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Static and dynamic pupillometry data of healthy individuals

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Background: This study sought to determine normative static and dynamic pupillometry data in different age groups in a healthy population, and to investigate the effects of age on pupillometric characteristics.
Methods: Pupillometry measurements were undertaken on 155 healthy participants using an automatic quantitative pupillometry system. Static pupillometry measurements were undertaken; these included scotopic pupil diameter (PD), mesopic PD, low photopic PD and high photopic PD values. Dynamic pupillometry measurements were undertaken, including resting diameter, amplitude of pupil contraction, latency of pupil contraction, duration of pupil contraction, velocity of pupil contraction, latency of pupil dilation, duration of pupil dilation and velocity of pupil dilation.
Results: Overall, 69 (44.5 per cent) participants were male and 86 (55.5 per cent) were female, with a mean age of 29.7 $\pm$ 17.8 years. Neither static nor dynamic pupillometry measurements varied significantly between males and females. Age was inversely and moderately correlated with each of the static pupillometric characteristics ($p < 0.05$). Resting diameter, velocity of pupil contraction, and velocity of pupil dilation values were inversely and moderately correlated with age ($p < 0.001$, $r = -0.63$; $p < 0.001$, $r = -0.47$; and $p < 0.001$, $r = -0.34$, respectively). Latency of pupil contraction was positively and moderately correlated with age ($p = 0.002$, $r = 0.29$).
Conclusions: The current study presents population-specific normative data on static and dynamic pupillometry values in different age groups and the effect of age on pupillary characteristics.

Key words: dynamic pupillometry, normative data, pupil diameter, static pupillometry

Clinicians examine the pupil by observing and measuring pupil size, shape, symmetry, response to light and response to near reflex.[1–5] Pupillary examinations can help clinicians to diagnose many ocular and neurological disorders, and may relate to history of medication, surgery or trauma.[5–8] Analysis of pupillary light reflex (PLR) is one way to evaluate the integrity of afferent visual pathways, and it is an indicator of the balance between the sympathetic constrictor and parasympathetic dilator systems.[9]

Researchers have been able to detect deficits in patients with suspected preperimetric glaucoma and diabetes without retinopathy by examining changes in pupillary characteristics.[10,11] Moreover, Kardon et al.[12] showed that chromatic pupillometry could provide a novel, non-invasive method for clinicians to follow functional retinal status, especially in patients with severe retinitis pigmentosa. Pupillary characteristics and PLR are also important in patients with traumatic brain injuries, since pupil size and response to the light can provide clinicians with information concerning potential intracranial pathologies.[13–15]

There are several factors that may affect the human pupillary system, including pharmacological agents, arousal state and head trauma.[16–18] Age is another important factor affecting pupillary characteristics. In several studies, researchers have shown that baseline pupil diameters tend to get smaller with age[16,19,20] and this age-related effect is seen over a wide range of ocular illuminance levels.[21] Herbst et al.[22] examined how age and *in vivo* measured lens transmission might affect pupil light responses and showed that the post-illumination pupil response (PIPR) is enhanced with ageing. Conversely, Kankipati et al.[23] revealed that the PIPR amplitude is independent of age using the plateau PIPR metric. Adhikari et al.[24] also confirmed the finding that there is no effect of ageing on the PIPR, indicating that the intrinsically photosensitive retinal ganglion cell inputs to the pupil control pathway show no change with age.

On the other hand, there are limited studies investigating the effect of ageing on pupillary dynamics, including pupil constriction velocity and re-dilation velocity. Pupillary constriction velocity is a function of the balance between sympathetic and parasympathetic tone in which increased sympathetic balance decreases the constriction velocity, whereas increased parasympathetic balance increases it.[1–3] The most well-known age-related change of the pupil is miosis, which possibly occurs owing to age-related atrophy of the dilator muscles of the pupil and decrease of sympathetic activity that lead to reduction of the dilator muscle tone.[1–3]

It also may be supposed that older subjects have shown slower pupillary responses, perhaps reflecting the consequences of senescence in the iris smooth muscles. Bitsios et al.[25] investigated the pupil dynamics

and ageing, and reported reduced maximum velocities of pupil constriction and dilation in older subjects. However, this study used closed-loop stimulus conditions where the smaller pupils of the elderly subjects might be allowed less light flux to elicit the reflex.

Subjective analysis of pupillary parameters can be affected by significant inter-observer variability due to factors such as differences in ambient illumination, intensity of light stimulus and observers' experiences. Recent developments to automated pupillometric devices have enabled quantitative, objective, non-invasive and repeatable measurements of pupil diameter (PD). These measurements can be taken statically with the conditions of scotopic, mesopic or photopic vision, and dynamically.[26–28]

The aim of this study is to determine normative pupillometry data for different age groups in a healthy population and to assess the effects of age on static and dynamic pupillometric characteristics.

Patients and methods

This cross-sectional study was carried out from March 2016 to December 2016 at a single institution. The study protocol was approved by the Ankara Numune Training and Research Hospital Ethics Committee, and we carried out the study in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants or their parents prior to enrolment. The number of participants studied was 155. Only data from right eyes were analysed.

Healthy participants were recruited, who were defined as those without any systemic disease and with a best-corrected visual acuity (BCVA) equal or greater than 6/6 according to the Snellen chart. Participants had no history of any ocular problem other than spherical or cylindrical refractive errors less than or equal to 1.00 D. Since smoking may be associated with changes in pupil size[29] only non-smokers were included in the study. Moreover, the following participants were excluded: those who had used drugs or consumed alcohol during the previous year; those with diagnosis of diabetic neuropathy; those who had taken systemic medications during the last three months; and those who had used any anti-prostate drugs such as prazosin, terazosin or tamsulosin.

Participants with any of the following conditions, which may affect pupillary motility, were also excluded: iris and/or pupil anomalies such as coloboma, anisocoria, synechia and sphincter tear; pseudoexfoliation syndrome; glaucoma, head or orbital trauma; uveitis; ocular or orbital inflammation; a history of previous ocular surgery or laser treatment; a history of orbital surgery; topical medications that may affect iris mechanics such as tropicamide, cyclopentolate, pilocarpine and narcotic-derived medications; neurological disease or other diseases of the visual pathways; and those who were not cooperative enough to undergo pupillometry examinations.

To grade lens opacities of the participants, we used the Lens Opacities Classification System III (LOCS III). We excluded participants who had cataracts graded greater than two on the LOCS III.

All participants underwent a comprehensive ophthalmic examination including BCVA testing using the Snellen chart at 6 m, gonioscopy with a Goldmann three-mirror lens, intraocular pressure measurement using a pneumotonometer, slitlamp biomicroscopy, and dilated fundus examination. Participants with three mean consecutive intraocular pressure readings greater than or equal to 21 mmHg were also tested with a Goldmann applanation tonometer (Haag–Streit, Bern, Switzerland).

Refraction measurements were performed on all participants using the same automatic refractor-keratometer device (Canon RF-K2 Full Auto Ref-Keratometer, Tokyo, Japan). Red–green colour deficiency was assessed using Ishihara cards. Eye movements in all aspects of view were evaluated. The clinical swinging-flashlight test was undertaken to determine afferent pupillary defects.

A single clinician performed pupillometry measurements using the same automatic quantitative pupillometry system (MonPack One, Vision Monitor System, Metrovision, Pérenchies, France) (Figure 1A). This system was equipped with near infrared illumination and a high-resolution camera (880 nm) that allowed the clinician to take measurements from binocular pupils under complete darkness and to provide precise control of stimulation parameters. The stimulus was white, obtained from a full-field backlight combining red (632 nm), green (523 nm) and blue (465 nm) light-emitting diode sources.

This pupillometry system allowed the clinician to take both static and dynamic pupillometry measurements and to perform accurate measurements of pupil size (accuracy = 0.1 mm).[8,30] The clinician performed three consecutive measurements for each participant and average values were selected for data analysis. Additionally, the clinician used the automatic-release mode of the device to minimise examiner-induced errors, and only the images with high quality were included in the study.

To minimise the effect of circadian variation on pupillary response[31] the clinician performed all pupillary measurements at the same time of day (between 10:00 and 12:00 hours) and in the same environmental conditions. To control fixation stability during pupil recording, we required participants to fixate on a target in the centre of the test field while stimuli were presented (Figure 1A). Furthermore, pupil recordings in the study analysis were only used if eye movements were within five degrees of the central fixation axis of the optical system and infrared camera plane.

During measurement, pupil contours of the participants were outlined on the image to allow us to control measurement accuracy and proprietary analysis. We used the proprietary analysis software of the device to conduct automatic static and dynamic pupillometry. This software automatically outlined the pupillary contours of the participants on the images, ensuring that measurements were accurate and taken under controlled lighting conditions (Figure 1B). Subsequently, the software performed an analysis of temporal and average response to successive visual stimuli with automated quantification of the following parameters: latency and duration of contraction and dilatation (ms); initial, minimum, maximum and mean PD (mm); amplitude of contraction (mm); and contraction and dilatation speed (velocity) of the pupil (mm/s) (Figure 1B).

Static pupillometry measurements were obtained under several illumination levels to measure pupil size in scotopic (0.1 cd/m^2), mesopic (1 cd/m^2), low photopic (10 cd/m^2), and high photopic (100 cd/m^2) vision conditions. Scotopic PD, mesopic PD, low photopic PD and high photopic PD values were recorded. In darkness, after five minutes of darkness adaptation, dynamic pupillometry measurements were obtained for a duration of 90 seconds. Participants were examined using white light flashes (stimulation ON time 200 ms, stimulation OFF time 3,300 ms; total luminance 100 cd/m^2; total intensity 20 lux). The images of both eyes were acquired and processed in real time

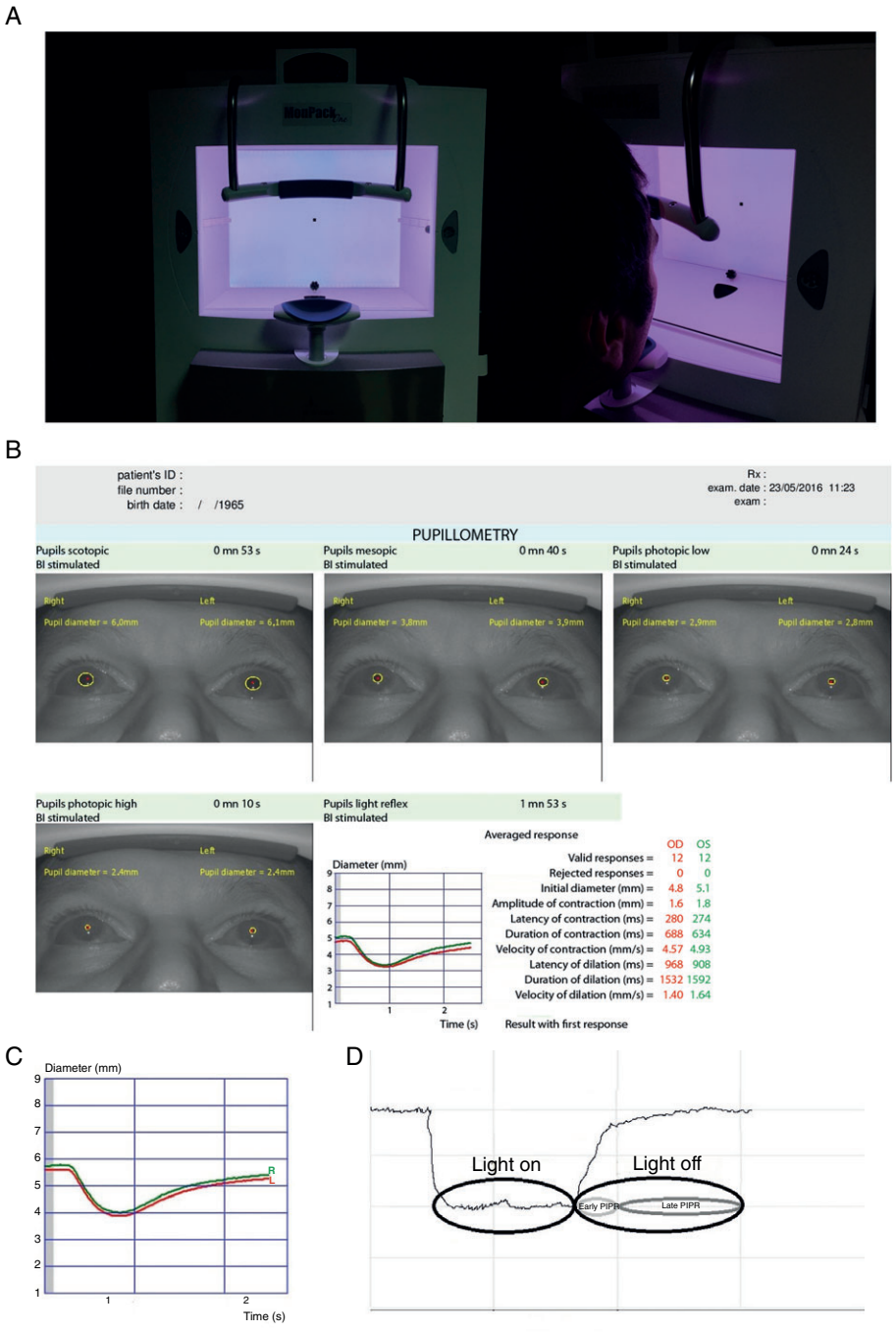

Figure 1. A: An image of the automatic quantitative pupillary measurement system (Vision Monitor System, Metrovision, France) is seen. B: An output of static and dynamic pupillary characteristics via the automatic quantitative pupillary measurement system (Vision Monitor System) is seen. C: A simultaneous measure of the pupil traces of each eye in a subject is seen. The R indicates the right eye, the L indicates the left eye. D: A diagram of the stimulus protocol and pupil response profile is seen. On the y-axis, the pupil size is expressed as normalised pupil diameter, and on the x-axis, the time is given in seconds. PIPR: post-illumination pupillary response.

(30 images per second) (Figure 1C). Luminance output was measured using a Minolta LS100 luminance meter.

The average response to successive visual stimuli (light flashes) was quantified using the following parameters: resting diameter, amplitude of pupil contraction, latency of pupil contraction, duration of pupil contraction, velocity of pupil contraction, latency of pupil dilation, duration of pupil dilation and velocity of pupil dilation. Figure 1D is a diagram of the stimulus protocol and pupil response profile in the pupillometry system used in this work. The baseline PD decreases with age[16,19,23,24] and it affects the pupil contraction amplitude such that a smaller amplitude is observed with a smaller baseline diameter.[23,24] To counteract this effect, PD was normalised during light stimulation and after light offset to baseline PD. The amplitudes of pupil contraction values are presented in percentage of the baseline PD.

Statistical analysis

The data obtained from the study were entered into the computer and analysed using the Statistical Package for Social Sciences (SPSS) version 22.0 for Windows (IBM, Armonk, New York, USA). Descriptive statistics were presented as mean ± standard deviations, frequency distributions and percentages. Pearson's chi-square test and one-sample chi-square test were used in the analysis of categorical variables. The normal distribution of the variables was tested using visual (histogram and probability graphs) and analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk tests). Independent sample t-test was used to compare quantitative data and chi-square analysis was used for qualitative data. The correlations between age and pupillometry measurements were investigated by using Pearson correlation tests. The statistical significance was set at $p < 0.05$.

Results

Of the total number of participants in the study, 69 (44.5 per cent) were male and 86 (55.5 per cent) were female with a mean age of 29.7 ± 17.8 years and a range of 6–64 years. The mean age difference between males and females was not statistically significant ($p = 0.147$).

For the purpose of comparison, participants were divided according to their age decade, and this resulted in seven subgroups

starting from the first decade. Table 1 shows static and dynamic pupillometry measurements of these subgroups. Additionally, participants were divided by gender, and there was no significant variation in static or dynamic pupillometry measurements between males and females in the study sample ($p > 0.05$).

As illustrated in Figures 2A–D, age was statistically significantly correlated with all static PDs including scotopic, mesopic, low photopic, and high photopic PDs ($p < 0.001$, for each). Resting diameter, velocity of pupil contraction, and velocity of pupil dilation were inversely and moderately correlated with age ($p < 0.001$, $r = -0.63$; $p < 0.001$, $r = -0.47$; and $p < 0.001$, $r = -0.34$, respectively). Latency of pupil contraction was positively and moderately correlated with age ($p = 0.002$, $r = 0.29$). Amplitude of pupil contraction, duration of pupil contraction, latency of pupil dilation and duration of pupil dilation were not statistically significantly correlated with age ($p = 0.242$, $r = -0.08$; $p = 0.056$, $r = -0.17$; $p = 0.859$, $r = -0.03$; and $p = 0.822$, $r = -0.02$, respectively, as shown in Table 2).

Discussion

In this study, static and dynamic pupillometry was conducted on a cohort that included 155 healthy participants of different age groups to determine normative values for pupillometry and the correlation between pupillometric characteristics and age. This population-based study evaluating both static and dynamic pupil characteristics obtained using an automatic quantitative pupillometry system (Vision Monitor System, Metrovision) in healthy, emmetropic participants and quantifying these parameters specifically as a function of age.

Researchers can use a pupillometry device to obtain automatic, multiple, quantitative measurements of pupillary response to light under controlled, ambient lightening conditions. This improves the repeatability of the measurements, solves the problem of examiner-dependent errors and reduces false negative responses.[26–28] Factors that influence pupil size include the level of retinal illumination, accommodative status, and various sensorial and emotional conditions.[16–18,23] Age is another important factor affecting pupil size.[19–24,32] Many studies reported that after the pupil reached a peak baseline size during the adolescent period, pupil size decreased linearly with increasing age in healthy participants.[22,32,33] In this study, all static PDs including the scotopic, mesopic and photopic PDs were largest in participants aged 11–20 years (the adolescent period) and decreased as age increased. Moreover, males and females were found to have similar PDs.

Similar to these results, Winn et al.[16] investigated the effect of age, gender, refractive error and iris colour on light-adapted pupil size in healthy participants and found that while pupil size decreased linearly as a function of age at all illumination levels, gender, refractive status and iris colour had no significant effect on pupil size. Netto et al.[34] confirmed that there was an inverse correlation between pupil size and age but no relationship with gender or refractive status. Furthermore, the present study found that older participants had smaller resting PDs than younger ones. Since pupillary resting diameter reflects the balance between opposing sympathetic and parasympathetic autonomic systems, the decrease in PD as age increased might have been related to either increasing parasympathetic effects or decreasing sympathetic input. Additionally, in a recent study, Schroder et al.[35] showed that this decrease in PD with age is largest for scotopic (≈0.057 mm/year) and smallest for photopic illumination (≈0.025 mm/year).

Pupillometric dynamics such as amplitude, latency, duration and velocity have been investigated in a variety of systemic and ocular diseases, including demyelinating diseases, Alzheimer's disease, Leber's hereditary optic neuropathy, amblyopia, glaucoma, diabetes mellitus and retinitis pigmentosa.[10–12,36–40] However, as the present study revealed, these dynamic pupil parameters are also affected by ageing. This could be a confounding factor in clinical studies, thus the effect of ageing on pupil dynamics should be well known. The present findings revealed that the velocity of pupil contraction and velocity of pupil dilation values are significantly and inversely correlated with age. Several studies showed that the pupillary dynamics are shown to slow down with ageing.[25,34]

Kasthurirangan and Glasser[41] studied the dynamic accommodative and pupillary responses to step stimuli in 66 human subjects (ages: 14–45 years) and demonstrated

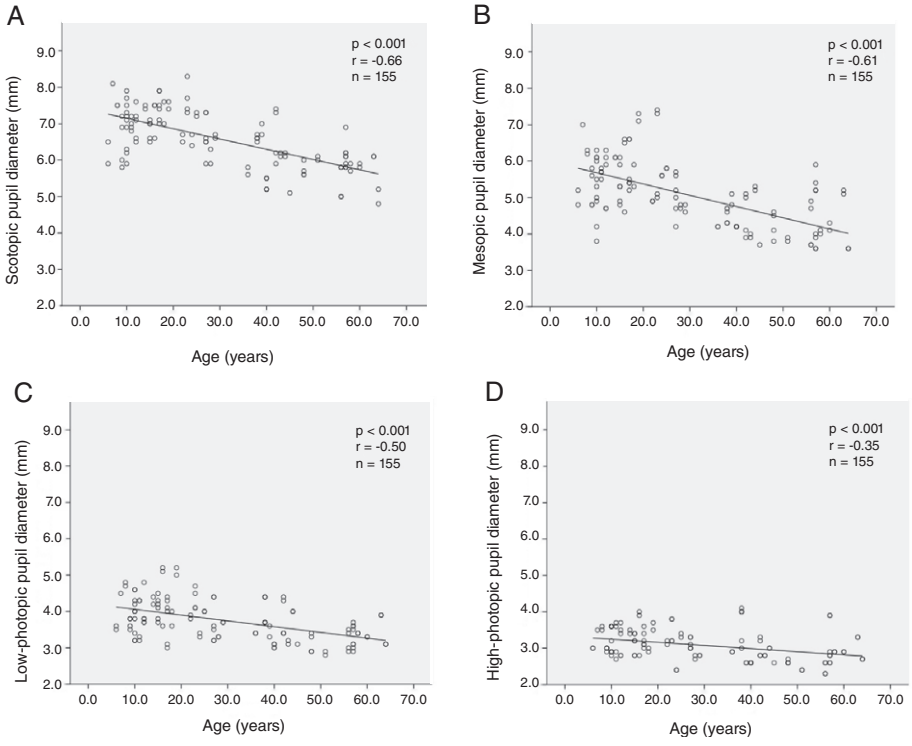

Figure 2. Scattering graphs showing the correlations of age with A: scotopic pupil diameter, B: the mesopic pupil diameter, C: the low-photopic pupil diameter and D: the high-photopic pupil diameter

Table 1. Static and dynamic pupillometry measurements of the study population in different age groups and in all participants

	0–10 years (n = 20) Mean ± SD	11–20 years (n = 30) Mean ± SD	21–30 years (n = 23) Mean ± SD	31–40 years (n = 22) Mean ± SD	41–50 years (n = 20) Mean ± SD	51–60 years (n = 20) Mean ± SD	61–70 years (n = 20) Mean ± SD	All participants (n = 155) Mean ± SD (range)
Scotopic PD (mm)	6.9 ± 0.7	7.2 ± 0.4	6.9 ± 0.6	5.9 ± 1.1	5.9 ± 0.9	5.8 ± 0.4	5.2 ± 0.7	6.6 ± 0.8 (4.8–8.3)
Mesopic PD (mm)	5.6 ± 0.8	5.9 ± 0.8	5.4 ± 0.7	4.4 ± 0.5	4.3 ± 0.6	4.3 ± 0.8	4.2 ± 0.8	5.0 ± 0.9 (3.6–7.4)
Low photopic PD (mm)	3.9 ± 0.5	4.1 ± 0.6	3.9 ± 0.4	3.5 ± 0.5	3.3 ± 0.6	3.3 ± 0.3	3.2 ± 0.6	3.7 ± 0.5 (2.8–5.2)
High photopic PD (mm)	3.1 ± 0.6	3.2 ± 0.8	3.0 ± 0.8	2.5 ± 1.1	2.3 ± 1.0	2.3 ± 1.1	2.3 ± 0.5	3.0 ± 0.7 (2.3–4.1)
Resting diameter (mm)	6.3 ± 0.6	6.5 ± 0.6	6.3 ± 0.6	5.2 ± 0.7	5.2 ± 0.8	5.2 ± 0.4	4.5 ± 0.7	5.8 ± 0.8 (4.1–7.7)
Amplitude of pupil contraction (% of baseline)	55.3 ± 6.7	57.1 ± 6.3	56.9 ± 7.0	56.1 ± 8.0	55.7 ± 6.9	54.7 ± 7.2	54.9 ± 6.2	55.8 ± 7.1 (50.2–60.5)
Latency of pupil contraction (ms)	261.6 ± 37.1	242.0 ± 48.3	239.0 ± 77.3	287.5 ± 26.7	263.6 ± 44.7	283.6 ± 23.2	284.5 ± 20.5	263.5 ± 38.6 (126–319)
Duration of pupil contraction (ms)	623.31 ± 67.8	590.8 ± 73.3	646.6 ± 90.0	550.7 ± 34.5	588.8 ± 62.5	596.3 ± 53.8	539.4 ± 36.1	596.4 ± 68.7 (458–770)
Velocity of pupil contraction (mm/s)	6.1 ± 0.6	6.2 ± 1.0	5.9 ± 1.0	5.8 ± 0.8	5.4 ± 0.6	5.3 ± 0.8	5.1 ± 0.7	5.8 ± 0.9 (4.1–7.9)
Latency of pupil dilation (ms)	873.3 ± 70.0	854.5 ± 77.3	886.3 ± 41.2	838.2 ± 45.0	852.4 ± 54.3	882.1 ± 62.1	825.4 ± 43.5	864.0 ± 63.1 (736–1,073)
Duration of pupil dilation (ms)	1,615.5 ± 66.2	1,606.6 ± 82.6	1,590.6 ± 61.4	1,615.6 ± 82.0	1,625.7 ± 83.1	1,595.3 ± 81.0	1,637.1 ± 74.2	1,607.6 ± 86.1 (1,136–1,764)
Velocity of pupil dilation (mm/s)	2.4 ± 1.1	2.4 ± 1.0	2.4 ± 0.8	1.9 ± 0.4	1.9 ± 0.3	1.9 ± 0.5	1.7 ± 0.3	2.1 ± 0.5 (1.36–3.84)

PD: pupil diameter, SD: standard deviation.

that the mean peak velocity of pupil constriction decreases significantly with age. The pupillary dynamics were also studied in guinea pigs, using a protocol that allows quantitative evaluation of the constriction and re-dilation response over time.[42] It was found that the constriction and re-dilation velocity significantly decrease in adult guinea pigs compared with juvenile ones.[42] On the other hand, Bremner[43] has investigated the correlations between the amplitude and peak velocity of constriction in the PLR of normal subjects to determine the effects of stimulus intensity, pupil size and age on this relationship. The results of the study revealed a strong linear correlation between the amplitude and peak velocity of constriction and this relationship is not affected by the stimulus intensity, size of the pupil or age of the subject.

The present study also showed that amplitude of pupil contraction, duration of pupil contraction, latency of pupil dilation and duration of pupil dilation were not statistically significantly correlated with age. Researchers have proposed that the reduction in light-stimulated pupil size with age is related to the decrease in resting diameter, which is due to iris atrophy and impaired sympathetic nerve supply to the iris that occurs with age.[1–3] However, the present results showed that when normalised to baseline PD, there was no significant effect of ageing on the amplitude of pupil contraction. Several studies also showed that amplitude of pupil constriction is independent of age.[23,24] Straub et al.[44] examined 103 healthy participants using modified infrared television pupillometry and found that maximal pupillary diameter, latency of light reflex, contraction and dilatation velocity are strongly age dependent. Further, Fotiou et al.[21] measured the pupillary dynamics of 100 healthy participants by dividing them into two groups according to age: Group 1 was 18–50 years of age and Group 2 was 51–81 years of age. They used a fast-video pupillometry device and revealed that while latency of pupil reaction is not affected by age, baseline pupil radius, maximum contraction velocity, maximum contraction acceleration and amplitude were significantly smaller in Group 2.

This population-based study showed findings that are important within the literature because a large number of participants were included. Further, this study investigated both static and dynamic pupillary characteristics using an automatic

Dynamic pupilometry characteristics	Age	
	p	r
Resting diameter (mm)	**< 0.001**	**−0.63**
Amplitude of pupil contraction (mm)	0.242	−0.08
Latency of pupil contraction (ms)	**0.002**	**0.29**
Duration of pupil contraction (ms)	0.056	−0.17
Velocity of pupil contraction (mm/s)	**< 0.001**	**−0.35**
Latency of pupil dilation (ms)	0.859	−0.03
Duration of pupil dilation (ms)	0.822	−0.02
Velocity of pupil dilation (mm/s)	**< 0.001**	**−0.34**

r: Pearson correlation co-efficient.
Bold values indicate statistically significant correlations.

Table 2. Correlations between the dynamic pupillometry characteristics and age in the study population

quantitative pupillometry system. On the other hand, this study had a number of limitations. For instance, only emmetropic healthy participants were included; thus, it is uncertain whether these findings are valid for ammetropic patients. As our pupillometry system included a fixation target in the centre of the test field, this would drive accommodation in those about 40 years and younger and bias the baseline PD toward the smaller side in all measurements. Another drawback of the study is that pupil recordings were only used if eye movements were within five degrees of the central fixation axis. A five degree fixation error may be significant, particularly in children. The recorded pupil size reduces when the fixation is eccentric, and this may be a confounding factor. Moreover, this study was performed cross-sectionally, so the generalisability of the present findings might be limited.

In conclusion, the current study offers population-specific normative data on static and dynamic pupillometry values in different age groups and shows the effect of age on pupillary characteristics. Further prospective, comprehensive, cohort studies including patients with different refractive errors are needed to confirm our findings.

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