

IMI Risk Factors for Myopia

Ian G. Morgan,^{1,2} Pei-Chang Wu,^{3,4} Lisa A. Ostrin,⁵ J. Willem L. Tideman,⁶⁻⁸ Jason C. Yam,⁹⁻¹¹ Weizhong Lan,¹²⁻¹⁵ Rigmor C. Baraas,¹⁶ Xiangui He,¹⁷⁻¹⁹ Padmaja Sankaridurg,^{20,21} Seang-Mei Saw,²²⁻²⁴ Amanda N. French,²⁵ Kathryn A. Rose,²⁵ and Jeremy A. Guggenheim²⁶

¹Research School of Biology, Australian National University, Canberra, ACT, Australia

²State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-Sen University, Guangzhou, China

³Department of Ophthalmology, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan

⁴Chang Gung University College of Medicine, Kaohsiung, Taiwan

⁵College of Optometry, University of Houston, Houston, Texas, United States

⁶Department of Ophthalmology, Erasmus MC, University Medical Centre, Rotterdam, The Netherlands

⁷Department of Epidemiology, Erasmus MC, University Medical Centre, Rotterdam, The Netherlands

⁸The Generation R Study Group, Erasmus MC, University Medical Centre, Rotterdam, The Netherlands

⁹Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong, China

¹⁰Hong Kong Eye Hospital, Hong Kong, China

¹¹Department of Ophthalmology and Visual Sciences, Prince of Wales Hospital, Hong Kong, China

¹²Aier School of Ophthalmology, Central South University, Changsha, China

¹³Aier School of Optometry, Hubei University of Science and Technology, Xianning, China

¹⁴Aier Institute of Optometry and Vision Science, Aier Eye Hospital Group, Changsha, China

¹⁵Guangzhou Aier Eye Hospital, Jinan University, Guangzhou, China

¹⁶National Centre for Optics, Vision and Eye Care, Faculty of Health and Social Sciences, University of South-Eastern Norway, Kongsberg, Norway

¹⁷Department of Preventative Ophthalmology, Shanghai Eye Disease Prevention and Treatment Center, Shanghai Eye Hospital, Shanghai, China

¹⁸Department of Ophthalmology, Shanghai General Hospital, Shanghai Jiao Tong University, Shanghai, China

¹⁹Shanghai Key Laboratory of Ocular Fundus Diseases, National Clinical Research Center for Eye Diseases, Shanghai, China

²⁰Brien Holden Vision Institute Limited, Sydney, Australia

²¹School of Optometry and Vision Science, University of New South Wales, Sydney, Australia

²²Saw Swee Hock School of Public Health, National University of Singapore (NUS), Singapore

²³Singapore Eye Research Institute, Singapore

²⁴Duke-NUS Medical School, Singapore

²⁵Discipline of Orthoptics, Graduate School of Health, University of Technology Sydney, Sydney, Australia

²⁶School of Optometry & Vision Sciences, Cardiff University, Cardiff, United Kingdom

Correspondence: Ian G. Morgan, Research School of Biology, Australian National University, Canberra, ACT 2601, Australia; ian.morgan@anu.edu.au.

Received: December 21, 2020

Accepted: December 24, 2020

Published: April 28, 2021

Citation: Morgan IG, Wu P-C, Ostrin LA, et al. IMI Risk factors for myopia. *Invest Ophthalmol Vis Sci.* 2021;62(5):3. <https://doi.org/10.1167/iovs.62.5.3>

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.

Keywords: myopia, prevention, circadian rhythms, prevalence, diet, risk factors, education, nearwork, time outdoors, screen time, Mendelian randomization, randomized clinical trials

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 myopia⁷ 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 oper-

ating 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 analysis²⁰ 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 alter-

native 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 Cohn⁷² 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

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 longitudinal⁷⁶ studies. Since then, a large body of epidemiological evidence on the protective effects of time outdoors has been accumulated⁷⁷ and a recent systematic review and meta-analysis has confirmed the association.⁷⁸ Importantly, increased time outdoors can reduce the impact of parental myopia⁷⁶ 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 randomization⁹³ 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 lighting¹⁰² 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 possibility¹⁰⁸ 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 Ireland¹¹⁵ (18.6%) and Australia¹¹⁶ (17.7%), but lower than the prevalence of myopia reported in Poland¹¹⁷ (34.1%), and, as expected, somewhat lower than meta-analysis estimates based on non-cycloplegic refractions¹¹⁸ (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 mid-winter. 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 study⁷⁹ 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 logger¹⁴⁸ 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 Tracker¹⁵⁰ 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 down-

ward 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 engage-

ment 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 Israel¹⁸⁵ and the United Kingdom¹⁸⁶ 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” mechanisms¹⁹⁰ 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

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](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 study²⁴² 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 Sydney²⁴² 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.

Acknowledgments

The authors thank Monica Jong for facilitation of the process.

Supported by the International Myopia Institute. The publication costs of the International Myopia Institute reports were

supported by donations from the Brien Holden Vision Institute, Carl Zeiss Vision, CooperVision, Essilor, and Alcon.

Disclosure: **I.G. Morgan**, None; **P.-C. Wu**, None; **L.A. Ostrin**, None; **J.W.L. Tideman**, None; **J.C. Yam**, None; **W. Lan**, None; **R.C. Baraas**, None; **X. He**, None; **P. Sankaridurg**, BHVI (E), co-inventor on multiple patents related to myopia (P); **S.M. Saw**, None; **A.N. French**, None; **K.A. Rose**, None; **J.A. Guggenheim**, None

References

- Dolgin E. The myopia boom. *Nature*. 2015;519:276–278.
- Morgan I, Rose K. How genetic is school myopia? *Prog Retin Eye Res*. 2005;24:1–38.
- Morgan IG, French AN, Ashby RS, et al. The epidemics of myopia: aetiology and prevention. *Prog Retin Eye Res*. 2018;62:134–149.
- Morgan IG, He M, Rose KA. Epidemic of pathological myopia: what can laboratory studies and epidemiology tell us? *Retina*. 2017;37:989–997.
- Morgan IG, Ohno-Matsui K, Saw SM. Myopia. *Lancet*. 2012;379:1739–1748.
- Pan CW, Ramamurthy D, Saw SM. Worldwide prevalence and risk factors for myopia. *Ophthalmic Physiol Opt*. 2012;32:3–16.
- Flitcroft DI, He M, Jonas JB, et al. IMI - defining and classifying myopia: a proposed set of standards for clinical and epidemiologic studies. *Invest Ophthalmol Vis Sci*. 2019;60:M20–M30.
- Jung SK, Lee JH, Kakizaki H, Jee D. Prevalence of myopia and its association with body stature and educational level in 19-year-old male conscripts in Seoul, South Korea. *Invest Ophthalmol Vis Sci*. 2012;53:5579–5583.
- Koh V, Yang A, Saw SM, et al. Differences in prevalence of refractive errors in young Asian males in Singapore between 1996-1997 and 2009-2010. *Ophthalmic Epidemiol*. 2014;21:247–255.
- Lin LL, Shih YF, Hsiao CK, Chen CJ. Prevalence of myopia in Taiwanese schoolchildren: 1983 to 2000. *Ann Acad Med Singapore*. 2004;33:27–33.
- Wu JF, Bi HS, Wang SM, et al. Refractive error, visual acuity and causes of vision loss in children in Shandong, China. The Shandong Children Eye Study. *PLoS One*. 2013;8:e82763.
- Holden BA, Fricke TR, Wilson DA, et al. Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. *Ophthalmology*. 2016;123:1036–1042.
- Hysi PG, Choquet H, Khawaja AP, et al. Meta-analysis of 542,934 subjects of European ancestry identifies new genes and mechanisms predisposing to refractive error and myopia. *Nat Genet*. 2020;52:401–407.
- Wojciechowski R. Nature and nurture: the complex genetics of myopia and refractive error. *Clin Genet*. 2011;79:301–320.
- Guggenheim JA, St Pourcain B, McMahon G, Timpson NJ, Evans DM, Williams C. Assumption-free estimation of the genetic contribution to refractive error across childhood. *Mol Vis*. 2015;21:621–632.
- Tedja MS, Haarman AEG, Meester-Smoor MA, et al. IMI Myopia genetics report. *Invest Ophthalmol Vis Sci*. 2019;60:M89–M105.
- Morgan IG, Iribarren R, Fotouhi A, Grzybowski A. Cycloplegic refraction is the gold standard for epidemiological studies. *Acta Ophthalmol*. 2015;93:581–585.
- Koh V, Yanf A, Saw SM, et al. Differences in prevalence of refractive errors in young Asian males in Singapore between 1996-1997 and 2009-2010: prevalence and risk factors of epiretinal membrane in Asian Indians. *Ophthalmic Epidemiol*. 2014;21:247–255.
- Adam D. The causation detector. *Nature*. 2019;576:196–199.
- Venkataramani AS, Bor J, Jena AB. Regression discontinuity designs in healthcare research. *BMJ*. 2016;352:i1216.
- Zadnik K, Sinnott LT, Cotter SA, et al. Prediction of juvenile-onset myopia. *JAMA Ophthalmol*. 2015;133:683–689.
- Wildsoet CF, Chia A, Cho P, et al. IMI - interventions for controlling myopia onset and progression report. *Invest Ophthalmol Vis Sci*. 2019;60:M106–M131.
- Rose KA, French AN, Morgan IG. Environmental factors and myopia: paradoxes and prospects for prevention. *Asia Pac J Ophthalmol (Phila)*. 2016;5:403–410.
- Skeller E. Anthropological and ophthalmological studies on the Angmagssalik Eskimos. *Meddr Gron*. 1954;107:187–211.
- Holm E. The ocular refractive state of the Palae-Negroids in French Equatorial Africa. *Acta Ophthalmol Suppl*. 1937;13:1–299.
- Mutti DO, Mitchell GL, Moeschberger ML, Jones LA, Zadnik K. Parental myopia, near work, school achievement, and children's refractive error. *Invest Ophthalmol Vis Sci*. 2002;43:3633–3640.
- Quek TP, Chua CG, Chong CS, et al. Prevalence of refractive errors in teenage high school students in Singapore. *Ophthalmic Physiol Opt*. 2004;24:47–55.
- Rosner M, Belkin M. Intelligence, education, and myopia in males. *Arch Ophthalmol*. 1987;105:1508–1511.
- Saw SM, Cheng A, Fong A, Gazzard G, Tan DT, Morgan I. School grades and myopia. *Ophthalmic Physiol Opt*. 2007;27:126–129.
- Peckham CS, Gardiner PA, Goldstein H. Acquired myopia in 11-year-old children. *Br Med J*. 1977;1:542–545.
- Mirshahi A, Ponto KA, Hoehn R, et al. Myopia and level of education: results from the Gutenberg Health Study. *Ophthalmology*. 2014;121:2047–2052.
- Mountjoy E, Davies N, Plotnikov D, et al. Education and myopia: a Mendelian randomisation study. *BMJ*. 2018;361:k2022.
- Morgan IG, Rose KA. Myopia and international educational performance. *Ophthalmic Physiol Opt*. 2013;33:329–338.
- Bez D, Megreli J, Bez M, Avramovich E, Barak A, Levine H. Association between type of educational system and prevalence and severity of myopia among male adolescents in Israel. *JAMA Ophthalmol*. 2019;137(8):1–7.
- Zylbermann R, Landau D, Berson D. The influence of study habits on myopia in Jewish teenagers. *J Pediatr Ophthalmol Strabismus*. 1993;30:319–322.
- Hawksworth NR, Headland S, Good P, Thomas NS, Clarke A. Aland island eye disease: clinical and electrophysiological studies of a Welsh family. *Br J Ophthalmol*. 1995;79:424–430.
- Sensaki S, Sabanayagam C, Verkicharla PK, et al. An ecologic study of trends in the prevalence of myopia in Chinese adults in Singapore born from the 1920s to 1980s. *Ann Acad Med Singapore*. 2017;46:229–236.
- Tsai TH, Liu YL, Ma IH, et al. Evolution of the prevalence of myopia among Taiwanese schoolchildren: a review of survey data from 1983 through 2017. *Ophthalmology*. 2021;128(2):290–301.
- Plotnikov D, Williams C, Atan D, et al. Effect of education on myopia: evidence from the United Kingdom ROSLA 1972 Reform. *Invest Ophthalmol Vis Sci*. 2020;61:7.
- Huang HM, Chang DS, Wu PC. The association between near work activities and myopia in children - a systematic review and meta-analysis. *PLoS One*. 2015;10:e0140419.

41. Mutti DO, Zadnik K. Has near work's star fallen? *Optom Vis Sci.* 2009;86:76–78.
42. Ip JM, Saw SM, Rose KA, et al. Role of near work in myopia: findings in a sample of Australian school children. *Invest Ophthalmol Vis Sci.* 2008;49:2903–2910.
43. Bedrossian RH. The effect of atropine on myopia. *Ann Ophthalmol.* 1971;3:891–897.
44. Chia A, Lu QS, Tan D. Five-year clinical trial on atropine for the treatment of myopia 2: myopia control with atropine 0.01% eyedrops. *Ophthalmology.* 2016;123:391–399.
45. Yam JC, Jiang Y, Tang SM, et al. Low-concentration atropine for myopia progression (LAMP) study: a randomized, double-blinded, placebo-controlled trial of 0.05%, 0.025%, and 0.01% atropine eye drops in myopia control. *Ophthalmology.* 2019;126:113–124.
46. Carr BJ, Mihara K, Ramachandran R, et al. Myopia-inhibiting concentrations of muscarinic receptor antagonists block activation of alpha2A-adrenoceptors in vitro. *Invest Ophthalmol Vis Sci.* 2018;59:2778–2791.
47. Carr BJ, Nguyen CT, Stell WK. Alpha2 -adrenoceptor agonists inhibit form-deprivation myopia in the chick. *Clin Exp Optom.* 2019;102:418–425.
48. McBrien NA, Moghaddam HO, New R, Williams LR. Experimental myopia in a diurnal mammal (*Sciurus carolinensis*) with no accommodative ability. *J Physiol.* 1993;469:427–441.
49. McBrien NA, Moghaddam HO, Reeder AP. Atropine reduces experimental myopia and eye enlargement via a nonaccommodative mechanism. *Invest Ophthalmol Vis Sci.* 1993;34:205–215.
50. Schaeffel F, Glasser A, Howland HC. Accommodation, refractive error and eye growth in chickens. *Vision Res.* 1988;28:639–657.
51. Schmid KL, Wildsoet CF. Effects on the compensatory responses to positive and negative lenses of intermittent lens wear and ciliary nerve section in chicks. *Vision Res.* 1996;36:1023–1036.
52. Schaeffel F, Troilo D, Wallman J, Howland HC. Developing eyes that lack accommodation grow to compensate for imposed defocus. *Vis Neurosci.* 1990;4:177–183.
53. Mutti DO, Mitchell GL, Jones LA, et al. Accommodation, acuity, and their relationship to emmetropization in infants. *Optom Vis Sci.* 2009;86:666–676.
54. Drobe B, de Saint-Andre R. The pre-myopic syndrome. *Ophthalmic Physiol Opt.* 1995;15:375–378.
55. Goss DA. Clinical accommodation and heterophoria findings preceding juvenile onset of myopia. *Optom Vis Sci.* 1991;68:110–116.
56. Gwiazda J, Thorn F, Held R. Accommodation, accommodative convergence, and response AC/A ratios before and at the onset of myopia in children. *Optom Vis Sci.* 2005;82:273–278.
57. Mutti DO, Mitchell GL, Hayes JR, et al. Accommodative lag before and after the onset of myopia. *Invest Ophthalmol Vis Sci.* 2006;47:837–846.
58. Allen PM, O'Leary DJ. Accommodation functions: co-dependency and relationship to refractive error. *Vision Res.* 2006;46:491–505.
59. Berntsen DA, Sinnott LT, Mutti DO, Zadnik K, CLEERE Study Group. Accommodative lag and juvenile-onset myopia progression in children wearing refractive correction. *Vision Res.* 2011;51:1039–1046.
60. Koomson NY, Amedo AO, Opoku-Baah C, Ampeh PB, Ankamah E, Bonsu K. Relationship between reduced accommodative lag and myopia progression. *Optom Vis Sci.* 2016;93:683–691.
61. Smith EL, 3rd. Prentice award lecture 2010: a case for peripheral optical treatment strategies for myopia. *Optom Vis Sci.* 2011;88:1029–1044.
62. Smith EL, 3rd, Hung LF, Huang J. Relative peripheral hyperopic defocus alters central refractive development in infant monkeys. *Vision Res.* 2009;49:2386–2392.
63. Atchison DA, Rosen R. The possible role of peripheral refraction in development of myopia. *Optom Vis Sci.* 2016;93:1042–1044.
64. Rosen R, Lundstrom L, Unsbo P, Atchison DA. Have we misinterpreted the study of Hoogerheide et al. (1971)? *Optom Vis Sci.* 2012;89:1235–1237.
65. Sng CC, Lin XY, Gazzard G, et al. Peripheral refraction and refractive error in Singapore Chinese children. *Invest Ophthalmol Vis Sci.* 2011;52:1181–1190.
66. Sng CC, Lin XY, Gazzard G, et al. Change in peripheral refraction over time in Singapore Chinese children. *Invest Ophthalmol Vis Sci.* 2011;52:7880–7887.
67. Aleman AC, Wang M, Schaeffel F. Reading and myopia: contrast polarity matters. *Sci Rep.* 2018;8:10840.
68. Boelen MK, Boelen MG, Marshak DW. Light-stimulated release of dopamine from the primate retina is blocked by 1-2-amino-4-phosphonobutyric acid (APB). *Vis Neurosci.* 1998;15:97–103.
69. Iuvone PM, Tigges M, Stone RA, Lambert S, Laties AM. Effects of apomorphine, a dopamine receptor agonist, on ocular refraction and axial elongation in a primate model of myopia. *Invest Ophthalmol Vis Sci.* 1991;32:1674–1677.
70. Goldschmidt E. The mystery of myopia. *Acta Ophthalmol Scand.* 2003;81:431–436.
71. Parssinen TO. Relation between refraction, education, occupation, and age among 26- and 46-year-old Finns. *Am J Optom Physiol Opt.* 1987;64:136–143.
72. Cohn HL. The hygiene of the eye in schools. English translation. Simpkin, Marshall and Co, London, 1886.
73. Parssinen O, Lyyra AL. Myopia and myopic progression among schoolchildren: a three-year follow-up study. *Invest Ophthalmol Vis Sci.* 1993;34:2794–2802.
74. Rose KA, Morgan IG, Ip J, et al. Outdoor activity reduces the prevalence of myopia in children. *Ophthalmology.* 2008;115:1279–1285.
75. Rose KA, Morgan IG, Smith W, Burlutsky G, Mitchell P, Saw SM. Myopia, lifestyle, and schooling in students of Chinese ethnicity in Singapore and Sydney. *Arch Ophthalmol.* 2008;126:527–530.
76. Jones LA, Sinnott LT, Mutti DO, Mitchell GL, Moeschberger ML, Zadnik K. Parental history of myopia, sports and outdoor activities, and future myopia. *Invest Ophthalmol Vis Sci.* 2007;48:3524–3532.
77. French AN, Ashby RS, Morgan IG, Rose KA. Time outdoors and the prevention of myopia. *Exp Eye Res.* 2013;114:58–68.
78. Xiong S, Sankaridurg P, Naduvilath T, et al. Time spent in outdoor activities in relation to myopia prevention and control: a meta-analysis and systematic review. *Acta Ophthalmol.* 2017;95(6):551–566.
79. He M, Xiang F, Zeng Y, et al. Effect of time spent outdoors at school on the development of myopia among children in China: a randomized clinical trial. *JAMA.* 2015;314:1142–1148.
80. Jin JX, Hua WJ, Jiang X, et al. Effect of outdoor activity on myopia onset and progression in school-aged children in northeast China: the Sujiatun Eye Care Study. *BMC Ophthalmol.* 2015;15:73.
81. Wu PC, Tsai CL, Wu HL, Yang YH, Kuo HK. Outdoor activity during class recess reduces myopia onset and progression in school children. *Ophthalmology.* 2013;120:1080–1085.

82. Ashby R, Ohlendorf A, Schaeffel F. The effect of ambient illuminance on the development of deprivation myopia in chicks. *Invest Ophthalmol Vis Sci.* 2009;50:5348–5354.
83. Ashby RS, Schaeffel F. The effect of bright light on lens compensation in chicks. *Invest Ophthalmol Vis Sci.* 2010;51:5247–5253.
84. Smith EL, 3rd, Hung LF, Huang J. Protective effects of high ambient lighting on the development of form-deprivation myopia in rhesus monkeys. *Invest Ophthalmol Vis Sci.* 2012;53:421–428.
85. Smith EL, 3rd, Hung LF, Arumugam B, Huang J. Negative lens-induced myopia in infant monkeys: effects of high ambient lighting. *Invest Ophthalmol Vis Sci.* 2013;54:2959–2969.
86. Norton TT, Siegwart JT. Light levels, refractive development, and myopia — a speculative review. *Exp Eye Res.* 2013;114:48–57.
87. Choi JA, Han K, Park YM, La TY. Low serum 25-hydroxyvitamin D is associated with myopia in Korean adolescents. *Invest Ophthalmol Vis Sci.* 2014;55:2041–2047.
88. Yazar S, Hewitt AW, Black LJ, et al. Myopia is associated with lower vitamin D status in young adults. *Invest Ophthalmol Vis Sci.* 2014;55:4552–4559.
89. McKnight CM, Sherwin JC, Yazar S, et al. Myopia in young adults is inversely related to an objective marker of ocular sun exposure: the Western Australian Raine cohort study. *Am J Ophthalmol.* 2014;158:1079–1085.
90. Sherwin JC, Hewitt AW, Coroneo MT, Kearns LS, Griffiths LR, Mackey DA. The association between time spent outdoors and myopia using a novel biomarker of outdoor light exposure. *Invest Ophthalmol Vis Sci.* 2012;53:4363–4370.
91. Zhang LM, Lu Y, Gong L. Pterygium is related to short axial length. *Cornea.* 2020;39:140–145.
92. Sun HP, Lin Y, Pan CW. Iris color and associated pathological ocular complications: a review of epidemiologic studies. *Int J Ophthalmol.* 2014;7:872–878.
93. Cuellar-Partida G, Williams KM, Yazar S, et al. Genetically low vitamin D concentrations and myopic refractive error: a Mendelian randomization study. *Int J Epidemiol.* 2017;46:1882–1890.
94. Guggenheim JA, Williams C, Northstone K, et al. Does vitamin D mediate the protective effects of time outdoors on myopia? Findings from a prospective birth cohort. *Invest Ophthalmol Vis Sci.* 2014;55:8550–8558.
95. Flitcroft DI. The complex interactions of retinal, optical and environmental factors in myopia aetiology. *Prog Retin Eye Res.* 2012;31:622–660.
96. Flitcroft DI, Harb EN, Wildsoet CF. The spatial frequency content of urban and indoor environments as a potential risk factor for myopia development. *Invest Ophthalmol Vis Sci.* 2020;61:42.
97. Read SA, Collins MJ, Vincent SJ. Light exposure and eye growth in childhood. *Invest Ophthalmol Vis Sci.* 2015;56:6779–6787.
98. Wu PC, Chen CT, Lin KK, et al. Myopia prevention and outdoor light intensity in a school-based cluster randomized trial. *Ophthalmology.* 2018;125:1239–1250.
99. Hua WJ, Jin JX, Wu XY, et al. Elevated light levels in schools have a protective effect on myopia. *Ophthalmic Physiol Opt.* 2015;35:252–262.
100. Sarfare S, Yang J, Nickla DL. The effects of brief high intensity light on ocular growth in chicks developing myopia vary with time of day. *Exp Eye Res.* 2020;195:108039.
101. Lan W, Feldkaemper M, Schaeffel F. Intermittent episodes of bright light suppress myopia in the chicken more than continuous bright light. *PLoS One.* 2014;9:e110906.
102. Pan CW, Wu RK, Liu H, Li J, Zhong H. Types of lamp for homework and myopia among Chinese school-aged children. *Ophthalmic Epidemiol.* 2018;25:250–256.
103. Rucker F. Monochromatic and white light and the regulation of eye growth. *Exp Eye Res.* 2019;184:172–182.
104. Hung LF, Arumugam B, She Z, Ostrin L, Smith EL, 3rd. Narrow-band, long-wavelength lighting promotes hyperopia and retards vision-induced myopia in infant rhesus monkeys. *Exp Eye Res.* 2018;176:147–160.
105. Smith EL, 3rd, Hung LF, Arumugam B, Holden BA, Neitz M, Neitz J. Effects of long-wavelength lighting on refractive development in infant rhesus monkeys. *Invest Ophthalmol Vis Sci.* 2015;56:6490–6500.
106. Torii H, Kurihara T, Seko Y, et al. Violet light exposure can be a preventive strategy against myopia progression. *EBio Medicine.* 2017;15:210–219.
107. Torii H, Ohnuma K, Kurihara T, et al. Violet light transmission is related to myopia progression in adult high myopia. *Sci Rep.* 2017;7:14523.
108. Jones-Jordan LA, Sinnott LT, Cotter SA, et al. Time outdoors, visual activity, and myopia progression in juvenile-onset myopes. *Invest Ophthalmol Vis Sci.* 2012;53:7169–7175.
109. Cui D, Trier K, Munk Ribell-Madsen S. Effect of day length on eye growth, myopia progression, and change of corneal power in myopic children. *Ophthalmology.* 2013;120:1074–1079.
110. Deng L, Gwiazda J, Thorn F. Children's refractions and visual activities in the school year and summer. *Optom Vis Sci.* 2010;87:406–413.
111. Donovan L, Sankaridurg P, Ho A, Naduvilath T, Smith EL, 3rd, Holden BA. Myopia progression rates in urban children wearing single-vision spectacles. *Optom Vis Sci.* 2012;89:27–32.
112. Gwiazda J, Deng L, Manny R, Norton TT, the CLEERE Study Group. Seasonal variations in the progression of myopia in children enrolled in the correction of myopia evaluation trial. *Invest Ophthalmol Vis Sci.* 2014;55:752–758.
113. Sanchez-Tocino H, Villanueva Gomez A, Gordon Bolanos C, et al. The effect of light and outdoor activity in natural lighting on the progression of myopia in children. *J Fr Ophthalmol.* 2019;42:2–10.
114. Hagen LA, Gjelle JVB, Arnegard S, Pedersen HR, Gilson SJ, Baraas RC. Prevalence and possible factors of myopia in Norwegian adolescents. *Sci Rep.* 2018;8:13479.
115. McCullough SJ, O'Donoghue L, Saunders KJ. Six year refractive change among white children and young adults: evidence for significant increase in myopia among white UK children. *PLoS One.* 2016;11:e0146332.
116. French AN, Morgan IG, Burlutsky G, Mitchell P, Rose KA. Prevalence and 5- to 6-year incidence and progression of myopia and hyperopia in Australian school children. *Ophthalmology.* 2013;120:1482–1491.
117. Czepita D, Mojsa A, Ustianowska M, Czepita M, Lachowicz E. Prevalence of refractive errors in schoolchildren ranging from 6 to 18 years of age. *Ann Acad Med Stetin.* 2007;53:53–56.
118. Williams KM, Bertelsen G, Cumberland P, et al. Increasing prevalence of myopia in Europe and the impact of education. *Ophthalmology.* 2015;122:1489–1497.
119. Greenwald SH, Kuchenbecker JA, Rowlan JS, Neitz J, Neitz M. Role of a dual splicing and amino acid code in myopia, cone dysfunction and cone dystrophy associated with L/M opsin interchange mutations. *Transl Vis Sci Technol.* 2017;6:2.
120. McClements M, Davies WI, Michaelides M, et al. X-linked cone dystrophy and colour vision deficiency arising from a

- missense mutation in a hybrid L/M cone opsin gene. *Vision Res.* 2013;80:41–50.
121. McClements M, Davies WI, Michaelides M, et al. Variations in opsin coding sequences cause x-linked cone dysfunction syndrome with myopia and dichromacy. *Invest Ophthalmol Vis Sci.* 2013;54:1361–1369.
 122. Hagen LA, Arnegard S, Kuchenbecker JA, et al. The association between L:M cone ratio, cone opsin genes and myopia susceptibility. *Vision Res.* 2019;162:20–28.
 123. Zhou N, Atchison DA, Zele AJ, Brown B, Schmid KL. Cone ratios in myopia and emmetropia: a pilot study. *Optom Vis Sci.* 2015;92:e1–5.
 124. Morgan RW, Munro M. Refractive problems in Northern natives. *Can J Ophthalmol.* 1973;8:226–228.
 125. Morgan RW, Speakman JS, Grimshaw SE. Inuit myopia: an environmentally induced “epidemic”? *Can Med Assoc J.* 1975;112:575–577.
 126. Skeller E. Anthropological and ophthalmological studies on the Angmagssalik Eskimos. *Meddr Gron.* 1954;107:187–211.
 127. van Rens GH, Arkell SM. Refractive errors and axial length among Alaskan Eskimos. *Acta Ophthalmol (Copenh).* 1991;69:27–32.
 128. Young FA, Leary GA, Baldwin WR, et al. The transmission of refractive errors within Eskimo families. *Am J Optom Arch Am Acad Optom.* 1969;46:676–685.
 129. Young FA, Leary GA, Box RA, et al. Comparison of cycloplegic and non-cycloplegic refractions of Eskimos. *Am J Optom Arch Am Acad Optom.* 1971;48:814–825.
 130. Wu PC, Chen CT, Chang LC, et al. Increased time outdoors is followed by reversal of the long-term trend to reduced visual acuity in Taiwan primary school students. *Ophthalmology.* 2020;127(11):1462–1469.
 131. Karupiah V, Wong L, Tay V, Ge X, Kang LL. School-based programme to address childhood myopia in Singapore. *Singapore Med J.* 2021;62(2):63–68.
 132. Jan C, Li L, Keay L, Stafford RS, Congdon N, Morgan I. Prevention of myopia, China. *Bull World Health Organ.* 2020;98:435–437.
 133. Jan CL, Congdon N. Chinese national policy initiative for the management of childhood myopia. *Lancet Child Adolesc Health.* 2018;2:845–846.
 134. Dirani M, Crowston JG, Wong TY. From reading books to increased smart device screen time. *Br J Ophthalmol.* 2019;103:1–2.
 135. Chiang SY, Weng TH, Lin CM, Lin SM. Ethnic disparity in prevalence and associated risk factors of myopia in adolescents. *J Formos Med Assoc.* 2020;119:134–143.
 136. Czepita M, Czepita D, Lubinski W. The influence of environmental factors on the prevalence of myopia in Poland. *J Ophthalmol.* 2017;2017:5983406.
 137. Enthoven CA, Tideman JWL, Polling JR, Yang-Huang J, Raat H, Klaver CCW. The impact of computer use on myopia development in childhood: the Generation R study. *Prev Med.* 2020;132:105988.
 138. Guan H, Yu NN, Wang H, et al. Impact of various types of near work and time spent outdoors at different times of day on visual acuity and refractive error among Chinese school-going children. *PLoS One.* 2019;14:e0215827.
 139. Huang L, Kawasaki H, Liu Y, Wang Z. The prevalence of myopia and the factors associated with it among university students in Nanjing: A cross-sectional study. *Medicine (Baltimore).* 2019;98:e14777.
 140. Ku PW, Steptoe A, Lai YJ, et al. The associations between near visual activity and incident myopia in children: a nationwide 4-year follow-up study. *Ophthalmology.* 2019;126:214–220.
 141. Liu S, Ye S, Xi W, Zhang X. Electronic devices and myopic refraction among children aged 6–14 years in urban areas of Tianjin, China. *Ophthalmic Physiol Opt.* 2019;39:282–293.
 142. Saxena R, Vashist P, Tandon R, et al. Incidence and progression of myopia and associated factors in urban school children in Delhi: the North India Myopia Study (NIM Study). *PLoS One.* 2017;12:e0189774.
 143. Singh NK, James RM, Yadav A, Kumar R, Asthana S, Labani S. Prevalence of myopia and associated risk factors in schoolchildren in North India. *Optom Vis Sci.* 2019;96:200–205.
 144. Williams KM, Kraphol E, Yonova-Doing E, Hysi PG, Plomin R, Hammond CJ. Early life factors for myopia in the British Twins Early Development Study. *Br J Ophthalmol.* 2019;103:1078–1084.
 145. Lanca C, Saw SM. The association between digital screen time and myopia: a systematic review. *Ophthalmic Physiol Opt.* 2020;40:216–229.
 146. Yam JC, Tang SM, Kam KW, et al. High prevalence of myopia in children and their parents in Hong Kong Chinese Population: the Hong Kong Children Eye Study [published online ahead of print January 24, 2020]. *Acta Ophthalmol*, <https://doi.org/10.1111/aos.14350>.
 147. Saw SM, Chua WH, Hong CY, et al. Nearwork in early-onset myopia. *Invest Ophthalmol Vis Sci.* 2002;43:332–339.
 148. Alvarez AA, Wildsoet CF. Quantifying light exposure patterns in young adult students. *J Mod Opt.* 2013;60:1200–1208.
 149. Read SA, Collins MJ, Vincent SJ. Light exposure and physical activity in myopic and emmetropic children. *Optom Vis Sci.* 2014;91:330–341.
 150. Verkicharla PK, Ramamurthy D, Nguyen QD, et al. Development of the FitSight fitness tracker to increase time outdoors to prevent myopia. *Transl Vis Sci Technol.* 2017;6:20.
 151. Wen L, Cao Y, Cheng Q, et al. Objectively measured near work, outdoor exposure and myopia in children. *Br J Ophthalmol.* 2020;104(11):1542–1547.
 152. Leung TW, Flitcroft DI, Wallman J, et al. A novel instrument for logging nearwork distance. *Ophthalmic Physiol Opt.* 2011;31:137–144.
 153. Williams R, Bakshi S, Ostrin EJ, Ostrin LA. Continuous objective assessment of near work. *Sci Rep.* 2019;9:6901.
 154. Bhandari KR, Ostrin LA. Validation of the Clouclip and utility in measuring viewing distance in adults. *Ophthalmic Physiol Opt.* 2020;40(6):801–814.
 155. Brotman DJ, Walker E, Lauer MS, O'Brien RG. In search of fewer independent risk factors. *Arch Intern Med.* 2005;165:138–145.
 156. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol.* 1986;51:1173–1182.
 157. Andersson T, Alfredsson L, Kallberg H, Zdravkovic S, Ahlbom A. Calculating measures of biological interaction. *Eur J Epidemiol.* 2005;20:575–579.
 158. Cortina-Borja M, Smith AD, Combarros O, Lehmann DJ. The synergy factor: a statistic to measure interactions in complex diseases. *BMC Res Notes.* 2009;2:105.
 159. Attebo K, Ivers RQ, Mitchell P. Refractive errors in an older population: the Blue Mountains Eye Study. *Ophthalmology.* 1999;106:1066–1072.
 160. Ip JM, Huynh SC, Robaei D, et al. Ethnic differences in refraction and ocular biometry in a population-based sample of 11–15-year-old Australian children. *Eye (Lond).* 2008;22:649–656.

161. He M, Huang W, Li Y, Zheng Y, Yin Q, Foster PJ. Refractive error and biometry in older Chinese adults: the Liwan eye study. *Invest Ophthalmol Vis Sci.* 2009;50:5130–5136.
162. He M, Zeng J, Liu Y, Xu J, Pokharel GP, Ellwein LB. Refractive error and visual impairment in urban children in southern China. *Invest Ophthalmol Vis Sci.* 2004;45:793–799.
163. Lyu IJ, Kim MH, Baek SY, Kim J, Park KA, Oh SY. The association between menarche and myopia: findings from the Korean National Health and Nutrition Examination, 2008–2012. *Invest Ophthalmol Vis Sci.* 2015;56:4712–4718.
164. Yip VC, Pan CW, Lin XY, et al. The relationship between growth spurts and myopia in Singapore children. *Invest Ophthalmol Vis Sci.* 2012;53:7961–7966.
165. Au Eong KG, Tay TH, Lim MK. Race, culture and Myopia in 110,236 young Singaporean males. *Singapore Med J.* 1993;34:29–32.
166. Dandona R, Dandona L, Srinivas M, et al. Refractive error in children in a rural population in India. *Invest Ophthalmol Vis Sci.* 2002;43:615–622.
167. Goh PP, Abqariyah Y, Pokharel GP, Ellwein LB. Refractive error and visual impairment in school-age children in Gombak District, Malaysia. *Ophthalmology.* 2005;112:678–685.
168. Murthy GV, Gupta SK, Ellwein LB, et al. Refractive error in children in an urban population in New Delhi. *Invest Ophthalmol Vis Sci.* 2002;43:623–631.
169. Saw SM, Goh PP, Cheng A, Shankar A, Tan DT, Ellwein LB. Ethnicity-specific prevalences of refractive errors vary in Asian children in neighbouring Malaysia and Singapore. *Br J Ophthalmol.* 2006;90:1230–1235.
170. Tedja MS, Wojciechowski R, Hysi PG, et al. Genome-wide association meta-analysis highlights light-induced signaling as a driver for refractive error. *Nat Genet.* 2018;50:834–848.
171. Cooper J, Tkatchenko AV. A review of current concepts of the etiology and treatment of myopia. *Eye Contact Lens.* 2018;44:231–247.
172. Edwards MH. Effect of parental myopia on the development of myopia in Hong Kong Chinese. *Ophthalmic Physiol Opt.* 1998;18:477–483.
173. Ip JM, Huynh SC, Robaei D, et al. Ethnic differences in the impact of parental myopia: findings from a population-based study of 12-year-old Australian children. *Invest Ophthalmol Vis Sci.* 2007;48:2520–2528.
174. Jiang X, Tarczy-Hornoch K, Cotter SA, et al. Association of parental myopia with higher risk of myopia among multiethnic children before school age. *JAMA Ophthalmol.* 2020;138:501–509.
175. Liang CL, Yen E, Su JY, et al. Impact of family history of high myopia on level and onset of myopia. *Invest Ophthalmol Vis Sci.* 2004;45:3446–3452.
176. Pacella R, McLellan J, Grice K, Del Bono EA, Wiggs JL, Gwiazda JE. Role of genetic factors in the etiology of juvenile-onset myopia based on a longitudinal study of refractive error. *Optom Vis Sci.* 1999;76:381–386.
177. Xiang F, He M, Morgan IG. The impact of parental myopia on myopia in Chinese children: population-based evidence. *Optom Vis Sci.* 2012;89:1487–1496.
178. Xiang F, He M, Morgan IG. The impact of severity of parental myopia on myopia in Chinese children. *Optom Vis Sci.* 2012;89:884–891.
179. GhorbaniMojarrad N, Williams C, Guggenheim JA. A genetic risk score and number of myopic parents independently predict myopia. *Ophthalmic Physiol Opt.* 2018;38:492–502.
180. Enthoven CA, Tideman JWL, Polling JR, et al. Interaction between lifestyle and genetic susceptibility in myopia: the Generation R study. *Eur J Epidemiol.* 2019;34:777–784.
181. Guggenheim JA, McMahon G, Northstone K, et al. Birth order and myopia. *Ophthalmic Epidemiol.* 2013;20:375–384.
182. Booth A, Kee HJ. Birth order matters: the effect of family size and birth order on educational attainment. *J Population Econ.* 2008;22:367–397.
183. Guggenheim JA, Williams C, UK Biobank Eye and Vision Consortium. Role of educational exposure in the association between myopia and birth order. *JAMA Ophthalmol.* 2015;133:1408–1414.
184. Zhao L, Zhou M. Do only children have poor vision? Evidence from China's One-Child Policy. *Health Econ.* 2018;27(7):1131–1146.
185. Mandel Y, Grotto I, El-Yaniv R, et al. Season of birth, natural light, and myopia. *Ophthalmology.* 2008;115:686–692.
186. McMahon G, Zayats T, Chen YP, Prashar A, Williams C, Guggenheim JA. Season of birth, daylight hours at birth, and high myopia. *Ophthalmology.* 2009;116:468–473.
187. Yang J, Bakshi A, Zhu Z, et al. Genetic variance estimation with imputed variants finds negligible missing heritability for human height and body mass index. *Nat Genet.* 2015;47:1114–1120.
188. Hauspie RC, Vercauteren M, Susanne C. Secular changes in growth and maturation: an update. *Acta Paediatr Suppl.* 1997;423:20–27.
189. Wong TY, Foster PJ, Johnson GJ, Seah SK. Refractive errors, axial ocular dimensions, and age-related cataracts: the Tanjong Pagar survey. *Invest Ophthalmol Vis Sci.* 2003;44:1479–1485.
190. Wallman J, Winawer J. Homeostasis of eye growth and the question of myopia. *Neuron.* 2004;43:447–468.
191. Saw SM, Chua WH, Hong CY, et al. Height and its relationship to refraction and biometry parameters in Singapore Chinese children. *Invest Ophthalmol Vis Sci.* 2002;43:1408–1413.
192. Ojaimi E, Rose KA, Morgan IG, et al. Distribution of ocular biometric parameters and refraction in a population-based study of Australian children. *Invest Ophthalmol Vis Sci.* 2005;46:2748–2754.
193. Rosner M, Laor A, Belkin M. Myopia and stature: findings in a population of 106,926 males. *Eur J Ophthalmol.* 1995;5:1–6.
194. Zadnik K, Manny RE, Yu JA, et al. Ocular component data in schoolchildren as a function of age and gender. *Optom Vis Sci.* 2003;80:226–236.
195. Mirshahi A, Ponto KA, Laubert-Reh D, et al. Myopia and cognitive performance: results from the Gutenberg Health Study. *Invest Ophthalmol Vis Sci.* 2016;57:5230–5236.
196. Saw SM, Tan SB, Fung D, et al. IQ and the association with myopia in children. *Invest Ophthalmol Vis Sci.* 2004;45:2943–2948.
197. Williams KM, Kraphol E, Yonova-Doing E, Hysi PG, Plomin R, Hammond CJ. Early life factors for myopia in the British Twins Early Development Study. *Br J Ophthalmol.* 2019;103(8):1078–1084.
198. Karlsson JL. Influence of the myopia gene on brain development. *Clin Genet.* 1975;8:314–318.
199. Polderman TJ, Benyamin B, de Leeuw CA, et al. Meta-analysis of the heritability of human traits based on fifty years of twin studies. *Nat Genet.* 2015;47:702–709.
200. Sauce B, Matzel LD. The paradox of intelligence: heritability and malleability coexist in hidden gene-environment interplay. *Psychol Bull.* 2018;144:26–47.

201. Shayer M, Ginsburg D. Thirty years on—a large anti-Flynn effect? (ID): 13- and 14-year-olds. Piagetian tests of formal operations norms 1976-2006/7. *Br J Educ Psychol*. 2009;79:409–418.
202. Shayer M, Ginsburg D, Coe R. Thirty years on - a large anti-Flynn effect? The Piagetian test Volume & Heaviness norms 1975-2003. *Br J Educ Psychol*. 2007;77:25–41.
203. Williams KM, Hysi PG, Yonova-Doing E, Mahroo OA, Snieder H, Hammond CJ. Phenotypic and genotypic correlation between myopia and intelligence. *Sci Rep*. 2017;7:45977.
204. Suhr Thykjaer A, Lundberg K, Grauslund J. Physical activity in relation to development and progression of myopia - a systematic review. *Acta Ophthalmol*. 2017;95:651–659.
205. Guggenheim JA, Northstone K, McMahon G, et al. Time outdoors and physical activity as predictors of incident myopia in childhood: a prospective cohort study. *Invest Ophthalmol Vis Sci*. 2012;53:2856–2865.
206. Lundberg K, Suhr Thykjaer A, Sogaard Hansen R, et al. Physical activity and myopia in Danish children - The CHAMPS Eye Study. *Acta Ophthalmol*. 2018;96:134–141.
207. Hansen MH, Laigaard PP, Olsen EM, et al. Low physical activity and higher use of screen devices are associated with myopia at the age of 16-17 years in the CCC2000 Eye Study. *Acta Ophthalmol*. 2020;98:315–321.
208. Ayaki M, Torii H, Tsubota K, Negishi K. Decreased sleep quality in high myopia children. *Sci Rep*. 2016;6:33902.
209. Jee D, Morgan IG, Kim EC. Inverse relationship between sleep duration and myopia. *Acta Ophthalmol*. 2016;94:e204–210.
210. Ostrin LA, Read SA, Vincent SJ, Collins MJ. Sleep in myopic and non-myopic children. *Transl Vis Sci Technol*. 2020;9:22.
211. Pan CW, Liu JH, Wu RK, Zhong H, Li J. Disordered sleep and myopia among adolescents: a propensity score matching analysis. *Ophthalmic Epidemiol*. 2019;26:155–160.
212. Wei SF, Li SM, Liu L, et al. Sleep duration, bedtime, and myopia progression in a 4-year follow-up of Chinese children: the Anyang Childhood Eye Study. *Invest Ophthalmol Vis Sci*. 2020;61:37.
213. Zhou Z, Morgan IG, Chen Q, Jin L, He M, Congdon N. Disordered sleep and myopia risk among Chinese children. *PLoS One*. 2015;10:e0121796.
214. Liu XN, Naduvilath TJ, Wang J, et al. Sleeping late is a risk factor for myopia development amongst school-aged children in China. *Sci Rep*. 2020;10:17194.
215. Ware J. Observations relative to the near and distant sight of different persons. *Phil Trans Roy Soc London*. 1813;103:31–50.
216. Lim HT, Yoon JS, Hwang SS, Lee SY. Prevalence and associated sociodemographic factors of myopia in Korean children: the 2005 third Korea National Health and Nutrition Examination Survey (KNHANES III). *Jpn J Ophthalmol*. 2012;56:76–81.
217. Shimizu N, Nomura H, Ando F, Niino N, Miyake Y, Shimokata H. Refractive errors and factors associated with myopia in an adult Japanese population. *Jpn J Ophthalmol*. 2003;47:6–12.
218. Sperduto RD, Seigel D, Roberts J, Rowland M. Prevalence of myopia in the United States. *Arch Ophthalmol*. 1983;101:405–407.
219. Varma R, Kim JS, Burkemper BS, et al. Prevalence and causes of visual impairment and blindness in Chinese American adults: the Chinese American Eye Study. *JAMA Ophthalmol*. 2016;134(7):785–793.
220. Theophanous C, Modjtahedi BS, Batech M, Marlin DS, Luong TQ, Fong DS. Myopia prevalence and risk factors in children. *Clin Ophthalmol*. 2018;12:1581–1587.
221. Tideman JW, Polling JR, Jaddoe VVW, Vingerling JR, Klaver CCW. Environmental risk factors can reduce axial length elongation and myopia incidence in 6- to 9-year-old children. *Ophthalmology*. 2019;126:127–136.
222. Jan C, Xu R, Luo D, et al. Association of visual impairment with economic development among Chinese schoolchildren. *JAMA Pediatr*. 2019;173:e190914.
223. Rahi JS, Cumberland PM, Peckham CS. Myopia over the life course: prevalence and early life influences in the 1958 British birth cohort. *Ophthalmology*. 2011;118:797–804.
224. Bann D, Johnson W, Li L, Kuh D, Hardy R. Socioeconomic inequalities in childhood and adolescent body-mass index, weight, and height from 1953 to 2015: an analysis of four longitudinal, observational, British birth cohort studies. *Lancet Public Health*. 2018;3:e194–e203.
225. Saw SM, Chia KS, Lindstrom JM, Tan DT, Stone RA. Childhood myopia and parental smoking. *Br J Ophthalmol*. 2004;88:934–937.
226. Iyer JV, Low WC, Dirani M, Saw SM. Parental smoking and childhood refractive error: the STARS study. *Eye (Lond)*. 2012;26:1324–1328.
227. Stone RA, Wilson LB, Ying GS, et al. Associations between childhood refraction and parental smoking. *Invest Ophthalmol Vis Sci*. 2006;47:4277–4287.
228. Nam GE, Hwang BE, Lee YC, et al. Lower urinary cotinine level is associated with a trend toward more myopic refractive errors in Korean adolescents. *Eye (Lond)*. 2017;31:1060–1067.
229. Cordain L, Eaton SB, Brand Miller J, Lindeberg S, Jensen C. An evolutionary analysis of the aetiology and pathogenesis of juvenile-onset myopia. *Acta Ophthalmol Scand*. 2002;80:125–135.
230. Gardiner PA. Observations on the food habits of myopic children. *Br Med J*. 1956;2:699–700.
231. Gardiner PA. The diet of growing myopes. *Trans Ophthalmol Soc U K*. 1956;76:171–180.
232. Gardiner PA. Dietary treatment of myopia in children. *Lancet*. 1958;1:1152–1155.
233. Gardiner PA. Protein and myopia. *Proc Nutr Soc*. 1960;19:96–100.
234. Burke N, Butler JS, Flitcroft I, Loughman J. The relationship between serum zinc levels and myopia. *Clin Exp Optom*. 2021;104(1):28–34.
235. Burke N, Butler JS, Flitcroft I, McCartney D, Loughman J. Association of total zinc intake with myopia in U.S. children and adolescents. *Optom Vis Sci*. 2019;96:647–654.
236. He M, Huang W, Zheng Y, Huang L, Ellwein LB. Refractive error and visual impairment in school children in rural southern China. *Ophthalmology*. 2007;114:374–382.
237. Pan CW, Wu RK, Li J, Zhong H. Low prevalence of myopia among school children in rural China. *BMC Ophthalmol*. 2018;18:140.
238. Zhao J, Pan X, Sui R, Munoz SR, Sperduto RD, Ellwein LB. Refractive error study in children: results from Shunyi District, China. *Am J Ophthalmol*. 2000;129:427–435.
239. Lin LL, Shih YF, Hsiao CK, Chen CJ, Lee LA, Hung PT. Epidemiologic study of the prevalence and severity of myopia among schoolchildren in Taiwan in 2000. *J Formos Med Assoc*. 2001;100:684–691.
240. Dandona R, Dandona L, Naduvilath TJ, Srinivas M, McCarty CA, Rao GN. Refractive errors in an urban population in Southern India: the Andhra Pradesh Eye Disease Study. *Invest Ophthalmol Vis Sci*. 1999;40:2810–2818.
241. Morris TT, Guggenheim JA, Northstone K, Williams C. Geographical variation in likely myopia and environmental risk factors: a multilevel cross classified analysis of a UK cohort. *Ophthalmic Epidemiol*. 2020;27:1–9.
242. Ip JM, Rose KA, Morgan IG, Burlutsky G, Mitchell P. Myopia and the urban environment: findings in a sample of

- 12-year-old Australian school children. *Invest Ophthalmol Vis Sci.* 2008;49:3858–3863.
243. Zhang M, Li L, Chen L, et al. Population density and refractive error among Chinese children. *Invest Ophthalmol Vis Sci.* 2010;51:4969–4976.
 244. Dadvand P, Sunyer J, Alvarez-Pedrerol M, et al. Green spaces and spectacles use in schoolchildren in Barcelona. *Environ Res.* 2017;152:256–262.
 245. Dadvand P, Nieuwenhuijsen MJ, Basagana X, et al. Traffic-related air pollution and spectacles use in schoolchildren. *PLoS One.* 2017;12:e0167046.
 246. Wei CC, Kung YJ, Chen CS, et al. Allergic conjunctivitis-induced retinal inflammation promotes myopia progression. *E Bio Medicine.* 2018;28:274–286.
 247. Choi KY, Yu WY, Lam CHI, et al. Childhood exposure to constricted living space: a possible environmental threat for myopia development. *Ophthalmic Physiol Opt.* 2017;37:568–575.
 248. Choi KY, Mok AY, Do CW, Lee PH, Chan HH. The diversified defocus profile of the near-work environment and myopia development. *Ophthalmic Physiol Opt.* 2020;40:463–471.
 249. Chakraborty R, Ostrin LA, Nickla DL, Iuvone PM, Pardue MT, Stone RA. Circadian rhythms, refractive development, and myopia. *Ophthalmic Physiol Opt.* 2018;38:217–245.
 250. Nickla DL. Ocular diurnal rhythms and eye growth regulation: where we are 50 years after Lauber. *Exp Eye Res.* 2013;114:25–34.
 251. Stone RA, Khurana TS. Gene profiling in experimental models of eye growth: clues to myopia pathogenesis. *Vision Res.* 2010;50:2322–2333.
 252. Stone RA, Pardue MT, Iuvone PM, Khurana TS. Pharmacology of myopia and potential role for intrinsic retinal circadian rhythms. *Exp Eye Res.* 2013;114:35–47.
 253. Feldkaemper M, Schaeffel F. An updated view on the role of dopamine in myopia. *Exp Eye Res.* 2013;114:106–119.
 254. Quinn GE, Shin CH, Maguire MG, Stone RA. Myopia and ambient lighting at night. *Nature.* 1999;399:113–114.
 255. Chapell M, Sullivan B, Saridakis S, et al. Myopia and nighttime lighting during sleep in children and adults. *Percept Mot Skills.* 2001;92:640–642.
 256. Czepita D, Mojsa A, Czepita M, Lachowicz E. Myopia and night lighting. Investigations on children with negative family history. *Klin Oczna.* 2012;114:22–25.
 257. Guggenheim JA, Hill C, Yam TF. Myopia, genetics, and ambient lighting at night in a UK sample. *Br J Ophthalmol.* 2003;87:580–582.
 258. Saw SM, Zhang MZ, Hong RZ, Fu ZF, Pang MH, Tan DT. Near-work activity, night-lights, and myopia in the Singapore-China study. *Arch Ophthalmol.* 2002;120:620–627.
 259. Zadnik K. Association between night lights and myopia: true blue or a red herring? *Arch Ophthalmol.* 2001;119:146.
 260. Zadnik K, Jones LA, Irvin BC, et al. Myopia and ambient night-time lighting. CLEERE Study Group. Collaborative longitudinal evaluation of ethnicity and refractive error. *Nature.* 2000;404:143–144.
 261. Zadnik K, Mutti DO. Darkness and myopia progression. *Ophthalmology.* 2003;110:1069–1070; author reply 1071–1062.
 262. Nickla DL, Totonelly K. Brief light exposure at night disrupts the circadian rhythms in eye growth and choroidal thickness in chicks. *Exp Eye Res.* 2016;146:189–195.
 263. Burfield HJ, Carkeet A, Ostrin LA. Ocular and systemic diurnal rhythms in emmetropic and myopic adults. *Invest Ophthalmol Vis Sci.* 2019;60:2237–2247.
 264. Kearney S, O'Donoghue L, Pourshahidi LK, Cobice D, Saunders KJ. Myopes have significantly higher serum melatonin concentrations than non-myopes. *Ophthalmic Physiol Opt.* 2017;37:557–567.
 265. Flanagan SC, Cobice D, Richardson P, Sittlington JJ, Saunders KJ. Elevated melatonin levels found in young myopic adults are not attributable to a shift in circadian phase. *Invest Ophthalmol Vis Sci.* 2020;61:45.
 266. Chakraborty R, Micic G, Thorley L, et al. Myopia, or near-sightedness, is associated with delayed melatonin circadian timing and lower melatonin output in young adult humans. *Sleep.* 2021;44(3):zsa208.
 267. Herbort CP, Papadia M, Neri P. Myopia and inflammation. *J Ophthalmic Vis Res.* 2011;6:270–283.
 268. Lin HJ, Wei CC, Chang CY, et al. Role of chronic inflammation in myopia progression: clinical evidence and experimental validation. *E Bio Medicine.* 2016;10:269–281.
 269. Shafer BM, Qiu M, Rapuano CJ, Shields CL. Association between hay fever and high myopia in United States adolescents and adults. *Eye Contact Lens.* 2017;43:186–191.
 270. Kung YJ, Wei CC, Chen LA, et al. Kawasaki disease increases the incidence of myopia. *Biomed Res Int.* 2017;2017:2657913.
 271. Ait-Khaled N, Pearce N, Anderson HR, et al. Global map of the prevalence of symptoms of rhinoconjunctivitis in children: The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three. *Allergy.* 2009;64:123–148.
 272. Gordon-Shaag A, Millodot M, Shneur E, Liu Y. The genetic and environmental factors for keratoconus. *Biomed Res Int.* 2015;2015:795738.
 273. Guggenheim JA, Williams C, UK Biobank Eye and Vision Consortium. Childhood febrile illness and the risk of myopia in UK Biobank participants. *Eye (Lond).* 2016;30:608–614.
 274. Landis EG, Yang V, Brown DM, Pardue MT, Read SA. Dim light exposure and myopia in children. *Invest Ophthalmol Vis Sci.* 2018;59:4804–4811.