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Associations with Intraocular Pressure in Latinos: The Los Angeles Latino Eye Study

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INTRODUCTION

Although intraocular pressure (IOP) is no longer included in the definition of open-angle glaucoma (OAG), it remains as the only modifiable and a major risk factor for the development and progression of the disease.^{1, 2} Several studies have identified characteristics associated with elevated IOP in persons of African, European and Asian ancestries.^{3–7} Reported factors include older age, ^{3, 4, 6–13} gender, ^{3, 6, 8, 14, 15} race (African ancestry), ^{11, 14} blood pressure (BP), ^{1, 3, 6, 9, 11, 14–18} diabetes, ^{1, 3, 6, 19–21} pulse rate, ^{3, 6} body mass index (BMI), ^{3, 4, 6} nuclear sclerosis, ^{3, 5} iris color, ^{5, 22} myopia, ^{5, 7} use of alcohol, ^{5, 6, 17} smoking⁶ and family history of glaucoma. ^{5, 6, 13}

To our knowledge there are no reports on the factors associated with IOP in the Latino population, which is the largest and fastest growing minority group in the US.²³ Latinos of predominantly Mexican ancestry in Los Angeles have high rates of OAG, similar to those of African-Americans and significantly higher than non-Hispanic whites in the US.²⁴ The Los Angeles Latino Eye Study (LALES), a population-based study of Latinos of mostly Mexican ancestry in Los Angeles County that was initiated to better understand health care and eye disease in Latinos,²⁵ provided us with opportunity to evaluate the biological factors associated with higher IOP in this population.

MATERIALS AND METHODS

The University of Southern California's Institutional Review Board approved the study, and all procedures were in accord with the standards of the Declaration of Helsinki for research involving human subjects. Informed consent was obtained from all study participants. Details of the study design, sampling plan, and baseline data are reported elsewhere.²⁵ In brief, the study population consisted of self-identified Latinos (primarily Mexican American), aged \geq 40 years, living in six adjacent census tracts in the city of La Puente, California. All self identified Latinos aged 40 years and older (n=7789) were invited to complete an in-home questionnaire

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and a complete clinical and ocular examination. Of the eligible participants, 6357 (82%) completed both the in-home questionnaire and the clinical exam. Of these 6357 persons, 399 had a prior history of ocular hypotensive medication use, laser or incisional surgery and were excluded from the study. Of the remaining 5958 participants without a prior history of glaucoma treatment, 281 met the LALES criteria for definite or probable OAG and 215 met the criteria for ocular hypertension. These individuals were included in the analysis. In brief, definite or probable OAG was defined as the presence of an open angle and (1) evidence of characteristic or compatible glaucomatous optic disc damage on stereo fundus photography in at least one eye; and/or (2) congruent, characteristic, or compatible glaucomatous visual field abnormality. The IOP level was not considered in establishing the diagnosis of OAG. Ocular hypertension was diagnosed in individuals with an IOP of >21 mmHg and the absence of either of the above mentioned criteria for OAG.

The IOP data provided here is from a randomly selected eye of each participant. Three measurements of IOP were obtained using the Goldmann applanation tonometry (Haag-Streit, Bern, Switzerland) and averaged.

Risk Factor Assessment

Candidate risk factors were grouped into demographic, medical, and ocular factors. The demographic information obtained from the in-home questionnaire included age and gender. During the in-home interview, the following clinical and ocular history information was obtained from the participants: previous diagnosis of diabetes or hypertension, previous history of other cardiovascular disease such myocardial infarction, angina or cerebrovascular accident, history and extent of tobacco and alcohol use, current or previous use of any type of corticosteroids, family history of glaucoma in first degree relatives and history of eye trauma.

Medical characteristics obtained from clinical examination included weight and height for calculation of body mass index (BMI), pulse (beats/minute), random blood glucose level (using the Hemocue B-Glucose Analyzer), glycosylated hemoglobin (used the DCA 2000+ System), and systemic blood pressure. Body mass index was defined as weight (in kilograms) divided by the square of the height in meters (kg/m²). Participants were considered to have diabetes if (1) they self-reported a history of diabetes and were under treatment with oral hypoglycemic medications, insulin, or diet alone; or (2) if they had a hemoglobin A₁C (HbA1C) level of 7.0% or higher or (3) if they had a random blood glucose of 200 mg% or higher. Each participant had two blood pressure and heart rate measurements taken while sitting. The mean of these two measurements were used in the statistical analysis.

The ocular characteristics were obtained from a comprehensive eye examination where all procedures were performed in a standardized manner by one of three LALES ophthalmologists and trained ophthalmic technicians. Details of the complete clinical protocol have been described previously.²⁵ The pertinent ocular factors evaluated here included measurements of central corneal thickness (CCT), axial length, grading of nuclear cataract²⁶ and iris color.²⁷

Statistical Analyses

The means and standard deviations of IOP, stratified by both age and gender, were calculated. Additional means and standard deviations were calculated while stratifying by each categorical predictor. Analysis of variance technique (ANOVA) was done for each demographic, medical, and ocular predictor versus IOP. Partial r-square values were reported for continuous covariates. The variables that were significant from the univariate ANOVA analysis (p<0.05) were entered into a multivariable regression model and those that remained significant (p<0.05) were kept in the final model. All analysis was done using SAS version 9 (SAS Institute Inc., Cary, NC).

We also modeled the nature of the relationship between the various significant risk factors and IOP by plotting the LOWESS (locally weighted least squares) fit²⁸ for age, systolic BP, BMI, and CCT after adjusting for all other variables. The predicted median IOP for a particular level of a risk factor was determined from the multivariable regression model after adjusting for other covariates. The estimated median IOP was then plotted against the variable of interest (e.g., systolic blood pressure) and a locally weighted regression line was fitted using S-PLUS (Insightful Corporation, Seattle, WA).

RESULTS

From the 6357 participants, the cohort for this study includes 5958 participants who had completed the interview and clinical examination and did not have a prior history of glaucoma treatment. The majority of participants were female (58%); the average age (\pm standard deviation) was 54.9 \pm 10.9 years. The mean IOP for the entire study population was 14.5 \pm 3.2 mm Hg.

The mean IOP values increased from 14.0 ± 2.8 mm Hg at the age of 40 to 49 years to 15.1 ± 3.7 mm Hg at 70 years of age or older (P < 0.0001, Table 1) Overall women had slightly higher IOPs than men (P < 0.0001). Table 2 provides the result of the univariate analysis for categorical variables associated with IOP as a comparison of means. Significant factors include female gender, history of hypertension and diabetes, nuclear sclerosis and brown iris color. The results of the univariate analysis for continuous variables associated with IOP are listed in Table 3. Factors associated with elevated IOP include older age, higher BMI, elevated systolic and diastolic BP, faster pulse rate, higher glycosylated hemoglobin (HbA1C) and thicker CCT.

Factors found to be significant in the univariate analysis were included the final step-wise multivariable regression model. Because of the high inter-correlation between systolic BP, diastolic BP and hypertension, and HbA1C and diabetes, hypertension and HbA1C were removed from this model. Variables that continued to be associated with elevated IOP in the final model were age, female gender, diabetes, higher systolic and diastolic blood pressure, elevated BMI, nuclear sclerosis, brown iris color and thicker CCT (Table 4). All of the factors combined, only explained 10% of the variation in IOP. Higher systolic BP and thicker CCT were the most significant factors associated with IOP, each explaining approximately 4% of IOP variance. The final multivariable regression analysis was repeated after excluding the 281 individuals with the diagnosis of OAG; the variables associated with elevated IOP remained unchanged.

Figure 1–Figure 4 illustrate the relationship between IOP and age, systolic BP, BMI and CCT, respectively, after adjusting for all other variables. The plots for SBP and DBP (not shown) suggest that there is an essentially linear relationship between these variables and IOP after adjusting for other risk factors. A 10 year difference in age is associated with a 0.34 mm Hg difference in IOP (Figure 1). A 20 mm Hg higher systolic or diastolic BP is associated with a 0.7 and 0.9 mm Hg higher IOP respectively (Figure 2).

DISCUSSION

We set out to identify biological factors associated with IOP in this Latino population without a prior history of glaucoma treatment.

Age

Several cross-sectional studies have shown a higher IOP with older age.⁶, 12, 22, 29 This has been attributed to significant reduction in outflow facility counteracting the reduced production of aqueous with age.³⁰, ³¹ Other studies have found no correlation or even a negative

correlation of IOP with age.^{3, 4, 17, 19, 32} It has been suggested that the rise in IOP that is observed in aging populations may be related to other factors such as a concomitant rise in blood pressure and/or BMI.^{4, 10, 18, 33} In our cross-sectional data IOP does vary with age and age remains a significant factor in the analysis even after adjusting for all other variables. Figure 1 plots the independent relationship between median IOP and age after controlling for other variables. There is slow rise in IOP with age. The variation is small, equaling slightly more than 1 mm Hg for those > 70 years of age compared to those 40–49 years of age (Table 1).

Gender

Results of previous studies evaluating gender differences in IOP are inconsistent.^{3–6, 15} We find a small but statistically significantly higher IOP in females than males although this difference is clinically insignificant. The relationship between gender and IOP is difficult to interpret. Women are believed to possibly have a more marked tendency for increase in IOP with age with peaking at a higher age than in men.^{34, 35} Other possible explanations for this include the higher level of obesity and hypertension in women or a longer life expectancy.

High Blood Pressure

High blood pressure is a well recognized risk factor for elevated IOP. Numerous studies have reported a consistent positive correlation between systolic blood pressure and IOP³, 4, 6, 9, 10, 12, 14–16, 18 although the association with diastolic BP is less consistent.³, 11, 14, 15, 18 Here we find a statistically significant association of elevated systolic and diastolic BP with IOP. Although arterial blood pressure and IOP both increase with age, this association in our data remains significant even when the data is adjusted for age. Figure 2 demonstrates the relationship between systolic BP and median IOP while controlling for all other variables. As systolic BP increases, IOP increases in linear fashion.

The mechanism responsible for elevated IOP with increasing BP is not well understood but increasing aqueous humor production by ultrafiltration as a result of elevated ciliary artery pressure or a generalized increased sympathetic tone and elevated serum corticosteroid levels resulting in simultaneous increase in BP and IOP together has been postulated.⁴, 10, 14 Regardless of the mechanism of IOP elevation, given the fact that BP is amendable to therapy and that IOP is a major risk factor for OAG, BP may potentially be a modifiable risk factor for OAG.

Diabetes Mellitus

Numerous large population-based studies have documented an association between diabetes, HbA1C and elevated IOP.³, 6, 10, 19 In this study our criteria for diagnosis of diabetes mellitus were stringent and based either on a history of currently being treated for DM and/or defined by a blood glucose and HbA1C testing. Those with a diagnosis of diabetes mellitus had a significantly higher IOP than those who did not. Although a physiologic explanation for this finding is unclear several theories have been proposed. The elevated blood glucose level in diabetes may induce an osmotic gradient and attract fluid into the intraocular space, resulting in elevated IOP.³⁴ Alternatively, diabetes related autonomic dysfunction or genetic factors may play a role.³⁶, 37

Although the positive association between diabetes and IOP is well documented, the relationship between diabetes and glaucoma is more controversial. Although several studies have shown diabetes to be a risk factor for the development of OAG,³³, ^{38–40} others have found no association between diabetes and OAG.²¹, ⁴¹ Diabetes mellitus, in the Latino population, has been found to be an independent risk factor for the development of OAG,³⁸ thus, diabetes, similar to BP, may be a modifiable risk factor for IOP and potentially for OAG.

Interestingly, in our study those with higher HbA1C values also had a higher IOP (Table 3) suggesting that improved blood sugar control may indeed help improve IOP control. We removed HbA1C from our final regression model, however, due to its high inter-correlation with diabetes.

Body Mass Index

Body mass index, a measure of obesity was positively correlated with IOP. Although obesity is correlated with elevated blood pressure and diabetes, the association between BMI and higher IOP was found independently of these 2 variables. In interpreting these results, however, the difficulty of obtaining accurate applation tonometry in some obese individuals must be considered. Other cross-sectional studies have also found similar associations between IOP and BMI.³, 6, 10, 12, 42 It has been suggested that increased orbital pressure due to excess orbital fat may increase episcleral venous pressure and result in a decrease of outflow facility. ⁴ Alternatively, the deposition of lipids may reduce outflow facility for the aqueous, resulting in higher IOP.¹⁴ Figure 3 plots the variation in IOP with increasing BMI. IOP is elevated by slightly more than one mmHg, as BMI increases by a massive amount (30 kg/m²). This association in clinical practice is likely insignificant.

Iris Color

Interestingly, we found a significant positive association of IOP with darker iris pigmentation. Other studies have also found a similar association.⁵, ²², ⁴³ Although pigment dispersion syndrome is thought to be related to the release of pigment and mechanical obstruction of the trabecular meshwork by pigment, in the absence of characteristics of pigment dispersion the relationship is difficult to interpret. Although we excluded cases with definite pigment dispersion, it is possible that subtle cases of the syndrome may have been missed. The differences in mean IOP between people with lighter colored irides and those with darker color irides, however, is very small and not clinically relevant.

Nuclear Lens Opacity Grade

The severity of nuclear sclerosis was also correlated with increasing IOP. Those with a II–III grade of nuclear sclerotic cataracts had on average a 1.3 mmHg increase in intraocular pressure compared to those with no cataracts, independently of other variables. A plausible explanation for this association is the mechanical effect of thicker lenses on the angle with subsequent compromise of aqueous outflow facility. IOP has been noted to reduce significantly after cataract extraction in several studies^{44, 45} and has been attributed to improvement of aqueous outflow facility by widening the drainage angle.⁴⁶

Central Corneal Thickness

The relationship between CCT and IOP as measured by applanation tonometry has been well studied.^{47–51} Since Goldmann based his readings on the assumption that the mean normal corneal thickness is approximately 500 μ m,⁵² the intraocular pressure readings obtained by the Goldmann applanation tonometry (GAT) for an eye with average CCTs has good accuracy. For significantly thinner or thicker corneas, however, Goldmann tonometry tends to underestimate or overestimate, respectively, the true intraocular pressure. Our results confirm this positive correlation of increasing IOP as measured by GAT with increasing CCT (Figure 4).

To the best of our knowledge, this is the first study to report on the factors associated with elevated IOP in the Latino population. Many of the variables that had been found to be significantly associated with IOP in previous studies in other populations were also found to be significant in this population. Age, female gender, higher systolic and diastolic BP, diabetes,

larger BMI, darker colored irides, nuclear sclerosis and thicker CCTs were significant factors contributing to an elevated IOP. It should however be emphasized that the overall difference in IOP among individuals with specific characteristics is small and in some cases clinically insignificant. Nevertheless, recognition and identification of these variables allows for better understanding of IOP determinants and more importantly allows us to define specific subgroups of individuals who are at high risk of having increased IOP and possible progression to OAG.

Since elevated IOP is a major risk factor for the development of OAG it is reasonable for one to assume that the two conditions have similar risk profiles. Diabetes in the Latino population, for example, has been shown to be a risk factor for the development of OAG.³⁸ This association, however, is independent of IOP. The relationship between OAG in the LALES population and other variables discussed here has not been elucidated and is currently under investigation.

The association of some variables such as systolic and diastolic blood pressure, diabetes and BMI with elevated IOP introduces the suggestion that perhaps individuals who are screened for these conditions should also be evaluated for elevated IOP and referred for further assessment and treatment if necessary. It is conceivable that by identifying such individuals, we may be able to decrease the burden of undetected eye disease in this fastest growing segment of the US population.

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Contributions: design and conduct of the study (RV, SA); collection, management, analysis, and interpretation of the data (FM, RV, SA, MYL); and preparation, review, or approval of the manuscript (RV, SA, FM, MYL).

Statement about Conformity: The study protocol was approved by the Institutional Review Board (IRB)/Ethics Committee at the University of Southern California and all study procedures adhered to the recommendations of the Declaration of Helsinki. Written consent was obtained from all participants.

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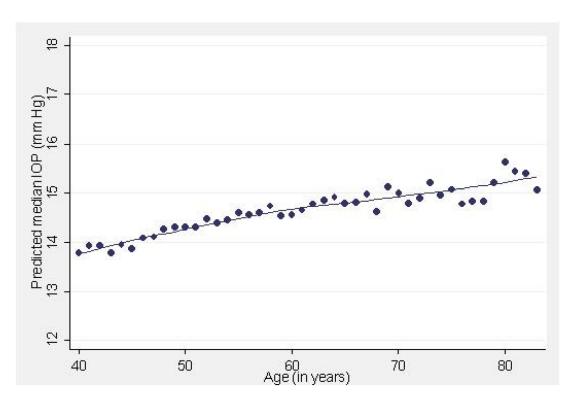


Figure 1.

Predicted median intraocular pressure (IOP, mmHg) in relation to age (years) in participants of the Los Angeles Latino Eye Study.

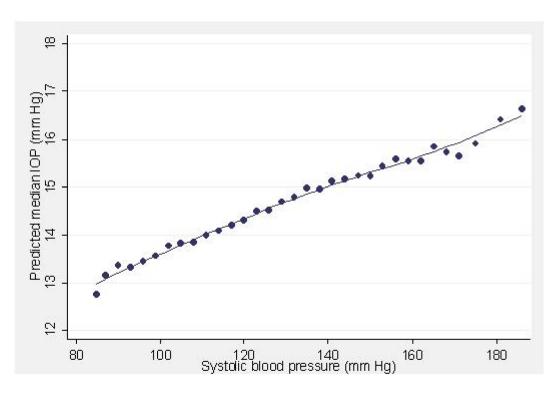


Figure 2.

Predicted median intraocular pressure (IOP, mmHg) in relation to systolic blood pressure (mmHg) in participants of the Los Angeles Latino Eye Study.

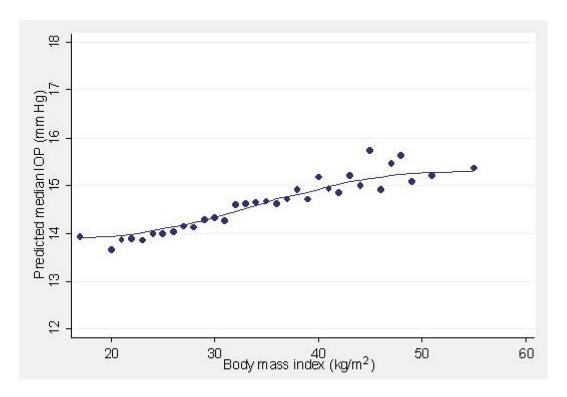


Figure 3.

Predicted median intraocular pressure (IOP, mmHg) in relation to body mass index (kg/m^2) in participants of the Los Angeles Latino Eye Study.

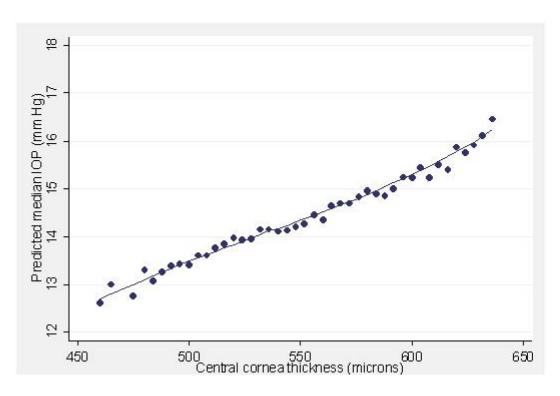


Figure 4.

Predicted median intraocular pressure (IOP, mmHg) in relation to central corneal thickness (μ) in participants of the Los Angeles Latino Eye Study.

 Table 1

 Age and Gender Specific Distribution of Intraocular pressure (IOP) in participants of the Los Angeles Latino Eye Study

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949 13.9 (3.0) 1 748 14.4 (3.4) 1 474 14.5 (3.4) 2 204 14.0 2.6	(dc -) unate u	$n \qquad Mean (\pm SD)$
748 14.4 (3.4) 1 474 14.5 (3.4) 1 201 14.0 2.5	1341 14.1 (3.7)	2290 14.0 (2.8)
474 14.5 (3.4) 204 14.0.2.5	1058 14.8 (3.0)	1806 14.6 (3.2)
304 14073 6	688 15.0 (3.5)	1162 14.8 (3.4)
J04 14.2 (J.U)	396 15.3 (3.7)	700 15.1 (3.7)
All ages 2475 14.3 (3.3) 32	3483 14.6 (3.1)	5958 14.5 (3.2)

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SD = standard deviation; IOP = intraocular pressure (mm Hg).

Table 2

Univariate Associations with Intraocular Pressure (IOP) in participants of the Los Angeles Latino Eye Study

Risk Factors [†]	N	<i>IOP (mm Hg)</i> *	P-value
Gender			
Female	3483	14.6 ± 3.1	
Male	2475	14.3 ± 3.3	< 0.0001
Family History of Glaucoma			
Yes	467	14.4 ± 2.9	
No	5203	14.5 ± 3.2	0.77
Hypertension			
Yes	2318	15.0 ± 3.3	
No	3640	14.1 ± 3.0	< 0.0001
Diabetes			
Yes	1416	15.2 ± 3.3	
No	4542	14.2 ± 3.1	< 0.0001
History of Tobacco			
Never	3624	14.5 ± 3.2	
Ex-smoker	1460	14.4 ± 3.2	
Current	848	14.7 ± 3.2	0.20
History of Alcohol			
Never	2303	14.4 ± 3.2	
Occasional	1783	14.5 ± 3.1	
Regular	774	14.6 ± 3.3	
Ex-Drinker	1080	14.5 ± 3.2	0.66
History of Steroid Use			
Never	3642	14.4 ± 3.1	
Used in past	188	14.5 ± 4.0	
Current use	59	14.3 ± 2.8	0.90
Cardiovascular Disease			
Yes	442	14.4 ± 3.3	
No	5516	14.5 ± 3.2	0.86
History of Eye Trauma			
Yes	1189	14.5 ± 3.0	
No	4769	14.5 ± 3.2	0.76
Nuclear Cataract Grading ^{\ddagger}			
Grade 0	1956	14.0 ± 2.9	
Grade 0–I	3362	14.6 ± 3.1	
Grade I–II	357	15.2 ± 3.6	
Grade II–III	83	15.3 ± 4.0	
>III	17	18.0 ± 9.0	< 0.0001
Pseudophakics	184	15.0 ± 4.0	
Iris Color			
Blue/Green/Hazel	2080	14.2 ± 3.1	
Light Brown	3125	14.3 ± 3.3	
Dark Brown	747	14.6 ± 3.1	0.0009

 $\frac{1}{1}$ Table 2 includes categorical variables.

*Mean (± SD).

≠ Lens Opacity Classification System II.

Table 3

Univariate Associations with Intraocular Pressure (IOP) in participants of the Los Angeles Latino Eye Study

Risk Factors ^{\dagger}	$r^{2}(\%)^{*}$	P-value
Age	0.01 (1.0)	< 0.001
BMI (kg/m^2)	0.003 (0.3)	< 0.0001
Systolic BP (mm Hg)	0.04 (4.0)	< 0.0001
Diastolic BP (mm Hg)	0.02 (2.0)	< 0.0001
Pulse (beats/min)	0.005 (0.5)	< 0.0001
CCT (µ)	0.03 (3.0)	< 0.0001
HbA1C (%)	0.02 (2.0)	< 0.0001
Axial Length (mm)	0.0004 (0.04)	0.13
Axiai Lengui (IIIII)	0.0004 (0.04)	0.15

⁷Table 3 includes continuous variables.

*Coefficient of determination.

BMI = body mass index, BP = blood pressure, CCT = central corneal thickness.

Table 4

Multivariable Associations with Intraocular Pressure (IOP) in participants of the Los Angeles Latino Eye Study

Risk Factors	Partial r^2 (%) [*]	P-Value
Age	0.002 (0.2)	< 0.0001
Gender	0.005 (0.5)	0.0001
Diabetes	0.008 (0.8)	< 0.0003
Nuclear Cataract Grading \ddagger	0.003 (0.3)	< 0.0002
Iris Color	0.001 (0.1)	0.009
BMI (kg/m ²)	0.001 (0.2)	0.0009
Systolic BP (mm Hg)	0.04 (4.0)	< 0.0001
Diastolic BP (mm Hg)	0.0009 (0.09)	0.02
CCT (µ)	0.04(4.0)	< 0.0001

Coefficient of partial determination.

Lens Opacity Classification System II.

BMI = body mass index, BP = blood pressure, CCT = central corneal thickness.

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