Age-Related Change and Sex Difference over 60s in Disc-Fovea Angle in Japanese Population: The Nagahama Study

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ABSTRACT

Purpose:

To analyse the disc-fovea angle (DFA) by age group, and to compare sex differences in each age group in a large cohort population

Methods:

This community-based cross-sectional cohort study included 9,682 eyes of 9,682 volunteers (aged 30–75 years). We measured the DFA, which is the angle between a horizontal line and a line connecting the fovea with the centroid of an optic disc on fundus photographs of the right eye. We manually marked the fovea and surrounded the optic disc. The centroid of an optic disc and the DFA were automatically calculated using originally developed software. We compared the DFA between age groups in 10-year increments, and investigated sex differences of DFA in each age group.

Results:

Overall mean DFA was 6.32 ± 3.53°. The DFA of older subjects was significantly larger than that of younger subjects ($P < 0.001$). The DFA of women was larger than that of men in their 60s and 70s ($P < 0.001$ for both), but not in subjects in their 30s, 40s, and 50s.

Conclusions:

Larger DFA in women than in men in their 60s and 70s suggests the possibility that age-related excyclo-shift occurs more easily in postmenopausal women compared to men of the same age.

Key words:

disc-fovea angle, menopause, objective ocular torsion, sex difference, age-related change, Nagahama Study

INTRODUCTION

Disc-fovea angle (DFA), which is the angle between a horizontal line and a line connecting the fovea with the centroid of an optic disc, can be measured from fundus photography images. The angle is also called objective ocular torsion (Morton et al. 1983; Madigan & Katz 1992; Ehrt & Boergen 2001; Felius et al. 2009; Kushner & Hariharan 2009) as opposed to subjective ocular torsion, which can be measured using clinical instruments including the synoptophore, Maddox rod, and Harms' tangent scale (Schworm et al. 1995; Schworm et al. 1997; Sharma et al. 2008). Even a small change in ocular torsion is thought to affect slant perception as depth perception (Brodsky 2002; Miyata et al. 2005). Therefore, estimation of such a small change in ocular torsion is important to understand changes in visuospatial perception. The change in ocular torsion can be analysed objectively by measuring the change in DFA. Furthermore, the DFA is recently getting increasingly more attention for its role in adjusting the circumpapillary retinal nerve fibre layer thickness profile of optical coherence tomography, particularly for patients with glaucoma (Choi et al. 2014; Jonas et al. 2015; Mayama et al. 2015; Yamashita et al. 2015; Mwanza et al. 2016; Resch et al. 2016).

There are many diseases exhibiting ocular torsion, including superior oblique palsy and ocular tilt reaction. Recently, age-related orbital connective tissue attrition of the lateral rectus and superior rectus (LR-SR) band, which is associated with excyclo-shift, has been demonstrated using magnetic resonance imaging (MRI) (Kono et al. 2002; Demer 2008). The LR-SR band is composed of collagen, elastin, and smooth muscle (Demer et al. 1995). We speculated that estrogen and progesterone may play important roles for stabilizing the LR-SR band, and a decrease in their level may affect objective ocular torsion, particularly after menopause. Although the prevalence of strabismus in children aged 6 to 72 months is similar between boys and girls (Chia et al. 2010), sex differences in cyclovertical strabismus have not been studied in children, nor in adults.

To date, only the Beijing Eye Study has reported DFA data from a large cohort; the mean DFA of 3,052 Chinese volunteers (age range, 50–91 years) was $7.76 \pm 3.63°$ as measured using fundus photography, and multivariate analysis revealed a positive association between DFA and age (Jonas et al. 2015). However, the authors did not include subjects younger than 50 years, neither did they compare the DFA between age groups, or between men and women in each age group. Therefore, the purporse of this study was to analyse DFA by age group, and to investigate sex difference in each age group of a large cohort population with a wider age range.

METHODS

All protocols and informed consent procedures were approved by the ethics committee of Kyoto University Graduate School of Medicine and by the Nagahama Municipal Review Board. This study adhered to the tenets of the Declaration of Helsinki. The nature of the study and the possible consequences of participation were explained to all candidate subjects, and written informed consent was obtained from all participants.

The Nagahama Study Population

The individuals studied were apparently healthy Japanese volunteers enrolled in the Nagahama Prospective Cohort for Comprehensive Human Bioscience (the Nagahama Study). Participants in this cohort study were recruited between 2008 and 2010 from the general population of Nagahama City, a rural city of 125,000 inhabitants located in central Japan. Community residents from 30–74 years of age, living independently and without physical impairment or dysfunction were eligible to participate in the study. Of the 9,804 included participants, nine withdrew consent to participate, and 26 were excluded because genetic analysis showed that they had another ethnic background.

Subjects

All participants underwent a structured questionnaire, systemic examinations, and comprehensive eye examinations including refraction test using an automatic refractometer (Autorefractor ARK-530; Nidek Co. Ltd., Aichi, Japan), axial length (AL) measurement (IOL Master; Carl Zeiss AG, Oberkochen, Germany), and fundus photography using a digital retinal camera (CR-DG10; Canon Inc., Tokyo, Japan) in a darkened room. For fundus photography, the subject's head was placed carefully in a fixed position, as perpendicular as possible, which was achieved using a front headrest. The inclusion criterion in this study was the availability of fundus photography images. The exclusion criteria were non-analysable, low-quality fundus photography images due to miosis, cataract, asteroid hyalosis, or a dislocated fovea around the centre of the image; and severe macular haemorrhage, epiretinal membrane, or exudative lesions.

Analysis of DFA

We analysed the DFA as the angle between a horizontal line and a line connecting the fovea with the centroid of an optic disc on fundus photography according to the previous reports (Figure 1) (Choi et al. 2014; Jonas et al. 2015; Mayama et al. 2015; Yamashita et al. 2015; Mwanza et al. 2016; Resch et al. 2016). As a first step, we manually marked the fovea and surrounded the optic disc. As a second step, the centroid of an optic disc and the DFA were automatically calculated originally using developed software. If the fovea was located below the horizontal line crossing the centroid of the optic disc, the value was noted as positive, while if the fovea was located above the line, the value was noted as negative. We analysed the results by age group in 10-year increments.

Statistical Analysis

Data are presented as means ± standard deviations where applicable. All statistical analyses were performed using SPSS (Version 21; IBM, New York, USA). We examined the distribution of DFA using the Kolmogorov–Smirnov (KS) test. Comparisons of differences in DFA between the two sexes in each age group were performed using the *t*-test. One-way analysis of variance (ANOVA) was performed to compare DFA among each age group, and post-hoc comparisons were made using Tukey's honestly significant difference test or Games–Howell test according to the results of Levene's test. A P-value of < 0.05 was considered statistically significant. As the KS test is oversensitive (Parikh et al. 1999; Lampariello 2000), a cut-off P-value of < 0.01 was applied for this test.

RESULTS

We included 9,769 right eyes of 9,769 Japanese volunteers (6,560 women and 3,209 men). Exclusion criteria were met in 87 eyes. A total of 9,682 eyes of 9,682 volunteers were analysed (6,505 women and 3,177 men). Mean age was 55.57 ± 13.41 years (range, 30–75 years), and axial length (n = 9,662) was 24.06 ± 1.41 mm (range, 16.47–33.28 mm).

Analysis of DFA

Table 1 shows DFA values according to age and sex. In total, DFA was 6.32 ± 3.53° (range, -9.66°– 24.68°). DFA was normally distributed in each age group ($P = 0.090$, 0.93, 0.08, 0.36, and 0.53, respectively; Kolmogorov–Smirnov test) and in the overall population ($P = 0.028$, Figure 2). The DFA increased with age from 5.76 ± 3.35 in the 30s group to 6.90 ± 3.82 in the 70s group (Table 1). There were significant differences of the DFA among each age group ($P < 0.001$; one-way ANOVA).Post-hoc comparisons among each age group confirmed the significant differences among most age groups (30s vs. 50s, 30s vs. 60s, 30s vs. 70s, 40s vs. 50s, 40s vs. 60s, and 40s vs. 70s: $P < 0.001$; 30s vs. 40s: $P = 0.24$; 50s vs. 60s: $P = 0.99$; 50s vs. 70s: $P = 0.06$; and 60s vs. 70s: $P = 0.10$; Games–Howell test).

The DFA was significantly greater in women than in men (6.42 ± 3.59° and 6.10 ± 3.39°, respectively, $P < 0.001$). The subsequent age group analysis revealed that the DFA was not significantly different between women and men in their 30s, 40s, and 50s ($P = 0.13$, 0.11, and 0.051, respectively), while there were significant differences in the DFA in the 60s and 70s age groups (Figure 3, $P < 0.001$ for both).

DISCUSSION

The present study showed that there were no significant sex differences of DFA in subjects in their 30s, 40s, and 50s; however, there were significant sex differences of DFA in subjects in their 60s and 70s, when we separated the population into age groups using 10-year increments. The DFA increased in elderly women aged 60 years or older compared to men of the same age. Furthermore, the sex difference of the DFA in subjects in their 70s was larger than in subjects in their 60s. Although the mean menopausal age is reported to be 45.59 ± 5.59 (Ahuja 2016), actual menopausal effect on clinical features would be delayed and gradually increased. The menopause may affect the DFA about 10 years after its onset. The present study first suggested the probability of a sex difference after menopause in the ophthalmology field, although the differences of osteoporosis and osteoarthritis are known widely.

The increase in the DFA could be explained by three overlapping possibilities. The first possibility is the age-related attrition of orbital connective tissue (Kono et al. 2002; Demer 2008). The LR-SR band, which is composed of musculofibroelastic tissues (Demer et al. 1995), becomes more relaxed with age. Although the LR-SR band is equivalent to the medial rectus and superior rectus (MR-SR) band in thickness and collagen content, elastin content of the LR-SR band is about one fourth of that of the MR-SR band (Kono et al. 2002). Therefore, the LR-SR band is less stiff. Recently, the possibility of sagging eye syndrome has been propounded (Chaudhuri & Demer 2013), which is due to degeneration of the LR-SR band, which permits inferior sag of the LR pulley, thus causing excyclo-shift. Gradual age-related increase of the DFA is consistent with the gradual age-related attrition of orbital connective tissue. On MRI scanning with 2- to 3-mm sections, 12.5% of normal elderly orbits showed LR-SR band attrition including thinning, discontinuity, or displacement (Rutar & Demer 2009). The second possibility is the increasing incidence of acquired cyclovertical strabismus including idiopathic cyclovertical strabismus, traumatic and ischemic trochlear palsy, and ocular tilt reaction. Martinez-Thompson et al. reported the incidence and types of adult-onset strabismus in a geographically defined population (Martinez-Thompson et al. 2014). They showed that the total lifetime risk of being diagnosed with adult-onset strabismus was 4.0% in women and 3.9% in men. The incidences of paralytic, cyclovertical strabismus, and thyroid-associated ophthalmopathy were 44.2%, 13.3%, and 2.8%, respectively. Rowe et al. reported that the prevalence of trochlear palsy was 16% in ocular motor cranial nerve palsy (Rowe 2011). In total, risk ratios of idiopathic cyclovertical strabismus, trochlear palsy, and thyroid-associated ophthalmopathy were 0.53%, 0.28%, and 0.11%, respectively, which were low. According to the above rates, we consider that the former possibility of attrition of LR-SR band strongly affects the increase of the DFA. The third possibility is a slight overaction of the inferior rectus (IR) muscle. Guyton reported that prolonged use of the eyes in downgaze, especially in convergence, has an extorting effect on the IR muscles (Guyton 1994). Converging in down gaze may increase with age, and possibly more in women than in men.

One of the causes for the DFA increase in elderly women (≥60 years) compared to men of the same age may be the rapid decrease of female sex hormones, including progesterone and estrogen, after menopause. These hormones are important to maintain dermal collagen content (Kanda & Watanabe 2005). Progesterone suppresses the expression of matrix metalloproteinases (MMPs), which degrade fibroblast-derived extracellular matrix proteins including collagen and elastin (Saito et al. 2004), and stimulate the production of tissue inhibitor of metalloproteinase (TIMP), which inhibits MMP, in fibroblasts (Sato et al. 1991). Estrogen increases collagen content in the dermis and maintains skin thickness in postmenopausal women (Shah & Maibach 2001). Although a decrease of female sex hormones has not been proven to affect the collagen content in orbital tissue directly, particularly after menopause, collagen as the main component of the LR-SR band is speculated to be decreased due to age-related decrease of female sex hormones. The LR-SR band may be weaker in elderly women compared to men of the same age, and this might cause the DFA to be larger. Further basic study researching the correlation between the orbital connective tissue and female sex hormones is necessary.

There are two significant differences concerning the DFA betweenthe present study and the Beijing Eye Study, although the two studies used similar methods. First, in the Beijing Eye Study, the DFA was 7.76 ± 3.63° (Jonas et al. 2015), which was larger than that in the present study (6.32 ± 3.53°). Shin et al. reported that ocular torsion of normal children between 4 and 15 years was 5.13 ± 2.79° (Shin et al. 2013). Age was significantly correlated with the DFA both in the Beijing Eye Study and in the present study. Therefore, we considered that the difference of age (63.6 ± 9.3 years vs. 55.6 ± 13.4 years) might explain the differences of ocular torsion between the two studies. Second, the Beijing Eye Study showed no significant correlation between the

DFA and sex. In the present study, there was no difference in the DFA between the two sexes in the younger population, and the difference in ocular torsion between the two sexes was small in the overall population; however, a significant difference was observed only in older population. We consider that the cause might be the absence of investigation in each age generation in the Beijing Eye Study.

Guyton's grading system for objective ocular torsion based on fundus landmarks is the standard system in use at present (Guyton 2008). In this grading system, the normal range for the fovea is within the lower third of the optic disc. In the present study, a positive value was assigned for a subject with normal ocular torsion by Guyton's grading system because the ocular torsion measurements were simply obtained based on ruler measurements. Although definition of a zero-point objective ocular torsion as the average value for the subjects' age group may prevent confusion of this paradigm shift, we used DFA not to mislead readers in the present study, instead of objective ocular torsion.

This study had some limitations. First, we did not perform any strabismological examinations. Ocular torsion does not often occur alone but is complicated with vertical deviation. If strabismological examinations were undertaken, diseases inducing ocular extorsion such as superior oblique palsy, trochlear palsy, sagging eye syndrome, and ocular tilt reaction could have been identified. The results in the present study might include the above diseases. If larger ocular torsion such as trochlear palsy increased the average value, the sample would not show normal distribution. However, the sample in the present study showed normal distribution among each age group; therefore, we considered that these diseases did not affect the overall outcome. Second, DFA were measured for right eyes. A previous report using scanning laser ophthalmoscopy showed that when comparing right and left eyes of the same individual, there was higher concordance of the horizontal and vertical angular distance between the fovea and the centre of the optic disc in normal volunteers; i.e. there was no difference of the location of the fovea between the right and left eyes (Rohrschneider 2004). Furthermore, the head was carefully fixed so as not to be tilted when fundus photographs were taken, although compensatory torsional eye movement (counterroll) can reduce the effect of head tilt on DFA (Hamasaki et al. 2010; Lim et al. 2017). In the epidemiology field, one eye is often included per patient (de Jong et al. 2008; Tan et al. 2008; Kumagai et al. 2015), because presentation of data from both eyes is redundant and complicated statistically. We believe one-eye data are sufficient to evaluate the DFA. Fourth, we analysed only Japanese subjects. Further studies including other races to investigate possible ethnic differences are necessary.

In conclusion, we present the mean DFA by age group in a Japanese population. The angle was larger in older subjects than in younger ones. The DFA was significantly larger in women than in men in their 60s and 70s, but not in their 30s, 40s, and 50s. These results suggest the possibility that age-related excyclo-shift occurs more easily in postmenopausal women compared to men of the same age. This is the first report to show a sex difference after menopause in the ophthalmology field.

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REFERENCES

Ahuja M (2016): Age of menopause and determinants of menopause age: A PAN India survey by IMS. J Midlife Health **7**: 126-131.

Brodsky MC (2002): Do you really need your oblique muscles? Adaptations and exaptations. Arch. Ophthalmol. **120**: 820-828.

Chaudhuri Z & JL Demer (2013): Sagging eye syndrome: Connective tissue involution as a cause of horizontal and vertical strabismus in older patients. JAMA Ophthalmology **131**: 619-625.

Chia A, M Dirani, YH Chan, et al. (2010): Prevalence of amblyopia and strabismus in young singaporean chinese children. Invest. Ophthalmol. Vis. Sci. **51**: 3411-3417.

Choi JA, J-S Kim, H-YL Park, H Park & CK Park (2014): The Foveal Position Relative to the Optic Disc and the Retinal Nerve Fiber Layer Thickness Profile in Myopia. Invest. Ophthalmol. Vis. Sci. **55**: 1419-1426.

de Jong FJ, MW Vernooij, MK Ikram, et al. (2008): Arteriolar oxygen saturation, cerebral blood flow, and retinal vessel diameters. The Rotterdam Study. Ophthalmology **115**: 887-892.

Demer JL (2008): More respect for connective tissues. J. AAPOS **12**: 5-6.

Demer JL, JM Miller, V Poukens, HV Vinters & BJ Glasgow (1995): Evidence for fibromuscular pulleys of the recti extraocular muscles. Invest. Ophthalmol. Vis. Sci. **36**: 1125-1136.

Ehrt O & KP Boergen (2001): Scanning laser ophthalmoscope fundus cyclometry in near-natural viewing conditions. Graefes Arch. Clin. Exp. Ophthalmol. **239**: 678-682.

Felius J, KG Locke, MA Hussein, DR Stager, Jr. & DR Stager, Sr. (2009): Photographic assessment of changes in torsional strabismus. J. AAPOS **13**: 593-595.

Guyton DL (1994): Sensory torsion as the cause of primary oblique muscle overaction/underaction and Aand V patterns. Binocul Vision Eye Muscle Surg Quart **9**: 211-235.

Guyton DL (2008): Ocular Torsion Reveals the Mechanisms of Cyclovertical Strabismus The Weisenfeld Lecture. Invest. Ophthalmol. Vis. Sci. **49**: 847-857.

Hamasaki I, S Hasebe, T Furuse & H Ohtsuki (2010): Relationship between Static Ocular Counterroll and Bielschowsky Head Tilt Phenomenon. Invest. Ophthalmol. Vis. Sci. **51**: 201-206.

Jonas RA, YX Wang, H Yang, JJ Li, L Xu, S Panda-Jonas & JB Jonas (2015): Optic Disc - Fovea Angle: The Beijing Eye Study 2011. PLoS One **10**: e0141771.

Kanda N & S Watanabe (2005): Regulatory roles of sex hormones in cutaneous

biology and immunology. J. Dermatol. Sci. **38**: 1-7.
Kono R, V Poukens & JL Demer (2002): Quantitative Analysis of the Structure of the Human Extraocular Muscle Pulley System. Invest. Ophthalmol. Vis. Sci. **43**: 2923-2932.
Kumagai K, Y Tabara, K Yamashiro, et al. (2015): Central blood pressure relates more strongly to retinal arteriolar narrowing than brachial blood pressure: the Nagahama Study. J. Hypertens. **33**: 323-329.
Kushner BJ & L Hariharan (2009): Observations about objective and subjective ocular torsion. Ophthalmology **116**: 2001-2010.
Lampariello F (2000): On the use of the Kolmogorov-Smirnov statistical test for immunofluorescence histogram comparison. Cytometry **39**: 179-188.
Lim HW, JH Kim, SH Park & SY Oh (2017): Clinical measurement of compensatory torsional eye movement during head tilt. Acta Ophthalmol **95**: e101-e106.
Madigan WP, Jr. & NN Katz (1992): Ocular torsion-direct measurement with indirect ophthalmoscope and protractor. J. Pediatr. Ophthalmol. Strabismus **29**: 171-174.
Martinez-Thompson JM, NN Diehl, JM Holmes & BG Mohney (2014): Incidence, Types, and Lifetime Risk of Adult-Onset Strabismus. Ophthalmology **121**: 877-882.
Mayama C, H Saito, H Hirasawa, et al. (2015): Diagnosis of Early-Stage Glaucoma by Grid-Wise Macular Inner Retinal Layer Thickness Measurement and Effect of Compensation of Disc-Fovea Inclination. Invest. Ophthalmol. Vis. Sci. **56**: 5681-5690.
Miyata M, S Hasebe, H Ohtsuki & M Sato (2005): Assessment of cyclodisparity-induced slant perception with a synoptophore. Jpn. J. Ophthalmol. **49**: 137-142.
Morton GV, N Lucchese & BJ Kushner (1983): The role of funduscopy and fundus photography in strabismus diagnosis. Ophthalmology **90**: 1186-1191.
Mwanza J-C, G Lee & DL Budenz (2016): Effect of Adjusting Retinal Nerve Fiber Layer Profile to Fovea-Disc Angle Axis on the Thickness and Glaucoma Diagnostic Performance. Am. J. Ophthalmol. **161**: 12-21.e12.
Parikh HH, WC Li & M Ramanathan (1999): Evaluation of an alternative to the Kolmogorov-Smirnov test for flow cytometric histogram comparisons. J. Immunol. Methods **229**: 97-105.
Resch H, I Pereira, J Hienert, S Weber, S Holzer, B Kiss, G Fischer & C Vass (2016): Influence of disc-fovea angle and retinal blood vessels on interindividual variability of circumpapillary retinal nerve fibre layer. Br. J. Ophthalmol. **100**: 531-536.

Rohrschneider K (2004): Determination of the Location of the Fovea on the Fundus. Invest. Ophthalmol. Vis. Sci. **45**: 3257-3258.

Rowe F (2011): Prevalence of ocular motor cranial nerve palsy and associations following stroke. Eye **25**: 881-887.

Rutar T & JL Demer (2009): "Heavy Eye" syndrome in the absence of high myopia: A connective tissue degeneration in elderly strabismic patients. J. AAPOS **13**: 36-44.

Saito T, H Mizumoto, R Tanaka, S Satohisa, K Adachi, M Horie & R Kudo (2004): Overexpressed progesterone receptor form B inhibit invasive activity suppressing matrix metalloproteinases in endometrial carcinoma cells. Cancer Lett. **209**: 237-243.

Sato T, A Ito, Y Mori, K Yamashita, T Hayakawa & H Nagase (1991): Hormonal regulation of collagenolysis in uterine cervical fibroblasts. Modulation of synthesis of procollagenase, prostromelysin and tissue inhibitor of metalloproteinases (TIMP) by progesterone and oestradiol-17 beta. Biochem. J. **275 (Pt 3)**: 645-650.

Schworm HD, KP Boergen & S Eithoff (1995): Measurement of subjective and objective cyclodeviation in oblique eye muscle disorders. Strabismus **3**: 115-122.

Schworm HD, S Eithoff, M Schaumberger & KP Boergen (1997): Investigations on subjective and objective cyclorotatory changes after inferior oblique muscle recession. Invest. Ophthalmol. Vis. Sci. **38**: 405-412.

Shah MG & HI Maibach (2001): Estrogen and skin. An overview. Am J Clin Dermatol **2**: 143-150.

Sharma P, S Thanikachalam, S Kedar & R Bhola (2008): Evaluation of subjective and objective cyclodeviation following oblique muscle weakening procedures. Indian J. Ophthalmol. **56**: 39-43.

Shin KH, HJ Lee & HT Lim (2013): Ocular torsion among patients with intermittent exotropia: relationships with disease severity factors. Am. J. Ophthalmol. **155**: 177-182.

Tan AG, P Mitchell, G Burlutsky, E Rochtchina, G Kanthan, FM Islam & JJ Wang (2008): Retinal vessel caliber and the long-term incidence of age-related cataract: the Blue Mountains Eye Study. Ophthalmology **115**: 1693-1698, 1698 e1691.

Yamashita T, T Sakamoto, H Terasaki, M Tanaka, Y Kii, E Uchino, T Hisatomi & K Nakao (2015): Association of retinal thickness and optic disc-to-fovea angle to axial length of young healthy eyes. Clin Ophthalmol **9**: 2235-2241.

FIGURE LEGENDS

Figure 1. Representative post-assessment fundus photography images.
We analysed the disc-fovea angle (DFA), which is the angle between a horizontal line and a line connecting the fovea with the centroid of an optic disc on fundus photography. If the fovea was located below the horizontal line crossing the centroid of the optic disc, the value was noted as positive, while if the fovea was located above the line, the value was noted as negative. (A) Representative images of a subject with DFA of 6.90°. (B) Representative images of a subject with DFA of 22.29°. (C) Representative images of a subject with DFA of -8.13°.

Figure 2. Histograms of distribution of disc-fovea angle.
Disc-fovea angle (DFA) was normally distributed in each age group and in the overall population. Distribution of DFA in the overall population (n = 9,682; A) and in subjects in their 30s (n = 2,318; B), 40s (n = 1,356; C), 50s (n = 1,881; D), 60s (n = 3,072; E), and 70s (n = 1,055; F).

Figure 3. Mean sex differences of disc-fovea angle among each age group.
There were significant differences in disc-fovea angle between male and female subjects in their 60s and 70s, but not between male and female subjects in their 30s, 40s, and 50s. Error bars are two-sided 95% confidence intervals.

Table1. Disc-Fovea Angle According to Age and Sex

Age range (years)	Total	Male	Female	*P*
30–39				
Mean (°)	5.76 ± 3.35	5.59 ± 3.34	5.82 ± 3.35	0.125
Range (°)	-8.13 to 20.68	-8.13 to 20.68	-5.20 to 18.54	
n, eyes	2,318	668	1,650	
40–49				
Mean (°)	6.00 ± 3.44	5.85 ± 3.19	6.05 ± 3.54	0.112
Range (°)	-6.97 to 16.26	-3.47 to 14.57	-6.97 to 16.26	
n, eyes	1,356	379	977	
50–59				
Mean (°)	6.51 ± 3.60	6.25 ± 3.40	6.61 ± 3.66	0.051
Range (°)	-9.66 to 24.68	-4.18 to 19.51	-9.66 to 24.68	
n, eyes	1,881	477	1,404	
60–69				
Mean (°)	6.57 ± 3.48	6.29 ± 3.40	6.74 ± 3.53	< 0.001*
Range(°)	-7.81 to 22.29	-4.52 to 19.75	-7.81 to 22.29	
n, eyes	3,072	1,185	1,887	
70–75				
Mean (°)	6.90 ± 3.82	6.40 ± 3.51	7.29 ± 4.01	< 0.001*
Range (°)	-6.53 to 24.08	-6.53 to 18.35	-5.71 to 24.08	
n, eyes	1,055	468	587	
Total				
Mean (°)	6.32 ± 3.53	6.10 ± 3.39	6.42 ± 3.59	< 0.001*
Range (°)	-9.66 to 24.68	-8.13 to 20.68	-9.66 to 24.68	
n, eyes	9,682	3,177	6,505	

Data are presented as mean ± standard deviation where applicable.
+; excyclo-direction, -; incyclo-direction
*; statistical significance ($P < 0.05$, *t*-test)

Figure 1

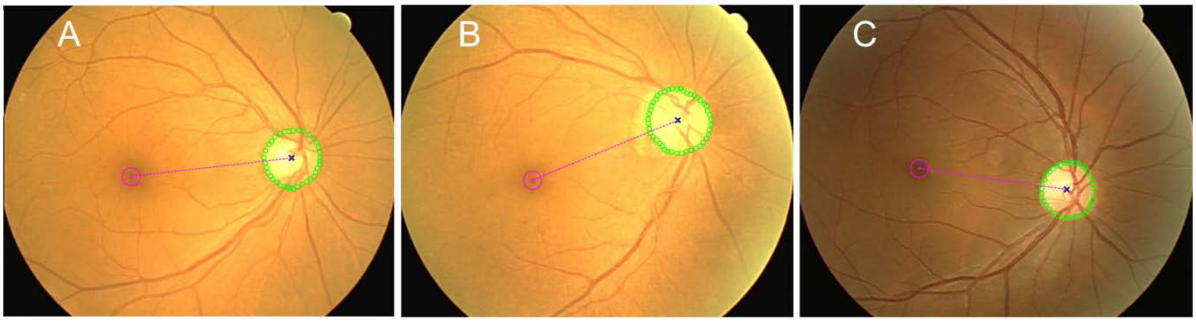


Figure 2

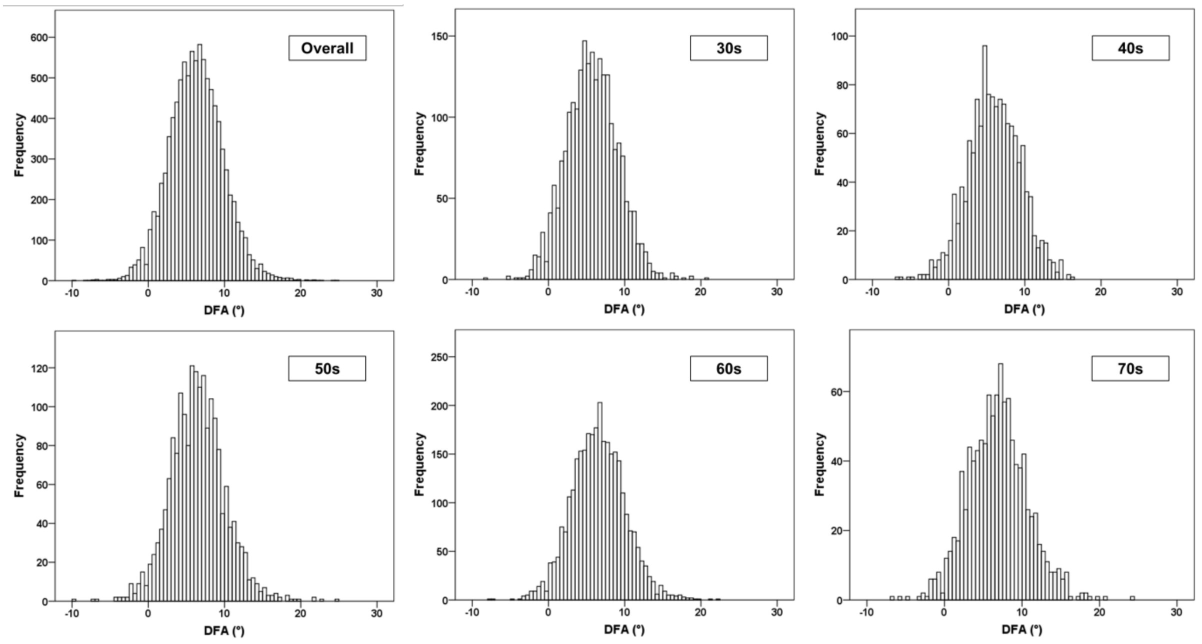
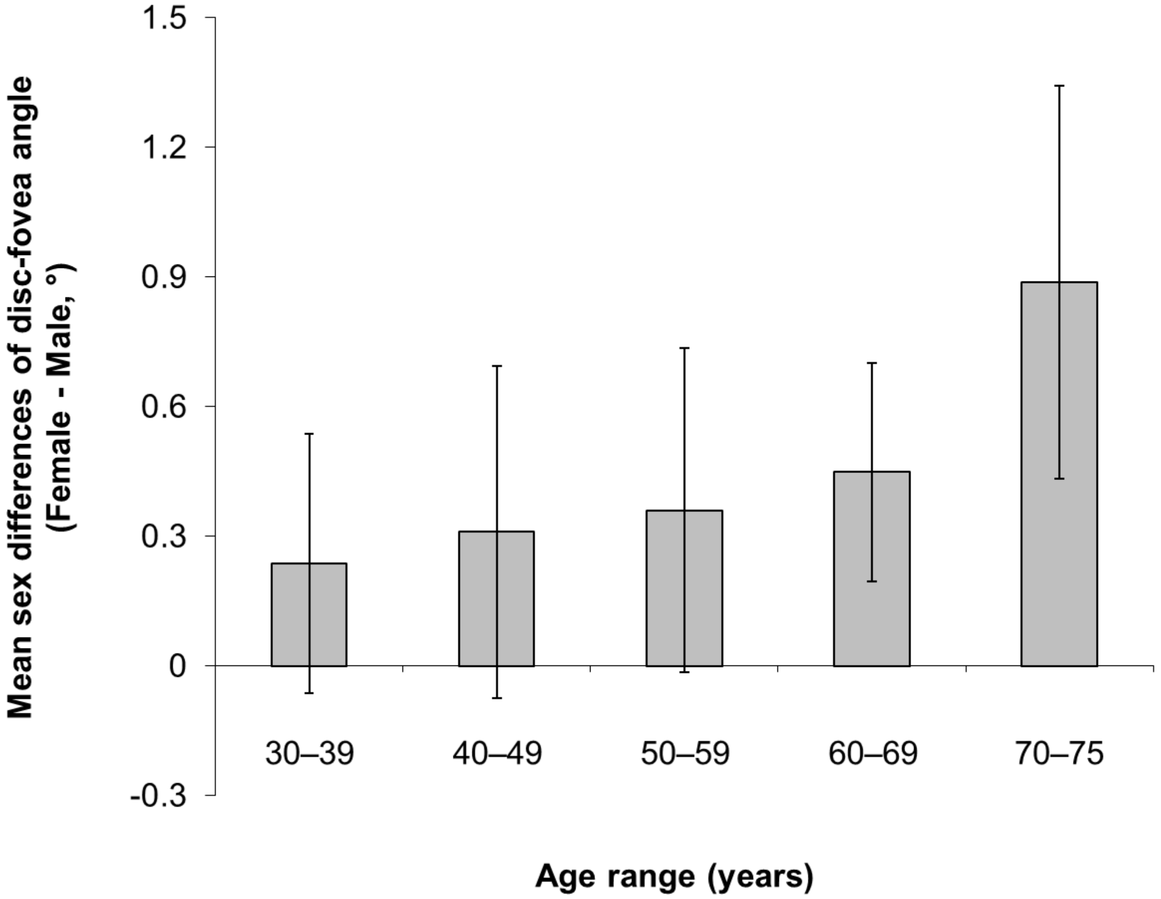


Figure 3


1.5
1.2
0.9
0.6
0.3
0
-0.3
Mean sex differences of disc-fovea angle (Female - Male, °)
30–39
40–49
50–59
60–69
70–75
Age range (years)