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ORIGINAL RESEARCH

Presbyopia, Dry Eye, and Retinal Thickness in the Middle-Aged Population: Focusing on Sex Differences

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Purpose: Risk factors for presbyopia have not been fully determined although previous studies suggested presbyopia was associate with age, dry eye, and retinal ganglion cell complex thickness (GCC). We accessed these signs and common ocular symptoms in the middle-aged population focusing on sex differences when women have drastic hormonal change.

Methods: This cohort study consecutively enrolled 2743 patients aged 36–45 years (n=1000), 46–55 years (n=1000), and 56–65 years (n=743). All underwent ocular surface tests and had near add power and GCC measured. Common ocular symptoms were asked using questionnaire.

Results: Among female participants, visual symptoms (eye strain and photophobia) were more prevalent in the age group 46–55, whereas non-visual symptoms (dryness, irritation, and pain) were not. We identified symptomatic presbyopia (near add power ≥ 1.5D) in 14.4%, 73.8%, and 97.8%, positive corneal staining in 29.1%, 23.8%, and 23.9%, and a mean GCC of 98.2 μm, 105.3 μm, and 89.6 μm in the age groups 36–45, 46–55, and 56–65, respectively. Mean tear break-up time were 3.3, 3.5, and 3.3 seconds, respectively. Results indicated a large progression of presbyopia ($P<0.01$) from the period of 36–45 years onward and significantly increased GCC ($P<0.01$) in women of age group 46–55. No notable tendency was observed in symptoms and GCC for male participants.

Conclusion: Visual symptoms in women were worse between 46 and 55 years than before or after these ages. The increase of symptomatic presbyopia and GCC may be contributing to visual symptoms in addition to menopausal transition symptoms in this age group.

Keywords: presbyopia, sex difference, near add power, menopause, eye strain

Introduction

Many middle-aged women may suffer ocular symptoms of early presbyopia and dry eye (DE) which are common age-related ocular disorders. Presbyopia is a natural aging process in the lens and other accommodation-related tissues. Presbyopia is characterized by the gradual loss of the ability to focus on nearby objects and usually becomes noticeable in the 40s.[1–3] Symptoms of presbyopia include blurred vision, difficulty reading small print, and eye strain. Aging is a well-known risk factor for presbyopia,[1,2] and, within similar age groups, dry eye (DE),[4,5] glaucoma medication,[6,7] and thinning of retinal ganglion cell complex (GCC)[6,7] have been also suggested as risk factors. However, clinical factors for presbyopia progression have not been fully determined.

DE is a multifactorial ocular surface disorder presenting with tear deficiency, poor quality tears, and decreased function of corneal and conjunctival epithelium.[8] Symptoms of DE include dryness, blurred vision, eye strain, irritation, pain, and photophobia. Among common ocular problems in middle-aged individuals, visual problems due to DE may appear, which are more prevalent in women and worsen during the menopausal period.[9,10] DE is an aging disease[11] and the symptoms of DE can be relieved by using topical medications.

Menopause is a natural biological process that marks the end of menstrual cycles. After 12 months without a menstrual period, menopause is confirmed. Women usually enter menopause in their 40's or 50's, and the average age of confirmation is 49.5 years in Japan and 51 years in the United States.[12,13] The common physical symptoms of

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menopause are sleep disorders, hot flashes, and mood changes resulting in lower energy or worse emotional health.[1,2] The ocular status during menopause has been investigated in several studies, including intra-ocular pressure (IOP) and corneal thickness,[14] DE,[15] age-related macular degeneration, cataract, and diabetic retinopathy.[16] In particular, the risk of glaucoma has been repeatedly documented in association with menopause.[17–19] Additionally, the condition of ocular surface and its symptoms change around the menopausal period[11] and many individuals with presbyopia may start using near eyeglasses in this crucial period.[20] However, no study has focused on sex differences in this particular period when presbyopia and common ocular symptoms usually develop and progress thereafter.

The aim of this study was to examine common visual symptoms, presbyopia, DE, and retinal thickness in the middle-aged population, as previous studies have reported associations between presbyopia, eye strain, and retinal thickness.[21,22] We recruited participants between 36 and 65 years and classified them into three groups: age group 36–45 to provide normative data for both sexes, age group 46–55 corresponding to the menopausal period for women, and age group 56–65 serving as a more advanced stage. We compared the prevalence of ocular symptoms and measured various parameters to explore the severity and age-dependency of ocular status across age groups.

Methods

Study Design and Participants

We conducted a clinic-based, retrospective, cross-sectional study involving healthy participants attending Tsukuba Central Hospital and Otake Eye Clinic from Oct 2015 to Sept 2023. The study was approved by the Institutional Review Board and Ethics Committee of the Tsukuba Central Hospital (approved on December 12, 2014, permission number 141201) and Kanagawa Medical Association (approved on November 12, 2018, permission number krec2059006). This study was carried out in accordance with the Declaration of Helsinki. Due to its retrospective nature, the Institutional Review Board and Ethics Committee approved an opt-out method instead of patients providing active consent. Additionally, the Institutional Review Board and Ethics Committee of Keio University School of Medicine approved this study (approval date: June 28, 2021; approval number 20210080) to permit authorship for authors (KN, AH and MA) appointed at the Keio University School of Medicine. The protocol was registered with the UMIN Clinical Trials Registry (UMIN000051891) on August 15, 2023. The data were accessed for research purposes from Oct 2023 to Dec 2023.

Inclusion and Exclusion Criteria

We included participants aged 36 to 65 years with bilateral phakic eyes and best-corrected visual acuity above 20/30. We excluded individuals with glaucoma, vitreoretinal disease, any ocular surgery in the previous month, or acute ocular disease in the previous two weeks. We also excluded patients with any ocular surface abnormalities such as abnormal tear film and corneal pathology.

Patient Interviews for Common Ocular Symptoms

Patients were asked about their experience regarding six common eye symptoms, namely dryness, irritation, and pain as non-visual symptoms, and eye strain, blurring and photophobia as visual symptoms. These questions were retrieved from the Dry Eye Questionnaire (DEQS)[23] and the six most prevalent symptoms reported by dry eye patients who had visited the Dry Eye Clinic in the Department of Ophthalmology at Keio University Hospital from January 1st, 2014, to December 31st, 2014.

Ophthalmological Examinations

All patients were examined by board-certified ophthalmologists. Ophthalmological evaluation consisted of best-corrected visual acuity (Vision Chart, SSC-370^{R}, Nidek Co., Ltd., Gamagori, Japan), autorefractometry (Tonoref^{TM} II, Nidek Co., Ltd., Aichi, Japan), slit-lamp biomicroscopy, funduscopy, and IOP measurements (Tonoref^{TM} II, Nidek Co., Ltd., Aichi, Japan). The examiner measured binocular near add power at a distance of 30 cm using a Bankoku near-acuity chart (Handaya Inc., Tokyo, Japan).[6] After determining the patient's refractive correction of distance vision, the examiner

measured the minimal additional power required to achieve near acuity above 20/25 at 30 cm in 0.25 D increments, and recorded it as near add power. The prevalence of symptomatic presbyopia (near add power≥1.50D) was calculated. Ocular surface examinations were performed according to standard procedures[24,25] and consisted of tear break-up time (BUT) and a corneal staining test. BUT was defined as the time taken for the first black spot to appear on the stained ocular surface after the last complete blink observed using cobalt-blue filter of the slit lamp. Three consecutive measurements were acquired and the mean value was calculated and recorded. A BUT measurement below or equal to five seconds was determined as a short BUT. Corneal staining was used to detect corneal epitheliopathy by grading the stain intensity one minute after administering fluorescein dye in the eye using the slit lamp's cobalt blue illumination and a yellow barrier filter. Diagnosed DE was determined according to the recently proposed criteria by the Asia Dry Eye Society,[8] whereby DE is defined as a multifactorial disease characterized by unstable tear film causing a variety of symptoms and/or visual impairment, potentially accompanied by ocular surface damage and the diagnostic criteria include instability of the tear film measured with BUT as well as the presence of subjective symptoms.

OCT (RS-3000, Nidek, Aichi, Japan) was used to measure macular retinal nerve fiber layer (mRNFL), ganglion cell layer (GCL) and inner plexiform layer (IPL) (GCL/IPL), mRNFL+GCL+IPL [ganglion cell complex (GCC)], and full macula thickness of the maps based on macular cube scans of a 6×6 mm square area centered on the fovea. For peripapillary RNFL imaging, raster scanning over a 6×6 mm^2 area centered on the optic disc center was conducted at a scan density of 512 A-scans (horizontal) × 128 B-scans (vertical). Peripapillary RNFL measurements were performed along a 3.45-mm diameter circle automatically positioned around the optic disc. The numbering of the 12 (30-degree size) RNFL sectors was initiated at the 1 o'clock position. The peripapillary protocol scan circle did not pass over any parapapillary atrophy in any case. OCT images were excluded if the image quality was <30.

Statistical Analysis

In order to compare both sexes at the same age, participants were divided into three age groups. We selected the central period as 46 to 55 years because most women experience menopause in this age range and the age group in this menopausal period was classified as age group 46–55[2]. Patients 45 years or younger were assigned to the age group 36–45 and patients 56 years or older were assigned to the age group 56–65.

The sample size was calculated with a 0.05 margin of error and 95% confidence interval. Effect size was derived from a measured value in the current study. Based on an effect size of 0.367 in GCC thickness, we determined an appropriate sample size of 161 with actual power of 0.950 for comparison of the female age groups 36–45 and 46–55.

Where appropriate, data are given as the mean ± SD. We analyzed the data from the right eye for BUT, corneal staining, IOP, and refraction. For OCT, the mean result of both eyes was analyzed. The signs and symptoms among age groups were compared using one-way analysis of variance (ANOVA) and the Mann Whitney *U*-test. A regression line for each age group was computed for age and near add power by the least-squares method. The difference in slope (rate of presbyopia progression) among three regression lines and standardized correlation coefficient were analyzed by a *t*-test. All statistical tests were two-sided, and the significance level was set to an α of 0.05 using StatFlex^R (Atech, Osaka, Japan).

Results

This study enrolled 2743 consecutive patients. Patient demographics are shown in Table 1. Refraction was significantly less myopic in the age group 56–65 than the other two groups in both sexes (Table 1) and astigmatic error increased with age in both sexes. The near add power and the prevalence of symptomatic presbyopia significantly increased across age groups. Results for women and men did not differ significantly except for the spherical equivalent in the age group 56–65.

The ocular surface did not worsen from the age group 36–45 to the age group 46–55 in women, whereas results in men worsened in an age-dependent fashion. All ocular surface parameters were worse in women than in men across all age groups. IOP decreased from the age group 36–45 to the age group 46–55 in women, whereas IOP did not change across men's age groups. There was no difference in IOP between women and men.

GCC was thickest in the 46–55 age group for women and the GCC of women was thicker than the men's in the 46–55 (P<0.01) and 56–65 age groups (P<0.05) (Figure 1). GCC thickness did not differ among men's age groups. RNFL

Table 1 Patient Demographics and Ophthalmological Parameters

Parameters and number of cases in age groups (n=2743)	Women				Men			
	36–45y (n=500)	46–55y (n=500)	56–65y (n=500)	*P*-value†	36–45y (n=500)	46–55y (n=500)	56–65y (n=243)	*P*-value†
Age, y	42.5 (2.0)	50.4 (2.9)	60.0 (2.8)	<0.01	41.1 (2.7)**	50.5 (2.8)	60.2 (2.9)	<0.01
Spherical equivalent, D (n=2681)	−3.76 (2.93)*	−3.74 (3.23)	−1.87 (3.05)*	<0.01	−3.97 (3.64)	−3.74 (3.36)	−2.52 (3.35)*	<0.01
Astigmatic errors, D (n=2681)	0.47 (0.61)	0.56 (0.55)	0.60 (0.41)	<0.01	0.57 (0.81)	0.65 (0.89)	0.68 (0.73)	0.14
Anisometropia, D (n=2681)	0.54 (0.64)	0.54 (0.64)	0.51 (0.72)	0.71	0.65 (1.19)	0.66 (0.96)	0.62 (0.95)	0.40
Near add power, D (n=2205)	0.65 (0.61)	1.73 (0.65)	2.57 (0.52)	<0.01	0.73 (0.61)	1.76 (0.60)	2.61 (0.43)	<0.01
Prevalence of symptomatic presbyopia[A], % (n=2205)	14.5	76.0	98.0	<0.01	15.3	79.3	98.8	
Ocular surface parameters and intra-ocular pressure								
Tear break-up time, s (n=2230)	3.3 (2.1)**	3.5 (2.0)**	3.0 (1.9)**	<0.01	4.7 (2.0)	4.5 (2.3)	4.4 (2.2)	<0.01
Corneal staining, % (n=2524)	29.3**	26.5**	29.7**	0.50	13.1	14.7	9.0	0.11
Diagnosed dry eye, % (n=2230)	54.8**	53.5**	59.6**	0.19	26.3	30.0	37.7	<0.05
Intra-ocular pressure, mmHg (n=2592)	15.0 (2.9)	14.2 (2.7)	14.9 (3.0)	<0.01	14.9 (3.4)	14.8 (3.0)	14.9 (3.3)	0.79
Retinal thickness								
Macular ganglion cell complex thickness, μm, mean (n=950)	98.2 (19.7)	105.6 (18.1)**	92.6 (14.7)*	<0.01	94.1 (15.8)	90.2 (23.9)**	88.8 (15.7)*	0.07
Superior	96.3 (18.1)	102.1 (17.8)	92.2 (14.6)	<0.01	94.3 (14.9)	89.4 (15.9)	89.1 (14.5)	0.02
Inferior	100.0 (22.9)	109.1 (20.9)**	93.3 (16.4)*	<0.01	93.8 (17.5)	91.9 (39.0)**	88.5 (17.9)*	0.16
Peripapillary retinal nerve fiber layer thickness, μm, mean (n=711)	120.9 (21.4)	116.7 (15.8)	120.4 (17.4)**	0.43	116.5 (18.3)	112.3 (19.8)	111.4 (19.2)	<0.05
Superior	119.7 (22.2)	114.8 (18.1)	117.1 (20.2)*	0.41	116.1 (18.9)	112.0 (20.2)	111.5 (19.7)*	0.13
Inferior	122.3 (24.3)	118.7 (16.9)	123.8 (20.3)**	0.29	117.0 (20.9)	112.8 (22.8)	111.3 (23.0)**	<0.05
Full retinal thickness of whole macula, μm (n=426)	262.3 (20.0)	259.4 (24.4)	252.9 (27.8)**	0.29	269.6 (35.1)	266.7 (27.5)	270.6 (25.0)**	0.40

Notes: Values are mean (standard deviation) unless indicated. * *P*<0.05, ** *P*<0.01, Women vs men, unpaired *t*-test or chi-squared test, as appropriate. †ANOVA or Mann-Whitney *U*-test as appropriate. [A](near add power ≥ 1.5D), 1= age group 36–45, 2= age group 46–55, 3= age group 56–65.

thickness did not differ among women's groups, whereas it decreased with age in men. The full retinal thickness of the whole macula decreased with age in both women and men without reaching statistical significance. GCC and RNFL thickness were generally thicker in women than men; in contrast, the full retinal thickness of the whole macula was higher in men than women, especially after 56 years of age ($P<0.01$).

The prevalence of visual symptoms in women peaked in age group 46–55; 46.2% experienced eye strain, 19.2% photophobia, and 29.1% blurring (Figure 2). Regarding non-visual symptoms, irritation was most prevalent in age group 56–65. In contrast, the prevalence of men's visual symptoms did not reach a peak in age group 46–55. Regarding men's non-visual symptoms, irritation was most prevalent in the older age group. Generally, all symptoms were more prevalent in women than men. The *P*-values for the multiple comparison test for the prevalence of symptoms in women and men

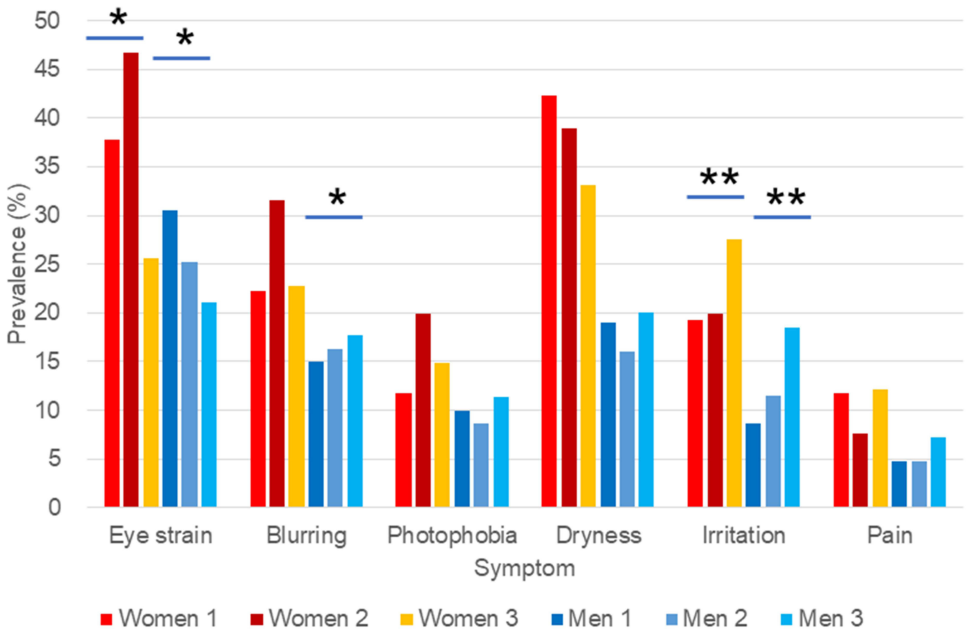

Figure 1 Retinal thickness in each age group and sex. Note greatest GCC thickness in the female age group 46–55 (**P<0.01, ANOVA) and age-dependent RNFL thickness in men's groups (*P<0.05, ANOVA). GCC= ganglion cell complex, NFL=nerve fiber layer, Full macula=full retinal thickness of whole macula. 1= age group 36–45, 2=age group 46–55, 3=age group 56–65.

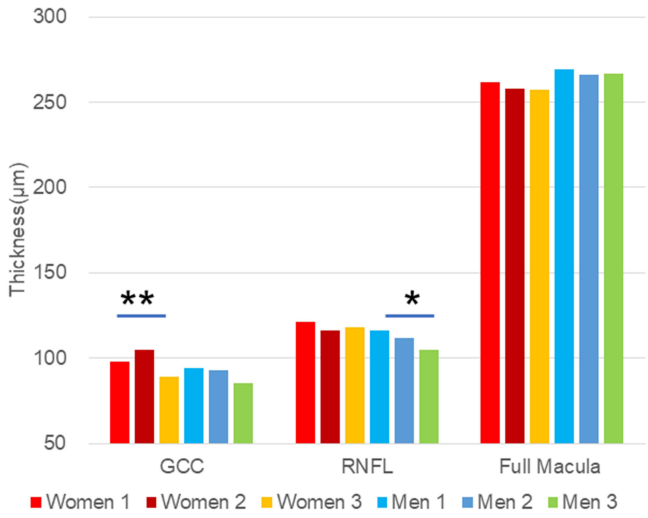

Figure 2 Prevalence of ocular symptoms in each age group and sex. Note the highest prevalence of visual symptoms (eye strain, blurring, and photophobia) in women of age group 46–55, whilst apparent age-dependency was found in men. Non-visual symptoms (dryness, irritation, and pain) were reported equally by women and men. *P<0.05, **P<0.01, Mann–Whitney U-test. 1= age group 36–45, 2=age group 46–55, 3=age group 56–65.

were 0.01 and 0.04 for eye strain, 0.29 and 0.76 for photophobia, 0.39 and 0.04 for blurring, 0.07 and 0.84 for dryness, <0.01 and <0.01 for irritation, and 0.37 and 0.37 for pain, respectively.

Regression analysis of age and near add power revealed that the mean progression rate of near add power (D/y) significantly increased from age group 46–55 to the older age group in both sexes (P<0.01, both groups; Table 2, Figure 3). The standardized correlation coefficient between age and near add power was greatest in the age group 46–55 in both sexes (P<0.01). There was no difference between women and men among the three groups in the progression rate of near add power and standardized correlation coefficient.

Table 2 Comparison of Parameters in Regression Lines with Near Add Power and Age

	Women			Men		
	36–45	46–55	56–65	36–45	46–55	56–65
Progression of presbyopia (D/y)	0.115	0.124	0.047††	0.101	0.114	0.050††
Standardized correlation coefficient between age group and near add power	0.372††	0.574	0.256††	0.323††	0.540	0.349††

Notes: ††P<0.01, vs age group 46–55, t-test. 1= age group 36–45, 2=age group 46–55, 3= age group 56–65.

Discussion

The current study revealed that women reported the highest prevalence of visual symptoms during the age of menopause, including eye strain, blurring, and photophobia, whereas non-visual symptoms, such as dryness, irritation, and pain, did not increase in women of the same age group. The present results suggest menopause-related ocular changes may predominantly involve visual function rather than non-visual sensations. It could be hypothesized that prevalent visual symptoms in menopausal women may be due to rapidly progressing presbyopia, thickening of GCC, and underlying DE. Of these, GCC and DE are etiologies more pronounced in women as indicated by the current study. Presbyopia is a serious burden in life and work that negatively influences quality of life.[26] The present results reveal that near add power progression was greatest and most age-dependent in women and men between 46 and 55 years, indicating that age was the largest factor to determine near add power in this age group, resulting in a rapidly increased prevalence of symptomatic presbyopia. Previous studies suggested that thickened GCC may be associated with eye strain.[21,22] In addition, another investigation described that glaucoma patients with thinning of the GCC have fewer ocular symptoms.[27] The synchronized peaking of both the prevalence of eye strain and GCC thickening in menopausal women could well fit with this hypothesis, although the association of thickened GCC with other visual symptoms, including blurred vision and photophobia, is still debatable Visual disturbance is a common problem in DE[28,29] due to an impaired functional visual acuity, irregular astigmatism, and higher-order aberration. DE should be a significant underlying factor for worsened visual symptoms in women, although the severity of non-visual parameters did not change noticeably between 36 and 65 years except for a worsening of BUT in women over 56 years of age.

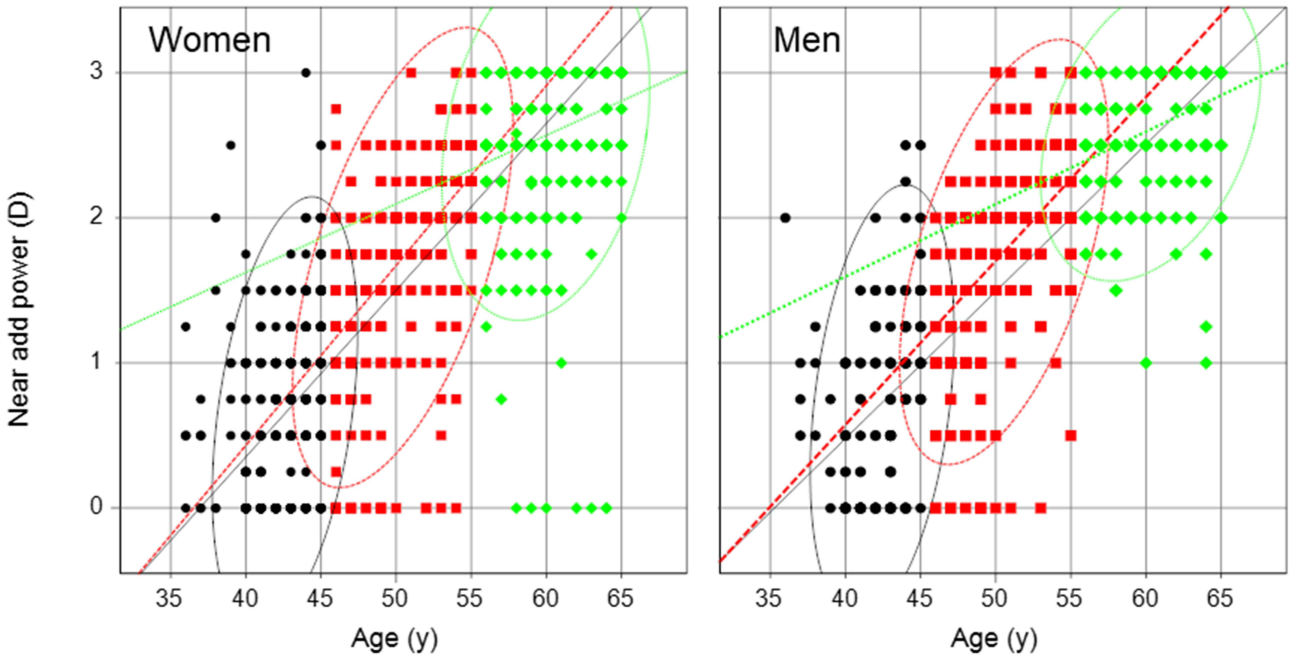

Figure 3 Scatter plots and regression lines with probability ellipses (confidence interval 95%) showing the age-related distribution of near add power in women and men. Note many plots are overlapped and small number appears in the graph. Black circles and line = age group 36–45, red squares and line = age group 46–55, green diamonds and line = age group 56–65y.

It has not previously been described that the GCC thickness in women increased in the menopausal period and decreased thereafter. Iron deficiency anemia (IDA) is a common comorbidity in women of reproductive age and often ameliorates after menopause. Several investigations have indicated that GCC and RNFL tend to thin in women with IDA and recovered with treatment.[30–32] Coskun et al compared retinal thickness between control and women with IDA and found the thicknesses of RNFL and GC-IPL were lower in the IDA group.[30] Çoban et al found a significant difference in OCT findings in choroidal and RNFL thicknesses before and after treatment of IDA, even though there was no difference in central macular thickness.[31] Cikmazkara et al compared female subjects with IDA and control subjects and found that RNFL thicknesses of the IDA group were reduced.[32] The authors also identified a positive correlation between mean NFL thickness and hemoglobin, iron, ferritin, and transferrin saturations. A Japanese survey[33] reported lifetime HRT was 13.6%, indicating hormone levels may be low in menopausal and postmenopausal Japanese women in this study. The decrease of estrogen levels may be apparently associated with a loss of neuroprotective effects; however, GCC thickness paradoxically increased during menopause as shown in the present study. Presumably, a recovery from iron deficiency may have positive effects on GCC that outweigh the decrease in estrogen. A long-term neuroprotective effectiveness of estrogen was also suggested since only retinal nerve thickness showed sex-specific differences given that RNFL was thicker in women, whereas full macular thickness was greater in men.

There may be racial differences in menopausal manifestations.[13] Although IOP has been reported to rise after menopause in non-Asian populations,[17–19] the present results did not show such an increase and were rather consistent with a large Asian study[34] reporting a marked sex difference; in women, the average annual IOP change was −0.006 mmHg, with a relatively flat association in the age range of 30 to 59 years, while in men, the average annual IOP change was −0.093 mmHg throughout follow-up. In our study, men's visual and non-visual symptoms were generally age-dependent without significant changes in the age group 46–55, which was an obvious difference from women. Those changes may be partly due to meibomian gland dysfunction and low androgen level[35] that is linked to ocular surface disorders and visual disturbances.

The strength of this study is a large sample size with sufficient statistical power. Participants were distributed in a wide range of ages, from 36 to 65 years, and excluded those with glaucoma and pseudophakic eyes. The present study addressed a significant gap in the understanding of ocular health during the menopausal period, particularly focusing on presbyopia and its associated symptoms. By segmenting the participants into distinct age groups, the current study aimed to provide a comprehensive analysis of how visual symptoms and ocular conditions, such as DE and changes in retinal thickness, manifest and evolve in middle-aged individuals. The inclusion of sex differences was crucial as it may reveal important variations in ocular health that may be influenced by hormonal changes during menopause. This approach may inform better clinical practices and interventions for those experiencing presbyopia and other related ocular symptoms in this age group.

This study also has several limitations. For accuracy, each woman should have been asked for her exact age of menopause, and hormone levels should have been measured to precisely classify the study groups. Accordingly, an analysis with a hormone-based classification would disclose a clear association between hormone levels and ocular signs and symptoms. Nevertheless, the present age-based classification enabled us to compare women and men to reveal clearer differences in retinal thickness and ocular surface results. Consequently, the current study suggests an age-related tendency in ocular symptoms and signs with distinct sex differences in the middle-aged population, and we believe the results from our age-based classification would be consistent with those of a hormone-based classification. Further investigation including the concrete menopausal status would be warranted to draw definitive conclusions since some of the results are not fully explained. The definition of symptomatic presbyopia is a refractive one in this study. Information of habitual near correction would be helpful to access the presence of functional symptom with presbyopia in their normal environment.

In conclusion, women of age group 46–55 reported more severe visual symptoms compared to those in the age groups 35–45 and 56–65. Presbyopia, GCC thickening, and DE could worsen these visual symptoms in addition to the effects of menopause. On the other hand, the observed signs and symptoms in men within the same age groups were simply age-dependent. It is hypothesized that sex differences may be due to alterations in hormonal balances and iron levels.

Data Sharing Statement

The data collected during the current study are available from the corresponding authors upon reasonable request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflicts of interest to declare in this work.

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