

Validation of Mahajan's formula for scaling ocular higher-order aberrations by pupil size

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Purpose: Zernike polynomials for describing ocular higher order aberrations are affected by pupil aperture. The current study aimed to validate Mahajan's formula for scaling Zernike polynomials by pupil size. **Methods:** Higher order aberrations for 3 intraocular lens models (AcrySof IQ IOL SN60WF, Technis ZA9003, Adapt Advanced Optics) were measured using the Zywave aberrometer and a purpose-built physical model eye. Zernike coefficients were mathematically scaled from a 5 mm to a 3 mm pupil diameter (5:3 mm), from a 5 mm to a 2 mm pupil diameter (5:2 mm), and from a 3 mm to a 2 mm pupil diameter (3:2 mm). Agreement between the scaled coefficients and the measured coefficients at the same pupil aperture was assessed using the Bland–Altman method in R statistical software. **Results:** No statistically significant mean difference (MD) occurred between the scaled and measured Zernike coefficients for 21 of 23 analyses after Holm-Bonferroni correction ($P > 0.05$). Mean differences between the scaled and measured Zernike coefficients were clinically insignificant for all aberrations up to the fourth order, and within 0.10 μm . Oblique secondary astigmatism (Z_4^{-2}) was significantly different in the 5:3 mm comparison (MD = -0.04 μm , $P < 0.01$). Horizontal coma (Z_3^1) was significantly different in the 3:2 mm comparison (MD = -0.07 μm , $P = 0.03$). There were borderline statistical differences in both vertical (Z_3^{-1}) and horizontal coma (Z_3^1) in the 5:3 mm comparison (MD = 0.02 μm , -0.09 μm , $P = 0.05$, 0.05, respectively). **Conclusion:** A formula for the scaling of higher order aberrations by pupil size is validated as accurate. Pupil scaling enables accurate comparison of individual higher order aberrations in clinical research for situations involving different pupil sizes.

Key words: Aberrations, higher order aberrations, ocular aberrations, optics, pupil size, Zernike polynomials

In the absence of corneal or lenticular opacity, ocular higher order aberrations (HOA) are the single most important factor in reducing the quality of the retinal image when the pupil size exceeds 3.0 mm in diameter.^[1] Accurate description of HOA can be achieved with Zernike polynomials, which are a set of orthogonal basis functions over a circle of unit radius.^[2,3] Aberrometers, such as the Zywave (Bausch and Lomb, Rochester, NY), directly measure HOA and report their magnitude using coefficients for individual Zernike polynomials.^[3] The advantages of utilizing Zernike polynomials in this manner include their mutual orthogonality and comparability. A disadvantage of Zernike polynomials is that they are dependent on pupil aperture.

Many clinical aberrometers are capable of scaling the aberrations for pupil size within their software; however, this is not a universal capability. In classical Hartmann-Shack aberrometers, algorithms for pupil scaling use a large number of sensor elements for calculating the aberrations for the maximum natural pupil size and a smaller number of sensor elements for the simulated, smaller pupil size.^[4]

Other approaches to mathematically scale Zernike coefficients have been proposed, and progressively simplified.^[5-13] These formulas use differing algebraic, recursive, or matrix methods, but all are equivalent.^[14] In theory, scaling Zernike coefficients to a smaller diameter has no error.^[14] The previous studies have applied scaling formulas to standardize ocular aberrations prior to statistical analysis.^[15,16] Moreover, two studies have validated alternative versions of HOA scaling formulas in human eyes, for both decreases and increases in pupil aperture.^[4,14]

The aim of the current study was to clinically validate a recently published HOA scaling formula, which expresses a scaled Zernike radial polynomial as a linear combination of the unscaled radial polynomials.^[13] To the best of our knowledge, this is the first study to apply to the scaling formulas to a validated HOA model, for which the pupil aperture can be exactly controlled, and for which all possible instrument sensors were used at every given pupil aperture.

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Methods

The university of Auckland model eye

The current study took place in Auckland, New Zealand. A physical model eye platform to analyze wavefront aberrations introduced by intraocular lenses (IOLs) was designed and constructed for use with the Zywave aberrometer (Bausch & Lomb, Rochester, NY) as previously described.^[17,18] The model consists of a Boston XO 45.0-diopter (D) corneal lens with an adjustable iris incorporating fixed pupil diameters at 5 mm, 3 mm, and 2 mm suspended on a digital vernier scale (accurate to 0.01 mm). Intraocular lenses were fitted to the mounting plate and were secured by elastic fasteners over the haptics to avoid physical distortion of the optic. The model eye was calibrated to remove tilt and decentration and then filled with Millipore-filtered (Millipore Corp., Billerica, MA) water to emulate aqueous fluid before aberrometry measurements for this study.

Aberrometry

A Zywave (Bausch & Lomb, Rochester, NY) Hartmann-Shack aberrometer (model 1.0, software version 5.09) was used for all aberrometry measurements. Prior to the study, the aberrometer was calibrated by an experienced Bausch & Lomb technician. All results were exported as raw data so that individual Zernike terms could be analyzed independently. The Zernike terms spanned HOAs from Z_2^0 through Z_5^{-5} .

Intraocular lenses

The IOLs selected for the study were acrylic with a power of 20 D to approximate the power of the average human lens. Three models from 3 manufacturers were selected for comparison, with 12 individual IOLs being assessed ($n = 4$ for each IOL model). The following IOL models were selected for the study: AcrySof IQ IOL SN60WF aspheric single-piece with blue-light filtration (Alcon, Hünenberg, Switzerland), Technis ZA9003 aspheric (Advanced Medical Optics), and Adapt Advanced Optics (Bausch and Lomb).

Measurements

All measurements were performed in a darkened room under the same conditions. Each IOL was selected in turn and inserted into the IOL mounting bracket while ensuring correct positioning and alignment. The model eye was adjusted to reach emmetropia (determined by the aberrometer); each IOL was centered and aligned so that there was no tilt or decentration. Aberrometry data were collected using the standard protocol for the aberrometer outlined by the manufacturer. Each IOL was measured once at each pupil aperture (2-mm, 3-mm, 5-mm diameter). After each IOL measurement, the IOL mounting bracket was removed from the model; the IOL then was removed from the mounting bracket and replaced with subsequent IOLs of the same model and power for repeat measurements (4 in total for each model). Using this procedure, all 4 identical IOLs of the 3 different models were assessed. After all aberrations were measured, the data were exported into Microsoft Excel (Microsoft Corp., Redmond, WA) and formatted for statistical analysis using the R statistical analysis package (R Foundation for Statistical Computing, Vienna, Austria). The model was tested repeatedly for reproducibility and error on a single IOL as documented previously.^[17] Briefly, repeat measurements of the same IOL were used to assess variability in HOAs (Z_2^0 through Z_5^{-5}) associated with repeated

measurements and varying degrees of disassembly of the model eye required for fitting and measuring different IOLs.

Scaling

Pupil scaling as described by Mahajan was implemented in R version 3.3.0 (R Foundation for Statistical Computing, Vienna, Austria) and applied retrospectively to the data.^[13,18] Zernike coefficients were scaled to 2 and 3 mm pupils using the measured data from the 3 and 5 mm pupils. The 2 mm pupil was too small for aberrations above primary spherical aberration (Z_4^0) to be detected by the aberrometer. Therefore, only the second and third order HOAs were scaled for any comparisons involving the 2 mm pupil. When scaling to a 3 mm pupil, only second-, third-, and fourth-order Zernike coefficients were analyzed because the coefficients were negligible for the fifth to seventh orders.^[14]

Statistical analysis

All statistical analyses were completed using R (R Foundation for Statistical Computing, Vienna, Austria). Data normality was assessed using the Wilks-Shapiro test and visual assessment of histograms. The scaled data were compared to the raw aberrometer measurements for a given pupil size. For example, in the 5:2 mm analysis, data scaled from a 5 mm to a 2 mm diameter pupil were compared to the aberrometer-reported 2 mm pupil results. Bland-Altman plots were used to visually compare measurements between device pairs by plotting the differences between measurements against their mean along with lines representing the limits of agreement.^[19,20] The 95% limits of agreement (mean difference $\pm 1.96 \times$ standard deviation) define the range within which most differences between measurements from the 2 devices will lie. To review fixed biases in the data, one-sample *t*-tests with were conducted with the test value equal to zero. Proportional biases were assessed with Pearson's correlation coefficient, and 95% limits of agreement for proportional biases were calculated using regression analysis according to Bland and Altman.^[19] *P* values were recorded before and after Holm-Bonferroni corrections.^[21]

Results

Analysis of raw data demonstrated the presence of some artifactual outliers in excess of two standard deviations from the mean that were removed prior to mathematical scaling. In total, twenty-three of 336 raw data points (6.8%) were removed as outliers prior to scaling and analysis. The comparisons of observed and scaled Zernike coefficients for data scaled from a 5:3 mm pupil are summarized in Table 1. After Holm-Bonferroni correction, there were no statistically significant fixed biases in 10 out of 11 measured higher order aberrations. The single statistically significant fixed bias occurred in oblique secondary astigmatism [mean difference (MD) = $-0.04 \mu\text{m}$, $P_{\text{Holm}} < 0.01$]. The comparisons of observed and scaled Zernike coefficients for data scaled from 5:2 mm and 3:2 mm are summarized in Table 2. Horizontal coma (Z_3^1) has a statistically significant fixed bias in the 3:2 mm analysis difference (MD = $-0.07 \mu\text{m}$, $P_{\text{Holm}} = 0.03$). When data were scaled from 5:2 mm, 4 out of 6 analyses were not statistically different; however, borderline significant fixed biases occurred in vertical coma (Z_3^{-3}) and horizontal coma (Z_3^3) MD = $0.02 \mu\text{m}$, $-0.09 \mu\text{m}$; $P_{\text{Holm}} = 0.05$, 0.05 ; respectively. Statistically significant proportional biases were identified in almost all comparisons, indicating that

Table 1: Mean differences between scaled 5 mm aberrations and observed 3 mm aberrations

| Mode | Classical name | M.D. | LoA (M.D.) | P | P_{Holm} | R | LoA (R) | P (R) |
|------|--------------------------------|-------|------------|-------|------------|-------|---------|-------|
| Z221 | Oblique astigmatism | 0.05 | 0.14 | 0.21 | 1.00 | -0.60 | 0.07 | 0.24 |
| Z220 | Vertical astigmatism | 0.02 | 0.14 | 0.40 | 1.00 | -1.60 | 0.14 | <0.01 |
| Z311 | Vertical coma | 0.02 | 0.05 | 0.01 | 0.08 | -0.05 | 0.05 | 0.88 |
| Z310 | Horizontal coma | -0.08 | 0.10 | 0.03 | 0.24 | -1.85 | 0.09 | 0.22 |
| Z331 | Vertical trefoil | -0.01 | 0.08 | 0.59 | 1.00 | -0.76 | 0.08 | 0.35 |
| Z330 | Oblique trefoil | -0.03 | 0.10 | 0.16 | 0.95 | -1.33 | 0.06 | <0.01 |
| Z400 | Primary spherical | 0.01 | 0.08 | 0.34 | 1.00 | -1.20 | 0.08 | <0.01 |
| Z421 | Vertical secondary astigmatism | 0.00 | 0.05 | 0.66 | 1.00 | -1.93 | 0.05 | <0.01 |
| Z420 | Oblique secondary astigmatism | -0.04 | 0.04 | <0.01 | <0.01 | -1.58 | 0.04 | <0.01 |
| Z441 | Vertical quatrefoil | -0.03 | 0.07 | 0.05 | 0.41 | -1.91 | 0.07 | <0.01 |
| Z440 | Oblique quatrefoil | -0.03 | 0.08 | 0.09 | 0.62 | -1.91 | 0.08 | <0.01 |

M.D.: Sample mean difference; LoA: 95% limits of agreement; LoA (R): Regression based 95% limits of agreement; P: Probability value; PHolm: Probability value after Holm-Bonferroni correction; P (R): Probability value for the correlation coefficient; R: Correlation coefficient (Pearson's R)

Table 2: Mean differences between scaled aberrations and observed 2 mm aberrations

| Mode | Classical name | M.D. | LoA (M.D.) | P | P_{Holm} | R | LoA (R) | P (R) |
|--|----------------------|-------|------------|-------|------------|-------|---------|-------|
| Comparison of Scaled 3 mm Data with Observed 2 mm Data | | | | | | | | |
| Z221 | Oblique astigmatism | -0.02 | 0.15 | 0.40 | 0.81 | -0.77 | 0.07 | <0.01 |
| Z220 | Vertical astigmatism | 0.03 | 0.06 | 0.01 | 0.06 | -0.71 | 0.04 | 0.01 |
| Z311 | Vertical coma | 0.01 | 0.04 | 0.23 | 0.68 | -1.09 | <0.01 | <0.01 |
| Z310 | Horizontal coma | -0.07 | 0.12 | <0.01 | 0.03 | -1.09 | <0.01 | <0.01 |
| Z331 | Vertical trefoil | -0.03 | 0.09 | 0.07 | 0.28 | -1.09 | <0.01 | <0.01 |
| Z330 | Oblique trefoil | -0.04 | 0.10 | 0.04 | 0.18 | -1.09 | <0.01 | <0.01 |
| Comparison of Scaled 5 mm Data with Observed 2 mm Data | | | | | | | | |
| Z221 | Oblique astigmatism | 0.05 | 0.25 | 0.26 | 0.53 | -1.71 | 0.09 | <0.01 |
| Z220 | Vertical astigmatism | 0.04 | 0.14 | 0.11 | 0.46 | -1.85 | 0.04 | <0.01 |
| Z311 | Vertical coma | 0.02 | 0.05 | 0.01 | 0.05 | -0.05 | 0.05 | 0.88 |
| Z310 | Horizontal coma | -0.09 | 0.17 | 0.01 | 0.05 | -2.15 | 0.03 | <0.01 |
| Z331 | Vertical trefoil | -0.01 | 0.06 | 0.31 | 0.53 | -1.86 | 0.03 | <0.01 |
| Z330 | Oblique trefoil | -0.03 | 0.10 | 0.15 | 0.46 | -1.81 | 0.02 | <0.01 |

M.D.: Sample mean difference; LoA: 95% limits of agreement; LoA (R): Regression based 95% limits of agreement; P: Probability value; PHolm: Probability value after Holm-Bonferroni correction; P (R): Probability value for the correlation coefficient; R: Correlation coefficient (Pearson's R)

the differences between the scaled and observed values grew proportionally to the magnitude of the observed aberrations.

Bland-Altman plots for the scaled and measured HOA pair comparisons (Z^{-2}_2 through Z^3_3) are demonstrated in Fig. 1. Data are generally tightly clustered around the line of no difference with outlying data points predominantly causing widening of the limits of agreement. Fig. 2 displays the agreement between scaled and measured fourth order aberrations for 5:3 mm analysis. These data are more centrally clustered than the lower order aberrations, with much narrower limits of agreement, all less than $\pm 0.1 \mu\text{m}$. Fig. 3 demonstrates the effect of the scaling function on individual second- and third-order aberrations in the 5:3 mm analysis.

Discussion

The aim of the current study was to verify Mahajan's pupil scaling formula for HOAs using a validated physical model eye and a clinical aberrometer.^[17,18] It has been demonstrated

that there are no significant fixed differences between the scaled data and the raw data for aperture ratios as low as 0.4 for all second order aberrations, excluding defocus (Z^0_2). Most third and fourth order aberration comparisons were also not significantly different; however, one significant difference in coma and one significant difference in oblique secondary astigmatism were noted.

Bland-Altman plots demonstrated that differences between the values produced by each method were tightly clustered around zero. The widest 95% limits of agreement approached $\pm 0.25 \mu\text{m}$ for oblique astigmatism; however, most were within $\pm 0.15 \mu\text{m}$. In the largest study to date, the median just-noticeable difference between two images occurred with $0.091 \mu\text{m}$ of aberration for astigmatism, $0.059 \mu\text{m}$ for coma, and $0.108 \mu\text{m}$ for trefoil, with a large interindividual spread.^[22] In a smaller study, a just-noticeable difference occurred with a spherical aberration coefficient of $0.07 \mu\text{m}$.^[23] The amount of aberration required to make this blur objectionable is least double this amount, and therefore

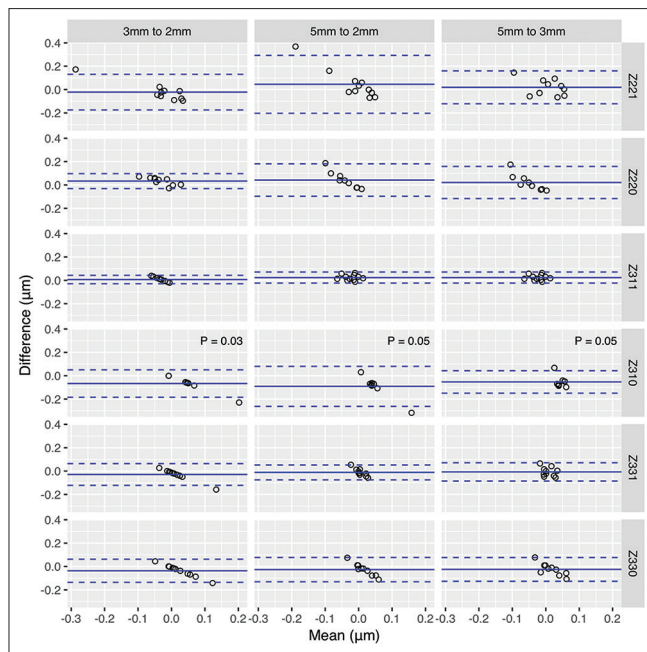


Figure 1: Bland–Altman plots showing the agreement of mathematically scaled and measured Zernike coefficients (micrometers) for different pupil sizes. The central line represents the mean of the difference between the two devices. Dashed lines represent 95% limits of agreement. Significant differences following Holm–Bonferroni correction are indicated with printed *P* values

outside most of the limits of agreement produced in the current study.^[24]

The findings of the current study agree with a previous study which demonstrated no statistically significant differences for scaled second, third, and fourth order aberrations in human eyes.^[4] The mean mesopic natural pupil size in that study was 5.39 mm and ranged between 5.00 and 6.26 mm with a mean aperture ratio of approximately 0.56 (range 0.48–0.60). In the current study, the most comparable results are therefore the 5:3 mm comparison with an aperture ratio of 0.6, in which there was only a single measured Zernike polynomial with a statistically significant fixed difference to that predicted using mathematical scaling.

A majority of comparisons in the current study show a strong proportional bias, indicating that the differences between the scaled and observed aberrations grew proportionally to the magnitude of the observed aberrations. Considerable variance in higher-order aberration measurements with Hartmann–Shack aberrometers has been previously shown with pupil apertures of 3 mm and below.^[25] This variance is attributed to fitting error caused by the small number of sensor elements involved in measuring wavefront inclination at smaller pupil sizes, which in turn reduces the signal-to-noise ratio.^[25] The signal-to-noise ratio also reduces with the radial order of the coefficient, and these factors combined may explain why proportional biases occurred more frequently in analyses involving smaller pupil sizes and coefficients with higher radial orders.^[25] The proportional biases demonstrated are in keeping with one previous study which reported correlation coefficients ranging between 0.695 and 0.999 when scaling second, third, and fourth order higher order aberrations.^[4]

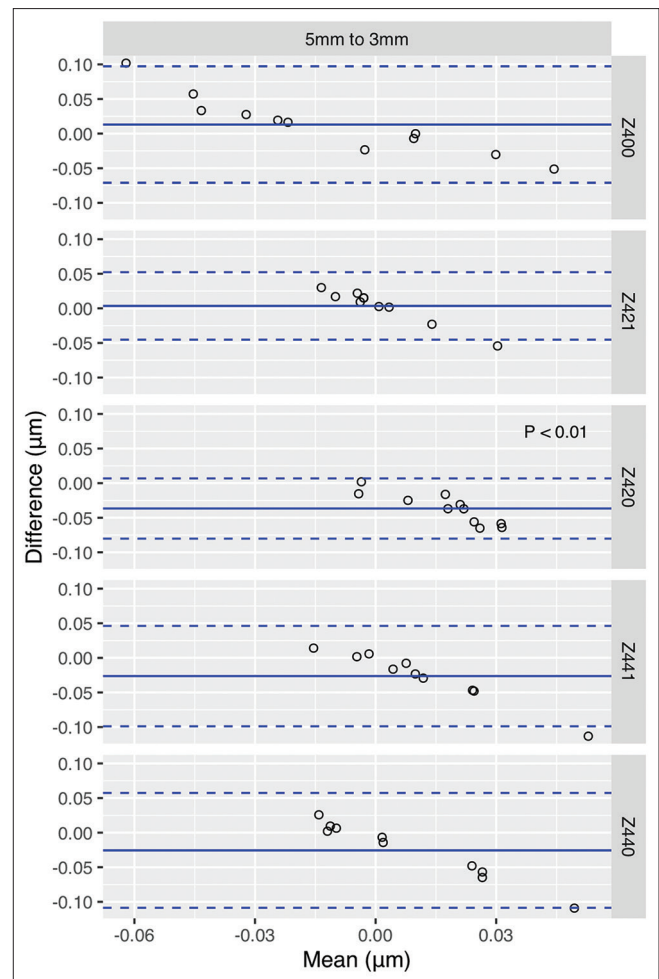


Figure 2: Bland–Altman plot showing the agreement of Zernike coefficients scaled from a 5 mm pupil to a 3 mm pupil (micrometers). The central line represents the mean of the difference between the two devices. Dashed lines represent 95% limits of agreement. Significant differences following Holm–Bonferroni correction are indicated with printed *P* values

The number of statistically significant analyses increased as the aperture ratio decreased to 0.4 (5:2 mm analysis). The formula must account for larger differences at smaller pupil ratios; however, scaling from large to very small pupil sizes should not reduce the accuracy of scaled HOAs.^[14] At small pupil sizes, the measured HOAs may be less accurate than those measured at, or scaled from, larger pupil sizes. As pupil size decreases, the number of sensors recruited, and the amount of data collected by the aberrometer is exponentially decreased. The smaller effective array used with a 2 mm aperture is likely to be relatively more sensitive to peripheral sensor dropout, signal noise, and optical interference compared to the larger 3 mm pupil. The previous studies using the same physical model eye have also demonstrated minimal overall HOA with a 2 mm pupil, suggesting Hartmann–Shack aberrometers may start to become diffraction limited at this point.^[18] Therefore, it is possible that the observed statistically significant differences involving the 2 mm pupil aperture are due to error associated with measurement at this pupil size using the clinical aberrometer rather than error introduced by the scaling function.

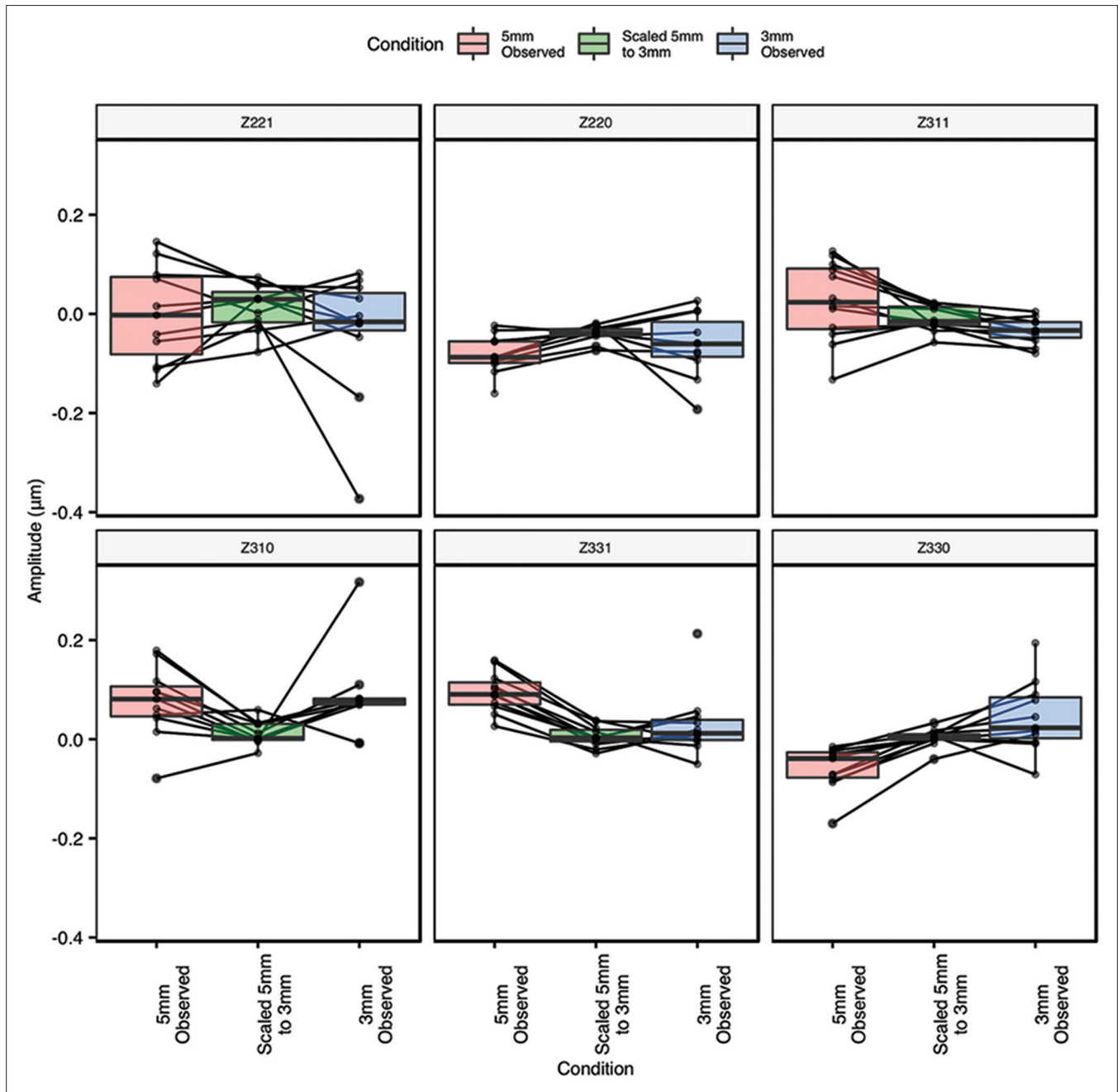


Figure 3: Boxplots with pairwise comparisons showing the agreement of mathematically scaled and measured Zernike coefficients (micrometers) for second- and third order aberrations at different pupil sizes. Lines connect data points corresponding to the same intraocular lens. 5 mm Observed, observed aberrations with a 5-mm pupil; Scaled 5 mm to 3 mm, 5 mm aberrations mathematically scaled to a 3 mm pupil; 3 mm Observed, observed aberrations with a 3-mm pupil

The agreement of scaled aberrations decreased with increasing radial degree in a previous study.^[4] This effect has also been noted in the current study whereby the comparisons involving aberrations from the highest radial degrees were the most likely to present significant differences.^[4] The reduction in agreement likely occurs because the absolute values of higher order aberrations decrease as the radial degree increases. These small aberrations may test the limits of accuracy of the aberrometer.

Limitations of the current study are the small number of measurements, and lack of repeated measurements for each

individual IOL. Repeated measures have been previously completed using the same experimental model eye and the system has been validated as accurate.^[17] Strengths include fine granular control over all factors affecting the optics of the system. The pupil aperture was perfectly consistent and circular in all circumstances which will not be the case for human-based studies. The lenses in the study were not decentered or tilted. This makes the model an ideal test-case for the formula selected; however, pupil scaling for decentered, tilted, and non-circular pupils has also been described.^[7,10,11]

The aperture dependent nature of Zernike polynomials requires special consideration when measurements from different instruments or participants are compared, for example, in repeatability and agreement studies. The ability to precisely predict the extent of HOA reduction at specific pupil sizes will enable clinicians to assess the likely efficacy of pinhole piggyback lenses to reduce visual symptoms associated with HOA. In addition, accurate aberration data relative to pupil size is critical when the measurements are used in planning for surgery such as the use of aspheric intraocular lenses or the selection and placement of intracorneal ring segments.

Conclusion

The accuracy of the pupil scaling formulas for aberrations above Defocus (Z_0^2) for pupil aperture ratios above 0.4 has been confirmed, with a model that ensures consistent and accurate pupil size. The validation of this formula enables the comparison of HOAs between patients or aberrometers. Because many HOAs cannot be measured with a 2 mm pupil, and scaling formulas appear to be less accurate with small pupils, it is likely good practice to avoid pupil sizes less than 3 mm when investigating higher order aberrations with Hartmann-Shack aberrometers.

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Conflicts of interest

There are no conflicts of interest.

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