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What can anisometropia tell us about eye growth?

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Synopsis/Precis:

In young children, the presence of small degrees of anisometropia is associated with impaired emmetropisation, suggesting that, in addition to environmental and genetic influences on eye growth, stochastic processes contribute to refractive development.

Competing Interests: There are no competing interests for any author

Abstract

Background/Aims: Both eyes of one individual share the same environment and genes. We examined interocular differences in biometry to determine the potential role of other factors in refractive development.

Methods: 362 subjects (6-7 years) from the Northern Ireland Childhood Errors of Refraction (NICER) study were studied. Cycloplegic autorefraction was measured with a Shin-Nippon open-field autorefractor. Axial length and corneal curvature were measured with a Zeiss IOLmaster.

Results: 257 subjects had an interocular difference of < 0.50D (ISO group) and 105 (29%) a difference of ≥ 0.50D (ANISO group). Twenty-five subjects (6.9%) had anisometropia ≥ 1.00D and 9 (2.5%) had anisometropia ≥ 1.50D. The two groups, ISO and ANISO, showed different refractive distributions (P = 0.001) with the ISO group showing a nearly Gaussian distribution and the ANISO group showing positive skew, a hyperopic shift and a bi-Gaussian distribution. A marker of emmetropisation is the poor correlation between refraction and corneal curvature seen in older children. There was no significant correlation between refraction and corneal curvature of each eye in the ISO group (r = 0.09, P = 0.19) but these parameters were significantly correlated in the ANISO group (r = 0.28, P = 0.004).

Conclusion: In young children, small degrees of anisometropia (≥ 0.5D) are associated with impaired emmetropisation. This suggests that anisometropia is a marker for poorly regulated eye growth, indicating that, in addition to environmental and genetic influences on eye growth, stochastic processes contribute to refractive outcomes.

Introduction:

The debate over the aetiology of myopia has largely focussed on the relative contributions from genetics ('nature') and the environment ('nurture') in guiding or driving an eye towards myopia[1]. The rapid rise in prevalence in certain countries over a generation points strongly towards environmental factors as the primary driver in the increasing the number of individuals exhibiting myopia. Conversely, twin studies and, more recently, genome-wide association studies (GWAS) have demonstrated the influence of genetics[2]. An emerging unifying factor are the gene-environment interactions identified for certain genes[3,4]. In addition, many myopia-associated genes are involved in retinal processing, which provides a link between human myopia and animal studies where eye growth is modulated by manipulation of the retinal image[5]. A factor that has received little attention in eye growth research is the role of stochastic factors, i.e. variability that comes about from randomness or noise within the biological mechanisms controlling eye growth. Inclusion of this element changes the question from nature versus nurture, to nature, nurture or chance[6].

What evidence is there for stochastic factors in eye growth? Such influences should introduce biological 'noise' or errors which are not correlated in the two eyes. In the absence of stochastic processes, the interaction of genes and the environment should produce identical refractions in a pair of eyes. Overall, there is a strong correlation in refractive parameters between the eyes[7], which can be taken as evidence that such shared genetic and environment factors have a dominant role. A neglected facet of refractive development provides the best evidence for a stochastic element of eye growth, namely the existence of anisometropia[8].

In early childhood, anisometropia tends to decline in the first few years of life during the process of emmetropisation [9,10]. Although the prevalence remains reasonably stable during early childhood, as many children lose anisometropia as develop it[11]. This period of early childhood is the time during which the process of emmetropisation is largely completed. In older children, the development of myopia is associated with a later development of increased anisometropia [12,13]. This suggests that most persistent hyperopia is the result of a primary failure of emmetropisation and myopes a failure to maintain emmetropia [14].

The aim of this study was to examine the biometric basis of anisometropia in a well-defined, population-based sample of 6-7 year children[15] in order to test the hypothesis that stochastic factors play a role in refractive development. At this age myopia is relatively uncommon and most eyes have demonstrated a significant level of emmetropisation compared to neonatal refractions[16–18]. If anisometropia is indeed an indicator of stochastic rather than regulated growth, it is expected that anisometropia should be associated with biometric and refractive evidence of a failure of emmetropisation.

Methods

The Northern Ireland Childhood Errors of Refraction (NICER) study is an ongoing study of refractive error in children and young adults in Northern Ireland. The study methods have previously been described in detail[19]. In brief, Phase 1 of the NICER study was a cross-sectional epidemiological study investigating the prevalence of refractive error in 6-7 and 12-13 year-old children in Northern Ireland conducted between 2006 and 2008. Participants were chosen using stratified random sampling of schools from geographic areas characteristic of Northern Ireland to obtain a representative sample of schools and children from urban/rural and deprived/non-deprived areas. Data collection occurred at the child's school during the school day. Data collection included assessment of logMAR crowded monocular acuity at 3 m (unaided and with spectacles if worn) and heterophoria/tropia carried out at distance (at least 3 m) and near (33 cm) using the cover/uncover test (unaided and with spectacles if worn). Cycloplegia was induced by one drop of 1.0% cyclopentolate hydrochloride, after corneal anaesthesia with one drop of 0.5% proxymetacaine hydrochloride. Autorefraction was performed using a binocular open-field autorefractor (SRW-5000, Shin-Nippon, Tokyo, Japan) at least 20 minutes after the instillation of drops. No less than five readings were taken from which the 'representative value' as determined by the instrument was used for further analysis. The representative value is widely used as an output value for this instrument and has been shown to be comparable to other methods of averaging refractive error[20]. The Zeiss IOLMaster (Carl Zeiss Meditec, Oberkochen, Germany) was used to measure axial length and corneal curvature. At least three measurements of axial length and corneal curvature readings were taken. Only axial length measurements with a signal-to-noise ratio greater than two were considered valid for subsequent analysis[21].

Data Selection

Of the 399 6-7-year-old subjects recruited and tested for the initial phase of the NICER study, a subset of 362 children with complete cycloplegic refractive data in both eyes and, in order to exclude possible amblyopes, best corrected visual acuity of better than 0.3 LogMAR (i.e. better than 6/12) in both eyes was extracted.

Criteria for Anisometropia

Significant anisometropia is often defined as a spherical equivalent, interocular difference of ≥ 1.00D. In this analysis, where anisometropia is being analysed as a marker of biological noise rather than for its optical significance, a lower threshold of 0.50D was selected. A sensitivity analysis was performed to determine whether the threshold unduly influenced the observed results.

Data Analysis

Data analysis was performed with R version 3.5.1 (R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/). Dual Gaussian fits of the refractive distribution data were achieved using non-linear optimisation[22]. These two sub-distributions were labelled 'Good Emmetropisers', characterised by a mean in the range 0 to 1.5D and 'Poor Emmetropisers', characterised by a mean greater than 1.5D and a larger standard deviation, as previously described[14].

Ethical approval

The NICER study was approved by the University of Ulster's Research Ethics committee and adhered to the tenets of the Declaration of Helsinki (Ulster University Research Ethics Committee Study number: REC/05/121 "Epidemiology of Myopia in a UK child Population"). Written informed consent was obtained from parents or guardians and verbal or written assent was obtained from participants on the day of the examination.

Results

Spherical Equivalent Refraction

The majority of the 362 subjects whose data were analysed were hyperopic with a mean (SD) spherical equivalent refraction of +1.31D (1.21) and +1.35D (1.24) in the right and left eyes, respectively. Within the total sample, there was no significant difference in the refractions of the two eyes (Wilcoxon rank sum test, P=0.66). As shown in Figure 1, the refractive distributions of right and left eyes were not normally distributed (Shapiro-Wilk test, $P < 10^{-15}$), with evidence of positive skew (+1.99). There was no difference in the overall shape of the distribution between left and right eyes (Kolmogorov-Smirnov test, P-value = 0.99).

Figure 1: Histograms of the spherical equivalent refraction of the right and left eyes of all subjects

The distribution of the mean spherical equivalent refraction of the two eyes, though not normal, could be accurately modelled as a combination of two gaussians with means of +1.01 D and +3.12D (see Figure 2).

Figure 2 Mean spherical equivalent refraction of all subjects

Anisometropia

257 subjects showed an interocular difference less than 0.50D (ISO group) and 105 (29%) had a difference of ≥ 0.50D (ANISO group). Twenty-five subjects (6.9%) had anisometropia ≥ 1.00D and 8 (2.2%) had anisometropia >1.50D. Figure 3 shows scatter plots of the right and left eye spherical equivalent refraction. As shown in Table 1, there were no differences in the mean age or gender ratio of subjects in the ANISO compared with the ISO group. Significant

differences were found for spherical equivalent, anisometropia and cylindrical component of refraction.

Table 1. Comparison of the ISO and ANISO group. Significance testing for gender: Chi-squared test. All other parameters: Wilcoxon signed rank test.

	ISO Group		*ANISO Group*		*Significance*
Total number of subjects	257		105		
Female (n)	132		52		
Male (n)	125		53		0.75
	mean	sd	mean	sd	
Age (years)	7.07	0.39	7.07	0.37	0.92
Average SE Refraction (D)	1.19	1.04	1.67	1.47	0.01*
SE Right Eye (D)	1.18	1.05	1.65	1.49	0.01*
SE Left Eye (D)	1.20	1.04	1.70	1.59	0.01*
Absolute Interocular Difference (D)	0.18	0.12	0.82	0.44	<1e-04*
Average Cylinder (D)	0.62	0.37	0.75	0.49	0.01*
Interocular Cylinder Difference (D)	0.31	0.29	0.43	0.42	0.02*
Average Axial Length (mm)	22.59	0.71	22.42	0.76	0.06

Figure 3 Scatter plots of the spherical equivalent refraction of the right and left eyes in the two groups.

The two groups at the 0.50D threshold (ISO and ANISO) showed different refractive distributions (Kolmogorov-Smirnov test, P = 0.001) with the average spherical equivalent of the ISO group showing a nearly normal distribution and the average spherical equivalent of the ANISO group showing a distinctly non-normal distribution. The two populations were fitted with a double gaussian (Figure 4) in the same manner as the overall population. Both groups shared a component centred at approximately +1.00 D, but most of the hyperopescontributing to the positive skew in Figure 2 were from the ANISO group. Within the ISO group 94% of the eyes fell within the 'Good Emmetropiser' sub-population, as compared with only 73% of the ANISO group.

Figure 4a Mean spherical equivalent refraction of both eyes in the ISO group (interocular difference < 0.50D)

Figure 4b. Mean spherical equivalent refraction of both eyes in the ANISO group (interocular difference ≥ 0.50D)

The pattern observed with the mean interocular spherical equivalent refraction remained whether the most hyperopic, least hyperopic eye, right eyes or left eyes were analysed. In the ISO group there was no significant correlation between refraction and corneal curvature of right eyes (r = 0.09, P = 0.16, Spearman's rank correlation) but in the ANISO group these features were significantly correlated (r = 0.34, P = 0.004, Spearman's rank correlation). In relation to axial length and refraction, the ISO group showed the expected inverse correlation (r = -0.33, $P < 10^{-07}$) as did the ANISO group (r = -0.37, P < 0.0001). Correlation between corneal radius and axial length was stronger in the ISO group (r = 0.75, $P < 10^{-15}$) than in the ANISO group (r = 0.54, $P < 10^{-8}$).

To assess whether the observed differences between the two groups reflect emmetropisation or the pre-myopic phase of myopia development, the two main predictors of future myopia (number of myopic parents and emmetropia at a young age) were examined. There was no significant difference in the mean number of myopic parents per subject (0.52 for the ISO group and 0.58 for the ANISO group, P = 0.57). The proportion of the two groups that fell within the definition of pre-myopia[23] was not significantly different in the two groups (37% for ISO group and 30% for the ANISO group, chi-square 1.64, P = 0.20).

Discussion

In this population, lack of anisometropia appears to be a marker for successful emmetropisation. The ISO group of non-anisometropes showed a narrow range of refractive error centred at +1.00D. In contrast, anisometropes showed a broader range of mostly hyperopic refractive errors. In addition to anisometropia, the ANISO group also demonstrated increased levels of astigmatism in terms of mean cylindrical power and increased interocular difference in cylindrical power. These features would all suggest a reduced level of regulated eye growth in the ANISO group up to the age of seven years. The hypothesis that anisometropia, even at low levels, is a marker of poor emmetropisation is supported by the observation that, in the ANISO group, refraction is significantly correlated with corneal curvature. In the ISO group there is no significant correlation between corneal curvature and refraction. Achieving emmetropia requires the regulation of axial length growth to match the optics of the eye. As corneal curvature changes little after 2 years of age, this principally reflects changes in axial length.[16] This growth pattern results in a poor correlation between refraction and corneal radius but a strong correlation between corneal curvature and axial length. The ANISO group showed a significant, if modest, correlation between both refraction and corneal curvature as well as a correlation between axial length and corneal curvature. This is similar to

the pattern observed in young infants[16]. In contrast, the ISO group, showed no significant correlation between refraction and corneal curvature, but a strong correlation between axial length and corneal curvature.

These observations are consistent with the hypothesis that anisometropia is a marker for a reduced degree of optically regulated eye growth. In the absence of well-regulated eye growth, stochastic factors would be expected to produce a range of interocular asymmetries as is observed in this sample. It is possible that rather than being a consequence of less tightly regulated eye growth, anisometropia may be the cause of abnormal eye growth. A high level of anisometropia is a well-known risk factor for amblyopia, which in turn has been demonstrated to influence eye growth by an, as yet, unidentified pathway[24]. In addition, clinical studies indicate emmetropisation in amblyopic eyes with anisometropia and/or strabismus is influenced by the quality of binocular alignment; with more aligned eyes demonstrating greater reductions in childhood hyperopia[25]. However, in the present analysis, likely amblyopes were excluded from the analysis and only eight subjects displayed a level of anisometropia usually considered as a risk factor for amblyopia (> 1.50D). All children also underwent a cover test, and, once amblyopes were excluded only, only 7 subjects had a manifest squint on cover test. Of these 3 were within the ANISO group and 4 four were within the ISO group. The small numbers and equal division by group indicate this is not a significant biasing factor in this study. It remains possible that milder degrees of impaired binocular function associated with anisometropia could have compromised the control of eye growth. Considering asymmetries in refractive error between monozygotic (MZ) twins provides a situation where the interocular effect of amblyopia can be excluded. MZ twins share the same genes and are usually exposed to similar, although not identical, environmental factors. A study in China has found that known environmental factors influencing refractive development cannot explain the discordance in

MZ twins, raising the possible contribution of stochastic factors[26]. These findings by no means prove that anisometropia is the result of stochastic growth, but certainly indicate that this hypothesis warrants further consideration.

The present analysis examined children at six and seven years of age in a population where very little myopia had yet emerged. There are many unanswered questions regarding whether achieving emmetropia by 6 or 7 and maintaining that status during school (i.e. avoiding becoming myopic) involve the same of different mechanisms.[14] In relation to future risks of myopia, the two strongest predictors for future myopia are early emmetropia and myopic parents.[27] The ISO and ANISO groups showed no significant differences in either the number of myopic parents, or the proportion that fell within the definition of pre-myopia. This suggests that, in our study population, the results of emmetropisation can be observed without the complicating factor of myopic eye growth. However, as 6-7 years was the youngest age of subjects participating in the NICER study, longitudinal data are lacking from birth up to this age. This limits the ability of our analysis to determine whether anisometropia is a consequence of stochastic processes during eye growth or a factor which disrupts eye growth. In either scenario, the asymmetry of spherical refraction and astigmatism still points to an under-appreciated role for stochastic elements in eye growth.

Conclusions: In young children, the presence of small degrees of anisometropia (≥ 0.50D) is associated with impaired emmetropisation. This suggests that anisometropia of this degree is a marker for poorly regulated eye growth, indicating that, in addition to environmental and genetic influences on eye growth, stochastic processes contribute to refraction.

Contributors: DIF, SmC and KJS: conception or design of the work, or the acquisition, analysis or interpretation of data; drafting the work or revising it critically for important intellectual content; final approval of the version published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Ethics Approval: The NICER study was approved by the University of Ulster's Research Ethics Committee Ref number: REC/05/121.

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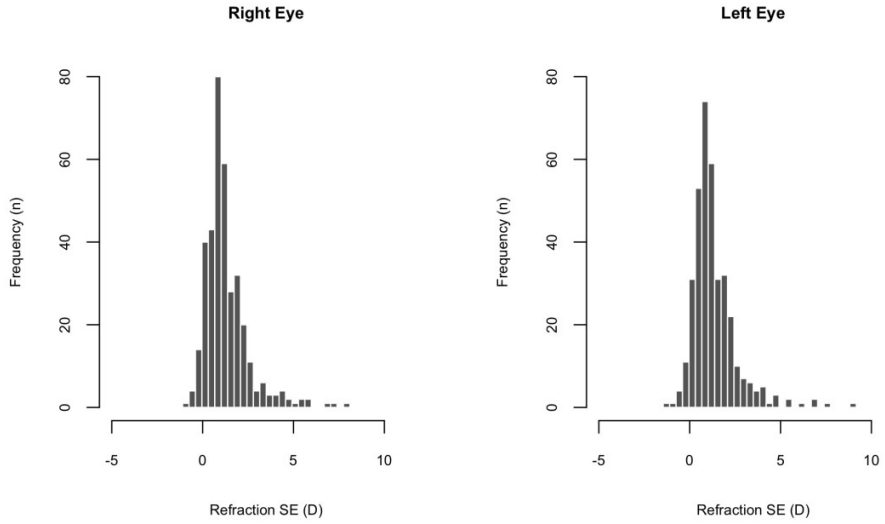

Figure 1: Histograms of the spherical equivalent refraction of the right and left eyes of all subjects

199x119mm (300 x 300 DPI)

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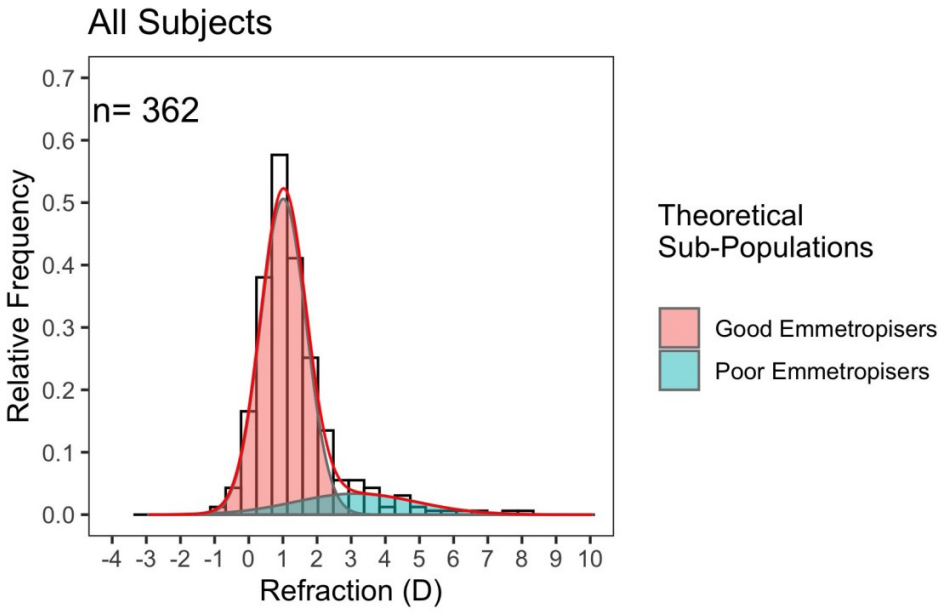


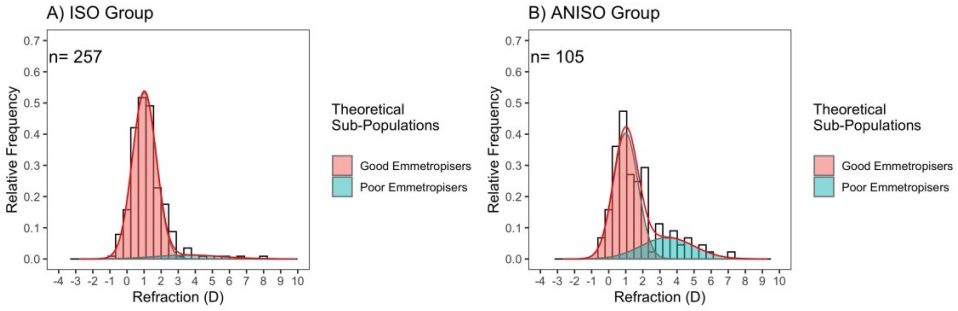
Population	Proportion	Mean	SD
Good Emmetropisers	0.85	1.01	0.67
Poor Emmetropisers	0.15	3.12	1.78

Figure 2 Mean spherical equivalent refraction of all subjects

139x119mm (300 x 300 DPI)

Figure 3 Scatter plots of the spherical equivalent refraction of the right and left eyes in the two groups.

199x119mm (300 x 300 DPI)



Population	Proportion	Mean	SD
Good Emmetropisers	0.94	1.02	0.70
Poor Emmetropisers	0.06	3.61	1.99

Population	Proportion	Mean	SD
Good Emmetropisers	0.73	0.99	0.72
Poor Emmetropisers	0.27	3.44	1.55

Figure 4a Mean spherical equivalent refraction of both eyes in the ISO group (interocular difference < 0.50D)

Figure 4b. Mean spherical equivalent refraction of both eyes in the ANISO group (interocular difference ≥ 0.50D)

279x119mm (300 x 300 DPI)