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Glaucoma

Associations of Midlife and Late-Life Blood Pressure Status With Late-Life Retinal OCT Measures

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Purpose: To explore the relationship of long-term blood pressure (BP) patterns with late-life optical coherence tomography (OCT) structural measures reflecting optic nerve health.

Methods: Participants in this community-based cohort study of black and white individuals were part of the Atherosclerosis Risk in Communities study and the nested Eye Determinants of Cognition (EyeDOC) study. Participants had BP measured six times from 1987 to 2017 and were categorized into five BP patterns: sustained normotension; midlife normotension, late-life hypertension (systolic BP [SBP] >140 mmHg or diastolic BP [DBP] >90 mmHg or antihypertensive medication use); sustained hypertension; midlife normotension, late-life hypotension (SBP <90 mmHg or DBP <60 mmHg); and midlife hypertension, late-life hypotension. Multivariable linear regression modeling was used to evaluate associations between BP patterns and late-life OCT ganglion cell complex (GCC) and peripapillary retinal nerve fiber layer (RNFL) thickness.

Results: In total, 931 eyes of 931 participants (mean age at EyeDOC visit = 80 years; 63% female; 45% black) were included. Mean GCC and RNFL thicknesses in the sustained normotension pattern were 90.8 ± 10.3 µm and 89.9 ± 11.2 µm versus 89.4 ± 11.9 µm and 90.1 ± 12.2 µm in the sustained hypertension pattern ($P > 0.05$). Compared to the sustained normotension pattern, no significant differences in GCC or RNFL thickness were found for any anomalous BP pattern.

Conclusions: Assessment of long-term BP status showed no significant associations with late-life OCT structural measures.

Translational Relevance: OCT imaging results in our population-based sample suggest that neither hypertension, even when present in midlife, nor late-life hypotension are significant risk factors for late-life optic nerve damage.

Introduction

Hypertension affects 33.2% of Americans aged 40 to 59 years and 63% of those aged 60 years and older.[1] While hypertension can be addressed with antihypertensive medications,[2,3] data suggest only 48% of adults with hypertension in the United States have their hypertension well controlled with medication.[1] In both cross-sectional studies of midlife blood pressure (BP) and long-term studies evaluating BP in midlife and late life, hypertension has been shown to impact late-life health outcomes, including cardiovascular disease and mortality,[4–6] stroke,[7] type 2 diabetes mellitus,[8] hearing loss,[9] and dementia,[10] suggesting that the effects of hypertension may develop over many years.

Research evidence remains mixed on the relationship between hypertension and retinal ganglion cell/optic nerve health, which can be assessed using optical coherence tomography (OCT). Some studies

have found an association of hypertension with thinner retina thickness[11] and increased prevalence of retinal nerve fiber layer (RNFL) defects.[12] Hypertension and higher BP have been both positively[13–15] and negatively[16] correlated with glaucoma, but most studies argue against an association between the two.[17–20] Hypotension, which can be the result of overtreating hypertension using antihypertensive medications, has also been linked to structural eye changes. Some reports have associated low diastolic blood pressure (DBP),[15] low perfusion pressure (BP – intraocular pressure [IOP]),[15,16] and low diastolic perfusion pressure (DBP – IOP) with primary open-angle glaucoma (POAG).[13,15,16,20,21] One analysis, among 232 participants of the Thessaloniki Eye Study, associated having DBP <90 mmHg due to antihypertensive treatment with decreased optic disc rim area,[22] but a more recent analysis of the data found no association between antihypertensive treatment and POAG among 2554 participants.[23] Conflicting findings from cross-sectional studies may be due to study limitations. In particular, the cross-sectional use of blood pressures may poorly represent long-term BP trends that influence the development of health outcomes and diseases in late life.[24–26] Longitudinal BP measures are a better assessment of cardiovascular health,[27] which may lead to conditions such as optic nerve damage over a period of many years.

The connection between long-term BP status and late-life optic nerve measures remains unknown, but elucidating this relationship is crucial to understanding the ocular benefits and risks of BP status and any subsequent late-life eye outcomes. To explore this association, we utilized data from the Atherosclerosis Risk in Communities (ARIC) and Eye Determinants of Cognition (EyeDOC) studies. Participants in the ARIC study had their BP recorded over nearly three decades. OCT retinal measures, including macula thickness of the ganglion cell complex (GCC) and peripapillary RNFL thickness, were obtained from EyeDOC, a later ancillary study of ARIC participants. Here, we examine the relationship of long-term BP status, accounting for both midlife and late life, with these late-life OCT measures of optic nerve structure.

Methods

Participants

The ARIC study is an ongoing cohort study that recruited 15,792 participants from four communities in the United States between 45 and 64 years of age from 1987 to 1989.[28] BP measures were taken at six visits from 1987 to 2017 (Fig. 1). The EyeDOC study ($n = 1073$) is an ancillary study of ARIC participants who were enrolled and examined between May 2017

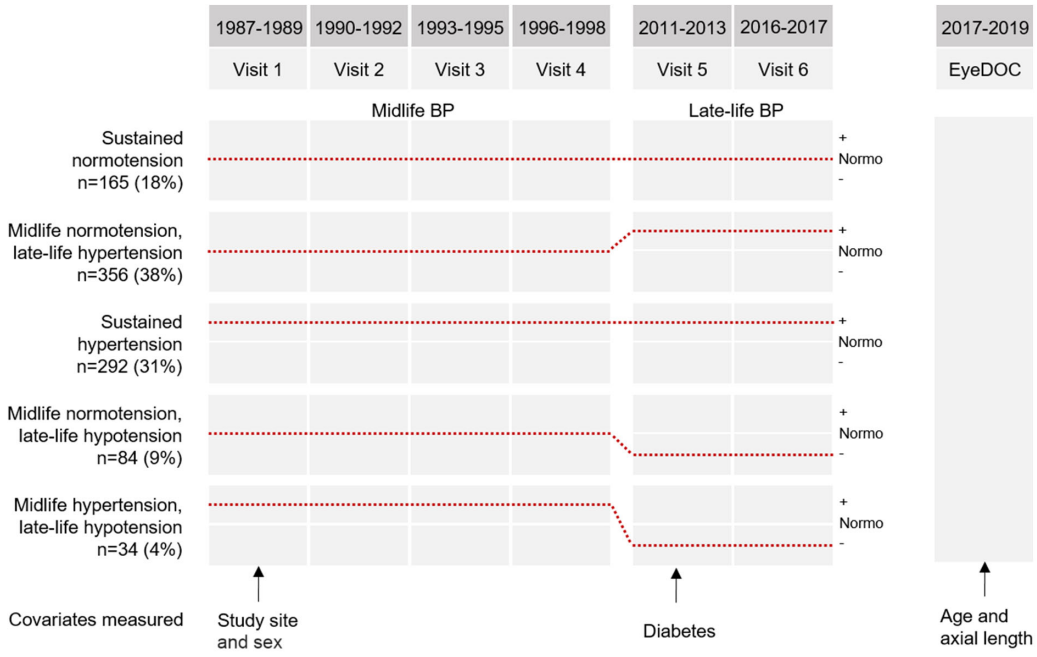

Figure 1. ARIC and EyeDOC study timelines and long-term blood pressure patterns ($n = 931$). +, hypertension; Normo, normotension; −, hypotension. *Dotted red line*: relative BP level. Participants with midlife hypertension/late-life normotension were not included in the primary analysis because of small sample size ($n = 6$). Blood pressures were grouped as midlife (visits 1–4) and late life (visits 5–6).

and June 2019. EyeDOC participants included black individuals from Jackson, Mississippi, and mostly white individuals from Washington County, Maryland. Thus, study site was tied to race. Visual function measures and retinal imaging were taken at the EyeDOC visit and retinal pathology was assessed by ophthalmologists at the Wilmer Eye Institute using criteria from the Early Treatment Diabetic Retinopathy Study Retinal Grading Protocol, the International Vitreomacular Traction Study Group Classification of Macular Hole, and the system of International Nomenclature for Optical Coherence Tomography Panel.[29–31] Institutional review board/ethics committee approval was obtained for the ARIC study and EyeDOC study at the respective ARIC sites, and all participants gave written informed consent at each ARIC and EyeDOC visit. Research adhered to the tenets of the Declaration of Helsinki.

Inclusion and Exclusion Criteria

The study sample included all those enrolled in the EyeDOC study with at least two consecutive BP measures from visits 1 to 4 and BP measures at both visits 5 and 6 ($n = 1032$), with the following exceptions. Participants with indications of overt retinal eye disease other than glaucoma (e.g., macula edema, age-related macular degeneration, diabetic retinopathy, proliferative retinopathy, and retinal vessel occlusion) were excluded ($n = 31$) in this study, since these conditions may affect OCT retinal outcomes. Glaucoma was not excluded because its occurrence may be related to BP status. Eight nonwhite participants in Washington County, 60 participants without quality OCT imaging, and 8 participants with axial length (AL) <19 mm were excluded for a final analytic sample of 931 eyes of 931 participants (Supplementary Fig. S1). Note that some participants were excluded based on more than one criterion. Participants without GCC measures were excluded from GCC analyses ($n = 13$), and participants without RNFL measures were excluded from RNFL analyses ($n = 76$). In the adjusted analyses, participants missing information for diabetes ($n = 17$) at visit 5 were also excluded.

Blood Pressure Measurements and Classification

Systolic blood pressure (SBP) and DBP were measured at visits 1 to 4 with a random zero sphygmomanometer and at visits 5 and 6 with an automated sphygmomanometer. BP was assessed with seated participants after a 5-minute rest period. At each visit, two to three BP measures were taken with at least 30 seconds separating each measure. BP was calculated as the mean of the final two measurements. At each visit, hypertension was defined as SBP >140 mmHg or DBP >90 mmHg or if participants reported use of antihypertensive medication in the past 2 weeks. Hypotension was defined as SBP <90 mmHg or DBP <60 mmHg, regardless of use of antihypertensive medication and superseding hypertension classification.[10,32]

BP measures were categorized as midlife from visits 1 to 4, between the mean ages of 50.7 and 59.6 years, and late life from visits 5 to 6, between the mean ages of 74.2 and 79.1 years, similar to prior reports linking long-term BP status with hearing and cognition.[9,10] In midlife, participants were assigned as having midlife hypertension if they satisfied criteria for hypertension at two or more consecutive visits and were otherwise considered to have midlife normotension, consistent with Walker et al.[10] Hypotension was not delineated in midlife since it is rarely seen. Classifications for late-life BP status incorporated data from both visits 5 and 6, providing increased confidence about late-life BP status compared to using data from a single visit. This contrasts with Walker et al.,[10] who used only visit 5 data for late life, and Ting et al.,[9] who used only visit 6 data for late life. Late-life hypertension was defined as meeting the definition for hypertension at both visits 5 and 6, and late-life hypotension was defined as meeting the definition for hypotension at both visits 5 and 6. The remaining participants with BP measures at both visits 5 and 6 were considered late-life normotensive. Participants missing BP measures at either visit 5 or 6 were excluded from the study. Using these definitions, participants were grouped into one of five long-term BP patterns (Fig. 1 and Supplementary Table S1): sustained normotension, defined as normotension in midlife and late life; midlife normotension, late-life hypertension; sustained hypertension, defined as hypertension in midlife and late life; midlife normotension, late-life hypotension; and midlife hypertension, late-life hypotension.

Midlife and late-life SBP and DBP were defined as the mean of available SBP or DBP measures from visits 1 to 4 for midlife and visits 5 and 6 for late life. Mean arterial pressure (MAP) for each visit was calculated using the following formula: $MAP = (2/3)DBP + (1/3)SBP$. Midlife and late-life MAP were defined as the mean of available MAP measures from visits 1 to 4 for midlife and visits 5 and 6 for late life.

OCT Retinal Measures

Total thickness of the macular GCC and peripapillary RNFL was obtained from OCT scans of one

eye of each participant, captured with an RTVue-XR Avanti system spectral OCT system (OptoVue; AngioVue, Fremont, CA, USA). Both eyes were scanned in a random 10% sample of study participants, and one eye was scanned in the remaining 90% sample of study participants.[33] The study eye, one eye for each participant, was chosen based on a participant's ARIC study ID: if the last digit in the ARIC ID was odd, the left eye was chosen, and if the last digit in the ARIC ID was even, the right eye was chosen. Scans were obtained after pupillary dilation with the patient positioned in the instrument, per protocol. The scan had an A-scan rate of 70,000 scans/s using a light source centered on 840 nm. Scans were screened for quality based on signal strength index ([SSI], SSI $\geq$44 for GCC; SSI $\geq$37 for RNFL).[34] Ocular biometry (IOL Master V.5.4; Carl Zeiss, Meditec, Oberkochen, Germany) was used to determine AL (mm). Participants with AL <19 mm were excluded. AL was imputed in nine eyes from nine participants, who were missing AL measures, using the mean AL measures from other eyes with the same spherical equivalent.

RNFL was normalized by AL using the following formula: RNFL(AL normalized) = RNFL(machine exported) $\times$ AL(biometry measured)/23.7 mm; 23.7 mm is the AL from a standard eye. Based on findings from the Advanced Imaging for Glaucoma Study Group that RNFL thickness depended significantly on AL,[35] RNFL thickness was normalized to obtain a true RNFL measure.

Covariates

Adjusted analyses accounted for age; AL; sex; study site, which was tied to race; and diabetes. Age and AL were obtained at the EyeDOC visit. Diabetes was defined at visit 5 as fasting glucose $\geq$126 mg/dL or nonfasting glucose $\geq$200 mg/dL or use of medication for diabetes or self-report of a physician's diagnosis of diabetes.

Statistical Methods

One-way analysis of variance testing was used to look for differences in continuous variables across BP patterns while χ^2 testing was used for categorical variables. Fisher's exact test was used to compare use of antihypertensive medication at any visit across BP patterns due to expected small frequency (<5) in the midlife hypertension/late-life hypotension pattern.

To visualize the relationship between BP as a continuous variable and OCT measures (GCC and RNFL thickness), locally weighted scatterplot smoothing (LOWESS) was used with MAP measures from midlife and late life.

To assess the relationship between long-term BP patterns and late-life OCT measures, multivariable linear modeling was used with the sustained normotension pattern as the reference. Beta coefficients were calculated, which are reported as deltas—the difference in GCC or RNFL thickness between the reference and the long-term BP pattern being analyzed. Unadjusted and adjusted models were evaluated. Analyses were also stratified by study site/race. Analyses were conducted using Stata version 17 (StataCorp, College Station, TX, USA).

Sensitivity Analyses

To explore how measured BP, regardless of antihypertensive medication treatment, was associated with late-life OCT measures, hypertension was redefined as SBP >140 mmHg or DBP >90 mmHg, regardless of use of antihypertensive medication.

Results

In total, 1,073 eyes of 1,073 participants were examined in the EyeDOC study. Of these, 1,032 participants had BP measures at both visits 5 and 6; 101 participants were removed, mostly because of low-quality OCT imaging or having retinal pathology other than glaucoma (Supplementary Fig. S1). Due to small sample size, participants with midlife hypertension/late-life normotension were excluded from the primary analysis ($n = 6$). The final analytic sample consisted of 931 eyes of 931 participants—918 (99%) had GCC measured and 855 (92%) had RNFL measured. Compared to participants in the final analytic sample, excluded participants were older, more likely to have diabetes at visit 5, and more likely to report use of antihypertensive medication at visit 1. Excluded participants also had higher mean SBPs in midlife and late life, along with higher mean DBPs in midlife.

Figure 1 shows the prevalence of each long-term BP pattern, and Table shows participant characteristics, grouped by BP pattern. Mean age at the EyeDOC visit was 80.4 $\pm$ 4.3 years (standard deviation), 63% were female, and 45% self-identified as black. Mean follow-up time from visit 1 to the EyeDOC visit was 29.7 $\pm$ 1.0 years, and mean follow-up time from visits 1 to 6 was 28.4 $\pm$ 0.9 years. Of the participants, 35% had

Table. Demographic and OCT Measures Among All Participants by Long-Term Blood Pressure Pattern ($n = 931$)

Characteristic	Sustained Normotension	Midlife Normotension, Late-Life Hypertension	Sustained Hypertension	Midlife Normotension, Late-Life Hypotension	Midlife Hypertension, Late-Life Hypotension	*P* Value
Number[a]	165	356	292	84	34	
Demographics						
Age, mean (SD), y	79.7 (4.1)	80.2 (4.4)	80.3 (4.1)	81.9 (4.4)	82.3 (4.8)	<0.001
Female, *n* (%)	100 (60.6)	209 (58.7)	198 (67.8)	54 (64.3)	24 (70.6)	0.14
Male, *n* (%)	65 (39.4)	147 (41.3)	94 (32.2)	30 (35.7)	10 (29.4)	
Community (race), *n* (%)						
Jackson, MS (black)	50 (30.3)	154 (43.3)	191 (65.4)	13 (15.5)	9 (26.5)	<0.001
Washington County, MD (white)	115 (69.7)	202 (56.7)	101 (34.6)	71 (84.5)	25 (73.5)	
Health, *n* (%)						
V5 diabetes	29 (17.7)	130 (37.0)	116 (40.9)	27 (32.5)	17 (53.1)	<0.001
Baseline[b] use of antihypertensive medication	2 (1.2)	24 (6.7)	164 (56.2)	2 (2.4)	17 (50.0)	<0.001
Use of antihypertensive medication at any visit	52 (31.5)	350 (98.3)	291 (99.7)	69 (82.1)	34 (100.0)	<0.001
Blood pressure, mean (SD), mmHg						
Midlife SBP	106.4 (8.2)	117.2 (8.9)	130.7 (13.7)	113.9 (12.4)	127.9 (12.4)	<0.001
Midlife DBP	66.3 (6.4)	71.9 (6.6)	80.0 (8.0)	66.2 (6.5)	72.8 (6.4)	<0.001
Late-life SBP	126.0 (10.2)	132.6 (13.4)	136.1 (15.2)	121.5 (14.3)	126.9 (17.2)	<0.001
Late-life DBP	66.6 (6.7)	67.4 (7.0)	69.6 (7.8)	53.2 (3.3)	53.8 (3.8)	<0.001
OCT measures and ocular characteristics, mean (SD)						
GCC thickness, µm	90.8 (10.3)	90.1 (10.3)	89.4 (11.9)	91.1 (12.3)	90.4 (7.7)	0.62
RNFL (AL normalized) thickness, µm	89.9 (11.2)	91.2 (11.6)	90.1 (12.2)	90.6 (11.2)	86.8 (12.0)	0.31
Axial length,[c] mm	23.6 (1.2)	23.6 (1.0)	23.6 (1.0)	23.5 (1.1)	23.6 (1.4)	0.89

Percentages (%) are in reference to the total number of participants within a blood pressure pattern. V5, visit 5.

[a]There were 17 participants missing information for diabetes who were excluded in adjusted analyses. Thirteen participants missing GCC measures were excluded in GCC analyses, and 76 participants missing RNFL measures were excluded in RNFL analyses.

[b]Baseline use of antihypertensive medication was measured at visit 1 (1987–1989).

[c]AL was assessed when measuring GCC thickness and when measuring RNFL thickness. AL assessed when measuring RNFL thickness was used if available. Otherwise, AL assessed when measuring GCC thickness was used for the remaining participants ($n = 76$).

diabetes at visit 5, and 86% of participants reported use of antihypertensive medication at any visit, including most participants with late-life hypotension (82% of participants with midlife normotension/late-life hypotension and 100% of participants with midlife hypertension/late-life hypotension). In a sensitivity analysis where hypertension was redefined using BP measures alone (SBP >140 mmHg or DBP >90 mmHg), the distribution of participants in BP patterns markedly changed compared to the distribution in the primary analysis (Supplementary Fig. S2).

Associations Between BP Patterns and GCC Thickness

Mean GCC thickness was 90.1 ± 10.9 µm for all participants, 90.8 ± 10.3 µm for those with sustained

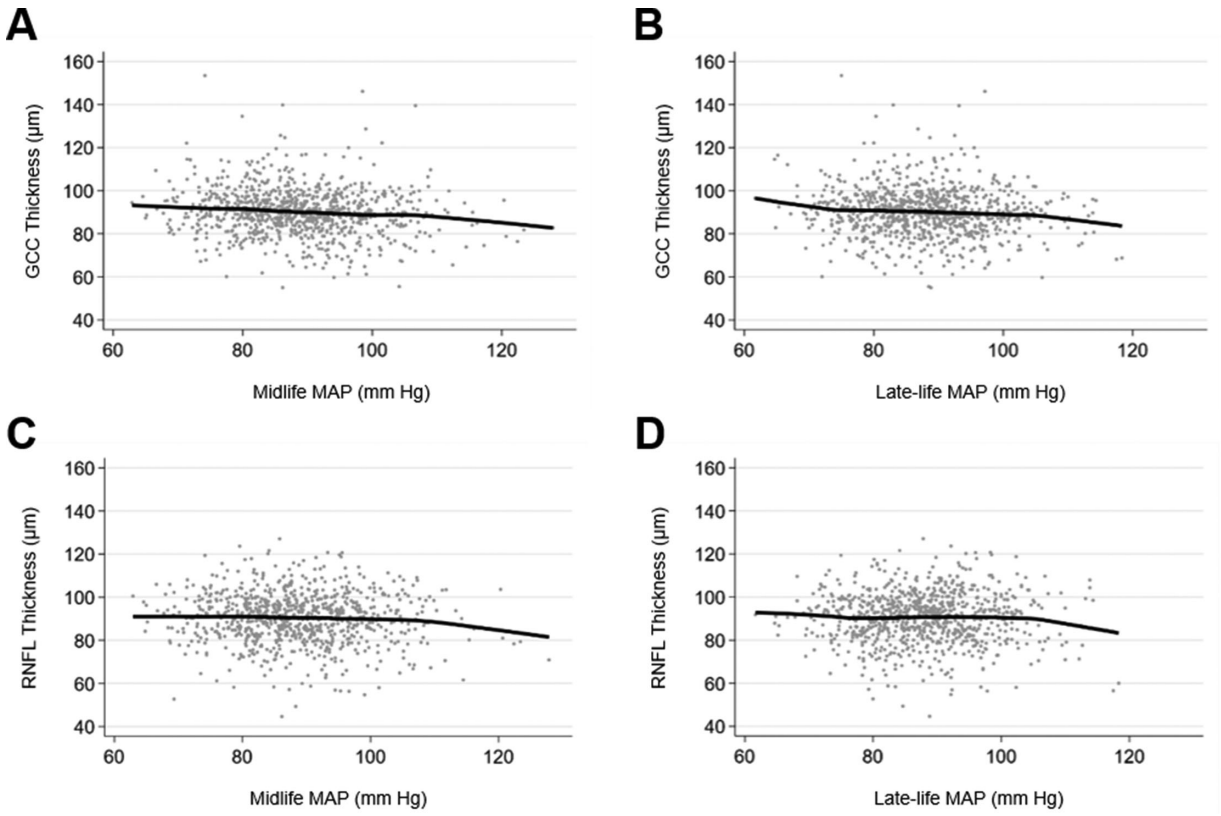

Figure 2. Scatterplots with LOWESS of late-life OCT measures and midlife and late-life MAP. Scatterplots with LOWESS of (A) GCC thickness with midlife MAP, (B) GCC thickness with late-life MAP, (C) RNFL thickness with midlife MAP, and (D) RNFL thickness with late-life MAP. *Dots*: individual MAP measures with corresponding late-life OCT measure; *line*: LOWESS. All RNFL measurements were normalized by axial length.

normotension, 90.1 ± 10.3 µm for those with midlife normotension/late-life hypertension, 89.4 ± 11.9 µm for those with sustained hypertension, 91.1 ± 12.3 µm for those with midlife normotension/late-life hypotension, and 90.4 ± 7.7 µm for those with midlife hypertension/late-life hypotension, with no statistically significant differences between groups (Table). No associations were found between long-term BP and GCC thickness, as judged by visual inspection of LOWESS lines on scatterplots of MAP and GCC thickness, which showed little variation of GCC thickness with changes in MAP (Figs. 2A, 2B). In the unadjusted and adjusted multivariable linear models, participants in the four anomalous BP patterns did not have differences in GCC thickness as compared to participants with sustained normotension (Fig. 3). For example, in the adjusted analyses, participants with sustained hypertension had no significant difference in GCC thickness compared to participants with sustained normotension (delta = 0.17 µm; 95% confidence interval [CI], −2.01 to 2.35), nor did participants with midlife hypertension/late-life hypotension (delta = −0.43 µm, 95% CI, −4.58 to 3.72) (Fig. 3B). The unadjusted and adjusted analyses stratified by site (Fig. 3), along with adjusted analyses with IOP as an additional covariate (data not shown), yielded similar results. Sensitivity analyses, one that defined hypertension by blood pressure alone and another that only included normative participants without glaucoma (Supplementary Fig. S3 and Supplementary Fig. S4), also yielded similar results.

Associations Between BP Patterns and RNFL Thickness

Mean RNFL thickness was 90.4 ± 11.7 µm for all participants, 89.9 ± 11.2 µm for those with sustained normotension, 91.2 ± 11.6 µm for those with midlife normotension/late-life hypertension, 90.1 ± 12.2 µm for those with sustained hypertension, 90.6 ± 11.2 µm for those with midlife normotension/late-life hypotension,

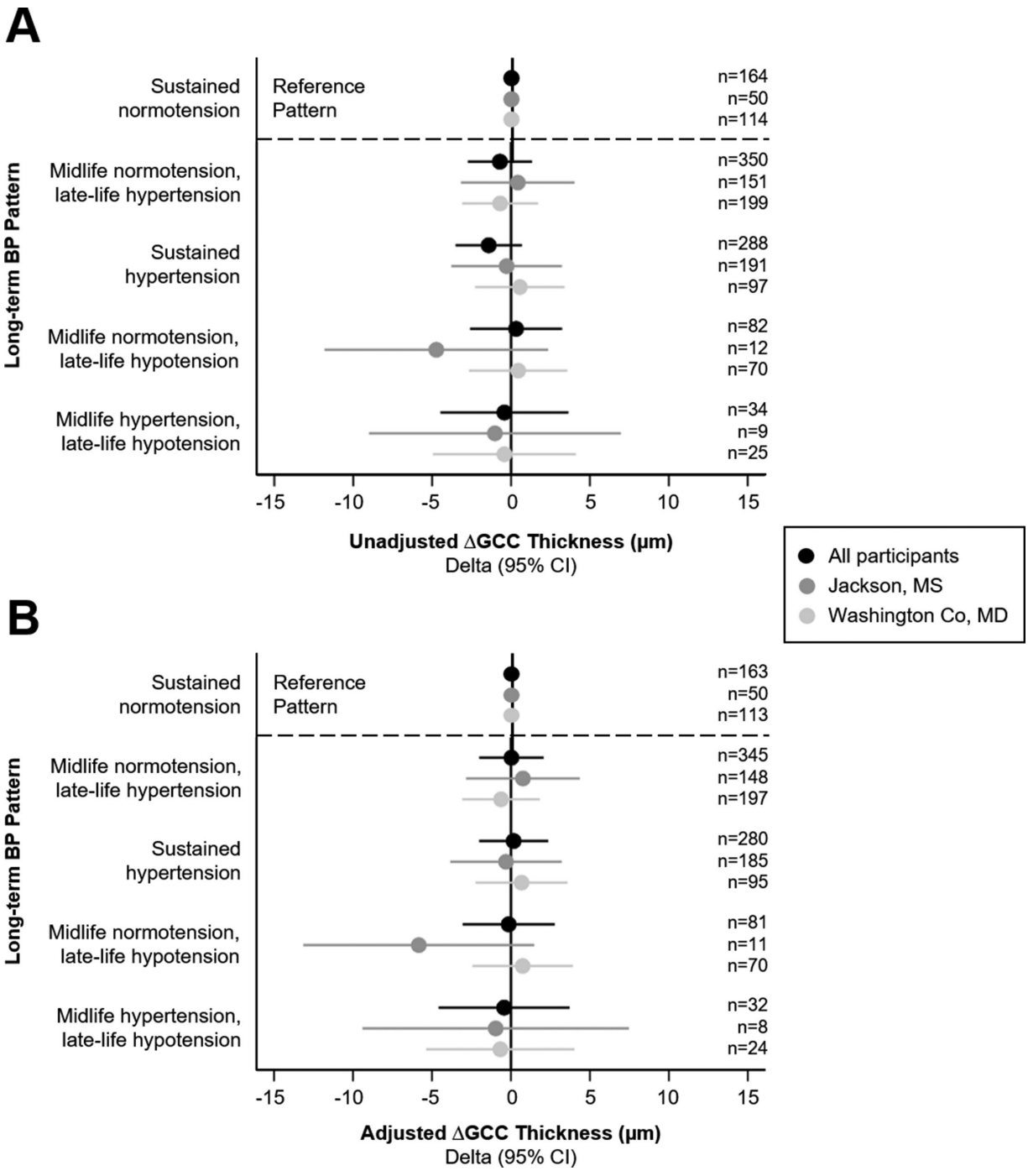

Figure 3. Association of late-life GCC thickness with long-term blood pressure pattern in (A) unadjusted ($n = 918$) and (B) adjusted analyses ($n = 901$). Co, county. Multivariable linear modeling was used to evaluate associations between BP patterns and late-life GCC thickness. Adjusted analyses accounted for the following covariates: age at EyeDOC visit, study site (for all participants), sex, axial length assessed when measuring GCC thickness, and diabetes at visit 5. The adjusted analysis had 17 fewer participants, who were missing information for diabetes. Site-specific analyses were conducted among Jackson participants only and Washington County participants only.

and 86.8 ± 12.0 µm for those with midlife hypertension/late-life hypotension, with no statistically significant differences between groups (Table). No associations were found between long-term BP and RNFL thickness, as judged by visual inspection of LOWESS lines on scatterplots of MAP and RNFL thickness, which showed little variation of RNFL thickness with changes in MAP (Figs. 2C, 2D). In the unadjusted and adjusted multivariable linear models, participants in the four anomalous BP patterns did

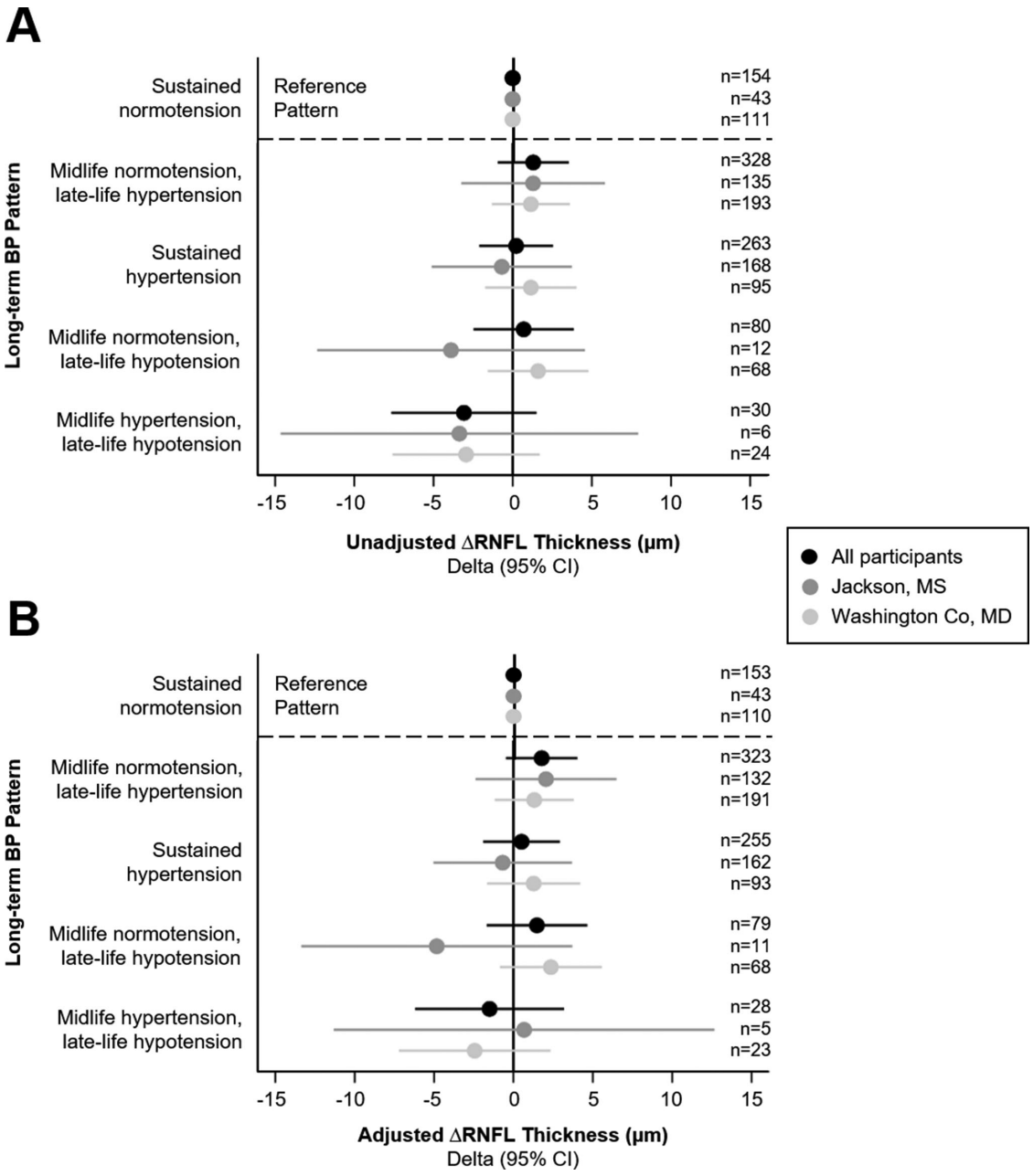

Figure 4. Association of late-life RNFL thickness with long-term blood pressure pattern in (A) unadjusted ($n = 855$) and (B) adjusted analyses ($n = 838$). Multivariable linear modeling was used to evaluate associations between BP patterns and late-life RNFL thickness. Adjusted analyses accounted for the following covariates: age at EyeDOC visit, study site (for all participants), sex, axial length assessed when measuring RNFL thickness, and diabetes at visit 5. The adjusted analysis had 17 fewer participants, who were missing information for diabetes. Site-specific analyses were conducted among Jackson participants only and Washington County participants only. All RNFL measurements were normalized by axial length.

not have differences in RNFL thickness as compared to participants in the sustained normotension pattern (Fig. 4). For example, in the adjusted analyses, participants with sustained hypertension had no significant difference in RNFL thickness compared to participants with sustained normotension (delta = 0.51 μm; 95% CI, −1.91 to 2.92), nor did participants with midlife hypertension/late-life hypotension (delta = −1.50 μm, 95% CI, −6.20 to 3.19) (Fig. 4B). The unadjusted and adjusted analyses stratified by site (Fig. 4), along with adjusted analyses with IOP as an additional covariate (data not shown), yielded similar results. Sensitivity analyses, one that defined hypertension by blood pressure alone

and another that only included normative participants without glaucoma (Supplementary Fig. S5 and Supplementary Fig. S6), also yielded similar results.

Discussion

In this study of a large sample of community-based black and white older adults, no relationship was found between long-term BP patterns, which consisted of various combinations of hypertension, hypotension, and normotension, and late-life OCT measures of optic nerve structure. Compared to the sustained normotension BP pattern, none of the four anomalous BP patterns had differences in GCC or RNFL thickness that were significant or clinically meaningful, defined as a difference in GCC or RNFL thickness of ≥8 µm.[36] These findings from a large, population-based survey of black and white individuals suggest that in most cases, neither anomalous BP nor its management should be considered a meaningful risk factor for optic nerve damage.

Some definitions are important in interpreting the results of this study. First, the definition of a clinically meaningful difference in GCC or RNFL thickness, which was a difference ≥8 µm, was based on a previous study that found that a mean decrease of 8 µm in RNFL thickness, compared to the mean RNFL thickness of healthy subjects, was associated with initial visual field loss.[36] We note that this 8-µm threshold for a clinically meaningful difference may not be generalizable to GCC thickness. Second, use of antihypertensive medication was included in the definition of hypertension because an individual with nonhypertensive BP (SBP <140 mmHg and DBP <90 mmHg) on these medications is biologically different from an individual with nonhypertensive BP not on these medications. For example, Topouzis et al.[22] observed differences in optic disc rim area and cup area between participants with normal DBP (DBP <90 mmHg) as a result of antihypertensive medication treatment and participants with normal DBP not due to treatment.

Our results add to the limited literature examining associations between BP and OCT measures of optic nerve structure. Jung et al.[11] examined the relationship between cross-sectional BP and structural eye measures of the retina, including thickness of the total retina, RNFL, ganglion cell layer, and inner plexiform layer. They found that increasing DBP was correlated with thinner ganglion cell and inner plexiform layers, but these findings are limited by use of BP at a single time and a small sample of 62 participants.[11] In contrast, we found that no hypertensive BP pattern (midlife normotension/late-life hypertension, sustained hypertension, midlife hypertension/late-life hypotension) was correlated with GCC or RNFL thickness.

Hypotension can occur due to antihypertensive medication overuse, and in this study, most participants with late-life hypotension reported use of antihypertensive medication during at least one visit (Table). Analyses associating hypotension, lower blood pressures, or antihypertensive treatment with optic nerve measures and disease have mixed results.[15,22,23,37] In 2006, Topouzis et al.[22] found that participants with DBP <90 mmHg as a result of antihypertensive medication treatment had decreased optic disc rim area and increased cup area compared to those with DBP <90 mmHg not on antihypertensive medication. More recently, Jammal et al.[37] associated lower MAP and DBP, when adjusted for IOP, with greater rates of RNFL loss. In contrast, we found that no hypotensive BP pattern (midlife normotension/late-life hypotension and midlife hypertension/late-life hypotension) was correlated with GCC or RNFL thickness.

A major reason behind the different results in our study compared to the study from Jammal et al.[37] could be differences in participant population. Jammal et al.[37] examined a clinical population in which 57% of participants were diagnosed as glaucoma suspect and 24% of participants were diagnosed as having POAG. On the other hand, our study consisted of a population-based sample in which only 5% of participants ($n = 48$) had glaucomatous optic nerve damage. There are many differences between clinical populations and population-based samples, which tend to be hard to assess. One possible explanation is that the relationship between BP and OCT retinal structural measures is different in the setting of disease, such as glaucoma, as opposed to the setting of a general population. Additionally, Jammal et al.[37] adjusted for IOP in their analyses, which yielded significant associations. Given the large number of participants who had glaucoma or were glaucoma suspect, many of the participants in their study were likely taking medication to treat IOP. We caution adjusting for IOP as a covariate when participants are being treated for IOP. For example, if treated eyes were found to have lower IOP than nontreated eyes, the results from an analysis may be influenced by IOP. Lastly, we would like to acknowledge differences in sample sizes and follow-up time between the two studies. Jammal et al.[37] used a large clinical sample, 7501 eyes of 3976 participants, compared to our sample of 931 eyes of 931 participants, and had a mean follow-up time of 4.0 years for BP measures, compared to our mean follow-up time of 28.4 years for BP measures.[37]

While we found no significant associations of long-term BP with late-life OCT measures in primary and sensitivity analyses, there were some associations of note. When hypertension was defined by BP measures alone in adjusted analyses, RNFL thickness of participants with midlife hypertension/late-life normotension ($n = 57$) was 3.04 µm thinner (95% CI, −6.21 to 0.13) compared to that of participants with sustained normotension ($n = 587$) (Supplementary Fig. S5B). Similar results were obtained when IOP was added as an additional covariate (data not shown). Overall, our results indicate that BP did not impact structural optic nerve measures in late life in this population. BP measures, irrespective of antihypertensive medication use, showed no relationship with late-life GCC or RNFL thickness.

In our community-based sample of black and white individuals, we found no significant or clinically meaningful associations between long-term BP and late-life measures of optic nerve structure in what is the first study, to our knowledge, to investigate the relationship between the two. These results support prior studies that found no relationship between hypertension or antihypertensive treatment and glaucoma, suggesting that BP is not a significant risk factor for optic nerve damage in the general population.

Strengths and Limitations

Strengths of this study are the assessment of BP over almost 30 years and use of a large, community-based sample of black and white participants aged over 70 years. Standardized protocols were utilized to assess structural eye measures, and OCT scans were screened for image quality and retinal pathology.

This study has several limitations. There is evidence of a U-shaped association between blood pressure and glaucoma, with both high BP and low BP associated with an increased risk of glaucoma,[38] and our study may be limited in detecting associations at the more extreme ends of the BP spectrum (Fig. 2). Additionally, our study sample may suffer from selection bias since it only includes those who survive into their upper 70s/80s, with the mean age of participants being 80.4 years. Third, some analyses had modest sample sizes, limiting our ability to detect moderate differences in OCT thickness (below 5 µm) between long-term BP patterns. Fourth, dips in MAP that are undetected in this study may be important to optic nerve structure. Melgarejo et al.[39] utilized 24-hour ambulatory BP monitoring, a method we did not use, and found that longer and deeper dips in MAP were associated with increased risk of open-angle glaucomatous optic neuropathy. Fifth, the criteria used to define BP patterns resulted in some intrapattern heterogeneity. For example, a participant could be hypotensive at visit 5 and hypertensive at visit 6 or vice versa, but that participant would be classified as having late-life normotension ($n = 11$). Sixth, this study did not include data regarding the use of ocular hypotensive medications, which would have been used as an additional covariate in sensitivity analyses with IOP as a covariate. Seventh, this study lacks information on the specific antihypertensive medication patients were taking, dosing, and whether medication regimens were changed over the 30-year study period. Lastly, most participants in this study were on antihypertensive medication, including most late-life hypotensive participants, lowering study power by making the reference BP pattern (sustained normotension) smaller.

Conclusion

Findings from this community-based sample of older adults suggest that hypertension, even when present in midlife, and late-life hypotension do not appear to be a significant risk factors for late-life optic nerve damage. When caring patients, practitioners should be hesitant in attributing abnormalities in optic nerve structural measures to hypertension, hypertensive treatment, or hypotension.

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References

1. Fryar CD, Ostchega Y, Hales CM, Zhang G, Kruszon-Moran D. Key findings data from the National Health and Nutrition Examination Survey. *NCHS Data Brief*. 2017;(289):1.
2. Elliott WJ. Systemic hypertension. *Curr Probl Cardiol*. 2007;32(4):201–259.
3. Messerli FH, Williams B, Ritz E. Essential hypertension. *Lancet*. 2007;370(9587):591–603.
4. Petruski-Ivleva N, Viera AJ, Shimbo D, et al. Longitudinal patterns of change in systolic blood pressure and incidence of cardiovascular disease. The Atherosclerosis Risk in Communities (ARIC) study. *Hypertension*. 2016;67(6):1150.
5. Yano Y, Stamler J, Garside DB, et al. Isolated systolic hypertension in young and middle-aged adults and 31-year risk for cardiovascular mortality: the Chicago Heart Association Detection Project in Industry Study. *J Am Coll Cardiol*. 2015;65(4):327.
6. McAreavey D, Vidal JS, Aspelund T, et al. Midlife cardiovascular risk factors and late-life unrecognized and recognized myocardial infarction detect by cardiac magnetic resonance: ICELAND-MI, the AGES-Reykjavik Study. *J Am Heart Assoc*. 2016;5(2):1–10.
7. Portegies MLP, Mirza SS, Verlinden VJA, et al. Mid-to late-life trajectories of blood pressure and the risk of stroke: the Rotterdam study. *Hypertension*. 2016;67(6):1126–1132.
8. Kramer CK, Von Mühlen D, Barrett-Connor E. Mid-life blood pressure levels and the 8-year incidence of type 2 diabetes mellitus: the Rancho Bernardo Study. *J Hum Hypertens*. 2009;24(8):519–524.
9. Ting J, Jiang K, Du S, et al. Longitudinal blood pressure patterns from mid- to late life and late-life hearing loss in the Atherosclerosis Risk in Communities Study. *Journals Gerontol Ser A*. 2022;77(3):640–646.
10. Walker KA, Sharrett AR, Wu A, et al. Association of midlife to late-life blood pressure patterns with incident dementia. *JAMA*. 2019;322(6):535–545.
11. Jung S, Bosch A, Kohler N, et al. Evidence of neurodegeneration in individuals with only mildly elevated blood pressure. *J Hypertens*. 2019;37(12):2389–2397.
12. Jie R, Xu L, Wang YX, et al. Ten-year incidence of retinal nerve fiber layer defects: the Beijing Eye Study 2001/2011. *Invest Ophthalmol Vis Sci*. 2015;56(9):5118–5124.
13. Bonomi L, Marchini G, Marraffa M, Bernardi P, Morbio R, Varotto A. Vascular risk factors for primary open angle glaucoma: the Egna-Neumarkt Study. *Ophthalmology*. 2000;107(7):1287–1293.
14. Langman MJS, Lancashire RJ, Cheng KK, Stewart PM. Systemic hypertension and glaucoma: mechanisms in common and co-occurrence. *Br J Ophthalmol*. 2005;89(8):960.
15. Memarzadeh F, Ying-Lai M, Chung J, Azen SP, Varma R. Blood pressure, perfusion pressure, and open-angle glaucoma: the Los Angeles Latino Eye Study. *Invest Ophthalmol Vis Sci*. 2010;51(6):2872.
16. Leske MC, Wu SY, Nemesure B, Hennis A. Incident open-angle glaucoma and blood pressure. *Arch Ophthalmol*. 2002;120(7):954–959.
17. Wang S, Xu L, Jonas JB, et al. Major eye diseases and risk factors associated with systemic hypertension in an adult Chinese population: the Beijing Eye Study. *Ophthalmology*. 2009;116(12):2373–2380.
18. Deb A, Kaliaperumal S, Rao V, Sengupta S. Relationship between systemic hypertension, perfusion pressure and glaucoma: a comparative study in an adult Indian population. *Indian J Ophthalmol*. 2014;62(9):917.
19. Wong T, Mitchell P. The eye in hypertension. *Lancet*. 2007;369(9559):425–435.
20. Quigley HA, West SK, Rodriguez J, Munoz B, Klein R, Snyder R. The prevalence of glaucoma in a population-based study of Hispanic subjects: Proyecto VER. *Arch Ophthalmol (Chicago, Ill 1960)*. 2001;119(12):1819–1826.
21. Tielsch JM, Katz J, Sommer A, Quigley HA, Javitt JC. Hypertension, perfusion pressure, and primary open-angle glaucoma: a population-based assessment. *Arch Ophthalmol*. 1995;113(2):216–221.
22. Topouzis F, Coleman AL, Harris A, et al. Association of blood pressure status with the optic disk structure in non-glaucoma subjects: the Thessaloniki Eye Study. *Am J Ophthalmol*. 2006;142(1):60–67.e1.
23. Topouzis F, Wilson MR, Harris A, et al. Association of open-angle glaucoma with perfusion pressure status in the Thessaloniki Eye Study. *Am J Ophthalmol*. 2013;155(5):843–851.e1.
24. Fuchs FD, Whelton PK. High blood pressure and cardiovascular disease. *Hypertension*. 2020;75(2):285–292.
25. Lim HM, Chia YC, Ching SM, Chinna K. Number of blood pressure measurements needed to estimate long-term visit-to-visit systolic blood pressure variability for predicting cardiovascular risk: a 10-year retrospective cohort study in a primary care clinic in Malaysia. *BMJ Open*. 2019;9(4):25322.

26. Brueren MM, Van Limpt P, Schouten HJA, De Leeuw PW, Van Ree JW. Is a series of blood pressure measurements by the general practitioner or the patient a reliable alternative to ambulatory blood pressure measurement? A study in general practice with reference to short-term and long-term between-visit variability. *Am J Hypertens*. 1997;10(8):879–885.
27. Pickering TG, Hall JE, Appel LJ, et al. Recommendations for blood pressure measurement in humans and experimental animals: Part 1: Blood pressure measurement in humans—a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. *Circulation*. 2005;111(5):697–716.
28. Wright JD, Folsom AR, Coresh J, et al. The ARIC (Atherosclerosis Risk In Communities) Study: JACC Focus Seminar 3/8. *J Am Coll Cardiol*. 2021;77(23):2939–2959.
29. Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs—an extension of the modified Airlie House Classification: ETDRS Report Number 10. *Ophthalmology*. 2020;127(4):S99–S119.
30. Staurenghi G, Sadda S, Chakravarthy U, Spaide RF. Proposed lexicon for anatomic landmarks in normal posterior segment spectral-domain optical coherence tomography: the IN•OCT consensus. *Ophthalmology*. 2014;121(8):1572–1578.
31. Duker JS, Kaiser PK, Binder S, et al. The International Vitreomacular Traction Study Group classification of vitreomacular adhesion, traction, and macular hole. *Ophthalmology*. 2013;120(12):2611–2619.
32. Oyetunji TA, Chang DC, Crompton JG, et al. Redefining hypotension in the elderly: normotension is not reassuring. *Arch Surg*. 2011;146(7):865–869.
33. Dong Y, Guo X, Arsiwala-Scheppach LT, et al. Association of optical coherence tomography and optical coherence tomography angiography retinal features with visual function in older adults. *JAMA Ophthalmol*. 2022;140(8):809–817.
34. Zhang X, Iverson SM, Tan O, Huang D. Effect of signal intensity on measurement of ganglion cell complex and retinal nerve fiber layer scans in Fourier-domain optical coherence tomography. *Transl Vis Sci Technol*. 2015;4(5):7.
35. Huang D, Chopra V, Lu ATH, Tan O, Francis B, Varma R. Does optic nerve head size variation affect circumpapillary retinal nerve fiber layer thickness measurement by optical coherence tomography? *Invest Ophthalmol Vis Sci*. 2012;53(8):4990–4997.
36. Alasil T, Wang K, Yu F, et al. Correlation of retinal nerve fiber layer thickness and visual fields in glaucoma: a broken stick model. *Am J Ophthalmol*. 2014;157(5):953.
37. Jammal AA, Berchuck SI, Mariottoni EB, Tanna AP, Costa VP, Medeiros FA. Blood pressure and glaucomatous progression in a large clinical population. *Ophthalmology*. 2022;129(2):161–170.
38. Leeman M, Kestelyn P. Glaucoma and blood pressure. *Hypertens (Dallas, Tex 1979)*. 2019;73(5):944–950.
39. Melgarejo JD, Eijgen J V, Maestre GE, et al. Open-angle glaucomatous optic neuropathy is related to dips rather than increases in the mean arterial pressure over 24-h. *Am J Hypertens*. 2022;35(8):703–714.