# Longitudinal Study of Iris Concavity, Corneal Biomechanics, and Correlations to Ocular Biometry in a Cohort of 10- to 12-Year-Old UK Schoolboys: 2-Year Follow-up Data

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**Purpose.** To explore changes in iris curvature over a 2-year period. To investigate associations between iris curvature and ocular biometric parameters. To explore relationships between a number of nonocular measurements and ocular biometric parameters.

**Methods.** Schoolboys enrolled 2 years previously were invited to return for anterior segment optical coherence tomography, corneal hysteresis (CH), corneal resistance factor (CRF), and axial biometric measurements. Refractive error was assessed and measures of height, weight, waist circumference, digit ratio, and percentage body fat taken.

**Results.** Mean spherical equivalent refraction reduced by 0.76 diopters and mean iris concavity, defined as a measurement of less than or equal to −0.1 mm, increased by 0.018 mm at distance fixation and 0.04 mm on accommodation. Compared with 2 years previously, the prevalence of iris concavity increased from 24% to 32% on distance fixation and from 65% to 84% on accommodation. Variables significantly associated with nonaccommodating iris curvature were anterior chamber depth (ACD, $P = 0.029$) and mean scleral spur angle ($P = 0.0001$). Variables significantly associated with accommodating iris curvature were ACD ($P = 0.02$), lens vault ($P = 0.047$), and scleral spur angle ($P < 0.0001$). Significant association was again found between CH and accommodating spur-to-spur distance ($R^2 = 0.13$, $P = 0.007$).

**Conclusions.** Iris concavity was more prevalent in this cohort of schoolboys than 2 years earlier. The degree of concavity remains related to ACD and lens vault. The association between spur-to-spur distance and CH was similar at baseline and after 2 years.

Keywords: anterior segment optical coherence tomography, iris concavity, pigment dispersion, corneal hysteresis, refractive error

Iris concavity is implicated in the pathogenesis of pigment dispersion syndrome (PDS), but published data indicate that it is also found in healthy subjects.[1] Yttrium aluminum garnet laser iridotomy has been proposed as a treatment to reverse the iris concavity in PDS and thereby halt disease progression, and several studies have investigated its efficacy.[1–4] There are no published data on iris curvature in a young healthy population. In December 2009, we conducted a cross-sectional study to estimate the prevalence of iris concavity in 10- to 12-year-olds attending a local boys' secondary school (City of London School, London, UK). Iris concavity was assessed using anterior segment optical coherence tomography (AS-OCT) and the relationship between iris curvature and components of refractive error was explored. Ninety-six boys from two consecutive-year groups took part. The baseline data are presented in an accompanying manuscript[5] and are summarized as follows. The prevalence of iris concavity was 24% at distance fixation and 65% at near fixation. Lens vault (LV), defined as the perpendicular distance between the anterior pole of the crystalline lens and the horizontal line joining the scleral spur, was significantly associated with nonaccommodating iris curvature ($R^2 = 0.23$, $P = 0.028$), whereas anterior chamber depth (ACD), LV, and scleral spur angle were significantly associated with accommodating iris curvature ($R^2 = 0.33$, $P = 0.009$, 0.047, and $< 0.001$, respectively, $R^2 = 0.33$). Significant association was also detected between corneal hysteresis (CH) and nonaccommodating spur-to-spur distance ($R^2 = 0.07$, $P = 0.025$, result for accommodating spur-to-spur distance was similar).

The original cohort was revisited in December 2011 in an effort to determine the prevalence of iris concavity 2 years from the time of the previous examination.

Corneal hysteresis has been significantly associated with longer axial length (AL),[6] but it is unclear whether eyes with lower CH are at greater risk for axial elongation or changes in CH are secondary to axial elongation. The relationship between baseline CH and changes in AL over the 2-year interval was therefore also investigated.

In addition to the data collection previously described in the baseline article, the opportunity was taken to collect data on birth weight (parental reporting), digit ratio, height, weight, waist circumference, and bioimpedance. Birth weight has been

TABLE 1. Summary Characteristics for Cohort in December 2011

| Parameter | *n* | Mean | SD |
|---|---|---|---|
| Axial length, mm | 62 | 24.01 | 1.04 |
| Spherical equivalent, diopters | 62 | −1.09 | 1.91 |
| Iris curvature A, mm | 57 | −0.25 | 0.17 |
| Iris curvature NA, mm | 59 | −0.019 | 0.14 |
| Spur-to-spur distance A, mm | 60 | 12.1 | 0.48 |
| Spur-to-spur distance NA, mm | 61 | 12.1 | 0.47 |
| Mean digit ratio | 62 | 0.95 | 0.033 |
| Height, cm | 62 | 164.45 | 8.58 |
| Corneal hysteresis, mm Hg | 58 | 11.4 | 1.64 |
| Corneal resistance factor, mm Hg | 58 | 11.5 | 1.98 |
| Weight, kg | 62 | 53.7 | 11.38 |
| Waist circumference, cm | 62 | 72.3 | 7.93 |
| Percentage body fat | 62 | 16.2 | 6.24 |
| Birth weight, kg | 61 | 3.34 | 0.78 |

A, accommodating; NA, nonaccommodating.

associated with refractive error[7] and AL.[8] There is evidence that control of eye growth differs between men and women.[9] By collecting data on digit ratio, a putative marker for prenatal androgen exposure,[10–12] we explored whether eye growth differs between boys with greater or lesser exposure to maternal levels of androgens. Bioimpedance analysis measures body composition, in particular the percentage of body fat. Height, weight, percentage body fat, and waist circumference provide an indication of general metabolic status and may reflect long-term insulin levels. Epidemiological evidence implicates a role for chronic hyperinsulinemia in juvenile-onset myopia.[13] We therefore investigated these easily measured parameters in our cohort.

## METHODS

### Recruitment

Letters were written to the 96 students from the original cohort inviting them to participate. Information leaflets were provided and informed consent was taken from both the pupils and their parents. The study adhered to the tenets of the Declaration of Helsinki and was approved by a regional ethics committee.

### Ocular Measurements

Visual acuity (VA), refraction, axial biometry, ocular response analyzer (ORA) measurements (ORA, Reichert, Inc., Depew, NY, USA) and Visante anterior segment imaging (Carl Zeiss Meditec, Dublin, CA, USA) were conducted as previously described. In brief, logMAR distance VA was measured in each eye at 4 m. Noncycloplegic ocular refraction was measured using an autorefractor (manual focimetry was performed where spectacles were worn). The room in which the study was conducted overlooked the Thames River and the autorefractor was set up such that the subject fixated on a designated target on a building on the opposite bank of the river to minimize accommodation. One eye of each participant from the original cohort had been randomly selected and designated as the study eye. The AL of the study eye was measured using laser interferometry and the ORA was used to obtain at least three good-quality CH and corneal resistance factor (CRF) measurements from the study eye. Anterior segment OCT imaging was performed under accommodative and nonaccommodative conditions in the horizontal meridian.

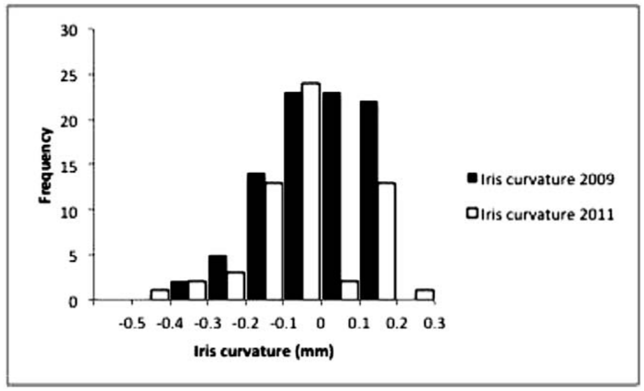


FIGURE 1. Histogram to show distribution of nonaccommodating iris curvature in 2009 and 2011.

### Nonocular Data Collection

Waist circumference was measured at the midpoint between the lower border of the rib cage and the iliac crest.

Weight and percentage body fat were determined using the Tanita BC543 Body Composition Analyzer (Tanita Corp., Tokyo, Japan). The subject was instructed to stand on the device after removing shoes and socks. Age and height were entered when prompted. Weight and then percentage body fat were returned on a digital display.

Hand scans were taken using an Epson Perfection 1650 scanner (Seiko Epson Corporation, Nagano, Japan). Right hand digit ratio was measured using ImageJ version 1.45s (http://imagej.nih.gov/ij/; provided in the public domain by the National Institutes of Health, Bethesda, MD, USA) to measure the lengths of the index and ring fingers from the middle of the basal crease to the tip of the finger in pixels. Digit ratio was obtained by dividing the length of the right hand index finger by the length of the right hand ring finger.

### Statistics

To determine which variables were associated with iris curvature, multiple regression analysis was performed using six variables (spur-to-spur distance, ACD, LV, mean scleral spur angle, spherical equivalent refractive error (SE), and AL). Linear regression analysis was used to investigate the relationship between CH/CRF and spur-to-spur distance (dependent variable). The relationship between ocular and nonocular parameters was also explored. Paired Student's *t*-test was used to compare measurements between the two time points. Analyses were performed using Prism version 6.0c for Mac OS X (GraphPad Software, La Jolla, CA, USA, www.graphpad.com) and MedCalc for Windows, version 12.2.1.0 (MedCalc Software, Mariakerke, Belgium).

## RESULTS

Of 96 pupils invited to take part, 62 (64.6%) agreed and took part. Near and distance scans from one student and the near scan from another were excluded due to poor image quality. Iris curvature measurements were not possible in an additional three accommodative scans and two nonaccommodative scans, due to difficulty identifying the posterior iris pigment epithelium. Ocular response analyzer measurements from four subjects were excluded, as waveform scores were consistently less than 4. Summary data are shown in Table 1. All parameters were normally distributed based on the Kolmogorov-Smirnov test, except for iris curvature in distance fixation, which showed a longer tail at lower values of iris curvature. There

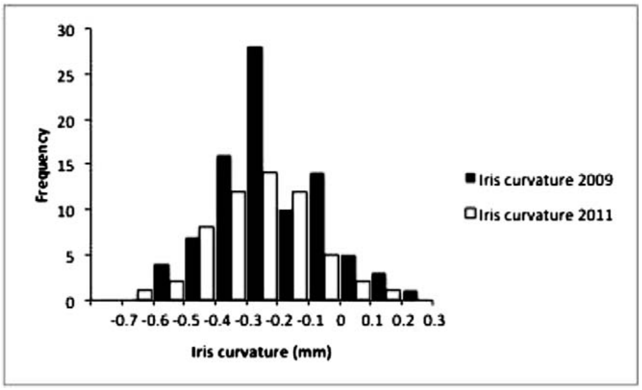


FIGURE 2. Histogram to show distribution of accommodating iris curvature in 2009 and 2011.

was no significant difference in refractive error between those who participated 2 years later and those who did not (mean SE –0.44 diopters and –0.37 diopters, respectively, $P = 0.86$).

For the purposes of this study, iris concavity was defined as iris curvature of –0.1 mm or less. The distribution of nonaccommodative and accommodative iris curvature is shown in Figures 1 and 2, respectively. The prevalence of iris concavity was 19 (32%) of 59 at distance fixation and 49 (84%) of 58 at near fixation (McNemar test $P < 0.0001$). The effect of changing this cutoff on prevalence values is shown in Table 2.

Variables significantly associated with nonaccommodating iris curvature were ACD ($t = 2.25$, $P = 0.029$) and mean scleral spur angle ($t = -4.11$, $P = 0.0001$). For both variables acting jointly, $R^2$-adjusted = 0.59. Variables significantly associated with accommodating iris curvature were ACD ($t = 2.34$, $P = 0.02$), lens vault ($t = -2.01$, $P = 0.047$), and scleral spur angle ($t = -7.30$, $P < 0.0001$). For both variables acting jointly, $R^2$-adjusted = 0.62.

Significant association was found between CH and nonaccommodating spur-to-spur distance ($R^2 = 0.07$, $P = 0.047$), as well as CH and accommodating spur-to-spur distance ($R^2 = 0.13$, $P = 0.0067$) (Fig. 3).

Angle-opening distance (AOD), trabecular–iris space area (TISA), LV, and scleral spur angle all show significant increases on accommodation (Table 3), a finding that was also noted in the 2009 cohort.

A comparison of ocular parameters between 2009 and 2011 using only individuals present in both cohorts is shown in Table 4. There was a mean increase in AL of 0.22 mm (paired $t$-test, $P < 0.0001$) and mean decrease in SE of 0.70 diopters compared with 2009 (paired $t$-test, $P < 0.0001$). Mean iris curvature at distance fixation reduced from –0.002 mm in 2009 to –0.02 in 2011 ($P = 0.40$) and at near fixation reduced from –0.21 in 2009 to –0.25 in 2011 ($P = 0.19$).

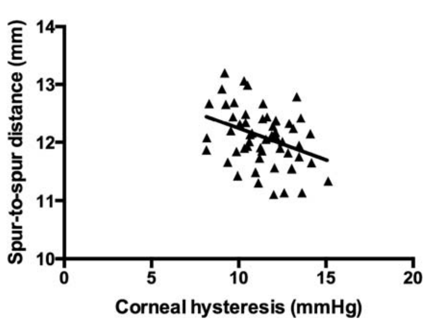


FIGURE 3. Scatterplot of corneal hysteresis against spur-to-spur distance on accommodation. *Regression line*: $y = -0.11x + 13.3$.

TABLE 2. Prevalence of Iris Concavity According to Iris Curvature Cutoff Used

| Iris Curvature Cutoff, mm | Prevalence Nonaccommodating, % | Prevalence Accommodating, % |
|---|---|---|
| ≤–0.1 | 32 | 84 |
| ≤–0.2 | 10 | 64 |
| ≤–0.3 | 5 | 40 |
| ≤–0.4 | 2 | 19 |
| ≤–0.5 | 0 | 5 |

No significant association was found between any ocular and nonocular measurements. There was no statistically significant difference between CH/CRF values in 2009 and 2011. No significant association was detected between CH/CRF and AL/SE. Histograms were constructed to investigate the distribution of these parameters to determine whether lack of a statistically significant association might be due to an insufficient range of the data points. All histograms showed relatively broad distributions. The distribution of AL is shown in Figure 4.

No significant association was detected between baseline CH, baseline CRF, or nonocular measurements and change in AL, SE, and spur-to-spur distance. No significant association was detected between change in CH/CRF and change in AL/SE over 2 years.

## DISCUSSION

The prevalence of iris concavity in this cohort was greater in 2011 (32% at distance fixation and 84% at near fixation) compared with 2009 (24% and 65%, respectively), although there was no statistically significant difference in iris curvature measurements over the 2-year period for boys with data available from both visits. We considered whether the higher prevalence may reflect a selection bias, whereby those with myopia may have been more interested (either through parental encouragement or independently) in taking part in the second visit compared with those without myopia. However, analyzing the 2009 cohort revealed no significant difference in refractive error between those who participated 2 years later and those who did not and so such selection bias appears unlikely. Figures 1 and 2 demonstrate a similar distribution of iris curvature in 2009 and 2011, supporting the view that selection bias is unlikely. Selection bias also may have occurred at enrollment into the baseline study, with pupils with eye problems such as myopia potentially being more likely to participate. A slideshow presentation was given to all potential participants before the start of the baseline study. This generated interest in the anatomy and optics of the eye, as well as a degree of excitement in engaging with the devices used in the study. It was felt that this interest, together with the knowledge that their classmates were participating in the study, were the main drivers in encouraging the boys to participate, rather than whether the boys themselves had eye problems.

A limitation common to the present study and the baseline study is that the autorefractor may have overestimated the degree of myopia, given that eyes were not cyclopleged. Entering this refraction value into the AS-OCT may have induced accommodation unintentionally. A subanalysis of 25 subjects from the baseline study revealed that on average autorefraction overestimated myopia by only 0.4 diopters compared with focimetry in the right eye, whereas no significant difference was found in the left eye. Thus, it appears that the autorefractor overestimates myopia by only a modest amount compared with focimetry.

TABLE 3. Summary Data for AS-OCT Parameters

| | Nonaccommodating, $n = 61$ | | Accommodating, $n = 60$ | | |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | $P$* |
| CCT, μm | 531.7 | 30.1 | 528.5 | 32.1 | 0.07 |
| ACD, mm | 3.38 | 0.28 | 3.14 | 0.31 | <0.0001 |
| Lens vault, μm | −176.2 | 217.6 | 59.3 | 223.4 | <0.0001 |
| Temporal AOD 500, μm | 822.4 | 318.4 | 907.8 | 379.0 | 0.0016 |
| Temporal AOD 750, μm | 1084.5 | 366.8 | 1185.5 | 398.7 | 0.0006 |
| Temporal TISA 500, mm$^2$ | 0.295 | 0.122 | 0.315 | 0.136 | 0.036 |
| Temporal TISA 750, mm$^2$ | 0.536 | 0.210 | 0.580 | 0.237 | 0.006 |
| Temporal scleral spur angle, deg | 55.8 | 10.5 | 57.6 | 11.5 | 0.03 |
| Nasal AOD 500, μm | 794.3 | 312.2 | 946.1 | 330.0 | <0.0001 |
| Nasal AOD 750, μm | 1069.1 | 362.6 | 1233.3 | 392.1 | <0.0001 |
| Nasal TISA 500, mm$^2$ | 0.277 | 0.112 | 0.312 | 0.115 | 0.0014 |
| Nasal TISA 750, mm$^2$ | 0.512 | 0.199 | 0.591 | 0.203 | <0.0001 |
| Nasal scleral spur angle, deg | 55.5 | 11.0 | 60.4 | 9.4 | <0.0001 |
| Spur-to-spur distance, mm | 12.17 | 0.48 | 12.10 | 0.48 | 0.78 |

CCT, central corneal thickness.
* Paired *t*-test.

Significant association was found between iris curvature and ACD in both accommodative and nonaccommodative states, indicating that relative lens position may influence iris curvature.

The study presented an opportunity to collect additional data that were potentially relevant to ocular growth. Rahi et al.[7] found that myopia was positively associated with low birth weight for gestational age, whereas Saw et al.[8] report that across the normal birth weight range, longer AL is associated with greater birth weight. However, Dirani et al.[14] analyzed data from 1224 twins from the Genes in Myopia twin study and found no significant association between birth weight and myopia.

The digit ratio is the ratio of the lengths of different digits or fingers typically measured from the bottom crease, where the finger joins the hand, to the tip of the finger. It has been suggested that the ratio of two digits (D) in particular, the second (index finger; 2D) and fourth (ring finger; 4D), is affected by exposure to androgens; for example, testosterone while in the uterus and that this 2D:4D ratio can be considered a putative marker for prenatal androgen exposure, with lower 2D:4D ratios pointing to higher androgen exposure.[10–12] Interestingly, the differences are more pronounced in the right hand.[15–17] There is evidence that control of eye growth differs between men and women[9] and by collecting data on digit ratio we aimed to explore whether eye growth differs between boys with greater or lesser exposure to maternal levels of androgens. Birth weight and digit ratio are both markers of intrauterine experience, and Barker's theory[18] suggests that intrauterine experiences have a lifelong impact on health. Bioimpedance monitors have been developed that can distinguish between lean and fat tissue based on differences in their conductance and impedance characteristics. They are simple to use, cost-effective, portable, and noninvasive. Excellent correlation has been shown between bioimpedance and fat-free mass as measured by hydrodensitometry[19] and its use has been validated in children.[20,21] Height, weight, percentage body fat, and waist circumference provide an indication of general metabolic status and may reflect long-term insulin levels. Epidemiological evidence implicates a role for chronic hyperinsulinemia, secondary to the refined sugars and starch in Western diets, in juvenile-onset myopia because of its interaction with hormonal regulation of vitreal chamber growth.[13]

No significant correlation was demonstrated between any of the above nonocular parameters and AL, SE, CH, and CRF (nor change in these parameters over the 2 years). The study was not powered to detect such associations, so this part of the study was considered exploratory, given the clinical importance of identifying risk factors for myopia.

TABLE 4. Comparison of Parameters Between 2009 and 2011 Cohorts

| Parameter | Mean Value 2009 | Mean Value 2011 | $n$ | Difference | $P$ |
|---|---|---|---|---|---|
| Axial length, mm | 23.79 | 24.01 | 62 | 0.22 | <0.0001 |
| Spherical equivalent, diopters | −0.39 | −1.09 | 62 | −0.7 | <0.0001 |
| Corneal hysteresis, mm Hg | 11.6 | 11.4 | 58 | −0.2 | 0.35 |
| Corneal resistance factor, mm Hg | 11.7 | 11.5 | 58 | −0.2 | 0.25 |
| Iris curvature NA, mm | −0.016 | −0.019 | 59 | −0.003 | 0.77 |
| Iris curvature A, mm | −0.198 | −0.25 | 57 | −0.048 | 0.11 |
| Anterior chamber depth NA, mm | 3.37 | 3.39 | 61 | 0.02 | 0.17 |
| Anterior chamber depth A, mm | 3.14 | 3.15 | 60 | 0.01 | 0.61 |
| Scleral spur angle NA, deg | 58.4 | 56.6 | 61 | −1.8 | 0.02 |
| Scleral spur angle A, deg | 60.4 | 58.4 | 60 | −2 | 0.11 |
| Lens vault NA, μm | −165.6 | −179.2 | 61 | −13.6 | 0.52 |
| Lens vault A, μm | 64.3 | 58 | 60 | −6.3 | 0.8 |
| Spur-to-spur distance NA, mm | 12.06 | 12.13 | 61 | 0.07 | 0.13 |
| Spur-to-spur distance A, mm | 12.05 | 12.12 | 60 | 0.07 | 0.08 |

Mean values are given for subjects who participated at both time points. Values shown for scleral spur angle represent temporal quadrant. Values for nasal angle were similar. $n$, number of eyes.
* Paired *t*-test.

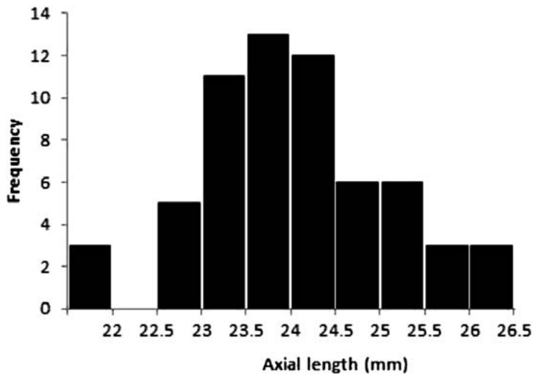


FIGURE 4. Histogram to show distribution of axial length in 2011 cohort.

Corneal hysteresis is a parameter that is thought to reflect the dampening or viscoelastic properties of the cornea.[22] Song et al.[6] reported on 1153 secondary school children in rural China and found lower CH to be significantly associated with longer AL. Poor correlation has been reported between CH and refractive error (as a continuous variable) in adult studies, although lower CH has been consistently reported in high myopia compared with low myopia or emmetropia. The fact that CH and spur-to-spur distance were consistently associated at both time points in our relatively small sample is noteworthy and suggests that corneal biomechanical properties, as measured by the ORA, are associated with anterior segment geometry. Interestingly, no association was detected between CH/CRF and AL, or between baseline CH/CRF and changes in AL or spur-to-spur distance over the 2-year interval. Thus, we did not find evidence that baseline corneal biomechanical parameters predict ocular growth, although the study was not powered to answer this question.

Iris concavity appears to be a frequent finding in this cohort at both time points. It is likely that the prevalence of iris concavity will fall as the cohort approaches adulthood on the basis that iris concavity in adults appears to be uncommon.[1] With regard to the significance of iris concavity in PDS, the persistence of iris concavity into adulthood is likely to confer an anatomical predisposition to pigment shedding from the posterior iris pigment epithelium. Whether pigment dispersion occurs entirely as a result of iris concavity or whether there is additionally an intrinsic susceptibility of the iris to pigment shedding is unclear.

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