Special Issue

IMI Risk Factors for Myopia

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Risk factor analysis provides an important basis for developing interventions for any condition. In the case of myopia, evidence for a large number of risk factors has been presented, but they have not been systematically tested for confounding. To be useful for designing preventive interventions, risk factor analysis ideally needs to be carried through to demonstration of a causal connection, with a defined mechanism. Statistical analysis is often complicated by covariation of variables, and demonstration of a causal relationship between a factor and myopia using Mendelian randomization or in a randomized clinical trial should be aimed for. When strict analysis of this kind is applied, associations between various measures of educational pressure and myopia are consistently observed. However, associations between more nearwork and more myopia are generally weak and inconsistent, but have been supported by meta-analysis. Associations between time outdoors and less myopia are stronger and more consistently observed, including by meta-analysis. Measurement of nearwork and time outdoors has traditionally been performed with questionnaires, but is increasingly being pursued with wearable objective devices. A causal link between increased years of education and more myopia has been confirmed by Mendelian randomization, whereas the protective effect of increased time outdoors from the development of myopia has been confirmed in randomized clinical trials. Other proposed risk factors need to be tested to see if they modulate these variables. The evidence linking increased screen time to myopia is weak and inconsistent, although limitations on screen time are increasingly under consideration as interventions to control the epidemic of myopia.

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There is now an epidemic of myopia in several countries in East and Southeast Asia,[1–6] In this part of the world, the prevalence of myopia in young adults who have completed 12 to 13 years of schooling is now 70 to 90%, up from 20 to 30% two or three generations ago. In addition, the prevalence of high and potentially pathological myopia in excess of -6D of myopia[7] is of the order of 10 to 20%.[8–11] Some projections suggest that by the year 2050, nearly 50% of the world's population could be myopic, with around 10% highly myopic.[12]

Epidemiologists and geneticists[2,3,13,14] agree that the speed with which the prevalence of myopia has increased in these locations is not compatible with myopia developing purely or predominantly due to genetic determination. But this does not mean that genetic factors play no role, and it has been demonstrated that genetic variation accounts for at least 12% of the variance in mean spherical equivalent refraction (SER) in populations of European ancestry today,[13] and probably 30% or more.[15] The evidence on genetic factors and myopia has been summarized in another paper in the IMI series.[16] Although gene pools change little between generations, changes in both the natural and the social environment can take place much more rapidly. This emphasizes the need to define the environmental exposures responsible for the rapid increases in prevalence of both mild to moderate and high myopia, because modifiable environmental risk factors provide an important basis for the design of preventive interventions.

Risk factors are most commonly identified by associations with the condition or disease in cross-sectional or preferably longitudinal cohort studies on defined populations. In cross-sectional designs, the association is with prevalence of myopia, whereas in longitudinal designs that define the temporal sequence, the association is with incident myopia. Alternatively, associations with axial length or changes in axial length can be studied. However, with "observational" studies of this kind, there is inevitably risk of confounding due to correlations between a measured factor, and other, sometimes unmeasured factors that may mediate the effects. Associations also raise the problem of reverse causation. For example, in relation to myopia, the association between less myopia and more time outdoors could be explained by a protective effect of time outdoors, or by myopic children having a tendency to spend less time outdoors. Even with very careful and thoughtful statistical analysis, it remains impossible to distinguish definitively between simple correlation and causality, although evidence for a plausible causal pathway increases the likelihood that an association is causal, and help to define the direction of causation.

More rarely, the search for risk factors makes use of ecological comparisons, where prevalence and risk factor exposures are compared between different populations. This sort of design is less commonly used because of what is known as the ecological fallacy – the false conclusions that can be drawn from simplistic comparisons between two locations without knowledge about other risk factors operating within the populations. Nevertheless, in combination with other information on risk factors, ecological comparisons can provide powerful insights.

Some fundamental aspects of study design are important for critical assessment of the literature.

- How myopia is measured and defined is clearly very important. The gold standard is cycloplegic refraction,[7,17] but many studies measure noncycloplegic refraction, resulting in overestimation of myopia and misclassification of other refractive categories. When combined with imprecise estimates of risk factors, such as nearwork and time outdoors, these errors can contribute to failure to detect risk factors, although they are less likely to lead to false positive identifications. We have tried to cite data based on cycloplegic refraction, except where no data meets this standard.
- Reduced visual acuity has also been used as a proxy measure of myopia, sometimes in combination with viewing through concave and convex lenses. This approach is particularly problematic for children of preschool and early primary age, because of cognitive limits on performance with eye charts. These less accurate approaches to determination of myopia tend to be used more commonly in large surveys, raising the question of whether smaller but methodologically better surveys would be more useful.
- Some of the limitations of these non-gold standard approaches can be overcome if axial length (AL), or the corneal radius of curvature (CR) are measured. These measures are not affected by lack of cycloplegia, and AL and the AL/CR ratio correlate highly with SER.
- Because age and years of schooling correlate highly with refraction in most studies of refractive development in children, a study design that uses a large homogenous sample of children of a given age or grade, rather than one that uses a similarly large but more heterogenous sample of children, will generally have greater power in detecting other associations.

In the emerging era of precision medicine, it is important to focus on school myopia, because different etiologies will often mean different approaches to prevention and clinical control of progression; the risk factors, preventive approaches, and treatment will differ between the axial myopia that develops in school-age children, and the nonaxial myopia that develops in children with keratoconus, or in association with cataract in the elderly. Even axial myopia is etiologically heterogeneous, consisting of a large number (at least 200–300) of individually rare forms of myopia that are genetically determined by specific mutations, and much less affected by environmental factors. These are estimated to account for myopia in fewer than 1% of any population.[3] In some societies, where the total prevalence of myopia is

low, school myopia affects only a small part of the population, but in East Asia and parts of Southeast Asia at the end of senior high school, around 80% of children may be affected by myopia.[8,10,11,18]

Establishing causality is crucial to translating information about associations into preventive interventions. Identifying a plausible mechanism linking the risk factor to the control of eye growth is important. Whether the risk factors identified are likely to be proximal (i.e. close to the relevant biological pathways that control eye growth, such as exposures to bright light or retinal defocus), or more likely to be distal factors that influence exposure patterns, such as attitudes to children spending time outdoors, after school, on the weekends, or during holidays, is an important consideration. Individual and social beliefs about the importance of education are also important, as are legislative policies that promote early onset of a highly competitive education.

The ultimate "gold standard" test of causality is a randomized clinical trial, but these are often not possible ethically. For example, it would not be ethically acceptable to allow education for some children and not for others on a randomized basis. Fortunately, there are other approaches. Where there is sufficient information on genetic contributions to identified risk factors, the technique of Mendelian randomization can be applied.[19] There is also a range of social "experiments" that provide information about causality. For example, although it would be unethical to give children different levels of education on a random basis, in most societies, variations in exposures of this kind occur "naturally" but without randomization, and can provide insight into causal relationships. Where policy changes that influence access to education are involved, the technique of regression discontinuity analysis[20] can be applied, both qualitatively and quantitatively, to myopia. This approach is particularly powerful when policy changes impose new patterns of behavior on all children.

In this paper, we review the scientific evidence on risk factors, taking account the issues discussed above. We have not considered refraction and biometric parameters as risk factors for myopia, because myopic shifts in refraction, increases in axial length, and decreases in lens power occur as part of the process of the development of an elongated myopic eye. While this makes them potentially very useful as predictors of subsequent myopia,[21] they are unlikely to be independent modifiable risk factors. Instead, we focus on the strength of the evidence for potentially modifiable risk factors, whether the associations are likely to be directly causal, or mediated by other risk factors, and whether the mechanism underlying any causal link is understood. Where knowledge about risk factors has been translated into preventive interventions, this will be noted, but the topic will not be reviewed in detail because it has been covered in another paper in the IMI series.[22]

Education and Time Outdoors: The Two Major Risk Factors for School Myopia

In modern societies, most human myopia appears over the time during which children attend school, whereas children who do not go to school rarely become myopic.[3] This indicates that it is the experience of the lifestyle of a school-aged child that leads to myopia. Abolishing school or education is certainly not an option for preventing myopia, so the problem is to determine which of the many things that change in a child's life when they start going to school actually lead to myopia.

Education

There has been speculation about the role of education in relation to myopia for at least several hundred years. The association between education and myopia can be seen at a number of levels, and has been extensively reviewed.[3,23]

There are three main lines of evidence:

- Although good historical data are sparse, there appears to be very little myopia in societies in which children do not go to school,[24,25] and the prevalence of myopia increases in societies as national education systems develop and more children attend school and complete more years of schooling.[3]
- Within a given location or school system, the prevalence of myopia increases as children get older and complete more schooling. At a given age, children who are enrolled in more academically oriented classes or schools, or who achieve higher grades, tend to be more myopic.[26–29]Superior academic performance appears in children before the onset of myopia.[30]Adults who have completed more years of schooling or have higher educational qualifications also tend to be more myopic.[31,32]
- Ecological studies show that the countries that currently have an epidemic of myopia stand out in international comparisons of educational outcomes. They tend to have a pattern of early onset of educational pressures, with homework starting in the preschool years and extensive use of tutorial classes outside of school hours.[33]

Despite the comprehensive nature of this evidence, the issue of causality has constantly been debated. Although some have argued that educational pressures cause myopia, others have argued that those who are predisposed genetically to myopia might selectively take up educational opportunities. Just as the rapid emergence of an epidemic of myopia in East and Southeast Asia is difficult to explain in genetic terms, so the historical pattern of increasing myopia over the last couple of hundred years as societies have developed school systems is similarly hard to explain in genetic terms. It is, of course, possible to argue that high selective pressure favoring myopia-predisposing gene variants has occurred in recent decades, but genetic analysis does not support this hypothesis.[13]

The very high prevalence of myopia seen in Israeli Jewish boys attending Orthodox or Ultra-Orthodox schools, compared with that in their sisters, or other children receiving more secular education, is also difficult to explain in genetic terms.[34,35]Again, it is possible to postulate that there is a sex-linked gene variant that predisposes to myopia segregating at a high frequency in Orthodox or Ultra-Orthodox Jewish communities in Israel, and indeed there are examples of rare, sex-linked forms of high myopia.[36] With modern molecular genetic techniques it would be relatively straightforward to identify such a gene variant should it exist; but to date there is no evidence that this is the case.

Further evidence on causality comes from the impact of policy interventions on the development of myopia. In qualitative terms, these can be seen in the historical patterns of the development of myopia in parallel with the development

of school systems, and the explosion of myopia in young adults (from 20–30% prevalence up to 70–80%) that occurred in mainland China over 20 years after the end of the Cultural Revolution in 1978, when there was a change in policy that made academic performance the main criterion for access to higher education, accompanied by a massive expansion of enrollments in higher educational institutions.[3] Similar impacts of educational policy changes on myopia have been documented in Singapore and Taiwan.[37,38] The quantitative technique of regression discontinuity analysis can be applied to data of this kind, and a recent study has examined the impact of increasing the mandatory length of schooling on development of myopia in the United Kingdom.[39] This policy resulted in a marked decrease in mean SER. Overall, policy innovations that have led to more children experiencing more intense educational pressures have led to an increase in the prevalence and severity of myopia, providing strong evidence of causality.

The classical epidemiological evidence strongly suggests that education has a causal role in relation to myopia. When this information is combined with Mendelian randomization analysis that supports a causal role,[32] then the associations are clearly causal. It should be noted that the Mendelian randomization study does not mean that years of schooling or myopia are strongly genetically determined, because the known genetic variation accounts for only a low percentage of the variance in each trait. The logic is that when a child's genetic profile "predisposes" them to undertake more schooling, then they are more likely to be myopic, whereas a genetic profile that "predisposes" them to be more myopic does not lead to them undertaking more schooling.

The mechanism by which this causal link is established is not clear. It has generally been assumed that reading and writing (nearwork) that are an integral part of education, provide the link. Many but not all studies have found associations between nearwork and myopia, and, in general, the associations have been weak and inconsistent, although meta-analysis suggests that the effects, while small, are real.[40] In contrast, others have concluded that nearwork plays little if any role.[41] Some studies have suggested that continuous nearwork or working distance may be more important than total duration,[42] but no randomized trials have been conducted to evaluate if limiting the amount of nearwork, limiting continuous periods of nearwork, or controlling working distance reduces the development of myopia. Nevertheless, interventions of this kind are often considered as potential strategies for myopia control. One possibility that could explain the weak association of nearwork with myopia is that when using imprecise questionnaires, it may be difficult to achieve statistical significance because the data are too noisy. More quantitative measures are now becoming available, and this may help to clarify these issues (see below).

The first specific hypothesis about a more proximal mechanism was that nearwork required more accommodation that would stimulate eye growth. This hypothesis appeared to have gained strong support when it was shown that atropine, a muscarinic antagonist that blocks accommodation, also blocked the development of myopia.[43] This line of research has developed into the effective control of myopia progression with atropine,[44,45] although the current evidence suggests that the drug may block eye growth by acting on nonmuscarinic receptors.[46,47] A range of other evidence suggests that accommodation is not involved in the effects of atropine[48–52] This triggered a search for alternative mechanisms, although it should be noted that there is some evidence that accommodation may play some role in early refractive development.[53]

Given that animal experiments have shown that imposed hyperopic defocus stimulated eye growth,[50] attention then shifted to the lag of accommodation and resulting hyperopic defocus that occurs during nearwork. Results of a critical test of this hypothesis, namely whether lag of accommodation develops before or after the onset of myopia, have been conflicting.[54–57] In addition, reports on an association between accommodative lag and progression of myopia are also conflicting.[58–60]

A particular variant of this hypothesis is that the development of peripheral hyperopic defocus, prior to the onset of myopia, leads to the development of myopia.[61] Animal experiments have shown that destruction of the central retina does not prevent normal regulation of eye growth,[62] demonstrating a role for the peripheral retina, although it is less certain that the central retina has no role at all.[62] The early evidence for the peripheral hyperopic defocus hypothesis has been contested,[63,64] and more recent work suggests that peripheral hyperopic defocus does not predict the development of myopia,[63,64] but develops after the onset of myopia in humans.[65,66] This would not exclude a role for peripheral hyperopic defocus in stimulating progression of myopia.

More recently, Schaeffel and colleagues have suggested that the use of black print on white paper may have a role.[67] This hypothesis was based on evidence that activity in the retinal OFF-pathway is stimulated by the use of black on white stimuli. Because activity in the parallel ON-pathway stimulates dopamine release,[68] an increase in relative activity in the OFF-pathway could lead to increased axial elongation, given the evidence from animal studies that dopamine acts as an inhibitor of eye growth.[69] However, this interesting hypothesis has not yet been tested on humans.

In summary, there is a large body of consistent evidence suggesting that there is a causal association between more education and more myopia. However, the mechanism involved is not clear, although the visual tasks of reading and writing may be contributors. Whereas this association suggests a wide variety of potential interventions, ranging from very distal societal interventions to regulate the amount of homework or to reduce the competitive nature of education pathways, through to interventions to prevent continuous nearwork or increase viewing distance, none has been validated in controlled trials.

Protection by Time Outdoors

Solid evidence that time outdoors was an important factor in the development of refractive error only became available over the last 20 years. Before that, there was often very weak evidence that time outdoors or physical activity was in some way protective from myopia, based generally on the lower prevalence of myopia in rural areas and in outdoor workers.[70,71] Related hypotheses were that people would have long viewing distances outdoors and hence use less accommodations, but there was no serious experimentation in this area. An emphasis on lighting also developed through the work of Cohn[72] who advocated for improved lighting in schools. This work was very influential in stimulating the development of lighting standards for schools, but the evidence base for much of this advocacy was weak, because methods for measuring light intensity and

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performing epidemiological surveys were poorly developed at the time.

A stronger evidence base has been developed more recently, starting with two seminal papers,[26,73] and followed by evidence from cross-sectional,[74] ecological,[75] and longitudinal[76] studies. Since then, a large body of epidemiological evidence on the protective effects of time outdoors has been accumulated[77] and a recent systematic review and meta-analysis has confirmed the association.[78] Importantly, increased time outdoors can reduce the impact of parental myopia[76] and higher levels of nearwork.[74] The evidence for causality now includes school-based intervention trials that have shown that increases in time outdoors of 40 to 80 minutes per day produced significant reductions in incident myopia,[79–81] consistent with the expectations from the epidemiological data.

Rose et al.[74] postulated that brighter light outdoors during daylight hours led to more dopamine release in the retina, which in turn inhibited axial elongation. This hypothesis has been supported by animal experiments demonstrating that bright light inhibits the development of form-deprivation myopia under laboratory conditions, and that the protective effect involves D2-dopamine receptors in chickens, monkeys, and tree-shrews.[82–84] The effects of bright light on lens-induced myopia were more limited and inconsistent; in both chickens and monkeys, the final compensation point was not affected, but in chickens it was approached at a slower rate, whereas no change in rate was observed in monkeys.[83,85] In contrast, bright light reduced the level of lens-induced myopia achieved after 28 days of exposure in tree-shrews.[86]

One plausible alternative hypothesis was that lower vitamin D levels, naturally observed in children who spend less time outdoors, play a causal role in relation to myopia. It has been shown that children or adolescents with myopia often have lower vitamin D levels.[87,88] Myopic subjects also have less conjunctival ultraviolet autofluorescence (CUVAF)[89,90] and a lower prevalence of pterygia,[91] both of which are associated with UV exposures. Because of these associations, it has been suggested that the development of CUVAF might provide a method for quantifying time outdoors. However, although this may provide a semiquantitative approach, CUVAF is not observed before the age of 8 years, it depends to some extent on skin color, and the kinetics of its development over time are not known.[92]

Despite these associations, a causal role for vitamin D has not been supported by more detailed analysis, including Mendelian randomization[93] and detailed longitudinal survival analysis.[94] Other hypotheses are that the protective effects of bright outdoor light on myopia might be due to a different balance of hyperopic and myopia defocus outdoors as compared with indoors, or that the greater uniformity of dioptric power outdoors may be an important factor.[95] The former is plausible in terms of the results of animal experimentation, but there is little evidence for uniformity detection of this kind. More recently, it has been suggested that the different spatial frequency compositions of indoor and outdoor scenes may play a role.[96] These hypotheses now need to be assessed more systematically.

The question of causality has been settled with the randomized intervention trials in children. However, some issues are still unclear. Initial epidemiological studies were based on distinctions between time spent outdoors and indoors, using an operational definition of being outdoors (during the day) as defined by light intensities over 1000 Lux, based on validation studies. Animal studies suggest that light intensities considerably higher, at least 10 to 20,000 Lux, might be required to produce significant inhibitory effects on eye growth, but there is suggestive evidence that lower light intensities (2–5,000 Lux) may be effective in humans.[97,98] One intervention trial has even suggested that modest increases in classroom lighting strongly inhibit the development of myopia.[99] This study has significant limitations, but requires replication because of its significant implications for interventions. It would not be surprising if animal experiments overestimated the light exposures required for protection in school-aged children, given that the stimulus for eye growth in the experiments is strong and constant, whereas signals in humans may be more intermittent.

It has also been suggested that the timing of the exposures,[100] or their frequency,[101] may also be important. There is only limited experimental support for these ideas, and they have not yet been tested in humans. The type of lighting[102] and parameters, such as spectral composition,[103] may also be important. Studies in rhesus monkeys have shown that rearing in narrowband long wavelength light promotes hyperopic shifts in refraction and protects from myopia.[104,105] If more subtle spectral variations to lighting are shown to be effective in preventing myopia, they might provide the basis for school-based preventive strategies. It has also been suggested that exposures to violet light may be important for the prevention of myopia,[106,107] but more follow-up work is required. Interventions of this kind may be particularly important if myopia prevention needs to rely on artificial light sources.

There is also controversy over whether increased time outdoors reduces progression as well as the onset of myopia. The initial epidemiology did not support this possibility[108] and a recent meta-analysis reached the same conclusion.[78] However, there is strong evidence that the rate of progression can be regulated, because seasonal differences in progression have been documented, with progression slower in summer than in winter. This suggests that progression may be regulated by environmental factors, and in a way that is generally consistent with the effects of nearwork and time outdoors.[109–112] Some epidemiological reports have suggested that more time outdoors does slow progression,[73,98,113] and more definitive work in this area is required.

Hagen et al.[114] have raised the question of whether controls over the development of myopia are compromised at extreme latitudes, where hours of light are limited during the winter months. In their study, the prevalence of myopia, measured with cycloplegia, in Norwegian 17 to 19 year old subjects was 16%. This is not significantly different to the prevalence of myopia measured under cycloplegia in samples of similar age of European ancestry in Northern Ireland[115] (18.6%) and Australia[116] (17.7%), but lower than the prevalence of myopia reported in Poland[117] (34.1%), and, as expected, somewhat lower than meta-analysis estimates based on non-cycloplegic refractions[118] (27.4%). Unfortunately, cycloplegic data on the prevalence of myopia in children of this age in Europe is very limited.

Hagen et al.[114] suggested that it might be necessary to invoke factors other than daylight exposures to explain the relatively low prevalence of myopia they reported, because of the limited daylight hours available in Norway in midwinter. However, it is not clear that this is the case, because at 60°N, where their study was performed, there are still

6 hours of daylight, even in mid-winter. It is important to note that the amount of daylight available is not necessarily made use of, either because of cultural preferences or because of conflicts with time devoted to education, and objective measures of light exposures may be required to resolve this issue. Hagen et al.[114] reported that Norwegian children spent 2–4 hours/days outdoors in preschool and throughout their school years, and that Norwegian child-rearing practices place emphasis on getting even very young infants outdoors. The study sample itself reported spending nearly 4 hours/day outdoors. In the context of the evidence that 2 hours outdoors per day can provide significant protection from myopia,[74,76,79,81,98] this amount of time may be sufficient to provide a large degree of control over the development of myopia, particularly since for most of the year, there seems to be ample daylight available.

Among the other factors, Hagen et al.[114] proposed that being adapted to extreme circannual variations might provide some protection, although there is little experimental evidence to support this idea. They also suggested that the specific L:M cone ratios and opsin characteristics of the population might render them less susceptible to developing myopia. This hypothesis was based on evidence that these characteristics have been associated with some syndromic forms of myopia,[119–121] and it has been proposed (by Neitz and Neitz [2015] "Methods for diagnosing and treating eye-length disorders," United States Patent US895172982) that variations in these characteristics might play a wider role in the etiology of myopia. In support of this idea, Hagen et al.[122] presented metadata showing differences in L:M cone ratios and opsin characteristics between Northern Europeans and East Asians. However, a more extensive study of correlations between these characteristics and the prevalence of myopia, taking into account other myopiagenic factors, will be required to establish such a link. The only experimental test of this hypothesis obtained largely negative results and concluded that a large longitudinal study would be required to test it more fully.[123]

The situation at 60°N can be contrasted with the situation at even more extreme latitudes. Early studies on Eskimo and Inuit populations living further north at around 70°N, where around 1 hour or less of daylight is available in mid-winter, showed that the prevalence of myopia was very low (1–2%), before the local populations had been moved into settlements and formal education introduced.[124–129] This observation is not surprising, because if there is little pressure to become myopic, exposure to protective factors may not be required. However, after these changes, the prevalence of myopia rapidly increased within one generation in younger people to over 50%, suggesting that once environmental pressure to develop myopia had been introduced, the low level of access to daylight at 70°N was insufficient to prevent the development of myopia. It is important to note that changes taking place were likely to place further restrictions on time outdoors, as well as introducing educational pressures, and, indeed, some of the authors noted anecdotally that myopia still seemed to be prevented in boys who attended school less regularly.[125] These observations suggest that further exploration at extreme latitudes of the balance between myopiagenic factors, such as education and environmental factors such as time outdoors, would be useful.

In summary, there is considerable evidence to support the idea that increased time outdoors delays the onset, and perhaps slows the progression of myopia, and that the association is causal. There is considerable evidence that the mechanism may involve stimulation of retinal dopamine release by brighter light outdoors, although other postulated mechanisms require further testing. School-based interventions to increase time outdoors have been implemented across the school system in Taiwan, with evidence of initial reductions in levels of reduced visual acuity, a proxy in school-aged children for myopia.[130] Promotion of increased time outdoors is also a central part of Singapore's myopia prevention strategy,[131] and initiatives to promote time outdoors form part of mainland China's myopia prevention plan.[132,133]

Use of Computers and Smart Phones

In the last 2 decades, use of computers and smart phones has become a routine part of daily life, with digital devices integrated into schooling in many countries. Dirani et al.[134] have recently proposed that increased digital screen time might now be "the single modifiable risk factor for myopia," accounting for "increased near-work activity and decreased outdoor activity." Taiwan has introduced laws controlling the amount of digital screen time that younger children are allowed (https://www.theatlantic.com/education/archive/2015/01/how-taiwan-is-curbing-childrens-daily-technology-exposure/384830/, accessed October 10, 2020). How regulations of this kind could be enforced is not clear. Similarly, in mainland China, limiting screen time in schools is being implemented to control myopia.[132,133]

The current evidence implicating digital devices is sparse and far from consistent. The epidemic of myopia appeared well before the common use of electronic devices, because the prevalence of myopia was already high in Taiwan and Singapore for children born in the early 1960s,[10,37] whereas the internet did not become available to the general public until 1993. It is certainly possible that digital devices have now come to constitute a significant form of nearwork, and their use may correlate closely with education and myopia.[135–144] This topic has been recently reviewed.[145]

However, the historical perspective is important in considering preventive interventions. Given that the first epidemics of myopia predated the widespread use of digital devices, if limits are now placed on their use, children may simply revert to traditional forms of nearwork, such as reading printed material. In addition, if digital devices encourage even more time indoors, active steps may need to be taken to get children to break with recently established behavior patterns, and spend more time outdoors. Over emphasis on digital screen time may in fact have negative consequences if it leads to neglect of other important factors. There is currently no evidence that time using digital devices is more dangerous than a similar amount of time reading, but more work in this area is clearly required.

The evidence is equivocal as to whether recent increases in the use of digital devices are associated with increases in the prevalence of myopia. Data from Taiwan suggest that there has been a steady increase in the prevalence of myopia in very recent years,[38] particularly in younger children, which could be attributed to increasing screen time. This is not inconsistent with the more recent decreases reported after the introduction of increased time outdoors in schools.[130] In contrast, data from Hong Kong suggest that the prevalence of myopia in 6 to 8 year old children has, if anything, slightly decreased in the last 20 years, despite an undoubted increase in the use of digital devices.[146] It may be that in places, such as Hong Kong, the capacity

to produce more myopia has reached its limits, and more definitive evidence may be obtained from locations where the prevalence of myopia is much lower. Recently, the World Health Organization (WHO) has recognized gaming disorders as a disease in the 11th revision of the International Classification of Diseases-11, and the impacts on the development of myopia of extreme screen time on those of school age, possibly combined with marked deprivation of time outdoors, have the potential to be severe. Given the interest in this topic among the public, as well as public health and education authorities, this is an area that requires more attention.

Measurement of Nearwork and Time Outdoors

One of the problems with work in this area is that nearwork and time outdoors have primarily been estimated with questionnaires. These are inevitably subject to problems of recall and secondary reporting by parents or teachers. In addition, the amount of detail that can be asked is limited; for example, it is unlikely that respondents would be able to give an accurate picture of changes in light intensity and duration of specific exposures.

Questionnaires started out short, with only a few questions on nearwork, and even less on time outdoors.[26,73,147] The questionnaire used in the Sydney Myopia Study had a much larger set of questions, but identified that the important factor was total time outdoors, and that indoor sport was not protective.[74] The WHO then sponsored the development of a simpler questionnaire to be used in subsequent studies, and this has been further developed by adopting a more diary-like format to apply time constraints to answers. The questionnaire used in the GOALS study[79] is an example that is available online.

None of the questionnaires has been validated against objective measures. Several attempts have been made to assess how accurate questionnaire answers are by comparing the results to objective measurements. Limited use has been made of objective light sensors, such as the HOBO data logger[148] and the Actiwatch,[149] and the agreement between questionnaire estimates and the more objective measurements is only limited. One of the important differences may be that the questionnaires ask for estimates of average activity patterns, generally discriminating among weekdays, weekends, and school holidays. In contrast, objective devices collect data on specific days. Because behavior almost certainly varies by season, in relation to weather and in school holidays, estimates of averages are bound to differ from specific measures. In the SCORM study,[147] the questionnaires were supplemented with activity diaries, and there is some evidence that diaries and questionnaires asking about a specific period show somewhat better agreement.

Objective measures obtained with wearable devices are likely to provide more reliable data. Other devices are now available to quantify light exposures, such as the FitSight Fitness Tracker[150] and the Clouclip device.[151] One of the features of the data collected with these devices is that the light exposures are generally significantly lower than measures of ambient light intensities. This is probably because ambient light intensities vary depending on the direction of collection. For example, when looking at the sky versus toward the ground, intensities may vary by at least an order of magnitude. Outdoors, people rarely gaze for long periods at the horizon or the sky, but spend much more time interacting with their peers, often with a slightly downward gaze. In this respect, devices mounted on the arms of spectacles may have an advantage over other devices, because they measure light intensity along the line of sight. A general problem with all devices is that wearing them may affect behavior, and in the case of the Clouclip device, children without glasses are required to wear frames. Protection from the damaging effects of UV exposures is often required outdoors, and it has been shown that the use of sunglasses and hats results in only slight reductions in exposure.

Attempts to quantify nearwork through measurement of viewing distance have been less common. An early instrument does not appear to have been used for research purposes.[152] However, the Clouclip device has this capacity, as does the RangeLife.[153] The Clouclip device has been independently validated for distance measurements.[154]

Wearable sensors are likely to be used more systematically in the future, but the logistics of their use on large samples is likely to be very challenging. Because they give a discrete sample in time, some sort of experience sampling regime may need to be applied to estimate longer-term patterns of use. With measurement along the line of sight, interpretation of the results in terms of viewing distance may be relatively straightforward, but the interpretation of this as nearwork may be more complicated.

One of the most fundamental problems with objective measures of activities may be that changes in well-measured parameters still need to be translated into changes in refraction and axial length. Although quality data are currently in short supply, initial data suggests that as children progress through schooling, the amount of nearwork they perform increases, whereas the time spend outdoors decreases. From this pattern, it would simplistically be expected that myopic refractive shifts and perhaps progression of myopia would increase as children enter higher year grades of schooling, but in fact these changes generally decrease after the early primary years. It seems likely that age limits the plasticity of axial growth rates, complicating the interpretation of the results by requiring age-specific translation of exposures into refractive and biometric changes. These are challenges that still need to be addressed, but appropriately used, objective devices have the potential to make a significant contribution.

Other Risk Factors for Myopia

A range of other risk factors reported to be associated with myopia have been documented, but whether they are independently associated with myopia, mediated by other factors, or are surrogates of other factors is generally not clear. Given the strength and consistency of the evidence for education and time outdoors as risk factors, it is particularly important to consider whether any of the other associations with myopia are mediated by these two exposures.

Perhaps the most common approach is to put all the risk factors significantly associated with myopia on univariable analysis into a multivariable regression, and label all those that remain significant as independent. However, this approach has significant limitations, related to variable collinearity, the need to include all relevant variables, and inaccurate measurement of variables.[155] In practice, statistical adjustment tends to perform poorly because exposures are difficult to measure and because models typically assume simple linear relationships between variables. Patterns of confounding can be complex, and it is unlikely that all relevant confounders are known, let alone measured.

Approaches based on "mediation analysis" (inclusion and removal of variables to look for changes in the associations between the dependent variable and independent variables) can suffer from similar problems.[156] The issues surrounding analysis of interactions between variables are similarly complex, and there is considerable debate about when additive and multiplicative models should be considered.[157,158] A crucial part of any analysis requires careful thought about plausible causal mechanisms, and careful statistical testing of specific hypotheses.

Basic Birth Parameters

Sex. Many studies have compared the prevalence of myopia in male and female subjects. In older studies, the prevalence in male subjects tends to be higher, whereas more recent studies more commonly report higher prevalences in female subjects. For example, the Blue Mountains Eye Study reported that the prevalence of myopia was higher in older male adults than in female adults,[159] but the situation was reversed in the Sydney Myopia Study on children.[160] Similarly, the Liwan Eye Study reported that sex differences in older adults were marginal,[161] but in more recent cohorts in China, girls are more likely to be myopic than boys.[11,162] The extremely large difference in the prevalence of myopia in girls and boys in Orthodox Jewish communities in Israel, where the boys undergo very intensive education from an early age, shows this trend in reverse,[34,35] and contrasts with the similarity of boys and girls receiving more secular education. This variability does not suggest a direct biological link between sex and myopia, but rather suggests that the associations may be mediated by social factors, such as access to education for girls, which varies markedly between locations and has improved considerably in many places in recent decades. The relationship is highly confounded, and may be influenced by differential engagement of the sexes in outdoor and nearwork activities, irrespective of whether they are biologically or socially determined. Some links to growth spurts or puberty[163,164] have been reported, and these may explain some of the differences in prevalence of myopia between girls and boys, who will be at different stages of puberty and growth spurts at the same age.

Ethnicity. Ethnicity or race has often been proposed as a risk factor for myopia, and indeed as evidence for genetic determination of myopia. It is important to note that the terms race and particularly ethnicity cover both genetic differences, which are small in magnitude compared with the genetic commonalities across all human populations, but can be measured very precisely, and cultural differences, that can be large, but are harder to quantify.

Epidemiological evidence shows major differences between ethnic groups in the prevalence of myopia, but more detailed analysis shows that these differences may be mediated by environmental exposures. For example, the prevalence of myopia is high in the three major ethnic groups resident in Singapore, Chinese, Indian, and Malay,[9,165] but in India and Malaysia, the population prevalence is much lower.[166–169] This suggests that it is the environment of Singapore, probably the education system and the limited time spent outdoors, that is responsible for the higher prevalences.[2,3,5] The prevalence of myopia is higher in children of Chinese ethnicity in Singapore, but the gap has narrowed over recent years. In addition, it is known that Chinese children currently have higher engagement in education, and currently achieve higher outcomes, whereas children of Malay ethnicity report spending more time outdoors. Adjustment for the differences in educational achievements narrows the gap between the ethnic groups, but adjustment for time outdoors has not yet been performed.

Consistent with the epidemiological analysis, genetic studies have not found major differences between East Asian and European ethnic groups in the levels of myopia-associated single-nucleotide polymorphisms (SNPs).[170] It should be noted, however, that the East Asian sample was relatively small and the study did not include analysis of the sex chromosomes. Nevertheless, genetic factors accounted for a lower percentage of variance in the East Asian sample, as would be expected if environmental factors played a larger part in East Asia. Although genetic aspects of race and ethnicity are not modifiable, cultural aspects of ethnicity are potentially more modifiable, although the difficulties of changing cultural patterns of behavior should not be underestimated.

Parental Myopia. One of the best documented risk factors for myopia is having parents with myopia. Although the consistent impact of parental myopia can be explained by parents with myopia passing on genetic variants that predispose their children to myopia, it is also likely that parents with myopia will be more well educated on average. Hence, parents with myopia may also pass on a myopiagenic lifestyle, in addition to shared genes. The conclusion that myopia must be a genetic phenomenon alone, because it runs in families, is simplistic, but this idea still persists.[171]

A purely genetic explanation for rare, monogenic (syndromic) forms of myopia is clear, but the impact of parental myopia is also seen for school myopia. Studies covering a range of different ethnic groups have shown that having one or two parents with myopia increases the risk of myopia in children,[26,172–178] although the relative risk is naturally lower in populations with a high baseline prevalence of myopia.

So far, using data from risk factor questionnaires, there is no evidence that children with parents with myopia are more exposed to risk factors, such as nearwork and limited time outdoors. However, a recent study found that children with parents with myopia had a greater risk of myopia even after accounting for the increased risk conferred by the SNPs they inherited (having parents with myopia and inheriting myopia-predisposing SNPs were independently associated with myopia).[179] This implies that environmental risk factors may also be involved. Similar conclusions were reached by Enthoven et al.[180] More accurate objective measures of nearwork and time outdoors may be required to measure differences in environmental exposures between children with and without parents with myopia.

Birth Order. Associations between myopia and birth order have been reported in several cohort studies, with first-born children tending to be more myopic.[181] In educational studies, it is well-documented that first-born children generally get more education,[182] which would tend to produce more myopia. A subsequent study on the UK Biobank dataset showed that the association between myopia and birth order was reduced but not eliminated after adjusting for years of education.[183] In addition, in China, children from one child families were more myopic than children with siblings, which the authors attributed to greater parental support for their child's education.[184] However, the sociology of these differences is very complex, and more work

needs to be done to establish whether birth order is an independent risk factor.

Date or Season of Birth. Season of birth has also been associated with myopia in several studies. There is a higher prevalence of high myopia in children born in Israel[185] and the United Kingdom[186] in the summer months, but differences in the prevalence of mild myopia were slight and inconsistent, as were correlations with photoperiod. In the Israeli study, the sample consisted of young male adults (military conscripts), whereas the UK sample covered the age 18 to 100 years. A more recent paper from the UK TEDS study reported that children born in the summer months were more myopic, but again perinatal photoperiod effects were not significant.[144] The authors proposed a link to the age of starting school, with children born in the summer months tending to start school younger by up to 1 year because of age cutoffs for school enrollment, and progression of myopia tending to be more rapid at younger ages.

Summary. The factors discussed in the section are set at birth, and are not modifiable per se. However, if the differences in the prevalence of myopia that emerge during childhood associated with these factors are mediated by cultural or social attitudes or rules that lead to differential exposures, it may be possible to devise interventions to limit the development of myopia.

Other Personal Factors

Height. Height is similar to myopia in that it has quite a high heritability, although not as high as that of myopia.[187] Like myopia, it is also subject to environmental influences, with significant increases in height seen in many populations over the past century.[188] These have been generally attributed to more adequate nutrition. Rare and often deleterious mutations can also cause extreme variation in height.

It has been argued that associations between height and myopia might be expected, given that taller people have longer axial lengths (see for example ref. 189), but this argument does not take into account that "emmetropization" mechanisms[190] should produce substantial convergence of refractive status, despite differences in body stature. Although it has been reported that that height is a risk factor for myopia in children,[191] the evidence on this is inconsistent.[192] In fact Rosner et al.[193] reported that Israeli male military conscripts who were not myopic, were taller and weighed more than those who were myopic – the reverse of some expectations. Another inconsistency lies in the difference in prevalence of myopia between male and female subjects, with a higher prevalence of myopia being commonly reported in girls in recent studies (see above), despite their smaller stature and shorter axial lengths.[194] In general, there appears to be a tight biological link between height and axial length, but not with refraction. Social factors affecting nutrition and education may be significant confounders. Mean height varies considerably between populations, (https://worldpopulationreview.com/country-rankings/average-height-by-country), but the countries known to have a high prevalence of myopia do not stand out through differences in height in the way that they do in relation to educational achievement.[33]

Intelligence. Higher intelligence or IQ, and some other cognitive measures, are generally associated with myopia.[195–197] Initially, this link was conceptualized in terms of dominant genetic effects within a rather simplistic big brain-big eye hypothesis,[198] although it is not clear that bigger brains are associated with higher intelligence, or that bigger, rather than relatively elongated, eyes are associated with myopia.

Intelligence or general cognitive function show high heritability in twin studies, although not as high as the heritability of myopia.[199] Genetic variants with large effects on intelligence or cognitive capacity are rare and deleterious, providing an interesting analogy between rare mutations that cause intellectual disability and rare mutations that cause early onset high myopia. However, whether intelligence or cognitive capacity exert effects independent of education and perhaps time outdoors is not clear. As is the case with myopia, there is considerable evidence that these traits can be modified environmentally[199–202] and a long-term trend toward increasing population IQ levels has been reported,[201,202] although it is much less dramatic than the changes in myopia in East and Southeast Asia.

In the SCORM study, both academic grades and IQ scores were reported to be independently associated with myopia,[29,196] and the same result has been obtained in a very large study of Israeli conscripts.[28] Both cognitive performance and years of education were associated with myopia in the Gutenberg Health Survey, but the association with years of education was stronger.[31,195] Williams et al.[203] reported that the phenotypic correlation between myopia and IQ was low but significant, and that most of it could be explained by genetic differences, although the proportion of variance explained by genetic factors was small for both phenotypes. This is an area in which thoughtful mediation analysis or a Mendelian randomization analysis would be particularly useful. The potentially bidirectional links among intelligence, cognition, education, and academic performance are not well understood. In addition, whatever subsequent research reveals about these links, it does not seem likely that this research will lead to interventions to prevent myopia.

Physical Activity. A number of papers have reported associations between increased physical activity and less myopia, but this association is confounded, given that increased physical activity is often performed outdoors. A systematic review has concluded that although most studies reported a negative association between increased physical activity and myopia, most did not rule out mediation by time outdoors, and several concluded that the important factor was time outdoors.[74,204,205] A recent detailed investigation concluded that there was no significant protective association of increased physical activity with myopia,[206] whereas a more recent paper has reported more robust associations but without ruling out time outdoors.[207] Further studies with more objective measures of activity and time outdoors are important because interventions aimed at promoting indoor physical activity rather than time outdoors may have little effect in preventing myopia, although they may be easier to implement.

Sleep. Associations between sleep and myopia have also been reported, but the evidence is quite inconsistent.[208–213] A large longitudinal study from Shanghai reported consistent significant associations of going to sleep late with greater myopia prevalence at baseline, incident myopia, and myopic shift in refraction, after adjustment for several variables including age, but did not find that sleep duration was an important factor.[214] The authors noted that going to sleep late was more prevalent in children who lived in urban areas, were older, had more parents with myopia, had better educated parents, tended to wake up late, spent more time

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reading and on screens, and spent less time outdoors – all characteristics that were also identified as risk factors for myopia. The analysis is thus highly confounded, and the evidence on causality is not strong. The authors suggested that their results might also implicate circadian rhythms. Children who have heavy study loads after school are probably likely to get less sleep, both because there is less time available, and also because mental activity close to bed time can disrupt sleep. This suggests that lack of sleep is more likely to be a problem in the senior years of school, when homework loads in many parts of East and Southeast Asia are very high. However, sleep deprivation may be less common in the early primary years, when myopia first appears.

Summary. Many of the associations reported in this section are not consistent across studies, suggesting that direct biological links may not be involved. In most cases, causality has not been demonstrated. The inconsistent findings suggest that many of the associations are affected by social factors and could have arisen due to confounding. There is too little data related to the role of circadian rhythms to make any firm conclusions, however, one of the benefits of natural daytime light is to maintain healthy diurnal rhythms. Thus, the effects of outdoor time on myopia may be related to whether diurnal rhythms of ocular growth are disrupted or not, and this may again be related to seasonal behavioral changes. Physical activity would seem to be a readily modifiable factor, but the available evidence currently does not suggest that interventions based on increasing physical activity, without increasing outdoor time, are likely to be effective.

Family Characteristics and Environment

Socio-economic Status. Since James Ware reported to the Royal Society in 1813 on the greater need for and use of corrections for near-sightedness in "persons of the higher ranks in life" as compared to "persons in the inferior stations of life,"[215] a large body of evidence has been accumulated showing that family income, as well as parental education and parental myopia, are associated with an increased prevalence of myopia in children. Other research has consistently shown that young adults engaged in continuing study or in occupations that involve nearwork indoors have a higher prevalence of myopia.[70] These associations have been observed in a wide range of populations.[216–219] Exceptions to this observation are rare,[220,221] and may possibly be associated with recent groups of migrants on low incomes pursuing intensive education for their children.

The possibility of a link between income and myopia has also been suggested by the recent epidemic of myopia in parts of East and Southeast Asia that have seen marked increases in per capita income, producing some of the wealthiest countries in the world. Jan et al.[222] have shown that, in mainland China, increases in the prevalence of visual impairment (a proxy measure for myopia) between provinces correlate with increases in gross domestic product (GDP) per capita at the province level. The potential for confounding in these analyses is obvious, and it is hard to understand how rising income could translate directly into biological changes in eye growth. Income is, however, a possible covariate of both education and nearwork. Although the association between socio-economic status (SES) and myopia is generally strong within a society at a given time, high per capita incomes were achieved in many Western societies with only modest prevalences of myopia, well before East Asian societies achieved similar income levels, but with much higher prevalences of myopia.[3] Within East and Southeast Asia, the prevalence of myopia is now similar in China, Japan, South Korea, and Singapore,[3] but per capita income and GDP are still much lower in China (https://en.wikipedia.org/wiki/List_of_countries_by_GDP_(nominal)_per_capita, accessed May 12, 2020). A more consistent association is with the intensity of the education system as shown in the PISA studies of educational outcomes.[33] This is an area in which more quantitative analysis would be very useful.

As another example of the potential for confounding, Rahi and colleagues reported that maternal height and age were associated with more myopia.[223] In the United Kingdom, height differs by SES, with mean heights greater in higher SES groups.[195,224] The same is true for maternal age, with women in higher SES groups tending to have children later in life (https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/livebirths/articles/anoteonchildbearingbysocioeconomicstatusandcountryofbirthofmother/2016#socio-economic-status-and-average-age-of-mother-for-uk-and-non-uk-born-women, accessed May 12, 2020). Given that children from higher SES groups are generally more myopic, these associations could have arisen due to confounding.

Smoking. Maternal smoking was associated with a lower risk of myopia in the SCORM study from Singapore, but there was no association with paternal smoking, and the number of mothers who smoked was small.[225] In the subsequent STARS study, a stronger negative association with maternal and paternal smoking was reported.[226] A similar protective relationship was reported in a sample from a pediatric ophthalmology clinic, which largely persisted after adjustment for a range of factors, including child's nearwork activity and parental myopia and education.[227] A detailed study from South Korea reported consistent results for exposure to passive smoke estimated from urinary cotinine level,[228] supporting the suggestion that nicotinic pathways are involved in the regulation of eye growth. In contrast, Rahi et al. reported an association between maternal smoking in early pregnancy and more myopia.[223] Although some of the associations reported are substantial, given the associations of smoking with SES and education, and lower gestational weight, these studies are at high risk of confounding.

Diet. Over the ages during which myopia develops in children, diets are largely set by family characteristics, including family wealth and cultures. Changes in diet have often accompanied economic development, as reflected in the secular increases in height that have been reported in many parts of the world. It should be noted that there is a need to carefully distinguish between dietary change associated with increased height as compared to that associated with an increase in obesity. Nevertheless, Cordain et al., taking a broad anthropological perspective, argued that dietary change could have contributed to the increased prevalence of myopia, and supported this argument with a plausible hypothesis linking insulin resistance, chronic hyperinsulinemia, increased circulating IGF-1, decreased circulating growth hormone, and decreased retinoid receptor signaling to increases in scleral growth.[229] However, expected associations of height, weight, body mass index (BMI), and obesity with myopia have not been consistently observed. Improved diet has been associated with greater height and axial length, but, as noted above, this does not

appear to have produced increased myopia because of the powerful eye growth control mechanisms that exist.

International variations in mean height do not parallel variations in the prevalence of myopia. Similarly, international variations in the prevalence of people in the overweight and obesity categories do not parallel the international distribution of myopia, with none of the countries with a high prevalence of myopia making the list of the top 20 countries ranked by percentage of obesity (https://www.who.int/gho/ncd/risk_factors/overweight/en/, accessed January 30, 2019). Thus, there is little support for a tight biological link between diet and myopia.

Another problem in this area is the sheer diversity of the components of diet and the difficulty of measuring lifetime exposures. Few dietary nutrients and micronutrients have been examined in detail. However, over 50 years ago, Gardiner explored the relationship between diet and myopia, particularly protein, with suggestive results, but this work does not appear to have been followed up.[230–233] More recently, studies examining dietary zinc and myopia suggested no association.[234,235] At present, there is no strong evidence implicating dietary change in the epidemic of myopia.

Summary. The association of family income with myopia in children is largely consistent. Although it is difficult to test formally, it seems likely that most of the data can be explained by associations between family income and education of the children, rather than a direct link between income and education. However, further work is needed for a more comprehensive understanding of the causal and noncausal pathways linking family income to myopia.

Aspects of the Lived Environment

Urban/Rural Differences. Urban-rural differences in the prevalence of myopia have been frequently reported, with large differences appearing when the level of economic development is markedly different in the different locations. Studies from mainland China,[11,162,236–238] Taiwan,[239] and India[166,168,240] have shown marked differences in the prevalence of myopia, with the prevalence higher in urban than rural areas. It has generally been assumed that these differences can be explained by differences in educational outcomes and time spent outdoors, but this assumption has never been systematically tested. However, a detailed analysis of data from the ALSPAC study has suggested other factors, such as population density, might be more important, at least in the prosperous Avon Valley region.[241] Population density has also been invoked as a factor in an Australian study[242] and in China.[243] In the latter study, the prevalence of myopia was high across a wide range of population densities, suggesting that other factors were more important.

Even within cities, regional differences in prevalence of myopia have been reported. The Sydney Myopia Study reported that the prevalence of myopia was highest in inner city areas.[242] Access to green space has also been linked to lower use of spectacles, as a proxy for myopia,[244] but there are many confounding effects in studies of this kind, such as where do higher SES families live, and where do the families of children achieving higher educational outcomes live. It does seem plausible that greater access to green space for play might provide an opportunity for more time outdoors and the prevention of myopia, but other factors, including safety, weather, pollution, and cultural attitudes, may determine whether it is used effectively.

Pollution. Pollution is one of the factors that has increased markedly since the Second World War in parts of East and Southeast Asia. One of the problems in this area is that there are many forms of pollution, but most attention has been devoted to air pollution. In international terms, air pollution is more extreme in many cities in South Asia and the Middle East than in Chinese cities, although their prevalence of myopia is much lower than in Chinese cities (https://www.who.int/airpollution/data/cities/en/, accessed May 12, 2020). Increased use of spectacles, presumably for myopia, has also been associated with traffic-related pollution,[245] but the effect is weak and may be related to the association between urban residence and more myopia, as well as links to SES, area of residence, and education, rather than to a direct effect of pollution. An association between myopia and traffic pollution was also reported from Taiwan. These studies are also highly confounded. The Taiwanese group has reported that concentrated atmospheric pollution applied to the eyes in animal experiments promotes the development of myopia,[246] but whether this simply represents a form of form-deprivation myopia is not clear.

Housing. Type of housing, particularly its size, has also been suggested as a factor, particularly the idea that living in small apartments might promote myopia. However, the results in this area are currently inconsistent. In Singapore, more spacious housing was associated with more myopia,[27] possibly because of a causal chain involving SES, housing, and its associations with education. In contrast, in both Sydney[242] and Hong Kong,[247] small apartment dwelling has been associated with more myopia. A detailed study in Hong Kong has suggested that home size and aspects of the home defocus environment may be associated with myopia.[248]

Circadian Rhythms. A large body of evidence from animal experiments supports the idea that there are circadian or diurnal rhythms in parameters, such as axial length and choroidal thickness, and that abnormal light exposures, such as constant light and dark, lead to changes in eye growth in animals.[249,250] In addition, studies examining gene expression in animal models of myopia have reported changes in expression of mRNAs associated with circadian clock genes,[251,252] and genomewide association studies (GWAS) have reported SNPs in similar genes associated with myopia.[13]

A fundamental problem in interpreting these observations is that dopaminergic function, through its interaction with melatonin, is an integral part of circadian and diurnal pathways. Given the evidence for a major role of dopamine release in the control of eye growth,[253] it is difficult to determine whether changes in light-regulated dopamine release or perturbations of broader circadian pathways have a primary role in leading to excessive axial elongation. In the animal experiments, it is possible that changes in dopamine release led to changes in the expression of clock genes, and it is equally possible that mutations in clock genes may lead to perturbed dopamine synthesis and release.

An environmental exposure that disrupts circadian rhythms in humans, leading to the development of myopia, has not been identified. An early report that children who slept with night lights became very myopic generated considerable interest.[254] However, attempts to replicate this finding in a range of populations found little or no effect.[255–261]One epidemiological phenomenon that may give some support to this hypothesis is the emergence of an

epidemic of myopia in Inuit and Eskimo populations when they were moved into settlements and received somewhat rudimentary education, far less intensive than that required to produce an epidemic of myopia in East and Southeast Asia.[124,125,128]

Based on evidence that brief exposure of chickens to light at night disrupted growth rhythms,[262] it has been suggested that increased use of artificial lighting and the consequent rise of light pollution might be a cause of myopia, although rhythms in humans seem to be more robust.[263] However, light pollution maps show similar levels of light pollution in East Asia, Europe, and North America (https://www.lightpollutionmap.info, accessed October 12, 2020) although the prevalences of myopia in these regions are quite different. It is therefore difficult to attribute the increased prevalence of myopia in East Asia to increased light pollution, and other factors seem likely to play a major role.

Kearney et al.[264] have recently reported that myopes in the NICER study have higher morning levels of serum melatonin, although this finding was not replicated in a US study.[263] More recently, this group reported that circadian rhythms in melatonin levels were not altered in myopes as compared with emmetropes.[265] In contrast, a more recent paper reported that melatonin levels were lower, and that there were phase shifts in rhythms.[266] At this stage, it is not clear whether these observations suggest a role for circadian rhythms, or whether the changes in melatonin levels are secondary to changes in dopamine metabolism.

Miscellaneous Risk Factors

Allergic Conjunctivitis, Hay Fever, and Kawasaki Disease. In 2011, Herbort et al. proposed an association of myopia with inflammatory conditions affecting the choriocapillaris.[267] An association between myopia and ocular inflammatory conditions, such as uveitis, was subsequently demonstrated,[268] and a higher risk of myopia was associated with allergic conjunctivitis, and less so allergic rhinitis, atopic dermatitis, and asthma.[246] A large population-based study using the US National Health and Nutrition Examination Survey (NHANES) dataset showed that hay fever was also associated with a higher prevalence of high myopia.[269] A recent report has also associated increased myopia with Kawasaki disease,[270] which has conjunctivitis as one of its core diagnostic criteria.

These associations raise the intriguing possibility of a link between ocular allergic responses and the development of myopia. Using an animal model, Wei et al. have proposed a potential molecular mechanism involving increased tumor necrosis factor (TNF)-alpha and interleukins.[246] It does not seem likely that a link between ocular inflammation and myopia can explain the epidemic of myopia in East and Southeast Asia, because there is no parallel between the international distribution of myopia and that of allergic rhinoconjunctivitis in children.[271] One possibility is that eye rubbing may lead to myopic refractions through corneal changes, as may be the case with keratoconus,[272] but a US study on hay fever did not support this hypothesis.[269] The possibility that children with these conditions tend to spend less time outside should be examined. It is also plausible that allergic conditions might add to the incidence and progression of myopia, without being the primary determinant of myopia onset. Another possible factor may be the drugs used to control allergies, although there is currently no evidence for this.

Febrile Diseases. Using data from the UK Biobank, Guggenheim et al. reported associations between several childhood diseases and myopia. From a list including pneumonia, encephalitis, meningitis, rheumatic fever, measles, rubella, mumps, diphtheria, and pertussis, myopia was associated with rubella, and mumps and pertussis were associated with any myopia, whereas measles, rubella, and pertussis were associated with high myopia.[273] The authors argued against a link to educational disruption or limited time outdoors, because not all serious childhood diseases were linked to myopia. This link, whatever its causes, is unlikely to explain the emergence of the epidemic of myopia, because, in general, childhood vaccination has increased over time in many countries, including in East and Southeast Asia since the Second World War, yet the prevalence of myopia has increased. However, these findings may have clinical implications that need to be explored.

Fertility Treatment. The British TEDS study has documented a standard range of social variables, with level of maternal education, summer birth, and hours spent playing computer games surviving full multivariate regression analysis, with associations with SES, educational attainment, reading enjoyment, and cognitive variables showing associations at multiple stages in the life-course analysis. A unique feature of the analysis was the protective associations of fertility treatment detected in the final analysis.[197] The authors ruled out associations with parental education, and the explanation for this finding remains obscure.

Popular Beliefs About the Causes of Myopia

There are many popular beliefs about the causes of myopia around the world, which have presumably arisen because the development of myopia and its progression is often observed by parents, who naturally seek explanations. In the Western world, a common belief is that reading in dim light, or under the bed-clothes causes vision to deteriorate, but this outcome, and these behaviors might indeed be common in those who like reading books, and read a lot, without indicating a causal connection. Scientific evidence in this area is very limited, and although animal experiments suggest that chickens exposed to constant dim light may slowly develop myopia, objective measurements on children suggests that children with myopia are less exposed to dim lights as well as brighter lights than nonmyopic children.[274] We have not attempted a systematic survey in this area, but in China, there seems to be many beliefs of this kind, perhaps because the prevalence of myopia has increased so conspicuously. One commonly encountered belief is that myopia is associated with reading and writing postures that violate the "foot, fist, inch" rule, that is the eyes should be one foot from the book, the chest should be one fist from the desk, and the fingers should be one inch from the nib of the pen. This is a variant on the idea that bad posture while reading leads to the development of myopia, which has widespread currency, but has never been rigorously tested. A similar common belief is that reading while riding on public transport is dangerous, but again this has never been tested. Other ideas include the development of myopia in children who read on their back, or their front, or who read extracurricular books with font sizes greater than standard text-books. These proposed factors need to be subjected to thorough epidemiological investigation. If they stand up to scrutiny, they need to be evaluated in carefully designed randomized clinical trials. Unfortunately, several such recommendations

TABLE. Summary of Factors Associated With Myopia

Factor	Evidence/Causal Relationship	Confounding Issues
Major factors		
Education	Strong and causal	Time outdoors
Time outdoors	Strong and causal	Role of light (intensity, duration, spectrum)
Screen time	Equivocal	Nearwork
Basic birth factors		
Sex	Weak	Social factors
Ethnicity	Inconsistent	Cultural attitudes or genetics
Parental myopia	Strong	Genetics or myopiagenic environments
Birth order	Weak	Years of education
Birth season	Weak	Years of education
Other personal factors		
Height	Weak	Social factors
Intelligence	Moderate	Education, time outdoors
Physical activity	Moderate	Time outdoors
Sleep	Weak	Educational pressures
Family characteristics		
Socio-economic status	Moderate	Education
Smoking	Weak	Education, SES
Diet	Weak	Education, SES
Environment		
Urban/rural	Moderate	Education, SES, time outdoors
Pollution	Weak	SES
Housing	Weak	Education, SES
Circadian rhythms	Weak	Dopamine
Night light	Negative	
Light spectrum	Weak	Limited data
Miscellaneous factors		
Allergic conjunctivitis, hay fever, Kawasaki disease, febrile diseases	Weak	Limited data, time outdoors
Fertility treatment	Weak	Limited data
Common beliefs		
Reading in dim light, under bed-clothes or in transport	Weak	Limited data
Posture in reading/writing and holding pen, font size in book	Weak	Limited data

have been written into China's National Myopia Prevention Plan as advice to parents, without a solid scientific basis.

CONCLUSIONS

This overview of risk factors for myopia has identified education and limited time outdoors as major risk factors for myopia. These two factors offer the prospect of identifying evidence-based approaches to the control of myopia, such as increased time outdoors and, possibly, decreased nearwork time. How these two factors act to regulate eye growth is largely unknown, but in the case of time outdoors it appears to involve regulation of the rate of dopamine release, and possibly other factors. Animal studies relevant to these pathways have been reviewed in another article in this series.[16] To date, only the negative (protective) association of increased time outdoors with myopia has been translated into a proven preventive intervention.

Myopia is often described as a complex multifactorial condition, and many other risk factors for myopia have been proposed. The Table lists these factors, and the quality of the evidence that currently documents them. The majority of them may involve more distal social factors, such as parental and social attitudes to education, provision of educational opportunities, and organization of school systems, and may be mediated by the exposures to educational pressures and time outdoors that children receive. So far, few have been translated into a preventive intervention that has been validated in a controlled trial, although several have obvious potential.

Future studies in this area need to become more rigorous. Cycloplegia needs to follow the required standard. Statistical adjustment for potential confounders, and mediation analysis, need to become more systematic, and to be conducted with greater thought about potential causal pathways. Measurement of the major identified risk factors, education or nearwork, and time outdoors, needs to become more accurate. New studies should therefore collect data on education, nearwork exposures and time outdoors, ideally using the objective sensors that are becoming available. Where possible, the powerful techniques of Mendelian randomization and regression discontinuity analysis should be applied. These improvements are required if studies on risk factors are going to provide a reliable basis for the development of future preventive interventions.

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