Review Article

Title: Myopia: precedents for research in the 21st Century

Running Head: Myopia Research Review

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Abstract

The myopic eye is generally considered to be a vulnerable eye and at levels greater than 6D, one that is especially susceptible to a range of ocular pathologies. There is concern therefore that the prevalence of myopia in young adolescent eyes has increased substantially over recent decades and is now approaching 10-25% and 60-80% respectively in industrialized societies of the West and East. Whereas it is clear that the major structural correlate of myopia is longitudinal elongation of the posterior vitreous chamber, other potential correlates include profiles of lenticular and corneal power, the relationship between longitudinal and transverse vitreous chamber dimensions and ocular volume. The most potent predictors for juvenile-onset myopia continue to be a refractive error $\leq$ +0.50D at 5 years-of-age and family history. Significant and continuing progress is being made on the genetic characteristics of high myopia with at least four chromosomes currently identified. Twin studies and genetic modeling have computed a heritability index of at least 80% across the whole ametropic continuum. The high index does not, however, preclude an environmental precursor, sustained near work with high cognitive demand being the most likely. The significance of associations between accommodation, oculomotor dysfunction and human myopia is equivocal despite animal models which have demonstrated that sustained hyperopic defocus can induce vitreous chamber growth. Recent optical and pharmaceutical approaches to the reduction of myopia progression in children are likely precedents for future research: for example progressive addition spectacle lens trials and the use of the topical M1 muscarinic antagonist pirenzepine.

Key Words: Myopia; epidemiology; biometry; heredity; accommodation,ocular.

INTRODUCTION

Myopia: the clinical and academic challenge

The indications are that the prevalence of myopia in young adolescent eyes has increased substantially over recent decades and is now approaching 10-25% and 60-80% respectively in industrialized societies of the West and East [1]; worldwide, the condition is considered to be the leading cause of visual impairment. [2] In clinical terms it is widely acknowledged that the myopic eye is a vulnerable eye, especially at levels greater than 6D, and one that is especially susceptible to a range of ocular pathologies. [3-6] These features have promoted research into the biological, neurophysiological and environmental bases for myopia onset and development and myopia laboratories throughout the world are mapping pathways to therapy. Pharmaceutical, optical and microsurgical treatment modalities for myopia thought improbable just a decade ago are now seen as likely options for future clinical management. The clinical challenge of myopia is therefore both appealing and demanding: patients are increasingly well aware, often via the Internet, of its epidemiology, hereditary characteristics and pathological ramifications. The academic challenge has been facilitated by the convergence of disciplines such as ophthalmology, optometry, orthoptics, molecular biology, biomaterials, genetics, wave front optical analysis and information technology.

A new era for myopia research

The final quarter of the 20th Century witnessed a renaissance in how the scientific and clinical communities viewed the influential biometric, heredity and epidemiological studies of Sorsby [7,8], Goldschmidt [9], Larsen [10], and their colleagues. The consensus was that co-ordinated growth of refractive components towards emmetropia was an active rather than passive process and importantly one that was altered by visual experience. [11]

That the concept could also be extended to the onset and development of myopia was evident from the seminal work of Wiesel and Raviola [12] in 1977 which demonstrated that manipulation of the visual environment by lid fusion could induce substantial myopia in monkey. The nature *versus* nurture debate, at least for moderate non-pathological levels of myopia, was thus rekindled and continues unabated. [13]

Much has followed since [14-20] and the purpose of this review is to provide a synopsis of prospects for myopia research in the 21st Century. Precedents set by current and previous literature have generated compelling research questions. For example: many Asian societies have prevalence levels far in excess of their Caucasian counterparts; could this be attributed to inherent ocular structural differences (possibly heredity-based) exacerbated by the visual environment? Is an increase in posterior chamber depth the sole structural correlate of myopia or, given advances in ocular imaging and optical wave front analysis, could others be equally prescriptive? Does the potent influence of heredity preclude serious consideration of environmental factors such as sustained near work that involves high levels of cognitive demand? Can animal models genuinely lay the foundations for long-term optical or pharmaceutical methods of treating myopia onset and progression in children? The review will address these and other topical questions within the framework of current perspectives on myopia concerning its prevalence, biometric parameters, putative precursors and prevention.

PREVALENCE

Comparative studies on myopia prevalence

As noted in Weale's [21] recent comprehensive review, assimilation of data on the epidemiology of refractive errors is confounded by limitations and inconsistencies in technical and statistical procedures. Saw [1] also highlights the difficulties specific to

myopia particularly with regard to comparisons across nations, offset in part by international initiatives to standardise sampling and measurement protocols. [22,23]

For example Negrel *et al.* [22] proposed obtaining population-based cross-sectional samples of children aged 5 to 15 years of age through cluster sampling with main outcome measures to include uncorrected and best-corrected visual acuity and cycloplegic autorefraction. The results of six studies [24-29] adopting the Refractive Error Study in Children (RESC) [22] protocol are summarised in Table 1. Comparison of prevalence data at 5 years and 15 years reveal substantial geographical and socio-economic differences between populations. The standardised methodology used in these studies will assist greatly identification of the aetiological bases for these differences such as, for example, changes in diet and educational provision. [30] In addition uncorrected refractive error as a cause of visual impairment ranged from 56.3% (of 1285 children) in Chile to 89.5% (of 1236 children) in China which was considered by McCarty and Taylor [30] to be support for the selection of refractive error as a priority for Vision 2020.

Table 2 provides examples of studies on myopia prevalence reported over the last three years and illustrates the difficulty in effectively comparing data for studies having substantially different methodologies. Nevertheless it can be seen that prevalence levels across all age ranges of ~ 60% to 80% have been reported for urban areas of Asia such as Taiwan, Hong Kong and Singapore and indications are that similar trends, albeit at more modest levels (~ 10% to 25%), are apparent for Australia, Europe and the USA. [31-41] The data summarised in Table 2 [33,34-37,40,41] demonstrate that whereas the evidence for high prevalence is unequivocal for East Asia it is less clear for USA and European societies with Denmark, for example, presenting a prevalence level approaching that seen in East Asia. It would be of value to extend the RESC approach

to prevalence levels and progression rates across different categories of myopia (see below), across nations of the West and East, (including within-nation ethnic groups) and, where appropriate, across different occupational and educational demands.

A central research question is whether myopia prevalence in Australia, Europe and the USA will increase to levels currently seen in East Asia. [39] It has been proposed that the declining prevalence of myopia in USA adults is due to age-related hypermetropization, rather than to an increasing prevalence in more recent age cohorts [42], although Rose *et al.* [39] have presented evidence to the contrary but for prevalence levels much less spectacular than for East Asian societies. Of special interest is whether inherent structural differences (possibly heredity-based) between East Asian and Caucasian eyes might be exacerbated by environmental differences, notably the educational pressures and high urbanisation evident in East Asian society.

Longitudinal data on rate of myopia progression in children are characterised by significant inter-subject variability owing to a variety of factors such as age-of-onset, ethnicity, gender and visual environment. [43] Taking account of this variability is clearly important in terms of optimising the design and data analysis of clinical trials for myopia control. [44] For example whereas it is expedient, and common, to match treatment and control groups for mean spherical equivalent myopic error, the procedure does not take account of either inherent differences in rate of myopia progression or their interaction with age-of-onset. Further there is evidence that response profiles differ between stable and progressing adult myopes for both accommodation stimulus-response curves and near work induced transient myopia. [45,46]

Future clinical designs are therefore likely to take account of reports on the dynamics of myopia progression using exponential growth functions to fit individual longitudinal refractive data.[47,48] Despite significant individual variation, it has been shown that a Gompertz double exponential growth function closely fits the time course of the refractive data of individuals developing myopia [48]. It has been shown that in most subjects the onset of myopia is abrupt but not instantaneous. In addition, it appears that myopia slows more rapidly than is predicted by a simple ballistic asymptote which implies that a dampening factor is needed to explain the rapidity of myopia cessation that was seen in most subjects. [48]

A recent report of cross-sectional data on myopia progression in 7376 UK children of mixed gender and ethnicity aged between 5 and 15 years of age has shown significant linear and inverse quadratic effects (linear $P = 0.007$; quadratic $P = 0.002$) across the whole age range sampled. [49] The trends indicated by the data suggest that optimum entry age for clinical trials aiming to control juvenile myopia progression is 9 years which would preclude the potential compliance and ethical constraints associated with younger children.

Classification of myopia

Most workers generally use Grosvenor's [50,51] classification system which is based on the age at which the myopia was first identified or corrected, albeit not necessarily the same as the true age-of-onset. Although age ranges differ somewhat between workers, the approach has operational value and indicates that, for the USA population, around 60% of myopia can be classified as early - onset (or school/juvenile) myopia; that is onset typically between 9 and 11 years of age with progression throughout the early teenage years which reduces in the late teens or early twenties to stabilise at a relatively

modest level of 3 to 4D. Myopia is generally classified as high myopia when it exceeds 6D [3] and has prevalence levels in young adolescents estimated at 1% and 15% respectively in Caucasian and East Asian populations.

Late-onset myopia

Although it seems clear that co-ordinated biological growth of the eye ceases around 15 years of age [8,40] a substantial proportion of myopes, estimated at between 8 and 15%, can be classified as late-onset (or early-adult onset); that is, onset typically between 15 and 18 years-of-age (and occasionally in the early twenties) with slow progression to levels rarely in excess of 2D. Late-onset myopia is therefore often attributed, especially by patients, to sustained near work, or to a change in the nature of near work (e.g. to electronic visual displays) especially when the work has high levels of cognitive demand although the research data are equivocal. [52,53] Late-onset myopia can be considered a proper sub-set of early onset myopia in that its principle structural correlate is an increase in length of the posterior vitreous chamber. [54,55] The rate of progression *per annum* in late-onset myopia is however relatively modest, around one third [56] (~ 0.16D) that of early-onset myopia. [57]

Other categories of myopia

Congenital myopia, myopia associated with systemic disease [58,59] and myopia associated with lenticular changes in the sixth decade of life [60] constitute the remainder of the myopic categories. We have observed myopic shifts of between 0.50D and 0.75D in the incipient phase of presbyopia (unpublished data), that is the 4 to 5 year period before an actual near reading addition is prescribed. The shift occurs in around 15% of individuals and appears to be more marked in existing myopes. Using high resolution measures of axial length (Zeiss *IOLMaster*, see later) our laboratory is investigating

whether the shift can be correlated with axial length elongation which would imply an aetiology linked to retinal defocus rather lenticular change.

BIOMETRIC PARAMETERS

Emmetropisation

The initial work of Sorsby *et al.* on ocular growth and refractive error was based mainly on cross-sectional studies on 1500 individuals aged between 3 and 22 years of age [7] but it was the subsequent longitudinal study on 440, 3 to 15-year old children which was of special interest. [8] In summary, eye growth was shown to consist of a rapid infantile phase whereby, in the first three years of life, the cornea and the lens had to compensate 20D or so for an increase in axial length of 5mm, adult dimensions almost being reached by two years of age. There follows a slow juvenile phase between 3 and 13 years or so whereby the compensation of lens and cornea has only to be approximately 3D for around a 1mm increase in axial length. The longitudinal data demonstrated an inter-relationship between refractive components indicating that eye growth is a co-ordinated process rather than a haphazard collection of individually-varying components; a process now generally described as emmetropisation. Importantly the data also indicate that ocular growth ceases by around 14 to 15 years of age.

Axial length: the principle structural correlate of myopia

Sorsby *et al.* [7,8] considered that changes in axial length were crucial in determining the architecture of the globe and that myopia resulted from a failure of the cornea and lens to compensate for axial length elongation. Compensatory changes in cornea power are approximately 1/3 those of the crystalline lens and both trail changes in axial length.

Although it was acknowledged that the emmetropization process could break down and produce errors in the 'normal' range of +/- 4D, it was, in the main, considered to be a successful process in that the distribution of refractive error showed leptokurtosis, that is, a marked bias to emmetropia in the population. Errors in this range were considered low and due simply to a mismatch between a number of structural components (*viz* correlation ametropia) rather than attributable to a single component such as axial length (*viz* component ametropia) which lay outside of the normal range observed in emmetropic individuals and comprised less than 3% of the total population examined.

The key role of axial length in emmetropisation is evident from the significant correlation between axial length and refractive error reported in many studies. Cross sectional data from our own centre at Aston University is illustrated in Figure 1: a coefficient of determination of 0.52 and 2.5D *per* mm of axial length is typical for this type of sample. Axial length data were the mean of three measurements using partial coherent interferometry with the commercially available Zeiss *IOLMaster* (see later comments). Mean sphere refraction was plotted from sph/cyl data recorded using the Shin-Nippon infra-red open view autorefractor (mean of 5 readings). Data were for right eye only of 169 University entrants, age range 17 – 35 (mean 19.5 +/- 4.8; 97 males, 72 females). Mean sphere for the group was -0.76D +/- 1.95; range +3.62 to -9.12D. Mean axial length was 23.88mm +/- 1.08; range 21.05 to 28.04mm. The preponderance of myopes is a consequence of the sample being drawn from a University population but there is evidence that hyperopia is also chiefly axial in nature with a weakly significant increase in corneal radius as hyperopia increases. [61]

The CLEERE study on ocular components in juvenile myopia

The USA CLEERE study (Collaborative Longitudinal Evaluation of Ethnicity & Refractive Error) extends significantly our database on ocular components in the developing eye. [40] The study is a multi-centre, 6-year study (commencing 1997) on normal ocular growth in 2583 children aged 6 to 14 years and is an extension of its predecessor, the Orinda Longitudinal Study of Myopia (which commenced in 1989). [62] The CLEERE cross sectional ocular component data is illustrated in Figure 2 and demonstrates how a mean refractive shift towards myopia of 1.13D between 6 and 14 years can be accounted for in large part by the difference between the mean reduction in lens power (due to lens thinning) of 1.85D and mean increase in vitreous chamber depth of 0.94mm (equivalent to 2.35D assuming 1mm = 2.5D). Generally most of the change in ocular components was shown to occur between 6 and 9 years-of-age. Corneal power and anterior chamber depth did not differ significantly over the 8 year period. A subsequent analysis of the CLEERE data in relation to the prevalence of refractive error and ethnicity is included in Table 2. [41]

In an attempt to quantify the expandability of the eye in childhood myopia, Schmid *et al.* [63] have combined standard ocular biometry with measures of intraocular pressure, equatorial scleral rigidity and outer wall thickness on the right eyes of 20 myopic (spherical equivalent -3.08 +/- 1.03D) and 20 non-myopic children (spherical equivalent +0.35 +/-0.29D) aged between 8 and 12 years. Although no significant differences could be demonstrated between the two groups, more precise data may be forthcoming with refinement of the approximations made for outer wall stress.

Biometric interactions and asymmetry of ocular stretch

Despite the longevity [64] and predominance of axial length as the principle structural correlate of myopia, its role has to be placed in the context of the eye as a composite refracting structure. Wildsoet [65] considers the issue in her comprehensive review of the structural correlates of myopia and separately examines the role of axial length in the developing human eye, myopia onset in the adult eye, and myopia induced in animal eyes. For example, the work of Scott and Grosvenor [66] is cited which used a multiple sample analysis technique on data from 42 emmetropic and 42 myopic eyes (aged between 17 and 26 years) and demonstrated that all refractive components except anterior chamber depth contributed to myopia with corneal radius and vitreous chamber depth being the main determinants. In addition, Wildsoet examined whether there was an axial bias to vitreous chamber enlargement such that axial dimensions exceeded transverse dimensions as myopia progresses. Early studies suggest this not to be the case for moderate degrees of myopia (i.e. 5 to 6.5D on average) [67] but that differences of 2mm could occur in high myopia (~12D). [68] Using a CT scanner Wang *et al.* [69] showed a mean difference (mm) between antero-posterior and lateral transverse dimensions of +1.56 for myopia, -0.29 for emmetropia and -0.98 for hyperopia. Thus in contrast to the emmetropic or hyperopic eye the myopic eye is a longer than it is wider, that is prolate in shape (see later comment).

Weale [21] indicates that an increase in transverse diameter is likely to lead to an increase in zonular tension with consequent decrease in thickness (and power) of the crystalline lens, an effect that will offset in part the increase in antero-posterior length, the implication being that myopia will ensue should equatorial stretch fail to match antero-posterior stretch. The observation is relevant to the report by Mutti *et al.* [70] that advances a lenticular-based hypothesis to account for the significantly higher response

AC/A (accommodative convergence/accommodation) ratio that occurs prior to myopia onset in children (see later). The authors cite previous work [71,72] on crystalline lens thinning in children to support their proposal that the disparity between growth in equatorial and longitudinal dimensions induces a pseudocycloplegia during the incipient phase of myopia development. To maintain constancy in accommodation:convergence synergy, the pseudocycloplegia prompts additional accommodative effort and hence an increase in AC/A ratio.

Biometry of anisomyopia

Models of human myopia need to resolve the issue of anisomyopia whereby substantial disparities in ocular growth can occur between eyes that have been exposed to the same genetic and environmental influences. Logan *et al.* [73,74] have used Caucasian and Taiwanese-Chinese eyes exhibiting early-onset iso- and anisomyopia to examine the relationship between axial and equatorial dimensions in myopia. The use of significant levels of anisomyopia (taken as ≥ 2D) is a valuable experimental paradigm as the least myopic eye can be used as a control. In summary, a special computing technique was used in iso- and anisomyopes (N=56) to generate estimates of posterior retinal shape for nasal and temporal sectors 35/40 degrees either side of the fovea. Estimates were based on measurements of corneal curvature, A-scan ultrasound and central/peripheral open-view automated infra-red refraction. [75] The presence and size of optic disc crescents were also assessed as indicators of retinal stretch in myopia.

In all cases there was a significant positive correlation between the degree of anisomyopia and differences in axial length between the two eyes. Anterior chamber dimensions remained the same between anisomyopic eyes. When comparing more myopic *versus* less myopic eyes, the former were elongated and distorted into a more

prolate shape for both the Caucasian and Taiwanese-Chinese subjects. In addition, Taiwanese-Chinese eyes displayed greater stretch in relative terms, and in these eyes, higher myopia was associated with larger optic disc crescents. A nasal-temporal axial asymmetry was also evident in the Caucasian eyes, reflecting a greater enlargement of the nasal sector. We have extended the calculations used to determine retinal shape in anisomyopia to estimate ocular volume and pulsatile ocular blood flow [76]. The correlation between choroidal volume and ocular volume, the interposition of the choroid between retina and sclera, and its very major role in mediating intraocular blood flow in humans (~ 80%) [77] place choroidal function at the centre of our understanding of myopia. [78-81]

There is scope for investigating the interactions between asymmetries of receptor orientation and retinal shape in the myopic eye. A recent study [82] used Stiles-Crawford functions to show nasal tilting of receptors in the more myopic eye of a 3D anisomyopic subject. Further, a recent study of form deprivation myopia on infant monkeys (*Macaca mulatta*) suggests that peripheral image quality could contribute to anomalous, vision-dependent refractive errors in children [83].

High resolution ocular biometry

Although advances in opto-electronics and digital signal processing will continue to extend greatly the range and scope of ocular biometry of the anterior segment [84,85] and wave front aberration in the myopic eye [86,87], longitudinal measurement of axial length remains the principal structural index of myopic change. In this regard the advent of a commercially available device for measuring axial length, the Zeiss *IOLMaster*, has attracted great interest in the myopia research community. The device, principally designed to calculate accurately intra-ocular lens power following refractive surgery, uses partial coherent interferometry rather than traditional ultrasound to provide high

resolution measures of axial length, anterior chamber depth and corneal radius. Although at the present time it is not possible to measure crystalline lens thickness (and hence vitreous chamber depth), with a dioptric resolution of approximately 0.03D (an order of magnitude better than 10Hz ultrasound) and, as non-contact, elimination of the need for corneal anaesthesia, the *IOLMaster* is likely to become a permanent resident in most myopia laboratories. [88]

Continued developments in whole-eye depiction of the myopic eye using high-resolution ocular magnetic resonance imaging (MRI) will, when combined with the new instrumentation described above, prove to be a valuable biometric adjunct to prospective clinical trials for myopia treatment. Simple measures of peripheral refraction[89,90] and associated computations [73-75] provide limited estimates of peripheral ocular shape but recent MRI studies [91,92] extend earlier work on 7 myopic eyes (MRI, T1) [93], and the newly established Aston Academy of Life Sciences is shortly to develop an optimised ocular surface-coil for use with the Siemens Trio 3-Tesla MRI. The application of high-resolution ocular MRI in anisomyopic subjects will provide a special opportunity for inter-eye biometric and accommodative comparisons. [94]

PRECURSORS

Axial length:corneal radius ratio

The ability to predict the onset of myopia before it is clinically measurable by conventional refractive methods enhances greatly the efficacy of clinical trials that aim to treat myopia. Although a variety of biometric and oculomotor indexes have been examined, the ratio between axial length and corneal radius (AL:CR) and the accommodative convergence: accommodation ratio (AC/A) have probably received

most attention although data are equivocal. Grosvenor [95] compared AL:CR data on emmetropic Melanesian children from a remote South Pacific island island, Vanuatu [96], with those taken on emmetropic British children by Sorsby *et al.* [8] and observed that the ratio was consistently higher in the British children than in the Melanesian children. Given the marked difference in prevalence of myopia between the two groups – ~3% for the Melanesian group, ~12% for the British group – it was proposed that a high AL:CR ratio in emmetropes (that is a ratio greater than 3) may qualify as a risk factor in the development of myopia. The proposal was subsequently tested in a three year longitudinal study on 87 emmetropic USA children between 9 and 14 years of age. [97] Cycloplegic refraction and ultrasound measures of axial length were taken every 6 months. Over the three year period, 29 of the 87 children became myopic up to a mean of 1 D. It was found that 88% of the myopic eyes had vertical axial length:corneal radius ratios that initially exceeded 3.0 whereas 90% of the eyes that remained emmetropic over the period had ratios less than 3.0. The result could not however be confirmed in a later USA study [98] on 554 emmetropic children (mean age 8.6 years) enrolled on the Orinda Longitudinal Study of Myopia. The authors proposed that the discrepancy was attributable to the earlier study [97] predicting myopia onset too close (i.e. 6 months prior) to the actual onset of myopia.

Accommodative convergence: accommodation ratio

It has been reported that Caucasian children with myopia have significantly elevated age-adjusted response AC/A ratios, with least squares mean values being recorded respectively for hypermetropes, emmetropes and myopes as 3.40, 3.94 and 6.39 Δ/D. [70] The authors used 828 children aged 6 to 14 years drawn from the Orinda Longitudinal Study of Myopia and accommodation was measured objectively by video phakometry. Non-myopic children having an AC/A ratio of 5.54 Δ/D or more, or a unit increase in

the AC/A ratio, elevated the risk of myopia development within 1 year by 22.5 times (95% CI: 7.12-71.1); behaviour of the AC/A ratio after the onset of myopia was less clear. [70] The higher ratios may be associated with reduced accommodative response at near or enhanced accommodative convergence. [99] It has also been proposed that AC/A ratios in myopes might reduce once the myopia stabilises owing to an enhanced accommodative response or an exophoric shift in the near 'phoria. [100] The biometric correlates of high AC/A ratios prior to myopia onset referred to earlier [77] appear well founded although high ratios have not been found in Hong Kong children despite the high prevalence of myopia in this group. [101]

Refraction at 5 years: a potent predictor

Improved and extended methods of measurement of both ocular components and oculomotor function will in future refine data sufficiently to examine further the predictive utility or otherwise of AL:CR and AC/A ratios [84-88,102], especially when incorporated into longitudinal experimental designs. Although Mutti and colleagues have recently shown differences in rates of change of axial and lenticular components to have value as longitudinal predictors of myopia onset [103], they have previously demonstrated clearly that the best single predictor of future myopia onset is initial cycloplegic autorefraction. [98] Hyperopia of 0.75D or less at a mean age of 8.6 years was shown to have a sensitivity of 86.7% and specificity of 73.3%. [98] This finding supports the early study of Hirsch [104] on USA children (The Ojai Longitudinal Study of Refraction) which showed that children with a spherical equivalent error of less than +0.5D at 5/6 years of age are likely to present with at least 0.5D of myopia at 13/14 years of age (see Figure 3).

Heritability: low to moderate myopia

The longitudinal study of Pacella *et al.* [105] highlights the potent influence of parental myopia on the development of myopia in offspring. Data for 277 children are illustrated in Figure 4 and are derived from a 24-year longitudinal study [at Massachusetts Institute of Technology (MIT)] which commenced in infancy (age 6 to 12 months) in a cohort of 609 largely Caucasian children. The mean age of the group was 13.3 years and data were taken from a mean of 15 non-cycloplegic refractions between 5 and 24 years from commencement. The odds ratio for two myopic parents *versus* no myopic parents demonstrates clearly the impact of parental myopia on moderate levels of child myopia (5.09; 95% CI: 1.69-15.49; p=<0.007; mean spherical equivalent on last refraction for the children was -2.46D, range -0.51 to -9.00). Interesting ocular biometric features may also accompany familial predisposition. For example, a study of non myopic children found increased eye size for those with myopic parents compared to those whose parents were not myopic. [106] A group of 662 children again drawn from the Orinda Longitudinal Study of Myopia, showed that when school grade and amount of near work was controlled, children with two myopic parents had significantly longer eyes and less hyperopic error than children with only one myopic parent or no myopic parents. [106]

Genetics of high myopia

The inexorable advance in information on the human genome will inevitably extend our knowledge of the genetics of myopia. Presently several loci have been identified for high myopia (i.e. < -6D) on a series of chromosomes (e.g. 18p; 12q; 7q36; TGIF) [107-109] although two of these, chromosomes 12 and 18, do not appear to be linked to juvenile myopia.[110] Two comprehensive twin studies have suggested that additive genetic factors are responsible for over 80% of the variation in refractive error in European populations. [104,105] The UK-based study by Hammond *et al.* [111] used genetic modelling to analyse

data for 226 monozyotic twins and 280 dizygotic twins (all female aged between 49 and 79 years) across a wide ametropic range (including emmetropia). The authors proposed that, despite the high heritability index, heredity could still be susceptible to environmental influences and identified near work as a major influence in producing what they termed adaptive myopia.

Heritability and environmental influences

Rose *et al*. [113] have examined further the issue of whether high heritability of myopia precludes rapid changes in prevalence induced by environmental influences. Using as a principle reference source an earlier analysis by Guggenheim *et al.* [114], data on heritability estimates are reanalysed and illustrated for twin studies and for myopia grouped by within-family correlations (i.e. parent-offspring or inter-sibling) for different ethnicities. The data analysis highlights the impact of the environment on myopia prevalence in communities of East Asian origin where rapid increases in prevalence have been evident. For example, heritability derived from inter-sibling correlations (where shared environment normally predominates) was found to be uniformly high (0.50-0.98; maximum heritability = 1.0) compared to that derived from parent-offspring correlations (0.04-0.49). The environmental risk factors for myopia most often cited include education, urbanization and near work but the nature of their interaction with genetic factors remains obscure. [1]

Myopia and near work: association or causation?

The strong association between near work and myopia has been evident for many years [115,116] being first recognized by Kepler in the 16th Century. Sustained near vision is a subtle and complex integration of psychophysiological responses and presents special difficulties in terms of experimental design and control. Further, the composite near

response is greatly influenced by the cognitive demand of the task and its medium. Specialised electronic displays pervade practically all modern day activities in education, communication, commerce and technical/health services. Our understanding of the characteristics of accommodative and oculomotor responses to these displays needs to be consolidated, especially as a new generation of virtual reality and three-dimensional displays is imminent. Given its intricate nature, it is comprehensible that the significance of near work as a genuine causative factor in myopia onset and development is ill-defined even in ethnic groups especially susceptible to myopia. [1] Recent studies have, however, shown Hong Kong children to be particularly susceptible to near-work induced transient myopia [117] a phenomenon which is itself enhanced by increasing levels of cognitive demand (see below). [118] The perplexing issue of assessing the influence of cognitive load on near work and myopia development has also been demonstrated in work on adolescent rhesus monkey eyes. [119] Substantial near work induced myopic shifts (with correlated change in axial length) were evident when monkeys participated in complex computer-based visual tasks but the shifts appeared to be independent of accommodation as they occurred when accommodation was neutralised with positive lenses during the tasks.

In terms of the structural changes that might be induced by accommodation, partial coherent interferometry techniques have shown that substantial accommodative effort does elongate the eye but that the elongation is more pronounced in emmetropes than in myopes. [120] Furthermore, sustained accommodative effort of has been shown to reduce intra-ocular pressure: using a Goldmann applanation tonometer 3.5 minutes of sustained accommodation induce reductions in IOP of 2.15 mmHg and 2.38 mmHg for, respectively, accommodation stimulus levels of 1.5D and 4D. [121] There is recent evidence of a relationship between IOP and myopia in a Japanese population [122] (after

adjusting for age and central corneal thickness) but no evidence of a link with developing myopia in Hong Kong[123] or Chinese [124] children.

Saw *et al.* [125] reported that the number of books read per week was associated with higher levels of myopia in 1005 Singaporean children (aged 7 to 9 years) independent of other related factors such as socioeconomic class and history of light exposure (see later). Quantitative measures of near work (e.g. reading in hours per day) were related to myopia >3D but the associations did not remain after multivariate adjustment. The authors considered that whereas they had provided evidence for a somewhat stronger correlation between near work and myopia than previously reported, their data did not unambiguously resolve whether near work is a genuine risk factor or a surrogate for other environmental or genetic factors. A more recent study has examined the prevalence of refractive error using non-cycloplegic refraction in 946 Singapore children aged 15 to 19 years. [126] The prevalence level reported was high at 73.9% (CI: 71.0-76.7). The amount of reading and writing done currently, as a measure of near work, was shown to be positively associated with myopia in addition to being of Chinese ethnicity, reading and writing at a close distance, a better educational stream and better housing type. The prevalence of hyperopia (spherical error of $\geq$ +0.50D) was found to be only 1.5%; that of anisometropia to be 11.2% (CI: 9.3-13.4) for a spherical error difference of at least 1D and 2.7% (CI: 1.8 -4.0) for a spherical error difference of at least 2D. Interestingly anisometropia of at least 2D was found to be greater in females (4.0%, CI: 2.1-5.9) than in males (1.7%, CI: 0.6-2.8). In contrast anisometropia $\geq$ 2D in Caucasian populations has a prevalence of around 1.5%. [74] Table 3 compares risk factors for myopia in terms of odds ratios after adjusting for age and gender. Of particular interest is that for this East Asian population $\geq$ 20.5 hours of

reading and writing per week and reading at close distances (i.e. < 30cms) was positively linked to myopia.

Parental myopia, near work and school achievement

Using cross-sectional data, Mutti *et al.* [127] have quantified the degree of association between juvenile myopia, parental myopia, near work [based on a task- and distance-weighted metric of dioptre-hours per week (D/hrs/wk) spent studying], reading for pleasure, watching television, playing video games or computer work, and hours per week playing sports. School achievement scores [based on the Iowa Tests of Basic Skills (ITBS)] were assessed in 366 Caucasian children drawn from the Orinda Longitudinal Study of Myopia (mean age 13.7 +/- 0.5 years; mean spherical equivalent refraction -0.17 +/- 1.56D). Table 4 summarises the odds ratio data for univariate and multivariate analyses of parental myopia, near work, sports and ITBS data. The univariate analysis supports the marked effect of parental myopia referred to earlier. [105] An odds ratio of 1.02 for near work indicates that the chance of developing myopia increases by a modest 2% for every D/hour of near work during the week; sports and basic skills both have a low level effect. Odds ratios for a sub-sample of children carrying out near work for greater than a median level of 50D/hrs/wk shows an increase in susceptibility to myopia but, in contrast to the report of Saw *et al.* [125] susceptibility is not affected by parental myopia. Of special interest is that odds ratios were not significantly modified following analysis using a multivariate logistic regression model, thus indicating that the four characteristics examined were essentially acting independently in terms of susceptibility to myopia. Although the authors emphasised the need to carry out longitudinal follow-up analyses, their data indicate that heredity is the single most important factor associated with juvenile myopia and further that there

was no evidence that children inherit a myopigenic environment or a susceptibility to the effects of near work from their parents.

Near work induced transient myopia

The delay in the relaxation of accommodation back to a baseline level following a sustained near vision task (i.e. a short-term myopic shift in the far point of accommodation) has been termed near-work induced transient myopia (NITM). [128] It has been proposed that the retinal defocus and degradation in retinal image contrast induced by NITM may be sufficient to trigger compensatory blur-driven growth of the posterior vitreous chamber in susceptible individuals. [128] On average, the magnitude of NITM is 0.40D with a range from 0.12 to 1.30D and a time course ranging from several seconds for a relatively short task, to as long as a few hours for longer task durations. [128] It has been shown that myopes specifically have a propensity to NITM when compared to emmetropes and hypermetropes.[129,130] Ciuffreda and Wallis [129] found a mean NITM of ~0.35 D for both their early-onset (N=13) and late-onset (N=11) young adult myopic groups. Neither the emmetropic group (N= 11) nor the hyperopic group (N = 9) exhibited significant NITM. The myopic groups were distinguished, however, by differences in the time taken subsequently to reach a stable baseline optimum level of accommodation for distance vision. Late-onset myopes were found to take almost twice as long to reach these distance accommodation levels than early-onset myopes (i.e. 63 seconds *versus* 35 seconds).

It has been shown that NITM is significantly greater in myopic than in emmetropic Hong Kong Chinese children (aged 6 to 12 years) with a mean level of ~ 0.52 +/-0.44D (compared to ~ 0.10 +/-0.45D) still evident after 3 minutes following sustained fixation

of a 5.00 D near task for 5 minutes. [117] In a recent report [118] young Caucasian adult myopes were again shown to be more susceptible to NITM than emmetropes but the susceptibility was especially pronounced in early-onset myopes when a near task of relatively high cognitive demand was followed by a passive distance task.

Putative precursors: night-time lighting and nutrition?

Two further putative precursors to myopia development have attracted attention. Quinn and co-workers [131] reported an association between myopia development and night-time light exposure during the first two years of childhood. There were found to be five times more children with myopia among those who slept with room lights on than in those who slept in the dark, and an intermediate number among those sleeping with a dim night light. The findings could not however be replicated in either USA children (e.g the CLEERE and MIT studies cited earlier), [132] UK children [133] nor in studies on rhesus monkey. [134,135] A recent study [136] has identified the number of hours exposure to daily darkness to be a risk factor for myopia progression in adults attending a USA law school: myopic progression was significantly increased when the number of hours of daily darkness was < 5.6 *per* 24 hour day.

Cordain *et al.* [137] have presented an interesting evolutionary analysis of the aetiology and pathogenesis of juvenile-onset myopia and argue that the nation-wide transition in modern times to a diet rich in refined sugar and processed cereals may account for the respective increases in myopia prevalence. It is shown that high consumption of carbohydrates instigates a sequence of events: disruption of glycaemic control; promotion of insulin resistance; a compensatory hyperinsulinaemia; an increase in free IGF-1 (insulin growth factor); a possible decrease in retinoid receptor signalling; and

finally, unregulated and enhanced tissue growth manifested as an increase in axial length.

PREVENTION

Near work, accommodative error and retinal defocus

Despite the fact that myopia was identified by Aristotle (384-322) more than 2300 years ago [9], an effective treatment still eludes the clinician. Early attempts at myopia control in humans were equivocal and often involved ocular pharmaceutical agents such as atropine or additional positive lens power for near work using bifocal lenses, [138,139] the implication being that the accommodation system was somehow deficient, not an unreasonable assumption given the clear association between myopia and near work. [115] Thus it has been proposed that myopia can be induced by hyperopic and myopic retinal blur due to inaccurate accommodation, [140,141,45] lag of accommodation at near, [142], transient myopia following sustained near vision,[117,130] and deficits in integrative/adaptive oculomotor responses which incorporate accommodation as a response component.[115,143,144] An important and perplexing issue is whether accommodative dysfunction in myopia is a cause or a consequence of the condition. It has been demonstrated that excess accommodative lag accompanies but does not precede the onset of myopia and therefore has limited use as a precictor. [145,146] Using monocular accommodative responses for letter targets at 0D and 4D for 903 children drawn from the Orinda Longitudinal Study of Myopia, odds ratios (adjusted for refractive error) associated with a 0.5D unit increase in accommodative lag did not indicate a significantly increased chance of developing myopia for each of the three years preceding actual myopia onset. [145] The mean adjusted odds ratio just one year prior to onset was also found to be insignificant at 1.02 (95% CI: 0.69 to 1.51). Of note

was the finding that adjusted least-square mean values for lag were significantly greater (~0.24D) for children who became myopic compared to those who remained emmetropic [145] a finding contrary to that found in a previous study which found no difference in accommodative lag between the two refractive groups. [147]

Retinal defocus and blur detection in humans

Recent advances in theoretical modelling of refractive error development [148-151] include the incremental retinal defocus theory proposed by Hung and Ciuffreda [150] which considers the myopigenic nature of retinal defocus. The critical element of the theory as it relates to near work is that the detection mechanism triggering ocular growth does not depend on the sign of the retinal blur, but rather on the change in blur magnitude during genetically programmed ocular growth - rate of ocular growth is dependent on the change in magnitude of retinal-defocus regardless of how it is generated. The notion was recently examined in the context of whether refractive under correction, compared to full correction, was able to reduce myopia progression in a two-year prospective study on 94 myopic children of Malay and Chinese origin (aged 9 to 14 years). [152] The treatment group comprised 47 myopic children who were under corrected by approximately +0.75D. Contrary to the animal data (see below), under correction (i.e. myopic defocus) enhanced rather than inhibited myopia development, the increases in refractive correction being correlated with change in axial length.

The ability to detect blur may however be altered in both adult and child myopia.[153,154] Schmid *et al.* [154] investigated blur detection thresholds in childhood myopia for two different black and white targets (text and scenes) and illumination conditions for a cohort of 20 myopic and non-myopic Hong Kong children aged 8 to 12

years. There was no correlation between blur thresholds and refractive error magnitude, refractive error progression (over the previous year) or contrast sensitivity. It was noted that blur detection ability showed significantly greater individual variability in myopic children which led the authors to suggest that sub-groups may differ in their ability to detect blur.

Animal models of retinal defocus

Whereas in qualitative terms the association between accommodation and myopia development in humans is well established, experimental paradigms for the control of eye growth in animals has provided valuable quantitative data. [155] Hyperopic defocus produced by negative lenses results in increased rates of eye growth in monkey, [156,157] blocked it appears by limited periods of interposed normal vision.[158] The significance of brief intervening periods of normal unrestricted vision is especially interesting as in form deprivation experiments on infant rhesus monkey it has been shown that as little as 1 hour per day of unrestricted viewing can reduce by over 50% the myopia induced by a 17-week period of deprivation. [159] In contrast to hyperopic defocus, myopic defocus produced by positive lenses decreases eye growth [160] even for relatively short exposure conditions. [161,162] Whether the spatiotopic and retinotopic operating characteristics of the human accommodation response system in terms of contrast, pupil size, depth-of-focus, temporal response and binocularity are sufficient to detect the sign of defocus, and hence modulate eye growth, is a challenging research question, [163] but one that has to take account of observations that complete elimination of accommodative signals fails to prevent induced eye growth in animals. [164,165] Additionally, it appears that regulation of eye growth in animals can occur independently of central processes [148] which further lessens the likelihood of a contribution from centrally-driven accommodation. Recent evidence in selective lesions on chick eye suggests however

that whereas an intact retina-brain link is not a requirement to compensate for hyperopic lens defocus, the emmetropisation set-point might be re-calibrated after optic nerve section and further the ciliary nerve itself may mediate inhibition of eye growth. [167]

In his comprehensive and absorbing review Crewther [168] proposes three control mechanisms for experimentally induced refractive error. One of these utilises the Stiles-Crawford effect to detect retinal defocus through analysis of spatio-temporal contrast within the sub-retinal space, a process which subsequently results in changes in ionic and fluid balance. Crewther demonstrates that the mechanism could conceivably modulate eye growth when incorporated with saccade-induced outer segment movement.

Interventions to retard myopia progression in children

Saw *et al.* [169] have recently reviewed ten published clinical trials of different interventions to retard myopia progression in children. The trials examined the efficacy of a variety of eye drops, bifocal and progressive addition spectacle lenses and soft contact lenses. The authors concluded that, at best, the available evidence for myopia intervention in children was inconclusive owing to the magnitude of the intervention effect being small compared with the control together with the likelihood of high dropout rates and low compliance. It was recommended that all future trials should incorporate double-masked randomized designs with optimum optical refraction data and sufficient follow-up time. The review did acknowledge the reported efficacy of atropine eye drops in retarding myopia progression. Figure 5 illustrates the results of a longitudinal study (over 1.5 years) by Shih [170] and his colleagues on myopia progression in 188 Taiwanese children aged 6 to 13 years. The treatments were single vision lenses alone (N=61), progressive addition lenses alone (N=61), and progressive addition lenses

combined with topical instillation of 0.5% atropine (N=66). Cycloplegic autorefraction was carried out and initial mean refraction for the group was - 3.28 +/- 0.13D. The mean myopia progression found over 18 months was: single vision lenses - 1.40 +/-0.09D; progressive addition lenses - 1.19 +/-0.07D; progressive addition lenses combined with atropine - 0.42 +/- 0.07D.

Muscarinic receptor antagonists and myopia control

Although the data in the Shih *et al.* [170] study support earlier human [171-173] and animal [174,175] investigations, it appears that the myopia reduction may occur via a non accommodative mechanism. [176] Further, the actual site(s) of action of atropine, a non-selective muscarinic cholinergic antagonist, is still unresolved as atropine can prevent form deprivation myopia in animals even when cholinergic cells and receptors are absent from the retina. [177] The apparent efficacy of atropine in myopia control is therefore countered by uncertainty over its mechanism of action. Saw *et al.* [169] strongly advocate follow-up studies to determine the possible long-term adverse reactions to atropine (e.g. cataract and retinal toxicity) and acquisition of data on myopia progression after cessation of atropine therapy.

Other muscarinic receptor antagonists that effectively prevent form deprivation myopia in animals, again with uncertainty regarding respective sites of action, are pirenzepine (M1 selective)[178], himbacine (M4 selective) [179] and oxyphenonium (non-selective). [177] The effect of 2% pirenzepine ophthalmic gel on myopia reduction in children has recently been tested on groups in the USA [180] (2 year duration) and Asia. [181] (one year duration). Both studies were multi-centre, randomized, double masked and placebo-controlled. Table 5 summarises the data and demonstrates a significant and proportionally equal maximum reduction (~ 50%) in myopia progression for both

groups. The placebo data also highlight the significant difference in myopia progression between East Asian and USA groups which may account for why a positive correlation between axial length and reduction in myopia progression could only be shown for the Asian group. Although less effective than atropine in reducing myopia progression, both pirenzepine trials reported relatively innocuous adverse reactions compared to atropine. These interesting findings will no doubt instigate further clinical trials on the efficacy of pirenzepine and other muscarinic receptor antagonists in inhibiting myopia progression in children.

Adrenergic control of accommodation

Whereas ocular accommodation is mediated principally by muscarinic receptors following parasympathetic innervation of ciliary smooth muscle, Gilmartin and colleagues have used non-selective and selective topical beta adrenoceptor drugs to demonstrate that the ciliary muscle also receives a supplementary inhibitory sympathetic innervation which is mediated by inhibitory beta-2 adrenoceptors [138, 182, 183] and possibly inhibitory alpha-1 adrenoceptors. [184] The principal features of sympathetic control are that it is inhibitory, relatively small (probably no more than -2 D) and is relatively slow (time courses range between 20 and 40 s compared with the 1 or 2 s for the parasympathetic system). A significant attribute of sympathetic inhibition is that it is augmented by concurrent parasympathetic (i.e. accommodative) activity.[185] The basis of this augmentation is first, sympathetic inhibition will only become apparent when there is something to inhibit and hence there is a base-line requirement for concurrent parasympathetic activity; second, parasympathetic activity above this level appears to augment sympathetic input directly, but not to an extent greater than 2 D, even for very high parasympathetic levels. [138]

Sympathetic deficit: a precursor for myopia development?

The properties of sympathetic innervation are consistent with the requirements of an adaptive facility which complements the fast reflexive nature of parasympathetic innervation. These properties have been linked to a number of general accommodative response characteristics [186-188] but are especially pertinent to our ability to adapt successfully to sustained near vision tasks. [115,183] Given the clear association between sustained near vision and the onset and development of myopia [115], sympathetic inhibition may thus have a putative aetiological role in development of certain classes of myopia in predisposed individuals. [129,130,189,190] In this context the role of sympathetic innervation of the ciliary muscle may be, for example, to attenuate the retention of accommodative tone induced by periods of intense close work and thus reduce the risk of latent post-task transitory pseudo-myopic changes. Without this attenuation, a series of micro-adaptation processes could accumulate to a critical level, perhaps via an iterative ratchet-type response with regard to accommodative gain, which when exceeded causes structural recalibration, that is, an increase in vitreous chamber length. A variety of techniques have been employed [184,187,188,190] using topical beta-adrenoceptor antagonists to demonstrate that sympathetic inhibition is present in around 30 to 40% of individuals.[190,191] Current longitudinal studies on refractive changes in young adults are examining whether an absence or deficit in sympathetic inhibition is a putative precursor for myopia onset and development. [191]

Bifocal and progressive addition spectacle lens trials

Despite the somewhat tenuous causal link between accommodation responses and the development of myopia, the rationale for the use of positive lens additions in myopia control is to optimise accommodative accuracy for near tasks such that retinal blur is minimised. Grosvenor [192] has reviewed previous studies to demonstrate equivocal

results and a lack of consistency in experimental designs. Of note however are the well-controlled bifocal spectacle lens longitudinal studies of Grosvenor *et al.* [193], Parsinnen *et al.* [194] and Jensen [195] although none could demonstrate significant effects against distance corrected single vision controls. The finding by Jensen that bifocals appeared to be more successful in reducing myopia progression in subjects having IOPs greater than 17 mmHg [195] warrants further investigation as her later report [196] on a sub-set of 49 of the 145 Danish children used in the original study, showed the rate of myopia progression in children with an IOP above 16 mmHg to be significantly greater than those with an IOP of 16 mmHg or less: 0.66 D/year *versus* 0.43 D/year respectively. The more recent randomised trial undertaken by Fulk and his colleagues [197] investigated the effect of single vision *versus* bifocal lenses on myopia progression in 84 children with near point esophoria. A modest but significant slowing in myopia progression of 0.25D was demonstrated over the 30 month test period.

Of three recent reports assessing the efficacy of progressive addition spectacle lenses (PALs) for myopia control in children [170,198,199], only the study of Gwiazda *et al.* [199] (COMET: Correction of Myopia Evaluation Trial), was able to show a statistically significant, albeit small (0.20 +/- 0.08D; p=0.004) slowing of progression. The retardation, which was not deemed sufficient to warrant a change in clinical practice, occurred during the first year of a three year trial and stabilised thereafter. The data illustrated in Figure 6 were generated by a randomised double-masked single vision controlled trial on 462 children (mixed ethnicity) aged 6 to 11 years with myopia between -1.25 and 4.50 spherical equivalent (cycloplegic autorefraction). Mean changes in axial length correlated with those in refractive error and interaction analyses have subsequently indicated that a sub-set of children with poor accommodative accuracy

and near esophoria may benefit significantly from PALs in clinical terms, a feature noted following an earlier PAL study on Hong Kong children. [200,201]

Contact lens control of myopia progression

Whereas soft contact lenses do not appear to affect myopia progression compared to spectacle correction, [202] an ongoing 3-year study [The Contact Lens and Myopia Progression (CLAMP) Study] [203] is due to report in 2004 on the efficacy of rigid gas-permeable contact lenses in myopia control. The study is supported by the USA National Eye Institute and extends previous studies where treatment outcomes were equivocal. [204-206] Presently 116 children (mean age 10.5 years at the baseline visit, range 8 to 11 years) are enrolled. The primary outcome measure will be the change over 3-years in cycloplegic autorefraction; the secondary outcome measures will include annual measures of corresponding changes in axial length, peripheral autorefraction, crystalline lens curvatures, corneal curvature and thickness, accommodation, and intraocular pressure. [203]

Ocular aberrations and myopia

The literature cited above has established the importance of retinal image quality in modulating eye growth in myopia and retinal defocus associated with astigmatic error has been examined by Gwiazda *et al.* [201] in 245 individuals after having carried out an initial refraction in the first year of life and follow-up refractions extending over the subsequent 6 to 23 years. Infantile astigmatism, in particular against-the-rule, was found to be associated with an increase in astigmatism and myopia during the school years although the mechanisms underlying the association remain obscure. Recent work on infant rhesus monkey has investigated whether developing primate eyes are capable of growing in a manner that eliminates astigmatism. The results indicate that visual

experience can alter corneal shape, but there was no evidence that primates have an active, visually regulated 'sphericalization' mechanism.[208]

The review ends with a brief note on the potential role of monochromatic aberrations in myopia onset and development. Whereas the effects of chromatic aberration have been assessed in chick eye [209] few have reported directly on monocromatic aberrations in humans. [210] The measurement of wave-front aberration has now become more accessible and work has examined the effect of variations in accommodative demand [211], differences between emmetropes and myopes,[87,212] and the potential interaction between accommodative demand and refractive error. [213] Given the association between sustained accommodation and myopia this interaction is of special interest as one might speculate whether wave-front modulated refractive surgery may at some point in the future be used to optimise retinal image quality during sustained near vision.

CONCLUDING COMMENT

The prospects for research in the 21st Century are intriguing and will challenge both imagination and comprehension as the nature of myopia is exposed to inexorable advances in the biological sciences. [18,155] Continued collaboration between inter-related disciplines and eye-care professions both within and between continents is an essential pre-requisite for success. [214] Whereas the likely outcome is further confirmation that heredity predominates in the genesis of myopia, genomic and proteomic scanning techniques will be used to map pathways to effective pharmaceutical intervention [155] possibly delivered via novel contact or implanted corneal lens biomaterials that concurrently correct lower and higher order ocular aberrations.

Of special significance is the continuing need for systematic appraisal of causal criteria adopted by investigators in the evaluation of epidemiological associations for myopia. McCarty [215] lists nine such criteria including for example consistency of findings, specificity and biological gradient (i.e. dose response). Particular attention is drawn to the criterion of temporality, that is change over time, and the importance of reporting negative results in order to refine research directions. Finally, a recent UK study has shown high myopia to have an adverse effect on quality-of-life equivalent to that of keratoconus [216] a feature not always fully appreciated but one that is increasingly recognised by health authorities in terms of health management and social services. [217,218]

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FIGURE LEGENDS

Figure 1. Example of the significant ($P < 0.001$) correlation between axial length and refractive error for cross-sectional data from a population of young adult University students. The correlation demonstrates that axial length is the principle structural correlate of myopia.

Figure 2. Summary of the main findings of the CLEERE study (Collaborative Longitudinal Evaluation of Ethnicity & Refractive Error), a USA multi-centre 6-year study on normal ocular growth in 2583 children aged 6 to 14 years. Ocular components illustrated are spherical equivalent refractive error (Rx), corneal power (CP), anterior chamber depth (AC), vitreous chamber depth (VC) and crystalline lens power (LP). Computed and redrawn from Zadnik *et al.* 2003. [40] Reproduced with permission from: Zadnik K, Manny RE, Yu JA, *et al.* Ocular component data in schoolchildren as a function of age and gender. *Optom Vis Sci* 2003; **80**(3): 226-36. © The American Academy of Optometry, 2003.

Figure 3. Spherical equivalent refractive error found at 13/14 years of age compared with that found at 5/6 years of age. Children with a spherical error of less than +0.5D at 5/6 years of age are likely to present with at least 0.5D of myopia at 13/14 years of age. Redrawn from Hirsch 1964.[104] Reproduced with permission from: Hirsch MJ. Predictability of refraction at age 14 on the basis of testing at age 6 - interim report from the Ojai Longitudinal Study of Refraction. *Am J Optom Arch Am Acad Optom* 1964; **41**: 567-73. © The American Academy of Optometry, 1964.

Figure 4. The influence of parental myopia on the development of myopia in offspring. Children with two myopic parents have a greatly increased chance of being myopic. Redrawn from Pacella *et al.* 1999 [105] Reproduced with permission from: Pacella R, McLellan J, Grice K, *et al.* Role of genetic factors in the etiology of juvenile-onset myopia based on a longitudinal study of refractive error. *Optom Vis Sci* 1999; **76**(6): 381-386. © The American Academy of Optometry, 1999.

Figure 5. A longitudinal study (over 1.5 years) on myopia progression in 188 Taiwanese children aged 6 to 13 years. The treatments were single vision spectacle lenses alone (SV), progressive addition spectacle lenses alone (PALs), and PALs

COUNTRY	SAMPLE SIZE	MYOPIA PREVALENCE (%; [95% CI])

combined with topical instillation of 0.5% atropine. Significant slowing of myopic progression was evident with atropine. Redrawn from Shih *et al.* 2001 [170] Reproduced with permission.

Figure 6. Results of the COMET trial (Correction of Myopia Evaluation Trial): a longitudinal study (over 3 years) on myopia progression in 462 children (mixed ethnicity) aged 6 to 11 years. The treatments were single vision spectacle lenses alone (SV) and progressive addition spectacle lenses alone (PALs). A statistically significant, but clinically small slowing of progression of 0.20 +/- 0.08D (p=0.004) occurred during the first year of the trial but stabilised thereafter. Redrawn from Gwiazda *et al*. [181]

Table 2. Selection of recent studies on the prevalence of myopia and hyperopia in children and young adolescents.

		5yrs	15yrs
CHINA [23]	5884	M + F: 0.0	M: 36.7 [29.9 – 43.4]
Shunyi District			F: 55.0 [49.4 – 60.6]
(rural)			
NEPAL [24]	5067	M + F: ~ 0.5	M: ~ 2.9
Mechi Zone			F: ~ 1.0
(rural)			extrapolated data
CHILE [25]	5303	M + F: 3.4	M: 19.4 [13.6 – 25.2]
La Florida		[1.72 –5.05]	F: 14.7 [10.1 – 19.2]
(suburban)			
INDIA [26]	4074	M + F: 2.80	M + F: 6.72
Andra Pradesh		[1.28 – 4.33]	[4.31 – 9.12]
(rural)			
INDIA [27]	6447	M + F: 4.86	M + F: 10.80
New Delhi		[2.54 – 6.83]	[6.71 – 14.80]
(Urban)			
SOUTH AFRICA [28]	4890	M + F: 3.2	M + F: 9.60
Durban	African	[0.6 – 5.7]	[6.4 – 12.7]
(Metropolitan)			

Table 1. Studies on the prevalence of myopia in children (< - 0.50D spherical equivalent cycloplegic autorefraction in either eye; 5 to 15 years-of-age; M: male; F: female) using the Refractive Error Study in Children sampling and measurement protocols (Negrel *et al.* 2000 [22]).

COUNTRY	N	Age (years)	Prevalence of Myopia (%) (criteria)	Prevalence of Hyperopia (%) (criteria)
UK [33]	7600	7	1.1 (<-1.00D)	5.9 (>+2.00D)
SWEDEN [34]	1045	12-13	45 (≤-0.50D)	8.4 (≥+1.00)
USA [40]	2583	6 - 14	10.1 (≤-0.75D)	8.6 (≥+1.25)
USA [41]	2523	5-17	9.2 (≤-0.75D)	12.8 (≥+1.25D)
African American	534		6.6	6.4
Asian	491		18.5	6.3
Hispanic	463		13.2	12.7
White	1035		4.4	19.3
AUSTRALIA [36]	2571	5	2.8 (<-0.50D)	46.1 (>+0.50D)
		12	8.7 (<-0.50D)	24.1 (>+0.50D)
SINGAPORE [35]	1453	7	29.0 (≤ 0.50D)	Data not reported
		8	34.7(≤ 0.50D)	
		9	53.1(≤ 0.50D)	

		13-15	Data not reported
HONG KONG [37]			
Local school	335	85 to 88	
International school	789	43 in non Chinese 65 in mixed Chinese 80 in Chinese	

Table 3. Risk factors associated with myopia in 946 Singaporean children (after Quek *et al.* 2004 [126]). Reproduced with permission.

Risk Factor	Hours per week spent	Age and gender adjusted odds ratios (95% CI)	*P*-value
Education stream			
Normal technical		1.00	
Normal academic		1.68 [1.15-2.46]	0.007
Express		3.03 [2.05-4.47]	<0.001
Reading and writing			
At present	≤ 20.5	1.00	
	> 20.5	1.12 [1.04-1.20]	0.003
At age 12	≤ 6.5	1.00	
	> 6.5	1.21 [0.90-1.64]	0.21
At age 7	≤ 4	1.00	
	> 4	1.34 [1.00-1.79]	0.05
Reading at close distances			
Never		1.00	
Sometimes		1.16 [1.13-2.28]	0.008
Often		1.80 [1.12-2.90]	0.015
Computer usage	≤ 6	1.00	
	> 6	1.23 [0.91-1.65]	0.17

Use of handheld electronic devices	≤ 3.5	1.0	
	> 3.5	0.78 [0.59-1.05]	0.10
Parental history			
No parents with myopia		1.00	
At least one parent with myopia		1.21 [0.84-1.74]	0.31

Table 4. Univariate and multivariate odds ratios and confidence intervals for the association between children's myopia and various risk factors (after Mutti *et al.* 2002. [127])

Risk Factor		**Univariate Analysis mean odds ratio [95% CI]**	**Multivariate Analysis mean odds ratio [95% CI]**
Number of myopic parents (unadjusted for amount of near work)	One	3.31 [1.32-8.30]	3.32 [1.18-9.37]
	Two	7.29 [2.84-18.7]	6.40 [2.17-18.87]
Near work ≥ 50 D-hrs/week (adjusted for number of myopic parents)	None		2.09 [0.36-12.00]
	One		2.22 [0.94-5.25]
	Two		1.57 [0.60-4.09]
Near work Dioptre-hours/week		1.02 [CI: 1.01-1.03]	1.02 [1.01-1.03]

Sports /hr/week	0.94 [0.89-0.98]	0.92 [0.86-0.97]
ITBS reading local percentile score /% score	1.01 [1.00-1.02]	1.01 [1.00-1.03]

Table 5. Clinical trials on myopia progression in young children comparing instillation of 2% pirenzepine (PIR) ophthalmic gel with placebo (PL).

	Age (years)	Trial	Sample Size	Mean myopic progression over 1 year
USA Siatkowski *et al.* 2004 [180]	8-12	PL *b.i.d.*	53	0.99(+/-0.68)
		PIR *b.i.d.*	31	0.58 (+/-0.53)*
ASIA Tan *et al.* 2003 [181]	6-12	PL *b.i.d.*	71	0.84
		PIR *q.d.*	141	0.70
		PIR *b.i.d.*	141	0.47**

PIR *b.i.d. versus* PL *b.i.d.* ** $P < 0.001$; * $P = 0.008$

Figure1

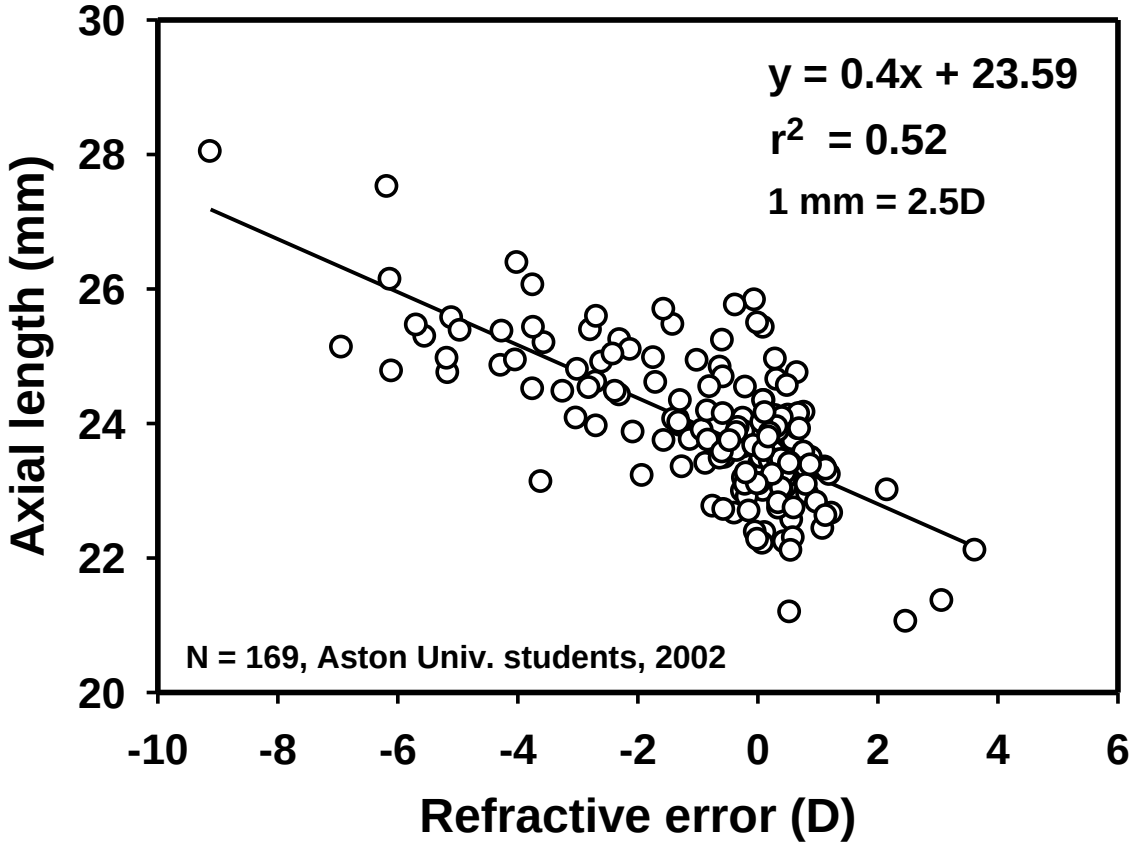
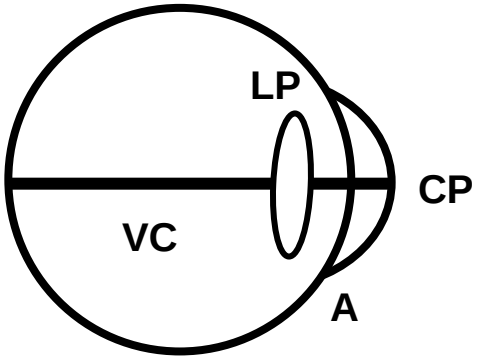

y = 0.4x + 23.59
r2 = 0.52
1 mm = 2.5D
N = 169, Aston Univ. students, 2002
Axial length (mm)
Refractive error (D)
30
28
26
24
22
20
-10
-8
-6
-4
-2
0
2
4
6

Figure 2

CLEERE study



most rapid changes between 6 & 9 yrs

Mean data pooled for gender, ethnicity & corneal meridians, (mean sds)

6 yrs	14 yrs
Rx (D)	
+ 0.85 ***(0.86)***	**- 0.28** ***(2.48)***
CP	
43.67 ***(1.48)***	**43.37** ***(2.48)***
AC	
3.54 ***(0.25)***	**3.66** ***(0.29)***
VC	
15.50 ***(0.61)***	**16.44** ***(1.19)***
LP	
24.23 ***(2.16)***	**22.38** ***(2.09)***

Figure 3

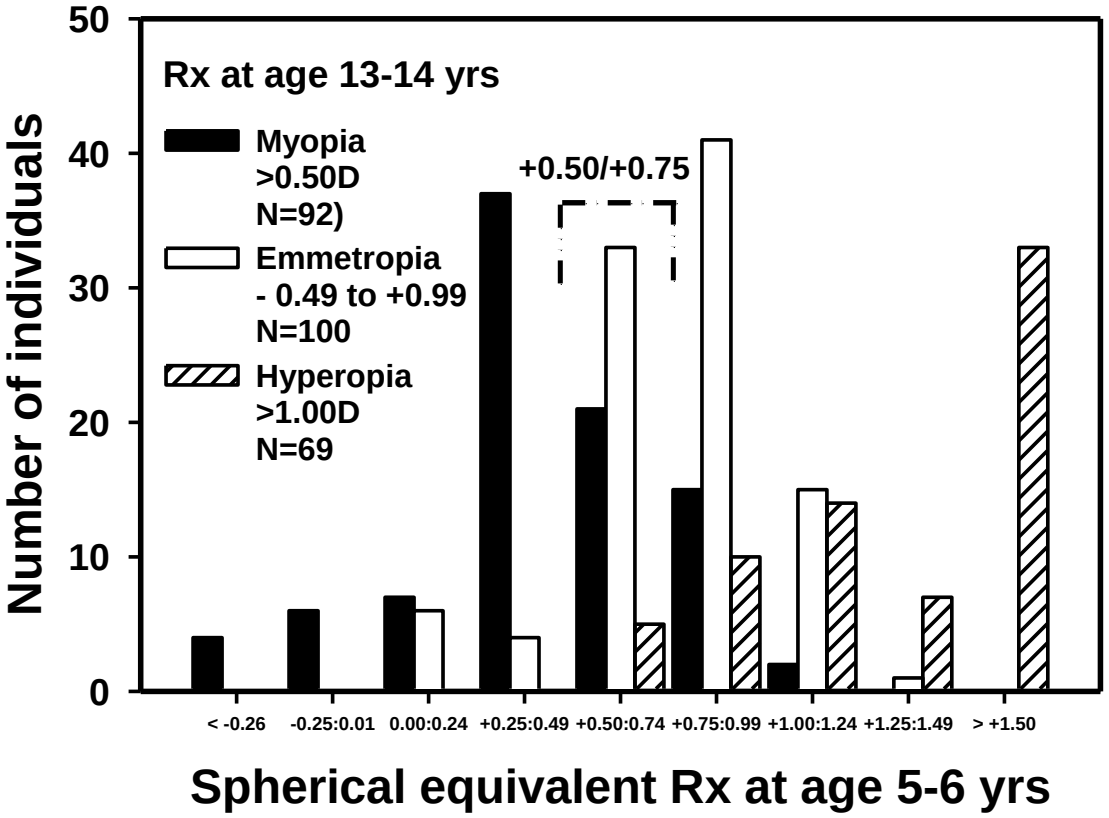

Rx at age 13-14 yrs
Myopia
>0.50D
N=92)
Emmetropia
- 0.49 to +0.99
N=100
Hyperopia
>1.00D
N=69
+0.50/+0.75
Number of individuals
50
40
30
20
10
0
< -0.26
-0.25:0.01
0.00:0.24
+0.25:0.49
+0.50:0.74
+0.75:0.99
+1.00:1.24
+1.25:1.49
> +1.50
Spherical equivalent Rx at age 5-6 yrs

Figure 4

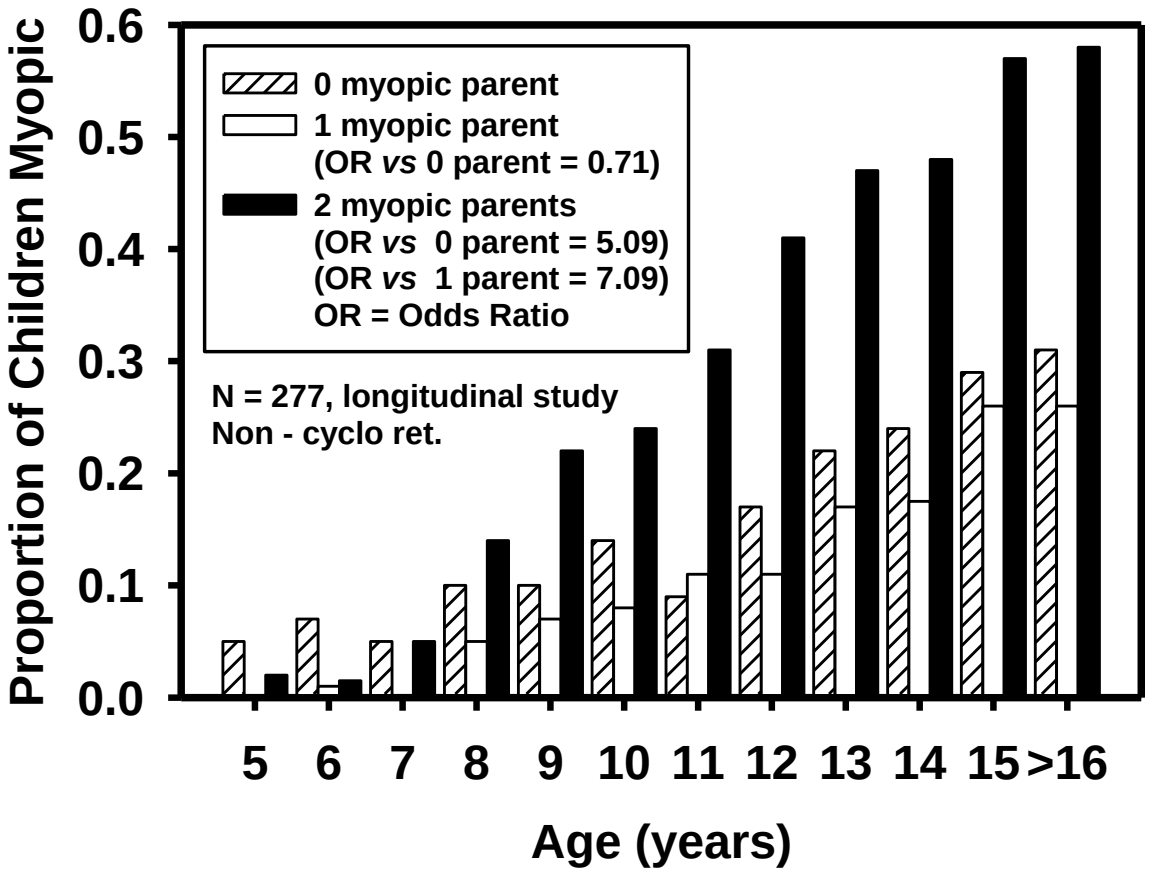

Proportion of Children Myopic
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0 myopic parent
1 myopic parent
(OR vs 0 parent = 0.71)
2 myopic parents
(OR vs 0 parent = 5.09)
(OR vs 1 parent = 7.09)
OR = Odds Ratio
N = 277, longitudinal study
Non - cyclo ret.
5 6 7 8 9 10 11 12 13 14 15 >16
Age (years)

Figure 5

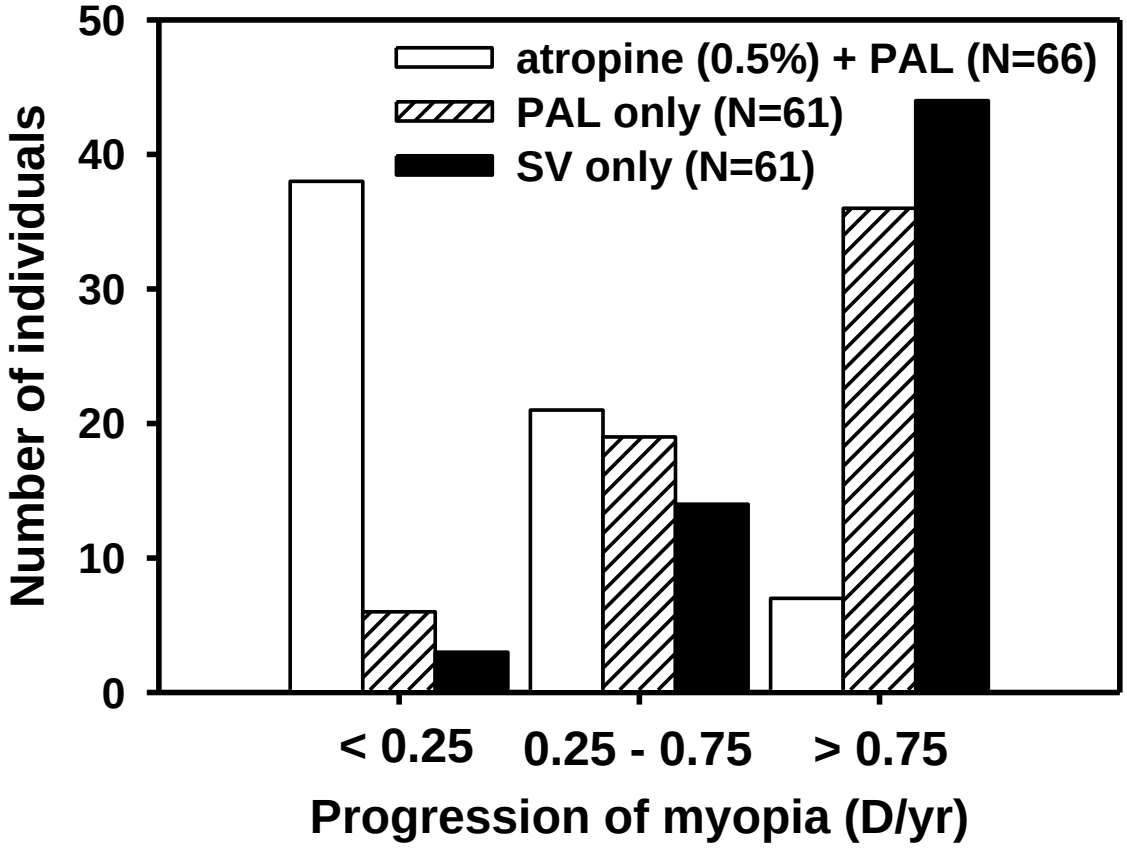
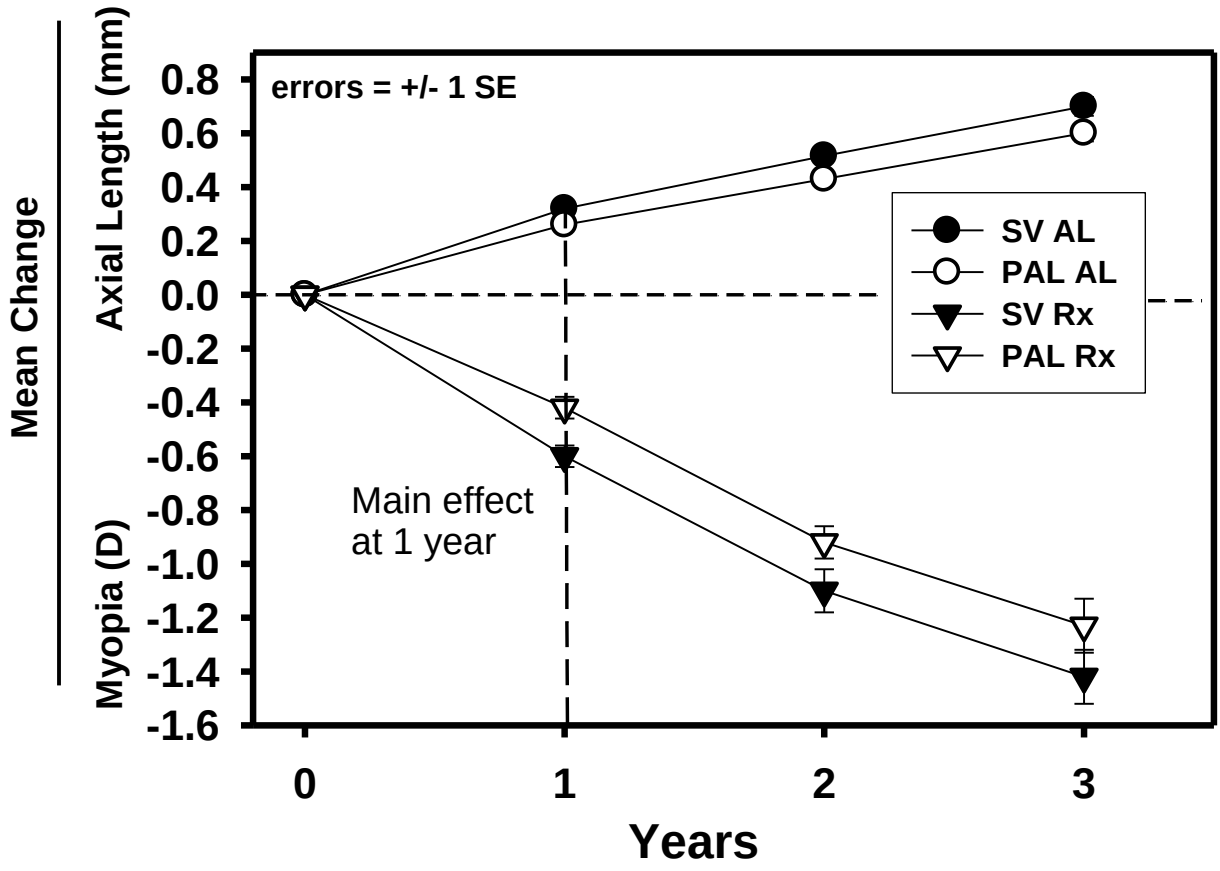

atropine (0.5%) + PAL (N=66)
PAL only (N=61)
SV only (N=61)
Number of individuals
50
40
30
20
10
0
< 0.25
0.25 - 0.75
> 0.75
Progression of myopia (D/yr)

Figure 6


Mean Change
Axial Length (mm)
Myopia (D)
errors = +/- 1 SE
0.8
0.6
0.4
0.2
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
-1.2
-1.4
-1.6
SV AL
PAL AL
SV Rx
PAL Rx
Main effect
at 1 year
0
1
2
3
Years