Published in final edited form as:
Am J Ophthalmol. 2015 March ; 159(3): 445–456.e1. doi:10.1016/j.ajo.2014.11.025.

Retinal Thickness Measured by Spectral Domain Optical Coherence Tomography in Eyes without Retinal Abnormalities: the Beaver Dam Eye Study

Chelsea E. Myers, **Barbara E. K. Klein**, **Stacy M. Meuer**, **Maria K. Swift**, **Charles S. Chandler**, **Yijun Huang**, **Sapna Gangaputra**, **Jeong W. Pak**, **Ronald P. Danis**, and **Ronald Klein**
Department of Ophthalmology and Visual Sciences, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, USA

Abstract

Purpose—To examine relationships of age, sex, and systemic and ocular conditions with retinal thickness measured by spectral-domain ocular coherence tomography (SD-OCT) in participants without retinal disease.

Design—Longitudinal study.

Setting: Population-based cohort.

Study Population: Persons aged 43-86 years living in Beaver Dam, Wisconsin in 1988-1990.

Observation Procedures: Retinal thickness was measured via SD-OCT at the Beaver Dam Eye Study examination in 2008-2010. Retinal disease was determined by ophthalmoscopy, fundus photography, or SD-OCT.

Main Outcome Measures: Retinal thickness from the inner limiting membrane to Bruch's membrane.

Results—The retina was thickest in the inner circle (mean 334.5 μm) and thinnest in the center subfield (285.4 μm). Mean retinal thickness decreased with age in the inner circle (P<0.0001) and outer circle (P<0.0001). Adjusting for age, eyes in men had thicker retinas than eyes in women in the center subfield (P<0.001) and inner circle (P<0.001). Sex, axial length/corneal curvature ratio, and peak expiratory flow rate were associated with center subfield thickness. Sex and peak expiratory flow rate were associated with retinal thickness in the inner circle. Alcohol

Correspondence: Chelsea E. Myers, MStat, University of Wisconsin School of Medicine and Public Health, Department of Ophthalmology and Visual Sciences, 610 N. Walnut Street, 4th Floor WARF, Madison, WI 53726-2336, Phone: (608) 263-0280, Fax: (608) 263-0279, myers@epi.ophth.wisc.edu.

c. *Contributions of Authors:* design and conduct of the study (RK, BEKK, SMM, MKS, YH); collection, management, analysis, and interpretation of the data (CEM, SMM, BEKK, RK, YH); and preparation, review, or approval of the manuscript (CEM, BEKK, SMM, MKS, CSC, YH, SSG, JWP, RPD, RK).

b. *Financial Disclosures:* All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and had no financial disclosures to make.

consumption, age, axial length/corneal curvature ratio, cataract surgery, ocular perfusion pressure, and peak expiratory flow rate were associated with retinal thickness in the outer circle.

Conclusions—This study provides data for retinal thickness measures in eyes of individuals aged 63 years and older without retinal disease. This information may be useful for clinical trials involving the effects of interventions on retinal thickness and for comparisons with specific retinal diseases affecting the macula.

INTRODUCTION

Spectral-domain optical coherence tomography (SD-OCT) is a noninvasive, quantitative method of imaging that is widely used in clinical practice.[1,2] SD-OCT has been used in clinical trials to measure retinal thickness of the macula and document the presence of anatomic changes in retinal diseases.[1,2] Description of SD-OCT changes in eyes with and without retinal disease has been limited, coming largely from small studies of select groups of patients often younger than 75 years of age who attended ophthalmology clinics or participated in clinical trials where severe disease was over-represented.[3-11] Additionally, normative data provided by SD-OCT manufacturers are limited because details about the populations used to create these datasets are not publicly available.

There are few SD-OCT measurements in the general population of morphological features of eyes with and without retinal disease and these reports are especially lacking for persons aged 85 years and older, who are particularly at risk of developing age-related retinal disease. Because SD-OCT thickness of the macula is the primary outcome measure in many current clinical trials, a well described set of retinal thickness data would be of value for purposes of planning these trials and evaluating their findings. In this report, we examine relationships of age, sex, and systemic and ocular conditions with SD-OCT measured retinal thickness in participants aged 63 years and older without retinal disease in the Beaver Dam Eye Study.

METHODS

Population

Methods used to identify the population and descriptions of the population have appeared in previous reports.[7,12-15] In brief, there were 5924 persons identified in a private census of whom 4926 participated in the baseline examination between March 1, 1988 and September 15, 1990. Subjects were invited to 4 follow-up examinations spaced 5 years apart. The analyses and findings reported here are limited to the 3032 eyes from 1544 individuals who participated in the 20-year follow-up in 2008-2010, the first examination at which SD-OCT scans were obtained. Comparisons between participants and nonparticipants at each examination have appeared elsewhere.[12-16] Ninety-nine percent of the population was white. Approval for this study was granted by the Institutional Review Board at the University of Wisconsin. Informed consent was obtained from each participant before every examination. The tenets of the Declaration of Helsinki were observed.

Procedures

A standardized interview and examination were administered. Information on demographic characteristics and other risk factors, including smoking and drinking habits, were obtained from the questionnaire. Height, weight, refraction, blood pressure, pupil size, peak expiratory flow rate, and visual acuity were measured by trained examiners. Refraction was only measured in individuals who did not have a history of cataract surgery.[17] Stereoscopic 30° color fundus photographs centered on the disc (Diabetic Retinopathy Study standard field 1) and macula (Diabetic Retinopathy Study standard field 2) were obtained for each eye. Intraocular pressure was measured by applanation tonometry using a Goldmann tonometer. Axial length and corneal curvature were measured by the Zeiss IOL Master (Carl Zeiss Meditec Inc., Dublin, California, USA). Glycosylated hemoglobin A1c was measured by RXL Dimension immunoassay. Oxygen saturation was measured by pulse oximetry.

Methods used to photograph and grade the lens for cataract and the retina for retinal disease have been described in detail elsewhere.[17-23] Presence of cataract surgery was determined by history along with the date of surgery and was corroborated by red reflex photographs. Retinopathy was graded in a masked fashion using an abbreviation of the modified Airlie House classification scheme.[24]

SD-OCT images were obtained at the 20-year examination using the Topcon SD-OCT (Topcon 3D-OCT 1000-Mark II) and were processed with Topcon 3D-OCT software (version 3.32). Using a universal OCT viewer, the grader centered an Early Treatment of Diabetic Retinopathy Study grid on the center of the fovea, at which point the thickness of the retina was measured between the internal limiting membrane and Bruch's membrane using the Topcon 3D-OCT segmentation algorithm. The grader then reviewed the segmentation in the scan and assessed the reliability of the retinal and retinal pigment epithelium (RPE) thickness segmentation in the central subfield, the inner circle, and the outer circle. Each region (central, inner, and outer) was graded as “acceptable”, “unacceptable”, or “cannot grade”. Any region for which the grade was “unacceptable” or “cannot grade” was excluded for analysis for all subfields within the region (e.g., if the grade for the inner circle was unacceptable, then the grade for all four subfields within the inner circle as well as the inner subfield thickness average was excluded from analysis). The Tissue Contrast Index (TCI),[25] which measures image quality based on the signal to noise ratio in the image, was calculated by the Universal OCT software. Eyes with TCI <5, corresponding to the threshold SD-OCT manufacturers recommended for use of an image, were excluded from analyses.

Definitions

Retinal thickness was defined as the thickness of the retina between the internal limiting membrane and Bruch's membrane. Mean arterial blood pressure (MABP) was defined as systolic blood pressure+ (2 × diastolic blood pressure) ÷3. Pulse pressure was defined as the systolic minus the diastolic blood pressure. Ocular perfusion pressure in each eye was defined by the following formula: OPP=(D+[S-D]÷3)-lOP, where OPP=ocular perfusion pressure, S=systolic blood pressure, D=diastolic blood pressure, and IOP=intraocular pressure.[26] Diabetes status was defined as self-report of physician diagnosis with or without

use of hypoglycemic medications or elevated (≥6.5%) glycosylated hemoglobin level. Body mass index was calculated by dividing a participant's weight in kilograms by height in meters squared. Current smokers were identified as persons having smoked ≥100 cigarettes in their lifetime and were smoking at the time of the examination. Past smokers had smoked in the past but had stopped at the time of the examination. Pack-years smoked was defined as the average number of cigarettes smoked in a day divided by 20 and multiplied by the number of years the individual smoked. Never smokers were considered to have smoked 0 pack-years. Current heavy drinking was defined as consuming 4 or more servings of alcoholic beverages daily; a serving was defined as 12 fluid ounces of beer, 4 fluid ounces of wine, or 1.5 fluid ounces of liquor. Past heavy drinkers had consumed 4 or more servings of alcohol per day in the past but had stopped by the time of the examination.

Eyes with moderate early or more severe age-related macular degeneration (levels 30-50 on the Three Continent Consortium severity scale),[23] epiretinal membranes, macular holes or cysts, posterior vitreoretinal traction, moderate nonproliferative or more severe diabetic retinopathy (more severe than Early Treatment of Diabetic Retinopathy severity level 31), macular edema, focal or scatter laser treatment in the macula, retinal vein or arterial occlusion, macular dystrophy, myopic degeneration, histoplasmosis or toxoplasmosis, retinal and chorioretinal inflammatory conditions, and coloboma/staphyloma as determined by ophthalmoscopy, fundus photography or SD-OCT were considered to have retinal disease. An individual with at least one eye with retinal disease was considered to have retinal disease. The axial length/corneal curvature ratio was defined as the axial length divided by the corneal curvature measurement.

Statistical Analysis

Measures of retinal thickness and covariates were obtained at the fifth Beaver Dam Eye Study examination and analyzed cross-sectionally. Thickness measures from the center subfield, the average of the four inner subfields (inner circle), and the average of the four outer subfields (outer circle) were used in analyses. Analyses were done in each eye separately, and relationships between each covariate and retinal thickness measure were modeled using generalized estimating equations with an exchangeable working correlation structure to account for correlation between the two eyes from a single participant. Relationships of covariates to each retinal thickness measure (center subfield, inner circle, and outer circle) were first modeled linearly adjusting only for age and sex. Quadratic and third order terms were tested for continuous risk factors, and significant higher order associations, adjusted for age and sex, were plotted for ease of interpretation. Because it is highly dependent on age and sex,[27] peak expiratory flow rate was analyzed in sex-specific quartiles comparing the highest 3 quartiles to the lowest quartile.

We then created a separate multivariate model for the thickness measure in each subfield/region in 4 steps. First, we compared the Quasi likelihood under the Independence model Criterion (QIC)[28] for each age-sex adjusted model to determine which measure of eye size and shape (axial length alone, corneal curvature alone, axial length and corneal curvature as independent terms in the same model, or axial length/corneal curvature ratio) best captured the association of eye size and shape to each thickness measure. We did not consider models

with refraction because refraction was not measured in eyes with a history of cataract surgery. Second, we added to each model all the other factors that were associated with the thickness measure, including significant higher-order terms, in age-sex adjusted analyses (full model). Third, we used backward selection to arrive at a final multivariate model for the retinal thickness measure in each subfield/region (reduced model). Finally, because peak expiratory flow rate is highly correlated with age, sex, and body size,[27] model selection was done without peak expiratory flow rate as a covariate. SAS version 9.3 (SAS Institute, Cary NC, USA) was used for all analyses.

RESULTS

Participant characteristics

There were 3032 eyes from 1544 individuals who had macular SD-OCT scans at the 20-year follow-up. Of these, 95 eyes were excluded because the grader could not appropriately center the grid or determined that all measurements in the center subfield and inner and outer circles were unreliable, and 171 eyes were excluded for having TCI less than 5. Of the 2766 eyes with gradable scans, 928 eyes were considered to have a retinal disease or condition. Twenty had macular edema, 31 had a traumatic injury, 19 had laser treatment, 6 had a retinal vein occlusion, 7 had macular dystrophy, 8 had myopic degeneration, 5 had presumed ocular histoplasmosis syndrome, 1 had a chorioretinal inflammatory condition, 609 had an epiretinal membrane, 292 had moderate early or more severe age-related macular degeneration, 71 had a macular hole, 89 had a retinal cyst, 25 had posterior vitreoretinal traction, and 60 had moderate or more severe diabetic retinopathy greater than level 31 (not mutually exclusive). Further, 68 center subfields, 27 inner circles, and 94 outer circles were excluded for poor reliability leaving 1838 eyes (1770 center subfields, 1811 inner circles, and 1744 outer circles) from 977 individuals eligible for analyses. The mean TCI for these images was 6.36 (standard deviation [SD]=0.56). Reliability was graded as very reliable (there were no complications in scan quality, e.g., mirror or motion artifact) in 1680, 1716, and 1217 images and moderately reliable (there was a complication in scan quality but it did not affect the reliability of the thickness measures) in 90, 95, and 527 images in the center subfield, inner circle, and outer circle, respectively.

Compared to individuals/eyes excluded from analyses, those included were younger (mean age 72.6 vs. 76.4 years) and, after adjusting for age and sex, had lower glycosylated hemoglobin (mean 5.9% vs. 6.0%), a smaller axial length/corneal curvature ratio (mean 3.08 vs. 3.09), better contrast sensitivity (mean 1.6 vs. 1.5 log contrast sensitivity), a higher TCI (mean 6.36 vs. 6.18), and a thinner retina in the center subfield and inner and outer circles (Table 1). Individuals/eyes included were less likely to have had cataract surgery (18.3% vs. 34.3%), have diabetes present (17.3% vs. 23.0%), have an increasing number of “C” risk alleles for *Complement Factor H* Y402H rs1061170 gene (11.8% vs. 15.8% with the C/C genotype), have an increasing number of “T” risk alleles for *Age-related Maculopathy Susceptibility 2* rs10490924 gene (3.3% vs. 6.1% with the T/T genotype), and have visual impairment (1.4% vs. 6.3%). There were no significant differences found between those included and excluded from analyses in sex distribution, smoking status, history of cardiovascular disease, or presence of nuclear cataract.

Variability of retinal thickness by subfield, age and sex

Figure 1 shows the distribution of retinal thickness in the center subfield and inner and outer circles. The retina was thickest in the inner circle (mean 334.5 μm, median 334.8 μm) and thinnest in the center subfield (285.4 μm, median 285.0 μm). Retinal thickness was most variable in the center subfield (SD 22.3 μm, range 172–368.0 μm) and least variable in the outer circle (SD 13.6 μm, range 238.0–331.0 μm). The retina was thickest in the nasal subfield (341.3 ±17.9 μm and 306.0 ±17.0 μm) in the inner and outer circles, respectively, and was thinnest in the temporal subfield in the inner circle (329.0 ±17.2 μm) and in the inferior region of the outer circle (281.3 ±14.7 μm, Table 2). Retinal thickness was highly symmetric between eyes of the same subject. The correlation in thickness measures between the eyes was 0.89 for the center subfield and 0.87 and 0.88 for the inner and outer circles, respectively.

Mean retinal thickness decreased with age in the inner circle (youngest vs. oldest age group, P value for trend per increasing age group: 337.8 vs. 325.7 μm, P<0.0001) and outer circle (292.4 vs. 282.7 μm, P<0.001) but not the center subfield (286.9 vs. 279.9 μm, P=0.07; Table 3). Adjusting for age, men had thicker retinas than women in the center subfield (men vs. women, P value: 289.5 vs. 273.8 μm, P<0.001) and inner circle (337.1 vs. 332.5 μm, P<0.001) but not the outer circle (290.7 vs. 288.9 μm, P=0.08). Adjusting for age, macular thickness in women taking oral estrogen (N=38) was on average 4.0 μm, 3.3 μm, and 4.4 μm greater in the center subfield, inner circle, and outer circle, respectively, than in women not taking oral estrogen, although these differences were not statistically significant.

Relationships of retinal thickness with ocular and systemic characteristics

Adjusting for age and sex, a greater axial length (P=0.03) and a greater axial length/corneal curvature ratio (P=0.0001) were linearly associated with a thicker retina in the center subfield. A greater corneal curvature (P=0.005), being a past compared to never smoker (P=0.004), having a greater number of pack-years smoked (P=0.02), and having a lower peak expiratory flow rate (P=0.002) were linearly associated with a thinner retina in the center subfield (Table 4). More hyperopic refraction (P<0.001) was linearly associated with a thicker retina in the inner circle, and a longer axial length (P<0.001), a greater corneal curvature (P=0.01), a greater number of pack-years smoked (P=0.01), a history of past heavy drinking (P=0.04), and a lower peak expiratory flow rate (P<0.001) were associated with a thinner retina in the inner circle. A more hyperopic refraction (P<0.001) and a history of current heavy drinking (P=0.005) were linearly associated with a thicker retina in the outer circle and a longer axial length (P<0.001), a greater corneal curvature (P<0.001), a greater axial length/corneal curvature ratio (P<0.0001), a history of cataract surgery (P=0.003), a higher ocular perfusion pressure (P=0.01), a higher MABP (P=0.02), and a lower peak expiratory flow rate (P<0.001) were associated with a thinner retina in the outer circle. The relationship of peak expiratory flow rate to retinal thickness in the inner and outer circles remained after further adjustment for oxygen saturation level and when analyses were restricted to non-smokers. No associations were found between pupil size, intraocular pressure, height, body mass index, weight, current history of diabetes or glycosylated hemoglobin in non-diabetic persons and any of the retinal thickness measures.

There was a cubic relationship between axial length and retinal thickness in the inner and outer circles. Adjusting for age and sex, retinal thickness in the inner circle increased with increasing axial length up to 22 mm and then decreased with longer axial length (Figure 2). Retinal thickness in the outer circle decreased slightly when axial length increased from 21 mm and then decreased more rapidly with axial length longer than 22 mm (Figure 3). There were no other higher order associations found between any of the risk factors and any of the retinal thickness measures (data not shown).

Because there was a cubic relationship between axial length and retinal thickness in the inner and outer circles, axial length was entered as a cubic term in these models comparing measures of eye size and shape to include in the multivariate models. Adjusting for age and sex, models with the axial length/corneal curvature ratio had a lower QIC compared to models with just axial length, just corneal curvature, or axial length and corneal curvature entered as independent terms (data not shown).

In multivariate analyses, the full model for center subfield thickness included age, sex, axial length/corneal curvature ratio, pack-years smoked, and peak expiratory flow rate (Table 5, full model 1). After backward selection, only male sex and a greater axial length/corneal curvature ratio were independently associated with a thicker retina in the center subfield and a lower peak expiratory flow rate was associated with a thinner retina in the center subfield (Table 5, reduced model 1). When pack-years smoked was replaced by smoking status in the full model, it did not remain independently associated with central subfield thickness after backward selection (data not shown).

The full model for the inner circle included age, sex, axial length/corneal curvature ratio, linear, quadratic and cubic terms for vertical cup/disc ratio, pack-years smoked, history of heavy drinking, and peak expiratory flow rate. After backward selection, male sex was associated with a thicker retina in the inner circle, and older age and a lower peak expiratory flow rate were associated with a thinner retina in the inner circle. When pack-years smoked was replaced by smoking status in the full model, it did not remain independently associated with central subfield thickness after backward selection (data not shown).

The full model for the outer circle included age, sex, axial length/corneal curvature ratio, history of cataract surgery, ocular perfusion pressure, history of heavy drinking, MABP, and peak expiratory flow rate. After backward selection, a history of current heavy drinking was associated with a thicker retina in the outer circle, and older age, a greater axial length/ corneal curvature ratio, a history of cataract surgery vs. no cataract, higher ocular perfusion pressure, and lower peak expiratory flow rate were independently associated with a thinner retina in the outer circle.

When peak expiratory flow rate was excluded from the full model, the other terms in the reduced models for center subfield and outer circle thickness remained the same (Table 5, reduced model 2). However, when peak expiratory flow rate was excluded from the full model for retinal thickness in the inner circle, a greater number of pack-years smoked was independently associated with a thinner retina in the inner circle and a current history of heavy drinking was independently associated with a thicker retina in the inner circle.

DISCUSSION

Our results provide normative values of SD-OCT macular thickness measures in an older cohort. We report the distribution of macular thickness in eyes without retinal diseases or conditions in a population based cohort of adults aged 63 years and older and examine relationships with age, sex, and other ocular and systemic covariates. These data may help provide needed estimates when starting a clinical trial studying the effects of an intervention on macular thickness and for comparisons of the effect of specific retinal diseases and macular thickness.

We have found that, with older age, the retina was thinner in the inner and outer circles but not the center subfield, which is consistent with several previous SD-OCT studies in healthy eyes.[29-32] This corresponds to histologic studies that found that outside the foveal center, photoreceptor and RPE cell density decreased significantly with increasing age.[33,34]

We did not find an association of age with center subfield thickness as was reported in some clinic-based studies[35-37] of healthy eyes. We speculate on two possible reasons for this difference. First, the participants in the clinic-based studies were, on average, younger than participants in our study (Demirkaya et al.[35] mean age 46.9 years, age-range 18 to 81 years, Ooto et al.[36] mean age 55.5 years, range 20 to 70+ years, Eriksson et al.[37] mean age 34.4 years, range 12-74 years). The central subfield is the most variable SD-OCT measure, and older individuals may have more difficulty fixating on the target thus introducing variability to our measurements of central subfield thickness, which would bias our results to the null. Second, we analyzed the thickness of the retina as a whole rather than analyzing each individual layer, each of which may be affected differently, i.e., some layers may become thicker while others may become thinner with age. Demirkaya et al. report a relationship of increasing age associated with a decrease in retinal thickness in the outer segment layer and an increase in retinal thickness in the RPE in the fovea (corresponding to the center subfield in our study) and Ooto et al. report that increased age was associated with thinner retinal layers, excepting the outer plexiform and outer nuclear layers in the center subfield of the retina.[35,36]

Our finding that men had thicker retinas than women in the center subfield and inner circle is consistent with several previous reports.[29,31,36,38-40] This finding of foveal thinning in women compared to men has been attributed to hormonal changes at menopause, and this may help to explain why women are at higher risk for developing macular holes than men.[41,42] In the Beaver Dam Eye Study, adjusting for age, macular thickness in women taking oral estrogen was on average 4 μm greater than in women not taking oral estrogen, although this difference did not reach statistical significance. The lack of significance may be due to the fact that only 38 participants were taking these medications.

In multivariate analyses, male sex and a greater axial length/corneal curvature ratio were independently associated with a thicker retina in the center subfield, and lower peak expiratory flow rate was independently associated with a thinner retina in the center subfield. Male sex was independently associated with a thicker retina in the inner circle, and older age and lower peak expiratory flow rate were independently associated with a thinner

inner circle of the retina. Being a current heavy drinker was independently associated with a thicker retina in the outer circle compared to never having been a heavy drinker, and older age, a greater axial length/corneal curvature ratio, a history of cataract surgery compared to no cataract, a higher ocular perfusion pressure, and a lower peak expiratory flow rate were independently associated with a thinner outer circle of the retina.

In analyses adjusted for age and sex, higher peak expiratory flow rate was associated with increased retinal thickness in all three regions of the retina. This relationship remained for the inner and outer circles after adjusting for other factors as well as when analyses were restricted to non-smokers. Hypoxia has been found to induce apoptotic damage to RPE cells.[43] If decreased peak expiratory flow rate is a systemic marker of hypoxia in the retina, lower peak expiratory flow rate may be associated with thinning of the RPE due to cell death. However, senescence of the RPE may contribute to decreased expression of angiogenesis inhibitors, such as pigment epithelium-derived factor, further increasing the risk of neovascular age-related macular degeneration,[44] which would have the effect of thickening rather than thinning the retina. When peak expiratory flow rate was not included as a covariate, pack-years smoked was associated with a thinner retina in the inner subfield, which is consistent with the hypothesis that hypoxia is related to thinning of the retina. However, oxygen saturation as measured from a finger was not associated with any of the retinal thickness measures in the Beaver Dam Eye Study adjusting for age and sex, and adding oxygen saturation to a model with age, sex, and peak expiratory flow rate did not change the association of peak expiratory flow rate to any of the retinal thickness measures. The relationship of peak expiratory flow rate to retinal thickness may also be due to uncontrolled confounding from differences in diet (i.e., people with higher peak expiratory flow rate may consume a diet richer in antioxidants that protects against cell death in the retina) or may reflect biological aging beyond what is expected for a given chronological age.

We have found measures of eye size and shape (axial length, corneal curvature, and axial length/corneal curvature ratio) to be related to retinal thickness. Modeling eye size and shape with the axial length/corneal curvature ratio was determined to have the best fit. This indicates that it is the degree of myopia rather than just axial length (which is also determined by height) that is most strongly associated with retinal thickness. Our findings of an association of a longer axial length and a greater axial length/corneal curvature ratio to a thicker retina in the center subfield and thinner retina in the inner and outer circles is consistent with other studies[29,45-47] of axial length, refractive status (myopic) and retinal thickness, and histological findings of increasing retinal thinning in myopic eyes.[48] Wu and colleagues[47] speculate that increased axial length results in mechanical stretching of the sclera, which could cause retinal thinning, and that the stretching and flattening tendency of the internal limiting membrane and the centripetal force of the posterior vitreous may result in elevation of the foveola and fovea.

We have found an absence of cataract surgery compared to no cataract and a higher ocular perfusion pressure to be associated with a thinner retina in the outer circle and history of current heavy drinking to be associated with a thicker retina in the outer subfield in multivariate analyses. Few studies have examined the relationship of these factors to retinal

thickness. The Singapore Chinese Eye Study did not find an association of any of these factors to total retinal thickness[29] or to thickness of the ganglion cell inner plexiform layer.[49] These relationships may be due to chance given the number of factors studied. Further studies are needed to examine the relationships of ocular and systemic factors to retinal thickness.

Our study's strengths include a large population-based cohort of persons with no clinical retinal diseases or conditions in individuals aged 63 years and older who underwent a standardized examination. One limitation is that we did not examine associations of age, sex, and other factors to the thickness of individual layers of the retina. We may not have found associations with various factors due to the fact that they only affect certain layers of the retina, or they affect different layers of the retina differently (i.e., some layers may become thicker while others may become thinner) with exposure to the risk factor. A second limitation is that retinal thickness in this study was measured using only one SD-OCT instrument, which may limit our ability to make generalizations about our estimates of retinal thickness measures and the relationships we report. Because our findings of associations of retinal thickness with age and other systemic factors reported herein are similar to those found in other studies using different machines to measure thicknesses from SD-OCT scans, we speculate that the information we report is likely to be found by and be informative to clinicians using different SD-OCT equipment.

In conclusion, this study provides data for retinal thickness measures in the macular area of eyes free of clinical signs of retinal disease from individuals aged 63 years and older. These data may benefit those who are planning clinical trials or making comparisons with specific retinal diseases. We have confirmed the findings of other studies of relationships of age, sex, and myopia to macular thickness. The relationships of peak expiratory flow rate, ocular perfusion pressure, diabetes status, and history of current heavy drinking to retinal thickness measures need to be replicated.

ACKNOWLEDGEMENTS

a. *Funding/Support:* The Beaver Dam Eye Study was supported by National Institutes of Health grant EY06594 (BEK Klein and R Klein) and by an unrestricted grant from Research to Prevent Blindness, New York, NY. The National Eye Institute provided funding for entire study including collection and analyses of data; Research to Prevent Blindness provided additional support for data analyses.

d. *Other Acknowledgments:* The authors thank Topcon Corporation (Tokyo, Japan) for providing the SD-OCT equipment used in this study.

Biography

AJO Brief Biosketch

Chelsea E. Myers is a biostatistician in the Department of Ophthalmology and Visual Sciences at the University of Wisconsin-Madison. Her research interests include statistical methods in the study of age-related eye disease.

REFERENCES

1. Kawasaki, M., editor. Optical Coherence Tomography. InTech; Rijeka, Croatia: 2013. p. 1-185.
2. Kharousi, N.; Upender, K.; Azeem, S. Current applications of optical coherence tomography in ophthalmology.. In: Kawasaki, M., editor. Optical Coherence Tomography. InTech; Rijeka, Croatia: 2013. p. 3-31.
3. Baumann B, Gotzinger E, Pircher M, et al. Segmentation and quantification of retinal lesions in age-related macular degeneration using polarization-sensitive optical coherence tomography. J Biomed Opt. 2010; 15(6):061704. [PubMed: 21198152]
4. Bearelly S, Chau FY, Koreishi A, Stinnett SS, Izatt JA, Toth CA. Spectral domain optical coherence tomography imaging of geographic atrophy margins. Ophthalmology. 2009; 116(9):1762–1769. [PubMed: 19643488]
5. Jain N, Farsiu S, Khanifar AA, et al. Quantitative comparison of drusen segmented on SD-OCT versus drusen delineated on color fundus photographs. Invest Ophthalmol Vis Sci. 2010; 51(10): 4875–4883. [PubMed: 20393117]
6. Landa G, Rosen RB, Patel A, et al. Qualitative spectral OCT/SLO analysis of drusen change in dry age-related macular degeneration patients treated with Copaxone. J Ocul Pharmacol Ther. 2011; 27(1):77–82. [PubMed: 21254921]
7. Linton KL, Klein BE, Klein R. The validity of self-reported and surrogate-reported cataract and age-related macular degeneration in the Beaver Dam Eye Study. Am J Epidemiol. 1991; 134(12):1438–1446. [PubMed: 1776618]
8. Menke MN, Dabov S, Sturm V. Features of age-related macular degeneration assessed with three-dimensional Fourier-domain optical coherence tomography. Br J Ophthalmol. 2008; 92(11):1492–1497. [PubMed: 18703554]
9. Pieroni CG, Witkin AJ, Ko TH, et al. Ultrahigh resolution optical coherence tomography in non-exudative age related macular degeneration. Br J Ophthalmol. 2006; 90(2):191–197. [PubMed: 16424532]
10. Schlanitz FG, Ahlers C, Sacu S, et al. Performance of drusen detection by spectral-domain optical coherence tomography. Invest Ophthalmol Vis Sci. 2010; 51(12):6715–6721. [PubMed: 21123769]
11. Zweifel SA, Imamura Y, Spaide TC, Fujiwara T, Spaide RF. Prevalence and significance of subretinal drusenoid deposits (reticular pseudodrusen) in age-related macular degeneration. Ophthalmology. 2010; 117(9):1775–1781. [PubMed: 20472293]
12. Klein R, Klein BE, Linton KL, De Mets DL. The Beaver Dam Eye Study: visual acuity. Ophthalmology. 1991; 98(8):1310–1315. [PubMed: 1923372]
13. Klein R, Klein BE, Lee KE. Changes in visual acuity in a population. The Beaver Dam Eye Study. Ophthalmology. 1996; 103(8):1169–1178. [PubMed: 8764783]
14. Klein R, Klein BE, Lee KE, Cruickshanks KJ, Chappell RJ. Changes in visual acuity in a population over a 10-year period : The Beaver Dam Eye Study. Ophthalmology. 2001; 108(10): 1757–1766. [PubMed: 11581046]
15. Klein R, Klein BE, Lee KE, Cruickshanks KJ, Gangnon RE. Changes in visual acuity in a population over a 15-year period: the Beaver Dam Eye Study. Am J Ophthalmol. 2006; 142(4): 539–549. [PubMed: 17011842]
16. Klein R, Lee KE, Gangnon RE, Klein BE. Incidence of visual impairment over a 20-year period: the Beaver Dam Eye Study. Ophthalmology. 2013; 120(6):1210–1219. [PubMed: 23466270]
17. Klein, R.; Klein, BE. The Beaver Dam Eye Study. Manual of Operations, Revised. National Technical Information Service; Springfield, VA: 1991.
18. Klein R, Davis MD, Magli YL, Segal P, Klein BE, Hubbard L. The Wisconsin age-related maculopathy grading system. Ophthalmology. 1991; 98(7):1128–1134. [PubMed: 1843453]

19. Klein, R.; Davis, MD.; Magli, YL., et al. The Wisconsin Age-Related Maculopathy Grading System. National Technical Information Service; Springfield, VA: Jul. 1991
20. Klein R, Klein BE, Linton KL. Prevalence of age-related maculopathy. The Beaver Dam Eye Study. Ophthalmology. 1992; 99(6):933–943. [PubMed: 1630784]
21. Klein R, Klein BE, Jensen SC, Meuer SM. The five-year incidence and progression of age-related maculopathy: the Beaver Dam Eye Study. Ophthalmology. 1997; 104(1):7–21. [PubMed: 9022098]
22. Klein R, Myers CE, Meuer SM, et al. Risk alleles in CFH and ARMS2 and the long-term natural history of age-related macular degeneration: the Beaver Dam Eye Study. JAMA Ophthalmol. 2013; 131(3):383–392. [PubMed: 23494043]
23. Klein R, Meuer SM, Myers CE, et al. Harmonizing the classification of age-related macular degeneration in the Three-Continent AMD Consortium. Ophthalmic Epidemiol. 2014; 21(1):14–23. [PubMed: 24467558]
24. Klein BE, Davis MD, Segal P, et al. Diabetic retinopathy. Assessment of severity and progression. Ophthalmology. 1984; 91(1):10–17. [PubMed: 6709313]
25. Huang L, Li Y, Singleton AB, et al. Genotype-imputation accuracy across worldwide human populations. Am J Hum Genet. 2009; 84(2):235–250. [PubMed: 19215730]
26. Grunwald JE. Effect of topical timolol on the human retinal circulation. Invest Ophthalmol Vis Sci. 1986; 27(12):1713–1719. [PubMed: 2947874]
27. Gupta CK, Mathur N. Statistical models relating peak expiratory flow rates to age, height, and weight in men and women. J Epidemiol Community Health. 1982; 36(1):64–67. [PubMed: 7069358]
28. Pan W. Akaike's information criterion in generalized estimating equations. Biometrics. 2001; 57(1):120–125. [PubMed: 11252586]
29. Gupta P, Sidhartha E, Tham YC, et al. Determinants of macular thickness using spectral domain optical coherence tomography in healthy eyes: the Singapore Chinese Eye study. Invest Ophthalmol Vis Sci. 2013; 54(13):7968–7976. [PubMed: 24222307]
30. Manassakorn A, Chaidaroon W, Ausayakhun S, Aupapong S, Wattananikorn S. Normative database of retinal nerve fiber layer and macular retinal thickness in a Thai population. Jpn J Ophthalmol. 2008; 52(6):450–456. [PubMed: 19089565]
31. Song WK, Lee SC, Lee ES, Kim CY, Kim SS. Macular thickness variations with sex, age, and axial length in healthy subjects: a spectral domain-optical coherence tomography study. Invest Ophthalmol Vis Sci. 2010; 51(8):3913–3918. [PubMed: 20357206]
32. Sung KR, Wollstein G, Bilonick RA, et al. Effects of age on optical coherence tomography measurements of healthy retinal nerve fiber layer, macula, and optic nerve head. Ophthalmology. 2009; 116(6):1119–1124. [PubMed: 19376593]
33. Gao H, Hollyfield JG. Aging of the human retina. Differential loss of neurons and retinal pigment epithelial cells. Invest Ophthalmol Vis Sci. 1992; 33(1):1–17. [PubMed: 1730530]
34. Panda-Jonas S, Jonas JB, Jakobczyk-Zmija M. Retinal photoreceptor density decreases with age. Ophthalmology. 1995; 102(12):1853–1859. [PubMed: 9098287]
35. Demirkaya N, van Dijk HW, van Schuppen SM, et al. Effect of age on individual retinal layer thickness in normal eyes as measured with spectral-domain optical coherence tomography. Invest Ophthalmol Vis Sci. 2013; 54(7):4934–4940. [PubMed: 23761080]
36. Ooto S, Hangai M, Tomidokoro A, et al. Effects of age, sex, and axial length on the three-dimensional profile of normal macular layer structures. Invest Ophthalmol Vis Sci. 2011; 52(12): 8769–8779. [PubMed: 21989721]
37. Eriksson U, Alm A. Macular thickness decreases with age in normal eyes: a study on the macular thickness map protocol in the Stratus OCT. Br J Ophthalmol. 2009; 93(11):1448–1452. [PubMed: 19019921]
38. Adhi M, Aziz S, Muhammad K, Adhi MI. Macular thickness by age and gender in healthy eyes using spectral domain optical coherence tomography. PLoS One. 2012; 7(5):e37638. [PubMed: 22629435]

39. Duan XR, Liang YB, Friedman DS, et al. Normal macular thickness measurements using optical coherence tomography in healthy eyes of adult Chinese persons: the Handan Eye Study. Ophthalmology. 2010; 117(8):1585–1594. [PubMed: 20472290]
40. Bressler NM, Edwards AR, Antoszyk AN, et al. Retinal thickness on Stratus optical coherence tomography in people with diabetes and minimal or no diabetic retinopathy. Am J Ophthalmol. 2008; 145(5):894–901. [PubMed: 18294608]
41. Risk factors for idiopathic macular holes. The Eye Disease Case-Control Study Group. Am J Ophthalmol. 1994; 118(6):754–761. [PubMed: 7977602]
42. Evans JR, Schwartz SD, McHugh JD, et al. Systemic risk factors for idiopathic macular holes: a case-control study. Eye (Lond). 1998; 12(Pt 2):256–259. [PubMed: 9683950]
43. Castillo M, Bellot JL, Garcia-Cabanes C, Miquel J, Orts A, Palmero M. Effects of hypoxia on retinal pigmented epithelium cells: protection by antioxidants. Ophthalmic Res. 2002; 34(6):338–342. [PubMed: 12483020]
44. Schlingemann RO. Role of growth factors and the wound healing response in age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol. 2004; 242(1):91–101. [PubMed: 14685874]
45. Lam DS, Leung KS, Mohamed S, et al. Regional variations in the relationship between macular thickness measurements and myopia. Invest Ophthalmol Vis Sci. 2007; 48(1):376–382. [PubMed: 17197557]
46. Lim MC, Hoh ST, Foster PJ, et al. Use of optical coherence tomography to assess variations in macular retinal thickness in myopia. Invest Ophthalmol Vis Sci. 2005; 46(3):974–978. [PubMed: 15728555]
47. Wu PC, Chen YJ, Chen CH, et al. Assessment of macular retinal thickness and volume in normal eyes and highly myopic eyes with third-generation optical coherence tomography. Eye (Lond). 2008; 22(4):551–555. [PubMed: 17464309]
48. Apple, DJ.; Fabb, MF. Clinicopathologic Correlation of Ocular Disease: a Text and Stereoscopic Atlas. CV Mosby; St. Louis: 1978.
49. Koh VT, Tham YC, Cheung CY, et al. Determinants of ganglion cell-inner plexiform layer thickness measured by high-definition optical coherence tomography. Invest Ophthalmol Vis Sci. 2012; 53(9):5853–5859. [PubMed: 22836772]

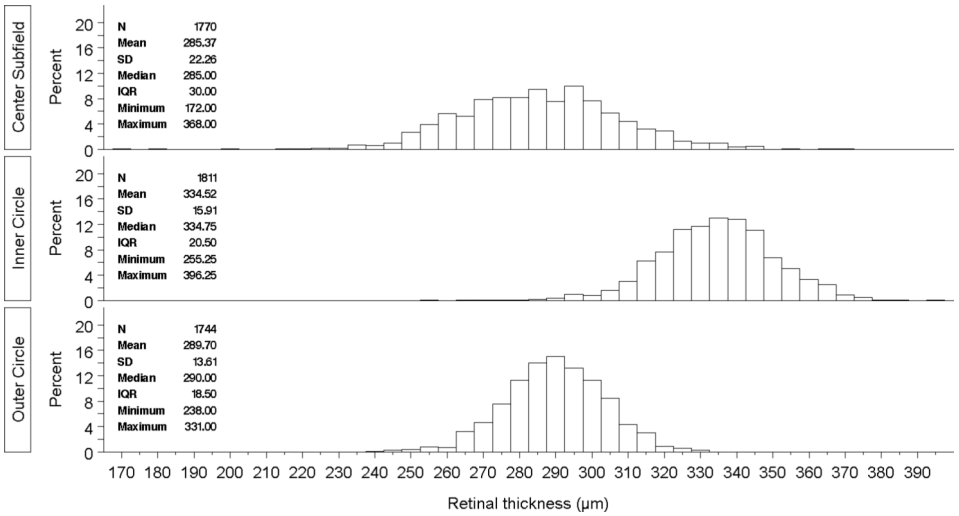

Figure 1.

Distribution of retinal thickness measured by spectral-domain optical coherence tomography in the center subfield and inner and outer circles. IQR, interquartile range; SD, standard deviation.

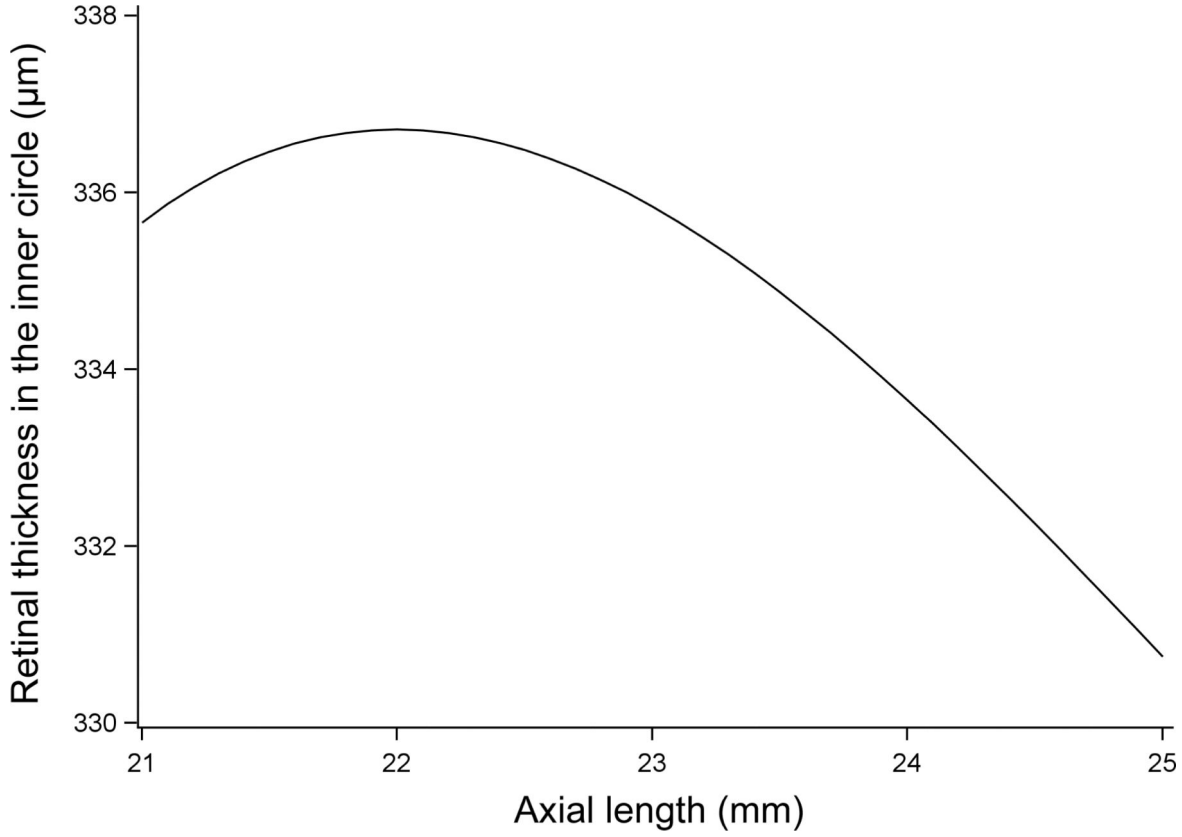

Figure 2.
Age-sex adjusted estimate of retinal thickness in the inner circle for a given axial length.

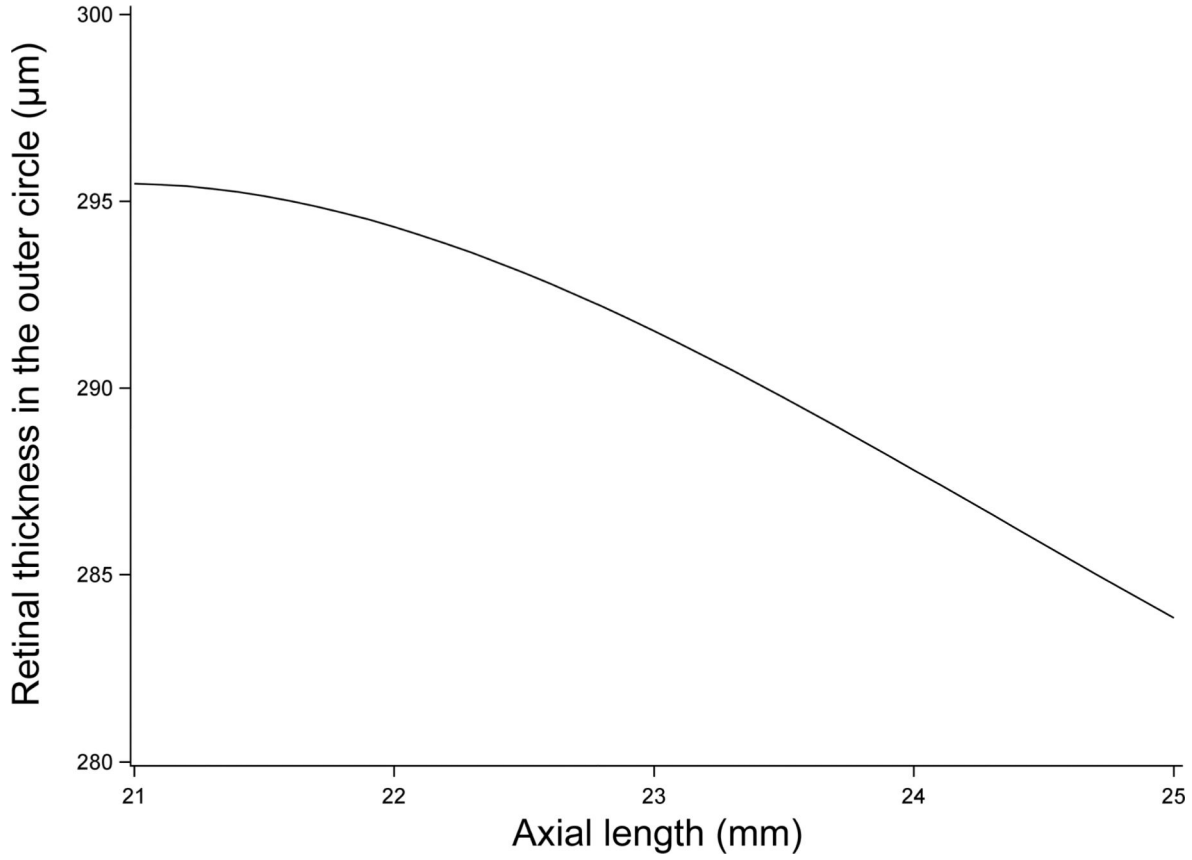

Figure 3.
Age-sex adjusted estimate of retinal thickness in the outer circle for a given axial length.

Table 1

Characteristics of Individuals Included and Excluded from Analyses of Retinal Thickness Measured by Spectral Domain Optical Coherence Tomography, Beaver Dam Eye Study, 2008-2010.

Covariate	Mean (SD), %, or ratio		P value[a]
	Included N=977 individuals/1838 eyes	Excluded N=525 individuals/928 eyes	
Age, years	72.6 (6.3)	76.4 (7.5)	0.001
Sex, male	44.6	41.9	0.76
Height, in	64.8 (3.8)	64.3 (4.0)	0.94
Weight, lb	182.8 (42.1)	177.3 (42.0)	0.89
Body mass index, kg/m^2	31.3 (6.3)	30.8 (6.2)	0.89
Positive history of current smoking	7.3	6.1	0.95
Pack-years smoked	14.4 (23.9)	13.3 (24.5)	0.84
Glycosylated hemoglobin A1c, %	5.9 (0.7)	6.0 (0.8)	0.02
Diabetes present	17.3	23.0	0.01
Mean arterial blood pressure, mmHg	93.4 (11.0)	91.5 (10.7)	0.11
Intraocular pressure, mmHg	15.8 (3.0)	15.5 (2.8)	0.30
Ocular perfusion pressure, mmHg	46.6 (7.5)	45.5 (6.9)	0.16
Vertical cup-to-disc ratio	0.4 (0.1)	0.4 (0.1)	0.02
Peak expiratory flow rate, L/min	362.4 (134.7)	336.2 (129.8)	0.95
Cardiovascular disease present	14.6	18.5	0.24
Positive history of myocardial infarction	9.2	11.8	0.33
Positive history of stroke		2.5	0.72
Positive history of angina	7.1	9.2	0.59
Refraction, diopters	0.6 (2.2)	0.3 (2.6)	<0.001
Axial length/corneal curvature ratio	3.1 (0.1)	3.1 (0.1)	0.006
Pupil size, cm	0.6 (0.1)	0.6 (0.1)	>0.99
Central cataract present	18.6	26.5	0.63
Positive history of cataract surgery	18.3	34.3	<0.001
Visual impairment worse than 20/40	1.4	6.3	<0.001
Contrast sensitivity, Log CS	1.6 (0.1)	1.5 (0.2)	<0.001
CFH genotype			0.03[b]
T/C	47.9	48.1	
T/T	11.8	15.8	
ARMS2 genotype			0.03[b]
G/T	36.9	38.7	
T/T	3.3	6.1	
Center subfield thickness, μm	287.5 (27.0)	294.1 (39.9)	<0.001
Inner circle thickness, μm	335.0 (17.2)	335.7 (22.6)	0.04
Outer circle thickness, μm	289.9 (14.5)	291.5 (16.3)	0.003
Tissue contrast index	6.4 (0.6)	6.2 (0.6)	<0.001

ARMS2, age-related maculopathy susceptibility 2; *CFH*, complement factor H; Log CS, logarithm of contrast sensitivity

[a] Adjusts for age and sex.

[b] Test of trend per increasing # of risk alleles.

Table 2

Mean Retinal Thickness (μm) Measured by Spectral Domain Optical Coherence Tomography in the Center Subfield and Each Subfield of the Inner and Outer Circles.

Subfield	Mean	SD	Minimum	Maximum
Center (1770 eyes)	285.4	22.3	172.0	369.0
Inner (1811 eyes)				
Inferior	332.9	17.2	226.0	480.0
Nasal	341.3	17.9	113.0	400.0
Superior	334.9	15.9	243.0	387.0
Temporal	329.0	17.3	180.0	384.0
Outer (1744 eyes)				
Inferior	281.3	14.7	206.0	341.0
Nasal	306.0	17.0	181.0	355.0
Superior	288.3	13.8	205.0	335.0
Temporal	283.2	15.1	194.0	332.0

SD, standard deviation.

Table 3

Mean Retinal Thickness (μm) Measured by Spectral Domain Optical Coherence Tomography by Age and Sex in the Center Subfield and Inner and Outer Circles, Beaver Dam Eye Study, 2008-2010

Area of Measurement	Age, years	Male			Female			Overall			P values	
		N	Mean	SD	N	Mean	SD	N	Mean	SD	Age trend	Male vs. Female*
Center subfield	63-69	342	295.3	21.8	360	279.0	20.0	702	286.9	22.4	0.07	<0.001
	70-74	215	290.9	20.8	289	278.1	20.1	504	283.6	21.4		
	75-79	122	290.6	21.7	161	281.8	23.6	283	285.6	23.2		
	80-84	71	287.7	24.4	131	285.4	22.1	202	286.2	22.9		
	≥85	31	289.5	18.9	48	273.8	18.8	79	279.9	20.3		
	Overall	781	292.4	21.8	989	279.8	21.0	1770	285.4	22.3		
Inner circle	63-69	351	340.8	16.0	364	334.8	14.9	715	337.8	15.7	<0.001	<0.001
	70-74	216	336.0	16.8	299	332.0	14.5	515	333.7	15.6		
	75-79	127	332.1	15.5	165	332.4	14.8	292	332.2	15.1		
	80-84	73	333.2	15.0	135	331.4	15.6	208	332.0	15.4		
	≥85	31	331.1	17.9	50	322.4	16.6	81	325.7	17.5		
	Overall	798	337.1	16.5	1013	332.5	15.2	1811	334.5	15.9		
Outer circle	63-69	336	293.6	13.0	351	291.2	13.4	687	292.4	13.3	<0.001	0.08
	70-74	208	290.1	13.8	289	288.5	13.0	497	289.2	13.4		
	75-79	125	287.0	13.4	161	287.8	12.4	286	287.5	12.8		
	80-84	68	288.0	14.2	128	287.5	13.6	196	287.7	13.8		
	≥85	31	284.5	18.3	47	281.5	13.8	78	282.7	15.7		
	Overall	768	290.7	13.9	976	288.9	13.3	1744	289.7	13.6		

SD, standard deviation.

*Adjusted for age.

Table 4

Age and Sex Adjusted Associations of Covariates to Retinal Thickness Measured by Spectral Domain Optical Coherence Tomography in the Center Subfield and Inner and Outer Circles, Beaver Dam Eye Study, 2008-2010

	Center subfield				Inner circle				Outer circle			
Covariate	**N**	**Mean (SD)**	**β (95% CI)**	**P value[a]**	**N**	**Mean (SD)**	**β (95% CI)**	**P value[a]**	**N**	**Mean (SD)**	**β (95% CI)**	**P value[a]**
Axial length, per mm			1.3 (0.1, 2.4)	0.03			−1.8 (−2.7, −0.9)	<0.001			−3.1 (−3.9, −2.4)	<0.001
Corneal curvature, per mm			−6.4 (−10.8, −1.9)	0.005			−5.4 (−8.7, −2.1)	0.002			−6.3 (−9.2, −3.5)	<0.001
Axial length / corneal curvature ratio, per mm			18.0 (8.8, 27.2)	<0.001			−5.7 (−12.0, 0.5)	0.07			−13.8 (−19.3, −8.4)	<0.001
Refraction, per diopter			−0.4 (−0.9, 0.1)	0.11			0.8 (0.4, 1.2)	<0.001			1.1 (0.8, 1.5)	<0.001
Cataract status												
None	1191	286.3 (22.0)	Referent		1212	336.1 (15.8)	Referent		1182	291.2 (13.2)	Referent	
Nuclear cataract	253	282.7 (21.3)	0.1 (−3.3, 3.5)	0.97	264	332.1 (14.6)	−0.2 (−2.1, 1.7)	0.86	248	288.0 (13.8)	−0.7 (−2.2, 0.8)	0.34
Cataract surgery	320	284.1 (23.8)	0.7 (−3.6, 5.0)	0.74	329	330.7 (16.6)	−1.7 (−4.4, 1.1)	0.23	308	285.4 (14.1)	−3.2 (−5.4, −1.1)	0.003
Pupil size, per mm			−0.9 (−16.5, 14.7)	0.91			4.2 (−7.3, 15.8)	0.47			−1.8 (−12.0, 8.5)	0.73
IOP, per 5 mmHg			0.7 (−0.7, 2.2)	0.33			−0.2 (−1.4, 1.0)	0.77			0.6 (−0.5, 1.7)	0.29
OPP, per 5 mmHg			−0.7 (−1.5, 0.1)	0.10			−0.3 (−0.9, 0.3)	0.36			−0.7(−1.2, −0.8)	0.01
Smoking status												
Never	868	285.8 (22.0)	Referent		883	335.1 (15.5)	Referent		849	290.0 (13.8)	Referent	
Past	772	285.4 (22.4)	−3.7 (−6.3, −1.1)	0.005	795	333.9 (16.4)	−1.9 (−3.8, −0.0)	0.05	765	289.3 (13.6)	−0.6 (−2.3, 1.1)	0.47
Current	130	282.2 (23.5)	−3.6 (−8.9, 1.6)	0.18	133	334.1 (15.7)	−1.7 (−5.4, 2.0)	0.37	130	289.8 (12.5)	−1.0 (−4.0, 1.9)	0.49
Pack-years smoked, per 5			−0.3 (−0.5, −0.0)	0.02			−0.3 (−0.5, −0.1)	0.005			−0.1 (−0.2, 0.1)	0.45
History of heavy drinking												
Never	1527	284.4 (22.2)	Referent		1566	334.5 (15.7)	Referent		1506	289.7 (13.6)	Referent	
Past	218	290.7 (22.4)	−0.3 (−4.3, 3.8)	0.91	220	333.8 (17.4)	−3.7 (−6.9, −0.5)	0.02	213	288.7 (13.9)	−2.5 (−5.1, 0.1)	0.06
Current	24	297.0 (18.8)	4.7 (−4.8, 14.2)	0.33	24	343.7 (12.3)	7.1 (−0.7,14.9)	0.07	24	298.3 (8.4)	7.7 (2.4, 13.0)	0.005
Height, per in			−0.3 (−0.8, 0.2)	0.17			−0.0 (−0.4, 0.3)	0.92			−0.1 (−0.4, 0.19)	0.47
BMI, per 3 kg/m^2			−0.1 (−0.67, 0.51)	0.79			−0.3 (−0.7, 0.2)	0.26			−0.1 (−0.5, 0.3)	0.53
Weight, per 10 lb			−0.1 (−0.5, 0.2)	0.46			−0.1 (−0.4, 0.1)	0.27			−0.1 (−0.3, 0.1)	0.38
Diabetes status												
Absent	1413	285.1 (22.5)	Referent		1449	334.8 (16.2)	Referent		1394	290.1 (13.8)	Referent	

Covariate	Center subfield				Inner circle				Outer circle			
	N	Mean (SD)	β (95% CI)	P value[a]	N	Mean (SD)	β (95% CI)	P value[a]	N	Mean (SD)	β (95% CI)	P value[a]
Present	309	287.7 (21.4)	0.7 (−2.5, 4.0)	0.66	312	333.2 (15.1)	−1.9 (−4.2, 0.5)	0.13	301	288.0 (13.0)	−1.9 (−4.0, 0.1)	0.07
HbA1c, per %[b]			−1.3 (−6.4, 3.8)	0.63			1.7 (−2.0, 5.5)	0.36			2.3 (−0.8, 5.3)	0.15
MABP, per 5 mmHg			−0.4 (−1.0, 0.2)	0.23			−0.2 (−0.7, 0.2)	0.27			−0.4 (−0.8, −0.1)	0.03
PEFR, L/min												
F: >241, M: >371	1291	286.9 (22.4)	Referent		1317	336.6 (15.3)	Referent		1274	291.1 (13.1)	Referent	
F: ≤240, M: ≤370	467	281.2 (21.5)	−5.5 (−8.4, −2.6)	<0.001	481	328.9 (16.5)	−6.5 (−8.7, −4.2)	<0.001	457	285.7 (14.4)	−4.4 (−6.4, −2.4)	<0.001
Oxygen saturation, per %			0.2 (−0.4, 0.9)	0.50			0.1 (−0.4, 0.6)	0.74			−0.0 (−0.5, 0.4)	0.84

β, beta estimate; BMI, body mass index; CI, confidence interval; F, female; HbA1c, glycosylated hemoglobin A1c; IOP, intraocular pressure; M, male; MABP, mean arterial blood pressure; OPP, ocular perfusion pressure; PEFR, peak expiratory flow rate; SD, standard deviation.

[a] Adjusted for age and sex.

[b] In persons without diabetes.

Table 5

Multivariate Associations of Covariates to Retinal Thickness Measured by Spectral Domain Optical Coherence Tomography in the Center Subfield and Inner and Outer Circles, Beaver Dam Eye Study, 2008-2010

	Full Model 1[a]		Reduced Model 1[b]		Full Model 2[c]		Reduced Model 2[d]	
	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value
Center subfield								
Age, per age group	0.3 (−0.8, 1.4)	0.58			−0.2 (−1.3, 0.8)	0.66		
Sex, male vs. female	12.3 (9.7, 14.8)	<0.001	12.0 (9.5, 14.5)	<0.001	12.4 (9.9, 14.9)	<0.001	12.0 (9.6, 14.5)	<0.001
Axial length/corneal curvature ratio	17.5 (8.2, 26.7)	<0.001	17.3 (8.2, 26.5)	<0.001	17.7 (8.5, 26.9)	<0.001	18.1 (9.0, 27.2)	<0.001
Pack-years smoked, per 5	−0.1 (−0.4, 0.1)	0.37			−0.2 (−0.5, 0.0)	0.08		
PEFR, lowest vs. upper 3 quartiles	−4.6 (−7.5, −1.6)	0.003	−4.4 (−7.1, −1.7)	0.002				
Inner circle								
Age, per age group	−1.6 (−2.4, −0.7)	<0.001	−1.5 (−2.3, −0.7)	<0.001	−2.3 (−3.0, −1.5)	<0.001	−2.4 (−3.1, −1.6)	<0.001
Sex, male vs. female	4.9 (2.9, 6.8)	<0.001	4.3 (2.5, 6.1)	<0.001	5.2 (3.2, 7.1)	<0.001	5.1 (3.2, 7.0)	<0.001
Axial length/corneal curvature ratio	−6.5 (−12.8, −0.2)	0.04			−6.2 (−12.5, 0.2)	0.06		
Pack-years smoked, per 5	−0.1 (−0.3, 0.1)	0.25			−0.2 (−0.4, −0.0)	0.02	−0.3 (−0.5, −0.1)	0.009
History of heavy drinking								
Past vs. never	−1.9 (−5.0, 1.2)	0.22			−2.5 (−5.7, 0.7)	0.12	−2.8 (−6.0, 0.4)	0.08
Current vs. never	8.4 (1.1, 15.7)	0.02	−6.5 (−8.7, −4.2)	<0.001	8.1 (0.6, 15.5)	0.03	8.3 (0.7, 15.8)	0.03
PEFR, lowest vs. upper 3 quartiles	−5.7 (−7.9, −3.4)	<0.001						
Outer circle								
Age, per age group	−1.3 (−2.1, −0.4)	0.003	−1.2 (−2.0, −0.4)	0.003	−1.7 (−2.5, −0.9)	<0.001	−1.7 (−2.4, −0.9)	<0.001
Sex, male vs. female	1.6 (−0.1, 3.4)	0.06			1.8 (0.0, 3.5)	0.05		
Axial length/corneal curvature ratio	−14.5 (−20.1, −9.0)	<0.001	−14.1 (−19.7, −8.6)	<0.001	−14.2 (−19.7, −8.6)	<0.001	−13.7 (−19.3, −8.1)	<0.001
History of cataract/cataract surgery								
Nuclear cataract vs. no cataract	−0.7 (−2.2, 0.8)	0.35	−0.8 (−2.3, 0.7)	0.28	−0.9 (−2.4, 0.6)	0.26	−1.0 (−2.5, 0.5)	0.20
Cataract surgery vs. no cataract	−2.9 (−5.1, −0.8)	0.01	−3.1 (−5.3, −1.0)	0.005	−3.2 (−5.3, −1.0)	0.004	−3.4 (−5.6, −1.3)	0.002
OPP, per 5 mmHg	−0.7 (−1.8, 0.4)	0.19	−0.9 (−1.4, −0.3)	0.002	−0.9 (−2.0, 0.3)	0.13	−0.8 (−1.4, −0.3)	0.003
History of heavy drinking								
Past vs. never	−1.5 (−4.1, 1.1)	0.25	−0.8 (−3.3, 1.7)	0.54	−2.2 (−4.8, 0.4)	0.10	−1.4 (−3.9, 1.1)	0.27
Current vs. never	8.7 (3.7, 13.8)	<0.001	9.6 (4.6, 14.6)	<0.001	8.1 (3.1, 13.0)	0.001	9.0 (4.1, 13.9)	<0.001

	Full Model 1[a]		Reduced Model 1[b]		Full Model 2[c]		Reduced Model 2[d]	
	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value
MABP, per 5 mmHg	−0.1 (−0.9, 0.6)	0.75			−0.0 (−0.8, 0.7)	0.98		
PEFR, lowest vs. upper 3 quartiles	−4.1 (−6.1, −2.1)	<0.001	−4.2 (−6.2, −2.2)	<0.001				

β, beta estimate; CI, confidence interval; MABP, mean arterial blood pressure; OPP, ocular perfusion pressure; PEFR, peak expiratory flow rate.

[a] Includes age, sex, axial length/corneal curvature ratio, and all terms that were significant in age-sex adjusted models.

[b] Reduced Model 1 includes only the terms from Full Model 1 that remained statistically significant after backwards selection.

[c] Full Model 2 includes all the terms from Full Model 1 except for PEFR.

[d] Reduced Model 2 includes only the terms from Full Model 2 that remained statistically significant after backwards selection.