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The Association among Blood Pressure, Blood Pressure Medications, and Glaucoma in a Nationwide Electronic Health Records Database

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Purpose: To measure the association among blood pressure (BP), BP medications, and glaucoma using the All of Us Research Program database.

Design: A retrospective, longitudinal cohort study leveraging a national electronic health record (EHR) database administered by the National Institutes of Health.

Participants: Eye patients in the All of Us Research Program database with at least 15 months of follow-up and 1 BP measurement.

Methods: Univariable and multivariable Cox regression models predicted the risk of developing incident open-angle glaucoma (OAG). Mean arterial pressure (MAP) and the number of BP medication classes were entered as time-varying predictors to account for changes over time.

Main Outcome Measures: The risk of developing incident OAG, as defined by billing diagnosis codes.

Results: Of 20 815 eligible eye patients who qualified for this study, 462 developed OAG. Low BP (MAP $<$ 83.0 mmHg) was associated with increased risk of developing OAG (hazard ratio [HR], 1.32; 95% confidence interval [CI], 1.04−1.67). High BP (MAP $>$ 101.3 mmHg) and the number of BP medication classes were not associated with OAG after adjustment for covariates. Other risk factors associated with OAG included being Black (HR, 3.31, 95% CI, 2.63−4.17), Hispanic or Latino (HR, 2.53, 95% CI, 1.94−3.28), Asian (HR, 2.22, 95% CI, 1.24−3.97), older in age (80+ years, HR, 20.1, 95% CI, 9.10−44.5), and diabetic (HR, 1.32, 95% CI, 1.04−1.67). Female gender was associated with decreased hazard of developing OAG (HR, 0.66, 95% CI, 0.55−0.80). No significant interaction was observed between MAP and the number of BP medications on the risk of developing OAG.

Conclusions: We found that low BP is associated with increased risk of developing OAG in a national longitudinal EHR database. We did not find evidence supporting a differential effect of medically treated and untreated low BP. This study adds to the body of literature implicating vascular dysregulation as a potential etiology for the development of OAG, particularly emphasizing the lack of influence of BP medications on this relationship. *Ophthalmology 2022;129:276-284 © 2021 by the American Academy of Ophthalmology*

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Open-angle glaucoma (OAG) is the leading cause of irreversible blindness and affects more than 58 million individuals worldwide.[1,2] Despite this high prevalence, the specific pathogenesis of OAG remains unclear. Numerous large-scale prevalence and epidemiology studies have attempted to identify risk factors contributing to the development of OAG.[3,4] Consistently identified risk factors include age,[2,5,6] high intraocular pressure (IOP),[6–8] family history,[9–11] Black race,[5,12,13] and high myopia.[14–16]

An important and potentially modifiable but inconsistently identified risk factor is aberrant blood pressure (BP). In a follow-up analysis of the Barbados Eye Study, systemic hypertension was associated with decreased risk of developing OAG.[17] Graham et al[18] described how the physiologic nocturnal reduction in BP may be an additional risk factor for glaucoma. These and other studies support the hypothesis that vascular factors may contribute to OAG pathogenesis, because low BP could result in decreased ocular perfusion pressure (OPP), defined as the difference between BP and IOP, and subsequent ischemic damage to the optic nerve.[19–23] Conversely, the Beaver Dam Eye Study found increased BP to be correlated with high IOP, suggesting that optic nerve damage results from systemic hypertension.[24] Further complicating these hypotheses is the role of BP medications and how therapeutically lowered BP compares with physiologically low BP, which has yet to be studied. Clarification of the relationship among BP, BP medications, and incident OAG is critical to understand the underlying pathogenesis of the disease and has

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significant clinical relevance because hypertension and the use of BP medications is highly prevalent among individuals at risk of glaucomatous disease, particularly the elderly.[25]

A new resource that is uniquely suited to address this question is the All of Us Research Program, supported and administered by the National Institutes of Health.[26] Although previous studies have been limited by sample size or cross-sectional experimental design, the All of Us Research Program offers longitudinal and comprehensive health information of more than one-quarter million individuals across the United States. The goal of this study was to use this nationwide database to assess the relationship between BP and the development of incident OAG and identify whether BP medications modify this relationship.

Methods

We conducted a retrospective, longitudinal cohort study using the All of Us Research Program database to assess the effect of BP and BP medications on the risk of developing incident OAG. Because only deidentified data were analyzed, this study is exempt from Stanford University Institutional Review Board approval and is compliant with the requirements of the Declaration of Helsinki.

Data Source

The All of Us Research Program is an effort by the National Institutes of Health to create a longitudinal database of clinical, environmental, lifestyle, and genetic data for 1 million or more people living in the United States.[26] Participants aged older than 18 years living in the United States can join the All of Us Research Program directly through their website (JoinAllOfUs.org) or through over 60 health care provider organizations, which include academic hospital networks, primary care organizations, and the U.S. Department of Veteran Affairs (the complete list can be found at https://www.joinallofus.org/health-care-provider-organizations). Participants are asked to create an All of Us account, consent to share their electronic health record (EHR) and get DNA results, and answer health surveys. Currently, patients who are prisoners, who cannot give consent, and who are younger than 18 years cannot enroll. Data are collected from EHRs, surveys, and other measures to ensure comprehensive and accurate health information. International Classification of Diseases 9th Revision (ICD-9) or 10th Revision (ICD-10) and Systematized Nomenclature of Medicine (SNOMED) diagnosis codes for each clinical encounter were available. Blood pressure records, BP medication history, age, gender, race, smoking status, and diabetes mellitus diagnosis were also available and used in the analyses.

Inclusion/Exclusion Criteria

This study included eye patients, defined as individuals who had seen an eye care provider. All patients were required to have at least 15 months of follow-up constituting a baseline 15-month lookback period before the index date of the study. Patients with baseline OAG during the lookback period were excluded to ensure subsequent OAG diagnoses were incident. Only patients with at least 1 BP recorded were included. Patients with other forms of glaucoma besides OAG were excluded. Patients also filled out past medical history surveys indicating whether they had an OAG diagnosis. Patients with positive survey responses but without concordant OAG billing codes before their survey responses were excluded. Patients with missing BP values (systolic or diastolic) or BP values outside a 0 to 400 mmHg range were excluded. Patients younger than 40 years of age at baseline or missing gender information were also excluded. The cohort design and filtering criteria for the study population are summarized in Figure 1. All ICD-9, ICD-10, and SNOMED codes used in cohort design are listed in Table S1 (available at www.aaojournal.org).

Outcomes

The primary outcome variable was the development of incident OAG, identified by the assignment of an ICD-9, ICD-10, or SNOMED diagnosis code for OAG at any point after the lookback period.

Measures

The primary predictors were BP and number of BP medication classes. The systolic and diastolic BPs over a given month were averaged and converted to mean arterial pressures (MAPs) using the formula:

$$\text{MAP} = \tfrac{1}{3} * \text{systolic BP} + \tfrac{2}{3} * \text{diastolic BP}$$

The MAPs were then divided into quintiles and categorized as low (first quintile), medium (second to fourth quintiles), or high (fifth quintile), with medium as the reference standard. Each patient's oral antihypertensive medications based on EHR and prescription records were grouped into classes and the total number of classes counted for each month, with zero classes as the reference. The following classes were used to group BP medications: thiazide or thiazide type diuretics, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, calcium channel blockers, diuretics, beta-blockers, direct renin inhibitors, alpha-1 blockers, central alpha-2 agonists and other centrally acting drugs, and direct vasodilators. Blood pressure medication classes were adapted from the 2017 Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.[27]

Other variables included age, gender, race, smoking status, and diabetes mellitus diagnosis. Age was recorded as the patient's age at the index date and grouped into 10 year categories, with 40 to 49 years old as the reference comparator. Gender was recorded as male or female. Race was recorded as White, Asian, Black or African American, Hispanic or Latino, or unavailable/other, with White as the reference comparator. Patients without race data were grouped into "Unavailable/Other." Patients were considered diabetic if there was evidence of a diabetes diagnosis via billing codes during the lookback period. Diabetes diagnoses were further verified with past medical history survey responses. Patients were considered smokers if they provided a smoking history of any kind (cigar, hookah, electronic) in a series of smoking-related surveys.

Data Analysis

Data analyses were performed on the All of Us data release version 3.0. Characteristics of the study population that were continuous variables were summarized with mean/standard deviation and compared using the Student *t* test, and categorical variables were summarized with frequency/percentage and compared using the chi-square test. Univariate and multivariate Cox regression models were used to predict the development of incident OAG, with MAP category and number of BP medication classes as primary predictors. A sensitivity analysis was performed by repeating multivariate Cox regression analysis on patients who did not take any BP medications. Secondary

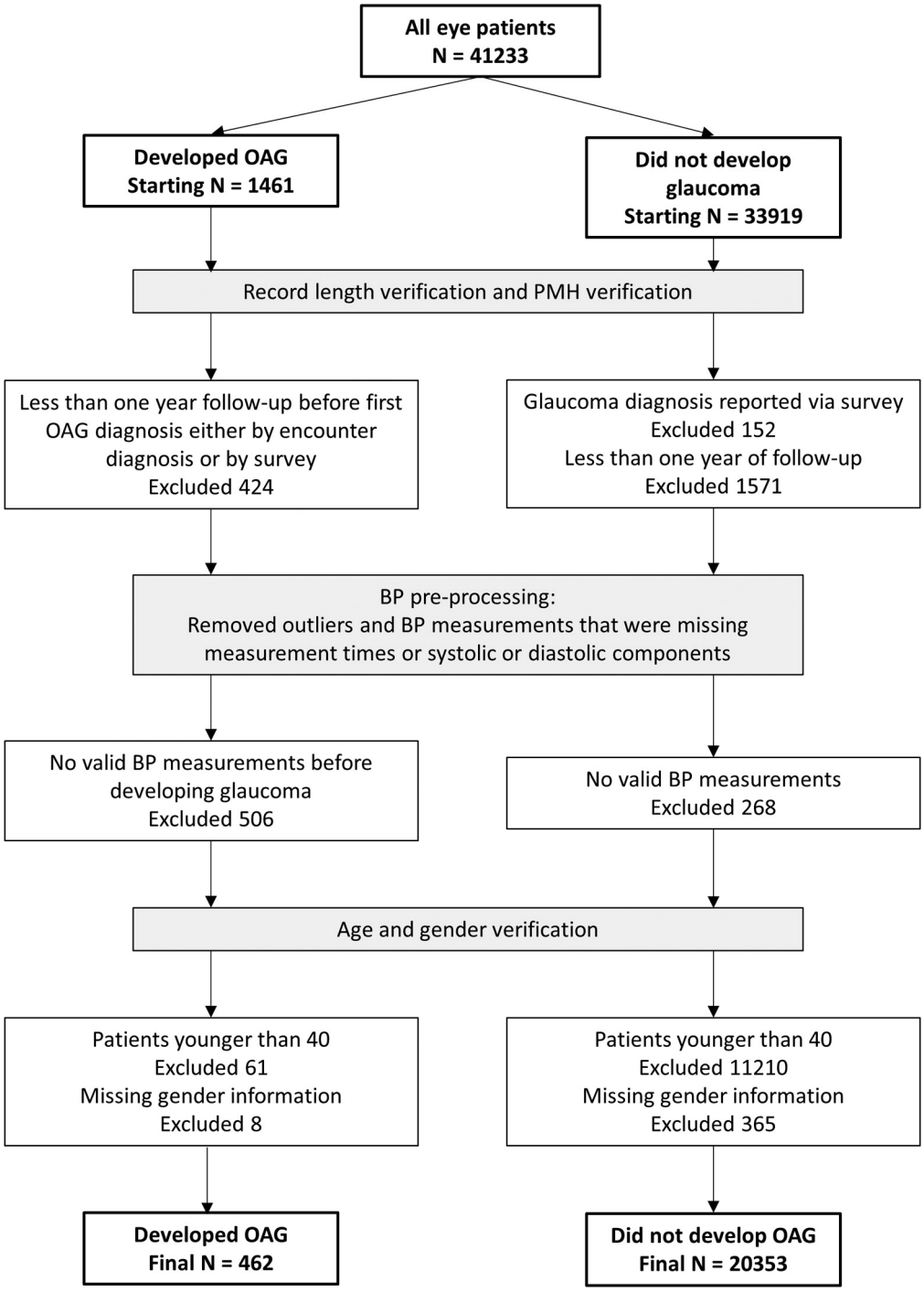

Figure 1. Flowchart illustrating the cohort inclusion and exclusion criteria. BP = blood pressure; OAG = open-angle glaucoma; PMH = past medical history.

analysis was also performed to examine whether any interaction existed between MAP and the number of BP medication classes (0, 1, 2, or 3+) to influence the development of OAG. Because patients had changing BP and medication regimens over time, these variables were entered as time-varying predictors rather than single static values in the regression analyses. This is a standard method to include time-varying predictors in Cox proportional hazards models. Other static predictors included age, gender, race, smoking status, and diabetes diagnoses. For all analysis, $P < 0.05$ was considered statistically significant.

Data preparation and Cox regression analyses were performed using the Python[28] (version 3.7.10) packages, pandas[29] (version 1.2.4) and lifelines[30] (version 0.25.10). Student *t* tests and chi-square tests were performed using the Python scipy[31] (version

1.6.2) package and R survey[32] (version 4.0) package. Second order tests were performed using R[33] (version 4.0.3).

Results

Population Characteristics

There were 20 815 eligible subjects who had undergone eye examinations, among whom 462 developed OAG during the follow-up period. Table 1 summarizes and compares the baseline characteristics of patients who developed OAG compared with nonglaucoma patients. Months of follow-up was significantly shorter in OAG patients compared with nonglaucoma patients (86.0 ± 77.6 and 104.6 ± 74.8, respectively; $P < 0.0001$), because follow-up in OAG patients ended with the first diagnosis of OAG. There was a slight predominance of female gender in nonglaucoma patients compared with OAG patients (65.0% and 56.1%, respectively; $P < 0.0001$). Patients with OAG were significantly older than nonglaucoma patients, with a larger percentage of patients older than 60 years (47.4% and 33.4%, respectively; $P < 0.0001$). The majority of patients were White, and there were significant differences in overall race distribution between OAG and nonglaucoma patients ($P < 0.0001$). There was a greater likelihood of a diabetes diagnosis in OAG patients compared with nonglaucoma patients (21.9% and 17.8%, respectively; $P = 0.0242$), but no significant differences in the percentage of tobacco/nicotine users between the 2 groups. There were also no significant differences between OAG patients and nonglaucoma patients in average MAP or the distribution of low/medium/high MAP categories. Overall, a greater proportion of nonglaucoma patients did not use any BP medications compared with patients who developed OAG (78.0% and 72.7%, respectively; $P = 0.0274$).

Development of Incident OAG

We examined how the development of OAG is related to MAP, BP medication use, and other covariates in both univariable and multivariable Cox proportional hazards regression models. Univariable Cox regression results are presented in Table 2. In univariable analyses, the number of BP medication classes was associated with significantly increased hazard of developing OAG with a dose-response relationship. Each additional class of such medications resulted in a greater hazard ratio (HR) for the development of OAG (1 class: HR, 1.45, 95% confidence interval [CI], 1.12−1.87, $P = 0.00442$; 2 classes: HR, 1.84, 95% CI, 1.40−2.43, $P < 0.0001$; 3+ classes: HR, 2.20, 95% CI, 1.70−2.84, $P < 0.0001$). Neither low nor high MAP was significantly associated with hazard of developing OAG. Being Black or African American race (HR, 2.50, 95% CI, 2.01−3.11, $P < 0.0001$), Hispanic or Latino race (HR, 1.99, 95% CI, 1.54−2.56, $P < 0.0001$), or Asian race (2.04, 95% CI, 1.14−3.66, $P = 0.0163$) were all associated with significantly increased hazard of developing OAG relative to White race. Other measures associated with increased hazard of developing OAG included older age (80+ years: HR, 16.7, 95% CI, 7.64−36.7, $P < 0.0001$) and having diabetes (HR, 2.07, 95% 1.65−2.59, $P < 0.0001$). Female gender was associated with decreased hazard of developing OAG (HR, 0.67, 95% CI, 0.56−0.80, $P < 0.0001$). Being a smoker was not associated with the hazard of developing OAG.

Multivariable Cox proportional hazards models investigated the impact of MAP and BP medications on incident OAG while adjusting for demographic characteristics and the other study measures (Table 2). In contrast to univariable regression, the multivariable regression revealed low MAP to be significantly associated with increased hazard of developing OAG (HR, 1.32, 95% CI, 1.04−1.67, $P = 0.0227$). The association between incident OAG and high MAP remained statistically insignificant (HR, 0.89, 95% CI, 0.71−1.13, $P = 0.336$). The number of BP medication classes was no longer significantly associated with hazard of developing OAG after adjustment for covariates (1 class: HR, 1.13, 95% CI, 0.87−1.46, $P = 0.37$; 2 classes: HR, 1.25, 95% CI, 0.94−1.65, $P = 0.184$; 3+ classes: HR, 1.28, 95% CI, 0.98−1.67). Consistent with univariable models, being Black or African American race (HR, 3.31, 95% CI, 2.63−4.17, $P < 0.0001$), Hispanic or Latino race (HR, 2.53, 95% CI, 1.94−3.28, $P < 0.0001$), or Asian race (HR, 2.22, 95% CI, 1.24−3.97, $P = 0.00756$) remained significantly associated with increased hazard of developing OAG relative to White race. Likewise, older age (80+ years: HR, 20.1, 95% CI, 9.10−44.5, $P < 0.0001$) and having diabetes (HR, 1.32, 95% CI, 1.04−1.67, $P = 0.0209$) also remained associated with increased hazard of developing OAG, and female gender continued to confer decreased hazard of developing OAG (HR, 0.66, 95% CI, 0.55−0.80, $P < 0.0001$). Being a smoker was still not associated with increased hazard of developing OAG.

Sensitivity analysis was performed using the 8728 patients who were not taking any BP medications in the primary analysis, of whom 185 developed OAG. In this cohort, low MAP was associated with an increased risk of developing OAG (HR, 1.33, 95% CI, 0.94−1.89), although the association was not significant. High MAP remained unassociated with risk of developing OAG. The full results of the sensitivity analysis can be found in Table S2 (available at www.aaojournal.org).

To investigate whether the relationship between MAP and OAG may differ between those taking BP medications to pharmacologically lower their BP and those with naturally low BP without BP medications, we performed a secondary analysis to identify whether the interaction between MAP and the number of BP medication classes significantly affected the development of OAG. No significant interaction between MAP and treatment for BP was observed (HR, 1.00, 95% CI, 0.99−1.02, $P = 0.81$).

Discussion

This study uses a nationwide longitudinal database to assess the relationship among BP, the use of BP medications, and the development of incident OAG. Study results demonstrated that low BP was significantly associated with increased hazard of developing OAG. In contrast, high BP was not associated with the development of OAG. Based on the study population characteristics, the upper MAP cutoff for low BP was 83.0 mmHg (~110/70 mmHg) and the lower MAP cutoff for high BP was 101.3 mmHg (~155/75). Although mean MAP appeared not to be significantly different between patients who developed OAG and those who did not develop OAG, the effect of MAP on the development of OAG was significant after controlling for confounding factors. Increasing number of BP medication classes appeared to be associated with increased hazard of developing OAG until other factors were adjusted for in multivariable regression. These results suggest that all other factors being equal, lower BP is associated with increased risk of developing incident OAG.

This study also examines the difference between therapeutically low and naturally low BP on the risk of developing incident OAG. Because no significant interaction was identified between MAP and the number of BP medication

Table 1. Population Characteristics of Eye Patients in the All of Us Database

Demographics	Developed OAG (n = 462) Number (%)	Did not develop OAG (n = 20 353) Number (%)	P
Follow up (months), mean ± SD (median)	86.0 ± 77.6 (63)	104.6 ± 74.8 (87)	<0.0001
Age (years)			<0.0001
40 − 49	84 (18.4)	6259 (30.8)	
50 − 59	159 (34.4)	7287 (35.8)	
60 − 69	158 (34.2)	5031 (24.7)	
70 − 79	54 (11.7)	1627 (8.0)	
80+	7 (1.5)	149 (0.7)	
Gender			<0.0001
Male	203 (43.9)	7133 (35.0)	
Female	259 (56.1)	13 220 (65.0)	
Race/ethnicity			<0.0001
White	212 (45.9)	11 909 (58.5)	
Black or African American	139 (30.1)	3986 (19.6)	
Hispanic or Latino	85 (18.4)	3174 (15.6)	
Asian	12 (2.6)	450 (2.2)	
Unavailable/Other	14 (3.0)	834 (4.1)	
Active tobacco/nicotine use	126 (27.3)	6034 (29.7)	0.269
Diagnosis of diabetes	101 (21.9)	3622 (17.8)	0.0242
BP measurements (mmHg)			
Systolic, mean ± SD (median)	130.6 ± 18.2 (129)	129.0 ± 17.8 (128)	0.0680
Diastolic, mean ± SD (median)	76.7 ± 10.7 (76)	76.6 ± 11.1 (76)	0.713
MAP, mean ± SD (median)	94.7 ± 11.8 (93.5)	94.0 ± 11.9 (93.3)	0.246
MAP level			0.191
Low (MAP < 83.0 mmHg)	64 (13.9)	3476 (17.0)	
Medium (83.0 ≤ MAP ≥ 103.3)	284 (61.5)	11 949 (58.7)	
High (MAP > 103.3)	114 (24.7)	4937 (24.3)	
Patients taking BP medications at baseline	126 (27.3)	4480 (22.0)	0.00707
Number of BP medication classes at baseline			0.0274
0	336 (72.7)	15 873 (78.0)	
1	60 (13.0)	2340 (11.5)	
2	37 (8.0)	1288 (6.3)	
3+	29 (6.3)	852 (4.2)	

BP = blood pressure; MAP = mean arterial pressure; OAG = open angle glaucoma; SD = standard deviation.

classes on the development of OAG, we did not find that low BP due to BP medication use confers different risk of developing OAG compared with naturally low BP.

The existing literature is inconclusive regarding the impact of aberrant BP on the risk of developing incident OAG. Several cross-sectional studies have assessed the association between BP and IOP, a known risk factor for the development of OAG and OAG progression.[22,24,34,35] The Rotterdam study found the presence of hypertension to be associated with a higher mean IOP of 0.66 mmHg (95% CI, 0.39−0.93) but not to be significantly associated with primary OAG prevalence.[34] In the Egna-Neumarkt Study, 10 mmHg increases in systolic and diastolic BPs were associated with 0.24 and 0.4 mmHg increases in IOP, respectively. However, only a weak association between systolic BP and primary OAG was observed, which became insignificant when diastolic BP was included.[35] The Beaver Dam Eye study observed 0.21 (95% CI, 0.16−0.27) and 0.43 (95% CI, 0.35−0.52) mmHg increases in IOP for every 10 mmHg increase in systolic and diastolic BP, respectively, but the effect of these IOP changes on the development or progression of OAG was not examined.[24] Although these studies consistently showed a positive association between increasing BP and IOP, a corresponding increase in the development or progression of OAG was not demonstrated, as these studies were cross-sectional in design and could not measure the risk of developing incident OAG. Furthermore, these studies were composed of ethnically homogenous populations, so it is unclear if their results can be broadly extrapolated to the general population.

Several longitudinal population-based studies have found an association between low BP and increased risk of glaucoma, consistent with the findings in our work. In analyses of the 4- and 9-year follow-up data from the Barbados Incidence Study of Eye Diseases I and II, increasing systolic BP was positively correlated with increased IOP.[36,37] However, further analysis of systemic hypertension in these studies revealed a negative association between hypertension and risk of developing OAG, with the 4-year follow up study showing a relative risk of 0.49 (95% CI, 0.29−0.85) and the 9-year follow up study showing a

Table 2. Univariable and Multivariable Cox Proportional Hazards Models for the Development of Incident OAG

Covariates	Univariable Results		Multivariable Results	
	Hazard Ratio (95% CI)	P	*Hazard Ratio (95% CI)*	P
Age (reference = 40 − 49 years)				
50 − 59 years	2.25 (1.71−2.96)	<0.0001	2.42 (1.84−3.18)	<0.0001
60 − 69 years	4.06 (3.06−5.37)	<0.0001	4.70 (3.52−6.28)	<0.0001
70 − 79 years	5.81 (4.06−8.31)	<0.0001	6.86 (4.74−9.93)	<0.0001
80+ years	16.7 (7.64−36.7)	<0.0001	20.1 (9.10−44.5)	<0.0001
Gender (reference = male)	0.67 (0.56−0.80)	<0.0001	0.66 (0.55−0.80)	<0.0001
Race (reference = White)				
Black or African American	2.50 (2.01−3.11)	<0.0001	3.31 (2.63−4.17)	<0.0001
Hispanic or Latino	1.99 (1.54−2.56)	<0.0001	2.53 (1.94−3.28)	<0.0001
Asian	2.04 (1.14−3.66)	0.0163	2.22 (1.24−3.97)	0.00756
Unavailable/other	1.12 (0.65−1.92)	0.682	1.22 (0.71−2.10)	0.464
Diabetes	2.07 (1.65−2.59)	<0.0001	1.32 (1.04−1.67)	0.0209
Smoking	0.90 (0.73−1.10)	0.294	0.97 (0.79−1.20)	0.782
BP medication classes (reference = 0)				
1	1.45 (1.12−1.87)	0.00442	1.13 (0.87−1.46)	0.37
2	1.84 (1.40−2.43)	<0.0001	1.25 (0.94−1.65)	0.184
3+	2.20 (1.70−2.84)	<0.0001	1.28 (0.98−1.67)	0.0742
MAP (reference = medium)				
Low (MAP < 83.0 mmHg)	1.26 (0.99−1.59)	0.0560	1.32 (1.04−1.67)	0.0227
High (MAP > 101.3 mmHg)	0.98 (0.78−1.23)	0.86	0.89 (0.71−1.13)	0.336

BP = blood pressure; CI = confidence interval; MAP = mean arterial pressure; OAG = open angle glaucoma.

relative risk of 0.8 (0.50−1.20).[4,36] Likewise, analysis of the patients in the Early Manifest Glaucoma Trial after 11 years of follow-up showed higher systolic BP (>160 mmHg) to be protective against OAG progression (HR, 0.71, 95% CI, 0.46−1.10).[38] Like the present study, the design of these previous longitudinal studies allows the measurement of incident glaucoma and identification of risk factors for incident glaucoma. The results of our study are consistent with and expand on the existing body of literature supporting systemic hypotension as a potential risk factor for the development of incident OAG.

Fewer studies have assessed the role of BP medications in OAG. A subset analysis of the Rotterdam study[39] by Müskens et al[40] examined the association between BP medication classes and incident OAG. Although they found a 1.8-fold (95% CI, 1.04−3.2; $P = 0.037$) increased risk of developing OAG in patients taking calcium-channel blockers, this association was unchanged after adjusting for MAP or the number of simultaneously used BP medications, and no other specific BP medication classes were implicated. Consistent with the results of the present study, increased number of BP medication classes did not confer a greater risk of developing incident OAG. These findings support the hypothesis that the risk of developing OAG might be due primarily to low BP, irrespective of therapeutic or natural causes. Although this study did not examine the effect of specific BP medication classes on the development of incident OAG, the positive association with calcium channel blockers Müskens et al[40] identified was contradicted by several other studies and may reflect characteristics of sample size and population.[41,42]

As in previous epidemiological studies, the associations described in this study do not provide conclusive evidence with regard to causation of glaucomatous disease, but rather add to the evidence supporting vascular risk factors as possible contributors to OAG pathogenesis. In the vascular dysregulation hypothesis of OAG, the relationships among BP, IOP, and OPP are implicated in adversely impacting ocular blood flow and thus damaging the optic nerve.[43] Ocular perfusion pressure is a surrogate measure of ocular blood flow, and animal studies have demonstrated cessation of choroidal blood flow when OPP is reduced to zero.[44] In healthy eyes, ocular blood flow can be autoregulated to meet the metabolic demands of the eye across a range of OPP.[44,45] However, dysregulation of ocular blood flow could lead to inadequate ocular perfusion and eventual ischemic injury of the optic nerve. Elevated concentrations of the vasoconstrictor endothelin-1 have been reported in aqueous humor of glaucoma patients, supporting the possibility that optic nerve ischemia is a causal mechanism for OAG.[46] A study of rat models overexpressing endothelin-1 found loss of retinal ganglion cells, although without a change in blood flow.[47] A challenge in testing the hypothesis that inadequate ocular blood flow causes ischemic damage to the optic nerve is the inability to accurately measure ocular arterial pressure in humans.[43] Advancements in the ability to measure ocular blood flow, rather than surrogate measures such as vessel caliber and flow velocity, are necessary before the vascular dysregulation hypothesis can be adequately tested in mechanistic studies.

The overall prevalence of OAG in U.S. adults (>40 years) is estimated to be approximately 1% to 2%.[48] In contrast, the prevalence of hypertension was 29.0% among U.S. adults (>18 years) in 2016, and the estimated percentage of affected men and women being treated for hypertension was 49.3% and 55.2%,

respectively.[25,49] Given the known and significant consequences of uncontrolled hypertension, including coronary artery disease, congestive heart failure, peripheral vascular disease, and stroke,[50,51] the findings of this study should by no means lead to a broad reduction in the treatment of hypertension in an effort to reduce glaucoma risk. The associated risk of incident OAG with hypotension, while statistically significant, would likely not outweigh the risks of uncontrolled hypertension. Further confirmation including a better understanding of the pathophysiology of OAG is necessary before adjustment of hypertension management for OAG prophylaxis can be considered.

Although some reviews have noted the contradictory results of previous studies as a reason to discount aberrant BP as a risk factor for OAG,[19,22] this study has several strengths that distinguish it from prior efforts. Most notably, the participants in this study came from the All of Us Research Program database, which is the largest and most racially diverse population to date for such analysis. More than 50% of participants were from racial and ethnic minorities, and more than 80% were from populations underrepresented in research.[26] Furthermore, the cohort size of more than 20 000 in this study was significantly larger than most previous studies. These factors increased the likelihood that true population-wide associations were captured rather than characteristics specific to a particular demographic group. Additionally, the All of Us Research Program is composed of longitudinal EHR data, which provide information not commonly available in insurance claims data alone. Clinical information and past medical history information such as diabetes diagnosis or smoking status are further verified with self-reported data from surveys, adding an extra layer of verification of the data. Finally, by only including eye patients in the study cohort, the number of false-negatives (patients who developed undiagnosed OAG) should have been minimized, because glaucoma would be less likely to go undiagnosed in patients who have seen an eye care provider.

Study Limitations

Several limitations of this study should be acknowledged. Although generally comprehensive, the All of Us database does not provide certain relevant clinical factors such as IOP, central corneal thickness measurements, refractive error, or family history of glaucoma. As discussed previously, the relationship among IOP, BP, and OPP underlies the vascular dysregulation hypothesis, so the lack of IOP measurements in this database prevents the direct examination of this interaction. Additionally, BP medication use records were derived from prescription fill and medication order records in their EHRs. However, medication compliance could not be verified with the available data, and it is always possible that EHR records are incomplete for some orders or prescription fills. Furthermore, although the study population was drawn from a large and diverse nationwide cohort of patients, it did not adhere to a specific sampling scheme designed to produce population representative estimates; therefore, results in this study should not necessarily be construed as being broadly generalizable and accurate to the entire U.S. population. Finally, OAG diagnoses were based on ICD coding, which is susceptible to errors.[52] However, the use of survey verification should have mitigated cases of mislabeling.

In conclusion, this study identified low BP to be a significant risk factor for the development of incident OAG in a nationwide longitudinal EHR database. High BP and the number of BP medications were not associated with OAG. This study also especially investigates the influence of BP medications and found no difference between therapeutically low and naturally low BP on the risk of developing OAG. Future research can leverage genetic and free-text records data that will eventually be available in the All of Us Research Program database to potentially study the mechanistic etiology of OAG.

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Footnotes and Disclosures

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All authors have completed and submitted the ICMJE disclosures form

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HUMAN SUBJECTS: Human subjects were not included in this study. Only deidentified data was analyzed, and this study is exempt from Stanford University Institutional Review Board approval and is compliant with the requirements of the Declaration of Helsinki. The requirement for informed consent was waived because of the retrospective nature of the study.

No animal subjects were used in this study.

Author Contributions:

Conception and design: Lee, Hu, Wang

Data collection: Hu, Wang

Analysis and interpretation: Lee, Hu, Singh, Wang

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Abbreviations and Acronyms:
BP = blood pressure; **CI** = confidence interval; **EHR** = electronic health record; **HR** = hazard ratio; **ICD-9** = International Classification of Diseases 9th Revision; **ICD-10** = International Classification of Diseases 10th Revision; **IOP** = intraocular pressure; **MAP** = mean arterial pressure; **OAG** = open-angle glaucoma; **OPP** = ocular perfusion pressure; **SNOMED** = Systematized Nomenclature of Medicine.

Keywords:
Blood pressure, Blood pressure medications, Electronic health records, Glaucoma, Risk factors.

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