Morphological characteristics of the optic nerve head and impacts on longitudinal change in macular choroidal thickness during myopia progression

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ABSTRACT.

Purpose: The aim of this study was to investigate the association between morphological characteristics of Bruch's membrane opening distance (BMOD), border length (BL), border tissue angle (BTA), peripapillary atrophy (PPA) as well as axial length (AL) and incident decreased macular choroidal thickness (mChT) in young healthy myopic eyes.

Methods: A total of 323 participants aged 17–30 years were included in the current 2-year longitudinal study. Each participant underwent detailed ocular examinations at baseline and follow-up. Data of AL, refraction error, PPA area, BMOD, BL, BTA and mChT were measured individually. Incident decreased mChT was defined as follow-up mChT of participants decreased into the lowest quartile of baseline mChT.

Results: Subjects with longer AL, longer BMOD were more likely to have incident decreased mChT (odds ratio [OR], 1.56; 2.09, respectively, per 1 Z-score increment), whereas larger BTA was less likely to develop decreased mChT (odds ratio [OR], 0.51, per 1 Z-score increment). The area under the receiver operating curve (AUROC) of basic risk model for incident decreased mChT was 0.6284. After adding BMOD, BTA and AL separately to the basic risk model, the AUROC of the combination could reach 0.6967, 0.6944 and 0.7383, respectively. After combining BMOD, BTA and AL to the basic model, the AUROC of the combination showed the highest AUROC of 0.7608.

Conclusions: Bruch's membrane opening distance and AL are significant risk factors for incident decreased mChT, whereas BTA played protective role in the deterioration of mChT. In addition, a combination of BMOD, BTA and AL could serve as earlier predictors of the attenuation of mChT in myopia progression.

Key words: Bruch's membrane opening distance – border tissue angle – choroidal thickness – risk factors – prediction model

Introduction

Myopia is a global major public health problem, whose prevalence among 18-year-old young adults in East Asia varies between 80% and 90% (Saw et al. 2006; Rudnicka et al. 2016). Optic nerve head (ONH) changes including optic disc tilt (Choi et al. 2014; Lee et al. 2015) and torsion (Jonas et al. 2016; Sung et al. 2016), peripapillary atrophy (PPA) (Dai et al. 2013; Jonas et al. 2016; Vianna et al. 2016) and focal lamina cribrosa (LC) defects (Han et al. 2016; Sawada et al. 2017) occur and were relatively common in highly myopic young adults, whereas myopic maculopathy was relatively rare. It can be concluded from the previous studies that optic disc tilt and PPA were observed initially, followed by posterior staphyloma and lacquer cracks, and the authors observed the occurrence of chorioretinal atrophy ultimately (Kim et al. 2012; Koh et al. 2016; Chen et al. 2019). Therefore, it is important to elucidate the morphological characteristics of the ONH accompanied with axial elongation in young myopic patients at an early stage.

Growing evidence suggests that choroid thinning, which has been defined as a significant structural change during myopia progression, may contribute to myopic pathogenesis (Ho et al. 2013; Wei et al. 2013), including myopic macular maculopathy (Fang et al. 2019) and myopic choroidal neovascularization (Neelam et al. 2012; Ohno-Matsui et al. 2015; Koh et al. 2016), either of which may result in severe visual impairment. Pathologic myopia is dependent on the duration of disease and increases in prevalence with age due to global axial elongation (Chang et al. 2013). Therefore, long-term and regular screening of young myopic eyes is needed to detect the early-risk patients who may have myopia-related fundus lesions in myopia progression.

Several studies considered Bruch's membrane (BM) as the biomechanically supporting structure and the primary driver elongating the globe (Jonas et al. 2017; Wu et al. 2019; Jonas et al. 2020), whereas there is little information on morphological characteristics of the optic nerve head, especially on ultra-structural changes related to BM in highly myopic eyes of young adults during myopia progression. Previous two prospective cohort studies conducted in Korea demonstrated that temporal border tissue configuration changed during axial elongation in childhood (Kim et al. 2018; Kim et al. 2021). However, the impact of border tissue (BT) configuration characteristics on choroidal thickness (ChT) remains unclear. Our previous cross-sectional study firstly reported an association between Bruch's membrane opening distance (BMOD), border tissue angle (BTA) and macular choroidal thickness (mChT) in young healthy high-myopic patients (Hu et al. 2020). No study has prospectively examined the associations between the attenuation of mChT and morphological BT features in the ONH or the peripapillary structure during young adult myopia progression. In the present study, we aimed to investigate association between morphological characteristics of BT configuration, BMOD, BL, BTA and AL, with macular choroidal thinning in young healthy myopic eyes.

Methods

Study population

The Shanghai High Myopia Study for Adults (SHMSA) is an ongoing population-based, myopic cohort study (NCT03446300), including individuals aged ≥16 years with high myopia, which was started in 2016 in Shanghai, China. This prospective, longitudinal, observational study as a part of SHMSA, adhered to the tenets of the Declaration of Helsinki and was authorized by the Institutional Review Board of Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine (Approval number: 2015KY156). All enrolled participants were briefed on the study protocol and signed informed consent forms.

As a complement of our previous cross-sectional study, the current 2-year longitudinal study was a follow-up investigation of 423 participants selected from Shanghai University between September 2016 and September 2018. Baseline examinations of 821 participants were conducted in the period October–November 2016. Two years later, 423 (51.5%) participants of the same cohort were enrolled, and the same examinations were performed.

Inclusion and exclusion criteria

Subjects with an age of 16 years or older and an AL ≥ 24 mm were included in this study. Additionally, all of them had BCVA of 20/30 or better; an intraocular pressure (IOP) of ≤ 21 mm Hg; a normal depth of the anterior chamber; and a healthy ONH without glaucomatous optic disc damage, including neuroretinal rim notching or thinning, concentric cup enlargement or shallowing, peripapillary haemorrhage, localized pallor and peripapillary retinal nerve fibre layer thickness (pRNFLT) changes on both eyes. The following exclusion criteria were applied: (1) history of glaucoma among first-degree family members; (2) history of major systemic or ocular diseases including congenital cataract, glaucoma, hypertension and diabetes; (3) history of intraocular or refractive surgery; (4) evidence of retinal pathology; and (5) evidence of optic nerve disease known to affect the optic nerve head structure (e.g. glaucoma, ischemic optic neuropathy, optic neuritis, papilledema and optic nerve drusen). In general, except for optic disc and peripapillary changes related to myopia, the patients had no other ocular comorbidities. Poor-quality images for more than two sections of SS-OCT (swept-source optical coherence tomography) scans and any images lost due to the eye movements or blinks were not included in the study. Only the right eye of each participant was selected for statistical analysis.

Definition of decreased mChT

Average mChT of 423 initial participants was stratified into 4 quartiles. Baseline and incident decreased mChT was defined as the upper quartiles of baseline mChT (≥188.71 μm). In detail, baseline decreased mChT was defined as participants in the lowest quartile of mChT at baseline (<188.71 μm). Incident decreased mChT was defined as follow-up mChT of participants decreased into the lowest quartile of baseline mChT (<188.71 μm). In the prospective analysis, those who had decreased mChT at baseline were excluded in the statistical analysis.

Examination procedures

The protocol for this prospective study was consistent with the ones used in previous studies (Chen et al. 2019; He

et al. 2019), approved by the Ethics Committee of the Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, and following the tenets of the Declaration of Helsinki.

Detailed examination procedures have been described previously (Hu et al. 2020). Briefly, each participant underwent a thorough ophthalmic examinations, including measurement of refractive error, best-corrected visual acuity (BCVA), intraocular pressure (IOP), anterior chamber depth (ACD), central corneal thickness (CCT), lens thickness (LT), axial length (AL), slit-lamp biomicroscopy, colour fundus examination and measurement of the thickness of choroid using SS-OCT. Refraction was examined using an auto-refractor (KR-8900; Topcon, Tokyo, Japan) without cycloplegia. IOP was measured using noncontact tonometry (Full Auto Tonometer TX-F; Topcon), and ACD, CCT, LT and AL were measured using optical low-coherence reflectometry (Aladdin; Topcon). All examinations for each patient were completed on the same day. Subjective refraction was performed by a trained optometrist. The spherical equivalent refraction (SER) was defined as the sphere plus half a cylinder. The BCVA was converted into the logarithm of minimal angle resolution (logMAR). Height and weight were measured as well, and body mass index (BMI) was calculated using the formula: weight(kg)/[height(m)^2]. A detailed medical history was also obtained for each participant.

SS-OCT imaging

The ONH and macular areas were imaged using SS-OCT (model DRI OCT-1 Atlantis; Topcon). The scan protocol used the 12-line radial scan pattern with a resolution of 1024×12 centred on the fovea and optic disc. The SS-OCT examinations were performed by one experienced examiner from 10:00 AM to 3:00 PM each day to minimize the influence of diurnal variation (Tan et al. 2012; Deng et al. 2018). The follow-up mode was selected for the examinations in the follow-up visits to ensure that the follow-up scans were from the same location as the baseline measurements. Both baseline and follow-up visits were performed by one experienced technician. The ChT was

defined as the vertical distance between BM and the choroidal-scleral interface. The tomography maps were overlaid with an Early Treatment Diabetic Retinopathy (ETDRS) Study grid (6×6 mm) that was focused on the macula using a built-in software. The placement of the circle was manually adjusted, if necessary. Each layer was automatically segmented with built-in software. However, the process was inaccurate, leading to measurement artifacts. Therefore, manual segmentation was carried out. Each scan was divided into three concentric circles with nine regions. The diameters of the central foveal circle, parafoveal circle and perifoveal circle were 1, 3 and 6 mm, respectively, and they were further subdivided into four quadrants, namely temporal, superior, nasal and inferior quadrants. The average choroidal thickness in each sector of the grid was automatically calculated using built-in software. In the macular region, the average thicknesses were calculated for all nine sectors of the grid.

Peripapillary atrophy area measurements

The PPA area was defined as an inner crescent of chorioretinal atrophy with good visibility of the large choroidal vessels and the sclera and measured as described previously (Fig. 1A; Dai et al. 2013; Vianna et al. 2016). PPA area was measured as the total number of pixels using ImageJ software, version 1.60 by 2 independent, masked, well-trained observers (L.M. and Y.Y.), and averaged data were used in the final analysis. The magnification was corrected for each AL using the Littmann's formula (Bennett et al. 1994). The area was converted from pixels into millimetres squared.

BMOD, BL and BTA measurements

The BMOD, BL and BTA of the optic disc were measured as described previously using horizontal cross-sectional OCT images (Hosseini et al. 2013; Park et al. 2015; Sung et al. 2018). The Bruch's membrane opening (BMO) was defined as the innermost termination of BM. Bruch's membrane opening distance was defined as the length of the line between the two BMO points. The BMO reference plane was considered as the line connecting both ends of the BMO. Then, the BT at the temporal

optic disc margin was marked on the horizontal cross-sectional OCT images, when the BT was present at the temporal optic disc margin. The linear distance between the temporal BMO point and the BT/scleral end was defined and measured as the BL (Kim et al. 2018; Lee et al. 2018), where the γ-zone PPA was located. A built-in calliper tool within SS-OCT was used to measure the BMOD and BL. The angle between the BMO reference plane and the BT was defined as the BTA (Kim et al. 2018). To measure the BTA, the images were analysed within ImageJ, and their degrees were determined using the protractor tool within ImageJ (Fig. 1B). To assess the reproducibility of the measurements, 100 randomly selected images were re-examined by the same examiner (YY) one month after the initial analysis. The BMOD, BL and BTA were highly reproducible, with an ICC of 0.95 for the BMOD, 0.89 for the BL and 0.87 for the BTA.

Statistical analysis

Statistical analysis was performed using the Statistical Analysis System, version 9.4 (SAS Institute, NC, USA). The demographic and optic characteristics were reported as counts or proportions for categorical data and as means ± standard deviation for continuous data. The intra-observer (two consecutive measurements) and inter-observer (measurements by YY and LM) agreements were determined with the intra-class correlation coefficient (ICC) using the absolute agreement model to measure PPA area, BMOD, BL and BTA for all participants. Differences in continuous variables and categorical variables between groups were compared using the one-way analysis of variance test and chi-square test, respectively (Table 1). A two-sided P value < 0.05 was considered as statistically significant. The differences between the baseline and follow-up data were assessed by paired t-tests. Partial correlation analysis was applied to investigate the relationship between BMOD, BTA and AL at baseline with the change in mChT as well as mChT at follow-up adjusted for sex.

Odds ratios (95% confidence intervals) were acquired using multivariate logistic regression analysis. Model 1. Unadjusted; Model 2. Adjusted for
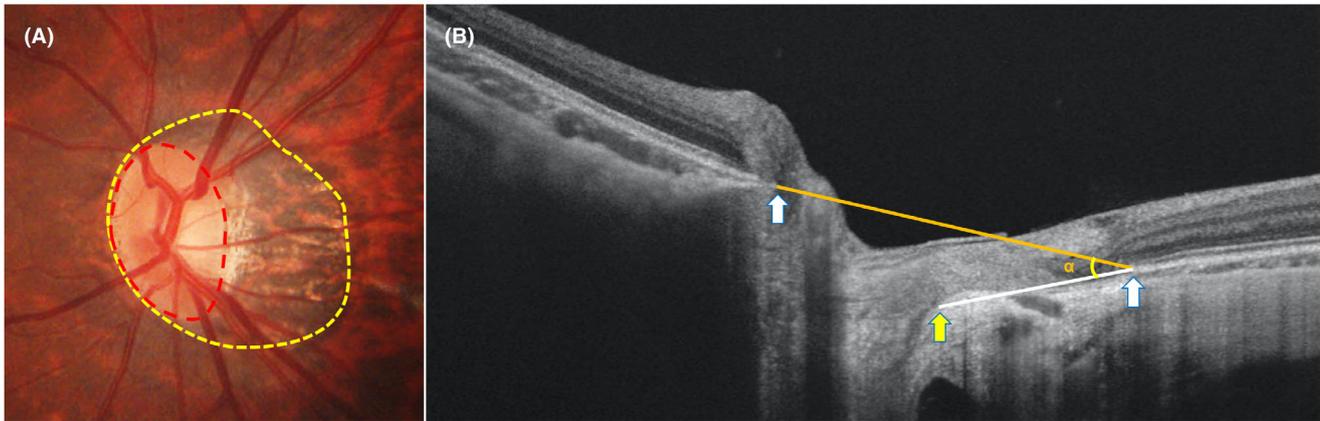
Fig. 1. Representative fundus photographs and swept-source optical coherence tomography (SS-OCT) image for measurement of peripapillary atrophy (PPA) area (A), Bruch's membrane opening distance (BMOD), border length (BL), border tissue angle (BTA) (B). The PPA area was outlined manually (area between the yellow dotted line and red dotted line), and the pixel area was calculated automatically using the software. BMOD, BL and BTA were measured on a horizontal SS-OCT B-scan. The nasal and temporal Bruch's membrane opening (BMO) points (white arrows) were connected to define the BMO reference plane. The distance between the two BMO points was defined as the BMOD (orange line). The angle α between the BMO reference plane and the temporal border tissue of Elschnig (yellow arrow) was defined as the BTA. The length from the temporal BMO to the border tissue scleral end was defined as the BL (white line).

Table 1. General and ocular characteristics of study eyes at baseline ($n = 323$).

Variable	Total ($n = 323$)	Non-decreased mChT group ($n = 302$)	Decreased mChT group ($n = 21$)	P value
Age, y	19.65 ± 2.12	19.64 ± 2.10	19.81 ± 2.40	0.519
Female, n (%)	154 (47.7%)	148 (49.2%)	6 (28.6%)	0.075
BMI	20.98 ± 2.92	20.96 ± 2.85	21.25 ± 3.87	0.663
SBP, mmHg	122.17 ± 16.40	121.88 ± 16.34	126.33 ± 17.09	0.259
PR,	73.40 ± 14.68	73.42 ± 14.97	73.14 ± 9.69	0.933
SER, D	−3.53 ± 2.45	−3.45 ± 2.47	−4.75 ± 1.87	0.018
AL, mm	25.00 ± 1.11	25.00 ± 1.11	25.86 ± 0.82	<0.0001
BCVA, logMAR	0.94 ± 0.16	0.94 ± 0.16	0.94 ± 0.11	0.911
IOP, mmHg	14.22 ± 2.97	14.22 ± 2.97	13.84 ± 2.27	0.565
CCT, µm	539.38 ± 47.55	540.12 ± 48.22	539.08 ± 49.00	0.287
ACD, mm	3.70 ± 0.34	3.69 ± 0.34	3.59 ± 0.34	0.247
LT, mm	3.49 ± 0.37	3.49 ± 0.38	3.55 ± 0.29	0.963
mChT, µm*	254.54 ± 47.20	258.46 ± 46.26	198.04 ± 8.12	<0.0001
PPA area, mm²	0.43 ± 0.39	0.42 ± 0.39	0.57 ± 0.39	0.079
BMOD, µm	2100.31 ± 452.62	2086.28 ± 452.24	2616.41 ± 462.44	0.034
BL, µm	411.61 ± 243.24	405.21 ± 244.18	503.77 ± 213.79	0.073
BTA, °	97.49 ± 44.51	98.79 ± 45.05	78.82 ± 30.96	0.010

ACD = anterior chamber depth, AL = axial length, BCVA = best-corrected visual acuity, BMOD = Bruch's membrane opening distance, BL = border length, BTA = border tissue angle, CCT = central corneal thickness, D = diopter, IOP = intraocular pressure, LT = lens thickness, LogMAR = logarithm of the minimum angle of resolution, mChT = macular choroidal thickness, PPA = peripapillary atrophy, SER = spherical equivalent refraction.
* Average thickness of macular choroidal.

age; Model 3. Further adjusted for sex, body mass index, and systolic blood pressure. Stratification analysis according to baseline sex, BMI and AL was performed to further investigate the association between BMOD, BTA and AL with the incident of decreased mChT. The multivariate adjusted model including age, sex, BMI and SBP for strata.

The receiver operative curve (ROC) and C-statistic measures concordance between model-based risk estimates and observed incident decreased mChT. Net reclassification improvement (NRI) and integrated discrimination improvement (IDI) measure the incremental prognostic effect that a new biomarker will have when added to an existing prediction model. The

basic prediction model including conventional risk factors for decreased mChT, including age, sex, BMI and SBP at baseline. BMOD, BTA and AL were added separately and combined in the prediction model for incident decreased mChT. A two-sided P value < 0.05 was considered as statistically significant.

Results

Baseline characteristics

Among 430 participants enrolled in the current study, three were excluded for losing fundus examinations, another four for poor SS-OCT imaging quality to improve measurement accuracy, but no obvious staphyloma was detected. The data of 423 (98.3%) students were included in the following analysis. Finally, after excluding those with decreased mChT at baseline ($n = 100$), 323 participants were included in the prospective analysis. The mean age of the study participants was 19.52 ± 2.15 years (range, 17–30 years) at baseline; 154 (47.7%) were female; the mean AL was 25.00 ± 1.11 mm (range, 21.98–29.39 mm), and the mean SER was −3.53 ± 2.45 D (range, 2.25 D to −12.625 D). Among all the participants in the prospective cohort, 302 (93.5%) remained as non-decreased mChT group during follow-up. The BMOD, BL and BTA were highly reproducible, with an ICC of 0.95 for

the BMOD, 0.89 for the BL and 0.87 for the BTA (*n* = 100).

The baseline general and ocular clinical characteristics including PPA area, BMOD, BL, BTA and topographic characteristics of mChT of the included participants are presented as total, decreased mChT and non-decreased mChT (Table 1). At baseline, participants with decreased mChT had significantly longer AL (*P* < 0.0001), more myopic SER (*P* = 0.018) and smaller mChT (*P* < 0.0001) compared with those without decreased mChT, whereas no significant difference was observed in the age, sex, BMI, SBP, PR, BCVA, IOP, CCT and LT at baseline in different mChT shift groups (*P* > 0.05). Furthermore, among the morphological characteristics of ONH at baseline including PPA area, BMOD, BL and BTA, BMOD was significantly longer and the BTA was significantly smaller in decreased mChT group compared with non-decreased mChT group. No significant differences in the PPA area and BL were observed between the groups.

After a median of 2-year follow-up, a significant axial elongation of the eye and an average myopic shift were found in all participants, with a mean change of 56.87 ± 129.84 μm (95% CI: 42.26 to 71.09 μm) and an average myopic shift of −0.33 ± 0.93 D (95% CI: −0.43 to −0.22 D), respectively. Similarly, significant difference was observed in axial elongation, average myopic shift between non-decreased and decreased mChT groups (Table S1).

Factors associated with longitudinal changes in average mChT

The values of the partial correlation coefficients between the longitudinal changes in average mChT and follow-up average mChT after adjusting for sex are listed in Table 2. The change in the average mChT was significantly negatively correlated with the baseline AL (*r* = −0.26) and baseline BMOD (*r* = −0.14), but significantly positively correlated with the baseline SER (*r* = 0.15; all *P* < 0.01; Table 2, Fig. 2), whereas in these ONH parameters, the PPA area and BTA had no significant association with the changes of mChT. The follow-up average macular choroidal thickness was significantly negatively correlated with the baseline BMOD (*r* = −0.44), baseline AL (*r* =

Table 2. Partial correlation analysis between changes and follow-up of macular choroidal thickness and ocular parameters adjusted for sex (*n* = 323).

Variable	Changes of mChT, μm*		Follow-up mChT, μm*	
	r	*P* value	*r*	*P* value
Age, baseline, y	−0.14	0.015	−0.01	0.945
AL, baseline, mm	−0.26	<0.0001	−0.42	<0.0001
SER, baseline, D	0.15	<0.009	0.32	<0.0001
BCVA, baseline, logMAR	−0.06	0.301	0.02	0.771
IOP, Baseline, mmHg	0.01	0.799	0.04	0.513
ACD, Baseline, mm	−0.06	0.258	−0.02	0.748
CCT, Baseline, μm	0.02	0.717	0.01	0.805
LT, Baseline, mm	0.07	0.231	0.09	0.106
mChT, Baseline, μm*	−0.06	0.299	0.93	<0.0001
PPA area, Baseline, mm²	−0.08	0.134	−0.35	<0.0001
BMOD, Baseline, μm	−0.14	0.012	−0.44	<0.0001
BL, Baseline, μm	−0.09	0.120	−0.29	<0.0001
BTA, Baseline, °	0.08	0.154	0.44	<0.0001

ACD = anterior chamber depth, AL = axial length, BCVA = best-corrected visual acuity, BMOD = Bruch's membrane opening distance, BL = border length, BTA = border tissue angle, CCT = central corneal thickness, D = diopter, IOP = intraocular pressure, LT = lens thickness, LogMAR = logarithm of the minimum angle of resolution, mChT = macular choroidal thickness, PPA = peripapillary atrophy, SER = spherical equivalent refraction.
* Average thickness of macular choroidal.

−0.42), baseline PPA area (*r* = −0.35) and baseline BL (*r* = −0.29), but significantly positively correlated with the baseline mChT (*r* = 0.93) and baseline BTA (*r* = 0.44; all *P* < 0.0001; Table 2, Fig. 2).

The association between ocular parameters and change in average mChT in multivariate logistics regression

Table 3 shows the multivariate logistic regression analysis for the risk factors of incident decreased mChT. Our results showed longer AL, longer BMOD, smaller BTA were more likely to have decreased mChT during the 2-year follow-up. The risk of developing decreased mChT increased by 2.09 times for each z-score increment in AL (95% confidence interval [CI]: 1.30, 3.38) and by 1.56 times for each z-score increment in BMOD (95% confidence interval [CI]: 1.04, 2.35). However, BTA exhibited 49% protective effect for incident decreased mChT (odds ratio [OR] 0.51; 95% confidence interval [CI]: 0.28, 0.94) after adjusting for sex, body mass index and systolic blood pressure.

Stratification analysis of the association between BMOD, BTA and AL with incident decreased mChT according to baseline BMI, sex and AL

The effect of AL, BMOD and BTA on the presence of decreased mChT in

this group of young adults is further illustrated in Fig. 3 and Table S2, stratified by BMI, sex and AL. We found that among the participants with BMI < 24, AL < 26 mm and females, the association between BMOD and the incident of decreased mChT was stronger, which means that among subjects with BMI < 24, AL < 26 mm, females, with each z-score increment in BMOD, the risk of incident decreased mChT increased by 59%, 93% and 108%, respectively. Similarly, we found that the association between BTA and incident decreased mChT was stronger in the subjects with BMI < 24, AL < 26 mm, females. However, the association between AL and incident decreased mChT was stronger in males.

ROC analyses to predict incident decreased mChT

Receiver operating curve and C-statistical analyses were performed to concordance between estimates of model-based risk and observed incident decreased mChT (Table 4, Fig 4). Basically, age, sex, BMI and SBP at baseline were included in the basic risk model, BMOD, BTA and AL were further included in the prediction model for the ROC analyses. The area under the receiver operating curve (AUROC) of basic model for incident decreased mChT were 0.6284 (95% CI:

(A)

(B)

(C)

(D)

(E)

(F)
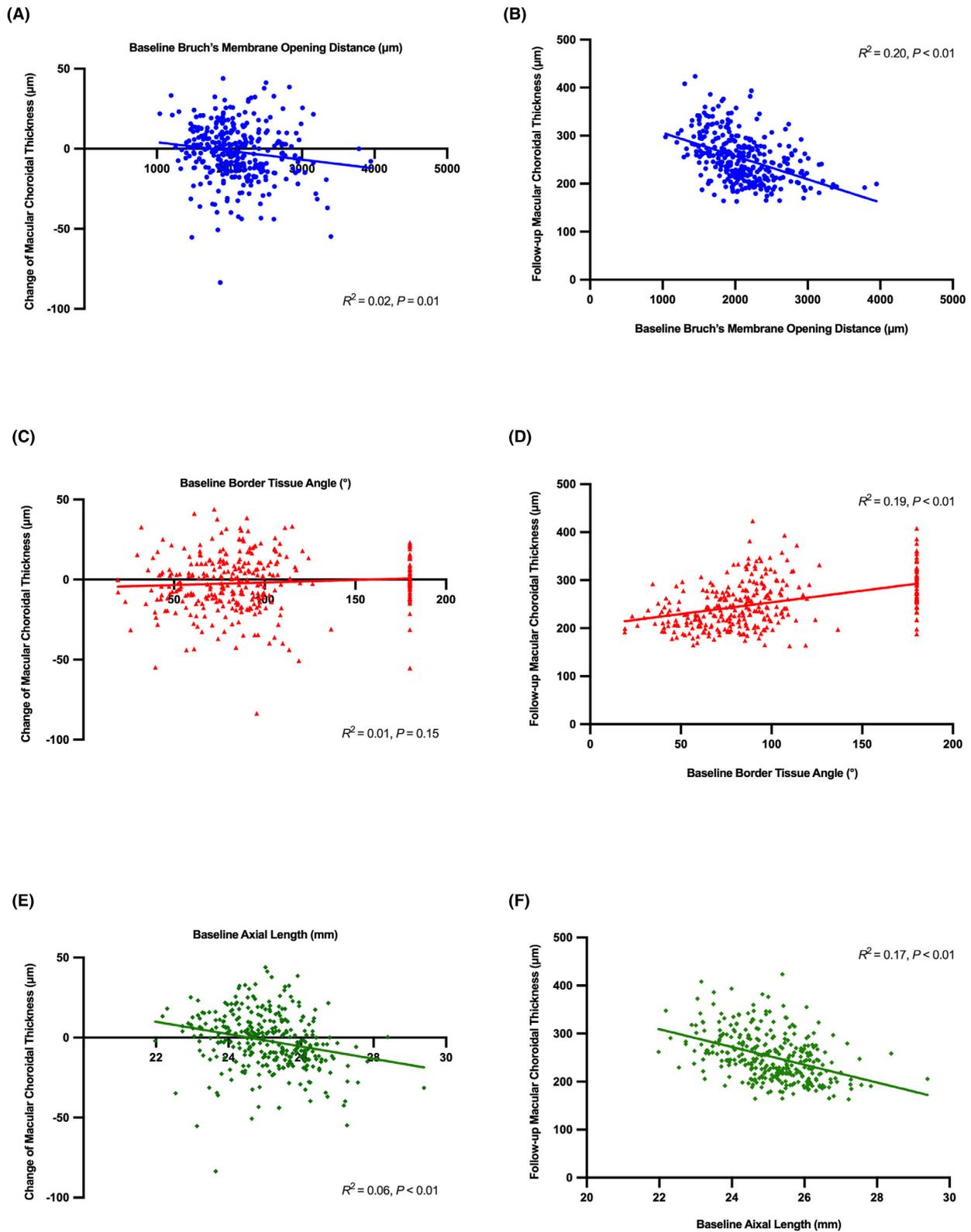
Fig. 2. Linear correlation between the changes, follow-up of average mChT and baseline characteristic of BMOD, BL and BTA in all subjects.

0.5035, 0.7534). After adding BMOD, BTA and AL separately to the basic model for predicting the incidence of decreased mChT, the AUROC of the combination could reach 0.6967, 0.6944 and 0.7383, respectively. After combining BMOD, BTA and AL to the basic model, the AUROC of the combination showed the highest and fairly good AUROC of 0.7608, (95% CI: 0.6724, 0.8492) in predicting possible incident decreased mChT.

Next, we compared the performance of BMOD, BTA and AL and combination of all three parameters with basic risk model in predicting incident decreased mChT. Adding BMOD, BTA or AL separately or in

Table 3. Odds ratios (95% confidence interval) of Z-score transformed measurements of BMOD, PPA, BTA, LT, ACD, CCT, BCVA, BL, AL for the presence of decreased mChT during follow-up (defined as the level of mChT decreased from the 2nd, 3rd, 4th quartile at baseline to the 1st quartile at follow-up visit).

Per 1 z-score increment	Model*	Model†	Model‡
BMOD	**1.53 (1.03–2.27)**	**1.53 (1.03–2.27)**	**1.56 (1.04–2.35)**
PPA	1.44 (0.95–2.17)	1.44 (0.95–2.18)	1.45 (0.95–2.19)
BTA	0.56 (0.31–1.01)	0.56 (0.31–1.00)	**0.51 (0.28–0.94)**
LT	1.01 (0.64–1.61)	0.995 (0.62–1.59)	0.97 (0.58–1.62)
ACD	1.50 (0.81–2.79)	1.52 (0.81–2.83)	1.39 (0.74–2.63)
CCT	0.85 (0.61–1.16)	0.85 (0.62–1.17)	0.86 (0.62–1.18)
BCVA	1.03 (0.65–1.64)	1.02 (0.64–1.62)	1.02 (0.63–1.64)
BL	1.54 (0.96–2.47)	1.54 (0.96–2.47)	1.57 (0.98–2.53)
AL	**2.21 (1.39–3.51)**	**2.21 (1.39–3.51)**	**2.09 (1.30–3.38)**

* Univariate.
† Adjusted for age.
‡ Adjusted for sex, body mass index and systolic blood pressure.
Bold indicates statistically significant values (p < 0.05).

combination into the basic risk model, slightly but significantly improved C-statistics, IDI and NRI compared with the basic risk model alone. (all *P* values < 0.05, except for C-difference for BMOD and BTA; Table 4).

Discussion

To the best of the authors' knowledge, this is the first longitudinal study to investigate the relationship between incident decreased mChT with baseline morphological characteristics of the ONH and peripapillary structure, especially the BT morphology, as well as AL, during early myopic progression in young healthy myopic eyes. This prospective study found that subjects with decreased mChT had longer AL, longer BMOD, smaller SER, BTA and mChT at baseline and the changes in mChT were significantly negatively associated with the baseline AL and BMOD. We demonstrated that eyes with a longer AL and BMOD had a higher risk of incident decreased mChT, whereas larger BTA had a lower risk of incident decreased mChT after adjusting for age, sex, BMI and SBP. There were no significant associations between PPA area and decreased mChT. We further found that association between BMOD, BTA and incident decreased mChT was stronger in the subjects with BMI < 24, AL < 26 mm, females. Moreover, BMOD and BTA when separately or in combination added could significantly improve NRI and IDI based on the basic prediction model. These findings indicated that BMOD
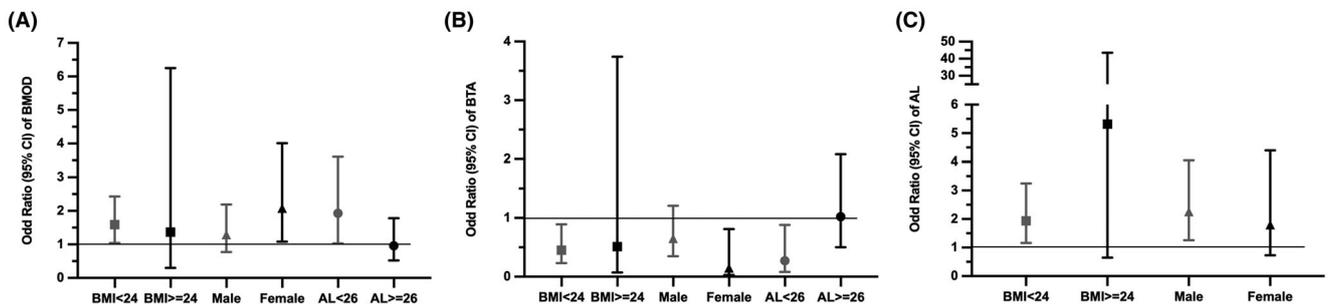
Fig. 3. Stratification analysis according to baseline sex, body mass index (BMI), and axial length (AL) to investigate the association between BMOD, BTA and AL with the presence of decreased macular choroidal thickness (mChT) in the multivariate logistic models adjusted for age, sex, BMI and systolic blood pressure (SBP).

Table 4. C-statistics, C-difference, Net Reclassification Improvement (NRI), and Integrated Discrimination Improvement (IDI) of BMOD, BTA and AL for the prediction of developing decreased average thickness macular choroidal thickness.

	C-statistics (95% CI)	C-difference (95% CI)	*P*	NRI	*P*	IDI	*P*
Basic model	0.6284 (0.5035, 0.7534)	–	–	–	–	–	–
BMOD + basic model	0.6967 (0.5946, 0.7988)	0.0683 (−0.0289, 0.1654)	0.1687	44.2857 (0.599, 87.9724)	<0.0001	1.1347 (−0.2253, 2.4947)	<0.0001
BTA + basic model	0.6944 (0.5988, 0.7901)	0.0660 (−0.0341, 0.1662)	0.1963	63.7143 (25.5853, 101.8432)	<0.0001	1.5163 (0.0722, 2.9604)	<0.0001
AL + basic model	0.7383 (0.6368, 0.8397)	0.1098 (0.0214, 0.1983)	0.0149	62 (20.2435, 103.7565)	<0.0001	3.2508 (1.0569, 5.4447)	<0.0001
BMOD, BTA, AL + basic model	0.7608 (0.6724, 0.8492)	0.1324 (0.0352, 0.2296)	0.0076	77.0476 (38.9994, 115.0959)	<0.0001	3.5294 (1.3562, 5.7026)	<0.0001

ROC curve
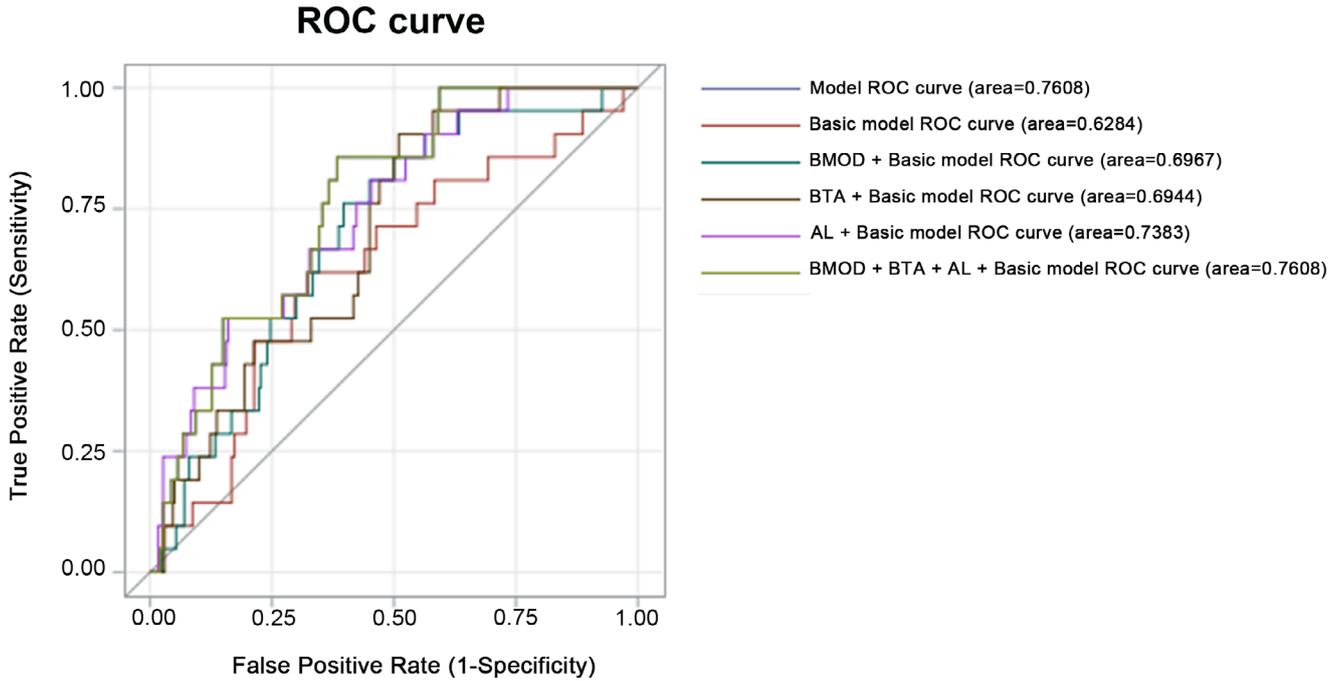
Fig. 4. Area under the receiver operating curve (AUROC) of basic risk model (including age, sex, BMI and SBP at baseline), BMOD, BL and BTA separately and BMOD, BL and BTA in combination added into the basic model for incident decreased mChT.

and BTA could be served as new biomarkers additional to AL for young myopic eyes at risk of developing decreased mChT and myopia-related fundus lesions in the future.

Earlier two prospective cohort studies from Korea (Kim et al. 2018; Kim et al. 2021) both revealed that the change in BTA in the temporal region showed a significant correlation with the changes in AL in the eyes with axial elongation. Differently, Kim et al. (2021) established that BMOD had a significant positive correlation with the AL changes, whereas Kim et al. (2018) found relatively stable BMOD, even in eyes with ONH and peripapillary change during axial elongation. The findings of our previous cross-sectional study (Hu et al. 2020) supported the results of Kim et al. (2021) elucidating that individuals with longer AL presented with a longer BMOD and BL. Furthermore, our cross-sectional results also revealed that a negative correlation was observed between mChT and BMOD and positive correlations among mChT and BTA during the early myopic progression in young healthy highly myopic eyes. To demonstrate the hypothesis and making up the limitation of our previous cross-sectional study (Hu et al. 2020), we did the 2-

year longitudinal study of the same population.

Our study supports the hypothesis that BM and both peripapillary BT are the biomechanically supporting structure and the primary driver elongating the globe, leading to a compression of the posterior choroid and a passive thinning of the posterior sclera (Jonas et al. 2017), highlighting the importance to pay more attention to the peripapillary BT configuration, especially BMOD and BTA in young myopic patients on OCT scans at an early stage. Compared with the sclera, BM appears to be better suited as the structure elongating the eye. This hypothesis is supported by several anatomical observations. Recent studies have reported the biomechanical strength of BM in relationship to its thickness was about 50–100 times stronger as compared to the strength of the sclera (Girard, personal communication; Jonas et al. 2020). Another anatomical finding suggests that it is not the sclera (separated from the photoreceptor outer segments by the spongy choroid) but rather the BM which determines the length of the optical axis (which ends at the photoreceptor outer segments close to BM) appears to be more suitable as the structure elongating the eye (Jonas

et al. 2017). The hypothesis also includes that if the BMO enlargement in ONH was not sufficient to reduce the strain within BM, additional BM defects may develop in the macular region (categories 3 and 4 of myopic maculopathy; Ohno-Matsui et al. 2015; Jonas et al. 2017; Wang et al. 2021).

Although in population-based studies, myopic maculopathy and posterior staphyloma, which were late signs of pathologic myopia and were much more common in elders (age >50 years), are not very prevalent in young age group, but myopic macular maculopathy is time-dependent and increases in prevalence with age as the axial length elongation (Asakuma et al. 2012; Chang et al. 2013). Koh et al. (2016) reported that reduced central ChT as well as age and AL were the risk factors for developing myopic maculopathy, and further demonstrated a significant association between reduced central ChT with poorer BCVA, even in young adults without obvious macular pathology. Fang et al. (2019) use the subfoveal ChT for diagnosing and classifying myopic maculopathy, indicating that progressive and continuous choroidal thinning plays a role critical to the progression from no maculopathy to tessellation and to diffuse atrophy.

These finds highlight the importance of long-term and regular screening of young myopic eyes, especially to detect the early-risk patients who may have incident decreased ChT in myopia progression to identify early-risk populations with myopia-related fundus lesions.

In the present study, multivariate logistics regression revealed that the PPA area could be a less sensitive independent factor associated with incident decreased mChT compared with the BMOD, BTA and AL. This finding is consistent with our previous cross-sectional study findings (Hu et al. 2020). The reason why BMOD and BTA were more sensitive predictor of decreased mChT might be that BMOD is a comprehensive variable, responding to the severity of the BM defect on bilateral ONH and deformation of deep structures of the ONH based on three dimensions. However, PPA area may only respond to the absence of retinal pigment epithelium and BM defect in 2D (Dai et al. 2013; Vianna & Nicolela 2016). In addition, the limitation of PPA is that the measurement of PPA area is only based on fundus photography, while measurements of BMOD and BTA were based on SS-OCT with higher resolution, so the results were relatively more objective and accurate.

The stratification analysis revealed that among the participants with BMI < 24, AL < 26 mm and females, the association between BMOD and BTA and the incident of decreased mChT were stronger. We could speculate that BMOD and BTA could be strong predictors for the incident decreased mChT for those with BMI < 24, AL < 26 mm and females.

Our team's previous study (Lyu et al. 2021) have reported that the proportion of fundus tessellation significantly decreased with higher BMI, probably due to the support effect of adipose tissue and its function in preventing the elongation of the globe. Singapore studies (Saw et al. 2002; Li et al. 2011) have revealed that both children and adults with higher BMI tend to have more hyperopic refractions in the eyes. These findings indicate that subjects with lower BMI are more likely to develop myopia and myopia-related fundus lesions and even pathologic myopia, which may depend on the combination of socioeconomic factors, genetic factors and environmental influences (documentation of near work activities). Our team's recent study has shown that females tended to have thinner choroid compared with males in elderly subjects without PM, consistent with our previous study (Xie et al. 2022). Higher prevalence of myopia and high myopia (Wong et al. 2000), higher rates of progression of myopia and higher prevalence of degenerative myopia in women than in men have been reported in several population-based studies (Angle & Wissmann 1980; Krause et al. 1982). Barteselli et al. (2012) and Li et al. (2011) separately reported that choroidal volume and choroidal thickness in men were greater compared those in women. It has been revealed that sex and hormonal status especially oestrogens may influence choroidal blood flow that may be responsible to changes in choroidal volume and choroidal thickness (Ooto et al. 2015). Furthermore, BMOD and BTA were more strongly correlated with incident decreased mChT in non-high myopic eyes (AL < 26 mm) rather than high myopic eyes. This may be due to the fact that ChT was already very small in high myopic eyes and could not further decrease with age and axial elongation (Xie et al. 2022).

Our study found that BMOD, BTA and AL could be widely used as ocular biometrics for incident decreased mChT, especially the combination of BMOD, BTA, AL and basic model. A combination of BMOD, BTA, AL and basic model including age, sex, BMI and SBP resulted as highest and fairly good accurate for detecting decreased mChT (95% CI of AUROC = 0.6724, 0.8492). Furthermore, BMOD and BTA when separately or in combination added could significantly improve NRI and IDI compared with the basic prediction model alone, indicating that BMOD and BTA could be served as new biomarkers additional to AL for young myopic eyes at risk of developing decreased mChT and myopia-related fundus lesion in the future.

This study had several limitations. Firstly, the relatively short follow-up period is a main limitation. It is expected that longer observations would reveal more obvious characteristics of choroidal changes and myopia-related fundus lesions. Secondly, a prior analysis was not performed at the design stage of study, though the post hoc power analysis revealed that the power of ROC analysis of BMOD, BL and BTA in combination added into the basic model could achieve to 98%, when tested with chance level of 0.5 (Hajian-Tilaki 2013). Thirdly, the subjects in the present study were all Chinese, whereas, reportedly, the biomechanical properties of the ONH may vary by race; thus, the present findings cannot be generalized to other races. Fourthly, due to the lack of wide-field imaging system, not all patients with staphyloma might have been removed because staphylomas located outside the posterior pole might have been missed. Finally, the present study included only young adult healthy eyes and not pathologic myopic eyes. The prevalence of pathologic myopia in young age group was very low, suggesting that the elderly population and may need to be included to further explore the associations between BMOD, BTA and presence of pathologic myopia in our future follow-up studies.

In conclusion, in this prospective, longitudinal study, we found BMOD and AL are significant risk factors for incident decreased mChT, whereas BTA played protective role in the deterioration of mChT during myopia progression in young healthy adults. Furthermore, the combination of BMOD, BTA, and AL could be served as ocular earlier predictors of the attenuation of mChT and myopia-related fundus lesion for young myopic eyes. Thus, young myopic patients with BT configuration change, especially with greater BMOD or small BTA, should be paid more attention and given long-term and regular screening.

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commercial interest in any materials discussed in this manuscript. All authors attest that they meet the current ICMJE criteria for authorship.

Ethics statement

The study was designed following the ethical standards of the declaration of Helsinki and approved by the ethical committee of Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China.

Authors' contributions

GH, QC, ML, YS, JX, LY, HL, JH, JZ, YF and XX were involved in study design and conduct. GH, QC, JH, YY, LY, HZ, JH and JZ were involved in data collection, management and analysis. GH and ML interpreted the data. GH, QC, JH and YF were involved in manuscript preparation, review, or approval.

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Supporting Information

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

Table S1. General and ocular characteristics of study eyes ($n = 323$).

Table S2. Stratification analysis of the association between BMOD, BTA and AL at baseline with decreased mChT during follow-up according to baseline.