Variations in Eye Volume, Surface Area, and Shape with Refractive Error in Young Children by Magnetic Resonance Imaging Analysis

Laurence S. Lim,1 Xianfeng Yang,2 Gus Gazzard,1,5 Xiaoyu Lin,4 Chelvin Sng,5 Seang-Mei Saw,1,4 and Anqi Qiu2,6,7

PURPOSE. To determine variations in eye volume, surface area, and shape with refractive error in young children using a three-dimensional magnetic resonance imaging (MRI) model.

METHODS. A subset of Singaporean Chinese boys enrolled in the population-based Strabismus, Amblyopia, and Refractive Error in Singapore (STARS) study underwent MRI using a 3-Tesla whole body scanner with a 32-channel head coil. Eye volume and surface area were measured. Eye shape was assessed qualitatively from the three-dimensional models and quantitatively by measurement of the longitudinal axial length (LAL), horizontal width, and vertical height along the cardinal axes.

RESULTS. One hundred thirty-four eyes of 67 subjects (mean age, 77.9 ± 3.9 months) were analyzed. The mean spherical equivalent (SE) refraction was 0.65 ± 0.92 D (range, −2.31 to 4.13 D). More myopic SE was associated with larger surface area (−20.59 [−37.09 to −4.10] mm²/D; P = 0.01) but not volume. In age-height adjusted models, more myopic SE was associated with longer LAL (−1.94 [−2.47 to −1.41] mm/D; P < 0.001) and greater width (−1.12 [−1.26 to −0.99] mm/D; P < 0.001) but not height (0.64 [−2.55 to 3.82] mm/D; P = 0.70). In nonmyopic subjects, less hyperopic SE was associated with longer AL (−0.40 [−0.71 to −0.10] mm/D; P = 0.01), width (−0.59 [−0.84 to −0.34] mm/D; P < 0.001), and height (−0.40 [−0.64 to −0.17] mm/D; P = 0.001). In three-dimensional models, myopic eyes conformed to an axial elongation model with a prolate profile in the axial plane, whereas nonmyopic eyes showed global expansion.

CONCLUSIONS. Eye surface area increases with myopia in young children. Eye shape is different in myopia, even in its early stages. Axial globe enlargement occurs in myopic eyes leading to a prolate shape, whereas nonmyopic eyes enlarge globally in length, width, and height. (Invest Ophthalmol Vis Sci. 2011; 52:8878–8883) DOI:10.1167/iovs.11-7269

The reported prevalence of myopia varies widely, with particularly high rates among Chinese East Asian populations such as those in Taiwan and Singapore.1–3 Understanding the pathogenesis of myopia is important for formulating prevention strategies. Pathologic myopia is associated with potentially blinding complications such as retinal detachment, choroideal neovascularization, and macular holes,4–6 and even less severe forms of myopia predispose to glaucoma and cataract in adulthood.7,8 Furthermore, the lifetime socioeconomic costs of myopia are considerable.9–11 Several risk factors for myopia in children have been identified in large-scale epidemiologic studies. These include a genetic basis for myopia susceptibility12–13 and a diverse range of environmental factors such as near work, outdoor activity, socioeconomic background, and nutrition.14–19 Yet the pathogenetic mechanisms underlying myopia development remain poorly understood. Longer axial globe dimensions have long been recognized to be associated with myopia, but the anatomic deviation from normal ocular anatomy involves more complex three-dimensional shape changes than are captured in a single-dimension axial measurement previously possible with ultrasound or partial coherence interferometry.20 Thus, the three-dimensional shape of the eye is an important area of myopia research.21 Studies on peripheral refraction have shown relative peripheral myopia and hyperopia horizontally in hypermetropic and myopic eyes, respectively,22–27 suggesting an oblate shape in the former and a prolate shape in the latter.25 In the vertical meridian, however, both myopic and hyperopic eyes show relative myopia, further illustrating the need for a three-dimensional appreciation of eye shape in ametropia.

The advent of high-resolution magnetic resonance imaging (MRI) and computer software for three-dimensional modeling has allowed for the direct study of eye shape in vivo. Cheng28 found that myopic eyes had the same spheroidal-elliptical shape as hyperopic and emmetropic eyes. Atchison29 studied the shape of the retinal surface in hyperopia and myopia and found that both emmetropic and myopic retinas were oblate. In another analysis30 on the shape of the globe imaged by MRI, the same authors found that myopic eyes were elongated more in length but that approximately equal proportions of myopic eyes fit global expansion and axial elongation models exclusively. An important question that has thus arisen from this work is whether and how the shape of a myopic eye differs from that of a nonmyopic eye.30

No study to date has assessed eye shape in young children using MRI, perhaps because of the obvious logistic difficulties. Evaluating this population may be particularly informative because it provides information on the earliest changes in the myopic eye. The aim of this study was to determine global variations in eye volume, surface area, and shape, as well as...
regional variations in the posterior globe, with refractive error in young children using a three-dimensional MRI model.

**Subjects and Methods**

**Subjects**

A subset of Singaporean Chinese boys aged 6 years (72 months) was recruited from the Strabismus, Amblyopia, and Refractive Error in Young Singaporean Children (STARS) study, a population-based survey of 3009 Singaporean children aged 6 to 72 months conducted in the southwestern part of Singapore. All study procedures were performed in accordance with the tenets of the Declaration of Helsinki as revised in 1989.

**Eye Examination**

Eye examinations in STARS were conducted by trained ophthalmologists, optometrists, and orthoptists. The study procedures have been described in detail elsewhere. Briefly, distance visual acuity measurements were obtained using a 4-m logarithm of the minimum angle of resolution (logMAR) visual acuity chart (nonilluminated ETDRS chart with Sloan letters). Cycloplegic objective refraction was performed using a keratometer (Autorefractor RK-F1; Canon, Tokyo, Japan). Cycloplegic objective refraction was assessed approximately 30 minutes after topical instillation of 3 drops of 1% cyclopentolate and 2.5% phenylephrine each, given 5 minutes apart. Five consecutive readings were obtained. Each autorefractor was calibrated before testing on a daily basis, and the same two autorefractors were used for all subjects throughout the study. Autorefractor readings were within ±0.25 diopters (D) of each other. If the autorefractive test failed, streak retinoscopy (Welch Allyn, Chessy, France) was performed by a trained study optometrist.

Axial length (AL) measurements were obtained using a noncontact partial coherence interferometer (IOLMaster; Carl Zeiss, Jena, Germany). Five consecutive readings were obtained for AL, with a signal-to-noise ratio >2.0.

**MRI Acquisition**

The children were asked to close the eye in the scanner so that less motion would occur during the fast image acquisition. Both T1-weighted magnetization prepared rapid gradient recalled echo (TR = 2000 ms; TE = 2.08 ms; flip angle = 9°) and double spin-echo T2-weighted and proton density (PD) images (TR = 3040 ms; TE1 = 11 ms; TE2 = 123 ms; flip angle = 120°) were acquired at the Clinical Imaging Research Centre at the National University of Singapore, on a 3-Tesla whole body scanner (Magnetom Trio Tim; Siemens, Washington, DC) with a 32-channel head coil. Each T2-weighted volume consisted of 190 sagittal slices of 1-mm thickness with no gap (FOV, 190 mm × 190 mm). Each T2-weighted volume consisted of 42 axial slices of 3-mm thickness with no gap (FOV, 220 mm × 220 mm). Both T1- and T2-weighted images covered both left and right eyes. The scanning time of the T1 and T2-weighted images were, respectively, 3 minutes 36 seconds and 2 minutes 16 seconds. For the T1 image, from top to bottom, the spatial resolution was 3 mm, whereas the resolution in-plane was 1 mm × 1 mm. For the T2 image, the spatial resolution was 1 mm × 1 mm × 1 mm.

Written informed consent from the parents of subjects and assent from the child when appropriate were obtained. The study was approved by the Institutional Review Board of the National University of Singapore.

**MRI Eye Segmentation Analysis**

We developed an atlas-based segmentation approach to automatically delineate the left and right eyes from the T2-weighted image. Within each subject, we first aligned the T2-weighted image to the T1-weighted image through a rigid transformation (rotations and translations) to compensate for the spatial resolution in the T2-weighted image. Then the T2-weighted image of one subject, whose left and right eyes were manually delineated, was chosen as the atlas image. We further used the affine and nonlinear transformations obtained from a large deformation diffeomorphic metric mapping to deform the atlas image (Fig. 1A) to be like the subject image (Fig. 1B). Finally, the surface of the atlas eye (Fig. 1C) was deformed through the affine and nonlinear transformations to approximate the eye shape of the subject (Fig. 1D). Validation of the segmentation was evaluated by comparing the ALs obtained from MRI and a partial coherence interferometer (PCI).

**Three-Dimensional Eye Coordinate System**

As illustrated in Figure 1, we constructed a three-dimensional coordinate system for each eye by first determining the long axis and then the horizontal and vertical axes. The assumption was that the shape of the eye could be characterized by two spheres: one modeled on the corneal region and the other modeled on the vitreous humor. One sphere encompassed the whole of the corneal region and the other encompassed the whole of the posterior chamber. The geometric center of the eye was then represented by the center of the sphere containing the vitreous humor. The long axis of the eyeball was defined as the line passing through the centers of the two spheres. The traditional AL was computed as distance between the most anterior and posterior points of the long axis. The vertical axis was then determined as the cross-product between the long axes of the left and right eyes. Finally, the...
horizontal axis of each eye was determined as the cross-product of the long and vertical axes.

**Eye Volume, Surface Area, and Shape Measurements**

The volume of the eye was computed as the number of voxels in the eye region (inside cyan contour in Fig. 1B), and the surface area of the eyeball was approximated as the area of the eye surface (Fig. 1D).

We further characterized the shape of the eye by ALs in the directions from the eye’s geometric center to posterior, from temporal to nasal, and from superior to inferior, respectively, referred to hereafter as longitudinal axial length (LAL), horizontal width, and vertical height.

We first measured the LAL at multiple locations on the sagittal and horizontal planes passing through the geometric center of the eye. As illustrated in Figure 2A, the vertical axis was evenly divided into 20 segments, where lines parallel to the long axis were drawn on the sagittal plane. The lengths of these lines from the vertical axis to the posterior boundary of the eye were computed and used to characterize the shape of the eye on the sagittal plane. In addition, we measured LAL on the horizontal plane passing the geometric center of the eye. As illustrated in Figure 2E, the horizontal axis was evenly divided into 20 segments, where lines parallel to the long axis were drawn. The lengths of these lines from the horizontal axis to the posterior boundary of the eye were computed and used to characterize the shape of the eye on the horizontal plane.

As illustrated in Figure 3A, we then measured the horizontal width at multiple locations on the horizontal plane, where the long axis from the eye’s geometric center to the posterior boundary of the eye was divided into 10 segments. The horizontal width at each location was measured as the distance between the most temporal and nasal points of the line parallel to the horizontal axis. Finally, we defined the vertical height at multiple locations on the sagittal plane where the long axis from the eye’s geometric center to the posterior boundary of the eye was divided into 10 segments. As shown in Figure 3E, the vertical height was calculated as the distance between the superior and inferior points of the line parallel to the vertical axis at each segment of the long axis.

**Statistical Analysis**

For the purposes of the study, myopia was defined as spherical equivalent refraction (SE) ≤ −0.5 D. Multivariable linear regression models were constructed with eye volume, surface area, and dimensions as the dependent variables and SE as independent variables, with adjustments for age and height. All probabilities quoted were two-sided, and all statistical analyses were undertaken using statistical analysis software (SPSS, version 16.0; SPSS Inc., Chicago, IL).

**RESULTS**

One hundred thirty-four eyes of 67 male Chinese subjects (mean age, 77.9 ± 3.9 months) were analyzed. The SE refraction was normally distributed with a mean of 0.65 ± 0.92 D (range, −2.31 to 4.13 D). The mean LAL, width, and height were 22.94 ± 1.01 mm, 21.90 ± 0.93 mm, and 23.91 ± 1.03 mm, respectively, and the average values of the eye volume and surface area were 6690.39 ± 623.23 mm³ and 1757.05 ± 109.58 mm², respectively. Five children were found to have myopia in at least one eye, and four had bilateral myopia. Myopic children were older (79.60 ± 3.44 months vs. 77.92 ± 3.80 months; P = 0.34) and shorter (97.16 ± 5.70 cm vs. 108.85 ± 4.84 cm; P < 0.001) than nonmyopic children. The mean SE in myopic eyes was −1.17 ± 0.63 D, whereas in nonmyopic eyes it was 0.78 ± 0.79 D (P < 0.001). To evaluate...
the accuracy of the MRI segmentation, the LAL obtained from MRI was compared with the AL using a PC; no significant differences were found.

Eye surface area (regression coefficient, −27.40 [95% confidence interval: −45.67 to −9.13]; P = 0.003) but not volume was significantly associated with SE. These relationships persisted in age- and height-adjusted models. More myopic SE was associated with larger surface area (−20.59 [−37.09 to −4.10] mm²/D; P = 0.01) but not volume.

In unadjusted analyses of myopic subjects (SE ≤ −0.5 D), more myopic SE was associated with longer LAL but not width or height. With age-height adjustment, more myopic SE was associated with longer LAL (−1.94 [−2.47 to −1.41] mm/D; P < 0.001) and greater width (−1.12 [−1.26 to −0.99] mm/D; P < 0.001) but not height (0.64 [−2.55 to 3.82] mm/D; P = 0.70).

In nonmyopic subjects, less hyperopic SE was associated with longer AL (−0.32 [−0.60 to −0.04] mm/D; P = 0.03), width (−0.50 [−0.69 to −0.32] mm/D; P < 0.001), and height (−0.33 [−0.54 to −0.12] mm/D; P = 0.002) in unadjusted analyses. These relationships persisted with age-height adjustment (−0.40 [−0.71 to −0.10] mm/D, P = 0.01; −0.59 [−0.84 to −0.34] mm/D, P < 0.001; and −0.40 [−0.64 to −0.17] mm/D, P = 0.001, respectively).

Figure 4 shows the three-dimensional models of myopic eyes that demonstrate the shape changes among myopic eyes, especially along the long axis. Myopic eyes conformed to an axial elongation model with a prolate profile in the axial plane and an increasing prolate profile with more myopic SE. Nonmyopic eyes, on the other hand, showed global expansion.

To quantify the shape of the back of the eye and its relationship with SE, we measured the long axis length, horizontal width, and vertical height at multiple locations (Figs. 2, 3).

Figures 2B and 2D illustrate the length of the long axis as a function of the locations at the normalized vertical axis (illustrated in Fig. 2A) and horizontal axis (illustrated in Fig. 2C). Red and black curves are the average lengths of the long axis within any location in nonmyopic subjects, but significant negative correlations were found at every location in myopic subjects. In myopic subjects, there was no significant correlation (P < 0.05) between SE and vertical height at any location in myopic subjects. However, in nonmyopic subjects, significant negative correlations (P < 0.05) were found between SE and vertical height at any location in nonmyopic subjects.

DISCUSSION

Eye surface area is larger with myopia in young children. The relationship between SE and eye shape in myopic subjects is different from that in nonmyopic subjects. Axial elongation and expansion in width occur in myopic eyes leading to a prolate shape, whereas nonmyopic eyes expand globally in length, width, and height with less hyperopic refraction. To the best of our knowledge, our study is the first to evaluate three-dimensional variations in eye dimensions and shape in vivo in young Asian children.

The extant data on variations in eye shape with refractive error are limited. The two main approaches that have been used in analyzing eye shape in vivo are indirect inferences from peripheral refraction and direct assessments from imaging. Extrapolating from the assumption that emmetropic eyes are spherical, Mutti25 suggested that hypermetropic eyes had to be oblate (wider equatorial diameter than AL) and myopic eyes to be prolate in the horizontal plane to account for peripheral refraction findings of relative peripheral myopia and hyperopia in hypermetropic and myopic eyes, respectively. Studies in other adult populations by Middordof59 and Athchison70 have also found peripheral refraction findings of relative peripheral myopia and hyperopia in hypermetropic and myopic eyes, respectively, whereas a recent publication27 from our cohort has demonstrated similar findings in children. In the vertical plane, however, the relative peripheral refraction profile has not demonstrated similar peripheral hyperopia in myopic eyes.22 41

In an X-ray study of 45 eyes of primarily adult subjects conducted in 1947, Deller28 reported that the longest dimension of myopic eyes was the AL, indirectly suggesting a prolate shape, whereas emmetropic and hypermetropic eyes were spherical, oblate, or prolate. More recently, MRI has been applied toward providing more detailed, higher resolution images of ocular anatomy. Cheng20 evaluated the globe dimensions along the three cardinal axes in a small cohort of eight hypermetropic eyes, six emmetropic eyes, and seven myopic eyes. Emmetropic and hyperopic eyes were similar in shape, and both had equatorial diameters that were longer than the axial and vertical diameters. However, myopic eyes, though larger than emmetropic
and hypermetropic eyes, did not deviate from the spheroidal shape of the latter. Based on the results of a study on eye shape in emmetropia and myopia conducted on 88 participants aged 18 to 36 years, Atchison considered three mechanisms of globe enlargement in myopia: equatorial elongation, global elongation, and posterior polar elongation. The equatorial elongation model is associated with increases in length but not width or height, whereas the global expansion model is defined by proportionate increases in all three dimensions. The posterior polar elongation model is associated with changes occurring in the most posterior locations of the globe. With increasingly myopic refraction, eyes became larger in all three dimensions, greater in length than height and in height than width. Based on height and length, 25% and 29% of myopic eyes exclusively fitted global expansion and axial elongation models, respectively, whereas based on width and length dimensions, 17% and 39% of myopic eyes exclusively fitted the global expansion and axial elongation models, respectively. In a subsequent study comparing the shape of the retinal surface in 21 emmetropic and 66 myopic eyes in subjects aged 18 to 36 years, the same authors reported that globe shapes were oblate in most of the emmetropic eyes, which meant that the axial dimensions were smaller than both the vertical and the horizontal dimensions. With increasingly myopic refraction, all ellipsoid dimensions increased with axial dimension increasing more than vertical dimension, which, in turn, increased more than horizontal dimension, indicating a decreasingly oblate profile. However, despite the inclusion of subjects with very high levels of myopia (up to −12D), few eyes were frankly prolate.

In our study, although eye volume and surface area increased with myopia in both myopic and nonmyopic eyes, our results indicate a contrast between refractive error and the globe dimensions along the cardinal axes for myopic and nonmyopic eyes. In myopic eyes, the overall refractive status of the eye was correlated with the length and the width but not the height of the globe, with greater changes in length than height per diopter of refractive error. Nonmyopic (emmetropic or hypermetropic) eyes, however, showed correlations with all three dimensions, with width showing the greatest change per diopter of refractive error, followed by height, and length showing the smallest change per diopter. Furthermore, by correlating the length, width, and height at multiple, equally spaced loci along the normalized cardinal axes with refractive error, our study has provided more comprehensive evidence that the changes in the shape of the myopic eye occur primarily in the central, posterior paraxial region of the retina, whereas the changes in the nonmyopic eye with less hyperopic/more myopic refraction are global. These changes, though grossly evident in pathologic myopia and in adulthood, were detectable in our population of young children with relatively low myopia.

Thus, nonmyopic eyes are expanded globally, but the myopic globe is primarily elongated and the eyeball assumes a prolate shape even at a very early age. This is consistent with clinical observations of the typical locations of posterior staphylomata in pathologic myopia and with the heavy eye phenotype of high myopia and is likely to be macular driven. The mechanisms regulating scleral expansion in myopia are still poorly understood. Asymmetric deformation has been reliably reproduced in chicks with a variety of experimental manipulations, including partial goggles and adjustments to the ground and sky, and biochemical studies have shown regional differences in the expression of proteolytic enzymes to lend mechanistic credence to these findings. The factors predisposing to myopia would seem to affect the elongation of globe AL in a myopic child at a very young age. The relative contributions of genetic and environmental risk factors in myopia are unclear, but the presence of differences in eye shape discernible at such an early age tend to suggest that genetic factors exert a greater influence.

The strengths of our study design include the availability of ocular measurements, including cycloplegic refraction performed according to a standardized protocol, and a relatively large population-based sample. MRI scans in young children are difficult to obtain because, in no small part, of the need for subject cooperation, and our study is the first to provide data on this population. Analyzing eye shape based solely on measurements along the cardinal axes, as in some earlier studies, does not provide information on regional variations, a limitation we have attempted to overcome by correlating measurements at multiple points with refractive error. General limitations include the cross-sectional nature of our study, which limited inferences of causation, and the relatively small proportion of myopic children. The results may also be biased because we analyzed only a subset of the total cohort, and the children who were excluded from our analyses may exhibit different patterns of eye shape. Other studies using MRI to analyze eye shape have also had higher resolution images than we had. This is, however, a nondifferential error that should not affect the relationships we found.

In conclusion, our study suggests that eye shape is different in myopic and nonmyopic children even at a very young age, with the former manifesting asymmetric axial globe elongation and the latter global expansion. These differences are evident even at low levels of ametropia. Studying young children is particularly advantageous because it minimizes the confounding effects of other ocular pathology, such as nuclear sclerosis on refractive error measurement, and it provides insights into the earliest changes of myopia. Further longitudinal study to determine whether evolution to pathologic myopia occurs in later life is warranted.

References
