Factors Associated With Retinal Vessel Diameters in an Elderly Population: the Thessaloniki Eye Study

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PURPOSE. To identify the factors associated with retinal vessel diameters in the population of the Thessaloniki Eye Study.

METHODS. Cross-sectional population-based study (age ≥ 60 years). Subjects with glaucoma, late age-related macular degeneration, and diabetic retinopathy were excluded from the analyses. Retinal vessel diameters were measured using the IVAN software, and measurements were summarized to central retinal artery equivalent (CRAE), central retinal vein equivalent (CRVE), and arteriole to venule ratio (AVR).

RESULTS. The analysis included 1614 subjects. The hypertensive group showed lower values of CRAE (P = 0.035) and AVR (P = 0.0351) compared to the normal blood pressure (BP) group. On the contrary, the group having normal BP under antihypertensive treatment did not have different values compared to the normal BP group. Diastolic BP (per mm Hg) was negatively associated with CRAE (P = 0.0001) and AVR (P < 0.0001), while systolic BP (per mm Hg) was positively associated with CRAE (P = 0.001) and AVR (P = 0.0096). Other factors significantly associated included age, sex, alcohol, smoking, cardiovascular disease history, ophthalmic medication, weight, and IOP; differences were observed in a stratified analysis based on BP medication use.

CONCLUSIONS. Our study confirms previous reports about the association of age and BP with vessel diameters. The negative correlation between BP and CRAE seems to be guided by the effect of diastolic BP as higher systolic BP is independently associated with higher values of CRAE. The association of BP status with retinal vessel diameters is determined by diastolic BP status in our population. Multiple other factors are also independently associated with retinal vessel diameters.

Keywords: retinal vasculature, hypertension, epidemiology, population-based, aging

The retinal vessels can be noninvasively visualized using modern fundus photography equipment, and retinal image analysis software have enabled the objective and accurate measurement of retinal vessel diameters.1 The retinal vasculature is considered a unique window to assess vascular health and to detect early structural changes and pathological features of the human microcirculation.1,2 Several systemic, environmental, and genetic factors have been shown to influence retinal vascular calibers, and results from population-based studies suggest that a wide range of subclinical and clinical cardiovascular diseases are associated with retinal vascular calibers.1,2 Moreover, there are reports in the literature about associations between ophthalmic diseases (glaucoma, age-related macular degeneration, diabetic retinopathy) and retinal vessel diameters.1 However, retinal vessel diameter measurements have not been introduced so far in the clinical setting of managing cardiovascular or ophthalmic patients.1 Nevertheless, the idea of introducing retinal vessel diameter measurements as a biomarker for cardiovascular patients may be promising. Moreover, association of retinal vascular caliber with the diagnosis or prognosis of ophthalmic diseases could provide insight for the pathogenetic mechanisms underlying the respective diseases.

The development of normative databases based on large population-based cohorts conducted in different populations is critical for the investigation of retinal vessel diameters in clinical settings.3 However, due to the numerous systemic and environmental factors affecting retinal vessel diameters, normative databases have not been developed so far. Retinal vessel diameters have been analyzed in previous population-based studies and associations with several factors have been identified. Specifically, narrower retinal arterial diameters and...
smaller arteriovenous ratio have been associated with older age, higher blood pressure, and obesity. On the contrary, wider retinal venular diameters have been associated with younger age, impaired fasting glucose and diabetes, dyslipidemia, obesity, systemic markers of inflammation, endothelial dysfunction, and cigarette smoking. Genetic factors and ophthalmic diseases have been also associated with retinal vessel diameters. However, it may be difficult to determine normal values across different individuals or populations and account for the confounding effect of systemic and ocular diseases. In addition, the confounding factors and their effect on retinal vessel diameters may differ among different populations.

The Thessaloniki Eye Study (TES) is a population-based study of the major eye diseases conducted in the Greek population. It is one of the few large population-based studies conducted in European populations and one of the few population-based studies conducted in a Mediterranean population. It is also the only population-based study where retinal vessel diameters were analyzed in a south-European, Mediterranean population. Apart from the detailed ophthalmic examination protocol, detailed history (including systemic and ophthalmic diseases, demographic factors, and lifestyle) was recorded for all the TES participants. Fundus photos were also obtained from TES participants. Therefore, the TES offers a unique opportunity to assess the distribution of retinal vessel diameters in an elderly south European–Mediterranean population and identify associations with ocular and systemic factors and disease biomarkers.

METHODS

The Thessaloniki Eye Study is a cross-sectional population-based study of chronic eye diseases in the population of Thessaloniki, which is the major urban center in Northern Greece. The study was approved by the Aristotle University Ethics Committee and the Institutional Review Board of the University of California, Los Angeles. All study procedures adhered to the principles outlined in the Declaration of Helsinki for research involving human subjects and all participants gave written informed consent before their participation.

Details about the recruitment process have been described previously. Briefly, the initial recruitment frame of the Thessaloniki Eye Study consisted of 5000 people 60 years of age or older who were selected randomly in February 1999 from approximately 321,000 persons registered in the municipality registers of the city of Thessaloniki. Randomization was provided by the municipality statistical service. Subjects from the Thessaloniki Eye Study recruitment group were contacted by phone or mail to ascertain their willingness to participate in the study. Subjects who agreed to participate were invited to the Thessaloniki Eye Study center at the Aristotle University of Thessaloniki for an extensive ophthalmic screening examination. A home visit eye examination was arranged for persons unable to visit the study examination center because of illness or major disability. Among the 3617 eligible subjects, 2554 participated in the study (participation rate, 71%); of these, 2261 (89%) had the clinic visit examination and 293 (11%) had the home visit examination. Only clinic-visit participants, who had fundus photography, were included in the present analyses.

All clinic visit participants were interviewed for demographic data (age, sex), ophthalmic and systemic diseases (hypertension, diabetes, cardiovascular disease, history of heart attack, coronary artery bypass or vascular surgery, and migraines), systemic medications (use of antihypertensive and diabetes treatment), and lifestyle (smoking, alcohol consump-
ment of the overlying grid centered on the optic disc, vessel type identification and width measurements for vessels. The manual components include the option to override any of the initial automated decisions or measurements. This would include adjusting the placement of the grid, changing the vessel type, deleting vessels, re-measuring vessels, and adding significant vessels missed in the initial calculation. The arteriole to venule ratio (AVR) was also calculated. A trained grader masked to participant characteristics, completed the retinal vessel diameter measurements in all TES participants. These measurements have been shown to be highly reproducible in previous studies. Following the training of the grader, a small reproducibility study was conducted to confirm the consistency of the measurements. This showed excellent values of intraclass correlation coefficient (>0.85) for all measured parameters (CRAE, CRVE, AVR). One fundus camera (Topcon Corp, Japan) was used for the purposes of the present study.

Details about glaucoma and pseudoexfoliation (PEX) definitions were described previously. Late age-related macula degeneration (AMD) was defined by the presence of either geographic atrophy (GA) or neovascular-exudative maculopathy (NV), as proposed by the International ARM Epidemiological Study Group.

Diabetic retinopathy was defined by the presence of typical retinopathy lesions of any stage (microaneurysms, hemorrhages, venous beading, intraretinal microvascular abnormalities, neovascularization of the disc or retina) as described by the Early Treatment Diabetic Retinopathy Study.

In TES three independent ophthalmologist graders were responsible for the assessment of the patients. A consensus agreement between at least two of them was required to assign any diagnosis. When disagreement between the graders existed, an open discussion for final classification and diagnosis was carried out. The principal investigator (ET) examined all study participants and was responsible for the final adjudication of diagnosis.

For the present study, all subjects with glaucoma, late AMD, or any stage of diabetic retinopathy in either eye were excluded from the analysis. Exclusion criteria also included subjects without fundus photo in at least one eye, subjects with no gradable fundus photo in at least one eye because of media opacities (cornea scarring, dense cataract, vitreous hemorrhage, etc.), and subjects in whom vessel diameters could not be measured in at least six arteries and veins in at least one eye.

Statistical Analyses

The CRAE, CRVE, and AVR were the dependent variables included in the analyses. Association of retinal vessel diameters (CRAE, CRVE, AVR) with demographic and lifestyle factors, BP, medical and ophthalmic history, intracocular pressure (IOP), and other ophthalmic variables was assessed in univariate analyses first. The continuous variables included in the analysis were height, weight, body mass index (BMI), sleep hours, systolic blood pressure (SBP), diastolic blood pressure (DBP), IOP, and mean perfusion pressure (MPP). The categorical variables included in the analysis were age (age groups: 60–69, 70–79, ≥80), sex, sleep in the afternoon, frequency of vegetable consumption, alcohol intake, smoking, history of hypertension, history of diabetes mellitus, history of cardiovascular disease, history of migraines, history of heart attack, history of coronary surgery; use of hypertension medication, use of diabetes medication (tablets), use of insulin, current systemic steroid use, past systemic steroid use, BP status, SBP status, DBP status, use of ophthalmic medication, iris pseudoexfoliation, lens pseudoexfoliation, any pseudoexfoliation (iris or lens), lens status (phakic, pseudophakic or aphakic), hormone replacement therapy (only in females).

Vegetable consumption data were grouped in the following groups: less than once a week, one to three times a week, at least once a day. Based on the answers provided by the participants, regular alcohol intake was defined as consumption of any type of alcohol greater or equal to once a month. Occasional alcohol intake was defined as consumption of any type of alcohol less than once a month. A subject was classified as a nonsmoker if he/she had smoked fewer than 100 cigarettes in his/her lifetime, as a former smoker if he/she had smoked more than this number of cigarettes in his/her lifetime but had stopped smoking at least 1 year prior to the examination, and as current smoker if he/she had not stopped smoking or stopped smoking less than 1 year prior to the examination.

BP, DBP, and SBP status were defined as following: DBP values lower than 90 mm Hg and SBP values lower than 140 mm Hg were considered normal. In evaluation of SBP, subjects were classified as having SBP within normal limits (SBP-WNL group), normal SBP as a result of antihypertensive treatment (SBP-WNL-Tx group), or high SBP regardless of treatment (SBP-Htn group). In evaluation of DBP, subjects were classified as having DBP within normal limits (DBP-WNL group), normal DBP as a result of antihypertensive treatment (DBP-WNL-Tx group), or high DBP regardless of treatment (DBP-Htn group). Similarly, subjects were classified in three groups by BP status (both SBP and DBP): BP (both SBP and DBP) within normal limits (BP-WNL group), normal BP (both SBP and DBP) as a result of antihypertensive treatment (BP-WNL-Tx group), high BP (SBP or DBP) regardless of treatment (BP-Htn group). Mean perfusion pressure (MPP) was also calculated as (2/3) X [DBP + (SBP - DBP)/3] – IOP and included in the analysis.

Pearson correlation coefficient was used to assess the association of quantitative variables with retinal vessel diameters (CRAE, CRVE, AVR), while univariate linear regression was used to assess the association of categorical variables with retinal vessel diameters. P values were considered statistically significant when less than 0.05. All variables with P value lower than 0.2 in the univariate models for any dependent variable (CRAE, CRVE, AVR) were included in the multivariable linear regression model.

RESULTS

From the 2261 clinic visit participants, subjects with glaucoma, late AMD, or any stage of diabetic retinopathy in either eye were excluded from the analysis, leaving data from 1772 subjects available for consideration of analysis. Subjects without fundus photos or subjects with no gradable fundus photo in either eye because of media opacities (cornea scarring, dense cataract, vitreous hemorrhage, etc.) were excluded from the analysis as were subjects in whom vessel diameters could not be measured in at least six arteries and veins in at least one eye. Thus a total of 1641 TES participants were included in the univariate analysis. The mean CRAE in our population was 148.61 μm (SD ± 14.29 μm), the mean CRVE was 227.44 μm (±21.16 μm), and the mean AVR was 0.66 (±0.06); 1614 subjects were included in the multivariable linear regression analysis as 27 participants had missing data in at least one of the variables included in the multivariable model.

The descriptive statistics for categorical and continuous variables included in the analyses are summarized in Tables 1 and 2, respectively. Table 3 summarizes the Pearson correlation coefficient between retinal vessel diameters and the continuous variables included in the analysis, and Table 4 summarizes
TABLE 1. Descriptive Statistics for Categorical Variables (Glucoma, AMD, and Diabetic Retinopathy Subjects Were Excluded)

<table>
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<tr>
<th>Variable</th>
<th>Category</th>
<th>Frequency</th>
<th>Percentage</th>
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</tr>
<tr>
<td></td>
<td>70–79</td>
<td>644</td>
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<tr>
<td></td>
<td>≥ 80</td>
<td>84</td>
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<td>Sex, N = 1641</td>
<td>Male</td>
<td>902</td>
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<td>Female</td>
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<tr>
<td></td>
<td>1–3 a week</td>
<td>907</td>
<td>55.27</td>
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<tr>
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<td>≥1 a day</td>
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<td>Current smoker</td>
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<td>Ex-smoker</td>
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<td>158</td>
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<td>Yes</td>
<td>843</td>
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<td>Diabetes medication, N = 1640</td>
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<td>13</td>
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<td>Steroid use at present, N = 1658</td>
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<td>Normal</td>
<td>363</td>
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<td>Normal with Tx</td>
<td>255</td>
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<tr>
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<td>High</td>
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<td>Normal with Tx</td>
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<td>Ophthalmic medication, N = 1641</td>
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TABLE 1. Continued

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<td>Lens status, N = 1641</td>
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<td>Pseudophakic</td>
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<tr>
<td></td>
<td>Aphakic</td>
<td>5</td>
<td>0.18</td>
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The results presented in Table 5 show that SBP, DBP, age, alcohol, smoking, BP status, history of cardiovascular disease, and ophthalmic medications are statistically significantly associated with CRAE in the univariate linear regression analysis. More specifically, higher SBP (per mm Hg) was associated with increased values of CRAE (slope estimate = SE 0.083 µm, P = 0.0011), while higher DBP (per mm Hg) was associated with decreased values (SE = −0.248 µm, P < 0.0001). Age 80 years or older was associated with decreased values of CRAE (SE = −3.884 µm, P = 0.025) compared to the reference group aged 60 to 69 years. Regular alcohol intake (SE = −2.109 µm, P = 0.017) was associated with decreased values of CRAE compared to no alcohol intake while current smoking was associated with increased values of CRAE (SE = 3.396 µm, P = 0.0033) compared to the nonsmoking group. High BP regardless of antihypertensive treatment was associated with decreased values of CRAE (SE = −3.396 µm, P = 0.0033) compared to normal BP without treatment. On the contrary, the group having SBP < 140 mm Hg and DBP < 90 mm Hg under antihypertensive treatment did not have different values compared to normal BP group (P = 0.2056). History of cardiovascular disease was associated with increased values of CRAE (SE = 2.371 µm, P = 0.0048). Use of ophthalmic medications was associated with increased values of CRAE (SE = 3.551 µm, P = 0.0217).

The results presented in Table 6 show that the factors statistically significantly associated with CRVE were DBP, age, sex, and smoking. Higher DBP (per mm Hg) was associated with decreased values of CRVE (SE = −0.143 µm, P = 0.0142). Age 80 years or older was associated with decreased values of CRVE (SE = −8.093 µm, P = 0.002) compared to the reference...
The slope estimate for continuous variables represents the amount change in the outcome variable with every one unit change in the predictor variable, while the estimate for categorical variables represents the amount change in the outcome variable between the corresponding group and the reference group.
The slope estimate for continuous variables represents the amount change in the outcome variable with every one unit change in the predictor variable, while the estimate for categorical variables represents the amount change in the outcome variable between the corresponding group and the reference group.

group age 60 to 69 years. Female sex was associated with decreased values of CRVE (SE = −3.221 μm, P = 0.0077) compared to male sex. Current smoking was associated with increased values of CRVE (SE = 6.962 μm, P < 0.0001) compared to the nonsmoking group.

The results presented in Table 7 show that the factors significantly affecting AVR were weight, SBP, DBP, IOP, sex, vegetable consumption, smoking, BP-WNL status, and cardiovascular disease history. Higher weight (per kg) was associated with decreased AVR (SE = −0.000259, P = 0.0482). Higher SBP (per mm Hg) was associated with increased AVR (SE = 0.000259, P = 0.0099), while higher DBP (per mm Hg) was associated with decreased AVR (SE = −0.000065, P < 0.0001). Higher IOP (per mm Hg) was also associated with increased values of AVR (SE = 0.000912, P = 0.041). Female sex was associated with increased AVR (SE = 0.013305, P = 0.0007) compared to male sex. Consuming vegetables less than once a week was associated with decreased AVR (SE = −0.012710, P = 0.0335) compared to vegetable consumption more than once a week. Current smoking was associated with decreased AVR (SE = −0.00887, P = 0.02) compared to nonsmoking. High BP regardless of antihypertensive treatment was associated with decreased AVR (SE = −0.009957, P = 0.0351) compared to the normal BP. On the contrary, the group having SBP < 140 mm Hg and DBP < 90 mm Hg under antihypertensive treatment did not have different values of AVR compared to the normal BP group (P = 0.2587). Individuals with a history of cardiovascular disease had increased AVR (SE = 0.009218, P = 0.0052) compared to those with no history of cardiovascular disease.

The results presented in Table 8 compare the factors affecting retinal vessel diameters in the participants receiving BP medication and the participants not receiving BP medication. In this stratified analysis, differences between the two groups were observed. Factors significantly associated with CRAE in individuals not receiving BP medication were DBP (per mm Hg, SE = −0.2903, P = 0.0092), ophthalmic medication use compared to no use (SE = 4.9202, P = 0.006) for the pseudophakic/aphakic group compared to the reference phakic group. Factors significantly associated with CRAE in individuals receiving BP medication were DBP (per mm Hg, SE = −0.2688, P < 0.0001), age (SE = −2.3041, P = 0.03 for the 70–79 group/ SE = −4.9693, P = 0.02 for the ≥80 group) compared to the 60 to 69 reference group, current smoking (SE = 3.7174, P = 0.008) compared to never smokers and history of cardiovascular disease compared to no history (SE = 2.3751, P = 0.03). Factors significantly associated with CRVE in participants receiving BP medication were age (SE = −2.9451, P = 0.002) and ophthalmic medication use compared to no use (SE = 4.9202, P = 0.006) for the pseudophakic/aphakic group compared to the reference phakic group. Factors significantly associated with CRVE in participants not receiving BP medication were DBP (per mm Hg, SE = −0.3016, P = 0.001) and smoking for current smokers (SE = 7.8440, P = 0.0001) compared to nonsmokers.

### Table 5. Multivariable Linear Regression Results for CRAE

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Slope Estimate</th>
<th>Pr &gt;</th>
<th>t</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (per cm)</td>
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<td>0.552</td>
<td>0.00087</td>
</tr>
<tr>
<td>Weight (per kg)</td>
<td>-0.0166995</td>
<td>0.6182</td>
<td>0.00087</td>
</tr>
<tr>
<td>SBP (per mm Hg)</td>
<td>0.082642</td>
<td>0.00011</td>
<td>0.0087</td>
</tr>
<tr>
<td>DBP (per mm Hg)</td>
<td>-0.2476165</td>
<td>&lt;0.0001</td>
<td>0.00011</td>
</tr>
<tr>
<td>IOP (per mm Hg)</td>
<td>0.1181001</td>
<td>0.2991</td>
<td>0.00087</td>
</tr>
<tr>
<td>Age: 70–79</td>
<td>-0.1085655</td>
<td>0.1502</td>
<td>0.000912</td>
</tr>
<tr>
<td>≥80</td>
<td>-3.8841049</td>
<td>0.025</td>
<td>0.000655</td>
</tr>
<tr>
<td>Sex: female vs. male</td>
<td>1.1265566</td>
<td>0.2958</td>
<td>0.000912</td>
</tr>
<tr>
<td>Sleep in the afternoon: yes vs. no</td>
<td>-0.8902254</td>
<td>0.2639</td>
<td>0.000912</td>
</tr>
<tr>
<td>Vegetable consumption</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 a week</td>
<td>-1.6371289</td>
<td>0.2812</td>
<td>0.000912</td>
</tr>
<tr>
<td>1–3 a week</td>
<td>1.2670733</td>
<td>0.0797</td>
<td>0.000912</td>
</tr>
<tr>
<td>≥1 a day</td>
<td>Reference</td>
<td></td>
<td>0.000912</td>
</tr>
<tr>
<td>Regular alcohol intake: yes vs. no</td>
<td>-2.1087241</td>
<td>0.017</td>
<td>0.000912</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
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</tr>
<tr>
<td>Current smoker</td>
<td>2.5825959</td>
<td>0.0068</td>
<td>0.000912</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>-0.4826856</td>
<td>0.5906</td>
<td>0.000912</td>
</tr>
<tr>
<td>Never</td>
<td>Reference</td>
<td></td>
<td>0.000912</td>
</tr>
<tr>
<td>HTN_BP_Meds</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP-WNL-Tx</td>
<td>-1.4739587</td>
<td>0.2056</td>
<td>0.000912</td>
</tr>
<tr>
<td>BP-HTN</td>
<td>-3.3959876</td>
<td>0.0033</td>
<td>0.000912</td>
</tr>
<tr>
<td>BP-WNL</td>
<td>Reference</td>
<td></td>
<td>0.000912</td>
</tr>
<tr>
<td>History of cardiovascular disease: yes vs. no</td>
<td>2.3709471</td>
<td>0.0048</td>
<td>0.000912</td>
</tr>
<tr>
<td>Heart attack history: yes vs. no</td>
<td>-0.274474</td>
<td>0.8351</td>
<td>0.000912</td>
</tr>
<tr>
<td>Coronary surgery history: yes vs. no</td>
<td>-0.1452581</td>
<td>0.9097</td>
<td>0.000912</td>
</tr>
<tr>
<td>Ophthalmic medication: yes vs. no</td>
<td>3.5507315</td>
<td>0.0217</td>
<td>0.000912</td>
</tr>
<tr>
<td>Lens: pseudophakic/aphakic vs. phakic</td>
<td>-2.1023192</td>
<td>0.1031</td>
<td>0.000912</td>
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</tbody>
</table>

### Table 6. Multivariable Linear Regression Results for CRVE

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Slope Estimate</th>
<th>Pr &gt;</th>
<th>t</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (per cm)</td>
<td>-0.0955916</td>
<td>0.2793</td>
<td>0.0087</td>
</tr>
<tr>
<td>Weight (per kg)</td>
<td>0.0730754</td>
<td>0.1485</td>
<td>0.0087</td>
</tr>
<tr>
<td>SBP (per mm Hg)</td>
<td>0.0374864</td>
<td>0.325</td>
<td>0.0087</td>
</tr>
<tr>
<td>DBP (per mm Hg)</td>
<td>-0.1434083</td>
<td>0.0142</td>
<td>0.0087</td>
</tr>
<tr>
<td>IOP (per mm Hg)</td>
<td>-0.1566071</td>
<td>0.3616</td>
<td>0.0087</td>
</tr>
<tr>
<td>Age: 70–79</td>
<td>-0.5566405</td>
<td>0.6242</td>
<td>0.0087</td>
</tr>
<tr>
<td>≥80</td>
<td>-8.0926895</td>
<td>0.002</td>
<td>0.0087</td>
</tr>
<tr>
<td>Sex: female vs. male</td>
<td>-3.3210524</td>
<td>0.0477</td>
<td>0.0087</td>
</tr>
<tr>
<td>Sleep in the afternoon: yes vs. no</td>
<td>-1.911443</td>
<td>0.112</td>
<td>0.0087</td>
</tr>
<tr>
<td>Vegetable consumption</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 a week</td>
<td>1.866383</td>
<td>0.4156</td>
<td>0.0087</td>
</tr>
<tr>
<td>1–3 a week</td>
<td>0.8172173</td>
<td>0.4538</td>
<td>0.0087</td>
</tr>
<tr>
<td>≥1 a day</td>
<td>Reference</td>
<td></td>
<td>0.0087</td>
</tr>
<tr>
<td>Regular alcohol intake: yes vs. no</td>
<td>-1.1709926</td>
<td>0.3797</td>
<td>0.0087</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>6.9618213</td>
<td>&lt;0.0001</td>
<td>0.0087</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>-0.1600185</td>
<td>0.9059</td>
<td>0.0087</td>
</tr>
<tr>
<td>Never</td>
<td>Reference</td>
<td></td>
<td>0.0087</td>
</tr>
<tr>
<td>HTN_BP_Meds</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP-WNL-Tx</td>
<td>-0.3656879</td>
<td>0.8351</td>
<td>0.0087</td>
</tr>
<tr>
<td>BP-HTN</td>
<td>-2.1030168</td>
<td>0.2281</td>
<td>0.0087</td>
</tr>
<tr>
<td>BP-WNL</td>
<td>Reference</td>
<td></td>
<td>0.0087</td>
</tr>
<tr>
<td>History of cardiovascular disease: yes vs. no</td>
<td>0.3736628</td>
<td>0.7681</td>
<td>0.0087</td>
</tr>
<tr>
<td>Heart attack history: yes vs. no</td>
<td>1.3821273</td>
<td>0.5086</td>
<td>0.0087</td>
</tr>
<tr>
<td>Coronary surgery history: yes vs. no</td>
<td>1.8092627</td>
<td>0.3493</td>
<td>0.0087</td>
</tr>
<tr>
<td>Ophthalmic medication: yes vs. no</td>
<td>4.2255252</td>
<td>0.0704</td>
<td>0.0087</td>
</tr>
<tr>
<td>Lens: pseudophakic/aphakic vs. phakic</td>
<td>-2.8365947</td>
<td>0.145</td>
<td>0.0087</td>
</tr>
</tbody>
</table>
Factors Associated With Retinal Vessel Diameters

### Table 7. Multivariable Linear Regression Results for AVR

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Slope Estimate</th>
<th>Pr &gt;</th>
<th>t</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (per cm)</td>
<td>3.40007E+05</td>
<td>0.8822</td>
<td></td>
</tr>
<tr>
<td>Weight (per kg)</td>
<td>−0.00025971</td>
<td>0.0482</td>
<td></td>
</tr>
<tr>
<td>SBP (per mm Hg)</td>
<td>0.000258799</td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td>DBP (per mm Hg)</td>
<td>−0.000655212</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>IOP (per mm Hg)</td>
<td>0.000917762</td>
<td>0.041</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>−0.003206388</td>
<td>0.2775</td>
<td></td>
</tr>
<tr>
<td>≥ 70–79</td>
<td>0.005777771</td>
<td>0.4547</td>
<td></td>
</tr>
<tr>
<td>≥ 60–69</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>−0.00989887</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>−0.002315531</td>
<td>0.5104</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HTN_BP_Meds</td>
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<td></td>
<td></td>
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<tr>
<td>BP-WNL-Tx</td>
<td>−0.005156696</td>
<td>0.2587</td>
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</tr>
<tr>
<td>BP-WNL</td>
<td>−0.009556077</td>
<td>0.0351</td>
<td></td>
</tr>
<tr>
<td>History of cardiovascular disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes vs. no</td>
<td>0.009217592</td>
<td>0.0052</td>
<td></td>
</tr>
<tr>
<td>Heart attack history: yes vs. no</td>
<td>−0.000432786</td>
<td>0.4257</td>
<td></td>
</tr>
<tr>
<td>Coronary surgery history: yes vs. no</td>
<td>−0.005321159</td>
<td>0.2894</td>
<td></td>
</tr>
<tr>
<td>Ophthalmic medication: yes vs. no</td>
<td>−0.003377499</td>
<td>0.5773</td>
<td></td>
</tr>
<tr>
<td>Lens: pseudophakic/aphakic vs. phakic</td>
<td>−0.000265428</td>
<td>0.9581</td>
<td></td>
</tr>
</tbody>
</table>

The slope estimate for continuous variables represents the amount change in the outcome variable with every one unit change in the predictor variable, while the estimate for categorical variables represents the amount change in the outcome variable between the corresponding group and the reference group.

#### DISCUSSION

Retinal vessel diameters have been measured in several population-based studies conducted in different populations and their measurements have been associated with ophthalmic and systemic diseases. However, different populations may differ in terms of genetic background and environmental exposures. The TES is the only population-based study conducted in the Greek population and, therefore, it is a unique opportunity to identify associations between retinal vessel diameters and ocular or systemic diseases in this population. It is also the only population-based study to analyze retinal vessel diameters in a south European or Mediterranean population.

Previous population based studies have associated higher BP values (systolic, diastolic, and mean BP) with decreased retinal arterial diameters. In these studies, the statistical approach was to use either mean BP as the only variable analyzed or to proceed to limited adjustment for some of the variables that could be affecting retinal vessel diameters (age, sex, body mass index, smoking history, education level). In our multivariable model, we considered additional potential factors as provided by the TES comprehensive data set. We found that SBP and DBP as continuous variables had an opposite effect on retinal vessel diameters. In our study, higher SBP was associated with increased CRAE and AVR values, while higher DBP was associated with decreased CRAE, CRVE, and AVR values. The negative association reported in the literature between BP and retinal arterial diameters seems to be guided by the effect of DBP. It is obvious from our results that CRAE and AVR are affected in a higher degree by DBP values than by SBP. SBP and DBP have been shown in the literature to be associated with a positive linear relationship. The analysis of our data allows the clarification of the effect of SBP and DBP on retinal vessel diameter measurements which, to the best of our knowledge, has not been studied in the literature before. The different role of SBP and DBP as prognostic factors for cardiovascular diseases has been analyzed in the literature, and the significance of SBP over DBP has been shown. To our knowledge, there are no previous studies assessing the relationship between BP status and retinal vessel diameters.

In our study, the hypertensive group showed lower values of CRAE and AVR compared to the group having normal BP without treatment. At the same time, the group having normal BP as a result of BP lowering treatment did not have significantly different CRAE and AVR values compared to the group having normal BP without treatment. This indicates that the association of BP status with retinal vessel diameters could be mainly affected by the current DBP level association, as analyzed before. In addition, the results suggest that the use of systemic antihypertensive medications effectively reducing BP within normal limits also preserves the diameters of main branches in the retinal vasculature.

The association between aging and retinal vessel diameters has been reported in the literature in several studies. Retinal arterial and venous diameters decrease 1.4 to 4.8 μm per decade of aging. The negative correlation between aging and retinal vessel diameters was confirmed in our population as well. However, it reached statistical significance only when comparing the groups 60 to 69 years old to those older than 80.

In our population, females showed decreased values of CRVE and increased values of AVR. Similar results have been reported by the Blue Mountains Eye Study, the Cardiovascular Health Study, and the Multi-ethnic Study of Atherosclerosis (MESA). Although estrogens have been proposed as the factor responsible for this difference observed between males and females, results in the literature are conflicting about this suggestion.

Current smoking was associated with increased values of CRAE and CRVE and decreased values of AVR in our results. Similar associations have been reported in the literature. Interestingly, ex-smokers did not have different values of retinal vessel diameters compared to nonsmokers in our study. On the contrary, the Rotterdam study reported increased values of CRAE and CRVE for ex-smokers compared to nonsmokers.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>CRAE</th>
<th>No HTN Meds, n = 798</th>
<th>HTN Meds, n = 833</th>
<th>CRVE</th>
<th>No HTN Meds, n = 798</th>
<th>HTN Meds, n = 833</th>
<th>AVR</th>
<th>No HTN Meds, n = 798</th>
<th>HTN Meds, n = 833</th>
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</thead>
<tbody>
<tr>
<td>Height (per cm)</td>
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<td>-0.0238, 0.77</td>
<td>-0.0413, 0.63</td>
<td></td>
<td>0.0158, 0.90</td>
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<td>-0.000256, 0.41</td>
<td>0.000280, 0.41</td>
</tr>
<tr>
<td>Weight (per kg)</td>
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<td></td>
<td>0.0605, 0.43</td>
<td>0.086, 0.21</td>
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<tr>
<td>IOP (per mm Hg)</td>
<td></td>
<td>0.1574, 0.34</td>
<td>0.0974, 0.54</td>
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<td>-0.0021, 0.99</td>
<td>-0.333, 0.15</td>
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<td>0.000691, 0.26</td>
<td>0.001290, 0.04</td>
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<tr>
<td>SBP (per mm Hg)</td>
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<td>0.0587, 0.08</td>
<td>0.0562, 0.051</td>
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<td>0.0852, 0.10</td>
<td>-0.029, 0.49</td>
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<td>0.000001, 0.99</td>
<td>0.000329, 0.004</td>
</tr>
<tr>
<td>DBP (per mm Hg)</td>
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<td>-0.2903, &lt;0.0001</td>
<td>-0.2688, &lt;0.0001</td>
<td></td>
<td>-0.3016, 0.001</td>
<td>-0.065, 0.40</td>
<td></td>
<td>-0.00391, 0.08</td>
<td>-0.00987, &lt;0.0001</td>
</tr>
<tr>
<td>Age 70–79</td>
<td></td>
<td>0.1852, 0.86</td>
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<td>-2.3404, 0.12</td>
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<td>-0.01566, 0.70</td>
<td>-0.005622, 0.19</td>
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<tr>
<td>Age ≥80</td>
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<td>-4.9693, 0.02</td>
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<td>-5.0576, 0.28</td>
<td>-9.213, 0.004</td>
<td></td>
<td>-0.00105, 0.99</td>
<td>0.005351, 0.70</td>
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<tr>
<td>Sleep in the afternoon: yes vs. no</td>
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<td>-1.8783, 0.10</td>
<td>0.0387, 0.97</td>
<td></td>
<td>-2.6986, 0.13</td>
<td>-1.111, 0.50</td>
<td></td>
<td>-0.000345, 0.95</td>
<td>0.015412, 0.01</td>
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<tr>
<td>Vegetable consumption: &lt;1 a week</td>
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<td>-1.2882, 0.56</td>
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<td>1.601, 0.63</td>
<td></td>
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<td>-0.009821, 0.27</td>
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<tr>
<td>Vegetable consumption: 1–3 a week</td>
<td></td>
<td>1.4085, 0.18</td>
<td>0.9089, 0.37</td>
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<td>1.507, 0.35</td>
<td>0.365, 0.81</td>
<td></td>
<td>0.001835, 0.64</td>
<td>0.003107, 0.45</td>
</tr>
<tr>
<td>Smoking status: Regular alcohol intake: yes vs. no</td>
<td></td>
<td>2.1561, 0.10</td>
<td>-2.3455, 0.054</td>
<td></td>
<td>-1.0317, 0.61</td>
<td>-0.852, 0.63</td>
<td></td>
<td>-0.007102, 0.15</td>
<td>-0.006888, 0.16</td>
</tr>
<tr>
<td>History of cardiovascular disease: yes vs. no</td>
<td></td>
<td>1.8556, 0.16</td>
<td>3.7174, 0.008</td>
<td></td>
<td>7.8410, 0.0001</td>
<td>6.784, 0.001</td>
<td></td>
<td>-0.014323, 0.004</td>
<td>-0.003279, 0.58</td>
</tr>
<tr>
<td>History of coronary surgery history: yes vs. no</td>
<td></td>
<td>-1.8120, 0.15</td>
<td>0.8825, 0.50</td>
<td></td>
<td>0.8027, 0.68</td>
<td>-0.819, 0.67</td>
<td></td>
<td>-0.010978, 0.02</td>
<td>0.005619, 0.28</td>
</tr>
<tr>
<td>History of ophthalmic medication: yes vs. no</td>
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<td>2.3571, 0.03</td>
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<td>0.017055, 0.0008</td>
<td>0.005041, 0.26</td>
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<td>History of ophthalmic surgery history: yes vs. no</td>
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<td>2.974, 0.27</td>
<td></td>
<td>0.003779, 0.64</td>
<td>-0.010270, 0.16</td>
</tr>
<tr>
<td>History of ophthalmic surgery history: yes vs. no</td>
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<td>3.1913, 0.35</td>
<td>0.909, 0.70</td>
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<td>-0.001813, 0.78</td>
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<td>Lens status: pseudo/aphakic vs. phakic</td>
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<td>4.9202, 0.03</td>
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<td>4.752, 0.13</td>
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<td>0.0108594, 0.21</td>
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<td></td>
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<td>-1.525, 0.55</td>
<td></td>
<td>-0.011747, 0.11</td>
<td>0.007196, 0.30</td>
</tr>
</tbody>
</table>

The slope estimate for continuous variables represents the amount change in the outcome variable with every one unit change in the predictor variable, while the estimate for categorical variables represents the amount change in the outcome variable between the corresponding group and the reference group.
Factors Associated With Retinal Vessel Diameters

Alcohol consumption was associated with decreased values of CRAE in our population; however, no association was found with CRVE and AVR. Similar associations have been reported previously by the MESA.12 On the contrary, the Rotterdam Study13 and the Atherosclerosis Risk in Communities Study (ARIC)14 found association of alcohol consumption with decreased values of AVR, while the mechanism responsible for this association has not been clarified. However, in our study, the association of alcohol consumption with decreased values of AVR did not reach statistical significance.

A self-reported history of cardiovascular disease was associated with increased values of CRAE and AVR. There are several studies in the literature associating retinal vessel diameters with atherosclerosis markers, inflammation and dysfunction of vessel endothelium, stroke, coronary heart disease, and death because of cardiovascular diseases.1,2 However, our results are not directly comparable with the results of these studies because the accuracy of self-reported history is different from the accuracy of objective disease markers used in those studies and because several confounders (e.g., systemic medication used) could be interfering with this relationship.

In our study, increased weight was associated with decreased values of AVR. On the contrary, weight was not associated with retinal arterial and venous diameters. The relationship between AVR and weight has been confirmed by several studies conducted in different populations, along with an association between weight and retinal arterial and venous diameters.15,19,25,27,28

In our population, the use of ophthalmic medications was associated with increased values of CRAE. Our analysis did not include subgroup analysis for different categories of ophthalmic medications used by the participants in TES. Investigations on the Beaver Dam Eye Study reported that the use of topical beta-blockers as IOP-lowering treatment was associated with narrowing of the retinal arterial and venous diameters.29 Although glaucoma patients were excluded from the analysis, there were participants overdiagnosed for glaucoma in our population.30 This explains that some of those included in the analysis were receiving ophthalmic medications (including IOP lowering medications).

Higher IOP was associated with decreased values of AVR in our population. This finding applies to individuals without glaucoma since glaucoma subjects were excluded from the analysis. To our knowledge, there are no previous population-based studies evaluating the effect of IOP on AVR. Increased IOP is known to be a risk factor for glaucoma.31 However, it is not clear from our study whether the effect of IOP on AVR is involved in the development of glaucomatous optic neuropathy.

Lower vegetable consumption (less than once a week) was associated with decreased values of AVR compared to the group consuming vegetables at least once a day. To our knowledge, there are no previous population-based studies assessing the effect of diet on retinal vessel diameters. Decreased AVR has been reported to be associated with several cardiovascular risk factors.3

The stratified analysis based on BP medication use (or not) revealed interesting differential findings regarding the factors affecting retinal vessel diameters. CRAE was associated with ophthalmic factors (ophthalmic medication and lens status) in the non-BP treated group only. Conversely, systemic factors (age and smoking) were associated with CRAE only in the group receiving BP treatment. CRVE was associated with CRVE in non-BP treated subjects but not in the BP treatment group. The opposite applied to subjects over 80 years of age. Weight, vegetable consumption, smoking and history of cardiovascular disease were associated with AVR only in the nontreatment BP group, while the opposite relationships were found when applied to IOP, SBP, and DBP.

It is not clear from our study if the presence of hypertension, antihypertensive treatment, or confounding variable is responsible for the differences observed between groups. Both the presence of hypertension itself and some types of treatment could be related with early changes in the structure and function of the retinal microcirculation.1,2 Moreover age may be a surrogate for the duration of hypertension or antihypertensive treatment thus potentially explaining the differences in the findings between those with and without antihypertensive treatment. DBP presented with different correlation with CRVE in those receiving or not receiving antihypertensive treatment (no significant correlation versus negative correlation respectively). Interestingly, we have previously reported association of DBP with optic disk structure in the nonglaucoma participants receiving antihypertensive treatment.3,2 In another analysis, we have found that diastolic ocular perfusion pressure was significantly associated with primary open angle glaucoma only in subjects receiving antihypertensive treatment.37 Considering the complexity of these issues, carefully designed research and more advanced mathematical analysis may further elucidate these relationships and any potential clinical significance.

Our results suggest that various factors are significantly associated with retinal vessel diameters differently based upon presence or absence of BP treatment. The factors significantly associated with retinal vessel diameters include: demographic data (age and sex), systemic factors (BP history of cardiovascular disease), ophthalmic factors (IOP and ophthalmic medication), and lifestyle (current smoking, alcohol consumption, weight, and vegetable consumption). One of the advantages of our study is that it is a random sample of the population in a defined geographical area. A limitation of our study is that the associations found may not be relevant to age groups younger than 60 years. Another limitation is the fact that the software used does not allow adjustment for the size of the optic disc, which could be a source of error since different disc sizes could affect the measurement of retinal vessel diameters. The measurement of the retinal vessels is a standardized distance from the disc, which may create an artifact in eyes with very large or small disc diameters.

Age and BP have been confirmed as factors statistically significantly associated with retinal vessel diameters across different studies and in our population as well. At the same time, the negative correlation between BP and CRAE reported in the literature seems to be guided by the effect of DBP as higher SBP independently is associated with higher values of CRAE. To our knowledge, our study is the first in the literature to analyze this association. Multiple other factors (including demographic, systemic, ophthalmic, and lifestyle factors) are independently associated with retinal vessel diameters in our population and BP medication use may affect this association as well. The associations we found may provide insights on the role of different factors in retinal vasculature diameters and its role as a potential biomarker in eye diseases and general health status. Further research to prospectively identify the impact of different factors on retinal vessels and analyze the relationship with ocular and systemic diseases is needed to this direction.

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