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# Optical 'dampening' of the refractive error to axial length ratio: implications for outcome measures in myopia control studies

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## Abstract

*Purpose:* To gauge the extent to which differences in the refractive error axial length relationship predicted by geometrical optics are observed in actual refractive/biometric data.
*Methods:* This study is a retrospective analysis of existing data. Right eye refractive error [RX] and axial length [AXL] data were collected on 343 6-to-7-year-old children [mean 7.18 years (S.D. 0.35)], 294 12-to-13-year-old children [mean 13.12 years (S.D. 0.32)] and 123 young adults aged 18-to-25-years [mean 20.56 years (S.D. 1.91)]. Distance RX was measured with the Shin-Nippon NVision-K 5001 infrared open-field autorefractor. Child participants were cyclopleged prior to data collection (1% Cyclopentolate Hydrochloride). Myopia was defined as a mean spherical equivalent [MSE] ≤−0.50 D. Axial length was measured using the Zeiss IOLMaster 500. Optical modelling was based on ray tracing and manipulation of parameters of a Gullstrand reduced model eye.
*Results:* There was a myopic shift in mean MSE with age (6–7 years +0.87 D, 12–13 years −0.06 D and 18–25 years −1.41 D), associated with an increase in mean AXL (6–7 years 22.70 mm, 12–13 years 23.49 mm and 18–25 years 23.98 mm). There was a significant negative correlation between MSE and AXL for all age groups (all $p < 0.005$). RX: AXL ratios for participant data were compared with the ratio generated from Gullstrand model eyes. Both modelled and actual data showed non-linearity and non-constancy, and that as axial length is increased, the relationship between myopia and axial length differs, such that it becomes more negative.
*Conclusions:* Optical theory predicts that there will be a reduction in the RX: AXL ratio with longer eyes. The participant data although adhering to this theory show a reduced effect, with eyes with longer axial lengths having a lower refractive error to axial length ratio than predicted by model eye calculations. We propose that in myopia control intervention studies when comparing efficacy, consideration should be given to the dampening effect seen with a longer eye.

## Introduction

It is widely acknowledged that alterations in eye size or its structural components are capable of actuating refractive change.[1,2] The most unmistakeable example of this is myopia, whereby development and progression are classically a corollary of excessive axial elongation. Manifest evidence exists in the well-documented, strong, correlation between refractive error and axial length.[1,3–8] Nonetheless, a consistent course of axial length change with age has not yet been established.[9–13] Similarly, the interactions of refractive error and axial length have not been wholly elucidated. However, what is evident, is the unstable relationship between other ocular components throughout emmetropisation and myopia development; most notably a gradual reduction in crystalline lens power with age.[14] It seems plausible to speculate that there may exist a collateral variation in the refractive error: axial length correlation at different stages of ocular development, as a result of changes in the compensatory relationship between the lens and ocular length. Therefore, it follows that assumptions made on observations of one specifically aged population may not be broadly applicable to others.

Proximate to its identification as the principal correlate responsible for myopia progression in children, axial length is increasingly used as a cardinal partner to mean spherical error [MSE] as a primary outcome measure in myopia control studies. To allow comparisons in myopia progression based on the primary outcomes of refractive error and axial length, an arbitrary numerical ratio is often used. Such values have been evidenced by previous studies, for example, Deller *et al.*[15] and Atchison *et al.*,[16] who cited values of 0.33 mm $D^{-1}$ (3.03 D $mm^{-1}$) and 0.35 mm $D^{-1}$ (2.86 D $mm^{-1}$) respectively and by modelling using the Bennett-Rabbetts emmetropic schematic eye (2.7 D $mm^{-1}$).[17] However, as both research studies examined exclusively adult participants, how appropriate such figures are to the populations of the age and refractive demographic characteristics commonly used in myopia control is unclear. To use such measurements and assumptions of axial length without an explicit understanding of the optical implications of a progressively elongating element to the refractive system risks obscuring the true nature of the optical and/or refractive change and may over or under estimate efficacy of myopia control interventions.

This study will provide a comparison between differences in the refractive error to axial length relationship as predicted by geometrical optics and actual refractive/biometric data collected from a cross-sectional sample of two groups of U.K. children and one group of U.K. adults.

## Methods

### Participant data collection

Cross-sectional data from children and young adults were obtained ($n$ = 760). Data from three specific age cohorts were taken, children aged 6–7 years inclusive ($n$ = 343), children aged 12–13 years inclusive ($n$ = 294) and young adult participants (age 18–25 years inclusive, $n$ = 123). Data for the child cohorts were taken from the Aston Eye Study (AES); a study designed to determine the prevalence and associated ocular biometry of refractive error in a multi-racial sample of school children from Birmingham, UK.[18] Adult participants were recruited from Aston University's Optometry student body. See *Table 1* for a breakdown of cohort demographics by age group.

Ethical approval was granted by Aston University Research Ethics Committee. The research adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from adult participants and each child's parent or guardian before participation in the study. Verbal and/or written assent was given by each child participant prior to data collection.

**Table 1.** Cohort demographics

| | Number | Age (years) | | Ethnicity (%) | | Gender (%) | |
|---|---|---|---|---|---|---|---|
| 6–7 years | 343 | Mean | 7.1 | South Asian | 61.2 | Female | Male |
| | | S.D. | 0.35 | White | 19.2 | 48.1 | 51.9 |
| | | Range | 6.1 to 7.9 | Black | 12.5 | | |
| | | | | Mixed | 4.4 | | |
| | | | | Other | 1.8 | | |
| | | | | East Asian | 0.9 | | |
| 12–13 years | 294 | Mean | 13.1 | South Asian | 38.8 | Female | Male |
| | | S.D. | 0.32 | White | 38.4 | 55.4 | 44.6 |
| | | Range | 12.3 to 13.9 | Black | 13.6 | | |
| | | | | Mixed | 5.1 | | |
| | | | | Other | 2.4 | | |
| | | | | East Asian | 1.7 | | |
| 18–25 years | 123 | Mean | 20.6 | South Asian | 85.4 | Female | Male |
| | | S.D. | 1.91 | White | 7.3 | 54.5 | 45.5 |
| | | Range | 18.1 to 25.8 | Black | 2.4 | | |
| | | | | Mixed | 1.6 | | |
| | | | | Other | 2.4 | | |
| | | | | East Asian | 0.8 | | |

Refractive error was measured with an open-field autorefractor (Shin Nippon, Rexxam, Japan, http://www.shin-nippon.jp/) while AXL was assessed with an IOL*Master* 500 (Carl Zeiss, GmbH, Jena, https://www.zeiss.com/meditec/int/home.html). One drop each of Proxymetacaine Hydrochloride (0.5%) and Cyclopentolate Hydrochloride (1%; Minims, Bausch and Lomb) were administered to child participants before measurement. Participants were instructed to focus on a Maltese cross target placed at a distance of four metres. The average was taken from a minimum of five reliable readings for both refractive and AXL data. Corneal radius was measured using the IOL*Master* 500 (6–7 years $n$ = 336; 12–13 years $n$ = 293; 18–25 years $n$ = 117). Mean corneal curvatures (CR) were calculated for each participant as the average of steepest and flattest corneal meridians measured in millimetres. Data for the right eye are presented.

### Optical modelling

Calculations are based on the manipulation of Gullstrand reduced model eye (GME) parameters (power 60 D;

 

refractive index, 1.33; corneal radius; 5.5 mm; axial length, 22.22 mm; see *Figure 1* for schematic illustration).

Theoretical axial length values are inputted into the ray trace calculations to produce refractive errors ranging from hyperopia to myopia. Refractive error is then plotted as a function of axial length.

### Comparison of GME and actual data points

To enable comparison between the relationship between RX and AXL from the predicted GME and that from the data, each individual's ratio was calculated by dividing their MSE (D) as measured by autorefraction by their IOL*Master* obtained axial length measurement (mm). For clarity this will be herein referred to as 'actual' ratio. A theoretical ratio was then calculated for each participant by inputting their axial length in to the GME ray trace calculation to determine their predicted refractive error. The predicted refractive error was then divided by the axial length to determine their predicted ratio (henceforth termed 'GME predicted' ratio). Actual vs GME predicted ratios for each individual were then plotted graphically to facilitate analysis.

### Statistical analysis

*A priori* power analysis was performed using G*Power 3.[20] A two-tailed, linear bivariate regression (one group, size of slope) with an $\alpha$ level of 0.05 and a $\beta$ level of 0.2 was performed to compute required sample size. Calculating for a medium effect size of 0.3 resulted in a total required sample size of 82 in each group.[21,22] Division by the asymptotic relative effectivity correction (ARE 0.91) for non-parametric data adjusted the sample size to a total requirement of 91 participants per group.

For this study, myopia was defined as MSE refraction (sphere + (cylinder/2)) $\leq -0.50$ D, emmetropia as MSE $> -0.50$ D to $< +2.00$ D, and hyperopia as MSE $\geq +2.00$ D. All confidence intervals (CI) are 95%. The axial length-to-corneal radius ratio (AXL/CR ratio) was defined as the mean AXL (mm) divided by the mean corneal radius of curvature (mm).

## Results

### Optical ray-trace output

A line of best fit plotted through the data demonstrates the non-linearity and non-constant nature of the relationship (*Figure 2*). Optical calculations based on the manipulation of Gullstrand reduced model eye parameters predict a reduction in RX: AXL ratio as the axial length of the eye is increased. Modelling also shows that there is a predicted reduction in the RX: AXL ratio with increasing axial length.

### Refractive characteristics

The prevalence of myopia (MSE $\leq -0.50$ D) was 8.8% (CI, 5.8–11.7) in the 6–7 years cohort, 26.5% (CI, 21.5–31.6) in the 12–13 years cohort and 54.5% (CI, 45.7–63.3) for the 18–25 years group. For all groups, the mean spherical refractive error was not normally distributed (Shapiro–Wilk $p < 0.05$). Axial length was normally distributed in all groups (6–7 years, $p = 0.15$, 12–13 years $p = 0.56$ and adult group $p = 0.61$). See *Table 2* for mean and median MSE and mean AXL values by cohort.

### Correlation between MSE and axial length

A significant negative correlation between MSE and axial length was found in all three groups (Spearman's Rank 6–7 years $r_s$ (341) = −0.37, $p < 0.005$; children aged 12–13 years, $r_s$ (292) = −0.48, $p < 0.005$ and adults, $r_s$ (121) = −0.68, $p < 0.005$; see *Figure 3*).

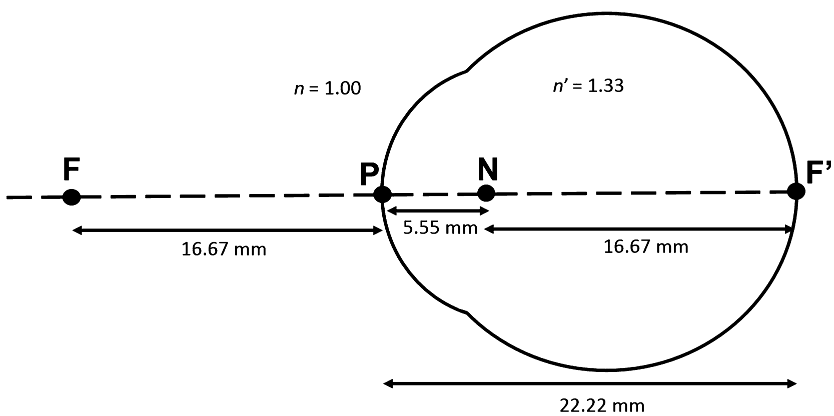


**Figure 1.** Schematic illustration of Gullstrand reduced eye model redrawn from Elmsley.[19] Here, *F* is the first focal point, *F'* the second focal point, *P* the principal point, *N* the nodal point, *n* the refractive index of air and *n'* the refractive index of the eye. The model has a total axial length of 22.22 mm, a corneal radius of 5.55 mm, and an overall power of 60 D.

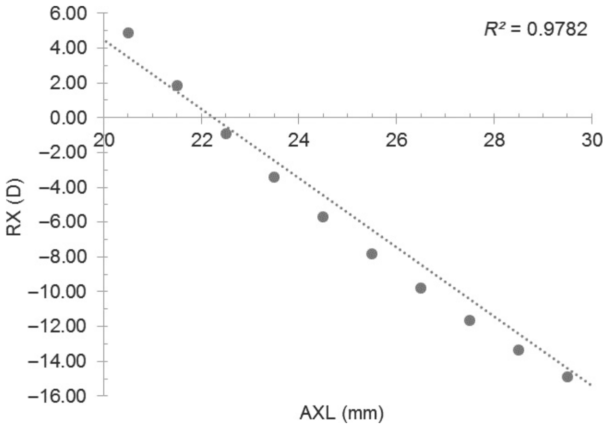


**Figure 2.** The relationship between axial length (AXL) and refractive error (RX) as predicted from calculations using Gullstrand reduced model eye parameters.

### Refractive error and axial length relationship for varying axial lengths

The inverse of the regression slopes for each data set as presented in *Figure 3* were calculated. For the specific cohorts, 1 mm difference in axial length equates with −3.58 D [Fisher's transformation *z*-score ($z$) 0.55, S.E. 0.05] of refractive error difference for the 6–7-year-olds, −3.10 D ($z$ 0.59, S.E. 0.06) for the 12–13-year-olds and −2.49 D ($z$ 0.87, S.E. 0.09) for the young adult group. To enable comparison with previous studies, this is equivalent to values per dioptre of myopia of 0.28 mm for the 6–7-year-olds, 0.32 mm for the 12–13-year-olds and 0.40 mm for the 18–25-year-olds.

Linear regression adjusted for age showed that a 0.05 decrease in RX: AXL ratio ($p < 0.001$) was observed per 1 mm increase in axial length. RX: AXL ratio was less negative than predicted from GME modelling with increasing AXL (see *Figure 4*). Decision Tree Analysis (DTA) found ethnicity and sex to have no significant impact on ratio (all $p > 0.05$).

### Refractive error and axial length relationship for low and high levels of myopia

We are specifically interested in the relationship between refractive error and axial length in lower levels of myopia vs higher levels. To address this, data for all myopes were split into two groups: (1) low myopia MSE between −0.50 D and <−3.00 D ($n$ = 123), (2) high myopia MSE −3.00 D or greater ($n$ = 45).

The relationship between myopia and axial length was derived by calculating the inverse of the regression slopes for each data set for low and high myopia. For the specific cohorts, 1 mm difference in axial length was associated with −3.13 D of refractive difference ($z$ = 0.47, S.E. 0.09) for the low myopes and −1.72 D ($z$ = 0.54, S.E. 0.15) for the high myopes.

### Corneal curvature and AXL/CR Ratio

Mean corneal radii were as follows: 6–7 years mean = 7.78 mm (S.D. 0.27); 12–13 years mean = 7.77 mm (S.D. 0.28), 18–25 years mean = 7.81 mm (S.D. 0.28). AXL/CR ratio values were as follows: 6–7 years = 2.92 (S.D. 0.16); 12–13 years = 3.02 (S.D. 0.12), 18–25 years = 3.06 (S.D. 0.14). See *Figure 5* for graphical representation of AXL/CR ratio plotted against MSE. A significant negative correlation between MSE and AXL/CR ratio was found in all three groups (Spearman's Rank 6–7 years, $r_s$ (334) = −0.51, $p < 0.005$, 12–13 years, $r_s$ (291) = −0.61, $p < 0.005$ and adults, $r_s$ (115) = −0.81, $p < 0.005$) (see *Figure 5*).

## Discussion

This study is the first to explicitly illustrate the optics of dampening in the context of the relationship between refractive error and axial length, as well as the extent to which these predictions are mirrored in actual data collected from the human eye. Additionally, through presenting data for a large group of ethnically diverse U.K. children and adults with a wide range of ametropias, this study highlights the complexities related to making inter-age-group comparisons. Furthermore, though there is clearly a place for approximate estimation values of Dioptres mm$^{-1}$, the findings of this study illustrate the intrinsic difficulties associated with doing so, and underlines that they should only be used with caution and an awareness of their limitations, particularly so when used for the purpose of assessment of any myopia control outcome.

**Table 2.** Mean and median MSE and mean AXL values for each cohort

| Age group | Mean MSE (D) | S.D. | Range (D) | Median MSE (D) | IQR | Mean AXL (mm) | S.D. | Range (mm) |
|---|---|---|---|---|---|---|---|---|
| 6–7 | +0.87 | 1.39 | +7.60 to −8.81 | +0.81 | 1.04 | 22.70 | 0.78 | 19.66 to 25.26 |
| 12–13 | −0.06 | 1.42 | +5.56 to −5.66 | +0.15 | 1.16 | 23.49 | 0.86 | 20.56 to 26.09 |
| 18–25 | −1.41 | 1.95 | +3.08 to −10.48 | −0.70 | 2.13 | 23.98 | 1.12 | 21.40 to 27.70 |

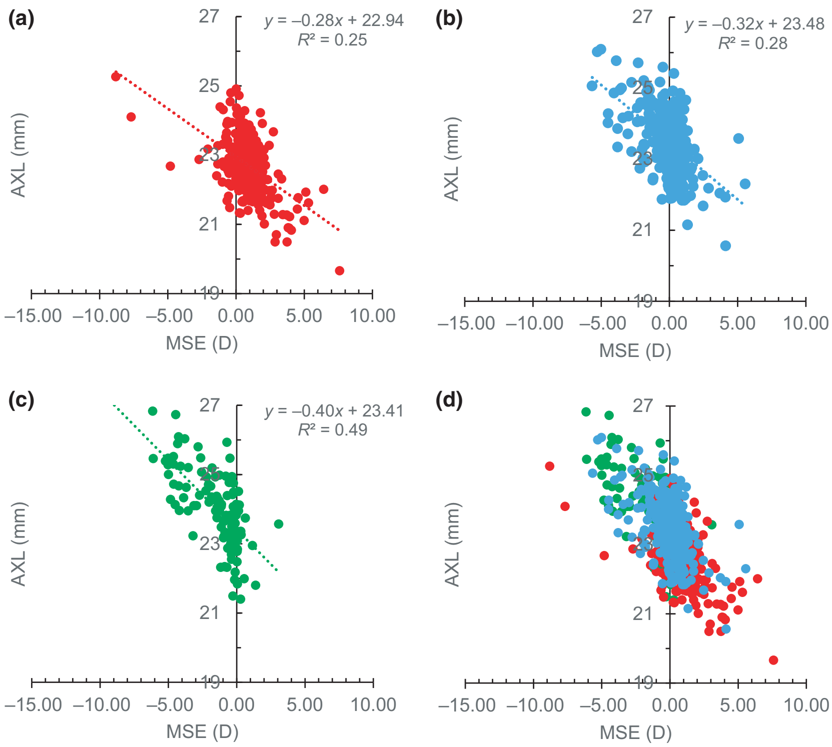


**Figure 3.** The correlation between MSE (D) and AXL (mm) for (a) 6–7-year-old participants (red markers), (b) 12–13-year-old participants (blue markers) and (c) 18–25-year-old participants (green markers). (Panel d) presents a composite graph of data for all cohorts.

The GME modelling data suggest that the relationship between refractive error and axial length should show a characteristic non-linearity and non-constancy (see *Figure 2*). Both of these patterns are evidenced in the human eye data in all cohorts (see *Figure 3*). An additional prediction of the modelling is that as axial length is increased, less myopia is induced per mm of axial length and the RX: AXL ratio becomes more negative (see GME model data, *Figure 4*). Again, the human eye data adhere to this pattern, showing that there is indeed a reduction in RX: AXL ratio with increasing axial length ($p < 0.001$) (see *Figure 4*). However, the effect was found to be less marked than the modelling would predict, indicated by the increasing disparity between the actual and predicted data points plotted on *Figure 4*. Accordingly, it seems that effectivity does produce a dampening of the RX: AXL relationship with increasing axial length, however this cannot be predicted solely on the basis of theoretical calculations and is not as extreme in the human eye as pure optics would suggest. Nonetheless, the level of dampening observed is still significant, and as such, holds potential implications when using axial length as an outcome measure in clinical trials of myopia control.

In the current study, the coefficient of determination between axial length and mean spherical error became stronger for each increasing age group both considering all refractive errors (6–7 years $R^2 = 0.25$; 12–13 years $R^2 = 0.28$ and 18–25 years $R^2 = 0.49$) and for myopes only (6–7 years $R^2 = 0.21$; 12–13 years $R^2 = 0.24$ and 18–25 years $R^2 = 0.45$). Previous studies of child populations have also evidenced the strong correlation between refractive error and axial length.[5,23–25] Range of refraction has been speculated as the reason for differences in correlation between some studies, with a low range giving a lower correlation coefficient.[26] From the values given for the relationship between refractive error and axial length for lower and higher levels of myopia in the current study (−3.13 D of refractive change for the low myopes and −1.72 D for the high myopes), it would appear that for lower levels of myopia 1 mm difference in axial length has a more profound effect on refractive error than for higher levels of myopia. This is also reflected in the predicted reduction in RX: AXL ratio forecast by the optical modelling presented. However it needs to be quantified that estimations made for the difference in eye size per dioptre increase in myopia are related to the distribution and magnitude of myopia in a population. Though arguably arbitrary and theoretical, such figures are useful and commonly used a clinical approximation to help to understand and estimate the link between axial length and refractive error. The illustrations made in the current study lead us to make the recommendation that caution should be taken when applying these

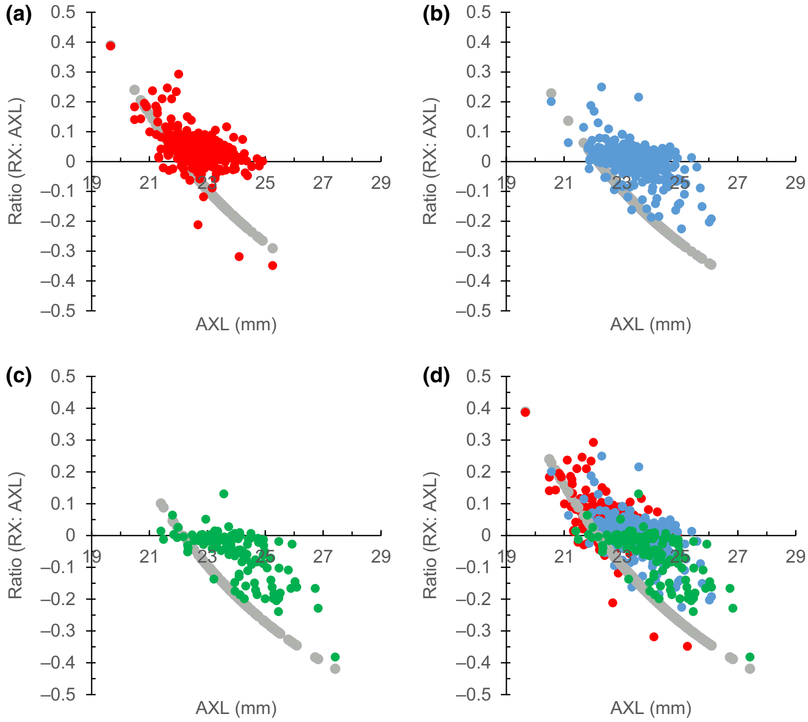


**Figure 4.** RX:AXL ratio (coloured markers) plotted as a function of AXL for (a) 6–7-year-old participants (red markers), (b) 12–13-year-old participants (blue markers) and (c) 18–25-year-old participants (green markers). Panel (d) presents a composite graph of data for all cohorts. Also plotted on each panel is the RX:AXL ratio as predicted from Gullstrand model eye calculations based on each participant's axial length – these are shown in grey for the purpose of comparison.

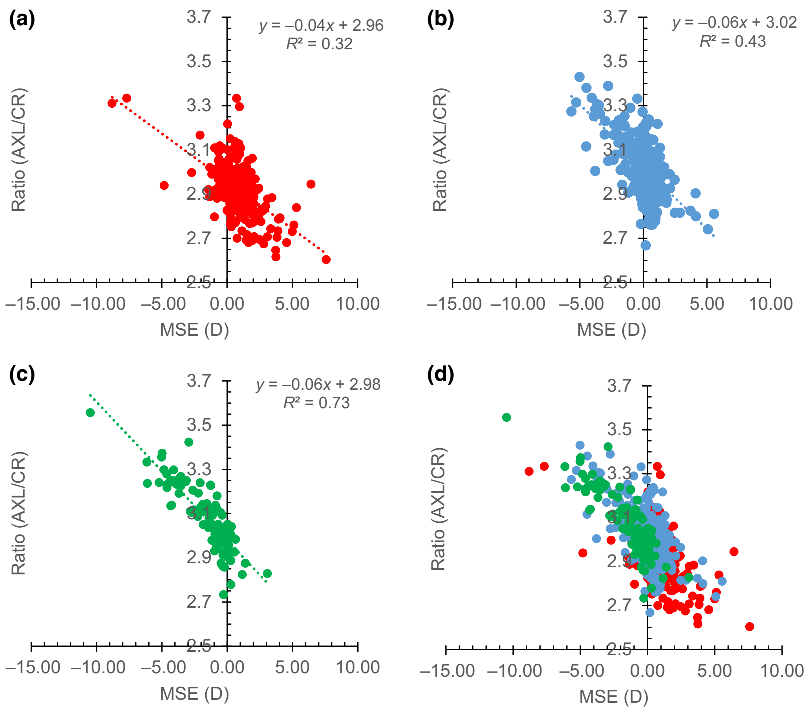


**Figure 5.** The association between MSE (D) and AXL/CR ratio for (a) 6–7-year-old participants (red markers), (b) 12–13-year-old participants (blue markers) and (c) 18–25-year-old participants (green markers). (Panel d) presents a composite graph of data for all cohorts.

assumptions to populations with different refractive characteristics, as one standard approximation figure is not universally applicable and is not necessarily representative, given the changing prevalence of refractive error with ocular development and growth. Instead, an appropriately matched figure should be used, as the failure to do so to approximate the efficacy of myopia control interventions has the potential to confound the effect of the treatment modality in question.

One limitation of this work is that cross-sectional data have been used, and as such we are unable to report specific change in refractive error with axial length for an individual. However the findings contained herein may allude to potential ramifications for longitudinal data which examine axial growth under myopia control conditions. By way of illustration, one dioptre of myopic progression in a shorter eye would correspond with less axial growth than would occur for the same refractive change in a longer eye. There are also particular consequences here for interventions or monitoring conducted in clinical practice, where comparisons cannot easily be drawn with matched groups. In terms of research studies, if we are comparing efficacy across a range of baseline levels of myopia, potentially a dioptre change for eyes with lower myopias would have less associated growth, whereas the same change in eyes with higher myopias would show a greater increase in length. This perhaps suggests that it is not necessarily appropriate to consider refractive error and axial length as interchangeable outcome measures. Another point to consider related to interchangeable measures is that data for the current study report refractive error measures taken with an autorefractor whose measurements are taken over approximately a 3 mm area and compares the data with axial length measured at the fovea.

Ocular growth and refraction are dynamic and change irregularly over the period leading to ocular maturity.[24,27,28] Studies have shown that despite the fact that corneal power does not alter significantly following the first few years of life,[14,25,29–31] the crystalline lens has been shown to undergo several substantial age related changes in the early years[14,27] which continue into school-age,[24,25] namely a flattening of surface curvatures,[14,32,33] decrease in refractive index,[14,29-30,] decrease in lens thickness[14,30,33–35] and resultant loss of power.[14,29,30,33] This fluidity in the coordination of ocular components may be sufficient to cause dissimilar relationships between axial length and refractive error in eyes at different stages of development. Longitudinal[36] and cross-sectional studies[14] have shown that in terms of refraction and ocular growth, the older eye cannot be considered as a simple scaled up version of the infant eye. The current study concludes that the longer eye cannot be assumed to have the same mathematical relationship between refractive error and axial length as a shorter eye. However, the discrepancy between modelled and actual data points expose that there may be some intrinsic compensatory mechanism from other ocular refractive structures which can wholly or in part account for optical dampening. In conclusion, these findings are further testimony as to how interlinked the optics, physiology and aetiology of the myopic eye are, and affirms the importance of understanding it as a whole to underpin the ever-evolving landscape of myopia control and to ensure that interventions are evaluated in the most appropriate fashion possible.

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## Disclosure

The authors report no conflicts of interest and have no proprietary interest in any of the materials mentioned in this article.

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