PERSPECTIVE

Myopia Control in Children through Refractive Therapy Gas Permeable Contact Lenses: Is it for Real?

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• PURPOSE: **To compare the safety and efficacy of orthokeratology as a nonsurgical treatment for myopia in children with alternate methods, such as soft contact lenses, rigid gas permeable lenses, and spectacles, throughout multiple studies.**
• DESIGN: **Perspective with literature review.**
• METHODS: **Analysis of recent studies to determine the safety and effectiveness of orthokeratology versus soft contact lenses, rigid gas permeable lenses, and spectacles in children.**
• RESULTS: **In all of the studies reviewed, the use of orthokeratology lenses proved to reduce myopia, to improve visual acuity, and, with the exception of the SMART study, to reduce the rate of axial elongation. Orthokeratology has been shown to be as effective as other methods in treating myopia and to be more effective at treating axial elongation. There were no major adverse events in any of the studies comparing orthokeratology with other methods of myopia treatment.**
• CONCLUSIONS: **Studies show that the use of orthokeratology is a safe and efficacious nonsurgical treatment for myopia and that it is capable of slowing axial elongation, making it an effective myopic treatment for children. (Am J Ophthalmol 2013;156:1076–1081.**

UNCORRECTED REFRACTIVE ERRORS ARE THE world's leading cause of visual impairment, with myopia estimated to be the leading form of refractive error worldwide.[1,2] Nearly 30% of Americans and up to 85% of the East Asia population are affected by myopia. Instances of myopia in 19-year-old Korean males reached 96.54% in a recent study. The study also showed that myopia increased with education levels, indicating a positive correlation between myopia and educational achievement.[3] Many efforts have been made to try to suppress and even reverse myopic development, including pharmaceutical, surgical, and corrective lens solutions. The most successful of these treatments was the use of antimuscarinic medications, such as atropine, pirenzepine gel, and cyclopentolate. However, this approach led to adverse side effects of light sensitivity and blurred vision. The drugs required were not readily available to the patient, making the treatment costly and impractical.[4] Orthokeratology, or the more current technique of corneal reshaping or refractive therapy, is a more effective strategy for addressing myopia up to −5 diopters (D) and astigmatism up to 1.5 D. It alters how light is refracted by reshaping the cornea into a flatter surface while slowing axial length elongation in younger patients. It is reversible, so if the patient is unhappy with the treatment, they can simply discontinue wearing the lenses.

Accepted for publication Apr 30, 2013.
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DEVELOPMENT OF ORTHOKERATOLOGY

ORTHOKERATOLOGY WAS FIRST NOTED IN THE 1950S BY Wesley and Jessen when their patients were experiencing what they called spectacle blur caused by reshaping of the cornea after wearing hard contact lenses.[5] Although spectacle blur was seen as a nuisance at the time, it was the springboard for later studies. In the 1960s, Jessen created the first orthokeratology lenses out of polymethyl methacrylate, a hard plastic that was uncomfortable and did not allow oxygen to reach the cornea, preventing orthokeratology from expanding as a common practice.[6] Orthokeratology continued in the 1970s with the use of tight and flat-fitting rigid contact lenses. These lenses were able to reduce myopia only by approximately 1 D and were ineffective at allowing oxygen to pass through the lens, making orthokeratology more of a novelty. The late 1970s ushered in a new era of contact lens materials. Rigid gas permeable lenses were designed from new plastic materials that allowed oxygen to reach the cornea, improving comfort and safety. However, the lenses still remained incapable of effectively correcting myopia, and the orthokeratology trend began to die down.[7] In 1989, the first reverse geometry lens was designed by Richard Wlodyga. The lens gave the secondary curve a steeper slope than the base curve, accelerating the time for the lens effect

0002-9394/$36.00
http://dx.doi.org/10.1016/j.ajo.2013.04.039

to occur, while improving correction from −1 D to −1.7 D of myopia and improved lens centration.[8] Using a higher Dk lens, which represents higher oxygen permeability, different reverse geometry rigid gas permeable lens designs, and advances in corneal topography, Contex was able to obtain approval for their orthokeratology design for daily wear from the Food and Drug Administration (FDA) in 1998. Many other investigators followed with their creative designs for better centration and astigmatism control. In 2002, the FDA approved an overnight wear contact by Paragon Vision Sciences, which revitalized this industry and was called corneal refractive therapy. Overnight wear, higher oxygen permeability, and accelerated results allowed corneal refractive therapy to become more popular to the eye care professional and the public.[9] Orthokeratology lenses represented more than 5% of the rigid gas permeable lens market in 2011, with double-digit growth in sales over the last few years.[10]

HOW ORTHOKERATOLOGY LENSES WORK

REVERSE GEOMETRY GAS PERMEABLE LENSES ARE USED TO reshape the cornea of a myopic eye. A normal cornea is steep centrally and gradually flattens to the periphery, causing light to be focused before it is able to reach the macula centrally and behind the retina in the periphery (peripheral hyperopia). These reverse geometry lenses differ from standard rigid gas permeable lenses because the central base curve is much flatter than the secondary curve. The reverse geometry lenses produce flattening of the central cornea, which allows light to be focused on the retina instead of in front of the retina. The lens creates a positive pushing pressure against the central cornea and a negative pulling pressure against the mid peripheral cornea, redistributing the epithelial cells to the mid periphery while flattening the central cornea via a thinning of the epithelial layer.[11] These 2 pressures give the cornea a more plateau shape.[12] The plateau shape allows for light to be refracted simultaneously onto the mid peripheral retina and macula, correcting myopia.

Orthokeratology lenses also are linked to slowing axial length elongation, a major cause of myopia, by treating peripheral hyperopia. A study by Smith and associates showed the relationship of peripheral vision and axial length elongation. In the study, the authors ablated the fovea and macula of monkeys with a laser, leaving the peripheral retina intact, and compared this group with another group in which they ablated the mid periphery of the retina, leaving the fovea and macula intact. Elongation occurred only in the monkeys that had damage to the mid periphery of the retina. The group that had macular damage showed no increase in axial length.[13]

These results were confirmed in a study that gave chicks a 2-zone lens that mimicked central hyperopia, central myopia, peripheral hyperopia, and peripheral myopia. The lenses that altered vision in the periphery had the most effect in stimulating eye growth. The lenses that affected only the central vision did not show a significant change in eye growth.[14] Because emmetropization is now thought to be linked to peripheral vision, focusing light on to the central retina will temporarily fix the myopia only and will not slow its progression.[15] The orthokeratology lens design reduces peripheral hyperopia by aligning the image shell on to the mid-peripheral retina, allowing eyes to move toward the ideal optical state. Myopic eyes treated with spectacles or conventional contact lenses do not correct peripheral hyperopia, causing elongation to continue.

EFFICACY OF ORTHOKERATOLOGY

THE EFFICACY OF ORTHOKERATOLOGY TREATMENT HAS been long debated because of early studies showing only slow improvement in patients with low degrees of myopia and increased rates of infection.[16] However, development of reverse geometry lenses, materials that improve oxygen permeability, and better training in orthokeratology fitting and patient compliance have led to increased benefits and safety of this procedure.

The Contact Lens and Myopia Progression study by Walline and associates was conducted to determine how conventional rigid gas permeable lenses affected myopia progression in children versus soft contact lens wearers. The initial mean cycloplegic retinoscopy of both groups was −2.09 D. After 3 years of wear, the cycloplegic retinoscopy of rigid gas permeable wearers was −1.56 D, whereas the soft contact lens cycloplegic retinoscopy was −2.19 D. The study showed a 29% slower progression of myopia in the rigid gas permeable group when compared with the soft contact lens group. The results were significant with a P value of 0.002 This study also showed that there was no significant difference in axial length ($P = 0.72$) between the two groups, but the soft contact lens group demonstrated greater corneal steepening than the rigid gas permeable group, which likely was the cause of the worsened myopia.[17] The Contact Lens and Myopia Progression study revealed that wearing spherical rigid gas permeable lenses was an ineffective treatment for slowing the progression of myopia and that it required something beyond spherical rigid gas permeable lenses.

The Longitudinal Orthokeratology Research in Children (LORIC) study, conducted by Cho and associates, was a 2-year pilot study in Hong Kong to determine if orthokeratology can treat and prevent myopia. The orthokeratology treatment was conducted by the same examiner to improve accuracy, and the spectacle control data were

provided by a previous study conducted by Edwards.[18] The children all had a spherical equivalent refraction between −0.25 D and −4.50 D, with astigmatism of less than 2.00 D. After the 2-year study had been completed, the spherical equivalent refraction error for the orthokeratology group showed a mean myopic reduction of 2.09 ± 1.34 D, whereas the spectacle group showed a mean myopic increase of 1.20 ± 0.61 D. The axial length change was 0.29 ± 0.27 mm, with a vitreous chamber depth change of 0.23 ± 0.25 mm for the orthokeratology group and 0.54 ± 0.27 mm for axial length, with a vitreous chamber depth change of 0.48 ± 0.26 mm for the spectacle group. The axial length and vitreous chamber depth change in the orthokeratology group were half of that of the spectacle group, which was statistically significant with a *P* value of 0.005. This study showed that orthokeratology not only was an effective treatment of myopia up to −4.00 D, but also that it can prevent myopia by slowing axial length and vitreous chamber growth.[19]

The purpose of the Children's Overnight Orthokeratology Investigation (COOKI) study, conducted by Walline and associates, was to determine the spherical equivalence refraction change and safety of orthokeratology treatment over a period of 6 months. The COOKI study showed that the mean spherical equivalence refraction error changed from −2.44 ± 1.38 D at baseline to −0.16 ± 0.66 D at 6 months in the orthokeratology wearers. Of the eyes tested, 47.4% had 20/20 visual acuity or better and 100% achieved 20/40 visual acuity or better. Ideal visual acuity levels were obtained after 1 week of wear, with the effect lasting throughout the day at two weeks.[20] This time was reduced from previous studies that required up to 300 days of wear for spherical lenses and 40 days for early reverse geometry designs.[21] The COOKI study showed that use of orthokeratology lenses was more effective than spherical rigid gas permeable lenses at treating myopia in children and that it was safe for overnight use.

Walline and associates also conducted the Corneal Reshaping and Yearly Observation of Nearsightedness (CRAYON) study to determine the efficacy of the LORIC study, which indicated that orthokeratology lenses can treat myopia and slow axial length elongation. The CRAYON study compared orthokeratology lenses with soft contact lens. The study showed a mean change in axial length of 0.16 mm less in the orthokeratology group, which was statistically significant with a *P* value of 0.0004. The mean change in vitreous chamber depth was 0.10 mm less in the orthokeratology group, a statistically significant difference with a *P* value of 0.006.[22] The CRAYON study confirmed the results of the LORIC study by Cho and associates that showed that orthokeratology lenses can reduce axial length elongation by half and are an effective preventative treatment for myopia progression.

The Stabilizing Myopia by Accelerated Reshaping Technique (SMART) study was the first large-scale study to determine if wearing reverse geometry overnight orthokeratology lenses would slow the progression of myopia in children. The SMART study enlisted 162 children to test the efficacy of orthokeratology. The orthokeratology lenses were compared with soft contact lens that were changed every month. The SMART study was conducted in 10 clinics throughout the United States. After the 3-year study, 85% of orthokeratology patients achieved an uncorrected visual acuity of 20/20 or better and 99% achieved an uncorrected visual acuity of 20/40 or better. The 3-year test results of the SMART study showed that the orthokeratology group was less myopic than the soft contact lens group, with a mean change spherical equivalence refraction for the orthokeratology group being −0.19 D in the right eye and −0.15 D in the left eye at the end of the third year. These readings were obtained after the orthokeratology lenses were removed from the patients and their refraction and topography were allowed to stabilize at two separate time points. The mean change in spherical equivalence refraction for the soft contact lens groups was −1.00 D in the right eye and −1.02 D in the left eye at the end of the third year. The SMART study did show a statistically significant difference in spherical equivalent refraction, but did not show any significant change in axial length between the orthokeratology and soft contact lens group. Lack of change of the axial length between the two groups is considered to be the result of the study being conducted by different practices with different techniques and machines for determining axial length (Gerowitz RS. Contact Lens and Anterior Eye 2012(35):E-Abstract 40).

Another study that validates the efficacy of orthokeratology treatment on myopic children titled "Influence of Overnight Orthokeratology on Axial Elongation in Childhood Myopia" was conducted in Japan to compare axial length in orthokeratology patients versus in those with spectacles. The baseline data for the orthokeratology group included a mean spherical equivalence refraction of −2.55 ± 1.82 D, a mean uncorrected visual acuity of 0.80 ± 0.32 D, and a mean axial length of 24.66 ± 1.11 mm. The baseline data for the spectacle group included a mean spherical equivalence refraction of −2.59 ± 1.66 D, a mean uncorrected visual acuity of 0.83 ± 0.31 D, and a mean axial length of 24.79 ± 0.80 mm. After two years, the spherical equivalence refraction for the orthokeratology group improved to a mean of −0.68 ± 1.02 D and had a mean axial length change of 0.39 ± 0.27 mm. The spectacle group spherical equivalence refraction dropped to −3.83 ± 1.76 D and had an axial length change of 0.61 ± 0.24 mm. The difference was statistically significant, with a *P* value of less than 0.0001.[23] Axial length measurements were tightly controlled using the IOL Master by Carl Zeiss Meditec and one technician to perform all the measurements. The results from the "Influence of Overnight Orthokeratology on Axial Length Elongation in Childhood Myopia" study confirm the results of the LORIC and CRAYON

TABLE. Orthokeratology Lenses Compared against Various Control Groups

Study	Age of Patients (y)	Change in Axial Length in Orthokeratology Patients (mm)	Change in Axial Length in Control Group (mm)	Method of Control	Length of Study (y)	Difference between Orthokeratology and Control Groups (%)	P Value
LORIC	7 to 12	0.29	0.54	Glasses	2	46.30	0.005
CRAYON	8 to 11	0.25	0.57	Soft contact lens	2	56.14	0.0004
IOOALECM	8 to 16	0.39	0.61	Glasses	2	36.00	0.0001
MCOS	6 to 12	0.47	0.69	Glasses	2	31.88	0.001
IOOALECM 5-y follow-up	8 to 16	0.99	1.41	Glasses	5	29.79	0.863
ROMIO	6 to 10	0.36	0.63	Glasses	2	57.14	0.001

CRAYON = Corneal Reshaping and Yearly Observation of Nearsightedness; IOOAECM = Influence of Overnight Orthokeratology on Axial Elongation in Childhood Myopia; LORIC = Longitudinal Orthokeratology Research in Children; MCOS = Myopia Control with Orthokeratology Contact Lenses in Spain; ROMIO = Retardation of Myopia in Orthokeratology. Each study showed that the group with orthokeratology treatment showed a reduction in axial length.

studies showing that that orthokeratology treatment reduces the rate of elongation of axial length and helps to treat myopia. There was published a 5-year follow-up of the "Influence of Overnight Orthokeratology on Axial Length Elongation in Childhood Myopia" study showing that orthokeratology was effective in long-term treatment. After 5 years, the mean change in axial length for the orthokeratology group was 0.99 ± 0.47 mm and that for the spectacle group was 1.41 ± 0.68 mm. The changes in axial length over each year were significantly different at the third year, with a *P* value of 0.0385. However, at year 5, the changes in axial length were no longer significantly different, with a *P* value of 0.8633.[24]

A recent study called "Myopia Control with Orthokeratology Contact Lenses in Spain," by J Santodomingo-Rubido and associates, was conducted to determine the effect of orthokeratology lenses on axial growth when compared with single-vision spectacles. The study found that the mean change in axial length over a 2-year period for the orthokeratology group was 0.47 mm and that for the spectacle group was 0.69 mm, which was statistically significant with a *P* value of less than 0.001.[25] These results show that orthokeratology has a slowing effect on axial length elongation when compared with the control group.

Finally, a randomized 2012 study conducted by Cho and Cheung assessed the effectiveness of orthokeratology and at what age orthokeratology most benefitted the patient. The study included 102 subjects 6 to 10 years of age. The study concluded that axial length elongation was slowed by 43% in children who wore orthokeratology lenses, a statistically significant difference with a *P* value of less than 0.001. At the end of the 2-year study, the average increase in axial length elongation of orthokeratology patients was 0.36 ± 0.24 mm and the average increase in the spectacle control group was 0.63 ± 0.26 mm. The study also concluded that children 7 to 8 years of age had a faster rate of axial length elongation than older children. This finding determined that younger children at approximately age 7 years benefitted to a greater degree from orthokeratology treatment.[26]

Each of these studies shows that orthokeratology has a sizable advantage in correcting and treating myopia when compared with single-vision spectacles, soft contacts, and standard rigid gas permeable lenses (Table).

SAFETY OF ORTHOKERATOLOGY LENSES

ADVANCEMENT IN LENS MATERIAL NOT ONLY HAS increased the rate at which orthokeratology can reach its maximum effect, but also it has increased safety. The original lens material used in orthokeratology, polymethyl methacrylate, had a negligible oxygen transmission (Dk = 0), causing them to be unsafe for extended wear. The material used in today's overnight extended wear gas permeable lenses have a Dk value ranging from 49 to 163, indicating high oxygen permeability and reduced risk of infection. There have been a total of 123 instances of microbial keratitis in orthokeratology patients reported between 1997 and 2007. Most of the reported cases were found in East Asian children ranging in age from 9 to 15 years of age. Common organisms found were *Pseudomonas aeruginosa* and *Acanthamoeba*. Risk factors determined in this study were inappropriate lens care, patient not following practitioner's instructions, and continuation of lens wear despite discomfort.[27] There is rising support for the safety of orthokeratology as a safe overnight treatment as patient compliance continues to improve. Orthokeratology does not seem to have an increased role in developing microbial keratitis as long as there is proper care for the lenses.[28]

The safety of orthokeratology also was evaluated in the SMART study, the COOKI study, a study at the Ohio State

University School of Optometry, and the Paragon Vision Sciences FDA postmarket surveillance. The SMART study found that there were 13 instances of grade 2 or higher biomicroscopic events in the orthokeratology group and 12 instances in the soft contact lens group. The soft contact lens group was the only group to show signs of corneal infiltrative keratitis (Gerowitz RS. Contact Lens and Anterior Eye 2012(35):E-Abstract 40). The COOKI study showed that 3 of 5 of the patients had fluorescein staining in the morning and 1 of 3 had staining in the afternoon. The mean staining rating was a 1.60 on a scale from 1 to 4, and none of the incidences was serious enough to stop use of the lenses. Walline and associates report low severity of staining in orthokeratology wearers and no reason to associate a high risk with overnight orthokeratology.[17] The FDA report for the Paragon Corneal Reshaping Therapy lens showed no slit-lamp instances that were worse than grade 2, and all instances could be corrected with no other complications.[9] It also showed that the orthokeratology lenses had no effect on intraocular pressure. Santodomingo-Rubido and associates evaluated the number of adverse events in orthokeratology patients versus a spectacle group. The study found that 9 of 61 patients experienced an adverse event and that 3 of those patients experienced adverse events not attributable to orthokeratology lens wear.[29]

The instances of microbial keratitis initiated a postmarket study conducted by the FDA and the Ohio State University. The results showed 7.7 instances of microbial keratitis per 10 000 person-years of wear, making orthokeratology wearers only slightly more susceptible to infection than daily soft contact lens wearers at 4.1 per 10 000 (Bullimore MA. Optom Vis Sci 2009;86:E-Abstract 90583). The original study by Schein and associates estimated the rate of microbial keratitis in 30-day extended wear silicone hydrogel lens wearers to be 14.4 per 10 000 person-years of wear.[30] The low instances and severity of adverse events in orthokeratology indicate that the method is safe for treating myopia in children. The lenses are worn for 6 to 8 hours per night and are made of a high Dk material, providing the eye with proper oxygenation. The lenses are also 10 mm in diameter and do not cover the limbus, preventing damage to stem cells. The lenses only change the shape of the epithelium and do not alter or damage the endothelium.

Training and certifications in fitting orthokeratology lenses, as required by the FDA, also has improved safety. Previously, orthokeratology lenses were able to be fit by anyone trained in rigid gas permeable lenses, but now certification is required by the companies to fit their orthokeratology lens design. Requiring a separate certification reduces the chance of a poor lens fit, another risk factor for microbial keratitis. Patient compliance is improving because of an effort by practitioners in promoting proper lens care, reducing the number of infections seen recently in orthokeratology wearers.

DEVELOPING APPLICATIONS OF ORTHOKERATOLOGY

ORTHOKERATOLOGY PROMISES TO IMPROVE ON ITS current standard by accelerating the time for the lenses to affect the cornea, better lens centration, greater safety with higher Dk valued lenses, and improved solutions for proper lens care. Lenses that are able to correct higher degrees of astigmatism also are being developed to allow more patients to wear orthokeratology lenses. There are also studies being conducted to make orthokeratology a treatment for keratoconus using the technique to reshape the cornea and then applying riboflavin and ultraviolet A light to stabilize the new shape of the cornea and to prevent further development of keratoconus.[31] Despite early trials being unsuccessful at stabilizing the cornea's shape, the orthokeratology lenses did flatten the cornea, reducing keratoconus in the patient. Advancements in collagen cross-linking materials would improve the success rate of the treatment. Recently, El Hage and Seiler presented 5 patients of who successfully underwent cross-linking with riboflavin and ultraviolet A light, combined with orthokeratology to treat myopia.[32] Koffler and associates showed in 1999 that a plateau-shaped gas permeable contact lens could be used to modify the shape and resultant refraction of undercorrected radial keratotomy eyes. The use of this orthokeratology method in postsurgical patients combined with cross-linking needs to be investigated further.[33] Another treatment being investigated is using orthokeratology to treat hyperopia by steepening the cornea. A study was conducted that showed that the use of hyperopia orthokeratology does steepen the cornea and produces the desired shape change in cats.[34]

CONCLUSIONS

THE INITIAL PRACTICE OF ORTHOKERATOLOGY PROVED TO be ineffective, but with new development of lens material and designs especially for overnight wear, orthokeratology has developed into a viable and effective treatment for myopia. Studies suggest that current techniques are highly effective at treating myopia of up to −6.00 D and astigmatism of up to −1.75 D. Orthokeratology is an effective option in slowing the progression of myopia by redirecting the image shell onto both the central and mid-peripheral retina, thereby producing emmetropization. Improved training, better lens hygiene, and patient compliance have promoted the safety of orthokeratology to make it as safe as other overnight methods. The future will bring further applications of orthokeratology to treat other refractive errors. Orthokeratology is a very useful tool in combating refractive errors in myopic children and, with further studies, should prove to be useful in a wide range of other refractive disorders.

ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST and the following were reported. Bruce Koffler has received speaking fees and honoraria for from Paragon Vision Sciences, Alcon, Bausch & Lomb, and Merck. James Sears has not received any support.

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Biosketch

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Atropine for the Treatment of Childhood Myopia: Safety and Efficacy of 0.5%, 0.1%, and 0.01% Doses (Atropine for the Treatment of Myopia 2)

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Purpose: Our previous study, Atropine for the Treatment of Myopia 1 (ATOM1), showed that atropine 1% eyedrops were effective in controlling myopic progression but with visual side effects resulting from cycloplegia and mydriasis. The aim of this study was to compare efficacy and visual side effects of 3 lower doses of atropine: 0.5%, 0.1%, and 0.01%.

Design: Single-center, double-masked, randomized study.

Participants: A total of 400 children aged 6–12 years with myopia of at least −2.0 diopters (D) and astigmatism of −1.50 D or less.

Intervention: Children were randomly assigned in a 2:2:1 ratio to 0.5%, 0.1%, and 0.01% atropine to be administered once nightly to both eyes for 2 years. Cycloplegic refraction, axial length, accommodation amplitude, pupil diameter, and visual acuity were noted at baseline, 2 weeks, and then every 4 months for 2 years.

Main Outcome Measures: Myopia progression at 2 years. Changes were noted and differences between groups were compared using the Huber–White robust standard error to allow for data clustering of 2 eyes per person.

Results: The mean myopia progression at 2 years was −0.30±0.60, −0.38±0.60, and −0.49±0.63 D in the atropine 0.5%, 0.1%, and 0.01% groups, respectively (P=0.02 between the 0.01% and 0.5% groups; between other concentrations $P > 0.05$). In comparison, myopia progression in ATOM1 was −1.20±0.69 D in the placebo group and −0.28±0.92 D in the atropine 1% group. The mean increase in axial length was 0.27±0.25, 0.28±0.28, and 0.41±0.32 mm in the 0.5%, 0.1%, and 0.01% groups, respectively ($P < 0.01$ between the 0.01% and 0.1% groups and between the 0.01% and 0.5% groups). However, differences in myopia progression (0.19 D) and axial length change (0.14 mm) between groups were small and clinically insignificant. Atropine 0.01% had a negligible effect on accommodation and pupil size, and no effect on near visual acuity. Allergic conjunctivitis and dermatitis were the most common adverse effect noted, with 16 cases in the 0.1% and 0.5% atropine groups, and no cases in the 0.01% group.

Conclusions: Atropine 0.01% has minimal side effects compared with atropine at 0.1% and 0.5%, and retains comparable efficacy in controlling myopia progression.

Financial Disclosure(s): The author(s) have no proprietary or commercial interest in any materials discussed in this article. *Ophthalmology 2012;119:347–354 © 2012 by the American Academy of Ophthalmology.*

Atropine eyedrops were first proposed as a treatment of myopia in the 1920s.[1] Since then, there have been numerous studies on this subject.[2–12] However, evidence from randomized control trials has become available only over the last 2 decades.[13–18] These trials confirm that atropine eyedrops are effective in the control of myopia in a dose-related manner.[13–18] Our previous randomized trial, Atropine for the Treatment of Myopia 1 (ATOM1), involving 400 children aged 6 to 12 years found that, over 2 years, atropine 1% slowed myopia progression (mean ± standard deviation) to −0.28±0.92 diopters (D) in children, compared with −1.20±0.69 D in the placebo group ($P < 0.001$).[16] Shih et al[14] showed that the myopic progression in Taiwanese children was −0.04±0.63, −0.47±0.91, and −0.47±0.91 D/year in the 0.5%, 0.25%, and 0.1% atropine groups, respectively, compared with −1.06±0.61 D/year in their tropicamide (control) group. Liang et al,[17] in a smaller study of 65 children, demonstrated myopic progression of −0.15±0.15, −0.38±0.32, and −0.21±0.23 D/year in the 0.5%, 0.25%, and 0.25% atropine plus auricular pressure groups, respectively.

In the second study, Atropine for the Treatment of Myopia 2 (ATOM2), we examined the effect of lower doses of atropine to determine whether these concentrations could result in efficacy in preventing myopia progression, with

ISSN 0161-6420/12/$–see front matter
doi:10.1016/j.ophtha.2011.07.031

less visual side effects (i.e., pupil dilation, loss of accommodation, and near vision blur). The ATOM2 study comprises 2 phases: a treatment phase lasting 24 months, followed by a washout period of 12 months, and then a second phase in which children showing myopic progression will recommence taking atropine at a dosage found optimal in the first phase. This article presents results in the first 24 months (first phase) of the ATOM2 study.

Materials and Methods

Children aged 6 to 12 years with myopic refraction of at least 2.0 D in both eyes, astigmatism of less than 1.5 D, and documented myopic progression of at least 0.5 D in the past year were enrolled in a double-masked, single-center clinical trial. Excluded were those with ocular pathology (e.g., amblyopia, strabismus), previous use of atropine or pirenzepine, an allergy to atropine, or systemic ill health (e.g., cardiac or respiratory illness). Written informed consent was obtained from parents or guardians, and verbal assent was obtained from children. The study was conducted according to the tenets of the Declaration of Helsinki, with ethics approval from the Singapore Eye Research Institute Review Board. This study was registered with the ClinicalTrial.gov website (registration no: NCT00371124).

Participants were randomized to receive 0.5%, 0.1%, or 0.01% atropine once nightly in both eyes at an allocation ratio of 2:2:1 in 6 strata defined by gender and age groups of 6 to 7, 8 to 10, and 11 to 12 years, respectively, to ensure gender and age balance across the 3 treatment arms. Trial medications were prepackaged so that bottles were prelabeled with subject number and of similar appearance. Trial medication consisted of the appropriate dose of atropine sulfate with 0.02% of 50% benzalkonium chloride as a preservative (Ashwood Laboratories Ltd., Macau, China).

After assessment at the time of recruitment (baseline), children were reassessed 2 weeks after starting atropine (baseline 2) and then at 4, 8, 12, 16, 20, and 24 months. At each visit, distance best-corrected visual acuity (BCVA) logarithm of the minimum angle of resolution (logMAR) was assessed by an optometrist using the Early Treatment Diabetic Retinopathy study chart. Near visual acuity was assessed using best-corrected distance spectacle correction with a reduced logMAR reading chart placed at 40 cm under well-lit conditions. The near point of accommodation was measured using a Royal Air Force near point rule using best-corrected distance spectacle correction. Children were instructed to move the target inward until the N5 print became slightly blurred and then outward until it just became clear. Accommodation amplitude was calculated as the inverse of near point of accommodation. Mesopic pupil size was measured with the Procyon 3000 pupillometer (Lion House, Red Lion Street, London, UK), using the Meso-Hi (4 lux) setting. Photopic pupil size was measured using the Neuroptics pupillometer (Neuroptics Inc., Irvine, CA), while children were viewing a target placed at 3 m, after at least 10 seconds of exposure to lamps providing 300 lux of luminance. In both cases, at least 5 pupil size readings (with range <0.5 mm) were recorded and averaged.

Cycloplegic autorefraction was determined 30 minutes after 3 drops of cyclopentolate 1% (Cyclogyl, Alcon-Convreur, Rijksweg, Belgium) were administered at 5 minutes apart using a Canon RK-F1 autorefractor (Canon Inc. Ltd., Tochigiken, Japan). Five readings, all of which had to be less than 0.25 D apart, were obtained and averaged. Spherical equivalent was calculated as sphere plus half cylinder power. The Zeiss IOLMaster (Carl Zeiss Meditec Inc., Dublin, CA), a non-contact partial coherence interferometry, was used to measure the ocular axial length. Five readings, with a maximum-minimum deviation of 0.05 mm or less, were taken and averaged.

Parents or guardians, children, and study investigators were kept masked to the assigned dosage of trial medications. Each child kept a diary of use of the trial medication. Compliance level of each subject was classified according to the mean number of frequency of using atropine per week as reported by participants over the first 24 months. Subjects with 75% compliance rate ($\geq$5.25 days/week) were considered compliant.

Children were also offered photochromatic glasses (which darken on exposure to ultraviolet or sunlight) if they experienced glare or their parents were worried of excessive light exposure, or progressive glasses (reading add) if children experienced difficulty with near vision.

The primary end point was myopia progression over 2 years. Because a hyperopic shift may occur after commencing atropine, myopic progression was calculated from the second baseline, when children had been taking trial medication for 2 weeks. Level of myopia progression in each eye was further categorized as mild ($<$0.5 D), moderate (0.5–0.99 D), or severe ($\geq$1.0 D).

Secondary end points included myopia progression at 1 year, change in axial length at 1 and 2 years, and side effect parameters, such as changes in accommodation amplitude, mesopic and photopic pupil size, and distance and near BCVA. Myopia and axial changes were noted from second baseline, whereas accommodation, pupil size, and visual acuity were monitored from the first baseline.

During each visit, children and parents were given an open-ended opportunity to report any medical illness or side effects. They were also specifically asked about symptoms related to allergy, blurred near vision, glare, or visual loss, and if children had been ill or hospitalized since the last visit. Any adverse events, regardless of whether they appeared relevant to atropine use, were documented.

Statistic Analysis

On the basis of findings from the various studies, it was estimated that the myopia progression rate for 0.5%, 0.1%, and 0.01% atropine would be -0.04, -0.47, and -0.76 D, respectively.[13–18] To achieve 90% power using a 2:2:1 randomization for 0.5%: 0.1%:0.01%, a sample size of 325 subjects (130:130:65) is needed. By factoring in an attrition rate of 20%, a sample size of 400 subjects (i.e., 160:160:80) is needed.

All analyses were based on intention-to-treat principle and performed with Stata statistical software (version 10.1, StataCorp., College Station, TX). For demographic and other person-level data, such as compliance and ever experiencing adverse events, the Fisher exact test was used to test for the difference in the proportion of subjects between treatment groups, and analysis of variance was used for the difference in means between treatment groups. End points from both eyes were pooled in a combined analysis using the Huber–White robust standard errors to allow for the correlation between eyes within person.[19] The results on left and right eyes were similar. For example, the mean difference (95% confidence interval [CI]) in 2-year myopia progression between left and right eyes was -0.01 (-0.06 to 0.03). For brevity and better precision, this report shows analyses pooling both eyes with robust standard errors for clustered data. The global null hypothesis of no difference among 3 treatment groups was tested first, followed by pairwise comparisons. A nominal level of statistical significance (P value) was reported, i.e., no adjustment for multiple comparison. Interpretation will begin with considering the global null hypothesis among 3 groups to prevent inflated type I

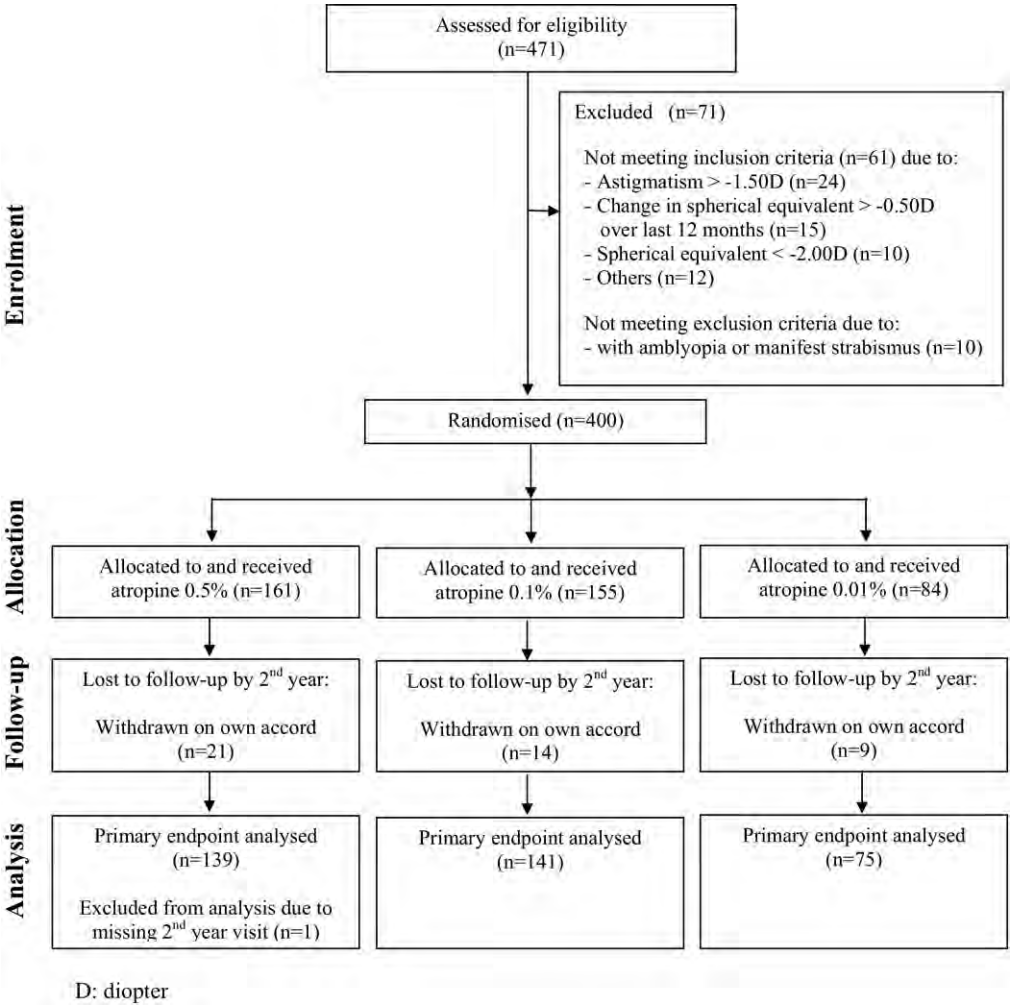

Figure 1. ATOM2 subject flow chart. ATOM = Atropine for the Treatment of Myopia.

error rate. Placebo and atropine-treated eyes in ATOM1 were used for reference in the secondary analyses.

Results

A total of 400 children were recruited into the study, with 161, 155, and 84 children in the 0.5%, 0.1%, and 0.01% atropine treatment arms, respectively (Fig 1). There were almost equal numbers of male and female children, and 91% of children were of ethnic Chinese origin (Table 1). No differences were noted in demographics, baseline refractive error, accommodation, pupil diameter, or BCVA among groups (Table 1). The correlation between change in spherical equivalent and axial length over 2 years was high (correlation coefficient = 0.82, $P < 0.001$), suggesting good measurement validity.

Two-year primary end point data were available for 355 of 400 subjects (88.8%). Forty-four subjects withdrew participation on their own accord: 9 (10.7%), 14 (9.0%), and 21 (13.0%) from the 0.01%, 0.1%, and 0.5% treatment groups, respectively ($P=0.43$); 1 participant did not attend the second year assessment. Compliance, defined as >75% expected use, was 98.7%, 96.8%, and 98.8% in the 0.5%, 0.1%, and 0.01% arms, respectively ($P=0.53$), in the 2-year period.

Change in Myopic Progression and Axial Length

A dose-related response on myopia was noted among the 3 treatment arms, but differences between treatment arms were clinically small (Fig 2). An initial hyperopia shift of 0.3 to 0.4 D was noted in the 0.1% and 0.5% groups but not in the 0.01% group (Table 1). At the end of 1 year, there was a significant difference in myopia progression between the 0.5% atropine group and the 0.01% ($P < 0.001$) and 0.1% ($P=0.01$) groups, but there was no statistical significant difference between the 0.01% and 0.1% groups. The final myopia progression over 2 years was -0.49 ± 0.60, -0.38 ± 0.60, and -0.30 ± 0.63 D in the atropine 0.01%, 0.1%, and 0.5% groups, respectively ($P=0.07$), with a significant difference only between the 0.01% and 0.5% groups (Table 2). There was no significant difference in spherical equivalent levels between groups ($P=0.20$). Fifty percent of the 0.01% group had progressed by less than 0.5 D, compared with 58% and 63% in the 0.1% and 0.5% groups, respectively, with approximately 18% progressing by ≥1.0 D in all 3 groups (Fig 3).

With regard to axial length, change at 1 year was larger in the 0.01% group (0.24 ± 0.19 mm) than in the 0.1% (0.13 ± 0.18 mm) and 0.5% (0.11 ± 0.17 mm) groups ($P < 0.001$) (Fig 4). Pairwise comparison showed a statistically significant difference between

Table 1. Characteristics at Baseline and Second Baseline (i.e., 2 Weeks after Starting Trial Medication)

Variables	Atropine(A) Dose			P Value*
	A 0.01% (n = 84)	*A 0.1% (n = 155)*	*A 0.5% (n = 161)*	
Age (yr), mean (SD)	9.5 (1.5)	9.7 (1.6)	9.7 (1.5)	0.95
Female, %	48.8	46.5	47.2	0.95
Chinese %	90.5	92.3	90.0	0.99
Spherical equivalent (D)				
-baseline	−4.5 (1.5)	−4.8 (1.5)	−4.7 (1.8)	0.40
-second baseline	−4.5 (1.5)	−4.5 (1.4)	−4.3 (1.8)	0.67
Axial length (mm)				
-baseline	25.1 (1.0)	25.2 (0.8)	25.2 (0.9)	0.94
-second baseline	25.2 (1.0)	25.1 (0.8)	25.1 (0.9)	0.93
Accommodation (D)				
-baseline	16.2 (3.4)	16.7 (3.0)	15.8 (3.4)	0.01
-second baseline	11.3 (4.3)	3.8 (2.5)	2.2 (1.2)	<0.001
Mesopic pupil diameter (mm)				
-baseline	3.9 (0.6)	3.9 (0.6)	4.0 (0.7)	0.21
-second baseline	5.2 (0.8)	7.2 (0.7)	7.8 (0.5)	<0.001
Photopic pupil diameter (mm)				
-baseline	4.7 (0.7)	4.6 (0.7)	4.6 (0.7)	0.63
-second baseline	5.8 (0.8)	7.4 (0.7)	7.9 (0.6)	<0.001
Distant BCVA (logMAR)		0.01	0.01	
-baseline	0.01 (0.05)	0.02 (0.06)	0.02 (0.06)	0.56
-second baseline	0.01 (0.05)	0.03 (0.05)	0.01 (0.06)	0.86
Near vision (logMAR)				
-baseline	0.04 (0.09)	0.04 (0.08)	0.04 (0.07)	0.38
-second baseline	0.06 (0.08)	0.29 (0.18)	0.48 (0.16)	<0.001

SD = standard deviation.
*Fisher exact test for binary demographic variables; analysis of variance for age; Huber–White robust standard error for clustered data (both eyes pooled) on ocular parameters.

the 0.01% group and the other 2 groups ($P < 0.001$). This difference persisted to the end of the 24-month period (Table 2).

Changes in Accommodation, Pupil Diameter, and Visual Acuity

There was no difference in accommodation, mesopic, and photopic pupil diameter among groups at baseline (Table 1). However, significant dose-related differences quickly became evident by the second baseline visit (Table 1). Changes within the 0.01% group were significantly less than in the 2 other groups. Accommodation amplitude in the 0.01% group was reduced to only 11.3 D compared with 3.8 D and 2.2 D in the 0.1% and 0.5% groups, respectively (Table 1). In functional terms, this meant that near visual acuity was not significantly impaired in the 0.01% group, whereas deficiencies were noted in the 2 other groups. Mean best-corrected distant visual acuity was not affected by atropine use (Table 2), although 10% of children did encounter mild distance blur (Table 3).

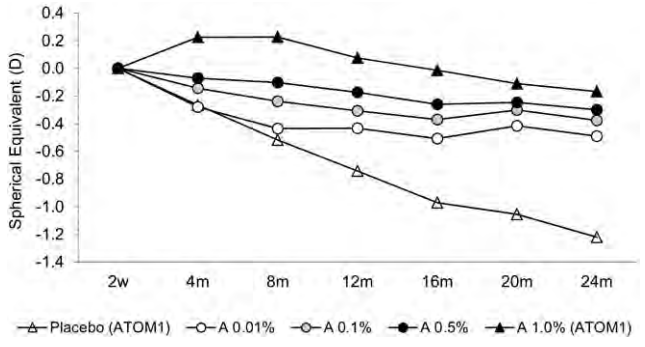

Figure 2. Mean change in spherical equivalent for groups from baseline, 2 weeks, and 4 to 24 months with atropine 0.01%, 0.1%, and 0.5% from the ATOM2 study, and placebo and atropine 1.0% from the ATOM1 study. A = atropine; ATOM = Atropine for the Treatment of Myopia; D = diopter; m = month; w = week.

Pupil size, under both photopic and mesopic conditions, in the 0.01% group increased by only 1 mm, whereas pupils in the 0.1% and 0.5% groups were ~3 mm larger (Table 2). Although the atropine effect on pupil diameter remained unchanged over time, the accommodation appeared to improve in the 0.1% and 0.5% groups over time (Table 2). The mean accommodation amplitude in the 0.5% group, for example, decreased from 15.8 D at baseline to 2.2 D at the second baseline visit but increased to 3.6 D and 4.1 D by the end of the first and second years, respectively. Changes in the 0.01% group were less, varying from 16.2 to 11.3, 11.7, and 11.8 D over the same time period.

Children receiving lower concentrations of atropine were less likely to require progressive lens power in their glasses. For example, in the 234 children aged 8 to 10 years at the start of study, 70%, 61%, and 6% of the children receiving atropine 0.5%, 0.1%, and 0.01%, respectively, requested combined photochromatic progressive glasses, whereas the remainder opted for single-vision photochromatic glasses.

Table 2. Ophthalmology Parameters at Second Annual Visit

	Atropine (A) Dose, Mean (SD)			
	A 0.01%	*A 0.1%*	*A 0.5%*	**P Value**
Spherical equivalent (D)				
-at 1 yr	−4.9 (1.5)	−4.8 (1.4)	−4.6 (1.9)	0.26
-at 2 yrs	−5.1 (1.5)	−4.9 (1.3)	−4.7 (1.7)	0.20
-mean change over 1 yr	−0.43 (0.52)	−0.31 (0.50)	−0.17 (0.47)	<0.001*,‡
-mean change over 2 yrs	−0.49 (0.63)	−0.38 (0.60)	−0.30 (0.60)	0.07*
Axial length (mm)				
-at 1 yr	25.4 (1.0)	25.3 (0.8)	25.3 (0.9)	0.36
-at 2 yrs	25.7 (1.0)	25.4 (0.8)	25.4 (1.0)	0.08†
-mean change over 1 yr	0.24 (0.19)	0.13 (0.18)	0.11 (0.17)	<0.001*,†
-mean change over 2 yrs	0.41 (0.32)	0.28 (0.27)	0.27 (0.25)	0.002*,†
Accommodation (D)				
-at 1 yr	11.7 (4.3)	6.0 (3.4)	3.6 (3.2)	<0.001*,†,‡
-at 2 yrs	11.8 (3.2)	6.8 (3.4)	4.0 (2.6)	<0.001*,†,‡
-mean change over 1 yr	−4.4 (4.9)	−10.9 (4.0)	−12.4 (3.3)	<0.001*,†,‡
-mean change over 2 yrs	−4.6 (4.2)	−10.1 (4.3)	−11.8 (4.4)	<0.001*,†,‡
Mesopic pupil size (mm)				
-at 1 yr	5.1 (0.9)	6.7 (1.0)	7.5 (1.1)	<0.001*,†,‡
-at 2 yrs	5.1 (0.9)	6.7 (1.1)	7.5 (1.2)	<0.001*,†,‡
-mean change over 1 yr	1.15 (0.78)	2.77 (1.03)	3.50 (1.05)	<0.001*,†,‡
-mean change over 2 yrs	1.15 (0.71)	2.71 (1.12)	3.56 (1.14)	<0.001*,†,‡
Photopic pupil size (mm)				
-at 1 yr	5.6 (0.8)	7.0 (1.0)	7.7 (1.0)	<0.001*,†,‡
-at 2 yrs	5.5 (0.8)	6.9 (1.0)	7.8 (1.1)	<0.001*,†,‡
-mean change over 1 yr	0.91 (0.78)	2.42 (0.91)	3.11 (1.08)	<0.001*,†,‡
-mean change over 2 yrs	0.74 (0.75)	2.25 (1.01)	3.11 (1.10)	<0.001*,†,‡
Distant BCVA (logMAR)				
-at 1 yr	−0.005 (0.042)	−0.003 (0.054)	−0.003 (0.054)	0.99
-at 2 yrs	−0.001 (0.057)	0.005 (0.054)	0.011 (0.057)	0.25
-mean change over 1 yr	−0.02 (0.05)	−0.02 (0.06)	−0.03 (0.05)	0.21
-mean change over 2 yrs	−0.02 (0.06)	0.01 (0.06)	−0.01 (0.06)	0.44
Near vision (logMAR)				
-at 1 yr	0.03 (−0.06)	0.15 (0.15)	0.35 (0.18)	<0.001*,†,‡
-at 2 yrs	0.01 (0.07)	0.10 (0.13)	0.29 (0.18)	<0.001*,†,‡
-mean change over 1 yr	−0.01 (0.10)	0.10 (0.16)	0.32 (0.19)	<0.001*,†,‡
-mean change over 2 yrs	−0.02 (0.08)	0.06 (0.13)	0.25 (0.19)	<0.001*,†,‡

SD = standard deviation.
Myopia progression and axial length: change from second baseline; other parameters: change from initial baseline. *P* values for test of global null hypotheses of all groups being the same are shown. Pairwise comparison *P* values are represented by*significant ($P < 0.05$) difference between atropine 0.01% and 0.5%;†significant difference between atropine 0.01% and 0.1%; and‡significant difference between atropine 0.1% and 0.5%.

Adverse Events

The majority of the adverse events were deemed to be unrelated to study treatment (e.g., flu-like illness) (Table 3). Adverse reactions directly attributable to atropine included allergic conjunctivitis, which occurred in 13 children (4.1%) in the atropine 0.1% and 0.5% groups. In 3 subjects (1.2%), symptoms were severe enough to warrant ceasing trial medication. Four children in the 0.1% and 0.5% groups (1.3%) had allergy-related dermatitis of the eyelids. Six children had other eye symptoms, 5 of which could be attributed to atropine, including 1 case of irritation and 1 case of blur in the atropine 0.01% group, and 2 cases of ocular irritation and 1 case of intolerable glare in the atropine 0.5% group.

Seven children had a severe adverse event requiring hospitalization. In the 0.01% group, 1 child had acute gastric pain. In the 0.1% group, there was 1 case each of appendicitis, respiratory infection, and Ewing's sarcoma. In the 0.5% group, there was 1 case each of tachycardia, dengue fever, and gastroenteritis. None of these events are thought to be associated with atropine.

Discussion

Childhood myopia is a major public health problem in Singapore. In a recent Strabismus, Amblyopia and Refractive Error in Singaporean Children study (2005–2009) involving preschool Chinese children, myopia (spherical equivalence, ≤−0.5 D) was already present in 7% of 4- to 5-year-old children.[20] The prevalence of myopia in the Singapore Cohort Study of Risk Factors for Myopia study (1999–2003) was noted to be 28%, 32%, and 43% in 7-, 8-, and 9-year-old children, respectively, with a subsequent 3-year cumulative myopia progression of −2.4 D (95% CI, −2.6 to −2.2), −2.0 D (95% CI, −2.1 to −1.8), and −1.7 D (95% CI, −2.0 to −1.4) in each group, respectively.[21] By the time children were aged 12 years, 61% were myopic and 10% were highly myopic (<−6 D) (Saw SM, personal communication, 2011). Army-based studies (1996–1997)

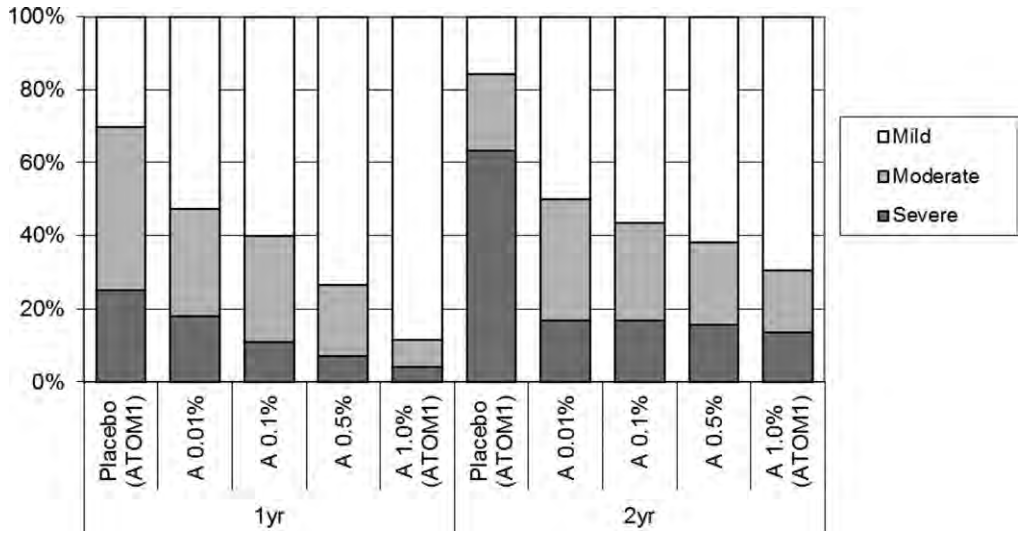

Figure 3. Progression of myopia according to severity (pooled eyes) with atropine 0.01%, 0.1%, and 0.5% from the ATOM2 study, and placebo and atropine 1.0% from the ATOM1 study, at 1 and 2 years. Myopia progression from baseline 2 if >1 D (severe), 0.5–0.99 D (moderate), and <0.5 D (mild). A = atropine; ATOM = Atropine for the Treatment of Myopia; D = diopter.

place the prevalence of myopia in young male conscripts at 79%, with 13% being highly myopic.[22]

Atropine is a nonspecific muscarinic antagonist.[1,23] It is uncertain how atropine acts to inhibit myopia progression.[1,24–28] Initially, inhibition of accommodation was thought to be important, but subsequent studies have shown that atropine also inhibits myopia in animals (e.g., in chickens) that have no accommodative facility.[24] One theory is that atropine and other muscarinic antagonists may have biochemical effects on the retina or sclera, which in turn affect remodeling of the sclera.[25,26] Another theory suggests that increased ultraviolet exposure (secondary to pupil dilation) may increase collagen cross-linking within the sclera, thereby limiting scleral growth.[28]

Atropine at 1.0% and 0.5% has been demonstrated through randomized trials to be effective in slowing myopia progression.[13–18] However, the safety profile of atropine (i.e., its effect on pupil size and accommodation) often has been a source of concern and deterred many from using this medication. Every unit increase in pupil size results in an exponential increase in the amount of light entering the eye, and this can cause glare and potential phototoxicity. Atropine also decreases accommodation amplitude and near vision so that children may require bifocal or progressive glasses to read. The ideal atropine dose would be one with the best balance between efficacy and safety.

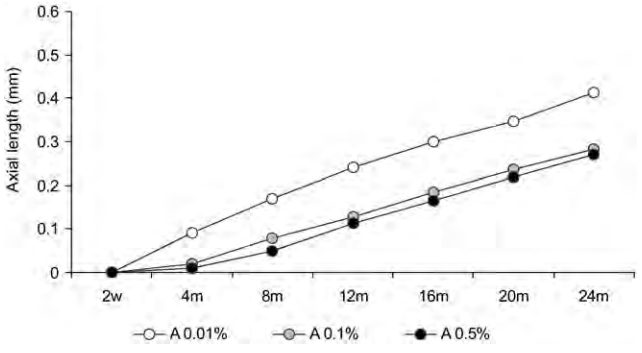

Figure 4. Mean change in axial lengths for groups from baseline, 2 weeks, and 4 to 24 months. A = atropine; ATOM = Atropine for the Treatment of Myopia; m = month; w = week.

In the ATOM1 study, 400 children aged 6–12 years with spherical equivalents of −1.00 and −6.00 D were randomly assigned to atropine 1% and placebo medication in 1 eye.[16] These children were slightly younger (9.2 vs. 9.6 years) and had lower spherical equivalents (−3.4 vs. −4.7 D) and smaller axial lengths (24.8 vs. 25.2 mm) than those in the ATOM2 group. Axial lengths were also measured differently between studies, with the A-scan ultrasonography used in ATOM1 and the IOLMaster used in ATOM2. At the end of 2 years, the mean myopia and axial length progression in the ATOM1 study were −0.28±0.92 D and −0.02±0.35 mm, respectively, in the atropine 1% eyes compared with −1.20±0.69 D and 0.38±0.38 mm, respectively, in the placebo eyes. The progression of myopia in the ATOM2 subjects lies in a dose-related manner between these 2 extremes (Fig 2). Such a dose-related effect on myopia progression was also noted in other studies.[14,15,17]

In ATOM2, the progression of myopia on atropine 0.5% was −0.17±0.47 D over 1 year and −0.30±0.60 D over 2 years. This was similar to the progression noted in children receiving atropine 1% in the ATOM1 study (Fig 2), and within the ranges noted in studies using atropine 0.5%. Shih et al[14] noted a 0.04±0.63 per year progression in 41 children aged 6–13 years. In a later study, Shih et al[15] noted progression of 0.41±0.07 D over an 18-month period in 66 children aged 6–13 years, whereas Liang et al[17] obtained 0.15±0.15 per year in 22 school-aged children.

Changes in myopia and axial lengths outcome in the atropine 0.1% group were similar to those in the 0.5% group. The myopia progression was initially larger in the

Table 3. Adverse Event and Serious Adverse Events

	Atropine (A) Dose			Exact Test
	No. of Episode/No. of Children (% Children)			
	A 0.01% (n = 84)	*A 0.1% (n = 155)*	*A 0.5% (n = 161)*	**P Value***
Adverse events				
Allergic conjunctivitis	0/0 (0)	7/6 (4)	7/7 (4)	0.16
Dermatitis involving eyelids	0/0 (0)	2/1 (1)	4/3 (2)	0.54
Stye/chalazion	2/2 (2)	16/12 (8)	16/12 (7)	0.22
Loss of distant BCVA >1 line	11/11 (13)	20/20 (13)	13/13 (8)	0.38
Others, eye related	2/1 (1)	2/2 (2)	3/3 (2)	1.00
Others, non–eye related	306/69 (82)	470/122 (78)	477/132 (82)	0.73
Severe adverse events				
Events requiring hospitalization	1/1 (1)	3/3 (2)	3/3 (2)	1.00

*Fisher exact test for proportion of children with adverse events.

atropine 0.1% group at 1 year (−0.31 vs. −0.17 D, $P=0.01$), but this gap had closed by 2 years (−0.38 vs. −0.30 D, $P=0.25$). This level of progression was less than the −0.47 D per year noted in children treated with 0.1% drops in Taiwan.[14] In terms of effect on other ocular parameters, accommodation (−10.9 vs. −2.4 D), mesopic pupil diameter (2.7 vs. 3.5 mm), and photopic pupil diameter (2.2 vs. 3.1 D) were also significantly less in the 0.1% group compared with the 0.5% group, making the overall efficacy side effect profile of atropine 0.1% better than atropine 0.5%.

In designing this study, atropine 0.01% was initially assumed to have minimal effect and act as a potential control, thus, the lower allocation of subjects to this group. However, contrary to expectations, atropine 0.01% also had significant clinical effects as evident by its effect on myopia progression, accommodation, and pupil size. The myopia progression rate in this group (−0.49±0.63 D/2 years) was less than the −1.20±0.69 D/2 years in the ATOM1 placebo groups.[16] It was also less than the cumulative progression over 2 years of −1.3 D (95% CI, −1.24 to −1.37), −1.07 D (95% CI, −1.01 to −1.13), and −0.78 D (95% CI, −0.72 to −0.85) in 8-, 9-, and 10-year-old myopic children, respectively, from the Singapore Cohort Study of Risk Factors for Myopia study (Saw SM, personal communication, 2011). Compared with the 2 higher doses, the difference in myopia progression at 2 years in the 0.01% group was statistically significant compared with the 0.5% group. Likewise, the difference in axial length increase was statistically larger than in both the 0.1% and 0.5% groups. However, absolute differences between groups were clinically small with differences in myopic progression and axial length increase of only 0.19 D and 0.13 mm, respectively, over 2 years (Table 2, Figs 2 and 4). In addition, the ocular side effect profile was significantly better with accommodation remaining at 11.8 D, a mean pupil size of 5 mm, and a mean near logMAR vision of 0.01.

There are no published data on atropine 0.01% for direct comparison. However, in a nonrandomized study, Lee et al[11] found that myopia in 21 children aged 6–12 years receiving atropine 0.05% progressed at a rate of 0.28±0.26 D per year, compared with 0.75±0.35 D per year in 57 consecutive untreated clinic patients. In a retrospective review of 50 pre-myopia children, 24 of whom were started on atropine 0.025%, Fang et al[29] noted that subsequent myopia shift was less (−0.14±0.24 D) in the atropine 0.025% groups compared with controls (−0.58±0.34 D).

Overall, atropine-related adverse effects were uncommon at the 0.01% dose. Allergic reactions were most frequent, with 3.2% experiencing allergic conjunctivitis and 0.8% experiencing an allergy-associated dermatitis, all of which were in the 0.1% or 0.5% groups. A number of children (11%) also noted at least 1 line loss in distance BCVA (Table 3). These effects are reversible on stopping medication.[18] There are no long-term studies on the effect of atropine on the eye, and continued vigilance is necessary. However, atropine has been clinically available since the early 1900s, and so far there are no known long-term adverse effects associated with its use.[23]

The strength of this study was its randomized double-blind design and low dropout rate, whereas an acknowledged weakness of the study was the lack of a placebo control group, necessitating use of external (historical and population) controls. The non-inclusion of a placebo group was a decision based on findings from the ATOM1 study, which clearly showed the efficacy of atropine treatment compared with placebo, rendering a placebo arm unethical. The more important aspect of this trial remained the comparison of low dose versus high dose in terms of not only the efficacy but also the visual side effects of atropine. ATOM2 was otherwise designed to have largely similar study parameters so that direct comparison with ATOM1 was deemed appropriate.

In conclusion, our results suggest that 0.5%, 0.1%, and 0.01% atropine remain effective in reducing myopia progression, compared with placebo treatment, and that the clinical differences in myopia progression among these 3 groups are small. The lowest concentration of 0.01% atropine thus seems to retain efficacy and is a viable concentration for reducing myopia progression in children, while attaining a clinically significant improved safety profile in terms of accommodation, pupil size, and near visual acuity, and subsequently reduced adverse impact on visual function. Moreover, the 0.01% formulation exhibited fewer ad-

verse events. Atropine 0.01% is currently not commercially available. However, these findings collectively suggest that a nightly dose of atropine at 0.01% seems to be a safe and effective regimen for slowing myopia progression in children, with minimal impact on visual function in children.

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Footnotes and Financial Disclosures

Originally received: April 5, 2011.
Final revision: July 20, 2011.
Accepted: July 20, 2011.
Available online: October 2, 2011. Manuscript no. 2011-538.

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Financial Disclosure(s):
The author(s) have no proprietary or commercial interest in any materials discussed in this article.

Supported by grants from the National Medical Research Council (MH 95:03/1-23) and SingHealth (SHF/FG039/2004 and TEST 08-03).

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Atropine for the Treatment of Childhood Myopia

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Purpose: To evaluate the efficacy and safety of topical atropine, a nonselective muscarinic antagonist, in slowing the progression of myopia and ocular axial elongation in Asian children.

Design: Parallel-group, placebo-controlled, randomized, double-masked study.

Participants: Four hundred children aged 6 to 12 years with refractive error of spherical equivalent −1.00 to −6.00 diopters (D) and astigmatism of −1.50 D or less.

Intervention: Participants were assigned with equal probability to receive either 1% atropine or vehicle eye drops once nightly for 2 years. Only 1 eye of each subject was chosen through randomization for treatment.

Main Outcome Measures: The main efficacy outcome measures were change in spherical equivalent refraction as measured by cycloplegic autorefraction and change in ocular axial length as measured by ultrasonography. The primary safety outcome measure was the occurrence of adverse events.

Results: Three hundred forty-six (86.5%) children completed the 2-year study. After 2 years, the mean progression of myopia and of axial elongation in the placebo-treated control eyes was −1.20±0.69 D and 0.38±0.38 mm, respectively. In the atropine-treated eyes, myopia progression was only −0.28±0.92 D, whereas the axial length remained essentially unchanged compared with baseline (−0.02±0.35 mm). The differences in myopia progression and axial elongation between the 2 groups were −0.92 D (95% confidence interval, −1.10 to −0.77 D; $P<0.001$) and 0.40 mm (95% confidence interval, 0.35–0.45 mm; $P<0.001$), respectively. No serious adverse events related to atropine were reported.

Conclusions: Topical atropine was well tolerated and effective in slowing the progression of low and moderate myopia and ocular axial elongation in Asian children. *Ophthalmology 2006;113:2285–2291 © 2006 by the American Academy of Ophthalmology.*

Myopia is the most common eye disorder in humans, affecting up to 80% of young adults in some East Asian countries such as Singapore and Taiwan,[1,2] and between 25% and 50% of older adults in the United States and Europe.[3–5] Studies indicate that the incidence rates of myopia in East Asia and other parts of the world are rising.[1,6,7] In addition to the decreased visual function from optical defocus, myopia is associated with an increased lifelong risk of irreversible blinding conditions such as myopic macular degeneration, retinal detachment, and glaucoma.[8–10] The risk of these complications rises with increasing severity of myopia. The widespread prevalence and the rising rates, the associated visual morbidity and consequent diminution of quality of life and social disability, and the substantial costs incurred for its correction make myopia a significant public health concern.

Although the cause of myopia has not been identified and the search for effective measures to prevent its onset remain elusive, an effective treatment that can halt or slow the progression of myopia, which typically occurs during childhood, would represent a significant advance in the management of myopia.

Recent clinical trials of a variety of interventions, such as progressive addition lenses and rigid gas-permeable contact lenses, have yielded disappointing results or positive results of marginal clinical significance.[11–13] To date, only topical atropine, a nonselective muscarinic antagonist, has been demonstrated through relatively small randomized trials to have some clinical effect on the progression of myopia.[14–16] However, these atropine studies suffered from various methodological shortcomings such as lack of regular and detailed follow-up examinations, absence of appropriate clinical controls, and absence of masking of participants and investigators. Additionally, the safety of prolonged atropine treatment was largely ignored. In a recent evidence-based review of myopia trials, the authors concluded that there was as yet insufficient evidence to support any interven-

Originally received: August 29, 2005.
Accepted: May 25, 2006. Manuscript no. 2005-819.

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Supported by the National Medical Research Council, Singapore (grant no.: SERI/MG/97-07/0008).

The authors have no commercial or financial interest in any of the material discussed in the article.

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ISSN 0161-6420/06/$–see front matter
doi:10.1016/j.ophtha.2006.05.062

tions, including atropine, to prevent the progression of myopia in children.[17] Consequently, we undertook a study designed to evaluate further whether pharmacologic intervention with topical atropine can reduce the progression of myopia in children over a 2-year period and to assess the safety of the treatment.

Patients and Methods

Study Design

The Atropine in the Treatment of Myopia study was a randomized, double-masked, placebo-controlled trial designed primarily to study whether topical atropine can prevent the progression of low and moderate myopia effectively and safely in children between 6 and 12 years of age. The study and protocol conformed to the tenets of the Declaration of Helsinki and was approved by the Singapore Eye Research Institute Review Board. Recruitment of participants was from the general public, primary schools, and ophthalmology practices through the distribution of standardized brochures and letters describing the Atropine in the Treatment of Myopia study as well as public talks. The participants were children aged between 6 and 12 years with refractive error of spherical equivalent between −1.00 and −6.00 diopters (D) who met the eligibility criteria listed in Table 1. Every child gave assent, and written informed consent was obtained from the parents or legal guardians after thorough explanation of the nature and risks of the study before enrollment. Overall study performance and child safety were reviewed by an independent data and safety monitoring committee.

Randomization

Assignments to treatment were allocated with concealment according to a computer-generated randomization list after eligibility criteria were verified. The children had an equal probability of assignment to either the atropine group or the placebo-control group. Only 1 eye of each child was chosen for treatment. The chosen eye also was selected using the randomization process. A child was considered to be enrolled in the study once the randomization assignment and study number were issued and the child received the assigned eye drops, which were handed out on the spot promptly after randomization.

Table 1. Eligibility Criteria for the Atropine in the Treatment of Myopia Study

Children aged 6 to 12 years
Refractive error of spherical equivalent between −1.00 D to −6.00 D in each eye as measured by cycloplegic autorefraction
Anisometropia of spherical equivalent less than or equal to 1.50 D as measured by cycloplegic autorefraction
Astigmatism of −1.50 D or less as measured by cycloplegic autorefraction
Distance vision correctable to logMAR 0.2 or better in both eyes
Normal intraocular pressure of <21 mmHg
Normal ocular health other than myopia
In good general health with no history of cardiac or significant respiratory diseases
No allergy to atropine, cyclopentolate, proparacaine, and benzalkonium chloride
No previous or current use of contact lenses, bifocals, progressive addition lenses, or other forms of treatment (including atropine) for myopia
Normal binocular function and stereopsis
No amblyopia or manifest strabismus, including intermittent tropia
Willing and able to tolerate monocular cycloplegia and mydriasis

D = diopters; logMAR = logarithm of the minimum angle of resolution.

Intervention

The eyes assigned for treatment were treated with either 1% atropine sulfate or vehicle eye drops once nightly for 2 years. Both the atropine and vehicle eye drops, the latter consisting of 0.5% hydroxypropyl methylcellulose and 1:10,000 benzalkonium chloride, were specially prepared by Alcon Laboratories (Puurs, Belgium). To aid and monitor compliance with the treatment regimen, each child was given a small calendar to tick off the days when the eye drops were used. In addition, all bottles were weighed before dispensing to, and after collection from, the parent or guardian at each visit. All children, regardless of treatment allocation, were prescribed photochromatic lenses (SOLA Transitions Single Vision Lenses, Lonsdale, Australia) for the correction of their refractive errors.

Masking

To minimize observational bias, neither the study participants nor the investigators responsible for measuring the study outcomes were aware of the intervention given. Several steps were taken to preserve and monitor masking. The atropine and placebo eye drops were packaged in identical bottles so that no one was able to identify the contents. Labels on the bottle had only the study number, the eye to be treated, and the expiration date. Parents or guardians were asked to seek advice from only the coordinating investigator regarding matters pertaining to their child's treatment and not to discuss any issues related to the study with the investigators measuring the study outcomes. To mask these study investigators, both pupils of every child were dilated fully and checked by the coordinating investigator before being seen by the study investigator.

Study Procedures

Cycloplegic autorefraction was used to assess refractive errors before enrollment as well as the progression of myopia. As with all data collection procedures, autorefraction was performed only by investigators who were trained and certified on study protocols. A Canon RK5 autorefractor-autokeratometer (Canon Inc. Ltd., Tochigiken, Japan) was used throughout the study to take 5 reliable readings, both before and after cycloplegia. All 5 readings had to be 0.25 D or less apart in both the spherical and cylindrical components before they were accepted. The cycloplegic regimen consisted of 1 drop of proparacaine hydrochloride (Alcaine, Alcon-Couvreur, Puurs, Belgium) followed by 3 drops of 1% cyclopentolate hydrochloride (Cyclogyl, Alcon-Couvreur), administered approximately 5 minutes apart. Cycloplegic autorefraction measurements were taken at least 30 minutes after instillation of the third drop of cyclopentolate. Cycloplegic subjective refraction also was performed primarily for the purpose of prescribing spectacles.

After cycloplegic refraction, ocular biometry (anterior chamber depth, lens thickness, vitreous chamber depth, and overall axial length) was measured by A-scan ultrasonography with the Nidek US-800 EchoScan (Nidek Co. Ltd., Tokyo, Japan). Six measurements were obtained for each eye. The axial length measurement was based on the average of the 6 values with a standard deviation of less than 0.12 mm. Measurements were obtained independently by the masked study investigators.

Sample Size and Power

Postulating that the eyes in the placebo-control group would progress by a mean of −1.00 D per year,[15] and anticipating a projected effect difference of 20% (with standard deviation of 0.5 D) between the atropine versus the placebo-control group and allowing a 15% attrition rate, 400 children would be sufficient for a power of 90% with a 2-sided test of 5%.[18]

Outcome Measures

Efficacy. The primary outcome was progression of myopia, defined as the change in spherical equivalent refractive error (SER) relative to baseline. The baseline assessment took place 2 weeks after commencement of treatment, that is, the pretreatment visit. This was necessary because atropine induces an additional cycloplegic effect that could lower further the SER. As such, a run-in period allowed for stabilization of the cycloplegic effect, thus making comparison of SER between the baseline and subsequent visits more meaningful. The SER was calculated for each of the 5 cycloplegic autorefraction measurements per eye, and the mean of the 5 SER measures then was computed. Progression of myopia was analyzed by expressing refractive error as 3 components: M (spherical equivalent), J0 (dioptric power of a Jackson cross cylinder at axis 0), and J45 (dioptric power of a Jackson cross cylinder at axis 45), as determined by Fourier decomposition.[19] The secondary outcome was change in axial length during follow-up relative to baseline measured by A-scan ultrasonography.

Safety. The primary safety outcome monitored was the occurrence of adverse events. The relationship of the event to the study medication was assessed by the investigators as none, unlikely, possible, probable, or definite. Other safety variables monitored included best-corrected visual acuity using the Early Treatment Diabetic Retinopathy Study chart, intraocular pressure (using noncontact tonometry), slit-lamp biomicroscopy, and fundus examination. In addition, multifocal electroretinography was used to assess the retinal function in a subset of children in each of the 2 groups. This has been previously described.[20]

Statistical Analyses

All statistical analyses were based on the intention-to-treat principle and performed using SPSS software version 11.5 (SPSS Inc., Chicago, IL). The clinical baseline measurements and demographic characteristics between the 2 treatment groups were evaluated by 2-sample *t* tests or Mann–Whitney *U* tests for continuous variables, depending on satisfaction of the normality and homogeneity assumptions, and the association with categorical variables was assessed using a chi-square or Fisher exact test. The analysis for efficacy outcomes was based on evaluation of the magnitude of change in SER and axial length between follow-up and baseline using a paired *t* test or Wilcoxon signed rank test. A multiple regression model was used to evaluate the association between changes in SER and axial length, adjusting for relevant covariates. There were no interim analyses of efficacy.

Results

Between April 1999 and September 2000, 400 children were enrolled in the study, with equal randomization to the atropine group and to the placebo-control group. In each group of 200 children, 100 right eyes and 100 left eyes were assigned for treatment. At the initial pretreatment visit, there were no significant differences between the groups in mean age, gender, and racial distribution (Table 2). Likewise, there were no significant differences between the groups in terms of refractive and biometric characteristics. Mean myopia in the atropine-treated eyes was −3.36±1.38 D, and in the placebo-treated eyes it was −3.58±1.17 D. The mean myopia in the fellow untreated eyes of those children in the atropine group and placebo group was −3.40±1.35 D and −3.55±1.21 D, respectively. The atropine-treated eyes and placebo-treated eyes had identical mean axial lengths of 24.80 mm. This was comparable with the mean axial lengths of 24.81 mm and 24.76 mm in fellow untreated eyes in the atropine and placebo group, respectively.

Three hundred forty-six (86.5%) children completed the 2-year study. Of the 44 who did not, 10 were from the placebo-control group and 34 from the atropine group. The mean pretreatment refractive and biometric characteristics of the children who were lost to follow-up were similar to that of the entire treatment group to which they belonged. At 1 year, the mean progression of myopia in the placebo-treated eyes was −0.76±0.44 D. In the atropine-treated eyes, however, there was a reduction of myopia by 0.03±0.50 D ($P<0.001$; Fig 1). Concomitantly, the mean axial elongation in the placebo-treated eyes was 0.20±0.30 mm, but in the atropine-treated eyes there was a slight reduction in axial length by −0.14±0.28 mm ($P<0.001$; Fig 2).

At 2 years, the mean progression of myopia and axial elongation in the placebo-treated eyes was −1.20±0.69 D and 0.38±0.38 mm, respectively. In the atropine-treated eyes, myopia progression was only −0.28±0.92 D, whereas the axial length remained essentially unchanged compared with baseline (−0.02±0.35 mm). The differences in myopia progression and axial elongation

Table 2. Pretreatment Characteristics of the Atropine in the Treatment of Myopia Study Patients

Characteristic	Placebo Group (n = 200)		Atropine Group (n = 200)	
	Treated Eye (n = 200)	*Untreated Eye (n = 200)*	*Treated Eye (n = 200)*	*Untreated Eye (n = 200)*
Mean age (yrs)	9.2		9.2	
Male (%)	52.5		57.5	
Chinese race (%)	93.0		95.0	
Indian race (%)	5.0		3.0	
Right eye	100	100	100	100
Left eye	100	100	100	100
Refractive error (D)	−3.58±1.17	−3.55±1.21	−3.36±1.38	−3.40±1.35
Axial length (mm)	24.80±0.84	24.76±0.86	24.80±0.83	24.81±0.84

D = diopters.

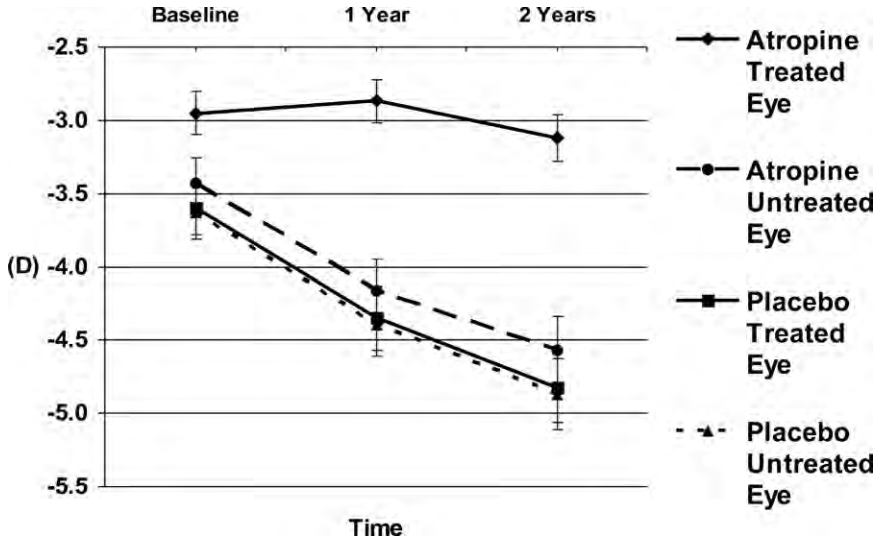

Figure 1. Graph showing mean spherical equivalent change from baseline. D = diopters.

between the 2 groups were −0.92 D (95% confidence interval, −1.10 to −0.77 D; $P<0.001$) and 0.40 mm (95% confidence interval, 0.35–0.45 mm; $P<0.001$), respectively. The changes in refractive error and axial length in the nontreated eyes of children in both the atropine group and placebo-control group paralleled that of the placebo-treated eyes (Figs 1, 2).

At the end of the 2-year treatment period, almost two thirds (65.7%) of atropine-treated eyes had progressed less than −0.50 D, whereas 13.9% had progressed more than −1.00 D. In contrast, 16.1% and 63.9% of placebo-treated eyes had progressed less than −0.50 D and more than −1.00 D, respectively. Figure 3 summarizes the frequency of distribution of the various rates of progression of myopia after 1 and 2 years.

No serious adverse events related to atropine were reported. Reasons for withdrawal were: allergic or hypersensitivity reactions or discomfort (4.5%), glare (1.5%), blurred near vision (1%), logistical difficulties (3.5%), and others (0.5%). There was no deterioration in best-corrected visual acuity. Similarly, intraocular pressure changes were within 5.5 mmHg, with no absolute readings of more than 21 mmHg. No lenticular, optic disc, or macular changes were reported.

Discussion

Key Findings

The results of our study indicate that a once-nightly dose of 1% atropine eye drops achieved a reduction in progression of low and moderate childhood myopia compared with placebo treatment that is both statistically and clinically significant. Over a 2-year period, atropine treatment achieved approximately a 77% reduction in mean progression of myopia compared with placebo treatment. This finding is strongly corroborated by the concomitant findings in ocular biometry, where there was essentially no change in mean axial length in the atropine-treated eyes compared with a

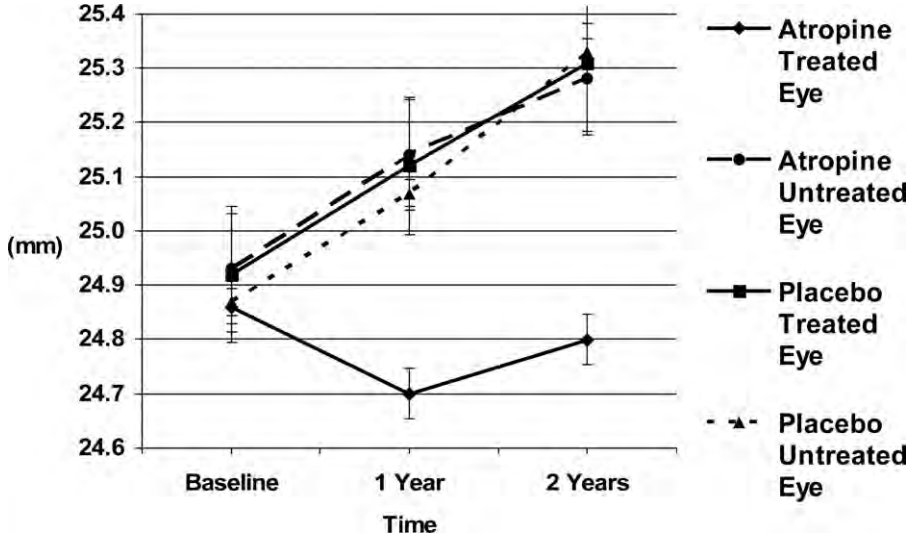

Figure 2. Graph showing mean axial length change from baseline.

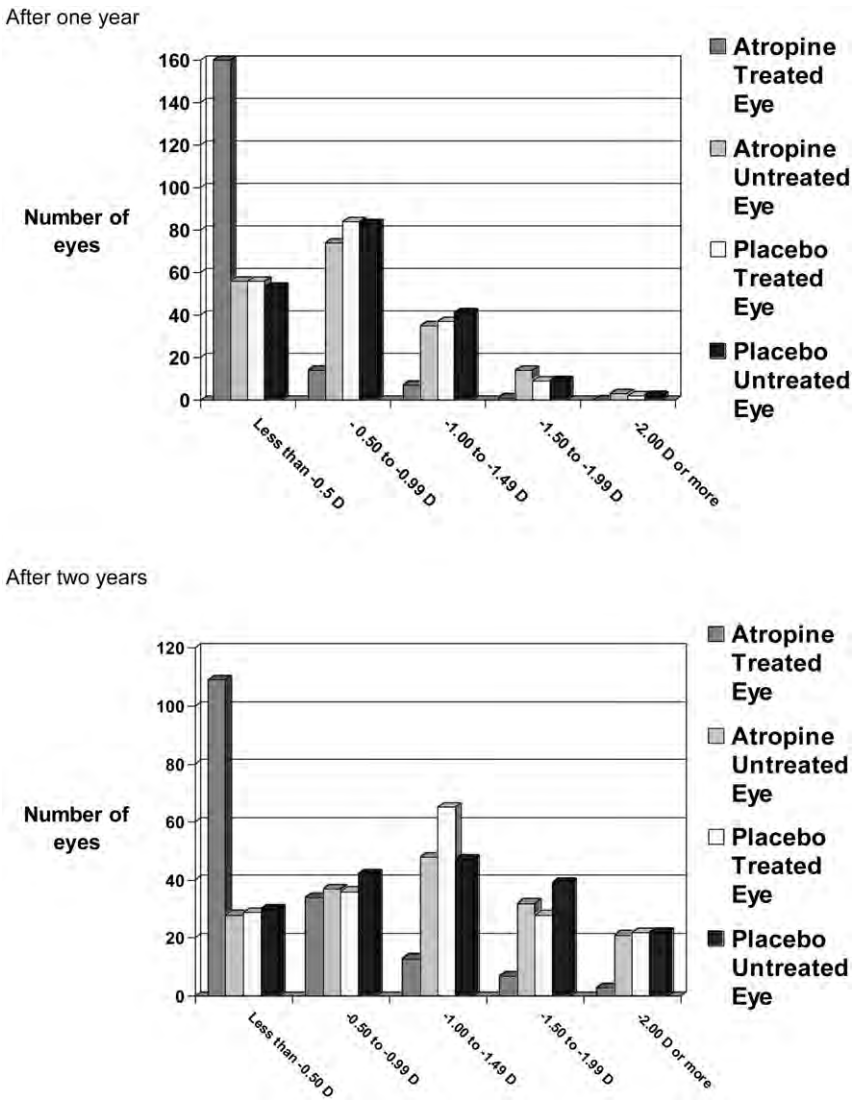

Figure 3. Graphs showing distribution of progression of myopia after 1 and 2 years. D = diopters.

mean increase of approximately 0.38 mm in the placebo-treated eyes and the untreated fellow eyes in both atropine and placebo groups. Our study also showed that atropine treatment was well tolerated generally and that no serious adverse effects were observed. This is supported by our electrophysiological assessment of a subset of study patients in which multifocal electroretinography results indicated that long-term atropine use had little effect on retinal function, with the retina-on response affected more than the retina-off response.[20]

Possible Mechanisms

Much like the cause of myopia, the mechanism of action of atropine in retarding progression of myopia and axial elongation is not understood clearly. Initially, its use was based on the putative role of excessive accommodation in causing myopia.[21] However, atropine also is effective in preventing myopia in animal models, where myopic eye growth can develop even after abolition of accommodation has been achieved by destruction of the Edinger-Westphal nucleus or after optic nerve section.[22] These results suggest alternative mechanisms and sites of action for atropine at, for example, either the retina or the sclera.

Comparison with Other Studies

The first report of atropine treatment for myopia was by Wells in the nineteenth century.[23] Since then, a number of other studies also have evaluated the efficacy of atropine in preventing the progression of childhood myopia. However, a recent literature search to identify articles for inclusion in an evidence-based review revealed the scarcity of well-designed randomized controlled trials of atropine treatment.[17] A range of concentrations (0.1%–1%) of atropine eye drops was evaluated in 3 separate, relatively small trials involving schoolchildren in Taiwan, and the rate of progression of myopia in the atropine group was significantly lower

compared with that of the control group. In one of these studies, the mean progression of myopia in eyes treated with 1% atropine was −0.22 D, versus −0.91 D in the eyes treated with normal saline.[14] Almost similar results were obtained in 2 subsequent studies of 0.5% atropine, where the progression rate of myopia in eyes treated with atropine was −0.28 D per year and −0.93 D per year in eyes not receiving treatment.[15,16] The magnitude of efficacy (0.79 D) seen in the first 12 months of the present study is just slightly larger than that in previously published studies.

Previous assessment of safety of atropine treatment was restricted to the recording of known side effects of atropine, but the reported rates of complications or adverse events were highly variable. For example, in the study by Yen et al,[14] every participant receiving 1% atropine had photophobia, whereas another study also using 1% atropine reported an incidence of photophobia of only 18%.[24] In our study, glare and photophobia were greatly minimized with the use of photochromatic lenses.

Strengths and Limitations

In addition to the merits of a randomized, double-masked, placebo-controlled trial design, a strength of our study is the presence of several controls: the untreated fellow eye of children in the atropine group, the placebo-treated eyes, and the untreated eyes of children in the control group. Further strengths include the use of cycloplegic autorefraction to assess primary efficacy outcomes. More significantly, we also assessed a secondary outcome by performing ocular biometry in all participants. The other strengths of the study are a larger sample size and higher retention rate compared with previous studies.

A weakness of any randomized study with atropine eye drops, including our study, is the potential for unmasking of the participants attributable to the atropine-induced mydriasis and cycloplegia. In the atropine group, children who covered their untreated eye noted the blurring of near vision in the atropine-treated eye, whereas astute parents might have noted the anisocoria, although the dark brown irises of our study population make the cursory identification of anisocoria somewhat more difficult. Investigators responsible for assessing both efficacy outcomes, however, always remained masked because they performed the refraction and biometry only after the child had received the bilateral cyclopentolate regimen, which, like atropine, induces mydriasis and cycloplegia.

The treatment regimen adopted in the study has 2 clinical side effects, however, that may be ameliorated in a clinical context. First, long-term uniocular treatment of myopia is impractical and unsatisfactory because the myopia in the untreated fellow eye may continue to progress, thus resulting in anisometropia and aniseikonia. Moreover, the risk of myopic complications in the untreated eye remains undiminished. In the clinical situation, bilateral treatment will obviate this problem. However, the primary reason for adopting a uniocular treatment design in this study was because bilateral atropine treatment would result in bilateral blurred near vision with functional consequences such as difficulty with near work activity, that is, reading, writing, and so forth. To overcome this problem, participants would have to use either bifocal or progressive addition lenses. This would mean introducing a potential treatment confounder into the study because progressive addition lenses were, at that time, being evaluated as an intervention for slowing myopia progression.[11,12]

Second, treatment with an atropine concentration of 1% produces some unwanted side effects, such as glare and photophobia because of pupillary dilatation and blurring of near vision resulting from induced cycloplegia. In view of the limitations and problems associated with uniocular 1% atropine treatment, further dose-determining studies are needed to identify an optimal atropine regimen for bilateral treatment.

The duration of atropine treatment in this study was only 2 years, and therefore we could not assess whether atropine will continue to have an effect on progression of myopia beyond 2 years of treatment. This information on the durability of atropine is important because the period of myopia progression and ocular axial growth commonly seen in Asian children extends beyond 2 years. Additionally, this paper has not addressed the refractive changes after cessation of atropine treatment. It is not known if the slower rate of myopia progression and axial elongation will be maintained or if there will be a rebound phenomenon that would negate the positive treatment effects.

To this end, we have embarked on a new randomized clinical trial to assess the efficacy, safety, and functional impact of 3 different atropine concentrations for the bilateral treatment of childhood myopia. This study will be longer than the present study and also will evaluate the changes in progression of myopia after cessation of atropine treatment.

In summary, the Atropine in the Treatment of Myopia study provides strong evidence that the progression of low and moderate childhood myopia can be slowed pharmacologically. Further research is required to elucidate the mechanism of action, to evaluate the safety and efficacy of bilateral atropine treatment beyond 2 years, and to identify characteristics of children who will derive maximum benefit from treatment.

Acknowledgment. The authors dedicate the article to the late Sek-Jin Chew, who conceived of and laid the foundation for this study.

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Five-Year Clinical Trial on Atropine for the Treatment of Myopia 2

Myopia Control with Atropine 0.01% Eyedrops

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Purpose: To compare the safety and efficacy of different concentrations of atropine eyedrops in controlling myopia progression over 5 years.

Design: Randomized, double-masked clinical trial.

Participants: A total of 400 children originally randomized to receive atropine 0.5%, 0.1%, or 0.01% once daily in both eyes in a 2:2:1 ratio.

Methods: Children received atropine for 24 months (phase 1), after which medication was stopped for 12 months (phase 2). Children who had myopia progression (≥ -0.50 diopters [D] in at least 1 eye) during phase 2 were restarted on atropine 0.01% for a further 24 months (phase 3).

Main Outcome Measures: Change in spherical equivalent and axial length over 5 years.

Results: There was a dose-related response in phase 1 with a greater effect in higher doses, but an inverse dose-related increase in myopia during phase 2 (washout), resulting in atropine 0.01% being most effective in reducing myopia progression at 3 years. Some 24%, 59%, and 68% of children originally in the atropine 0.01%, 0.1%, and 0.5% groups, respectively, who progressed in phase 2 were restarted on atropine 0.01%. Younger children and those with greater myopic progression in year 1 were more likely to require re-treatment. The lower myopia progression in the 0.01% group persisted during phase 3, with overall myopia progression and change in axial elongation at the end of 5 years being lowest in this group (-1.38 ± 0.98 D; 0.75 ± 0.48 mm) compared with the 0.1% (-1.83 ± 1.16 D, $P = 0.003$; 0.85 ± 0.53 mm, $P = 0.144$) and 0.5% (-1.98 ± 1.10 D, $P < 0.001$; 0.87 ± 0.49 mm, $P = 0.075$) groups. Atropine 0.01% also caused minimal pupil dilation (0.8 mm), minimal loss of accommodation (2–3 D), and no near visual loss compared with higher doses.

Conclusions: Over 5 years, atropine 0.01% eyedrops were more effective in slowing myopia progression with less visual side effects compared with higher doses of atropine. *Ophthalmology 2015;■:1–9 © 2015 by the American Academy of Ophthalmology.*

Several studies have shown that atropine eyedrops are effective in slowing myopia progression in young children.[1–19] In our past Atropine for the Treatment of Myopia (ATOM) 1 and 2 (phases 1 and 2) clinical trials, we demonstrated a dose-related response to atropine, with higher doses inhibiting myopia progression to a slightly greater degree than lower doses, although the myopia progression of −0.49 diopters (D), −0.38 D, and −0.30 D in the atropine 0.01%, 0.1%, and 0.5% groups, respectively, were not significantly different at 24 months.[16,19] However, when atropine was stopped for 12 months after 24 months of treatment (phase 2 of ATOM2), there was a rapid increase in myopia in children originally treated with higher concentrations of atropine, whereas those receiving the lowest concentration of 0.01% showed minimal change.[18,20] This resulted in myopia progression being significantly lower in children previously assigned to the 0.01% group (−0.72 D) at 36 months compared with that in the 0.1% (−1.04 D) and 0.5% (−1.15 D) groups. In addition, the lowest dose also caused less photopic pupil dilation (0.74 mm, compared with 2.25 and 3.11 mm in the 0.1% and 0.5% groups, respectively) and no clinically significant loss in accommodation or near visual acuity (4.6 D, compared with 10.1 and 11.8 D in the 0.1% and 0.5% groups, respectively).[20]

Although proven effective and safe in the short-term, there was concern about the long-term effectiveness of atropine, particularly in children who experienced an increase in myopia after atropine was stopped. In the final phase (phase 3), spanning the fourth and fifth years of the ATOM2 study, children who continued to progress (>0.5 D/year) during phase 2 (the washout year) were re-treated with atropine 0.01%. The aim of this study was to evaluate the efficacy and safety of atropine over this last phase and the entire 5-year study period.

Methods

In phase 1 of the ATOM2 study (treatment phase), 400 Asian children (aged 6–12 years) with myopia of −2.00 D or worse in each eye were randomized to receive atropine 0.01%, 0.1%, and 0.5% once nightly in both eyes for 2 years. Children were assigned to treatment in a 1:2:2 ratio, stratified by 6 gender and age strata. In

http://dx.doi.org/10.1016/j.ophtha.2015.07.004
ISSN 0161-6420/15

phase 2 (washout phase), atropine was stopped and children were monitored for 12 months. In phase 3 (re-treatment phase), children who exhibited myopia progression of −0.50 D or more in at least 1 eye during the washout phase were restarted on atropine 0.01% for a further 24 months.

Written informed consent was obtained from parents and verbal assent was obtained from children before randomization. The investigators, study team performing the ocular measurements, parents, and children were masked to an initial dose of atropine throughout the entire 5-year study, and the study team was also blinded to whether or not children were restarted on atropine during the last phase of the study.

After assessment at a screening visit, children were reassessed again after they had been receiving atropine for 2 weeks (baseline visit). Children were then reviewed every 4 months during phase 1, at 26, 32, and 36 months during phase 2, and all children, including those who were not restarted atropine treatment, were reviewed every 6 months during phase 3 and then again in 2 months after all medication had been stopped.

At each visit, cycloplegic autorefraction, axial length (AL), mesopic and photopic pupil size, accommodation and distance, and near logarithm of the minimum angle of resolution visual acuity were measured.[19,20] Cycloplegia was achieved using 3 drops of cyclopentolate 1% administered 5 minutes apart, and cycloplegic autorefraction was measured, 30 minutes after the last drop, using a Canon RK-F1 autorefractor (Canon Inc. Ltd., Tochigiken, Japan). Five readings, all of which were within 0.25 D apart, were averaged. Spherical equivalent was calculated as the sphere plus half cylindrical power. Axial length was obtained using the Zeiss IOL Master (Carl Zeiss Meditec Inc., Dublin, CA). Five readings, all within 0.05 mm or less, were averaged. The photopic pupil size was measured using the Neuroptics pupillometer (Neuroptics Inc., Irvine, CA) at 300 lux of luminance. Accommodation was measured using the Royal Air Force rule while the subjects used their best-corrected distance spectacles. Distance and near vision were measured using logarithm of the minimum angle of resolution Early Treatment Diabetic Retinopathy Study charts.

The primary outcome was progression of myopia, defined as change in spherical equivalent over phase 3 and the entire 5-year study period. The secondary outcome was change in AL. Other study variables include changes in photopic pupil size, accommodation, and distance/near visual acuity.

The study was conducted according to the tenets of the Declaration of Helsinki. Ethics approval was obtained from the Singapore Eye Research Institute Review Board, and the study was registered with the ClinicalTrial.govwebsite (registration no: NTC00371124).

Statistical Analysis

All analyses were based on an intention-to-treat principle and performed using the statistical software SASv9.3 (SAS Inc., Cary, NC). Data were summarized by initial atropine treatment group in the re-treated and untreated children at the phase 3 stage. For person-level data such as gender, the Fisher exact test was used to test for the difference in proportion of children between groups, and analysis of variance was used for the difference in means between groups. Data of ocular parameters from both eyes were pooled in a combined analysis using the Huber−White robust standard errors to allow for correlation between eyes within a person.[21] Although P values (without adjustment for multiple comparison) were obtained for both the global null hypothesis of no difference among treatment groups and the pairwise comparison, interpretation only began with considering the global null hypothesis to prevent inflation of type I error rate.

Results

Among the 400 children enrolled in the study, 44 were lost in phase 1 and 11 were lost in phase 2, with 345 (86%) continuing to phase 3 (Fig 1). Children still in the study at the start of phase 3 were more myopic at baseline but had less myopic progression over the first year compared with children who were lost to follow-up (Table 1). The majority of the children (91%) were of ethnic Chinese origin.

Of the 345 children, 192 (56%) were restarted on atropine 0.01% because they had progressed 0.5 D or more during the preceding phase 2 washout year; this included 17 of 70 children (24%) in the 0.01% group, 82 of 139 children (59%) in the 0.1% group, and 93 of 136 children (68%) in the 0.5% group (Fig 2). Compared with children who were not restarted on atropine, those restarted on treatment were younger, had less myopia and shorter AL at baseline, but had greater myopia progression and change in AL during the first year of the study (Table 1). Multivariate analysis revealed that younger age and assignment to higher initial atropine dose predisposed children to greater myopic progression in phase 2 (Table 2) and thus more likely to be re-treated with atropine 0.01% in phase 3.

Myopia Progression

Children who required re-treatment had higher rates of myopia progression during the first 24 months (phase 1) and in the washout phase (phase 2) compared with those who did not require re-treatment (Table 3). In the re-treated children, mean annual myopia progression during phase 3 (−0.38 to −0.52 D) was lower than in the preceding phase 2 period (−0.62 to −1.09 D) in all 3 atropine groups, but higher than those who did not require re-treatment (−0.30 to −0.38 D) (Table 3). The overall mean myopia progression in phase 3 was −0.69±0.46 D, −0.81±0.57 D, and −0.84±0.61 D in the atropine 0.01%, 0.1%, and 0.5% groups, respectively ($P = 0.09$) (Fig 3). In contrast, the mean myopia progression over the entire 5 years was less in the 0.01% group (−1.38±0.98 D) than in the 0.1% (−1.83±1.16 D, $P = 0.003$) and 0.5% (−1.98±1.10 D, $P < 0.001$) groups.

The rate of myopic progression in children restarted on atropine slowed in phase 3. The mean increase in myopia over the fourth and fifth years (−0.86±0.56 D in 0.01% group, −0.87±0.59 D in 0.1% group, −0.90±0.66 D in 0.5% group) was similar to that in children originally assigned to the 0.01% group, who required re-treatment during phase 1 (−0.77±0.49 D, $P > 0.286$), suggesting that re-treatment with 0.01% was as effective as primary treatment with atropine 0.01% (Table 3).

Overall, fewer eyes progressed by ≥2.0 D in the original atropine 0.01% (27%) group compared with those in the 0.1% (41%) and 0.5% (47%) groups at the end of the study ($P = 0.006$) (Fig 4). The percentages of high myopia (myopia ≥6.0 D) in both eyes was 44%, 49%, and 50% in the atropine 0.01%, 0.1%, and 0.5% groups, respectively ($P = 0.70$). Very high myopia (myopia of ≥8.0 D in both eyes) was noted in 7%, 9%, and 17% of children in the 0.01%, 0.1%, and 0.5% groups, respectively ($P = 0.07$).

Change in Axial Length

There was no significant difference in AL in all 3 atropine groups at the start of phase 3 ($P = 0.653$) (Fig 5). However, by the end of phase 3, the mean change in AL was smaller in the 0.01% group (0.19±0.18 mm) compared with the 0.1% (0.24±0.21 mm, $P = 0.042$) and 0.5% (0.26±0.23 mm, $P = 0.013$) groups (Table 3). The mean overall change in AL over 5 years was 0.75±0.48

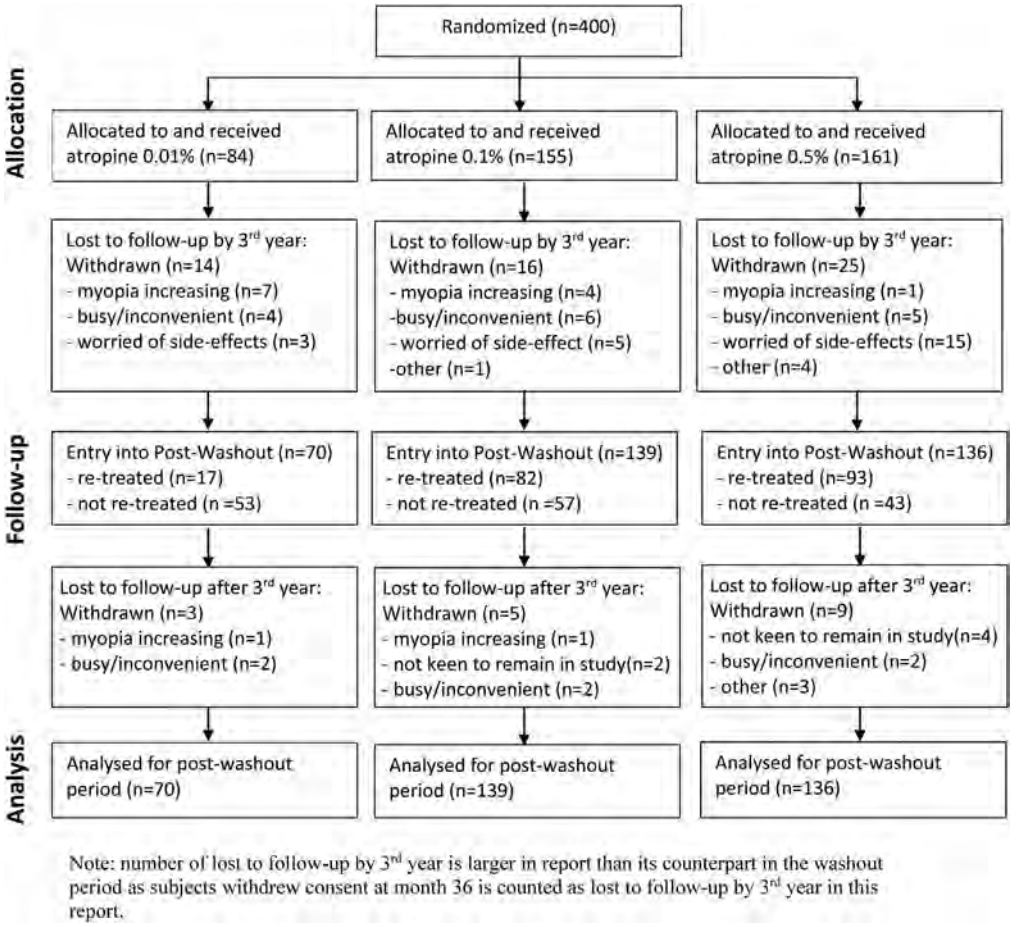

Figure 1. Subject flowchart of Atropine for the Treatment of Myopia (ATOM) 2.

mm, 0.85±0.53 mm, and 0.87±0.49 mm in the 0.01%, 0.1%, and 0.5% groups, respectively ($P = 0.185$).

In the children who were not restarted on atropine, AL elongation gradually slowed during phase 3 and there was no difference in AL among groups at 5 years ($P = 0.555$) (Table 3). In children in whom atropine was restarted, AL elongation slowed in all groups (0.32±0.22 mm in 0.01% group, 0.27±0.25 mm in 0.1% group, 0.29±0.25 mm in 0.5% group) over phase 3 to a rate lower than that noted during phase 1 in the 0.01% group that required re-treatment (0.58±0.27 mm, $P < 0.001$).

Change in Pupil Size, Accommodation, and Distance/Near Vision

At 36 months, before restarting children on atropine, the pupil size, accommodation, and near vision were similar in all 3 groups

Table 1. Comparison of Subjects Who Required Re-treatment and Those Who Did Not, and Those Still in Study and Those Lost To Follow-up at 3 Years

	Re-treated Children n = 192 (55.6%)	Untreated Children n = 153 (44.4%)	*P* Value	Still in Study (at 3 Years) n = 345 (86.2%)	Lost to Follow-up n = 55 (13.8%)	*P* Value
Age at screening, yrs, mean (SD)	9.1 (1.3)	10.5 (1.2)	<0.001	9.7 (1.5)	9.5 (1.9)	0.329
Male, n (%)	104 (54.2)	75 (49.0)	0.386	179 (51.9)	32 (58.2)	0.467
Spherical equivalent (D)						
Baseline, mean (SD)	−4.34 (1.64)	−4.70 (1.51)	0.031	−4.50 (1.59)	−3.89 (1.71)	0.018
Change at 1 yr	−0.30 (0.47)	−0.20 (0.48)	0.033	−0.25 (0.48)	−0.64 (0.66)	0.003
AL (mm)						
Baseline, mean (SD)	25.05 (0.91)	25.30 (0.86)	0.008	25.16 (0.90)	25.00 (0.92)	0.225
Change at 1 yr	0.17 (0.17)	0.10 (0.16)	<0.001	0.14 (0.17)	0.28 (0.29)	0.008

AL = axial length; SD = standard deviation.

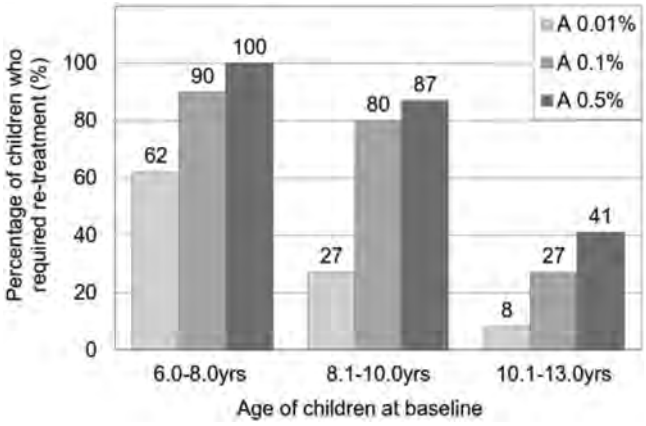

Figure 2. Percentage of children in each atropine group who required re-treatment at 3 years with atropine 0.01%, 0.1%, and 0.5% because they had progressed by more than 0.50 diopters (D) during the washout period (phase 2).

(Table 4). On restarting atropine 0.01%, there was a mean increase in photopic pupil size of approximately 1 mm and a loss of accommodation of 2.00 to 3.00 D, which were similar to the change noted in eyes treated with atropine 0.01% during phase 1 (Table 4). These mild side effects were deemed clinically insignificant, because there was no change or loss in distance or near visual acuity. Children were offered progressive addition or photochromatic (tinted) glasses if they encountered near blur or glare. During phase 1, 7% of children receiving atropine 0.01% requested glasses,[19] but no child who was restarted on atropine 0.01% requested glasses during phase 3. Pupil size and accommodation returned to levels similar to those in untreated children at the final visit (2 months after stopping atropine).

Discussion

In our first randomized placebo-controlled clinical trial using atropine eyedrops to control myopia progression in children (ATOM1), we established the clinical safety and efficacy of atropine 1% at least in the short term.[16,18] In phase 1 of ATOM2, we established that atropine 0.01% was almost as effective in reducing myopia progression as higher concentrations but with minimal pupil dilation accommodation and near vision loss.[19,20] In phase 2, we further established that children receiving lower doses had less myopic progression after atropine was stopped,[20] resulting in 0.01% being more effective in reducing myopia progression at 3 years.

In the last phase of ATOM2 (phase 3), all children with myopia progression of −0.50 D or more in the washout year were restarted on atropine 0.01% for a further 24 months. Fewer children in the 0.01% group (24%) needed re-treatment compared with children in the 0.1% (59%) and 0.5% (68%) groups (Fig 2). By the end of the study, the overall 5-year progression of myopia was less in the 0.01% group (−1.38±0.98 D) compared with the 0.1% (−1.83±1.16, $P = 0.003$) and 0.5% (−1.98±1.10 D, $P < 0.001$) groups (Fig 3). This was largely because fewer children in the 0.01% group progressed after atropine was stopped, and the rate of progression in the washout year in those who needed re-treatment was also less in the 0.01% group (−0.63 D, −0.94 D, and −1.09 D in the 0.01%, 0.1%, and 0.5% groups, respectively) (Table 3). The subsequent myopic progression in children who required re-treatment was similar between groups over the last 2 years (−0.86 to −0.91 D), which was also similar to that in children in the 0.01% group who required re-treatment over the first 2 years (−0.79 D). This suggests that re-treatment with atropine 0.01% could be as effective as primary treatment with atropine 0.01%, and that clinicians may be able to titrate treatment by stopping and restarting treatment according to individual progression rates (Table 3).

Findings from the ATOM1 and ATOM2 studies are summarized in Figure 6. Conducted a few years apart, both studies had similar study designs, with the main differences being that children in the ATOM2 study were slightly older (9.7 vs. 9.2 years) and had slightly higher levels of baseline myopia (−4.7 D vs. −3.5 D).[16,19,20] By combining the 2 studies, we found that in the initial 8 months, there was a hyperopic shift in the 1.0% group and continued myopic progression in the other groups, which was greater in the lower doses, before growth slowed between the 8- and 24-month periods. By the end of phase 1, there was clustering of mean myopia progression between 0.2 and 0.5 D in the atropine-treated eyes, compared with 1.2 D in the placebo eyes.[16,19] This plateauing of myopia progression in the second year suggests that there may be a maximal effect

Table 2. Regression Analysis of Myopic Rebound (Change in Spherical Equivalent) during Phase 2 (Washout) Period

	Unadjusted Analysis		Adjusted Analysis	
Baseline Characteristics	*Coefficient (95% CI)*	P *Value*	*Coefficient (95% CI)*	P *Value*
Age	0.16 (0.13–0.19)	<0.001	0.16 (0.13–0.18)	<0.001
Gender				
Female	0.03 (−0.07 to 0.14)	0.529	0.02 (−0.06 to 0.10)	0.584
Male	0	-	0	-
Spherical equivalent	−0.03 (−0.06 to −0.003)	0.031	−0.01 (−0.04 to 0.01)	0.229
Treatment group				
Atropine 0.01%	0	-	0	-
Atropine 0.1%	−0.40 (−0.50 to −0.31)	<0.001	−0.40 (−0.49 to −0.31)	<0.001
Atropine 0.5%	−0.60 (−0.70 to −0.49)	<0.001	−0.60 (−0.70 to −0.51)	<0.001

CI = confidence interval.

Table 3. Demographics and Changes in Spherical Equivalent and Axial Length in Children within Different Atropine Groups (0.01%, 0.1%, and 0.5%) Who Were Re-treated and Who Did Not Require Re-treatment

	Re-treated Children				Untreated Children			
	Atropine 0.01% N = 17 (24.3%)	*Atropine 0.1% N = 82 (58.9%)*	*Atropine 0.5% N = 93 (68.4%)*	***P* Value**	*Atropine 0.01% N = 53 (73.5%)*	*Atropine 0.1% N = 57 (41.1%)*	*Atropine 0.5% N = 43 (31.6%)*	***P* Value**
Age at screening, yrs, mean (SD)	8.6 (1.1)	9.0 (1.3)	9.2 (1.4)	0.261	10.0 (1.3)	10.7 (1.2)	10.9 (1.0)	<0.001
Male, n (%)	9 (52.9)	43 (52.4)	52 (55.9)	0.908	27 (50.9)	31 (54.4)	17 (39.5)	0.317
SE, D, mean (SD)								
Baseline	−4.07 (1.26)	−4.31 (1.40)	−4.41 (1.89)	0.617	−4.80 (1.55)	−4.76 (1.35)	−4.49 (1.65)	0.593
24 mos	−4.84 (1.22)	−4.84 (1.29)	−4.74 (1.76)	0.898	−5.12 (1.63)	−4.88 (1.30)	−4.63 (1.61)	0.332
36 mos	−5.47 (1.27)	−5.78 (1.28)	−5.83 (1.78)	0.554	−5.27 (1.64)	−5.18 (1.36)	−5.05 (1.54)	0.772
48 mos	−5.76 (1.42)	−6.16 (1.48)	−6.28 (1.93)	0.406	−5.58 (1.81)	−5.54 (1.51)	−5.46 (1.75)	0.939
60 mos	−6.20 (1.59)	−6.63 (1.67)	−6.77 (2.19)	0.428	−5.86 (1.85)	−5.91 (1.75)	−5.80 (1.83)	0.948
Change in SE, D, mean (SD)								
Baseline to 12 mos	−0.54 (0.43)	−0.41 (0.47)	−0.16 (0.45)	<0.001	−0.31 (0.45)	−0.14 (0.51)	−0.13 (0.44)	0.055
12−24 mos	−0.24 (0.36)	−0.12 (0.41)	−0.17 (0.40)	0.419	−0.01 (0.36)	0.02 (0.37)	−0.05 (0.37)	0.638
24−36 mos	−0.63 (0.31)	−0.94 (0.33)	−1.09 (0.43)	<0.001	−0.16 (0.24)	−0.30 (0.30)	−0.38 (0.34)	<0.001
36−48 mos	−0.42 (0.47)	−0.38 (0.50)	−0.42 (0.51)	0.880	−0.30 (0.39)	−0.36 (0.42)	−0.38 (0.37)	0.575
48−60 mos	−0.44 (0.48)	−0.52 (0.44)	−0.49 (0.56)	0.762	−0.34 (0.38)	−0.36 (0.42)	−0.32 (0.34)	0.910
Baseline to 60 mos	−2.25 (1.11)	−2.34 (1.07)	−2.32 (1.04)	0.950	−1.12 (0.77)	−1.13 (0.88)	−1.27 (0.86)	0.631
AL, mm, mean (SD)								
Baseline	24.97 (0.84)	24.97 (0.81)	25.14 (0.99)	0.419	25.37 (0.98)	25.32 (0.78)	25.21 (0.81)	0.654
24 mos	25.55 (0.89)	25.33 (0.83)	25.45 (1.05)	0.506	25.68 (1.06)	25.47 (0.81)	25.38 (0.84)	0.274
36 mos	25.89 (0.92)	25.76 (0.85)	25.87 (1.06)	0.659	25.82 (1.10)	25.66 (0.85)	25.56 (0.85)	0.385
48 mos	26.01 (0.94)	25.92 (0.91)	26.08 (1.10)	0.581	25.91 (1.10)	25.79 (0.87)	25.66 (0.86)	0.442
60 mos	26.16 (0.98)	26.07 (0.95)	26.20 (1.14)	0.692	25.96 (1.11)	25.86 (0.88)	25.74 (0.88)	0.555
Change in AL, mm, mean (SD)								
Baseline to 12 mos	0.30 (0.15)	0.18 (0.17)	0.13 (0.16)	<0.001	0.18 (0.15)	0.05 (0.16)	0.06 (0.15)	<0.001
12−24 mos	0.28 (0.15)	0.19 (0.13)	0.18 (0.11)	0.020	0.14 (0.13)	0.10 (0.11)	0.11 (0.10)	0.183
24−36 mos	0.34 (0.13)	0.43 (0.14)	0.42 (0.18)	0.007	0.14 (0.09)	0.18 (0.12)	0.17 (0.14)	0.093
36−48 mos	0.17 (0.15)	0.15 (0.15)	0.17 (0.16)	0.742	0.08 (0.09)	0.13 (0.10)	0.10 (0.09)	0.018
48−60 mos	0.15 (0.11)	0.12 (0.12)	0.12 (0.13)	0.572	0.06 (0.08)	0.07 (0.09)	0.08 (0.10)	0.550
Baseline to 60 mos	1.21 (0.54)	1.08 (0.53)	1.03 (0.47)	0.372	0.60 (0.35)	0.54 (0.34)	0.54 (0.34)	0.495

AL = axial length; D = diopter; SD = standard deviation; SE = spherical equivalent.

after which higher doses are ineffective. After stopping atropine, there was a significant myopic progression in eyes receiving higher doses with myopia than in eyes previously receiving atropine 1.0%, almost approaching that of placebo eyes, with less change noted in lower doses.[18,20]

Much of the changes noted could be explained by the pharmacologic effect of atropine on the actively growing myopic eye. Although the exact mechanism of atropine is not known, it is believed that atropine acts directly or indirectly on the retina or scleral, inhibiting thinning or stretching of the scleral, and thereby eye growth.[20,22] This eye growth possibly involves a series of biochemical steps, and atropine presumably inhibits 1 or more steps along this pathway, creating changes in the feedback mechanisms and up- or downregulating other receptors both up- and downstream. When atropine is withdrawn, it is not surprising that there may be a sudden growth spurt as the inhibitory action is released. If the process involved a simple inhibition of growth, then one would expect that after a sudden increase, eyeball growth would then slow to a rate appropriate for age. However, the rate of growth seemed to continue at a steady pace over the washout year in children previously receiving the higher 0.1% and 0.5% doses of atropine, slowing only when atropine 0.01% was restarted. This suggests that the effects, particularly of higher doses of atropine, may be more complex than we think, possibly causing change or modification of the mechanism regulating eye growth at different anatomic and biochemical levels.[20,22] It is uncertain whether these changes could be permanent (e.g., resulting in sustained acceleration of myopia even years after stopping atropine), the system will reset itself, or we can modulate subsequent eye growth (e.g., by tapering atropine more slowly over time). Somewhat reassuring is the finding that the proportion of children who progressed >0.5 D in the washout year (i.e., requiring re-treatment) decreased with increasing age in all 3 treatment arms (Fig 2). From clinical experience, we also note that by slowly tapering the frequency of atropine, we can dampen the change in myopia and retain the beneficial effect on myopia progression. In contrast, the change in myopia progression after stopping atropine 0.01% seemed less marked, and it is hoped as AL growth slowed naturally, as it did during phase 3, that atropine could be safely stopped (e.g., by the mid to late-teens).

On the basis of these results, we conclude that low-dose (0.01%) atropine for periods up to 5 years is a clinical viable

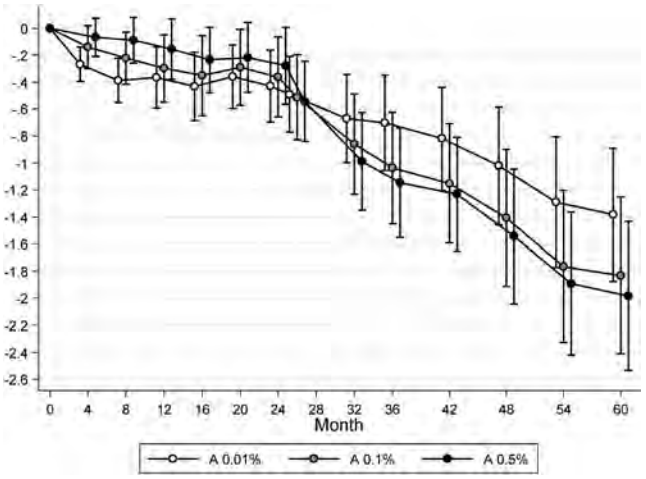

Figure 3. Mean change in spherical equivalent over time within different treatment groups (atropine 0.01%, 0.1%, and 0.5%). Error bars represent 1 standard deviation.

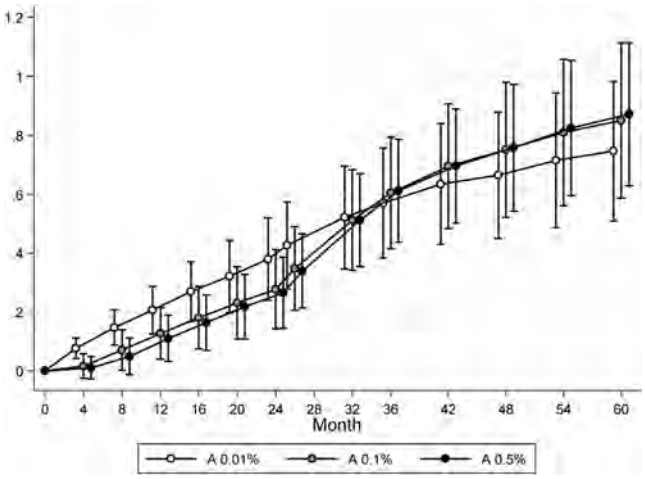

Figure 5. Mean change in axial length (AL) over time within different treatment groups (atropine 0.01%, 0.1%, and 0.5%). Error bars represent 1 standard deviation.

treatment of myopia with the best sustained effect on myopia retardation. The mean myopia progression at 5 years (−1.38 D) in children initially randomized to atropine 0.01% was similar to that in placebo eyes at 2.5 years (−1.40 D), suggesting that atropine 0.01% slowed myopia progression by 50% (Fig 6).[18] The gradual slowing of the myopia progression and corresponding AL change in the later years in phase 3 (i.e., 54−60 months) in the 0.01% group suggested that eye growth was slowing and that a long-term sustained effect was possible, as suggested in several other studies.[4,8,23]

In establishing clinical treatment algorithms, however, questions remain on which children would best benefit from treatment (e.g., in terms of age, level of myopia, rate of progression, and family risk factors), when atropine should be started and stopped, and for how long it should be used. In our studies, children underwent a washout period of a full 1 year after 2 years of treatment, which clinically would not be necessary, and it is possible that if atropine had been continued longer, particularly in children whose myopia increased after atropine was stopped, then the overall effect may have been even better. Although one may speculate as to the safety and efficacy profiles of other low doses (e.g., 0.005% or 0.05%), the 0.01% dose appears to offer an appropriate risk−benefit ratio, with no clinically significant visual side effects balanced against a reasonable and clinically significant 50% reduction in myopia progression. This is corroborated by cohort studies that show that doses of 0.025% to 0.05% could be very effective.[23] Further studies could explore if there is still a role for high-dose atropine (e.g., for rapid progressors) and the additive effect of combining atropine with other emerging myopia therapies (e.g., peripheral defocus contact lenses or spectacles) and environmental interventions (e.g., increased outdoor time).[24]

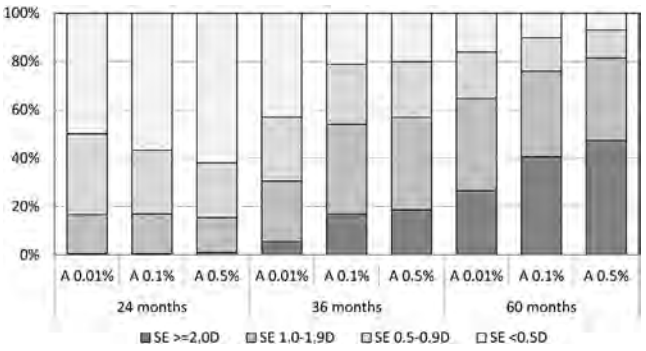

Figure 4. Myopic progression in eyes within each atropine group at the end of phase 1 (24 months), phase 2 (36 months), and phase 3 (60 months). D = diopter; SE = spherical equivalent.

Within the confines of our finding, we propose that a daily dose of atropine 0.01% is an effective first-line treatment in children aged 6 to 12 years with documented myopic progression of ≥0.5 D in the preceding year with few side effects. Because atropine appeared more effective in the second year than the first, treatment initially should be continued for at least 2 years. If there is a good response to atropine 0.01% (e.g., almost no progression or progression <0.25 D in the second year) especially in older children aged >13 years, then atropine 0.01% could be stopped. If an increase in myopia then occurs, then children could be restarted on atropine. If the initial response to atropine was more moderate (e.g., progression of 0.25−0.75 D in the second year), then one could consider continuing atropine 0.01% for a longer period until progression slows to <0.25 D per year, as it might do in the mid to late teens.

However, there may be children who are poor responders to atropine. In phase 1, 9.3% of children in the 0.01% group, 6.4% of children in the 0.1% group, and 4.3% of children in the 0.5% group had myopia progression ≥1.5 D over the first 2 years of treatment. In children who respond poorly to atropine 0.01% (e.g., progress >0.75 D per year in the second year), it may be possible that they would also not respond to higher doses and that atropine should be stopped.

Table 4. Changes in Pupil Size, Accommodation, and Visual Acuity in Children within Different Atropine Groups (0.01%, 0.1%, and 0.5%) Who Were Re-treated and Who Did Not Require Re-treatment

	Re-treated Children				Untreated Children			
	Atropine 0.01% (N = 17)	*Atropine 0.1% (N = 82)*	*Atropine 0.5% (N = 93)*	***P* Value**	*Atropine 0.01% (N = 53)*	*Atropine 0.1% (N = 57)*	*Atropine 0.5% (N = 43)*	***P* Value**
Photopic pupil size, mm, mean (SD)								
Screening	3.93 (0.56)	4.01 (0.62)	3.98 (0.63)	0.872	3.89 (0.58)	3.86 (0.67)	4.02 (0.60)	0.363
24 mos	5.18 (1.02)	6.76 (1.04)	7.65 (1.06)	<0.001	5.02 (0.92)	6.46 (1.07)	7.28 (1.46)	<0.001
36 mos	3.78 (0.58)	3.76 (0.57)	3.76 (0.63)	0.993	3.73 (0.58)	3.59 (0.49)	3.74 (0.47)	0.193
48 mos	4.89 (0.99)	4.78 (0.87)	4.86 (0.95)	0.775	3.63 (0.52)	3.59 (0.51)	3.68 (0.40)	0.633
60 mos	5.13 (0.89)	4.79 (0.90)	4.77 (0.98)	0.275	3.58 (0.59)	3.48 (0.49)	3.58 (0.46)	0.448
Final visit	3.81 (0.59)	3.59 (0.54)	3.56 (0.51)	0.264	3.58 (0.59)	3.48 (0.49)	3.58 (0.46)	0.448
Accommodation, D, mean (SD)								
Screening	17.29 (3.24)	17.13 (3.12)	15.95 (3.68)	0.041	15.99 (3.15)	16.83 (2.72)	15.93 (2.76)	0.149
24 mos	10.88 (4.01)	6.18 (2.76)	3.89 (2.33)	<0.001	11.95 (2.73)	7.53 (3.58)	4.55 (3.16)	<0.001
36 mos	13.55 (2.49)	14.58 (2.79)	13.30 (2.96)	0.010	14.18 (3.04)	14.26 (2.29)	13.07 (2.17)	0.015
48 mos	11.37 (3.21)	11.66 (2.62)	11.17 (3.11)	0.530	13.61 (2.60)	13.42 (2.81)	12.34 (2.10)	0.013
60 mos	11.01 (3.20)	10.92 (2.45)	10.57 (2.83)	0.638	12.98 (2.58)	12.56 (2.48)	12.29 (2.13)	0.348
Final visit	13.44 (2.48)	12.93 (2.28)	12.26 (2.87)	0.107	12.98 (2.58)	12.56 (2.48)	12.29 (2.13)	0.348
Distance visual acuity, logMAR, mean (SD)								
Screening	0.02 (0.03)	0.02 (0.07)	0.03 (0.06)	0.527	0.01 (0.05)	−0.00 (0.06)	0.00 (0.05)	0.333
24 mos	0.01 (0.05)	0.01 (0.05)	0.02 (0.06)	0.539	−0.01 (0.06)	−0.01 (0.06)	−0.01 (0.05)	0.992
36 mos	−0.01 (0.05)	0.00 (0.05)	0.00 (0.05)	0.700	−0.01 (0.05)	−0.02 (0.05)	−0.01 (0.05)	0.843
48 mos	−0.00 (0.04)	0.00 (0.05)	0.00 (0.05)	0.822	−0.02 (0.05)	−0.02 (0.06)	−0.01 (0.04)	0.867
60 mos	−0.01 (0.05)	−0.01 (0.05)	0.00 (0.05)	0.120	−0.02 (0.05)	−0.02 (0.06)	−0.03 (0.05)	0.286
Final visit	−0.02 (0.04)	−0.02 (0.05)	−0.01 (0.05)	0.444	−0.02 (0.05)	−0.02 (0.06)	−0.03 (0.05)	0.286
Near visual acuity, logMAR, mean (SD)								
Screening	0.04 (0.08)	0.07 (0.08)	0.04 (0.07)	0.059	0.03 (0.06)	0.02 (0.07)	0.02 (0.06)	0.440
24 mos	0.03 (0.07)	0.13 (0.13)	0.30 (0.16)	<0.001	0.01 (0.07)	0.07 (0.12)	0.27 (0.22)	<0.001
36 mos	0.00 (0.05)	−0.01 (0.06)	−0.00 (0.06)	0.434	−0.02 (0.05)	−0.02 (0.06)	−0.02 (0.06)	0.676
48 mos	−0.01 (0.06)	0.01 (0.05)	0.01 (0.07)	0.728	−0.01 (0.05)	−0.02 (0.06)	−0.03 (0.06)	0.049
60 mos	0.01 (0.06)	−0.01 (0.06)	−0.00 (0.07)	0.535	−0.02 (0.05)	−0.02 (0.06)	−0.04 (0.05)	0.191
Final visit	−0.00 (0.05)	−0.02 (0.06)	−0.01 (0.06)	0.451	−0.02 (0.05)	−0.02 (0.06)	−0.04 (0.05)	0.191

D = diopters; logMAR = logarithm of the minimum angle of resolution; SD = standard deviation.

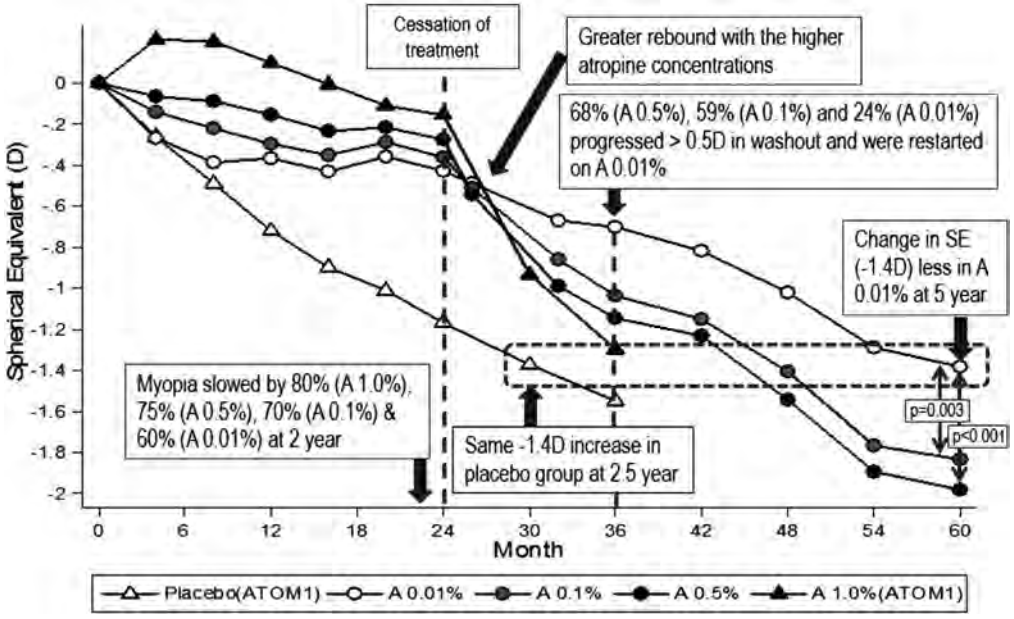

Figure 6. Summary of findings from the ATOM1 and ATOM2 studies: change in spherical equivalent (SE). ATOM = Atropine for the Treatment of Myopia; D = diopter.

An ultimate goal of myopia control therapy would be to slow myopic progression during the years of most active eye growth so that the eventual level of myopia was lower than if the eye was allowed to grow naturally (i.e., to reduce the incidence of high myopia). If less people developed high or pathologic myopia, then less might also develop the potentially blinding myopic complications, such as posterior staphyloma, macula choroidal neovascularization, retinal detachment, and glaucoma.[25–27] In a recent review, pathologic myopia was estimated to have a global prevalence of 0.9% to 3.1% and to be the cause of low vision or blindness in 5.8% to 7.8% in European populations and 12.2% to 31.3% in East Asian populations.[26] Given the increasing prevalence of myopia in East Asia, where the prevalence of myopia in young adults now approaches 80% and high myopia rates exceed 20%, it is thought that the disease burden and cost of pathologic myopia will continue to increase over time.[27] The availability of an effective and low-cost myopia-retarding medication such as atropine 0.01% is timely and could make both clinical and economic sense as a public health measure. The role of higher doses of atropine remains debatable, and care should be taken in stopping it suddenly, particularly in younger children. The strength of this study is in its randomized double-blind design, its relatively low loss to follow rate, and its long duration. Unfortunately, the lack of a control group in this study severely limited our ability to evaluate the full effect of atropine, necessitating comparison with historic and population-based data. Further studies are still needed to determine how eye growth is altered in the long term in children treated with varying doses of atropine so as to better assess the true long-term efficacy and safety of this medication.

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Footnotes and Financial Disclosures

Originally received: June 25, 2014.
Final revision: June 8, 2015.
Accepted: July 2, 2015.
Available online: ■■■. Manuscript no. 2014-1001.

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Financial Disclosure(s):
The author(s) have no proprietary or commercial interest in any materials discussed in this article.

Supported by grants from the National Medical Research Council (MH 95:03/1-23) and SingHealth (SHF/FG039/2004 and TEST 08-03).

Author Contributions:

Conception and design: Chia, Lu, Tan

Data acquisition and/or research execution: Chia, Lu, Tan

Analysis and interpretation: Chia, Lu, Tan

Obtained funding: Tan

Overall responsibility: Chia, Lu, Tan

Abbreviations and Acronyms:
AL = axial length; **ATOM** = Atropine for Treatment of Myopia; **D** = diopters.

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Progress in Retinal and Eye Research 31 (2012) 622–660

Contents lists available at SciVerse ScienceDirect

Progress in Retinal and Eye Research

journal homepage: www.elsevier.com/locate/prer

The complex interactions of retinal, optical and environmental factors in myopia aetiology

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ARTICLE INFO

Article history:
Available online 4 July 2012

Keywords:
Myopia
Myopia aetiology
Physiological myopia
Pathological myopia
Retina
Myopic progression
Myopia prevention
Myopia treatment

ABSTRACT

Myopia is the commonest ocular abnormality but as a research topic remains at the margins of mainstream ophthalmology. The concept that most myopes fall into the category of 'physiological myopia' undoubtedly contributes to this position. Yet detailed analysis of epidemiological data linking myopia with a range of ocular pathologies from glaucoma to retinal detachment demonstrates statistically significant disease association in the 0 to −6 D range of 'physiological myopia'. The calculated risks from myopia are comparable to those between hypertension, smoking and cardiovascular disease. In the case of myopic maculopathy and retinal detachment the risks are an order of magnitude greater. This finding highlights the potential benefits of interventions that can limit or prevent myopia progression.

Our understanding of the regulatory processes that guide an eye to emmetropia and, conversely how the failure of such mechanisms can lead to refractive errors, is certainly incomplete but has grown enormously in the last few decades. Animal studies, observational clinical studies and more recently randomized clinical trials have demonstrated that the retinal image can influence the eye's growth. To date human intervention trials in myopia progression using optical means have had limited success but have been designed on the basis of simple hypotheses regarding the amount of defocus at the fovea.

Recent animal studies, backed by observational clinical studies, have revealed that the mechanisms of optically guided eye growth are influenced by the retinal image across a wide area of the retina and not solely the fovea. Such results necessitate a fundamental shift in how refractive errors are defined. In the context of understanding eye growth a single sphero-cylindrical definition of foveal refraction is insufficient. Instead refractive error must be considered across the curved surface of the retina. This carries the consequence that local retinal image defocus can only be determined once the 3D structure of the viewed scene, off axis performance of the eye and eye shape has been accurately defined. This, in turn, introduces an under-appreciated level of complexity and interaction between the environment, ocular optics and eye shape that needs to be considered when planning and interpreting the results of clinical trials on myopia prevention.

Contents

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[1] Percentage of work contributed by the author in the production of the manuscript is as follows: D.I. Flitcroft: 100%.

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http://dx.doi.org/10.1016/j.preteyeres.2012.06.004

1. Introduction

More than twenty years ago in a mini-review on the aetiology of myopia, Phillips wrote that 'the retina may not be the passive victim of scleral growth, but may conceivably be the author of its own destruction' (Phillips, 1990). Over the intervening years the evidence that refractive error can wreak 'destruction' upon the eye has grown considerably. As well as the long recognised association of high myopia with retinal detachment and myopic maculopathy, evidence now points to associations between myopia and the far more prevalent conditions of glaucoma and cataract. Such findings have not however gained much prominence in the field of ophthalmology. The situation would most certainly be very different if refractive error represented a modifiable risk factor for ocular disease in the way that hypertension is for cardiovascular disease. To that end a small community of scientists have, for the last few decades, being exploring different facets of the biology of refractive error with a view to ultimately preventing or limiting myopia. These studies have revealed a complex web of interactions involved in the optical control of eye growth and, in fulfilment of the above speculative comment, have indeed demonstrated the central role of the retina and intra-retinal processing in the control of eye growth.

While the refraction of the eye can be modified in animals over a wide dioptric range by a variety of interventions that alter eye growth (as reviewed by Wallman and Winawer, 2004), the same is not yet possible in humans. It is one of the challenging aspects of this field that when simple hypotheses, well supported by highly

controlled animal studies, have been tested in a clinical setting the results have generally been disappointing and at times contradictory. Nevertheless a variety of optical and pharmacological interventions have been demonstrated to have some impact on refractive development, and more importantly eye growth, in humans (reviewed by Leo and Young, 2011; Walline et al., 2011). This disparity is not the only paradox in myopia research; perhaps the greatest paradox is the mismatch between the strong epidemiological associations with near work and the poor correlation of near work metrics with myopia progression and the limited effect of bifocal or varifocal glasses. Also whereas twin studies show an apparent high heritability of refractive errors, the prevalence of myopia appears to be increasing over the matter of decades, a change that can't be explained by changes in the gene pool. Adding to the complexity of this field are recent findings that time spent outside appears to limit myopic progression.

The purpose of this review is not to exhaustively review the entire field but to unify disparate strands of myopia research. This unification requires combining topics that are frequently addressed in separate papers such as epidemiology, interventional clinical trials, basic animal studies and applied optics. While this approach may be unusual, it is essential to make sense of the complexity and breadth of this topic. To that end the main part of this review is divided into three sections. Section 2 deals primarily with the epidemiological association of refractive error with ocular disease. This section is intended to demonstrate the potential public health benefits of treatments that can slow or prevent myopic progression. Such treatments are most likely to arise from research into the biological mechanisms of refractive error development. This is the purpose of Section 3, which reviews such mechanisms from both a clinical and animal model perspective. Together, Sections 2 and 3 of this review address the two issues raised in the opening paragraph, namely the nature and magnitude of the 'destructive' force of refractive errors and the role of the retina in this process. Section 4 addresses the optical issues involved in refractive error development and how these may interact with known biological mechanisms. These are far more complex than generally appreciated and a full understanding of the nature of the interactions between the environment, the optics of the eye and image quality across the retina is essential to make sense of existing research and in the planning of future studies.

In relation to the role of the retina, it has become apparent that the extra-foveal retina plays as important, if not a more important role than the fovea, in controlling eye growth. This stands in stark contrast to how the refractive state of the eye is both tested and quantified, which considers only foveal refraction. So while optically guided eye growth requires a pan-retinal or retinocentric perspective on refraction, the definition of myopia used in clinical studies of myopia and clinical refraction is entirely foveocentric. This raises the intriguing possibility that at least some of the conflicts within the field of myopia research represent a classical logical paradox and at the heart of every true paradox is an invalid assumption. In the case of myopia research this invalid assumption is that foveal refraction is the relevant parameter for understanding how the growth of the human eye will respond to visual tasks and optical interventions.

Section 4 of this review sets out to challenge the standard foveocentric definition of refraction and attempts to map out the full implications of a retinocentric view of both refraction and eye growth. Unfortunately abandoning the reassuring and familiar foveocentric definition of refraction reveals a highly complex set of interactions between the physical environment, optics of the eye, eye shape and the mechanisms controlling eye growth. While this analysis reveals an unsuspected and indeed daunting level of complexity, it provides a comprehensive framework for future research and may ultimately help to explain some of the paradoxes of myopia research.

2. The association of myopia and ocular disease

One of the factors that has held back research into the biological basis of refractive errors is the broadly held perception that, apart a very small minority of high myopes, refractive error is merely an optically correctable inconvenience (Saw, 2006). This commonly held viewpoint has undoubtedly impacted upon levels of research funding and drug development. The perception that myopia is an 'optical inconvenience' can be challenged on two grounds; firstly in terms of the impact of refractive errors optically, particularly in the developing world, and secondly on the basis of the public health impact of refractive errors. On a global perspective uncorrected refractive errors represent a major cause of loss of vision, particularly in developing countries, and refractive errors have been listed as one of the five priority conditions in the World Health Organizations 'Vision 2020' (Pararajasegaram, 1999).

In more developed countries the vast majority of myopes will have normal visual acuity with appropriate optical correction but myopia still has significant public health consequences from a variety of perspectives; financial, psychological, quality of life, direct and indirect risks of blindness. Direct and indirect costs of myopia in the US population were estimated for 1990 at US$4.8 billion (Javitt and Chiang, 1994). High levels (>10 D) of myopia are associated with an impact on quality of life comparable with keratoconus (Rose et al., 2000). But the most important impact of myopia, in terms of public health, is as a risk factor for other potentially blinding ocular pathologies. Myopic maculopathy, a condition associated with significant risks of visual loss (Hayashi et al., 2010) and measurable reductions in quality of life (Takashima et al., 2001), is the most obvious linkage between myopia and ocular pathology. However, as will be reviewed below, epidemiologists have also compiled an impressive array of data indicating that refractive errors are a highly important risk factor for a range of ocular diseases including retinal detachment, glaucoma and cataract.

2.1. Physiological vs. pathological myopia

The question whether myopia is merely an inconvenience or a 'disease' is often answered by dividing myopia into physiological myopia and pathological myopia (Curtin, 1985). Although this is a long-standing concept, it is still actively promoted by researchers in this field (e.g. Morgan et al., 2012). The cut-off between the two is conventionally, though arbitrarily, set at a spherical refractive equivalent of −6 Dioptres. Under this classification, physiological myopia represents an inconvenience correctable by optical or surgical means and pathological myopia is a medical condition subject to the complications of extreme levels of myopia. If this distinction was truly valid, low myopes would have no additional ocular disease risks over emmetropes. As the following analysis demonstrates significant disease associations exist even at low levels of myopia. Furthermore there is no evidence of a safe threshold level of myopia for any of the known ocular diseases linked to myopia including myopic maculopathy.

It is important to note that the following analysis addresses the potential disease associations of refractive errors. Low levels of myopia may certainly have some benefits in daily life, especially in later life after the onset of presbyopia (Rose and Tullo, 1998). Furthermore, as is discussed below, physiological mechanisms may create myopia as a consequence of optically misguided emmetropization. Neither of these possibilities prevents myopia also having adverse consequences for ocular health, which is the fundamental reason for rejecting the concept of 'physiological myopia'.

2.1.1. Myopic maculopathy

The most characteristic and common complication of high levels of myopia is atrophic myopic maculopathy/retinopathy. This is a slowly progressive and sight threatening condition in which visual loss develops from atrophy of the retinal pigment epithelium and/or secondary complications such as sub-retinal neovascularization (Hayashi et al., 2010). Far from rare, this condition is currently the fourth commonest cause of visual impairment in the UK ahead of diabetic eye disease (Evans et al., 2004). The same situation prevailed 45 years ago when Sorsby (1966) reported on UK blindness statistics. Despite the major progress in the intervening years in the management and treatment of conditions such as glaucoma, cataract and age-related macular degeneration, no such progress has been made in relation to atrophic myopic maculopathy. These findings are similar or worse in other countries, it being the third most common cause of blindness in the working age population in Ireland (Kelliher et al., 2006) and Israel (Avisar et al., 2006). In Beijing myopic maculopathy is the second commonest cause of low vision (Xu et al., 2006). Despite its importance in terms of public health, atrophic myopic maculopathy stands out as the only disease amongst the top five causes of blindness that remains entirely untreatable.

As part of the extensive Blue Mountains Eye Study, 3654 subjects were examined for evidence of myopic retinopathy (Vongphanit et al., 2002). This study showed a marked and highly non-linear relationship between refraction and the prevalence of myopic retinopathy. Myopes of less than 5 Dioptres had a myopic retinopathy prevalence of 0.42% as compared to 25.3% for myopes with greater than 5 Dioptres of myopia, i.e. a 60 fold (5924%) increase in risk in higher myopes. Beyond 9 D of myopia greater the prevalence exceeded 50%. Despite the far higher prevalence of myopic retinopathy with increasing myopia, the far higher proportion of low myopes (less than 5 D of myopia) in the population resulted in this group contributing 43% of the cases, though these might be expected to be of lesser severity. Thus the so-called 'physiological myopes' in this study contributed almost as many cases as the pathological myopes, a finding that reinforces the arbitrary nature of this old division in public health terms. Calculations of the odds ratio for myopic maculopathy as a function of refractive status are shown in Fig. 1 in the form of a forest plot. These values, and all other calculated or derived statistics in this paper, have been calculated from the reported incidence data using the statistical and meta-analysis functions of R: A language and environment for statistical computing (R Development Core Team, 2012).

2.1.2. Retinal detachment

A similar relationship has been observed between increasing myopia and disease in terms of the increased risk of retinal detachment. Ogawa and Tanaka (1988) provided details of the refraction of 1166 cases of non-traumatic detachment and 11,671 clinic controls. Compared to emmetropes and hyperopes, this Japanese population showed an odds ratio of 3.14 for retinal detachment in low myopes in the range −0.75 to −2.75 D. The odds ratio rose steeply with increasing myopia to greater than 80 for myopia in excess of −15 D. In the US the Eye Disease Case-Control Study (The Eye Disease Case-Control Study Group, 1993) compared 253 patients with idiopathic retinal detachment and 1138 controls. Refraction was identified as the major identifiable risk factor for retinal detachment, with an adjusted odds ratio for refractions in the range −1 to −3 D of 4.4 (95% Confidence Interval (CI) 2.9–6.6), increasing to 9.9 (95% CI 6.6–14.8) in the range −3 D to −8 D. For any degree of myopia (above −1 D) the corrected odds ratio was 7.8 (95% CI 5.0–12.3). These results are presented graphically in Fig. 2, again in the form of a forest plot. From the Eye Disease Case-Control Study it was estimated that in the US 55% of non-traumatic detachments in eyes without previous surgery are attributable to myopia. In contrast to the Japanese study, the Eye Disease Case-Control Study excluded high myopes (more than 8 D), but the risk estimates from the two studies are not significantly different in myopia up to −8 D.

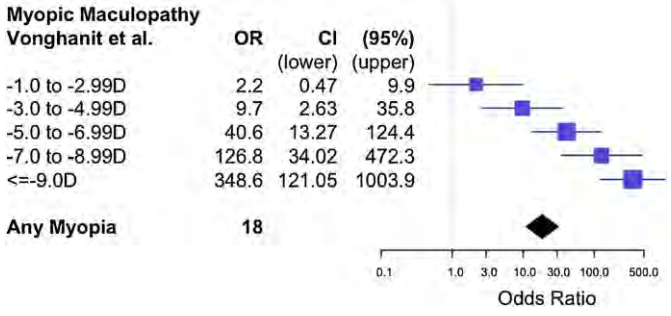

Fig. 1. Forest plot of odds ratio for myopic maculopathy for different refractive states derived from the Blue Mountains Eye Study. The horizontal lines in this type of plot represent the 95% confidence intervals and the size of the square the sample size in each group.

2.1.3. Glaucoma and cataract

Myopia also has been demonstrated to have a statistically significant association with two of the commonest ocular pathologies, namely glaucoma and cataract. In the Blue Mountains Eye Study, for example, the relationship between glaucoma and myopia was maintained after adjusting for known glaucoma risk factors. This study reported an odds ratio (OR) for low myopia of 2.3 (95% CI 1.3–4.1) (Mitchell et al., 1999). The relationship was stronger for eyes with moderate-to-high myopia (OR 3.3; 95% CI 1.7–6.4). A recent meta-analysis of myopia as a risk factor for glaucoma pooled data from 11 different studies and concluded that for low myopia (myopia up to −3 D) the odds ratio was 1.65 (95% CI 1.26–2.17) and for higher levels of myopia (in excess of −3 D) the odds ratio was higher still at 2.46 (95% CI 1.93–3.15) (Marcus et al., 2011).

For cataract the picture is complicated by the fact that the relationship with refraction varies somewhat between different types of cataract and that myopic shifts can accompany the development of nuclear cataracts. The Lens Opacities Case-Control Study addressed the latter issue by using use of distance glasses before 20 years of age as a surrogate for myopia and showed an increased odds ratio risk of mixed cataract of 1.44 (Leske et al., 1991). The Blue Mountain Eye Study has also provided valuable data on this question (Lim et al., 1999), showing that early onset myopia before age 20 years and posterior subcapsular cataract (PSC) showed the strongest association (OR 3.9; 95% CI 2.0–7.9) and hyperopia appeared protective of PSC (OR 0.6; 95% CI 0.4–0.9). As with the other conditions described above a dose–response relationship was apparent with increasing risk of PSC with increasing levels of myopia. The odds ratio for PSC increases from 2.1 (95% CI 1.4–3.5) for low myopia to 3.1 for moderate myopia (95% CI 1.6–5.7), and 5.5 for high myopia (95% CI 2.8–10.9). A similar, though steeper, dose–response relationship between myopia and PSC was found in the Salisbury Eye Evaluation (SEE) project (Chang et al., 2005). In this latter study the odds ratio for PSC was 1.59 (95% CI 0.90–2.80) for myopia between −0.50 D and −1.99 D, 3.22 (95% CI 1.53–6.79) for myopia between −2.00 D and −3.99 D, 5.36 (95% CI 2.17–13.26) for myopia between −4.00 D and −5.99 D, and 12.34 (95% CI 4.85–31.42) for myopia −6.00 D or greater. The Salisbury Eye Evaluation Study found weaker associations with nuclear cataract and no association between myopia and cortical cataract. The Tanjong Pagar survey also reported significant associations

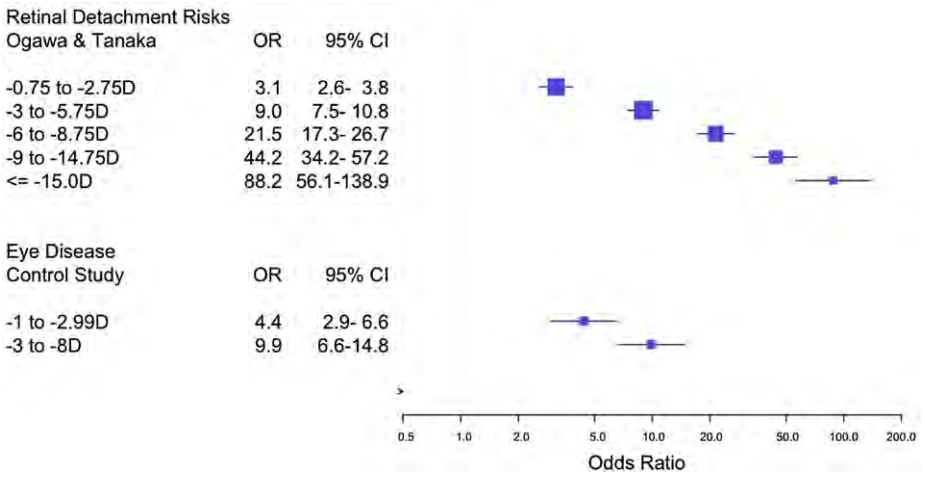

Fig. 2. Forest plot showing the odds ratio for retinal detachment as a function of refraction from Ogawa and Tanaka (1988) and the Eye Disease Control Study (1993).

between nuclear cataract and posterior subcapsular cataract but not cortical cataract (Wong et al., 2003).

A simpler, more binary division has been employed in a more recent Blue Mountains Study in which cataract surgery was used as a criterion. Appropriately adjusted for confounding effects such as severity of nuclear opacity, a significant association was identified between cataract surgery and any degree of myopia (OR 2.1, 95% CI 1.1–4.2). Once again a dose–response relationship was found but this was not as dramatic as seen in retinal detachment surgery with moderate myopia (−3.5 to −6 D) having an odds ratio of OR 2.9 (95% CI 1.2–7.3) and high myopia 3.4 (95% CI 1.0–11.3) (Younan et al., 2002). Some studies have failed to find an association with PSC, notably the Beaver Dam Eye Study in which significant associations with myopia were only reported for nuclear cataract and cataract surgery (Wong et al., 2001).

2.1.4. Hyperopia and disease risk

Myopia is not the only refractive error that is associated with altered disease risk. As noted above hyperopia appears to be protective for some types of cataract (Lim et al., 1999). Conversely, several studies have shown that eyes with a short axial length, a surrogate for hyperopia, are at increased risk of certain retinal disorders and angle close glaucoma, which also means that myopes are at lower risk.

A study from Singapore demonstrated that eyes with myopic spherical equivalent were less likely to have any degree of diabetic retinopathy (odds ratio OR, 0.90; 95% confidence interval CI, 0.84–0.96; $p = 0.002$, per 1-Dioptre decrease) and less likely to have vision-threatening diabetic retinopathy (OR, 0.77; 95% CI, 0.67–0.88; $p < 0.001$, per 1-Dioptre decrease) (Lim et al., 2010). A similar relationship was observed for axial length with significant risk reductions with each 1 mm increase in axial length. Hyperopia and short axial lengths have also been found to be associated with higher rates of exudative age-related maculopathy (Lavanya et al., 2010). In this Asian population hyperopia, when compared with myopia, was associated with early age-related macular degeneration (OR 1.54; 95% CI, 1.00–2.36) as was shorter axial length (OR, 1.91; 95% CI, 1.05–3.46), after adjustment for age, sex, smoking, education, height, and systolic blood pressure. No refractive or axial length association was found with late AMD was found in this study.

Angle closure glaucoma is another condition that has been associated with hyperopia (Lowe, 1970). The association between hyperopia and angle closure glaucoma may be stronger in Caucasian populations than Asian populations (Congdon et al., 1997). The Beijing Eye Study confirmed the association between hyperopia and a shallow anterior chamber, a primary risk factor for angle closure glaucoma (Xu et al., 2008). For angle closure glaucoma rather than just shallow anterior chambers, population surveys have shown a stronger association with axial length than refraction. The Kandy Eye Study (Casson et al., 2009) found the axial length was significantly shorter in eyes with angle closure (21.99 mm) compared with eyes with open angles (22.47 mm; $p < 0.001$) with an odds ratio of 2.04 (95% CI 1.45–2.94) per millimetre reduction in axial length. Despite this association, refractive error itself was not significantly correlated with the incidence of angle closure, OR per 1.0 Dioptre increase = 1.022 (95% CI 0.93–1.12). A population survey from India, the Andhra Pradesh Eye, also found that no statistically significant association between angle closure and hyperopia when considered as a categorical variable, OR = 1.66 (95% CI 0.91–3.04) (Senthil et al., 2010).

So for several conditions hyperopia has increased risk and hence myopia could be considered protective. However, the identified risk levels for hyperopia are smaller than the risks identified for myopia. The stronger correlation with axial length than refraction found in angle closure glaucoma reinforces the biological relevance of axial length, the primary determinant of most refractive errors, in terms of ocular health. In relation to ocular disease risk, refractive error may therefore merely be a surrogate variable for axial length.

2.1.5. Comparison of myopia with hypertension as disease risk factor

Out of context, the relevance of such data for public health can be hard to grasp. Comparison of the risks identified for ocular disease from myopia with the risks from hypertension for cardiovascular disease provides an illuminating benchmark. It took decades of research to fully elucidate the risks posed by hypertension for cardiovascular disease (Shea et al., 1985; Stamler et al., 1993). Comparison of hypertension and myopia as risk factors requires determination of disease incidence in untreated patients and normal controls. Since long-term observation of hypertension without treatment would be considered unethical at this stage, this limits available comparative cardiovascular data to a few large case control studies. A particularly relevant and well powered case control study in the UK examined the risks for stroke according to the quality of blood pressure (BP) control and showed an odds ratio of 3.2 for systolic BP > 160 (95% CI 1.8–5.6) (see Fig. 3) (Du et al., 1997). This study was a based on a yearlong review of a population of 388,821 in which 267 cases of stroke were identified from the regional stroke register and compared with 534 controls.

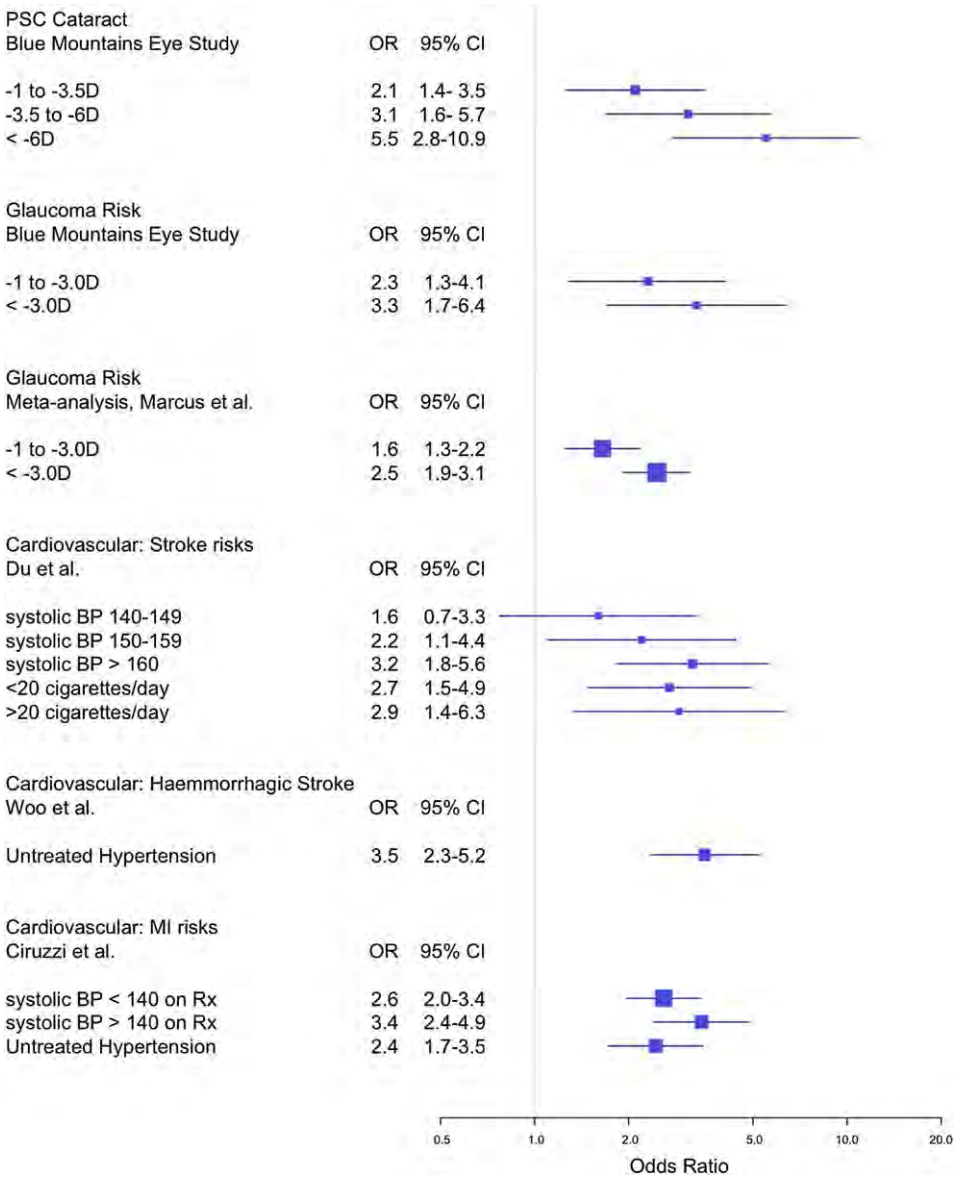

Fig. 3. Forest plot showing the odds ratio for glaucoma and cataract as a function of refraction and, comparison, the odds ratio for stroke and myocardial infarction (MI) associated with poorly controlled hypertension and smoking.

Another large population based case control study from Cincinnati identified 549 cases of haemorrhagic stroke over 5.5 years and demonstrated that the odds ratio for untreated hypertension as 3.5 (95% CI 2.3–5.2; $p < 0.0001$) (Woo et al., 2004). An Argentinian multicentre case control study that examined the risks for myocardial infarction from untreated or treated hypertension collected 939 cases over almost 3 years and demonstrated a range of odds ratios from 2.4 to 3.4 (see Fig. 3) (Ciruzzi et al., 2001). The odds ratios described above for glaucoma and cataract vary from 1.5 to 3.4, which is comparable to the odds ratios for the increased incidence of cardiovascular events in the presence of untreated hypertension. Therefore myopia in the so-called 'physiological range' represents a major risk factor for ocular disease that is comparable with the risks associated with hypertension for cardiovascular disease. The myopia risks for glaucoma and cataract were also comparable with the risks of stroke from smoking >20 cigarettes per day. For retinal detachment and myopic maculopathy, myopia carries a risk far in excess of any identified population risk factor for cardiovascular disease.

2.1.6. Is there a safe physiological threshold for myopia and ocular disease?

If 'physiological' myopia is a valid concept there should be a demonstrable, safe level of myopia without increased risk of other pathology. For both cataract and glaucoma there is evidence that low myopes in the range −1 to −3 D, which is in the lower half of the range of what is conventionally considered 'physiological', have increased risk. For these two diseases myopia has generally been pooled into low, moderate and high myopia for analysis; a stratification that limits detailed analysis of the dose–response relationship between ocular disease and refraction. For retinal detachment and myopic maculopathy published risk data exists that provides more granularity in relation to refraction. This allows mathematical models to be fitted to the data so as to determine the asymptotic value of refraction for which no risk is seen.

Fig. 4A and B show the risk data calculated for retinal detachment and myopic maculopathy plotted conventionally (as opposed to the forest plots) on linear and logarithmic scales on the basis of

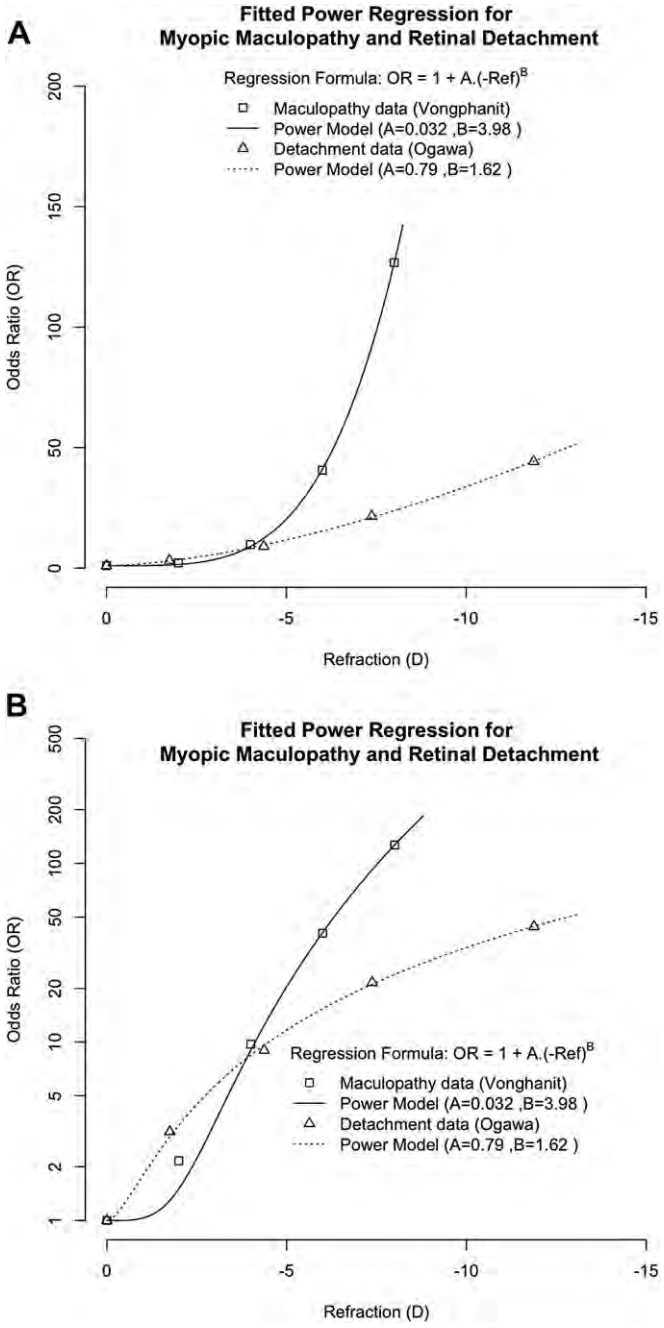

Fig. 4. A. The odds ratio for myopic maculopathy and retinal detachment for the centroid values of the refraction ranges quoted in the two studies plotted on a linear scale for the odds ratio. B. The data from A replotted using a logarithmic scale for the odds ratio. If the relationship were exponential, these data would fall on a straight line. This indicates that a power relationship is a much better representation than a simple exponential model.

mid points of the refractive ranges or estimated median in the case of the maximal myopic group. The relationship is clearly shown in Fig. 4A to be non-linear and exponential in nature but Fig. 4B shows that the relationship remains non-linear when risk is plotted logarithmically indicating this is not a true exponential relationship. Comparison of an exponential non-linear optimization with other two-parameter models (power, linear and exponential) shows that the risk, as defined by odds ratio, is best described by a power model of the form:

$$\mathrm{OR} = 1 + A(-\mathrm{Ref})^B$$

where OR = odds ratio, A is a scaling constant, Ref = refraction in Dioptres and B is the power coefficient. The sign of refraction is reversed in this model to capture the concept of risk increasing with increasing myopia. It is therefore designed only for myopic refractions. The plotted lines in Fig. 4A and B are the fitted models according to the parameters shown in Table 1.

For the retinal detachment data there is convincing evidence that there is no safe level of myopia with any myopic refraction having an odds value of greater than 1. For myopic maculopathy the existence or absence of a safe threshold is less clear-cut. Calculation of an odds ratio requires a comparison or control group. This creates problems if the incidence of a disease in the control population (i.e. emmetropes in this case) approaches zero, as is the case with myopic maculopathy. Using prevalence and/or incidence data can circumvent this problem, though such data can only be reliably acquired from population-based surveys. For myopic maculopathy there are two well-conducted population surveys in which prevalence data for myopic maculopathy has been measured as a function of refraction (Liu et al., 2010; Vongphanit et al., 2002). The data from each is plotted in Fig. 5 along with best-fit exponential and power functions. The nature of the relationship is best seen on a logarithmic scale as shown in Fig. 5B. Beyond −5 D both models describe the data well but at lower refractions the power model provides a much better fit and this fitted model has an asymptotic zero risk at emmetropia. So even in myopic maculopathy it appears there is no safe threshold for myopic refractive errors, although the absolute risk falls rapidly in low myopia.

2.2. Public health implications

The above analysis serves to indicate that myopia is an important independent risk factor for a range of ocular diseases. For certain conditions such as retinal detachment and myopic maculopathy refraction appears to be the dominant risk factor and for others, e.g. cataract and glaucoma, second only to age. Taking the risks of hypertension as a reference point, myopia poses an equal or even greater risk to ocular health as hypertension does for cardiovascular health.

Epidemiological studies can demonstrate statistical association but are not suited to determine causation. Whether myopia has a direct causal role in the above conditions has not yet been proven but there are several factors supporting such an interpretation. Firstly myopia generally predates the onset of these other conditions by many decades. Secondly alterations in the anatomy of the posterior segment that are typical of higher levels of myopia provide a plausible mechanism for increasing the risks of retinal detachment, maculopathy and glaucoma. So for at least three conditions there are plausible, if unproven, aetiological hypotheses. The aetiological linkage, if any, between cataract and myopia is less clear but the Tanjong Pagar Survey included detailed ocular biometric data (Wong et al., 2003). This study indicated that for

Table 1
Regression value and statistics for a power model fitting the relationship between myopic maculopathy and myopia and retinal detachment and myopia. Regression Formula: $\mathrm{OR} = 1 + A\,(-\mathrm{Ref})^B$.

	Estimate	Std error	t value	p value
Myopic maculopathy				
Parameter A	0.032104	0.003294	9.748	0.00229**
Parameter B	3.978256	0.049981	79.596	4.37e−06***
Retinal detachment				
Parameter A	0.78586	0.07046	11.15	0.00154**
Parameter B	1.62057	0.03779	42.88	2.79e−05***

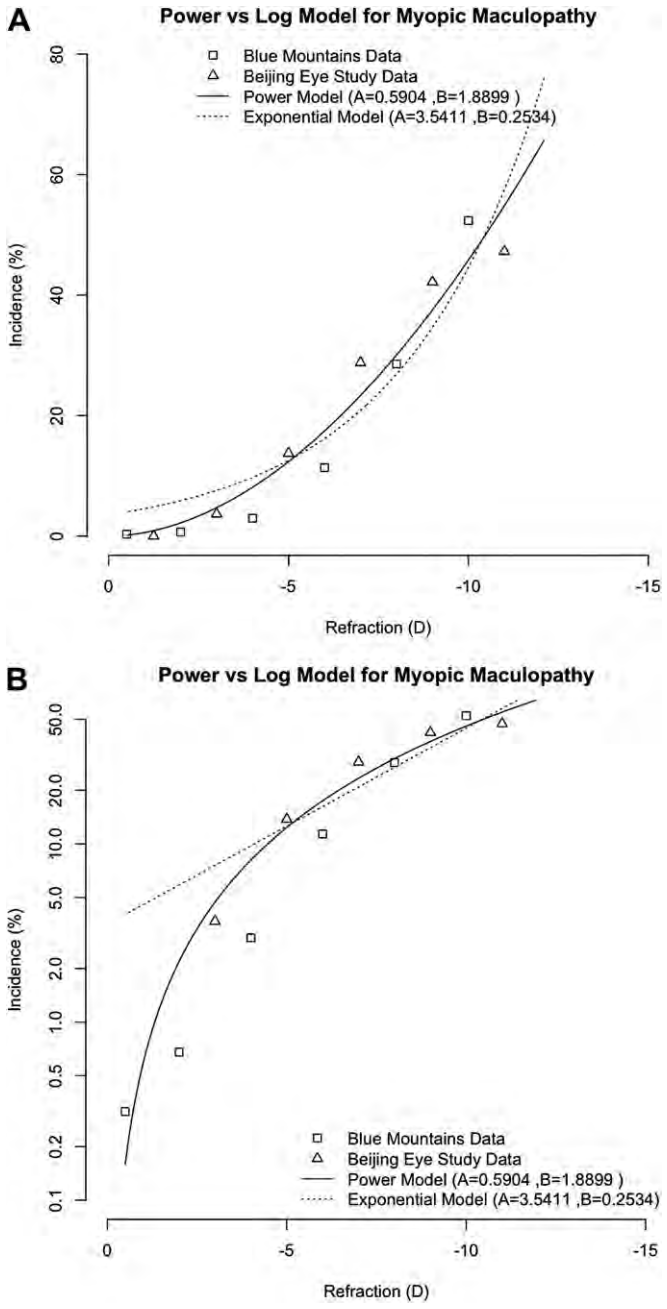

Fig. 5. Plots of the incidence of myopic maculopathy from two studies on linear (A) and log–linear axes (B). The power model (solid line) provides a better fit of the data and demonstrates an asymptotic intercept at emmetropia.

posterior subcapsular cataract (PSC), but not nuclear cataract, there were significant associations with axial length, a thin lens and deep anterior chamber. This points to a causal linkage between ocular shape, which is defined early in life, and PSC, which develops later in life. No such structural factors were found for nuclear cataract where index myopia might explain much of the association. Similar structural associations have been reported in glaucoma (Kuzin et al., 2010). Thirdly is the existence of a dose–response effect for all these conditions, i.e. that increased levels of myopia are associated with increased risk of associated disease.

However, the crucial test of causation is whether reducing the degree of myopia reduces the risk of these associated pathologies. Such a study will be hard to perform due to the long time lag between the development of myopia and the associated pathology. An alternative indirect test of causation involves determining if population shifts in myopia prevalence are followed, in future years, by increases in the incidences of glaucoma, cataract, retinal detachment and myopic maculopathy that match predictions made on the basis of available risk data. As discussed below there are global shifts in myopia prevalence that may facilitate such an approach.

2.2.1. The increasing prevalence of myopia

The prevalence of myopia varies with age, geography, educational achievement, occupation and birth cohort being important parameters. Myopic prevalence in children has been correlated with increasing urbanization in both the far east (Yang et al., 2007; Zhan et al., 2000), Greece (Paritsis et al., 1983) and Australia (Ip et al., 2008). Amongst the school population there is a huge range internationally with a reported myopia prevalence of 2.9% in Melanesian school children (Garner et al., 1988). At the other extreme, developed countries in the Far East now have levels of myopia in excess of 80% amongst school children (Lin et al., 1999).

In more developed countries myopia prevalence seems to be rising quite considerably over the last few decades. The most commonly cited prevalence figure for the West derives from the National Health and Nutrition Examination Survey (NHANES) in 1972 which gave a population prevalence figure of 25% for the USA (Sperduto et al., 1983). A follow up study that replicated the methodology of the 1972 survey to ensure comparability demonstrated a significantly higher myopia prevalence in the 12–54 years age group in 1999–2004 compared to 1971–1972 (41.6% vs. 25.0%, respectively; $p = 0.001$) (Vitale et al., 2009), adding credence to earlier studies showing increased myopia in younger US population cohorts (The Framingham Offspring Eye Study Group, 1996). In terms of the degree of myopia amongst the myopic population the NHANES studies have also demonstrated that the observed change corresponds approximately to a 1 D shift towards increasing myopia within the population.

Similar or even greater increases in myopia prevalence over time have been seen in other countries. Singapore has experienced a large increase in myopia in recent decades with myopia prevalence amongst 15–25 year olds rising from 26.3% in 1974–1984 to 43.3% in 1987–1991 (Tay et al., 1992). A study of 919,929 16–22 year olds in Israel based on sequential cross-sectional surveys over 13 years showed an increase in myopia prevalence from 20.3% in 1990 to 28.3% in 2002 (Bar Dayan et al., 2005). A dramatic rise has been observed within Inuit Eskimo populations over two generations. This has been linked with the introduction of westernized patterns of living and education for younger cohorts with no significant refractive shift in the older generation over the same time period (Morgan et al., 1975; Norn, 1997; Young et al., 1969). Increased myopia in younger populations has been claimed to be an artefact induced by an age induced hyperopic shift in adulthood (Mutti and Zadnik, 2000; Park and Congdon, 2004). Such criticism only applies to single cross-sectional studies. The findings of longitudinal studies and cross-sectional studies repeated over a number of years, such as those cited above provide robust indications that the prevalence of myopia is increasing in specific populations.

2.2.2. Possible implications of increasing myopia prevalence

To understand how an increasing prevalence of myopia may contribute to an increased burden of ocular disease it is necessary to consider the nature of the relationship between disease risk and increasing myopia. The dose–response relationship observed between disease risk and increasing myopia means that the attributable risk for ocular disease from myopia will depend on both the number of myopes and their degree of myopia. This in turn

means that an increasing prevalence of myopia will increase the overall population disease risk. It also means that a small population shift in refraction such as the −1 Dioptre shift noted in the NHANES study can lead to significant increases in disease risk, as all myopic subjects are pushed into a higher risk band. Conversely, if the degree of myopia in a population were reduced by interventions to limit progression, then even without any change in overall prevalence the population disease risk would be lowered.

Shifting patterns of disease incidence are, of course, compounded by the ageing population profile in developed countries but examples of increasing disease incidence for myopia-associated conditions have been described in some populations. For example in Scotland over a twenty year period the incidence of retinal detachment has increased over 45% with an annualised rate of 1.9%/year but a lack of population refraction data over the same period means that there is no evidence that Scotland has experienced the same increases in myopia prevalence that have been observed in other countries (Mitry et al., 2011). Careful evaluation of trends in disease incidence in countries with well-defined changes in refractive distribution over time will provide the best indicator whether the observed relationship between refraction and ocular disease prevalence is causal.

This leads onto the central question of this review – 'Is myopia a modifiable risk factor?' If it is then the dose–response relationships observed in epidemiological studies would indicate that there would be benefits not only in reducing the number of myopes but also in reducing the degree of myopia even the overall incidence of myopia is unaltered. This is an important observation as any intervention strategy is most likely to be applied once a person has already become myopic. To that end a comprehensive understanding of the underlying biological mechanisms of eye growth and refractive development, which is the topic of next section, provides the best hope of finding therapeutic interventions.

3. The role of the retina in controlling eye growth

3.1. Experimental myopia in animal models

The development of animal models of refractive errors has made a huge contribution to our understanding of the regulation of eye growth. This field has also generated a huge literature and in the following sections citations have been chosen to exemplify a specific aspects of this research rather than aiming to be exhaustive.

3.1.1. Deprivation myopia

The first evidence that visual experience has an influence on eye growth arose serendipitously from early lid-suture studies into amblyopia. Wiesel and Raviola (1977) discovered that the sutured eyes of monkeys developed myopia associated with expansion of the posterior segment both equatorially and axially. Wiesel and Raviola postulated that this was due to lack of a clear retinal image. As lid closure may induce a range of effects, as well as preventing vision, additional studies showed that this change was light dependent (Raviola and Wiesel, 1978) and that similar changes in refraction were induced without lid closure but with the induction of corneal opacities (Wiesel and Raviola, 1979). It soon became clear that this phenomenon was present in other species including the tree shrew (Sherman et al., 1977) and chickens (Wallman et al., 1978) and both species have since become important animal models in the field of experimental myopia in recent years.

3.1.2. Impact of spectacles lenses on eye growth

The next major advance in experimental myopia was the demonstration that eye growth can be altered by lenses place on or in front of the eyes (Irving et al., 1991, 1992; Schaeffel et al., 1988). Such compensatory eye growth has now been demonstrated in a range of vertebrate species including the rhesus monkey (Hung et al., 1995), marmoset (Whatham and Judge, 2001), tree shrew (McBrien et al., 1999; Shaikh et al., 1999), guinea pig (McFadden et al., 2004) and even in fish (Shen and Sivak, 2007). The presence of this phenomenon in such a wide range of species suggests it is fundamental aspect of eye growth that has been conserved during vertebrate evolution. In lens rearing studies the induced changes in eye size and refraction represent an appropriate compensation for the sign and amount of defocus induced by the lens in front of the eye. A negatively powered lens in front of the eye induces hyperopic defocus in the retinal image that results in axial elongation, compensating for the optical effects of the lens. Once the lens is removed after such compensation has taken place the increased axial length renders the eye myopic. Such induced myopia will generally show a significant degree of recovery over time when the lens is removed due to marked reductions in axial elongation compared to the fellow eye and hence is a phenomenon best demonstrated in young eyes that are still actively growing. The mechanisms that mediate lens compensation have been suggested to be a fundamental biological feedback loop in ocular growth that drives the statistical phenomenon of emmetropization (Schaeffel and Howland, 1988), a concept derived from clinical studies that was first described almost a century previously (Straub, 1909).

An important finding in lens rearing studies is that the changes in refraction are primarily due to changes in axial length though the growth mechanisms are somewhat different in birds and mammals. In mammals growth in vitreous chamber size results from alterations in the turnover of extra-cellular matrix materials leading to loss of proteoglycans and scleral thinning (McBrien et al., 2000). Birds have a partially cartilaginous sclera and growth is associated with active growth with increased extra-cellular matrix materials in the cartilaginous layer (Nickla et al., 1997). The fibrous part of the avian sclera has, however, been found to demonstrate similar changes to mammalian sclera during myopic growth (Marzani and Wallman, 1997). Birds and mammals also differ in the range over which compensation occurs, a finding which may reflect differences in the visual neurophysiology of different species (Flitcroft, 1999).

3.1.3. Evidence for local growth signals

The optically dependent growth mechanisms appear to operate predominantly within the eye without dependence upon the central nervous system (CNS). This has been demonstrated by the fact that experimental changes in axial length and refraction, including local growth changes in response to partial form deprivation and lens compensation, could still be induced in the chick after the optic nerve has been cut (Troilo et al., 1987). This is not true for all primate species however, optic nerve section prevents deprivation myopia in the stump tailed macaque but not the rhesus macaque (Raviola and Wiesel, 1990). In the chick the accuracy and time course of the growth responses is changed by optic nerve section (Troilo, 1990), so although not essential the central nervous system would appear to have an influence on these mechanisms. In addition to disconnecting the eye from the CNS, optic nerve section may also have a direct impact within the eye from retrograde degeneration of ganglion cells once their axons are severed or by alteration in the blood supply to the retina due to damage to blood vessels passing within the optic nerve or its associated pial covering. So optic nerve section not only separates the eye from the CNS but may also have significant intraocular consequences on the inner retinal layers, complicating the interpretation of such studies. The use of neurotoxins has provided additional evidence for the role of the retina in controlling eye growth which circumvent these issues.

Deprivation myopia and post-deprivation emmetropization are still demonstrable even after intraocular injection of tetrodotoxin (TTX), which blocks action potentials (McBrien et al., 1995; Norton et al., 1994; Wildsoet and Wallman, 1995). The majority of processing within the retina involves graded potentials, with only retinal ganglion cells and some classes of amacrine cell generating action potentials. Therefore the preservation of at least some aspects of the retinal control of eye growth following TTX injections indicates that such control is largely mediated by intra-retinal processing without the involvement of ganglion cells.

Additional evidence for the role of the retina in the process has derived from pharmacological studies. Manipulations leading to myopic eye growth cause large increases in the levels of the neurotransmitter VIP (vasoactive intestinal peptide) which is localised within a class of amacrine cell (Raviola and Wiesel, 1990). Dopaminergic mechanisms have also been shown to have a role in the optical regulation of eye growth and indicate that separate mechanisms exist for deprivation myopia and lens induced myopia (McCarthy et al., 2007; Nickla and Totonelly, 2011; Schaeffel et al., 1994a; Stone et al., 1990). Dopamine is limited to amacrine cells in the mammalian retina, notably the A18 (or CA1) cell (Kolb et al., 1981). In primates a second type of dopaminergic amacrine has also been described, the CA2 cell (Hokoc and Mariani, 1987). Perhaps the most direct evidence that the retina responds to defocus has been the observation that gene expression of the transcription factor ZENK within glucagonergic amacrine cells is altered within 40 min of inducing retinal defocus with a contact lens and that the nature of the response is different with positive and negatively powered lenses (Bitzer and Schaeffel, 2002). Changes in ZENK expression caused by occlusion of an eye have also been found to be rapidly reversed by muscarinic antagonists and dopamine agonists which block the development of deprivation myopia, whereas ZENK expression in undeprived eyes is unaltered (Ashby et al., 2007). Retinal amacrine cells are a highly varied cell class whose overall role in visual physiology remains far from clear, but these studies suggest that specific subpopulations of amacrine cell are likely to play a pivotal role in the optical regulation of eye growth.

3.1.4. Active involvement of the choroid in eye growth regulation

A role for the retina requires a signalling mechanism between the retina and sclera that can pass through the choroid. One of the most surprising findings in experimental myopia was the discovery that transient alterations in choroidal thickness, a structure previously considered solely as a vascular layer, precede changes in axial length/vitreous chamber enlargement attributable to changes in the sclera (Nickla and Wallman, 2010; Wallman et al., 1995; Wildsoet and Wallman, 1995). This was first noted in the chick but it was subsequently confirmed that similar changes of smaller magnitude are found in primates (Hung et al., 2000; Troilo et al., 2000). Imposed defocus has also been shown to produce rapid, if small, changes in choroidal thickness in humans within 60 min of lens wear (Read et al., 2010).

A linkage between the retinal image, choroid and sclera (where permanent growth changes in the eye are manifest) requires communication between these three layers. One candidate signalling molecule between the retina, choroid and sclera is retinoic acid, a compound actively synthesized within choroid. The levels of retinoic acid in the retina and choroid change in opposite directions with imposed myopic and hyperopic defocus (McFadden et al., 2004). Furthermore choroidal retinoic acid is detectable in the sclera at levels that inhibit proteoglycan synthesis (Mertz and Wallman, 2000). This sequence of interactions makes retinoic acid a leading candidate as an intraocular growth-signalling molecule.

The choroid also contains neurons, so called intrinsic choroidal neurons (ICN), which have been described in birds and higher primates including humans (Schrodl et al., 2003, 2004; Stubinger et al., 2010). The role of these choroidal neurons remains enigmatic but they represent another potential signalling mechanism between the retina and sclera. These neurons stain for both vasoactive intestinal peptide (VIP) and neural nitric oxide synthase (nNOS) (Stubinger et al., 2010). Both of these transmitter systems have been implicated in refractive development (Fujikado et al., 1997; Seltner and Stell, 1995).

3.1.5. Circadian rhythms and eye growth

A close link has been identified between circadian rhythms and eye growth. The induction of myopia in animals by visual deprivation has been found to alter diurnal rhythms in retinal dopamine by reducing daytime dopamine concentrations (Iuvone et al., 1989; Stone et al., 1989; Weiss and Schaeffel, 1993). No such effect was noted during induction of myopia by lens rearing, which suggests deprivation and lens-induced myopia involved different retinal pathways (Bartmann et al., 1994). Choroidal thickness shows a circadian rhythm in chicks, marmosets and humans (Brown et al., 2009; Nickla et al., 1998, 2002; Papastergiou et al., 1998). In chicks there is a close phase relationship between the diurnal changes in choroidal thickness and axial length changes during normal and myopic eye growth suggesting these rhythms play an important role in regulating eye growth (Nickla et al., 1998). Manipulation of factors that affect circadian rhythms such as altering the daily light–dark cycle or rearing under constant light has also been found to produce a range of changes in eye growth. Constant light limits the development of myopia from deprivation but was reported not to affect lens induced changes in refraction (Bartmann et al., 1994), though another study found constant light did impair compensatory growth responses to negatively powered lenses (Padmanabhan et al., 2007). Constant light also affects the anterior segment in chicks producing corneal flattening and hyperopia despite an increase in axial length (Stone et al., 1995).

3.1.6. Role of the central nervous system

Although there is ample evidence for a local feedback loop from the sensory retina, most probably involving several classes of amacrine cell, via the choroid to the sclera, the central nervous system (CNS) does appear to have at least a modulatory influence on eye growth and emmetropization. As already noted optic nerve section does not abolish compensatory growth but it does alter the response and in the chick an intact optic nerve appears necessary to achieve emmetropia or accurate compensation (Troilo, 1990) and optic nerve section in chicks appears to alter the set-point of the regulatory process (Wildsoet, 2003). This points to some contribution from the central nervous system.

The most obvious manner in which the central nervous system might influence eye growth is via the accommodation system, yet ablation of the Edinger–Westphal nucleus which controls accommodation does not prevent lens compensation (Schaeffel et al., 1990). The so-called ‘accommodation hypothesis’ in which the active accommodation of near work was the driver for myopia was also initially supported by early clinical trials in which atropine, a potent cycloplegic, appeared to limit myopic progression in humans (Bedrossian, 1979) and was also found to prevent deprivation myopia in monkeys (Raviola and Wiesel, 1985). Atropine also limits or prevents experimental myopia in chickens but the ciliary muscle in chickens has striated muscle and is unaffected by atropine pointing to a non-accommodative mechanism of action (McBrien et al., 1993; Stone et al., 1991). The effectiveness of pirenzepine, a primarily M1 muscarinic receptor antagonist, in suppressing experimental myopia suggested the M1 receptor was the

primary target for the effectiveness of non-selective cholinergic antagonists such as atropine (Stone et al., 1991). Further work has indicated that the chick lacks the M1 receptor (Yin et al., 2004) and more recently the M4 receptor has been identified as a more likely site of action at least in chicks (McBrien et al., 2011). The observation that atropine alters electrical activity of the retina at concentrations required to suppress myopia, points to a retinal site of action (Schwahn et al., 2000) though a wide range of muscarinic receptor subtypes are expressed in both the retina and sclera (Fischer et al., 1998; Qu et al., 2006).

One of the more challenging concepts in this field is the suggestion that amblyopia can prevent normal emmetropization. Monkeys with induced strabismic or anisometropic amblyopia both displayed hyperopia in the amblyopic eye which correlated with the density of the amblyopic deficit (Kiorpes and Wallman, 1995). Monkeys that failed to show compensatory growth to imposed anisometropia were found to have developed amblyopia in the non-compensated eye (Smith et al., 1999). In humans the situation is less clear cut but several small clinical studies have suggested that anisometropia may be a consequence of amblyopia as much as a cause. It was claimed as long ago as 1975 that amblyopic eyes showed less emmetropization than the normal fixing eye (Lepard, 1975) and confirmed independently (Nastri et al., 1984). It was later demonstrated by ultrasonography that this reflected different patterns of vitreous chamber growth (Burtolo et al., 2002).

The mechanisms by which amblyopia might influence eye growth remain unclear but, if a true phenomenon, this would point to the possible involvement of retinopetal (or centrifugal) projections from the CNS to the retina. Such fibres have been identified in a range of species including humans but no role has yet been determined for them (Halpern et al., 1976; Simon et al., 2001; Wolter, 1978; Wolter and Knoblich, 1965). In primates both histaminergic and serotonergic retinopetal projections have been identified which terminate predominantly in the inner retina (Gastinger et al., 2006b). The serotonergic fibres appear to project from the Dorsal Raphe Nuclei, creating a circuit between the retina, Dorsal Raphe Nuclei and the suprachiasmatic nucleus and hence they may play a role in circadian rhythm regulation (Frazao et al., 2008; Gastinger et al., 2005). Histaminergic retinopetal fibres originating from the hypothalamus have been identified in guinea pigs and primates (Airaksinen and Panula, 1988; Gastinger et al., 1999). In primates these fibres are thought to terminate on ON-bipolar terminals but histamine receptors have been noted on dopaminergic amacrine cells in rats (Gastinger et al., 2006a). There is currently no evidence of a direct role of these retinopetal fibres in regulating eye growth, but the links with ON-bipolar cells, dopamine and circadian rhythms are intriguing since all three, as discussed in this review, have been implicated in the refractive development of the eye.

3.2. The role of the retina and retinal image in controlling human refraction

3.2.1. Role of a clear retinal image in human eye growth

The first evidence in humans that a degraded retinal image can produce myopia came from the natural experiments offered by a range of ocular diseases. Shortly after the publication demonstrating that lid suture leads to myopia in monkeys (Wiesel and Raviola, 1977) the same phenomenon was described in naturally occurring clinical situations (O'Leary and Millodot, 1979). Clinical disorders that prevent the formation of a clear retinal image were found to replicate the experimental conditions that had been seen to produce deprivation myopia in animal models. A later paper published distribution data on refractions of 73 infants with a range of clinical disorders that prevented the formation of a clear retinal

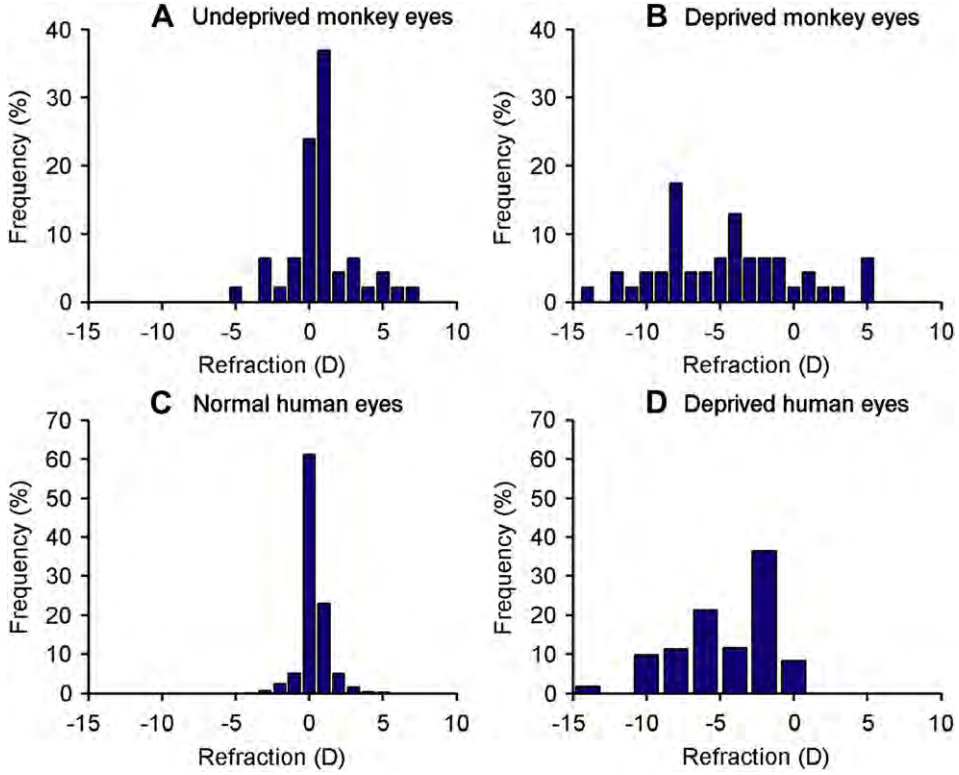

Fig. 6. Panels A and B are redrawn from Raviola and Wiesel (1985) and show the distribution in refraction of 46 eyes with and without visual deprivation (note an apparent error in vertical scaling in the original source paper has been corrected in these graphs). Panels C and D are redrawn from Rabin et al. (1981).

image and demonstrated a myopic shift compared to normal infants (Rabin et al., 1981). The data from this clinical study have been replotted in Fig. 6 alongside the data from Wiesel and Raviola (1977). The refractive distribution of human infants with an impaired retinal image and normal controls can be seen to display a remarkably similar pattern to that seen in monocularly deprived monkeys and normal monkeys.

3.2.2. Impact of spectacle corrections on human eye growth

Animal studies demonstrating that lens-induced hyperopic defocus promotes myopic growth together with studies indicating that myopes tend to under-accommodate for near (Gwiazda et al., 1993; McBrien and Millodot, 1986) led to the development of the accommodative-lag hypothesis. This hypothesis states that under-accommodation for near promotes myopia development by creating hyperopic blur during near work. A logical prediction of this hypothesis is that reducing such accommodative lag for near by reducing accommodation demand with a bifocal or varifocal near add should reduce myopic progression. Several clinical trials have been conducted which have demonstrated either no impact of bifocals on progression (Grosvenor et al., 1987), or statistically significant but small reductions in myopia progression and most importantly in axial elongation (Cheng et al., 2010; Fulk et al., 2000; Gwiazda et al., 2003). While such studies have not changed clinical practice they do provide evidence that human eye growth can be modified by optical means alone.

In animal studies, myopic defocus limits eye growth and promotes the formation of hyperopia in growing eyes. In humans, myopic defocus can be created by under-correcting pre-existing myopia. Deliberate under-correction of myopic children should on that basis slow myopic progression and conversely optically correcting myopes may promote myopic progression by eliminating myopic blur. In fact the opposite effect was observed on both refraction and axial length in one study with fully corrected eyes progressing slower than under-corrected eyes (Chung et al., 2002) and a small but statistically insignificant effect seen in another (Adler and Millodot, 2006). This finding might indicate that, in humans, under-correction promotes myopia progression via a mechanism akin to deprivation myopia (as demonstrated in Fig. 6) that outweighs the effect of myopic defocus. Alternatively humans, in contrast to other species, may respond to hyperopic defocus but be relatively insensitive to myopic defocus by the time myopia has developed. A counter to that argument is found in a recent contact lens trial. A multi-zone contact lens designed to superimpose an in-focus image together with an image having myopic defocus has demonstrated significant reductions in myopic progression and axial elongation, indicating that myopic defocus can reduce myopic progression in humans (Anstice and Phillips, 2011). An earlier study in chicks demonstrated that the growth response to simultaneous exposure of hyperopic and myopic defocus favoured the myopic defocus (i.e. a hyperopic growth response) (Tse et al., 2007). While reconciling these studies remain challenging they do at least demonstrate that human eye growth is sensitive to optical manipulation in a similar manner to animal models.

3.2.3. Retinal disorders and eye growth in humans

Further evidence of the role of the retina in influencing the refractive state derives from the range of retinal abnormalities that are associated with abnormal refractive states. These conditions include myelinated nerve fibres (Tarabishy et al., 2007). Perhaps the clearest evidence for a role of the retina in regulating eye growth is rarely mentioned in papers or reviews on myopia, namely the existence of a distinct class of retinal dystrophies which have been classified as the “ametropic dystrophies” (Laties and Stone, 1991).

Table 2 provides a list of recognised ametropic dystrophies along with the associated gene abnormalities where known. The data in this table were extracted from the full-text files provided by OMIM (Online Mendelian Inheritance in Man) database using dedicated scripts written by the author. These scripts are written in AWK and allow identification of retinal diseases where refractive errors are listed as a clinical feature and the associated genes were then extracted from the OMIM gene map files. Despite the relative neglect of such conditions in the myopia literature, there is a certain irony that the first claimed myopia locus MYP1, is in fact one such ametropic dystrophy, also known as Bornholm Eye Disease (Young et al., 2004). However, a recent Chinese linkage study has suggested that non-syndromic myopia may also be associated with this locus

Table 2
Retinal disorders associated with ametropia.

Condition	OMIM Ref #	Linkage	Gene symbols	Dominant refractive error
Achromatopsia 3	262300	8q21.3	CNGB3, ACHM3, ACHM1	Myopia
Aland island eye disease	300600	Xp11.23	CACNA1F, CSNB2, CORDX3, CSNB2A, AIED, OA2	Myopia
Alport syndrome, X-linked	301050	Xq22.3	COL4A5, ATS, ASLN	Myopia
Aplasia cutis congenita, high myopia, and cone-rod dysfunction	601075			Myopia
Bornholm eye disease	300843	Xq28	BED	Myopia
Chorioretinal atrophy, progressive bifocal	600790	6q14-q16.2	PBCRA, CRAPB	Myopia
Cone-rod dystrophy, X-linked, 1	304020	Xp11.4	RPGR, RP3, CRD, RP15, COD1, CORDX1	Myopia
Fundus dystrophy, pseudoinflammatory, recessive form	264420			Myopia
Gyrate atrophy of choroid and retina	258870	10q26.13	OAT, GACR	Myopia
Lymphoedema, microcephaly, chorioretinopathy syndrome	152950			Myopia
Myelinated retinal nerve fibres	N/A			Myopia
Night blindness, congenital stationary, type 1A	310500	Xp11.4	NYX, CSNB1A, NBM1	Myopia
Night blindness, congenital stationary, type 1B	257270	5q35.3	GRM6, MGLUR6, CSNB1B	Myopia
Retinitis pigmentosa 2	312600	Xp11.23	RP2	Myopia
Sveinsson chorioretinal atrophy	108985	11p15.3-p15.2	TEAD1, TCF13, REF1	Myopia
Dominant macular dystrophy, cystoid	153880	7p21-p15	MDDC	Hyperopia
Leber congenital amaurosis	204000	various	LCA, *RPE65*, *RDH12*, *CRB1*, *AIPL1*, *GUCY2D*, *CRX*, *RPGRIP1*	Hyperopia
Pigmented paravenous chorioretinal atrophy	172870	1q31.3	CRB1, RP12, LCA8	Hyperopia
Retinopathy, pericentral pigmentary, autosomal recessive	268060			Hyperopia
Retinoschisis of fovea	268080			Hyperopia

(Guo et al., 2010). Of the ametropic dystrophies, one in particular can be closely linked to the body of research from animal studies, namely congenital stationary night blindness (CSNB). Defects in several different genes have been found to create this phenotype and they are expressed within the ON-bipolar cell within the retina. This type of neuron is part of a sub-retinal circuit that also involves the AII and dopaminergic A18 amacrine cell which has been implicated in refractive development on the basis of pharmacological studies (Kolb et al., 1991). A mouse knockout (nob) has been created with a mutation in the NYX gene, the same gene that is defective in human CSNB1. This mouse has been found to be less hyperopic than wild-type mice and develop form deprivation at a much faster rate with form deprivation (Pardue et al., 2008). Retinal dopamine and 3,4-dihydroxyphenylacetic acid (DOPAC, a dopamine metabolite) were also found to be lower in these mice, which provides a direct link between the retinal on-pathway, dopamine and refractive development.

While the vast majority of the ametropic dystrophies produce myopia, some dystrophies are also associated with high hyperopic errors notably certain mutations that cause Leber's congenital amaurosis (LCA). In addition to specific retinal dystrophies that are linked to large refractive errors, retinal dysfunction appears to be broadly associated with increased levels of ametropia. An electrophysiological study of children with reduced best corrected visual acuity demonstrated that myopia, astigmatism and hyperopia were all associated with a significantly higher rate of retinal abnormalities as determined by the ERG (Flitcroft et al., 2005). A detailed analysis of refractive errors in retinitis pigmentosa (RP), one of the commonest retinal dystrophy phenotypes, was published in 1978 (Sieving and Fishman, 1978), following on from earlier published observations dating back as far as 1935. Whereas 12% of a normal clinical population were observed to have myopic refractions, myopia was found in 75% of 268 eyes of RP patients and in 95% of 41 eyes of X-linked RP patients. The spherical errors describe a single-peaked, skewed distribution, with a mean of −1.86 Dioptres that is significantly more myopic, by −2.93 D ($p < 0001$), than that of a normal population (Fig. 7). The X-linked genetic group has a spherical mean of −5.51 D that is significantly more myopic than the non-X-linked RP population ($p < 0\ 01$). This paper also demonstrated that the refractive abnormalities extended to astigmatism. Astigmatic refractive errors greater than 0.5 D are found in 47% of this RP population, considerably in excess of the 19% of a normal population with such astigmatic errors, though as astigmatism tends to increase along the spherical component of refractive errors this may be a consequence of increased myopia rather than an independent phenomenon.

It is clear that a huge amount of clinical and genetic data is available from retinal disease research that has application in terms of understanding the regulation of refraction development. This stands in stark contrast to the lack of identified genes identified from myopia linkage studies. As indicated above this association of refractive errors and genetic retinal disease has received remarkably little attention in the last decade and represents a potentially important area for future work. In particular, advances in the understanding of how different retinal cells and pathways are affected in retinal dystrophies with and without characteristic refractive errors may reveal a great deal about how the retina influences refraction in humans.

3.3. Evidence for a role of the peripheral retina in refractive development

3.3.1. Animal models

The neural mechanisms by which the retina can process image quality remain uncertain (Wallman and Winawer, 2004) as does the communication processes by which any defocus signal is transmitted to the sclera though several candidate messaging molecules have been identified including retinoic acid (Mertz and Wallman, 2000). What is clear from chick studies is that, whatever the mechanism, the effect is relatively local to the overlying sclera. In experiments where only half the visual field is affected by a lens or diffuser, only the corresponding half of the sclera shows the growth changes resulting in local, predominantly off-axis myopia (Diether and Schaeffel, 1997; Hodos and Kuenzel, 1984; Wallman et al., 1987). This indicates that the retina can modify the growth of the adjacent sclera in response to changes in retinal image quality on a local basis. This type of local growth response has now been demonstrated in the rhesus monkey (Smith et al., 2009a, 2010).

In primates evidence that the peripheral retinal image can influence eye growth has recently been provided by experiments in rhesus monkeys (Smith et al., 2005, 2007). These experiments demonstrated that deprivation of the peripheral retina can stimulate axial eye growth despite normal central vision and indicates that influences on the peripheral retina can outweigh signals from the central retina. Furthermore foveal ablation in one eye demonstrated that the periphery could produce the emmetropization-like responses seen during recovery from induced refractive errors, showing that central vision is not essential for emmetropization. More recently lens induced peripheral hyperopia has been demonstrated to produce foveal myopia with and without functioning foveal vision (Smith et al., 2009b).

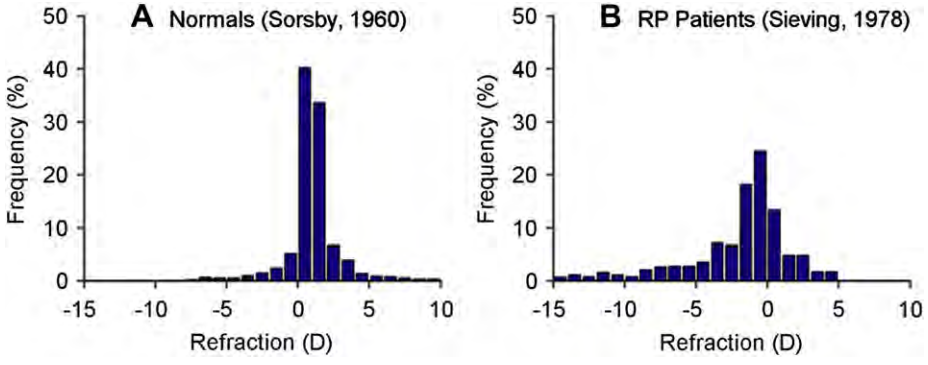

Fig. 7. Comparison of the distribution of refractions in a normal population (from Sorsby et al., 1960) and a population of RP patients (268 eyes). There is both an increased overall variation, increase in variance, and a shift of the mean refraction in the myopic direction.

3.3.2. Peripheral refraction and human eye growth

In humans, studies on the role of the peripheral retina in relation to refractive error and eye growth have largely been descriptive with numerous studies examining the relationship between foveal refraction and off-axis refraction (Ehsaei et al., 2011; Ferree et al., 1931; Millodot, 1981; Mutti et al., 2000; Rempt et al., 1971; Seidemann et al., 2002). The interesting aspect of studies is that myopes, emmetropes and hyperopes show a different pattern of off-axis refraction with myopes showing relative off-axis hyperopia (i.e. they get less myopic off-axis), the majority of emmetropes remain approximately emmetropic off-axis and hyperopes show a tendency to relative myopia (i.e. they get less hyperopic off-axis). The largest sample (822 children from 5 to 14 years of age) was provided by Orinda Longitudinal Study of Myopia (Mutti et al., 2000). Categorized by central refraction values, these children showed the following relative peripheral refractions (mean ± S.D.) at 30° nasally: myopic eyes: relative peripheral refraction of +0.80 ± 1.29 D; emmetropic eyes: relative peripheral refraction of −0.41 ± 0.75 D; hyperopic eyes: relative peripheral refraction of −1.09 ± 1.02 D. While statistically significant these findings demonstrate a wide range of variation and considerable overlap in each refractive group. The tendency for myopes to be hyperopic in the periphery fits with the observed shape of myopic eyes which commonly demonstrate greater elongation axially than equatorially though again marked variation in eye shape was noted within different refractive groups (Atchison et al., 2004; Singh et al., 2006).

In relation to the aetiology of myopia the question arises of whether the observed patterns of off-axis refraction are merely the consequence of the growth patterns that produce myopia. A study of pilots conducted over 40 years ago (Hoogerheide et al., 1971) has attracted a lot of attention in recent years as it addresses this question. This study is significant in that, for the first time, it demonstrated that emmetropes with off-axis hyperopia had a greater risk of developing myopia in subsequent years than emmetropes who were relatively emmetropic or myopic off-axis. More recently it has been demonstrated that children who became myopic had more hyperopic relative peripheral refractive errors than those that remained emmetropic and that this difference was apparent from 2 years prior to the onset of myopia (Mutti et al., 2007). Mutti et al. (2011b) have recently published contrary data thought this is based on a single peripheral measure at 30° in the nasal field. A recent study from Singapore has also indicated that peripheral refraction did not predict future myopic progression in their study population (Sng et al., 2011).

Overall the data from off-axis refraction is suggestive that eye shape is a relevant factor in myopia aetiology rather than just a consequence of myopic eye growth. Nevertheless the variability of results and existence of contradictory evidence clearly indicates that other factors must also play a role and therefore eye shape and peripheral refraction cannot be said to the primary or dominant determinant of final refraction.

Another surprising line of evidence for an impact of peripheral refraction in humans has come from studies of old method of myopia control, orthokeratology. In orthokeratology overnight wear of very flat fitting, reverse-geometry, rigid contact lenses induces corneal deformation with central flattening of the cornea. This flattening corrects the refractive aspect of myopia on-axis but by inducing peripheral corneal steepening induces off-axis myopia. Rather than just alter the anterior segment as originally anticipated, there is now good evidence that overnight orthokeratology reduces myopic progression by altering vitreous chamber growth and it is proposed that this effect derives from the impact of peripheral cornea steepening on off-axis refraction (Cho et al., 2005; Kakita et al., 2011; Walline et al., 2009). However, a trial of aspheric spectacle lens designs intended to manipulate off-axis refraction so as to limit myopic progression has not demonstrated significant effects on eye growth (Sankaridurg et al., 2010).

A failing of all these studies is that they attempt to correlate off-axis refraction and/or eye shape with refraction while missing an essential determinant of local retinal image quality, the structure of the environment. If an essential factor in determining local retinal image defocus is not measured in such studies it is hardly surprising that peripheral refraction fails completely to predict or inconsistently predicts future refractive development. This issue is addressed in detail in Section 4 of this review.

4. A retinocentric view of refraction and eye growth

Having established a central role for the retina in regulating eye growth and, in particular, the importance of the peripheral retinal image, the next issue to be considered is what determines retinal image quality at each point on the retina. As discussed above, this is the stage at which the standard description of refraction fails us entirely.

4.1. Challenging the standard definition of myopia

Myopia is classically defined optically as a mismatch between the optical power of the eye and the axial length where the posterior focal point is in front of the retina. This definition is encapsulated in the classical graphic representation shown in Fig. 8 where in an uncorrected myopic eye (top panel) rays from distant objects are brought into focus in front of the retina, a situation correctable with a negatively powered or concave lens placed in front of the eye (lower panel).

It is not uncommon in reviews or research articles on myopia to include a section on the definition of myopia. Such sections often point to the inconsistencies in definitions and methodologies of measurement. The principal areas of variation between different studies are the use or non-use of cycloplegia, choice of cycloplegic agent, measurement method or device and thresholds for myopia. Various refraction techniques have been employed in studies including auto-refractors, objective refraction (manual) and or subjective refraction. Once a sphero-cylindrical refraction has been

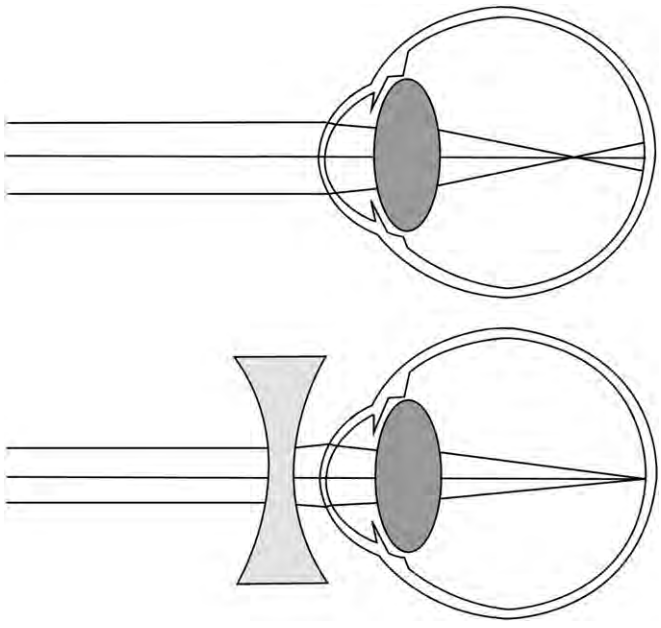

Fig. 8. Standard representation of the optical basis of myopia and its optical correction.

obtained, there is additional variation in terms of use of the spherical equivalent refraction or least myopic meridian, thresholds for myopia and limits on allowable levels of astigmatism. Such methodological considerations are generally as far as criticism of the definition of myopia extends.

In essence myopia is defined as either a binary variable, (i.e. present or absent) or as continuous variable (typically as spherical equivalent refraction). This reduces myopia to a one-dimensional variable, i.e. a single refractive description of a single point on the retina at a single point in time. The implicit but unstated assumptions in the standard definition of myopia are:

- Optically the eye can be considered as a purely paraxial optical system
- The world is reduced to a single point which varies only by distance from the eye
- Extra-foveal refraction is irrelevant

This one-dimensional concept has certainly stood the test of time and represents the basis of optical correction in ophthalmological and optometric practice so why abandon it? At the heart of the analysis in this paper is the concept that the beguilingly simple definition of myopia is inappropriate when it comes to analysing the aetiology of refractive errors. The errors and contradictions that the standard foveocentric definition of refraction introduces vastly outweigh any possible errors from measurement. Indeed several of the paradoxes of myopia research may arise precisely because the unstated assumptions behind the standard definition of myopia have not been challenged.

In relation to refractive correction the simple definition of refractive error works both practically and intuitively because human vision is foveocentric. In stark contrast the biological mechanisms that have been discovered to influence eye growth and hence refractive development are, as reviewed above, retinocentric or pan-retinal. To summarize several decades of research into a single sentence, this means that the retina has a central role in optically regulating eye growth and that each area of retina processes the retinal image and influences the growth and/or biomechanics of the overlying sclera. The existence of such mechanisms points to a highly complex interaction between the optics of the eye, the shape of the posterior segment and the physiological mechanisms responsible for eye growth. To fully appreciate the degree of complexity it is necessary to be aware of the multiple interactions that exist between the following:

- The image quality across the retina as determined by:
  - The geometry of the visual environment
  - Optics (on- and off-axis)
  - Curvature of the retina (hence eye shape)
- The neural elements that are involved in visual guidance of eye growth
- The growth patterns and shape changes involved in refractive development which impact upon retinal curvature and to a lesser extent off axis optical performance of the eye.

4.2. Determinants of the optical properties of the retinal image

In the traditional foveocentric view of refraction with the simplification of paraxial optics the transformation from the world to the retinal image is reduced to a reassuringly simple formula, a simple rearrangement of the Gaussian lens formula, where f = focal length of the eye, v = distance from second nodal plane of the eye to the fovea (i.e. essentially vitreous chamber depth) and obj is the distance to the object being fixed upon.

$$\text{Refractive error} = 1/f - 1/v - 1/\text{obj}$$

This creates a single refractive error, which is valid for foveal refraction, but for the retinal image the calculation must be extended to calculate the error for each point across the visual field. Far from being able to describe the retinal image in terms of a single dioptric value, the retinal surface is a curved plane onto which light from a three dimensional word is mapped by the optical surfaces of the eye. This transforms the traditional definition of refraction from a single dimensional variable to a two-dimensional plane mapped onto a three dimensional surface. Determination of the local focus error in the retinal image therefore requires knowledge of three dimensional structure of the scene or more specifically the distance of each point in the visual field from the eye, the imaging properties of the eye's optics for light arising from each point in that scene (i.e. off-axis imaging properties of the eye) and the shape/position of the retina at each point across the visual field.

Two of these factors, the off-axis optics of the eye and the shape of the retina have been the subject of great interest in the field of myopia but the relevance of the three-dimensional structure of the environment has received minimal attention. In considering the implications of eye shape and off axis refraction for eye shape there has been an almost universal assumption that the off axis refraction is a representation of the level of dioptric blur within the retinal image at any given point on the retina with no reference to the structure of the environment. If all three factors are not considered together then any inferences about the relevance of eye-shape or indeed even off-axis refraction on the retinal image blur are inherently invalid. Current discussions of off-axis refraction in relation to myopia aetiology make the tacit assumption that if the off-axis refraction is relatively hyperopic then the retinal image in that location is subject to that degree of hyperopic defocus with the converse being true of off-axis myopic errors. For this to be true the following conditions must be met:

- The eye is fully corrected for its axial ametropia
- The eye is accurately accommodated for the foveal fixation distance
- The visual world is dioptrically uniform

The first of these conditions is usually true. The second is often not true with a large literature indicating that normal subjects show small lags of accommodation for near targets and myopes often display large lags at least under certain circumstances (Gwiazda et al., 2004) though under binocular free-space viewing conditions accommodation lags appear small (Seidel et al., 2005). As will be demonstrated in the following section the third is most certainly not true for indoor settings and only an approximation for outdoor settings.

4.3. Optical structure of the environment

Several early studies that predate the current interest in off axis refraction, have pointed to a possible influence of the structure of the environment on eye growth in the form of lower field myopia, a phenomenon first described in pigeons by Catania (1964). In a more detailed analysis it has been shown that the refraction of pigeon eyes is essentially uniform off-axis in the superior visual field but shows progressive myopia up to 5 Dioptres which closely followed the geometric distance from the pigeon's eye to the ground suggesting it is an adaptive phenomenon (Fitzke et al., 1985). Lower field myopia is a phenomenon that has now been described in a range of ground feeding bird species (Hodos and Erichsen, 1990) and amphibians (Schaeffel et al., 1994b) but not in raptor bird species that spend little time on the ground (Murphy

et al., 1995). Young (1961, 1963) demonstrated that rearing monkeys in highly restrictive visual environments led to myopia, a finding that was an extension of a much earlier study in German by Levinsohn published in 1919. Studies in chicks have also demonstrated that rearing in a low ceiling environment creates the inverse of lower field myopia with development of myopia in the superior field associated with local expansion of the inferior sclera (Miles and Wallman, 1990).

In humans, there is some limited evidence that the local environment influences refractive development. Time spent in restrictive environments such as submarines or underground ballistic missile installations has been found to associated with increased rates of myopia as compared to military personnel in more usual working environments (Greene, 1970; Kinney et al., 1980). Rural populations have been observed in epidemiological studies to have very low levels of myopia as compared to urban populations. For example school children in rural Melanesia have a reported myopia prevalence of only 2.9% (Garner et al., 1988) as compared to a myopia rate in Taiwanese cities of 12% at the age of 6 increasing to 84% by age 16–18 (Lin et al., 1999). Myopic prevalence in children has been correlated with increasing urbanization in both the far east (Yang et al., 2007; Zhan et al., 2000), Greece (Paritsis et al., 1983) and Australia (Ip et al., 2008). Intriguing recent results have demonstrated that time spent outdoors (Rose et al., 2008) is associated with refractive status. Children who spent little time outdoors and large amount of time on near-work activities were more likely to be myopic than the control group (odds ratio = 2.6; 95% CI, 1.2–6.0). Yet the group who were in the highest third for near work and highest third for outdoor activity had no significant increased myopia risk suggestive of a protective effect of time outdoors. The authors proposed light exposure as the most likely factor in preventing myopia progression. An alternative possibility that merits consideration, and one that will be considered in detail in this section, is that the three dimensional structure of the environment is an important factor due to the impact this has on the patterns of defocus across the retina.

4.3.1. Methodology

To understand the optical structure of the environment it is necessary to visualize the world in dioptric terms. This requires the removal of all luminance and chromatic information from a scene and calculating the reciprocal of the distance of each point from the eye. Extracting distance from a scene could be done using stereoscopic images but this is computationally intense and generates rather noisy distance maps. I have developed an alternative approach in which artificial scenes are generated using computer-generated images (CGI) from which a precise geometric distance from the eye to each point on the image can be generated. In all the following examples the images are entirely computer generated and created using an open source scripting language POVRAY (Persistence of Vision™ Raytracer, Persistence of Vision Pty. Ltd.).

The images used in these calculations were created from a range of POVRAY files that are publicly available in source code format (see Acknowledgements). The depth information is extracted using the post-processing features of an unofficial extension of POVRAY, MEGAPOV (http://megapov.inetart.net). The resulting depth maps, once corrected for internal gamma correction to create geometrical distance have then been imported into Matlab™ (The MathWorks Inc.) for all subsequent analysis which incorporates the effects of accommodation, fixation position, off-axis refraction and the impact of optical corrections such as bifocal glasses. The author is happy to share programming details and source code for all aspects of this modelling on request.

4.3.2. Dioptric structure of the environment

The image shown in Fig. 9 shows three computer-generated images of a complex office environment with camera location set at the height appropriate for an adult sitting at a desk. This construct allows precise calculations of viewing distance during different indoor tasks such as reading on a desk, using a computer or looking at a distant object through a window while indoors.

The first thing that can be taken from such images is that the indoor environment (Fig. 9D–F) is much more dioptrically varied than the outdoor environment (Fig. 9A–C). Fig. 9E shows a simple example of reading a book or journal while sitting at a table. At a viewing distance of 40 cm this would, in the traditional concept of refraction, indicate an accommodation stimulus of 2.5 D. As can be seen from this figure, increasing distance from the centre of fixation is associated with a decrease in the dioptric values, despite the flat nature of the desktop. When reading a computer screen the marked variations in dioptric value across the visual scene are even greater with a variation of several Dioptres in the periphery compared with the value at the point of fixation. Both these near tasks share the characteristic that away from the point of fixation the dioptric value falls. The opposite situation applies when looking a distance object indoors as for example looking out of a window (see Fig. 9F). In this situation more peripheral objects have a greater dioptric value (i.e. are nearer). Indoors the world is essentially never optically flat. Indeed the only way a scene can be optically flat is if the viewing plane were a curved surface with a radius that equals the viewing distance, i.e. if a person were suspended in the centre of a spherical but otherwise feature-less room.

Outdoors, the world is just as complex a three-dimensional construct but the vast majority of that structure is sufficiently distant that the conversion from distance to Dioptres renders the outside world dioptrically much flatter than interior scenes. In a park setting (Fig. 9A) the world is mostly uniform with the majority of the scene less than a few tenths of a Dioptre. In more complexly structured urban scenes (Fig. 9B and C) the world is still, in dioptric terms, almost flat with the entire scene less than 0.5 D. What can be seen from these images is the outdoors the world is generally uniform though there is small loss of uniformity in more crowded settings.

4.4. Impact of 3D structure on the retinal image – accommodation and fixation

To understand the implications for eye growth we need to determine the impact of the three dimensional world's structure on the retinal image. As discussed above this requires integration of the optics of the eye and eye shape. As a first step it will help to omit consideration of eye shape and consider first the impact of accommodation and to convert the dioptric world maps in accommodation error maps across the retina. These maps represent the mismatch between the accommodation stimulus across the field and the accommodation response, which is primarily determined by the foveal accommodation stimulus. They therefore represent an estimate of the pattern of retinal defocus assuming no off-axis refractive error. For clarity the images have not been inverted to the orientation within the eye and references in the text below to superior and inferior relate to the position within the visual field.

4.4.1. Accommodation on and off-axis

Peripheral retinal defocus is dependent on the point of fixation as the accommodation system responds primarily to central stimuli (Gu and Legge, 1987) and fixation targets less than 15 min of arc can provide accommodation responses as accurate as extended targets such as a Maltese cross (Kruger et al., 2004). This shows that the

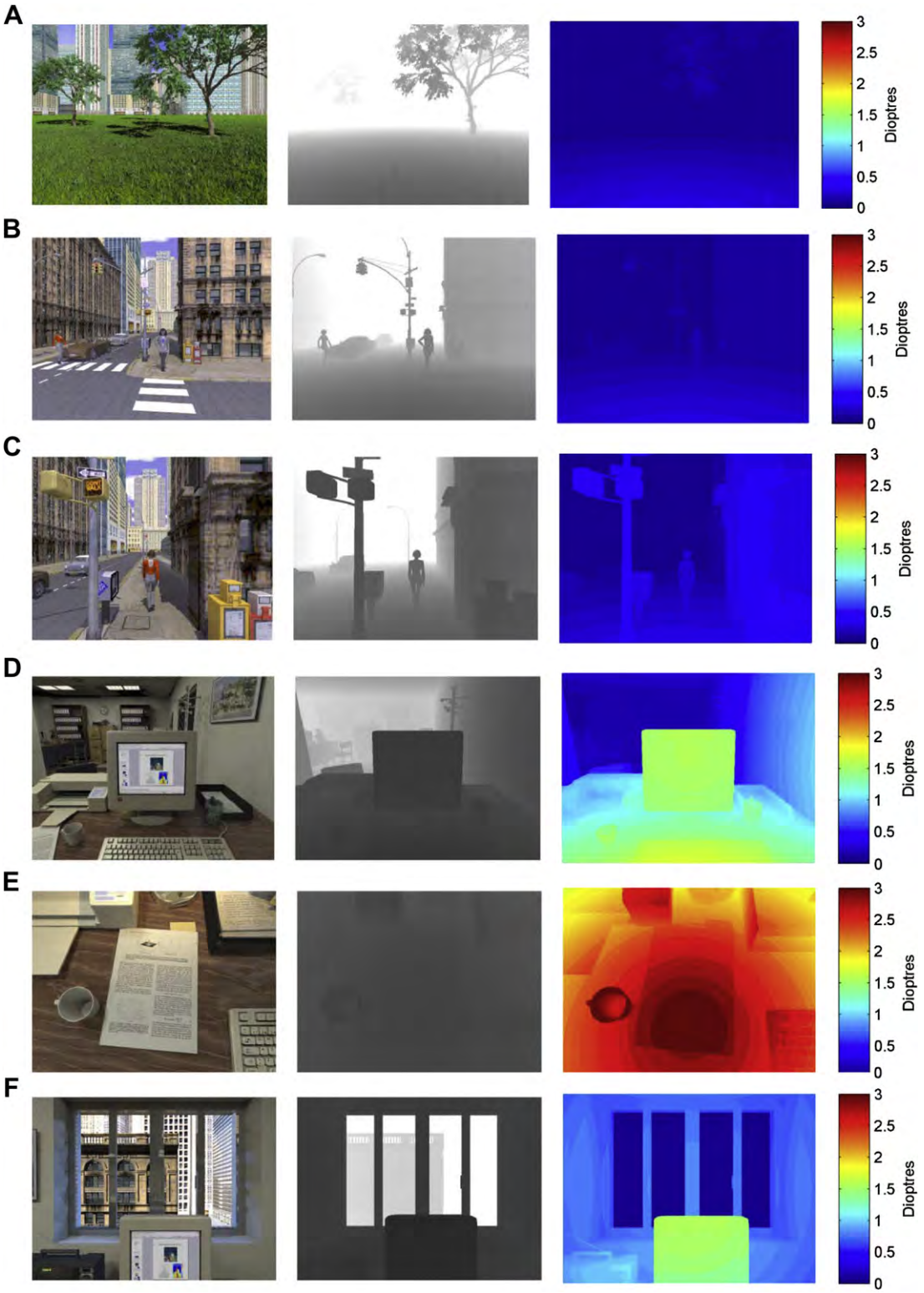

Fig. 9. The first column of this figure shows the rendered image of the scenes and the second column a grey scale image where the intensity of each pixel relates solely to the distance from the eye (the brighter the intensity the greater the distance) in metres. The third column shows the impact of transforming distance into Dioptres (i.e. the reciprocal of the distance in metres) on a colour scale that varies from blue at 0 D to red at the maximum of the scale (3 D).

accommodation system is foveocentric in operation. Since the refractive change caused by accommodation applies across the entire visual field this means that accommodation minimizes foveal defocus but not peripheral defocus. Another well defined feature of the accommodation system is 'lag', the progressive under-accommodation for increasingly near targets (Toates, 1972). This lag has been found to be greater in myopic subjects and incipient myopes at least for monocular viewing (Gwiazda et al.,

1993). However, in binocular viewing conditions the responses of emmetropes and myopes are comparable (Seidel et al., 2005), presumably by the additional contribution of convergence-accommodation in binocular viewing during near work (Wick and Currie, 1991).

An extra level of complexity relates to whether the change in optical power induced by accommodation is uniform across the visual field. It remains unclear how relative off-axis refraction is altered during accommodation. Calver et al. (2007) found changes in off-axis astigmatism and a small relative myopic shift off axis in emmetropes but not myopes. Two studies found no significant relative refractive changes off-axis with accommodation in emmetropes (Mathur et al., 2009; Tabernero and Schaeffel, 2009). Davies and Mallen (2009) studied both emmetropes and myopes and found only small changes in astigmatism off-axis with increasing accommodation. Other studies have found that accommodation produces a relative peripheral myopic shift in myopes (Whatham et al., 2009). The exact opposite has been described in another study with accommodation augmenting the existing tendency for off-axis hyperopia in myopes (Walker and Mutti, 2002). Lundstrom et al. (2009) studied both emmetropes and myopes and found a peripheral relative myopic shift in emmetropes whereas myopes showed no shift or a small hyperopic shift. The lack of consistency between various studies points to inter-study methodological variations, high levels of inter-subject variability or a combination of both. In any case the magnitude of any off-axis effects appear small so as a first approximation the refractive shift induced by accommodation can be considered to affect the whole retinal image. In light of these uncertainties, the off-axis impact of accommodation in the following calculations has therefore been modelled on the basis measured binocular human accommodation performance for fixation at different distances.

4.4.2. Comparison of different visual tasks and points of fixation

Fig. 10 demonstrates the pattern of retinal defocus taking into account the structure of the world and accommodation. In these images the colour scale ranges from white when in focus to red for hyperopic defocus and blue for myopic defocus according to the vertical colour scale to the right of each image. The left panel shows the image scenes and the right panel the dioptric error maps with the point of fixation used for calculation marked by an arrow. In addition these images have been extended to provide a 120° projection of the visual field, giving a better concept of the pan-retinal image at the expense of some distortion. Fig. 10A and B demonstrates the impact of accommodation and fixation in an office environment. When looking at a computer screen there is a small amount of hyperopic focus, on the scale of a few tenths of a Dioptre, in the central field. At computer reading distances accommodative lags are relatively small as the accommodative demand (typically 2–2.5 D) is only slightly greater than the resting level of accommodation (typically 1–1.5 D). Such accommodative lags are far smaller than the errors in the periphery, which experiences increased hyperopic defocus inferiorly and often large myopic errors further off-axis especially laterally. A change of fixation to a distant target in this environment causes a dramatic shift in the pattern of defocus with increasing hyperopic defocus inferiorly and to a lesser extent superiorly with dioptric errors minimized in the central and lateral fields. These changes occur with a change in foveal defocus of only a few tenths of a Dioptre. In an interior environment distant viewing involves either looking at a distant point within the room or looking at far distant targets through a window. For both types of indoor distant viewing the level of defocus at the point of fixation is very small, but large amounts of peripheral hyperopic defocus are generated with the three dimensional structure of the environment.

So indoors the retinal image contains a great deal of hyperopic defocus irrespective of whether the task is reading or distant viewing. The amount of defocus across the visual field also varies considerably and the vast majority of this is attributable to the structure of the environment rather than the performance of the accommodation system. The accommodation system can minimize defocus at the fovea to within a few tenths of a Dioptre in binocular viewing but the periphery will, under most indoor viewing conditions, experience far greater levels of defocus. One important consequence of this is that as fixation moves around an interior scene the peripheral retina will be subject to far greater levels of dioptric variation over time than the fovea. The central retina may change over the range of a few tenths of a Dioptre apart from larger transitory changes while the accommodation responds after a change in fixation. At the same time a change in fixation and accommodation from a near point to distant viewing may create sustained changes in the peripheral retinal image of several Dioptres, i.e. ten times greater than that experienced at the fovea.

Reading at a desk (Fig. 10C), as compared to reading on a computer monitor, will be associated with less eye-movement dependent shifts in defocus in the periphery but is associated with large constant amounts of myopic defocus peripherally and small amounts of hyperopic defocus centrally due to accommodation lag. If the observer directs their gaze slightly forwards, as opposed to looking vertically down at a page, then there will also be increased hyperopic defocus in the inferior field.

As already demonstrated in Fig. 9 there is far less dioptric variation outdoors than indoors. When the accommodation response is included, as shown in Fig. 11, it can be seen that outdoor viewing is associated with a far more uniform pattern of retinal focus than indoors. One of the principal differences between indoor and outdoor activities is that indoors we are most commonly seated and outdoors most commonly standing. This difference alone has significant implications for the pattern of retinal defocus. When standing in an uncluttered environment outdoors the ground will the closest object and the distance depends on a person's height and angle of the light rays reaching the eye. This creates the pattern of defocus seen in Fig. 11A with a small degree of inferior hyperopic defocus of the order of a few tenths of a Dioptre which reduces with increasing elevation to emmetropia or a very small degree of myopic defocus for distance, reflecting the performance attributes of the accommodation system for distant fixation. A very similar pattern is seen even in more complex scenes outdoors (Fig. 11B and C).

When seated indoors the ground is nearer than it is when standing and the presence of a desk or similar working surface creates an image plane which is even closer. For near fixation this produces a far greater degree of inferior hyperopia than can be experienced outdoors. When fixating on a distant point indoors an even greater degree of inferior field hyperopic defocus is generated. There is also a smaller degree of superior hyperopic defocus due to proximity of the ceiling (compare Fig. 10A with Fig. 10B), an effect that obviously does not apply outdoors (see Fig. 11A–C).

4.5. Impact of the eye's optical performance and eye shape across the retinal image

The variation of dioptric power shown above is determined solely by the structure of the environment combined with accommodation. Determination of the impact of such variation on the retinal image requires incorporation of the impact of optics of the eye and eye shape. Together these two factors determine how the refractive power of the eye varies across the retina. Human eyes have two dominant features in their off-axis optical performance, a curved image shell and high levels of off-axis astigmatism. Ocular shape also shows significant variations between subjects, which

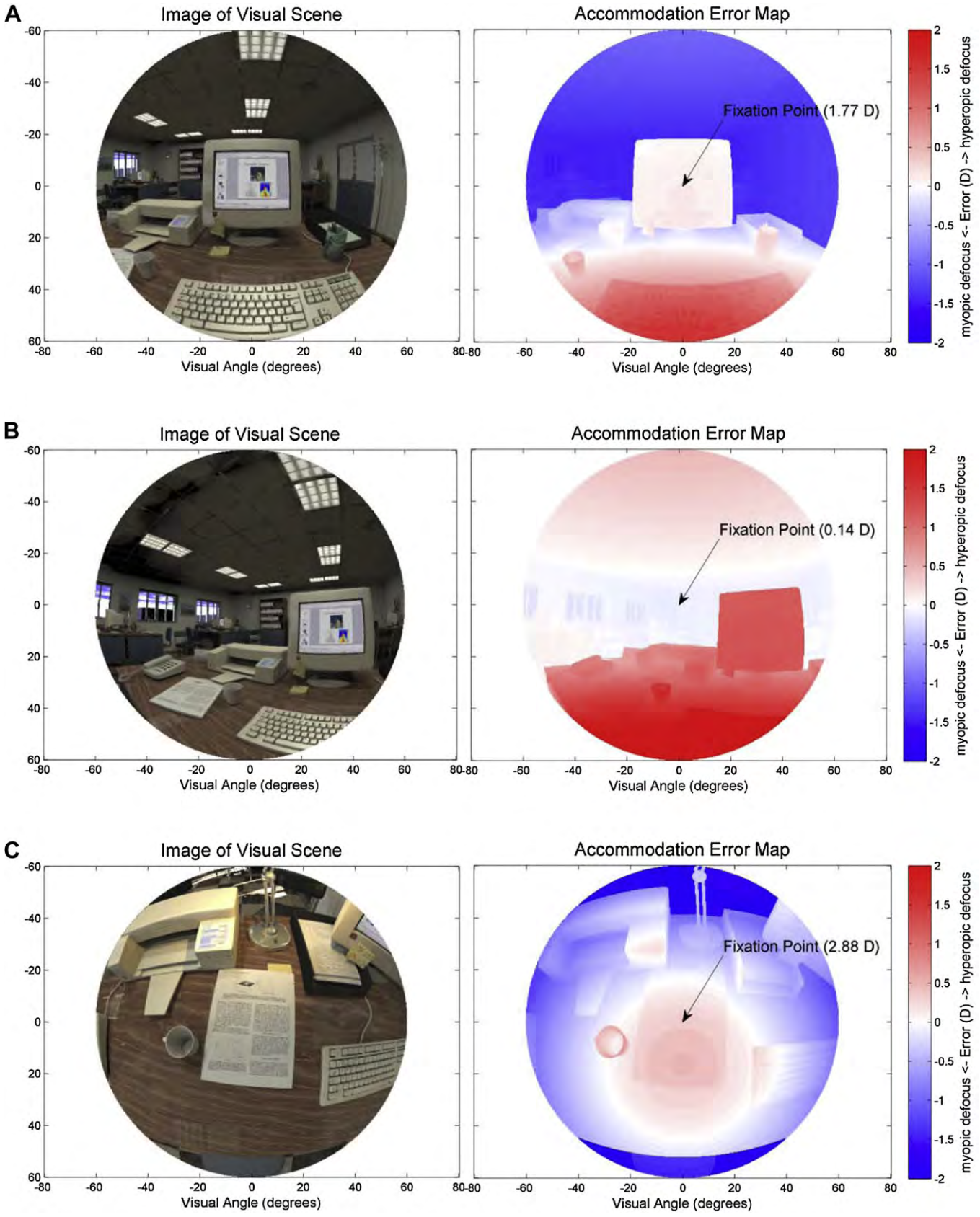

Fig. 10. Dioptric error maps taking into account of the accommodation response and the point of fixation for three indoor scenarios. The colour coded dioptric maps show hyperopic defocus in red and myopic defocus in blue. The term "Accommodation Error Map" is used to indicate the mismatch between the accommodation response and the accommodation demand across a visual scene. The eye is in these representations assumed to be emmetropic or optically fully corrected for foveal refraction.

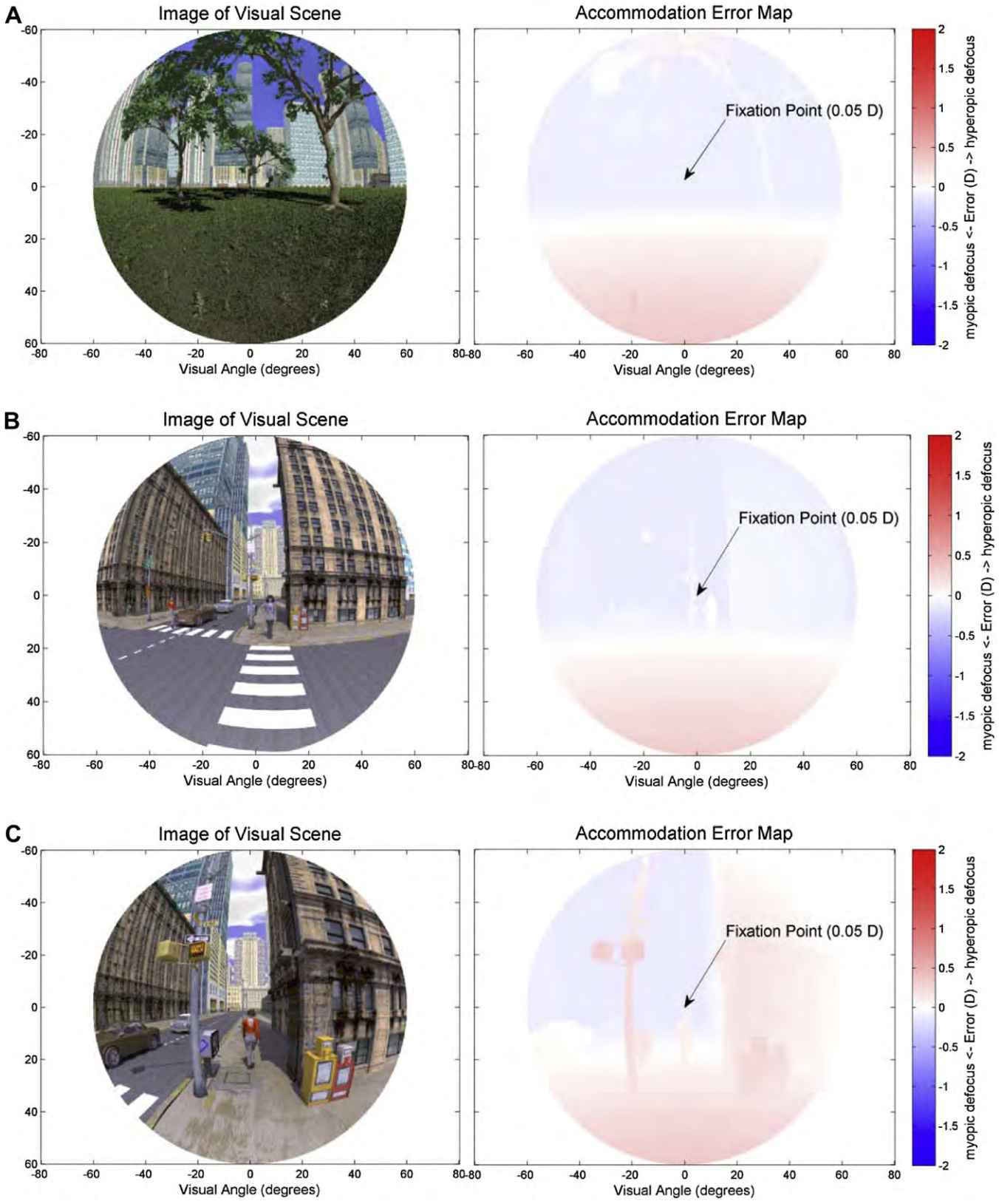

Fig. 11. Dioptric error maps taking into account of the accommodation response and the point of fixation for three outdoor scenarios. The same colour scale has been used in this figure as Fig. 10 to allow direct comparison. The very washed out colours of the error maps reflects the much lower degree of dioptric variation outdoors.

correlate to some degree with the on-axis refraction of the eye. In general, more myopic eyes are less oblate or more prolate than emmetropic or hyperopic eyes (Atchison et al., 2004). The terms oblate and prolate are often applied to eye shape and relate to deviations from a purely spherical shape. An oblate eye indicates that the sclera shell has a greater equatorial diameter than an axial diameter i.e. is axially flattened. Conversely a prolate eye has a scleral shell that has a greater axial than equatorial diameter, i.e. is axially elongated.

4.5.1. Off axis-astigmatism

One of the most striking features of the human eye, and indeed most vertebrate eyes, is the presence of off-axis or oblique astigmatism (Gustafsson et al., 2001). Rather than a single image shell most optical systems create two image surfaces for the tangential and sagittal axes of astigmatism. This means that off-axis bundles of rays aligned radially in respect to the centre of the cornea are focussed differently to ray bundles aligned circumferentially (or sagittally) to the pupil. These two image surfaces differ greatly in curvature with the tangential shell having a curvature that is usually steeper than the retina and the sagittal shell a curvature flatter than the retina. Both off-axis astigmatism and field curvature potentially have great relevance to the optical regulation of eye growth.

4.5.2. Off-axis astigmatism and retinal image neural processing

Off-axis astigmatism could potentially represent both a cue to guide refractive eye growth (Wallman, 1993) or a hindrance (Fulton et al., 1982). The two image shells effectively allow the retinal image contrast to be measured at two different focus levels. Potentially, if the retina could extract the differences in image contrast in radial and circumferential contours, this could provide a cue to both the sign and magnitude of defocus by estimation of the slope of the modulation transfer function with respect to refraction in a similar manner to that previously proposed for chromatic cues in the accommodation system (Flitcroft, 1990). Conversely the degree of image degradation from off-axis astigmatism could act as a barrier to local defocus processing. A third alternative is that the image degradation associated with off-axis astigmatism is mitigated by mechanisms that selectively respond to one or other of the two image shells. Processing cues from astigmatism or minimizing the impact of it would be expected to depend upon orientation-selective neurons. Classically most retinal receptive fields do not display significant orientation selectivity, a feature more typically seen in the visual cortex. However a degree of orientation tuning has been detected in both amacrine cells and ganglion cells in several mammalian species. To selectively respond to tangential or sagittal blur neurons would optimally be tuned to an orientation along an axis radial to the fovea or tangential. A radial orientation preference for receptive field elongation was first noted in the cat for ganglion cells more than 2° from the area centralis (Levick and Thibos, 1982). This selectivity has been demonstrated in the primate retina using single cell recording techniques, with the two most frequent orientations being with ±15 degrees of the radial and tangential directions with respect to the fovea (Passaglia et al., 2002). Such neurons would, in terms of image processing, be preferentially stimulated by either the sagittal image shell or tangential image shell (Fig. 12).

That this spatial tuning reflects neural processing rather than an artefact of off-axis astigmatism *per se* is supported by the fact that a similar orientation can be seen in the dendritic trees of some classes of amacrine and ganglion cells (Bloomfield, 1991, 1994). In the cat the dendritic trees of ganglion cells outside the area centralis, which had been retrogradely labelled with horse radish peroxidase (HRP), were found to be arranged radially 'like the spokes of a wheel having the area centralis at its hub' (Leventhal and Schall, 1983). The finding has been replicated in the primate retina (Schall et al., 1986).

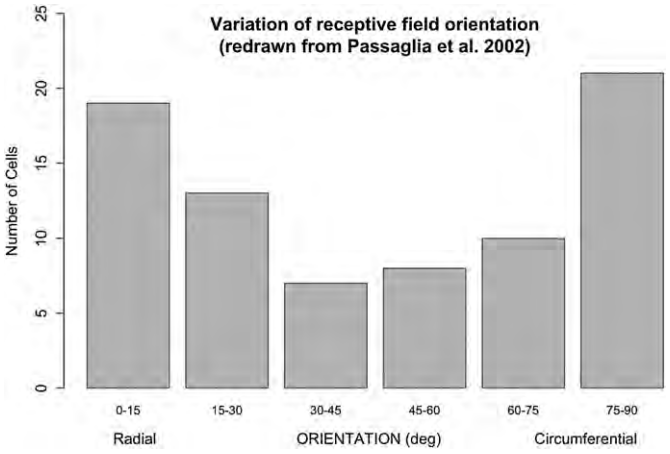

Fig. 12. This shows the preferred orientation preference of primate retinal ganglion cells with respect to fovea. The orientation is specified as the difference in degrees between the preferred stimulus orientation and a radial line to the fovea so the 0–15° category represents cells aligned along a radial axis with respect to the fovea and 75–90 those aligned circumferentially.

The fact that foveal ablation doesn't prevent emmetropization or lens rearing responses in primates (Smith et al., 2009b) points to the fact that either off axis astigmatism does not degrade the retinal image sufficiently to prevent extraction of a local defocus cue or orientation-selective mechanisms serve to enhance image contrast sufficiently. We have insufficient evidence to know the relevance, if any, of retinal orientation selectivity of amacrine cells and ganglion cells for the processing of defocus signals, though the orientation of the receptive fields and the fact they are only located outside the central retina provides a potential neural basis for off axis astigmatism being a cue for eye growth. This is certainly an intriguing possibility that has received little attention in the field of myopia research.

4.5.3. Impact of imposed astigmatism on eye growth

The impact of imposed astigmatism on eye growth has been examined in both the chick and monkey by rearing animals with cylindrical or sphero-cylindrical lenses. In one study in the chick imposition of +10 or −10 cylindrical lenses did not induce compensation to the spherical equivalent refraction (i.e. +5 or −5) but rather to the myopic meridian (Schmid and Wildsoet, 1997). Another study using cross-cylinders with no overall optical power found only a small bias towards the imposed myopic meridian, i.e. the eyes became only slightly hyperopic. Furthermore this study showed that combining large (±5 D) cross cylinders with spherical lenses did not prevent accurate compensation to the spherical lenses (McLean and Wallman, 2003). In the monkey eyes exposed to cross-cylindrical lenses with zero spherical equivalent power did not remain emmetropic but become myopic or hyperopic apparently showing adaptive growth to one or other of the astigmatic meridian, though the least hyperopic or most myopic meridional power was preferred (Kee et al., 2004). Imposed astigmatism often led to induced corneal astigmatism but there was no correlation between the imposed and induced astigmatic axis (Kee et al., 2003). This suggests that there is no visually guided mechanism to eliminate corneal astigmatism. It should be noted that in both species imposed astigmatism seemed to disrupt emmetropization with eyes showing more variability in growth response than is typically seen in spherical lens rearing studies.

It is worth noting that these studies were designed and analysed in terms of the impact of the imposed astigmatism on central

refraction. The orientation of the axes of spectacle lens or indeed corneal astigmatism is consistent across the visual field whereas both the axis and magnitude of tangential and sagittal off-axis astigmatism vary with retinal location. For example at a retinal level a cylindrical lens with an axis at 90° has opposite effects on tangential and sagittal astigmatism along the vertical and horizontal meridians but at oblique angles i.e. an axis of 45° and 135° the imposed astigmatism will not affect the tangential or sagittal image shells as the cylindrical lens has no power along these oblique meridians. In addition, the magnitude of off-axis astigmatism increases with eccentricity so the centre of the visual field will be dominated by the imposed astigmatism, the mid-peripheral field will experience a varying range of astigmatism which varies between different meridians due to the interaction of corneal and off-axis astigmatism and the periphery will be increasingly dominated by off-axis astigmatism. Hence the presence of corneal or imposed astigmatism significantly disrupts the pattern of off-axis astigmatism across the retina. If off-axis astigmatism were used as a cue to control eye growth then large amounts of corneal or lenticular astigmatism would be expected to detrimentally affect processes such as emmetropization or lens adaptation.

In humans the process of natural emmetropization, i.e. the reduction of spherical refractive errors and astigmatism over time that has been well documented in longitudinal studies appear to proceed relatively independently of each other (Ehrlich et al., 1997). Nevertheless it has long been observed that astigmatism is associated with ametropia (Green, 1871). An association between early astigmatism and later myopic progression has also been described (Fulton et al., 1982; Gwiazda et al., 2000a) supporting the notion of a causal link. Does persistent astigmatism during infancy reflect deficient emmetropization mechanisms from the outset or does pre-existing astigmatism detrimentally influence eye growth leading to later myopia? The evidence from animal studies does suggest that imposed astigmatism reduces the accuracy of emmetropization and does not lead to compensation towards the spherical equivalent refraction but to one of the astigmatic meridians. This suggests that astigmatism can affect eye growth but it also possible that increasing ametropia *per se* leads to astigmatism.

Another under-explored question in relation to off-axis refraction is whether the eye will regulate its growth off-axis towards the optimal spherical equivalent refraction or to one or other of the tangential and sagittal image shells in the manner that has been observed for imposed astigmatism (Kee et al., 2004; Schmid and Wildsoet, 1997). The eye may regulate its growth to the most myopic/least hyperopic shell as seen in animal studies or alternatively may regulate to the image shell that is most in focus i.e. closest in position to the retina. The tangential image shell is more steeply curved than the sagittal shell so would typically follow the retinal contour of a prolate eye and conversely the flatter sagittal shell would follow the contour of an oblate eye. The starting shape of the posterior segment, which may be genetically defined, combined with the off-axis astigmatism determined by the refracting surfaces may therefore interact so as to promote a particular retinal profile as the eye grows. Like so much in this field, such issues remain unresolved but merit further study.

4.5.4. Field curvature and eye shape

Measurements of off-axis refractive error combine the two factors of optical field curvature and the three dimensional shape of the posterior segment because off-axis refraction represents the mismatch of the field curvature and the curvature of the retina. Shape is often inferred from off-axis refraction on the basis that the optics of the eye produce a spherical image shell. Optical models such as the classic schematic eyes of Gullstrand and others have been optimized for paraxial optics but have off axis performance that is radically un-physiological, principally on account of the fact that spherical refractive surfaces are used for computational simplicity. Schematic eyes with aspheric surfaces have been developed which provide good approximations of off-axis performance of the human eye (Drasdo and Fowler, 1974; Escudero-Sanz and Navarro, 1999; Navarro et al., 1985; Pomerantzeff et al., 1971, 1984). For any given paraxial focal length and standard clinical refraction, the profile of peripheral field curvature is sensitive to the asphericity of the corneal and lenticular surfaces. Fig. 13 shows how changes in both eye shape and ocular surface asphericity can alter the off-axis spherical equivalent refraction without changing on-axis refraction. These calculations were generated using the ray tracing program Zemax™ (Radiant Zemax) and an aspheric model eye based on the wide-angle model of Escudero-Sanz and Navarro (1999).

Fig. 13C shows the standard model with a spherical shape for the posterior sclera and a normally aspheric cornea. The four other model eyes showing the effect of making the anterior surface cornea more prolate (Fig. 13A), oblate (Fig. 13E) or changing just the shape of the posterior sclera making it more prolate (Fig. 13B) or oblate (Fig. 13D). In essence prolate corneal and scleral profiles both create relative peripheral hyperopia and an oblate cornea/sclera profile creates a more myopic off-axis refraction pattern. Therefore in the absence of information about the degree of off-axis astigmatism and field curvature, it is impossible to reliably infer off-axis refraction from eye shape data alone. Similarly it is not valid to infer eye shape from off-axis refraction.

4.6. The combined effects of the environment, eye shape and optics

An accurate calculation of the pattern of defocus across the retinal image requires integration of all of the above factors, i.e. 3D structure of the environment, accommodation, fixation distance and off-axis refraction as determined by the optics and shape of the eye. A further complication is that, as discussed in Section 3.3.2 above, differences have been found in off-axis refraction between adult emmetropes and adult myopes as well as younger subjects who are destined to become myopic in later years. This evidence is at least suggestive that eye shape might influence later eye growth, but animal studies demonstrate that eye shape can be altered by optically driven eye growth so that in humans it is likely that eye shape in adults may also reflect the consequences of optically driven growth.

4.6.1. Is off-axis defocus affected by the structure of the environment?

The simulations shown in Figs. 10 and 11 show the variations in the pattern of defocus across the visual field. The greatest degree of hyperopic defocus is seen inferiorly for indoor distance viewing and the second greatest superiorly for the same the viewing condition. This should lead to the situation where the inferior and superior off-axis refractions are more myopic than central refraction. Such an adaptive growth response is analogous to the lower field myopia seen in animals that live close to the ground. Fig. 14 shows the results of applying the same methodology of Figs. 10 and 11 to the phenomenon of lower field myopia in pigeons. Fig. 14A demonstrates a wide-angle (120°) computational model of a park scene from the perspective of pigeon at an eye height of 19 cm though the dioptric scale has been resized (from ±2 D to ±5 D) to take into account the much higher levels of inferior hyperopia when an eye is close to the ground. This map assumes that there is no consistent change in refraction off-axis.

To relate this to the phenomenon of lower field myopia Fig. 14B shows the individual refraction data for pigeons across the vertical visual field re-plotted from Fitzke et al. (1985). The black line represents the trigonometric model described by Fitzke, as

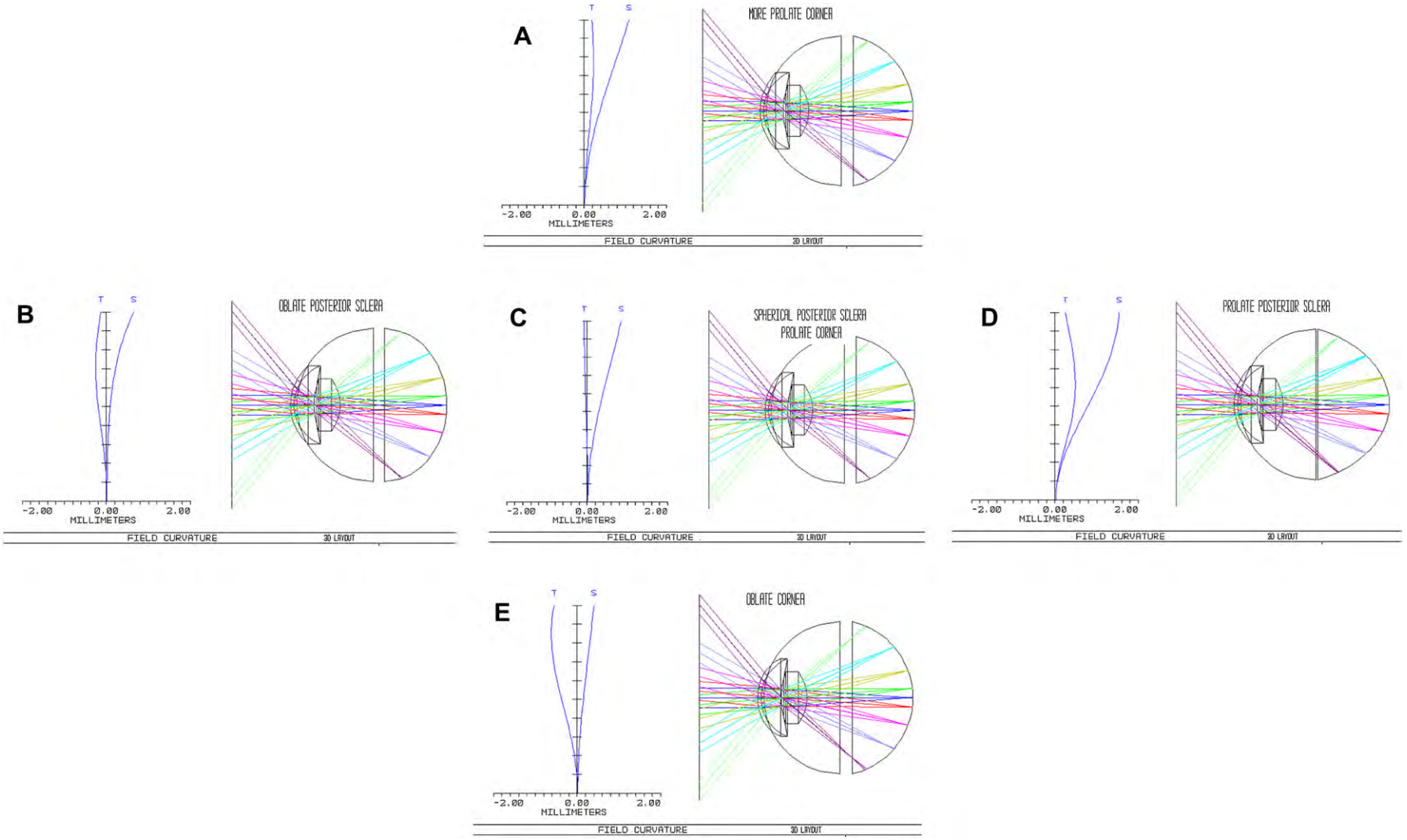

Fig. 13. Demonstration of the impact of posterior sclera shape and cornea asphericity on image curvature in the human eye. The graphs of field curvature show the position of the tangential astigmatic image shell (labelled 't') and the sagittal astigmatic image shell (labelled 's') relative to the retina. Positive values along the horizontal indicate the image plane is posterior to the retina (i.e. at the retina the image will experience hyperopic defocus) and negative values indicate the image plane is anterior to the retina (i.e. at the retina the image will experience myopic defocus). The vertical axis represents visual angle up to a maximum of 50°. Axial length and overall optical power of the eye is the same in all these models. Prolate corneal and scleral profiles both create relative peripheral hyperopia and an oblate cornea/sclera profile creates a more myopic off-axis refraction pattern.

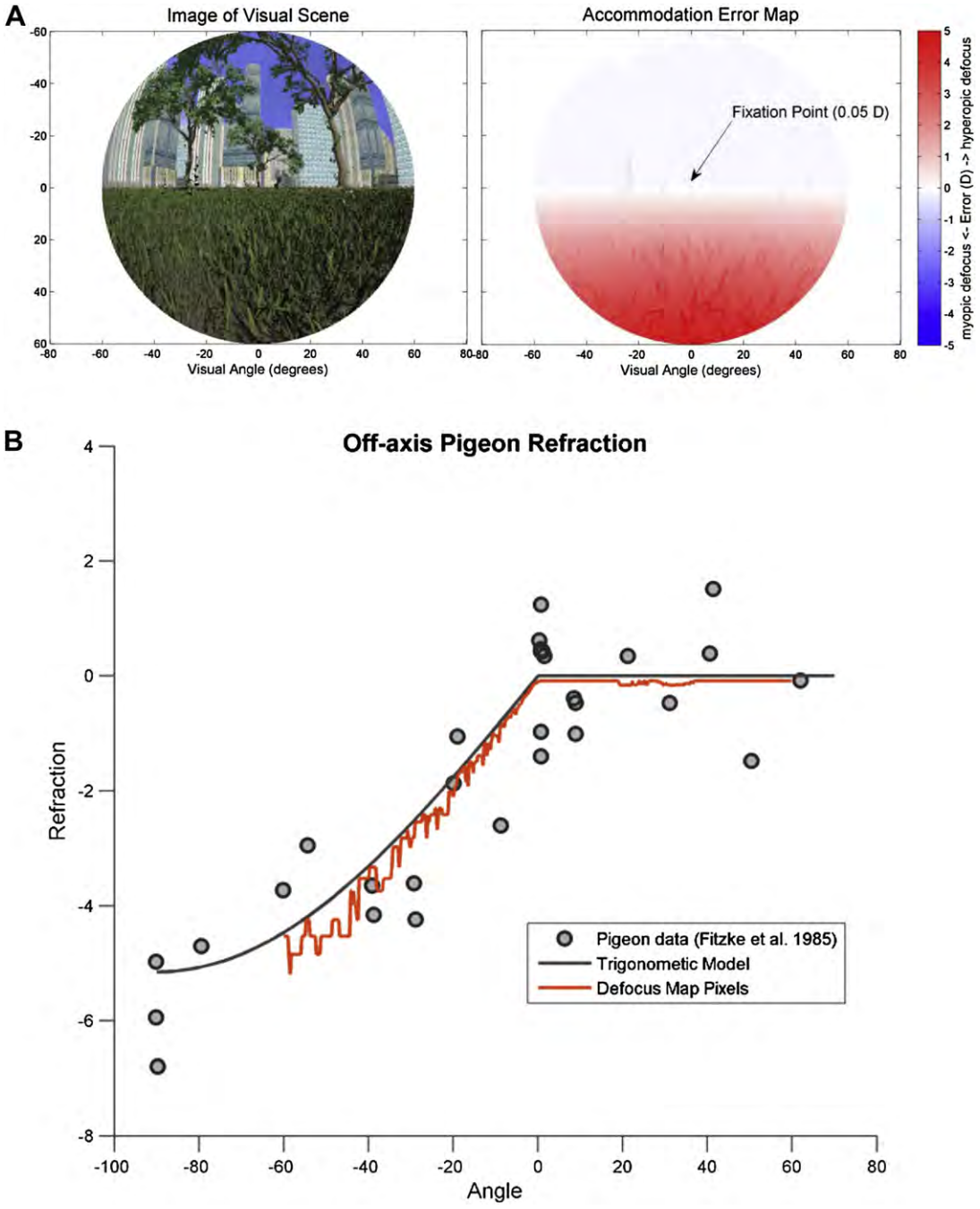

Fig. 14. Dioptric map of a park scene from the perspective of a pigeon (A) and the representation of the dioptric values along the vertical midline meridian plotted against actual off-axis pigeon refraction data from Fitzke et al. (1985).

described by the equation Ref = (100/H) × sine θ where Ref = refractive state, H = the eye-ground height in cm (19.4), and θ = elevation below horizon. The red line represents the dioptric error values from Fig. 14A in pixels along the central vertical meridian. This graph demonstrates very clearly the accurate correspondence of the pigeon's off-axis refraction with its typical visual environment as well providing a calibration for the optical transformations used in these simulations.

4.6.2. Do humans show any correlate of lower field myopia?

In humans the combination of the greater distance of the eye from the ground with the reciprocal relationship between Dioptres and distance means that the visual scene outdoors is much more uniform as already shown in Fig. 11 (though note the different dioptric scale in the Figs. 11 and 14). As discussed above the act of sitting, particularly at a desk creates a 'ground' level much closer to the eye. In particular Fig. 10A and B show significant amounts of inferior hyperopic defocus and for distant fixation indoors a small amount of superior defocus due to the ceiling.

Does human eye growth show any compensatory growth patterns akin to lower field myopia in birds and other species? Studies of off-axis refraction cited above in Section 3.3.2 have typically considered only the horizontal meridian and sometimes only a single off-axis measurement. In humans there has been little

study of refractive variation in the vertical meridian though Seidemann et al. (2002) was the first study to demonstrate a small degree of inferior field myopia. A larger study by Atchison et al. (2006) concluded that humans did not display lower field myopia but as the data was presented in the form of absolute rather than relative peripheral refraction the small effect that is evident in this study was not easily apparent. Their paper provided polynomial fits for both vertical and horizontal meridians. Using these functions refraction maps across the visual field, analogous to the maps shown for defocus above, can be constructed from the horizontal and vertical data provided by Atchison by extrapolation. Fig. 15 shows the resulting maps calculated by pooling the data into high myopes (−5 to −8), low myopes (−1 to −4) and emmetropes. While emmetropes demonstrated relative off-axis myopia with the exception of the region around the optic nerve (approximately 15° temporal to fixation), myopes showed a progressive hyperopic shift along the horizontal meridian with vertical relative myopia greater in the inferior than the superior field. A nasal-temporal variation along the horizontal meridian has been a consistent finding in a wide range of studies. The fact that this asymmetry is mirror symmetric in the two eyes indicates that this cannot relate to any feature or attribute within the environment since the nasal field of one eye views the same part of the environment as the temporal field of the other eye. Accurate measurements of eye shape in the posterior pole with partial coherence interferometry indicate that the optic nerve, which inserts into the nasal retina, contributes to this asymmetry (Schmid, 2003, 2011). An observation reinforced by the fact that the location of the small hyperopic shifts often seen in temporal field/nasal retina of emmetropes is located at the angular position of the optic nerve (Atchison et al., 2006; Shen et al., 2010).

These findings have recently been replicated in another much larger study of 85 myopic children who showed relative peripheral hyperopia along the horizontal meridian (+0.56 D at 30° nasally and +0.61 D at 30° temporally) and relative peripheral myopia along the vertical meridian which was more pronounced inferiorly (−0.36 D at 30° superiorly and −0.48 D at 20° inferiorly) (Berntsen et al., 2010). However another study has failed to demonstrate this effect along the vertical meridian (Ehsaei et al., 2011).

If the pattern of off axis refraction demonstrated for myopes in the studies of Seidemann et al., Atchison et al. and Berntsen et al. were a compensatory growth response then this would most closely match the compensation pattern expected for indoor distance viewing. The red hyperopic areas superiorly and inferior in Fig. 10B should promote myopic growth on the basis of animal models leading to the blue myopic areas seen in Fig. 15C. Understanding whether such patterns reflect compensatory growth will clearly need far more detailed studies ideally of a longitudinal nature in which all the factors discussed here are measured, i.e. visual tasks analysed in terms of the 3D structure of the world (not just near work or distance), optics of the eye, eye shape and accommodation performance. But for now the limited available data provides an intriguing indication of how being indoors as compared to outdoors might promote myopic growth.

4.6.3. Relevance of peripheral refraction prior to the onset of myopia

Another question arises from the findings of Hoogerheide et al. (1971) and others who have shown that the pattern of off-axis refraction in emmetropes appears to be associated with increased risk of myopia in later years. How do different patterns of off-axis refraction interact with the dioptric maps presented so far? In this case the horizontal and vertical variations in off-axis refraction don't apply, as this feature, where it has been seen, appears to be a feature of myopic eyes. In emmetropes the horizontal and vertical field are very similar with the exception of the variation around the optic nerve, but since this corresponds to the physiological blind spot this area cannot have any input to the process of retinally guided eye growth. Examples of hyperopic and myopic off-axis have therefore been modelled on the basis of rotationally symmetric representations of off-axis refraction up to 60° based on the data of Millodot (1981) as shown in Fig. 16 (note the angular dimensions of these wide angle maps are twice that of Fig. 15).

The results of combining off-axis refraction with 3D structure, accommodation and fixation are shown in Fig. 17. Fig. 17 panels A–D represent different scenes. The first panel shows the rendered image from the 3D model, column 2 represents the impact of a myopic off-axis refraction profile, column 3 an emmetropic profile and column 4 a hyperopic off-axis profile on retinal defocus. As in previous figures, the retinal image calculations are not inverted to allow easy comparison with the visual scene.

The situation outdoors is relatively simple since in such environments the dioptric structure of the world is very uniform so that in this environment off-axis refraction is the dominant determinant of retinal defocus off-axis (see Fig. 17 panels A1–4).

In the presence of physiological levels of peripheral myopia (Fig. 17, column 2) the retinal image is dominated by myopic defocus with the greatest levels experienced off-axis when reading on a flat surface such as a desk (Fig. 17 panel D2). When there is no variation of spherical equivalent refraction with eccentricity (Fig. 17, column 3) the off-axis refraction is primarily determined by the 3D structure of the environment, accommodation and fixation point. With off-axis hyperopia, the retinal image in most scenes is dominated by off-axis hyperopia with some para-central myopic blur in some conditions (Fig. 17 panel C4). The greatest total amount of hyperopia in this condition is experienced for indoor distance viewing (Fig. 17 panel B4) and the least for reading on a flat surface (Fig. 17 panel D4), which can be construed to indicate that off-axis hyperopia is optimally adapted for reading. These calculations demonstrate that the impact of off-axis refraction on retinal defocus is task and environment dependent and that the relative importance of environment or off-axis refraction depends on the sign (i.e. whether myopic or hyperopic) of peripheral refraction and will also depend on its magnitude, the greater the degree of peripheral refractive error the more dominant this feature becomes. The implications of these patterns of defocus are discussed further in Section 4.7.3 below.

As has been previously noted (Stone and Flitcroft, 2004) one important aspect of off-axis refraction data is often masked by presentation of mean data, that is the degree of variability. Taking one the largest available samples as an example (the Orinda Eye Study, Mutti et al., 2000), the degree of overlap and variation between emmetropes, myopes and hyperopes can be visualized by plotting the probability distribution functions based on the observed mean and standard deviation for each group (see Fig. 18) assuming a normal distribution pattern. Amongst the emmetropic group which are often considered to have a single pattern of off-axis refraction 45.2% would be expected to have more than 0.5 D of myopia at 30° from the measured mean and standard deviation, 43.5% to be within ±0.5 D of emmetropia and 11.3% more than 0.5 D of hyperopia. Fig. 18 also indicates the significant overlap of myopes and hyperopes who are often considered to have different off-axis refractive profiles. When considering Fig. 18 together with the retinal defocus calculations shown in Fig. 17 it should be clear that it is impossible to infer what the actual pattern of off axis retinal defocus will be in a myopic or hyperopic subject without knowing both the individual's off-axis refraction and viewing habits. This shows that inferring the pattern of off-axis retinal defocus on the basis of mean off-axis refraction of a particular group or demographic is invalid. Hence the determination of the pattern of off-axis retinal defocus needs to be made on an individual basis.

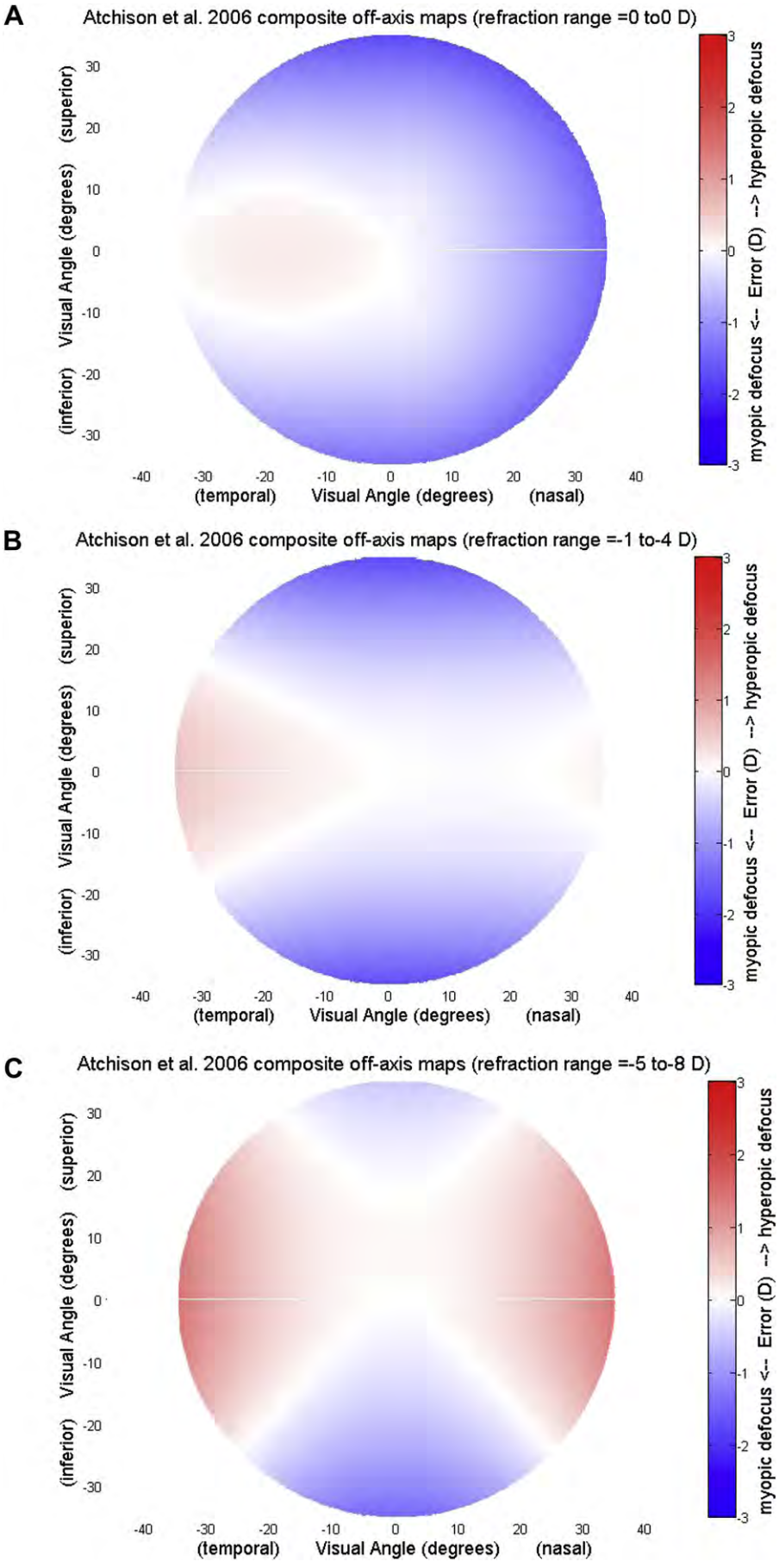

Fig. 15. Extrapolated maps of off-axis refraction for emmetropes, low myopes and high myopes (calculated from data published by Atchison et al., 2006).

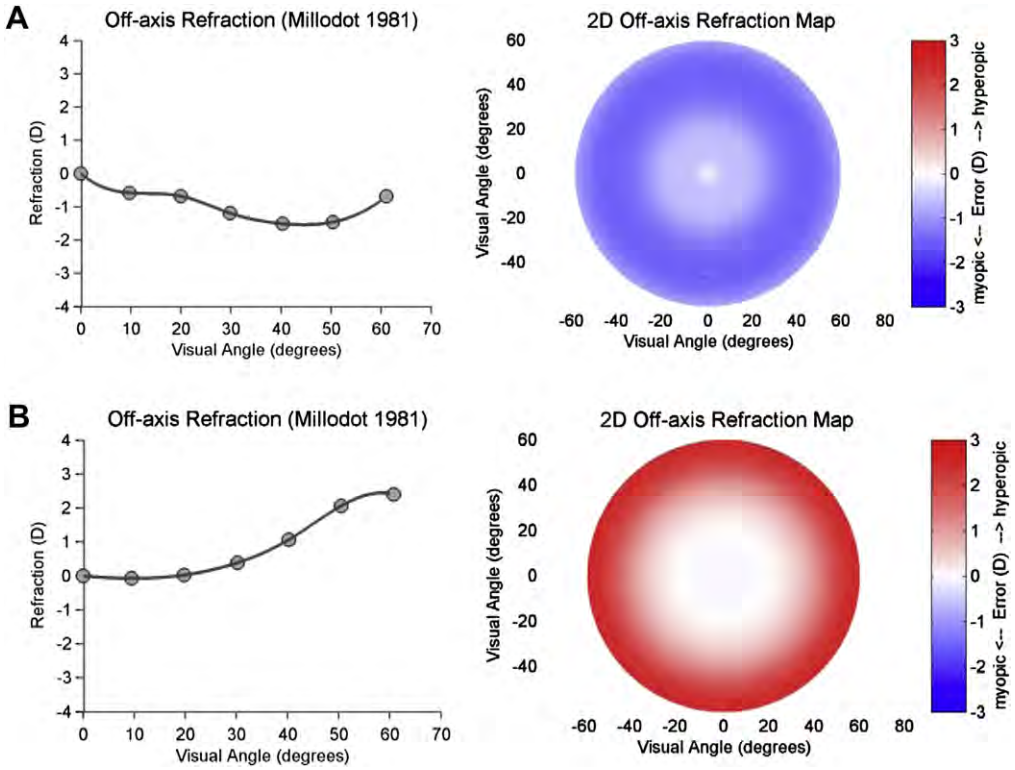

Fig. 16. Hypothetical off-axis two-dimensional profiles based on clinical data for off-axis myopic (A) and hyperopic (B) profiles from Millodot (1981). The left panel of each row shows the off-axis refraction measurements from Millodot (1981) and the right panel the equivalent 2-dimensional maps.

4.7. Implications for understanding eye growth

On the basis of our understanding of the visual guidance of eye growth the above analysis has significant implications. These include a better appreciation of why bifocals glasses for near work have limited impact on progression, a potential explanation for the impact of time spent outdoors on myopia progression and implications for myopia control strategies based on manipulation of peripheral refraction with spectacle lenses or contact lenses.

4.7.1. Impact of bifocal glasses on dioptric error maps

A core assumption of the bifocal and varifocal glasses intervention trials is that providing a near-add for close work creates the optical equivalent of distant viewing by reducing accommodation demand and also accommodative lag. While the latter is certainly true for the retinal image at the fovea, across the retina this is most certainly not true. The impact of 'executive' bifocals with near addition of +1.5 D is demonstrated in Fig. 19. The 'executive' style of bifocal glasses has traditionally been used in children and involves a horizontally split lens where the entire lower portion of a lens has additional dioptric power. These calculations assume that when fixating for near the subject fixates 20° below the line dividing the near and distant part of the glasses and when fixating for distance fixates 20° above the dividing line. Outdoors (Fig. 19A), with distant fixation, bifocals produce a pattern that differs from that shown in Fig. 17 by having an area of myopic defocus in the inferior field. This is a reversal of the small degree of inferior hyperopic defocus usually seen outdoors. Indoors the pattern of defocus on the peripheral retina is also changed. During distant viewing indoors while sitting at a desk (Fig. 19B), bifocals reduce the amount of hyperopic blur in the inferior field (compare with Fig. 17B3 but note the different Dioptric scale). In terms of retinal area this is a far greater effect than the reduction in central hyperopic defocus that is typical of reading, i.e. the classical accommodation-lag (Fig. 19D). Reading a computer screen with bifocals reduces the amount of superior myopic defocus this condition usually generates. On a flat surface, the reduced level of ocular accommodation with the bifocal lens creates a zone of hyperopic blur superiorly in the field (Fig. 19D).

It should be noted that in addition to the differences induced by the visual task, the defocus pattern across the visual field/retina will also depend on the fixation point in the two lens zones and the design of a bifocal/varifocal lens. Nevertheless, it is clear that bifocals change the pattern of defocus but certainly do not eliminate hyperopic defocus. In particular bifocals do not change the retinal defocus pattern during reading into the pattern see for distance viewing. Overall the level of hyperopic defocus is reduced centrally during reading and in the inferior field during distant viewing indoors, but it is increased in the superior field during reading. If the pattern of defocus across the retina is an important parameter in human refractive development then these calculations help to explain why bifocals have had limited success in reducing myopia progression.

4.7.2. Protective effect of being outside on myopic progression

One of the more intriguing findings in recent years has been the demonstration from a detailed population based study that time spent outdoors appears to be protective of myopic progression (Rose et al., 2008), an association first noted in boys in Finland (Parssinen and Lyyra, 1993). Light exposure has been suggested as the protective factor and yet light exposure has also been suggested as a causative factor in myopia progression (Mandel et al., 2008; Quinn et al., 1999) though the evidence has been contradictory in humans (Gwiazda et al., 2000b; Saw et al., 2001; Zadnik et al., 2000). Constant light rearing in chickens leads to enlargement of the vitreous chamber despite a hyperopic refraction since the

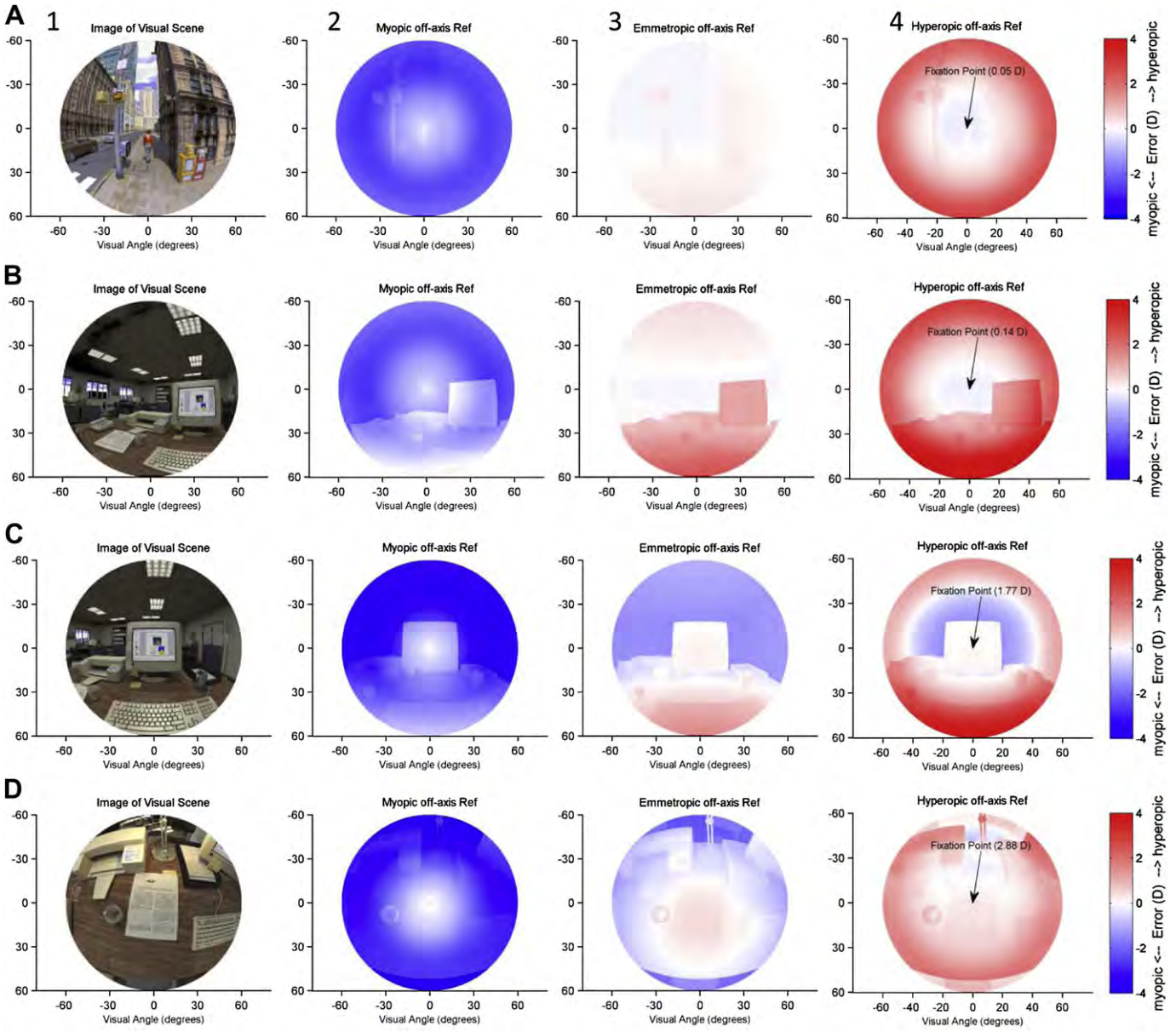

Fig. 17. Off-axis retinal defocus patterns including 3D structure of the environment, fixation, accommodation, and off-axis refraction. Figures A–D represent different scenes and column 2 shows the impact of myopic off-axis refraction, column 3 emmetropic off-axis refraction and column 4 hyperopic off-axis refraction. Specific images are referred to in the text by row and column e.g. top right images is referred to as A4.

cornea flattens dramatically under such conditions (Liu et al., 2004; Stone et al., 1995). Animal studies with both chickens (Ashby et al., 2009) and rhesus monkeys (Smith et al., 2012) have demonstrated that high ambient light levels (15,000–25,000 lux) for periods of the day retard the development of deprivation myopia. In chickens high light levels also slow the development of myopia during compensation to negatively powered lenses but augment hyperopic compensation to positively powered lenses, though in both cases full compensation was still observed (Ashby and Schaeffel, 2010). Despite current interest in high light levels (comparable to full sunlight), constant light of lower intensity has previously been found to have similar effects on deprivation and lens rearing as shorter periods of bright light (Bartmann et al., 1994; Padmanabhan et al., 2007). This suggests that light may impact eye growth by influencing circadian rhythms, which have long been known to be important in ocular growth (Nickla et al., 1998).

The attention on light has led to researchers to consider vitamin D levels and receptors. Associations have been found between myopia and polymorphisms within the vitamin D receptor gene (Annamaneni et al., 2011; Mutti et al., 2011a) and differences noted in vitamin D levels in myopes and emmetropes (Mutti and Marks, 2011), yet myopia is not a typical feature of severe vitamin D deficiency in the form of rickets (Reddy et al., 1979). In relation to the regulation of eye growth the challenge in relation to light exposure is that the amount of light received by the retina or in the case of vitamin D the amount of light received by the skin has no bearing on the refraction of the eye and *vice versa*. In engineering terms light is an open loop stimulus. It is therefore difficult to create a regulatory hypothesis for how light levels could regulate growth of the eye to the precision to maintain emmetropia (i.e. regulate axial length within ±200 μm which corresponds approximately to ±0.5 D).

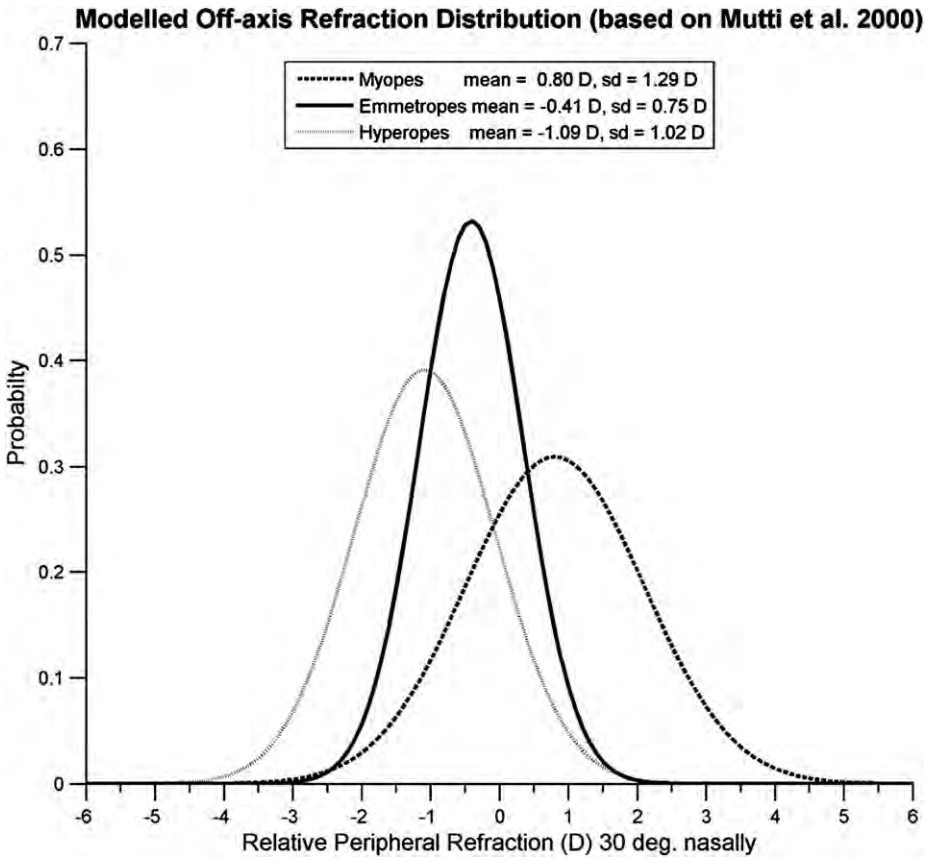

Fig. 18. Probability distributions demonstrating the degree of overlap of different refractive groups in the Orinda Eye Study (calculated from data derived from Mutti et al., 2000).

This is not to say that light exposure can't affect the mechanisms involved in the optical regulation of eye growth. As indicated above, recent animal studies in chickens do suggest that light might differentially affect the mechanisms responsible for myopic and hyperopic compensation, altering the dynamics of the responses to myopic and hyperopic defocus (Ashby and Schaeffel, 2010). Constant light also has significant impact on dopamine levels in the retina, a neurotransmitter linked to ocular growth mechanisms (Bartmann et al., 1994). Light would also be expected to impact on defocus via constriction of the pupil which increases the depth of focus and hence reduces retinal sensitivity to focus errors (Blackie and Howland, 1999).

An alternative or additional possibility for the impact of being outdoors on myopic progression may be the profound differences in the pattern of retinal defocus generated indoors and outdoors. On the basis of animal studies, sustained hyperopic defocus should promote local eye growth and myopia. Contrasting indoor scenes with outdoors reveals a marked increase in the level of hyperopic defocus for both near and distant fixation while indoors. Being outdoors may therefore be protective on the basis that it provides minimal amounts of peripheral defocus and hence may provide a so-called STOP signal for eye growth. Even if the human eye were responding only to the amount of blur and not its sign, the amount of blur across the retina and indeed its variation with eye movements is far less outdoors than indoors. This optical effect may indeed be further enhanced by the impact of light levels on pupil size which would be expected to be much smaller outdoors so light might interact with peripheral defocus via the depth of focus changes induced by pupil constriction.

4.7.3. Temporal variations in defocus

The spatial and optical analysis presented in this paper is complex but it must be noted that an additional dimension, that of time will also need to be incorporated into a full understanding of eye growth. While the effects of sustained periods of myopic or hyperopic defocus have been well defined in animal studies, it has recently been shown that the effects of different signs of defocus do not interact in a simple linear fashion over time. Such studies have demonstrated that short periods of myopic defocus, or a clear retinal image, can block the myopic growth response from longer periods of hyperopic defocus (Kee et al., 2007; Shaikh et al., 1999; Winawer and Wallman, 2002; Winawer et al., 2005; Zhu et al., 2003).

Changing fixation, particularly in a visually cluttered office or school environment can create large and rapid shifts in off axis refraction over the time frame of a single saccade. The accommodation system ensures that foveal refractive errors are minimized, though not totally eliminated, when fixing at objects at different distances. This means that the variation of foveal refractive error between the different viewing and off-axis refraction conditions is much smaller than the dioptric variations seen peripherally. This is well demonstrated by comparing image Fig. 17 panel D2 (desk reading in an eye with off-axis myopic refraction) with Fig. 17 panel B4 (distant viewing indoors with an off-axis hyperopic refraction). As a result the peripheral retina will experience a far more complex temporal pattern of changing blur than the fovea.

Outdoors the more uniform dioptric environment means that eye movements would generate little temporal variation in retinal defocus. In primate studies brief periods of clear vision appear to be

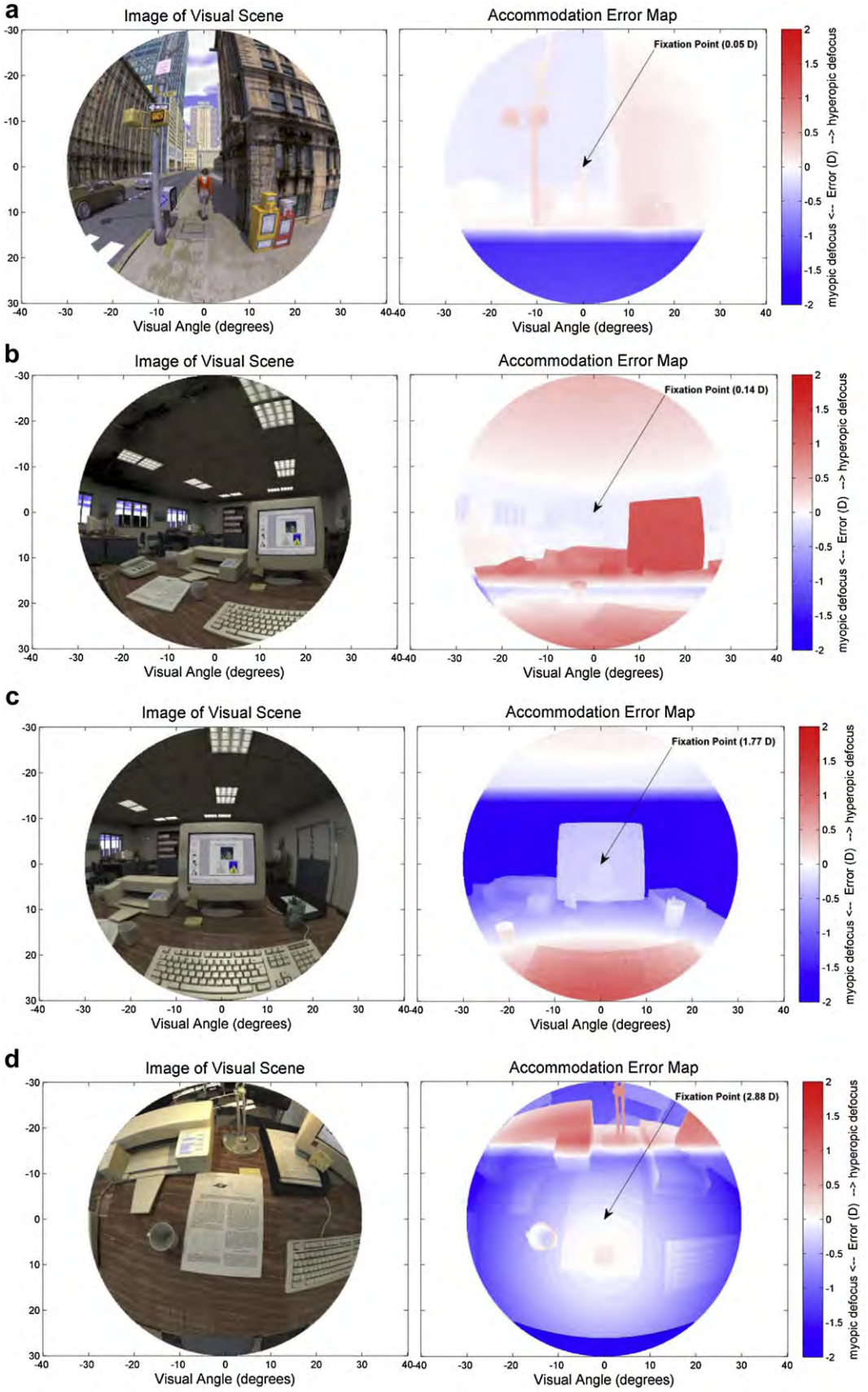

Fig. 19. Impact of +1.5 D executive bifocal on retinal defocus incorporating 3D structure of the environment, fixation and accommodation performance.

able to counteract the effect of sustained periods of hyperopic defocus (Kee et al., 2007). These findings may help to explain why simple correlates of near work such as total amount of time may correlate poorly with myopic progression, pointing to the need for more sophisticated methods of recording viewing distance with detailed time resolution (Leung et al., 2011). Only with clinical data indicating fixation information down to a temporal resolution of minutes or less can some of the rapid temporal interactions observed in animal studies be incorporated into a comprehensive spatial and temporal model of human eye growth.

4.7.4. Eye shape and off axis refraction

The calculations shown in Fig. 17 have wide ranging implications in terms of understanding eye growth. These simulations demonstrate that, in the absence of off-axis refractive errors, environmental structure is the primary determinant of the pattern of retinal defocus and that physiological amounts of off-axis refractive error have a significant impact on changing retinal defocus patterns. This implies that the refractive development of eyes with more emmetropic off-axis refractions may be more influenced by the structure of the local environment and hence time spent in different environments.

The condition that produces minimum dioptric blur is outdoor viewing of a distant fixation point in an eye with no consistent off-axis spherical error (Fig. 17 panel A3). In the presence of hyperopic (Fig. 17 panels A4–D4) or myopic off-axis refraction (Fig. 17 panels A2–D2), all viewing conditions will produce significant off-axis defocus (note the scale in these images is ±4 Dioptres). In the presence of hyperopic off-axis refraction, the viewing state that minimizes off-axis errors the most is reading on a flat surface (Fig. 17 panel D3) and the condition that compounds the off-axis hyperopia the most is distant viewing indoors (Fig. 17 panel B4). With off-axis emmetropia it is also distant viewing indoors that creates the greatest amount of hyperopic blur across the retina (Fig. 17 panel B3).

In relation to myopic progression, it is hyperopic defocus that is expected to maximally promote eye growth. Therefore it is potentially very significant that the condition that would be expected to maximally promote eye growth is being indoors rather than reading. In relation to reading, Fig. 17 panel D4 shows that hyperopic off-axis refraction leads to the least amount of defocus during reading on a flat surface as the geometry of this task leads to peripheral myopic defocus in the absence of any significant off-axis refractive error. Reading in the absence of off-axis refractive errors (Fig. 17 panel D3) creates a pattern of central hyperopia and peripheral myopia. On the basis of animal studies, this should promote increased growth at the posterior pole and reduced growth peripherally, which will create a more prolate scleral profile. Therefore as well as a prolate eye shape and off-axis hyperopia promoting myopic progression, it is possible that prolonged reading may itself contribute to the formation of a prolate eye. Such a growth shift, in the absence of changes in the anterior segment, should lead to relative peripheral hyperopia.

Once an eye has developed relative peripheral hyperopia the one condition that can create minimal blur across the retina, i.e. distant viewing outdoors, no longer does so (see Fig. 17 panel A4). Instead outdoor viewing now generates peripheral hyperopic defocus across the peripheral retina. Even brief periods of a clear retinal image have been shown to allow animals exposed to hyperopic defocus to achieve emmetropia (Kee et al., 2007). Therefore the loss of the one condition (Fig. 17 panel A3) that produce a clear image across the retina could create a positive feedback situation accelerating a shift towards increasing myopia even before the onset of myopia itself. A rapid acceleration at the start of myopic progression, which can start even before an eye becomes myopic, has been observed in longitudinal studies but no clear explanation has yet been found for this phenomenon (Mantyjarvi, 1983; Thorn et al., 2005). Consideration of retinal defocus maps therefore helps to explain the pattern myopic progression and indicate that such progression can be both a consequence and cause of a prolate eye shape and off-axis hyperopia.

The interaction of off-axis refraction and the visual environment also has implications for clinical studies. Analysing progression data solely on the basis of off-axis refraction without detailed temporal information on time spent outdoors and indoors and definition of the nature of the visual tasks performed indoors may hide any true effect. An eye with no significant off-axis spherical error exposed to a lot of distance viewing indoors may experience more peripheral hyperopic defocus than an eye with low levels of off-axis hyperopia exposed to prolonged reading at a desk or flat surface. Such effects are particularly relevant when the overlap between the off-axis refractions in hyperopes, emmetropes and myopes is appreciated as shown in Fig. 18. The interactions between off-axis refraction and the visual environment have not been adequately explored at present. The existence of such interactions points to the need to stratify analyses according to the pattern of retinal defocus rather than just the off-axis refraction or time spent indoors or outdoors.

4.7.5. Optical manipulations of off-axis refraction for myopia control

Recent animal studies have created a lot of interest in the prospect of manipulating off-axis refraction with aspheric designs of spectacle lenses (Sankaridurg et al., 2010) or contact lenses. As demonstrated in Fig. 13, changes in the asphericity of the anterior cornea can create a peripheral myopic shift in the image shell. In terms of the peripheral retinal image this would appear to offer an ideal method of countering the effects of a prolate sclera shape and eliminate off-axis hyperopia. However changes in sclera shape alter off-axis refraction without impacting on the optical quality of the retinal image. In contrast changing cornea asphericity, in particular making the cornea more oblate, can create large amounts of higher order aberrations, notably spherical aberration – an effect that increases with increasing pupil size. The impact of changing corneal shape and scleral shape on the foveal point spread function calculated using the ray tracing program Zemax™ (Radiant Zemax) using the wide-angle model of Escudero-Sanz and Navarro (1999) as a starting point is shown in Fig. 20. A significant change in off-axis refraction by corneal manipulation with contact lenses will inevitably have some consequences for foveal vision that may limit acceptability. The issues created by such lenses are not unlike the problems created during the early days of corneal refractive surgery with small treatment zones, where patients with large pupils under mesopic conditions experienced a lot of glare. Many patients may tolerate this well but others will not.

The interaction of eye shape, optics, and the visual environment also dictate that a single pattern of off-axis refraction will not necessarily suit all eyes. Achieving the goal of minimizing hyperopic blur or creating defined amounts of myopic blur peripherally will require customised lenses, or targeting specific groups of myopes on the basis of their eye shape, optics and behaviour patterns.

5. Discussion

This review is intended to set out the complexity of what has often been considered to be a simple concept. Myopia can be reduced to a simple binary difference from emmetropia, an eye is either myopic or it isn't, and condensed into a diagram as simple as

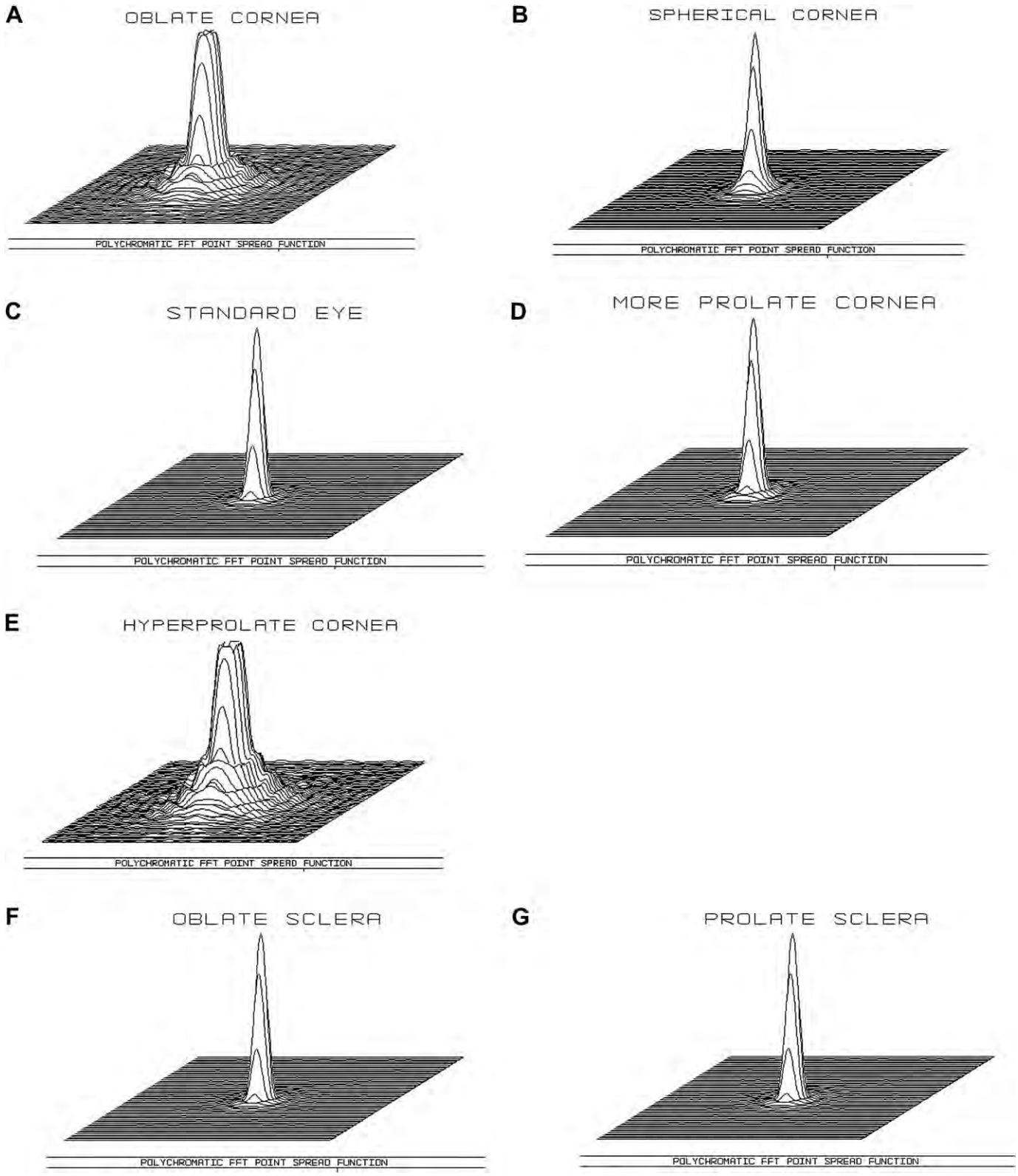

Fig. 20. Impact of changing corneal shape (A–E) and scleral shape (F and G) on the foveal point spread function. Changing scleral shape has no impact on foveal point spread functions, but changing corneal shape leads to significant degradation.

that shown in Fig. 8. From such simplicity comes the expectation that simple interventions can prevent myopia and that simple theories can explain its aetiology. The last twenty years of myopia research have amply proved both these statements to be false. These last two decades have also demonstrated that the control mechanisms for eye growth are highly complex, to which complexity we must now add consideration of defocus across the retinal image.

From the point of view of clinical refraction and conventional measures of visual performance such as visual acuity, vernier acuity and contrast sensitivity, the foveocentric view provides an adequate description of the optical performance of the eye. On the basis of recent animal studies, clinical studies and the optical analysis presented in this paper a retinocentric view should now be considered essential for a full understanding of optical regulation of eye growth. Table 3 summarizes the distinctions between the foveocentric and retinocentric view of the refraction. It is certainly true that changing from a foveocentric to retinocentric perspective brings with it considerable complexity, since it extends refraction into a multi-dimensional realm. While appreciation of such complexity makes the prospect of simple interventions less likely, and helps to explain the failings of such simple interventions, it also provides a basis to plan future interventions.

5.1. Future directions

An appreciation that the peripheral retina plays a role in controlling ocular growth has provided a new impetus into the development of myopia control strategies. In relation to potential treatments or strategies to limit myopic progression, the central question is 'to what benefit?' The analysis presented in Section 2 of this review indicates that even if the proportion of myopes in a population remained stable, i.e. if no method is found to prevent myopia, then reducing the degree of myopia by limiting the rate of progression may have significant public health benefits. The principle caveat to this claim is the question of causation, which has yet to be proven and remains an important topic for future research. However, several features of the statistical association of myopia and ocular disease do favour causation: myopia develops prior to the onset of disease, greater degrees of myopia are associated with higher risk and in terms of the mechanical consequences of augmented ocular growth (principally sclera thinning) there are plausible mechanisms whereby myopia could promote retinal detachment, macula atrophy and increase the optic nerve's sensitivity of the damaging effects of increased intraocular pressure. Investigation of the question of causation represents one of the most important areas in this field as it represents the basis on which medical intervention in myopia can be justified. Investigation of how refractive error can interact with such a wide range of diseases may also provide more direct routes to intervene in the pathological processes involved outside the question of preventing myopic progression.

Table 3
Comparison of foveocentric and retinocentric views of refraction.

Foveocentric view	Retinocentric view
An eye has a single refraction	An eye has a graded, complex pattern of refractions across the retinal surface
Refraction and retinal image blur are defined at a single point (the fovea)	Refraction and retinal image blur are defined across a 3-dimensional curved plane (the retina)
Spatial structure of the visual environment irrelevant	Spatial structure of the environment contributes to the defocus of the image at each point in the retinal image
Ocular shape unimportant apart from axial length	Three dimensional ocular shape is fundamentally important
Paraxial optics provides an adequate description of the eye's optics	Wide-angle ray tracing needed to fully define the eye's optics
Near work with a bifocal add is optically equivalent to far work	Near work with a bifocal add is not optically equivalent to far work
Relevant for visual acuity and accommodation	Relevant for understanding optical regulation of eye growth

Progress in our understanding of the control mechanisms of eye growth may in the near future lead to myopia being as treatable a risk factor for ocular health as hypertension is for cardiovascular health. Although the health consequences of myopia may be less serious than is seen in cardiovascular medicine, prevention or reduction of myopia will have secondary benefits for patients in a way that having lower blood pressure in an otherwise healthy person does not. The majority of patients treated for high blood pressure will no perceive no difference in their daily life. In contrast all myopes with a reduced level of myopia will benefit from improved unaided visual acuity during their early adult years as well as potentially reduced risks of sight loss in later life.

5.1.1. Optical strategies

Many different optical interventions have been investigated in the search for a preventive strategy for myopia from varifocals, bifocals to novel contact lens designs. Many of these trials have shown a statistically significant slowing of myopic progression that indicates that human eye growth responds to optical cues. This has been considered insufficient to merit changing optical prescribing patterns from the standard clinical practice of providing single vision lenses, but if limiting the degree of myopia does indeed have future ocular health benefits this view may need to be reconsidered. A recent trial of combined prisms and bifocals has demonstrated a reduction of myopic progression over two years of almost 50% (−1.55 D for single-vision lenses compared with −0.70 D for bifocals with incorporated prisms) (Cheng et al., 2010).

Most of the optical interventions have, to date, been solely based on refraction at the fovea. Novel types of optical interventions are currently being evaluated that include consideration of the refraction across the retina. This provides a degree of optimism that newer optical interventions will prove more effective than those of the past. The impact of the environment and its three dimensional structure have still to be taken into account in such designs. A specific lens design will have different impact on off-axis retinal blur when used for reading than for outdoors for example. This suggests that lenses designed for specific tasks may be more appropriate than a general-purpose lens. This may be a practical option for glasses but is less practical for contact lenses. A combination of contact lenses for general use with additional glasses that correct detrimental patterns of retinal defocus for specific tasks may prove to be a workable solution. Considering the variability of off-axis refraction additional customisation of optical corrections may also be required to take account of this variability, necessitating individualized corrections both on-axis and off-axis. Incorporation of the full range of interactions detailed in this paper into optical strategies should provide a method of designing appropriate corrections for different tasks, viewing conditions and eye shapes.

5.1.2. Behavioural strategies

A better understanding of the retinal defocus patterns generated during different tasks may lead to better methods of eliminating those that contribute to myopic progression. So rather than have different optical interventions for different tasks another approach is design a single optical correction and modify the environment or the behaviour of people in a given environment such as a school or class room. New approaches to the ergonomics of the working environment such as curved computer monitors/work stations that recreate the optics of outside viewing in intensive work environments are conceivable. Further investigation of the basis of the protective effect of being outdoors certainly merits investigation. This may provide simple behavioural means for limiting

progression, though the history of myopia research would suggest that simple interventions rarely result in simple results.

5.1.3. Pharmacological strategies

Of all myopia control strategies examined to date atropine, a drug which has been suggested for myopia control for over 30 years (Dyer, 1979), remains the most effective. A series of studies has culminated in the Atropine in the Treatment of Myopia (ATOM) study which demonstrated in a randomized controlled trial over two years that 1% atropine drops profoundly reduced the rate of axial elongation (-0.02 ± 0.35 mm vs. 0.38 ± 0.38 mm in the control group) and myopic progression (-0.28 ± 0.92 D vs. -1.20 ± 0.69 D in the control group) (Chua et al., 2006). Despite this effectiveness during the treatment period a rebound acceleration in myopia progression was noted on termination of treatment (Tong et al., 2009). Atropine is still not considered suitable for widespread use despite some claims to the contrary (Romano, 2001) due to the profound cycloplegia and concerns of the long term effects of retinal phototoxicity. In that regard, an extension of the ATOM trial (ATOM2) has demonstrated that doses of atropine as low as 0.01% are almost as effective as 1% yet have minimal effects on accommodation and pupil size and high tolerability, a finding that may lead to low dose atropine finding broader clinical acceptance (Chia et al., 2012).

Other muscarinic antagonists that have shown promise for myopia control are drugs that are selective for one or more of the muscarinic receptor subtypes so as to minimize cycloplegia, most notably pirenzepine. Clinical trials in the far east and the US have demonstrated reductions of almost 50% in the rate of myopia progression and axial elongation over the course of one and two year randomized trials (Siatkowski et al., 2004, 2008; Tan et al., 2005), yet despite this effectiveness against myopia progression and the minimal effects pirenzepine has on accommodation and pupil size the drug appears to be no longer in active development as a therapy. This drug and others in its class certainly merit further investigation. Although categorized as an M1antagonist, pirenzepine's second strongest binding effect is on the M4 receptor subtype. As discussed above, animals studies in chicks have demonstrated that it is the M4 receptor that is principally involved in the anti-myopic effects of atropine and pirenzepine (McBrien et al., 2011). This opens up the possibility that other selective muscarinic antagonists may prove to be useful potential treatment options in myopia. It will undoubtedly be challenging to get new chemical entities through the entire drug development process to treat a condition such as myopia. This makes exploration of existing drugs, already safety tested but licenced for another indication, the most likely approach to the development of an eye drop or oral preparation to prevent myopia.

5.1.4. Combined strategies

To what degree are the reductions seen in optical and pharmacological studies additive? If they are acting on different mechanisms or even different parts of the same control mechanism there is hope that the effects may summate at least to some degree. In years to come we are likely to see trials of low dose atropine combined with optical interventions such as bifocal glasses or myopia control contact lenses such as those used by Anstice and Phillips (2011) that produce simultaneous myopic defocus for both near and distance viewing. It may make sense to combine different approaches into a single therapeutic product. Possibilities include medicated contact lenses that release anti-muscarinic drugs such as low dose atropine (e.g. 0.01% as used in the ATOM2 trial), pirenzepine or more selective m4 antagonists. In the context of pirenzepine, which achieved an almost 50% reduction in myopia progression despite poor ocular penetration as a drop preparation, using slow release from drug impregnated therapeutic myopia control contact lenses (either daily use lenses, or by incorporation of an active drug into the storage solution) may both enhance the ocular penetration and provide a greater level of progression control than either intervention by itself. A lower concentration of pirenzepine in such a combination may also enhance tolerability. On the basis of the impact of individual interventions the prospect of suppression of myopia progression by combination approaches appears possible. The complex condition of myopia almost certainly has multiple aetiological factors, even in a single person, so the combined approach also has the benefit that multiple factors might be addressed in a single treatment plan.

5.1.5. Ensuring full control of all the variables in future trials

In planning human intervention trials all relevant variables need to be considered to prevent studies being based on unstated but seemingly reasonable assumptions that may be false. To date randomized controlled trials in myopia prevention have not controlled for all of variables that determine retinal defocus. As a result what is presented as a controlled trial may have a raft of unknown confounders. Under such circumstances it is no surprise that the results are often inconsistent.

Complex as it is, trial design should attempt to incorporate all aspects of the visual environment, as well as proper characterization of visual tasks both spatially and temporally. In addition, the impact of eye shape and optics need to be considered on an individual rather than a pooled basis due to the complex nature of the interactions between these parameters and the large amounts of inter-subject variability.

5.1.6. Conclusions

Myopia should not be considered as a simple trait defined by a single parameter. It is the end result of a complex process that has elements of regulated growth and unregulated or pre-programmed growth. The refraction of an eye is not a one dimensional number but a two dimensional plane, in a three dimensional eye in which the retinal image defocus can only be determined once the 3D viewing structure, off axis performance of the eye and eye shape have been accurately defined.

In light of the evidence linking myopia of any degree with serious ocular pathology the notion of physiological myopia should be abandoned. With that comes the impetus to find safe, well-tolerated and effective methods to prevent or limit myopic progression. The range of potential treatments for myopia is broader today than it has ever been, leading to he expectation that individually, or in combination, clinically useful interventions will enter clinical practice in the coming years. A better understanding of the patterns of defocus across the retina may positively contribute to the development of such treatment modalities provided that the complex interactions between the environment, optics of the eye, eye shape and retinal function are taken into account.

Acknowledgements

I would like to acknowledge many years of inspirational conversation with Josh Wallman, to whom this review is dedicated. I would also like to thank the reviewers and the patience of the editor of the journal. The CGI simulations of the environment were built upon open source software from several authors. The office scenes are modified versions of a scene originally created by Jaime Vives Piqueres. The street scenes were derived from code elements originally created by Gilles Tran and human figures derived from code elements created by Peter Houston.

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