Determinants of Macular Thickness Using Spectral Domain Optical Coherence Tomography in Healthy Eyes: The Singapore Chinese Eye Study

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Purpose. We determined ocular and systemic factors influencing macular thickness measured by spectral-domain optical coherence tomography (SD-OCT) in a population-based sample of healthy eyes.

Methods. We recruited 490 healthy Chinese adults, aged 40 to 80 years, from the Singapore Chinese Eye Study, a population-based survey. All participants underwent a comprehensive eye examination and a standardized interview. The SD-OCT (Cirrus HD-OCT, software version 6.0) was used to measure a range of macular thickness parameters (central foveal subfield thickness, average inner macular thickness, average outer macular thickness, overall average macular thickness, and overall macular cube volume). Linear regression analyses were performed to examine the effects of various ocular and systemic factors on macular thickness.

Results. The mean (standard deviation) age of the subjects was 53.17 (6.14) years and 50.0% of them were male. The mean central foveal subfield, average inner, and average outer macular thicknesses were 250.38 (20.58), 319.33 (14.40), and 276.67 (11.94) μm, respectively. The overall average macular thickness was 280.25 (11.42) μm and overall macular cube volume was 10.09 (0.41) mm^3. Sex, age, and axial length (AL) are the factors that influenced macular thicknesses. Thinner overall average macular thickness was associated with female sex (4.46 μm thinner compared to males, $P < 0.001$), older age (0.38 μm decrease per each year increase in age, $P < 0.001$), and longer AL (2.34-μm decrease per each mm increase in AL, $P < 0.001$), whereas thinner central foveal subfield thickness was associated with female sex (13.5 μm thinner compared to males, $P < 0.001$) and shorter AL (3.33-μm decrease per each mm increase in AL, $P < 0.001$).

Conclusions. Female sex, older age, and longer AL were associated independently with thinner overall average macular thickness, whereas female sex and shorter AL were associated with thinner central foveal thickness in ethnic Chinese. These factors should be taken into consideration when interpreting macular thickness measurements with SD-OCT.

Keywords: macular thickness, spectral-domain OCT, population-based study

Macular thickness is a reliable surrogate marker for diagnosing and evaluating the efficacy of treatment of various ocular diseases involving macular changes, such as macular edema.[1] Thus, the knowledge of normal macular thickness and its distribution is essential for assessing macular thickening in various ocular pathologies.

Optical coherence tomography (OCT) is a noninvasive imaging technique that enables clinicians to detect and monitor subtle changes in macular thickening quantitatively and reliably.[1–6] The development of spectral-domain OCT (SD-OCT, or high-definition OCT [HD-OCT]), now allows faster scanning speed (27,000 axial scans per second) and even higher image resolution (axial resolution up to 5 μm) compared to that of conventional time-domain OCT,[7,8] providing more accurate and reproducible macular thickness measurements.[9–13]

Although previous studies have examined the factors affecting macular thickness measurement using OCT,[14–21] these studies only considered few factors (such as age, sex, and axial length [AL]/refractive errors) that might influence thickness measurements. Moreover, such studies have been limited by inclusion of highly selected clinic- or volunteer-based samples, which are prone to selection bias. To the best of our knowledge, only one population-based study has described normal macular thickness measurements in rural Chinese adults using the older generation time-domain OCT.[22] There is lack of population-based data reporting a series of comprehensive ocular (e.g., refractive error, IOP, anterior chamber depth, corneal curvature, corneal thickness, presence of cataract, and

so forth) and systemic (e.g., body mass index [BMI], blood pressure [BP], level of blood glucose, presence of diabetes, cholesterol, and so forth) factors that may influence macular thickness measurements using SD-OCT. Knowledge of such factors is crucial before drawing inferences on macular thickness by SD-OCT.

The aim of our study was to determine ocular and systemic factors influencing macular thickness measured by SD-OCT (Cirrus HD-OCT; Carl Zeiss Meditec, Inc., Dublin, CA) in a population-based sample of healthy eyes of Chinese adults.

Materials and Methods

Study Population and Design

The data for this study were derived from the Singapore Chinese Eye Study (SCES), a population-based cross-sectional study of eye diseases in Chinese adults aged 40 to 80 years living in the southwestern part of Singapore between February 2009 and December 2011. Details of the study design, sampling plan, and methodology have been reported previously.[23,24] In total, 3353 participants took part in the study, representing a 72.8% participation rate. Approval for the study was granted by the Singapore Eye Research Institute Institutional Review Board, and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants before enrollment.

Study Subjects

The SD-OCT substudy was conducted between June 2009 and June 2011, and subjects were recruited consecutively during this period. Based on biomicroscopic examination and OCT scans, for our analyses, we excluded subjects based on the following: best corrected logMAR visual acuity (VA) $>$ 0.50 (for proper fixation); evidence of macular or vitreoretinal diseases; previous retinal or refractive surgery; past history of intraocular surgery, neurologic diseases, or clinical features compatible with a diagnosis of a glaucoma suspect or glaucoma; and Cirrus HD-OCT imaging with signal strength less than six. A glaucoma suspect was defined as having any of the following criteria in the presence of normal visual field: IOP $>$ 21 mm Hg, signs consistent with pseudoexfoliation or pigment dispersion syndrome, narrow angles (posterior trabecular meshwork visible for $<$180° during static gonioscopy), and findings consistent with secondary glaucoma.[25] Of the total 3353 subjects included in SCES, 916 subjects underwent visual field examination (with reliable and normal results) and Cirrus OCT. Of these 916 subjects, 426 subjects were excluded based on the above criteria, leaving 490 subjects with healthy eyes for final analysis.

Measurement of Ocular Factors

All participants underwent an extensive and standardized examination procedure, which included measurement of their presenting and best corrected VA (BCVA) using a logarithm of the minimum angle of resolution (LogMAR) number chart (Lighthouse International, New York, NY) at a distance of 4 m. Intraocular pressure was measured with a Goldmann applanation tonometer (GAT; Haag-Streit, Bern, Switzerland) before pupil dilation. The static refraction of each eye was measured using an autorefractor (Canon RK 5 Auto Ref-Keratometer; Canon, Inc., Ltd., Tochigiken, Japan). Spherical equivalent refraction was calculated as the sum of the value of the spherical value and half of the cylindrical value. Central corneal thickness (CCT) was measured with an ultrasound pachymeter (Advent; Mentor O & O, Norwell, MA), and the mean of five measurements was used in the analysis. Axial length, corneal curvature, and anterior chamber depth (ACD) were measured with a noncontact partial coherence laser interferometry (IOLMaster V3.01; Carl Zeiss Meditec AG, Jena, Germany), and the mean of five measurements was used in the analysis. Lens opacity was assessed by two trained ophthalmologists during the visit using the Lens Opacities Classification System (LOCS) III[26] with a Haag-Streit slit-lamp microscope (model BQ-900) in comparison with standard photographic slides for nuclear opalescence (NO), nuclear color (NC), and cortical and posterior subcapsular (PSC) cataract. Standardized visual field testing was performed with static automated white-on-white threshold perimetry (SITA Standard 24-2, Humphrey Field Analyzer II; Carl Zeiss Meditec, Inc.). All subjects included for the final analysis had a reliable and normal visual field (without a visual field defect).

OCT Imaging

An experienced operator performed the macular thickness map after pupil dilation using tropicamide 1% and phenylephrine hydrochloride 2.5%. Cirrus HD-OCT (software version 6.0; Carl Zeiss Meditec, Inc.) was used to acquire 1 macular scan in an area of 6 $\times$ 6 mm^2 using the macular cube 200 $\times$ 200 scan protocol in each study eye. The built-in software was used to produce retinal thickness maps, which then were averaged over nine retinal subfields in a 6-mm diameter circle centered at the true fovea location, as defined by the Early Treatment Diabetic Retinopathy Study.[27] The standard retinal subfields are central, inner superior, inner nasal, inner inferior, inner temporal, outer superior, outer nasal, outer inferior, and outer temporal (see Figure). The inner and outer subfields are bounded by the 3- and 6-mm diameter circle, respectively. The central foveal subfield is bounded by the innermost 1-mm diameter circle. The average of the four-quadrant macular thicknesses in the inner (1–3 mm) and outer (3–6 mm) rings was calculated as average inner macular thickness and average outer macular thickness, respectively. Overall average macular thickness and overall macular cube volume over the entire grid area also were obtained from the computational software output.

In brief, during image acquisition, the subject's pupil first was centered and focused in the iris viewport, and the line-scanning ophthalmoscope with "auto focus" mode then was used to optimize the view of the retina. The "center" and "enhance" modes were used to optimize the Z-offset and scan polarization, respectively, for the OCT scan to maximize the OCT signal.

OCT Image Evaluation

After each capture, motion artifact was checked with the line-scanning ophthalmoscope image with the OCT en face overlaid. Rescanning was performed if a motion artifact (indicated by blood vessels discontinuity) was detected. Centration was checked to confirm whether the central subfield aligned to center of fovea correspondingly. In addition, each of 200 B-scans were scrutinized manually in each eye by trained technicians and checked for segmentation boundaries displayed. Images with motion artefact, centration error, or macular algorithm segmentation failure were excluded from the analysis. All the OCT scans included in the study had signal strength of at least six, and we selected one eye from each participant for final analysis.

Measurement of Systemic Factors

All participants underwent a detailed interview using standardized questionnaires. Information on sociodemographic

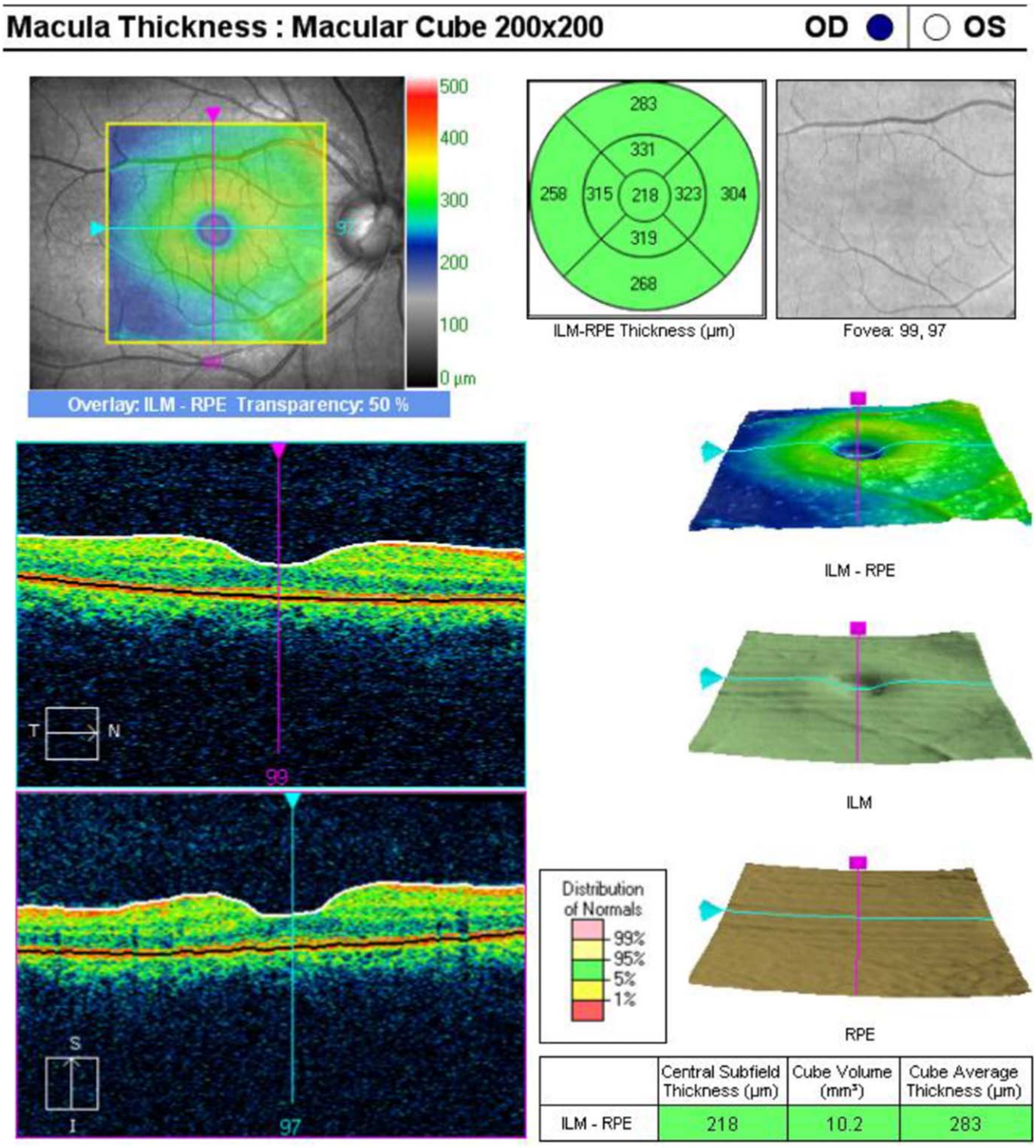

FIGURE. Example of macular thickness measurements obtained with Cirrus SD-OCT system. Representative OCT image (macular cube 200 × 200 scan) from one randomly selected subject in the Singapore Chinese Eye Study.

status, lifestyle risk factors (e.g., smoking, alcohol consumption), medication use, and self-reported history of systemic disease were collected. Systolic and diastolic BPs were measured using a digital automatic BP monitor (Dinamap model Pro Series DP110X-RW, 100V2; GE Medical Systems Information Technologies, Inc., Milwaukee, WI), after subjects were seated for at least 5 minutes with legs uncrossed. A total of three measurements was taken, and the average of the two closest BP readings was taken as each participant's BP. The BMI was calculated as body weight (in kilograms) divided by body height (in meters) squared. Smoking status was defined as those currently smoking, ex-smokers, and nonsmokers. The

Table 1. Baseline Characteristics of Included and Excluded Subjects

	Included, $n = 490$	Excluded, $n = 426$	*P*
Age, y	53.17 (6.14)	54.82 (6.79)	<0.001
Sex, *N* (% male)	245 (50.00)	217 (50.94)	0.777
IOP, mm Hg	14.49 (2.77)	14.34 (3.09)	0.424
Spherical equivalent, D	−0.94 (2.34)	−0.71 (2.27)	0.130
Best corrected visual acuity, logMAR	0.03 (0.06)	0.06 (0.12)	<0.001
Axial length, mm	24.10 (1.22)	23.92 (1.33)	0.038
Anterior chamber depth, mm	3.31 (0.32)	3.30 (0.39)	0.694
Central corneal thickness, μm	559.25 (33.51)	552.78 (31.81)	0.003
Corneal curvature, mm	7.69 (0.26)	7.65 (0.27)	0.036
LOCS III nuclear opalescence	1.74 (0.71)	1.86 (0.76)	0.012
LOCS III nuclear color	1.82 (0.69)	1.90 (0.76)	0.081
LOCS III cortical	0.81 (0.86)	0.88 (0.89)	0.207
LOCS III PSC	0.18 (0.22)	0.24 (0.48)	0.013
Systolic blood pressure, mm Hg	131.12 (17.05)	129.98 (17.81)	0.322
Diastolic blood pressure, mm Hg	77.79 (9.73)	77.33 (9.69)	0.472
Body mass index, kg/m^2	23.36 (3.46)	23.71 (3.66)	0.145
Serum glucose, mmol/L	6.00 (2.18)	6.23 (2.05)	0.107
HbA1c, *N* (%)	5.94 (0.73)	5.97 (0.75)	0.495
HDL cholesterol, mmol/L	1.31 (0.37)	1.32 (0.40)	0.905
LDL cholesterol, mmol/L	3.35 (0.86)	3.41 (0.89)	0.280
Triglycerides, mmol/L	1.79 (1.28)	1.83 (1.22)	0.662
Blood creatinine, mmol/L	70.10 (16.63)	72.55 (24.24)	0.074
Current smoking, *N* (%)	72 (14.69)	59 (13.85)	0.716
Diabetes mellitus, *N* (%)	32 (6.65)	41 (9.83)	0.082

Data are mean (±SD), except for sex, HbA1c, current smoking, and diabetes, which are expressed as number (%).

number of packs smoked per week was recorded. Nonfasting venous blood samples were analyzed at the National University Hospital Reference Laboratory for biochemical testing of serum total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, glycosylated hemoglobin (HbA1c), glucose, and creatinine.

Statistical Analysis

Statistical analysis was performed using SPSS version 17.0 (SPSS, Inc., Chicago, IL). The mean and standard deviation of the following parameters were calculated: ocular variables (corneal curvature, IOP, spherical equivalent, BCVA, AL, ACD, CCT, LOCS III score, and signal strength), systemic variables (age, sex, systolic BP, diastolic BP, BMI, smoking, serum glucose, HbA1c, HDL cholesterol, LDL cholesterol, triglycerides, and creatinine), and macular thickness (foveal, average inner, average outer, and overall average) measured with Cirrus HD-OCT. Univariate and multiple linear regression analyses were performed to determine ocular and systemic factors (independent variables) association with macular thickness measurements (dependent variables). For multiple linear regression, age, signal strength, and ocular and systemic parameters with $P < 0.10$ found in univariate linear regression analysis were included. For all analysis, a *P* value of less than 0.05 was considered to be significant.

Results

A total of 916 subjects had undergone SD-OCT and visual field testing in the SCES substudy. Among these 916 subjects, data from 490 subjects (53.49%) who met the study inclusion criteria were analyzed. Table 1 shows the baseline characteristics of the included and excluded subjects. The mean age of the subjects included in the study was 53.17 ± 6.14 years (range, 44.51–75.66 years) and 245 (50.0%) were male. When compared to those excluded, included participants were significantly younger, had less cataract, better VA, longer AL, and more curved cornea (all $P < 0.05$).

Table 2 shows the distributions of macular thickness and volume measurements. The macular center was the thinnest (250.38 ± 20.58 μm) and the inner region was thickest (319.33 ± 14.40 μm), and then the thickness decreased in the outer region (276.67 ± 11.94 μm). Among the inner and outer regions, the nasal quadrant was the thickest, followed by the superior and inferior quadrants, with the temporal quadrant the thinnest. The central foveal subfield, average inner, overall average macular thicknesses, and overall macular cube volume were significantly greater in men than in women ($P \leq 0.005$), whereas no significant difference was observed in outer region.

Table 2. Distribution of Macular Thickness and Volume Measurements in Healthy Eyes by Sex

Macular Thickness, μm	Total, $n = 490$	Male, $n = 245$	Female, $n = 245$	*P* for Sex Differences
Central macular, 1 mm	250.38 (20.58)	257.78 (18.70)	242.99 (19.73)	<0.001
Inner region, 3 mm				
Temporal	310.00 (14.45)	314.96 (13.53)	305.03 (13.62)	<0.001
Superior	323.11 (15.10)	327.36 (14.23)	318.86 (14.77)	<0.001
Nasal	325.14 (15.77)	330.10 (14.71)	320.19 (15.26)	<0.001
Inferior	319.09 (14.55)	323.12 (13.75)	315.05 (14.23)	<0.001
Average inner macula	319.33 (14.40)	323.89 (13.42)	314.78 (13.93)	<0.001
Outer region, 6 mm				
Temporal	261.48 (12.21)	264.02 (11.81)	258.94 (12.09)	<0.001
Superior	279.62 (13.06)	279.93 (13.02)	279.31 (13.11)	0.595
Nasal	299.38 (14.17)	300.62 (14.49)	298.14 (13.75)	0.053
Inferior	266.19 (12.66)	266.23 (12.94)	266.14 (12.39)	0.940
Average outer macula	276.67 (11.94)	277.70 (12.06)	275.63 (11.76)	0.056
Overall average macula	280.25 (11.42)	281.73 (11.36)	278.77 (11.30)	0.005
Overall macular cube volume, mm^3	10.09 (0.41)	10.14 (0.41)	10.04 (0.41)	0.004

Data are mean (±SD).

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Table 3. Distribution of Macular Thickness and Volume Measurements by Age Group

Macular Thickness, μm	Age Group, y			*P* for Trend for Age	
	40–49, *n* = 196	50–59, *n* = 218	60+, *n* = 76	Unstandardized β Coefficient	*P*
Central macular, 1 mm	251.38 (20.86)	249.16 (19.96)	251.34 (21.63)	−0.50	0.704
Inner region, 3 mm					
Temporal	311.46 (14.62)	308.83 (14.67)	309.58 (13.16)	−1.31	0.157
Superior	325.40 (14.91)	321.98 (15.68)	320.43 (13.18)	−2.69	0.005
Nasal	326.63 (15.75)	324.13 (15.91)	324.21 (15.32)	−1.50	0.140
Inferior	320.33 (14.51)	317.91 (14.80)	319.25 (13.85)	−0.96	0.307
Average inner macula	320.96 (14.41)	318.21 (14.69)	318.37 (13.29)	−1.61	0.081
Outer region, 6 mm					
Temporal	263.17 (12.38)	259.89 (12.52)	261.68 (10.23)	−1.30	0.096
Superior	281.94 (13.34)	278.40 (13.09)	277.14 (11.32)	−2.65	0.002
Nasal	301.85 (14.27)	298.16 (13.93)	296.51 (13.74)	−2.90	0.001
Inferior	267.58 (12.49)	265.45 (13.16)	264.70 (11.36)	−1.59	0.050
Average outer macula	278.64 (12.01)	275.47 (12.11)	275.01 (10.67)	−2.11	0.006
Overall average macula	282.18 (11.40)	279.14 (11.66)	278.46 (10.10)	−2.12	0.004
Overall macular cube volume, mm^3	10.16 (0.41)	10.05 (0.42)	10.03 (0.37)	−0.08	0.004

Data are mean (±SD).

Table 3 shows the variation in macular thickness and volume measurements by age groups. With increase in age, there was no difference in central and inner macular thicknesses (except superior region). However, age was correlated inversely with average outer macular thickness ($\beta = -2.11$, $P = 0.006$), overall average macular thickness ($\beta = -2.12$, $P = 0.004$), and overall macular cube volume ($\beta = -0.08$, $P = 0.004$).

Table 4 shows the univariate analysis between ocular and systemic factors with macular thickness. The AL was correlated positively with central foveal subfield thickness ($P < 0.001$, $\beta = 5.07$), whereas it was found to be associated negatively with average outer and overall average macular thickness (both $P < 0.001$). Age was associated significantly with thinner macula (except in the central foveal subfield region). Female sex also was associated with thinner macula (except for average outer region). However, macular thickness was not significantly influenced by most of the systemic factors, like BMI, systolic BP, LDL cholesterol, triglycerides, serum blood glucose level, HbA1c, and diabetes mellitus.

Table 5 shows the multiple linear regression analysis of ocular and systemic parameters with macular thickness. Thinner overall average macular thickness was associated with female sex (4.46 μm thinner compared to males, $P < 0.001$), older age (0.38 μm decrease per each year increase in age, $P < 0.001$), and longer AL (2.34 μm decrease per each mm increase in AL, $P < 0.001$), whereas thinner central foveal subfield thickness was associated with female sex (13.5 μm thinner compared to males, $P < 0.001$) and shorter AL (3.33 μm decrease per each mm increase in AL, $P < 0.001$).

Table 6 gives the summary of the studies reporting determinants of macular thickness measurements in healthy eyes using OCT.

Discussion

Our study reports the distributions of normal macular thickness, and its ocular and systemic determinants measured by SD-OCT in a population-based sample of Chinese adults. We found that thinner overall average macular thickness was associated independently with older age, female sex, and longer AL. Such findings are of potential significance in clinical interpretation of SD-OCT–based macular thickness measurements.

To our knowledge, this is the first population-based investigation on determinants of macular thickness in healthy eyes using SD-OCT. The majority of the previous studies were hospital- or university-based and, hence, were subject to selection bias and they used time-domain OCT. Although direct comparison of our results with other reported studies is limited due to differences in ethnicity of study participants, age groups, study inclusion and exclusion criteria, and different types of OCT (time-domain versus spectral-domain) used in various studies. Nevertheless, we observed similar trends in distributions of macular thickness as reported in previous studies. Our findings that macular thickness was thinnest at the fovea, followed by outer region and thickest in inner region are in line with those in previous reports.[12,16,28] We identified the nasal quadrant to be the thickest in the inner and outer regions, consistent with the anatomic relationship of the converging of nerve fibers with the optic disc. This is followed by superior and inferior quadrants, presumably from the superior and inferior arcuate bundling of the nerve fibers.[29]

However, our measurement values of macular thickness using SD-OCT are larger (foveal thickness, 250.38 ± 20.58 μm) when compared to that reported by the Handan Eye Study[22] (foveal thickness, 176 ± 17.5 μm), a Chinese population-based study using time-domain OCT, but similar to that obtained in other studies using SD-OCT.[10,12,14] First, this variation in macular thickness measurements could be due to differences in definitions of the posterior retinal boundary used in different OCT instruments.[9,10,16] Second, macular thickness map in time-domain OCT is derived from fewer data points (768 axial scans/image, obtained from six 6-mm linear scans over a 360° area) requiring mathematic interpolations to obtain thickness estimations for the spaces in between.[30] However, SD-OCT allow detailed mapping of the macula, wherein macular thickness is derived from much more data points, (total 40,000 axial scans/image in 200 × 200 scan prototype) leading to more reliable and reproducible measurements.[11]

Our results showed that the macular thickness was influenced significantly by age, sex, and AL in healthy eyes. Older age was associated with thinner average outer macular thickness, overall average macular thickness, and overall

Table 4. Univariate Analysis Between Ocular and Systemic Factors With Macular Thickness

	Central Macular, 1 mm		Average Inner Macula, 3 mm		Average Outer Macula, 6 mm		Overall Average Macula	
	Unstandardized β Coefficient	*P* Value	Unstandardized β Coefficient	*P* Value	Unstandardized β Coefficient	*P* Value	Unstandardized β Coefficient	*P* Value
Ocular factors								
IOP, mm Hg	−0.49	0.148	−0.18	0.447	−0.03	0.882	−0.04	0.825
Axial length, mm	5.07	<0.001	1.04	0.053	−2.41	<0.001	−1.52	<0.001
Central corneal thickness, μm	0.002	0.938	0.02	0.396	0.02	0.178	0.02	0.210
Corneal curvature, mm	3.55	0.153	−4.56	0.026	5.54	0.118	−2.64	0.179
OCT signal strength	−0.75	0.447	−0.71	0.306	0.73	0.201	0.30	0.588
LOCS III nuclear opalescence	0.23	0.863	−2.12	0.021	−1.75	0.021	−1.74	0.017
LOCS III nuclear color	0.47	0.730	−1.92	0.041	−1.70	0.030	−1.69	0.023
LOCS III cortical	−0.13	0.902	−0.84	0.270	−0.99	0.117	−0.91	0.130
LOCS III PSC	−5.14	0.221	−4.33	0.140	−1.22	0.616	−2.15	0.356
Systemic factors								
Age, y	−0.10	0.503	−0.28	0.007	−0.33	<0.001	−0.33	<0.001
Sex, female vs. male	−14.78	<0.001	−9.11	<0.001	−2.07	0.056	−2.96	0.004
Body mass index, kg/m^2	0.04	0.872	0.11	0.556	−0.14	0.379	−0.10	0.523
Systolic blood pressure, mm Hg	0.03	0.598	0.05	0.179	0.02	0.501	0.02	0.441
Diastolic blood pressure, mm Hg	0.22	0.023	0.21	0.001	0.10	0.081	0.11	0.036
Smoking status, yes vs. no	3.03	0.248	3.01	0.102	0.97	0.527	1.03	0.482
Presence of diabetes mellitus	−0.20	0.958	0.04	0.988	0.47	0.830	0.40	0.849
Serum blood glucose, mmol/L	−0.09	0.844	−0.08	0.806	−0.07	0.791	−0.09	0.721
HbA1c, %	−0.65	0.616	−0.59	0.513	−0.52	0.486	−0.43	0.548
HDL cholesterol, mmol/L	−8.11	0.001	−4.41	0.012	−0.36	0.808	−1.35	0.338
LDL cholesterol, mmol/L	0.86	0.433	0.74	0.337	0.59	0.355	0.58	0.338
Triglycerides, mmol/L	−0.18	0.808	0.20	0.704	−0.05	0.915	−0.07	0.870
Blood creatinine, mmol/L	0.34	<0.001	0.18	<0.001	0.002	0.961	0.02	0.460

macular cube volume. There was no significant correlation in thickness for the fovea and inner macula, although a trend of decrease in thickness with age was seen, which probably could be due to fewer retinal cell layers at the fovea compared to the rest of the macula. Our results were consistent with previous studies reporting significant decrease in macular thickness with age,[14,15,31–33] and also correspond to histologic studies that have demonstrated a decrease in density of photoreceptors, ganglion cells, retinal pigmented epithelium, and optic nerve fibers with age.[34,35]

Compared to females, male subjects had significantly thicker macula in the foveal, inner, and overall macular regions, but there was no significant difference in the outer region (although a similar trend was evident). Our finding of reduced foveal thickness in women was in alignment with the observations in other studies[14,36,37] that reported that women have thinner macular measurements. This may explain why certain macular conditions, such as macular hole, occur more frequently in women.[38,39]

Among the ocular factors, macular thicknesses are influenced by AL and lens opacity. In general, greater AL (except central foveal subfield thickness) and presence of lens opacity were associated with a thinner macula. Our results were compatible with histologic findings that in eyes with greater AL, the elongation of the eyeball leads to mechanical stretching, and thinning of the sclera and retina,[40] and a clinical study that demonstrated more frequent chorioretinal atrophy in the posterior pole in eyes with longer AL.[41] Taken together, the results of our study were in agreement with the

Table 5. Multiple Linear Regression Analysis Between Ocular and Systemic Factors With Macular Thickness

	Central Macular, 1 mm		Average Inner Macula, 3 mm		Average Outer Macula, 6 mm		Overall Average Macula	
	β Coefficient	*P* Value	β Coefficient	*P* Value	β Coefficient	*P* Value	β Coefficient	*P* Value
Age, y	−0.11	0.460	−0.31	0.004	−0.37	<0.001	−0.38	<0.001
Sex, female vs. male	−13.50	<0.001	−10.64	<0.001	−4.15	<0.001	−4.46	<0.001
Diastolic blood pressure, mm Hg	−0.09	0.375	0.05	0.515	0.08	0.168	0.07	0.198
HDL cholesterol, mmol/L	0.52	0.845	0.82	0.668	–	–	–	–
Blood creatinine, mmol/L	−0.004	0.957	−0.05	0.418	–	–	–	–
Axial length, mm	3.33	<0.001	−0.30	0.613	−3.16	<0.001	−2.34	<0.001
OCT signal strength	0.14	0.886	−1.10	0.111	−0.32	0.564	−0.62	0.256
LOCS III nuclear opalescence	–	–	−1.91	0.033	−1.29	0.076	−1.28	0.070
Corneal curvature, mm	–	–	−1.41	0.605	–	–	–	–

Table 6. Summary of Studies Reporting Determinants of Macular Thickness Measurements in Healthy Eyes Using OCT

Study	Ethnicity	Study Design	Sample Size	OCT Used	Factors Studied, Ocular and Systemic
Current study	Chinese	Population-based	416	Spectral-domain	Age,* sex,* BMI, SBP, DBP, smoking, DM, serum blood glucose, HbA1c, HDL/LDL cholesterol, triglycerides, blood creatinine, AL,* IOP, CCT, corneal curvature, OCT-signal strength, and cataract*
Duan XR, Liang YB, Friedman DS, et al.[22]	Chinese	Population-based	2230	Time-domain	Age,* sex,* RE, AL,* fasting plasma glucose,* BMI
Adhi M, Aziz S, Muhammad K, et al.[16]	Pakistanese	Clinic-based	220	Spectral-domain	Age, sex*
Song WK, Lee SC, Lee ES, et al.[14]	Korean	Clinic-based	198	Spectral-domain	Age,* sex,* RE, AL*
Ooto S, Hangai P, Tomidokoro A, et al.[19]	Japanese	Clinic-based	248	Spectral-domain	Age,* sex,* AL
Sung KR, Wollstein G, Bilonick RA, et al.[20]	Whites	Clinic-based	226	Time-domain	Age*
Errikson U, Alm A[15]	Whites	Clinic-based	67	Time-domain	Age*
Lam DS, Leung KS, Mohammad S, et al.[18]	Chinese	Clinic-based	26	Time-domain	Age, sex,* RE,* AL*
Chan A, Duker JS, Ko TH, et al.[28]	Whites	Clinic-based	37	Time-domain	Age

RE, refractive error; SBP, systolic BP; DBP, diastolic BP; DM, diabetes mellitus.
* Indicates significant determinants of macular thickness.

trend of recent studies that outer macular thickness decreases with increasing AL.[14,17,18]

In addition, an interesting observation in our study is that the central subfield foveal thickness increased with increase in AL, whereas average outer and overall average macular thicknesses decreased with increase in AL. Our results were concurrent with previous studies in children[42] and adults.[17,18,43] Lim et al.[17] suggested that this association may be due to poorer and off-foveola fixation in highly myopic eyes. However, in our current study, we have checked the central subfield alignment during OCT imaging for each subject and, therefore, off-foveola fixation was unlikely present in this study. Other possible reasons for the positive correlation between central foveal thickness and AL are retinomotor movements of the photoreceptors,[18] or stretching tendency of the internal limiting membrane and centripedal force of the posterior vitreous,[43] which could result in elevation of foveal thickness. We also speculated that this could be due to myopic foveoschisis and vitreomacular traction in elongated eyeballs, which could result in foveal thickening. The underlying mechanisms of foveal thickening with AL remain unclear and, thus, further studies are needed.

In the multiple regression analysis, we found that macular thickness was not significantly influenced by other ocular factors, such as IOP, CCT, corneal curvature, and signal strength, as well as systemic factors, such as BMI, systolic and diastolic BP, HDL-cholesterol, LDL-cholesterol, triglycerides, creatinine, blood glucose levels, HbA1C, diabetes mellitus, and smoking. Thus, these measurements appear to be robust in subjects with a wide range of systemic factors. Nevertheless, our findings are important in helping clinicians to understand the pattern of regional variation in macular thickness. The observations suggested that it is essential to adjust for age, sex, and AL when conducting analyses of SD-OCT–based macular thickness measurements. However, these associations may not be extrapolated to other ethnic groups and further studies in other ethnic populations are warranted to confirm the results.

The strengths of this study include its large population-based sample, which minimizes the selection bias inherent in previous hospital- and university-based studies; standardized assessment of wide range of systemic and ocular factors; and the inclusion of laboratory investigations. However, our study had some limitations. First, macular thickness measurements were obtained from subjects with an age range between 40 and 75 years. Their associations with sex and ocular factors may not be extrapolated to other age groups. Second, only ethnic Chinese were examined in this study, and the findings may vary in other ethnic groups. Third, due to strict study inclusion criteria, only normal healthy eyes were included. Almost half (46.51%) of our study subjects were excluded in the final analysis; thereby, the generalizability of our study results may be limited. Fourth, due to the cross-sectional nature of our study, the causal relationships between macular thickness and the factors studied cannot be established. Last, there may be residual confounding factors that we have not controlled for, such as diurnal variation and other systemic diseases (e.g., multiple sclerosis), that could have biased or modified the associations observed in our sample.

In conclusion, female sex, older age, and longer AL are the factors that were associated with thinner overall average macular thickness, whereas female sex and shorter AL were associated with thinner central foveal thickness measures with SD-OCT in ethnic Chinese. As the current normative database in the Cirrus OCT database does not take these factors into account (except age), clinicians should be aware of the effect of such factors and, therefore, should take them into account when interpreting Cirrus HD-OCT–based macular thickness measurements.

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