Blood Pressure Measures and Incident Primary Open-Angle Glaucoma

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Received: August 29, 2022
Accepted: November 14, 2022
Published: December 5, 2022

Citation: Macri C, Wong CX, Tu SJ, et al. Blood pressure measures and incident primary open-angle glaucoma. *Invest Ophthalmol Vis Sci.* 2022;63(13):3. https://doi.org/10.1167/iovs.63.13.3

Purpose. To investigate the association of systemic blood pressure and incident primary open-angle glaucoma (POAG) using a large open-access database.

Methods. Prospective cohort study included 484,268 participants from the UK Biobank without glaucoma at enrollment. Incident POAG events were recorded through assessment visits, hospital inpatient admissions, and primary care data. Blood pressure measures included systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP), and mean arterial pressure (MAP). Repeated measurements throughout the study period were analyzed as time-varying covariables. The parameters were modeled as both categorical and continuous nonlinear variables. The primary outcome measure was the relative hazard of incident POAG.

Results. There were 2390 incident POAG events over 5,715,480 person-years of follow-up. Median follow-up was 12.08 years. In multivariable analyses, compared to SBP and PP in the normal range (SBP, 120–130 mmHg; PP, 40–50 mmHg), higher SBP and PP were associated with an increased risk of incident POAG (linear trend $P = 0.038$ for SBP, $P < 0.001$ for PP). Specifically, SBP of 130 to 140 mmHg or 140 to 150 mmHg was associated with a 1.16 higher hazard of incident POAG (95% CI, 1.01–1.32 and 1.01–1.33, respectively), whereas a PP of greater than 70 mmHg was associated with a 1.13 higher hazard of incident glaucoma (95% CI, 1.00–1.29). In multivariable models, no statistically significant associations were found for DBP or MAP with incident glaucoma. These findings were similar when blood pressure measures were modeled as continuous variables.

Conclusions. Higher SBP and PP were associated with an increased risk of incident POAG. Further studies are required to characterize these relationships better.

Keywords: blood pressure, pulse pressure, arterial pressure, open-angle glaucoma, UK Biobank

Glaucoma is the leading cause of irreversible blindness worldwide.[1] Primary open-angle glaucoma (POAG) is the most common type,[2] with an estimated global burden of 65.5 to 79.6 million afflicted people in 2020.[2,3] Despite extensive investigation, intraocular pressure (IOP) is currently the only modifiable risk factor to prevent disease progression.[4] The development and progression of POAG are influenced by complex gene/environment interactions,[5] as well as non-modifiable factors, including IOP, age, family history, central corneal thickness, and optic disc features.[6]

The relationship between blood pressure and POAG remains poorly understood. Incident POAG has previously shown associations with diurnal low ocular perfusion pressure and low systolic blood pressure (SBP).[7] Furthermore, systemic hypertension[8] and nocturnal dips in SBP[9] have been associated with visual field progression. The effect of these vascular parameters is thought to be mediated by influencing ocular blood flow; however, the mechanisms contributing to possible glaucomatous damage are not well defined.[10] Evidence supporting an association between blood pressure and POAG is largely derived from cross-sectional studies, although most have not shown a significant relationship.[11] Similarly, the few longitudinal studies that exist have observed inconsistent associations.[7,12–14] Comparing results among studies is complicated by their different approaches to representing blood pressure, inconsistent definitions of high and low blood pressure, incomplete range of blood pressure parameters included, and boundaries used to discretize categories. Pulse pressure (PP) is often not examined, despite a clear relationship with cardiovascular disease and mortality.[15] Where mean arterial pressure has been included, variable formulas have been used.[16] Furthermore, linearity is often assumed when blood pressure has been examined as a continuous variable,[16] despite a hypothesized U-shaped association.[17] In the current study, we aimed to investigate the strength and shape of the

associations among the full range of blood pressure parameters, including systemic SBP, diastolic blood pressure (DBP), mean arterial pressure (MAP), and PP with incident POAG in participants of the UK Biobank.

Methods

The UK Biobank study is a prospective cohort study including over 500,000 participants 40 to 69 years of age, recruited between 2006 and 2010 across the United Kingdom.[18] Subjects were recruited by postal invitation sent to individuals proximate to one of 22 assessment centers throughout England, Wales, and Scotland. The North-West Multicentre Research Ethics Committee approved the UK Biobank study. This research was conducted using the UK Biobank Resource under Application Number 62103.

All participants attended an initial assessment center visit. During this visit, participants completed a touchscreen questionnaire and verbal interview to collect baseline sociodemographic, lifestyle, and health information. In addition, baseline standardized anthropomorphic and blood pressure measurements were recorded.

A subset of participants returned for further visits after the baseline assessment visit. Additional interview data and physical measurements were collected after the baseline assessment visit during a repeat assessment visit between 2012 and 2013, an imaging visit (for non-ophthalmic radiological imaging) in 2014, and a repeat imaging visit in 2019. The additional and subsequent measurements of blood pressure were included in the analysis as a time-varying covariable.

The latest update of UK Biobank participant data at the time of writing was March 31, 2021. Prospective hospital inpatient data including diagnostic and operation codes are available via linked national databases and updated periodically. In addition, linked primary care data are currently available for approximately 45% of the UK Biobank participants. The primary care data provide information on clinical events such as diagnostic and operation codes and were included in the analyses. Primary care data linkage for the rest of the cohort is currently ongoing.

Participants

All participants of the UK Biobank were considered for eligibility. Participants were included in the study if they had at least one systolic and diastolic automated or manual blood pressure reading at baseline. Participants were excluded if they had glaucoma of any type at baseline (identified from self-report touchscreen questionnaire, verbal interview, linked hospital inpatient data, and linked primary care data) or had prior glaucoma surgery (determined from linked hospital inpatient data, linked primary care data, or self-report). The specific codes identifying these cases are listed in the Supplementary Material.

Assessment of Blood Pressure

SBP and DBP were measured by a registered nurse on the seated individual from the right brachial artery using the Omron 705 IT electronic blood pressure monitor (Omron Healthcare Europe BV, Hoofddorp, Netherlands). If the largest cuff size was too small for the participant, or if the electronic blood pressure monitor failed to produce a reading, a sphygmomanometer with an inflatable cuff was used with a stethoscope. Automated blood pressure readings were preferred when available; otherwise, manual measures were used for analyses. Two sets of systolic and diastolic blood pressure measurements were recorded in the baseline visit. The first measurement was taken at the beginning of the visit after the first interview section. The second measurement was taken at the end of the visit. Two sets of blood pressure measurements were also taken at any subsequent assessment or imaging visits after the baseline visit. The final SBP and DBP for a visit were calculated as the average of the two measurements taken during that visit. MAP was calculated from the final averaged SBP and DBP readings using the formula MAP = DBP + 1/3(SBP − DBP).[19] Similarly, PP was calculated as PP = SBP − DBP.[20] Routine blood pressure measurements were recorded at the initial assessment visit, follow-up assessment visit, initial imaging visit, and follow-up imaging visit.

Assessment of Other Covariates

Body mass index (BMI) was calculated using the height and weight measurements taken during the initial assessment center visit: BMI = weight (kg)/height (m^2). Standing height was measured using a seca 202 device (seca, Hamburg, Germany). Weight was measured using the Tanita BC-418MA body composition analyzer (Tanita, Tokyo, Japan), or standard scales for participants that were medically unsuitable or refused the analyzer. BMI was then categorized according to the World Health Organization definition into underweight (BMI < 18.5), healthy weight ($18.5 \leq$ BMI < 25), overweight ($25 \leq$ BMI < 30), or obese (BMI ≥ 30).

Prevalent diabetes and cataract surgery were noted from self-report, hospital inpatient data, and primary care data. The codes used to identify these cases are listed in the Supplementary Material. Education was categorized as secondary (Advanced [A] levels/Advanced Subsidiary [AS] levels or equivalent, Ordinary [O] levels/General Certificate of Secondary Education [GCSE] or equivalent, Certificate of Secondary Education [CSE] or equivalent), tertiary (National Vocational Qualification [NVQ] or Higher National Diploma [HND] or Higher National Certificate [HNC] or equivalent, college or university degree), other (other professional qualifications), or none of the above.

Assessment of Outcomes

Incident cases of POAG were identified as the first occurrence of the diagnostic code for POAG in hospital inpatient or primary care data, if available. The codes used to identify POAG are listed in the Supplementary Material. Subsequent occurrences of POAG in the same patient were not included.

Statistical Analyses

Participant characteristics were presented by status of incident POAG. The distributions of the continuous variables were visually inspected for symmetry using density plots. All plots were adequately symmetric, and continuous variables were summarized with mean, standard

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deviation (SD), and range and compared using linear model ANOVA. Categorical variables were summarized by number and proportion and compared using the χ^2 test.

Cox regression was used to assess the effect of SBP on the risk of incident POAG. Blood pressure was included as a time-updated variable to account for updated measurements collected through additional subsequent measurements taken during repeat visits. Participants were considered at risk from the initial assessment center visit until either diagnosis of POAG or censorship. Participants were censored by death, loss to follow-up, or end of available follow-up. The end of available follow-up was defined as the date of the latest available Showcase data update of hospital inpatient admission data (March 31, 2021).

Analyses with blood pressure represented as categorical predictors were conducted for SBP (<120, 120–130, 130–140, 140–150, ≥150 mmHg), DBP (<70, 70–80, 80–90, 90–100, ≥100 mmHg), MAP (<90, 90–100, 100–110, 110–120, ≥120 mmHg), and PP (<40, 40–50, 50–60, 60–70, ≥70 mmHg). Blood pressure was included in the model as a time-updated variable. This updates the value of the blood pressure measure for participants who had routine blood pressure recorded at subsequent study visits. Multivariable models included adjustment for age, gender, ethnicity (white, asian, black, other), BMI (underweight, healthy weight, overweight, obese), and education (secondary, tertiary, other, none of the above), Townsend deprivation index quintiles (index of material deprivation based on census variables describing car and house ownership, overcrowding, and unemployment), smoking status (never, previous, current), alcohol status (never, previous, current), diagnosis of diabetes at baseline, and prevalent cataract surgery at baseline. These covariates were included as baseline variables only and were not time-updated. Results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs), including a *P* value for the linear trend of ordered categories for blood pressure parameters.

The second analysis included blood pressure parameters as continuous variables. SBP, DBP, MAP, and PP were included in the aforementioned multivariable model as time-updated continuous predictors modeled as restricted cubic splines with four knots placed at the 5th, 35th, 65th, and 95th percentiles, defined a priori.[21] The relative hazard ratios and 95% CIs for POAG were plotted on the *y*-axis as a function of SBP, DBP, MAP, or PP on the *x*-axis. The normal blood pressure values of SBP = 120 mmHg, DBP = 80 mmHg, MAP = 93.3 mmHg, and PP = 40 mmHg were used as reference values. Dashed vertical lines represent the knot locations for the restricted cubic splines.

The proportional hazards assumption was tested graphically using Schoenfeld residuals. No violations were present. A two-tailed *P* value was set at 0.05 for statistical significance. Analyses were performed using R 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria) with the packages *rms* (v6.2-0)[22] and *survival* (v3.2-11).[23]

We conducted a further sensitivity analysis excluding participants who had taken antihypertensive medication anytime during the study. The antihypertensive medication classes included angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, and diuretics (thiazide and thiazide-like diuretics, loop diuretics, and potassium-sparing diuretics). The codes used to identify these medications are listed in the Supplementary Material.

Results

Baseline Characteristics

The study population consisted of 484,268 participants after the exclusion of 1834 who did not have at least one SBP or DBP measurement at baseline, 5071 who had any type of glaucoma diagnosis at baseline, 189 who had prevalent glaucoma surgery, and 11,128 missing other variables (stepwise exclusion of 2356 for ethnicity, 1883 for smoking, 532 for alcohol, 607 for Townsend deprivation index, 3692 for education, and 2058 for BMI). The mean age was 56.5 years, and 54.5% were female. Mean ± SD baseline SBP parameters were SBP = 137.8 ± 18.6 mmHg, DBP = 82.3 ± 10.1 mmHg, MAP = 100.8 ± 12.0 mmHg, and PP = 55.6 ± 13.6 mmHg. There were 2390 incident POAG events over 5,715,480 person-years of follow-up with a median follow-up duration of 12.08 years. The baseline characteristics of the study participants are presented in Table 1. All participants had baseline SBP and DBP measurements. Over the study period, 43,642 participants recorded two SBP measurements, 9396 had three, and 494 had four. Similarly, 43,645 participants recorded two DBP measurements, 9400 had three, and 494 had four. Primary care data were available for 223,335 of the included participants (46.1%).

Categorical Analyses

Kaplan–Meier plots shown in Figure 1 demonstrate statistically significant differences in incident POAG associated with SBP, PP, and MAP ($P < 0.001$ for all) but not DBP ($P = 0.79$). Overall higher SBP, PP, and MAP were associated with higher rates of incident POAG. In univariate analyses, there was a statistically significant increased risk of incident POAG for SBP > 130 mmHg compared to an SBP of 120 to 130 mmHg (Table 2). This finding remained statistically significant in multivariable analyses for SBP from 130 to 150 mmHg and was statistically significant for linear trend across all categories after adjustment for age, gender, ethnicity, BMI, education, Townsend deprivation index, smoking status, alcohol status, diabetes, and previous cataract surgery ($P = 0.038$). In comparison, there was no statistically significant association between DBP and the risk of incident POAG in the unadjusted models ($P = 0.46$) or adjusted models ($P = 0.80$).

In univariate analyses, compared to a pulse pressure of 40 to 50 mmHg, PP < 40 mmHg was associated with a reduced risk of incident POAG, whereas PP categories > 50 mmHg were associated with incrementally higher hazards of incident POAG (Table 2). In multivariable analyses after adjustment for confounders, only PP ≥ 70 mmHg remained significantly associated with an increased hazard of incident POAG, although the linear trend remained significant across all categories ($P = 0.015$). Compared to a MAP of 90 to 100 mmHg, lower MAP (<90 mmHg) was associated with a reduced risk of incident POAG, whereas MAP between 100 and 120 mmHg was associated with a higher hazard of incident POAG in univariate analyses, but these associations were no longer statistically significant in multivariable analyses once adjusted for confounders.

Continuous Analyses

Figure 2 depicts the HRs and 95% CIs for each blood pressure parameter modeled as continuous variables and

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Table 1. Comparison of Baseline Characteristics Between Participants With and Without Incident POAG

	No POAG (n = 481,878)	POAG (n = 2390)	P
Age (y), mean ± SD	56.5 ± 8.1	61.7 ± 6.2	<0.001
Female, n (%)	262,873 (54.6)	1219 (51.0)	<0.001
Ethnicity, n (%)			<0.001
White	456,634 (94.8)	2216 (92.7)	
Asian	10,659 (2.2)	56 (2.3)	
Black	7482 (1.6)	85 (3.6)	
Other	7103 (1.5)	33 (1.4)	
Smoking, n (%)			<0.001
Never	264,207 (54.8)	1299 (54.4)	
Previous	166,886 (34.6)	915 (38.3)	
Current	50,785 (10.5)	176 (7.4)	
Alcohol use, n (%)			0.037
Never	21,121 (4.4)	111 (4.6)	
Previous	17,079 (3.5)	107 (4.5)	
Current	443,678 (92.1)	2172 (90.9)	
Townsend deprivation index, n (%)			0.91
1st quintile	97,487 (20.2)	471 (19.7)	
2nd quintile	96,714 (20.1)	496 (20.8)	
3rd quintile	96,585 (20.0)	483 (20.2)	
4th quintile	96,409 (20.0)	473 (19.8)	
5th quintile	94,683 (19.6)	467 (19.5)	
Diabetes, n (%)	24,537 (5.1)	187 (7.8)	<0.001
Education, n (%)			<0.001
None	81,480 (16.9)	529 (22.1)	
Other	29,745 (6.2)	190 (7.9)	
Tertiary	188,296 (39.1)	843 (35.3)	
Secondary	182,357 (37.8)	828 (34.6)	
Prior cataract surgery, n (%)	9676 (2.0)	93 (3.9)	<0.001
BMI, n (%)			0.001
Healthy weight	157,209 (32.6)	830 (34.7)	
Underweight	2505 (0.5)	13 (0.5)	
Overweight	20,4921 (42.5)	1049 (43.9)	
Obesity	117,243 (24.3)	498 (20.8)	
Baseline SBP, mean ± SD	137.8 ± 18.6	141.9 ± 18.3	<0.001
Baseline DBP, mean ± SD	82.3 ± 10.1	82.1 ± 9.8	0.55
Baseline MAP, mean ± SD	100.8 ± 12.0	102.1 ± 11.4	<0.001
Baseline PP, mean ± SD	55.5 ± 13.6	59.8 ± 14.2	<0.001

after adjustment for confounders. Compared to SBP of 120 mmHg, SBP < 120 mmHg showed a statistically significant decreased risk of incident POAG, whereas SBP >120 mmHg was associated with a statistically significant increased risk of incident POAG up to a SBP of approximately 185 mmHg, after which there was no association (Fig. 2). Compared to a DBP of 80 mmHg, a lower DBP between 55 and 70 mmHg was associated with a small statistically significant increased risk of incident POAG but was otherwise statistically nonsignificant for all other ranges. A PP between 50 and 100 mmHg was associated with a statistically significant increased hazard of incident glaucoma compared to a PP of 40 mmHg, but no statistically significant associations were found for MAP. The above findings were not greatly altered after excluding participants who had taken antihypertensive medication in the sensitivity analysis.

Discussion

In this longitudinal cohort analysis of 484,268 UK Biobank participants investigating the full range of blood pressure parameters modeled as both categorical and continuous nonlinear variables, we found that higher SBP and PP were associated with an increased risk of incident POAG. In contrast, no statistically significant association was found with DBP or MAP. In multivariable analyses, SBP of 130 to 150 mmHg (vs. normal 120–130 mmHg) was associated with a 1.16 higher hazard of incident POAG, whereas a PP of greater than 70 mmHg (vs. normal 40–50 mmHg) was associated with a 1.13 higher hazard of incident glaucoma. Furthermore, we performed two different types of blood pressure modeling, with secondary analyses of blood pressure parameters as continuous variables confirming that higher SBP and PP showed a statistically significant higher risk of incident POAG. These findings suggest that, among the various blood pressure indices, SBP and PP may more strongly impact glaucoma risk compared to DBP and MAP. The varied prognostic significance of these differing blood pressure parameters appears to mirror that seen for systemic cardiovascular risk in older patients and adds weight to the potential role of systemic vascular dysfunction in the pathogenesis of POAG.[24–26] Systolic hypertension may thus represent a potential modifiable risk factor for POAG, although further studies are required to characterize this relationship better.

There is substantial heterogeneity in the statistical representation of systemic blood pressure across previous stud-

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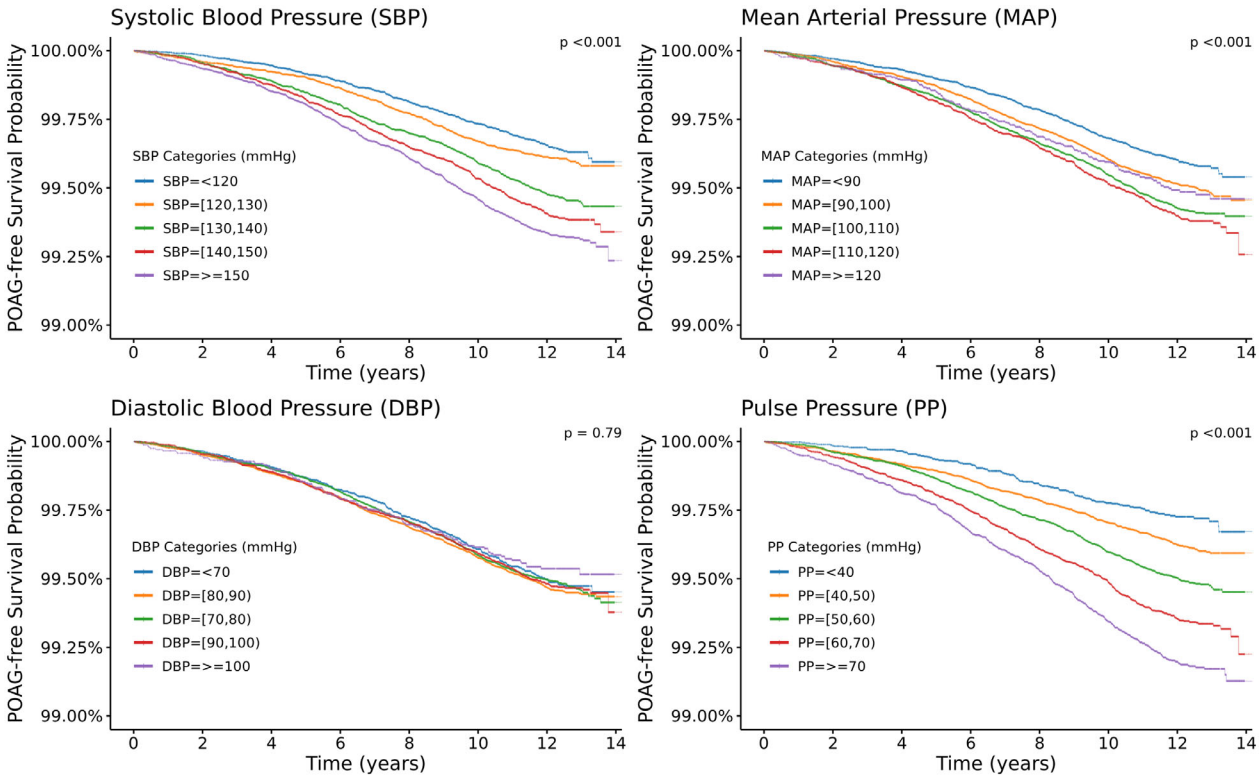

Figure 1. Kaplan–Meier curves for systemic blood pressure parameters.

Table 2. Results of Categorical Analysis

	Analysis			
	Univariate		Multivariate	
Pressure (mmHg)	**HR (95% CI)**	***P* for Linear Trend**	**HR (95% CI)**	***P* for Linear Trend**
SBP		**<0.001**		**0.038**
<120	0.89 (0.76–1.04)		1.02 (0.86–1.19)	
120–130	Reference		Reference	
130–140	**1.34** (1.17–1.53)		**1.16** (1.01–1.32)	
140–150	**1.51** (1.32–1.73)		**1.16** (1.01–1.33)	
≥150	**1.70** (1.5–1.93)		1.12 (0.99–1.28)	
DBP		0.46		0.80
<70	0.96 (0.83–1.1)		0.95 (0.82–1.1)	
70–80	0.97 (0.88–1.07)		0.99 (0.90–1.09)	
80–90	Reference		Reference	
90–100	0.98 (0.87–1.10)		0.99 (0.88–1.11)	
≥100	0.88 (0.72–1.08)		0.93 (0.75–1.14)	
MAP		**<0.001**		0.65
<90	**0.82** (0.73–0.93)		0.92 (0.81–1.05)	
90–100	Reference		Reference	
100–110	**1.16** (1.05–1.28)		1.05 (0.95–1.17)	
110–120	**1.23** (1.09–1.38)		1.05 (0.93–1.19)	
≥120	1.04 (0.87–1.24)		0.86 (0.71–1.03)	
PP		**<0.001**		**0.015**
<40	**0.74** (0.61–0.90)		0.90 (0.74–1.10)	
40–50	Reference		Reference	
50–60	**1.34** (1.19–1.5)		1.05 (0.93–1.18)	
60–70	**1.72** (1.53–1.94)		1.09 (0.96–1.24)	
≥70	**2.15** (1.90–2.42)		**1.13** (1.00–1.29)	

Bold indicates statistical significance.

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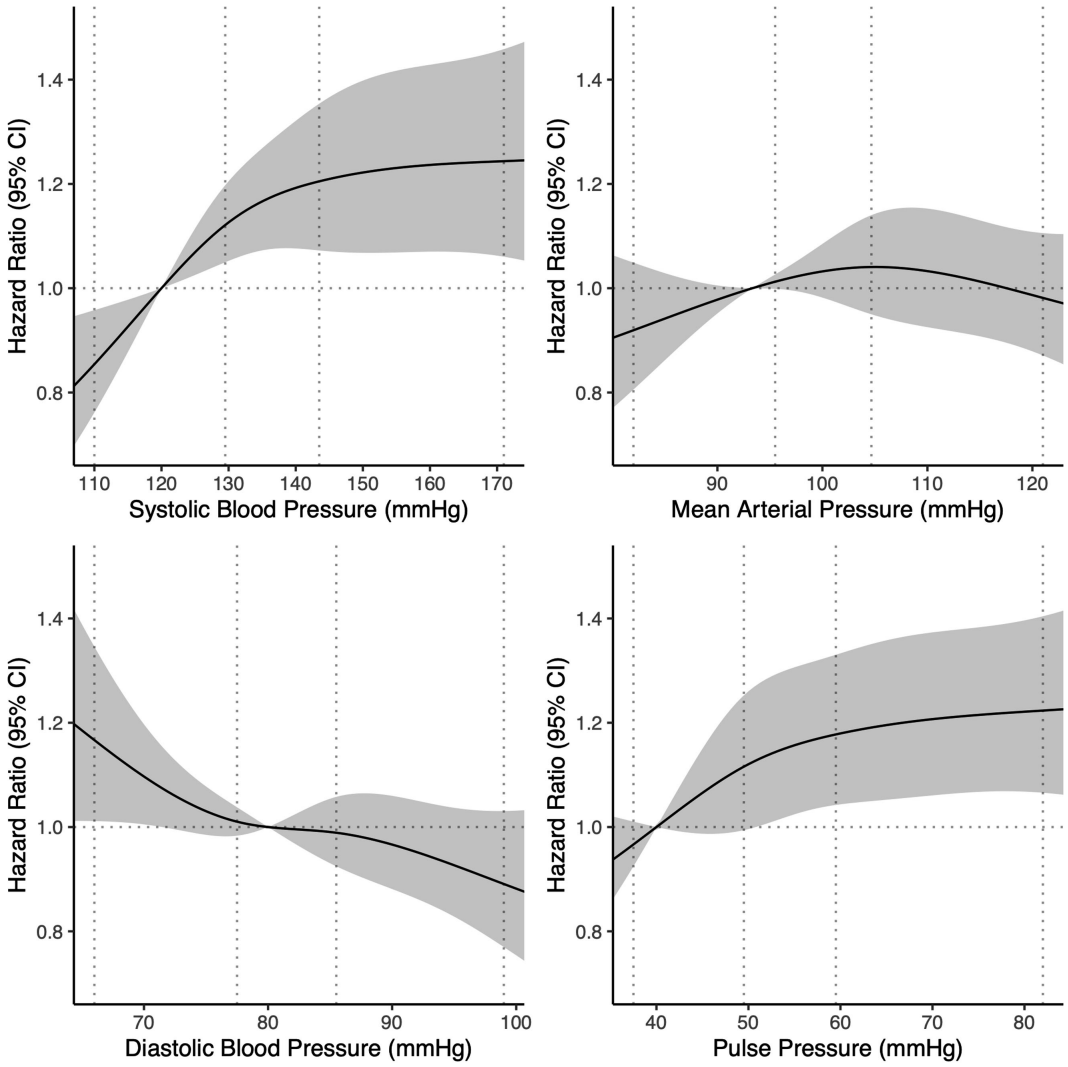

Figure 2. Hazard ratio curves for incident POAG and systemic blood pressure parameters. Blood pressure measures truncated at the 5th and 95th percentiles. The *gray band* represents the 95% confidence interval, and the *Vertical dotted lines* are the knot locations (5th, 35th, 65th, and 95th percentiles).

ies investigating an association with open-angle glaucoma.[16] This variation may contribute to the inconsistent findings and impedes study comparison. Approaches used by previous longitudinal cohort studies have included dichotomization using a cut-point value to determine hypertensive status,[7,27] discretization of blood pressure ranges into categories,[7,13,27] and determining hypertensive status using diagnostic codes or use of antihypertensive medication found in medical records.[28,29] Variation exists even within these approaches. For example, discretization has been defined using quantiles,[7] combinations of quantiles,[7,13] or prespecified ranges.[27] This variation is similarly mirrored in cross-sectional and case-control studies.[16] We modeled blood pressure parameters as both categorical and continuous nonlinear variables. To the best of our knowledge, the latter has not been described before in incident POAG studies. As performed in our analysis, representing blood pressure as restricted cubic splines preserved the continuous nature of the measurement without assuming linearity and was particularly useful in confirming parameters of significance—namely, higher SBP and PP, which were consistently associated with a higher hazard of incident POAG across both analyses.

Our study further supports existing data showing an association between systolic hypertension and an increased risk of POAG. A 2014 meta-analysis by Zhao et al.[11] found greater risk with each 10-mmHg increase in SBP (relative risk [RR] = 1.01; 95% CI, 1.00–1.03) in a dose–response analysis. This estimate, however, was pooled from predominantly cross-sectional and case-control studies. The same meta-analysis found an increased pooled relative risk for POAG comparing participants with hypertension (RR = 1.16; 95% CI, 1.05–1.28) to those without. However, definitions of hypertension differed considerably across study designs, using cut-point values of SBP ranging from >130 to >160 mmHg, antihypertensive medication use, medical records, self-report, and studies including DBP in diagnostic criteria. Most reported positive associations between systemic hypertension and incident POAG are largely derived from cross-sectional studies,[11] with most longitudinal studies unable to confirm such an association.[7,12–14] In contrast, in a longitudinal cohort study of the Korean National Health Insurance System, Jung

et al.[27] found that hypertension (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg) conferred an increased risk of POAG (hazard ratio [HR] = 1.68; 95% CI, 1.53–1.84). Additionally, in a managed care network data study, Newman-Casey et al.[29] found a statistically significant association between hypertension defined by diagnostic coding and incident POAG (HR = 1.17; 95% CI, 1.13–1.22). A detailed characterization of the influence of blood pressure on POAG risk, beyond the presence or absence of hypertension defined by a varying blood pressure level, has thus far been greatly limited. Similarly, exploration of a dose–response relationship is limited by the representation of blood pressure in categories or assuming linearity and by a lack of longitudinal studies. In our study, we analyzed blood pressure indices as both categorical and continuous variables, with both approaches showing that higher SBP, particularly >130 mmHg, was associated with an increased risk of incident POAG. We found no statistically significant association between DBP and incident POAG, in keeping with both the Barbados Eye Study[7] (DBP quartiles of ≤73, 73–80, 80–88, and >88 mmHg, and per 10-mmHg increase) and Rotterdam Eye Study[30] (DBP of <65, 65–74, 75–85, and >85 mmHg, and per standard deviation). These findings complicate the interpretation of incident POAG studies that use elevated DBP as part of the criteria for systemic hypertension if the risk of disease is mediated by SBP alone.

Together with the available literature, our findings suggest that systolic hypertension may represent a modifiable risk factor for glaucoma. It is also possible that hypertension and other cardiovascular risk factors may increase the risk of glaucoma progression.[8] More aggressive hypertension management may be warranted in patients at high risk of POAG, analogous to findings of the SPRINT trial, which showed a reduced risk of fatal and nonfatal cardiovascular events seen with lower blood pressure targets in those at high cardiovascular risk without diabetes.[31] However, overtreatment may complicate aggressive blood pressure lowering, given evidence of disease progression with nocturnal dips in blood pressure.[9] Optimal blood pressure targets for patients with glaucoma remain unclear, and additional prospective studies are required to evaluate this relationship further.

PP represents the difference between SBP and DBP and is considered an index of arterial stiffness, with elevated PP increasingly recognized as a risk factor for cardiovascular disease.[15] The existing literature regarding PP and POAG is mixed. Although the Barbados Eye Study found no apparent relationship between PP (as PP categories of ≤41, 41–51, 51–64, and >64 mmHg, and per 10-mmHg increase) and incident POAG,[7] the Rotterdam Eye Study found a statistically significant association between standard deviations of PP and hypertensive POAG.[32] In a further categorical analysis, compared to PP < 55 mmHg, PPs of 65 to 80 mmHg and >80 mmHg were associated with 2.81 (95% CI, 1.35–5.82) and 2.87 (95% CI, 1.34–6.17) higher odds, respectively, of POAG.[32] Similarly, we found that higher PP, particularly greater than 70 mmHg, was associated with an increased risk of incident POAG, with the relationship appearing to mirror that of SBP. Previous studies have shown that PP may be a better predictor of cardiovascular risk and mortality in older patients compared to the other blood pressure parameters,[33,34] with one study demonstrating that patients 65 and older with PP > 77 mmHg had a 57% increased risk of cardiovascular death compared to those in the lowest quintile.[34] Given the derivation of PP from SBP and DBP, these findings may in part reflect the association between SBP and POAG, but also suggest a potential pathological role for arterial stiffness and subsequent hemodynamic instability in POAG development.

The findings of previous studies examining the association between MAP and incident POAG are also varied. We found no statistically significant association for MAP in our analysis, consistent with Leske et al.,[7] who similarly found no statistically significant association per 10-mmHg increase or by quartiles (MAP of ≤89, 89–98, 98–107, or >107 mmHg). In contrast, in a longitudinal cohort study of the All of Us Research database, Lee et al.[13] observed that low MAP (<83.0 mmHg) was associated with an increased risk of incident POAG (HR = 1.32; 95% CI, 1.04–1.67) compared to medium MAP (83.0 ≤ MAP ≤ 103.3 mmHg). In addition, the authors found no association with high MAP (MAP >103.3 mmHg). At the same time, another longitudinal analysis of participants of the Nurses' Health Study and Health Professionals Follow-Up Study found an increased risk of incident POAG with increasing MAP (HR = 1.05; 95% CI, 1.01–1.09, per 5-mmHg).[35] The conflicting findings in the literature and the lack of association in our study suggest that further investigation is required to understand this relationship better. Several previous studies have shown that the prognostic significance of MAP and DBP in cardiovascular disease decreases with increasing age,[24–26] and this may also be the case for glaucoma. Furthermore, DBP plays the predominant role in the derivation of MAP compared to SBP, which may also account for the lack of association, given that both our study and previous longitudinal studies have found no association between DBP and incident POAG.

Low systemic blood pressure is associated with disease progression among patients diagnosed with POAG, predominantly with low IOP.[4,36,37] Similarly, nocturnal dips in systemic blood pressure are a risk factor for glaucoma progression.[9] Given that systemic hypertension is endemic in many populations,[38] it is not known whether those with untreated low blood pressure fare better, worse, or the same with regard to disease progression relative to those who are treated, and sometimes overtreated, for systemic hypertension. Findings from the Low-Pressure Glaucoma Treatment Study showed that antihypertensive medication was associated with disease progression.[39] One hypothesis for such a relationship is that hypertension results in vascular harm to the optic nerve and that subsequent lowering of blood pressure with treatment results in further limitation of blood flow to the nerve in the setting of vascular dysregulation.[40] We found a linear trend in categorical SBP analyses but an apparent lower hazard compared to normal SBP in continuous modeling. Similarly, the Barbados Eye Study found a trend toward increased hazard of POAG per 10-mmHg SBP increase ($P = 0.05$),[7] although these results were not statistically significant in quantiles or categorical analyses. Our findings suggest that high SBP may be a more important determinant of incident glaucoma risk than low SBP, although the potential protective nature of low SBP requires further investigation. High SBP perhaps leads to initial optic nerve vascular compromise, which is subsequently further exacerbated by low blood pressure, either systolic or diastolic, based on prior work.

Our study has several limitations. First, incident POAG was defined by the presence of diagnostic codes in hospital inpatient admission data or primary care data; therefore, assessment of the primary outcome relies on accurate and comprehensive diagnostic coding. We could not

account for errors or delays in diagnostic coding. In addition, detecting incident POAG in those without primary care data relies on participant inpatient hospital admissions. Similarly, we could not account for undiagnosed cases at baseline or during follow-up. Due to these coding limitations, it is possible the associations seen are with seeking early care or receiving more care due to higher blood pressure rather than POAG. We did not adjust for IOP, refractive error, central corneal thickness, or for cerebrospinal fluid pressure, as these data were only available for a small proportion of UK Biobank participants. Although blood pressure was included as a time-varying variable where available, unfortunately the vast majority of patients did not have repeat blood pressure measurements; therefore, longitudinal changes in blood pressure could not be accounted for in most participants. Finally, it is important to consider that the UK Biobank does not represent the entire UK population, comprised of a predominantly Caucasian population. Overall, 95% of the included cohort were of Caucasian ethnicity. Hypertension prevalence and severity are greater among minority ethnic groups,[41] who also have a greater risk of POAG.[42] Furthermore, participants enrolled were between the ages of 40 and 70 years, thus excluding older adults who may have developed incident glaucoma and may also have higher rates of hypertension. The associations observed in this cohort require further evaluation in other diverse age and ethnic cohorts. In addition, the study exhibits a "healthy volunteer" selection bias,[43] and caution should be used when generalizing findings to the population level. Our analysis also has several strengths, including a standardized and comprehensive collection of sociodemographic, lifestyle, anthropomorphic, and medical information in a large sample size; standardized measurement of blood pressure with large and repeated samples over a long follow-up period of 12 years; and the examination of continuous, nonlinear associations.

In summary, we found that higher SBP and PP were associated with a higher risk of incident POAG, whereas the roles of DBP and MAP were less significant. Systolic hypertension may thus represent a potential modifiable risk factor for POAG, although further studies are required to better characterize these associations.

Acknowledgments

The sponsor or funding organizations had no role in the design or conduct of this research.

Disclosure: **C. Macri**, None; **C.X. Wong**, None; **S.J. Tu**, None; **R. Casson**, None; **K. Singh**, Alcon (C), Allergan (C), Glaukos (C), Ivantis (C), Santen and Sight Sciences (C); **S.Y. Wang**, None; **M.T. Sun**, None

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