Hypertension

ORIGINAL ARTICLE

Blood Pressure Polygenic Score Predicts Long-Term Blood Pressure Control and Treatment-Resistant Hypertension

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BACKGROUND: Suboptimal blood pressure (BP) control remains a major cardiovascular disease risk factor. Whether genetically predicted BP independently predicts long-term BP control is unknown. We examined the associations of BP polygenic scores (PGSs) with long-term BP control and treatment-resistant hypertension.

METHODS: We identified 22 456 Mass General Brigham Biobank participants with hypertension. Longitudinal BP control was defined as the percentage of time above-target systolic BP (SBP) ≥130 mm Hg or diastolic BP (DBP) ≥80 mm Hg over 5 years. Using multivariable regression, we assessed the associations of BP PGS with duration above-target BP and lifetime treatment-resistant hypertension incidence. Incremental prognostic utility of BP PGSs was assessed based on the discrimination C-index, Brier score, and net reclassification index. Validation was performed in the population-based UK Biobank cohort using the SBP/DBP ≥140/90 mm Hg threshold.

RESULTS: Among 10 853 (48.3%) were female, the mean SBP/DBP (SD) at index date was 132 (18)/75 (11) mm Hg, and 4126 (18.4%) developed treatment-resistant hypertension over lifetime. In reference to the low (<20th percentile) PGS group, the high (≥80th percentile) BP PGS was associated with 8.01 (95% CI, 6.68%–9.34%) longer duration with above-target SBP and 6.19 (95% CI, 5.05%–7.33%) with high DBP. Each high SBP and DBP PGS conferred 2.36 (95% CI, 2.07–2.68) and 1.75 (95% CI, 1.55–1.99)-fold higher odds of treatment-resistant hypertension. Adding BP PGSs to traditional risk factors improved treatment-resistant hypertension prediction from C-index (95% CI), 0.74 (0.73–0.75) to 0.78 (0.77–0.79). BP PGSs consistently predicted longitudinal BP management to a comparable extent in the UK Biobank.

CONCLUSIONS: Harnessing BP PGSs may inform anticipated trends in BP control to warrant vigilant monitoring and augment prioritization of intensive therapy. ***(Hypertension.* 2026;83:00–00. DOI: 10.1161/HYPERTENSIONAHA.125.26399.)**
• **Supplement Material**.

Key Words: blood pressure ■ cardiovascular disease ■ hypertension ■ prognosis ■ risk factors

High blood pressure (BP) is a major driver of cardiovascular disease (CVD)-related mortality and disability worldwide.[1] As such, sustained achievement of optimal BP is fundamental for CVD prevention. Observational studies demonstrate a log-linear association of both systolic BP (SBP) and diastolic BP (DBP) with CVD, even among young adults[2] or individuals without modifiable risk factors, such as hypertension, dyslipidemia, diabetes, and current tobacco use.[3] With clinical trials[4–7] establishing lower rates of major adverse cardiovascular events from intensive SBP lowering below <120 mm Hg compared with the standard (<140 mm Hg) treatment, contemporary clinical guidelines[8,9] have adopted a starkly lower BP target (<130/80

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NOVELTY AND RELEVANCE

What Is New?

Blood pressure (BP) polygenic scores PGSs may augment clinical actionability for hypertension management—especially for high-risk patients warranting more vigilant monitoring and frequent risk reassessments towards optimal BP preservation.

What Is Relevent?

In both US health care-based and UK population-based cohorts, high BP polygenic scores were independently associated with longer duration lived with above-target BP level and higher odds for developing treatment-resistant hypertension regardless of demographics, BP-lowering treatment intensity and regimen, or history of cardiorenal diseases.

BP polygenic scores improved the prediction of long-term BP control, cumulative BP burden, treatment intensity, and treatment-resistant hypertension beyond phenotypic risk factors.

Clinical/Pathophysiological Implications?

BP polygenic scores may augment prioritization of patient subgroups that are likely to derive greater benefit from a specific therapy when other phenotypic risk factors are equalized.

Nonstandard Abbreviations and Acronyms

BP	blood pressure
CVD	cardiovascular disease
DBP	diastolic blood pressure
PGS	polygenic score
SBP	systolic blood pressure

mm Hg) for the general population as well as individuals with concurrent cardiorenal conditions.

Nevertheless, suboptimal BP management remains highly prevalent and imposes substantial risk for CVD events.[10] The extent of BP control significantly varies across geographic regions, demographics, and comorbidities.[11] Based on the 2017 to 2020 National Health and Nutrition Examination Survey, US adults prescribed antihypertensives had varying rates of adequate BP control across sociodemographics.[12] In addition, the prevalence of treatment-resistant hypertension was significantly higher among individuals with concurrent cardiometabolic comorbidities, including diabetes (48.1% versus 23.5% in normoglycemia), chronic kidney disease (50.8% versus 26.5% in normal kidney function), and CVD (40.8% versus 18.4% without).[13] However, environmental, contextual, clinical, and diurnal influences contribute to substantial intraindividual measurement variability,[14] thereby challenging timely hypertension detection and treatment. Furthermore, rare or ancestry-specific genetic variants modify BP-associated pathophysiological pathways, including mineralocorticoid and glucocorticoid production, β-1 adrenergic receptor encoding, natriuretic peptides clearance, and conversion of angiotensin II to angiotensin III.[15] However, whether commonly occurring genetic variations are associated with prolonged suboptimal BP management is incompletely understood.

Given the increasing consensus for rigorous BP management yet pervasively suboptimal control, identifying novel risk factors influencing BP control may further optimize timing and course of BP-lowering treatment. Prior literature has illustrated that genetically predicted BP independently predicts midlife measured BP and provides incremental discrimination ability for lifetime CVD prediction beyond lifestyle and clinical factors.[16] Nevertheless, whether BP genetic risk is associated with long-term BP stability remains unknown. Understanding the associative and prognostic utility of genetic tools in predicting long-term BP control and treatment-resistant hypertension may improve identification of high-risk individuals warranting earlier and intensive preventive strategies. Here, we examined whether a BP polygenic score (PGS) independently predicts longitudinal BP control and lifetime incidence of treatment-resistant hypertension in adults with hypertension.

METHODS

Per the Health Insurance Portability and Accountability Act, requests to access the Mass General Brigham Biobank data from qualified researchers trained in human subject confidentiality protocols may be sent to Mass General Brigham Biobank at https://biobank@partners.org. UK Biobank data are available to researchers by application at https://ukbiobank.dnanexus.com.

Study Populations

The Mass General Brigham Biobank is a volunteer health care-based cohort comprising 8 tertiary care and affiliated community hospitals in New England.[17] Through genotyping and linkage to electronic health records, its objective is to study clinical, genetic, lifestyle, and socioenvironmental risk factors on health outcomes and disease pathophysiology. The protocol was approved by the Massachusetts General Hospital institutional review board (2018P001236). Informed consent was provided by all participants.

To account for temporal changes in BP clinical guidelines, we assessed long-term BP control after the adoption of the 2017 American College of Cardiology/American Heart Association BP guidelines[9] endorsing uniform SBP/DBP thresholds of <130/80 mm Hg irrespective of demographic characteristics or underlying comorbidities. We identified 22 456 participants (1) aged 18–79 years; (2) with physician-diagnosed hypertension; (3) at least 3 distinct outpatient BP measurements with <2 years gap between each encounter; and (4) without heart failure with reduced ejection fraction, or end-stage renal disease at the beginning of assessment period (ascertainment of diseases in the Supplemental Methods; Figure S1).

Validation analyses were performed on a healthier, population-based UK Biobank observational cohort. The UK Biobank is a prospective cohort study of 0.5 million adults aged 40 to 69 years at recruitment between 2006 and 2010.[18] Among 151 747 participants with linkage to general practitioner data and genotype information, we identified 27 856 participants with hypertension before enrollment (Figure S2). The UK Biobank study protocol was approved by the North West Multi-center Research Ethics Committee (11/NW/0382), and the secondary data usage (UK Biobank application no. 7089) was approved by the Massachusetts General Hospital institutional review board (2021P002228). All participants provided signed informed consent. The present study followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Construction of BP PGS

Details on central quality control, imputation of genotypic data, and BP PGS construction and predictive performance are elaborated in[17,18] and construction of blood pressure polygenic scores in the Supplemental Methods. Briefly, PGSs were derived from multiancestral genome-wide association study results[19–23] based on >1.2 million Hapmap3 variants. Single-nucleotide polymorphisms were extracted from the genome-wide association study data and processed with the LDpred2 framework.[24] Given the high genetic diversity observed, we applied the Genetic Distance-assisted PRS Combination Pipeline for Diverse Genetic Ancestries[25] framework to generate a harmonized BP PGS for all individuals via linear interpolation. Here, we leveraged multiple PGS weights that were fine-tuned within single ancestry samples and the genetic ancestry continuum information to yield high-accuracy estimation. The scores were calculated based on the 4 sets of single-nucleotide polymorphism effect sizes (AFR, EAS, EUR, and SAS), regressed on the first 10 principal components, and rescaled to a mean of 0 and SD of 1. The combination weights were derived based on the genetic distance, computed via principal component analysis, between the target individual and the AFR, EAS, EUR, and SAS fine-tuning data sets. Fine-tuning to generate BP PGSs in Mass General Brigham Biobank was performed on UK Biobank samples and vice versa.

Demographics, Lifestyle, and Clinical Risk Factors

In the Mass General Brigham Biobank, covariates were extracted from electronic health records 1 year prior to and the most proximate to the beginning of the 5-year BP management assessment period (index date). Blood biochemistry and anthropometry measurements were collected during routine outpatient encounters. History of atherosclerotic CVD was recorded for participants with diagnostic or procedural codes pertaining to myocardial infarction, stroke, peripheral artery disease, percutaneous coronary intervention, or coronary artery bypass grafting.

In the UK Biobank, covariates were measured at the cohort enrollment (index date). Current smoking was defined as lifetime smoking of at least 100 cigarettes without indication of cessation. Body mass index was measured using a Tanita BC-418MA body composition analyzer (Tanita, Tokyo, Japan). Blood biochemistry was assayed within 24 hours of nonfasting sample collection.

Outcomes

BPs were measured using automated oscillometric or aneroid auscultatory devices used during routine care; BPs collected during invasive procedures, ambulatory BP monitoring, or pregnancy were excluded. To avoid introducing spurious readings, we excluded measurements with SBP ≥240 mm Hg or <60 mm Hg, or DBP ≥160 mm Hg or <30 mm Hg.[26]

Two primary outcomes were studied. First, the time above target BP was calculated by re-zeroing the interpolated BP values above SBP ≥130 mm Hg and DBP ≥80 mm Hg, separately, such that only the duration spent above the thresholds contributes to the cumulative BP burden (Figure 1). We performed linear interpolation on all BP measurements to connect the measured values throughout the 5-year BP control assessment period. Graphically, the time above target represents the sum of duration lived between SBP readings ≥130 mm Hg and 130 mm Hg or DBP readings ≥80 mm Hg and 80 mm Hg. Second, apparent treatment-resistant hypertension was defined as either (1) having SBP/DBP ≥140/90 mm Hg despite the concurrent use of 3 or more antihypertensive agents of different classes, including a long-acting calcium channel blocker, renin-angiotensin system inhibitor, and a diuretic at maximally tolerated dose; (2) use of 4 or more antihypertensives medication classes; or (3) *International Classification of Diseases*-10 of I1A.0.[27] We estimated the lifetime cumulative incidence of treatment-resistant hypertension.

Three secondary outcomes were examined. First, time-averaged BP was assessed to account for differences in measurement interval by averaging the cumulative BP from adjacent consecutive health care visits indexed to the 5-year assessment period. Second, cumulative BP level above target was calculated by annualizing the sum of the difference between ≥130 mm Hg and 130 mm Hg or ≥80 mm Hg and 80 mm Hg thresholds. Third, we categorized and summed the different antihypertensive medication classes.

To reflect differences in clinical practice, the validation analyses using the UK Biobank applied SBP/DBP thresholds of 140/90 mm Hg in adherence to the 2006 National Institute for Health and Clinical Excellence hypertension guidelines, in alignment with the UK Biobank enrollment era.[28] Enrollment BP was measured on 2 consecutive occasions with a 1-minute interval using Omron 705 IT electronic BP monitor (OMRON Healthcare Europe, Hoofddorp, the Netherlands) after 5 minutes of seated rest; office BP measurements differed by local primary care practices.

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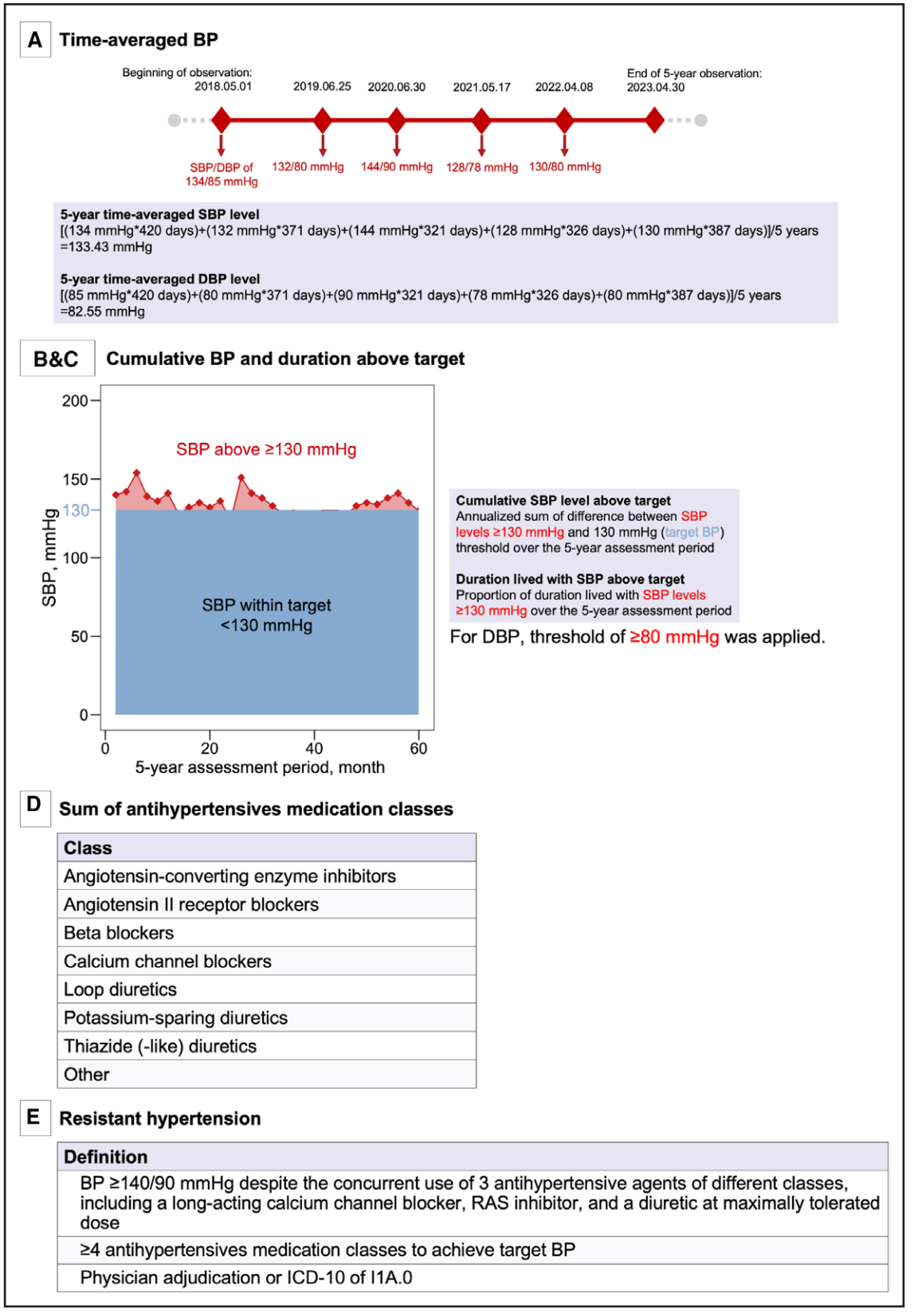

Figure 1. Definitions of long-term blood pressure (BP) control measures.
Time-averaged BP, cumulative BP levels, and duration above target BP were assessed over the 5-year period. The maximum number of antihypertensive classes prescribed and treatment-resistant hypertension were curated over the lifetime. The extent of BP control was quantified in adherence to the 2017 American College of Cardiology/American Heart Association BP guidelines for Mass General Brigham Biobank and the 2004 National Institute for Health and Care Excellence guideline for UK Biobank. DBP indicates diastolic blood pressure; ICD, *International Classification of Diseases*; RAS, renin-angiotensin system; and SBP, systolic blood pressure.

Statistical Analysis

The βs or odds ratios (95% CIs) for time above target BP and the cumulative incidence of treatment-resistant hypertension were calculated across decile and low (<20th percentile; reference), intermediate (20–<80th percentile) and high (≥80th percentile) SBP and DBP PGS groups of normalized PGS using 1-way ANOVA tests. In parallel, the continuous association was also examined per 1 SD increase in BP PGS using multivariable linear or logistic regression. All models were adjusted for age, sex, first 10 principal components, genotyping array, self-identified race and ethnicity, measured BPs, body mass index, total and high-density lipoprotein cholesterols, estimated glomerular filtration rate, cigarette smoking, lipid-lowering medication, diabetes, history of CVD, and number of antihypertensives medication classes (except in the case of treatment-resistant hypertension as the outcome) as a time-varying covariate. Given PGS has different explainability for a trait in the context of primary or secondary CVD prevention, comorbidities, and demographics,[29,30] we performed sensitivity stratified analyses by age, sex, genetic ancestry, number of health care utilization with BP readings, number of antihypertensive classes, and history of cardiometabolic diseases. Given varied definitions of drug-resistant hypertension across clinical guidelines, we further assessed the associations in alignment with the 2024 European Society of Cardiology.[31]

As long-term BP management contributes to CVD, we further assessed the associations between BP PGSs and lifetime risk of cardiovascular-kidney-metabolic syndrome, defined as diabetes, chronic kidney disease, atherosclerotic CVD, and heart failure among participants without subtype-specific conditions before the assessment period using Cox proportional hazards models adjusted for the covariates above.

To assess the clinical utility of BP PGS in enhancing the prediction of long-term BP management, we quantified improvements in discrimination, model fit, and net reclassification made by the genetic score. From the base model (demographics, lifestyle, clinical risk factors, comorbidities, and medications), we compared improvements in Harrell C-index by adding BP PGS. Improvements in discrimination were estimated based on a 2-sided *Z* test after bootstrap resampling of 1000 iterations. Likelihood ratio tests determined whether the inclusion of BP PGS significantly improved the model goodness-of-fit. Improvements in the Brier score captured the calibration and discrimination ability of BP PGSs in predicting long-term BP outcomes. Continuous net reclassification index quantified whether the addition of BP PGS yields clinically relevant improvements in prediction.

All statistical tests were 2-sided, and statistical significance was set at $P<0.05$. All analyses were performed using R version 4.3.3 (R Foundation for Statistical Computing, Vienna, Austria).

Table 1. Characteristics of MGB and UK Biobank Subcohorts With Hypertension and Longitudinal Health Records at the Beginning of 5-Year Assessment Period

Characteristics	MGB Biobank	UK Biobank (validation cohort)
Total number	22 456	27 856
Age, y, mean (SD)	63.91 (13.50)	61.54 (6.40)
Women	10 853 (48.33%)	12 578 (45.15%)
Self-reported race and ethnicity		
Hispanic or Latino	271 (1.21%)	N/A
Non-Hispanic Asian or Pacific Islander	343 (1.53%)	756 (2.71%)
Non-Hispanic Black or African American	1400 (6.23%)	150 (0.54%)
Non-Hispanic White	19 308 (85.98%)	26 270 (94.31%)
Uncategorized or multiple categories	1134 (5.05%)	680 (2.44%)
Body mass index, kg/m², mean (SD)	29.52 (6.05)	29.71 (5.24)
Total cholesterol, mg/dL, mean (SD)	183.20 (36.75)	198.21 (46.50)
High-density lipoprotein cholesterol, mg/dL, mean (SD)	55.01 (17.29)	51.46 (14.13)
Systolic blood pressure, mm Hg, mean (SD)	131.54 (17.73)	143.73 (18.59)
Diastolic blood pressure, mm Hg, mean (SD)	75.36 (10.57)	83.30 (10.33)
Number of antihypertensive classes		
0	1599 (7.12%)	851 (3.05%)
1	6311 (28.10%)	5356 (19.23%)
2	7208 (32.10%)	11 635 (41.77%)
≥3	7338 (32.68%)	10 014 (35.95%)
Prevalent treatment-resistant hypertension	2889 (12.87%)	1723 (6.19%)
Never smoker	15 278 (68.04%)	13 164 (47.26%)
Diabetes	7457 (33.21%)	2087 (7.49%)
Lipid-lowering medication	14 401 (64.13%)	14 643 (52.57%)
Annual number of BP measurements, median (IQR)	7.60 (3.60–13.20)	4.80 (3.20–6.40)
Average interval between each BP reading, days, median (IQR)	48.03 (27.65–101.39)	76.04 (57.03–114.06)

In MGB Biobank, characteristics at the beginning of the assessment period were extracted from electronic health records most proximate to and occurring within 1 year before the assessment period. In the UK Biobank, characteristics at the beginning of the assessment period correspond to baseline examination at cohort enrollment. IQR indicates interquartile range; and MGB, Mass General Brigham.

RESULTS

The study included 22 456 Mass General Brigham Biobank participants (mean [SD] age, 63.9 [13.5] years; 10 853 [48.3%] females) with hypertension presenting a mean (SD) SBP of 131.5 (17.7) mm Hg and DBP of 75.4 (10.6) mm Hg at the beginning of 5-year assessment window (Table 1; Tables S1 and S2). Participants contributed a median (IQR) of 7.6 (3.6–13.2) BP readings annually, with a median (IQR) of 48.0 (27.7–101.4) days between each reading (Figure S3). The UK Biobank cohort had a lower mean (SD) age of 61.5 (6.4) years but with a higher mean SBP (SD) of 143.7 (18.6) mm Hg and DBP (SD) of 83.3 (10.3) mm Hg at enrollment (Tables S3 and S4). Accounting for antihypertensive effects, each SD increase in SBP and DBP PGS was associated with cross-sectionally measured index date SBP (SE) of 1.86 (0.12) mm Hg and DBP of 0.97

(0.07) mm Hg in the Mass General Brigham Biobank and 2.95 (0.11) mm Hg and 1.46 (0.06) mm Hg in the UK Biobank, respectively (Table S5).

Distribution of Long-Term BP Control and Treatment-Resistant Hypertension Incidence Across BP PGS

The mean duration lived with above target SBP was incrementally longer across higher BP genetic risk, as represented by the highest PGS decile. This resulted, on average, in living above target SBP 51.1% of the time compared with the 40.9% in the lowest decile ($P<0.001$; Figure 2). Similarly, the highest DBP PGS decile had a significantly longer time with above target DBP compared with the lowest decile (32.3% versus 20.8%; $P<0.001$). In parallel, the proportion of participants achieving target BP for the entirety of the assessment period was incrementally lower across higher BP PGS deciles (P for trend <0.001; Tables S6 and S7). In secondary analyses, the lowest BP PGS decile had significantly lower mean time-averaged SBP (SD) of 128.2 (12.3) mm Hg and DBP (SD) of 72.9 (12.3) mm Hg compared with the highest decile (time-averaged SBP, 132.7 [12.8] mm Hg and DBP, 76.2 [12.8] mm Hg; $P<0.001$; Figures S4 and S5). Over a lifetime, the highest SBP PGS decile had a 2-fold higher likelihood of treatment-resistant hypertension compared with the lowest PGS group (24.7% versus 12.8%) and a higher proportion of individuals requiring triple or higher antihypertensive therapy (25.4% versus 41.6%; $P<0.001$).

Associations of BP PGS With 5-Year BP Control and Lifetime Treatment-Resistant Hypertension

BP PGS was independently associated with long-term BP stability and treatment-resistant hypertension (Figure 3A; Table S8). In reference to the low SBP PGS group, the intermediate and high SBP PGS groups conferred 3.21 (95% CI, 2.13%–4.29%) and 8.01 (95% CI, 6.68%–9.34%) longer duration spent with above target SBP, respectively. Simultaneously, higher SBP PGS associated with higher time-averaged SBP level (per SD increase, 1.41 [0.08] mm Hg) and cumulative SBP above target (3.34 [95% CI, 2.53–3.85] mm Hg/y). Similarly, the high DBP PGS group was also associated with 6.19 (95% CI, 5.05%–7.33%) longer duration lived with above target DBP. In alignment, the high SBP PGS group associated with 11.19 (95% CI, 10.03%–12.35%) longer duration spent with above target SBP ≥140 mm Hg in the UK Biobank cohort (Figure 3B; Table S9).

Compared with Mass General Brigham Biobank participants with low BP PGS, the high SBP PGS group had 2.36 (95% CI, 2.07–2.68)-fold greater odds for lifetime development of treatment-resistant hypertension, whereas the high DBP PGS strata exhibited 1.75 (95% CI, 1.55–1.99)-fold higher odds. As such, the odds ratios (95% CIs) for requiring triple or more intensive antihypertensive therapy were 1.31 (1.27–1.36) in high SBP and 1.22 (1.18–1.26) in high DBP PGS categories compared with the respective low PGS groups.

Subgroup analyses (Tables S10 through S28) showed that high SBP PGS is consistently associated with poor long-term hypertension control without significant heterogeneity by age ($P=0.122$) or antihypertensive treatment intensity and regimen ($P=0.145$). Furthermore, high genetically determined BP is associated with treatment-resistant hypertension irrespective of across sexes, health care utilization, underlying comorbidities, and varying clinical guidelines in both the Mass General Brigham Biobank and UK Biobank.

As such, BP PGSs were significantly associated with higher lifetime risk of cardiovascular-kidney-metabolic outcomes independent of measured BPs and phenotypic risk factors (Figures S6 through S9). In the Mass General Brigham Biobank, relative to the low PGS group, the high SBP genetic risk group was associated with hazard ratio (95% CI) of 1.36 (1.23–1.50) for chronic kidney disease, 1.19 (1.12–1.27) for atherosclerotic CVD, and 1.18 (1.09–1.28) for heart failure. Likewise, in the UK Biobank, the high SBP PGS group conferred 1.11-, 1.14-, and 1.18-fold higher risk for chronic kidney disease, atherosclerotic CVD, and heart failure, respectively.

Prognostic Utility of BP PGSs

Table 2 and Figure S10 illustrate the discrimination and net reclassification abilities of BP genetic scores beyond phenotypic risk factors. In addition to demographic, clinical, and lifestyle factors, SBP PGS enhanced the prediction of uncontrolled SBP from C-index (95% CI), 0.82 (0.81–0.83) to 0.84 (0.84–0.85; ΔC-index [95% CI], 0.02 [0.02–0.03]) and net reclassification index (95% CI) by 0.02 (0.01–0.03). Furthermore, BP PGSs significantly improved discrimination for treatment-resistant hypertension from C-index (95% CI) of 0.73 (0.72–0.74) to 0.76 (0.76–0.78; ΔC-index [95% CI], 0.04 [0.03–0.04]). BP PGSs consistently enhanced discrimination, calibration, and reclassification abilities for all long-term BP burden and treatment indices in the UK Biobank (Table S29; Figure S11).

DISCUSSION

In large prospective health care- and population-based cohorts of adults with hypertension, BP PGS was independently associated with and improved the prediction of long-term BP control, cumulative BP burden, treatment intensity, and treatment-resistant hypertension regardless of age or history of cardiorenal diseases. Since contemporary clinical guidelines underscore sustained achievement of target BP for primary and secondary

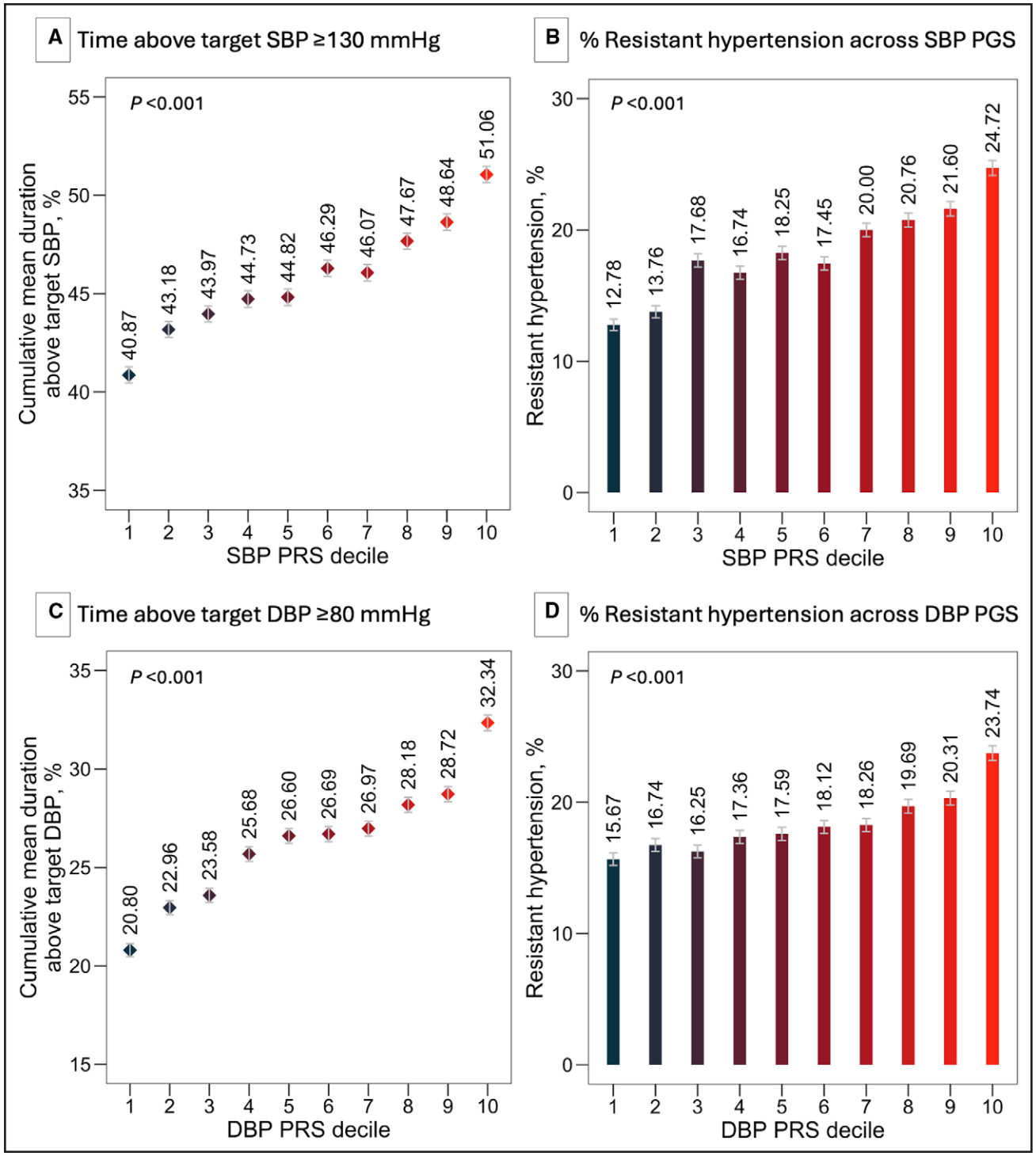

Figure 2. Proportion of time spent with above-target blood pressure (BP) and incidence of treatment-resistant hypertension across BP genetic score decile.

One-way ANOVA test was used to calculate the *P* value for the difference across the BP polygenic score (PGS) decile. DBP indicates diastolic blood pressure; and SBP, systolic blood pressure.

prevention of CVD, our findings permit several conclusions regarding the clinical utility of polygenic assessment toward optimal hypertension management.

First, genetic predisposition to elevated BP is associated with the extent of guideline-recommended target BP level achievement and cumulative BP burden over 5 years. These findings extend prior observations on how BP-associated genetic alleles independently associate with incident hypertension[32] and exhibit greater predictability for CVD.[16,33] A cross-sectional population

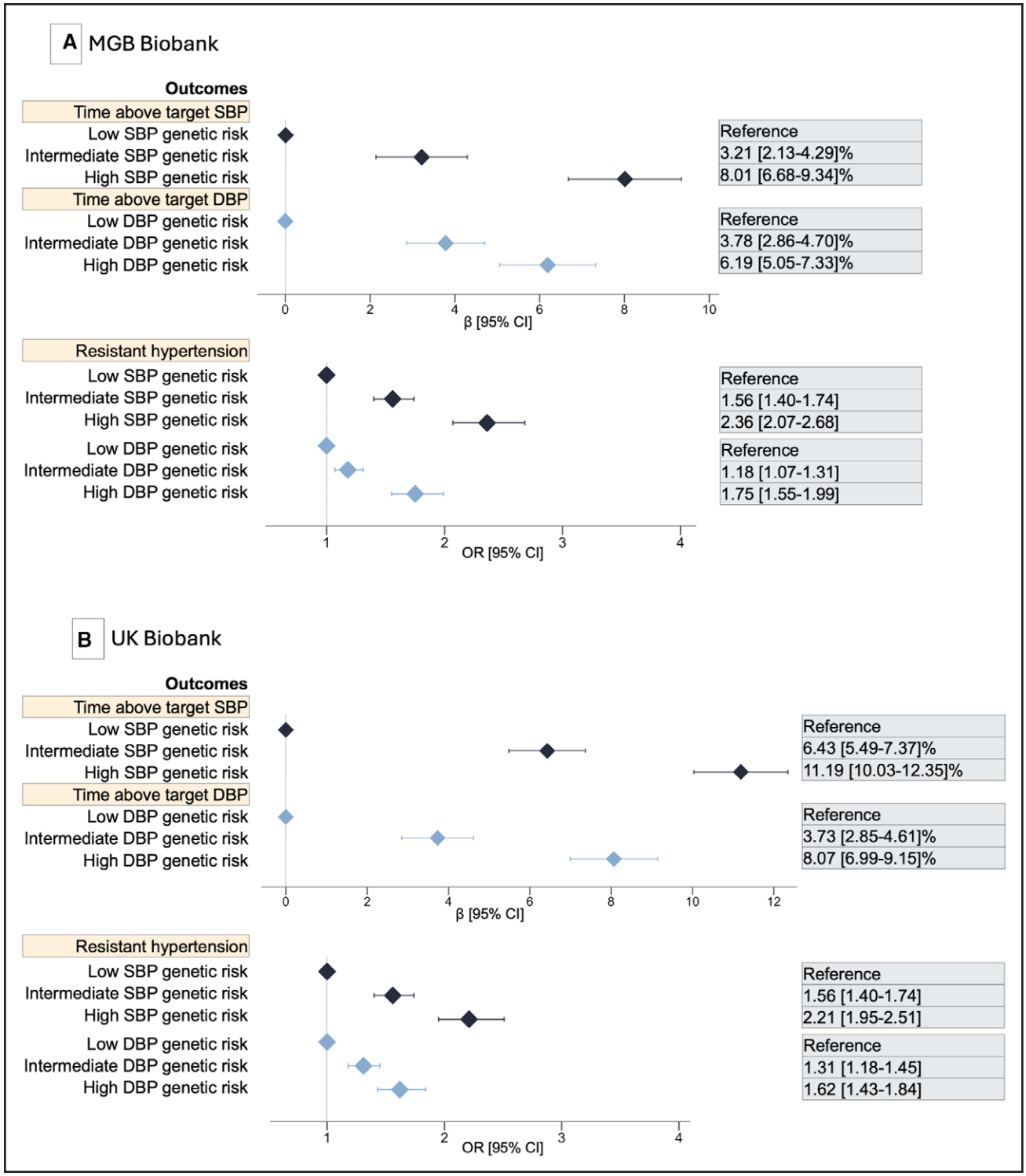

Figure 3. Associations of blood pressure (BP) polygenic score (PGS) with long-term BP control and treatment-resistant hypertension in (A) Mass General Brigham Biobank and (B) validation UK Biobank cohort.
Low BP genetic risk group corresponds to <20th PGS percentile; intermediate BP genetic risk group corresponds to 20th–<80th PGS percentile; high BP genetic risk group corresponds to ≥80th PGS percentile. Effect estimates are adjusted for age, sex, self-identified race and ethnicity, the first 10 principal components, genotyping array; BP levels at the beginning of the assessment period, total cholesterol, high-density lipoprotein cholesterol, body mass index, estimated glomerular filtration rate, diabetes, current smoking status, lipid-lowering medication, history of atherosclerotic cardiovascular disease, and number of antihypertensives medication class as a time-varying covariate. DBP indicates diastolic blood pressure; OR, odds ratio; and SBP, systolic blood pressure.

Table 2. Prognostic Value of Genetic Risk Score in Predicting Long-Term BP Control and Treatment-Resistant Hypertension

Long-term BP management outcome	Model	C-index (95% CI)	ΔC-index (95% CI)	Likelihood ratio test *P*	Brier score	NRI
Time-averaged, SBP ≥130 mm Hg	Base model	0.749 (0.742–0.757)	0.024 (0.020–0.028)	<0.001	0.294	0.029 (0.020–0.037)
	Base model+SBP PGS	0.773 (0.767–0.780)			0.245	
Time-averaged, DBP ≥80 mm Hg	Base model	0.843 (0.835–0.852)	0.023 (0.018–0.027)	<0.001	0.191	0.027 (0.019–0.036)
	Base model+DBP PGS	0.866 (0.859–0.877)			0.172	
Above target SBP over 5 years	Base model	0.819 (0.814–0.826)	0.023 (0.019–0.027)	<0.001	0.074	0.021 (0.012–0.030)
	Base model+SBP PGS	0.842 (0.835–0.852)			0.061	
Above target DBP over 5 years	Base model	0.771 (0.762–0.780)	0.022 (0.017–0.0.26)	<0.001	0.165	0.021(0.012–0.030)
	Base model+DBP PGS	0.793 (0.785–0.802)			0.156	
Triple therapy or higher	Base model	0.725 (0.717–0.735)	0.031 (0.027–0.035)	<0.001	0.252	0.030 (0.021–0.040)
	Base model+BP PGSs	0.757 (0.750–0.766)			0.236	
Treatment-resistant hypertension	Base model	0.737 (0.730–0.745)	0.042 (0.037–0.047)	<0.001	0.168	0.036 (0.029–0.043)
	Base model+BP PGSs	0.780 (0.772–0.790)			0.139	

The base model is adjusted for age, sex, total cholesterol, high-density lipoprotein cholesterol, body mass index, estimated glomerular filtration rate, diabetes, current smoking status, lipid-lowering medication, number of antihypertensive prescription classes (except for resistant hypertension as the outcome), history of atherosclerotic cardiovascular disease, and BP levels at the beginning of the assessment period. Delta C-index indicates additional discrimination ability that the genetic risk score contributes to predicting long-term BP management outcomes. Likelihood ratio test $P<0.05$ indicates that the inclusion of the corresponding BP PGS significantly improves the model goodness of fit compared with the base model. Continuous net reclassification index reflects the clinical significance of the genetic risk score by quantifying the magnitude of prediction improvement. BP indicates blood pressure; DBP, diastolic blood pressure; NRI, net reclassification index; PGS, polygenic score; and SBP, systolic blood pressure.

surveillance data identified sociodemographic (current or former marriage, consistent access to the same health care provider) and lifestyle (dietary sodium reduction, physical activity, weight management) factors associated with better BP control in US adults with hypertension.[34] We further observed a role for BP PGS to predict longitudinal BP control beyond established phenotypic risk factors using real-world health care utilization data and minimizing practical challenges of high BP measurement variability.[35] Given that (1) the risk of cardiovascular events increases log-linearly even below SBP of 120 mmHg[36] and (2) elevated BP is implicated with high population attributable risk across primordial[3] to secondary[37] CVD prevention, BP PGSs may augment clinical actionability for hypertension management—especially for high-risk patients warranting more vigilant monitoring and frequent risk re-assessments towards optimal BP preservation.

Second, BP PGSs may augment prioritization of patients benefiting from earlier or more intensive BP-lowering therapy. Current hypertension guideline acknowledges rare, monogenic forms of hypertension (ie, glucocorticoid-remediable aldosteronism, Liddle syndrome) but do not formally recognize BP PGS as a risk-enhancing factor due to the nominal contribution of individual BP loci to measured BP.[9] Nevertheless, we demonstrate that higher BP PGS is associated with 8% longer duration spent above target BP and 2.4-fold higher risk of treatment-resistant hypertension across health care and general populations, conferring a wide gradient of cardiorenal disease risk and comorbidities burden. Furthermore, using novel multiancestral PGSs, we establish the independent associations and robust predictive utility of both SBP and DBP PGSs in treatment-resistant hypertension prediction (ΔC-index [95% CI], 0.04 [0.04–0.05]), otherwise unobserved in prior studies.[38] Akin to our finding, a pharmacogenomic substudy of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial demonstrated that participants in the highest BP PGS quintile had 50% to 70% higher odds of having treatment-resistant hypertension compared with those at intermediate risk.[39] Such a finding suggests that BP-regulating genes and pathobiology (ie, vasodilation activation of the renin-angiotensin aldosterone system) may contribute to BP-lowering response[40] and implies prognostic utility of BP PGS for risk stratification beyond traditional risk factors.

Furthermore, BP PGSs significantly improved discrimination for stability of BP control and treatment-resistant hypertension, which may help to prioritize subgroups who are likely to derive greater benefit from a specific therapy when other phenotypic risk factors are equalized. Nevertheless, evidence of genetic interaction and heterogeneity of BP-lowering treatment effect across BP PGS remains scarce and inconsistent. Within a limited scope, current pharmacogenomics focuses on the identification of candidate genes responsible for interindividual variability in antihypertensives response. Few modestly powered epidemiological studies have demonstrated divergent findings on the effect of BP PGS on measured BP response to select antihypertensive classes. Whereas Black adults in the lowest SBP PGS quintile derived 3.5 mm Hg greater SBP reduction at 6 months from hydrochlorothiazide compared with the median PGS quintile,[39] nonsignificant effect modification was observed in the Finnish male population.[41] Furthermore, no associations

were observed between the SBP PGS and BP response to lisinopril[39] or diuretics.[41] The lack of high-powered, methodologically optimized, and diverse trials examining the treatment effect between BP PGSs and class-specific antihypertensives underscores the need to refine strategies to improve hypertension management in the context of heightened genetic risk. A recent primary and secondary prevention study[42] demonstrated that the atherogenicity of even moderately elevated low-density lipoprotein cholesterol is higher in individuals with a high PGSs. In this context, BP PGS may similarly identify an actionable genotype in whom targeted intensive BP-lowering therapy could derive the greatest absolute CVD risk reduction. Nevertheless, whether new modalities emerging for treatment-resistant hypertension, such as zilbesiran[43] and renal denervation,[44] will benefit those with high BP PGS to a greater extent, needs future investigations.

Strengths and Limitations

Based on multiancestry BP PGSs and rigorously characterized longitudinal BP control using international biobanks with linkage to electronic health records, we demonstrated the translational potential of BP genetic score in hypertension management. Nevertheless, our results have potential limitations. First, BPs were collected using varied devices and protocols under diverse contextual and physical environments. Therefore, direct comparison to studies using standardized BP measurements may be limited. Second, white-coat hypertension or masked hypertension may have led to misclassification of on-target BP achievement. Conversely, health care providers may have set higher target BPs to minimize adverse effects such as hypoperfusion, syncope, frailty, or electrolyte abnormalities; in such cases, pseudo-resistance is possible. Nevertheless, we have rigorously excluded patients with advanced cardiorenal conditions and further validated in the UK guideline, adhering to more liberal BP thresholds. Third, patients may have undergone BP measurement at out-of-network practices. Similarly, our results may have limited external generalizability across sociodemographically or clinically heterogeneous populations adhering to differing BP-lowering practices. Nevertheless, we expect missingness to be minimal as the Mass General Brigham is the largest multi-institutional health system in New England, and the National Health Service serves as the single-payer system for the UK Biobank. Lastly, our results may have limited generalizability across external populations with different population structures, BP distributions, and hypertension management practices.

In summary, BP PGSs exhibited discernible associations and predictive capabilities for long-term BP control and treatment-resistant hypertension in adults with hypertension. Given the ubiquity of suboptimal BP control, genetic assessment may augment opportunities for earlier treatment intensification for patients with high underlying risk, quantification of individualized treatment thresholds for more effective and safe hypertension management, and identification of candidates meriting novel BP-lowering modalities. With the increasing availability of large-scale multiancestral biobanks, the cost-effectiveness of the routine incorporation of BP genetic instruments into the clinical roadmap toward personalized hypertension management warrants future exploration.

Perspectives

Considering high genetically determined BP is associated with poorer long-term BP management and greater cumulative BP burden, patients with high BP PGS may benefit from more vigilant monitoring, frequent risk reassessments, and earlier antihypertensive medication initiation or intensification. Furthermore, these individuals are also predisposed to a higher treatment-resistant hypertension over their lifetime. As such, when other phenotypic risk factors are equalized, BP PGS may more efficiently prioritize high-risk patients who are likely to derive greater benefit from a specific therapy or identify candidates for novel BP-lowering interventions.

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REFERENCES

1. Martin SS, Aday AW, Almarzooq ZI, Anderson CAM, Arora P, Avery CL, Baker-Smith CM, Gibbs BB, Beaton AZ, Boehme AK, et al. 2024 Heart disease and stroke statistics: a report of US and global data from the American Heart Association. *Circulation*. 2024;149:e347–e913. doi: 10.1161/CIR.0000000000001209
2. Lee H, Yano Y, Cho SMJ, Park JH, Park S, Lloyd-Jones DM, Kim HC. Cardiovascular risk of isolated systolic or diastolic hypertension in young adults. *Circulation*. 2020;141:1778–1786. doi: 10.1161/CIRCULATIONAHA.119.044838
3. Whelton SP, McEvoy JW, Shaw L, Psaty BM, Lima JAC, Budoff M, Nasir K, Szklo M, Blumenthal RS, Blaha MJ. Association of normal systolic blood pressure level with cardiovascular disease in the absence of risk factors. *JAMA Cardiol*. 2020;5:1011–1018. doi: 10.1001/jamacardio.2020.1731
4. The SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. 2015;373:2103–2116. doi: 10.1056/NEJMoa1511939
5. Cheung AK, Rahman M, Reboussin DM, Craven TE, Greene T, Kimmel PL, Cushman WC, Hawfield AT, Johnson KC, Lewis CE, et al; SPRINT Research Group. Effects of intensive BP control in CKD. *J Am Soc Nephrol*. 2017;28:2812–2823. doi: 10.1681/ASN.2017020148
6. Liu J, Li Y, Ge J, Yan X, Zhang H, Zheng X, Lu J, Li X, Gao Y, Lei L, et al; ESPRIT Collaborative Group. Lowering systolic blood pressure to less than 120 mm Hg versus less than 140 mm Hg in patients with high cardiovascular risk with and without diabetes or previous stroke: an open-label, blinded-outcome, randomised trial. *Lancet*. 2024;404:245–255. doi: 10.1016/S0140-6736(24)01028-6
7. Bi Y, Li M, Liu Y, Li T, Lu J, Duan P, Xu F, Dong Q, Wang A, Wang T, et al; BPROAD Research Group. Intensive blood-pressure control in patients with type 2 diabetes. *N Engl J Med*. 2025;392:1155–1167. doi: 10.1056/NEJMoa2412006
8. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO 2021 clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Int*. 2021;99:S1–S87. doi: 10.1016/j.kint.2020.11.003
9. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Himmelfarb CD, DePalma S, Gidding S, Jamerson KA, Jones DW, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA 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. *Hypertension*. 2018;71:e13–e115. doi: 10.1016/j.jacc.2017.11.006
10. Aggarwal R, Yeh RW, Joynt Maddox KE, Wadhera RK. Cardiovascular risk factor prevalence, treatment, and control in US adults aged 20 to 44 years, 2009 to March 2020. *JAMA*. 2023;329:899–909. doi: 10.1001/jama.2023.2307
11. Zhou B, Perel P, Mensah GA, Ezzati M. Global epidemiology, health burden and effective interventions for elevated blood pressure and hypertension. *Nat Rev Cardiol*. 2021;18:785–802. doi: 10.1038/s41569-021-00559-8
12. Muntner P, Miles MA, Jaeger BC, Hannon L III, Hardy ST, Ostchega Y, Wozniak G, Schwartz JE. Blood pressure control among US adults, 2009 to 2012 through 2017 to 2020. *Hypertension*. 2022;79:1971–1980. doi: 10.1161/HYPERTENSIONAHA.122.19222
13. Carey RM, Sakhuja S, Calhoun DA, Whelton PK, Muntner P. Prevalence of apparent treatment-resistant hypertension in the United States: comparison of the 2008 and 2018 American Heart Association scientific statements on resistant hypertension. *Hypertension*. 2019;73:424–431. doi: 10.1161/HYPERTENSIONAHA.118.12191
14. Omboni S. Estimates of blood pressure variability obtained in different contexts are not interchangeable. *Hypertens Res*. 2021;44:1678–1680. doi: 10.1038/s41440-021-00778-z
15. Franceschini N, Chasman DI, Cooper-DeHoff RM, Arnett DK. Genetics, ancestry, and hypertension: implications for targeted antihypertensive therapies. *Curr Hypertens Rep*. 2014;16:461. doi: 10.1007/s11906-014-0461-9
16. Cho SMJ, Koyama S, Ruan Y, Lannery K, Wong M, Ajufo E, Lee H, Khera AV, Honigberg MC, Natarajan P. Measured blood pressure, genetically predicted blood pressure, and cardiovascular disease risk in the UK Biobank. *JAMA Cardiol*. 2022;7:1129–1137. doi: 10.1001/jamacardio.2022.3191
17. Koyama S, Wang Y, Paruchuri K, Uddin MM, Cho SMJ, Urbut SM, Haidermota S, Hornsby WE, Green RC, Daly MJ, et al. Decoding genetics, ancestry, and geospatial context for precision health. *medRxiv*. 2023. doi: 10.1101/2023.10.24.23297096
18. Bycroft C, Freeman C, Petkova D, Band G, Elliott LT, Sharp K, Motyer A, Vukcevic D, Delaneau O, O'Connell J, et al. The UK Biobank resource with deep phenotyping and genomic data. *Nature*. 2018;562:203–209. doi: 10.1038/s41586-018-0579-z
19. Evangelou E, Warren HR, Mosen-Ansorena D, Mifsud B, Pazoki R, Gao H, Ntritsos G, Dimou N, Cabrera CP, Karaman I, et al; Million Veteran Program. Genetic analysis of over 1 million people identifies 535 new loci associated with blood pressure traits. *Nat Genet*. 2018;50:1412–1425. doi: 10.1038/s41588-018-0205-x
20. Huang QQ, Sallah N, Dunca D, Trivedi B, Hunt KA, Hodgson S, Lambert SA, Arciero E, Wright J, Griffiths C, et al. Transferability of genetic loci and polygenic scores for cardiometabolic traits in British Pakistani and Bangladeshi individuals. *Nat Commun*. 2022;13:4664. doi: 10.1038/s41467-022-32095-5
21. Wojcik GL, Graff M, Nishimura KK, Tao R, Haessler J, Gignoux CR, Highland HM, Patel YM, Sorokin EP, Avery CL, et al. Genetic analyses of diverse populations improves discovery for complex traits. *Nature*. 2019;570:514–518. doi: 10.1038/s41586-019-1310-4
22. Sakaue S, Kanai M, Tanigawa Y, Karjalainen J, Kurki M, Koshiba S, Narita A, Konuma T, Yamamoto K, Akiyama M, et al; FinnGen. A cross-population atlas of genetic associations for 220 human phenotypes. *Nat Genet*. 2021;53:1415–1424. doi: 10.1038/s41588-021-00931-x
23. Major-Smith D, Heron J, Fraser A, Lawlor DA, Golding J, Northstone K. The Avon Longitudinal Study of Parents and Children (ALSPAC): a 2022 update on the enrolled sample of mothers and the associated baseline data. *Wellcome Open Res*. 2022;7:283. doi: 10.12688/wellcomeopenres.18564.2
24. Privé F, Arbel J, Vilhjálmsson BJ. LDpred2: better, faster, stronger. *Bioinformatics*. 2020;36:5424–5431. doi: 10.1093/bioinformatics/btaa1029
25. Ruan Y, Bhukar R, Patel A, Koyama S, Hull L, Truong B, Hornsby W, Zhang H, Chatterjee N, Natarajan P. Leveraging genetic ancestry continuum information to interpolate PGS for admixed populations. *medRxiv*. 2024. doi: 10.1101/2024.11.09.24316996
26. Cho SMJ, Lee H, Koyama S, Zou RS, Schuermans A, Ganesh S, Hornsby W, Honigberg MC, Natarajan P. Cumulative diastolic blood pressure burden in normal systolic blood pressure and cardiovascular disease. *Hypertension*. 2024;81:273–281. doi: 10.1161/HYPERTENSIONAHA.123.22160
27. Carey RM, Calhoun DA, Bakris GL, Brook RD, Daugherty SL, Dennison-Himmelfarb CR, Egan BM, Flack JM, Gidding SS, Judd E, et al; American Heart Association Professional/Public Education and Publications Committee of the Council on Hypertension; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Genomic and Precision Medicine; Council on Peripheral Vascular Disease; Council on Quality of Care and Outcomes Research; and Stroke Council. Resistant hypertension: detection, evaluation, and management a scientific statement from the American Heart Association. *Hypertension*. 2018;72:e53–e90. doi: 10.1161/HYP.0000000000000084
28. National Institute of Health and Clinical Excellence. *Hypertension: management of hypertension in adults in primary care*. Accessed 14 April 2025. https://www.nice.org.uk/guidance/cg34
29. Cho SMJ, Koyama S, Honigberg MC, Surakka I, Haidermota S, Ganesh S, Patel AP, Bhattacharya R, Lee H, Kim HC, et al. Genetic, sociodemographic, lifestyle, and clinical risk factors of recurrent coronary artery disease

events: a population-based cohort study. *Eur Heart J*. 2023;44:3456–3465. doi: 10.1093/eurheartj/ehad380
30. Ding Y, Hou K, Xu Z, Pimplaskar A, Petter E, Boulier K, Prive F, Vilhjalmsson BJ, Loohuis LMO, Pasaniuc B. Polygenic scoring accuracy varies across the genetic ancestry continuum. *Nature*. 2023;618:774–781. doi: 10.1038/s41586-023-06079-4
31. McEvoy JW, McCarthy CP, Bruno RM, Brouwers S, Canaan MD, Ceconi C, Christodorescu RM, Daskalopoulou SS, Ferro CJ, Gerdts E, et al. 2024 ESC guidelines for the management of elevated blood pressure and hypertension. *Eur Heart J*. 2024;45:3912–4018. doi: 10.1093/eurheartj/ehae178
32. Vaura F, Kauko A, Suvila K, Havulinna AS, Mars N, Salomaa V, Cheng S, Niiranen T; FinnGen. Polygenic risk scores predict hypertension onset and cardiovascular risk. *Hypertension*. 2021;77:1119–1127. doi: 10.1161/HYPERTENSIONAHA.120.16471
33. Clarke R, Wright N, Walters R, Gan W, Guo Y, Millwood IY, Yang L, Chen Y, Lewington S, Lv J, et al; China Kadoorie Biobank Collaborative Group‡. Genetically predicted differences in systolic blood pressure and risk of cardiovascular and noncardiovascular diseases: a Mendelian randomization study in Chinese adults. *Hypertension*. 2023;80:566–576. doi: 10.1161/HYPERTENSIONAHA.122.20120
34. He J, Muntner P, Chen J, Roccella EJ, Streiffer RH, Whelton PK. Factors associated with hypertension control in the general population of the United States. *Arch Intern Med*. 2002;162:1051–1058. doi: 10.1001/archinte.162.9.1051
35. McAlister FA, Lethebe BC, Leung AA, Padwal RS, Williamson T. Visit-to-visit blood pressure variability is common in primary care patients: retrospective cohort study of 221,803 adults. *PLoS One*. 2021;16:e0248362. doi: 10.1371/journal.pone.0248362
36. Malik R, Georgakis MK, Vujkovic M, Damrauer SM, Elliott P, Karhunen V, Giontella A, Fava C, Hellwege JN, Shuey MM, et al. Relationship between blood pressure and incident cardiovascular disease: linear and nonlinear Mendelian randomization analyses. *Hypertension*. 2021;77:2004–2013. doi: 10.1161/HYPERTENSIONAHA.120.16534
37. The Blood Pressure Lowering Treatment Trialists' Collaboration. Pharmacological blood pressure lowering for primary and secondary prevention of cardiovascular disease across different levels of blood pressure: an individual participant-level data meta-analysis. *Lancet*. 2021;397:1625–1636. doi: 10.1016/S0140-6736(21)00590-0
38. Breeyear JH, Shuey MM, Edwards TL, Hellwege JN. Blood pressure polygenic scores are associated with apparent treatment-resistant hypertension. *Circ Genom Precis Med*. 2022;15:e003554. doi: 10.1161/CIRCGEN.121.003554
39. Armstrong ND, Srinivasasainagendra V, Patki A, Jones AC, Parcha V, Pampana A, Broeckel U, Lange LA, Arora P, Limdi NA, et al. Utility of a systolic blood pressure polygenic risk score with chlorthalidone response. *JAMA Cardiol*. 2024;9:1134–1141. doi: 10.1001/jamacardio.2024.3649
40. El Rouby N, Cooper-DeHoff RM. Genetics of resistant hypertension: a novel pharmacogenomics phenotype. *Curr Hypertens Rep*. 2015;17:583. doi: 10.1007/s11906-015-0583-8
41. Tähtisalo HS, Ruotsalainen S, Mars N, Porthan K, Oikarinen L, Virolainen J, Fyhrquist F, Ripatti S, Kontula KK, Hiltunen TP. Human essential hypertension: no significant association of polygenic risk scores with antihypertensive drug responses. *Sci Rep*. 2020;10:11940. doi: 10.1038/s41598-020-68878-3
42. Marston NA, Kamanu FK, Melloni GEM, Schnitzler G, Hakim A, Ma RX, Kang H, Chasman DI, Giugliano RP, Ellinor PT, et al. Endothelial cell-related genetic variants identify LDL cholesterol-sensitive individuals who derive greater benefit from aggressive lipid lowering. *Nat Med*. 2025;31:963–969. doi: 10.1038/s41591-025-03533-w
43. Desai AS, Webb DJ, Taubel J, Casey S, Cheng Y, Robbie GJ, Foster D, Huang SA, Rhyee S, Sweetser MT, et al. Zilebesiran, an RNA interference therapeutic agent for hypertension. *N Engl J Med*. 2023;389:228–238. doi: 10.1056/NEJMoa2208391
44. Cluett JL, Blazek O, Brown AL, East C, Ferdinand KC, Fisher NDL, Ford CD, Griffin KA, Mena-Hurtado CI, Sarathy H, et al; American Heart Association Council on Hypertension; Council on Cardiovascular and Stroke Nursing; Council on the Kidney in Cardiovascular Disease; and Council on Peripheral Vascular Disease. Renal denervation for the treatment of hypertension: a scientific statement from the American Heart Association. *Hypertension*. 2024;81:e135–e148. doi: 10.1161/HYP.0000000000000240