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Variability in Objective Refraction for Persons with Down Syndrome

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Abstract

Purpose—Down syndrome (DS) is associated with ocular and cognitive sequelae, which both have the potential to influence clinical measures of refractive error. This study compares variability of autorefractometry among subjects with and without DS.

Methods—Grand Seiko autorefractometry was performed on 139 subjects with DS (age: 8 to 55, mean: 25±9 yrs) and 138 controls (age: 7 to 59, mean: 25±10 yrs). Subjects with 3 refraction measures per eye (DS: 113, control: 136) were included for analysis. Each refraction was converted to power vector notation (M , J_0 , J_{45}) and a difference in each component (ΔM , ΔJ_0 , ΔJ_{45}) was calculated for each refraction pairing. From these quantities, average dioptric strength ($\bar{D}_t$: square root of the sum of the squares of M , J_0 and J_{45}) and average dioptric difference ($\bar{D}_d$: square root of the sum of the squares of ΔM , ΔJ_0 and ΔJ_{45}) were calculated.

Results—The DS group exhibited a greater median $\bar{D}_t$ (1Q: 1.38D M: 2.38D 3Q: 3.41D) than control eyes (1Q: 0.47D M: 0.96D 3Q: 2.75D) ($p < 0.001$). Likewise, the DS group exhibited a greater median $\bar{D}_d$ in refraction (1Q: 0.27D M: 0.42D 3Q: 0.78D) than control eyes (1Q: 0.11D M: 0.15D 3Q: 0.23D) ($p < 0.001$) with 97.1% of control eyes exhibiting $\bar{D}_d \leq 0.50$ D, compared to 59.3% of DS eyes. An effect of $\bar{D}_t$ on $\bar{D}_d$ was not detected (p -value=0.3009) nor was a significant interaction between $\bar{D}_t$ and group detected (p -value=0.49).

Conclusions—In the current study, comparing three autorefractometry readings, median total dioptric difference with autorefractometry in DS was 2.8x the levels observed in controls, indicating greater potential uncertainty in objective measures of refraction for this population. The analysis demonstrates that J_{45} is highly contributory to the observed variability.

Keywords

Down syndrome; refraction; autorefraction; power vector

Down syndrome is a genetic condition associated with chromosome 21 (the presence of a complete or partial extra copy of this chromosome), with an overall incidence in the general population of 1 in 691 births.¹ One functional consequence of Down syndrome on vision is the presence of refractive error.^{2–6} da Cunha et al. demonstrated that only 2.0% of a sample of Down syndrome subjects exhibited emmetropia, 58.5% exhibited hyperopia or hyperopic astigmatism and 39.5% exhibited myopia or myopic astigmatism.⁷ Even in the presence of refractive corrections (typically delivered in the form of spectacles), Down syndrome subjects still perform worse than age-matched controls on many common visual performance tasks.^{8–11} Reduced visual performance (measured as grating acuity) has also been reported in children with Down syndrome that have no significant refractive error.¹²

The population of individuals with Down syndrome exhibit both increased refractive cylinder¹³ and higher order ocular aberration¹⁴ which has the potential to further compound the problems associated with subjective refraction as it relies entirely on patient feedback concerning perceived image quality. For typical eyes, where perceived image quality is predominantly a function of residual sphere and cylinder error, the optical parameters at the control of the clinician largely compensate for those impacting the subject's perceived visual quality. However, in the presence of elevated higher order aberration, this is not the case. The higher order aberration (spherical aberration, coma, trefoil, etc.) are not corrected with the optics in spectacle lenses (sphere and cylinder). Further, the interaction of aberration terms has a profound effect on perceived image quality,¹⁵ making the question "which is better, one or two?" more challenging to answer. Therefore, in the presence of elevated higher order aberrations, the typical refractive sequence may be less effective at guiding the clinician and patient toward the best refractive correction. Unlike in the eye with minimal higher order aberration, the clinician can no longer account for the full spectrum of optical defects that impacts perceived image quality. Evidence of this can be found in the population of individuals with the corneal disease keratoconus, where high levels of higher order aberration exist.¹⁶ In the keratoconus population, test-retest variability on subjective refraction is 4x to 6x worse than is seen in the myopic population.¹⁷

Among the population of individuals with Down syndrome, the presence of elevated higher order aberration and the cognitive demands of the refraction task present barriers to obtaining the best possible refractive correction.

As a step in evaluating the refractive sequence in the population of individuals with Down syndrome, this study examines repeatability of autorefraction data. Repeatability analyses are facilitated by first converting the refraction data from minus (or plus) cylinder forms to power vector form, which is an orthogonal representation of spherical and cylindrical components of the refraction and facilitates statistical analyses.^{17,18} From this representation, the study uses the metric dioptric difference to quantify the variability in repeated measures of autorefraction in subjects with and without Down syndrome.^{17,18}

METHODS

Recruitment of Human Subjects

The subject sample used here was also used in a previous study.¹³ Individuals with Down syndrome were recruited through two mechanisms: Down Syndrome Association of Houston (DSAH) events as well as Special Olympics Lion's Club International Opening Eyes (SOLCIE) vision screening events. All individuals with Down syndrome (as per parent / chaperone report) encountered by the research team at these events were invited to participate. Reported prior ocular surgery was used as an exclusion criterion. An age- and sex-matched control sample was recruited from the University of Houston faculty, staff, students, their family and their friends. Individuals with an Optometry degree, Optometry students and clinic subjects were ineligible for enrollment into the control sample to reflect similar representation of the general population. Prior ocular surgery and self-reported history of ocular disease were used as exclusion criteria in the control sample.

Protection of Human Subjects

This research was approved by the University of Houston Committee for the Protection of Human Subjects and adhered to the tenets of the Declaration of Helsinki. Parental/guardian permission was obtained for subjects recruited from the Down syndrome Association of Houston. A consent waiver was obtained for subjects recruited from SOLCIE vision screenings, and willingness to sit for the measurements served as patient assent. Informed consent was obtained for all controls 18 years of age and over, while parental permission and patient assent was obtained for subjects under the age of 18.

Collection of Autorefraction Data

For all subjects, autorefraction measurements were collected after removal of habitual spectacles or contact lenses, if present, (none of the individuals with Down syndrome recruited to participate were contact lens wearers) for each eye with a Grand Seiko WAM 5500 autorefractor (RyuSyō Industrial Co., Ltd. Hiroshima, Japan), which is an open-field autorefractor, allowing the subject to fixate a visual target during testing. All measurements were recorded in the absence of cycloplegia. In an attempt to decrease the possibility of accommodation during measurement, a movie was viewed during data collection for the majority of the subjects with Down syndrome. The movie was displayed on a laptop due to the need for portability. The laptop screen was 12" x 7". There was a small subset of subjects tested at DSAH who viewed a modest size TV screen (dimensions larger than the laptop) on a rolling cart. On a smaller subset of the sample (n = 9) collected at one of the SOLCIE vision screenings where equipment to play a movie was unavailable) a large, inflatable toy was placed at distance and the patient was repeatedly asked to locate and view that target. All targets used in the sample with Down syndrome were set at a 20' test distance, were high contrast and visually interesting. For controls, a large Bailey-Lovie letter chart was used as a fixation aid (top line = 1.0 logMAR) set for distance viewing. Each measurement was reported by the instrument in minus cylinder representation of the correcting lens in the corneal plane. Data were collected on 139 subjects with Down syndrome (age range: 8 to 55, mean: 25±9 yrs) and 138 controls (age range: 7 to 59, mean: 25±10 yrs). Right eye data were collected, followed by left eye data. The data collection

goal was acquisition of 5 measurements per eye, however this goal was not achieved on all subjects. Figure 1 reports the percentage of individuals from each group by number of successful paired captures (at least n captures in both eyes). In 13 subjects, it was not possible to record images on one or both eyes. Given the method of data collection, definitive diagnoses are not possible, but notes recorded regarding probable sources of inability to acquire measures included visible cataract (4), suspect cataract (5), suspect keratoconus (1), general fixation difficulty (1), unilateral ptosis (1) and pellucid marginal degeneration (1). Subjects for whom at least 3 repeated measures were recorded in both eyes (Down syndrome: 113 (81%) and control: 136 (98.6%)) were included in this study, and among these, the first 3 measurements were used in the analysis.

Conversion from Minus Cylinder Notation to Power Vector Notation

Each refraction was converted from minus cylinder notation (S' , C' , α) to power vector notation measured in Diopters (M , J_0 , J_{45}), as described by Thibos et al., where M is the spherical equivalent power of the correcting lens, while J_0 and J_{45} represent with/against the rule and oblique astigmatic powers of the correcting lens in diopters, respectively.¹⁸ Conversion to power vector notation allows the application of scalar mathematical methods such as addition, subtraction and averaging of the individual components of the refraction, which are not possible when the prescriptions are represented in minus or plus cylinder forms.^{17,18}

Total Dioptric Difference - The Difference in Two Refractions

In this study, we adopt the method of dioptric difference published by Raasch et al.¹⁷ which was originally used for examining the difference between two subjective refractions. Here, the method is adopted to examine variability across three objective refractions.

First, pairwise differences are calculated for each of the 3 refractions, (refraction 1 paired with refraction 2; refraction 1 paired with refraction 3; and refraction 2 paired with refraction 3) as:

$$\Delta M_{i,j} = |M_i - M_j| \quad (1)$$

$$\Delta J_{0i,j} = |J_{0i} - J_{0j}| \quad (2)$$

$$\Delta J_{45i,j} = |J_{45i} - J_{45j}| \quad (3)$$

where $i=1$ to 3 , $j=1$ to 3 , $i < j$.

Thus, total variability in the refraction ($D_{t_{ij}}$) for each pairwise refraction is calculated as:

$$\Delta D_{t_{i,j}} = \sqrt{\Delta M_{i,j}^2 + \Delta J_{0_{i,j}}^2 + \Delta J_{45_{i,j}}^2} \quad (4)$$

where $i=1$ to 3 , $j=1$ to 3 , $i < j$

Mathematically, $D_{t_{i,j}}$ is the total scalar distance between the heads of the two power vectors.

An example of the vector representation of three refractions in power vector notation and the resulting $D_{t_{i,j}}$ between them are pictorially represented in Figure 2.

The original application of dioptric difference was in determining test-retest reliability between two subjective refractions, when the refractions were performed during two separate visits. The technique is applied here as a measure of variability of multiple objective refraction measurements during a single data collection session. To form a conservative estimate, the average dioptric difference between three refractions was calculated for each eye as described in equation (5).

$$\Delta \bar{D}_t = \frac{\sum \Delta D_{t_{i,j}}}{3}, i=1 \text{ to } 3, j=1 \text{ to } 3, i < j \quad (5)$$

Dioptric Strength - Magnitude of the Refractive Correction

When the refraction is represented in power vector notation, the individual M , J_0 and J_{45} components of the refraction can be utilized to calculate the magnitude of the refractive correction for an arbitrary refraction (refraction i), as described by Raasch et al., and reported in equation (6) below.¹⁷

$$D_{t_i} = \sqrt{M_i^2 + J_{0_i}^2 + J_{45_i}^2}, i=1, 2, 3 \quad (6)$$

Equation (6) reduces the vector representation of the refractive correction to a scalar value (D_i), with increasing magnitude indicating increasing refractive power of the correction and average dioptric strength, $\bar{D}_t$, was calculated as:

$$\bar{D}_t = \frac{\sum D_{t_i}}{3}, i=1 \text{ to } 3 \quad (7)$$

Data Analysis

All statistical analyses were performed using Stata 13.1 (StataCorp, College Station, TX) or SAS version 9.4 (SAS Institute, Inc., Cary, NC) with two-sided statistical tests at a 0.05 significance level. Due to the skewness of the underlying distribution, distribution-free methods were used to compare group differences. Specifically, a Wilcoxon signed-rank test

was used to compare the within-eye difference in calculated measures of $\bar{D}_l$ and $\bar{D}_r$ and the clustered Wilcoxon rank sum test was used to compare $\bar{D}_l$ and $\bar{D}_r$ between subjects with Down syndrome and controls accounting for inter-eye correlation. A linear mixed-effects regression was used to determine if increase in $(\log(-D_l))$ was explained as a function of increased refractive error ($\bar{D}_l$) among the two groups. A similar analysis was performed to determine whether an increase in $(\log(-D_r))$ was explained as a function of increased age among the two groups.

We used a discriminant function analysis (DFA), to investigate which component of total refraction discriminates between the Down syndrome and typical subjects. DFA finds the linear combination of the specified quantitative variables that maximize the distance between (or separates) the two groups. We specified a total of six quantitative variables ($\bar{M}^2$, $\bar{J}_0^2$, $\bar{J}_{45}^2$) for left and right eyes, where for example $\bar{M}^2$ is the average pairwise difference between two time points squared. Both the within canonical structure and the within-subject standardized canonical coefficients were used to interpret this data. The within canonical structure describes the correlation between the variable of interest and the discriminant function. The higher the correlation, the stronger the contribution of that variable to discriminating between the groups. The within-subject standardized canonical coefficients are the raw coefficients relative to the standard deviation of the variable.

RESULTS

Objective Measurement of Spherical Equivalent Refractive Error

Figure 3 reports the objectively measured spherical equivalent refractive error for both samples. The Down syndrome sample has a mean spherical equivalent of -0.04 ± 3.54 D, whereas the control sample has a mean spherical equivalent of -1.32 ± 2.45 D. The values are statistically different, with the Down syndrome values being shifted toward more hyperopic values ($p < 0.001$)

Comparison of Mean Astigmatism Magnitude

Objectively measured mean astigmatic magnitude (magnitude in the astigmatic power vector plane) for both samples was calculated and compared. The Down syndrome sample has a mean astigmatic magnitude of 0.99 ± 0.64 D, whereas the control sample has a mean astigmatic magnitude of 0.34 ± 0.30 D. The mean values are statistically different ($p < 0.001$), indicating more astigmatism is present in the individuals with Down syndrome.

Refractive Variation in Down Syndrome and Control Groups

The median $\bar{D}_l$ in the right and left eyes of the subjects with Down syndrome were statistically different: 0.49D v. 0.39D, respectively ($p=0.024$) (Table 1). Median $\bar{D}_l$ for the right and left eyes of the control sample were not statistically different: 0.16D and 0.14D, respectively ($p = 0.058$).

Figure 4 is a cumulative frequency plot of $\bar{D}_l$ by group for all eyes. Plotting cumulative frequency allows one to judge the percentage of individuals (found on the vertical axis) that have a level of, in this case, $\bar{D}_l$ that is less than or more than a specific value (found on

horizontal axis). Subjects with Down syndrome exhibited elevated $\bar{D}_t$ ($p < .001$). The median value of $\bar{D}_t$ in subjects with Down syndrome was 0.42D compared to 0.15D observed in controls. Median $\bar{D}_t$ in the sample with Down syndrome for objective refraction was 2.8x the level observed in controls. In this sample, 97.1% of control eyes exhibited $\bar{D}_t \leq 0.50$ D, compared to only 59.3% of Down syndrome eyes. No control eye had $\bar{D}_t$ over 1.50D, whereas 8.4% of Down syndrome eyes exceeded that benchmark.

Magnitude of Refractive Error in Down Syndrome and Control Samples

There were no significant inter-eye differences in $\bar{D}_t$ detected in either the Down syndrome group (Right Eye: 2.43D; Left Eye: 2.32D; $p = 0.91$) or the control group (Right Eye: 0.96D, Left Eye: 0.99D; $p = 0.34$) (Table 2)

Overall, the median $\bar{D}_t$ was higher in the Down syndrome group than in the control group (2.38D v. 0.96D, $p < 0.001$). Figure 5 is a cumulative frequency plot of $\bar{D}_t$ for all eyes by group.

Dioptric Difference as a Function of Dioptric Strength

$\bar{D}_t$ was plotted as a function of $\bar{D}_t$ by group for all eyes (Figure 6). A significant relationship between $\bar{D}_t$ and $\bar{D}_t$ was not detected ($p = 0.30$), nor was a significant interaction between $\bar{D}_t$ and group detected ($p = 0.49$).

Dioptric Difference as a Function of Age

We did not observe a significant effect of age on $\bar{D}_t$ ($p = 0.1504$) after adjusting for group membership.

Multivariate Analysis

The within canonical structure that describes the correlations between the variable of interest and the discrimination function, we observed that $\bar{J}_{45}^2$ for left and right eyes had the highest correlations (Right Eye: 0.730; Left Eye: 0.81) with the discriminant function indicating that this component primarily defined the function. This was followed by $\bar{M}^2$ (Right Eye: 0.562), $\bar{J}_0^2$ (Left Eye: 0.494), $\bar{J}_0^2$ (Right Eye: 0.462), and $\bar{M}^2$ (Left Eye: 0.442). The results from the within standardized coefficients show consistent findings in that $\bar{J}_{45}^2$ has the largest unique contribution in both left eyes and right eyes relative to the other counterparts (coefficients: Right Eye: 0.832; 0.616).

DISCUSSION

Variability in refractive error was elevated in the Down syndrome sample, as compared to the control sample and this variability was driven by variability in the oblique astigmatism component. When dioptric difference was plotted as a function of dioptric strength, neither a significant effect of $\bar{D}_t$ on $\bar{D}_t$ nor a significant interaction between $\bar{D}_t$ and group were detected, demonstrating, increasing dioptric strength does not explain the increase in dioptric difference.

Potential sources of variability in the objective refraction include poor fixation, inattention to the visual target (possibly due to the visual angle subtended by the test object), and optical deficits in the cornea and lens. Given the method of data collection here, it is not possible to differentiate between these potential sources of variability.

To test whether the results might be affected by the number of successful captures used in the calculations, $\bar{D}_t$ was recalculated for the right eye of control subjects where 5 measures were successfully collected, and these values were compared to values calculated from values calculated from the first 3 measures. The values for $\bar{D}_t$ were not significantly different whether 3 or 5 measures were used ($p = 0.589$).

In our sample of Down syndrome subjects, there was a significant difference between the dioptric difference in right and left eyes, with right eyes being more variable. We hypothesize that this may be, in part, due to the fact that right eyes were always measured first. As the test involves a clinical instrument being placed in close proximity to the face of the subject, it is possible that this may have led to apprehension in some subjects with Down syndrome, resulting in poorer cooperation during the initial measurements, which were always performed on the right eye. As the number of trials increased, and the test was then performed on the left eye, the subject would have gained experience with the task which may have reduced the observed variability. That said, the difference in median values between the right and left eyes was 0.10D, which while statistically different, would likely not be considered clinically relevant. In a clinical context, the fact that increased variability was observed on the Down syndrome sample highlights the demands that testing may impose on individuals with Down syndrome.

Raasch et al. observed $\bar{D}_t$ in control subjects at 0.20D,¹⁷ which is comparable to the mean $\bar{D}_t$ found in the control sample in the current study of 0.15D. That said, important differences exist between the two reported measurements. The values reported by Raasch et al. reflect test-retest values (two measurements in total) for subjective refraction on separate days,¹⁷ whereas the $\bar{D}_t$ value in the current experiment is an average of objectively recorded value across three measurements that occurred on the same day in rapid succession. Further, the measurement reported here was objective (no patient feedback required). For this reason, one might anticipate that the value of $\bar{D}_t$ found here would be smaller than that observed by Raasch et al.¹⁷

Perhaps more clinically relevant to the practicing optometrist than the median values for variability in the population with Down syndrome are the values at the extremity of the distribution. It was noted that only 91% of subjects with Down syndrome were able to achieve at least 1 autorefraction capture on both eyes. This is in contrast to > 99% of the control population, whose measurements were limited only by optical opacities. Further, examination of Figure 3 shows that the variability in the refraction was over 1.5D in 8.4% of the Down syndrome eyes. This level of variability, coupled with other challenges associated with subjective refraction could lessen the possibility of the patient/clinician pairing arriving at the best possible refraction in a sizeable portion of the population with Down syndrome.

Data for this study were collected without the use of cycloplegia due to the fact that subjects were tested in a non-clinical setting without a comprehensive ocular health assessment. Performing autorefraction without cycloplegia is common clinical practice and thus the testing method employed here offers generalizable information regarding variability of multiple measures under the most typical use of this instrument. That said, the lack of cycloplegia in this study means that accommodation was active during measurements and thus could have contributed to some of the variability for either population. This concern is largely minimized by the type of autorefractor used in this study – an open-field design - that permits real distance viewing and thus encourages relaxation of accommodation. In addition, with respect to subjects with Down syndrome, it is well documented that these individuals can have poor accommodative function, even in childhood, and therefore the increased variability in the subjects with Down syndrome is unlikely to be attributed to fluctuations in accommodation during autorefraction measures.^{19–21} This expectation is also supported by our finding that oblique astigmatism contributed to the observed variability rather than spherical component variability.

What is the consequence of this variability? In the clinical setting, increased variability may result in a larger dioptric space that must be considered during the subjective refraction process. However, performing retinoscopy before subjective refraction is a standard clinical practice for individuals with Down syndrome, and may reduce the need to search an enlarged refractive space during the subjective refraction. If the refractive search space is not reduced by the use of retinoscopy, the clinician may have to provide the subject with a greater number of comparisons, or potentially alter the dioptric step size utilized during refraction, to identify the best possible sphero-cylindrical correction for the subject. In the research setting, increased variability would lead to less certainty in any average refraction that is calculated; meaning, the estimated refraction is less likely to represent the true refractive state of the eye.

It is hypothesized that increased variability in objective refraction in Down syndrome may lead to increased uncertainty in spectacle prescriptions for this patient population. Objective measures such as the open-field autorefractor used here have appeal, mainly due to the speed of data collection, and worked well for a large portion of this population. For those with increased variability, however, the uncertainty of the measures lead to limitations in its utility. If used as a starting point for subjective refraction, the measurement uncertainty, coupled with the cognitive demands of the subjective refraction task, may lead to an increased variability in the ending point of subjective refraction for the population with Down syndrome. If used in isolation as an objective tool for prescribing in patients who are unable to participate fully in subjective refraction, it could lead to suboptimal prescriptions. At present, these findings underscore the importance of utilizing multiple methods to measure refraction and corroborate findings across techniques (autorefraction, retinoscopy, subjective refraction, etc.). With respect to the future management of this population, the need exists for additional tools to provide objective measurements of refraction with greater certainty.

CONCLUSIONS

In the current study, comparing three autorefraction readings, median refractive variability in the population with Down syndrome for objective refraction as quantified with dioptric difference was 2.8x the levels observed in controls, and the analysis demonstrates that J45 is highly contributory to the observed variability.

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Figure 1.

The data collection goal was to collect 5 Grand-Seiko autorefraction measurements in both eyes of each subject. This was successfully completed on over 98% ($n = 136$) of control subjects. However, 5 autorefraction measures were recorded in both eyes of only 55% ($n = 77$) of the Down syndrome sample.

Power Vector Representation

Figure 2.

Power Vector Representation - Dioptric difference between any two refractive pairings is represented as a dashed arrow. Raasch et al¹⁶ described this quantity for comparing two refractions as a way to establish test-retest differences between 2 subjective refractions, with smaller values indicating less difference. Here dioptric difference is applied to 3 objective refractions, resulting in three values of dioptric difference for each eye.

Figure 3.
Objectively measured spherical equivalent refractive error for both the Down syndrome and control samples.

Figure 4.

Distribution of Dioptric Difference - Cumulative frequency distribution of total dioptric difference ($\bar{D}_t$) of control (gray line) and Down syndrome (DS), groups (black line). The DS group exhibits elevated variability when compared to the control group.

Figure 5. Distribution of Dioptric Strength - Cumulative frequency distribution of total dioptric strength ($\bar{D}_t$) of control (gray line) and Down syndrome (DS) group (black line).

Figure 6.

Dioptric Difference as a Function of Dioptric Strength - Variability in total refractive error ($\Delta \overline{D_t}$) is plotted as a function of magnitude of the total refractive error $\overline{D_t}$ for both the Down syndrome and control groups.

Table 1

Median total dioptric difference ($\bar{D}_l$) in DS and control samples by eye.

Wilcoxon Signed Rank	<u>Average Dioptric Difference</u>		
		Median (1Q, 3Q)	P
DS (n=113)	RE	0.49 (0.32, 0.84)	0.02
	LE	0.39 (0.25, 0.69)	
Control (n=136)	RE	0.16 (0.11, 0.24)	0.058
	LE	0.14 (0.10, 0.22)	

DS = Down Syndrome; RE = right eye; LE= left eye.

Table 2

Median total dioptric strength ($\bar{D}$) in Down syndrome and control samples by eye.

Wilcoxon Signed Rank	<u>Average Dioptric Strength</u>		
		Median (1Q, 3Q)	P
DS (n=113)	RE	2.43 (1.25, 3.35)	0.91
	LE	2.32 (1.57, 3.53)	
Control (n=136)	RE	0.96 (0.45, 2.82)	0.34
	LE	0.99 (0.50, 2.72)	

DS = Down Syndrome; RE = right eye; LE= left eye.