of myopia, it seems implausible that they alone can account for the recent dramatic increase in myopia prevalence. The visual environment and human behavior to which myopia is intimately tied likely hold additional clues to its development and/or progression.

ROLE OF VISUAL ENVIRONMENT

The role of the visual environment in myopia development has long been debated, and the list of potential environmental influences studied is long. Nonetheless, our understanding of the environmental factors influencing ocular growth regulation and/or myopia progression remains poor, owing in part to study design challenges (e.g., controlling for confounding factors, sampling methods, etc.). A recent review of several worldwide population-based epidemiological studies identified limited outdoor activity and increased amounts of near work as key environmental risk factors for myopia, yet it is not known whether these risk factors vary in their relative importance in different regions of the world (Ramamurthy et al. 2015). Reports of slower myopia progression during the summer months, when children

are presumably doing less near work and more outdoor activity, offer indirect support for these myopia risk factors (Cui et al. 2013, Fujiwara et al. 2012, Gwiazda et al. 2014). The following sections examine the evidence for and nature of environmental influences on human myopia development and progression, with emphasis on the factors most extensively studied.

Education and Intelligence Quotients

The first suggestion that something connected with education may be a risk factor for myopia development came from the classical epidemiological study of Alaskan Eskimo families by Young et al. (1969). They examined correlations between the refractive errors of parents and siblings in 41 family units (197 participants) and found the correlation among siblings was highest, thus suggesting environmental influences. Moreover, despite virtually no myopia in parents or grandparents, the prevalence of myopia in children was approximately 50%. The authors speculated that the advent of formal (classroom) education and/or recent dietary changes for the population might be to blame. Anecdotal evidence has also long suggested a link between education level/attainment and the development of myopia, and Mirshahi et al. (2014) recently confirmed this association.

As noted above, a recent gene–environment meta-analysis including cohorts of Asian and European ancestry indicates a connection between epigenetic influences and education (Fan et al. 2016). The effect of education level was greatest for East Asian individuals, especially for Singaporean Chinese (β coefficient = 1.09), compared with those of European descent (β coefficient = 0.49). However, the clinical significance of this difference is questionable, owing to substantial variability in the data. Yet, genes had a larger influence on Asian participants with higher levels of education versus those with lower levels of education, suggesting epigenetic influences. No significant interactions between single-nucleotide polymorphisms and education were identified for European participants.

Cohn (1883) first linked higher intelligence, as defined by intelligence quotient (IQ), to myopia, but contemporary studies have reported conflicting results. In the longitudinal Twin Early Development Study, IQ alone explained only 1.5% of refractive error variance, despite an apparent shared genetic risk for IQ and myopia (Williams et al. 2017). This result contrasts with those from the earlier Avon Longitudinal Study of Parents and Children, where the odds of being myopic (defined as −1.50 D or worse, noncycloplegic autorefraction) for 7–10-year-old children were significantly increased in those with higher verbal or performance IQ scores (Williams et al. 2008). Challenges in teasing apart possible confounding environmental influences in these studies make it difficult to draw conclusions from them.

Near Work and Myopia

The apparent link between education level and myopia may reflect a confounding influence of the increased near work associated with educational activities. In addition, reduced near work (possibly combined with an increase in outdoor activity) may contribute to the apparent slowing in myopia progression observed during the nonschool summer months (Fujiwara et al. 2012, Gwiazda et al. 2014, Tan et al. 2000). Numerous contributing

myopiagenic factors are likely associated with reading and other near-work activities. The amount of near work, accuracy of accommodation (a source of focusing errors), habitual working distance, and gaze behavior could each contribute to the risk for myopia development, as discussed further below. Although more attention has recently been paid to the role(s) of these factors, identifying one key causative risk factor related to near work has not yet been possible, likely reflecting the traditional use of artificial (lab-based) testing conditions and simple qualitative metrics in related studies.

To provide a modern context, we must recognize that the near work performed by children has evolved dramatically to include device use, head-mounted displays, and virtual/augmented reality. A recent 2017 survey of parents by the nonprofit Common Sense Media group (https://www.commonsensemedia.org) found that 49% of children 8 years and younger often or sometimes used a device in the hour before bedtime and were exposed to screen media for more than 2 h per day. Infants under 2 years of age also had significant daily exposure of approximately 42 min to screen media, an increase from 5 min per day noted in a 2011 survey. Regardless of whether increased device use is partly to blame for the current myopia epidemic, the approach to studying the relation between near work and myopia must evolve because children are not performing the same types of near work today as they did even a decade ago.

Potential Near Work Risk Factors

In general, the roles in myopia development of the amount versus nature of near work undertaken by a child remain unclear. Challenges in deciphering results from relevant studies include defining near work (e.g., reading, computer work, studying, etc.) and the metric used to quantify amount (e.g., time, number of books typically read), both of which vary across studies. Further complicating the literature, some studies used hybrid metrics such as diopter–hours, which take into account both working distance and time, whereas others included gaze breaks (between periods of continuous fixation) as another possible risk factor.

Because near work is one of the earliest environmental influences studied in relation to myopia, the body of literature is extensive but also challenging to navigate. To that end, Ramamurthy et al. (2015) summarized results from six key population-based epidemiological studies, all but one of which reported an association between increased amounts of near work and myopia. Including results from 11 studies, Huang et al. (2015) also found that increased hours of near work was associated with myopia, albeit to a small, non–clinically significant degree (summary odds ratio: 1.14). In addition, a separate analysis of three studies using the diopter–hours metric of near work found no significant effect of increased near work on future myopia development (Huang et al. 2015). Finally, Huang et al. (2015) found no clinically meaningful differences between myopes and nonmyopes in the time (mean hours) spent in various near-work activities (reading, watching TV, studying, playing computer/video games) when compared across all studies (mean differences approximately 30 min or fewer).

Increased accommodative lag, or underaccommodation (for near targets), may explain the apparent risk that near work conveys. With accommodative lags, the retina experiences

hyperopic defocus, which triggers increased (myopic) eye elongation in several animal species when imposed on normal eyes with defocusing lenses (reviewed in Wallman & Winawer 2004). However, some studies involving children have reported increased accommodative lags either prior to (Drobe & de Saint-André 1995, Goss 1991, Gwiazda et al. 2005) or after (Mutti et al. 2006, Nakatsuka et al. 2005) the onset of myopia. Three large clinical myopia trials (Berntsen et al. 2011, Gwiazda 2011, Koomson et al. 2016) and another longitudinal study (Weizhong et al. 2008) also failed to find any consistent relationship between lags of accommodation and myopia progression. Although methodological inconsistencies across studies (e.g., testing with habitual versus full spectacle correction) and the non-natural testing conditions used to evaluate accommodative responses (e.g., nonhabitual working distance, nonsustained task) may have contributed to the inconsistencies in study outcomes, no conclusion can be made at this time regarding the role of increased accommodative lags as a myopia risk factor.

These inconsistencies may also reflect, at least in part, the common practice of considering accommodation function separately from the vergence system. However, at least two indirect pieces of evidence indicate that these systems are intimately linked: (*a*) Progressive addition lenses used as myopia control treatments appear to be more effective in children with large lags of accommodation and near esophoria (Gwiazda 2011), and (*b*) near addition lenses with base-in prism incorporated to reduce both accommodative and vergence demands appear to be more effective than near addition lenses alone in controlling myopia progression in children with low accommodative lags (<1.01 D) (Cheng et al. 2014).

Potentially tied to increased accommodative lags, closer near working distances may be another risk factor for myopia development and progression Two studies reported an association between near working distances (<30 cm) and myopia presence/severity (Hartwig et al. 2011, Ip et al. 2008), and Gwiazda (2011) found that progressive addition lens treatments for myopia control were more effective, albeit to a small degree, in children with habitual near working distances of less than 30 cm. These results are also consistent with the findings of Zylbermann et al. (1993) showing that males in Israeli religious schools who were required to spend significant time reading while rocking back and forth in relation to the text (davening) were at greater risk of myopia compared with females in religious schools or those attending secular schools.

Per the clinical picture, a myopic child is an avid reader who never takes gaze breaks. This anecdotal evidence may have some truth, as children engaged in extended periods of near work develop myopia earlier and show more rapid myopia progression (Gwiazda et al. 2004). Providing more direct evidence implicating gaze behavior, Harb et al. (2006) found that myopic adults took significantly fewer fixation breaks during sustained near tasks compared with nonmyopic individuals. Because spending more time fixating at closer near working distances (where accommodative lags may be greater) exacerbates myopia, the retinal defocus pattern experienced when viewing far objects during gaze breaks, even if only for brief periods, may contribute to the protective effect of gaze breaks (see discussion below) (Wallman & Winawer 2004). Gaze behavior has rarely been monitored in past studies investigating near work and myopia, but collecting such data in future studies may

offer additional insights into individual differences in susceptibility to myopia development and/or progression.

Visual Environment, Retinal Defocus Patterns, and Eye Growth

As noted in the above discussion of emmetropization, decades of animal studies show that eye growth regulation is a local (ocular), visually mediated process (for a review, see Smith et al. 2014). The local nature of this process is best evidenced by the fact that an eye isolated from the brain by optic nerve section still responds to myopiagenic stimuli (e.g., form depriving diffusers and negative lenses) and axially elongates (Troilo et al. 1987, Wildsoet 2003, Wildsoet & Pettigrew 1988). Further indirect evidence also shows that local, regionally specific myopia-generating stimuli induce asymmetric ocular growth patterns (Diether & Schaeffel 1997, Smith et al. 2009a). Interestingly, the peripheral retina, which accounts for a large proportion of the overall retinal surface area, supports compensatory eye growth in the absence of a functional fovea in primate eyes (Huang et al. 2011; also reviewed in Wallman & Winawer 2004). Thus, the global retinal experience may be of greater relevance in considering influences on ocular growth. Observations that hyperopic defocus (plane of focus behind the retina) triggers a grow signal and myopic defocus (plane of focus in front of the retina) triggers a stop signal (discussed above) have provided the foundation for optical myopia control treatments targeting the peripheral retina, such as orthokeratology lenses and multifocal contact lenses (for a review, see Walline 2016).

Models included in a review by Flitcroft (2012) provide insights into differences in the defocus profiles and thus myopiagenic properties of indoor and outdoor environments (Figure 3). Hyperopic retinal defocus is more frequently encountered indoors than outdoors because objects nearer than the fixation distance are more likely encountered indoors. Therefore, more crowded indoor environments may also be more myopiagenic. However, given current technology, it is theoretically possible to create an indoor visual environment that surrounds and reduces or eliminates hyperopic defocus on the peripheral retina of an individual, thereby reducing the risk of myopia development and/or progression.

Outdoor Activity and Myopia Protection

The finding from the Sydney Myopia Study that children reporting low levels of outdoor activities combined with high levels of near work had the highest odds of being myopic (Rose et al. 2008) has drawn sustained attention worldwide to the possible protective effect of outdoor activity on the development and/or progression of myopia. Since this study, multiple studies have investigated the possible protective effect of increased time spent outdoors. However, differences in design, including the lack of consistency across relevant studies in how outdoor exposure is quantified, make comparisons across studies difficult and interpretation of collected data challenging. In fact, a recent systematic review of the methods used to measure time outdoors in myopia research involving children concluded that more integrated and objective methods are needed (Wang et al. 2018). For example, many studies have relied on either or both self and parental reports to estimate time spent outdoors. There are also inter-study differences in the criteria used to classify outdoor exposure. For example, in some but not all studies, outdoor sporting activities and time spent outdoors have been grouped together (Dirani et al. 2009), and leisure outdoor activities and

sporting activities have been separated into distinct categories (Jones et al. 2007). Weekend and weekday activities have also been distinguished in only some studies (Guggenheim et al. 2014).

Sherwin et al. (2012) provided one of the first relevant meta-analyses undertaken on seven cross-sectional pediatric studies (six involving school-aged and one involving 6–72-month-old children) and reported a protective effect of increased time outdoors, equal to approximately 2% decreased odds of having myopia for a weekly increase in outdoor exposure of 1 h. Their review of five prospective cohort studies (with >1 year of follow-up) also found myopes to engage in significantly less outdoor activity compared with nonmyopes (7.68 versus 11.65 h/week, respectively) and a 9% reduction in the odds of developing myopia (for the nonmyopic cohort) for every additional hour of outdoor activity per week. The US-based Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error Study was published around the same time and also found reduced time outdoors to be associated with the future development of myopia (Jones-Jordan et al. 2011).

Xiong et al. (2017) found similar trends in their meta-analysis of cohort studies investigating the role of outdoor activity in myopia development. In addition, they showed the protective effect of outdoors was more robust in younger compared with older children (aged 6 years versus 11–12 years). Two recently published longitudinal cohort studies involving school-aged children (Guo et al. 2017, Shah et al. 2017) reported an approximate 10% reduction in the hazard ratio of myopia (as measured by noncycloplegic autorefraction) for each hour of increased outdoor activity per day. Guo et al. (2017) also noted increased time outdoors was associated with reduced axial elongation over a 4-year follow-up period.

Recent Randomized Control Trials of Outdoor Exposure

To date, four randomized control trials, all in East Asia (two in China, two in Taiwan) where the myopia problem is most severe, have been completed. All studies targeted children aged 6–14 years (at baseline) along with a similar cluster-randomization design at the school level (He et al. 2015; Jin et al. 2015; Wu et al. 2013, 2018) and all used similar interventions, i.e., increased daily time outdoors by 40–80 min. However, their dosing strategies differed: He et al. (2015) administered time outdoors as one interval, but Jin et al. (2015) and Wu et al. (2013) distributed time outdoors across multiple intervals. Yet all the trials found similar effects (Figure 4); increased time outdoors reduced the overall incidence of myopia by approximately 5–10% but had little to no effect on myopia progression (or axial elongation) in already myopic children (at baseline). In their meta-analysis of these and other related studies, Xiong et al. (2017) likewise found no dose–response relationship between time outdoors and myopic progression in already myopic children.

To investigate further the protective effect of outdoors observed in the Taiwan-based study, Wu et al. (2018) initiated a follow-up randomized control trial in which participants wore a light sensor device around their necks during the school day. The authors accounted for approximately 20% of the cohort in their earlier study (Wu et al. 2013), and by excluding children receiving myopia control treatments, they substantially reduced the number of already-myopic participants (n = 73/693). Nonetheless, a reduction in myopia incidence was again observed, albeit smaller than previously found (3% versus 10%), and the effects on

myopia progression and axial elongation over the 1-year study period were also small in those children who were already myopic at baseline (0.23 D and 0.15 mm less, relatively). Interestingly, there were no significant differences between the treatment and control groups in their light exposure patterns (minutes of exposure to various light levels) by the end of the study. Yet, results may have been confounded because both groups recorded increases in bright light exposure over the study period, which offers indirect evidence for the effectiveness of a concurrent public health initiative aimed at increasing time outdoors for children.

Possible Outdoor Protective Factors and Mechanisms

The aspect(s) responsible for the observed protective effect of outdoor exposure against myopia remain to be determined. Potential contributing factors can be separated into lighting characteristics, activities, and visual experience. Whereas the first two have received significant attention as of more recently, outdoor visual experience has received little attention, despite suggestions from experimental animal studies that it may be important (Hess et al. 2006, Smith et al. 2014).

Yet, neither the nature nor the amount of physical activity appears to be critical to the protective effect of outdoors (Guggenheim et al. 2012, Read et al. 2014, Suhr Thykjær et al. 2017). Although disentangling physical from other outdoor activities in their pediatric longitudinal study is challenging, Jones-Jordan et al. (2011) reported an association between lower levels of outdoor/sports activities and an increased risk of developing myopia in children.

High light intensity may explain the protective effect of outdoors versus indoors. Studies have reported that monkeys (Smith et al. 2012) and chickens (Ashby et al. 2009, Stone et al. 2016) reared in bright light are afforded protection against form-deprivation myopia. However, in both cases, the same conditions offered significantly less protection against lens-induced myopia (Ashby & Schaeffel 2010, Smith et al. 2013). Zheng et al. (2018) also reported additive inhibitory effects of myopic defocus and bright light on eye growth in chickens. For protection against form-deprivation myopia in chickens, dosing characteristics (frequency of delivery and brightness) may be important. Very short, frequent periods of bright light may offer better protection than does continuous exposure (Lan et al. 2014), and the inhibitory effect may increase in parallel with intensity up to 10 klux (Zheng et al. 2018). However, methodological differences across studies, including in the brightness and spectral composition of lighting used, make it difficult to draw definitive conclusions from these animal studies.

The advent of commercially available light-sensing wearable technologies has also motivated more myopia-related studies, mostly involving children, aimed at objectively measuring light exposure (Cui et al. 2013, Ostrin et al. 2018, Read et al. 2015, Verkicharla et al. 2017). The general finding of these studies is that increased exposure to higher light levels outdoors has little to no effect on myopia progression and/or axial elongation (e.g., the latter decreased 0.07 mm or less over 6 months to 1 year) (Cui et al. 2013, Ostrin et al. 2018, Read et al. 2015).

The spectral composition of lighting also differs between indoor and outdoor environments, and outdoor conditions vary both seasonally and with time of day (Thorne et al. 2009). Interest in the potential influence of such differences stems in part from the recognition that the eye is subject to chromatic aberration, as different light wavelengths focus at different positions relative to the retinal plane (red behind blue). Because longitudinal chromatic aberration provides a defocus cue for accommodation (Kruger et al. 1995), it may also serve a similar role for emmetropization, albeit with a slower time constant.

Although animal studies have explored the influence of lighting wavelength on eye growth, their direct relevance to the outdoor protective effect is questionable because all have used unnatural monochromatic rearing conditions that children are unlikely to encounter. There is also little consistency in the responses to monochromatic rearing conditions across species. In brief, rearing animals in diurnal red (long wavelengths) and blue (short wavelength) lighting induces myopia and hyperopia, respectively, in chicks (Foulds et al. 2013) and guinea pigs (Liu et al. 2011, Qian et al. 2013). By contrast, red lighting induced hyperopia in both tree shrews and monkeys (Gawne et al. 2017, 2018; Hung et al. 2018; Smith et al. 2015). Regardless of the direction of eye growth, rearing an animal in narrow-band lighting disrupts emmetropization, suggesting the retina may use chromatic aberration to decode defocused images.

Increased retinal dopamine release and/or circulating vitamin D levels may also be involved in the protective effect of outdoors, where higher light intensities are experienced. First implicating dopamine in eye growth regulation, Stone et al. (1989) reported retinal dopamine levels and biosynthesis were reduced in form-deprived myopic chickens. Since then, several related reviews have considered whether this key retinal neurotransmitter functions as a signal molecule to regulate eye growth (see Feldkaemper & Schaeffel 2013, Norton & Siegwart 2013, Wallman & Winawer 2004, Zhou et al. 2017). Light-induced inhibition of form-deprivation myopia in chickens has also been linked to a partial rescue of the decreased dopamine release seen with form deprivation alone (Lan et al. 2016).

However, there are inconsistencies in the findings linking dopamine to protective effects. In a recent study, guinea pigs exposed to flickering lighting showed myopic changes, despite increased retinal dopamine release (Luo et al. 2017). Some chicken studies also showed that lens- and form-deprivation-induced myopia involve different retinal signal pathways (Dong et al. 2011, Nickla & Totonelly 2011). However, our understanding of the relation between myopia and retinal dopamine remains incomplete. For example, it is well known that many ocular parameters, including eye length, undergo diurnal variations, for which myopia-related changes have also been reported (for a review, see Chakraborty et al. 2018). Retinal dopamine may play a role in this process, as it does in entraining the intrinsic retinal rhythm to the light-dark cycle, where dopamine levels are typically higher during the day (opposite to the pattern for melatonin). Activated by elevated light levels, intrinsically photosensitive retinal ganglion cells may provide inputs to this dopaminergic pathway (for reviews, see Norton & Siegwart 2013, Zhou et al. 2017). Given the rapid advances in ocular imaging technology, it may become possible in the near future to evaluate retinal dopamine turnover in vivo and thus gain important insights into the role of retinal dopamine in the protective effect of outdoors against myopia in humans.

In a case series of myopic children, Laval (1938) first investigated the effect of vitamin D on eye growth and the impact of its deficiency on myopia (for a review, see Pan et al. (2017). The negative result reported therein is consistent with many but not all recent findings. For example, three large cohort studies report diverging conclusions with respect to a low level of circulating vitamin D being a risk factor for the development of myopia (Choi et al. 2014, Guggenheim et al. 2014, Tideman et al. 2016). No association between vitamin D serum levels and myopia presence or magnitude was found in a recent analysis of the US National Health and Nutrition Evaluation Survey data (Harb & Wildsoet 2016). Two small cross-sectional studies by Mutti & Marks (2011) and Mutti et al. (2007) also found no correlation in Caucasian subjects, but there were polymorphisms in the vitamin D receptors of participating low to moderate myopes. In the only animal study of direct relevance, vitamin D_3 supplementation did not inhibit experimentally induced myopia in tree shrews that were not initially vitamin D deficient (Siegwart et al. 2011). Making inter-study comparison difficult, the many possible confounders, including the use of sunscreen, latitude of residence, and race/ethnicity, as well as interstudy differences in how such factors are adjusted for, must be considered in human studies.

Less Commonly Considered Environmental Influences

Parental smoking, in particular maternal smoking during pregnancy, has been linked with a reduced prevalence of myopia and shorter axial length in offspring compared with children of non-smoking mothers. Specifically, three large population-based studies (based in the United States, Egypt, and Singapore) reported a similar significant association between parental smoking and hyperopia (Borchert et al. 2011, El-Shazly 2012, Iyer et al. 2012), whereas a UK-based study reported an association between parental smoking and high myopia (Rahi et al. 2011). However, a recent review by Ramamurthy et al. (2015) raised concern about a general lack of control for confounding factors such as parental education, income, socioeconomic status, myopia status, and birth weight across all these studies.

Maternal age (greater than 35 years) has been linked with increased odds of having myopic offspring. However, relevant studies are limited in number and results inconsistent: Some found a small increase in the odds of myopia (<1.10) (Rahi et al. 2011, Rudnicka et al. 2008), whereas others found no association (Borchert et al. 2011). Older mothers, as well as those who smoke, also tend to have babies of lower birth weight (Dennis & Mollborn 2013), which has been linked with an increased prevalence of myopia (Rahi et al. 2011).

Birth order has been suggested as another myopia risk factor. Guggenheim et al. (2013) reported a small but variable increase in myopia prevalence in first-born versus other children. However, the above four large epidemiological studies in their meta-analyses were not designed to investigate explicitly the role of birth order, and they used noncycloplegic methods to measure refractive errors, which may have led to misclassification of myopia. Thus, no well-defined hypothesis is available, and several confounders that typically present in first-born children (e.g., low birth weight, insulin resistance secondary to increased postnatal growth, higher education attainment) could be responsible for the small effect of birth order (Ramamurthy et al. 2015).

The season of birth may also affect myopia prevalence. It has been used as a marker for perinatal light exposure patterns to consider whether diurnal light–dark cycles, which influence the retinal melatonin–dopamine balance, may impact emmetropization (see Chakraborty et al. 2018). Mandel et al. (2008) and McMahon et al. (2009) found that summer versus winter birth was associated with a small increase in the odds (<0.24) of having more severe myopia. By contrast, Ma et al. (2014) reported children born in winter versus summer months showed clinically insignificant relative myopia (based on noncycloplegic autorefraction, judged against a background of largely hyperopic refractive errors). In interpreting these results, it is also important to consider that more babies are generally born in summer than winter months and the season of birth may have various influential confounders, including parental education.

Interestingly, the season of birth has also been considered as a marker for in utero vitamin D exposure, with important implications for later development. For example, a large UK Biobank study (n = 450,000) found children born in summer months had higher birth weights, started pubertal development later, and were taller as adults (Day et al. 2015). Evidence further links eye length with body height, albeit independent of refractive error (Wang et al. 2011, Zhang et al. 2011). However, because children born during summer months with longer daylight did not show a reduced risk of myopia, vitamin D may not provide a protective effect against myopia development.

More general interest in nutrition stems from an observed increase in myopia prevalence as native populations and countries have adopted more westernized diets. Cordain et al. (2002) proposed diets of high glycemic load as a risk factor for myopia and speculated that the associated hyperinsulinemia could modify scleral growth as an underlying mechanism. Offering at least a partial explanation for the link between diabetes and myopia (e.g., Fledelius 1986, Sjølie & Goldschmidt 1985), researchers found that transient changes in blood glucose levels induce changes in the index of refraction of the crystalline lens (Goldschmidt & Jacobsen 2014; also reviewed in Mäntyjärvi 1988).

Visual Environment and Myopia: Unanswered Questions

A significant deficiency in studies attempting to quantify the habitual visual environment of individuals has been the reliance on subjective reports, whose inaccuracy is well recognized (Alvarez & Wildsoet 2013, Chan et al. 2016, Ostrin et al. 2018). The ability of subjective reports to capture potentially critical details such as spatial and temporal exposure patterns (dosing), which have been influential in animal studies, is also limited (Backhouse et al. 2013, Lan et al. 2014, Nickla & Totonelly 2016, Nickla et al. 2017). Such deficiencies may explain why no consistent risk factors for myopia development and protection from it have emerged and further suggest that key aspects of indoor and/or outdoor environmental experiences have been missed.

Only with rare exceptions have wearable technologies been used to capture outdoor and indoor activities in adults (Harb et al. 2016) or children (Ostrin et al. 2018, Read et al. 2014). Such technologies may yield objective results and large dynamic data sets not possible with questionnaires. However, they have not been fully exploited in pediatric studies to investigate, for example, the dynamics of exposure to indoor and outdoor environments

(e.g., timing and intervals across the day rather than cumulative daily metrics) that may be important to ocular growth given previous animal research, as reviewed by Chakraborty et al. (2018) and Phillips et al. (2012).

Studies of the differences between indoor and outdoor visual environments to explain why outdoor activities are protective against myopia development have also received relatively little attention. For example, the spatial frequency and contrast content of visual stimuli as well as retinal defocus patterns are important in basic research [e.g., spatial frequency content (Hess et al. 2006) and peripheral defocus (Smith et al. 2009b)], but relevant studies have not collected corresponding data for habitual indoor and outdoor environments. Furthermore, whereas researchers have attempted to model the retinal defocus patterns of representative indoor and outdoor scenes (see Figure 3) (Charman 2011, Flitcroft 2012), the habitual visual indoor and outdoor environments of children have not been characterized nor their experiences quantified as predictors of future development of myopia. Because most individuals spend more time indoors than outdoors, dioptric variation is much greater in indoor versus outdoor settings, and reliance on electronic gadgets has increased largely in parallel with myopia prevalence, future research may benefit from focusing on indoor environments, at least initially.

CONCLUSION

In summary, uncorrected refractive errors are a leading cause of visual impairment around the world, and myopia is rapidly increasing in prevalence, especially in East Asia. Although genetic factors influence refractive errors, they alone cannot account for the rapidly changing prevalence statistics. This review has focused mainly on environmental factors pertaining to myopia, providing hints that certain features of indoor and outdoor behaviors are important for its development and/or progression (Figure 5). Slow progress toward a comprehensive understanding of the factors underlying eye growth regulation and thus refractive development and myopia in humans can be at least partly attributed to the reliance on insensitive subjective tools in related research. Advances in technology may change this picture, as future deployment of suitable tools and analytics to capture objective data on childhood indoor and outdoor behaviors may improve our understanding of the factors underlying the development of myopia.

The rapid increase in the prevalence of myopia is driving a paradigm shift in its clinical management. Eye care providers have increased their efforts beyond simply managing myopia in children to institute treatments aimed at slowing eye growth and, thus, myopia progression. The appearance of myopia control clinics offering optical (e.g., multifocal and orthokeratology contact lenses, bifocal spectacles) and pharmacological (e.g., atropine, including low-dose options) treatment options is further evidence of this shift (for comprehensive reviews, see Huang et al. 2016, Saw et al. 2002, Walline 2016, Walline et al. 2011). Currently, none of these treatment options provide total control of myopia progression. By improving our understanding of the environmental risk factors driving myopia development, such treatments may be further optimized to provide the basis for evidence-based, customized clinical management of myopia in which digital monitoring devices and behavioral modifications play integral roles.

Glossary

Myopia
nearsightedness arising when the axial length of the eye is too long for its optical power, creating blurred vision especially at far distance

Emmetropia
a perfect optical system, devoid of any refractive error

Hyperopia
farsightedness resulting from the axial length of the eye being too short for its optical power, creating blurred vision especially at near distance

Astigmatism
refractive error most typically caused by a non-spherical corneal surface, creating distorted vision at both far and near distances

Genome-wide association studies (GWAS)
seek to uncover variations in the human genome in the form of single-nucleotide polymorphisms as a possible explanation for diseases

Heritability
proportion of total variation between individuals in a given population that is due to genetic variation

Single-nucleotide polymorphisms
variations in a DNA building block (nucleotide); the most common form of genetic variation in humans

Epigenetics
study of phenotypic changes in an individual caused by modification of gene expression, possibly due to environmental influences, rather than genetic code alterations

Accommodative lag
underaccommodation for a given near target such that images are focused behind the plane of the retina (hyperopic defocus)

Hyperopic defocus
optical defocus where the theoretical image plane lies behind the retinal plane

Myopic defocus
optical defocus where the theoretical image plane lies in front of the retinal plane

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SUMMARY POINTS

1. The World Health Organization ranks uncorrected refractive errors as one of the leading causes of vision impairment worldwide, affecting 44% of people globally.
2. Myopia, or nearsightedness, which is mostly a product of excessive eye elongation, is seeing a rapid rise in prevalence worldwide, with 50% of the world's population predicted to be myopic by 2050.
3. Refractive errors, including hyperopia (farsightedness), are a common finding in the very young, but their persistence or reappearance in childhood or adolescence indicate a failure of emmetropization.
4. Emmetropization describes the developmental processes by which mismatches between the eye's optical power and its length are eliminated to achieve emmetropia; visual experience is now acknowledged to play a key role in emmetropization.
5. The rapidly rising prevalence of myopia worldwide requires explanations beyond genetics, with visual environmental influences playing major roles.
6. The advent of wearable technologies offers new capabilities, not possible with subjective questionnaires, to objectively quantify key elements of human behavior and may create new insights into the myopia epidemic.
7. The benefit of increased time outdoors as a myopia protection strategy has been confirmed in school-based randomized clinical trials in Asia, although underlying mechanisms remain unresolved.
8. The implications for myopia development of society's increasing dependence on electronic devices and time spent on them indoors remain to be addressed.

FUTURE ISSUES

1. Further exploration into the nature and dynamics of human indoor and outdoor behavior may offer new insights into modifiable behaviors that can be prescribed to reduce the incidence and progression of myopia.

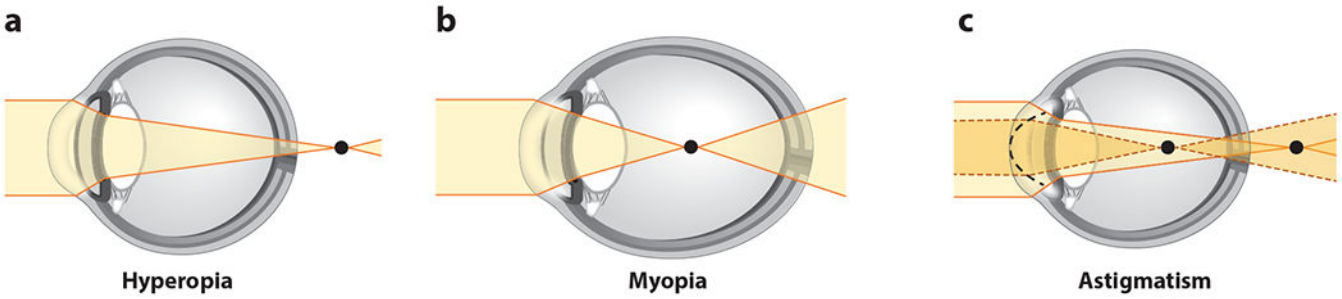

Figure 1.

Schematic diagram of refractive errors. (*a*) Hyperopia (farsightedness) results when the eye's optical focal plane lies beyond the retina; it is typically a product of a shorter than normal eye, rendering the eye relatively underpowered in an optical context. (*b*) Myopia (nearsightedness) results when the eye's optical focal plane lies in front of the retina; it is typically a product of a longer than normal eye, rendering the eye relatively overpowered. (*c*) Regular astigmatism generally results when one or more optical elements of the eye (most commonly, the cornea) have different curvatures (shapes) along different directions or meridians, one of which is steeper than the other (e.g., dashed versus solid corneal contours), thus giving rise to two focal planes instead of one, as in an eye without astigmatism. Hyperopic and myopic (as well as emmetropic) eyes may exhibit astigmatism.

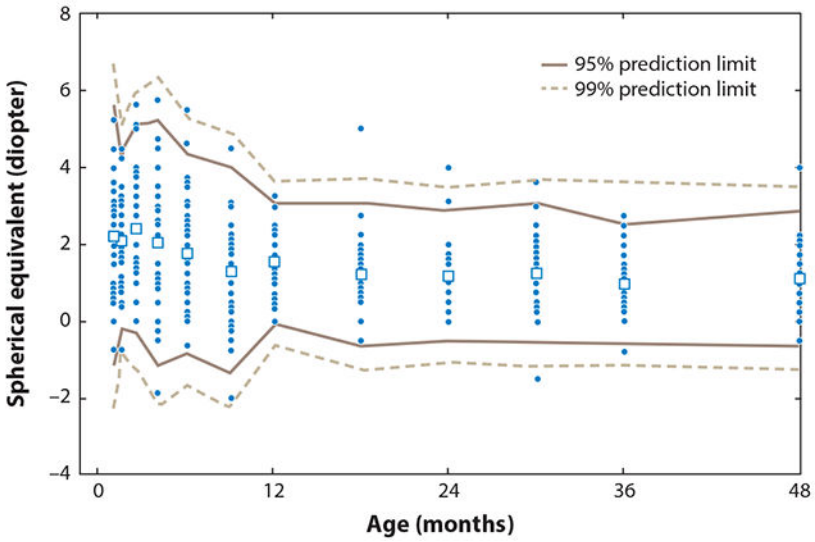

Figure 2.

Cycloplegic refractive error cross-sectional data for children aged 1–48 months. Spherical equivalent errors represent the average of the two meridians for eyes with astigmatism. Although young infants exhibit, on average, low (+2.0 D) hyperopia, the distribution of refractive errors is wide. Through emmetropization, the distribution narrows, and average error moves toward emmetropia (0 D) with increasing age over the first 2 years of life. Figure adapted with permission from Mayer et al. (2001).

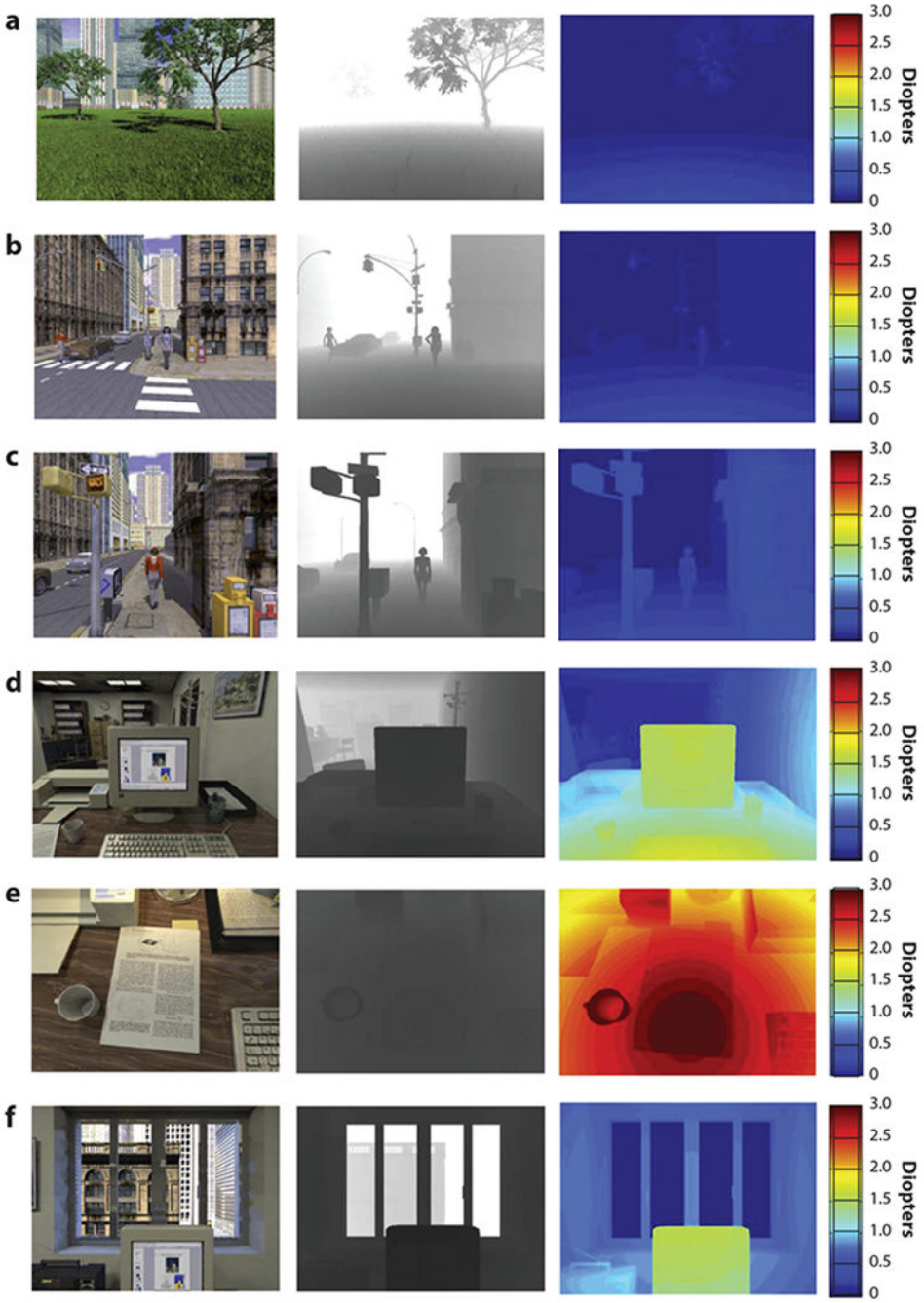

Figure 3.

Dioptric variation in indoor and outdoor visual scenes. (*First column*) Rendered images of (*a–c*) outdoor and (*d–f*) indoor visual scenes; (*second column*) gray-scale depth images of the same scenes, relative to the eye, with brighter intensities representing further distances (in meters); (*third column*) dioptric transformation of the respective scenes where cooler colors represent fewer diopters. In general, compared with outdoor scenes, indoor visual scenes have more dioptric variation, as indicated by the associated dioptric heat maps. Figure adapted with permission from Flitcroft (2012).

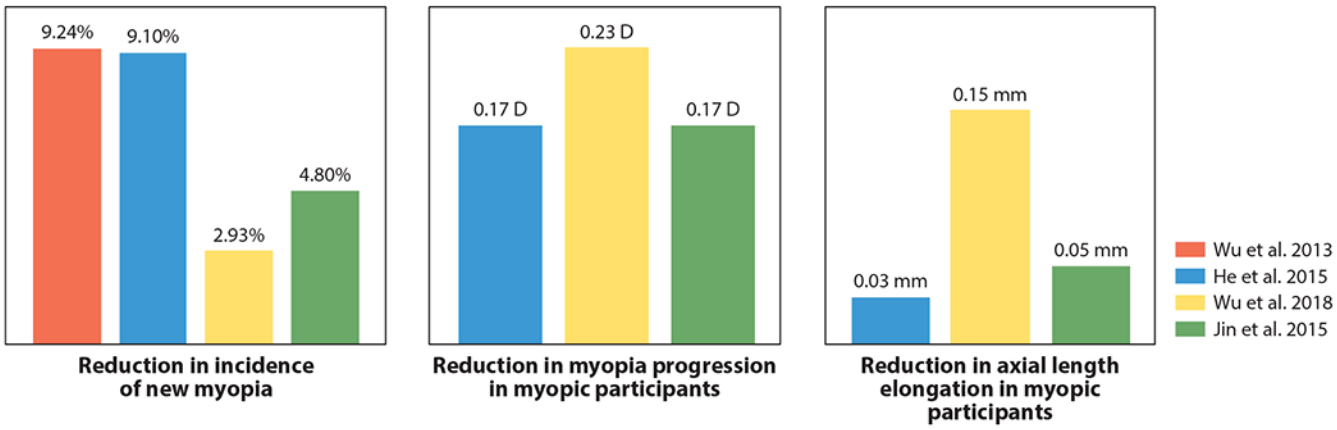

Figure 4.

Summary of results from four randomized control trials investigating the effects of increased outdoor recess time versus a traditional school day (control) as a myopia-controlling intervention in Asian schoolchildren. Bar graphs show effects of interventions expressed as relative change in intervention group compared to control group in response to interventions over 1-year (Jin et al. 2015, Wu et al. 2018) or 3-year trial periods (He et al. 2015).

All studies reported relative reductions in myopia incidence, albeit variable across studies, whereas myopia progression and axial length elongation were minimally controlled (no data reported in Wu et al. 2013).

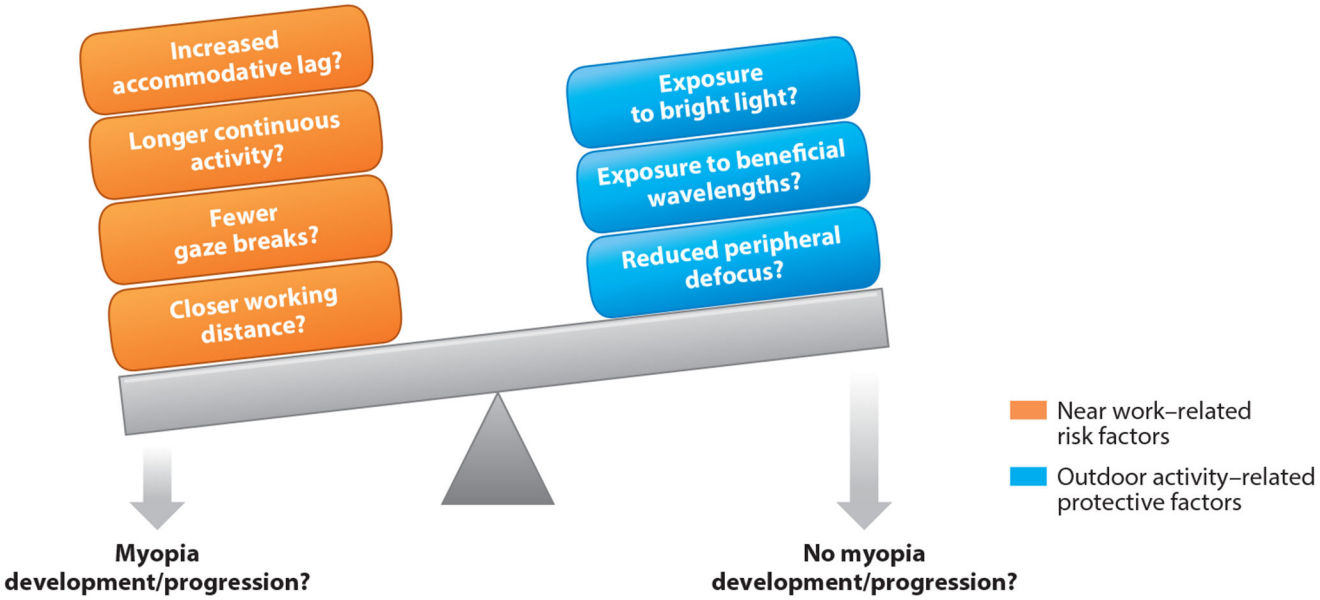

Figure 5.

Possible model of human myopia development, depicting the opposing influences of risk and protective factors related to near work and outdoor activity, respectively, and their impact on myopia development (incident myopia) and/or its progression. Data are based on current evidence from basic (animal model) and human studies, and conjectures are based on indirect evidence, where relevant data are not yet available.