ORIGINAL INVESTIGATION

Higher-order Aberrations in Children and Adolescents of Southwest China

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ABSTRACT

Significance: This study is the first study about higher-order aberrations distribution states in a larger number of Chinese children and adolescents. **Purpose:** To determine the distribution of higher-order aberrations (HOAs) of Han Chinese young subjects with normal vision and their relationship to age. **Methods:** Children and adolescents, aged from 3 to 17 years, with normal visual acuity were enrolled, and their wavefront aberrations for a 6-mm pupil were evaluated by the Zywave II aberrometer. Their correlations with age were analyzed. And the 95% statistical reference ranges were computed for each Zernike term. **Results:** A total of 1634 eyes (287 for preschool-age children, 897 for school age children and 450 for adolescents) were analyzed. There was a significant correlation with age and the root mean square (RMS) of total HOAs ($r=0.256$, $P<0.0001$), third-order aberrations ($r=0.062$, $P=0.029$), fourth-order aberrations ($r=0.197$, $P<0.0001$), fifth-order aberrations ($r=0.067$, $P=0.017$) and trefoil-like aberrations ($r=0.100$, $P<0.0001$) in the myopic group. There were significant differences in RMS values (except coma-like aberrations, $\chi^2=4.179$, $P=0.124$) as well as the Zernike coefficients among three different age groups. Therefore, the 95% statistical normal reference values were calculated separately for three age groups. **Conclusions:** The RMS value of total HOAs, coma-like, trefoil-like, third-order, fourth-order, and fifth-order aberrations are correlated with age, and the RMS values and Zernike coefficients of aberrations were different in different age stages of the subjects. This study described the distribution of HOAs in children and adolescents and established 95% statistical normal values of HOAs for different ages of children and adolescents by analyzing the HOAs in a large number of the Han Chinese clinical population.

Key words： aberration, coma-like aberration, children, refractive error, reference value

The human eye, despite an ingeniously designed optical system, still suffers imperfections known as aberrations. Traditional aberrations include lower-order aberrations usually called defocus (such as nearsightedness and farsightedness) and astigmatism as well as higher-order aberrations, which also affect the quality of vision.[1] Lower-order aberrations are now routinely corrected by conventional spectacles or contact lenses, but higher-order aberrations are still not so easily treated. Higher-order aberrations have gained increasing attention in the ophthalmology and optometry fields as new technology develops. When people trying to understand why refractive surgery patients continue to be dissatisfied with their vision after successful surgical correction of lower order aberrations, it was then found that the higher-order aberrations were another reason that causing poor retinal images.[2] Consequently, traditional methods of vision correction and technology for detecting the visual function of the eyes could not meet both the patients' and ophthalmologists' expectations, resulting in the rapid development of applications and detection technologies for higher-order aberrations.

Basic data concerning the distribution of the higher-order aberrations of the human eye and characteristics for higher-order aberrations are important not only for fundamental research but also for clinical practice. In the beginning, as refractive surgeries were limited to adults, a large number of studies focused mainly on the adult population. There are many studies on the distribution of the higher-order aberrations in normal adults.[2-5] For example, Salmon and Pol[6] established reference values for normal healthy adults by collecting 10 researchers' data in a large population (2560 eyes of 1433 subjects). Recently, Hashemi[7] described the distribution of higher-order aberrations in an Iranian population (577 citizens of Shahroud of Iran, aged from 40 to 60 years). However, there are few studies focusing on children. With the development of aberration detection technology, many clinicians and researchers in the fields of ophthalmology and vision science, which include refractive surgery, customized intraocular lens,[8, 9] specially designed contact lenses,[10] and adaptive optics technology,[1] extended the research of the aberrations into younger populations.

Though studies show that aberrations varied with age in adults, [11-13] there are fewer studies investigating the relationship of aberrations with age for young subjects. Similarly, even though the distribution of higher-order aberrations in adults have been established by many researchers, the distribution of aberrations in the young population and their characteristics have not been described and reported to date. Furthermore, studies showed that there are significant differences between higher-order aberrations for different ethnic backgrounds.[14, 15] To our knowledge, there are no studies aimed at the population of Han Chinese young population, which can serve as a reference for clinical use, and no clearly described data about the higher-order aberrations in children to date. Therefore, this study aimed to describe the distribution and establish a reference by investigating a large population of Han Chinese children and adolescents with normal vision.

METHODS

The study was approved by the ethics committee of Sichuan University, and performed in accordance with the Declaration of Helsinki. The parents or other guardians of the participants were informed of the details of the study before signing the informed consent documents. Subjects first received an ocular examination to ensure they had normal ocular health. Then, 1% Tropicamide eye drops were used to paralyze accommodation and dilate the pupil. Subjects were placed in one of three groups according to their spherical equivalent refraction: the myopic group (greater than -0.25D), the emmetropic group (spherical equivalent from -0.25D to +0.50D), and the hyperopic group (greater than +0.50D). The aberrations of the eyes for all subjects were measured using the Zywave II aberrometer (Bausch and Lomb, Rochester, NY, USA), which is a device based on the Hartmann-Shack principle. The repeatability of this device has been reported before.[16] In order to get reliable measuring results from children, at least 5 measuring were taken for each subjects, then the most repeatable 3 values will be chosen to calculate the average value, then making statistical analysis.

The exported data of Zywave are normalized Zernike polynomial coefficients, while the expressions used do not conform to OSA, ANSI and ISO standards.[17] In the present study, the Z_n^m represents the polynomial, which correspond to coefficient for C_n^m; and, as Zywave uses the opposite reference for the direction of wavefront propagation, therefore the sign of the coefficients was reversed. According to the operation manual of the Zywave aberrometer, Zernike polynomials of the aberrations were computed over a circular pupil of 6mm diameter, which is used widely in literatures reporting the aberrations. The Zernike values for 6 mm can be translated into values for others pupil sizes by a technique reported by Schwiegerling,[18] allowing them to be compared with other studies. Zernike coefficients up to the fifth-order were measured, and the root mean square (RMS) of total higher-order aberrations, coma-like aberrations, trefoil-like aberrations, and third- to fifth-order aberrations were calculated according to their coefficient values. For example, the root mean square of coma-like aberrations were the square roots of the sums of the squared coefficients of Z_3^{-1}, Z_3^1, Z_5^{-1}, and Z_5^1. Similarly, the root mean square value of trefoil-like aberrations was the square root of the sum of the squared coefficients of Z_3^{-3}, Z_3^3, Z_5^{-3}, and Z_5^3.

Data were analyzed using SPSS software (version 18.0; SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov statistics test was used to check whether the data were normally distributed. For the data that was normally distributed with homogeneity of variance, one-way analysis of variance (ANOVA) was used to test differences among different groups; while the Kruskal-Wallis test was used for analysis of the data that was not normally distributed. A *P* value of less than 0.05 was considered to represent a statistically significant difference. Correlations between age and root mean square of Higher-order aberrations were explored using Pearson's correlation coefficients (*r*) when the data were normally distributed, while the Spearman correlation was used for the results which were not normally distributed. If data was normally distributed, a parametric method was used to calculate the reference range. Thus, the reference range was defined as mean plus or minus standard deviations, which is displayed as: 95% reference range = ($\bar{\chi}$-1.96s，$\bar{\chi}$+1.96s). For the data that was not normally distributed, a non-parametric method was used for calculating the reference ranges. First, the results were arranged in order, and a rank was assigned to each value. Then, the ranks were calculated and found to correspond to the 2.5 and 97.5 percentiles for 95% reference range. Finally, the values that correspond to this rank were determined, and this value represented the upper and lower reference values.

RESULTS

A total of 1634 eyes were analyzed. Eye number, age range, and the refractive error range for the preschool-age and school age children and adolescents are described in Table 1. As the two eyes are highly correlated, we used the right eye of each subject in the analysis. A pre-analysis were done before computing the reference range, which aimed at evaluating whether there were differences between the three refractive groups, the results showed that there were no differences in Zernike coefficients and root mean square aberration values among these three refractive groups for the pre-school-age, school-age children or adolescents (ANOVA tests; $P>0.05$). Thus, it was not necessary to divide the population into different refractive groups. And the mean age for the three different refractive groups were: 10.1 ± 1.5, 9.4 ± 1.8 and 8.4 ± 1.6 years old.

In the myopic group: There was a significant correlation between age and the total RMS of higher-order aberrations (r=0.256, $P<0.0001$), RMS of third-order aberrations (r=0.062, $P=0.029$), fourth-order aberrations (r=0.197, $P<0.0001$), fifth-order aberrations (r=0.067, $P=0.017$), and trefoil-like aberrations (r=0.100, $P<0.0001$). For individual Zernike coefficients, there were significant correlations with the y-trefoil (r=0.214, $P<0.0001$), spherical aberration (r=-0.229, $P<0.0001$), x-secondary astigmatism (r=0.136, $P<0.0001$), x-quadrafoil (r=-0.085, $P=0.003$) and y- pentafoil (r=-0.057, $P=0.044$) with age.

In the emmetropic group: There were no significant correlation between age and RMS of all HOAs aberrations (spearman correlation, $P>0.05$). For individual Zernike coefficients, there were significant correlations with the y-trefoil (r=0.304, $P<0.0001$), spherical aberration (r=-0.381, $P<0.0001$) and y-secondary trefoil (r=-0.1780, $P=0.033$) with age.

In the hyperopic group: There was a significant correlation between age and the total RMS of higher-order aberrations (r=0.256, $P<0.0001$), fourth-order aberrations (r=0.224, $P=0.004$), fifth-order aberrations (r=0.216, $P=0.006$) and coma-like aberrations (r=0.186, $P=0.018$). For individual Zernike coefficients, there were significant correlations with the y-trefoil (r=0.298, *P*<0.0001), vertical coma (r=0.191, *P*=0.015), horizontal coma (r=0.106, *P*=0.006), spherical aberration (r=-0.336, *P* <0.0001) and x-secondary trefoil (r=-0.202, *P*=0.010) with age.

Moreover, significant differences were found in root mean square values (total higher-order aberrations: χ^2=38.979, *P* <0.001; trefoil-like aberrations: χ^2=22.444, *P* <0.001; third-order aberration: χ^2=10.470, *P* = 0.005; fourth-order aberrations: χ^2=38.979.179, *P* <0.001; fifth-order aberrations: χ^2=15.433, *P*<0.001.), except in coma-like aberrations (χ^2=4.179, *P* = 0.124), among the three age groups (Table 2). Similarly, six Zernike coefficients (Z_3^{-3}: χ^2=95.334, *P*<0.001; $Z3^{-1}$: χ^2=11.300, *P* = 0.002; Z_4^0: χ^2=91.553, *P*<0.001; Z_4^2: χ^2=35.424, *P*<0.001, Z_4^4: χ^2=14.700, *P* = 0.018; Z_5^{-3}; χ^2=4.179, *P*<0.001) were significantly different among the three age groups (Table 3). Therefore, in this study, normal reference values were established respectively for the three different age groups (see Appendix).

Mean and standard deviations of the Zernike coefficients and root mean square values of aberrations in the three different age groups are shown in Tables 2 and 3. Means of all Zernike coefficients were significantly different from zero in all three age groups (Table 3). For all three age groups, the third-order aberrations contributed the most to total higher-order aberrations. The contribution of the variences of third-order aberrations in the variences of total higher-order aberrations were: 66% (preschool age children), 59% (school age children) and 54% (adolescents). However, the contribution of the individual Zernike coefficient values in the total higher-order aberrations values were different in the three age groups. For preschool-age children, Z_3^{-1} , Z_3^{-3} and Z_4^0 comprised the largest part of the total higher-order aberrations. For school-age children, $Z_3^{-1}$and Z_4^0 comprised the largest part of the total higher-order aberrations, while Z_3^{-3} only made up a small part. For adolescents, Z_4^0 , Z_3^{-1} , and Z_3^{-3} were the largest proportions of the total higher-order aberrations.

Histograms were used to illustrate the frequency for each Zernike coefficient (from third- to fifth-order), as shown in Fig.1 (preschool-age children), Fig. 2 (school-age children), and Fig. 3 (adolescents), separately for the three age groups.

DISCUSSION

Higher-order aberrations of the human eye, as one of the factors that influence visual acuity and retinal image quality, have drawn wide interest from visual scientists in recent years. In previous research, reference values for adult eyes have been established by either directly measuring a large population of normal vision adults [3, 4] or by collecting data from multiple sites and using this information to calculate the reference values.[6] However, these values could not be used as references for children because higher-order aberrations vary with age.[12, 13] For example, Bisneto[19] measured higher-order aberrations of 312 eyes of people whose ages ranged from 7 to 62 years old, and the results revealed that there was a positive relationship between age and higher-order aberrations. Consequently, it is necessary to establish reference ranges of higher-order aberrations for children and adolescents.

The results of this study showed that the root mean square of higher-order aberrations were correlated with age, which is in agreement with previous studies for adults, [5, 11, 12] though the present results had some variations from them. For example, Atchison's[12] study on emmetropic subjects (aged from 17 to 70 years old) showed that higher-order root mean square aberrations increased by 26% with an age range of 20 to 70 years. In the present study, the higher-order aberrations increased about 40% with an age range of 3 to 17 years. Wan's[5] study on Chinese adults (aged from 31 to 86 years old) showed that the total root mean square of higher-order aberrations were not correlated with age. Only the vertical primary coma and spherical aberrations showed a correlation with age (r_{coma}=0.206 and $r_{spherical\ equivalent\ refraction}$=0.196). However, in the present study, not only coma and spherical, but also trefoil-like aberrations and root mean square of third- to fifth-order aberrations were also correlated with age. Additionally, the present study showed that there were significant differences between children of different ages. Correspondingly, we divided the whole population into three groups: pre-school children, school-age children, and adolescents, and computed the normal values for these three age groups separately. In Brunette's study,[20] children and adolescents were integrated into the same group, which seems to be too wide. Therefore, the determination of a reference range for higher-order aberrations at different stages in children and adolescents is meaningful for clinical practice.

Concerning there maybe differences in HOAs in different refraction groups, we compared the HOAs in different refractive errors groups, the results showed that there were no differences in Zernike coefficients and root mean square aberration values among these three refractive groups for the pre-school-age, school-age children or adolescents (ANOVA tests; P>0.05).

Although, at first, He et al [21] reported that the HOAs varied with different refraction error groups. But most research findings did not support this view.[5, 22] Several factors may have contributed to these controversial conclusions, such as differences in the sample sizes between studies, differences in measuring devices, and the effect of accommodation on the aberrations.[23] Among these factors, accommodation should be considered, as children demonstrated a higher amount of accommodation. Hence, the differences of higher-order aberrations values between the three refractive groups in He's[21] study, which did not take appropriate measures to control the children's accommodation, may have occurred due to accommodation factors. In this study, we paralyzed accommodation by instilling cycloplegic drugs, and thus helped to control their accommodation and dilate their pupils at the same time (and the potential effects of cycloplegic drugs on aberration will be discussed separately below). In addition, Hartwig's study[4] regarding adult's aberrations also reported findings opposite to those in this study. They used the near addition as a proxy for age, from which can be seen that most of the subjects were old person, which is different from our study's subjects; Moreover, their subjects may have included people who had undergone corneal surgery, or had binocular anomalies or ocular pathology; these factors would have influenced their final results. In our present study, the pre-analysis were made for pre-school age, school age and adolescents groups separately, we did not find any difference between the HOAs in different refractive error groups, whether in children or in adolescents age groups. Recent studies on Chinese adults[5] and children[22] displayed similar results, reporting that there were also no differences in higher-order aberrations among myopic, emmetropic, and hyperopic eyes. Hence, we believed that it was the accommodation or other factors, rather than refractive errors that contributed to the differences in higher-order aberrations in studies which reported differences on HOAs between difference refractive error groups. As refractive errors are low-order aberrations, they should not be factors affecting higher-order aberrations; hence, it was not necessary to calculate reference ranges for different refractive error groups.

In order to control the influence of accommodation on the HOAs in children, we used 1%

Tropicamide eye drops. While the questions of whether cycloplegic drugs impact on the measuring results of HOAs do not have a consistent result. For example, Carkeet [24] found that there were significant differences in HOAs when measuring with Zywave by using mydriatic drugs. But they used the phenylephrine and cyclopentolate, while in our study the Tropicamide were used. Another researcher[25] measuring the aberrometer with the Zywave aberrometer before and after 100 eyes dilated with Tropicamide 0.5% (as group I) and 100 eye with Tropicamide 0.5% + phenylephrine 2.5% (group 2) on a 5mm pupil size. They observed some HOAS terms (vertical trefoil, spherical, and quatrefoil) significantly changed after application of mydriatic eye drops. On the contrary, Awwad et al[26] had a different result. They measured the HOAs by using LADARWave and Visx WaveScan in pupil size of 6.0mm. The results showed, when measuring with Wavescan, at an optical zone of 6mm, the HOAs measured in eyes with physiologic pupils were similar to those in pharmacologically dilated pupils when the physiologic pupil center was taken as the reference. Their results showed that, dilation and mild cycloplegia did not clinically affect the wave measurement magnitude or pattern. Another study[27], which also using the same cycloplegic drug (Tropicamide, Santen Pharmaceutical Co., Shiga, Japan), showed (although there are differences of HOAs) the differences was lower than 0.1 μm before and after pharmacological pupil dilation when measuring with WaveScan (WaveScan 3.62; Santa Clara, California, US). We also agreed that, in adults, dilation with drugs to control accommodation is not necessary, as accommodation can be neglected during the wavefront aberration measuring with the WASCA (Ascelpion-Meditec-Zeiss, Jena, Germany) aberrometer.[28] And, as Taneri [25] and Awwad [26] also mentioned, when measuring the HOAs, the pupil center is shifted by dilation, so the using of cycloplegic drugs should be clearly concerned. While, until now, no study has investigated whether cycloplegic drugs have an impact on HOAs of children when measuring aberrations with Zywawe. Considering the larger amount of accommodation in children, so the cycloplegic drugs were used in this study.

Compared with Wei's study,[29] that included Chinese adult subjects (aged from 21.5 to 52.8 years) and used the same device as the one used in our study, the total root mean square values in the present study (preschool-age children were 0.34±0.13μm, school age children were 0.35±0.22μm and adolescents were 0.40±0.25μm) were less than his study (0.49±0.16 μm), indicating that higher-order aberrations in children were less than in adults, which matched our results that higher-order aberrations increase with age. Another study on aberration distribution of Chinese adults (age from 31 to 86 years old) showed that the total root mean square value of higher-order aberrations (0.296 ±0.147μm) was smaller than that shown in our present study, but they used a different aberrometer (iTrace Dynamic Laser Refraction system, Tracey Technologies, Corp. EyeSys Vision, Inc.) to measure the ocular aberration.[5] Their aberrometer was based on the ray-tracing principle, which differed from the Hartmann-Shack principle we used; therefore, the results of the two studies cannot be compared. The percentage and distribution of higher-order aberrations for adults have been well reported in the published literature, the trend for children (as seen in our present study) was similar to adults. For example, in Wan's[5] study, the predominant higher-order aberrations were coma-like (0.180±0.115 μm), trefoil (0.151±0.116 μm), and spherical aberrations (0.081±0.060 μm); similarly, in our present study, the predominant higher-order aberrations were coma-like, trefoil and spherical aberrations. However, there were variations, such as the percentages of each aberration were different in different age groups in our present study. For school-age and preschool-age children, the predominant aberration was coma-like, while for adolescents, spherical aberrations were predominant.

A random sampling method was not used here because of a lack of resources (time and expense), which influences the representativeness of the results. However, this influence was diminished through adopting and analyzing a large sample size, which had an equal amount of refractive error state distribution with the general population. The reference ranges established here will usually be applied in hospital or clinical situations. The results are therefore considered as representative of people who required diagnosis of their abnormal optics in clinics or hospitals.

In conclusion, this study described the distributions of higher-order aberrations in a large clinical population of Han Chinese children and adolescents. The aberrations increased with age. For the first time, this study established a statistical reference range of higher-order aberrations for preschool-age children, school-age children, and adolescents by analyzing the higher-order aberrations in a large clinical population of Han Chinese children and adolescents. We hope that this will provide basic information for further studies and serve as reference values for the eyes of normal, healthy children and adolescents.

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APPENDIX

Appendix lists the 95% reference range for Zernike coeffiecients (μm) for preschool-age children, school children and adolescents. As not all the data belong to normal distribution, the detailed results were liseted in Appendix for reference. For the data belonged to normal distribution, then (-1.96s, +1.96s) were used to calculate the 95% normal reference range, which were shown in bold. For data not belonged to normal distribution, the ranks were calculated, correspond to the 2.5 and 97.5 percentiles for 95%.

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Table 1. Eye number, age, and refractive error range for preschool-age children, school-age children, and adolescents (Mean ± Standard deviation)

	Preschool-age children	School-age children	Adolescents
Eyes (N)	287	897	450
Age (Year) (Range)	5.1±1.0 3 ≤ age < 7	9.9±1.6 7 ≤ age < 13	14.0±1.1 13 ≤ age < 17
SE (D)	-10.00 – +6.25	-9.25 – +8.25	-10.00 – +6.00

SE = spherical equivalent refraction

Table 2. The RMS values of HOAs in three different age groups

RMS of HOAs	Preschool-age children (N=287) (Mean ± SD)	School-age children (N=897) (Mean ± SD)	Adolescents (N=450) (Mean ± SD)	χ^2
Total HOA***	0.338±0.125	0.353±0.224	0.400±0.250	38.979
Coma-like	0.205±0.119	0.211±0.122	0.223±0.125	4.179
Trefoil-like***	0.177±0.103	0.164±0.086	0.191±0.105	22.444
Third-order**	0.275±0.130	0.271±0.125	0.295±0.135	10.470
Fourth-order***	0.157±0.074	0.169±0.087	0.201±0.092	57.645
Fifth-order***	0.076±0.039	0.073±0.035	0.084±0.057	15.433

** *P* value< 0.01; *** *P* value < 0.001. HOA = higher order aberration; RMS= root mean square; SD = standard deviation

Table 3. The Zernike coefficients of HOAs (up to fifth-order) in three different age groups.

Zernike term	Preschool-age children (N=287) (Mean ± SD)	School-age children (N=897) (Mean ± SD)	Adolescents (N=450) (Mean ± SD)	χ^2
Z_3^{-3}***	-0.054±0.154	0.001±0.140	0.064±0.158	95.334
Z_3^{-1}**	-0.068±0.196	-0.121±0.181	-0.116±0.193	11.300
Z_3^{1}	0.007±0.100	-0.008±0.097	-0.010±0.105	3.201
Z_3^{3}▲	0.012±0.115	0.002±0.114	0.004±0.122	1.375
Z_4^{-4}	-0.004±0.049	-0.004±0.051	-0.009±0.057	3.662
Z_4^{-2}	-0.007±0.046	-0.007±0.043	-0.003±0.051	2.286
Z_4^{0}***	-0.035±0.129	-0.083±0.125	-0.133±0.118	91.553
Z_4^{2}***	-0.015±0.064	0.001±0.069	0.017±0.074	35.424
Z_4^{4}*	-0.012±0.056	-0.020±0.063	-0.027±0.070	14.700
Z_5^{-5}	0.014±0.035	0.016±0.034	0.012±0.036	3.233
Z_5^{-3}***	0.002±0.038	-0.007±0.032	0.000±0.039	17.285
Z_5^{-1}	-0.010±0.050	-0.017±0.045	-0.020±0.052	8.219
Z_5^{1}	-0.006±0.024	-0.005±0.022	-0.007±0.028	0.404
Z_5^{3}	-0.002±0.024	0.002±0.021	0.001±0.023	3.734
Z_5^{5}	-0.002±0.026	-0.001±0.028	0.001±0.034	1.218

* *P* value < 0.05； ** *P* value < 0.01; *** *P* value < 0.001. HOA = higher order aberration; SD = standard deviation

Figure 1. Histogram about frequency of the Zernike coefficients of HOAs (third- to fifth-order) in preschool-age children (N=287).

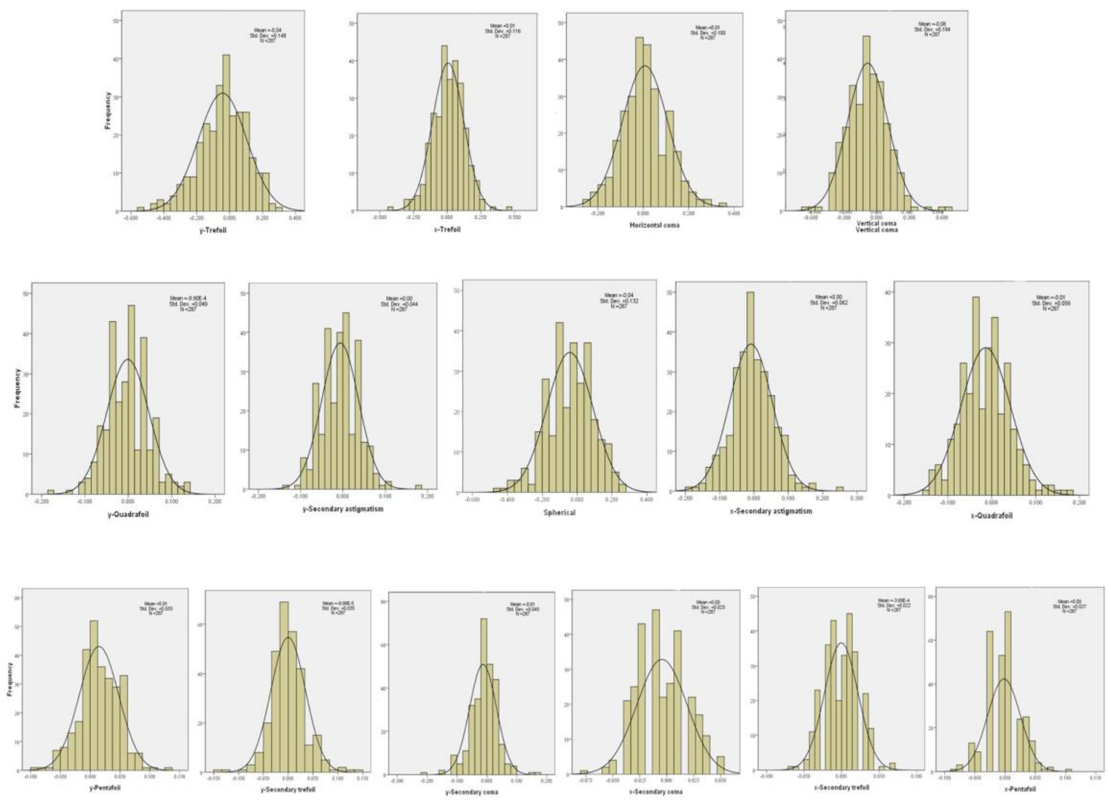

Figure 2. Histogram about frequency of the Zernike coefficients of HOAs (third- to fifth-order) in school-age children (N=897).

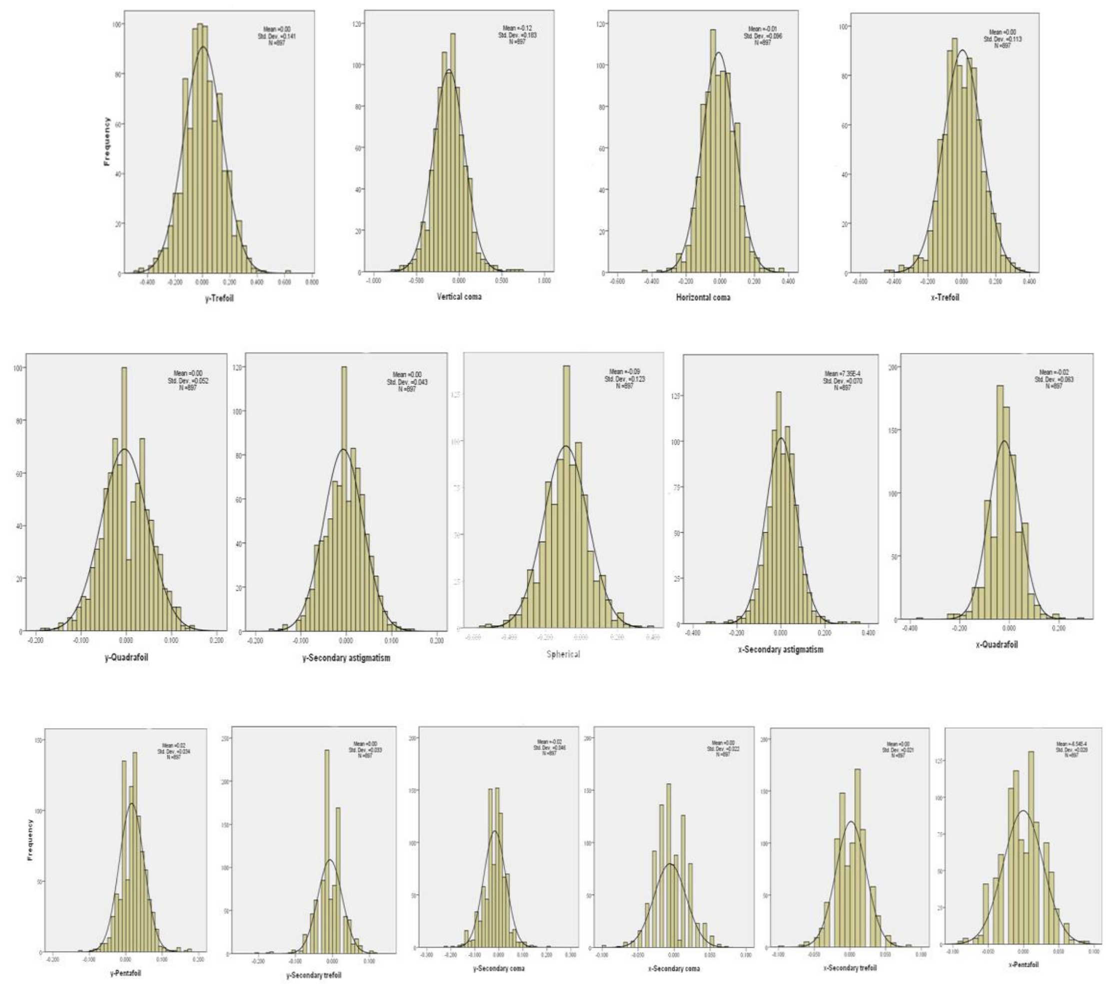

Figure 3. Histogram about frequency of the Zernike coefficients of HOAs (third-to fifth-order) in adolescents (N=450).

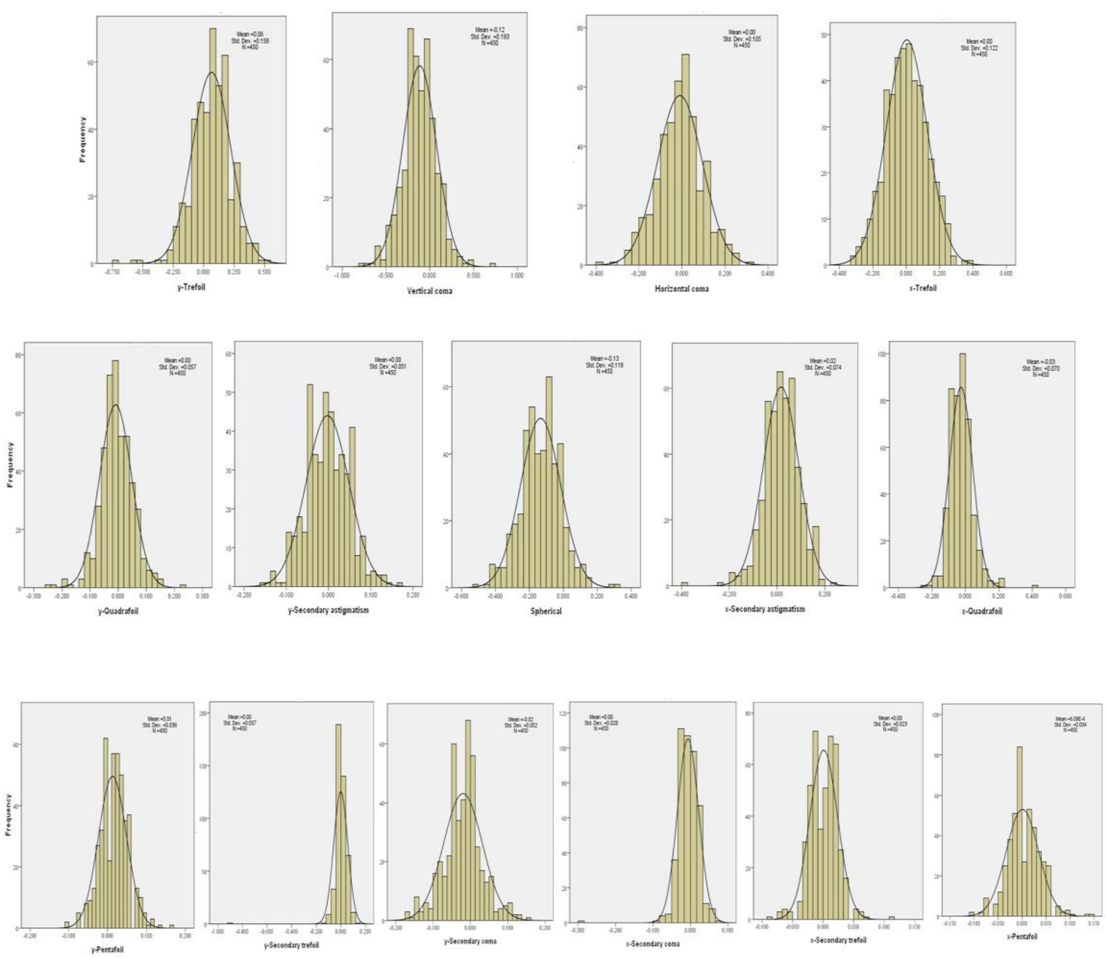

FIGURE LEGENDS

Figure 1. Histograms illustrating the frequency of the Zernike coefficients of higher order aberrations (third- to fifth-order) in preschool-age children (N=287).

Figure 2. Histograms illustrating the frequency of the Zernike coefficients of higher order aberrations (third- to fifth-order) in school-age children (N=897).

Figure 3. Histograms illustrating the frequency of the Zernike coefficients of higher order aberrations (third- to fifth-order) in adolescents (N=450).