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ASSOCIATION OF RISK FACTORS FOR CHOROIDAL NEOVASCULARIZATION IN AMD WITH DECREASED FOVEOLAR CHOROIDAL CIRCULATION

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Abstract

Purpose—To investigate the relationship between known risk factors for Age-related macular degeneration (AMD) progression and foveolar choroidal circulation in eyes with non-exudative AMD.

Design—A cross-sectional study in non-exudative AMD.

Methods—Laser Doppler Flowmetry (LDF) measurements of relative choroidal blood velocity (ChBVel), volume (ChBVol) and flow (ChBFlow) were obtained in the center of the fovea of 273 study eyes of 204 AMD patients investigated at the Scheie Eye Institute of the University of Pennsylvania Medical School. All study eyes had visual acuity of 20/40 or better, good fixation, no other intraocular pathology and no evidence of choroidal neovascularization. RPE hypertrophy was determined from color fundus photographs by trained masked graders at the Scheie Image Reading Center. Correlation analysis and multivariate linear regression analysis with adjustments for significant covariates were carried out.

Results—A significant inverse correlation was observed between age and ChBFlow ($r = -0.36$, $p < 0.0001$), and ChBVol ($r = -0.28$, $p < 0.0001$), but not for ChBVel. A significant inverse correlation was observed between spherical equivalent and ChBFlow ($r = -0.21$, $p = 0.006$), and ChBVol ($r = -0.14$, $p = 0.04$) but not for ChBVel. ChBFlow and ChBVol were significantly lower in patients with a history of hypertension ($p \leq 0.003$) and in eyes with RPE hypertrophy ($p \leq 0.04$), respectively.

Conclusions—All the above described risk factors for AMD development and progression are associated with decreased choroidal circulatory parameters, suggesting that decreases in choroidal circulatory parameters may be involved in the development of AMD.

Age-related macular degeneration (AMD) is the leading cause of severe visual impairment and blindness among the elderly worldwide and in the developed countries^{1–3}. In the United States, 1.75 million people are affected by AMD, and its incidence increases with age. By the year 2020, an estimated of 2.95 million people are expected to be affected by AMD^{3–5}.

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AMD is a multifactorial disease that involves a complex interaction of metabolic and functional changes and risk factors that affect the progression of the disease and its response to various treatment modalities^{6–7}.

The risk factors for AMD can be categorized as demographic, environmental, and genetic^{6–7}. The strongest risk factor associated with the development and progression of AMD is increasing age; all population based studies confirm that the incidence, prevalence, and progression of AMD increase with advancing age^{2–5}.

Another established risk factor is cigarette smoking; numerous case-control studies, cohort studies, and cross-sectional studies have found a statistically significant association between smoking and the development and progression of AMD⁸.

The association between AMD and Systemic Hypertension (SHTN) has also been investigated. Some studies have showed that SHTN is a strong risk factor for AMD and choroidal neovascularization^{9–13}, while other studies have failed to demonstrate statistically significant associations^{14–15}. History of kidney disease¹⁶, hyperopia¹⁷, retinal pigment epithelium (RPE) abnormalities, light iris color, and female gender have been shown to be associated with AMD or choroidal neovascularization (CNV) in different studies^{10, 18–19}.

Previous cross-sectional studies performed in our laboratory have suggested that foveolar choroidal blood flow progressively decreases with increasing severity of AMD^{20–21}. In addition, a longitudinal study has reported that lower baseline choroidal blood flow parameters are associated with future development of CNV and decrease in vision²². Furthermore, decreases in choroidal circulatory parameters were detected prior to the development of CNV²². All these findings have suggested a role for circulatory abnormalities in the development and progression of AMD. In an attempt to further elucidate this role, we have investigated the relationship between the above mentioned risk factors for AMD and foveolar choroidal circulation.

Methods

We included in the study AMD patients examined at Scheie Eye Institute, Department of Ophthalmology, University of Pennsylvania, who were 50 years or older. All subjects were informed about the study and were asked to sign appropriate consent forms prior to the enrollment. All study eyes had visual acuity equal to or better than 20/40, and had no evidence of CNV. A visual acuity of 20/40 or better was required in order to ensure appropriate fixation for optimal foveolar blood flow measurements. All subjects had clear ocular media, pupillary dilatation of 5 mm or more, steady fixation and intraocular pressure (IOP) < 21mmHg in the study eyes. Patients with intraocular pathology or history of intraocular disease other than AMD, as well as patients with Diabetes Mellitus were excluded from the study.

A structured questionnaire was used to obtain information on age, gender, race, history of smoking, medical history, including history of SHTN, cardiovascular disease and kidney disease; ocular history, including eye color, family history of AMD. All subjects had a complete ocular examination, including visual acuity, applanation tonometry, and slit lamp biomicroscopy. After pupillary dilatation with tropicamide 1% (Alcon, Fort Worth, TX) and phenylephrine hydrochloride 10% (Sanofi Winthrop, New York, NY), a fundus examination was performed by an ophthalmologist, and stereo fundus photography of the disc and macula were obtained by a trained photographer.

Laser Doppler Flowmetry measurements (Oculix Instrument, Huntingdon Valley, PA) of the choroidal circulation were performed in the center of the foveola to assess relative Choroidal blood velocity, choroidal blood volume and choroidal blood flow. These parameters mainly

represent choriocapillaris flow. Details about the method used have been described in previous publications^{23–24}. Subjects were seated in front of the Laser Doppler Flowmetry camera in a darkened room, and were asked to fixate for three periods of 30 seconds on the aiming laser beam. A 200µm diameter diode laser beam (670µm) with an intensity of 20microWatts at the cornea was delivered through a fundus camera (model TRC; Topcon, Tokyo, Japan). To enable the observation of the position of the laser on the foveola, light with a retinal irradiance of approximately 0.03mW/cm² and a wavelength of 570nm constantly illuminated the posterior retina (30° in diameter). Choroidal blood velocity and choroidal blood volume were independently obtained with the Laser Doppler Flowmetry instrument. Choroidal blood velocity was proportional to the mean velocity of the red blood cells (RBCs) within the volume sampled by the laser light, and choroidal blood volume was proportional to the number of RBCs in the measured sample. Choroidal blood flow was calculated by the instrument according to the formula: Choroidal blood flow= Constant × Choroidal blood velocity × Choroidal blood volume²⁵. Choroidal blood velocity, choroidal blood volume and choroidal blood flow are all shown in arbitrary units (A.U.)

Immediately after blood flow measurements, while subjects were still seated, brachial artery systolic and diastolic blood pressures were determined by sphygmomanometry (Accutorr 1A; Datascope, Paramus, NJ), using a standardized protocol. Intraocular pressure (IOP) was then measured by Goldmann applanation tonometry. The mean of brachial artery pressure (BPm) was calculated according to the formula: BPm = BPs + 1/3 (BPs – BPD).

Analysis of the blood flow data was performed by a masked observer using software specifically developed for the analysis of Doppler signals from ocular tissues²⁴. Only parts of the recordings that showed stable circulatory parameters were selected for analysis. An average of approximately 12 seconds of measurements for each study eye was analyzed. We calculated a coefficient of variability (CV) for each study eye derived from three subsequent measurements to assess the reproducibility of the blood flow data. CV was calculated by the formula: CV = (SD/mean) × 100%, where SD represents standard deviation from three replicated measurements. The mean CV was 12.8% (SD=8.4%) for choroidal blood volume, 8.7% (SD=6.8%) for choroidal blood velocity, and 9.9% (SD=6.4%) for choroidal blood flow.

An average of the three measurements for each choroidal circulatory parameter was calculated and was used in data analysis. Correlation analysis and multivariate linear regression analysis with adjustment for significant covariates were carried out. The association between each blood flow parameter and a specific risk factor was first tested separately by a univariate analysis. Risk factors with a p-value < 0.10 from univariate analysis were included in the multivariate regression analysis, which was further simplified by including only the significant risk factors with p<0.05. The association of circulatory parameters with each of studied risk factors was assessed by using the generalized estimating equations (GEE) approach to linear regression to adjust for the correlation between eyes of the same patient²⁶. Calculations were executed by using PROC GENMOD (SAS Version 9.1, SAS, Cary, NC), and exchangeable working correlation structure was used to describe the correlation in circulatory measurements between paired eyes of each patient²¹.

Fundus photographs were graded in a masked fashion at the Scheie Image Reading Center at the University of Pennsylvania by trained graders. Gradings of drusen characteristics and Retinal Pigment Epithelium (RPE) hypertrophic changes in the study eyes were performed according to the Complications of Age-Related Macular Degeneration Prevention Trial (CAPT) protocol²⁷.

Results

A total of 269 non-exudative AMD eyes from 204 participants were included in this study. Participant's age ranged from 50 to 87 years (mean=71, SD=8.9 years). One hundred ninety six (96.1%) were Caucasian, 6 were African American, 1 was Asian and 1 was Hispanic. One hundred fourteen (55.9%) Participants were female. Thirteen participants (6.4%) were currently smokers at the time of Laser Doppler Flowmetry measurement. A history of SHTN was present in 91 (44.6%) study participants; 126 (61.8%) participants had a history of cardiac disease, and 18 (8.8%) participants had a history of kidney disease. RPE hypertrophy was observed in 157 (58.4%) study eyes (Table 1).

A statistically significant association was observed between the risk factors; age, SHTN, spherical equivalent or RPE hypertrophy and choroidal blood volume or choroidal blood flow (Table 1, Figures 1 through 6). No significant associations were detected between the above risk factors and choroidal blood velocity (Table 1).

A significant inverse correlation was observed between age and choroidal blood flow ($r=-0.36$, $p<0.0001$) (Figure 1), and choroidal blood volume ($r=-0.28$, $p<0.0001$) (Figure 2). In other words, patients with increasing age tended to have lower choroidal blood flow and ChBVol. These significant associations were still maintained for choroidal blood flow ($p=0.004$), and for choroidal blood volume ($p=0.02$) after adjustments for other significant risk factors (Table 2).

A significant inverse correlation was observed between spherical equivalent and choroidal blood flow ($r=-0.21$, $p=0.006$) (Figure 3), and choroidal blood volume ($r=-0.14$, $p=0.04$) (Figure 4). In other words, patients with more hyperopia tended to have lower choroidal blood flow and choroidal blood volume. These significant associations were still maintained for choroidal blood flow ($p=0.02$), but not for choroidal blood volume ($p=0.28$) after adjustments by age, systemic hypertension, and RPE hypertrophy (Table 2).

Multivariate analysis also confirmed all other statistically significant associations observed in the univariate analysis. Patients with a history of SHTN had choroidal blood volume (Mean $\pm$ SE) of 0.21 ± 0.01 A.U. and choroidal blood flow 6.94 ± 0.31 A.U. that were significantly lower than those observed in patients without SHTN (choroidal blood volume 0.25 ± 0.01 , P-value = 0.007; and choroidal blood flow 7.97 ± 0.32 , P-value = 0.003). Patients with RPE hypertrophy had average choroidal blood volume (0.22 ± 0.01) and choroidal blood flow (6.94 ± 0.31), which were significantly lower than those of eyes without RPE hypertrophy (choroidal blood volume 0.25 ± 0.01 , P-value = 0.01 and choroidal blood flow 7.78 ± 0.32 , P-value = 0.04) respectively (Table 2).

We detected no significant associations between the risk factors: current smoking status, brachial artery systolic and diastolic blood pressures, gender, eye color, cardiac or kidney diseases, and choroidal blood flow parameters (Table 1).

Discussion

AMD is a multifactorial disease that affects primarily the photoreceptors and RPE, Bruch's membrane, and choriocapillaries. The pathophysiology of AMD is complex and includes genetic factors and other processes such as oxidative stress, inflammation and hypoxia^{6, 28}.

The results of our current study in AMD patient's showing decreasing choroidal blood flow and volume, but not velocity, with increasing age are consistent with our previous study in normal subjects²⁹. The decreases in choroidal blood volume and flow may be caused by age-

associated changes in capillary vessel structure and a decline in choriocapillary density and lumen diameter^{29–31}.

Systemic hypertension (SHTN) has been shown by many studies to be associated with an increased risk for the development of AMD or CNV^{9–13}. The presence of decreased choroidal blood volume and choroidal blood flow in the patients with history of SHTN in our current study is consistent with our previous findings in a smaller sample size³², suggesting that an ischemic mechanism may be involved in the etiology of this disease. Possibly, choroidal blood flow decreases could lead to imbalances in choroidal watershed vascular filling zones; the areas most prone to develop ischemia and hypoxia³³. As reported by Ross et al³³ CNV often develops in close proximity to choroidal watershed vascular filling zones, supporting our hypothesis that hypertension may contribute to the progression of AMD and the development of CNV³², through a decrease in choroidal blood flow.

Consistent with our previous report³², we found in our current study no significant correlation between choroidal blood flow and actual blood pressure at the time of the flow measurements (Table 1). This could be due to the fact that blood pressure was well controlled in the majority of the study patients and blood pressure in most cases was within the normal range at the time of the blood flow measurements. It is possible that a history of SHTN or the presence of high systemic blood pressure in the past may produce chronic effects on the choroidal vasculature that may have a stronger effect on flow than the actual blood pressure detected at the time of flow measurements³².

The presence of focal RPE hyperpigmentation in the macula has been associated with a greater risk of AMD and development of CNV²¹. RPE serves a variety of metabolic and supportive functions to retinal photoreceptors. The impairment of RPE cell function is probably a crucial initiatory factor that drives slowly to progressive accumulation of lipofuscin formation, to local chronic inflammation and then to drusen formation²⁸.

Our present results showing that the RPE hyperpigmentation is associated with decreased choroidal blood flow suggests that hypoxia may have a role in the formation of these RPE changes. Hyperpigmentation of the RPE is caused by hypertrophy of the RPE and the formation of clusters of pigmented cells in the subretinal space and the outer nuclear area³⁵. Possibly, ischemia may modulate RPE proliferation and migration leading to these changes. Because we demonstrate an association and not a causal relationship we cannot conclude with certainty whether reduced flow may cause RPE hyperpigmentation or the reverse.

A clear explanation for the relationship between hyperopia and decreased choroidal blood flow and their association with an increased risk of AMD remains elusive. Hyperopic eyes are smaller and have thicker, more rigid and compact sclerae³⁶. This generalized scleral stiffness may cause an increased choroidal vasculature resistance leading to perfusion abnormalities. This process could adversely affect the transportation of oxygen, nutrients, and metabolic products from the photoreceptors across the RPE, and result in accumulation of metabolic debris and drusen formation and thickening of Bruch's membrane^{17, 30, 37–39}.

Interestingly, we did not observe significant correlations between choroidal circulatory parameters and race, eye color or kidney disease. This lack of significant correlation may be due to the smaller number of patients with some of these attributes, a situation that limits our ability to detect associations.

We also did not find a correlation between smoking, cardiac disease or gender and choroidal blood flow. This lack of association could be due to the involvement of other pathogenetic mechanisms that are not related to ischemia or hypoxia. For example, chronic cigarette smoke has been associated with increased oxidative damage and ultrastructural degeneration of the

RPE and Bruch membrane, and RPE cell apoptosis⁴⁰. In addition, because smoking has an effect on the immune system, it is possible that part of the risk conferred by smoking funnels through inflammatory pathways⁶.

Control of modifiable risk factors such as smoking, SHTN, and dietary supplementation with antioxidants and minerals can reduce the risk of developing AMD and CNV^{7, 28}. Our current results show that several important demographic and environmental risk factors for AMD are associated with decreased choroidal circulatory parameters. This suggests that decreases in choroidal circulatory parameters may be involved in the etiology of AMD or CNV. This kind of information may be useful in both understanding the pathophysiology of AMD and in determining possible targets and strategies for intervention in the prevention and progression of AMD development.

In summary, our current results demonstrate an association between decreased choroidal circulation and a number of risk factor for the development of AMD. All these findings suggest a possible role for choroidal circulatory abnormalities in the development of AMD and CNV. The precise mechanism by which these AMD risk factors and blood flow parameters affect each other remains unclear and needs to be further investigated. Finally, interventions aimed at improving the foveolar choroidal circulation may perhaps have a role in the prevention of AMD development and progression.

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Biographies

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Dr. Wei Xu, MD, received her medical degree from Hunan Medical College and completed her medical residency at St. Luke Hospital in Shanghai, China. Dr. Xu has devoted her efforts to a career in biomedical research, both basic and clinical science. She has been working at the University of Pennsylvania School of Medicine for 6 years, and has been the first author for publications in national scientific journals. Her current interest is in clinical research.

Figure 1.

Scatterplot of Choroidal Blood Flow (**ChBFlow**) with **Age**. The linear correlation coefficient between Choroidal blood flow (ChBFlow) and Age is -0.36 ($p < 0.0001$). The linear equation regression between Choroidal blood flow (ChBFlow) and Age is: Choroidal blood flow (ChBFlow) $= 16.3 - 0.13 \times \text{Age}$. Choroidal blood flow (ChBFlow) is shown in arbitrary units (A.U.), and age is in years.

Figure 2.

Scatterplot of Choroidal Blood Volume (**ChBVol**) with **Age**. The linear correlation coefficient between Choroidal blood volume (ChBVol) and Age is -0.28 ($p < 0.0001$). The linear regression equation between Choroidal blood volume (ChBVol) and Age is: Choroidal blood volume (ChBVol) $= 0.44 - 0.0029 \times \text{Age}$. Choroidal blood volume (ChBVol) is shown in arbitrary units (A.U.), and age is in years.

Figure 3.

Scatterplot of Choroidal Blood Flow (**ChBFlow**) with **Spherical Equivalent**. The linear correlation coefficient between Choroidal blood flow (ChBFlow) and Spherical Equivalent is -0.21 ($p=0.006$). The linear regression equation between Choroidal blood flow (ChBFlow) and Spherical Equivalent is: Choroidal blood flow (ChBFlow) $= 7.44 - 0.31 \times$ Spherical Equivalent. Choroidal blood flow (ChBFlow) is shown in arbitrary units (A.U.), and Spherical Equivalent is in Diopters (D).

Figure 4.

Scatterplot of Choroidal Blood Volume (**ChBVol**) with **Spherical Equivalent**. The linear correlation coefficient between Choroidal blood volume (ChBVol) and Spherical Equivalent is -0.14 ($p=0.04$). The linear regression equation Choroidal blood volume (ChBVol) and Spherical Equivalent is: $\text{ChBVol} = 0.23 - 0.0065 \times \text{Spherical Equivalent}$. Choroidal blood volume (ChBVol) is shown in arbitrary units (A.U.), and Spherical Equivalent is in Diopters (D).

Figure 5.

Comparison of Choroidal Blood Volume (**ChBVol**) between eyes without and with retinal pigment epithelium (RPE) hypertrophy. Boxplot shows a statistically significant difference between the two groups in Choroidal blood volume (ChBVol) ($P=0.02$). Each boxplot includes the upper extreme (whisker, excluding outliers indicated as circles outside the box), upper quartile (top portion of box), median (horizontal line in box), lower quartile (bottom portion of box), and lower extreme (whisker).

Figure 6. Comparison of Choroidal Blood Volume (**ChBVol**) between eyes without and with retinal pigment epithelium (RPE) hypertrophy. Boxplot shows a statistically significant difference between the two groups in and choroidal blood flow (ChBFlow) ($P=0.03$). Each boxplot includes the upper extreme (whisker, excluding outliers indicated as circles outside the box), upper quartile (top portion of box), median (horizontal line in box), lower quartile (bottom portion of box), and lower extreme (whisker).

Table 1

Association between AMD risk factors and circulatory parameters: Univariate analysis.

Risk Factors	Number and distribution (%) of study patients or eyes	ChBV _{ol}		ChBV _{el}		ChBF _{low}	
		Mean(SE) ^a	P-value	Mean(SE) ^a	P-value	Mean(SE) ^a	P-value
Age (years)			0.03		0.91		0.002
50–60	22 (10.8)	0.29 (0.02)		0.39 (0.02)		9.58 (0.76)	
61–70	63 (30.9)	0.24 (0.01)		0.38 (0.01)		7.65 (0.44)	
71–80	86 (42.2)	0.21 (0.01)		0.38 (0.01)		6.90 (0.28)	
80 +	33 (16.2)	0.21 (0.01)		0.38 (0.01)		6.30 (0.38)	
Gender			0.40		0.45		0.87
Male	90 (44.1)	0.23 (0.01)		0.38 (0.01)		7.33 (0.29)	
Female	114 (55.9)	0.24 (0.01)		0.38 (0.01)		7.40 (0.33)	
Eye color			0.51		0.43		0.80
Blue	65 (31.9)	0.22 (0.01)		0.39 (0.01)		7.01 (0.28)	
Brown	71 (34.8)	0.24 (0.01)		0.37 (0.01)		7.55 (0.39)	
Hazel	41 (20.1)	0.23 (0.02)		0.38 (0.03)		7.54 (0.53)	
Green	20 (9.8)	0.24 (0.02)		0.38 (0.01)		7.30 (0.69)	
Gray/Unknown	7 (3.4)	0.24 (0.05)		0.37 (0.02)		7.96 (1.88)	
Current smoking			0.08		0.11		0.39
No	191 (93.6)	0.23 (0.01)		0.38 (0.01)		7.32 (0.23)	
Yes	13 (6.4)	0.27 (0.02)		0.36 (0.01)		7.97 (0.69)	
Systemic Hypertension			0.009		0.48		0.005
No	112 (54.9)	0.25 (0.01)		0.38 (0.01)		7.86 (0.31)	
Yes	91 (44.6)	0.21 (0.01)		0.38 (0.01)		6.67 (0.27)	
Cardiac disease			0.80		0.55		0.44
No	78 (38.2)	0.23 (0.01)		0.38 (0.01)		7.56 (0.34)	
Yes	126 (61.8)	0.23 (0.01)		0.38 (0.01)		7.23 (0.28)	
Kidney disease			0.09		0.41		0.15
No	186 (91.2)	0.24 (0.01)		0.38 (0.01)		7.44 (0.23)	
Yes	18 (8.8)	0.20 (0.02)		0.39 (0.01)		6.58 (0.52)	
Systolic BP (mmHg)			0.53		0.047		0.77
		−0.0002 (0.0003)		0.0005 (0.0002)		0.003 (0.01)	

Risk Factors	Number and distribution (%) of study patients or eyes	ChBV _{ol}		ChBV _{el}		ChBFlow	
		Mean(SE) ^a	P-value	Mean(SE) ^a	P-value	Mean(SE) ^a	P-value
Diastolic BP (mmHg)		−0.0001 (0.0005)	0.84	0.0014 (0.0004)	0.001	0.02 (0.02)	0.16
Mean BP (mmHg)		−0.0002 (0.0004)	0.65	0.0008 (0.0004)	0.04	0.01 (0.01)	0.31
RPE Hypertrophy			0.02		0.62		0.03
No	112 (41.6)	0.25 (0.01)		0.38 (0.01)		7.98 (0.39)	
Yes	157 (58.4)	0.22 (0.01)		0.39 (0.01)		6.91 (0.29)	
	Mean (SD) of risk factor						
Systolic BP (mmHg) (as continuous)	136 (21.6)	−0.0002 (0.0003)	0.53	0.0005 (0.0002)	0.047	0.003 (0.01)	0.77
Diastolic BP (mmHg) (as continuous)	74 (12.2)	−0.0001 (0.0005)	0.84	0.0014 (0.0004)	0.001	0.02 (0.02)	0.16
Mean BP (mmHg) (as continuous)	95 (14.0)	−0.0002 (0.0004)	0.65	0.0008 (0.0004)	0.04	0.01 (0.01)	0.31
Spherical equivalent (D) (as continuous)	0.51 (2.06)	−0.007 (0.003)	0.04	−0.004 (0.003)	0.16	−0.31 (0.11)	0.006

^aChBVol, ChBVel and ChBFlow are shown in arbitrary units (A.U.).

Table 2

Association between AMD risk factors and Choroidal Blood Volume (ChBVol) and Flow (ChBFlow):
Multivariate analysis ^b.

Risk Factors	ChBVol		ChBFlow	
	Mean (SE) ^c	P-value	Mean (SE) ^c	P-value
Age		0.02		0.004
50–60	0.29 (0.03)		9.41 (0.84)	
61–70	0.23 (0.01)		7.31 (0.35)	
71–80	0.21 (0.01)		6.71 (0.26)	
80 +	0.20 (0.01)		6.01 (0.32)	
Systemic Hypertension		0.007		0.003
No	0.25 (0.01)		7.97 (0.32)	
Yes	0.21 (0.01)		6.94 (0.31)	
RPE hypertrophy		0.01		0.04
No	0.25 (0.01)		7.78 (0.32)	
Yes	0.22 (0.01)		6.94 (0.31)	
Spherical equivalent (D) (as continuous)			−0.21	0.02

^bThe risk factors in the multivariate model include age, systemic hypertension and RPE hypertrophy for ChBVol, and include age, systemic hypertension, RPE hypertrophy, and spherical equivalent for ChBFlow.

^cChBVol and ChBFlow are shown in arbitrary units (A.U.).