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Spectral-Domain Optical Coherence Tomography Imaging in 67 321 Adults

Associations with Macular Thickness in the UK Biobank Study

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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.