

Macular thickness in healthy eyes of adults ($N = 4508$) and relation to sex, age and refraction: the Tromsø Eye Study (2007–2008)

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ABSTRACT.

Purpose: To provide sex-stratified normative data on retinal thickness and study the relationship with sex, age and refractive status.

Methods: Population-based study including 2617 women and 1891 men, aged 38–87 (mean 61 ± 8) years, without diabetes, glaucoma and retinal diseases, and spherical equivalent refraction (SER) within ± 6 dioptres. Retinal thickness was measured with optical coherence tomography (spectral domain Cirrus HD-OCT).

Results: Women had thinner retina than men. Retinal thickness was significantly associated with refraction, where mean change in retinal thickness per 1 D increase in SER was -1.3 (0.2) μm in the fovea, 0.7 (0.1) μm in the pericentral ring and 1.4 (0.1) μm in the peripheral ring. In the fovea, there was a non-monotonic curved relationship between retinal thickness and age in both sexes with a maximum at about 60 years ($p < 0.001$). In the pericentral ring, the mean reduction in retinal thickness per 10-year increase was 2.7 (0.3) μm in women and 4.0 (0.4) μm in men and corresponding results in the peripheral ring were 2.3 (0.3) μm in women and 2.6 (0.4) μm in men. In both regions, there was evidence for a nonlinear pattern with an increased rate of change with higher age. There was a significant interaction between sex and age for retinal thickness of the pericentral ring ($p = 0.041$).

Conclusion: Women had thinner retina than men, and thickness varied with refractive status. Retinal thickness was associated with age in all macular regions, and the rate of change in retinal thickness varied at different ages.

Key words: age – epidemiology – optical coherence tomography – population based – refraction – retina – sex

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Introduction

Optical coherence tomography (OCT) is a non-invasive imaging technology, widely used in clinical practice to evaluate retinal thickness and the presence of structural changes in retinal diseases. Normative data from OCT software are not publicly available. Further, available OCT devices differ in segmentation algorithms, so measurements are not directly comparable between instruments (Giani et al. 2010; Pierro et al. 2010; Tan et al. 2015).

Most studies on retinal thickness from OCT have been small and partly clinically based, while a few larger scale population-based studies have been published recently (Duan et al. 2010; Tariq et al. 2011; Gupta et al. 2013; Myers et al. 2015). There is good evidence that women have thinner retina than men (Kelty et al. 2008; Eriksson & Alm 2009; Duan et al. 2010; Ooto et al. 2010; Song et al. 2010; Adhi et al. 2012; Gupta et al. 2013; Myers et al. 2015). High age has been found to be associated with thinner retina in the peripheral macula in most studies while results considering the foveal thickness as well as change with age in younger adults have been

inconsistent (Duan et al. 2010; Ooto et al. 2010, 2011; Song et al. 2010; Adhi et al. 2012; Demirkaya et al. 2013; Gupta et al. 2013; Myers et al. 2015). Refractive status and axial length seem to affect retinal thickness in the macula (Lam et al. 2007; Duan et al. 2010; Song et al. 2010; Gupta et al. 2013; Myers et al. 2015). Studies have shown differences in retinal thickness between different ethnic populations (Kelty et al. 2008; Girkin et al. 2011; Tariq et al. 2011).

Reliable normative data are important in both scientific and clinical settings. We aimed to investigate the influence of sex, age and refraction on the retinal thickness of the macula in persons without retinal diseases in a large population-based study of women and men with a broad age span.

Subjects and Methods

Study sample

The Tromsø Eye Study is a substudy of the Tromsø Study, a population-based multipurpose longitudinal study from the municipality of Tromsø, Norway. Participants were identified through the Population Registry of Norway, and the study selection criterion has been a combination of total and random samples of birth cohorts of the inhabitants of Tromsø, with details published elsewhere (Jacobsen et al. 2012; Bertelsen et al. 2013). The Tromsø Eye Study 1 was conducted in 2007–2008 within the sixth survey of the Tromsø Study. A total of 7306 persons attended (attendance rate of 64%) and 91% reported Caucasian ethnicity. Optical coherence tomography (OCT) scan of at least one eye was carried out in 6279 participants. We excluded participants with glaucoma and/or diabetes ($n = 828$). We further excluded eyes with OCT scans of low quality or with pathology on scans, eyes with high refractive error (spherical equivalent refraction) $>+6.0$ dioptres (D) or <-6.0 D, and eyes with retinal vascular occlusion evaluated from fundus photo, leaving 2617 women and 1891 men who were included in the study (Fig. S1). The study adhered to the tenets of the Declaration of Helsinki and was approved by the Data Inspectorate of Norway and Regional Committee for Medical and Health Research Ethics.

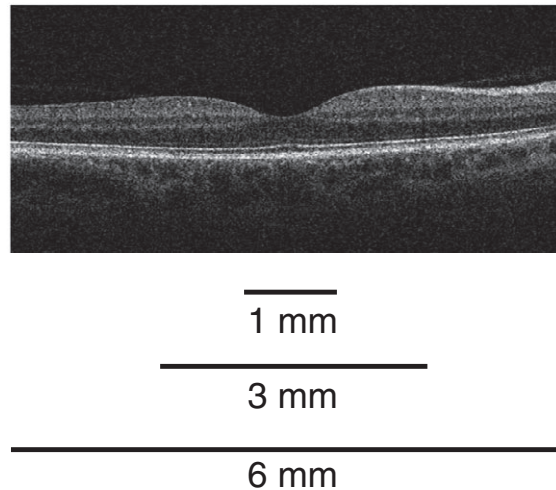
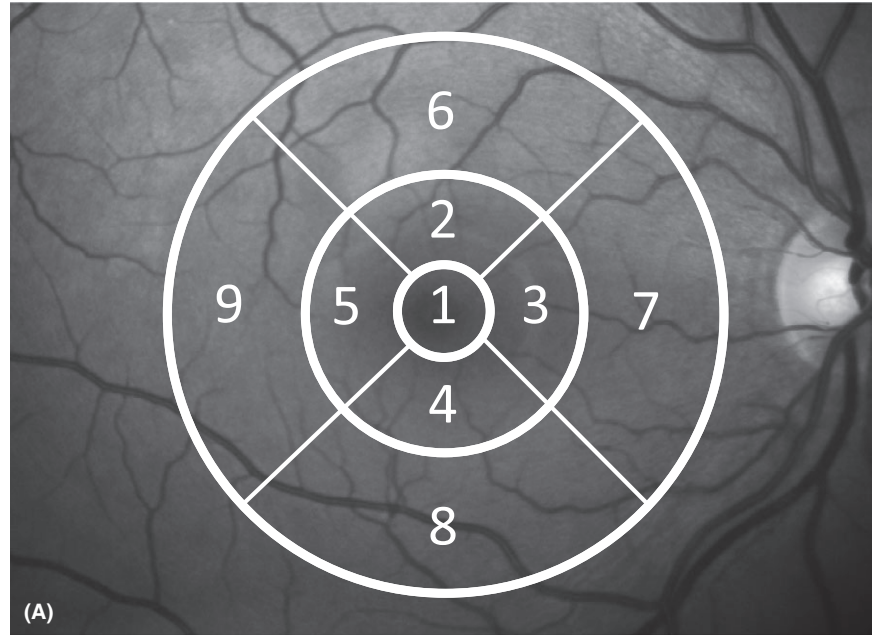


Fig. 1. Optical coherence tomography (OCT) scan and the nine sectors of the ETDRS grid. (A) The nine sectors of the ETDRS grid (right eye). Fovea (sector 1), pericentral ring (sectors 2–5) and peripheral ring (sectors 6–9). (B) Representative horizontal spectral domain Cirrus HD-OCT (Carl Zeiss Meditec) scan through the fovea from the right eye of a healthy subject.

Procedures

Refraction was measured by Nidek AR 660A auto refractor (Nidek CO., LTD., Gamagori, Japan). Spherical equivalent refraction (SER) was calculated as spherical power plus half the cylindrical power in dioptres. Both pupils were dilated with tropicamide 0.5% (Chauvin Pharmaceuticals Ltd., Kingston Upon Thames, Surrey, England). Five-field 45-degree retinal colour photographs were taken on both eyes with a Visucam PRONM (CZM) digital retinal camera. Optical coherence tomography scans were taken of both eyes with the spectral domain

(SD) Cirrus HD-OCT model 4000 (Carl Zeiss Meditec (CZM), Jena, Germany), using the standard '512 × 128 macular cube' scan protocol. CIRRUS HD-OCT research browser v.5.0 was used to evaluate scans (Bertelsen et al. 2013). A manual evaluation was performed to validate the automated lines for internal limiting membrane (ILM) and retinal pigment epithelium (RPE; segmentation line is drawn in the middle of the RPE band; Giani et al. 2010; Tan et al. 2015), and if scans were centred allowing measures of all nine sectors of the ETDRS (Early Treatment Diabetic Retinopathy Study) grid (Fig. 1). The presence of pathology on

OCT within the whole macular cube was manually evaluated in regard to drusen, pigment epithelial detachment, epiretinal fibrosis, oedema, atrophy of RPE or retina, vitreomacular traction and/or macular hole. Automated measurements of average retinal thickness between ILM and RPE of nine subfields of the ETDRS grid (Fig. 1), macular volume of the total ETDRS grid and OCT scan signal strength were exported for analyses, all algorithms were supplied by CZM. Good quality scan was defined as scan satisfying (I) no defects or errors in the automated lines for ILM and RPE and (II) well centred and (III) signal strength ≥ 5 .

Data on prevalent disease and cardiovascular risk factors were collected from questionnaires, laboratory testing and physical examinations, and details are given elsewhere (Jacobsen et al. 2012; von Hanno et al. 2014). The presence of glaucoma was based on self-report from questionnaires. Diabetes was defined as self-reported diabetes and/or use of diabetes medication and/or HbA1c $\geq 6.5\%$. Non-fasting blood samples were obtained by venipuncture, and laboratory measurements were performed at the University Hospital of North Norway. HbA1c was measured in EDTA whole blood by high-performance liquid chromatography (HPLC) using an automated analyser (Variant II, Bio-Rad Laboratories Inc., Hercules, CA, USA).

Statistical analyses

STATA/MP 14.0 for Mac (StataCorp, College Station, TX, USA) was used for all statistical analyses. p-Values < 0.05 were considered significant. Descriptive statistics were calculated for participant characteristics. Correlation between thickness measurements between right and left eyes was assessed with Pearson's correlation tests, and mean values of retinal thickness and refraction of both eyes were used when both eyes were available. Retinal thickness in nine sectors, the average of the four inner subfields (pericentral ring), the average of the four outer subfields (peripheral ring; Fig. 1) and retinal volume of the ETDRS grid were summarized and tested for gender difference in linear regression adjusted for age. Measurements were summarized in age groups < 50 years, ≥ 80 years and

Table 1. Macular thickness and volume in healthy eyes in women, by age groups. Tromsø Eye Study 2007–2008.

	Age groups (years)						Linear trend* p		
	< 50	50–55	55–60	60–65	65–70	70–75		75–80	≥ 80
Number of subjects	129	446	436	792	402	229	137	46	2617
Macular thickness (μm)									
Fovea (1 mm diameter)	259.5 (17.0)	259.6 (20.5)	261.9 (20.6)	261.3 (19.5)	259.5 (20.6)	257.3 (20.0)	254.7 (18.5)	251.9 (21.2)	0.002
Pericentral ring (3 mm diameter)									
Nasal	327.6 (14.1)	326.9 (15.5)	327.7 (14.4)	325.8 (14.4)	323.4 (15.4)	320.4 (14.4)	317.9 (13.8)	315.7 (16.5)	< 0.001
Temporal	312.1 (13.2)	311.2 (14.2)	313.0 (13.9)	311.7 (13.3)	309.8 (14.4)	307.9 (13.6)	305.8 (13.2)	304.4 (15.9)	< 0.001
Superior	324.6 (14.5)	324.2 (15.1)	324.8 (13.9)	323.4 (13.7)	320.8 (15.0)	318.0 (14.2)	315.0 (13.9)	312.1 (18.1)	< 0.001
Inferior	321.6 (13.8)	320.5 (15.1)	321.6 (14.5)	319.7 (14.1)	317.8 (15.0)	315.0 (13.4)	312.9 (14.0)	311.4 (15.5)	< 0.001
Average	321.5 (13.5)	320.7 (14.5)	321.7 (13.7)	320.1 (13.5)	318.0 (14.5)	315.3 (13.4)	312.9 (13.3)	310.9 (16.0)	< 0.001
Peripheral ring (6 mm diameter)									
Nasal	295.4 (15.5)	294.6 (15.4)	294.1 (14.5)	291.7 (14.5)	289.5 (15.7)	285.9 (13.9)	283.9 (15.0)	282.7 (16.6)	< 0.001
Temporal	259.7 (12.8)	259.8 (12.4)	260.9 (12.3)	259.6 (12.2)	258.5 (12.9)	258.3 (11.5)	256.9 (12.9)	257.2 (13.7)	0.002
Superior	277.8 (14.1)	277.9 (13.5)	277.8 (12.9)	276.4 (12.5)	274.7 (13.9)	273.1 (12.8)	271.2 (14.6)	270.8 (15.5)	< 0.001
Inferior	267.9 (13.1)	267.4 (14.0)	268.2 (13.1)	266.0 (13.4)	264.7 (14.0)	263.2 (12.5)	261.6 (13.4)	260.8 (13.8)	< 0.001
Average	275.2 (13.1)	274.9 (13.1)	275.2 (12.5)	273.4 (12.3)	271.8 (13.4)	270.1 (11.7)	268.4 (13.1)	267.9 (14.0)	< 0.001
Macular volume (mm^3)									
ETDRS grid	8.048 (0.356)	8.038 (0.363)	8.053 (0.343)	8.004 (0.341)	7.956 (0.371)	7.900 (0.327)	7.847 (0.355)	7.822 (0.397)	< 0.001

Numbers are presented as mean (standard deviation).
* Linear regression, age treated as continuous variable.

5 years age groups in between, stratified by sex, and tested for linear trend over age by linear regression. From inspection of age-stratified thickness measurements we suspected a nonlinear relationship with age, we thus performed sex-stratified fractional polynomial regression (mfp, Stata), which allows for nonlinear relationships (Royston et al. 1999; Royston & Sauerbrei 2008). Models, adjusted for refraction, were fitted by first (FP1, monotonic, linear/nonlinear) and second (FP2, non-monotonic, nonlinear) degree fractional polynomials, with powers from the set $\varphi = (-2, -1, -1/2, 0, 1/2, 1, 2, 3)$, giving in total 44 different models. The best model was chosen according to Royston & Sauerbrei (2008). The p-value in FP2-models was obtained by log-likelihood test statistics comparing the model with the null model (variable not included). Associations, based on best (chosen) model, were graphically shown as fitted line. Regression residual plots from models, including smoothed residuals, were explored to evaluate model fit (Royston & Sauerbrei 2011). We performed sensitivity analyses on the part of the population aged 50–80 years to evaluate whether model choice was driven by the youngest and/or oldest age groups. Association with refraction was analysed by linear regression adjusted for sex and age, as there was no evidence of nonlinear relationship. Media opacities may influence retinal thickness measures (Darma et al. 2015) and we performed sensitivity analyses by restricting analyses to scans with signal strength ≥ 8 to see whether that affected the association with age and/or refraction. Explained variance, R^2 , was calculated for each sex-stratified model and a supplemental model including both sexes, and separate contribution from age, refraction and sex was evaluated by a R^2 -like statistics (Royston & Sauerbrei 2008). *Post hoc* we investigated multiplicative interaction between age and sex and age and refraction (difference between women and men in shape and/or slope of association) by entering the cross-products in the regression models.

Results

Characteristics of study participants are presented in Table S1. Thickness measurements of right and left eyes were

Table 2. Macular thickness and volume in healthy eyes in men, by age groups. Tromsø Eye Study 2007–2008.

	Age groups (years)							Linear trend*	
	< 50	50–55	55–60	60–65	65–70	70–75	75–80	≥ 80	p
Number of subjects	59	336	369	548	244	199	102	34	1891
Macular thickness (μm)									
Fovea (1 mm diameter)	271.1 (18.3)	273.9 (21.5)	276.4 (19.4)	276.5 (19.4)	273.6 (20.9)	269.7 (20.5)	267.2 (22.3)	267.9 (20.1)	0.001
Pericentral ring (3 mm diameter)									
Nasal	333.0 (15.0)	334.2 (16.2)	333.0 (15.7)	331.6 (14.9)	327.6 (14.6)	323.8 (16.0)	321.5 (16.3)	323.6 (14.7)	<0.001
Temporal	316.7 (15.1)	318.8 (15.4)	318.1 (15.2)	318.0 (14.3)	315.7 (14.5)	311.5 (14.4)	308.8 (16.0)	309.5 (14.8)	<0.001
Superior	328.8 (15.0)	328.8 (16.0)	328.0 (15.6)	327.3 (14.5)	323.7 (15.0)	319.6 (15.9)	315.4 (15.8)	317.5 (15.6)	<0.001
Inferior	325.7 (14.0)	326.3 (15.6)	325.1 (15.6)	324.0 (14.8)	321.0 (14.5)	317.4 (15.3)	314.8 (16.6)	314.9 (15.7)	<0.001
Average	326.1 (14.3)	327.0 (15.3)	326.0 (15.1)	325.2 (14.2)	322.0 (14.2)	318.1 (15.0)	315.2 (15.7)	316.4 (14.7)	<0.001
Peripheral ring (6 mm diameter)									
Nasal	294.8 (14.9)	295.0 (15.9)	293.9 (15.6)	292.6 (15.2)	288.9 (14.4)	286.2 (15.3)	282.6 (16.0)	285.3 (16.8)	<0.001
Temporal	263.4 (11.9)	264.2 (12.8)	263.4 (12.7)	263.8 (12.2)	263.1 (12.4)	260.9 (12.2)	258.2 (12.8)	258.3 (14.0)	<0.001
Superior	276.7 (12.6)	277.1 (13.5)	276.6 (13.4)	276.5 (13.2)	274.3 (13.4)	272.4 (13.5)	268.9 (14.0)	269.2 (16.7)	<0.001
Inferior	267.4 (11.3)	267.4 (13.8)	267.3 (13.6)	266.3 (12.9)	264.8 (13.0)	263.3 (13.0)	261.0 (13.8)	260.0 (16.0)	<0.001
Average	275.6 (11.8)	275.9 (13.2)	275.3 (13.1)	274.8 (12.6)	272.8 (12.5)	270.7 (12.8)	267.7 (13.1)	268.2 (15.2)	<0.001
Macular volume (mm^3)									
ETDRS grid	8.096 (0.331)	8.111 (0.372)	8.093 (0.366)	8.078 (0.352)	8.011 (0.350)	7.940 (0.361)	7.857 (0.375)	7.876 (0.416)	<0.001

Numbers are presented as mean (standard deviation).
* Linear regression, age treated as continuous variable.

Table 3. Macular thickness and volume in healthy eyes, total and by sex and association with refraction. Tromsø Eye Study 2007–2008.

	Total*	Sex		p [†]	Refraction	
		Women*	Men*		β-coeff (SE) [‡]	p
Number of subjects	4508	2617	1891		4352	
Macular thickness (μm)						
Fovea (1 mm diameter)	265.9 (21.4)	259.9 (20.0)	274.1 (20.4)	<0.001	-1.30 (0.17)	<0.001
Pericentral ring (3 mm diameter)						
Nasal	327.2 (15.6)	325.0 (15.0)	330.3 (15.9)	<0.001	0.59 (0.13)	<0.001
Temporal	313.2 (14.7)	310.8 (13.9)	316.5 (15.1)	<0.001	0.55 (0.12)	<0.001
Superior	323.7 (15.2)	322.3 (14.6)	325.6 (15.8)	<0.001	0.86 (0.13)	<0.001
Inferior	320.7 (15.1)	319.0 (14.6)	322.9 (15.6)	<0.001	0.93 (0.13)	<0.001
Average	321.2 (14.7)	319.3 (14.1)	323.9 (15.1)	<0.001	0.73 (0.12)	<0.001
Peripheral ring (6 mm diameter)						
Nasal	291.4 (15.5)	291.4 (15.3)	291.5 (15.8)	0.61	1.11 (0.13)	<0.001
Temporal	260.9 (12.6)	259.4 (12.4)	263.0 (12.6)	<0.001	1.62 (0.10)	<0.001
Superior	275.8 (13.5)	276.0 (13.4)	275.4 (13.6)	0.13	1.37 (0.11)	<0.001
Inferior	265.9 (13.5)	265.9 (13.6)	265.8 (13.4)	0.89	1.47 (0.11)	<0.001
Average	273.5 (12.9)	273.2 (12.8)	273.9 (13.0)	0.04	1.39 (0.11)	<0.001
Macular volume (mm ³)						
ETDRS grid	8.016 (0.362)	7.993 (0.356)	8.049 (0.368)	<0.001	0.033 (0.003)	<0.001

* Numbers are presented as mean (standard deviation).

† Linear regression, adjusted for age.

‡ Difference, β-coefficient (standard error), in thickness/volume pr. One dioptre increase in spherical equivalent refraction, linear regression adjusted for age and sex.

highly correlated, with correlation coefficients in the range 0.86–0.94 (all $p < 0.001$) for corresponding nine sectors, pericentral ring and peripheral ring. Compared to those excluded, persons included were younger and had lower blood pressure, HbA1c and SER and higher OCT signal strength, while other differences were only slight (Table S1).

Age-stratified thickness and volume measures with linear trends are given for women (Table 1) and men (Table 2). Women had thinner retina in the fovea and pericentral ring than men; while in the peripheral ring, women had thinner retina in the temporal sector only (Table 3). In both the pericentral and peripheral ring, the nasal sector was thickest, followed by the superior, inferior and temporal sector. These regional patterns were similar in women and men.

Retinal thickness of the fovea was nonlinearly associated with age, with a gradual increase by age to a maximum at about 60 years, followed by a steeper decline with increasing age (Fig. 2, panels A and D). The vertex occurred slightly earlier in men than in women, but this difference was not significant (p for interaction 0.6). Residual plots and sensitivity analyses supported the curved relationship (not shown).

In the pericentral and peripheral ring, the retinal thickness declined with

age in both women and men (Tables 1 and 2). In the pericentral ring, the mean reduction in retinal thickness per 10 years was 2.7 (0.3) μm in women and 4.0 (0.4) μm in men and corresponding results in the peripheral ring were 2.3 (0.3) μm in women and 2.6 (0.4) μm in men. In women, the association between retinal thickness in the peripheral ring and age followed a nearly linear pattern with age above 60 years, corresponding to men (Fig. 2, panels C and F). Still there was evidence for a nonlinear pattern (Fig. 2, panels B, C and E), with an increased rate of change with higher age. The tendency of a maximum at lower ages (e.g. non-monotonic relationship) seen in women was less robust, where results in the peripheral ring were dependent on measurements from the youngest age groups (results not shown). There was a significant interaction between sex and age for retinal thickness of the pericentral ring ($p = 0.041$), while not the peripheral ring ($p = 0.7$).

There was a significant association between retinal thickness and refraction. Higher SER was associated with thinner fovea and thicker retina in the pericentral and peripheral ring in both women and men. There was no significant interaction between sex and refraction in association with the thickness in either region ($p > 0.3$ for all);

thus, results are shown for women and men together (Table 3).

Restricting analyses to scans with superior signal strength (≥ 8 ; $N = 3627$), the association with age and refraction remained (results not shown). The non-monotonic curvilinear association with age in the fovea remained in both women and men. In the pericentral and peripheral ring, the curvilinear pattern with age was diminished, in women the association changed to monotonic curved (FP1 3) in both, while in men the curved relationship in the pericentral ring changed to linear.

Thickness measures of the fovea had more variance than of the pericentral and the peripheral ring (Tables 1 and 2). Sex, age and refraction contributed most to the explained variance in the foveal thickness (13%), where sex was clearly the most important (Table S2).

Discussion

Our results provide sex-stratified normative data of spectral-domain optical coherence tomography (SD-OCT) macular thickness in an adult and old population. The results reflect a non-diabetic general population without retinal diseases in the age range 38–87 (mean 61 ± 8) years and we investigated the relationship with sex, age and refraction.

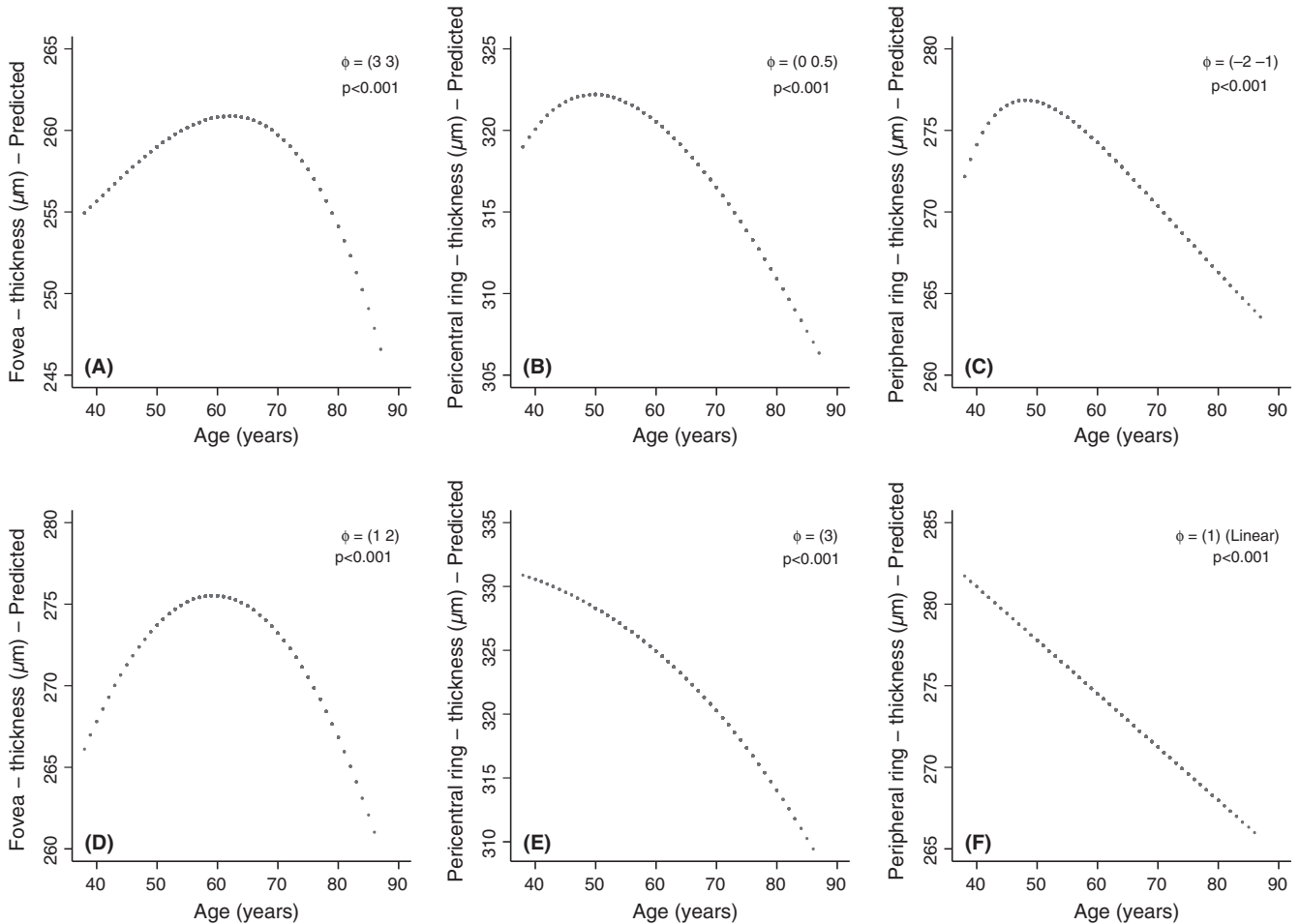


Fig. 2. Predicted relationship between age and retinal thickness in the fovea, pericentral and peripheral ring of macula, by use of fractional polynomial multiple linear regression. Women are displayed in panels A–C and men in panels D–F, p = level of significance, ϕ = powers of model. $\phi = (a)$: First-degree fractional polynomial (FP1) with the power a (describes a monotonic function). $\phi = (a\ b)$: Second-degree fractional polynomial (FP2) with powers a and b (describes a non-monotonic function). Models are adjusted for spherical equivalent refraction, and graphs centred at the sex-specific median. Tromsø Eye Study 2007–2008.

There are ethnic variances in macular retinal thickness, with Caucasians found to have thicker macular retina than African Americans and several ethnic Asian populations, even when accounted for refractive error (Kelyt et al. 2008; Girkin et al. 2011; Tariq et al. 2011). Further, OCT measurements are not directly comparable between devices, as they differ in segmentation algorithms (Giani et al. 2010; Pierro et al. 2010; Tan et al. 2015). The SD Cirrus HD-OCT software draws the outer limitation in the middle of the RPE band, while other algorithms draw the outer limitation at the upper border of the RPE band or at the RPE–Bruch’s membrane complex. This is probably why our thickness measures, despite similar ethnic composition, were slightly lower than those in the Beaver Dam study, as they measured between ILM and Bruch’s membrane (Myers et al.

2015). The Singapore Chinese Eye Study used the same OCT device as ours, implying that the slightly thinner measures probably are due to the ethnic component (Gupta et al. 2013). In the Handan study, thickness measures were considerably lower than in our study, probably due to both the ethnic component and the OCT device (CZM Stratus OCT), which draws the outer segmentation line at the interface of the inner and outer segments of the photoreceptors (Duan et al. 2010; Giani et al. 2010).

Age is an important risk factor for several retinal diseases. Our population covers an age range before diseases normally appear, which may be important to understand the age-related changes eventually leading to disease. We found that retinal thickness was associated with age in all macular areas. The non-monotonic curved

pattern with age was a robust finding for foveal thickness, not driven by potential error from media opacity or outliers in lower age groups where number of participants was low, especially in men. The decline in retinal thickness in the highest ages seen in all regions is possibly reflecting atrophic changes with age, while the thickening of fovea in the lower ages must reflect other ageing processes, possibly accumulation of extra- or intracellular debris (Ardeljan & Chan 2013; Zealley & de Grey 2013).

The thickening of the fovea in middle age corresponds with findings from the Handan study (Duan et al. 2010). In the Beaver Dam population, there was no significant association between age and retinal thickness in the fovea, which may be explained by the older population (Myers et al. 2015). Studies that include segmentation on

individual layers have been conflicting whether retinal thickness in the fovea changes with age. The study of Ooto et al. (2011) ($n = 256$) found increased retinal thickness of the fovea with significantly increased thickness of both photoreceptor outer segments and outer plexiform and nuclear layer by higher age, while the study of Demirkaya et al. (2013) ($n = 120$) found reduction in the retinal outer segment layer by higher age and no change in the other layers of the fovea. The segmentation algorithm of CZM Cirrus OCT draws the automated line of the outer retinal limit in the middle of the RPE; thus, changes in RPE may have contributed to our results. Still, the Handan study supports that our finding of foveal thickening in the lower age groups is due to increase in the retinal tissue, as their outer segmentation line was actually within the photoreceptor layer (Duan et al. 2010). Although not a significant finding, it is interesting to note that the vertex of the foveal thickness appeared slightly later in women than in men, which may reflect a slight delay in ageing changes in women as seen with cardiovascular disease appearing later in women than in men (Roger et al. 2012).

Women had thinner retina in the fovea and pericentral ring than men and was in accordance with results from different ethnic populations (Duan et al. 2010; Song et al. 2010; Adhi et al. 2012; Gupta et al. 2013; Myers et al. 2015). In the peripheral ring, women had thinner retina than men only in the temporal part. Ooto et al. (2010, 2011) reported similar results, which they related to the different distribution of RNFL between sectors, with thickest RNFL in the nasal, superior and inferior parts of the peripheral ring. As women had thicker RNFL than men, in these sectors this outweighed that other retinal layers were thinner than in men. A few studies on children have found that boys have thicker macula than girls, while several have found no gender difference (Molnar et al. 2015; Pérez-García et al. 2016). This may indicate a change during adolescence and/or adulthood, possibly due to hormonal influence.

Retinal thickness was associated with refraction in both women and men, with lower SER associated with thicker retina in the fovea and thinner retina in the pericentral and peripheral

ring. This mainly corresponds with results from other studies considering axial length, refraction and macular thickness (Lam et al. 2007; Duan et al. 2010; Gupta et al. 2013; Myers et al. 2015). Myopization correlates with axial elongation, and *in vivo* studies have shown a significantly lower photoreceptor packing density in myopic eyes, indicating a stretching and thus thinning of the myopic retina corresponding to our findings in the pericentral and peripheral ring (Grosvenor & Scott 1993; Chui et al. 2008). The mechanism for foveal thickening with higher degree of myopia is unclear. Wu et al. (2008) suggested that increased axial length could result in a stretching and flattening tendency of the ILM, resulting in an elevation of the fovea. A possible explanation by poorer fixation with high myopia as suggested by Lim et al. (2005) has been negated in studies that confirmed central fixation in each participant (Lam et al. 2007; Wu et al. 2008). Ocular magnification affects lateral measurements on OCT images (Sanchez-Cano et al. 2008). This will affect the ETDRS grid, with more of the margin zone of the pericentral ring included in the foveal zone with higher myopia. Still this is not the whole explanation as studies have shown the same correlation with increased central fovea (foveola) thickness in myopia (Lam et al. 2007; Wu et al. 2008).

An important limitation of this study is the cross-sectional design, which prohibits inferences about temporal and causal relationships. Our study provides data from a high number of subjects of both sexes, and the population-based design and the relatively high attendance rate are important means to control for selection bias. Study size is particularly important when exploring nonlinear associations, and our quite wide age range, ranging from middle to older age, is an important strength of our study, while we may not infer about age-related changes in earlier adulthood and childhood.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Flow chart of participants with optical coherence tomography (OCT) in healthy eyes in the Tromsø Eye Study 2007–08.

Table S1. Characteristics of included and excluded participants.

Table S2. Explained variance (R^2) of macular thickness in healthy eyes.