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How genetic is school myopia?

Ian Morgan[a,*], Kathryn Rose[b]

[a]Visual Sciences Group, Research School of Biological Sciences and Centre for Visual Science, Australian National University, GPO Box 475, Canberra City, ACT 2601, Australia
[b]Faculty of Health Sciences, School of Applied Vision Science, University of Sydney, Lidcombe, NSW 2141, Australia

Abstract

Myopia is of diverse aetiology. A small proportion of myopia is clearly familial, generally early in onset and of high level, with defined chromosomal localisations and in some cases, causal genetic mutations. However, in economically developed societies, most myopia appears during childhood, particularly during the school years. The chromosomal localisations characterised so far for high familial myopia do not seem to be relevant to school myopia. Family correlations in refractive error and axial length are consistent with a genetic contribution to variations in school myopia, but potentially confound shared genes and shared environments. High heritability values are obtained from twin studies, but rest on contestable assumptions, and require further critical analysis, particularly in view of the low heritability values obtained from parent–offspring correlations where there has been rapid environmental change between generations. Since heritability is a population-specific parameter, the values obtained on twins cannot be extrapolated to define the genetic contribution to variation in the general population. In addition, high heritability sets no limit to the potential for environmentally induced change. There is in fact strong evidence for rapid, environmentally induced change in the prevalence of myopia, associated with increased education and urbanisation. These environmental impacts have been found in all major branches of the human family, defined in modern molecular terms, with the exception of the Pacific Islanders, where the evidence is too limited to draw conclusions. The idea that populations of East Asian origin have an intrinsically higher prevalence of myopia is not supported by the very low prevalence reported for them in rural areas, and by the high prevalence of myopia reported for Indians in Singapore. A propensity to develop myopia in "myopigenic" environments thus appears to be a common human characteristic. Overall, while there may be a small genetic contribution to school myopia, detectable under conditions of low environmental variation, environmental change appears to be the major factor increasing the prevalence of myopia around the world. There is, moreover, little evidence to support the idea that individuals or populations differ in their susceptibility to environmental risk factors.

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*Corresponding author. Tel.: +61-2-61254671; fax: +61-2-61253808.
E-mail address: ian.morgan@anu.edu.au (I. Morgan).

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1. Introduction

Since it was first realised that highly educated people are more likely to be myopic than less educated people, there has been a continuing debate over whether myopia is inherited, or environmentally determined. This debate is encapsulated in two conflicting ideas; that those born to be myopic naturally gravitate to academic studies and near work occupations, or that engaging in these activities, particularly during development, causes myopia.

A comprehensive review of the literature led Curtin (1985) to the following conclusions:

> Recent investigations convincingly indicate that the development of refraction can be influenced to some extent, in that the eye seems to develop post-natally towards emmetropia. Certain environmental factors

appear capable of deranging this process and thereby produce myopia, often of high degree.

The debate around these propositions has not been settled, as the correspondence provoked by a recent clinical review (Fredrick, 2002) has demonstrated. However, the last 20 years has seen considerable clarification of some of the issues. It is now clear that myopia largely results from a failure of the eye growth control processes that normally adjust the axial length of the eye to its optical power. Excessive axial eye growth relative to the optical power of the cornea and lens is responsible for myopic refractive error, and excessive axial elongation is also responsible for myopia's longer-term pathological consequences.

It is also now clear that myopia is not one disorder, but can be classified into categories based on familial inheritance, severity, age of onset, progression and pathological consequences. This points to considerable heterogeneity in the underlying causes of the failure in control of eye growth. However, it should be cautioned that the distinctions between categories are not clear-cut. In particular, the severity of myopia does not provide a simple distinction between myopias of genetic and environmental origin.

The area of biggest concern, which will be the focus of this article, is juvenile-onset or school myopia. This category excludes early onset forms of high myopia that are often associated with clear familial inheritance (see Section 3.1), or with severe environmental distortions of visual input (see Section 5.2.3). In classical cases of school myopia, clinically significant myopic refractive errors appear over the ages 8–14, in the late primary school or early secondary school years. Further progression of myopia may occur over the next 10–15 years, up to the age of about 30, and incident cases of myopia may appear over this time. This form of myopia can affect a large proportion of the population, and is increasing dramatically in prevalence and severity in many parts of the world, in association with a decrease in the age of onset (see Sections 4.4.1 and 4.4.2).

The central issue is not whether genes are involved in the development of school myopia. Eye growth is a biological process, involving tissues such as the retina, choroid and sclera. Gene expression, and changes in gene expression must therefore be involved, and the involvement of a range of biochemical pathways in the control of eye growth in animal models has been documented (for recent reviews see Feldkamper and Schaeffel, 2003; McBrien and Gentle, 2003; Morgan, 2003; Schaeffel et al., 2003). However, this only establishes that there is a biological basis for a contribution of genetic variation to refractive error. The crucial question is to what extent do genetic differences actually contribute to variations in refractive status in humans. We will consider three major questions:

- To what extent does genetic variation contribute to individual differences in eye length and refractive error?
- To what extent does genetic variation between populations contribute to different prevalences in myopia in different populations in different parts of the world?
- Is the increasing prevalence of myopia seen in many parts of the world due primarily to environmental change?

2. Emmetropisation—a developmental process for matching eye length to optical power

Significant genetic contributions to eye size might be expected, in view of the abundant evidence for genetic contributions to growth processes which result, for example, in variations in height both within and between populations (Silventoinen et al., 2000; Silventoinen, 2003; Wu et al., 2003). However, the impact of differences in eye size on refractive error could be minimised due to emmetropisation—the process of eye development in both humans and other animals that involves an active matching of the axial length of the eye to the optical power of the cornea and lens (for review see Wildsoet, 1997). Emmetropisation should act to control eye growth and prevent the development of myopia, irrespective of other factors affecting eye growth, and thus could limit the impact of genetic variation on refractive error.

Normally, eye development proceeds from neonatal hypermetropia towards emmetropia, rapidly within the first year and then more slowly over most of the developmental period in humans (Gwiazda et al., 1993). However, it can be disrupted by environmental factors. In animal models, excessive axial elongation can be induced by lowering image contrast with diffusers placed over the eye (Sherman et al., 1977; Wiesel and Raviola, 1977; Wallman et al., 1978). The extreme plasticity of eye growth in experimental animals during development is also demonstrated by the compensatory growth responses induced by fitting positive and negative lenses, which slow and speed up eye growth respectively (Schaeffel et al., 1990; Irving et al., 1991, 1992, 1995; Schaeffel and Howland, 1991). These results suggest that eye growth in humans may be vulnerable to extreme environmental perturbation until growth ceases, and there is considerable evidence that this is the case (see Section 5.2.3). There is also considerable evidence that more subtle environmental variations also affect the process of emmetropisation (see Section 5.1).

The existence of emmetropisation raises two important issues. The first is whether there is genetic variation in the effectiveness of emmetropisation which could result in variations in refractive error. The second is whether there are differences in the sensitivity of emmetropisation to environmental impacts.

It is also possible that the term emmetropisation is misleading. Perhaps "emmetropisation" is a mechanism for adjusting eye size to the predominant plane of focus that is experienced during development, rather than a process aimed at achieving emmetropia per se. If this is the case, then it is possible that growth control is working correctly in producing myopia, and that the problem lies with the environmental exposures which lead the "emmetropisation" mechanism to produce an aberrant result.

3. Evidence for genetic determination of myopia and eye length

Evidence for genetic determination of biological characteristics comes in the first instance from studies of familial inheritance of those characteristics. This is usually followed by the search for chromosomal localisation and ultimately molecular characterisation of the gene or genes involved.

3.1. Genetically determined high myopia

There are a large number of clearly inherited syndromes, in which myopia is one of a complex of symptoms, where the underlying genetic defect has been identified. These include Marfan (Dietz et al., 1991), Weill–Marchesani (Faivre et al., 2003b), Stickler (Knowlton et al., 1989; Brunner et al., 1994) and Knobloch (Sertie et al., 2000) syndromes, as well as two forms of congenital stationary night blindness (Bech-Hansen et al., 1998; Pusch et al., 2000). Most of these are characterised by congenital or early onset high myopia, in association with a range of other abnormalities.

These syndromes include diseases based on characterised mutations related to connective tissue components, including a range of mutations in a variety of forms of collagen, as well as retinal structure and information processing (Table 1). Considerable genetic heterogeneity in the syndromes, sometimes associated with phenotypic variation, has been reported (Pulkkinen et al., 1990; Boycott et al., 2001; Suzuki et al., 2002; Faivre et al., 2003a; Biggin et al., 2004; Menzel et al., 2004).

Several chromosomal localisations for inherited non-syndromic high myopia have also been reported in genome-wide scans (Table 1). So far, specific genes associated with these conditions have not been identified. Similar localisations has been reported in East Asia (Lam et al., 2003b), but the localisations reported so far do not account for all cases of inherited non-syndromic high myopia in either Caucasian or East Asian populations. Thus there appears to be considerable genetic heterogeneity, even for this restricted non-syndromic phenotype. Candidate gene approaches to familial high myopia have also been reported, with positive results in relation to TGFβ (Lam et al., 2003a) and negative results in relation to TIGR (Leung et al., 2000).

Collectively, these syndromes and inherited non-syndromic high myopia account for only a few, generally highly myopic individuals in the population. These diseases and mutations will not be reviewed in

Table 1
Chromosomal localisations for non-syndromic autosomal dominant high myopia and some identified forms of syndromic high myopia

Non-syndromic autosomal dominant high myopia Chromosomal localisation			Reference
Between D18S59 and D18S11 on 18p11.31			Young et al. (1998b)
Between D18S63 and D18S52 on 18p11.31			Young et al. (2001)
Between D12S1684 and D12S1605 on 12q21–23			Young et al. (1998a)
Between D17S787 and D17S1811 on 17q21–22			Paluru et al. (2003)
Between D7S798 and the telomere on 7q36			Naiglin et al. (2002)
Identified forms of syndromic high myopia Syndrome	Locus	Gene	Reference
Marfan	15q15–q21.1	Fibrillin	Dietz et al. (1991)
Weill–Marchesani	15q15–q21.1	Fibrillin	Faivre et al. (2003b)
Stickler type1	12q13.1–q13.3	Collagen 2A1	Knowlton et al. (1989)
Stickler type2	6p21.3–p22.3	Collagen 11A2	Brunner et al. (1994)
Ehlers–Danlos type 4	2q24.3–q31	Collagen 3A1	Tiller et al. (1994)
Knobloch	21q22.3	Collagen18a1	Sertie et al. (2000)
Congential stationary night blindness 1	Xp11.4	Retinal nyctalopin	Pusch et al. (2000)
Congenital stationary night blindness 2	Xp11.23	Retinal Ca^{++} channelα1F	Bech-Hansen et al. (1998)

detail here, since they are apparently of little relevance to school myopia (Mutti et al., 2002b; Ibay et al., 2004), although they do demonstrate that myopia can result from mutations in proteins in specific biochemical pathways. The mutations detected will therefore provide information about some of the important pathways in the regulation of eye growth, complementing the dissection of the pathways that control eye growth that is currently being carried out in animal studies. They may also provide information about sites for pharmacological intervention designed to prevent the development of school myopia, even if school myopia does not result from genetic defects in those pathways.

Attempts to define genes associated with non-syndromic mild/moderate or common myopia are more limited. Using enrolment criteria designed to preferentially select families with a dominant mode of inheritance of a fairly high-penetrance susceptibility gene, Stambolian et al. (2004) found evidence of maximum linkage at marker D22S685 on chromosome 22q12.3, although the peak was broad. Weaker linkage was also found on chromosome 14q and even weaker linkage at 4q22-q28, 8q22.2, 10q22, 11q23, 13q22, 14q32 and 17qter.

3.2. Family correlations in school myopia

While family patterns of inheritance are clear in familial high myopia, there are also significant family correlations in refractive error in school myopia. In a large number of studies, children with myopic parents have been shown to be more likely to be myopic than those without myopic parents (see, for example, Ashton, 1985b; Goss et al., 1988; Mutti and Zadnik, 1995; Zadnik, 1997; Pacella et al., 1999; Wu and Edwards, 1999; Guggenheim et al., 2000; Saw et al., 2001b; Mutti et al., 2002a). Having two myopic parents generally poses a greater risk than one. These correlations are well-established in populations of both East Asian and Caucasian origin.

While these correlations are consistent with a genetic basis for myopia, they do not establish it. Correlations in refractive error between parents and their children, and heritability values calculated from those correlations, can reflect shared environments, as well as shared genes. Where commitment to education is part of family and community culture, this could result in high correlations between parents and children, without, at the limit, any role for shared genes.

Conversely, where there are major differences in the environments in which parents and their children grow up, as was the case with the Inuit (Young et al., 1969; Morgan et al., 1975; Alsbirk, 1979) during the process of acculturation, parent–children correlations, and the heritability values calculated from them, can become quite low (Guggenheim et al., 2000; Rose et al., 2002) (Fig. 1).

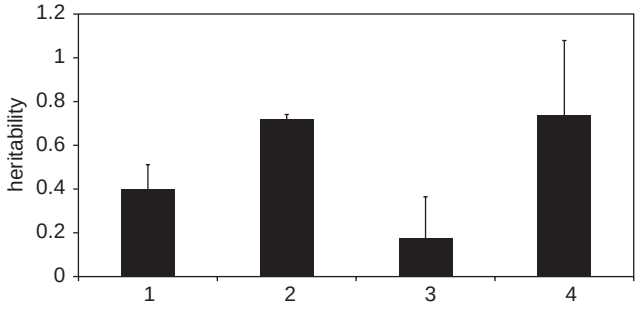

Fig. 1. Mean heritability calculated from correlations in refractive error from parent–offspring correlations and sib–sib correlations, under relatively stable or rapidly changing social environments. Error bars show the standard deviations.
Data are taken from Table 1 of Guggenheim et al. (2000), derived from the original sources cited below:

1. Parent–offspring; stable social environments (Sorsby et al., 1966; Keller, 1973; Hegmann et al., 1974; Ashton, 1985b).
2. Sib–sib; stable social environments (Sorsby et al., 1966; Ashton, 1985b).
3. Parent–offspring; rapid intergenerational change (Nakajima, 1968; Nakajima et al., 1968; Young et al., 1969; Young and Leary, 1972; Alsbirk, 1979; Johnson et al., 1979).
4. Sib–sib; rapid intergenerational change (Young et al., 1969; Alsbirk, 1979).

Note that the heritabilities calculated from sib–sib correlations are significantly higher than those calculated from parent–offspring correlations, and that the heritabilites derived from parent–offspring correlations decline in rapidly changing social environments. Both these observations suggest that the underlying correlations reflect shared environments as well as shared genes.

This also appears to be the case in parts of East Asia today. Wu and Edwards (1999) have documented a decline in the odds ratio for myopia with at least one parent myopic over three generations of Chinese, from 12.04 to 1.70 in the rural village of Ban Chau, from 5.34 to 1.34 in the provincial city of Tianjin, and from 4.38 to 1.61 in Hong Kong. A recent study of high school students in Singapore found an odds ratio for myopia with at least one parent myopic of 1.21, which was not significantly different from 1 (Quek et al., 2004).

These low recent values should be contrasted with the odds ratios reported for children in the Orinda Longitudinal Study of Myopia (1991–1996) of 3.32 for one parent myopic and 6.40 for both parents myopic, using multivariate analysis (Mutti et al., 2002a). In neither case was parental myopia directly assessed—in the Orinda Study, parents reported on their refractive status, whereas in the Singapore study, parental refractive status was reported by the high school students.

Because siblings tend to share the same environment, correlations between siblings would be expected to be

more consistent, and the available data suggest that this is the case (Fig. 1). However, the Framingham Offspring Eye Study (1996) has reported that the greater the gap in age between siblings, the lower the correlation in refractive error, with a gap of 15 years virtually eliminating the increased risk of myopia associated with having a myopic sibling. The interpretation of this result is complicated, since refractive error varies throughout life, and it is not necessarily indicative of cohort effects.

The impact of major environmental variation on family correlations and heritability indicates that the correlations confound shared environments with shared genes. This also means that, even when environmental variation is less extreme, the basic correlations are likely to be affected by shared environmental factors, and cannot be taken as unequivocal evidence for genetic determination.

3.3. Family correlations in eye size

In an important study, Zadnik and colleagues (Zadnik et al., 1994) have shown that children with myopic parents tend to have longer eyes than their peers without myopic parents, even before they become myopic themselves. This is often quoted as evidence of genetic determination, although it has been pointed out that the analysis does not clearly establish a genetic basis, in view of the possible confounding of shared genes and environments (Chew and Ritch, 1994; Wallman, 1994), in much the same way as with family correlations in refractive error.

In their response to the original critiques, Zadnik and colleagues argued that, given the evidence that longer eyes led to myopia, it could be assumed that disruption of the normal pattern of eye growth becomes more likely as the eye enlarges. Therefore, the larger the eye initially, the greater the risk of myopia.

Myopia is indeed associated with longer eyes in population studies (for detailed references, see Chapter 2 of Curtin, 1985). However, this association appears to be due to a failure to properly match axial length to optical power, which leads to myopic eyes being longer than eyes of similar optical power that are emmetropic. Myopic eyes are therefore, on average, larger than emmetropic eyes, but emmetropia can be associated with a range of axial lengths which overlaps significantly with the range that is associated with myopia (Tron, 1940; Stentstrom, 1947; van Alphen, 1961; Sorsby et al., 1962a).

Axial length is the actively regulated variable during development, as is indicated by the normal distribution curves demonstrated for corneal radius or power, lens power and anterior chamber depth. After eliminating cases of high myopia, axial length distributions also tend to be normal. However the distribution of refractive errors is leptokurtotic and skewed, apparently due to matching of axial length to corneal power (for detailed references, see Chapter 2 of Curtin, 1985). Animal studies point strongly to axial lenth as the regulated variable (Wallman, 1990).

However, when emmetropisation is effective, axial length can be appropriately adjusted to eye size and there should be no intrinsic association between large eyes and myopia. Males generally have larger eyes than females, yet there is no consistent link between gender and refractive error (Wang et al., 1994; Saw et al., 1996, 2002b; Attebo et al., 1999; Wong et al., 2000, 2001a, b, 2003). Similarly, there is no systematic link between height and myopia. Taller people, who tend to have larger eyes (Saw et al., 2002b; Wong et al., 2001a, b), may have a lower, the same or a higher prevalence of myopia (Rosner et al., 1995; Wong et al., 2001a, b). Children with larger birth weights, head circumferences, birth lengths, or gestational ages had deeper vitreous chambers and flatter corneas, but there were no significant associations with refraction at ages 7–9 (Saw et al., 2004).

Thus there is little evidence that larger eyes are more vulnerable to disruption of growth control. This is supported by the report that parental background of myopia, which correlates with longer eyes in children, does not produce a greater sensitivity to near work (Mutti et al., 2002a), although a greater sensitivity to other environmental factors has not been excluded.

The observation that children of myopic parents have longer eyes, even before they become myopic, may therefore be important in a quite different way to that originally postulated (Zadnik et al., 1994). If this correlation is partly due to shared environments rather than shared genes, the data could suggest that the impact of environmental factors can be seen well before the onset of myopia. This, in turn, would suggest that most of the existing epidemiological studies that examine environmental risk factors may be documenting them well after the process of developing myopia is initiated.

3.4. Does parental myopia interact with environmental risk factors?

It should be noted that parental myopia or eye length are not necessarily good measures of genetic background. If we assume that myopia results from both genetic and environment factors, then some of those in the parental generation who have "myopia genes" might not be myopic because of their lack of environmental exposure, while some might be myopic due to environmental exposure without "myopia genes". This is a particular problem in those situations where environmental exposures and the prevalence of myopia are changing rapidly between generations.

Bearing this qualification in mind, there are three important issues. The first is the extent to which parental myopia is a more, or less, important risk factor than the most commonly considered environmental risk factor, near work. Both factors have been documented in almost all studies. Parental myopia has sometimes been identified as the more important factor (Zadnik and Mutti, 1998; Mutti et al., 2002a), but this is not the case in studies from Singapore where the impact of parental myopia currently appears to be quite low (Quek et al., 2004).

The second issue is whether the effect of parental myopia may be associated with, or even mediated by, a differential sensitivity to environmental risk factors. In the Orinda study, the effect of near work on myopia was not significantly different between groups of children with no, one or two myopic parents (Zadnik, 1997; Mutti et al., 2002a). In contrast, Saw and colleagues have found that the effects of increased reading are greater in those who have two myopic parents (Saw et al., 2000; Saw, 2003).

This issue clearly needs further work, for the latter observation could indicate some difference in the sensitivity of the emmetropisation process to environmental pressures, which could be of genetic origin, although complex non-genetic familial effects would be hard to exclude. In contrast, the results of Mutti, Zadnik and colleagues give little support to the idea of genetic differences in sensitivity to environmental factors (Zadnik, 1997; Mutti et al., 2002a).

The third issue is whether parental myopia expresses itself through shared myopigenic environments. In the Orinda Study, although having myopic parents had a strong effect on the prevalence of myopia, and myopes performed significantly more near-work than emmetropes ($p<0.05$) and played significantly less sport ($p<0.005$), there was little correlation ($p=0.31$) between parental myopia and dioptre-hours of near-work performed by the children, suggesting that the children of myopic parents did not inherit myopigenic environments, characterised by intense near-work and less sport. The relationship between parental myopia and myopigenic environments needs to be tested in other studies, since, if the lack of correlation between parental myopia and myopigenic environments is confirmed, it will weaken the otherwise strong case for a role for shared environmental effects.

3.5. Twin studies and heritability

Correlations in refractive error between monozygotic twins are high, and higher than those seen in dizygotic twins (Sorsby et al., 1962b; Guggenheim et al., 2000; Hammond et al., 2001; Lyhne et al., 2001). This result has caused considerable confusion, because it has generally been interpreted as demonstrating a predominant role for genetic factors. For example, in commenting on the evidence for rapid changes in the prevalence of myopia in Eskimo communities during the settlement process, Sorsby (Sorsby and Young, 1970) stated that:

> The concordance shown in the substantial series of studies now available on uniovular twins have all without exception established as cumulative, direct and incontrovertible evidence that refraction is genetically determined.

However, twin studies do not provide a definitive way of separating the effects of shared genes and shared environments. When twin data on refractive error are analysed using correlational path models, the results are compatible with standard additive genetic correlations for monozygotic and dizygotic twins, using the assumption that the correlation in environments within monozygotic and dizygotic twin pairs is absolute (Table 2). However, equally good, and possibly better fits to the data could be obtained using different assumptions (Wilson, 1982).

Table 2
Heritability estimates for myopia from twin studies

Reference	Broad heritability
Sorsby et al. (1962b)	0.87
Nakajima (1968)	0.83
Nakajima et al. (1968)	0.73
Kimura (1965)	0.80
Hu (1981)	0.61
Lin and Chen (1987)	0.25
Teikari et al. (1991)	0.58
Angi et al. (1993)	0.11
Hammond et al. (2001)	0.84–0.86
	0.90 (myopia, binary trait)
	0.89 (hyperopia, binary trait)
Lyhne et al. (2001)	0.91

The data are derived from Table 2 of Guggenheim (Guggenheim et al., 2000), with the addition of more recent references.

The common environment assumption is not always valid, and needs to be critically tested (Hopper, 1992, 1993, 2000). One way of approaching this problem is to look at refractive error in separated twins. One very small study, carried out as a side-project for a larger study of psychiatric disorders, has reported that refractions were not different in separated twins (Juel-Nielsen, 1964).

Reports on the impact of discordant behaviours in twins are contradictory. One study reported that different study habits had little effect on correlations in twins (Jancke and Holste, 1941), but another reported that discordant reading habits significantly lowered the correlations in refractive error in both monozygotic and dizygotic twins, although monozygotic twins were always more similar than dizygotic (Chen et al., 1985). Lyhne et al. (2001) found that dizygotic twins were more

discordant than monozygotic twins in years of education, and also found evidence for gene–environment interactions. Given the strong effects of education on the prevalence of myopia (see Section 5.1.1), examination of correlation in length and outcomes of education could be usefully included in future twin studies.

There are other indications of environmental effects, such as the generally lower correlations for non-twin siblings and for parent–offspring than for dizygotic twins (Sorsby et al., 1966), which would not be expected from a simple additive genetic model where dizygotic twins, non-twin sibling pairs and parents and offspring have similar levels of shared genes. In addition, parent–offspring correlations in refractive error decline rapidly when there are major environmental differences between the generations (Guggenheim et al., 2000; Rose et al., 2002; and Fig. 1), and correlations between siblings decline with an increasing age gap (Framingham Offspring Eye Study, 1996). A early attempt at more rigorous analysis (Ashton, 1985b) excluded major gene effects, and did not favour polygenic models. Instead, it suggested that shared environmental effects were of major importance.

Thus, it is clear that more rigorous analysis of the high heritability values obtained in twin studies is required. More sophisticated design and analytical approaches, which can take account of a wider range of family relationships, shared environmental factors, interactions, covariation, non-random mating, and a range of other factors are now available (see, for example Harrap et al., 2000). Population-based twin registers, which avoid problems associated with attracting only twins who have maintained close contact, are also available (Boomsma et al., 2002). These more systematic approaches need to be applied to the analysis of refractive error, to determine if the assumption of a major contribution of genetic variation to variations in refractive error stands up to more rigorous testing.

Nevertheless, the correlations and heritability values calculated in twin studies on refractive error are high. If some or all of the correlations are due to shared genes, then dizygotic twins become an extremely useful population for carrying out genome-wide scans to localise and characterise the genes involved, precisely because the impact of environmental variation is minimised. Hammond et al. (2004) has used this approach to obtain evidence of linkage on chromosome 11p13, 3q26, 8p23 and 4q12. Pax-6 lies under the linkage peak on chromosome 11, but there are other candidate genes that are close to that region, and tests for association have so far not confirmed a role for Pax-6.

3.6. Heritability is a population-specific parameter

Even if more rigorous testing validates the assumptions on which the high heritability values have been calculated in twin studies, these values cannot be readily extrapolated to the general population. Twin studies tend to underestimate the importance of environmental factors, because the range of environmental variation between twins within pairs is likely to be much more limited than the range of variations between individuals and families present in society as a whole. To take just one relevant example, it may be rare to find one twin who has completed tertiary education while the other has dropped out of secondary school, yet this range of variation is common in society between individuals. This problem is exacerbated if discordant outliers are excluded from the analysis without a sound justification in terms of suspected aetiology, or if twins are recruited in ways that tend to select for those who have shared environments.

More generally, there is a common, but incorrect assumption that a heritability value specifies the contribution of genetic factors to variation in the characteristic in all circumstances. However, these values are specific to the population studied, and cannot be assumed to apply in other circumstances. For simple mathematical reasons, a high heritability calculated in circumstances of low environmental variation will inevitably drop, if relevant environmental variation increases.

Heritability is therefore not an invariant value associated with a phenotypic characteristic—in this case refractive error. Thus, there is no implication from a high heritability in twin studies that the phenotypic characteristic is under tight and invariant genetic control. There is therefore no incompatibility between high correlations, high heritability, and rapid environmental change of the kind documented in the following sections.

Height is a well-known example of a characteristic with relatively high heritability, where there has been a consistent trend of change across successive generations, probably associated with increased nutrition (Silventoinen et al., 2000; Silventoinen, 2003; Wu et al., 2003). In this case, the role of genetic background has been preserved, in that short parents tend to have short children, and tall parents tend to have tall children, but all children tend to be taller than their parents. This sort of pattern may also be seen for eye size, but emmetropisation appears to be able, under normal circumstances, to adjust the axial length to the changed optical power of the eye. Only when there is change in other environmental factors, which disrupt emmetropisation, is there likely to be an overall change in refraction.

3.7. Conclusion

While there is evidence for inherited high myopia, both as myopia associated with other syndromes, and as

non-syndromic high myopia, these forms of myopia only account for a very small percentage of total myopia. They are thus distinct from juvenile-onset myopia, and genetic analyses have so far shown no association between the mutations associated with inherited high myopia and school myopia.

Most of the evidence on school myopia, which is largely based on within-family correlations in refractive status, potentially confounds shared environments with shared genes. Twin studies are susceptible to such confounding, and calculation of heritability depends critically on the assumption that the correlation of environments for both dizygotic and monozygotic twin pairs is complete. Significant effects of shared environments on educational attainment have been reported in some twin studies (Miller et al., 2001), and educational attainment appears to be associated with refractive error (see Section 5.1.1). Nevertheless, the high heritability values calculated in twin studies are consistent with the idea that there may be a genetic contribution to refractive error, which can be seen when environmental variation is low. Genome wide scans on twins may therefore provide a useful paradigm for elucidating any genes involved.

However, twin, and other family studies, will tend to underestimate the impact of environmental variation on refractive error in the population as a whole, because of the limited environmental variation seen within twin pairs. There is evidence in the data from parent–offspring correlations, sibling correlations and twin studies that increased environmental variation reduces correlations and hence heritability estimates. Moreover, the high heritability values reported from twin studies do not mean that environmental factors are ineffective, but are quite consistent with rapid environmentally induced change.

Overall, the evidence points to problems with emmetropisation as the cause of school myopia. But there is little convincing evidence that the failure to achieve emmetropia is predominantly genetic in origin. In many cases, growth control may not actually be failing, but may be producing incorrect responses as a result of abnormal visual environments—that may be inherited through family structures, rather than genes.

4. Evidence for environmental factors in the development of school myopia

In contrast to the limited evidence for genetic determination of refractive error, there is considerable evidence of the importance of environmental factors. The first set of evidence comes from studies that have shown that the prevalence of myopia and high myopia is changing rapidly, at least in some parts of the world.

4.1. Issues in study design

There are considerable problems in interpreting the evidence available on the prevalence of myopia. There are significant methodological differences between studies, as well as differences in the definition of myopia. In addition, there are few genuinely longitudinal studies, with most of the available data being cross-sectional.

Many of the cross-sectional studies show higher prevalences of myopia in younger adult cohorts (with later birth dates). However, changes in refractive error occur throughout life (Slataper, 1950). Specifically, refractive measures shift in a myopic direction from the early childhood years until somewhat beyond adolescence, with the potential for some continuing development in adult life. A hypermetropic shift takes place roughly over the ages 40–60, and later still, there is a myopic shift (Lee et al., 1999, 2001, 2002; Guzowski et al., 2003). The later myopic shifts can be earlier in onset in developing countries, apparently due to an association with unoperated cataract.

An additional complexity is that some aspects of development, such as age of menarche, are changing, so the precise timing of developmental events may shift between different birth cohorts. Furthermore, in some countries in East Asia, where the prevalence of myopia is increasing, myopia is appearing much earlier (see below). Thus, details of the age norms are probably specific to particular populations in particular environments at particular times, although the general trends are likely to be reasonably constant.

The changes in refractive error in adults can be considerable, and could, over a 20-year period, lead to a hypermetropic shift of around 1*D* (Table 3). Shifts of this magnitude could significantly alter prevalence data, and indeed the 10-year cumulative incidence of hyperopia in the Beaver Dam Eye Study in the 40- to 70-year-old group appears to be around 25% (Lee et al., 2002).

Table 3
Longitudinal estimates of hypermetropic shifts in ageing populations

Age	5-year change (BMES)	5-year change (Beaver Dam)	10-year change (Beaver Dam)
43–54		0.23 (54)	
43–59			0.54 (51)
49–54	0.41 (66)		
55–64	0.30 (72)	0.21 (51)	
60–69			−0.03 (47)
65–74	0.04 (70)	−0.07 (50)	
70+			−0.41 (50)
75+	−0.22 (61)	−0.30 (43)	

Data from the Blue Mountains Eye Study (BMES) are taken from Guzowski et al. (2003). Data from the Beaver Dam Study are taken from Lee et al. (1999, 2001, 2002).

This means that a decline in the prevalence with myopia with increasing age in cross-sectional studies cannot be taken as evidence of an increasing prevalence of myopia. Mutti and Zadnik (2000) have shown that the adult hypermetropic shifts in several studies in the United States are similar across birth cohorts, using a normalisation procedure that demonstrates the similarity between studies, but obscures evidence of longitudinal changes in prevalence.

Ideally, systematic cross-sectional, population-based studies of refractive error, carried out on a longitudinal basis should be performed, so that the complexity of life-course changes in refractive error can be taken into account. There are few studies of this kind. However the available data permit some comparisons of different birth cohorts, at the same stage in their life cycle between different studies. This sort of comparison, provided that it is valid in terms of methodology, definition of refractive error, and population-basis, can provide valid evidence for or against changes in the prevalence of myopia.

Given the magnitude of the changes in refractive error with age, both during the juvenile period during which myopia develops, and in adult life, it is desirable that distributions of refractive error and the prevalence of myopia be reported for narrow age ranges. Ideally, data should be presented by year of age for periods of rapid development of myopia, as in the studies of the development of myopia in children using a common Refractive Error Study in Children protocol carried out in China (Zhao et al., 2000; He et al., 2004), Chile (Maul et al., 2000), Nepal (Pokharel et al., 2000), India (Dandona et al., 2002b; Murthy et al., 2002) and South Africa (Naidoo et al., 2003).

4.2. Definition of human populations

Studies on genetically related populations can provide considerable insight into aetiology of myopia, provided that the definition of populations is informed by recent progress in the molecular analysis of relatedness between populations. It should be noted that all these studies emphasise the common genetic heritage of the human species, with within-group variation far outweighing between-group variation. However, by focussing on the minor differences between groups, it is possible to produce a classification of human populations which is largely consistent with the archaeological, historical, cultural and linguistic record.

We will use the most recent classifications of human populations based on modern molecular biological analysis, particular of mitochondrial and Y-chromosome DNA (for reviews, see Cavalli-Sforza et al. (1994) and Cavalli-Sforza and Feldman, 2003) (Fig. 2). The classification of populations on a genetic and geographical basis has led to the recognition of five major

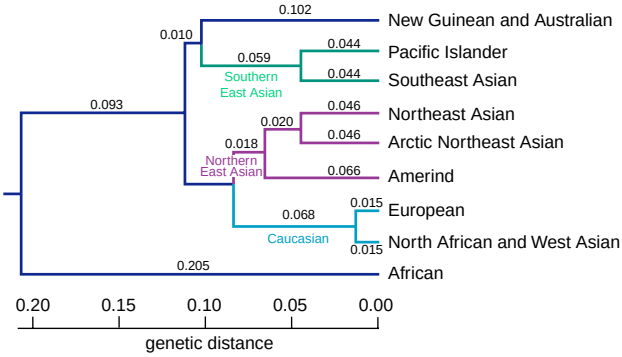

Fig. 2. Classification of human populations based on molecular differences, adapted from (Cavalli–Sforza et al., 1994; Cavalli-Sforza and Feldman, 2003). This classification is derived by focussing on the minor between-group genetic differences between human populations, and must be interpreted within the framework of the predominant pattern of shared genetic background for all human populations.

branches of the human species (African, Caucasian, Northern East Asian, Southern East Asian, and Australian and New Guinean), with more detailed sub-divisions of:

- Caucasian into European, and Non-European Caucasoid or North African/West Asian (Semitic),
- Northern East Asian into Northeast Asian, Arctic Northeast Asian and Amerind,
- Southern East Asian into Southeast Asian and Pacific Islander, which can in turn be sub-divided into Melanesian, Micronesian and Polynesian.

Each one of these population groups can be further divided into local populations, which often show coherent patterns of molecular genetic relatedness, which are to some extent consistent with linguistic and cultural/historical links.

It should be noted that some of the population affinities demonstrated with modern molecular techniques are not consistent with popularly held notions. For example, one of the most commonly recognised cultural/historical population groups, the Han Chinese, appears to be divided on genetic grounds into two groups, with north Chinese having greater genetic affinities with Japanese, Koreans and Tibetans, and ultimately with Caucasians, while south Chinese are more closely linked to the populations of Southeast Asia and the Pacific Islands (for a detailed analysis of the data see Cavalli-Sforza et al., 1994). While this view has been challenged (Ding et al., 2000), it still appears to be essentially valid (Karafet et al., 2001), and the strong historical, cultural and political links between the populations of north and south China should not obscure the different genetic backgrounds of the populations (Yao et al., 2002).

Table 4
Prevalence of myopia in 6- to 7-year-old children

Country	Locality	Year	Age	Prevalence (%)	Cut-off	Method	Reference
Japan	Nara, urban	1984	6	4	$\leqslant -0.5D$	Non-cycloplegic autorefraction	Matsumura and Hirai (1999)
Japan	Nara, urban	1996	6	4	$\leqslant -0.5D$	Non-cycloplegic autorefraction	Matsumura and Hirai (1999)
Nepal	Mechi zone, rural	1998	6	<1	$\leqslant -0.5D$	Cycloplegic autorefraction	Pokharel et al. (2000)
China	Xiamen, rural	1998	6–7	3.9	$\leqslant -0.5D$	Cycloplegic autorefraction	Zhan et al. (2000)
China	Xiamen, urban	1998	6–7	9.1	$\leqslant -0.5D$	Cycloplegic autorefraction	Zhan et al. (2000)
China	Shunyi, semi-rural	1988–1998	6	0–2	$\leqslant -0.5D$	Cycloplegic autorefraction	Zhao et al. (2000)
China	Guangzhou, urban	2003–2003	6	2.7–5.9	$\leqslant -0.5D$	Cycloplegic retinoscopy and autorefraction	He et al. (2004)
Taiwan	Diverse	1983	7	5.8	$\leqslant -0.25D$	Cycloplegic autorefraction	Lin et al. (2004)
Taiwan	Diverse	1986	7	3.0	$\leqslant -0.25D$	Cycloplegic autorefraction	Lin et al. (1988a)
Taiwan	Diverse	1990	7	5.3	$\leqslant -0.25D$	Cycloplegic autorefraction	Lin et al. (2004)
Taiwan	Diverse	1995	7	12.1	$\leqslant -0.25D$	Cycloplegic autorefraction	Lin et al. (1996)
Taiwan	Diverse	2000	7	20.2	$\leqslant -0.25D$	Cycloplegic autorefraction	Lin et al. (2001)
Hong Kong	Sha Tin, urban	1991	7	11	$\leqslant -0.5D$	Non-cycloplegic retinoscopy	Edwards (1999)
Hong Kong	Urban	1991	6–7	28	$\leqslant -0.5D$	Non-cycloplegic retinoscopy	Lam and Goh (1991)
Vietnam	Thai Nguyen, rural	2003	6–7	5.2	$\leqslant -0.5D$	Cycloplegic autorefraction	Unpublished
Vietnam	Thai Nguyen, urban	2003	6–7	11.1	$\leqslant -0.5D$	Cycloplegic autorefraction	Unpublished
Singapore	Urban	1998	6–7	12.3	$\leqslant -0.5D$	Cycloplegic autorefraction	Zhan et al. (2000)
Singapore	Urban	1999	7	27.8	$\leqslant -0.5D$	Cycloplegic autorefraction	Chua et al. (2000)
India	Andhra Pradesh, rural	1997–2000	7	2.8	$\leqslant -0.5D$	Cycloplegic retinoscopy	Dandona et al. (2002b)
India	Andhra Pradesh, urban	1996–1997	7	2.9	$\leqslant -0.5D$	Cycloplegic retinoscopy	Dandona et al. (1999)
India	New Delhi, urban	2000–2001	6	5.9	$\leqslant -0.5D$	Cycloplegic autorefraction	Murthy et al. (2002)
South Africa	Durban, diverse	2002	6	1.6–4.6	$\leqslant -0.5D$	Cycloplegic autorefraction	Naidoo et al. (2003)
Australia	Sydney, urban	2003	6–7	1.5	$\leqslant -0.5D$	Cycloplegic autorefraction	Unpublished
United States	Orinda, urban, high SES	1953–1954	6–7	2–3	$\leqslant -0.5D$	Non-cycloplegic autorefraction	Blum et al. (1959)
United States	Orinda, urban, high SES	1993	6–7	4–5	$\leqslant -0.5D$	Cycloplegic autorefraction	Zadnik (1997)
Canada	Province wide	1998	6	6	$<-0.25D$	Non-cycloplegic retinoscopy	Robinson (1999)
Chile	Santiago, urban	1998	6–7	5	$\leqslant -0.5D$	Cycloplegic autorefraction	Maul et al. (2000)

4.3. Comparative data on the prevalence of myopia

Bearing these qualifications in mind, we have summarised the evidence on the prevalence of myopia for four important age groups, 6–7 (Table 4), 11–13 (Table 5), 15–24 (Table 6) and 40–49 (Table 7), where there are significant amounts of comparative data. We have largely restricted our

Table 5
Prevalence of myopia in 11- to 13-year-old children

Country	Locality	Year	Age	Prevalence (%)	Cut-off	Method	Reference
Japan	Nara, urban	1984	12	39	$\leqslant -0.5D$	Non-cycloplegic autorefraction	Matsumura and Hirai (1999)
Japan	Nara, urban	1996	12	59	$\leqslant -0.5D$	Non-cycloplegic autorefraction	Matsumura and Hirai (1999)
Nepal	Mechi zone, rural	1998	11–13	2	$\leqslant -0.5D$	Cycloplegic autorefraction	Pokharel et al. (2000)
China	Shunyi, semi-rural	1998	12	18	$\leqslant -0.5D$	Cycloplegic retinoscopy	Zhao et al. (2000)
China	Guangzhou, urban	2002–2003	12	45.6–49.7	$\leqslant -0.5D$	Cycloplegic retinoscopy and autorefraction	He et al. (2004)
Taiwan	Diverse	1983	12	36.7	$\leqslant -0.25D$	Cycloplegic autorefraction	Lin et al. (2004)
Taiwan	Diverse	1986	12	29.0	$\leqslant -0.25D$	Cycloplegic autorefraction	Lin et al. (1988a)
Taiwan	Diverse	1990	12	39.1	$\leqslant -0.25D$	Cycloplegic autorefraction	Lin et al. (2004)
Taiwan	Diverse	1995	12	55.4	$\leqslant -0.25D$	Cycloplegic autorefraction	Lin et al. (1999)
Taiwan	Diverse	2000	12	60.7	$\leqslant -0.25D$	Cycloplegic autorefraction	Lin et al. (2001)
Hong Kong	Urban	1991	13	53	$\leqslant -0.5D$	Non-cycloplegic autorefraction	Lam and Goh (1991)
Hong Kong	Urban	2001	13	83	$\leqslant -0.25D$?	Subjective	Lam et al. (2004)
Vietnam	Thai Nguyen, rural	2003	12–13	8.8	$\leqslant -0.5D$	Cycloplegic autorefraction	Unpublished
Vietnam	Thai Nguyen, urban	2003	12–13	26.3	$\leqslant -0.5D$	Cycloplegic autorefraction	Unpublished
India	Andhra Pradesh, urban	1996–1997	12	10	$\leqslant -0.5D$	Cycloplegic autorefraction	Dandona et al. (1999)
India	Andhra Pradesh, rural	1997–2000	12	4.8	$\leqslant -0.5D$	Cycloplegic autorefraction	Dandona et al. (2002b)
India	New Delhi, urban	2000–2001	11–13	9.9–10.6	$\leqslant -0.5D$	Cycloplegic autorefraction	Murthy et al. (2002)
South Africa	Durban region, diverse	2002	11–13	4	$\leqslant -0.5D$	Cycloplegic autorefraction	Naidoo et al. (2003)
Finland	Rural	1980	11–12	7.2	$\leqslant -0.5D$	Cycloplegic Retinoscopy	Laatikainen and Erkkila (1980)
Sweden	Goteborg school district	2000	12–13	49.7	$\leqslant -0.5D$	Cycloplegic autorefraction	Villarreal et al. (2000)
United States	Orinda, high SES community	1953–1954	12	12.3	$\leqslant -0.5D$	Non-cylcoplegic retinoscopy	Blum et al. (1959)
United States	Orinda, high SES community	1993	12	28	$\leqslant -0.5D$	Non-cycloplegic autorefraction	Zadnik (1997)
Chile	Santiago, urban	1998	12	10	$\leqslant -0.5D$	Cycloplegic autorefraction	Maul et al. (2000)

selection of data to studies that have attempted to obtain population data, rather than data on selected or self-selected population sub-groups. The tables include the cut-off used to define myopia and the methodology for determining refractive error. Within each table, we have grouped the data in terms of currently accepted population classifications (Cavalli-Sforza et al., 1994; Cavalli-Sforza and Feldman, 2003), and within these classifications, we have grouped the data in chronological order.

4.4. High and rapidly increasing prevalence of myopia in East Asia

There have been rapid increases in the prevalence of myopia in a number of countries in East Asia and in populations of East Asian origin over the past 30–40 years documented below.

4.4.1. Taiwan

In Taiwan, five three large-scale population studies (Lin et al., 1988a, 1999, 2001, 2004) have demonstrated

Table 6
Prevalence of myopia in young adults (15–24)

Country	Locality	Year	Age	Prevalence (%)	Cut-off	Method	Reference
Japan	Nara, urban	1984	17	49.3	$\leqslant -0.5D$	Non-cycloplegic autorefraction	Matsumura and Hirai (1999)
Japan	Nara, urban	1996	17	65.6	$\leqslant -0.5D$	Non-cycloplegic autorefraction	Matsumura and Hirai (1999)
Nepal	Mechi zone, rural	1998	15	2	$\leqslant -0.5D$	Cycloplegic autorefraction	Pokharel et al. (2000)
China	Shunyi, semi-rural	1998	15	55(f); 36(m)	$\leqslant -0.5D$	Cycloplegic retinoscopy	Zhao et al. (2000)
China	Guangzhou, urban	2002–2003	15	73.1–78.4	$\leqslant -0.5D$	Cycloplegic retinoscopy and autorefraction	He et al. (2004)
Hong Kong	Urban	1991	16–17	56–77	$\leqslant -0.5D$	Non-cycloplegic autorefraction	Lam and Goh (1991)
Taiwan	Diverse	1983	17	74.3	$\leqslant -0.25D$	Cycloplegic autorefraction	Lin et al. (2004)
Taiwan	Diverse	1986	17	73.5	$\leqslant -0.25D$	Cycloplegic autorefraction	Lin et al. (1988a)
Taiwan	Diverse	1990	17	70.4	$\leqslant -0.25D$	Cycloplegic autorefraction	Lin et al. (2004)
Taiwan	Diverse	1995	17	84.1	$\leqslant -0.25D$	Cycloplegic autorefraction	Lin et al. (1999)
Taiwan	Diverse	2000	17	83.2	$\leqslant -0.25D$	Cycloplegic autorefraction	Lin et al. (2001)
Singapore	Male conscripts	1974–1984	17–19	26.3	$<6/18$	Visual acuity	Tay et al. (1992)
Singapore	Male conscripts	1987–1991	17–19	43.3	$<6/18$	Visual acuity	Tay et al. (1992)
Singapore	Male conscripts, Chinese	1987–1992	17–19	48.5	$<6/18$	Visual acuity	Au Eong et al. (1993b)
Singapore	Male conscripts, Chinese	1996–1997	17–19	82.2	$\leqslant -0.5D$	Non-cycloplegic autorefraction	Wu et al. (2001)
Singapore	Male conscripts, Indian	1987–1992	17–19	30.4	$<6/18$	Visual acuity	Au Eong et al. (1993b)
Singapore	Male conscripts, Indian	1996–1997	17–19	68.8	$\leqslant -0.5D$	Non-cycloplegic autorefraction	Wu et al. (2001)
Singapore	Male conscripts, Malay	1987–1992	17–19	24.5	$<6/18$	Visual acuity	Au Eong et al. (1993b); Wu et al. (2001)
Singapore	Male conscripts, Malay	1996–1997	17–19	65.0	$\leqslant -0.5D$	Non-cycloplegic autorefraction	Wu et al. (2001)
Singapore	Year 9/10 students	2002	15+	74.2	$\leqslant -0.5D$	Non-cycloplegic autorefraction	Quek et al. (2004)
India	Andhra Pradesh, urban	1996–1997	15	10	$\leqslant -0.5D$	Cycloplegic autorefraction	Dandona et al. (1999)
India	Andhra Pradesh, rural	1997–2000	15	4.8	$\leqslant -0.5D$	Cycloplegic autorefraction	Dandona et al. (2002b)
India	New Delhi, urban	2000–2001	15	10.8	$\leqslant -0.5D$	Cycloplegic autorefraction	Murthy et al. (2002)
South Africa	Durban region, diverse	2002	15	9.6	$\leqslant -0.5D$	Cycloplegic autorefraction	Naidoo et al. (2003)
United States	Population survey	1966–1970	17	33.2	Any myopic error	Statistically inferred	Angle and Wissmann (1980)
United States	NHANES	1971–1972	18–24	27.5	Any myopic error	Indirect determination	Sperduto et al. (1983)
Australia	Sydney, urban	2001	15–18	37	$\leqslant -0.5D$	Cycloplegic autorefraction	Rose et al. (2003)
Chile	Santiago, urban	1998	15	20(m); 15(f)	$\leqslant -0.5D$	Cycloplegic autorefraction	Maul et al. (2000)

Table 7
Prevalence of myopia in middle-aged adults

Country	Location and characteristics	Year	Age	Prevalence (%)	Cut-off	Method	Reference
Japan	Obushi and Higashiura-cho, males	1997–2000	40–49	70	$\leqslant -0.5D$	Non-cycloplegic autorefraction	Shimizu et al. (2003)
Japan	Obushi and Higashiura-cho, females	1997–2000	40–49	60	$\leqslant -0.5D$	Non-cycloplegic autorefraction	Shimizu et al. (2003)
Mongolia	Hovsgol and Omnogobi, males	1995–1997	40–49	11.8	$< -0.5D$	Non-cycloplegic autorefraction	Wickremasinghe et al. (2004)
Mongolia	Hovsgol and Omnogobi, females	1995–1997	40–49	18.4	$< -0.5D$	Non-cycloplegic autorefraction	Wickremasinghe et al. (2004)
Singapore	Urban males	1997–1998	40–49	45.2	$< -0.5D$	Subjective refraction	Wong et al. (2000)
Singapore	Urban females	1997–1998	40–49	51.7	$< -0.5D$	Subjective refraction	Wong et al. (2000)
United States	Framingham, high SES	1989–1991	35–44	52	$\leqslant -1D$	Non-cycloplegic autorefraction	(1996)
United States	Framingham, high SES	1989–1991	45–54	38	$\leqslant -1D$	Non-cycloplegic autorefraction	(1996)
India	Andhra Pradesh, urban	1996–1997	40–49	17.8	$< -0.5D$	Cycloplegic retinoscopy	Dandona et al. (1999)
India	Andhra Pradesh, rural	1996–1997	40–49	18.6	$< -0.5D$	Cycloplegic retinoscopy	Dandona et al. (1999)
Australia	Sydney, urban	1992–1994	49–54	30.4(m); 21.3(f)	$< -0.5D$	Non-cycloplegic autorefraction and subjective refraction	Attebo et al. (1999)
Australia	Melbourne, state-wide	1993	40–49	23.6	$\leqslant -0.5D$	Non-cycloplegic autorefraction and subjective refraction	Wensor et al. (1999)
United States	Beaver Dam, rural	1987–1988	43–54	37.8(m); 47.5(f)	$< -0.5D$	Non-cycloplegic autorefraction and subjective refraction	Wang et al. (1994)
United States	Beaver Dam, rural females	1987–1988	43–54	47.5	$< -0.5D$	Non-cycloplegic autorefraction and subjective refraction	Wang et al. (1994)
United States	Baltimore, urban, white	1985–1988	40–49	40.9	$< -0.5D$	Subjective refraction	Katz et al. (1997)
United States	Baltimore, urban, black	1985–1988	40–49	30.7	$< -0.5D$	Subjective refraction	Katz et al. (1997)
United States	NHANES	1971–1972	35–44	24.5	Any myopic error	Non-cycloplegic refractive error	Sperduto et al. (1983)
United States	Standardised data, white		40–49	46.33(f); 36.76(m)	$\leqslant -1D$	Non-cycloplegic refractive error	Kempen et al. (2004)
United States	Standardised data, black		40–49	18.38(f); 22.52(m)	$\leqslant -1D$	Non-cycloplegic refractive error	Kempen et al. (2004)
United States	Standardised data, Hispanic		40–49	25.13(f); 21.82(m)	$\leqslant -1D$	Non-cycloplegic refractive error	Kempen et al. (2004)
Barbados	Black	1987–1992	40–49	17	$< -0.5D$	Non-cycloplegic autorefraction	Wu et al. (1999)

a continuing increase in the prevalence of myopia over a 20 year period in school-age Taiwanese children. Using a definition of myopia as any refractive error $< -0.25D$, over 80% of adolescents completing secondary schooling are now myopic, with approaching 20% in the high myopia category ($\leqslant -6D$).

At the time of the initial survey in 1988, the prevalence of myopia in school-leavers was already high. It has increased somewhat, but a more important feature of the data is the appearance of a higher prevalence of myopia in younger age groups, which implies an increasingly early onset of myopia (Fig. 3). This would be consistent with the early impact of environmental factors.

Another characteristic and important feature of the data is that there has been a systematic shift in the mean refractive error, with the distribution of refractive errors becoming broader and flatter in the more recent birth cohorts, as the prevalence of myopia has increased (Fig. 4). An important feature of the data is the increasing prevalence of high myopia ($<-6D$). This, and other changes are particularly clear in the last two surveys, which may indicate an acceleration of change over the last decade.

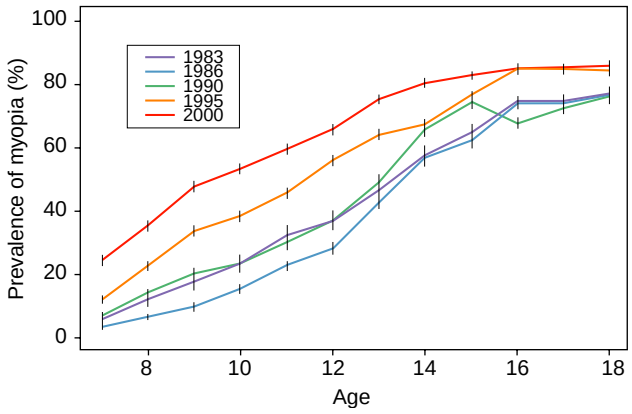

Fig. 3. Changes in prevalence of myopia ($\leqslant -0.25D$) in school-age children in Taiwan since 1983. Data taken from (Lin et al., 1988a, 1996, 1999, 2001, 2004). Note the marked changes in prevalence observed in the early school years, compared to the relatively stable prevalence of myopia in the older age groups.

There are marked differences in the prevalence of myopia between urban and rural areas, and between the Chinese and Aboriginal populations of Taiwan (Lin et al., 1988a, b; Chang et al., 1999), but myopia has been increasing in all areas and in all populations. These studies, which involve cycloplegic refractions of a large sample of Taiwanese school-children provide the strongest and most systematic longitudinal evidence for rapid increases in the prevalence of myopia. The prevalence of myopia in older adults appears to be much lower (Cheng et al., 2003).

4.4.2. *Singapore*

Data from Singapore are based on testing of male school leavers undertaking miliary service, in general at the age of 17–19 (Chew et al., 1988; Tay et al., 1992; Au Eong et al., 1993a; Saw et al., 1996; Seet et al., 2001). Early data were based on visual acuity measures rather than refraction, with the assumption that the majority of cases of low visual acuity were due to myopia. More recent data are soundly backed with cycloplegic or non-cycloplegic refractions.

The link between visual acuity and refractive error is not simple. The early data provides information on

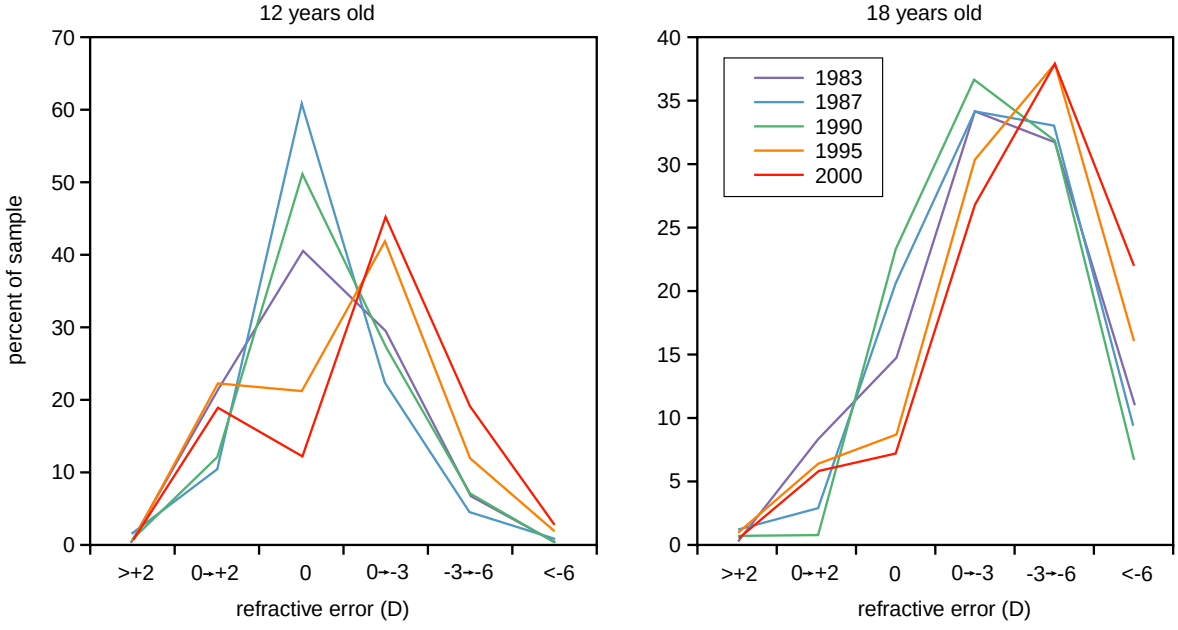

Fig. 4. Changes in distribution of refractive error in school-age children in Taiwan since 1983. Note the shift towards more myopic measurements over time, and the consequent spread in the distribution. Note that the data from the first 3 surveys is relatively similar, and that the data from the later two surveys has changed considerably. This can be seen particularly clearly in the changing prevalence of high myopia ($<-6D$) in the 18 years old. Data are taken from (Lin et al., 1988a, 1996, 1999, 2001, 2004).

visual acuity which can be improved with a pinhole test. The prevalences of myopia are plotted in Fig. 5, using two definitions of myopia; all visual acuities of $\leqslant 6/18$, or all visual acuities of $\leqslant 6/9$. High myopia was defined as visual acuities of $<6/60$.

Using these definitions, in the 1960s and 1970s, only 20–30% or 40–50% of male school leavers were myopic, depending on the visual acuity cut-off (Tay et al., 1992). This prevalence increased quite rapidly (Au Eong et al., 1993a). In more recent studies (Wu et al., 2001), myopic refractive errors were more precisely defined, with around 80% of males of school-leaving age with myopic refractive errors, and approaching 15% in the high myopia category. If a significant percentage of the low visual acuities in the earlier years were due to hyperopic errors, this would only increase the degree of the myopic shift that has occurred. This data therefore also provides strong evidence of rapid increases in prevalence, and makes studies on those of school leaving age, when refractive error has to some extent stabilised, important for international comparisons.

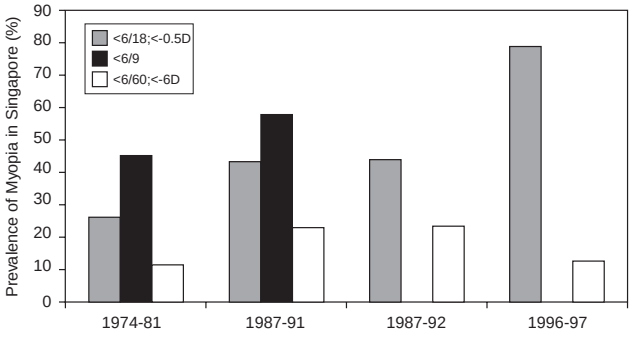

Fig. 5. Prevalence of myopia in male conscripts in Singapore (Tay et al., 1992; Au Eong et al., 1993a; Wu et al., 2001). In the early studies, myopia was defined as a visual acuity of $<6/18$ improvable with a pinhole. Data for a cut-off of $<6/9$ are also given. In the most recent study, it was defined as $<-0.5D$. High myopia was defined in the early studies as an improvable visual acuity of $<6/60$, and in the most recent study as $<-6D$. Whichever cut-off is used, the increase in the overall prevalence of myopia since 1974 is clear, and if there was substantial hyperopia or false low visual acuities due to "draft dodging" in the early data, this would only increase the change in prevalence. The early data also suggest an increase in the prevalence of high myopia based on visual acuity data, but this is not seen in the later data based on measurement of refractive error. In view of the marked changes seen in the prevalence of high myopia in Taiwan, this may indicate that the definition of high myopia as an improvable visual acuity of $<6/60$ over-estimates the prevalence compared to the $<-6D$ cut-off.

The prevalence of myopia has increased in school-leavers from the three major racial groups in Singapore, Chinese, Malays and Indians (Au Eong et al., 1993b; Wu et al., 2001) (Fig. 6). It is consistently, albeit only slightly, higher in those of Chinese, as compared to those of Indian and Malay origin. After adjusting for educational level, the differences between the racial groups are still evident, particularly in relation to the prevalence of high myopia. In those of Chinese ethnicity with tertiary education, the prevalence of high myopia approached 20%. The major difference between Indians growing up in India and Singapore is evidence of a powerful impact of environmental factors. The remaining differences between those of Chinese origin and those of Indian origin in Singapore may also indicate that there are some genetic differences. However, complete allowance for community attitudes to education, intensity of study habits, other near work activities and other aspects of life-style has not been possible.

A recent study has been carried out on Year 9 and 10 high schools students (Quek et al., 2004). The overall prevalence of myopia ($\leqslant -0.5D$) was 73.9%, with 5.7% high myopia ($\leqslant -6D$). The prevalence of myopia was higher in girls than boys, with the prevalence higher in Chinese than in Malays and Indians. There was a strong association of myopia with being in the "express educational stream", and a clear association with the academic as compared to the technical stream. There was also a clear association with reading more than 20.5 h a week, and reading at close distances. Differential computer usage had little effect, and there was an indication that use of handheld electronic devices might be negatively associated with myopia.

The Tanjong Pagar (Wong et al., 2000) study has examined Chinese adults over the age of 40 in

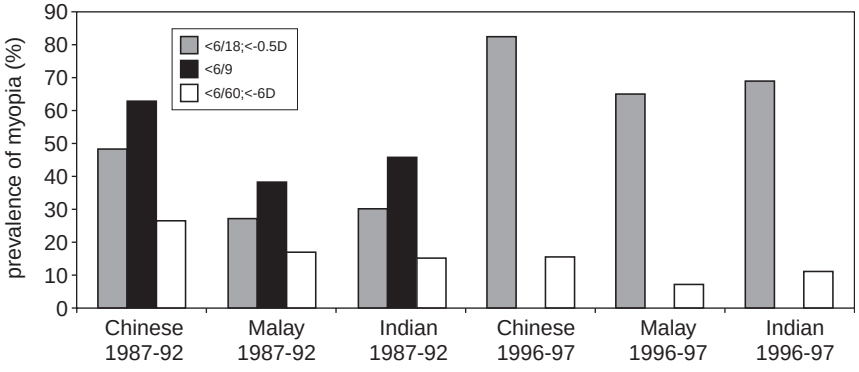

Fig. 6. Prevalence of myopia in three different population groups in Singapore; Chinese, Indians and Malays. Data taken from (Au Eong et al., 1993b) and (Wu et al., 2001). Note the similar changes in prevalence over time in the three groups.

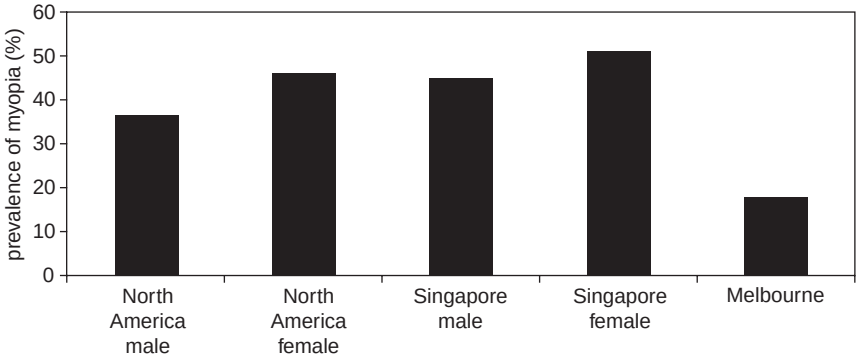

Fig. 7. Prevalence of myopia in the 40- to 49-year-old group in the North American white population (Kempen et al., 2004), in the Chinese population in Singapore (Wong et al., 2000), and in Australia (Wensor et al., 1999). Note the similarity in the prevalence in myopia in the North American white ($\leqslant -1D$) and Singaporean Chinese populations ($< -0.5D$), particularly given the different cut-offs for myopia, and the lower prevalence seen in Australia.

Singapore. The prevalence of myopia in the 40- to 49-year-old group was close to 50%, with a conservative definition of myopia as $< -1D$ (Fig. 7). The prevalence of myopia in the older age groups was lower than in younger groups.

4.4.3. China

In China, the prevalence of myopia in cities such as Guangzhou (He et al., 2004) and Hong Kong (Goh and Lam, 1994; Lam et al., 1994) is high, at levels comparable to those reported for Singapore and urban areas of Taiwan. Somewhat lower values have been reported in a population study of school-age children in Shunyi (Zhao et al., 2000, 2002), a semi-rural area on the outskirts of Beijing, and from both urban and rural areas of Xiamen (Zhan et al., 2000). Both the Shunyi and Xiamen studies were carried out on younger children, and thus the fully developed prevalence of myopia has not been documented. However, the data from Xiamen document a clear urban–rural difference in the prevalence of myopia.

The prevalence of myopia appears to have been increasing in school-age children in Hong Kong (Wu and Edwards, 1999), and cross-sectional studies on adult populations are consistent with rapid increases in prevalence (Goh and Lam, 1994; Lam et al., 1994). A more recent report indicates that the prevalence of myopia may have increased by around 25% in 13- to 15-year-old school students since 1991 (Lam et al., 2004).

Wu and Edwards (1999) have studied the prevalence of myopia across three generations in Hong Kong, Tianjin (a large provincial city close to Beijing) and a rural site, Ban Chau, near Tianjin. There were significant differences in the prevalence of myopia in the three sites, with the higher prevalences reported in the urban sites. In all sites, the prevalence of myopia increased significantly from one generation to the next. The sensitivity of the prevalence of myopia to more complex social factors is also indicated by the reported reduction in prevalence that has occurred in the generation whose education was disrupted by the Cultural Revolution (Hu, 1998).

The work of Rasmussen (1936), sometimes cited as indicating that there has been a high prevalence of myopia in China for many years, has been misinterpreted. Rasmussen did not carry out a population-based study of refractive error in China. Rather he surveyed the optical prescription records of some major westernised hospitals in China, finding that over 60% of the prescriptions were for myopic corrections. Given that the population studied was selected for clinical levels of refractive error, and for access to and willingness to use westernised facilities, these results cannot be taken as evidence of long-standing generalised high levels of myopia in China.

Despite the absence of large-scale population-based longitudinal studies of refractive error using cycloplegic refractions in China, the data suggest a long-term increase, complicated by the vast differences in economic development and educational achievements in different regions, and by political history—with high prevalences in urban areas similar to those reported from Singapore and Taiwan. It should be noted that the prevalence appears to be high in both northern and southern China, despite the evidence for population genetic differences between the two areas. Large-scale population-based studies would clearly be worthwhile, given the size of the Chinese population, and the impact on public health that a generalised high prevalence of myopia of the levels seen in Guangzhou, Hong Kong, Taiwan and Singapore would have.

4.4.4. Japan

Sato (1957) has shown that the prevalence of myopia was already increasing in school-children in Japan, especially in academically oriented classes, prior to the Second World War. This process appears to have been disrupted by changes in education policy in the lead-up

to the Second World War, and the war itself (Kamiya et al., 1985).

In more recent years, the prevalence of myopia has further increased rapidly on a population basis, from 49.3% to 65.6% in 17-year-old students over a 13 year period from 1984 to 1996 (Matsumura and Hirai, 1999). The data show a similar pattern to that observed in Taiwan, namely a spreading of the distribution of refractive errors, as refractions become more negative. However, the decrease in age of onset seen in the data from Taiwan is not seen in the Japanese data. This may be due to the less conservative cut-off used in the studies in Taiwan, and the tendency for early onset myopic refractive errors to initially cluster around low values of myopia. The prevalence of myopia appears to be significantly lower in rural areas (Watanabe et al., 1999). In adults, the prevalence of myopia in 40- to 45-year-old adults was over 60% in 1999 (Shimizu et al., 2003).

4.4.5. Vietnam

In Vietnam, the first study on the prevalence of myopia was carried out in 1964 using non-cycloplegic refraction. The prevalence rate reported for 6- to 17-year-old students was 5.2% for urban students and 1.0% for students in rural areas. By 1999, this had increased to 32% in students from Hanoi and 11.8% in rural areas. A much lower prevalence of myopia was reported in Hue at the same time. In none of the early studies was the definition of myopia specified, and cycloplegic refraction was not used. Most of the data is only available in conference reports in Vietnamese.

More recently, the prevalence of myopia in provincial urban and rural areas was estimated as 11.1% and 5.2% for 6–7 years old and 26.3% and 8.8% for 12–13 years old, using cycloplegic refraction with a definition of myopia as a refractive error of $\leqslant -0.5D$ (unpublished results).

4.4.6. Mongolia

A recent population study of adults in Mongolia reported much lower prevalences of myopia than are commonly reported in East Asian populations, with prevalences of only 11.8% in 40- to 49-year-old males and 18.4% in 40- to 49-year-old females (Wickremasinghe et al., 2004).

4.4.7. Studies on populations of Northeast Asian origin

The Inuit, and indeed all the North American native peoples, originate from population migrations out of North-east Asia in the last 10–30,000 years, and thus are genetically related to Northeast Asian populations (Cavalli-Sforza and Feldman, 2003). There is controversy over the timing and details of the migrations into the Americas, but there appear to have been at least two major migrations, of which the first primarily contributed to the populations which spread throughout the Americas, while the later migration contributed only to populations of North America (Bortolini et al., 2003).

Seminal studies on the prevalence of myopia were carried out on Inuit populations, both children and adults, where the prevalence of myopia increased spectacularly between generations as people moved into settlements (Young et al., 1969, 1971; Boniuk, 1973; Morgan et al., 1975; Alsbirk, 1979; van Rens and Arkell, 1991). All authors noted the link to acculturation and school attendance. Morgan et al. (1975) specifically noted the strong association between increased years of school attendance and increased prevalence of myopia, and the protective effects of frequent or prolonged absence from school.

These important observations were met with a strong critique of aspects of methodology (Sorsby and Young, 1970), and questioned largely on the basis that they were not consistent with the high heritability of myopia obtained from twin studies. Subsequent studies addressed these methodological problems, and the reality of these rapid changes is no longer disputed.

High and rapidly changing prevalences of myopia have also been reported in Amerindian populations in Canada, suggesting that all the Native Peoples of the American continent show sensitivity to environmental exposures (Woodruff and Samek, 1976, 1977). A high prevalence (44%) of myopia in 12–13 years old in an urban setting in Mexico (Villarreal et al., 2003) has also recently been reported. Genetic studies suggest that the dominant genetic contribution to modern Mexican populations comes from Amerindian populations, with some admixture of European and African origin (Green et al., 2000). These data suggest that sensitivity of emmetropisation to environmental change is shared by Amerindian populations with Arctic Northeast Asian and Northeast and Southeast Asian populations. Lower prevalence values have been reported in Santiago in Chile (Maul et al., 2000), but it is possible that the European genetic contribution to the population may be higher in this part of South America.

4.4.8. Conclusion

In a number of East Asian countries and populations of East Asian origin, the prevalence of myopia is high, and there is considerable evidence that there has been a 50-year trend towards increasing prevalence of myopia.

While this conclusion has been disputed (Park and Congdon, 2004), there is convincing longitudinal evidence of change for Taiwan, Singapore and Japan, and there is indicative evidence from Hong Kong, China, Vietnam and in the Native peoples of the Americas who are derived from population migrations out of North-east Asia. There are also isolated reports of significant levels of myopia in Indonesia (Saw et al., 2002b), with earlier lower levels reported from Malaysia (Garner

et al., 1990; Yeow, 1994), suggesting that the phenomenon of a high and increasing prevalence of myopia may be common to all the countries and populations of East Asia, both North and South. Given the significant population migrations out of East Asia in recent times, it is unfortunate that there are no reported studies on these immigrant groups in different environments that have controlled for place of birth and education.

4.5. The prevalence of myopia in other populations

4.5.1. The prevalence of myopia in populations of predominantly European origin

Comprehensive cross-sectional population studies have been carried out on adult populations of largely European origin in North America (Sperduto et al., 1983; Wang et al., 1994; Framingham Offspring Eye Study, 1996; Katz et al., 1997), Europe and Australia (Attebo et al., 1999; Wensor et al., 1999). In a valuable initiative, the data from several of the larger studies where the methodologies give comparable results (Baltimore Eye Study, Beaver Dam Eye Study, Proyecto VER, Rotterdam Eye Study, Blue Mountains Eye Study, Melbourne VIP, and Barbados Eye Study) have been collected, reporting against a common definition of myopia ($<-1D$) (Kempen et al., 2004).

In the most recent cohorts, the prevalence of myopia in the white population in Europe and North America is around 40–45% (Kempen et al., 2004), approaching that seen in similar birth cohorts at the same age in East Asia (Fig. 7). The prevalence of myopia was higher in the white population than in the Hispanic and the black populations.

There is considerable evidence of longitudinal increases in the prevalence of myopia in the United States. One of the strongest pieces of evidence comes from the Beaver Dam Eye Study, where changes in average refractive error of as much as $-1D$ per decade between different birth cohorts measured at the same age have been measured, with the changes appearing to be greatest in the younger birth cohorts (Lee et al., 2002). This evidence is consistent with recent reports of high prevalences of myopia, such as the prevalence of nearly 60% myopia in the Framingham Offspring Eye Study (1996) in 23- to 34-year-old cohort, using a conservative definition myopia as $<-1D$.

There is also some systematic information on myopia in school-age children in largely European populations in North America. Data from the Orinda Study suggest that over a period of 40 years, from 1953 to 1993, the prevalence of myopia in school-age children has almost doubled (Zadnik, 1997). This increase has been attributed to an increasing proportion of the population of Asian origin, however, the population data to support this conclusion has not been provided. Somewhat surprisingly, in view of the adult pattern, the CLEERE study has found higher prevalences of myopia in Hispanic and African American children than in whites, although the difference between African Americans and whites was not statistically significant (Kleinstein et al., 2003). Similarly, that the highest prevalence of hyperopia was found in white children, with less in Hispanic and even less in African American children is also unexpected.

Population data from Scandinavia give a similar picture. While older data suggest that there were not been significant changes in the prevalence of myopia over almost 100 years, more recent data suggest that there has been an increase in the prevalence of myopia (Goldschmidt, 1968, 1981, 2003). In contrast, a recent study of a population of 12- to 13-year-old Swedish students, found a prevalence of myopia of 49.7% (Villarreal et al., 2000), up from 10–15% 20 years ago (Laatikainen and Erkkila, 1980; Mantyjarvi, 1983). Since a continuing increase in the prevalence of myopia would be expected beyond the age of 12–13, the adult prevalence will be significantly higher, when these children mature, reaching levels that would be usually associated with East Asia. This is consistent with recent reports of higher than expected prevalences of myopia in young adult populations in Norway (Midelfart et al., 2002).

Contributions to the gene pools in these areas from Saame peoples (also known as Lapps), genetically an admixture of Mongoloid and Caucasoid people of roughly equal proportions, as well as from central Asian Uralic migrations to parts of Scandinavia, might contribute to these changes. However, the Goteborg school district studied by Villarreal and colleagues is likely to share the predominant genetic associations of the general Swedish population with Western Europe (for detailed analysis see Cavalli-Sforza et al., 1994), and thus provides strong evidence of a high prevalence of myopia in a population with European population genetic characteristics.

In Australia, in adult cohorts (Attebo et al., 1999; Wensor et al., 1999; Kempen et al., 2004), the prevalence of myopia appears to be lower than in North America and Europe (Fig. 7). The Blue Mountains Eye Study classified myopes into early onset (<21) and older-onset ($\geqslant 21$), finding that there was a systematic decline in the prevalence of early onset myopia in the older-age groups (Attebo et al., 1999). From data from the Melbourne Visual Impairment Project on the use of distance vision corrections at the age of 40 (Wensor et al., 1999), McCarty and Taylor (2000) estimated that there may have been a four-fold increase in the prevalence of myopia in Australia over the last century. While the data are subject both to problems with recall, and also to changing patterns of access to provision of optical corrections, the trends observed support the idea that

the prevalence of myopia has been increasing in Australia (Rose et al., 2001).

The prevalence of myopia in a self-selected population of school-age children in Australia has also been reported to be rather low (Junghans et al., 2002; Junghans and Crewther, 2003), compared to the data from North America (Zadnik, 1997). Some higher values have been reported in a more systematic population study (MacFarlane et al., 1987) and from a pilot study for the population-based Sydney Myopia Study (Rose et al., 2003). Preliminary data (see Table 4) are now available on myopia in 6–7 years old from the population-based Sydney Myopia Study of refractive error in school-children in Sydney, which will provide more definitive data in this area, including data on students of East Asian and Pacific Islander origin growing up in Sydney.

Given the predominantly European background of the major populations, the lower prevalence of myopia in Australia as compared to North America and Europe points to a considerable impact of environmental factors. The populations are not however identical in their origins, and some role for genetic differences is possible. In terms of environmental factors, there is, however, no evidence that educational pressures are less intense in Australia than in Europe and North America. Indeed, recent international comparative data suggest that educational outcomes in Australia are comparable to those in the most educationally successful European countries, and higher than those achieved in the United States (OECD, 2001; available as an e-book at www1.oecd.org/publications/e–book/9601141E.pdf). Thus, other environmental factors would seem to be implicated.

There are some common trends in the studies on populations of European origin. The population prevalence of myopia appears to have been generally low at the beginning of the 20th Century, with evidence for an increasing prevalence of myopia appearing first in the United States and Europe, and apparently even later in Australia. High prevalences have, however, been reported for highly educated sections of the population over a considerable time-period (Ware, 1813; Agnew, 1877; Tscherning, 1882; Cohn, 1886).

4.5.2. The prevalence of myopia in non-European Caucasoid (North African and West Asian or Semitic) populations

Only limited data are available on populations of North African and West Asian origin. The prevalence of myopia in Oman and Jordan (Lithander, 1999; Al-Bdour et al., 2001) has been reported to be very low, with significant urban–rural differences and effects of education. Other data have been reported from Egypt (Said et al., 1970, 1971; Gawdat, 1976) and Tunisia (Ayed et al., 2002), but do not provide up-to-date population data.

Older studies in Europe and the United States have documented somewhat higher prevalence rates in Jewish populations that in other population groups (Stephenson, 1892; Tenner, 1915; Pearson and Moul, 1928; Sourasky [later Sorsby], 1928; Sorsby, 1932). However, the impact of differential education was rarely taken into account. The admixture of European Caucasoid and Non-European Caucasoid genes in the European Jewish population has been extensively documented (Carmelli and Cavalli-Sforza, 1979; Livshits et al., 1991; Behar et al., 2004).

Large-scale studies have also been carried out in Israel. The general population shows a moderate prevalence of myopia (Hyams et al., 1977; Rosner and Belkin, 1987), but a particularly high prevalence has been reported for male Orthodox Jewish students (Berson et al., 1982; Zylbermann et al., 1993) (Fig. 8). Given the much lower prevalence of myopia in girls in Orthodox schools, Zadnik and Mutti (1998) have suggested that myopia may show genetically sex-linked characteristics. However, the lesser educational pressures on girls in Orthodox schools are also clear, and educational pressures thus remain an alternative, and less ad hoc, explanation.

4.5.3. The prevalence of myopia in Indian populations

Population-based studies on children and adults have been carried out in both northern and southern India. The prevalence of myopia is quite low in comparison to those reported from East Asia (Dandona et al., 1999, 2002a, b; Murthy et al., 2002), but there are no longitudinal data that allow for conclusions about changes in prevalence. There are, however, clear urban–rural differences. Detailed studies on the prevalence of myopia have also been carried out on Indian

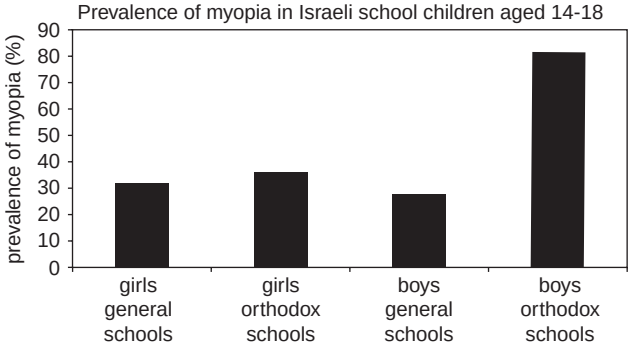

Fig. 8. Prevalence of myopia is Israeli school children aged 14–18. The prevalence of myopia is much higher in the boys attending Orthodox schools. While an explanation in terms of sex-linked myopia prevalent in the Orthodox community is possible, the known differences in intensity of study and study style provide an at least equally plausible explanation. Data taken from (Zylbermann et al., 1993).

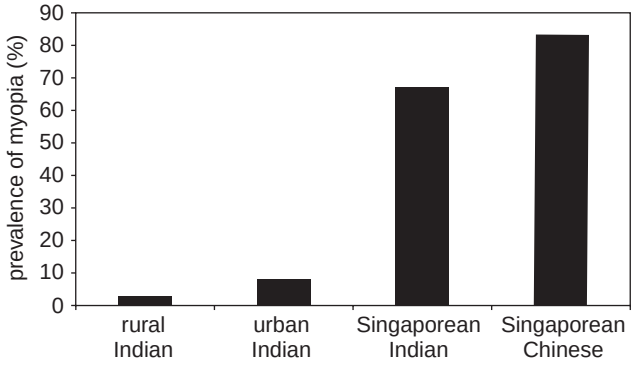

Fig. 9. Prevalence of myopia in populations of Indian origin of similar age living in India (Dandona et al., 1999, 2002a, b; Murthy et al., 2002) and Singapore (Wu et al., 2001). Note the markedly higher prevalences reported in Singapore.

populations in Singapore (Au Eong et al., 1993b; Wu et al., 2001), where the prevalence of myopia is very much higher than that reported in India (Fig. 9).

The population of India is generally regarded as Caucasian in genetic origin, although modern molecular approaches have given a more complex picture with a proto-Asian substrate, with a substantial admixture of Caucasian genetic markers that are stronger in higher castes and stronger in the north-western regions (Bamshad et al., 2001; Basu et al. 2003)., The Asian geographical location of India should not be confused with population genetic affinities with the populations of East Asia, for the genetic analysis of the origins of the Indian population indicates that Indians are not closely related to East Asians in terms of population genetics. For this reason, use of the geographic term ''Asian'' is ambiguous and confusing in relation to the aetiology of myopia, and should be avoided. In population genetic terms, the markedly higher prevalence of myopia in populations of Indian origin in Singapore compared to those reported from India suggests that there have been strong effects of living in ''East Asian'' urban environments on the prevalence of myopia in a population that is, in population genetic terms, of Caucasian origin.

4.5.4. The prevalence of myopia in African populations

Data on the prevalence of myopia from Africa is limited (Lewallen et al., 1995; Kawuma and Mayeku, 2002; Wedner et al., 2002; Naidoo et al., 2003; Av-Shalom et al., 1967), but generally suggests that the prevalence of myopia is low. There is limited data suggesting that the prevalence may be different in rural and urban areas (Lewallen et al., 1995b), and that those who are more highly educated have higher prevalences of myopia (Lewallen et al., 1995b; Wedner et al., 2002).

The values reported from studies in Africa are considerably lower than the prevalence of 30.7% for black persons aged in the Baltimore Eye Study (Katz et al., 1997) and around 20% in the predominantly black population studied in the Barbados Eye Study (Wu et al., 1999). Collectively, these data suggest an influence of education and place of residence on refractive error in populations of African origin.

4.5.5. The prevalence of myopia in indigenous Australian and New Guinean populations

There is even less systematic information on Australian and New Guinean populations, who appear to be derived from very early migrations out of Africa through Southeast Asia (Cavalli-Sforza et al., 1994; Cavalli-Sforza and Feldman, 2003).

There is no data on myopia in populations of New Guinean origin. There does, however, appear to have been a major myopic shift in the Aboriginal population of central Australia (Taylor, 1981; Taylor et al., 2003). Given that the baseline was a high level of hypermetropia, this has not yet produced an epidemic of myopia, although the mean refraction is now mildly myopic. Educational levels in these populations are still quite low, and further myopic shifts are likely as educational levels rise.

4.5.6. The prevalence of myopia in Pacific Islander populations

The Pacific Islander population group includes Melanesians, Micronesians and Polynesians. Most of the northern and eastern Pacific Islands have been settled by populations migrating out of Taiwan and parts of Southeast Asia, with an uncertain degree of admixture with Melanesian populations (Cavalli-Sforza et al., 1994; Cavalli-Sforza and Feldman, 2003).

The prevalence of myopia appears to be low in Pacific Islander populations. The reported prevalences of myopia are low in Vanuatu (Garner et al., 1985, 1988, 1990), Bougainville and the Solomon Islands (Verlee, 1968), and Fiji (Andrist and Yoton, 1986) in what are predominantly Melanesian populations, but there is no evidence of longitudinal change, or effect of education. The prevalence of myopia in the Polynesian Maori populations in New Zealand also seems to be low, although the data are old and there is no information on longitudinal changes and the effect of education (Grosvenor, 1965, 1966). Wensor et al. (1999) have reported higher values for Pacific Islanders living in Melbourne, Australia, but the population sample is far too small for definitive conclusions. There is no information on Micronesia.

It is unfortunate that the large Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) study (Kleinstein et al., 2003; Zadnik et al., 2003) is following National Institutes of Health and US Census Bureau classifications in combining East Asian and Pacific Islander populations into one group, despite the data which indicates that these populations have

similar population genetic origins, but, at present, very distinct prevalences of myopia, and probably very different patterns of education and environments. Studies on the prevalence of myopia in well-defined Pacific Islander populations living in different environments are therefore urgently required.

4.5.7. Conclusions

Where there is data which permits reasonable longitudinal comparisons, or comparisons of similar birth cohorts at the same age, there is considerable evidence that the prevalence of myopia in populations of European origin is high and increasing, particularly in North America and Europe. There is not sufficient evidence to draw conclusions for African or Pacific Islander populations, but there is clear evidence of a significant myopic shift in Australian Aboriginal populations.

4.6. Rapid changes in the prevalence of myopia are not compatible with simple genetic determinism

The rapidity of the changes that have been documented in some of these population studies, particularly those carried out in East Asia and on the Inuit in North America, is not compatible with a simple genetic determination of myopia which would require changes in gene pools, since gene pools in human populations do not change so rapidly. However, it is possible that some of these populations might have genetic characteristics that make them particularly sensitive to environmental pressures and a failure of emmetropisation in these circumstances. If this is the case, then, given the evidence for significant changes in prevalence, populations of Northeast Asian, Arctic Northeast Asian, Amerindian, Southeast Asian, Australian Aboriginal and Caucasian origin share this characteristic. The issue of population differences in susceptibility to environmental factors will be discussed in more detail later.

5. Environmental determinants of the prevalence of myopia

In the absence of sufficient information on longitudinal changes in the prevalence of myopia, evidence of the impact of environmental factors on the prevalence of myopia indicates that there is plasticity in refractive error and eye growth. Where these environmental factors are changing rapidly, it would be expected that the prevalence of myopia would change as well.

5.1. Evidence for environmental impacts on myopia

5.1.1. The effect of education

A consistent feature of studies that have examined the effect of education on the prevalence of myopia is the strong correlation between higher educational level and higher prevalence of myopia. There is evidence for an effect of educational level on the prevalence of myopia in populations of African (Lewallen et al., 1995; Wedner et al., 2002), North African and West Asian (Rosner and Belkin, 1987), European (Goldschmidt, 1968; Sperduto et al., 1983; Teasdale et al., 1988; Teasdale and Goldschmidt, 1988; Wang et al., 1994; Katz et al., 1997; Wensor et al., 1999), Northern East Asian (Shimizu et al., 2003), and Southern East Asian (Tay et al., 1992; Au Eong et al., 1993a; Wong et al., 1993, 2002) origin. An example of the correlations observed is shown in Fig. 10, which gives the prevalence of myopia in military conscripts in Singapore by educational level.

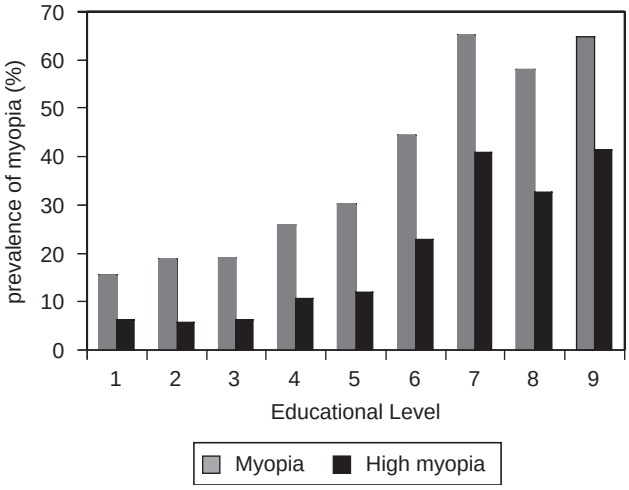

Fig. 10. Relationship between level of education and the prevalence of myopia and high myopia in male conscripts in Singapore (1987–1992). Note the increasing prevalence of myopia with higher educational level completed, and the greater increase in the prevalence of high myopia. Data taken from (Au Eong et al., 1993a).

1. No formal education.
2. Begun but not completed primary education.
3. Successfully completed 6–8 years of primary education.
4. Begun but not completed 4 years of secondary education.
5. Passed the General Certificate of Education (N Level Examination)—i.e. 4 years of secondary education.
6. Passed the General Certificate of Education (O Level Examination)—i.e. 4–5 years of secondary education.
7. Passed the General Certificate of Education (A Level Examination)—i.e. 2–3 years of pre-university education.
8. Successfully completed a 3 year diploma course.
9. Successfully completed 3–5 years of university education.

The effect of education subsumes two factors—formal years of study, and intensity of study as measured by educational outcomes at a particular level. Many studies have used years of study as a measure. However, there also appears to be a correlation between myopia and higher scores in academic tests at a given level of schooling (Grosvenor, 1970; Young et al., 1970; Ashton, 1985a; Rosner and Belkin, 1987; Teasdale et al., 1988;

Teasdale and Goldschmidt, 1988; Williams et al., 1988; Mutti et al., 2002a).

Highly educated sections of the population have shown high prevalences of myopia ever since they were first systematically studied (Ware, 1813; Agnew, 1877; Tscherning, 1882; Cohn, 1886), with clear correlations between occupational status and myopia (Tscherning, 1882; Goldschmidt, 1968). In general, higher socio-economic status is also associated with a higher prevalence of myopia. This could be explained in terms of the general association between higher socio-economic status and higher education.

Highly academic classes within schools or highly academic schools have also been shown to have high prevalences of myopia, in both European (Cohn, 1886), North American (Agnew, 1877) and East Asian (Sato, 1957) settings for many years. Currently, medical (Chow et al., 1990; Midelfart et al., 1992; Hansen et al., 1993; Lin et al., 1996; Fledelius, 2000), engineering (Kinge and Midelfart, 1994, 1999; Kinge et al., 1998, 1999, 2000) and law (Zadnik and Mutti, 1987; Loman et al., 2002) students have been reported to have high prevalences of myopia, which continue to increase after the school years.

It is clear that involvement in limited formal modern education per se does not necessarily lead to high prevalences of myopia, as the low prevalences of myopia in school children reported from Vanuatu (Garner et al., 1985, 1988, 1990) and rural areas of China (Zhan et al., 2000; Saw et al., 2001b), Vietnam (unpublished results), Taiwan (Lin et al., 1988a, 1999, 2001) and Nepal (Garner et al., 1999) indicate (Fig. 11). On the other hand, Inuit populations have shown massive increases in the prevalence of myopia within a generation (Young et al., 1969, 1971; Morgan et al., 1975; Alsbirk, 1979), associated with probably equally limited levels of engagement in schooling. These data, together with the significantly higher prevalences of myopia in North American populations of European origin and in European populations as compared to those in populations of European origin in Australia (Fig. 7), may point to major non-linearities in the interaction of educational pressures with other environmental factors.

Despite these complexities, there is also evidence that the link between educational pressures and eye growth can be quite tight. Thus, in both East Asian (Tan et al., 2000) and Caucasian (Goss and Rainey, 1998; Fulk et al., 2002) populations, within school systems, there is evidence that the rate of progression of myopia differs around the school year, with progression higher during periods of intense study and lower during long holiday periods. The consolidated data from North America and Europe show that in older cohorts, the prevalence of myopia is higher amongst males, but in younger cohorts, the prevalence is higher in females (Kempen et al., 2004). This may be related to the emergence of higher educational outcomes for girls that has taken place more recently in Western societies.

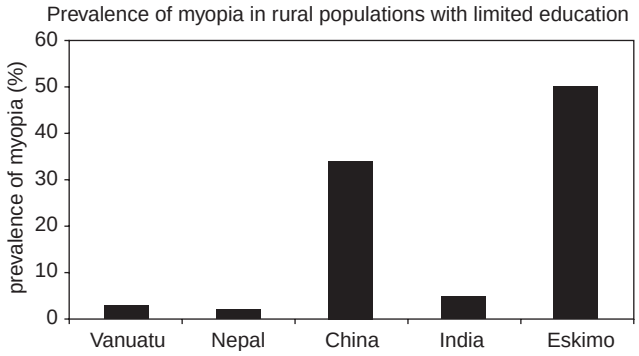

Fig. 11. Prevalence of myopia in school children from rural populations with limited education. While the data are not strictly comparable because of differences in age groups and other aspects of methodology, major differences in prevalence between different populations are nevertheless evident, particularly in the Eskimo population. This is not explicable in terms of population genetic background, at least in terms of major branches of the human population, since the Nepalese are predominantly of northern East Asian origin, as are the Chinese and Eskimo. There are no quantitative measures of the level of engagement in and intensity of education in the different populations, which could explain some of the differences. However, it seems unlikely that education was much more intensive in the recently settled Eskimo populations in North America than in the Chinese in semi-rural Shun-yi, close to Beijing. Other possible factors could include particular sensitivity to environmental pressures associated with founder effects in small populations, as is possible with the Northeast Asian settlers of the Americas, although this elevated sensitivity is not seen in other Native American populations. Alternatively, other environmental factors such as the nature of the light–dark cycles in Arctic regions could be involved.
Data taken from:

Vanuatu: (Garner et al., 1985, 1988, 1990)
Nepal: (Garner et al., 1999, 2004)
China: (Zhao et al., 2000)
India: (Dandona et al., 2002b)
Eskimo: (Young et al., 1969)

5.1.2. *A role for intelligence?*

Several studies have documented an association between myopia and higher scores on IQ tests of various kinds, which we will loosely term intelligence (Hirsch, 1959; Grosvenor, 1970; Rosner and Belkin, 1987; Cohn et al., 1988; Teasdale et al., 1988; Teasdale and Goldschmidt, 1988).

These data have led to hypotheses concerning links between big brains and big eyes (Miller, 1992). There is, however, no evidence linking variations in brain size to intelligence in humans, except in pathological and degenerative situations (Henneberg, 1998; Tramo et al., 1998), and the evidence that larger eyes are not necessarily associated with myopia if emmetropisation is operating normally, is summarised in Section 3.3.

More conservatively, a pleiotropic genetic relationship between myopia and intelligence has been supported by

some, on the basis of supposedly "convincing evidence from genetic studies that myopia is an inherited condition, probably transmitted as a recessive characteristic" (Karlsson, 1973, 1975), or in view of the high heritability reported for both (Cohn et al., 1988).

The issue of heritability of IQ has been extremely controversial, because of its suggested implications for educational policy (Jensen, 1973a, b). It should be noted that much of the evidence on IQ is flawed by the same issues of confounding shared genes and shared environments, although more work has been done on the genetics of intelligence with separated twins. Although some of the early evidence has been discredited (Kamin, 1974), a high heritability for IQ has now been generally agreed (Neisser et al., 1966).

Despite the agreed high heritability, there have been substantial increases in performance in IQ tests in a number of populations over the past decades (Flynn, 1999), demonstrating again that a high broad heritability does not set a limit to the potential impacts of environmental change. Dickens and Flynn (2001) have developed a sophisticated environmental multiplier model to explain how small differences, be they genetic or environmental in origin, might be selectively multiplied into large differences in outcomes. Aspects of this modelling might be applicable to the epidemiology of myopia, although in principle there is no theoretical incompatibility between high heritability and rapid change. All that is required in the case of myopia is a rapid change in relevant environmental variables, which could lead to a collapse of heritabilities calculated from parent–offspring correlations, while preserving high heritabilities calculated from sibling correlations and in twin studies—precisely the pattern that is seen in the case of myopia (see Sections 3.5 and 3.6).

Zadnik and Mutti (1998) have suggested, taking the high heritabilities of IQ and myopia as evidence for inheritance, that they may be "inherited via nearby alleles or genes, and thus intelligent, achieving children and adults tend to read more". This hypothesis suggests that the correlation of myopia with near work may not be causal, but may result from linked inheritance of myopia and intelligence, with higher intelligence leading to greater involvement in reading and education. However, it is premature to postulate linked simple inheritance of myopia and intelligence, when there is little evidence of simple inheritance of either characteristic.

School performance has also been analysed in twin studies, where the heritability also appears to be high (Heath et al., 1985; Tambs et al., 1989; Miller et al., 2001), although there have been clear longitudinal increases in school outcomes in most societies, consistent with the idea that high heritability does not set limits to the possibility of change.

We suggest, in the light of the evidence that is currently available, that school performance, performance on IQ tests and near work be regarded as potentially linked variables in epidemiological analysis. Performance on IQ tests might provide evidence of general preparation for academic pursuits. Near work might provide a measure of involvement in the activities that, combined with general preparation, would lead to higher educational attainments.

5.1.3. *Urban versus rural environments*

Another environmental risk factor is residence in urban versus rural areas. Studies on the prevalence of myopia in populations with very similar genetic backgrounds growing up in different environments in India (Dandona et al., 1999, 2002a, b), Nepal (Garner et al., 1999), China (Zhan et al., 2000), Taiwan (Chang et al., 1999) and Vietnam (unpublished results) have shown that those growing up in rural environments have a lower prevalence of myopia (Fig. 12).

This does not demonstrate that there is a direct myopigenic effect of growing up in built-up environments, since educational levels and socio-economic indices tend to be higher in urban as compared to rural environments, even if the minimum formal requirements of schooling are the same. There are thus differences in duration and intensity of study between students in urban and rural areas, and it is not clear whether the observed differences in refractive error can be explained purely in terms of education. Other factors that might be involved include exposure to long-distance viewing and time spent outdoors, where light intensities are generally higher and where optical depth of field is greater.

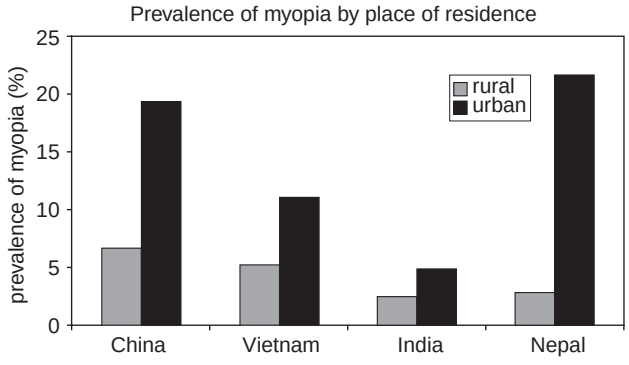

Fig. 12. Prevalence of myopia in closely related populations living in urban and rural environments. Note the vast differences in prevalence between urban and rural environments. Data are not necessarily comparable from one country to another because of methodological differences.
Data taken from:

China: (Zhan et al., 2000)
Vietnam: unpublished results
India: (Dandona et al., 1999, 2002a, b)
Nepal: (Garner et al., 1999)

Environments of this kind provide a favourable situation for exploring some of the factors that might be responsible for longitudinal change, for there are clearly major differences between urban and rural areas in exposure to potential risk factors such as near work, intensive education, television and computers, and to potentially protective factors such as time spent outdoors. In developing countries, these factors are changing with time, and differentially between the urban and rural environments, which can significantly aid analysis, despite the probable linkage of some of the variables. However, in the relatively homogenous environments encountered in modern cities and societies, such as the United States and Singapore, the impact of variables such as television, video games, or home computers may be minimal, as has been reported (Mutti et al., 2002a; Quek et al., 2004). This, of course, means that in those environments, continued longitudinal change would need to be explained through other mechanisms.

5.2. Mechanisms for environmental impacts on axial length and refractive error

In 1985, Curtin comprehensively reviewed the evidence for environmental impacts on myopia and axial length. He concluded that

> the obsessive quest for the mechanism of axial elongation became obtuse and contradictory and at times incorporated elements of high comedy…the number and disarray of such theories defy the talents of the most organised of minds…it would, however, be a serious mistake to reject all of these theories, since, as will be noted, recent laboratory studies give a degree of credence to theories that have often been alluded to with condescension or disdain.

A review of the more recent literature demonstrates that, despite some progress, the full story is still not understood.

5.2.1. The role of near work

Near work is generally regarded as one of the risk factors involved in the effect of education. We do not propose to review the evidence on near work and myopia in detail, except to note that near work has been documented as a risk factor in almost all studies that have examined the issue, although the association is weak and not always quantitative (for a review see Zadnik and Mutti, 1998).

There are considerable problems involved in quantifying the amount of near work, in units such as dioptre hours, an approach followed most rigorously by Zadnik, Mutti and colleagues. Thus, considerable further work to accurately quantify viewing distances and accommodation, and investigate possible non-linear relationships between near work and myopia in different ethnic groups, would be valuable. The problems in quantification could be magnified, if the most important factors are the early childhood determinants of myopic progression, which have hardly been studied.

Generally the association with near work is explained in terms of the growth induced by excessive accommodation, although a direct role for accommodation is not supported by animal studies (McBrien and Millodot, 1987; McBrien et al., 1993, 1995; Schmid and Wildsoet, 1996; Wildsoet, 2003), and the only limited success of attempts to limit the progression of myopia by reducing accommodative demands in humans (Grosvenor and Goss, 1988; Shih et al., 2001; Edwards et al., 2002; Gwiazda et al., 2003).

In view of the consistent correlation between myopia and education, and the relative weakness of the impact of near work, it is worthwhile investigating more intensely whether the inverse of near work, that is time devoted to distance viewing and outdoor activities also plays a role (Mutti et al., 2002a). Functionally, emmetropisation would appear to involve setting the eye up for distance vision, and letting accommodation do the rest. Thus insufficient viewing of distant objects might impair the process. This might contribute to the urban–rural differences that have been reported.

However, differences related to more open living environments in rural areas are unlikely to generate major differences in accommodative load expressed as dioptre hours, because clear vision beyond more than a few metres requires minimal accommodative load. However, as noted previously, living in rural areas may be associated with increased amounts of time spent outdoors, and the impact of the higher light levels outdoors, with resulting pupil constriction and increased depth of field may also be important.

5.2.2. Other environmental factors

Other factors, such as high glycaemic index diets, have also been postulated to play a role as risk factors in the aetiology of myopia, based on correlations between myopia and height, weight, body-mass-index, age of menarche and diabetes (Cordain et al., 2002). Changes in diet tend to occur in parallel with urbanisation and increased education, thus complicating the analysis, but this hypothesis requires detailed examination. A recent analysis of correlations between myopia and indicators of high glycaemic index diets in data from the Blue Mountains Eye Study did not support this idea (D. Morgan, personal communication).

Abnormal lighting conditions have also been postulated to play a role in the development of myopia. One specific hypothesis, that early exposure to night lights may be a crucial factor (Quinn et al., 1999), has not been supported in a series of subsequent studies (Chapell et al., 2001; Zadnik, 2001; Saw et al., 2002c). However,

studies on ocular development in experimental animals demonstrate that eye growth is perturbed by light–dark cycles that diverge markedly from 12:12 conditions. More than 4–6 h of dark every night seems to be required to support normal eye growth (Li et al., 1995, 2000). In many urban environments, artificial lighting may well have pushed growth control processes close to the limit. Thus a role for the increased light exposures that characterise urban environments is worth further consideration.

5.2.3. Blurred vision

In addition to the range of social factors described above, rare childhood conditions which blur vision also result in myopia. Children suffering from neonatal ptosis, fused eye-lids, cataracts or keratitis become myopic, and often extremely myopic, unless the blurred vision is relieved by medical treatment (Robb, 1977; Anderson and Baumgartner, 1980a, b; Hoyt et al., 1981; Gee and Tabbara, 1988). Some of these conditions may themselves be genetic in origin, but their impact on myopia is through environmental distortion of emmetropisation. While these conditions demonstrate the sensitivity of the emmetropisation process to visual blur, they are responsible for only a very small fraction of childhood myopia. Animal studies show that reduction of image contrast with diffusers leads to myopia in species as diverse as chickens (Wallman et al., 1978) and non-human primates (Wiesel and Raviola, 1977; Smith et al., 1987, 1999).

It has been postulated that the more transient blurring of distant objects in the peripheral visual field during near focus, or the blurring in central fields associated with accommodative lags and errors may contribute to the development of myopia. The effects of constantly blurred vision in humans provide some support for the postulated role of intermittently blurred vision in the development of myopia. However, one of the features of the form-deprivation paradigm in animals is that brief periods of unblurred vision prevent the development of myopia (Napper et al., 1995, 1997; Smith et al., 2002). It is not clear that blurring associated with differential focus and resolution during reading (Wallman et al., 1987), accommodative lag (Wildsoet, 1997), or high AC/A ratios (Gwiazda et al., 1999) could maintain blur consistently enough to produce myopia through a form-deprivation mechanism. Nevertheless, it has been reported that an elevated response AC/A ratio is a risk factor for the development of myopia (Mutti et al., 2000).

More recently, Wallman and colleagues (Kee et al., 2001; Winawer and Wallman, 2002; Zhu et al., 2003) have shown that the balance between hyperopic and myopic defocus may be important. In particular, brief periods of imposed myopic defocus are able to prevent the development of compensatory myopia in response to negative lenses. On the basis of these observations, Wallman et al. (2000) have suggested that the possibly protective effect of the myopic defocus of more distant objects, might be disrupted by close focus on a printed page, which obscures the myopic defocus of more distant objects. Wallman has therefore suggested that encouraging periods of myopic defocus might provide a useful prophylaxis against myopia (see also Morgan and Megaw, 2004). The balance between central and peripheral hyperopic and myopic focus may also be important in eyes that deviate from spherical (Stone and Flitcroft, 2004).

5.3. Conclusion

Irrespective of the causal factors involved, where there is no direct evidence for an increasing prevalence of myopia, dependence of the prevalence of myopia on educational level and place of residence provides evidence of sensitivity to environmental impacts. Evidence for dependence of the prevalence of myopia on environmental factors has been obtained for populations of African, Northeast Asian, Southeast Asian and Caucasian origin. This sort of dependence, where demonstrated, would suggest that these populations will show an increasing prevalence of myopia in environments characterised by increasing educational pressures and urbanisation.

6. Are there differences in the intrinsic prevalence of myopia or susceptibility to environmental impacts between population groups?

The prevalence of myopia varies significantly around the world, with significant differences between different racial and ethnic groups. This is often taken as evidence for genetic determination, either of refractive error, or of susceptibility to environmental factors, where the relevant genes are differentially distributed between different populations. However, this sort of analysis must take into account the different environments that exist around the world, including the level of educational pressure on children, as well as the possible differences in genetics.

We have outlined above the evidence for an increasing prevalence of myopia in populations of Northeast and Southeast Asian, Caucasian and Australian Aboriginal origin. Similar evidence is not available for the African and Pacific Islander populations. We have also outlined the case for taking evidence of dependence of myopia on educational level, or place or residence as evidence of susceptibility to environmental impacts. These effects have been documented for most of these populations, as well as for African populations.

Table 8

	Rapid changes in or high prevalence of myopia	Effect of education on prevalence	Urban–rural difference in prevalence
New Guinean and Australian	YES		
Pacific Islander			
Southern East Asian	YES	YES	YES
Northern East Asian	YES	YES	YES
Arctic Northern East Asian	YES		
Amerindian	YES		
European	YES	YES	YES
North African and West Asian		YES	YES
African		YES	YES

Examples of effects of educational level and place of residence on the prevalence of myopia, and/or examples of rapid changes in the prevalence which cannot be simply explained in genetic terms, are therefore available for populations from each of the major lines of the human family, with the exception of Pacific Islanders (Table 8). Since there is no negative evidence, but only an absence of evidence, this suggests that sensitivity to environmental risk factors may be a quite general characteristic of human populations.

6.1. *Are population differences in the prevalence of myopia maintained in different environments?*

A critical test of the relative roles of genes and environment can come from examining whether population differences in the prevalence of myopia are maintained in populations that have migrated to different environments. It should be noted that maintenance of population characteristics in other environments could be explained by preservation of cultural and social patterns, as well as in terms of genetic inheritance, whereas major changes in different environments can generally only be explained in terms of environmental influences.

There is some evidence that the prevalence of myopia in those of East Asian origin in North America (Cheng, 2002; Kleinstein et al., 2003) and Australia (Wensor et al., 1999) is higher than in the general population. However, these studies have not rigorously addressed the issue of where the populations have grown up, and where they have been educated. Nor have they addressed the issue of maintenance of cultural and social patterns.

Lam and colleagues (Lam et al., 2004) have determined the prevalence of myopia in students of Chinese origin in local and international schools, and in those of Caucasian origin in international schools. The prevalence of myopia was high in students of Chinese origin in both sorts of schools, whereas in students of Caucasian origin in the international schools, the prevalence of myopia was much lower. Since the prevalence of myopia in the European students was higher than that reported in some slightly older studies on students of similar age in Europe and North America, Lam and colleagues interpreted their results as indicating both an effect of the different genetic backgrounds of the groups of students, and an effect of the Hong Kong environment.

However, the prevalence of myopia in the students of European origin in Hong Kong is comparable to that reported in more recent European (Villarreal et al., 2000) and North American (Zadnik, 1997) student cohorts, which weakens the case for the effect of the Hong Kong environment. More information on the length of time the European students had lived in Hong Kong, and how long they had attended Hong Kong schools, as well as their academic results, is required so that the possible impact of more limited exposure to environmental risk factors, including less intensive study habits, can be assessed.

Several studies on the association of place of residence (rural versus urban) with markedly difference prevalences of myopia in genetically closely related populations suggest a major effect of environmental factors (see Section 5.1.3). One study on immigrant populations strongly suggests a major role for the environment. Indians show a very low prevalence of myopia in India (Dandona et al., 1999, 2002a, b; Murthy et al., 2002). Indeed the low prevalence of myopia in Indians in India in comparison to the high prevalence of myopia in Singaporean Chinese is sometimes cited as evidence of genetic determination of population differences. However, the prevalence of myopia in Indians in Singapore is very high, close to that in the Singaporean Chinese population (Au Eong et al., 1993b; Wu et al., 2001), with a similar correlation between myopia and educational level. Appropriate comparison of data (Fig. 9) therefore demonstrates the considerable impact of the environment, rather simple genetic determination. Whether the residual difference between those of Chinese and Indian origin is evidence of a role for genetic differences, or can be explained in terms of maintained cultural differences to education and outdoor activities, is still to be determined.

6.2. *Is the prevalence of myopia intrinsically higher in East Asian populations?*

It is commonly asserted that Chinese, or more generally East Asians, have an intrinsically higher

prevalence of myopia (see, for example (Park and Congdon, 2004). However, the prevalence of myopia in populations of northern East Asian origin can range from very low (Garner et al., 1999; Pokharel et al., 2000) as in rural parts of Nepal with populations of substantially Northeast Asian origin (Brega et al., 1986; Semino et al., 1991; Passarino et al., 1993; Cavalli–Sforza et al., 1994; Umemura et al., 1998; Pang et al., 2001), through moderate levels in Mongolia (Wickremasinghe et al., 2004), rural China (Zhan et al., 2000; Zhao et al., 2000, 2002) and rural Japan (Watanabe et al., 1999), through to the characteristically high prevalences observed in urban Japan (Matsumura and Hirai, 1999; Shimizu et al., 2003) and China (Wu and Edwards, 1999). Similarly, the prevalence of myopia in populations of predominantly southern East Asian origin can range from low as in rural Vietnam (unpublished results) and Taiwan (Chang et al., 1999), through to very high in urban Taiwan (Lin et al., 1988a, 1999, 2001, Chang et al., 1999; Cheng et al., 2003), Hong Kong (Goh and Lam, 1994; Lam et al., 1994; Edwards, 1999; Wu and Edwards, 1999; Goldschmidt et al., 2001), Guangzhou (He et al., 2004) and Singapore (Tay et al., 1992; Au Eong et al., 1993a; Wong et al., 2000; Wu et al., 2001).

Fig. 13 summarises the data on East Asian populations in a range of environments, for the 11- to 13-year-old group. Studies on adults in different environments in East Asia also demonstrate marked differences in the prevalence of myopia (Lam et al., 1994; Wong et al., 2000; Cheng et al., 2003; Shimizu et al., 2003; Wickremasinghe et al., 2004).

Studies on younger children give little support to an innate difference between racial groups. The average cycloplegic hyperopic refractive errors in 10- to 12-week-old infants in Hong Kong (Edwards, 1991) and Italy (Grignolo and Rivara, 1968) are very similar. Edwards and Lam (2004) note that in these two studies, there is quite rapid emmetropisation in the Chinese infants, but little change in the refractions of the infants in the Italian study over the first year after birth was reported. This contrasts with other observations of quite rapid post-natal emmetropisation in Caucasian infants (Fulton et al., 1980; Gwiazda et al., 1993; Mayer et al., 2001). In Chinese children, there then appears to be refractive stability until the age of about 5 years (Chan and Edwards, 1993; Edwards and Lam, 2004), as also appears to be the case in European infants (Fulton et al., 1980; Gwiazda et al., 1993; Mayer et al., 2001). More studies on the development of refractive error in infants and preschool children are required, particularly in view of the trend towards earlier onset of myopia observed recently in Taiwan, Hong Kong and Singapore.

The picture of a generally similar cohort effect in the prevalence of myopia in young people of European and East Asian origin is shown in Fig. 14, where the prevalence of myopia in Scandinavia and Taiwan for 11–13 years old is compared. Similarly, comparison of similar birth cohorts (1940–1950) at a similar age (40–49) in Singapore (Wong et al., 2000) and North America and Europe (Kempen et al., 2004), also suggest that the prevalence of myopia in these groups was similar (Fig. 7), particularly after allowing for the more conservative cut-off used in the NIH study.

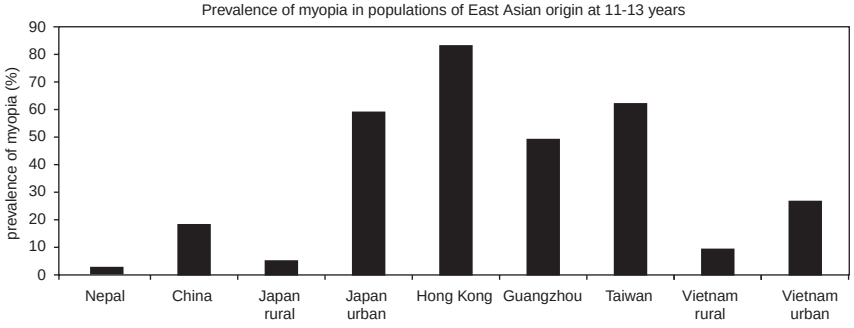

Fig. 13. Prevalence of myopia in populations of East Asian origin at 11–13 years old. Note that the prevalence can vary from extremely low as in Nepal to very high as in Singapore, Guangzhou, Taiwan and Hong Kong. The population of Nepal is heterogenous, but includes substantial elements of East Asian origin. Data taken from:

Nepal: (Pokharel et al., 2000)—see also Garner et al. (1999)
China: (Zhao et al., 2000)
Japan (rural): (Watanabe et al., 1999)
Japan (urban): (Matsumura and Hirai, 1999)
Hong Kong: (Lam and Goh, 1991; Goh and Lam, 1994)
Guangzhou: (He et al., 2004)
Taiwan: (Lin et al., 2001)
Vietnam (rural): unpublished results
Vietnam (urban): unpublished results

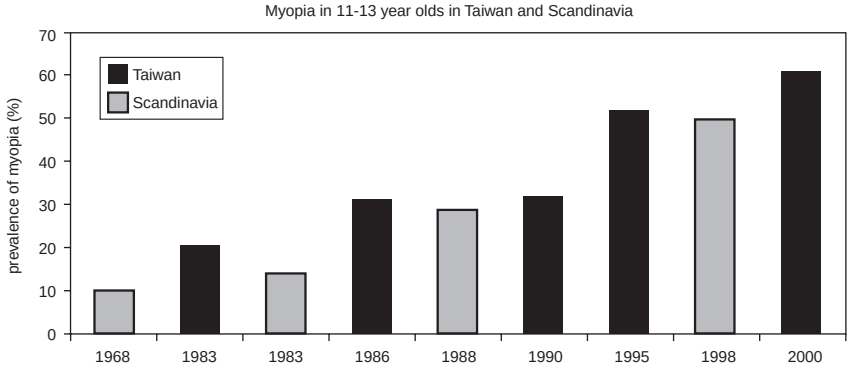

Fig. 14. Prevalence of myopia in late primary school children in Taiwan and Scandinavia. Note the similarity in temporal change in the Chinese population of Taiwan and the Caucasian population of Scandinavia.
Data are taken from: 1968: (Goldschmidt, 1968); 1983: (Lin et al., 2004); 1983: (Mantyjarvi, 1983); 1986: (Lin et al., 1988a); 1988: (Jensen, 1991); 1990: (Lin et al., 2004); 1995: (Lin et al., 1999); 1998: (Villarreal et al., 2000); 2000: (Lin et al., 2001).

Thus there is little evidence in most of the data for an intrinsically higher prevalence or myopia, or a greater susceptibility to environmental risk factors in populations of East Asian origin. However, the very recent data from Singapore, Taiwan and Hong Kong and Japan (Lin et al., 2004; Tay et al., 1992; Lam et al., 1994; Chua et al., 2000; Saw, 2003) suggest that the prevalence of myopia has further increased in later birth cohorts, with the change particularly evident in an earlier onset of myopia and an increasing prevalence of high myopia. There is little evidence that similar changes have taken place in North America and Europe. Whether this difference, if confirmed, is due to greater intrinsic susceptibility to extreme environmental factors in East Asians, or to greater exposure to environmental risk factors in East Asia, remains to be definitively established.

Two observations might however suggest that some specific populations of East Asian origin might have special characteristics. Firstly, the Inuit, of northern East Asian origin, showed a massive increase in the prevalence of myopia in only one generation, despite exposure to only relatively limited education. In acculturation, a number of variables can change in parallel, and changes in factors other than education might have been the cause of the massive changes in refractive error, although some of the authors noted the protective effects of absence from school. Another possibility is that the extremely variable light–dark cycles characteristic of extreme latitudes may interact with other environmental variables to create major change. An alternative possibility is that the extreme sensitivity of the Inuit to environmental change may be due to a founder effect related to the small population that migrated from Northeast Asia across the Behring Strait.

A very high prevalence of myopia, comparable to that observed in those of Malay origin in Singapore, has also been observed in 20- to 29-year-old Indonesians from a pooled rural–urban sample (Saw et al., 2002a). This is difficult to explain in terms of environmental factors, but other studies on populations of Malay origin outside Singapore have found lower values (Garner et al., 1990; Yeow, 1994). Non-cycloplegic refraction was used in the most recent studies, and the possibility of pseudomyopia therefore cannot be excluded.

Overall, therefore, there is no convincing evidence to support the idea that there is a differential distribution of genes specifying refractive error or conferring susceptibility to environmental risk factors between different racial and ethnic groups. The rapid and massive changes in prevalence seen in the Inuit is the evidence most likely to indicate some variation in sensitivity to environmental factors, but this is far from conclusive. The slight differences between Singaporean Chinese, Indians and Malays, in a relatively common environment, may be genetic in origin, but social influences have not been excluded. And they need to be contrasted to the major differences in the prevalence of myopia between Indians growing up in India, and those growing up in Singapore. If there is a greater sensitivity to environmental influences in populations of East Asian origin, it is clearly quantitative rather than qualitative.

6.3. Conclusion

Most of the evidence suggests that all the human population groups are sensitive to environmental pressures, and will develop high prevalences of myopia in the appropriate environments. There is a major gap in the evidence in relation to Pacific Islanders, and more extensive information on African and indigenous Australian and New Guinean populations would be valuable. At this stage, however, we conclude that sensitivity to the social and environmental risk factors

that have been identified as associated with an increased prevalence of myopia is more likely to be a common human characteristic. This would not be surprising, for the genetic evidence is that human populations are characterised more by their genetic similarities than by their differences, and that the differentiation of populations is only achieved by focussing on the minor differences (Cavalli–Sforza et al., 1994; Cavalli-Sforza and Feldman, 2003).

7. Conclusions

Overall, while there is good evidence for a major role for genetic variation in familial forms of early onset high myopia, there is little evidence for a major role for genetic determination in school myopia. The high heritabilities observed in twin studies suggest that genetic factors do have a role in school myopia, but the evidence from broader family studies suggests that some of the high correlations observed between genetically related family members may be due to shared environments as well as shared genes. This conclusion is supported by the much lower correlations reported when parents and offspring have been exposed to very different environments during development, and when siblings are very different in age. Thus genetic factors may be more important under conditions of relatively low environmental variation.

A limited role for genetic determination of refractive error is not surprising, because the active regulation of axial elongation integral to emmetropisation would eliminate many of the effects of genetic differences in general growth processes. In contrast, there is evidence for environmental risk factors which affect strongly the development of school myopia. While some of the environmental effects could be explicable in terms of ad hoc genetic explanations, the pattern of change and variation is more consistently explicable in terms of the impact of environmental factors. These include education and place of residence, but the mechanisms by which these environmental risk factors exert their effects are not clear.

This conclusion is almost the reverse of that found in the classic texts. For example, in Duke-Elder's Practice of Refraction (Duke-Elder, 1978), it is stated that:

> Simple refractive errors are thus largely hereditarily determined, owing to the co-ordinated combination of essentially normal elements of the optical system of the eye…Pathological refractive errors, on the other hand, are determined by abnormal development or acquired variations of the optical components of the eye…

In the light of the evidence now available, it is clear that this conclusion is not sustainable. The increasing prevalence of school myopia is clearly due to the impact of environmental risk factors. In contrast, genetic factors are responsible for the development of some pathological myopia, although environmental factors also seem to be able to induce pathological levels of myopia, as shown by effects of blurred vision and by the marked increases in the prevalence of high myopia in Singapore and Taiwan in the last decades.

Under the influence of environmental factors, over at least the last 50 years, the prevalence of myopia has been increasing. In parts of East Asia, these environmental pressures have already led to the majority of the younger population becoming myopic, irrespective of their genetic background. The description of the current situation as an epidemic is not universally accepted (Park and Congdon, 2004), but a comprehensive analysis of the situation in East Asia, and increasingly in other parts of the world, justifies the use of this term.

While there are currently major differences in the prevalence of myopia in different parts of the world, these appear to be predominantly associated with social and environmental differences, rather than with inherited differences in the prevalence of myopia, or in susceptibility to the environmental risk factors. There is evidence that most of the major branches of the human species, defined in terms of genetic associations, show marked increases in the prevalence of myopia, when exposed to particular environments. There is unfortunately no evidence on Pacific Islander populations, but it seems likely that sensitivity to environmental influences is a property that will prove to be shared by all the major branches of the human species. It would therefore be expected that the prevalence of myopia will increase in all parts of the world, and in all populations, as economic development continues.

This shared sensitivity to environmental risk factors appears to be associated with the process of emmetropisation, which has been designed by evolution to minimise refractive errors, despite variability in overall eye growth. However, in environments that are extreme in evolutionary terms, this process breaks down and appears to promote the development of myopic refractive errors.

Detailed analysis of the data from Taiwan and Japan shows that the distribution of refractive errors has broadened and flattened as the prevalence of myopia has increased. This would not be expected from a simple model, in which shared environmental pressures have added a constant amount to axial length and refractive error.

There are two possible explanations. The first is that the broadening of the distribution reflects differential exposure to the environmental risk factors. The continuing evidence of a relationship between educational levels and myopia is consistent with this explanation.

However, it is also possible that inherited differences between individuals in susceptibility to environmental factors may contribute to the broadening, although the evidence that the younger generations of some populations have become overwhelmingly myopic suggests that the differences between individuals in susceptibility are, at most, quantitative rather than qualitative. The search for differential sensitivity needs to pay particular attention to those who are very highly educated, but do not become myopic, and those who are very poorly educated, but who nevertheless become myopic in the absence of association with syndromic or non-syndromic familial myopia.

Individual differences in sensitivity, if they exist, are not significantly differentially distributed between different racial and ethnic groups. Common generalisations such as an intrinsically higher prevalence of myopia in East Asians (given the marked variations in prevalence seen in populations of East Asian origin in different environments), or greater susceptibility to environmental risk factors in East Asians compared to other racial groups (given the high prevalence of myopia seen in Indians in Singapore, and the evidence that the prevalence of myopia is increasing in other populations) cannot be sustained.

Overall, the answer to the question of whether it is genes or environment that is making more people more myopic is clear. Undoubtedly, the recent alarming trends are being driven by environmental change, predominantly changes in the social environment. This does not mean that the epidemic of myopia can be readily reversed, for the social risk factors involved seem to be quite intrinsic to modern economic development.

On an historical time-scale, the process may be captured in the following way. In low-pressure environments, where exposure to environmental risk factors is low, only those with clearly genetic high myopia would be myopic. In moderate pressure environments, typically those in Europe and North America in which the foundations of research on myopia were established, more people would develop school myopia. This would preferentially affect those more exposed to the environmental risk factors, which tend to run in families, and those with a genetic predisposition towards myopia, leading to the simultaneous observation of impact of parental myopia and education, with high familial correlations in refractive error. Finally, in high-pressure environments, with highly intensive mass-education systems in highly urbanised environments, almost everyone could become myopic, due to the impact of environmental factors, although patterns of familial inheritance might be preserved in measures of the severity of myopic. This is the situation that is being approached in East Asia, and apparently more slowly in other parts of the world.

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