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Spectral-Domain Optical Coherence Tomography Imaging in 67 321 Adults

Associations with Macular Thickness in the UK Biobank Study

*Praveen J. Patel, FRCOphth, MD(Res),[1] Paul J. Foster, PhD, FRCOphth,[1] Carlota M. Grossi, PhD,[1] Pearse A. Keane, MD, MRCOphth,[1] Fang Ko, MD,[1] Andrew Lotery, MD, FRCOphth,[2] Tunde Peto, MD, PhD,[1] Charles A. Reisman, MS,[3] Nicholas G. Strouthidis, PhD, FRCOphth,[1,4,5] Qi Yang, PhD,[3] on behalf of the UK Biobank Eyes and Vision Consortium**

Purpose: To derive macular thickness measures and their associations by performing rapid, automated segmentation of spectral-domain optical coherence tomography (SD OCT) images collected and stored as part of the UK Biobank (UKBB) study.

Design: Large, multisite cohort study in the United Kingdom. Analysis of cross-sectional data.

Participants: Adults from the United Kingdom aged 40 to 69 years.

Methods: Participants had nonmydriatic SD OCT (Topcon 3D OCT-1000 Mark II; Topcon GB, Newberry, Berkshire, UK) performed as part of the ocular assessment module. Rapid, remote, automated segmentation of the images was performed using custom optical coherence tomography (OCT) image analysis software (Topcon Advanced Boundary Segmentation [TABS]; Topcon GB) to generate macular thickness values. We excluded people with a history of ocular or systemic disease (diabetes or neurodegenerative diseases) and eyes with reduced vision (<0.1 logarithm of the minimum angle of resolution) or with low SD OCT signal-to-noise ratio and low segmentation success certainty.

Main Outcome Measures: Macular thickness values across 9 Early Treatment of Diabetic Retinopathy Study (ETDRS) subfields.

Results: The SD OCT scans of 67 321 subjects were available for analysis, with 32 062 people with at least 1 eye meeting the inclusion criteria. There were 17 274 women and 14 788 men, with a mean (standard deviation [SD]) age of 55.2 (8.2) years. The mean (SD) logarithm of the minimum angle of resolution visual acuity was −0.075 (0.087), and the refractive error was −0.071 (+1.91) diopters (D). The mean (SD) central macular thickness (CMT) in the central 1-mm ETDRS subfield was 264.5 (22.9) μm, with 95% confidence limits of 220.8 and 311.5 μm. After adjusting for covariates, CMT was positively correlated with older age, female gender, greater myopia, smoking, body mass index (BMI), and white ethnicity (all $P < 0.001$). Of note, macular thickness in other subfields was negatively correlated with older age and greater myopia.

Conclusions: We report macular thickness data derived from SD OCT images collected as part of the UKBB study and found novel associations among older age, ethnicity, BMI, smoking, and macular thickness. *Ophthalmology 2015;■:1−12 © 2015 by the American Academy of Ophthalmology.*

*Supplemental material is available at www.aaojournal.org.

Optical coherence tomography (OCT) imaging has transformed our understanding of macular structure in health and disease. This rapid, noninvasive imaging technique uses light in the near-infrared region and may be used to generate 3-dimensional images of the macula based on the optical reflectivity profile of macular tissue.[1] Changes in macular morphology and thickness occur in eyes with retinal disease, such as macular thickening in neovascular age-related macular degeneration and macular edema with conditions such as geographic atrophy and macular atrophy characterized by reduced macular thickness. Therefore, it is important to understand the range of normal macular thickness in populations and to identify major determinants of macular thickness. This knowledge is essential when attempting to distinguish disease-related changes in thickness from normal variability.

Despite the importance of OCT imaging−derived macular thickness measurements, there is a relative paucity of data relating to the description of normal macular thickness, with most studies conducted using the older time-domain

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OCT (TD-OCT) technology. We are aware of 2 population-based studies using the newer spectral-domain OCT (SD OCT) technology to image eyes of Singaporean Chinese adults[2] and adults in the United States (Beaver Dam Eye Study).[3] In total, these 2 studies assessed OCT images from 2034 people. The UK Biobank (UKBB) study is a large prospective cohort study of health and disease in 502 649 adults aged 40 to 69 years. More than 67 321 of these subjects had nonmydriatic SD OCT (Topcon 3D OCT-1000 Mark II; Topcon GB, Newberry, Berkshire, UK) imaging performed as part of the ocular assessment module in addition to visual acuity and intraocular pressure (IOP) measurement.

The UKBB study provides an opportunity to report normal macular thicknesses in a community-based study in the United Kingdom with a sample size 1 to 2 orders of magnitude larger than previous reports, and in this report we present the results of the analysis of macular thickness derived from SD OCT (Topcon 3D OCT-1000 Mark II; Topcon GB) in the UKBB study.

Methods

Study Population

The UKBB study is a large, multisite, community-based cohort study with the overarching aim of improving the prevention, detection, and treatment of a wide range of serious and life-threatening diseases. The study invited people aged 40 to 69 years to take part. All UK residents aged 40 to 69 years who were registered with the National Health Service and living up to 25 miles from 1 of the 22 study assessment centers were invited to participate. The North West Multi-centre Research Ethics Committee approved the study (REC reference number: 06/MRE08/65), in accordance with the principles of the Declaration of Helsinki. Detailed information about the study is available at the UKBB website (www.ukbiobank.ac.uk).

Measurement of Ocular Variables Data Set/ Ocular Examination Protocol

A total of 132 041 of the UKBB participants had ocular data collected; more than 67 321 participants had macular SD OCT imaging performed at 6 UKBB centers (Sheffield, Liverpool, Hounslow, Croydon, Birmingham, and Swansea). In this cross-sectional study, we report the analysis of macular thickness derived from SD OCT images in UKBB participants, concentrating on people with good vision and without self-reported macular or systemic disease (including diabetes, glaucoma, and neurodegenerative disease). The other relevant ocular variables included visual acuity measurement and Goldmann-corrected IOP, as measured using the Ocular Response Analyzer (Reichert, Depew, NJ).

Spectral-Domain Optical Coherence Tomography Imaging Protocol

The SD OCT imaging was performed using the Topcon 3D OCT-1000 Mark II and was performed after visual acuity, autorefraction, and IOP measurement. The SD OCT imaging was carried out in a dark room but without pupil dilation using the 3-dimensional 6×6-mm^2 macular volume scan mode (512 A scans per B scan; 128 horizontal B scans in a raster pattern). The right eye was imaged first, and the scan was repeated for the left eye.

Analysis of Macular Thickness

All OCT images were stored as .fds files, a proprietary image storage file format, on the UKBB supercomputers in Oxford, United Kingdom, with no prior analysis of macular thickness. Version 1.6.1.1 of the Topcon Advanced Boundary Segmentation (TABS) algorithm[4] was used to delineate the inner and outer retinal surfaces.

As part of the original UKBB data access rules and procedures for bulk data, the stored OCT files (source data) could not be copied, stored, or removed outside the local Oxford University network. Instead, researchers were given access to computers at the central Biobank data repository via remote, secure log-in and could then install any analysis software needed on the UKBB computers. A copy of each preexisting 3-dimensional OCT scan file was retrieved from the UKBB database before running the segmentation analysis software. The derived data were then extracted, after which the OCT scan file was deleted. Up to 12 log-ins were implemented in parallel, increasing the processing throughput by a nearly proportional factor.

Several segmentation indicators were calculated beyond the layer detection processing. In addition to the image quality score, these also served to identify poor scan quality or segmentation failures. These indicators included an inner limiting membrane (ILM) indicator, a validity count, and motion indicators. The ILM indicator was a measure of the minimum localized edge strength around the ILM boundary across the entire scan. It is useful for identifying blinks, scans that contain regions of severe signal fading, and segmentation errors. The validity count indicator is used to identify scans with a significant degree of clipping in the OCT scan's z-axis dimension. The motion indicators use both the nerve fiber layer and the full retinal thicknesses, from which Pearson correlations and absolute differences between the thickness data from each set of consecutive B-scans are calculated. The lowest correlation and the highest absolute difference in a scan serve as the resulting indicator scores. This last group of indicators serves to identify blinks, eye motion artifacts, and segmentation failures. It should be noted that the various indicators, including the image quality score, tend to be highly correlated with one another.

Inclusion and Exclusion Criteria

Macular thickness values from all eyes from patients who had SD OCT performed as part of the UKBB study were used as a starting point for this analysis (Fig 1). Patients were excluded from the analysis if they had withdrawn their consent, with further exclusions based on a per-eye assessment of missing thickness values from Early Treatment of Diabetic Retinopathy Study (ETDRS) subfield signal strength scans with an image quality score (signal strength) less than 45, poor centration certainty, and poor segmentation certainty using TABS software (poorest 20% of images excluded on the basis of each of the segmentation indicators). This led to the identification of the subset of participants with good-quality, well-centered images and central, stable fixation during the OCT scan. Participants with high refractive error ($>\pm 6$ diopters [D]) were then excluded. The next step excluded eyes with a visual acuity of worse than 0.1 logarithm of the minimum angle of resolution (20/32 Snellen equivalent), followed by exclusion of eyes with a Goldmann-corrected IOP >21 mmHg (or if 0 mmHg) with further sequential exclusion of eyes from patients with diabetes and neurodegenerative disease, and those with self-reported glaucoma, retinal, or macular disease. Finally, if both eyes of 1 patient were eligible for inclusion in this analysis, 1 eye was chosen at random.

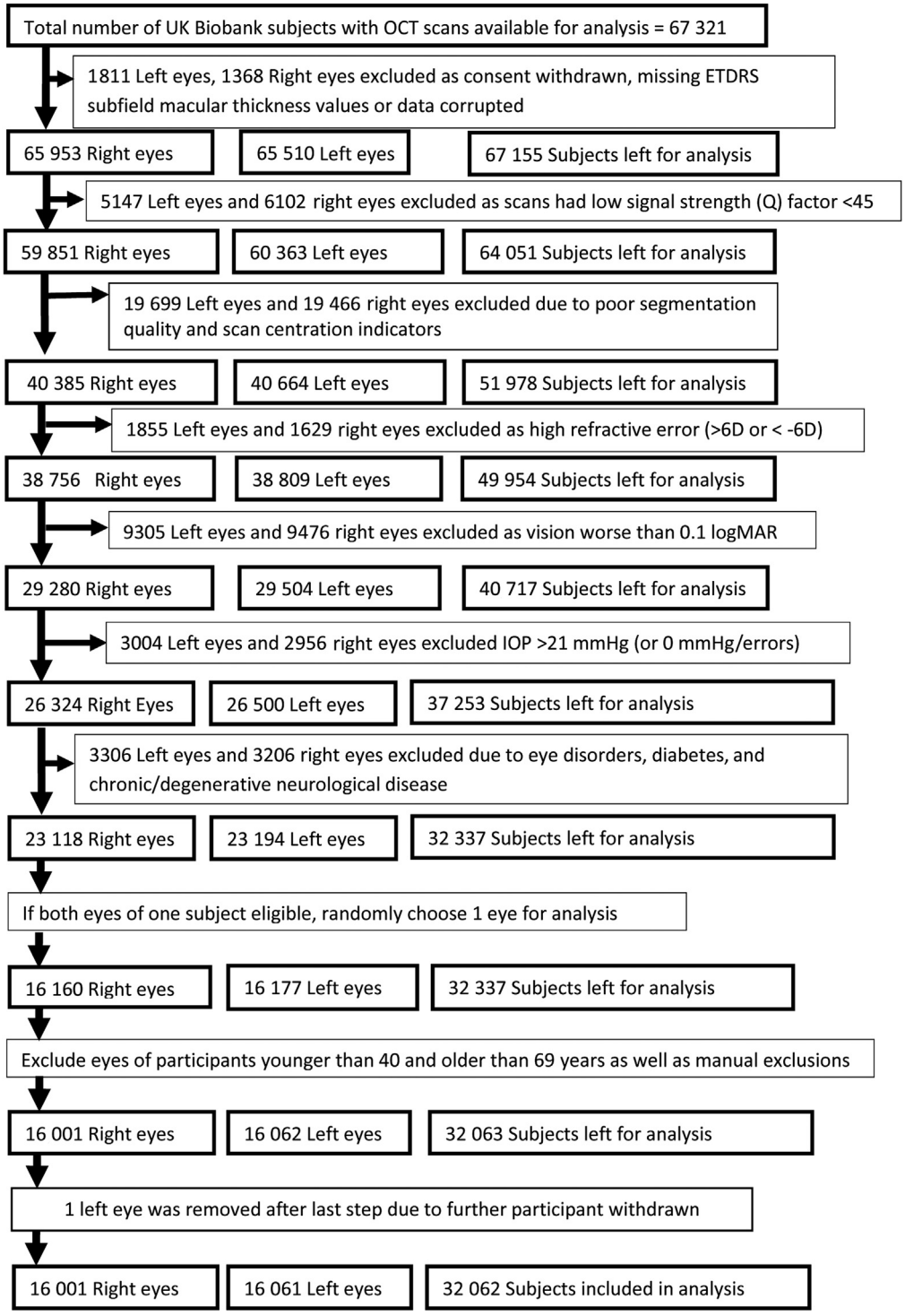

Figure 1. Methodology and exclusions. D = diopters; ETDRS = Early Treatment of Diabetic Retinopathy Study; IOP = intraocular pressure; logMAR = logarithm of the minimum angle of resolution; OCT = optical coherence tomography.

Manual Assessment of Outliers

Given the size of the cohort, it was not feasible to manually read all images for evidence of retinal morphologic abnormalities or segmentation error. Applying filters to the data in a stepwise manner will have led to the exclusion of scans of poor image quality, poor centration, poor segmentation certainty, and disease. However, despite this rigorous approach, a few outliers with disease or errors may have persisted, and to militate against this risk, a subset of selected images was manually graded by 2 observers independently to identify visible segmentation error in the central B-scan line and to detect evidence of abnormalities in retinal morphology.

Eyes were arranged in order of the magnitude of the central macular thickness (CMT), and the scan with the largest CMT was analyzed by P.J.P. and C.A.R. The next scan reviewed was the scan with the CMT closest to 1 standard deviation (SD) less than the largest CMT. If this was normal (no evidence of abnormality of macular morphology and no segmentation error on the central B-scan image), the next scan reviewed was the scan with CMT nearest to half an SD greater than the last image, whereas if the scan was not normal, the next scan to be reviewed was again the scan with CMT closest to 1 SD below the previous one. Once a normal scan was detected, the SD increment/decrement step size was cut in half with each ensuing step. This "staircasing" methodology based on fractions of the SD was used until 10 images were reviewed at the upper end of the CMT range. If the 10th scan was determined not to be normal, the manual grading was continued using the staircasing methodology until a normal image free from segmentation error and abnormalities of retinal morphology was identified. Then, all scans with CMT measurements greater than the highest normal CMT thickness determined via the staircasing methodology were excluded.

This process was then repeated, starting with the scan with the lowest CMT and moving toward reviewing scans with higher CMT, using the same staircasing methodology based on the SD and fractions of the SD of the CMT. This novel staircasing methodology approach to selecting images for manual review in this large data set based on the SD of the CMT variable was developed to deliver an efficient and effective way of excluding scans with segmentation error or disease in the final included cohort.

Statistical Analysis

For subjects in whom both eyes were eligible for analysis, 1 eye was randomly chosen to include in this study by generating a variable of random numbers uniformly distributed on the interval (0, 1) and selecting the left or right eye depending on the participant being assigned a value <0.5 or ≥ 0.5. We used descriptive statistics to report continuous variables, including demographic variables and macular thickness in each subfield, with mean, SD, and 95% confidence intervals (CIs) where appropriate. Categoric variables were reported with percentages and 95% CIs. Comparisons between groups were undertaken using analysis of variance or *t* test for continuous variables and chi-square or comparison of proportions tests for categoric variables. Univariable linear regression models were used to assess the associations of mean macular thickness in each ETDRS subfield with age, gender, ethnicity (self-reported), blood pressure, body mass index (BMI), smoking status, Biobank center, refraction, IOP, and visual acuity. All variables significant at a *P* value less than 0.001 level were then included in 1 multivariable linear regression model to further evaluate associations with macular thickness. Although we initially considered using scatter plots to illustrate the trend in association of macular thickness and other ocular and systemic variables given the large sample size, the density of the data makes it difficult to identify trends and associations using this approach. The figures presented in this article show mean values of macular thickness grouped by categorized variables and 95% CI error bars. Analyses were performed using STATA-12 and STATA-13 (StataCorp LP, College Station, TX). Excel (Microsoft Corp., Redmond, WA) was used to produce the figures. Age−macular thickness linearity was checked graphically by dividing the age variables in year categories and plotting thickness mean and 95% CI. Because the trends in the different subfields varied after the age of 60 years, a piecewise regression was performed in the multivariable analysis, using 2 linear splines variables for age with knot at 59 years. Normality of residuals and models' specification were checked after multivariable regression.

Results

A total of 67 321 participants had OCT imaging as part of the UKBB study. Of these, 32 062 healthy subjects with good-quality imaging were identified. Figure 1 shows a summary of the numbers of eyes and subjects selected and included. Figure 2 provides examples of excluded scans based on use of scan quality indicators. The mean ± SD age of subjects included in the analysis was 55.2±8.2 years, and 17 275 subjects (53.9%) were women. The demographics of the population included and excluded from this analysis are summarized in Table 1 (age, gender, ethnicity, laterality, visual acuity, refractive error, and Goldmann-correlated IOP). The subjects excluded from the analysis were significantly older, male, and more likely to be from a nonwhite, ethnic group, with poorer vision, greater myopia, and higher IOP.

The means and SDs of macular thickness by ETDRS subfield in the 32 062 normal participants are shown in Figure 3. Macular thickness by gender, age, and ethnicity is shown in Tables 2, 3, and 4, respectively. Men had greater mean retinal thickness in most ETDRS subfields compared with women, with means and 95% CIs for retinal thicknesses in each subfield shown in Table 2. Normal central subfield macular thickness values in this cohort range from 220.8 to 311.5 μm based on the 95% confidence limits for this measure.

Figure 4 shows that CMT increased linearly with age (until the age of 60 years), whereas macular thickness decreased with age in other subfields. Figure 5 shows that CMT increased linearly with greater myopia, and macular thickness decreased with greater myopia in other subfields.

With regard to self-reported ethnicity, the central macular subfield thickness was found to be greater in white UKBB participants compared with other ethnic groups with black UKBB participants having the thinnest CMT. This difference was also seen for other macular subfields, although the difference between ethnic groups was less marked than for the central macular subfield (Table 3).

Table 5 shows the univariable associations with macular thickness. In the multivariable analysis (Table 6), age, ethnicity, refraction, scan signal strength, BMI, and smoking status showed significant associations with macular thickness in each macular subfield. Older age was associated with an increase in CMT (2.05-μm increase per decade before 60 years) but was associated with a decrease in the average inner subfield (1.37-μm decrease per decade for those aged 40−59 years and 7.74 μm for those aged 60−69 years) and outer subfield (2.10-μm decrease per decade for those aged 40−59 years and 5.64 μm for those aged 60−69 years). White subjects had a thicker macula in each macular subfield compared with Asian subjects and black subjects. Subjects from a Chinese Asian ethnic group had a reduced CMT, but differences from white patients were not significant in other outer subfields. Increasing positive refractive error (relative hyperopia) was associated with a decrease in CMT (0.67-μm decrease for every diopter increase in positive refractive error), whereas the average inner macular subfields and outer macular subfields showed an increase in macular thickness (1.03-μm and 1.73-μm increase in thickness, respectively, per +1-D increase in refractive error). There was a statistically significant association between macular thickness and BMI, with increasing BMI associated with a reduction in macular thickness in all subfields. However, the magnitude of this association was small (0.87-μm reduction in CMT per 5 kg/m^2 increase in BMI).

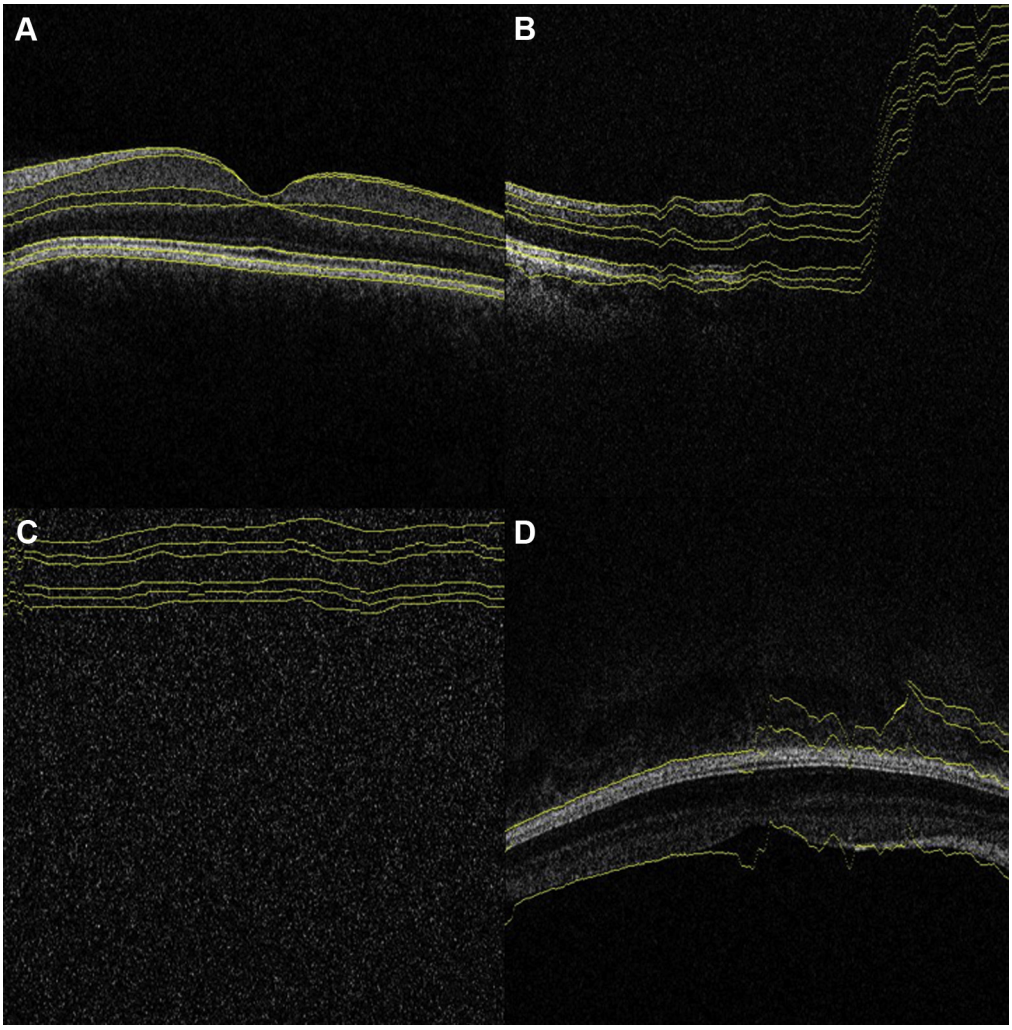

Figure 2. Example of B-scan images with segmented boundaries in accepted and rejected sample Biobank optical coherence tomography (OCT) data volumes. **A**, B-scan example in an accepted volume (included in the analysis). **B**–**D**, B-scan examples in 3 rejected sample volumes (excluded from the analysis).

There was also a statistically significant association between smoking and reduced macular thickness; however, the size of the association was small (subjects who smoked some or most days had a CMT 1.73 μm less than subjects who did not smoke). We also found a small but statistically significant relationship between visual acuity and macular thickness in the inner and outer subfields but no statistically significant association with CMT.

Scan-related factors such as signal strength and the UKBB center at which the scan was carried out also showed an association with macular thickness, but the magnitude of this association was generally small when compared with other continuous or categoric variables. The association between blood pressure and macular thickness was found to be significant in the univariate regression model for some of the macular subfields, but no significant association was seen in the multivariable regression model.

Discussion

The UKBB study provides a unique opportunity to explore determinants of macular morphology and thickness in a large cohort of patients aged 40 to 69 years. There were 67 321 subjects who had SD OCT imaging of the macula performed as part of the UKBB study. The results of remotely accessing the UKBB. fds Topcon 3D OCT-1000 files and applying automated segmentation to derive macular thickness measurements identified scans from 32 062 subjects with good visual acuity that were of high image quality. In this study, we report absolute average macular thickness values greater than in other smaller population-based studies using the older TDOCT imaging technology[5] and values closer to other reports using the Topcon OCT device[5] and other SD OCT devices.[3] We found that gender, age, ethnicity, and refraction were the most important factors associated with macular thickness in this analysis of SD OCT in the UKBB cohort, but there was also a statistically significant association between BMI and macular thickness and between smoking and macular thickness, although these associations were smaller.

There is a relative paucity of population-based or large cohort-based studies using SD OCT imaging. We report

Table 1. Demographic Characteristics of UK Biobank Subjects Included and Excluded from Analysis

	Included (N = 32 062)	Excluded (N = 34 901)	P Value
Age (yrs)	55.2 (±8.2)	58.0 (±7.8)	<0.001
Female gender, % (95% CI)	53.9 (53.3–54.4)	55.0 (54.5–55.5)	0.004
Ethnicity, % (95% CI)			
White	92.1 (91.8–92.4)	89.2 (88.8–89.5)	<0.001†
Mixed	1.0 (0.9–1.1)	0.8 (0.7–0.9)	
Asian	2.5 (2.3–2.6)	4.0 (3.8–4.2)	
Black	2.8 (2.6–3.0)	3.6 (3.4–3.8)	
Chinese	0.3 (0.3–0.4)	0.6 (0.5–0.7)	
Other	1.3 (1.1–1.4)	1.9 (1.7–2.0)	
Laterality, n (% right eyes)	49.9 (49.4–50.5)	50.4 (49.9–51.0)*	0.160
Visual acuity (logMAR)	−0.075 (±0.087)	0.089 (±0.230)	<0.001
Spherical equivalent (D)	−0.071 (±1.906)	−0.600 (±3.240)	<0.001
IOP (Goldmann corrected)	15.0 (±3.0)	16.3 (±4.5)	<0.001

D = diopters; IOP = intraocular pressure; logMAR = logarithm of the minimum angle of resolution.
Data are mean (±SD), except for gender and ethnicity, which are expressed as percentage and 95% CI. Excluded = individuals with both eyes excluded.
*Only comparing right and left eyes.
†For percentage of white subjects.

greater absolute mean macular thickness values (CMT of 266 μm in 29 427 white subjects) compared with some previous studies. However, several factors may underlie these differences. Previous population studies reporting macular thickness values have tended to use the older technology of TDOCT[5]; however, with the faster imaging speeds of SD OCT devices, more of the macula can be sampled with less interpolation between sampled points. This increases the accuracy of average macular thickness measurements and may partly explain differences in macular thickness reported in studies using TDOCT and SD OCT. In addition, although different automated segmentation algorithms agree on the boundary of the inner retina (inner surface of ILM), these analysis software algorithms differ in where the outer retinal boundary is determined (anywhere from the inner outer segment junction to the retinal pigment epithelium/Bruch membrane complex). This may go some way toward explaining why absolute macular thickness measurements vary from study to study and, together with differences in study inclusion criteria and subject demographics, means that direct comparison with other studies can be difficult. In this analysis of the UKBB OCT images, we applied the TABS algorithm to generate macular thickness, and this software attempts to calculate the distance between the inner surface of the ILM and the reflectance signal associated with the outer segments and retinal pigment epithelium (outer segment/retinal pigment epithelium) interface. Indeed, when we compare the values of macular

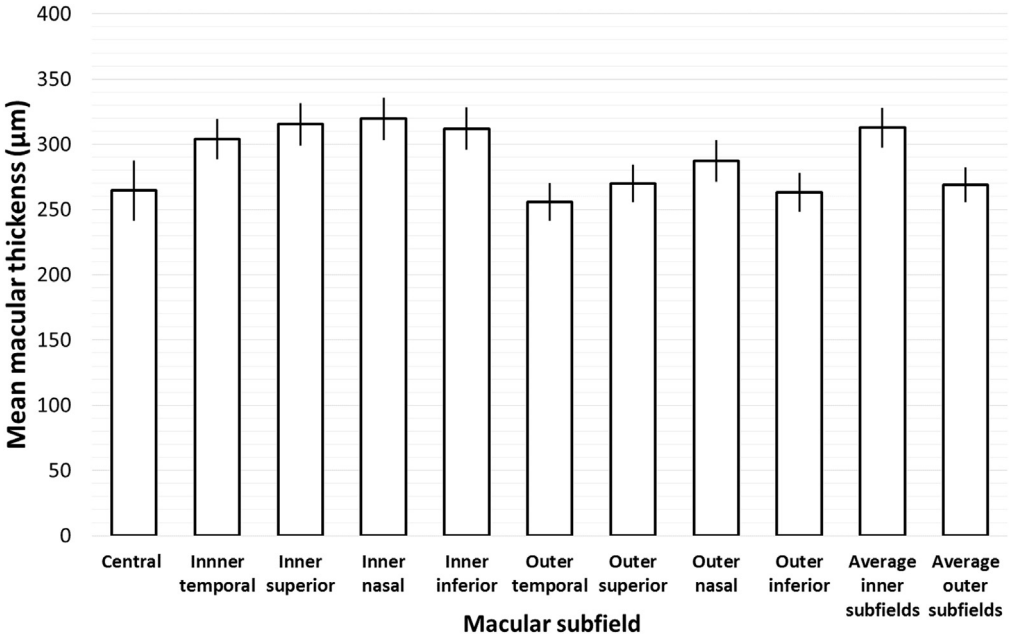

Figure 3. Mean macular thickness (±standard deviation) in different macular subfields.

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

Macular Thickness (μm)	Total (n=32 062)	Female (n=17 274)	Male (n=14 788)	*P* for Sex Differences
Central macular subfield	264.5 (±22.9)	259.8 (±22.6)	269.9 (±22.0)	<0.001
Inner subfields				
Temporal	304.0 (±15.5)	301.3 (±14.9)	307.1 (±15.6)	<0.001
Superior	315.3 (±16.1)	313.8 (±15.6)	317.0 (±16.5)	<0.001
Nasal	319.5 (±16.3)	317.3 (±15.8)	322.2 (±16.4)	<0.001
Inferior	311.9 (±16.2)	309.7 (±15.8)	314.5 (±16.3)	<0.001
Average inner subfields	312.7 (±15.2)	310.5 (±14.8)	315.2 (±15.4)	<0.001
Outer subfields				
Temporal	255.6 (±14.3)	254.2 (±14.3)	257.3 (±14.2)	<0.001
Superior	269.7 (±14.3)	270.3 (±14.4)	269.1 (±14.3)	<0.001
Nasal	287.2 (±15.8)	287.6 (±15.6)	286.7 (±16.0)	<0.001
Inferior	263.0 (±15.0)	263.6 (±15.0)	262.2 (±15.0)	0.001
Average outer subfields	268.9 (±13.2)	268.9 (±13.2)	268.8 (±13.3)	0.450
Overall average macula	278.5 (±13.0)	277.9 (±12.9)	279.2 (±13.1)	<0.001
Overall macular volume, mm^3	7.87 (±0.37)	7.86 (±0.36)	7.89 (±0.37)	<0.001

Data are mean (±SD).

thickness obtained in our study with that from more recent studies using SD OCT and a Topcon segmentation algorithm, as used in the Beaver Dam Eye Study,[3] we find macular thicknesses from the UKBB data set that are approximately 20 to 25 μm less than in the Beaver Dam Eye Study report. These differences could be explained by differences in the average age of patients in the 2 cohorts (older in the Beaver Dam Eye Study) and differences in older and newer Topcon segmentation algorithms (with the TABS algorithm used in the UKBB data set positioning the outer retinal boundary in a more anterior location). The values of macular thickness obtained in our study also are greater than values reported using the Cirrus SD OCT device in the Singapore Chinese Eye Study,[2] and this is explained to a large degree by the differences in ethnicity in the 2 cohorts (mainly white patients in the UKBB).

Sex and Macular Thickness

We found significant differences in macular thickness between men and women in most macular subfields, with men having a greater macular thickness than women in the central and inner 3-mm macular zone. However, macular thickness was more similar between men and women in the outer 6-mm macular subfields, as previously reported in population-based studies.[2,3,5] Previous studies have suggested that these differences may arise at the level of the inner nuclear layer or outer nuclear layer/outer plexiform layer, which may be thicker in the central and inner macular subfields in men.[6] Another explanation for some of the difference in central subfield macular thickness between men and women could be differences in foveal morphology, with steeper and less wide foveal pits in men, resulting in more parafoveal tissue

Table 3. Distribution of Macular Thickness and Volume Measurements in Healthy Eyes by Age

Macular Thickness and Volume Measurements	Age Group, yrs			Trend for Age	
	40–49 (n=9250)	*50–59 (n=10 875)*	*60–69 (n=11 937)*	*β Coefficient**	*P Value*
Central macular subfield	262.5 (±23.4)	264.7 (±22.8)	265.8 (±22.4)	1.7	<0.001
Inner subfields					
Temporal	305.0 (±15.7)	305.0 (±15.5)	302.3 (±15.2)	−1.5	<0.001
Superior	317.4 (±16.1)	316.4 (±16.0)	312.6 (±16.0)	−2.6	<0.001
Nasal	321.2 (±16.5)	320.6 (±16.2)	317.3 (±16.0)	−2.1	<0.001
Inferior	313.5 (±16.4)	312.7 (±16.2)	309.9 (±15.8)	−1.9	<0.001
Average inner subfields	314.3 (±15.4)	313.7 (±15.2)	310.5 (±15.0)	−2.0	<0.001
Outer subfields					
Temporal	256.6 (±14.3)	256.1 (±14.3)	254.5 (±14.3)	−1.1	<0.001
Superior	271.8 (±14.2)	270.6 (±14.2)	267.4 (±14.3)	−2.3	<0.001
Nasal	289.6 (±15.5)	288.1 (±15.7)	284.5 (±15.7)	−2.7	<0.001
Inferior	264.6 (±14.9)	263.3 (±15.1)	261.4 (±15.0)	−1.7	<0.001
Average outer subfields	270.7 (±13.1)	269.5 (±13.2)	266.9 (±13.1)	−1.9	<0.001
Overall average macula	280.1 (±12.9)	279.2 (±13.0)	276.6 (±12.9)	−1.9	<0.001
Overall macular volume, mm^3	7.92 (±0.37)	7.89 (±0.37)	7.82 (±0.36)	−0.05	<0.001

Data are mean μm (±SD) unless otherwise indicated.
*Linear regression – thickness variation per 10 years.

Table 4. Distribution of Macular Thickness (μm) by Ethnicity

	White	Mixed	Asian	Black	Chinese	Other	Total	P (ANOVA)
N	29 427	318	790	896	109	405	31 945	
Central subfield: mean	265.8	253.9	253.3	240.5	255.6	251.5	264.5	<0.001
SD	22.1	22.8	24.1	25.3	22.2	23.9	22.9	
Inner temporal: mean	304.6	302.2	296.9	291.8	301.7	298.3	304.0	<0.001
SD	15.2	15.8	16.0	17.2	14.0	17.4	15.5	
Inner superior subfield: mean	315.8	314.6	309.5	304.0	316.7	311.9	315.3	<0.001
SD	15.9	16.2	16.5	17.2	14.5	17.7	16.1	
Inner nasal subfield: mean	320.3	317.0	313.1	304.9	320.3	314.0	319.6	<0.001
SD	15.9	16.2	16.4	18.6	15.5	18.9	16.3	
Inner inferior subfield: mean	312.6	309.8	305.7	298.3	310.4	306.7	311.9	<0.001
SD	15.9	15.7	16.5	18.3	14.7	18.4	16.2	
Average inner subfields: mean	313.3	310.9	306.3	299.8	312.3	307.8	312.7	<0.001
SD	14.9	15.2	15.3	16.5	13.7	17.0	15.2	
Outer temporal subfield: mean	255.9	255.7	251.6	250.0	257.0	253.7	255.6	<0.001
SD	14.3	14.6	14.4	14.9	15.0	14.9	14.3	
Outer superior subfield: mean	270.1	270.4	265.0	262.8	271.7	267.8	269.8	<0.001
SD	14.2	14.6	14.5	14.3	15.6	16.2	14.3	
Outer nasal subfield: mean	287.5	287.3	284.7	278.6	292.1	285.6	287.2	<0.001
SD	15.6	15.8	15.9	16.4	16.6	16.7	15.8	
Outer inferior subfield: mean	263.2	262.6	260.6	258.2	265.5	262.8	263.0	<0.001
SD	15.0	15.8	15.6	15.5	16.2	16.4	15.0	
Average outer subfields: mean	269.2	269.0	265.5	262.4	271.6	267.5	268.9	<0.001
SD	13.2	13.4	13.2	13.2	13.9	14.1	13.2	
Total macular mean thickness	278.9	277.9	274.2	270.1	280.2	276.0	278.5	<0.001
SD	12.9	12.9	12.9	13.1	13.1	13.8	13.01	

ANOVA = analysis of variance; SD = standard deviation.

included in calculations of CMT, resulting in larger CMT values. However, other studies suggest that these differences may genuinely reflect macular thickness differences between the genders rather than simply arising from differences in the amount of parafoveal tissue included in the calculation of CMT.[7]

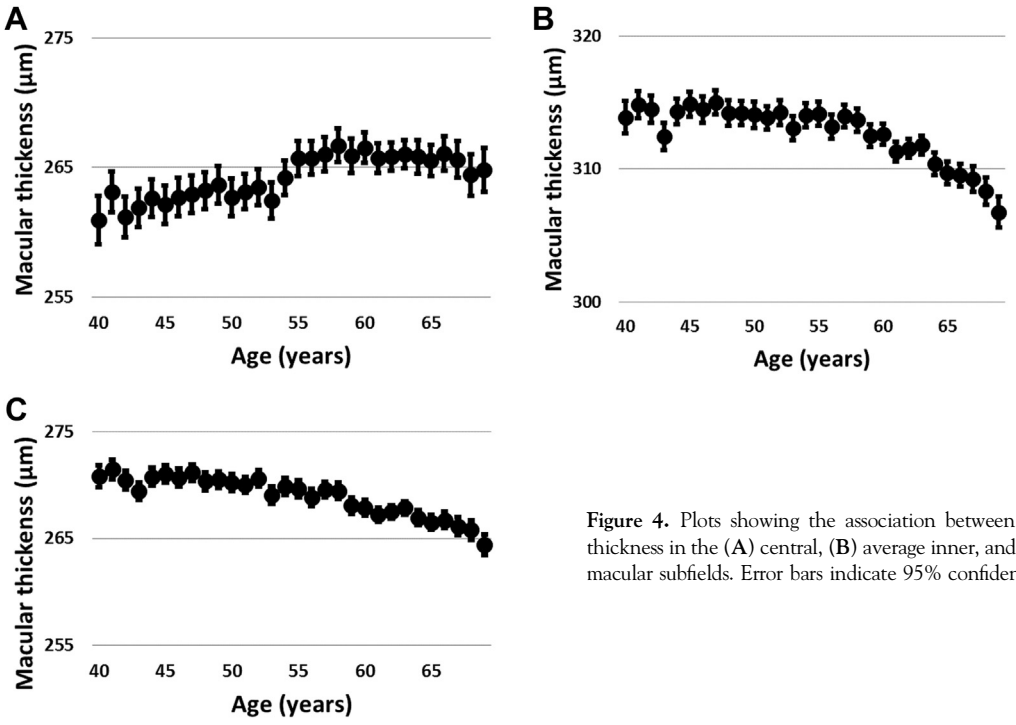

Figure 4. Plots showing the association between age and macular thickness in the (**A**) central, (**B**) average inner, and (**C**) average outer macular subfields. Error bars indicate 95% confidence intervals.

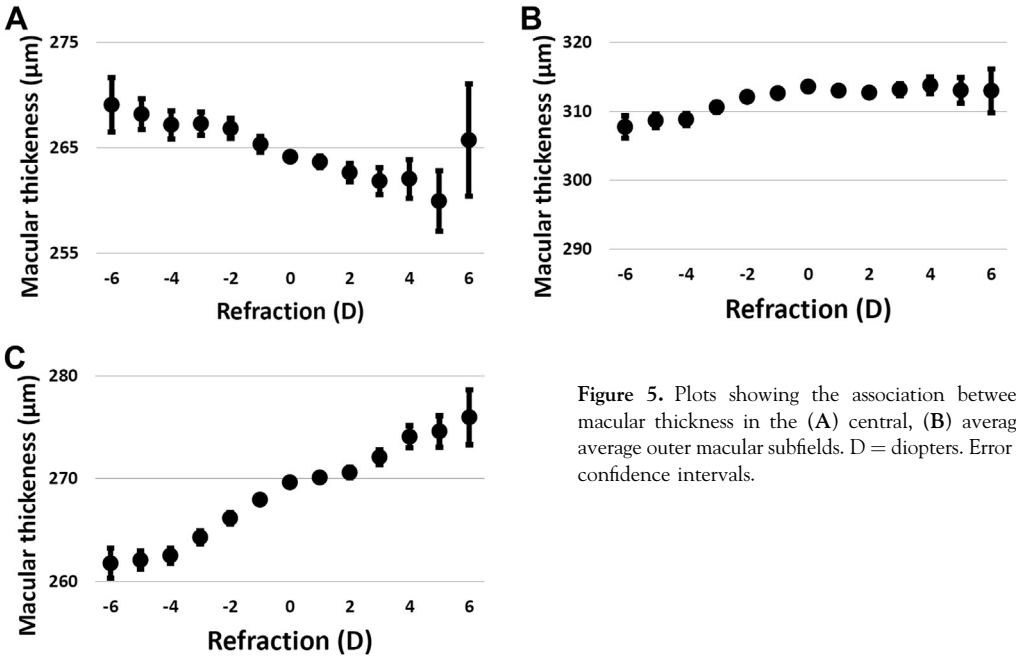

Figure 5. Plots showing the association between refraction and macular thickness in the (**A**) central, (**B**) average inner, and (**C**) average outer macular subfields. D = diopters. Error bars indicate 95% confidence intervals.

Table 5. Univariable Logistic Regression Results (Macular Thickness as the Dependent Variable)

	Central Subfield		Average Inner Subfields		Average Outer Subfields		Total	
	Coefficient	P *Value*	*Coefficient*	P *Value*	*Coefficient*	P *Value*	*Coefficient*	*P Value*
Ocular factors								
IOPg/mmHg	0.19	**<0.001**	0.00	0.940	−0.15	**<0.001**	−0.11	**<0.001**
Refractive error	−0.83	**<0.001**	0.51	**<0.001**	1.32	**<0.001**	1.08	**<0.001**
Signal strength	−0.35	**<0.001**	−0.17	**<0.001**	−0.04	**<0.001**	−0.08	**<0.001**
Visual acuity (per 0.1 logMAR)	−0.65	**<0.001**	−0.16	**<0.001**	−0.77	**<0.001**	−0.93	**<0.001**
Systemic factors								
Age/10 yrs (40–59)	2.49	**<0.001**	−0.56	0.003	−1.16	**<0.001**	−0.93	**<0.001**
Age/10 yrs (60–69)	−1.55	0.061	−5.21	**<0.001**	−2.70	**<0.001**	−3.23	**<0.001**
Gender (vs. female)	10.07	**<0.001**	4.70	**<0.001**	−0.09	0.550	1.26	**<0.001**
BMI/5 kg/m^2	−0.55	**<0.001**	−0.97	**<0.001**	−0.69	**<0.001**	−0.75	**<0.001**
SPB/10 mmHg	0.44	**<0.001**	−0.34	**<0.001**	−0.51	**<0.001**	−0.45	**<0.001**
DBP/10 mmHg	0.62	**<0.001**	−0.21	0.016	−0.61	**<0.001**	−0.49	**<0.001**
Smoking (most/all days vs. no)	−1.39	**<0.001**	−1.01	0.003	−0.52	0.090	−0.65	0.030
Ethnicity vs. white								
Mixed	−11.97	**<0.001**	−2.45	0.004	−0.20	0.794	−1.02	0.159
Asian	−12.47	**<0.001**	−7.08	**<0.001**	−3.72	**<0.001**	−4.71	**<0.001**
Black	−25.28	**<0.001**	−13.58	**<0.001**	−6.79	**<0.001**	−8.81	**<0.001**
Chinese	−10.20	**<0.001**	−1.08	0.412	2.39	0.072	1.27	0.311
Other	−14.35	**<0.001**	−5.58	**<0.001**	−1.71	0.015	−2.93	**<0.001**
UK Centre vs. Sheffield								
Liverpool	−2.26	**<0.001**	−2.56	**<0.001**	−3.64	**<0.001**	−3.36	**<0.001**
Hounslow	−1.37	**<0.001**	−1.78	**<0.001**	−0.95	**<0.001**	−1.15	**<0.001**
Croydon	−3.14	**<0.001**	−1.29	**<0.001**	−1.43	**<0.001**	−1.45	**<0.001**
Birmingham	0.31	0.404	−0.68	0.005	−0.79	**<0.001**	−0.73	**<0.001**
Swansea	0.52	0.831	−5.84	0.001	−4.15	0.003	−4.40	0.002

BMI = body mass index; DBP = diastolic blood pressure; IOPg = Goldmann-correlated intraocular pressure; logMAR = ogarithm of the minimum angle of resolution; SPB = systolic blood pressure.
$P < 0.001$ shown in boldface to indicate statistical significance; coefficient = regression coefficient.

Table 6. Multivariable Regression Analysis (Macular Thickness as the Dependent Variable)

	Central Subfield			Average Inner Subfields			Average Outer Subfields			Total		
	Coefficient	*P*	R^2 (%)*	*Coefficient*	*P*	R^2 (%)*	*Coefficient*	*P*	R^2 (%)*	*Coefficient*	*P*	R^2 (%)
Ocular factors												
IOPg/mmHg	0.05	0.206	0.00	0.03	0.261	0.00	−0.07	0.007	0.02	−0.04	0.087	0.01
Refractive error	−0.67	**<0.001**	0.28	1.03	**<0.001**	1.50	1.73	**<0.001**	5.65	1.51	**<0.001**	4.44
Signal strength	−0.29	**<0.001**	1.09	−0.22	**<0.001**	1.44	−0.12	**<0.001**	0.61	−0.15	**<0.001**	0.92
Visual acuity (0.1 logMAR)	−0.34	0.023	0.02	−0.84	**<0.001**	0.22	−0.31	**<0.001**	0.04	−0.42	**<0.001**	0.08
Systemic factors												
Age/10 yrs (40–59)	2.05	**<0.001**	0.20	−1.37	**<0.001**	0.20	−2.1	**<0.001**	0.62	−1.82	**<0.001**	0.48
Age/10 yrs (60–69)	−2.08	0.001	0.04	−7.74	**<0.001**	1.10	−5.64	**<0.001**	0.77	−6.00	**<0.001**	0.91
Gender vs. female	9.86	**<0.001**	4.34	4.94	**<0.001**	2.47	0.23	0.127	0.01	1.54	**<0.001**	0.33
BMI/5 kg/m^2	−0.87	**<0.001**	0.11	−1.08	**<0.001**	0.38	−0.57	**<0.001**	0.14	−0.69	**<0.001**	0.21
SBP/10 mmHg	−0.28	0.014	0.02	−0.11	0.169	0.01	−0.07	0.307	0.00	−0.08	0.21	0.00
DBP/10 mmHg	0.36	0.064	0.01	0.06	0.661	0.00	−0.08	0.461	0.00	−0.04	0.719	0.00
Smoking (most/all days vs. no)	−1.73	0.001	0.03	−2.1	**<0.001**	0.11	−1.42	**<0.001**	0.07	−1.58	**<0.001**	0.09
Ethnicity vs. white												
Mixed	−9.22	**<0.001**	0.16	−2.41	0.005	0.02	−0.98	0.193	0.01	−1.53	0.036	0.01
Asian	−12.73	**<0.001**	0.72	−8.38	**<0.001**	0.71	−4.83	**<0.001**	0.31	−5.84	**<0.001**	0.47
Black	−23.56	**<0.001**	2.71	−14.16	**<0.001**	2.21	−7.95	**<0.001**	0.92	−9.76	**<0.001**	1.44
Chinese	−10.14	**<0.001**	0.07	−1.11	0.407	0.00	2.67	0.041	0.01	1.47	0.24	0.00
Other	−12.62	**<0.001**	0.36	−5.81	**<0.001**	0.17	−2.79	**<0.001**	0.05	−3.73	**<0.001**	0.10
UK Center vs. Sheffield												
Liverpool	−2.75	**<0.001**	0.08	−2.8	**<0.001**	0.20	−3.73	**<0.001**	0.47	−3.49	**<0.001**	0.42
Hounslow	−0.83	0.032	0.01	−1.86	**<0.001**	0.16	−0.86	**<0.001**	0.05	−1.08	**<0.001**	0.07
Croydon	−1.36	**<0.001**	0.04	−0.22	0.324	0.00	−0.64	0.002	0.03	−0.57	0.005	0.02
Birmingham	0.10	0.796	0.00	−1.17	**<0.001**	0.07	−1.14	**<0.001**	0.08	−1.11	**<0.001**	0.08
Swansea	−1.40	0.590	0.00	−7.92	**<0.001**	0.06	−6.53	**<0.001**	0.05	−6.69	**<0.001**	0.05
Observations	30 097			30 097			30 097				30 097	
R^2	0.1145			0.1059			0.0928				0.0932	

BMI = body mass index; DBP = diastolic blood pressure; IOPg = Goldmann-correlated intraocular pressure; logMAR = logarithm of the minimum angle of resolution; SPB = systolic blood pressure.
$P < 0.001$ shown in boldface to indicate statistical significance.
*Semipartial correlation; coefficient = regression coefficient.

Ethnicity and Macular Thickness

Another striking finding in this analysis of macular thickness in the UKBB cohort was the significant difference between different ethnic groups with respect to macular thickness, with those from Afro-Caribbean and South Asian (Indian subcontinent) self-reported ethnicity having a reduced macular thickness in all macular subfields compared with their white counterparts. Comparison with previous work is confounded by the use of different OCT technologies and different segmentation algorithms (Table 7); however, ethnic differences in macular thickness in adult subjects have been reported.[8,9] Other smaller studies have reported that differences in macular thickness between African and African American subjects and white subjects from the United States may be limited to the CMT and that these differences may relate more to foveal pit morphology or dimensions rather than true differences between ethnic groups.[7] Subjects with a less broad foveal pit will have more parafoveal retinal tissue included in a calculation of CMT, leading to higher thickness values in this central subfield. African American subjects have been shown to have a broader foveal pit with shallower slopes when compared with white subjects. This finding, together with the finding in other studies that differences in macular thickness between African American and white subjects were found only in the central macular subfield, led researchers to suggest that it was the broader foveal pit that leads to smaller central thickness values in African American subjects and that this is not suggestive of true differences in macular thickness resulting from differences in macular sublayer thicknesses. In the UKBB cohort, differences in macular thickness between subjects from different self-reported ethnic groups are seen across all ETDRS macular subfields rather than being limited to just the central macular subfield. This suggests that the difference in macular thickness may well be due to true differences in retinal sublayer thicknesses rather than purely due to differences in foveal pit morphology. Subjects reporting to be from a South Asian (Indian subcontinent) background in the UKBB study also had reduced macular thickness when compared with subjects with a white self-reported ethnicity, although these differences were not as marked as for participants from a self-reported Afro-Caribbean background. The macular thickness results for subjects from an East Asian background should be viewed with caution given the relatively small number of subjects with this self-reported ethnic background,

Table 7. Summary of Large Community or Population-Based Studies Reporting Optical Coherence Tomography–Derived Macular Thickness in Healthy Adult Subjects

Study	Country	Year(s)	SD OCT or TD-OCT	OCT Device	Mean Age ± SD	No. Eyes/Subjects	CMT (mean μm ± SD)
Handan Eye Study	China	2006	TD	Stratus OCT (Zeiss, Oberkochen, Germany)	46.4±9.9	2230/2230	176.4±17.5
Singapore Chinese Eye Study[2]	Singapore	2009–2011	SD	Cirrus OCT (Zeiss)	53.2±6.1	490/490	250.4±20.6
Beaver Dam Eye Study	United States	2008–2010	SD	Topcon 3D-OCT Mark II (Topcon GB, Newberry, Berkshire, UK)	72.6±6.3	1838/977	285.4±22.3
UKBB	United Kingdom	2009–2010	SD	Topcon 3D-OCT Mark II (Topcon GB)	55.2 ±8.2	32 062 eyes of 32 062 included	264.5±22.9

CMT = central macular thickness; OCT = optical coherence tomography; SD = standard deviation; SD OCT = spectral-domain optical coherence tomography; TDOCT = time-domain optical coherence tomography; UKBB = UK Biobank.

but the values are similar to macular thickness reported in the Singapore Chinese Eye Study.[2]

Refraction and Macular Thickness

Macular thickness also varied with age and refraction, with a different association for the central 1-mm macular subfield compared with other subfields. Increased myopia was associated with an increase in CMT but a decrease in other macular subfield thicknesses. The association between increasing myopia and increasing CMT has been noted in studies with smaller sample sizes. This could be an artifact arising from differences in scaling of myopic eyes compared with hyperopic eyes with respect to lateral B-scan length (with a relative magnification of hyperopic eyes leading to more of the foveal depression included in the central macular subfield[10]). An alternative suggestion is that this is an adaptive or compensatory process in the fovea to minimize image blur and the effects of refractive error.[11]

Age and Macular Thickness

We report a biphasic association between central subfield macular thickness and age, with an increase in CMT from 40 to 59 years, but no further increase was found from 60 to 69 years. This contrasts with other studies: the Handan Eye Study reported an increase in CMT with age[5] and the Beaver Dam Eye Study[3] and the Singapore Chinese Eye Study[2] reported no relationship between CMT and age-reduced CMT with age. Relative differences in the associations of retinal sublayer thicknesses with age may underlie the biphasic relationship we describe between CMT and age. Reports from histology show that aged human rod photoreceptors show convolutions and other structural changes leading to increased length of outer segments with age,[12] and an increase in outer segment length may not be limited to rods but also may be seen in cones. These changes may partly explain the increased CMT noted with age and changes in foveal morphology leading to a less steep foveal pit with age.[5] Because each retinal sublayer may be affected differently by age, those sublayers that make a substantial contribution to the thickness of the central macular subfield, such as the outer nuclear layer, may drive the changes seen in the thickness of the central macular subfield in older subjects, resulting in reduced macular thickness after the age of 60 years.

Study Strengths and Limitations

Strengths of this study include the large sample size and the use of SD OCT in the UKBB study rather than TDOCT imaging. This is the largest report of macular thickness analysis to date, and this large sample size allows us to reveal weaker associations previously not seen in smaller data sets. An additional strength is the way in which OCT scan quality was controlled by first applying automated image quality criteria (using scan quality indices) before manual reading of images in a systemic way. Applying these exclusion criteria led to the exclusion of a large number of eyes from this analysis. However, in terms of the associations we describe, it is reasonable to assume the trends and associations among demographic, systemic, and ocular factors would still potentially hold true for cases that have been excluded on the basis of poor scan quality or segmentation error if a high-quality scan with accurate measurement of macular thickness could be obtained. One of the limitations of this analysis includes the cross-sectional nature of sampling. Another potential limitation is that although there was a sampling frame for the UKBB study based on general practitioner patient registers in the UK National Health Service, given the low response rate (5.5%), there is the potential for nonresponse bias, with UKBB participants likely to be more healthy than the general population of the United Kingdom. We detected and excluded macular disease, glaucoma, and other significant sight-involving disease directly and indirectly using a combination of approaches, including excluding eyes with visual acuity less than 20/32, excluding eyes with poor image quality by manual assessment of a proportion of scans, and excluding eyes from patients with self-reported ocular disease. Relying in part on self-reported ocular disease may have led to eyes from patients with undiagnosed glaucoma and retinal or macular disease being included in this analysis. However, the large sample size should help in minimizing the effects of inclusion of such cases on the reported macular thickness values.

In conclusion, we report macular thickness measurements from SD OCT imaging in the UKBB study, a large cohort

study of adults in the United Kingdom aged 40 to 69 years. In addition to confirming previous associations between gender and refraction with macular thickness, we show novel findings of an association between macular thickness, age, and ethnicity. This has implications for disease diagnosis, which should take normalized data regarding age- and ethnicity-related changes into account. Furthermore, this work provides baseline macular thickness measurements for the UKBB cohort, which will be of use in assessing changes in macular thickness as the study invites participants to take part in its longitudinal component.

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Footnotes and Financial Disclosures

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[1] NIHR Biomedical Research Centre at Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, London, United Kingdom.

[2] Clinical and Experimental Sciences, Faculty of Medicine, University Hospital Southampton, Southampton, United Kingdom.

[3] Topcon Advanced Biomedical Imaging Laboratory, Oakland, New Jersey.

[4] Singapore Eye Research Institute, Singapore.

[5] Discipline of Clinical Ophthalmology and Eye Health, University of Sydney, Sydney, New South Wales, Australia.

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Author Contributions:

Conception and design: Patel, Foster, Keane, Strouthidis, Yang

Data collection: Patel, Grossi, Ko, Reisman, Yang

Analysis and interpretation: Patel, Foster, Grossi, Ko, Lotery, Reisman, Strouthidis, Yang

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Overall responsibility: Patel, Foster, Keane, Ko, Lotery, Peto, Reisman, Strouthidis, Yang

Abbreviations and Acronyms:
BMI = body mass index; **CI** = confidence interval; **CMT** = central macular thickness; **D** = diopters; **ETDRS** = Early Treatment of Diabetic Retinopathy Study; **ILM** = inner limiting membrane; **IOP** = intraocular pressure; **OCT** = optical coherence tomography; **SD** = standard deviation; **SD OCT** = spectral-domain optical coherence tomography; **TABS** = Topcon Advanced Boundary Segmentation; **TDOCT** = time-domain optical coherence tomography; **UKBB** = UK Biobank.

Correspondence:
Praveen J. Patel, FRCOphth, MD(Res), Moorfields Eye Hospital NHS Foundation Trust, 162 City Road, London, EC1V2PD UK. E-mail: praveen.patel@moorfields.nhs.uk.