British journal of
OPHTHALMOLOGY

Estimation of ocular volume from axial length

Journal:	*British Journal of Ophthalmology*
Manuscript ID:	bjophthalmol-2013-304652.R1
Article Type:	Clinical science
Date Submitted by the Author:	26-May-2014
Complete List of Authors:	Nagra, Manbir; Aston University, School of Life and Health Sciences Gilmartin, Bernard; Aston University, Optometry Logan, nicola; Aston University, Optometry
Keywords:	Optics and Refraction, Eye (Globe), Imaging

Title: Estimation of ocular volume from axial length

Corresponding author details: Manbir Nagra

Postal Address: School of Life & Health Sciences, Aston University, Aston Triangle, Birmingham B4 7ET
UK

Email address: m.nagra@aston.ac.uk
Tel: 44 (0) 121 204 4171
Fax: 44 (0) 121 204 4048

Co-authors
Bernard Gilmartin
School of Life & Health Sciences, Aston University, Aston Triangle, Birmingham B4 7ET, UK

Nicola S Logan
School of Life & Health Sciences, Aston University, Aston Triangle, Birmingham B4 7ET, UK

Keywords:

myopia, ocular biometry, ocular volume, refractive error

Word count (excluding title page, abstract, references, figures and tables and figure/table legends): 1847 words

Title: Estimation of ocular volume from axial length

ABSTRACT

BACKGROUND/AIMS:

To determine which biometric parameters provide optimum predictive power for ocular volume.

METHODS: Sixty-seven adult subjects were scanned with a Siemens 3-T MRI scanner. Mean Spherical Error, MSE (D) was measured with a Shin-Nippon autorefractor and a Zeiss *IOLMaster* used to measure (mm) axial length (AL), anterior chamber depth (ACD) and corneal radius (CR). Total ocular volume (TOV) was calculated from T2-weighted MR images (voxel size 1.0mm^3) using an automatic voxel counting and shading algorithm. Each MR slice was subsequently edited manually in the axial, sagittal and coronal plane, the latter enabling location of the posterior pole of the crystalline lens and partitioning of TOV into anterior (AV) and posterior (PV) regions.

RESULTS: Mean values (±sd) for MSE (D), AL (mm), ACD (mm) and CR (mm) were -2.62±3.83, 24.51±1.47, 3.55±0.34, 7.75±0.28, respectively. Mean values (±sd) for TOV, AV and PV (mm^3) were 8168.21±1141.86, 1099.40±139.24, 7068.82±1134.05, respectively. TOV showed significant correlation with MSE, AL, PV (all $p<0.001$), CR ($p=0.043$), and ACD ($p=0.024$). Bar CR, the correlations were shown to be wholly attributable to variation in PV. Multiple linear regression indicated that the combination of AL and CR provided optimum R^2 values of 79.4% for TOV.

CONCLUSION: Clinically useful estimations of ocular volume can be obtained from measurement of AL and CR.

INTRODUCTION

A recent comprehensive review of factors contributing to the aetiology of myopia included an analysis of the association between myopia and ocular disease.[1] It was demonstrated that the risk of disease, traditionally linked to dioptric levels greater than 6D, was also significant between 1 and 3D, a level generally described as physiological myopia. [2] Further, the review demonstrated that risk was not confined to myopia as hyperopia is associated with higher rates of exudative age-related maculopathy and angle closure glaucoma.[1] Longitudinal axial length is the principal structural correlate for refractive error[3,4] and a recent cross-sectional study on 120 Hong Kong children used binary logistic regressions to demonstrate that after adjusting for myopia over -8D, age, gender, duration of myopia, family retinal history and intraocular pressure, an axial length longer than 26.5 mm was a significant risk factor for peripheral retinal changes, optic nerve crescents and white-without-pressure.[5]

Ocular volume is more directly relevant than longitudinal axial length to the structural and biomechanical integrity of the globe, particularly in myopia.[6] If the eye is treated as a simple sphere then a 12.8% increase in axial length from 23.5mm (typical for an emmetropic individual) to 26.5mm (typical for a highly myopic individual) results in an increase in ocular volume of 43.4% (i.e. from 6795 mm^3 to 9744 mm^3). A 6.4% decrease in axial length to 22mm (typical for a hyperopic individual) results in a decrease in volume of 17.9% (i.e. from 6795 mm^3 to 5575 mm^3). A systematic analysis of *in vivo* measures of ocular volume and longitudinal axial length has yet to be reported.

Ocular MRI has been used in ophthalmic research in areas such as accommodation[7, 8] and myopia.[9-12]Our laboratory was the first to use 3-D ocular MRI to report ocular volume in emmetropic and myopic eyes.[9,10] The technique can also account for the differences between emmetropia and myopia in the shape of the posterior vitreous chamber.[11] Our MRI studies to date have generated ocular volume data across a range of refractive error and the aim of the present study is to investigate the utility of generally available biometric measures in estimating ocular volume.

MATERIALS AND METHODS

The study was approved by the Aston University Research and Ethics Committee; all aspects of the investigation were carried out in accordance with the tenets of the Declaration of Helsinki. Informed consent was obtained from all subjects.

Subjects

Sixty-seven adult subjects were recruited from the Aston University student and staff population. Subject age ranged from 18 to 40 years (mean age 26.20±6.24 years); the cohort comprised of 23 males and 44 females of predominantly white European and South Asian ethnicities (54% white European; 40% South Asian; 3% African-Caribbean; 3% Chinese).

Refraction, axial length, keratometry, and anterior chamber depth measurements

Objective measurements of refractive error for both eyes were obtained under cycloplegia (one drop of tropicamide ophthalmic solution 0.5%, *Minims*® Bausch and Lomb, Surrey, UK). An open-view binocular infrared autorefractor (Shin Nippon SRW-5000, Ryusyo Industrial Co. Ltd, Osaka, Japan) was used to obtain five readings per eye and average refractive error expressed as Mean Spherical Error (MSE, D).

Partial coherence intereferometry (PCI) longitudinal axial length (AL) measurements, central corneal radius (CR) and anterior chamber depth (ACD) were determined (mm) using the Zeiss *IOLMaster* (Carl Zeiss Meditec, Inc., Dublin, California, USA). AL was expressed as the mean of five measurements. Mean CR was expressed as the mean of the horizontal and vertical corneal radii following three measurements, and a single capture automatically generated mean ACD based on five measurements.

Ocular volume

The MRI protocol, verification, and repeatability statistics for the MRI technique employed in this study have been previously reported.[9-11] Calculation of ocular volume followed the acquisition of T2-weighted MR images using a Siemens trio 3-T whole body MR scanner (Siemens Medical Systems, Iselin, NJ) with an eight phase head coil (voxel dimensions 1.0 x 1.0 x 1.0 mm). Images were optimised to reveal the fluid-filled

chambers of the eyes. An automatic voxel shading algorithm was applied and if required, shading was subsequently edited manually following visual inspection of each MR slice in each of the axial, sagittal and coronal planes (approximately 25 slices per plane). The program provided a standard voxel count to calculate volume.[9,10]

With reference to the longitudinal visual axis, the anterior volume was defined as the region from the posterior corneal surface to the posterior pole of the lens; the posterior volume was defined as the region from the posterior pole of the lens to the retinal surface (vitreous-retinal interface). The approximate location of the posterior pole of the lens was taken to be the first MR coronal slice to fall wholly within the posterior vitreous chamber i.e. the slice that indicated the delineation of the non-fluid lens from the fluid vitreous. Shaded voxels were then removed for slices in the coronal plane between the posterior corneal surface and the posterior lens pole (i.e. the anterior volume); the remaining voxels were counted by the *mri3dX* program (developed by Professor Krish Singh, 2005) to generate posterior volume in mm^3 (PV). Subtracting the posterior volume from the total volume (TOV) gave values for the anterior volume (AV). Correlations were calculated between MSE, AL, CR, ACD and volume (PV, AV, and TOV). All statistical analyses were undertaken using SPSS version 21.0 (IBM, IL, USA).

RESULTS

A two-tailed paired student's t-test for MSE, AL, CR, ACD, PV, AV and TOV showed no overall group difference between right and left eye data (all $p>0.05$). Right eye data are presented.

Mean data

Mean Spherical Error, MSE (D) mean -2.62±3.83 (range -10.56 to +4.38, see Figure 1), mean AL (mm) 24.51±1.47 (range 21.72 to 28.12), mean CR (taken as the mean of the horizontal and vertical corneal radii) were (in mm) 7.75±0.28 (range 6.95 to 8.38) and mean ACD (in mm) 3.55±0.34 (range 2.23-4.39).

Mean TOV (mm^3) was 8168.21±1141.86 (range 5036.00-11777.00); mean AV was 1099.40 ±139.24 (range 633.00-1422.00) and mean PV was 7068.82±1134.05 (range 4017.00-10646.00).

Pearson's correlation coefficients

A more negative MSE was significantly correlated with a longer AL ($p<0.001$, $R^2=0.76$), a steeper CR ($p=0.002$, $R^2=0.14$), and a deeper ACD ($p=0.046$, $R^2=0.06$). A greater TOV was also significantly correlated with a longer AL ($p<0.001$, $R^2=0.74$), an increasingly negative MSE ($p<0.001$, $R^2=0.43$), a flatter mean CR ($p=0.043$, $R^2=0.06$), and a deeper ACD ($p=0.024$, $R^2=0.08$). Mean CR was not correlated with AL ($p=0.91$, $R^2=0.002$), but a significant increase in ACD was noted with increasing AL ($p=0.006$, $R^2=0.11$).

Anterior ocular volume (AV)

AV did not bear any significant correlation with MSE, AL (Figures 2 and 3), CR, ACD, PV, or TOV (all $p>0.05$)

Posterior ocular volume (PV)

An increase in PV significantly correlated with a longer AL ($p<0.001$, $R^2=0.76$), an increase in negative MSE ($p<0.001$, $R^2=0.46$), a larger TOV ($p<0.001$ $R^2=0.99$) (Figure 2 and 3) and a deeper ACD ($p=0.030$, $R^2=0.07$), but the relationship with mean CR just failed to reach statistical significance ($p=0.060$, $R^2=0.05$).

Regression analysis

Simple linear regressions showed that mean CR accounted for 6.2% of the variance in TOV ($F=4.28$, $p=0.043$); ACD for 7.6% ($F=5.36$, $p= 0.024$), MSE for 42.6% ($F=48.32$, $p<0.001$), and AL for 73.8% of the variance in TOV ($F=183.08$, $p<0.001$).

A Stepwise method of multiple regression was employed; AL and corneal radius were automatically selected by SPSS as the predictors which created the best model of ocular volume prediction. AL alone contributed to 73.8% of the variance in TOV; mean

CR contributed a further 5.6%; hence both AL and mean CR could account for 79.4% of the variance in TOV.

Simple linear regressions showed that mean CR accounted for 5.3% of the variance in PV (F=3.67, p=0.060); ACD for 7% (F=4.91, p=0.030), MSE for 45.8% (F=55.03, p<0.001), and AL for 75.6% of the variance in PV (F=201.73, p<0.001).

Equations to determine ocular volume

From the multiple linear regression analysis, the following equation for TOV (in mm^3) was derived; AL and mean CR are expressed in mm:

$$TOV = -15565.86 + (662.62*AL) + (967.18*Mean\ CR) \quad Eq\ 1$$

The robustness of the equation may be gauged from examining the difference between unadjusted and adjusted R^2 values, 0.794 and 0.788, respectively. The difference of 0.006 thus indicates that that if the equation were derived from a larger population it would account for only 0.6% less variance.

From multiple linear regression analysis, the following equation for PV (in mm^3) was derived; AL and mean CR are expressed in mm:

$$PV = -16155.62 + (666.41*AL) + (889.41*Mean\ CR) \quad Eq\ 2$$

The R^2 for the PV multiple regression was 0.805 and the adjusted R^2=0.798; i.e. a difference of 0.007 (0.7%).

The regression equations in Table 1 may be used to calculate volumes in situations where only one biometric parameter may be available. Two-tailed significance p-values are shown in brackets.

Predictor	Posterior volume	Total volume
Axial length (mm)	y = 668.70x - 9319.50 R^2 = 0.76 (p<0.001)	y = 665.11x – 8132.00 R^2 = 0.74 (p<0.001)

MSE (D)	y = -200.65x + 6543.98 R^2 = 0.46 (p<0.001)	y = -194.83x + 7658.57 R^2 = 0.43 (p<0.001)
Anterior chamber depth (mm)	y = 890.29x + 3909.35 R^2 = 0.07 (p=0.030)	y = 933.54x + 4855.27 R^2 = 0.08 (p=0.024)
Mean corneal radius (mm)	y = 937.17x – 193.51 R^2 = 0.05 (p=0.060)	y = 1014.663x + 305.33 R^2 = 0.06 (p=0.043)

Total MRI derived volume was also compared to the equivalent volume for a sphere using the formula $^4/_3$ * pi * r^3 where 'r' is half the axial length. A paired Student's t-test indicated significant differences between the two volume datasets (p<0.001). Volume for eyes with axial lengths less than 26mm were underestimated by the sphere formula (by 17.54% for an axial length of 22mm) and overestimated for axial lengths greater than 26mm (by 6.43% for an axial length of 28mm) (see Figure 4 and Table 2).

PCI AL	MRI regression vol	Sphere regression vol	Difference (MRI-Sphere)	Percentage difference
22	6500.42	5360.34	1140.08	17.54
23	7165.53	6327.81	837.72	11.69
24	7830.64	7295.28	535.36	6.84
25	8495.75	8262.75	233.00	2.74
26	9160.86	9230.22	-69.36	-0.76
27	9825.97	10197.69	-371.72	-3.78
28	10491.08	11165.16	-674.08	-6.43

DISCUSSION

As expected, total ocular volume increased with a longer axial length. However, anterior volume bore no significant relationship to either axial length or to ametropia (expressed as MSE). Conversely, posterior eye volume showed a strong correlation with axial length and MSE, supporting previous findings[9,11,12] that an increase in posterior vitreous chamber depth is the main contributor to increased axial length in myopia.

Whereas the correlation between linear measurements of AL and ACD was calculated solely from measurements made using the Zeiss IOLMaster, the correlation between AL and AV was calculated from a combination of PCI (AL) and volumetric data based on an MRI 1mm^3 voxel count (AV). The resolution of volumetric data will thus be

significantly less than PCI data and less able therefore to reflect the significant correlation evident between AL and ACD.

Estimation of ocular volume from axial length may facilitate further investigation of the effect of intravitreal injection of ophthalmic drugs on intra ocular pressure (IOP).[13-17] Several reports have suggested a link between axial length, refractive error and IOP increase following injection,[15-17] but others have found evidence to the contrary.[18] Although injection volumes are generally small (of the order of 0.05ml) a recent study on post-mortem porcine globes demonstrated increases in IOP of approximately 15mmHg following one-second 15ml (0.015ml) micro-infusions of phosphate buffered saline.[19] A clinical research application of this study could be, therefore, to examine whether ocular volume is a structural correlate for IOP change following intravitreal injections.

Using a similar subject group to the present study Santodomingo et al[20] demonstrated that axial length determined using the Zeiss *IOLMaster* did not differ significantly from that determined by 10MHz A-scan applanation ultrasonography (Storz Omega Compu-Scan Biometric Ruler, Storz International, St Louis, MO, USA). Ultrasound measures of axial length can therefore be used to estimate total ocular volume and posterior ocular volume from Equations 1 and 2 respectively.

REFERENCES AND ACKNOWLEDGEMENTS

Acknowledgements: We acknowledge Krish D Singh, Elizabeth Wilkinson, Jade Thai, and Jon Wood for assistance with data collection. We thank Richard Armstrong and Chinyere Nzekwe-Excel for their advice on statistical analysis.

Funding: The College of Optometrists and The Lord Dowding Fund for Humane Research are acknowledged for funding support.

References

1. Flitcroft DI. The complex interactions of retinal, optical and environmental factors in myopia aetiology. *Prog Ret Eye Res.* 2012:31:622–660.
2. Curtin BJ. The Myopias: basic science and clinical management. Philadelphia: Harper & Row 1985.
3. Jones LA, Mitchell GL, Mutti DO et al. Comparison of ocular component growth curves among refractive error groups in children. *Invest Ophthalmol Vis Sci.* 2005;46:2317-2327.
4. Wong HB, Machin D, Tan SB et al. Ocular Component Growth Curves among Singaporean children with different refractive error status. *Invest Ophthalmol Vis Sci.* 2010;51:1341-1347.
5. Cheng SCK, Lam CSY, Yap MKH. Prevalence of myopia-related retinal changes among 12–18 year old Hong Kong Chinese high myopes. *Ophthal Physiol Opt.* 2013;33:652–660.
6. Saw SM, Gazzard G, Shih-Yen EC, et al. Myopia and associated pathological complications. *Ophthal Physiol Opt.* 2005;25:381–391.
7. Strenk SA, Semmlow JL, Strenk LM et al. Age-related changes in human ciliary muscle and lens: a magnetic resonance imaging study. *Invest Ophthalmol Vis Sci*. 1999;40:1162-1169.
8. Sheppard AL, Evans CJ, Singh KD et al. Three-dimensional magnetic resonance imaging of the phakic crystalline lens during accommodation. *Invest Ophthalmol Vis Sci*. 2011;52:3689-3697.

9. Singh KD, Logan NS, Gilmartin B. Three-dimensional modelling of the human eye based on magnetic resonance imaging. *Invest Ophthalmol Vis Sci.* 2006;47:2272-2279.
10. Gilmartin B, Logan NS, Singh KD. In vivo comparison of anterior and posterior ocular volume in human ametropia. *Invest Ophthalmol Vis Sci*. 2008;49:ARVO E-Abstract 3582.
11. Gilmartin B, Nagra M, Logan NS. Shape of the posterior vitreous chamber in human emmetropia and myopia. *Invest Ophthalmol Vis Sci.* 2013;54:7240-7251.
12. Atchison DA., Jones CE, Schmid KL et al. Eye shape in emmetropia and myopia. *Invest Ophthalmol Vis Sci.* 2004;45:3380-3386.
13. Adelman RA, Zheng Q, Mayer HR. Persistent ocular hypertension following intravitreal bevacizumab and ranibizumab injections. *J Ocul Pharmacol Ther.* 2010;26:105-110.
14. Jonas JB, Kreissig I, Degenring R. Intraocular pressure after intravitreal injection of triamcinolone acetonide. *Br J Ophthalmol.* 2003;87:24-27.
15. Kotliar K, Maier M, Bauer S et al. Effect of intravitreal injections and volume changes on intraocular pressure: clinical results and biomechanical model. *Acta Ophthalmol Scand* 2007;85:777-781.
16. Cacciamani A, Oddone F, Parravano M et al. Intravitreal injection of bevacizumab: changes in intraocular pressure related to ocular axial length. *Jpn J Ophthalmol* 2013;57:63-67.
17. He L, Wendt M, Glasser A. Manipulation of intraocular pressure for studying the effects on accommodation. *Exp eye res* 2012;102:76-84.

18. Goktas A, Goktas S, Atas M et al. Short-term impact of intravitreal ranibizumab injection on axial ocular dimension and intraocular pressure. *Cutan Ocul Toxicol* 2013;32:23-26.

19. Morris HJ, Tang J, Perez BC. Correlation between biomechanical responses of posterior sclera and IOP elevations during micro intraocular volume change. *Invest Ophthalmol Vis Sci* 2013;54:7215-7222.

20. Santodomingo-Rubido J, Mallen EAH, Gilmartin B et al. A new non-contact optical device for ocular biometry. *Br J Ophthalmol* 2002;86:458-462.

LEGENDS FOR DISPLAY ITEMS:

Fig 1 Histogram showing distribution of Mean Spherical Error (MSE, in D).

Fig 2 Anterior and Posterior ocular volume (mm^3) plotted as a function of MSE (D). Unfilled circles represent anterior volume; filled circles represent posterior volume.

Fig 3 Anterior and Posterior ocular volume (mm^3) plotted as a function of AL (mm). Unfilled circles represent anterior volume; filled circles represent posterior volume.

Fig 4 Total MRI volume (mm^3) plotted as a function of AL (mm) represented by the filled circles, and the equivalent volume of a sphere (mm^3) also plotted as a function of AL, represented by the unfilled circles.

Table 1 Linear regression equations for both total ocular volume and posterior ocular volume based on axial length and MSE.

Table 2 AL values (mm) from 22mm to 28mm were inputted into the linear regression equations representing total MRI volume (mm^3), and sphere formula volume (mm^3) from Fig 4.

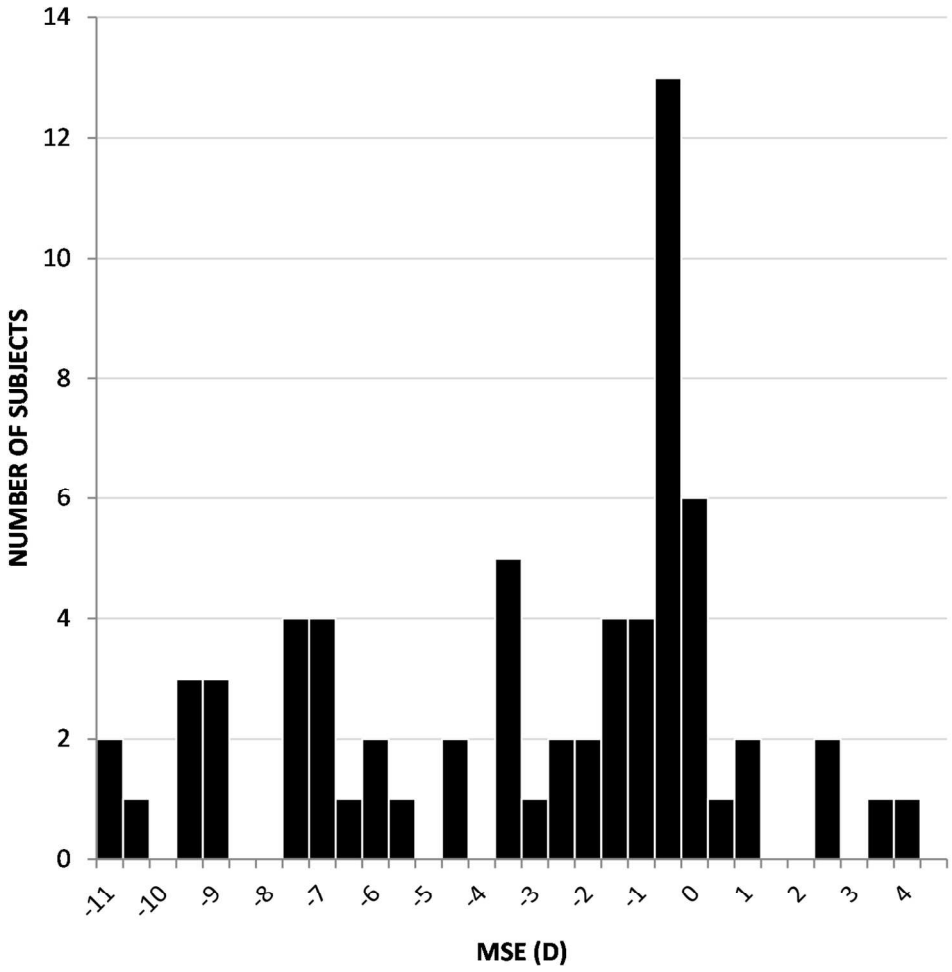

Fig 1 Histogram showing distribution of Mean Spherical Error (MSE, in D).
127x128mm (300 x 300 DPI)

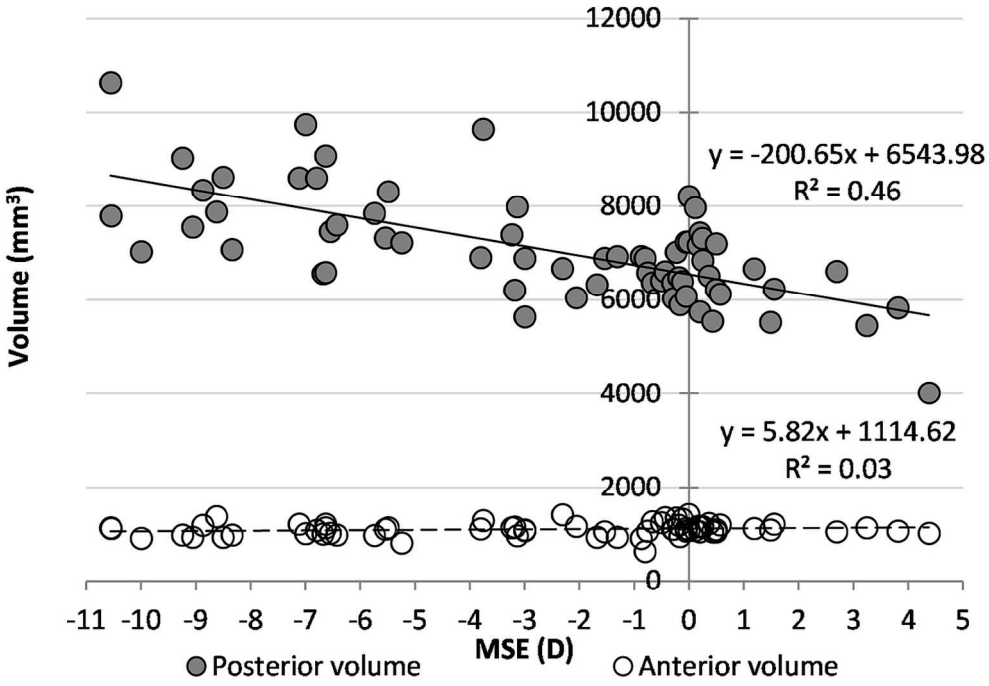

Fig 2 Anterior and Posterior ocular volume (mm3) plotted as a function of MSE (D). Unfilled circles represent anterior volume; filled circles represent posterior volume.
131x90mm (300 x 300 DPI)

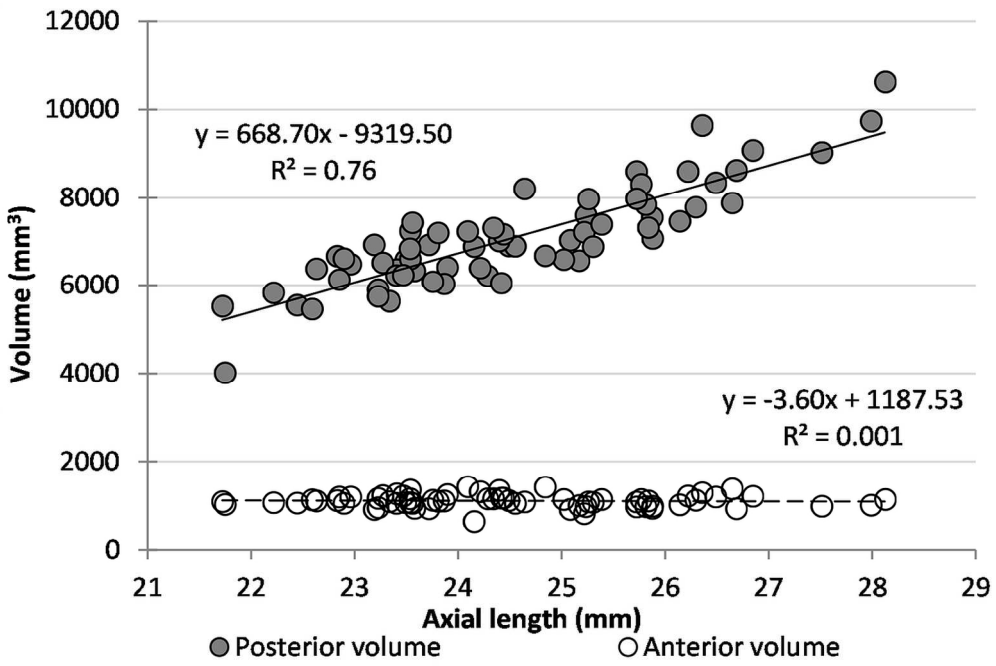

Fig 3 Anterior and Posterior ocular volume (mm3) plotted as a function of AL (mm). Unfilled circles represent anterior volume; filled circles represent posterior volume.
135x90mm (300 x 300 DPI)

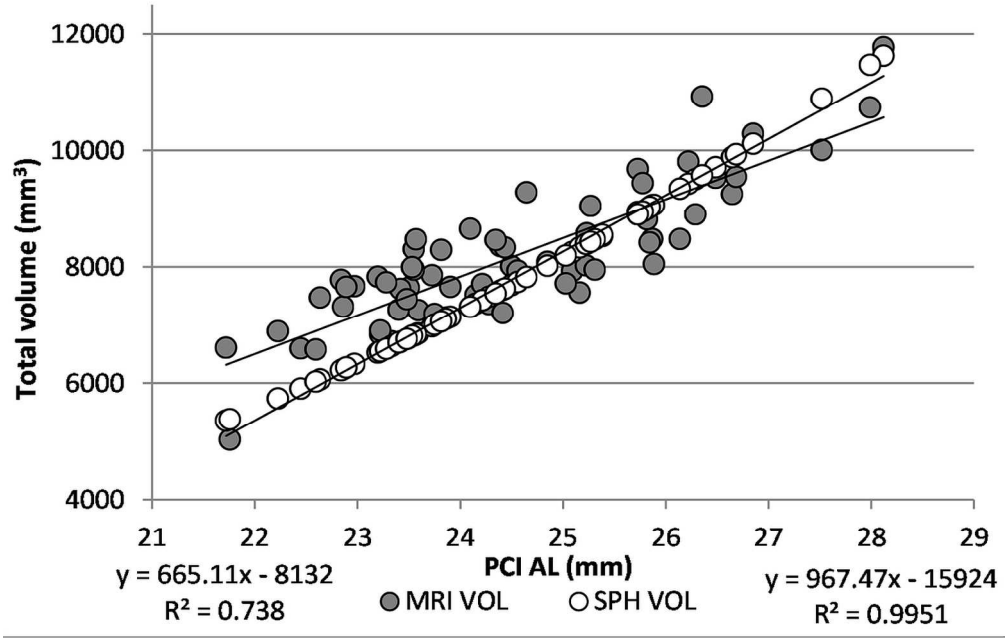

Fig 4 Total MRI volume (mm3) plotted as a function of AL (mm) represented by the filled circles, and the equivalent volume of a sphere (mm3) also plotted as a function of AL, represented by the unfilled circles.
140x90mm (300 x 300 DPI)