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Macular thickness and its associated factors in a Chinese rural adult population: the Handan Eye Study

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ABSTRACT

Purpose To describe the normal macular thickness and assess its associations.

Methods The Handan Eye Follow-up Study was conducted between 2012 and 2013. Macular thickness was scanned by spectral-domain optical coherence tomography (OCT). The built-in software generated a retinal thickness (RT) map, which was divided into three regions (central, internal and external regions) and nine quadrants (one in central and four in internal and external regions each).

Results For 5394 subjects in the Handan Eye Follow-up Study, 4793 received OCT examination, 2946 of whom (accounting for 61.46% of the total subjects, mean age 58.91±10.95, 55.6% were women) were included for analysis. The mean RT in central macula, inner and outer rings were (237.38 µm±23.05 µm), (309.77 µm±18.36 µm) and (278.29 µm±14.38 µm), respectively (overall difference, $p < 0.001$). In inner ring, the RT in temporal was thinnest, followed by nasal, superior and inferior. In outer ring, the RT in superior was thinnest, with the next subfields being temporal, inferior and nasal, respectively. The RT in central macula, inner and outer rings were significantly thicker in men than in women. Multivariate linear regression analysis showed that in central macula, RT increased in subjects younger than 60 years and thinned above the age of 60. In inner and outer rings, RT thinned along with age ($p < 0.001$).

Conclusions This study finds that RT in central macula is the thinnest, followed by the outer ring, the RT in the inner ring is the thickest. Age and gender are related to RT. These associated factors need to be considered when explaining RT.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Changes in macular thickness were important for predicting some retinal diseases, but there have been few spectral/Fourier domain optical coherence tomography (SD-OCT) measurements of normal eyes in the general population.

WHAT THIS STUDY ADDS

⇒ This study measured the normal macular thickness with SD-OCT and identified its related factors in a rural adult population in China.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Measurement of macular thickness using SD-OCT may build a normal reference range and offer a dataset for adult retinal thickness in China.

INTRODUCTION

As a rapid non-invasive imaging technique, optical coherence tomography (OCT) can present "optical biopsy" of the posterior segment of eyes and measure macular thickness in a quantitative way, which contributes to the diagnoses and follow-up of fundus oculi diseases.[1–3] The changes in macular thickness occur in eyes with retinal diseases, such as diabetic retinopathy (DR), neurovascular age-related macular degeneration and retinal vein occlusion, which could induce macular thickening or oedema and geographic atrophy, macular atrophy, which could induce macular thinning.

Initially, time-domain OCT (TD-OCT) systems like stratus OCT were used in clinical practice. Recently, spectral/Fourier domain OCT (SD-OCT) systems have been widely used in both scientific research and clinical practice. Compared with the conventional TD-OCT, the newly developed SD-OCT systems have higher sensitivity, far higher acquisition speed (~60 times faster) and up to five times higher resolution.[4–6] For this reason, it is important to acquire the normal range of macular thickness in populations with SD-OCT. This is essential for ophthalmologists to distinguish changes in disease-related retinal thickness (RT) caused by normal variability. In addition, it has become a primary means in many current clinical trials to use SD-OCT to measure the macular thickness, a well-described set of RT data will be valuable for the planning of these trials and the evaluation of their findings. However, so far, there have been few SD-OCT measurements of normal eyes in the general population.

This study aims to measure the normal macular thickness with SD-OCT and identify its related factors in a rural adult population in China, to prove a normal reference range for adult RT in China.

METHODS

Setting

As a population-based cross-sectional study, the Handan Eye Follow-up Study was conducted in Handan, Hebei Province, northern China in 2012–2013. Details have been described elsewhere.[7] Briefly, 6830 subjects aged 30 or above participated in the baseline study in 2006–2007. Participants who were still alive were invited to take part in the follow-up study 6 years later. The

research protocol was approved by the Ethics Committee of Beijing Tongren Hospital, Capital University of Medical Sciences (TREC2006-22) and written informed consents were signed by all participants, according to the Declaration of Helsinki. The protocol of follow-up study was similar to that of the baseline study and had been standardised. It consisted of extensive ocular examinations and questionnaires, which were performed by trained and experienced doctors and interviewers who participated in Handan Eye Baseline Study.

Eye examination and interview

First, the visual acuity was measured. If it was worse than 0.0 logMAR (Snellen 6/6 or 20/20), subjective refraction was performed by trained and certified optometrists.[8] Intraocular pressure (IOP) was measured by Kowa HA-2 applanation tonometer (Kowa Company, Tokyo, Japan) in cooperative subjects. Those who could not cooperate were measured by a Schiotz tonometer or digital palpation. Slit-lamp examination (Topcon SL-2F; www.global.topcon.com) was performed by ophthalmologists after pupil dilation. A 10 MHz A/B-mode ultrasound device (Cine Scan, www.quantel-medical.com) was used to measure axial length (AL). Colour retinal photographs were collected by a Canon CR 2 with a 20D SLR back (Canon, www.cacon.com).

Measurement procedures of OCT

Macular thickness was scanned by an experienced operator by dilating pupils using spectral-domain OCT (RTVue 100–2, Optovue, Fremont, California; V.4.0). The device used a scanning laser diode to emit infrared light source with a wavelength of 840 nm and acquired 26 000 A-scans per second, and the resolution of tissue depth was 5 µm. The MM6 mode was selected to complete 12 radiation scans within 0.27 s, with a length of 6 mm and centred on the fovea. Each scan consisted of 1024 equidistant transverse A scans. Up to three scans were obtained for each eye, and single scans with the best quality were selected for analysis. Those without artefacts (boundary errors or decentration) were accepted, and complete cross-sectional images were observed in all individual line scans. After images were acquired, all macular images were manually checked to ensure that the foveal depression was in the centre of the scan. The results were considered credible if signal strength index (SSI)≥55. Additionally, one retinal specialist reviewed these scans carefully for abnormalities, such as epiretinal membrane, retinoschisis and other retinopathies.

Demographic measurement and questionnaires

The height and weight of the subjects were measured by certified nurses based on a standardised protocol. In addition, a detailed questionnaire, which included demographic information, internal medicine diseases (diabetes, hypertension, drinking and smoking) as well as family history of eye diseases, was used. Furthermore, blood was collected for biochemical analysis including lipids (total cholesterol, total triglycerides, low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol), serum creatinine, blood urea nitrogen and fasting glucose.

Inclusions and exclusions

The inclusion criteria were as follows: (1) best-corrected visual acuity (BCVA) ≤0.3logMar, (2) spherical refractive error ≤±6 diopters (D) and the astigmatism ≤±3 D, (3) the IOP ≤21 mm Hg, (4) SD-OCT SSI ≥55. Subjects who met one of the following exclusion criteria were excluded: (1) any history or evidence of age-related macular degeneration, DR, glaucoma or other eye diseases affecting RT, (2) history of ocular trauma, (3) history of ocular surgery or retinal laser treatment other than uneventful cataract surgery or refractive surgery. Subjects with two eligible eyes were examined, whose both eyes were included in macular thickness analysis. For subjects with only one eligible eye, the data of that eye alone were included in statistical calculation.

Macular thickness measurement

The RT of RTVue was measured between the internal limiting membrane (ILM) and the edge defined by the mean value of the maximum reflectance of retinal pigment epithelium (RPE), which avoided detection errors at the outer border of RPE.[9] The built-in software was used to generate a RT map, where the common centre of three concentric circles was located in the macular fovea, and the diameters were 1 mm (innermost ring), 3 mm (inner ring) and 6 mm (outer ring), respectively. The 1 mm innermost ring was the central macular area, the 3 mm inner ring and the 6 mm outer ring were further divided into four equal areas. According to the definition of Early Treatment Diabetic Retinopathy Study, the nine subregions of macular RT were central macular areas, above the inner ring, below the inner ring, nasal side of the inner ring, temporal side of the inner ring, above the outer ring, below the outer ring, nasal side of the outer ring and temporal side of the outer ring (See figure 1).

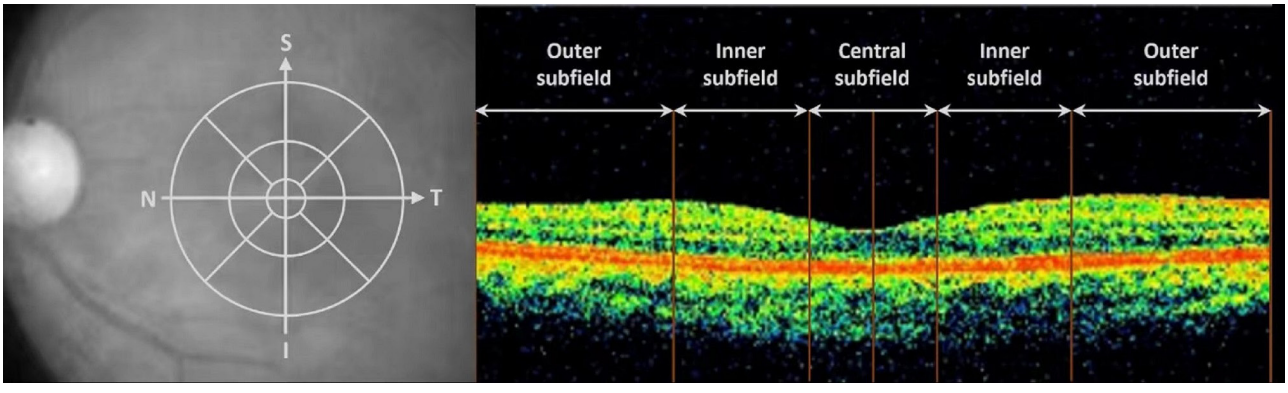

Figure 1 The three subfields (central subfield, inner ring and outer ring) and nine subregions of macular retinal in fundus photograph and OCT. OCT, optical coherence tomography.

Statistics

Statistical analysis was performed using software R (V.4.1.1; R Core Team, 2021). Descriptive statistics were adopted to describe demographic, RT and other parameters of the included and excluded groups. The normality distribution and variance homogeneity of continuous variables were measured, and then t test or Wilcoxon rank sum test was performed. χ^2 test was performed on categorical variables for ordered data, and non-parametric Wilcoxon rank sum test was performed for disordered data. Linear regression was used to analyse the correlation between age and macular thickness. Subsequently, univariate and multivariate linear regression models were used to investigate the associations between demographic, biochemical characteristics and RT (central macular subfield, average inner ring and average outer ring). To begin with, univariate regression model was used to estimate the correlation between demographic characteristics, medical history, behaviour, ocular parameters and central macula, inner and outer rings, respectively. Second, variables that were found statistically significant ($p \leq 0.05$) in the univariate model or those with clinical significance were further included in the multivariate regression model, in which a stepwise forward method was adopted for variable selection. A two-tailed p value of less than 0.05 was considered to be statistically significant.

RESULTS

In Handan Follow-up Study, 4793 of 5394 subjects received OCT examination, of whom 2946 with healthy eyes and good-quality imaging were identified. Table 1 shows a comparison of demographic characteristics, medical history, behaviour and ocular parameters between the included and excluded groups. It is seen from the table that age, gender, BMI, SBP, diastolic blood pressure (DBP), hypertension, coronary heart diseases, diabetes, HDL, LDL, SE OU (OU includes OD and OS), BCVA OU, IOP OU, CCT OU, AL OU and anterior chamber depth (ACD) OU were significantly different between the included and excluded groups. The subjects in the included group were older, with more hypertension and coronary heart diseases, higher SBP, HDL, LDL, SE OU, lower BMI, DBP, IOP OU, worse BCVA OU, thinner CCT OU, shorter AL OU, ACD OU and fewer diabetes compared with those in the excluded group. In addition, there was no significant difference between the two groups in terms of education, the number of current smokers, triglycerides, haemoglobin A1c (HbA1c), keratometry and vertical C/D.

The mean and SD, 1, 5, 50, 95 and 99 percentiles of the central macula, inner and outer rings of RT distribution are shown in online supplemental table 1. RT measurements were expressed as the mean±SD (M±SD). It can be seen that the RT of the central macula (237.38 μ^2±23.05 μ^2) was the thinnest, followed by that of the outer ring (278.29 μh±14.38 μh) and the RT of the inner ring (309.77 μ±18.36 μ) was thickest. In the inner ring, the RT of the temporal subfield (306.53 μh±19.39 μh) was the thinnest, followed by the nasal one (308.06 μh±19.54 μh), then the superior (311.12 μ±18.71 μ) and inferior ones (313.35±19.25μ). Compared with the RT of the inner inferior hemisphere (312.86 μ±19.07 μ), the RT of the superior one (306.68 μ±18.59 μ) was thinner. In the outer ring, the RT of the superior one (271.15 μh±13.89 μh) was the thinnest, and the next subfields were temporal (277.23 μe±16.59 μe), inferior (279.69±15.27 μ) and nasal ones (285.08 μ±16.63 μ), respectively. The RT of the outer superior hemisphere (270.94 μ±14.6 μ) was much thinner than that of the outer inferior one (285.64 μ^2±15.61 μ^2), similar to the pattern of the inner ring.

Table 1 Comparisons of demographic characteristics, medical history, behaviour and ocular parameters between the included and excluded individuals

Characteristic	Included (n=2946)	Excluded (n=1847)	t/x^2	P value
Age	58.91±10.75	53.95±11.06	−15.281	<0.001
Gender			10.741	0.001
Male	1307 (44.4)	909 (49.2)		
Female	1639 (55.6)	938 (50.8)		
Education			0.562	0.453
Below high school	2857 (97.0)	1784 (96.6)		
High school or above	89 (3.0)	63 (3.4)		
BMI	25.73±4.06	26.09±3.77	3.160	0.002
SBP	144.27±22.61	141.30±21.96	−4.508	<0.001
DBP	83.59±12.91	84.77±13.13	3.076	0.002
Hypertension			4.364	0.037
Yes	897 (33.0)	521 (30.0)		
No	1818 (67.0)	1213 (70.0)		
Coronary heart disease			3.877	0.049
Yes	244 (9.2)	129 (7.5)		
No	2418 (90.8)	1598 (92.5)		
Diabetes			5.539	0.019
Yes	120 (4.5)	104 (6.1)		
No	2564 (95.5)	1609 (93.9)		
Current smoker			0.193	0.660
Yes	749 (26.7)	470 (26.1)		
No	2055 (73.3)	1329 (73.9)		
Triglycerides	1.40±1.06	1.45±1.28	1.420	0.156
HbA1c	5.75±0.77	5.78±0.99	1.116	0.265
HDL	1.23±0.28	1.21±0.27	−2.047	0.041
LDL	2.69±0.75	2.63±0.75	−2.637	0.008
Keratometry OD	44.19±1.54	44.14±1.52	−1.124	0.261
Keratometry OS	44.19±1.57	44.10±1.53	−1.953	0.051
SE OD	0.40±1.89	−0.40±2.30	−10.899	<0.001
SE OS	0.43±1.90	−0.35±2.22	−11.215	<0.001
BCVA OD	0.72±0.17	0.40±0.25	−47.097	<0.001
BCVA OS	0.71±0.17	0.38±0.24	−50.777	<0.001
IOP OD	11.65±2.57	12.00±2.45	4.702	<0.001
IOP OS	12.17±2.33	12.56±2.61	5.268	<0.001
CCT OD	532.61±29.75	535.05±29.35	2.695	0.007
CCT OS	532.25±29.74	534.93±29.13	2.968	0.003
AL OD	22.81±1.05	22.95±1.05	4.195	<0.001
AL OS	22.76±0.90	22.92±0.94	5.675	<0.001
ACD OD	2.76±0.35	2.84±0.39	7.424	<0.001
ACD OS	2.75±0.35	2.85±0.36	8.792	<0.001
Vertical C/D OD	0.35±0.13	0.35±0.14	0.686	0.493
Vertical C/D OS	0.35±0.13	0.35±0.14	1.557	0.120

All data were shown as M±SD or n (%).
ACD, anterior chamber depth; AL, axial length; CCT, central corneal thickness; DBP, diastolic blood pressure; HDL, high-density lipoprotein; IOP, intraocular pressure; LDL, low-density lipoprotein; SBP, systolic blood pressure; SE, spherical equivalent; Vertical C/D, vertical cup disc ratio.

Table 2 shows the change of RT with age and gender in central macula, inner ring and outer ring (nine subfields). The variation trend with age in the nine subfields was significant. It is seen from the table that for subjects up to 70 years old, the RT of the central macula gradually increased with age. After 70 years old, it decreased with the increase of age. For different subfields of the inner ring, the variation trend with age was different. Among

Table 2 Distribution of macular thickness measurements in healthy eyes by age and gender

Characteristic	Age						Gender			
	<40 (N=436)	41–50 (N=528)	51–60 (N=1906)	61–70 (N=1536)	≥70 (N=494)	β coefficient	P value	Female (N=2722)	Male (N=2178)	t	P value
Central macular subfield	232.48±20.41	234.20±18.84	238.81±22.53	238.86±23.80	234.94±27.52	1.054	0.001	233.67±22.83	242.01±22.49	−12.794	<0.001
Inner rings											
Tempo	311.64±16.36	308.28±18.31	308.57±18.85	305.16±19.11	296.59±21.99	−3.132	<0.001	302.99±18.39	310.96±19.69	−14.501	<0.001
Superior	317.39±15.67	314.00±17.38	312.65±18.39	309.47±18.67	301.73±19.93	−3.401	<0.001	307.79±17.79	315.28±19.01	−14.211	<0.001
Nasal	312.81±16.93	309.81±17.35	309.91±19.06	307.08±19.85	297.94±21.11	−2.999	<0.001	304.74±19.28	312.21±19.06	−13.542	<0.001
Inferior	319.63±16.56	316.15±17.58	315.08±18.87	311.53±19.54	303.86±19.79	−3.461	<0.001	309.99±18.67	317.56±19.15	−13.946	<0.001
Superior hemisphere	312.12±15.67	309.08±17.54	308.41±18.05	305.41±18.50	296.57±20.36	−3.248	<0.001	303.34±17.71	310.85±18.83	−14.341	<0.001
Inferior hemisphere	318.61±16.76	315.04±17.37	314.69±19.12	311.21±18.72	303.49±19.91	−3.248	<0.001	309.42±18.42	317.16±19.01	−14.414	<0.001
Average thickness	315.37±15.99	312.06±17.16	311.55±18.12	308.31±18.10	300.03±19.33	−3.248	<0.001	306.38±17.51	314.00±18.52	−14.672	<0.001
Outer rings											
Tempo	282.23±13.65	279.18±15.15	278.88±15.77	275.94±17.30	268.42±17.74	−2.91	<0.001	275.38±16.61	279.55±16.28	−8.8153	<0.001
Superior	275.48±12.19	272.75±11.96	272.46±13.30	269.91±13.65	264.47±17.12	−2.375	<0.001	269.86±14.18	272.77±13.34	−7.3329	<0.001
Nasal	290.06±13.78	286.99±14.34	286.25±15.90	284.04±17.86	277.41±17.27	−2.629	<0.001	283.23±16.38	287.41±16.65	−8.8063	<0.001
Inferior	284.98±12.52	282.67±13.77	280.90±15.04	278.05±15.13	272.27±16.90	−2.904	<0.001	279.09±14.88	280.44±15.72	−3.0472	<0.001
Superior hemisphere	275.28±12.33	272.26±12.28	272.33±13.62	269.98±15.31	263.31±16.97	−2.443	<0.001	269.11±14.88	273.22±13.90	−9.902	<0.001
Inferior hemisphere	291.09±13.33	288.53±15.07	286.91±15.41	283.99±15.43	277.97±15.94	−2.966	<0.001	284.67±15.13	286.86±16.11	−4.8541	<0.001
Average thickness	283.19±12.40	280.40±12.99	279.62±13.94	276.98±14.43	270.64±15.57	−2.705	<0.001	276.89±14.21	280.04±14.40	−7.6696	<0.001

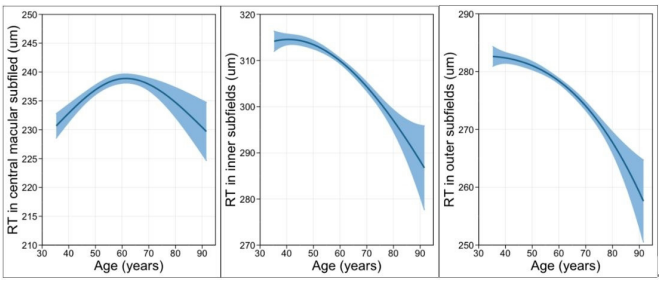

Figure 2 RT change in central macular, inner and outer rings along with age. The smooth curves in the figure represent the average RT in three subfields and the blue areas represent the 95% RT CI. RT retinal thickness.

them, the RT of the superior and inferior subfields showed a downward trend with age, while the RT of the nasal and temporal ones decreased with age before the age of 40, increased with age between 50 and 60 and decreased with age again after 60. The RT in superior hemisphere, inferior hemisphere and the whole inner ring showed the same variations as that of the superior and inferior subfields. In the outer ring, the RT in the four subfields all gradually decreased with age. The RT in the inferior hemisphere and whole outer ring showed the same variations as the four outer rings. While the RT in the superior hemisphere decreased before 50, increased slightly between 50 and 60, then decreased again after 60. It is seen from figure 2 that the RT changed with age intuitively. In the central macular subfield, RT increased with age before 60, and then decreased. While in inner and outer rings, RT decreased all the way with age.

It also is seen from table 2 that among all of the nine subfields, RT was thicker in men than in women, especially in central macula and inner ring, where the RT difference between men and women was around 7 µm to 8 µm. In the outer ring, however, the difference was smaller, around 1 µm to 4 µm. Figure 3 shows the differences. Besides, it can also be seen that in both men and women, the RT in central macula was the thinnest, followed by outer ring, and the RT in inner ring was the thickest. In the inner ring, the RT in the temporal was the thinnest, followed by nasal and superior and inferior. While in the outer ring, RT in the superior was the thinnest, followed by temporal, inferior and nasal.

The univariate linear regression model was used to estimate the correlation between demographic characteristics, medical history, behaviour, ocular parameters and the RT in central macula, inner and outer rings (see table 3). The results have demonstrated that age, gender, education, current smoker, BMI, HDL, spherical equivalent, AL, ACD and keratometry were significantly associated with the RT in central macular subfield ($p<0.05$). RT in the inner ring was correlated with age, gender, education, current smoker, BMI, SBP, diabetes, HbA1c, LDL, coronary heart disease, cataract surgery, spherical equivalent, AL, ACD, vertical C/D, keratometry and BCVA. In the outer ring, RT was correlated with age, gender, education, current smoker, BMI, SBP, diabetes, HbA1c, LDL, coronary heart disease, cataract surgery, AL, ACD, vertical C/D, keratometry and BCVA ($p<0.05$). However, other parameters had not shown any relationship with RT in those three areas.

Table 4 shows the results of multivariate linear regression, in which the association among the variables that were found statistically significant ($p\leq0.05$) in the univariate linear model or those with clinical significance and the RT in central macula, inner and outer rings were analysed. The results demonstrated that gender (B=6.53, $p<0.001$), BMI (B=–0.34, $p=0.005$), spherical equivalent (B=–0.57, $p=0.036$) and ACD (B=3.81, $p=0.004$) were significantly related to the RT in central macular subfield, while other variables became less significant.

In the inner ring, age (B =–0.44, $p<0.001$), gender (B=5.76, $p<0.001$), diabetes (B =–5.59, $p=0.001$), ACD (B=2.79, $p=0.005$) and BCVA (B =–7.80, $p<0.001$) were significantly related to RT. And in the outer ring, there was a significant correlation between age (B =–4.00, $p<0.001$), gender (B=3.71, $p<0.001$), education (B =–0.16, $p=0.027$), BMI (B =–0.16, $p=0.027$), AL (B=–0.83, $p=0.002$), vertical C/D (B=–7.71, $p<0.001$) and keratometry (B=0.73, $p<0.001$). It can be seen from the table that in the three subfields, namely, central macula, inner and outer rings, the multivariate linear regression demonstrated that gender was all correlated with the RT. Considering that some variables of significance in the univariate analysis showed non-significance in the multivariate regression due to their minor impact on the outcome variable by a stepwise method, some variables like current smoker and LDL were not selected in this analysis.

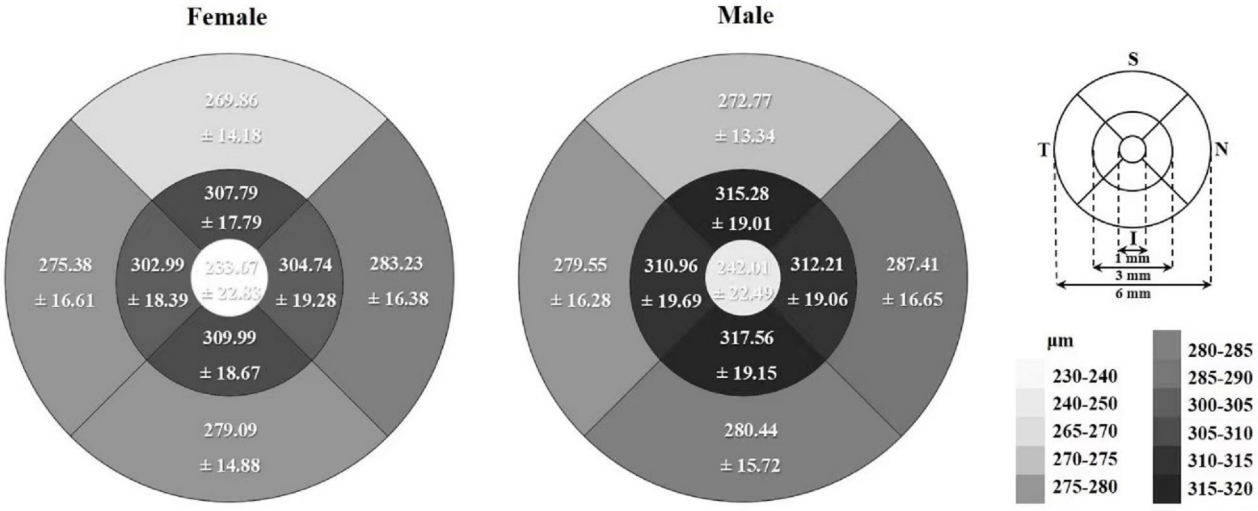

Figure 3 The RT distribution in nine sub-regions of macular retinal of male and female. RT retinal thickness.

Table 3 The univariate linear regression model for the association between demographic characteristics, medical history, behaviour, ocular parameters and central macular, inner and outer rings

	Central macular subfield				Inner rings				Outer rings			
Variables	B	SE	t	P value	B	SE	t	P value	B	SE	t	P value
Age	0.13	0.03	3.97	<0.001	−0.37	0.03	−14.43	<0.001	−0.30	0.02	−15.16	<0.001
Gender	8.34	0.65	12.79	<0.001	7.63	0.52	14.76	<0.001	3.15	0.41	7.67	<0.001
Education	−4.61	1.96	−2.35	0.019	−4.62	1.56	−2.96	0.003	−2.48	1.22	−2.02	0.043
Current smoker	6.31	0.74	8.50	<0.001	6.22	0.59	10.52	<0.001	2.95	0.47	6.32	<0.001
BMI	−0.37	0.08	−4.48	<0.001	−0.16	0.07	−2.42	0.016	−0.17	0.05	−3.4	0.001
SBP	0	0.023	0.02	0.985	−0.07	0.01	−5.67	<0.001	−0.06	0.01	−6.20	<0.001
DBP	−0.01	0.0	−0.28	0.778	0.02	0.02	0.78	0.436	−0.03	0.02	−1.81	0.070
Diabetes	−1.99	1.68	−1.19	0.236	−7.73	1.33	−5.81	<0.001	−4.20	1.04	−4.04	<0.001
HbA1c	−0.34	0.46	−0.75	0.453	−2.13	0.36	−5.89	<0.001	−1.21	0.28	−4.26	<0.001
HDL	−3.52	1.20	−2.93	0.003	0.07	0.95	0.07	0.943	0.85	0.74	1.15	0.252
LDL	−0.89	0.46	−1.96	0.050	−0.79	0.36	−2.19	0.029	−0.86	0.28	−3.08	0.002
Triglycerides	−0.43	0.32	−1.35	0.179	−0.23	0.25	−0.91	0.361	−0.14	0.20	−0.70	0.485
CHD	1.20	1.20	0.99	0.320	−3.17	0.98	−3.30	0.001	−2.44	0.76	−3.22	0.001
Cataract surgery	0.13	3.53	0.04	0.970	−6.72	2.81	−2.39	0.017	−4.59	2.2	−2.09	0.037
IOP	0.25	0.14	1.85	0.064	0.19	0.11	1.70	0.089	−0.09	0.09	−1.04	0.301
Spherical equivalent	−0.44	0.20	−2.18	0.029	−0.43	0.16	−2.71	0.007	−0.09	0.12	−0.70	0.482
AL	1.91	0.35	5.52	<0.001	1.41	0.27	5.16	<0.001	−0.76	0.21	−3.57	<0.001
CCT	−0.01	0.01	−0.74	0.459	0.01	0.01	1.39	0.166	−0.00	0.01	−0.39	0.699
ACD	5.33	0.96	5.52	<0.001	7.23	0.76	9.55	<0.001	2.78	0.60	4.66	<0.001
Vertical C/D	−0.26	2.52	−0.11	0.917	−4.82	2.00	−2.42	0.016	−8.06	1.56	−5.178	<0.001
Keratometry	−0.77	0.22	−3.59	<0.001	−0.91	0.17	−5.28	<0.001	0.55	0.14	4.063	<0.001
BCVA	−1.05	2.13	−0.49	0.623	−15.94	1.69	−9.46	<0.001	−8.24	1.32	−6.23	<0.001

Gender: male versus female; education: below high school versus high school or above.
ACD, anterior chamber depth; AL, axial length; BCVA, best-corrected visual acuity; BCVA, best-corrected visual acuity; BMI, body mass index; CCT, central corneal thickness; CHD, coronary heart disease; DBP, diastolic blood pressure; HDL, high-density lipoprotein; IOP, intraocular pressure; LDL, low-density lipoprotein; OCT, optical coherence tomography; SBP, systolic blood pressure; Vertical C/D, vertical cup disc ratio.

Figure 4 shows these relationships in an intuitive way. In the central macular subfield, the RT in the subjects increased before 60 years old and decreased with age after 60. In inner and outer rings, RT decreased all the time with age. Male subjects had thicker RT in all of the three subfields than women. Subjects who had higher education, smoked and did not have diabetes had thicker RT than others. However, BMI, SBP, HbA1c, AL, SE, ACD, keratometry and vertical C/D had inconsistent effects on RT in the three subfields and the details are shown in figure 4.

DISCUSSION

Our study has demonstrated normal distribution of macular RT by SD-OCT in a rural adult population in China, which showed that

Table 4 The multivariate linear regression model for the association between demographic characteristics, medical history, behaviour, ocular parameters and central macular, inner and outer rings

	Central macular subfield				Inner ring				Outer ring			
Variables	B	SE	t	P value	B	SE	t	P value	B	SE	t	P value
Age					−0.44	0.05	−9.44	<0.001	−4.00	0.04	−10.93	<0.001
Gender	6.53	0.92	7.09	<0.001	5.76	0.69	8.33	<0.001	3.71	0.56	6.66	<0.001
Education					−3.20	1.83	−1.75	0.080	−4.13	1.44	−2.87	<0.001
BMI	−0.34	0.12	−2.79	0.005	−0.16	0.09	−1.72	0.087	−0.16	0.07	−2.21	0.027
SBP					−0.03	0.02	−1.61	0.107	−0.02	0.01	−1.57	0.115
Diabetes					−5.5	1.62	−3.45	0.001	−2.21	1.27	−1.74	0.082
HDL	−3.23	1.67	−1.93	0.054								
Spherical equivalent	−0.57	0.27	−2.10	0.036								
AL									−0.83	0.27	−3.12	0.002
ACD	3.81	1.34	2.85	0.004	2.79	1.00	2.80	0.005				
Vertical C/D									−7.71	1.96	−3.94	<0.001
Keratometry									0.73	0.19	3.90	<0.001
BCVA					−7.81	2.04	−3.84	<0.001	−2.91	1.60	−1.83	0.068

Gender: male versus female; education: below high school versus high school or above.
ACD, anterior chamber depth; AL, axial length; BCVA, best-corrected visual acuity; BMI, body mass index; Vertical C/D, vertical cup disc ratio; HDL, high-density lipoprotein; SBP, systolic blood pressure.

Figure 4 The relationship between demographic characteristics, medical history, behaviour, ocular parameters and central macular, inner and outer rings in multivariate linear regression analysis.

RT in central macular subfield was the thinnest, followed by the outer ring, and that the RT in the inner ring was the thickest. The pattern of RT distribution was consistent with previous studies.[3 10 11]

The RT in central macular subfield, inner ring and outer ring were 237.38 µm±23.05 µm, 309.77 µm±18.36 µm and 278.29 µm±14.38 µm, respectively, which were thicker than those in Adhi M's study (229.0 µm, 292.6 μm, 268.5 μm, respectively)[3] and thinner than those in other previous studies (8 µm to 48 µm, 1 µm to 28 µm, 8 µm to 21 µm thinner, respectively)[3 10 12–15] by SD-OCT. The differences might be attributed to the different placement of the posterior boundary for measuring RT among SD-OCT instruments,[16] together with the differences in ethnic groups, subjects demographics and inclusion criteria of studies.[15 17] The RT measured by SD-OCT in our Handan follow-up study was much thicker than that measured by TD-OCT in our Handan baseline study (176.4 µm, 255.3 µm, 237.7 µm, respectively).[18] Masashi Kakinoki *et al* also discovered that similar to our study, the average RT measured with the SD-OCT was approximately 60 µm thicker than that measured with TD-OCT.[19] The difference was also attributed to different outer boundaries. The former was IS/OS, and the latter was OS/RPE mean reflectance location,[9] the distance between the IS/OS and the retinal pigment epithelium measured with SD-OCT was approximately 54 µm, which can explain the difference in RT between two OCT instruments.[19] In addition, the macular thickness map in TD-OCT was derived from fewer data points (768 axial scans/image, acquired from six 6 mm linear scans over a 3608 area), thus requiring mathematic interpolations to estimate the thickness for the spaces in between.[8] While SD-OCT got detailed mapping of the macula, wherein macular thickness was derived from far more data points (a total of 40 000 axial scans/images in 200×200 scan prototype), leading to more reliable and

Table 5 Summary of reports on macular thickness measurements in healthy subjects using different spectral domain-OCT device

Study	Country	Year	SD-OCT system	Mean age±SD	Number of eyes/subjects searched	Central macular thickness (mean µm±SD)	Foveal macular volume (mm^3)	Total macular volume (mm^3)	Repeatability of full-retinal layer thickness (ICC, 95% CI)
Hanno *et al*[22]	Norway	2007–2008	Cirrus HD-OCT (Carl Zeiss Meditec)	61.0±8.0	7686/4508	265.9±21.4	NA	8.02±0.36	NA
Hashemi *et al*[23]	Iran	2008–2009	Cirrus HD-OCT (Carl Zeiss Meditec)	54.2±5.6	3024/3024	255.4±23.8	NA	10.01±0.51	NA
Song *et al*[14]	Korea	2008–2009	Cirrus HD-OCT (Carl Zeiss Meditec)	55.6±16.4	198/198	253.9±24.2	NA	9.74±0.71	NA
Myers *et al*[24]	United States	2008–2010	Topcon 3D OCT-1000 Mark II	72.6±6.3	1838/977	287.5±27.0	NA	NA	NA
Adhi *et al*[3]	Pakistan	2009–2010	Topcon 3D OCT-1000 Mark II	45.3	220/220	229.0±20.5	NA	NA	NA
Patel *et al*[17]	United Kingdom	2009–2010	Topcon 3D OCT-1000 Mark II	55.2±8.2	32062/32062	264.5±22.9	NA	7.87±0.37	NA
Gupta *et al*[11]	China	2009–2011	Cirrus HD-OCT (Carl Zeiss Meditec)	53.2±6.1	490/490	250.4±20.6	NA	10.09±0.41	NA
Chua *et al*[25]	China, Malaysia and India	2009–2011	Cirrus SD-OCT (Carl Zeiss Meditec)	56.0±8.0	3043/2047	251.8±24.8	NA	NA	NA
Ooto *et al*[26]	Japan	2010	3D-OCT 1000	48.6	248/248	221.9±18.8	NA	NA	NA
Choovuthayakorn *et al*[27]	Thailand	2011	Spectralis (Heidelberg Engineering)	49.2±17.2	368/368	259.2±19.1	0.20±0.02	8.59±0.37	NA
Wang *et al*[28]	China	2011	Spectralis (Heidelberg Engineering)	60.0±8.0	384/384	259.8±18.9	NA	NA	NA
Pokharel *et al*[29]	Nepal	2013	Spectralis (Heidelberg Engineering)	21.2±6.8	126/63	247.7±19.9	0.20±0.02	8.49±0.31	NA
Natung *et al*[30]	India	2013–2014	Cirrus HD-OCT (Carl Zeiss Meditec)	38.1±12.1	800/400	240.4±18.3	NA	NA	NA
Al-Zamil *et al*[31]	Saudi	2015	Cirrus HD-OCT (Carl Zeiss Meditec)	29.9±7.85	158/158	244.8±23.6	0.20±0.02	8.48±0.35	NA
Invernizzi *et al*[32]	Italy	2017	Spectralis (Heidelberg Engineering)	39.9±13.9	200/200	280.1±17.5	NA	NA	0.995

ICC, intraclass correlation coefficient; OCT, optical coherence tomography.

reproducible measurements.[10] What is more, when compared with other SD-OCT systems from different companies, RTVue exhibited approximately 42 µm shorter than Spectralis in the measurement of central RT,[20] the latter was thought to have higher reproducibility than others.[21] This difference was induced by different outer retinal boundary definition of various OCT instruments.[21] The comparison of RTVue and other SD-OCT systems is summarised in online supplemental table 2. In addition, previous reports[3 11 14 17 22–32] on macular thickness measurements of healthy subjects with SD-OCT are exhibited in table 5.

The RT in the inner ring was temporal, nasal, superior and inferior from thin to thick and the RT in the outer ring was superior, temporal, inferior and nasal from thin to thick. The RT distribution pattern was consistent in both genders and across all age groups in our study as well as in previous studies with different types of OCT or RT analysers.[33–36] This might be attributed to the crowding of nerve fibres in the inner ring and along with the anatomy of the converging of nerve fibres around the optic disc.[36 37] Besides, it was also found that the RT in superior hemisphere in both inner and outer rings was thicker than that in inferior ones. The reason might be that the number of inferior arcuate bundling of the nerve fibres was greater than that of superior arcuate bundling because of gravity. However, more studies are necessitated to explore more possible reasons.

It was found in the study that RT changed with age, and the variation trends in different subfields were different. In central macula, the RT increased in subjects before 60 years old and decreased with age after 60. In inner and outer rings, the variation trends of RT were consistent, which showed that the RT decreased all the way with age. The results were consistent with those from several previous studies.[22 38] The decline in RT with age seen in inner and outer rings possibly reflects atrophic changes with age, which corresponds to histologic studies that has presented a decrease in density of photoreceptors, ganglion cells, retinal pigmented epithelium and optic nerve fibres as people grow older.[39 40] While the thickening of the central macular subfield in the lower ages may reflect other ageing processes, probably the accumulation of extracellular or intracellular debris. Nevertheless, the reason needs to be further explored.[41 42]

Our study has demonstrated that compared with female subjects, male subjects had significantly greater RT in the nine regions, which was more prominent in the central macula and inner ring. The findings were in alignment with the observations in several previous studies.[11 13 17] This may explain why certain macular conditions, such as macular hole, occur more frequently in women.[43 44] The animal model also showed that women had thinner retina than men, which might be attributed to the higher ratio of parvocellular retina ganglion cells to magnocellular retina ganglion cells in women than in men.[45]

It was found in the multiple regression analysis that except age and gender, other ocular and systemic parameters were associated with RT in macular retina. In central macular subfield, RT increased with the deepening of ACD and a low SE and decreased with the increase in BMI. The reason why RT changed with SE might be that decreased SE (higher myopia) usually existed with long AL, which could induce stretching tendency of the ILM and centripetal force of the posterior vitreous,[38] thereby resulting in the traction and elevation of RT in central macular subfield. Interestingly, the results were controversial from some previous studies,[46 47] which indicated that the precise explanation for the change of RT with SE was uncertain. Recently, Sun *et al* reported some new loci for myopia and relevant ocular biometric parameters,[48] suggesting us to take these genetic factors into account for the trend of RT variation. In addition, the reason why the RT in macular subfield associated with BMI and ACD might be accidental and the real causes should be explored. In the inner ring, the RT had a positive correlation with ACD and a negative correlation with diabetes and BCVA. Those with diabetes had a smaller RT in the inner ring. And in the outer ring, there was a positive correlation between keratometry and RT, while there was a negative correlation between RT and education, BMI, AL, vertical C/D. When the AL increased, the retina stretched with the eyeball, and the RT in the outer ring, thus, decreased.

Our study was a population-based study, which reduced the selection bias inherent in previous hospital-based or university-based studies. In addition, the correlation between RT and a wide range of ocular and systemic factors in a standardised way was analysed. However, there were several limitations in our study. First, it was a population-based study, in which the causal relationships between RT and the factors of interest cannot be established. Second, the RT measurements were obtained from subjects with an age over 36 years, which cannot be extrapolated to earlier adulthood and childhood. Third, due to the strict inclusion criteria, only normal healthy eyes were included, and nearly 40% of the subjects in our study were excluded from the final analysis. Therefore, the generalisability of our study results might be limited. The last but not the least, the subjects in our study consisted only Chinese, and the findings may differ in other ethnic groups.

In conclusion, our study has provided data for normal RT in macular area of eyes from individuals aged 36 years and above in an adult population in China. The data may be useful for those who are planning clinical trials or diagnosing retinal diseases. We have confirmed findings in other studies of the relationships between age, sex and RT. What's more, we have also found that education, BMI, diabetes, SE, AL, ACD, vertical C/D, keratometry and BCVA had some effects on RT in the central macula, inner ring and outer ring. When explaining the RT, the associated factors need to be considered.

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Supplementary Table 1. Distribution of macular thickness measurements in the health eyes

Variables	Mean	SD	Q0.01	Q0.05	Q0.5	Q0.95	Q0.99
Central macular subfields	237.38	23.05	180.15	201.83	236.86	273.19	297.29
Inner rings							
Tempo	306.53	19.39	245.49	275.96	307.37	335.46	349.58
Superior	311.12	18.71	257.71	280.19	311.97	339.08	352.59
Nasal	308.06	19.54	249.82	276.56	308.85	337.14	351.87
Inferior	313.35	19.25	254.53	282.82	313.93	342.78	353.5
Superior Hemisphere	306.68	18.59	251.66	275.92	307.35	334.75	346.78
Inferior Hemisphere	312.86	19.07	255.92	282.26	313.35	342.55	353.71
Average thickness	309.77	18.36	254.63	279.7	310.24	338.08	348.93
Outer rings							
Tempo	277.23	16.59	234.75	253.62	277.5	301.39	313.28
Superior	271.15	13.89	234.76	250.25	270.95	293.09	302.73
Nasal	285.08	16.63	242.54	260.9	284.94	309.37	321.03
Inferior	279.69	15.27	237.18	255.96	279.9	303.88	315.03
Superior Hemisphere	270.94	14.6	233.3	249.35	270.84	292.78	303.18
Inferior Hemisphere	285.64	15.61	247.47	261.56	285.8	309.89	321.25
Average Thickness	278.29	14.38	240.57	256.1	278.43	300.7	311.32

Note: SD: standard deviation; Q0.01: 1 percentile; Q0.05: 5 percentile; Q0.5: 50 percentile; Q0.95: 95 percentile; Q0.99: 99 percentile

Supplementary Table 2. Comparison of RTVue 100-2 OCT used in our study with other spectral domain-OCT instruments

Type of SD-OCT(company)	Axial Resolution (μm)	A-Scans per Second	Features
RTVue-100 (Optovue)	5	26000	Point-to-point tracking with eye movement; high resolution of anterior segment imaging
Cirrus HD-OCT (Carl Zeiss Meditec)	5	27000	Fixation-independent scan adjustment; high resolution of anterior segment imaging
Spectralis (Heidelberg Engineering)	7	40000	Point-to-point tracking with eye movement; high digital resolution; 6 kinds of diagnostic methods; advanced choroidal pattern
3D-OCT 1000	6	18000	With no need for mydriasis and color fundus photographs can be acquired
Spectral OCT/SLO (OPKO/OTI)	5	27000	Point-to-point tracking with eye movement; high resolution of anterior segment imaging; precise macular measurement
SOCT Copernicus (Optopol)	6	25000	Point-to-point tracking with eye movement; high resolution of anterior segment imaging; more accurate layers of retina; judgement of the intraretinal cyst volume
SDOCT (Bioptigen)	4	20000	Appropriate for pediatric patients and animal experiments; portable type; Doppler blood flow analysis of retina

Note: OCT stands for Optical coherence tomography.