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ORIGINAL RESEARCH

Normative Data of Higher-Order Aberrations in Healthy Caucasian Eyes and Their Correlation with Age, Gender, and Spherical Equivalent

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Purpose: To investigate the distribution of normative data for higher-order aberrations (HOA) among younger and older populations and identify their correlations with age, gender, and refractive errors.

Methods: This study analyzed healthy, phakic, treatment-naïve eyes from Caucasian participants examined at three European centers between July 2019 and July 2022. Total eye and corneal HOA were analyzed using a novel corneal tomographer with an integrated Hartmann-Shack aberrometer. Simple correlation analysis was conducted using the Pearson correlation coefficient, assuming a linear model.

Results: A total of 1075 eyes were analyzed. Mean age and spherical equivalent (SE) were 52.9 ± 19.5 years (range: 10–91 years) and −1.81 ± 3.76D (range: -17.11–+8.72D). A strong correlation was found between age and ocular RMS HOA ($r = 0.55$, $p < 0.001$) and the age-related effect on spherical aberration (SA) was moderate ($r = 0.30$, $p < 0.001$). There was a moderate positive correlation between age and corneal RMS HOA ($r = 0.46$, $p < 0.001$), horizontal coma ($r = 0.28$, $p < 0.001$), and SA at 4-mm ($r = 0.39$, $p < 0.001$) and 6-mm ($r = 0.55$, $p < 0.001$) zones, indicating that these aberrations increase with age. Weak correlations were observed between SE and ocular SA at 4-mm ($r = 0.27$, $p < 0.001$) and 6-mm ($r = 0.26$, $p < 0.001$) zones, with SE explaining only a limited proportion of the observed variability. Gender-dependent differences were small but identified between ocular vertical trefoil ($p < 0.01$), corneal RMS HOA ($p < 0.03$), horizontal coma ($p < 0.001$), and oblique secondary astigmatism ($p < 0.03$).

Conclusion: This large Caucasian cohort demonstrates the distribution of normative HOA data. Significant age, gender, and SE-dependent differences were identified that may be taken into consideration when mitigating HOA in clinical practice.

Translational Relevance: Our data demonstrates the distribution and normative values of HOA among healthy phakic eyes and may serve as a reference for mitigation of wavefront errors in clinical practice.

Keywords: higher order aberration, normative data, wavefront aberrations

Introduction

Higher-order aberrations (HOA) are complex distortions of the ocular wavefront caused by irregularities in the optical medium.[1,2] When severe, they cannot be readily compensated by conventional spherocylindrical correction and may cause detrimental visual impairment. Keratoconus, corneal scars, post-refractive surgical ectasia, and Fuchs endothelial dystrophy are among the notable ocular conditions known to increase HOA and degrade the image quality as well as high-contrast visual acuity.[3–6]

Such marked visual degradation underscores the importance of recognizing and reducing these wavefront aberrations. However, mitigating HOA can be challenging without the knowledge of normative HOA data. Previous research has demonstrated age-dependent differences in individual HOA values.[7–12] While several studies sought to analyze the

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distribution of HOA among healthy individuals, most of them are from single centers with restricted sample size, published prior to development of corneal tomography, and did not investigate potential correlations with demographic or refractive parameters.[12–22] Furthermore, ethnic differences in HOA components have also been reported, which complicates generalizability of the results.[18,19]

In this study, we aimed to establish a normative distribution of HOA in a large cohort of healthy Caucasian eyes by measuring their wavefront errors using a novel corneal topographer combined with a Hartmann-Shack aberrometer and to identify any correlations with age, gender, and refractive errors.

Materials and Methods

Subjects

This retrospective, multi-center study analyzed healthy Caucasian volunteers who presented to three large ophthalmology care centers in Europe (Department of Ophthalmology, University of Heidelberg, Heidelberg, Germany; IRCCS-G.B. Bietti Foundation, Rome, Italy; Department of Ophthalmology, Qvision Vithas Hospital Almería, Spain) and underwent ocular examination between July 2019 and July 2022. Eyes with any surgical history or ocular pathology except for age-related lenticular changes were excluded. Any participants who wore contact lenses within five days of the examination were also excluded. The presence of a dry eye or any ocular surface disease that may affect the wavefront aberration measurement was determined via comprehensive slit-lamp examination as well as corneal tomography and such eyes were excluded. Topical administration of mydriatic agents was unnecessary, as accommodation was controlled by the device through defocusing of the fixation target to prevent accommodative effort. A built-in fixation target was projected optically for distance viewing. Patients were included with the first measured eye only; no bilateral data were evaluated. Multiple examinations were performed per eye, from which only measurements with a good image quality were considered for analysis. All examinations were performed prior to topical administration of any diagnostic agents.

The study adhered to the Declaration of Helsinki, was approved by the local ethic committee of each study site, and written informed consent was obtained from all patients. The Institutional Review Board approval numbers were 24/15/FB for IRCCS Bietti Foundation (Comitato Etico Centrale IRCCS Lazio), 202499908562931 for Qvision at the Vithas Hospital (Comité de Ética de la Investigación Provincial de Almería), and S-392/2011 for the University Eye Hospital of Heidelberg (Ethics Committee of the Medical Faculty of Heidelberg University).

Pentacam AXL Wave

The Pentacam AXL Wave (Oculus Optikgeräte GmbH, Germany) is a novel diagnostic device that combines Scheimpflug tomography, optical biometry, and wavefront analysis to provide comprehensive data on the anterior and posterior corneal surfaces, anterior chamber, and lens. It is equipped with a 180-degree rotating Scheimpflug camera, a 470 nm blue LED light source, and a 1.45-megapixel camera that captures 138,000 precise corneal elevation points in just 2 seconds. The AXL Wave also integrates Hartmann-shack sensor, which consists of 420 lenslets covering a 7 mm pupil, providing sufficient spatial resolution for reliable analysis of ocular wavefront aberrations. The reliability as well as the repeatability of the device has already been reported in the literature.[23–25]

Primary Outcome

Primary outcome was the distribution of total ocular and corneal HOAs up to the 4th order. For the purpose of this study, all measurements were taken at central 4 mm zone under mesopic conditions, which is the standard measurement zone integrated in Pentacam AXL Wave and has been recommended by previous studies as primary zone of interest when considering implantation of multifocal IOLs.[26–28] Only spherical aberration (SA) was analyzed at both 4 mm and 6 mm zones as SA-correcting IOLs generally refer to the corneal SA value of ca. 0.27µm measured at 6 mm zone.[16,26,29] Secondary outcomes were the correlations between each HOA component and age, gender, and spherical equivalent (SE). SE was measured via clinical manifest refraction.

Statistical Analysis

Statistical analysis was performed using R statistical software (RStudio, Boston, MA, USA) and MATLAB R2024a (MathWorks Inc., Natick, MA, USA). Packages tidyverse and rstatix were used for R and statistics and machine learning toolbox for MATLAB. The data were provided as the mean, standard deviation (SD), median, minimum, maximum and 95% confidence interval (CI). Normality was assessed through visual examination of Q-Q plots, which given the large sample size, showed the data closely followed the reference line with only moderate deviations at the tails consistent with approximate normality for all variables. Still, for comparisons between genders, both the parametric *t*-test and non-parametric Mann–Whitney *U*-test were used to detect statistically significant differences, ensuring the robustness of results regardless of distributional assumptions. Simple correlation analysis was performed using Pearson correlation coefficient and linear regression model was assumed.

Results

Patient Demographics

A total of 1075 eyes of 1075 patients were included in the analysis, of which 629 (58.5%) were females and 621 (57.8%) right eyes. Figure 1A demonstrates the age frequency and distribution of the overall study population. Mean ages of the female and male patients were 51.2 ± 19.0 years (range: 10–91 years) and 55.5 ± 20.0 years (range: 11–89 years), respectively. Figure 1B demonstrates the frequency and distribution of SE values of the overall study population. Mean SE of the overall study population was −1.81 ± 3.76 D (range: −17.11 ± 8.72 D).

Normative HOA Values

Figures 2 and 3 show the arithmetic mean and root mean square (RMS) of total ocular and corneal HOA components, respectively. The corresponding values are listed in Supplementary Tables 1 and 2.

Correlation with Age

Figure 4 shows linear regression models of age-dependency for total ocular HOA parameters. RMS HOA ($r = 0.55$, $p < 0.001$) and SA ($r = 0.30$, $p < 0.001$) increased significantly with age, indicating a strong age-related increase in ocular HOAs, with age explaining roughly one-third of the variance in RMS HOA and a smaller, but still substantial, proportion of the variance in SA. Although vertical trefoil ($r = −0.16$, $p < 0.001$), vertical coma ($r = −0.18$, $p < 0.001$), and horizontal coma ($r = −0.09$, $p < 0.01$) also showed statistically significant correlations with age (Table 1), the impact of age on these aberrations was smaller, explaining less than about 4% of the variance in the population. Moreover, the negative correlations indicate an increase in the negative value of the corresponding aberration coefficients with age.

Figure 5 shows linear regression models of age-dependency for corneal HOA parameters. Significant positive correlations were found for RMS HOA ($r = 0.46$, $p < 0.001$), horizontal coma ($r = 0.28$, $p < 0.001$), as well as SA at both 4 mm ($r = 0.39$, $p < 0.001$) and 6 mm ($r = 0.55$, $p < 0.001$) zone diameters (Table 2). This analysis suggests that

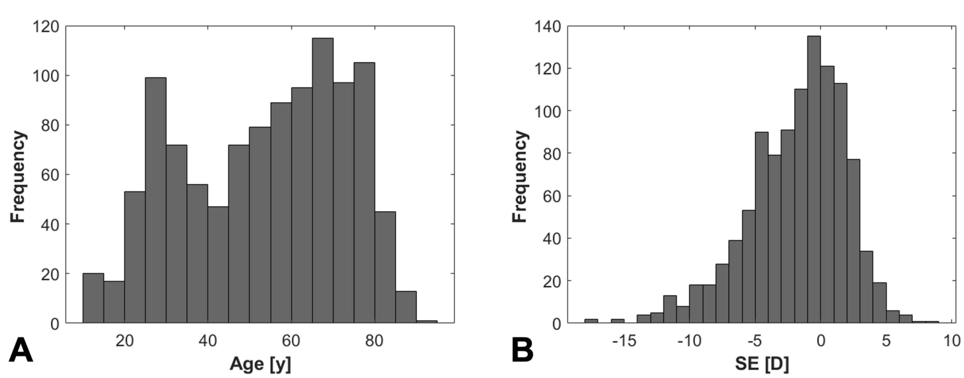

Figure 1 Histograms of the age (**A**) and spherical equivalent (**B**) distribution and frequency of the overall study population.

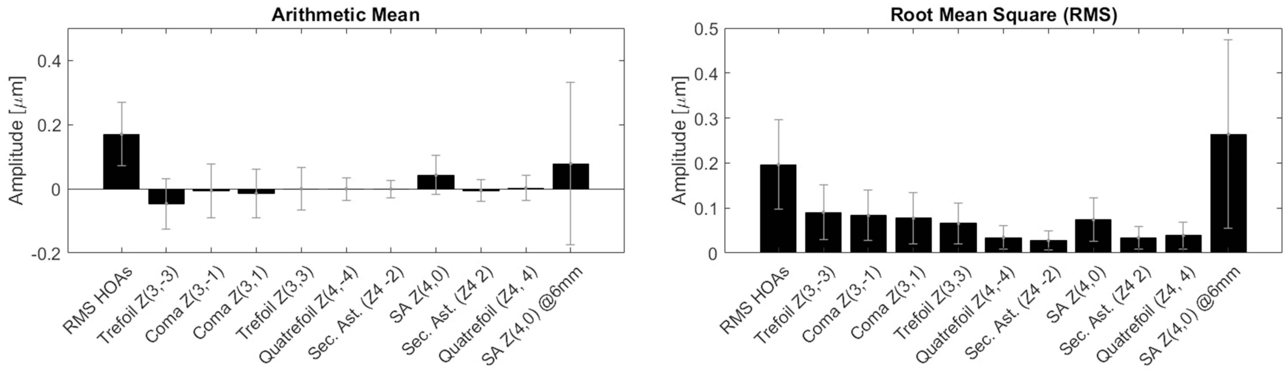

Figure 2 Bar plots of arithmetic mean (±standard deviation) and root mean square of total eye higher-order aberrations. All values are measured at 4 mm zone except for spherical aberration Z(4,0), which was measured at both 4 and 6 mm zone diameters.
Abbreviations: RMS, root mean square; SA, spherical aberration.

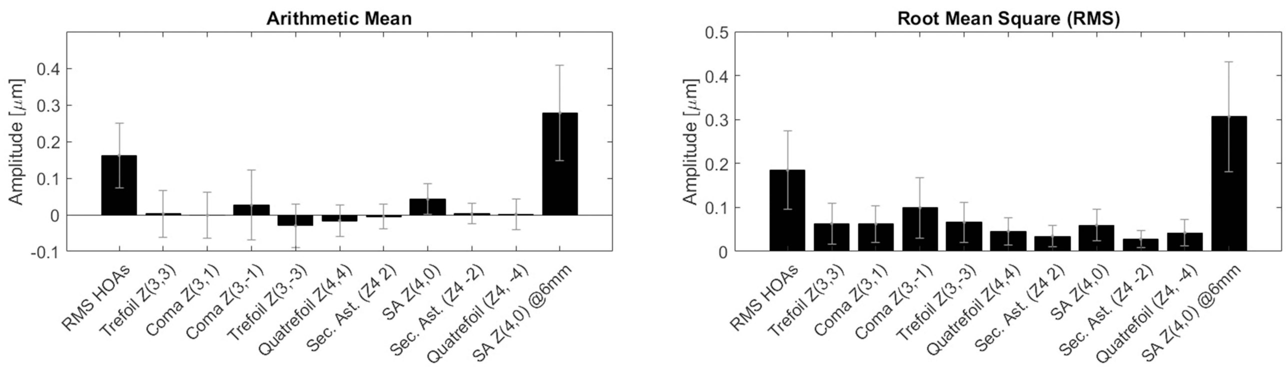

Figure 3 Bar plots of arithmetic mean (±standard deviation) and root mean square of corneal higher-order aberrations. All values are measured at 4 mm zone except for spherical aberration Z(4,0), which was measured at both 4 and 6 mm zone diameters.
Abbreviations: RMS, root mean square; SA, spherical aberration.

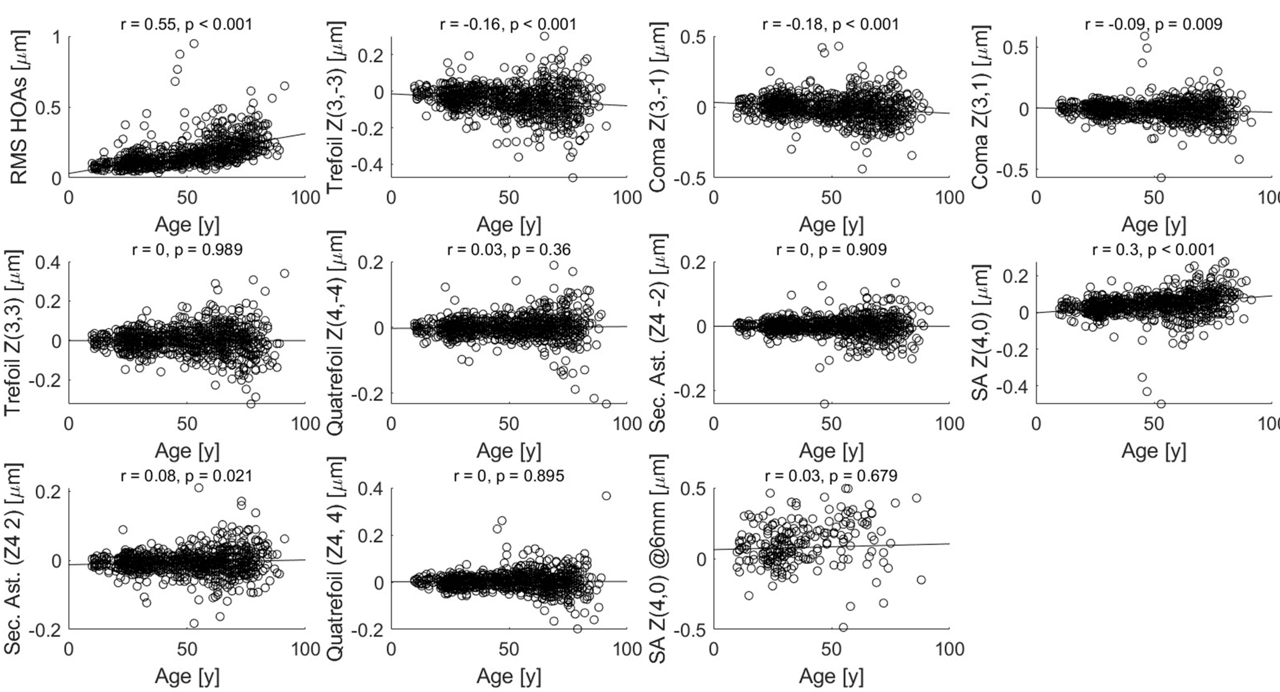

Figure 4 Linear regression models for correlations between age and total ocular higher-order aberration (HOA) parameters at 4 mm zone.
Abbreviations: RMS, root mean square; SA, spherical aberration.

Table 1 Linear Regression Model for Age-Dependency of Total Ocular Higher-Order Aberrations at 4 mm Zone

Parameter	Slope (95% CI)	Intercept (95% CI)	R^2
RMS HOA	0.003 (0.003, 0.003)	0.030 (0.014, 0.045)	0.303
Vertical Trefoil	−0.001 (-0.001, -0.000)	−0.014 (-0.028, 0.000)	0.027
VERTICAL COMA	−0.001 (-0.001, -0.000)	0.032 (0.017, 0.048)	0.032
HORIZONTAL COMA	−0.000 (-0.001, -0.000)	0.003 (-0.011, 0.017)	0.008
OBLIQUE Trefoil	−0.000 (-0.000, 0.000)	−0.000 (-0.013, 0.012)	0.000
OBLIQUE Quatrefoil	0.000 (-0.000, 0.000)	−0.003 (-0.010, 0.003)	0.001
OBLIQUE Sec. Astigmatism	−0.000 (-0.000, 0.000)	−0.001 (-0.006, 0.004)	0.000
PRIMARY SA	0.001 (0.001, 0.001)	−0.003 (-0.014, 0.007)	0.087
VERTICAL Sec. Astigmatism	0.000 (0.000, 0.000)	−0.013 (-0.019, -0.007)	0.006
VERTICAL Quatrefoil	0.000 (-0.000, 0.000)	0.002 (-0.005, 0.009)	0.000
PRIMARY SA*	0.000 (-0.002, 0.002)	0.063 (-0.015, 0.141)	0.001

Note: *measured at 6 mm zone.
Abbreviations: CI, confidence interval; RMS, root mean square; HOA, higher order aberrations; SA, spherical aberration.

horizontal coma and SA significantly increase with age, reflecting age-related changes in corneal optics. A weak negative correlation was observed for oblique trefoil ($r = -0.14$, $p < 0.001$), revealing slightly more negative oblique trefoil values in older eyes.

Correlation with Spherical Equivalent

Supplementary Figure 1 (Supplementary Table 3) and Supplementary Figure 2 (Supplementary Table 4) show the linear regressions models of SE-dependency for total ocular and corneal HOA parameters, respectively. For total ocular HOA, we observed small, yet statistically significant, positive correlations for vertical secondary astigmatism ($r = 0.12$, $p < 0.001$) and for SA at both 4 mm ($r = 0.27$, $p < 0.001$) and 6 mm ($r = 0.26$, $p < 0.001$) zone diameters (Supplementary Table 3). Negative correlations were found for vertical coma ($r = -0.16$, $p < 0.001$) and oblique quatrefoil ($r = -0.07$, $p < 0.03$), indicating a slight shift toward more negative coefficient values in more hyperopic eyes. For corneal HOA, there were significant positive correlations between SE and RMS HOA ($r = 0.13$, $p < 0.001$), horizontal coma ($r = 0.10$, $p < 0.001$), and SA for both 4 mm ($r = 0.13$, $p < 0.001$) and 6 mm ($r = 0.21$, $p < 0.001$) zones (Supplementary Table 4). However, the overall strength of these associations remained modest. Weak but significant negative correlations were measured for oblique secondary astigmatism ($r = -0.07$, $p < 0.02$) and vertical quatrefoil ($r = -0.09$, $p < 0.01$), suggesting that SE explains only a small portion of the variability in these aberrations.

Correlation with Gender

Table 3 shows gender-dependent differences between total ocular and corneal HOAs. For total ocular HOAs, statistically significant differences were only found for vertical trefoil (mean values of −0.04 ± 0.08 vs. −0.06 ± 0.07 for women and men, respectively; $p < 0.01$). For corneal HOAs, RMS HOA (0.16 ± 0.08 vs. 0.17 ± 0.10; $p < 0.03$), horizontal coma (0.02 ± 0.09 vs. 0.04 ± 0.10; $p < 0.001$), and oblique secondary astigmatism (−0.01 ± 0.03 vs. 0.00 ± 0.03; $p < 0.03$) demonstrated significant gender-dependent differences. These comparisons indicate that gender-related effects are small in magnitude, although statistically significant, and are most pronounced for asymmetric coma- and astigmatism-like aberrations.

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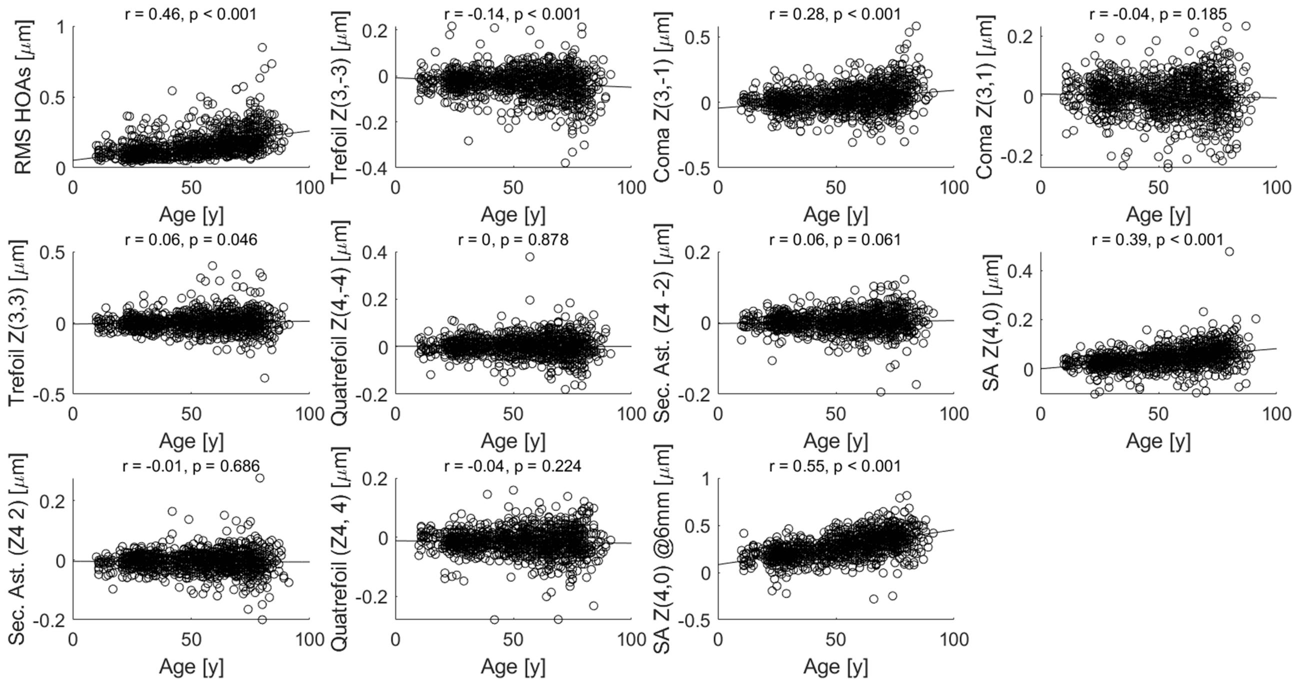

Figure 5 Linear regression models for correlations between age and corneal higher-order aberration (HOA) parameters at 4 mm zone.
Abbreviations: RMS, root mean square; SA, spherical aberration.

Supplementary Table 5 shows the gender-dependent differences between total ocular and corneal higher order aberrations for 6 mm zone.

Supplementary Figures 3 and 4 demonstrate the age-related change in SD for corneal HOA measured at 4 and 6 mm zones, respectively. Supplementary Figures 5 and 6 demonstrate the age-related variation in SD for total HOA measured at 4 and 6 mm zones, respectively.

Supplementary Figures 7–10 show equivalent data analysis for a subgroup of patients with 6 mm pupil.

Table 2 Linear Regression Model for Age-Dependency of Corneal Higher-Order Aberrations at 4 mm Zone

Parameter	Slope (95% CI)	Intercept (95% CI)	R^2
RMS HOA	0.002 (0.002, 0.002)	0.052 (0.038, 0.0657)	0.208
Vertical Trefoil	0.000 (0.000, 0.000)	−0.008 (-0.019, 0.003)	0.004
VERTICAL COMA	−0.000 (-0.000, 0.000)	0.006 (-0.005, 0.016)	0.002
HORIZONTAL COMA	0.001 (0.001, 0.002)	−0.045 (-0.061, -0.030)	0.076
OBLIQUE Trefoil	−0.000 (-0.001, -0.000)	−0.008 (-0.019, 0.002)	0.018
OBLIQUE Quatrefoil	−0.000 (-0.000, 0.000)	−0.012 (-0.020, -0.005)	0.001
OBLIQUE Sec. Astigmatism	−0.000 (-0.000, 0.000)	−0.004 (-0.010, 0.002)	0.000
PRIMARY SA	0.001 (0.001, 0.001)	−0.001 (-0.007, 0.006)	0.150
VERTICAL Sec. Astigmatism	0.000 (-0.000, 0.000)	−0.002 (-0.007, 0.003)	0.003
VERTICAL Quatrefoil	−0.000 (-0.000, 0.000)	0.002 (-0.005, 0.009)	0.000
PRIMARY SA*	0.004 (0.003, 0.004)	0.083 (0.064, 0.102)	0.306

Note: *measured at 6 mm zone.
Abbreviations: CI, confidence interval; RMS, root mean square; HOA, higher order aberrations; SA, spherical aberration.

Table 3 Gender-Dependent Differences Between Total Ocular and Corneal Higher Order Aberrations for 4 mm Zone

Parameter	Women	Men	p-Value*	P-VALUE†
Total Eye HOA	(Mean ± SD)	(Mean ± SD)		
Age, y	51.15 ± 18.98	55.45 ± 19.97	0.000	0.000
SE, D	−1.88 ± 3.8	−1.72 ± 3.57	0.501	0.957
RMS HOA	0.17 ± 0.10	0.17 ± 0.09	0.597	0.189
Vertical Trefoil	−0.04 ± 0.08	−0.06 ± 0.07	0.005	0.005
VERTICAL COMA	−0.01 ± 0.08	0.00 ± 0.08	0.163	0.056
HORIZONTAL COMA	−0.01 ± 0.08	−0.02 ± 0.07	0.374	0.338
OBLIQUE Trefoil	0.00 ± 0.06	0.00 ± 0.07	0.566	0.882
OBLIQUE Quatrefoil	0.00 ± 0.04	0.00 ± 0.03	0.142	0.228
OBLIQUE Sec. Astigmatism	0.00 ± 0.03	0.00 ± 0.03	0.109	0.177
PRIMARY SA	0.04 ± 0.06	0.04 ± 0.06	0.701	0.929
VERTICAL Sec. Astigmatism	−0.01 ± 0.03	−0.01 ± 0.04	0.664	0.492
VERTICAL Quatrefoil	0.00 ± 0.04	0.00 ± 0.04	0.567	0.408
PRIMARY SA*	0.08 ± 0.2	0.08 ± 0.19	0.871	0.419
Corneal HOA				
RMS HOA	0.16 ± 0.08	0.17 ± 0.10	0.023	0.131
Vertical Trefoil	0.00 ± 0.06	0.01 ± 0.07	0.195	0.325
VERTICAL COMA	0.00 ± 0.06	0.00 ± 0.06	0.127	0.216
HORIZONTAL COMA	0.02 ± 0.09	0.04 ± 0.10	0.000	0.000
OBLIQUE Trefoil	−0.03 ± 0.06	−0.03 ± 0.0	0.052	0.014
OBLIQUE Quatrefoil	−0.02 ± 0.04	−0.02 ± 0.05	0.206	0.370
OBLIQUE Sec. Astigmatism	−0.01 ± 0.03	0.00 ± 0.03	0.026	0.015
PRIMARY SA	0.04 ± 0.04	0.04 ± 0.04	0.614	0.468
VERTICAL Sec. Astigmatism	0.00 ± 0.03	0.00 ± 0.03	0.634	0.341
VERTICAL Quatrefoil	0.00 ± 0.04	0.00 ± 0.04	0.665	0.978
PRIMARY SA*	0.28 ± 0.13	0.28 ± 0.13	0.498	0.740

Notes: *measured at 6 mm zone. *T-test; †Mann–Whitney U-test.
Abbreviations: HOA, higher order aberrations; SE, spherical equivalent; RMS, root mean square; SA, spherical aberration.

Mixed Regression Model

Given the significant correlations and differences between total ocular and corneal HOAs with age, gender, and SE in linear regression models, a mixed regression model was performed. The prediction power remains largely comparable to the age-dependent linear model for corneal HOAs when all three variables were included into the mixed model analysis (Table 4), demonstrating that, among the examined parameters, age is the primary predictor of HOAs in non-pathological eyes. Still, a slight improvement was observed with total SA at 4- and 6-mm, increasing the explained variance by 3% and 6%.

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Table 4 Mixed Model Analysis for Correlations Between Higher Order Aberrations and Age, Gender, and Spherical Equivalent

	Parameter	Intercept	Intercept p-Value	Age Coefficient	Age p-Value	SE Coefficient	SE p-Value	Gender Coefficient	Gender p-Value	Adjusted R^2	Model p-Value
Total Ocular HOAs	RMS HOA	0.008	0.409	0.003	0.000	−0.004	0.000	0.005	0.430	0.320	0.409
	Vertical Trefoil	−0.017	0.055	−0.001	0.000	0.001	0.082	0.014	0.012	0.034	0.055
	Vertical Coma	0.027	0.004	−0.001	0.000	−0.002	0.002	−0.010	0.078	0.044	0.004
	Horizontal Coma	−0.001	0.952	0.000	0.019	0.000	0.787	0.004	0.476	0.005	0.952
	Oblique Trefoil	0.003	0.698	0.000	0.843	0.000	0.636	−0.003	0.560	−0.003	0.698
	Oblique Quatrefoil	−0.005	0.192	0.000	0.115	−0.001	0.010	−0.003	0.168	0.008	0.192
	Oblique Sec. Astigmatism	−0.002	0.564	0.000	0.778	0.000	0.364	0.003	0.113	0.000	0.564
	Primary SA (4,0)	0.012	0.071	0.001	0.000	0.003	0.000	0.001	0.875	0.119	0.071
	Vertical Sec. Astigmatism	−0.008	0.049	0.000	0.194	0.001	0.004	−0.001	0.755	0.012	0.049
	Vertical Quatrefoil	0.000	0.986	0.000	0.533	−0.001	0.083	−0.001	0.587	0.000	0.986
	Primary SA*	0.153	0.002	−0.001	0.559	0.019	0.000	0.000	0.994	0.059	0.002
Corneal HOAs	RMS HOA	0.054	0.000	0.002	0.000	0.000	0.842	−0.004	0.437	0.207	0.000
	Vertical Trefoil	−0.002	0.766	0.000	0.159	0.001	0.289	−0.004	0.299	0.003	0.766
	Vertical Coma	0.013	0.048	0.000	0.085	0.001	0.205	−0.007	0.081	0.003	0.048
	Horizontal Coma	−0.026	0.010	0.001	0.000	0.001	0.354	−0.021	0.000	0.083	0.010
	Oblique Trefoil	−0.008	0.180	0.000	0.000	0.001	0.136	0.006	0.125	0.021	0.180
	Oblique Quatrefoil	−0.011	0.021	0.000	0.096	0.001	0.048	0.003	0.253	0.004	0.021
	Oblique Sec. Astigmatism	−0.004	0.327	0.000	0.895	−0.001	0.018	−0.005	0.022	0.008	0.327
	Primary SA (4,0)	−0.003	0.415	0.001	0.000	0.000	0.623	0.005	0.038	0.150	0.415
	Vertical Sec. Astigmatism	−0.002	0.434	0.000	0.051	0.000	0.342	0.000	0.818	0.001	0.434
	Vertical Quatrefoil	−0.002	0.594	0.000	0.464	−0.001	0.003	−0.001	0.645	0.006	0.594
	Primary SA*	0.085	0.000	0.004	0.000	0.002	0.041	0.011	0.114	0.306	0.000

Notes: *measured at 6 mm zone. Intercept represents the estimated baseline value of each higher-order aberration when all predictors are zero. Regression coefficients indicate the magnitude and direction of change in the aberration per unit increase in age (years) or spherical equivalent (diopters), or between genders. Adjusted R^2 reflects the proportion of variance explained by the mixed regression model after accounting for the number of predictors. The model p-value indicates the overall statistical significance of the regression model.

Abbreviations: SE, spherical equivalent; RMS, root mean square; HOA, higher order aberrations; SA, spherical aberration.

Discussion

This retrospective study analyzed 1075 healthy, phakic, treatment-naïve Caucasian eyes at three large ophthalmology care centers in Europe and provides normative data of HOA for an age range of nine decades. To the best of the authors' knowledge, this is the largest sample size investigated for HOA normative data in European eyes using Pentacam AXL Wave as of November 2024, based on our literature search. Our analysis found statistically significant correlations between HOA and age, gender, and SE, which may serve as a reference database for clinicians and researchers, and can be directly implemented into the Pentacam AXL Wave device.

To date, several studies have published normative data on HOA and their association with age, gender, or SE in patients of different ages and ethnicities, with most reports dating from over a decade ago.[18,19,21,25,30–33] Although they share a similar study design, a direct comparison of the results may be challenging due to the differences in instrumentation, zone diameters, age groups, and refractive errors or statuses (eg, phakic vs. pseudophakic) of the study populations. Furthermore, ethnicities have also been reported to play a role in wavefront errors, which further limits the generalizability of the published results.[18,19,21,33]

In this study, optical aberrations were measured using a novel hybrid Scheimpflug tomographer that features a Hartman-Shack aberrometer, which has been shown to demonstrate high accuracy, repeatability, and even superiority compared to other currently available aberrometers.[25,34,35] To keep the study population and measurements consistent, we only studied phakic treatment-naïve eyes and performed the analysis at 4 mm central zone.

Previous research has shown a positive effect of age on total ocular HOA.[7–12,36] Fujikado et al measured total ocular HOAs in 66 eyes of normal subjects using Hartmann-Shack aberrometer at 4 mm and found significant age-related increases in total ocular HOA ($r = 0.43$), coma-like aberrations ($r = 0.27$), and spherical-like aberrations ($r = 0.53$).[9] Amano et al also reported age-dependent increase in ocular coma RMS ($r = 0.33$) and SA ($r = 0.31$) in their study involving 75 healthy eyes when measured at 6 mm using a videokeratography and Hartmann-Shack wavefront aberrometer.[36] In our study, we found significant increase in total ocular RMS HOA and SA with age, which is in alignment with previous research.[9,10,15,22,36] The progressive increase in total ocular SA is postulated to be related to anterior corneal surface[16,21,22,37,38] or optical alterations such as lenticular changes (eg, cataract).[36,39,40]

Regarding corneal HOA, there is a variation in the literature with some studies reporting age-related associations for coma and SA,[12,13,17,36,41] while no associations were found by Fujikado et al.[9] Our analysis demonstrated notable increase in corneal RMS HOA, horizontal coma, and SA at both 4 and 6 mm zones. While age had a weak positive effect on vertical trefoil, it was negatively correlated with horizontal trefoil. Some studies suggested that an increase in corneal coma with age may lead to concomitant increase in total ocular coma, though a significant correlation was not always observed.[9,15,36] In our study, we observed a slight age-dependent decrease in total ocular coma despite increasing corneal horizontal coma. While the reasons for the discrepancies are not clear, they may be ascribable to the differences in measured zones, devices, and sample sizes between studies.

Conflicting reports have also been published concerning the association between HOA and refractive errors.[12,32,42–44] He et al analyzed wavefront aberrations in 83 emmetropic and 87 myopic children as well as in 54 emmetropic and 92 myopic young adults using a customized optical bench and observed statistically significantly higher HOA values among myopic individuals compared to emmetropes regardless of age.[32] Paquin and associates also observed a particular increase in coma among myopic individuals.[43] This observation agrees with comatic aberrations commonly seen among keratoconic eyes.[3,45] In contrast, Hashemi et al measured the highest degrees of higher-order RMS among hyperopes compared to myopes or emmetropes in their Iranian population study.[21] Interestingly, Cheng et al and Kiuchi et al did not find any significant differences in HOA depending on the patients' refractive status.[12,44] Our study analyzed a wide range of SE and found moderately significant, positive correlations between SE and ocular SA at 4 and 6 mm zones as well as between SE and corneal SA at 6 mm zone diameter. Similar trends of SA becoming more negative with increasing myopia were also found in previous research.[42,46,47]

Only a few studies have investigated the gender effect on HOA. Reilly et al analyzed the differences in HOA between males and females and concluded that while the overall HOA did not show any sex-dependent differences, significant differences were found in individual Zernike polynomials including tetrafoil, secondary trefoil, secondary spherical, tertiary astigmatism, and secondary tetrafoil.[48] Hashemi et al observed significant sex-dependent differences in total

RMS trefoil and fourth-order aberration,[21] while Hughes et al did not report any gender effect on HOA in their non-myopic pediatric cohort.[49] In our study, we found significant gender-related differences in ocular vertical trefoil, corneal RMS HOA, corneal horizontal coma, and corneal vertical secondary astigmatism. While the small differences may appear clinically negligible, our results do suggest a possibility of differences in gender-dependent optical properties and further research is warranted to investigate the causes.

We also performed a mixed regression model to adjust for all three variables, namely age, gender, and SE, yet the prediction power did not result in a substantial improvement compared to the linear regression model that only accounted for age. Although a slight improvement was observed in predicting total eye SA, our study suggests that while age, SE, and gender are individually related to SA, combining them does not substantially enhance the predictive power. Therefore, the residual variation observed in the HOAs within our population remains largely unexplained.

Our study is not without limitations. First, its retrospective nature may limit the ability to control for all potential variables. We only analyzed the HOA components at 4 mm zone, which limits the comparability of our results to other studies conducted at different sizes. However, given that the average pupil diameter exceeds a 4 mm size only in about approximately 15% of patients older than 50 years of age, we contend that our outcomes are particularly relevant for this population.[50] Furthermore, given the reported ethnic differences in ocular aberrations, our results may also not be generalizable for non-Caucasian eyes. The fact that all study sites are based in European countries also does not guarantee that all test subjects were indeed Caucasians. No cycloplegia was given in younger populations; however, accommodation was controlled via defocusing of the fixation target to prevent accommodative effort. This study analysis also does not take into account the potential tear film variability and natural pupil size variability.

Statistical trends observed in this study, such as age-related decrease in coma or linear correlation between spherical aberration and spherical equivalent, warrant further investigations. Moreover, it remains to be seen in future studies whether the numerous weak statistical correlations we observed in the study indeed do demonstrate clinical significance. In our study, only one eye per subject was included in the analysis to avoid inter-eye correlation and ensure statistical independence of data points. Although this approach strengthens the validity of the correlation analyses, it prevents assessment of potential inter-ocular differences in higher-order aberrations, which may be of clinical interest. We have also limited our analysis to the 4th order Zernike terms because the most clinically relevant higher-order aberrations, such as coma, trefoil, and spherical aberration, are contained within the 3rd and 4th orders. Aberrations beyond the 4th order generally contribute negligibly to the overall wavefront error in healthy eyes, particularly when measured at the central 4 mm zone. Similar methodological cutoffs have been employed in previous normative and clinical studies, however, ensuring both comparability and clinical relevance of the results.

Nevertheless, the strengths of this study include the largest sample size yet on Caucasian normative HOA data with wide ranges of refractive errors and age, as well as the use of a novel measurement instrumentation. Integration of our data into diagnostic devices by comparing individual results to the average values observed in a normal population of the same age, along with their confidence bounds, may facilitate the data assessment and provide a tool for direct comparison. Still, before each patient's HOA component becomes available in such diagnostic devices as Pentacam AXL Wave, they can be manually calculated by using the following formula:

$$HOA = patient\ age \bullet slope + intercept$$

Each slope and intercept values for average and 95% CI estimates can be taken from Table 2 and Table 3, Supplementary Tables 4 and 5. For example, using this method, we can calculate the SA of a 50-year-old cornea and its normative distribution. By substituting data from Table 2, we obtain an SA value of 0.283 µm with a 95% CI [0.214, 0.302], which aligns well with the 0.28 µm SA reported by Wang et al for their 50-year-old patients at a 6-mm zone.[16] This approach can be similarly applied to calculate the average value of any HOA component for a given age or, by using information from Supplementary Tables 4 and 5, also SE.

In summary, our data demonstrates the distribution and normative values of HOA among healthy phakic eyes and may serve as a reference for mitigation of wavefront errors in clinical practice, including multifocal intraocular lens selection, preoperative risk assessment in refractive surgery, and HOA-targeted treatments or wavefront-guided corrections. Future prospective studies incorporating longitudinal follow-up, broader ethnic representation, and standardized pupil-size-dependent analyses are warranted to further validate these findings.

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Disclosure

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