High Blood Pressure and Intraocular Pressure: A Mendelian Randomization Study

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Purpose. To test for causality with regard to the association between blood pressure (BP) and intraocular pressure (IOP) and glaucoma.

Methods. Single nucleotide polymorphisms (SNPs) associated with BP were identified in a genome-wide association study (GWAS) meta-analysis of 526,001 participants of European ancestry. These SNPs were used to assess the BP versus IOP relationship in a distinct sample ($n = 70,832$) whose corneal-compensated IOP (IOPcc) was measured. To evaluate the BP versus primary open-angle glaucoma (POAG) relationship, additional Mendelian randomization (MR) analyses were conducted using published GWAS summary statistics.

Results. Observational analysis revealed a linear relationship between BP traits and IOPcc, with a +0.28 mm Hg increase in IOPcc per 10-mm Hg increase in systolic BP (95% confidence interval [CI], 0.26–0.29); for diastolic blood pressure (DBP) and pulse pressure (PP), these estimates were +0.41 mm Hg and +0.36 mm Hg, respectively. An inverse-variance weighted MR analysis did not support a causal relationship, as the estimated causal effect was +0.01 mm Hg IOPcc per 10-mm Hg increase in systolic blood pressure (SBP); +0.13 mm Hg IOPcc per 10-mm Hg increase in DBP; and +0.02 mm Hg IOPcc per 10-mm Hg increase in PP (all $P > 0.05$). With regard to the risk of POAG, MR analyse yielded causal effect estimate of odds ratio = 0.98 (95% CI, 0.92–1.04) per 10-mm Hg increase in SBP. Neither DBP nor PP demonstrated evidence of a causal effect on POAG.

Conclusions. A range of different MR analysis methods provided evidence, in general, that the causal effect of BP on IOP (and POAG) was modest, or even zero. However, interpretation was complicated by SNPs associated with BP potentially having pleiotropic effects on IOP.

Keywords: blood pressure, intraocular pressure, glaucoma, POAG, Mendelian randomization

Glaucoma is a complex disease with a progressive loss of retinal ganglion cells as its hallmark feature, which is visualized as optic nerve damage. Glaucoma is a significant public health problem; it remains one of the leading causes of irreversible blindness worldwide.[1] The most common form of the disease among individuals of European ancestry is primary open-angle glaucoma (POAG).[2] Elevated intraocular pressure (IOP) is the main risk factor for POAG.[3,4] There is a strong genetic correlation between IOP and POAG[5]; genetic variants identified in genome-wide association studies (GWASs) for IOP have been used successfully to predict individuals at high risk of glaucoma.[6]

Numerous epidemiological studies have reported a positive association between blood pressure (BP) and IOP.[7,8] One proposed mechanism for such a relationship is an effect via the autonomic nervous system leading to excessive production of aqueous humor and a decrease in aqueous outflow.[9] However, the relationship between BP and IOP inferred from cross-sectional and longitudinal observational studies (i.e., non-intervention studies) may be biased by the presence of imprecisely measured or unmeasured confounding factors, which makes it unclear if the relationship is truly causal.[10] The current study sought to assess the causality of relationship between BP and IOP, using the technique of

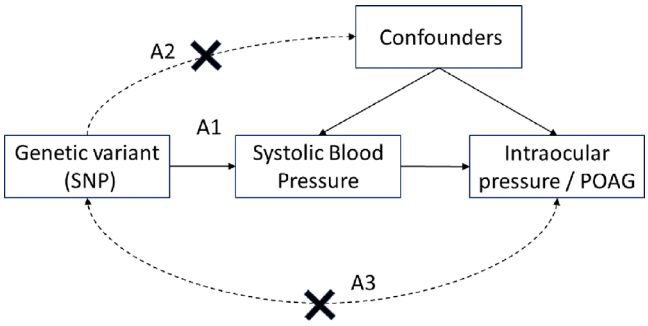

Figure 1. Diagram of MR assumptions. *Arrows* depict causal relationships among variables. A1 represents the causal path of the SNP on the exposure (SBP). A2 represents the causal path between the SNP and confounders that have effects on both SBP and IOP. A3 represents the causal path between the SNP and the outcome (IOP or POAG).

Mendelian randomization (MR). MR is a method for determining causal inference that leverages information from genetic variants within a framework of instrumental variables (IVs).[11] Genetic variants associated with the risk factor of interest are used to estimate the effect of the risk factor on the outcome that is free from bias due to reverse causality and—under a specific set of assumptions—free from bias due to unmeasured confounders.[12,13] The validity of causal estimates obtained using MR are dependent on three key assumptions: (1) the genetic variants used as instrumental variables are strongly associated with the risk factor (path A1 in Fig. 1), (2) the genetic variants are not associated with confounders of the risk factor–outcome association (path A2 in Fig. 1), and (3) the genetic variants affect the outcome only through the risk factor (path A3 in Fig. 1). Mendel's law of independent assortment states that the inheritance of alleles from a heterozygous parent to an offspring at conception is random and thus independent from, for example, the influence of confounders of the systolic blood pressure (SBP) versus IOP relationship.[12]

In this study, we used MR analyses to test whether or not the association between BP and IOP is causal and if the causal relationship of BP on IOP is linear. Finally, we used MR to investigate the causality of the relationship between BP and POAG.

Methods

Study Cohort

UK Biobank (UKB) is a longitudinal study in the United Kingdom examining the genetic and lifestyle influences on health and wellbeing. Physical assessments and questionnaire-based data were collected at baseline for approximately 500,000 participants 37 to 73 years old. Individuals were recruited during the period from 2006 to 2010, and assessments were undertaken at 22 centers across England, Wales, and Scotland.[14] Ethical approval was obtained from the National Health Research Ethics Service (Reference 11/NW/0382), and all participants provided (digital) written informed consent. The study adhered to the tenets of the Declaration of Helsinki.

Genotype Data

Genotype data were available for 488,377 participants. Prior to data release, UK Biobank researchers performed genotype imputation using the Haplotype Reference Consortium reference panel, followed by extensive quality control.[15] To avoid spurious associations due to population stratification, individuals not in the set of white British ancestry individuals defined by Bycroft et al.[16] were excluded. Participants who withdrew from the UK Biobank study after the baseline examination were also excluded.

BP Measurement

BP measurements were available for 475,166 participants. During the baseline assessment center visit, two automated readings were taken a few moments apart using an OMRON 705 IT electronic BP monitor (OMRON Healthcare Europe, Hoofddorp, Netherlands). An average value of the two readings was calculated and then adjusted for BP-lowering medication by adding 15 mm Hg, as described previously.[17] This antihypertensive medication–adjusted phenotype was used in all analyses. SBP, diastolic blood pressure (DBP), and pulse pressure (PP) were analyzed independently in order to understand the impact of different aspects of BP on IOP or glaucoma.

Ophthalmic Assessment

An ophthalmic assessment was introduced into UK Biobank in 2009, toward the latter stages of the recruitment period. Approximately 23% of participants underwent the ophthalmic assessment.[20] IOP was measured for each eye using an Ocular Response Analyzer non-contact tonometer (Reichert Technologies, Buffalo, NY, USA). We used corneal-compensated intraocular pressure (IOPcc) as our IOP phenotype. IOPcc was developed to correct for biomechanical properties of the cornea and has been used in previously reported GWASs for IOP.[6,21]

Study Sample

Participants were assigned to one of two non-overlapping subsamples. The first subsample included participants who had measures for both IOPcc and BP available; we refer to this sample as the IOP sample. The second subsample included participants with BP measures but without IOP information, which we refer to as the BP sample. The selection scheme is shown in Figure 2.

Genetic Association With BP

In the first stage, we performed three GWASs for SBP, DBP and PP in the BP sample (n = 226,997 UK Biobank participants; Fig. 2). A total of 7,458,361 imputed genetic variants with minor allele frequency $\geq$ 1%, missing genotype call rate < 1.5% and Hardy–Weinberg equilibrium P > 1.0E-06 were examined. Each genetic variant was tested for association with SBP using linear regression in PLINK 2.0.[24] Age, sex, genotyping array, body mass index (BMI), and the first five ancestry principal components (PCs) calculated by Bycroft et al.[16] were included as covariates in the analysis. To maximize the genetic effect of BP, in the second stage a meta-analysis was conducted to combine summary statistics from the first stage with GWAS for BP results obtained from International Consortium for Blood Pressure (ICBP).[19] The ICBP study sample had no overlap with UK Biobank.

Variants were selected for further analyses if they (1) were associated with BP traits at the level of P < 5E-09

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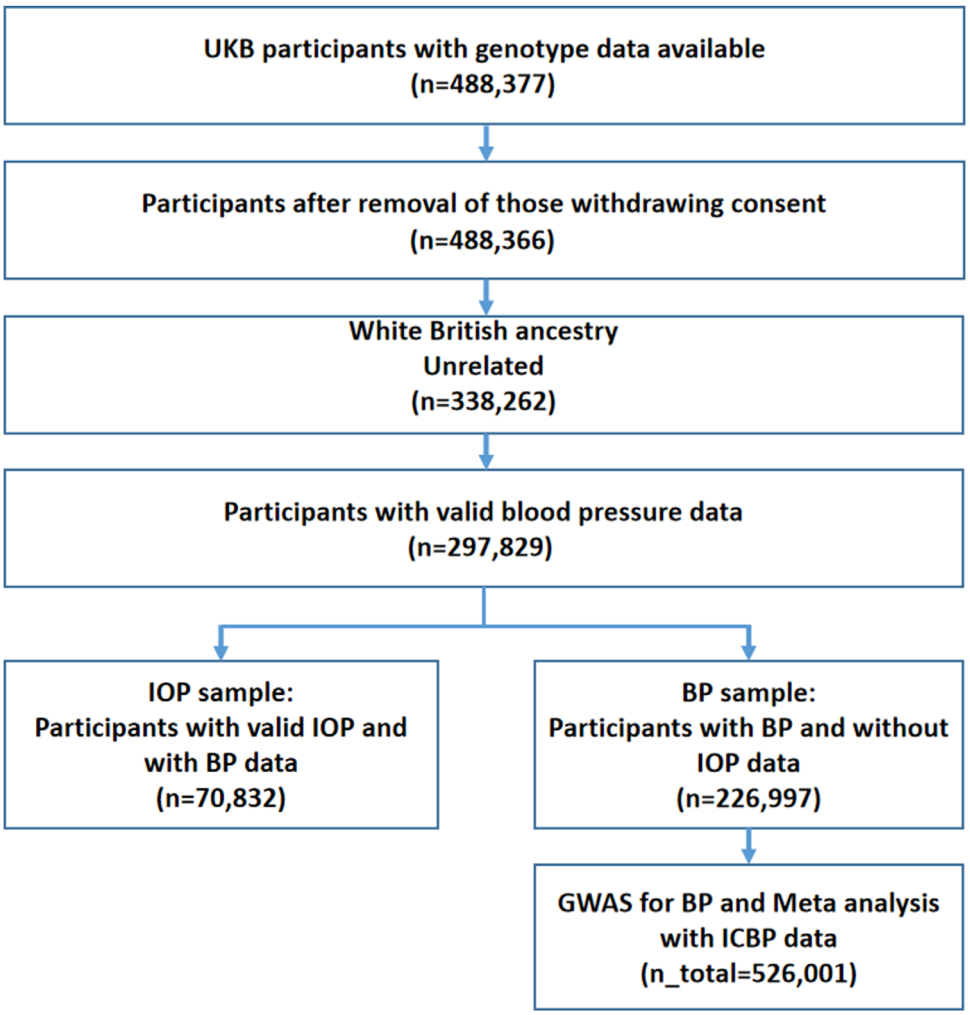

Figure 2. Selection of UK Biobank participants for GWAS for IOP and for MR analysis (n = 70,832; IOP sample) and for SBP (n = 226,997; BP sample).

in the UKB–ICBP meta-analysis, (2) had concordant direction of effect in both the UKB and ICBP studies, and (3) were associated with BP at a level of significance at least $P < 0.01$ in each study. These single nucleotide polymorphisms (SNPs) were used to derive a weighted polygenic risk score[25] for each participant in the IOP sample (n = 70,832 UK Biobank participants) (Fig. 2) using the –score command implemented in PLINK 2.0.

Genetic Association With IOPcc and With POAG

A GWAS for IOPcc was performed in the IOP sample of 70,832 UK Biobank individuals of European ancestry. Genotype quality control was the same as mentioned above. Age, sex, genotyping array, and the first five ancestry PCs were used as covariates in the association analysis. We used the SNP–POAG regression coefficients from the summary statistics from the first stage of the meta-analysis conducted in individuals of European ancestry only, reported by Gharahkhani et al.[22] UK Biobank participants were excluded, resulting in 15,229 cases and 177,473 controls.

Statistical Analyses

Linear regression was used to estimate the observational association between BP and IOPcc in the IOP sample. The model was adjusted for age, sex, genotyping array, BMI, and the first five ancestry PCs. To calculate the variance in BP explained by the polygenic risk score, we fitted two linear regression models: (1) a baseline model with one of the BP traits as the outcome variable and age, genotyping array, and the first five ancestry PCs as the explanatory variables; and (2) a full model that included the polygenic risk score and the baseline explanatory variables. The variance in BP traits explained by the polygenic risk score was calculated as the difference between the adjusted R^2 of the full and baseline models (this is also known as the incremental R^2).

To assess the causal effect of BP on IOP, a set of two-sample MR analyses was carried out using the R package MendelianRandomization. The SNP–exposure regression coefficients used in these MR analyses were those obtained from our UKB+ICBP meta-analysis for BP traits. The SNP–outcome regression coefficients for these MR anal-

yses were obtained using the IOP sample (n = 70,832), which had no overlap with the sample used for the GWAS for SBP. For the first analysis, the causal effect estimate results for the selected SNPs were combined using inverse-variance weighted (IVW) meta-analysis.[27] Next, the effects of the selected SNPs were combined using the MR-Egger,[28] weighted median,[29] or mode-based[30] meta-analysis methods as sensitivity analyses for the assumption of no unbalanced or horizontal pleiotropy in the IVW MR analysis. These tests provide a valid causal MR estimate even if a proportion of the SNPs associated with SBP are not valid instrumental variables. As a further sensitivity analysis for the assumption that all selected SNPs were valid instrumental variables, an MR-PRESSO analysis was performed.[31] The MR-PRESSO analysis provides an MR causal effect estimate that is designed to be valid if a proportion of the selected SNPs were invalid instrumental variables due to having strong (outlier) pleiotropic effects on IOP, such as affecting IOP by a route other than directly via BP.

To test the assumption of linearity of the putative causal relationship between BP and IOP, a nonlinear MR[32] analysis was conducted. In the first step, the UK Biobank IOP sample was stratified into 10 quantiles of residual BP (i.e., the BP of each participant after adjusting for the effects of the SNPs included in the polygenic risk score for BP). In the second step, an MR analysis examining the causal effect of BP on IOPcc was performed using the LIML estimator (ivmodel R package) within each of the 10 quantiles. The polygenic risk score for BP was used as a single instrument in this nonlinear MR analysis. Cochran's Q test (rma function in the metaphor R package) was used to assess the degree of heterogeneity in the MR causal effect estimate across deciles of residual BP.

We also performed a set of MR analyses to examine the causal relationship between BP and POAG (rather than between BP and IOP). Instrumental variables for BP traits were the same as mentioned above. The regression coefficients quantifying the SNP–outcome association were obtained from the GWAS for POAG reported by Gharahkhani et al.[22] IVW, MR-Egger, weighted median, mode-based, and MR-PRESSO analyses were performed.

Results

GWAS for BP Meta-Analysis

Meta-analysis of 526,001 European participants identified a total of 498 SNPs for SBP, 654 SNPs for DBP, and 289 SNPs for PP (Supplementary Tables S1–S3). In the independent IOP sample, the three polygenic risk scores constructed from these variants explained approximately 2% of the variance in SBP, DBP, and PP (all P < 2E-16). Specifically, the incremental R^2 = 1.99% (95% confidence interval [CI], 1.75–2.15) for SBP, R^2 = 2.47% (95% CI, 2.16–2.72) for DBP, and R^2 = 1.85% (95% CI, 1.52–1.96) for PP.

Observational Association Between BP and IOP

The observational association between BP and IOPcc was tested using linear regression in the IOP sample Supplementary Figure S1. An increase of 10 mm Hg in SBP was associated with a +0.28-mm Hg increase in IOPcc (95% CI, 0.26–0.29; P < 2E-16). For DBP and PP, the estimated observational associations with IOPcc were +0.10 mm Hg (95% CI, 0.38–0.43; P < 2E-16) and +0.36 mm Hg (95% CI, 0.34–0.39; P < 2E-16), respectively.

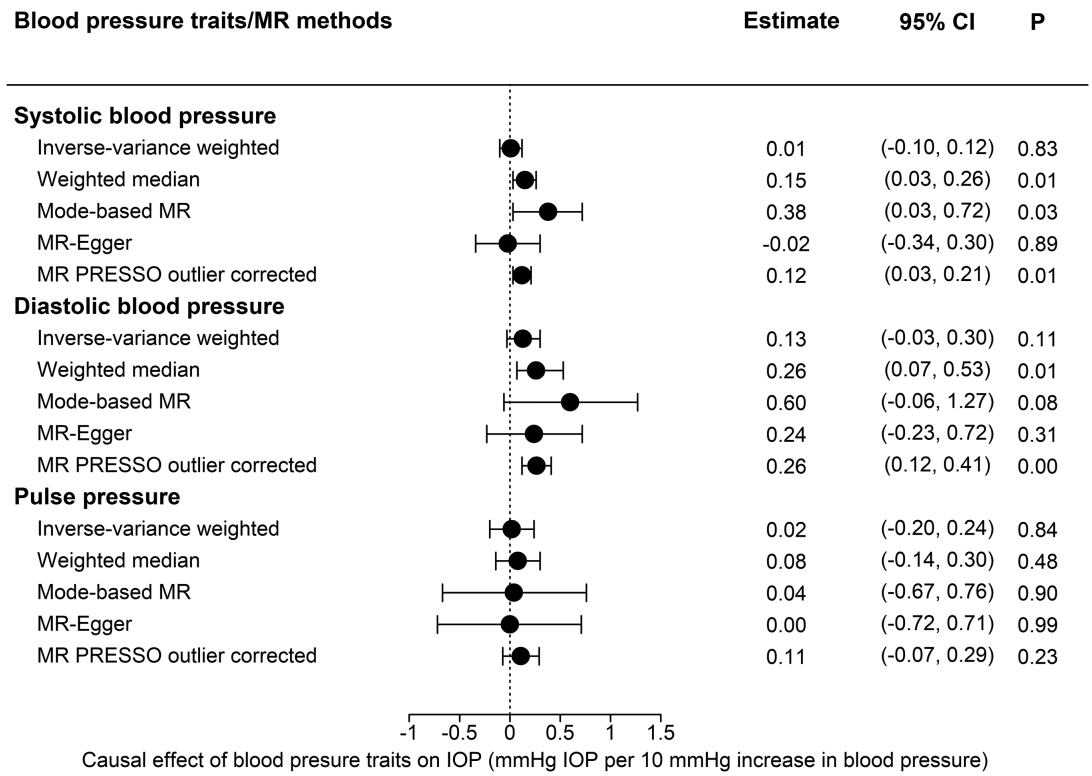

Figure 3. Association of genetically predicted BP traits with IOP.

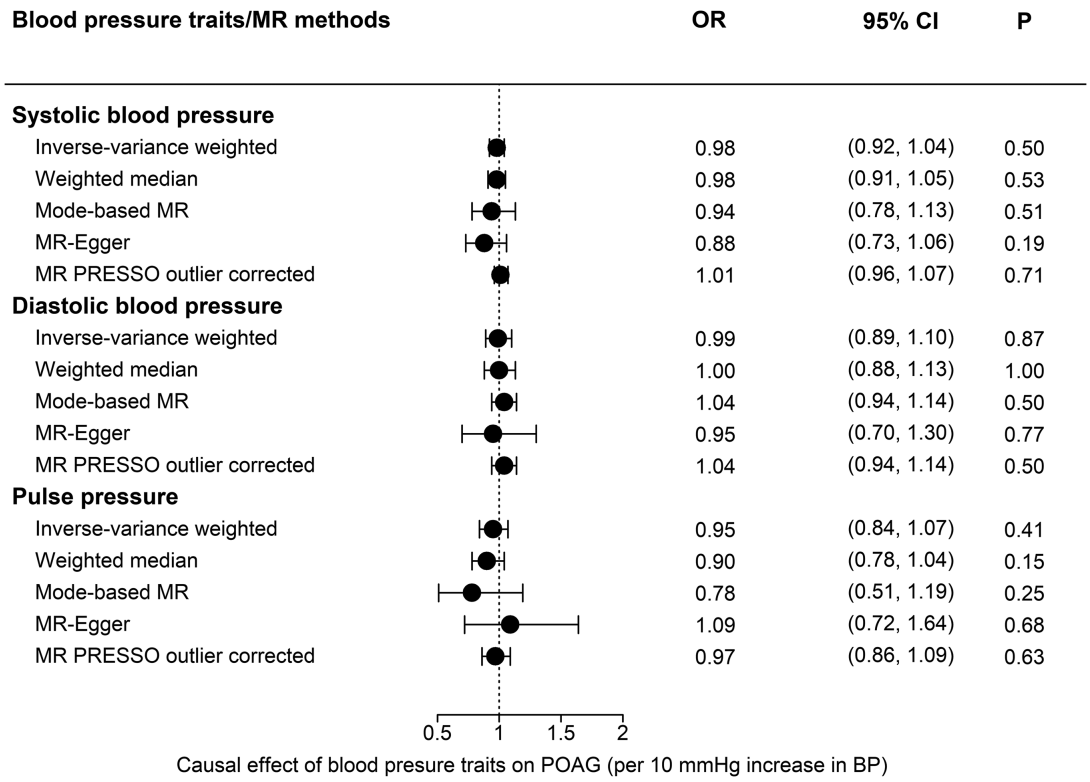

Figure 4. Association of genetically predicted BP traits with POAG.

Mendelian Randomization Analyses Assuming a Linear Exposure–Outcome Relationship

An IVW MR analysis estimated the causal effect of SBP on IOP to be +0.01 mm Hg IOPcc per 10-mm Hg increase in SBP (95% CI, –0.10 to 0.12; $P = 0.83$) (Fig. 3, Supplementary Table S4). An MR–Egger intercept test, which is a test for directional pleiotropy, yielded an estimate of –0.02 mm Hg IOP per 10-mm Hg increase in SBP, suggesting minimal evidence of such pleiotropy (Supplementary Table S4). The causal effects estimated using a weighted median and the mode-based MR analysis were +0.15 mm Hg (95% CI, 0.03–0.26; $P = 0.01$) and +0.38 mm Hg (95% CI, 0.03–0.72; $P = 0.03$), respectively. An MR-PRESSO analysis, which identified 16 SNP as outliers, yielded a causal effect estimate of +0.12 mm Hg IOP per 10-mm Hg increase in SBP (95% CI, 0.03–0.21; $P = 0.01$).

A summary of the results for DBP and PP is presented in Figure 3 and in Supplementary Tables S5 and S6. For DBP, 476 valid SNPs were included as IVs in the final analysis. The IVW MR estimated causal effect was +0.13 mm Hg per 10-mm Hg increase in DBP (95% CI, –0.03 to 0.30; $P = 0.11$). Sensitivity MR analyses yielded a slightly higher effect of DBP on IOPcc. For PP, the IVW MR estimated effect was +0.02 mm Hg (95% CI, –0.20 to 0.24; $P = 0.84$) per 10-mm Hg increase in PP. Likewise, MR sensitivity analyses did not support causality in the relationship between PP and IOPcc.

Nonlinear Mendelian Randomization Analyses

Nonlinear MR analyses in the IOP sample provided no evidence to reject the hypothesis that the causal effect of BP on IOP was linear (and there was little heterogeneity across strata, as Cochran's $Q = 14.4$ and $P = 0.11$). Notably, there was negligible evidence to support a non-zero causal effect in any of the 10 strata (Supplemental Table S7). Results of the nonlinear MR analyses for DBP and PP are presented in Supplementary Tables S8 and S9.

Mendelian Randomization Analyses With Glaucoma As an Outcome

An additional set of MR analyses was performed to test for a causal effect of BP traits on POAG rather than IOP. The results are presented in Figure 4 and Supplementary Tables S10–S12. For SBP, an IVW MR analysis yielded a causal effect estimate for the risk of POAG of odds ratio (OR) = 0.98 (95% CI, 0.91–1.05; $P = 0.50$) per 10-mm Hg increase in BP. For DBP, the IVW MR causal effect estimate was OR = 0.99 (95% CI, 0.89–1.10; $P = 0.87$) and for PP the IVW MR causal effect estimate was OR = 0.95 (95% CI, 0.84–1.07; $P = 0.41$). For all three BP traits, a range of sensitivity analyses also provided negligible evidence of a causal effect of BP on the risk of POAG (Fig. 4, Supplementary Tables S10–S12).

Discussion

A recent meta-analysis[34] of observational studies reported a pooled estimate of the association between SBP and IOP of +0.26 mm Hg (95% CI, 0.23–0.28) per 10-mm Hg increase in SBP. We calculated a very similar observational association of +0.28 mm Hg increase in IOPcc per 10-mm Hg increase in SBP. However, the influence of confounders may have led to bias in these observational estimates of association. One potential confounder is age, which has a

positive association with SBP.[35,36] Even if an observational study statistically adjusts for age, it is not possible to take into account all age-related risk factors, such as the putative role of inflammation in glaucoma development.[37] Recently, age-related impairment of the brain–retina barrier has been identified in animal models that may lead to an inflammatory response followed by pro-apoptotic responses in retinal ganglion cells.[38,39] Increased IOP can cause irreversible damage to retinal ganglion cells; therefore, identifying physiological risk factors that raise IOP is highly relevant to disease prevention and treatment. We carried out a series of Mendelian randomization analyses to assess the causality of the relationship between BP and IOP and between BP and POAG. We also tested the assumption of linearity of the former relationship.

An IVW MR analysis did not support the hypothesis that BP traits have a causal effect on IOP. IVW MR analysis provides relatively high statistical power, but this advantage comes at the expense of reliance on the assumption that all of the genetic variants used in the analysis are valid instrumental variables. Violation of this assumption may lead to bias in the estimated causal effect. The weighted median MR analysis method provides a consistent causal effect estimate even if less than a half of instrumental variables are valid, which makes this approach more robust to the effects of outliers than IVW MR. The mode-based MR method relies on the assumption that the most common effect estimate is a valid estimate of the true causal effect. This method can produce a reliable causal effect estimate even if the majority of instrumental variables are not valid. Both the weighted median and mode-based MR analyses supported the hypothesis of a causal effect of SBP on IOP, as did the outlier-robust MR-PRESSO method. The point estimates of the causal effect using these methods ranged from +0.12 to +0.38 mm Hg increases in IOPcc per 10-mm Hg increase in SBP (Supplementary Table S4). This range encompassed the observational association between SBP and IOPcc of +0.28 mm Hg IOP per 10-mm Hg increase in SBP. Together, our MR findings are consistent with a scenario in which a proportion of the SNPs used as instrumental variables for SBP exhibited horizontal pleiotropy (for example, influencing IOP directly or through a mechanism other than an effect on SBP). Such horizontal pleiotropy would violate the exclusion restriction assumption upon which MR relies. In summary, although our primary analysis did not support the hypothesis that SBP has a causal effect on IOP, some of our sensitivity analyses were consistent with SBP having a causal effect on IOP of sufficient magnitude to fully account for the observational association.

In addition to increased IOP and increased risk of POAG being associated with raised SBP,[40] it has also been suggested that the risk of POAG is higher in individuals with low SBP.[41,42] The "mechanical theory" of glaucoma focuses on a mechanistic link between increased IOP and damage to retinal ganglion cells.[9] By contrast, the "vascular theory" of glaucoma emphasizes the role of ocular perfusion pressure in relation to glaucomatous optic neuropathy, via insufficient blood supply of the optic nerve head, irrespective of whether this is caused by vascular dysregulation or increased IOP.[43] In clinical practice, it is commonly believed that lowering BP (for example, as a consequence of prescribing antihypertensive agents) increases the risk of glaucoma. This belief is supported by findings from the Thessaloniki Eye Study,[44] in which antihypertensive medication was associated with increased cupping and decreased rim area of the optic disc. Interestingly, Melgarejo et al.[45] reported that a 20% nighttime dip in SBP was associated with a 19-fold increased risk of glaucomatous damage. Moreover, in the Los Angeles Latino Eye Study, there was a U-shaped relationship between DBP and glaucoma prevalence, suggesting that both extremely high and extremely low BP were associated with an increased risk of glaucoma.[46] Here, our investigation of the linearity of the causal relationship between BP and IOP did not support the hypothesis that the relationship is nonlinear. Although this result argues against a major role of SBP on IOP, we urge caution in interpreting our findings, given that the statistical power of our nonlinear MR analysis was limited. As seen in the wide confidence intervals of the point estimates in Supplementary Tables S7, causal effects in the range of –0.33 to +0.37 mm Hg IOP per 10-mm Hg increase in SBP could potentially have gone undetected in our nonlinear MR analysis.

An additional limitation to acknowledge is that systemic beta-blockers, which are frequently prescribed in patients with hypertension, can exert an IOP-lowering effect that is independent of their effect on BP.[47] Although we accounted for the effect of antihypertensive drugs on BP (by adding 15 mm Hg to the measured SBP values in participants taking antihypertensive drugs) we did not take account of any potential direct lowering of IOP. To the date, there is no consensus on the extent to which systemic beta-blockers lower IOP directly versus indirectly via their effect on BP, nor the extent to which such responses are sustained during prolonged antihypertensive therapy. We were unable to exclude individuals taking antihypertensive medication from our analyses, as doing so could potentially bias the results of an MR analysis.[48]

The relationship among BP, IOP, and glaucoma is complex, and glaucomatous damage occurs in many patients whose IOP remains within the normal range. Clinically, the proportion of POAG patients with normal-tension glaucoma was approximately 32% in the Beaver Dam Eye Study[49] and was 39% in both the Rotterdam Study[50] and the Egna-Neumarkt Study.[51] In the EPIC-Norfolk Eye Study, 76% of patients who were newly diagnosed with POAG had an IOP within the normal range.[52] Nevertheless, in a recent study, the pooled relative risk for POAG was estimated as 1.01 (95% CI, 1.00–1.03) for each 10-mm Hg increase in SBP.[34] Our MR analyses were in accordance with a limited impact of BP on POAG risk, although we were unable to rule out a small causal effect. This was partly due to limited statistical power and partly due to suggestive evidence of horizontal pleiotropy in the effects of the instrumental variables for BP traits. Furthermore, we were unable to assess the linearity of the relationship between BP and the risk of POAG.

The major strength of the current study was the use of an analysis method, MR, that is not biased by reverse causation and that is prone to different sources of bias compared to observational studies. We also applied the nonlinear MR technique to investigate the shape of the causal relationship between BP and IOP. As with all MR analyses, a major limitation of the current study was that it was not possible to rule out the presence of horizontal pleiotropy—that is, the chance that some of the BP-associated genetic variants used as instrumental variables affected IOP through pathways distinct from a change in BP. The differing results obtained using MR methods with varying degrees of robustness to horizontal pleiotropy prevented us from drawing firm conclusions. A further limitation was that our study was restricted to participants of European ancestry; the

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observational and causal effects of BP on IOP may differ in other ethnic groups. Similar to our non-definitive findings regarding the relationship between BP and IOP, our MR analyses examining the relationship between BP and the risk of POAG were also inconclusive. In general, the MR analyses did not support a major causal role of BP on POAG, although once again the findings were challenging to interpret due to the potential existence of SNPs with pleiotropic effects on both BP and POAG. Thus, further work is needed to definitively address whether BP-lowering medication influences the risk of glaucoma progression.

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