Three-dimensional relationship between high-order root-mean-square wavefront error, pupil diameter, and aging

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We report root-mean-square (RMS) wavefront error (WFE) for individual aberrations and cumulative high-order (HO) RMS WFE for the normal human eye as a function of age by decade and pupil diameter in 1 mm steps from 3 to 7 mm and determine the relationship among HO RMS WFE, mean age for each decade of life, and luminance for physiologic pupil diameters. Subjects included 146 healthy individuals from 20 to 80 years of age. Ocular aberration was measured on the preferred eye of each subject (for a total of 146 eyes through dilated pupils; computed for 3, 4, 5, 6, and 7 mm pupils; and described with a tenth-radial-order normalized Zernike expansion. We found that HO RMS WFE increases faster with increasing pupil diameter for any given age and pupil diameter than it does with increasing age alone. A planar function accounts for 99% of the variance in the 3-D space defined by mean log HO RMS WFE, mean age for each decade of life, and pupil diameter. When physiologic pupil diameters are used to estimate HO RMS WFE as a function of luminance and age, at low luminance (9 cd/m^2) HO RMS WFE decreases with increasing age. This normative data set details (1) the 3-D relationship between HO RMS WFE and age for fixed pupil diameters and (2) the 3-D relationship among HO RMS WFE, age, and luminance for physiologic pupil diameters. © 2007 Optical Society of America

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1. INTRODUCTION

It is known that high-order root-mean-square wavefront error (HO RMS WFE) increases with age (see, for example, Refs. 1–10) and pupil diameter (see, for example, Refs. 9 and 11–16). However, the interdependent relationship among these variables has not previously been fully characterized by decade of age and pupil diameter in 1 mm steps, nor has the three-dimensional (3-D) relationship among RMS WFE, age, and pupil diameter for the individual components trefoil, coma, tetrafoil, secondary astigmatism, and spherical aberration. In addition, HO RMS WFE has not been published as a function of age and luminance for the physiologic pupil. Here we report mean and standard deviations of the HO RMS WFE for 3, 4, 5, 6, and 7 mm diameter pupils by decade for subjects between the ages of 20 and 80, using the recommended common language of the American National Standards Institute (ANSI) Z80.28 standard. We in turn use this data, combined with data from the literature on physiologic pupil diameter as a function of age and luminance, to estimate how HO RMS WFE varies as a function of age and luminance for physiologic pupil diameters. Such normative data sets are needed for a variety of purposes, including evaluating the ever-expanding variety of therapy designed to improve the optical properties of the eye with respect to age and pupil-matched norms, and the estimation of study sample sizes for parameters of interest to be

determined more accurately by providing the mean and standard deviation of the HO RMS WFE data as a function of age and pupil diameter.

2. METHODS

The tenets of the Declaration of Helsinki were followed, and the study was reviewed and approved by the University of Houston Institutional Review Board. Data from the Texas Investigation of Normal and Cataract Optics (TINCO study) were analyzed to establish relationships among pupil diameter, age, luminance, and HO RMS WFE. The TINCO study focused on the optical properties of the normal healthy eye as crystalline lens opalescence (nuclear cataract) increases naturally with age. Subjects were excluded if they had a crystalline lens with large amounts of cortical and/or posterior subcapsular cataract. The Lens Opacities Classification System—III (LOCS-III) was used to classify the opacification of each subject's crystalline lens.[17] This system provided a standardized method for scoring nuclear opalescence (NO) from 0.1 to 6.9, nuclear color (NC) from 0.1 to 6.9, cortical cataract (C) from 0.1 to 5.9, and posterior subcapsular cataract (P) from 0.1 to 5.9. The test eye pupil for each subject was dilated with one drop of 1% tropicamide and one drop of 5% neosynephrine. The HO RMS WFE was measured on the

preferred eye of each of 146 normal subjects between 20 and 80 years of age. All subjects had good systemic and eye health for their age.

The WFE was measured using a custom built Shack–Hartmann (SH) wavefront sensor. The operating principles of SH wavefront sensing have been previously described.[18–21] Briefly, the SH wavefront sensor used in this study images the entrance pupil of the subject through a 1:1 relay telescope onto a lenslet array. The lenslet array is a single optical element composed of a 65 × 65 matrix of small lenses, each having a pitch of 400 μm and a focal length of 24 mm. Each lenslet within the array samples a portion of the wavefront originating from a small retinal point source created by a superluminescent diode (SLD) ($\lambda = 830$ nm) and images the retinal point source onto a CCD camera. Subject alignment is maintained using a pupil camera, which allows the operator to align the subject's entrance pupil conjugate with the entrance aperture of the lenslet array. At least three measurements were taken on each eye. In each case the subject was asked to blink, and the measurement was taken between 2 and 5 s after the blink. Of these, we analyzed the best SH image as determined by eye. SH images with obvious image artifacts (lashes, mucous globs, etc.) were not considered valid for analysis.

The WFE was calculated for pupil diameters of 3, 4, 5, 6, and 7 mm. The center of the dilated pupil was used as the pupil center for all pupil diameters. The measured WFE was described by a normalized Zernike polynomial through the 10th radial order, and we report data through the sixth radial order following the convention set forth by the ANSI Z80.28 standard for specifying ocular WFE.

The Zernike coefficients for various pupil diameters (3, 4, 5, 6, 7 μm) were rescaled.[22,23] Rescaling has been argued to induce less error than limiting the data analysis to SH centroid data within the pupil borders of interest.[7] The Zernike coefficients for various pupil diameters were rescaled in the following manner:

1. Record x and y slopes for each sampled point.
2. Compute the normalized pupil sampling positions for each lenslet based on the system's magnification factor and the pupil diameter that you want to fit.
3. Compute the Zernike polynomials by fitting the derivative of the polynomial to the slopes using a least-squares fitting algorithm.
4. Use all of the sampled points to drive the fit, regardless of whether they fall within the normalized pupil radius.

Patients were grouped by age decade (20s, 30s, 40s, 50s, 60s, and 70s). Means and standard deviations of the HO RMS WFE were calculated for each age group for each pupil diameter. In addition, the mean RMS WFE was calculated for each component of the HO RMS WFE through the fourth radial order—trefoil, coma, tetrafoil, secondary astigmatism, and spherical aberration. To determine whether the third radial-order RMS WFE contributed more to the HO RMS WFE than did the fourth radial-order RMS WFE, we calculated the ratio of mean third to mean fourth radial-order RMS WFE for each decade of life and pupil diameter. To determine whether tre-

foil contributed more to the HO RMS WFE than did coma, we calculated the ratio of RMS WFE due to trefoil to RMS WFE due to coma for each decade of life and pupil diameter.

A three-step process was used to estimate the HO RMS WFE for typical physiologic pupil diameters as a function of luminance and age. The steps are first outlined and then described in detail in the following paragraphs:

1. Define the 3-D behavior of a typical physiological pupil diameter as a function of age and luminance from data available in the literature.[24]
2. Use the physiological pupil diameter for each age and luminance level of interest defined in step 1, and calculate the HO RMS WFE for each physiological pupil diameter of interest using the relationship among HO RMS WFE, age, and pupil diameter reported in this paper for the TINCO data set.
3. Plot the HO RMS WFE obtained in step 2 against the age and luminance that defined the physiologic pupil diameter in order to graphically display the 3-D relationship among HO RMS WFE, age, and luminance.

The first step was to define how the physiologic pupil diameter varied with age and luminance. According to the data of Winn *et al.*,[24] who measured pupil diameter for 5 luminance levels (9, 44, 220, 1100, and 4400 cd/m^2) of 91 individuals from 17 to 83 years of age (almost identical to the sample population of the current study), physiologic pupil diameter decreases linearly with increasing age for any given light level. The rate of change of pupil diameter as a function of age for the different luminance levels was not constant. As can be seen in Table 1, as luminance increases the rate of change in physiological pupil diameter as a function of age decreases. The 3-D relationship among physiological pupil diameter, age, and luminance derived from the Winn *et al.* study[24] is plotted in Fig. 1.

The second step was to determine the HO RMS WFE for physiologic pupil diameters for all age categories and luminance levels of interest. Two substeps [(2a) and (2b)] were used to accomplish this goal. The first substep (2a) defined the relationship among HO RMS WFE, age, and pupil diameter. This relationship was defined by fitting the mean HO RMS WFE as a function of pupil diameter for each age group (e.g., 20–29, 30–39, etc.) measured in the TINCO study with an exponential function. (Note: This aspect of the results is reported here as opposed to

Table 1. Slope, Intercept, and Coefficient of Determination (R^2) of the Linear Regression Describing How Pupil Diameter Changes as a Function of Age for Five Luminance Levels for 91 Subjects[a]

Luminance Level (cd/m^2)	Slope	Intercept	R^2
9	−0.043	8.046	0.557
44	−0.040	7.413	0.486
220	−0.032	6.275	0.377
1100	−0.020	4.854	0.226
4400	−0.015	4.070	0.214

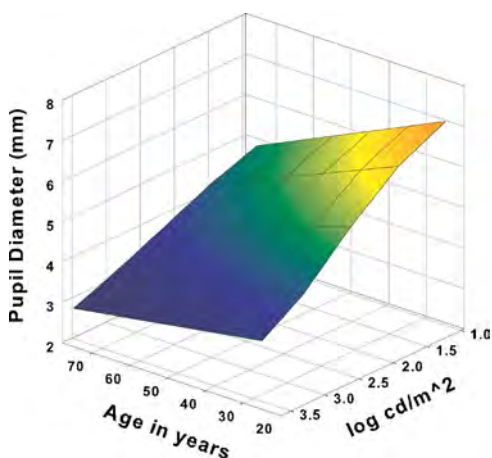[a]Data from Winn *et al.*[24] study.

Fig. 1. (Color online) Relationship among physiologic pupil diameter, age, and luminance derived from the data of Winn *et al.*[24]
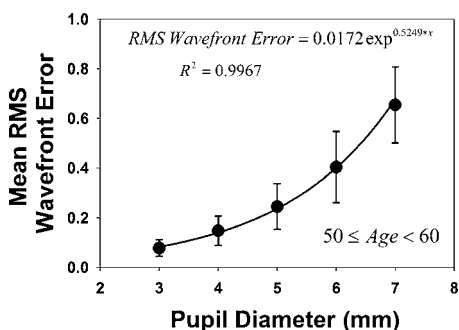

Fig. 2. HO RMS WFE as a function of pupil diameter for the decade of the 50s. All other decades between 20 and 80 are well represented by an exponential function, as can be seen in Table 2.

Table 2. For Six Different Age Groups, Parameters (*a* and *b*), and Coefficient of Determination (*R²*) of the Exponential Regression (HO RMS WFE=$a*\exp^{b*x}$) Describing the Relationship among the Mean HO RMS WFE and Any Given Pupil Diameter (*x*) and the Corresponding Coefficient of Determination (*R²*)

Mean Age±SD (Years)	*a*	*b*	*R²*
25.2±2.3	0.0114	0.5331	0.9875
35.0±2.4	0.0102	0.5623	0.9972
45.2±2.8	0.0130	0.5559	0.9952
54.4±2.9	0.0172	0.5249	0.9967
62.9±1.9	0.0187	0.5311	0.9881
72.9±2.4	0.0193	0.5735	0.9950

the results because it is part of the method used to calculate HO RMS WFE as a function of age and luminance.) As seen in Fig. 2 for the 50–59 age group, and in Table 2 for each age group, exponential functions of the form HO RMS WFE=$a*\exp^{b*x}$ fit the TINCO data extremely well (*R²* ranged between 0.9875 and 0.9972 depending on the decade of interest). The second substep (2b) was to substitute into these exponential functions the physiologic pupil diameters (*x*) for each age category and luminance level of interest to define the expected HO RMS WFE for any given physiologic pupil diameter.

On the assumption that the physiologic pupil diameters of our subjects behave in a manner similar to those in the Winn *et al.*[24] study, the third step was to plot the HO RMS WFE for each physiological pupil diameter of interest against the age and luminance that defined each of the physiologic pupil diameters.

3. RESULTS

Table 3 displays the age range forming each age group, the number of eyes and individuals, the mean age, the standard deviation, and the minimum and maximum ages in each age group. Table 4 displays the mean and standard deviation for each LOCS-III scoring category as a function of age. As anticipated, in normal healthy eyes, NO and NC increase with age. P and C were kept low by study design.

Table 5 displays by age group and pupil diameter the mean HO RMS WFE, the standard deviation, the minimum and maximum values of the HO RMS WFE, the number of eyes dilating to at least the desired pupil diameter, and the number of eyes that did not dilate enough to meet the qualifying pupil diameter. For the 6 mm pupil diameter, 2 of the 146 subjects' pupils did not dilate to at least 6 mm. For the 7 mm pupil diameter, 34 of the 146 subjects' pupils did not dilate to at least 7 mm. Interestingly, the failure to dilate to 7 mm affected all age groups, with the 50–60 year olds affected more than any other group, including the 60–70 year olds and the 70–80 year olds (see Table 5, last column). Wavefront data for eyes that did not dilate adequately could not be properly calculated and are excluded from the 6 and 7 mm pupil analyses. The 3, 4, and 5 mm diameter pupil data analyses include all 146 subjects. Some caution is therefore

Table 3. Label for Each Age Range, Age Range Forming Each Group, Mean Age, Standard Deviation (SD), and Minimum and Maximum Age

Age Label	Age (years)	Count[a]	Mean Age±SD (years)	Minimum Age (years)	Maximum Age (years)
20s	20–29	20	25.2±2.3	21.6	29.8
30s	30–39	18	35.0±2.4	30.1	38.7
40s	40–49	32	45.2±2.8	40.5	49.9
50s	50–59	32	54.4±2.9	50.5	58.7
60s	60–69	21	62.9±1.9	60.3	67.4
70s	70–79	23	72.9±2.4	70.0	78.4

[a]Details the number of eyes and individuals forming each group.

Table 4. LOCS-III Mean Score and Standard Deviation (SD) by Decade for NO, NC, C, and P

Label	NO Mean±SD	NC Mean±SD	C Mean±SD	P Mean±SD	Count[a]
20s	1.5±0.4	0.9±0.1	0.3±0.2	0.1±0.03	20
30s	2.0±0.4	1.2±0.5	0.3±0.2	0.1±0.10	18
40s	2.3±0.5	1.6±0.5	0.4±0.5	0.1±0.05	32
50s	2.5±0.4	2.4±0.6	0.4±0.4	0.2±0.40	32
60s	3.1±0.8	2.8±0.7	0.4±0.5	0.2±0.07	21
70s	3.4±1.0	3.4±1.0	0.9±0.7	0.3±0.40	23

[a]Shows the number of eyes and individuals in each age group.

**Table 5. Mean HO RMS WFE (Third–Sixth Radial Order), Standard Deviation, Minimum and Maximum
HO RMS WFE, and Number of Eyes Grouped by Age and Pupil Diameter[a]**

Age (years)	Pupil Diameter (mm)	HO RMS WFE Mean±SD (μm)	HO RMS WFE Minimum (μm)	HO RMS WFE Maximum (μm)	No. of Eyes	Eyes Not Fully Dilated
20–29	3	0.051±0.022	0.022	0.109	20	0
30–39	3	0.052±0.022	0.017	0.099	18	0
40–49	3	0.064±0.024	0.027	0.107	32	0
50–59	3	0.078±0.033	0.027	0.145	32	0
60–69	3	0.083±0.022	0.047	0.118	21	0
70–79	3	0.100±0.031	0.044	0.172	23	0
20–29	4	0.103±0.037	0.050	0.205	20	0
30–39	4	0.102±0.041	0.038	0.188	18	0
40–49	4	0.127±0.041	0.063	0.215	32	0
50–59	4	0.148±0.059	0.053	0.292	32	0
60–69	4	0.167±0.039	0.108	0.240	21	0
70–79	4	0.199±0.060	0.115	0.322	23	0
20–29	5	0.180±0.059	0.097	0.353	20	0
30–39	5	0.174±0.062	0.067	0.287	18	0
40–49	5	0.221±0.065	0.125	0.382	32	0
50–59	5	0.245±0.092	0.099	0.544	32	0
60–69	5	0.292±0.073	0.193	0.451	21	0
70–79	5	0.360±0.105	0.218	0.549	23	0
20–29	6	0.294±0.095	0.170	0.550	20	0
30–39	6	0.289±0.091	0.127	0.426	18	0
40–49	6	0.370±0.112	0.200	0.654	32	0
50–59	6	0.403±0.144	0.158	0.923	31	1
60–69	6	0.469±0.134	0.287	0.799	20	1
70–79	6	0.626±0.214	0.312	1.125	23	0
20–29	7	0.433±0.132	0.261	0.687	18	2
30–39	7	0.513±0.138	0.227	0.718	15	3
40–49	7	0.604±0.195	0.334	1.107	29	3
50–59	7	0.654±0.153	0.324	0.952	18	14
60–69	7	0.702±0.204	0.429	1.113	16	5
70–79	7	0.996±0.285	0.576	1.555	16	7

[a]Two eyes did not dilate to 6 mm, and 34 eyes did not dilate to 7 mm, as indicated in last column.

warranted for the 7 mm pupil data in that 23% of the subjects did not have pupils that dilated to at least 7 mm. In particular, for the 50–59 age group, 7 mm diameter, 44% of the eyes did not dilate to 7 mm.

Figure 3(A) displays the mean HO RMS WFE listed in Table 5 in a 3-D plot illustrating visually the relationship among age, pupil diameter, and HO RMS WFE. Starting at any given point on Fig. 3(A) (e.g., 5 mm pupil diameter, age 40 years), HO RMS WFE increases faster with increasing pupil diameter than with increasing age. Figure 3(B) displays in a 3D plot the relationship among RMS WFE of the third Zernike radial order, age, and pupil diameter. Figure 3(C) displays the RMS WFE for the fourth Zernike radial order in a similar manner. As with the total HO RMS WFE, RMS WFE for the third and fourth radial orders increases faster with pupil diameter for any given age than it does with age alone for any given pupil diameter. Figure 3(D) plots the ratio of the third radial-order mean RMS WFE to fourth radial-order mean RMS WFE as a function of mean age for each decade and pupil diameter. This figure illustrates that for almost all pupil diameters and age groups, third-order WFEs are larger than fourth-order WFEs [i.e., the ratio of third to fourth is always greater than 1 except for some of the largest (7 mm) pupil diameters].

Figure 4 fits an exponential to the mean HO RMS WFE as a function of age for each individual pupil diameter. Notice each exponential function fits the data extremely well. The parameters for each exponential function of Fig. 4, as well as the coefficient of determination, are given in Table 6.

The fact that RMS WFE increases exponentially with both mean age and pupil diameter suggested the need to replot the 3-D data of Fig. 3(A) as log HO RMS WFE as a function of age and pupil diameter to determine if such a transformation better defined the relationship among HO RMS WFE, pupil diameter, and age. Figure 5 graphically displays this relationship and defines a planar surface that accounts for 99% of the variance in the mean log HO RMS WFE, defined by the following formula:

log mean HO RMS WFE = 0.0063 × mean Age + 0.2374

× Pupil Diameter − 2.1233.

Table 7 lists for each decade and pupil diameter the mean and standard deviation (SD) of the RMS WFE for trefoil
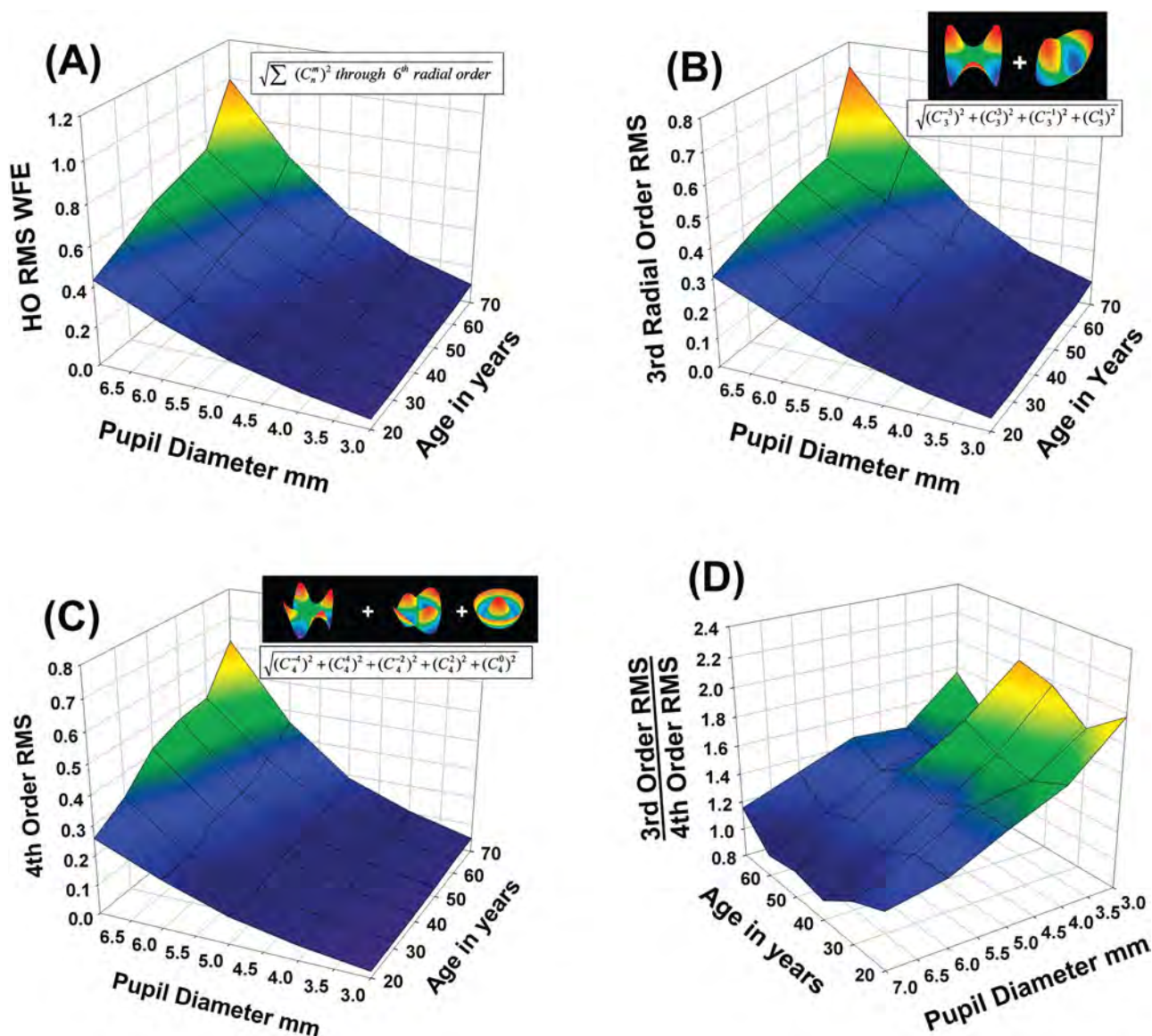
Fig. 3.   (Color online) Three-dimensional graphs illustrating HO RMS WFE as a function of age and pupil diameter: (A) third–sixth-order HO RMS WFE; (B) third radial-order RMS WFE; (C) fourth radial-order RMS WFE; (D) ratio of third-order RMS WFE to fourth-order RMS WFE.
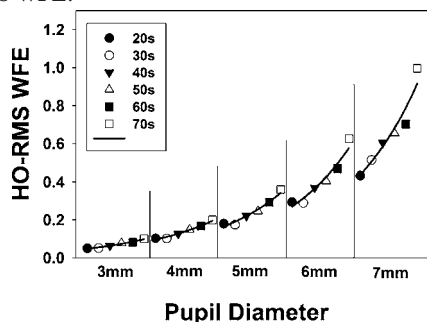

Fig. 4.   Mean HO RMS WFE as a function of age for each pupil diameter, where each pupil diameter is fit with an exponential function the parameters detailed in Table 6.

$[\sqrt{(C_3^{-3})^2+(C_3^3)^2}]$,   coma $[\sqrt{(C_3^{-1})^2+(C_3^1)^2}]$,   tetrafoil $[\sqrt{(C_4^{-4})^2+(C_4^4)^2}]$, secondary astigmatism $[\sqrt{(C_4^{-2})^2+(C_4^2)^2}]$, and spherical aberration $[\sqrt{(C_4^0)^2}]$.

   Figure 6(A)–6(E) displays the mean RMS WFE listed in Table 7 in 3-D graphs that illustrate how coma (A), trefoil

Table 6. Parameters (a and b) of the Exponential Function (HO RMS WFE=$a * \exp^{b*x}$) Describing the Mean HO RMS WFE for Each Age Group for a Given Pupil Diameter[a]

Pupil Diameter (mm)	Parameter		
	a	b	R^2
3	0.0329	0.0151	0.9683
4	0.0662	0.0148	0.9660
5	0.1109	0.0154	0.9453
6	0.1789	0.0160	0.9359
7	0.2899	0.0157	0.9481

[a]x is the average age of the patients in each decade group as given in Table 3.

(B), spherical aberration (C), tetrafoil (D), and secondary astigmatism (E) mean RMS WFE vary with mean age for each decade and pupil diameter. Panel (A) displays the RMS WFE for coma, which is the aberration with the
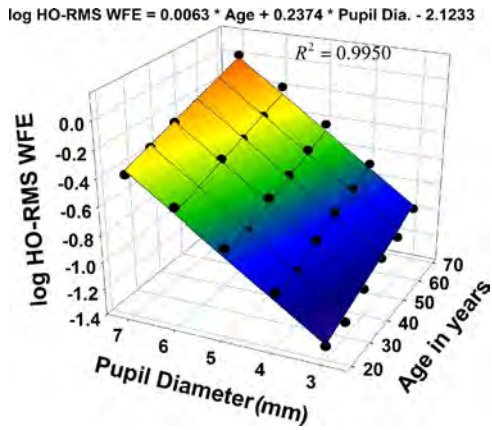
Fig. 5. (Color online) Mean log HO RMS WFE as a function of pupil diameter and age defines a plane ($R^2 = 0.99$). Solid circles are the mean log HO RMS WFE for each decade and pupil diameter.

largest average RMS WFE across all ages and pupil diameters. Panel (E) (secondary astigmatism) is the aberration with the lowest average RMS WFE across ages and pupil diameters. The mean of means of the RMS WFE for coma and trefoil are nearly identical. On average, coma is just slightly but not significantly ($p = 0.12$ paired t-test) larger than trefoil across conditions. This is illustrated in Fig. 6(F) which graphically displays the ratio of mean trefoil RMS WFE to mean coma RMS WFE, which is essentially unity across all ages and pupil diameters.

Figure 7 displays the calculated relationship among HO RMS WFE, luminance, and age for physiologic pupil diameters as they are likely to occur in the real world. Unlike the relationships in Figs. 3 and 4, where HO RMS WFE was measured for fixed pupil diameters regardless of age, Fig. 7 displays HO RMS WFE for physiologic pupil diameters that vary with age and luminance. Notice that

Table 7. Mean and Standard deviation (SD) of the RMS WFE is Displayed for Trefoil,[a] Coma,[b] Tetrafoil,[c] Secondary Astigmatism (2nd Astig.),[d] and Spherical Aberration (Sph. Ab.)[e] for Each Decade and Pupil Diameter

Age (years)	Pupil Diameter (mm)	RMS WFE (μm) Trefoil Mean±SD	RMS WFE (μm) Coma Mean±SD	RMS WFE (μm) Tetrafoil Mean±SD	RMS WFE (μm) 2nd Astig. Mean±SD	RMS WFE (μm) Sph. Ab. Mean±SD
20–29	3	0.029±0.018	0.028±0.019	0.011±0.010	0.011±0.007	0.013±0.013
30–39	3	0.027±0.017	0.031±0.022	0.010±0.004	0.015±0.008	0.014±0.010
40–49	3	0.038±0.023	0.036±0.020	0.014±0.008	0.014±0.009	0.016±0.011
50–59	3	0.043±0.027	0.048±0.028	0.019±0.016	0.018±0.011	0.014±0.011
60–69	3	0.041±0.021	0.047±0.026	0.023±0.019	0.017±0.011	0.027±0.013
70–79	3	0.059±0.031	0.055±0.026	0.024±0.014	0.020±0.010	0.030±0.022
20–29	4	0.056±0.033	0.051±0.033	0.024±0.018	0.025±0.016	0.032±0.028
30–39	4	0.051±0.034	0.055±0.043	0.018±0.010	0.030±0.014	0.034±0.017
40–49	4	0.071±0.043	0.065±0.037	0.028±0.015	0.027±0.017	0.045±0.025
50–59	4	0.077±0.047	0.083±0.053	0.034±0.030	0.032±0.021	0.041±0.026
60–69	4	0.076±0.048	0.093±0.045	0.043±0.030	0.035±0.023	0.062±0.033
70–79	4	0.107±0.059	0.099±0.048	0.049±0.024	0.040±0.025	0.075±0.046
20–29	5	0.091±0.059	0.087±0.049	0.034±0.023	0.044±0.028	0.065±0.057
30–39	5	0.085±0.058	0.090±0.062	0.031±0.018	0.042±0.018	0.064±0.041
40–49	5	0.120±0.059	0.104±0.059	0.044±0.024	0.044±0.023	0.097±0.057
50–59	5	0.121±0.067	0.129±0.090	0.049±0.037	0.045±0.030	0.097±0.055
60–69	5	0.129±0.077	0.161±0.077	0.060±0.040	0.063±0.038	0.123±0.073
70–79	5	0.182±0.100	0.193±0.075	0.073±0.039	0.063±0.045	0.145±0.086
20–29	6	0.141±0.089	0.137±0.076	0.051±0.025	0.063±0.035	0.132±0.108
30–39	6	0.139±0.089	0.136±0.087	0.056±0.030	0.055±0.027	0.130±0.090
40–49	6	0.187±0.083	0.169±0.089	0.073±0.048	0.071±0.037	0.193±0.110
50–59	6	0.189±0.097	0.198±0.145	0.072±0.051	0.073±0.039	0.197±0.115
60–69	6	0.196±0.115	0.238±0.134	0.088±0.068	0.097±0.070	0.235±0.141
70–79	6	0.292±0.175	0.339±0.170	0.113±0.064	0.093±0.060	0.311±0.153
20–29	7	0.197±0.114	0.205±0.123	0.091±0.033	0.087±0.043	0.195±0.167
30–39	7	0.239±0.135	0.235±0.124	0.110±0.053	0.083±0.053	0.269±0.176
40–49	7	0.270±0.129	0.261±0.133	0.126±0.079	0.117±0.058	0.355±0.214
50–59	7	0.310±0.152	0.269±0.124	0.106±0.062	0.116±0.066	0.401±0.177
60–69	7	0.259±0.168	0.308±0.208	0.137±0.087	0.153±0.091	0.406±0.237
70–79	7	0.458±0.274	0.505±0.213	0.179±0.100	0.127±0.077	0.563±0.251

[a] $\sqrt{(C_3^{-3})^2 + (C_3^3)^2}$.

[b] $\sqrt{(C_3^{-1})^2 + (C_3^1)^2}$.

[c] $\sqrt{(C_4^{-4})^2 + (C_4^4)^2}$.

[d] $\sqrt{(C_4^{-2})^2 + (C_4^2)^2}$.
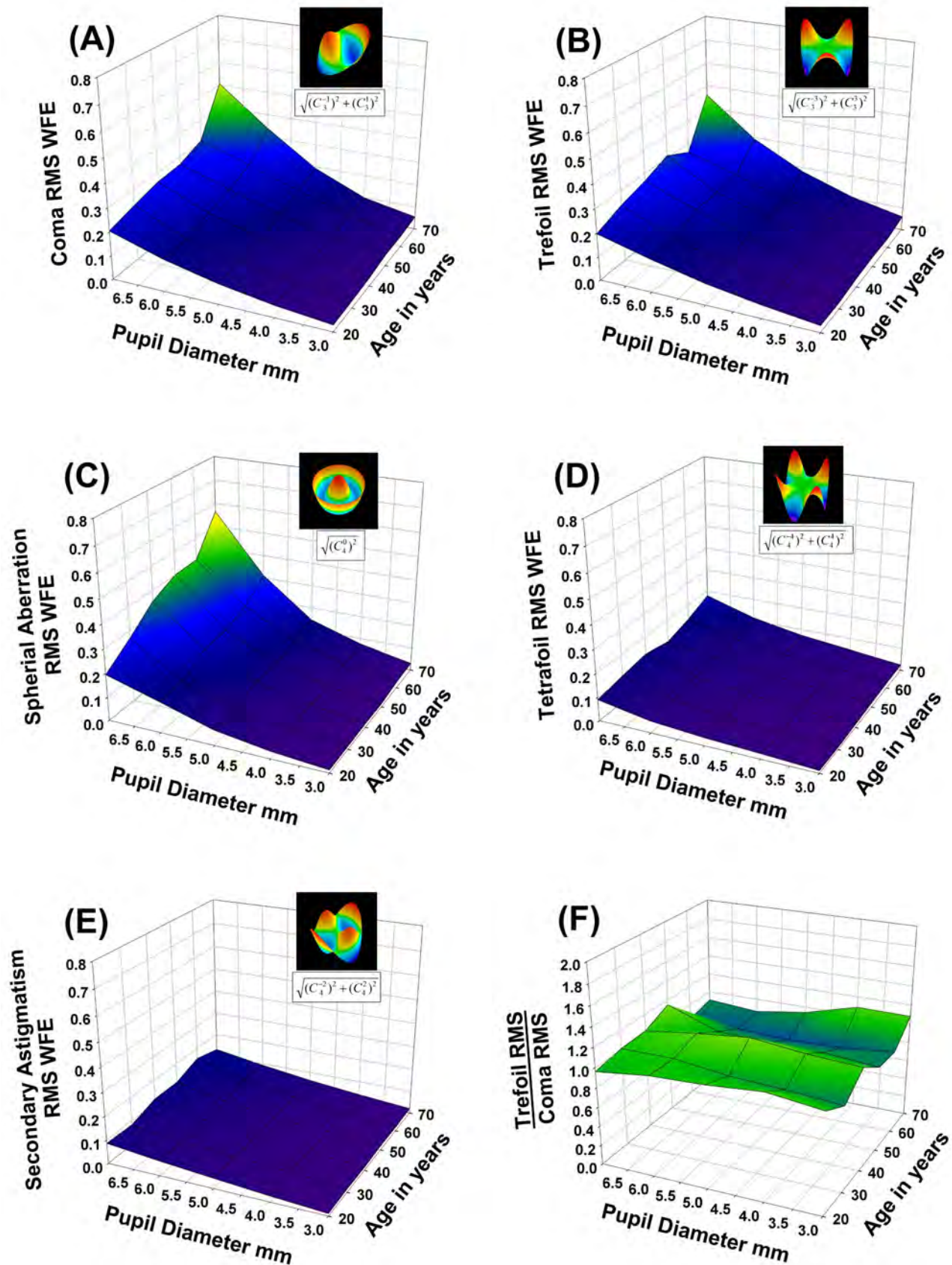
[e] $\sqrt{(C_4^0)^2}$.

Fig. 6.   (Color online) Mean RMS WFE as a function of mean age by decade and pupil diameter for (A) coma, (B) trefoil, (C) spherical aberration, (D) tetrafoil, and (E) secondary astigmatism. Panel (F) plots the ratio of trefoil RMS WFE to coma RMS WFE.
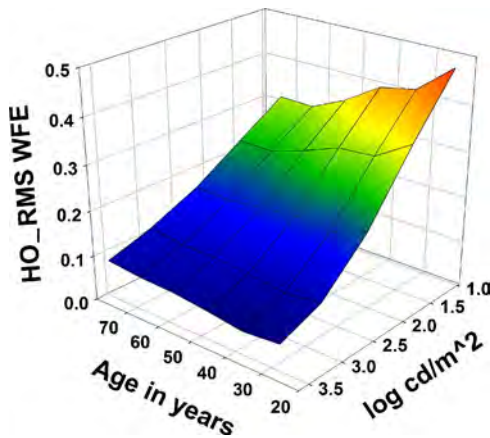
Fig. 7. (Color online) Estimated relationship among HO RMS WFE (third–sixth radial orders) age, and luminance through the physiologic pupil.

at low luminance, HO RMS WFE decreases with age. The HO_RMS WFE decreases because the physiologic pupil diameter decreases at a relatively fast rate with age (see Fig. 1) at low-luminance levels. However, for high-luminance levels, RMS WFE increases slightly with age because the rate with which the pupil diameter decreases with age at high-luminance levels is not sufficient to counteract the increase in HO RMS WFE with age.

4. DISCUSSION

There have been other large cross-sectional studies of HO RMS WFE (for example, Refs. 25 and 26). Results from these studies have been limited to a rather narrow age range of eyes studied[26] or to primarily one pupil diameter.[25] Here we have reported the HO aberrations as a function of pupil diameter and age for a large cohort of subjects and have used these data to estimate the relationship among HO RMS WFE, luminance, and age under physiologic pupil diameters, being careful to report the level of cataract as specified by LOCS III scores for NO, NC and to control for C and P.

Table 5 and Fig. 3(A) reveal that HO RMS WFE increases faster with pupil diameter for any given age than it does with age for any given pupil diameter. Therefore, a typical young individual with an inherently large natural pupil may habitually experience a larger HO RMS WFE than would a typical older individual with an inherently small natural pupil. When the data are reanalyzed as log HO RMS WFE (Fig. 5), the relationship is remarkably well predicted, accounting for 99% of the variance in the log of the mean HO RMS WFE across mean age (by decade) and pupil diameter.

Collectively, the data set provides normative data with which the mean HO RMS WFE and variance of any given individual at any given age and with any given pupil diameter can be compared, be it for the total HO RMS WFE (Table 5) or the RMS WFE for any particular aberration (Table 7) of interest through the fourth radial order. With respect to the design of future studies, this data set is particularly useful in sample size calculations that are needed to properly design and implement studies.

It is important to note in considering this data set that the aberration structure may not be random.[27] Consistent with these suggestions, eye aberrations do not appear to vary with eye length,[28] and it is certainly the case that although the Zernike terms are mathematically orthogonal optically, they can interact to improve or degrade optical quality.[29,30]

The ratio of average coma to trefoil remains essentially constant for each age group and pupil diameter [see Fig. 6(F)], indicating that both types of aberrations increase together as a function of pupil diameter and age. Corneal WFE has been shown to be reasonably stable as a function of age (HO RMS corneal first-surface WFE changes 0.08 from the 20s to the 70s over a 6 mm pupil),[3] compared with the change in total eye aberrations of 0.45 μm over a 5.9 mm pupil from the 20s to the 70s.[22] The relative stability of the corneal HO RMS WFE compared with the total eye HO RMS WFE suggests that aging of the crystalline lens affects both trefoil and coma equally. However, it does not mean that the orientation of these components is constant. Orientation of aberration is not addressed in this paper.

The result that the ratio of average third-order aberrations to average fourth-order aberrations decreases from approximately 2 to slightly greater than 1 [Fig. 3(D)] as pupil diameter increases from 3 to 7 mm is consistent with the observation that spherical aberration increases faster with increasing pupil diameter than do other aberrations. It is important to note again that in this paper we are looking at the magnitude of the aberration and not the sign of the individual components. It is well known that with age, spherical aberration shifts toward more positive values.[31] This should not be confused with the fact that in young eyes spherical aberration becomes more negative with increasing accommodation.[32]

The fact that third radial-order aberrations of coma and trefoil dominate the aberration structure of normal eyes was first reported by Howland and Howland.[33,34] This paper reconfirms this result and extends their finding by demonstrating in a large cross-sectional sample of people of varying age that third radial-order aberrations dominate fourth radial-order aberrations across all ages and all but the largest (7 mm) pupil diameters [see Fig. 3(D)].

The HO RMS WFE reported here as a function of age and pupil diameter examine the wave aberration in drug-dilated eyes as a function of five fixed pupil diameters having a common center (Figs. 3–5). However, the natural pupil center can vary with pupil diameter. (see, for example, Refs. 35 and 36). The pupil tends to shift a relatively small amount (average shift of 0.13 mm temporally) as the pupil dilates from photopic to mesopic light levels.[36] The effect that this shift has on the HO RMS WFE or the individual components of the WFE are not accounted for in the data reported here.

It is of particular interest to define HO RMS WFE as a function of age and luminance using physiologic pupil diameters. The reasons are simple. The HO RMS WFE is very dependent on pupil diameter, and we do not operate in the real world with a fixed pupil diameter. Two major drivers of physiologic pupil diameter are luminance and age. To define the relationship among HO RMS WFE, lu-

minance, and age, we first used data from Winn *et al.*[24] to understand the fundamental relationship among physiologic pupil diameter, age, and luminance. As can be seen in Fig. 1 and more clearly in Table 1, at the low-luminance level tested (9 cd/m^2) physiologic pupil diameter decreases by approximately 0.43 mm/decade of life, and at the highest luminance level (4400 cd/m^2) pupil diameter decreases at a much slower rate of 0.15 mm/decade. It is important to note that while physiologic pupil diameters as a function of age at any given luminance level are well represented by linear functions, Winn *et al.*[24] and Loewenfeld[37] (in a study of 1263 individuals) emphasized the fact that there is large variability in physiologic pupil diameter at all ages. For low-to-moderate luminance levels (room lighting) the physiologic pupil diameter can span a range of ±2 mm from the mean at any given age. For high-luminance levels (sunshine) the range of physiologic pupil diameter decreases to about ±1 mm from the mean for any given age. The large range in pupil diameter at any given age and luminance level (greater than 30% of the mean pupil diameter for any given age and luminance level) is important because it implies that it is impossible to predict the actual pupil diameter of an individual at a given age from the mean data presented in Fig. 1. Nonetheless, the relationship between pupil diameter and age for any given luminance level is important in that it defines useful population trends for real-world situations. Finally, before turning to how physiologic pupil diameters as a function of age and luminance affect HO RMS WFE, it is worth noting that although Winn *et al.*[24] found a significant relationship between pupil diameter and age for all luminance levels tested, they found no significant correlations between pupil diameter and iris color or refractive error.

To answer the question, What is the HO RMS WFE for the typical normal eye in real-world situations? we estimated the HO RMS WFE as a function of age and luminance for age- and luminance-appropriate physiologic pupil diameters. As illustrated in Fig. 7, at low-luminance levels, RMS WFE decreases with increasing age, whereas at the highest-luminance levels RMS WFE increases slightly with increasing age. Consequently, in the 60s and 70s, the rate at which RMS WFE increases as luminance decreases is slower than that in the 20s. Combining this fact with the observation that high-contrast photopic acuity is relatively insensitive to variations in HO RMS WFE (or other retinal image-quality metrics based on HO WFE) in the normal eye with good high-contrast visual acuity,[38] it is difficult to attribute decreasing acuity with increasing age[39–42] to an increase in aberration when acuities are measured under physiologic pupil conditions. Thus acuity loss with age in the normal aging eye is most likely due to neural changes (see, for example, Refs. 43–45) combined with other optical effects, including scatter[46,47] and decreased light transmission.[48–54]

5. CONCLUSION

Collectively, the data sets presented serve as normative data detailing of (1) how HO RMS WFE individually and collectively varies as a function of age by decade and pupil diameter in 1 mm steps from 3 to 7 mm, and (2) how HO RMS WFE varies as a function of luminance and age for physiologic pupil diameters. These normative data are particularly useful for determining sample sizes in study design and for evaluating therapy designed to improve the optical properties of the eye.

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