Higher Order Aberrations in Children with Down Syndrome

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Purpose. Down syndrome (DS) is associated with ocular abnormalities and reduced visual function. Studies report atypical optical structures in the DS eye such as thinner, steeper corneae and thinner crystalline lenses and, functionally, a degrading influence of the optics on acuity. This study further investigates optical quality in DS by comparing higher order ocular aberrations (HOAs) in DS and control eyes.

Methods. Participants were 44 children with DS (6–16 years) and 209 age-matched controls. All participants were free from corneal or lenticular pathology. HOAs were measured following cycloplegia using Shack-Hartmann aberrometry. HOAs were analyzed over a 3-mm and 5-mm pupil using Zernike polynomials from third-sixth order. Optical quality was explored using Visual Strehl ratios (VSX) and equivalent defocus values.

Results. HOAs were measured successfully from 68% of the DS group and 95% of controls. Root mean square of total combined HOAs, third, and sixth orders and coma were significantly greater in the DS group ($P < 0.005$). Significant differences were found between groups for Zernike coefficients Z_3^{-3}, Z_3^3, and Z_4^0 ($P < 0.013$). VSX and equivalent defocus values indicated significantly poorer optical quality in DS eyes ($P < 0.02$).

Conclusions. Children with DS have greater HOAs and reduced central optical quality compared with typically developing children. Whilst the differences in HOAs between the groups reached statistical significance, they were not of pathological proportions and the DS eye maintains relatively good optical quality considering the degree of ametropia and atypical optical structures often found amongst these children. The subtle reduction in optical quality may, however, compound the visuocortical deficits previously reported in DS. (*Invest Ophthalmol Vis Sci.* 2013;54:1527–1535) DOI:10.1167/iovs.12-10597

Down syndrome (DS) is associated with a range of ocular anomalies of both structure and function. Even with optimal refractive management, good vision care, and in the absence of pathology, children with DS show reduced visual function compared with their age-matched, typically developing peers.[1–3] The cause of this poor visual performance in DS is not yet fully understood but cannot be attributed to subject selection, attention, or motivational factors.[2,4]

Little et al.[5] demonstrated that an optical deficit may help to explain much of the reduced visual performance found in children with DS. They report a 4-fold improvement in visual performance when a visual stimulus that bypassed the optics of the eye (interferometric sinusoidal gratings) was used to assess resolution visual acuity. Previous studies have also commented on differences in the structure of the optical components of the DS eye when compared with the general population, such as thinner, steeper corneae,[6–9] thinner crystalline lenses,[6] reduced accommodative function,[10,11] and variations in tear film composition.[12,13] Authors have also reported an increased prevalence of disorders of the optical components in DS such as high levels of astigmatism,[8,9] keratoconus,[14,15] and cataract.[16–18] These variations in the optical and refractive components of the DS eye may influence optical quality and integrity and help to explain the poor visual performance found in this unique group.

Individuals with increased levels of higher order aberrations (HOAs) beyond the primary refractive errors have been reported to have degraded visual performances.[19,20] The aim of the present study was to quantify the optical quality of the eyes of children with DS for the first time, beyond primary refractive errors, by measuring their HOAs and to compare these with a typically developing reference group.

METHODS

Participants

Typically Developing Participants (Controls). Permission was granted from the regional Education and Library Boards to approach schools for recruitment of typically developing children. One postprimary (high school, grades 7 to 11) and two primary schools (elementary, grades 1 to 6) were contacted and principals agreed to send out information leaflets and consent forms to parents and guardians. Written informed consent was obtained from the parents/guardians of 209 children with a participation rate of 51.4%. The mean age was 11.4 ± 3.1 years, ranging from 5.8 to 16.9 years. Sex balance was 56% female.

DS Participants Group. Children with DS were invited to participate after identification by local pediatric clinicians and DS parent support groups. Information leaflets and consent forms similar to those used for the control group were posted to parents/guardians. Written informed consent was obtained from the parents/guardians of 44 children with DS with a participation rate of 55.2%. Mean age was 10.5 ± 3.1 years, ranging from 5.7 to 16.9 years. Sex balance was 46% female.

Participants from both groups were predominantly white (98%), reflective of the Northern Irish population.[21] Recruitment and experimental protocols complied with the Declaration of Helsinki. Ethical approval was obtained from the University of Ulster Research Ethics Committee and NHS Research Committees and Research Governance.

Children with DS who were known from their clinical notes to have corneal or lenticular pathology (such as keratoconus or cataract) were not invited to participate in the study. Parents/guardians were also asked to comment on the child's ocular history prior to testing and the quality of the retinoscopy reflex was used to screen for gross pathology. None of the participants from either group reported or were found to have such pathology.

Procedure

Testing of participants with DS was carried out at the University of Ulster optometry clinic or at the child's local health center. Testing of the control group took place on the participants' school premises, within school time. Test rooms were quiet and easily darkened. The same test apparatus and procedures were used across sites.

Monochromatic HOA were measured for both eyes using an aberrometer (IRX3 Shack-Hartmann; Imagine Eyes, Orsay, France) 30 minutes following the instillation of cycloplegic drops (1% cyclopentolate hydrochloride), which achieved pupil diameters of at least 5 mm. The aberrometer uses a 32×32 lenslet sampling array and a near infrared laser source of 780 nm wavelength. Refractive corrections were removed for HOA measurements. Participants were stabilized by the chin and forehead rest on the aberrometer and in some cases where necessary, the participant's head was supported by an examiner. Measurements were repeated three times for each eye, and the mean of the measurements was used for data analyses. Measurements of HOA were taken with the participant fixating on an internal target (black letter E) within the aberrometer (IRX3 Shack-Hartmann; Imagine Eyes).

Zernike polynomials were calculated over a fixed 3-mm and 5-mm pupil diameter centered on the participant's dilated pupil.[22] Zernike coefficients up to the sixth order were fitted to the aberration data using the standards recommended by the Optical Society of America.[23] The root mean square (RMS) of total coma, trefoil, spherical aberration, third, fourth, fifth, sixth orders, and total combined HOA (third to sixth orders) were also calculated. For both groups, a strong correlation was found for the RMS of total combined HOA between right and left eyes (DS: $r = 0.51$, $P = 0.01$; Control: $r = 0.77$, $P < 0.0001$), and therefore further analyses were performed for left eye data only.

The Strehl ratio is defined as a ratio of the peak intensity of the point spread function of an optical system compared with the intensity of a perfect optical system (diffraction-limited) for the same pupil size.[24] The Visual Strehl ratio (VSX), described in Thibos et al.,[25] incorporates a standardized neural weighting to the Strehl ratio and has been reported to show a stronger correlation with visual performance.[26] This yields a simple quantitative measure of optical quality. Visual Strehl ratios range from 0 to 1, with 1 being the equivalent of a perfect optical system. Visual Strehl ratios were calculated from HOA data from 3-mm and 5-mm pupil diameters using analytical software (GetMetrics 2.5; Visual Optics Institute, University of Houston, Houston, TX).

To further aid interpretation, the higher order coefficients were converted to an ophthalmic prescription using the equivalent defocus expression outlined in Thibos et al.[27]

$$\text{Equivalent defocus} = 4\pi\sqrt{3} \times \frac{RMS\ error}{Pupil\ Area}$$

Refractive error was assessed using cycloplegic retinoscopy following the measurement of HOA. Natural pupil size was measured prior to cycloplegia and dilation using a standard pupil card with printed semicircles increasing in 0.5-mm diameter steps.

Statistical Analyses

Statistical analyses were carried out using commercially available software (Intercooled Stata 10; StataCorp, College Station, TX). Data were tested for normalcy using the Shapiro-Wilk test. The raw data followed nonnormal distributions and were not improved by logarithmic transformations; therefore nonparametric analyses including the median, interquartile ranges (IQR), and ranges are presented. Kruskal-Wallis and Mann-Whitney U tests were used to compare medians between groups. Bonferroni correction factors were used for multiple comparisons of HOA between groups ($P < 0.05/n$, where $n = 17$ comparisons). Multiple linear regression analyses were performed between the Zernike coefficients from the third and fourth orders. This was used to investigate the contribution of each Zernike coefficient within the wavefront in predicting the other Zernike coefficients, whilst controlling for interdependent relations.

RESULTS

Success Rates

Three measurements of HOA were successfully measured from 198 (95%) controls and an average result calculated. Obtaining three reliable measurements for the participants with DS proved more difficult due to poorer cooperation. If the child was unable to cooperate for three readings, two—or in a few cases, one—measurement was recorded (Table 1). No statistically significant differences were found between the average RMS of combined HOA when data were included using one, two, or three readings (Kruskal-Wallis [K-W] = 0.57, $P = 0.75$). The majority of data from participants with DS were obtained from at least two HOA measurements (73%). All HOA measurements from participants with DS that were deemed reliable by a clinician (SJM) experienced with using the aberrometer (Imagine Eyes) were included in the results regardless of the number of repeat measurements obtained. This is supported by the work of Miranda et al.[28] who reported no significant difference between two measurements of HOA taken over a period of a few seconds using the aberrometer (IRX3 Shack-Hartmann; Imagine Eyes).

Age & Refractive Error

There was no statistically significant difference in the age of participants between groups (Mann Whitney [M-W] $z = -1.67$, $P = 0.09$).

The median spherical equivalent and astigmatic refractive errors for the control group were +0.75DS (IQR +0.25 to +1.38DS; range, −4.25 to +5.25DS) and −0.25DC (IQR −0.50 to 0.00DC; range, −2.25 to 0.00DC), respectively; and for the DS group, +2.63DS (IQR +0.75 to +5.25DS; range, −9.00 to +7.00DS) and −1.25DC (IQR −2.25 to −0.50DC; range, −4.00 to 0.00DC), respectively. Statistically significant differences were found between spherical equivalent and astigmatic errors between the two groups (M-W, spherical equivalent error $z = -5.74$, $P < 0.0001$; astigmatic error $z = 6.97$, $P < 0.0001$).

Pupil Size

Median pupil size for the control group was 5.5 mm (IQR 4.5–6.0 mm; range, 2.5–7.5 mm) compared with 6.0 mm for the DS group (IQR 5.0–6.5 mm; range, 4.0–8.0 mm). A statistically significant greater pupil size was found in the DS group (M-W, $z = -2.65$, $P = 0.0077$).

Tables 2 and 3 report the HOA data for 3-mm and 5-mm pupil diameters as median values, interquartile ranges, and minimum to maximum values (range) for the DS and control groups.

Multiple linear regression analyses revealed no statistically significant influence of age or refractive error on Visual Strehl ratio or the RMS of total combined HOA over 3-mm and 5-mm pupil diameters (all comparisons $P > 0.187$). Figure 1 plots the spherical equivalent refraction against the RMS of total combined HOA for individual control and DS data. Refractive errors were also classified into groups by spherical equivalent

TABLE 1. DS Group: HOA Measurement Success Rates

Number of Reliable Readings Obtained	Number of Participants, $n = 44$ (%)
0	14 (31.8)
1	8 (18.2)
2	6 (13.6)
3	16 (36.4)

Depicts number of aberrometry readings obtained from participants with DS.

refraction using the following definitions: myopic if less than or equal to −0.50 diopters (D); hyperopic if greater than or equal to +0.50 D; and emmetropic if greater than −0.50 D but less than +0.50 D.[29] No statistically significant differences were found between refractive error groups for the RMS of total HOA over both 3-mm and 5-mm pupil diameters for either the DS or control group (DS 3 mm, K-W = 2.89, $P = 0.235$; DS 5 mm, K-W = 1.69, $P = 0.43$; Control 3 mm, K-W = 1.62, $P = 0.446$; Control 5 mm, K-W = 0.86, $P = 0.650$).

Individual Zernike coefficients for the predominant HOA from third and fourth order (5-mm pupil data) are plotted against the RMS of total combined HOA for children within the DS and control groups (Figs. 2A–E). Linear regression analyses showed that 24.1% of the variance of the RMS of total combined HOA for the control group was due to Z_3^{-1} (vertical coma); 23.9% due to Z_4^0 (spherical aberration); 21.7% due to Z_3^{-3} (trefoil of the sine phase); and only 1.3% and 0.2% due to Z_3^3 (trefoil of the cosine phase); and Z_3^1 (horizontal coma), respectively. For the DS group, 24.6% of the variance of the RMS of total combined HOA was due to Z_3^1, 17.2% due to Z_3^{-1}, 11.7% due to Z_4^0, and only 6.4% and 4.3% due to Z_3^3 and Z_3^{-3}. However, it can be seen from Figure 2D that several outliers with greater amounts of negative Z_3^1 may be strengthening this result.

Interaction between Zernike Coefficients

To explore the influence of interactions between Zernike coefficients, multiple linear regression analyses were performed between the Zernike coefficients of the third and fourth orders to investigate the interdependent relations within the wave-

TABLE 2. Comparison of HOA Data between the DS and Control Groups over Fixed 3-mm Pupil Diameters

	3-mm Pupil Diameter				
	DS Group		Control Group		
Zernike Coefficient	Median, μm	IQR, μm, Min to Max	Median, μm	IQR, μm, Min to Max	Mann-Whitney *U* Test
Z_1^{-3}	−0.010	−0.04 to 0.02 −0.09 to 0.11	−0.035	−0.06 to −0.01 −0.12 to 0.09	$z = -2.65$, $P = 0.0081$*
Z_3^{-1}	0.030	−0.02 to 0.07 −0.10 to 0.11	0.015	−0.01 to 0.04 −0.11 to 0.13	$z = -1.34$, $P = 0.186$
Z_3^1	0.020	0.00 to 0.05 −0.04 to 0.07	0.010	−0.01 to 0.03 −0.09 to 0.11	$z = -1.55$, $P = 0.122$
Z_3^3	0.000	−0.02 to 0.05 −0.07 to 0.07	−0.010	−0.03 to 0.00 −0.08 to 0.10	$z = -3.66$, $P = 0.0003$*†
Z_4^{-4}	0.000	−0.01 to 0.01 −0.03 to 0.06	0.000	−0.01 to 0.01 −0.04 to 0.03	$z = -0.94$, $P = 0.344$
Z_4^{-2}	0.000	−0.01 to 0.01 −0.03 to 0.03	0.000	−0.01 to 0.01 −0.03 to 0.03	$z = 0.02$, $P = 0.981$
Z_4^0	0.000	−0.01 to 0.02 −0.04 to 0.05	0.020	0.01 to 0.02 −0.04 to 0.07	$z = 3.35$, $P = 0.0008$*†
Z_4^2	0.000	−0.02 to 0.01 −0.05 to 0.04	0.000	−0.01 to 0.01 −0.05 to 0.03	$z = -0.19$, $P = 0.849$
Z_4^4	−0.010	−0.01 to 0.01 −0.06 to 0.04	0.000	−0.01 to 0.01 −0.04 to 0.05	$z = 1.14$, $P = 0.255$
Trefoil	0.043	0.02 to 0.08 0.01 to 0.12	0.051	0.03 to 0.07 0.00 to 0.13	$z = 0.42$, $P = 0.677$
Coma	0.064	0.05 to 0.09 0.01 to 0.12	0.042	0.02 to 0.06 0.00 to 0.14	$z = -4.07$, $P < 0.0001$*†
Spherical	0.011	0.01 to 0.03 0.00 to 0.05	0.020	0.01 to 0.02 0.00 to 0.07	$z = -0.32$, $P = 0.751$
Third order	0.090	0.08 to 0.12 0.05 to 0.17	0.080	0.06 to 0.10 0.03 to 0.17	$z = -3.17$, $P = 0.0015$*†
Fourth order	0.050	0.04 to 0.06 0.02 to 0.09	0.040	0.03 to 0.04 0.01 to 0.09	$z = -4.88$, $P < 0.0001$*†
Fifth order	0.030	0.02 to 0.03 0.01 to 0.06	0.020	0.01 to 0.02 0.01 to 0.06	$z = -3.99$, $P = 0.0001$*†
Sixth order	0.020	0.01 to 0.02 0.01 to 0.03	0.010	0.01 to 0.02 0.01 to 0.06	$z = -3.23$, $P = 0.0012$*†
Combined HOA	0.110	0.10 to 0.14 0.06 to 0.20	0.090	0.07 to 0.11 0.04 to 0.18	$z = -3.93$, $P = 0.0001$*†

Medians, IQR, and minimum to maximum values (range) for the 3rd and 4th order Zernike coefficients, RMS values, and for the DS and control groups over a 3-mm pupil diameter.

* Denotes statistically significant differences between the two groups (M-W, $P < 0.05$).

† Denotes statistical significance with Bonferroni correction for multiple comparisons (M-W, $P < 0.05/n$, where $n = 17$ comparisons).

TABLE 3. Comparison of HOA Data between the DS and Control Groups over Fixed 5-mm Pupil Diameters

| Zernike Coefficient | 5-mm Pupil Diameter | | | | |
| | DS Group | | Control Group | | |
	Median, μm	IQR, μm, Min To Max	Median, μm	IQR, μm, Min To Max	Mann-Whitney U Test
Z_1^{-3}	−0.050	−0.12 to 0.08 −0.23 to 0.18	−0.095	−0.18 to −0.01 −0.50 to 0.24	$z = -2.43$, $P = 0.013$*
Z_3^{-1}	0.130	−0.01 to 0.28 −0.30 to 0.37	0.055	−0.04 to 0.14 −0.36 to 0.49	$z = -1.32$, $P = 0.186$
Z_3^1	0.075	−0.06 to 0.16 −0.61 to 0.27	0.010	−0.04 to 0.08 −0.53 to 0.52	$z = -5.45$, $P = 0.122$
Z_3^3	0.035	−0.04 to 0.08 −0.11 to 0.21	−0.040	−0.10 to 0.02 −0.31 to 0.34	$z = -4.21$, $P < 0.0001$*†
Z_4^{-4}	−0.030	−0.04 to 0.01 −0.13 to 0.11	−0.010	−0.04 to 0.01 −0.15 to 0.06	$z = 1.558$, $P = 0.119$
Z_4^{-2}	0.000	−0.04 to 0.03 −0.09 to 0.08	0.010	0.00 to 0.03 −0.08 to 0.10	$z = 0.95$, $P = 0.342$
Z_4^0	−0.025	−0.07 to 0.03 −0.19 to 0.15	0.060	0.02 to 0.10 −0.14 to 0.40	$z = 5.61$, $P < 0.0001$*†
Z_4^2	0.025	−0.04 to 0.06 −0.13 to 0.15	0.010	−0.03 to 0.04 −0.15 to 0.18	$z = -0.77$, $P = 0.437$
Z_4^4	−0.010	−0.08 to 0.03 −0.12 to 0.08	0.005	−0.02 to 0.03 −0.17 to 0.11	$z = 1.56$, $P = 0.119$
Trefoil	0.143	0.09 to 0.20 0.05 to 0.30	0.145	0.09 to 0.21 0.01 to 0.59	$z = 0.26$, $P = 0.793$
Coma	0.231	0.18 to 0.33 0.09 to 0.65	0.142	0.09 to 0.21 0.02 to 0.71	$z = -4.71$, $P < 0.0001$*†
Spherical	0.055	0.03 to 0.08 0.00 to 0.19	0.071	0.04 to 0.10 0.00 to 0.40	$z = 1.39$, $P = 0.166$
Third order	0.285	0.23 to 0.38 0.18 to 0.66	0.220	0.17 to 0.29 0.05 to 0.75	$z = -3.20$, $P = 0.0014$*†
Fourth order	0.115	0.09 to 0.15 0.05 to 0.24	0.110	0.09 to 0.15 0.04 to 0.41	$z = -0.49$, $P = 0.624$
Fifth order	0.070	0.06 to 0.09 0.04 to 0.08	0.060	0.05 to 0.08 0.02 to 0.22	$z = -1.64$, $P = 0.101$
Sixth order	0.055	0.04 to 0.06 0.03 to 0.12	0.040	0.03 to 0.05 0.02 to 0.12	$z = -4.39$, $P < 0.0001$*†
Combined HOA	0.340	0.26 to 0.41 0.22 to 0.70	0.280	0.22 to 0.34 0.12 to 0.88	$z = -2.84$, $P = 0.0046$*

Medians, IQRs, and minimum to maximum values range for the 3rd and 4th order Zernike coefficients, RMS values, and for the DS and control groups over a 5-mm pupil diameter.

* Denotes statistically significant differences between the two groups (M-W, $P < 0.05$).

† Denotes statistical significance with Bonferroni correction for multiple comparisons (M-W, $P < 0.05/n$, where $n = 17$ comparisons).

front. Similar relations were found for both groups with Z_3^{-1} (vertical coma) being significantly predicted by Z_3^{-3} (trefoil of the sine phase; DS $R^2 = 0.38$, $P = 0.002$; control $R^2 = 0.43$, $P < 0.0001$) and with Z_4^{-4} (quadrafoil of the sine phase) being significantly predicted by Z_4^{-2} (secondary oblique astigmatism; DS $R^2 = 0.25$, $P = 0.015$; control $R^2 = 0.14$, $P < 0.0001$). The Zernike coefficient Z_3^1 (horizontal coma) for the DS group was significantly predicted by Z_4^{-4} ($R^2 = 0.18$, $P = 0.046$); however, this differed from the control group where Z_3^1 was significantly predicted by Z_3^3 (trefoil of the cosine phase; $R^2 = 0.027$, $P = 0.022$) and Z_4^0 (spherical aberration; $R^2 = 0.04$, $P = 0.002$). Significant relations were also found between Z_4^0 for the control group and Z_3^{-3} ($R^2 = 0.026$, $P = 0.025$); Z_4^{-4} ($R^2 = 0.032$, $P = 0.013$); Z_4^2 (secondary Cartesian astigmatism; $R^2 = 0.031$, $P = 0.014$); and Z_4^4 (quadrafoil of the cosine phase; $R^2 = 0.031$, $P = 0.014$), whereas the only significant relation with Z_4^0 for the DS group was with Z_3^{-1} ($R^2 = 0.21$, $P = 0.028$).

## Visual Strehl Ratios and Equivalent Defocus Values

Table 4 outlines the VSX and equivalent defocus values for the control and DS groups over 3-mm and 5-mm pupil diameters.

For both 3-mm and 5-mm pupil diameters, the VSX and equivalent defocus are significantly poorer in the DS group compared with controls ($P < 0.03$ for all conditions).

Linear regression analysis showed a strong relation between Visual Strehl ratio for 3-mm and 5-mm pupil diameters for both groups of children (DS $F_{(1,28)} = 12.79$, $R^2 = 0.31$, $P = 0.0013$, control $F_{(1,196)} = 112.65$, $R^2 = 0.37$, $P < 0.0001$; Fig. 3). Within the DS group, 25 children (83%, 3-mm pupil data) showed a Visual Strehl ratio to be less than the average Visual Strehl ratio for the control group.

DISCUSSION

This is the first study to quantify the optical quality of the eyes of children with DS by measuring their HOA. Previous authors have reported that visual performance among children with DS improved when the optics of the eye were bypassed, suggesting degraded optical integrity may play some part in their reduced visual performance.[5] Within the present study, the children with DS were found to have statistically significantly greater combined HOA compared with the
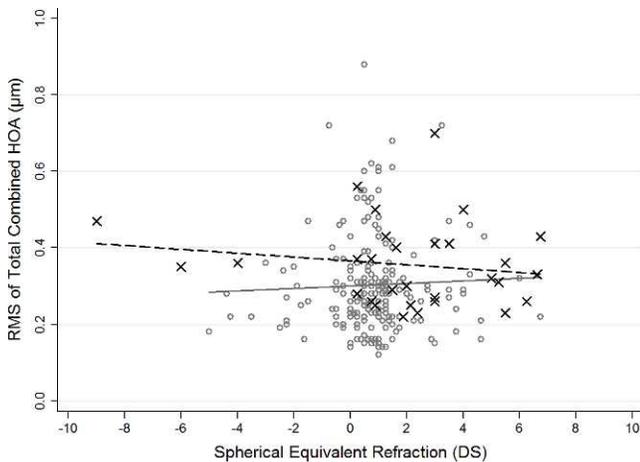
FIGURE 1. RMS of total combined HOA plotted against the spherical equivalent refraction for each child with DS (*black X*) and typically developing child (*gray O*). The *black dashed line* and *gray solid line* denote the linear regression for the DS data ($F_{[1,28]} = 0.72$, $R^2 = 0.025$, $P = 0.404$) and control data ($F_{[1,196]} = 0.34$, $R^2 = 0.017$, $P = 0.599$), respectively.

typically developing children. Statistically significantly greater amounts of the RMS values of third, fourth (3-mm pupil only), fifth, and sixth order aberrations and coma were also found in the DS group compared with control data. Differences were also found between the two groups in the variance of the RMS of total combined HOA from individual aberrations (Fig. 2). The Zernike coefficient Z_3^1 was the most influential explaining 24.6% of the variance of the RMS of total combined HOA for the DS group compared with only 0.2% for the controls. However, this result for the DS group may have been inflated due to outliers within the group with greater magnitudes of Z_3^1. Similar trends for both groups were found with the Zernike coefficient Z_3^{-1} explaining the majority of the variance of the RMS of total combined HOA.

Although the RMS values of HOA for the DS group were of significantly greater magnitude compared with the control data, they are not of the magnitude reported for eyes with pathology affecting the optical structures such as those with keratoconus or cataract.[30,31] Within the present study, the corneae and crystalline lenses of the DS group appeared clinically normal; therefore, the results are suggestive of subclinical imperfections in optical quality. Although refractive error (lower order aberrations) was significantly greater in the DS group, this cannot explain the greater magnitudes of HOA found within the DS eye (Fig. 1). The magnitude of HOA found within the control group of the present study is greater than that reported by other studies investigating HOA in typically developing children[22,29,32] and those reported for adult eyes using the same aberrometer.[28] Therefore, the greater magnitude of aberrations within the typically developing children of the present study may be somewhat masking the relative increase in HOA of those children with DS.

Visual Strehl ratios were significantly poorer over both pupil diameters for the DS group compared with the control data. Although there were subtle differences between the average values for each group, the majority of children with DS (83%) showed lower than the average Visual Strehl ratios for the control group. The reduction in optical quality for the DS group was greater over the central pupil area. This is more likely to have an impact on visual function for these individuals, as the Stiles-Crawford effect demonstrates that cone photoreceptors are more sensitive to light entering at the center of the pupil compared with rays entering at the

periphery[33]; and results from Applegate et al.[34] suggest that having a greater area in the center of the pupil where the wavefront is relatively flat will result in better visual performance. Natural pupil size was statistically significantly greater in the DS group (6.0 mm) compared with the controls (5.5 mm). Individuals with larger pupils will experience greater levels of aberrational blur and thus poorer optical quality even if HOA are similar under fixed pupil diameters.[35]

The equivalent defocus values (DS 3 mm, 0.34 D; 5 mm, 0.38 D; control 3 mm, 0.28 D; 5 mm, 0.31 D) suggest only a small clinically insignificant dioptric increase for the DS group, which does not fully explain the large reduction in visual performances reported to occur among these individuals.[2,3] From the results of Little et al.,[5] we may have expected the equivalent defocus or RMS of total combined HOA to be approximately four times greater than that of the control group. Although the difference between the two groups is not of this magnitude, the extra blur beyond refractive error may be important for the visual performance of children with DS who have coexisting visual processing difficulties and may find it more difficult to interpret images through the distortions caused by the aberrations.

The multiple regression analyses of the present study found significantly different interactions between the Zernike coefficients of the DS and control eyes. Differences were found between the groups for the prediction of Z_3^1 (horizontal coma) and Z_4^0 (spherical aberration), which also showed differing trends with the RMS of total combined HOA between groups. It is difficult to elicit how these interactions within the wavefront may help to improve or reduce image quality and thus visual performance. Applegate et al.[34] reported that aberrations two radial orders apart and with the same angular frequency combine to improve image quality and those within the same radial order combine to reduce image quality. Depending on the combination of the aberrations present within the wavefront, even without a change in the total combined HOA RMS, visual performance can vary by as much as two lines on an acuity chart.[36] These interactions cannot be easily elucidated using graphical or statistical analyses and McClellan et al.[37] suggested that while strong correlations can be found between particular pairs of aberrations, it is the interactions within the entire ensemble of aberrations that work together to improve the overall optical quality. Further work is required to simulate the HOA patterns present in DS eyes to fully understand their interactions and their impact on visual performance.

The somewhat reduced central optical quality present among the DS eyes may be suggestive of a lack of organization and compensation of the HOA between the cornea and internal optics. Children with DS fail to emmetropize[38]; similarly, the eye may also fail to fine-tune the position and shape of the optics to achieve optimum optical quality.[39] Internal compensation of HOA has been reported to occur through a passive mechanism due to the geometrical properties of the optics of the eye, with the optical shape of the cornea (meniscus) and the crystalline lens (biconvex) being the optimum geometrical shapes to automatically compensate for comatic aberration.[40] The shape of the optical components in the DS eye are reported to be atypical[6–9,14] and may, therefore, not facilitate a passive mechanism for optimal compensation. Greater magnitudes of coma were found for the DS group but the difference between the two groups was not statistically significant. Perhaps the most surprising result from this study is the absence of larger amounts of coma and overall HOA considering the level of ametropia and atypical optical structures commonly found in DS eyes.

The majority of children with DS (60%) were found to have negative Z_4^0 (spherical aberration) Z_4^0 compared with only 14% of the controls. The Z_4^0 data also showed a negative trend with
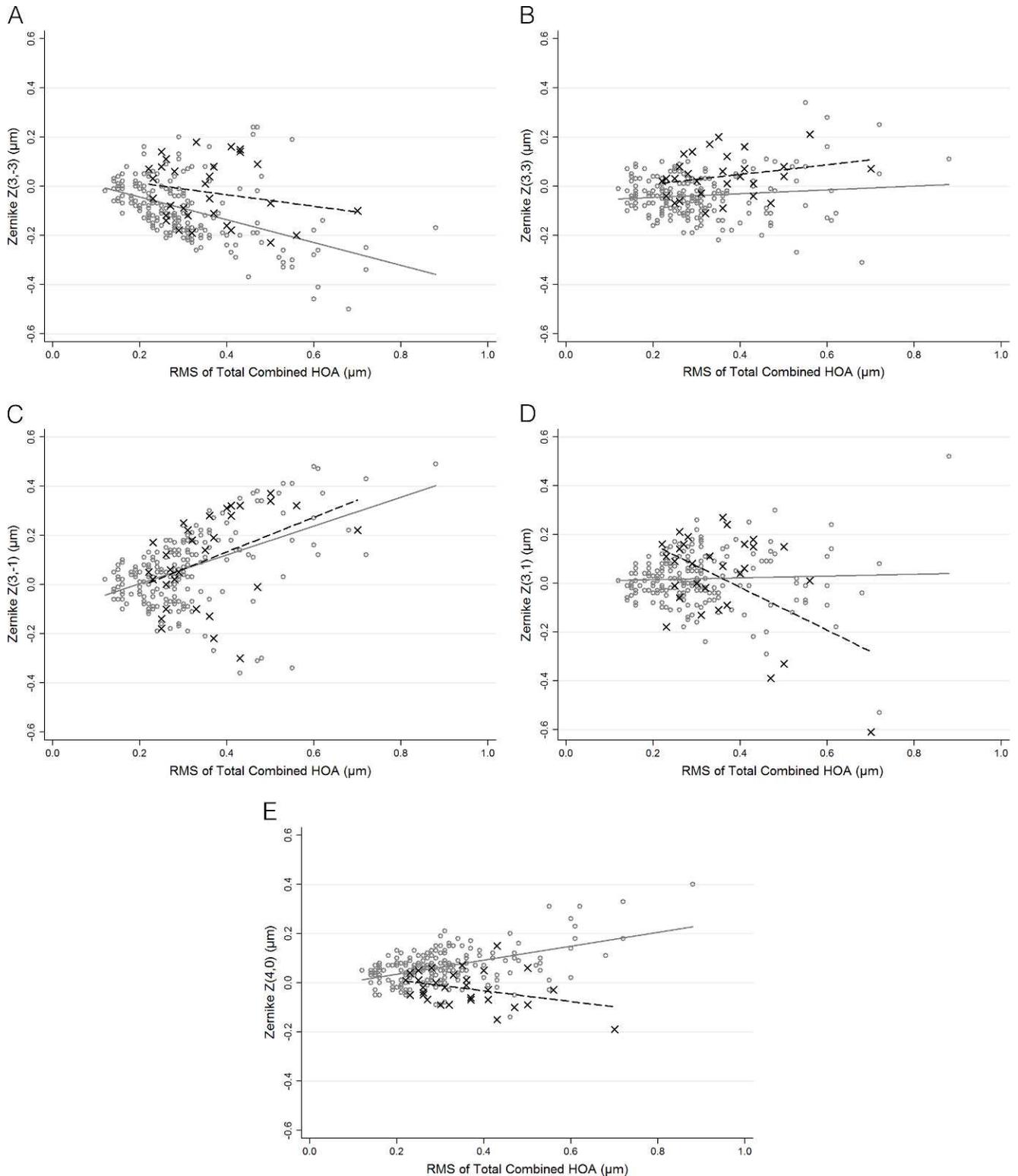
FIGURE 2. RMS of total combined HOA plotted against Zernike Coefficients. (**A**) Z_3^{-3} (trefoil of the sine phase). (**B**) Z_3^3 (trefoil of the cosine phase). (**C**) Z_3^{-1} (vertical coma). (**D**) Z_3^1 (horizontal coma). (**E**) Z_4^0 (spherical aberration) for each child with DS (*black X*) and each typically developing child (*gray O*). The *dashed black lines* represent the linear regressions for the DS data. (**A**) $F_{(1,28)} = 1.3$, $R^2 = 0.043$, $P = 0.27$. (**B**) $F_{(1,28)} = 1.9$, $R^2 = 0.064$, $P = 0.18$. (**C**) $F_{(1,28)} = 5.8$, $R^2 = 0.17$, $P = 0.023$. (**D**) $F_{(1,28)} = 9.1$, $R^2 = 0.25$, $P = 0.005$. (**E**) $F_{(1,28)} = 3.7$, $R^2 = 0.12$, $P = 0.064$. The *solid gray lines* represent the linear regressions for the control data. (**A**) $F_{(1,196)} = 54$, $R^2 = 0.22$, $P < 0.0001$. (**B**) $F_{(1,196)} = 2.5$, $R^2 = 0.013$, $P = 0.12$. (**C**) $F_{(1,196)} = 62$, $R^2 = 0.24$, $P < 0.0001$. (**D**) $F_{(1,196)} = 0.36$, $R^2 = 0.002$, $P = 0.55$. (**E**) $F_{(1,196)} = 62$, $R^2 = 0.24$, $P < 0.0001$.

TABLE 4. Medians, IQRs, and Minimum to Maximum Values for VSX and Equivalent Defocus Values for the DS and Control Groups over 3- and 5-mm Pupil Diameters

	DS Group		Control Group		
	Median	IQR Min to Max	Median	IQR Min to Max	Mann-Whitney U Test
3-mm pupil diameter					
VSX	0.884	0.80 to 0.91 0.68 to 0.98	0.922	0.89 to 0.95 0.76 to 0.98	$z = 4.24$, $P < 0.0001$*
Equivalent defocus	0.339 (D)	0.31 to 0.43 0.18 to 0.62 (D)	0.277	0.22 to 0.34 0.12 to 0.55 (D)	$z = -3.93$, $P = 0.0001$*
5-mm pupil diameter					
VSX	0.458	0.40 to 0.55 0.20 to 0.72	0.543	0.43 to 0.67 0.10 to 0.87	$z = 2.32$, $P = 0.020$*
Equivalent defocus	0.377 (D)	0.29 to 0.45 (D) 0.24 to 0.78 (D)	0.310 (D)	0.24 to 0.38 (D) 0.13 to 0.98 (D)	$z = -2.84$, $P = 0.0046$*

* Denotes statistically significant differences between the two groups (M-W, $P < 0.05$).

increasing magnitudes of the RMS of combined total HOA, in contrast to the positive trend shown by the results of the control group. Studies reporting HOA among populations of children and adults typically report spherical aberration Z_4^0 to be positive, between 0.04 μm and 0.06 μm over a 5-mm pupil,[22,29,41] in agreement with the average results of the control group. The more negative Z_4^0 present within the DS group is contradictory to what one might have expected for eyes that have been reported to have steeper than average corneae[42] and for individuals with greater amounts of hyperopia.[29] The more negative ocular spherical aberration in the DS eyes may therefore reflect differences in internal spherical aberration and relate to the shape of the crystalline lens. An increase in negative internal spherical aberration, which would overcompensate for positive corneal spherical aberration, is consistent with a flattening of the posterior surface of the crystalline lens (Marcos S, et al., *IOVS* 2002;43:ARVO E-Abstract 1510). Haugen et al.[6] reported a flatter anterior surface of the crystalline lens amongst the eyes of participants with DS compared with healthy controls; however there are currently no data reporting posterior lens shape in DS. One could hypothesize that a flatter crystalline lens in the DS eye in conjunction with negative Z_4^0 could provide an atypical stimulus cue for accommodation and may help to explain the poorer accommodative function commonly found in individuals with DS[2,10,11] Further investigation of the crystalline lens including density and refractive index gradient[43,44] and of peripheral cornea shape[42] in DS may help to explain the presence of negative spherical aberration found in this group.

Strengths & Limitations

This is the first report on HOA in DS. The majority of participants with DS within the present study were cooperative with the measurement of their HOA. A power calculation revealed that the sample size was appropriate for the detection of differences in the RMS of total combined HOA (3-mm pupil diameter) between the DS and control groups. For significance at the 5% level, the statistical power was 99.27%.

The children with DS within the present study had higher refractive errors than the control group. There is much debate in the literature on the influence of refractive error on HOA, with some studies reporting greater levels of HOA with increasing refractive error[42,45] and others reporting no significant relationships.[22,46,47] Within the present study, refractive error was not influential in inflating the HOA measurements within the DS group. Similarly, the control group did not demonstrate any associations with refractive error.

Variations in the composition of the tear film have been reported in the DS eye.[12,13] Studies have reported slightly greater amounts of spherical and comatic aberrations in dry eyes,[48] which become less stable and increase with the time delay postblink.[49] Within the present study, all efforts were made to encourage both groups of children to blink before the measurements were taken. Therefore, it is unlikely that the differences observed in HOA between the two groups were solely tear-film related.

CONCLUSIONS

Children with DS have significantly greater HOA and reduced central optical quality compared with typically developing children. While the differences in HOA between the DS and control group reached statistical significance, they were not of pathological proportions and the DS eye maintains relatively good optical quality considering the degree of ametropia and atypical optical structures. The subtle reduction in optical quality may, however, add to the visuocortical[3,4,50] and focusing deficits[2,10,11] previously reported in DS. Further work is required to fully explain reduced visual performance in these children.
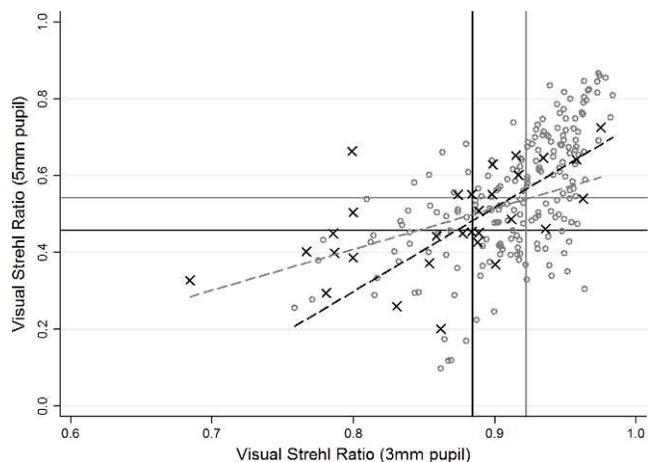

FIGURE 3. VSX for 3-mm pupil diameter plotted against VSX for 5-mm pupil diameter for the children with DS (*black X*) and typically developing children (*gray O*). *Vertical* and *horizontal lines* represent the group averages and *diagonal dashed lines* denote the linear regression of the data (DS, *black*; control, *gray*).

Acknowledgments

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