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Association of a Multi-Ancestry Genome-Wide Blood Pressure Polygenic Risk Score with Adverse Cardiovascular Events

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Abstract

Background ––Traditional cardiovascular (CV) risk factors and the underlying genetic risk of elevated blood pressure (BP) determine an individual's composite risk of developing adverse CV events. We sought to evaluate the relative contributions of the traditional CV risk factors to the development of adverse CV events in the context of varying BP genetic risk profiles.

Methods ––Genome-wide polygenic risk score (PRS) was computed using multi-ancestry genome-wide association estimates among US adults who underwent whole-genome sequencing in the Trans-Omics for Precision program. Individuals were stratified into high, intermediate, and low genetic risk groups (>80th, 20–80th, <20th centiles of systolic BP [SBP] PRS). Based on the ACC/AHA Pooled Cohort Equations (PCE), participants were stratified into low and high

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Supplemental Materials:
Supplemental Methods
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(10y-ASCVD risk: <10% or ≥10%) CV risk factor profile groups. The primary study outcome was incident CV event (composite of incident heart failure, incident stroke, and incident coronary heart disease).

Results ——Among 21,897 US adults (median age:56 years; 56.0% women; 35.8% non-White race/ethnicity), 1 SD increase in the SBP PRS, computed using 1.08 million variants, was associated with systolic BP (β:4.39 [95%CI:4.13–4.65]) and HTN (OR:1.50 [95%CI:1.46–1.55]), respectively. This association was robustly seen across racial/ethnic groups. Each SD increase in SBP PRS was associated with a higher risk of the incident CVD (HR_{adj}:1.07 [95%CI:1.04–1.10]) after controlling for ACC/AHA PCE risk scores. Among individuals with a high SBP PRS, low ASCVD risk was associated with a 58% lower hazard for incident CVD (HR_{adj}:0.42 [95%CI:0.36–0.50]) compared to those with high ASCVD risk. A similar pattern was noted in intermediate and low genetic risk groups.

Conclusions ——In a multi-ancestry cohort of >21,000 US adults, genome-wide SBP PRS was associated with BP traits and adverse CV events. Adequate control of modifiable CV risk factors may reduce the predisposition to adverse CV events among those with a high SBP PRS.

Keywords

Hypertension; Coronary Heart Disease; Genomics; Heart Failure; Polygenic Risk Score; Stroke; Precision Medicine

Introduction

High blood pressure (BP) is the leading modifiable cause of premature mortality globally.[1, 2] Elevated BP, with an estimated 30–50% heritability, is considered a precursor phenotype for the development of cardiovascular disease (CVD) events, including heart failure (HF), stroke, and coronary heart disease (CHD).[2–4]

A polygenic risk score (PRS) aggregates the risk conferred by multiple common DNA sequence variants into a single predictor, and a BP PRS can be used to estimate an individual's genetic risk of elevated BP and hypertension (HTN).[5–8] A genome-wide PRS integrates the cumulative effects of common genetic variants across the genome and provides a more inclusive understanding of the genetic risk of CV diseases. PRSs for BP (both genome-wide and genome-wide association study [GWAS]-significant variants only) have previously demonstrated efficacy in predicting adverse CV events in European ancestry populations.[5–9] Due to the predominantly European ancestry composition of existing genomic biobanks and GWAS populations, a multi-ancestry genome-wide BP PRS has not been evaluated for association with BP traits and adverse CV events.[9]

The ACC/AHA Pooled Cohort Equations (PCE), which includes BP, robustly predicts the risk of adverse CV events in the US population.[10, 11] To our knowledge, the relative contributions of traditional CV risk factors (captured using ACC/AHA PCE[11]) to the risk of developing adverse CV events in the presence of varying genetic risk of elevated BP (captured using a genome-wide BP PRS) has not been examined in a multi-ancestry population. Further, the incremental contribution of a genome-wide multi-ancestry BP PRS

beyond the ACC/AHA PCE for CVD risk prediction has not been assessed in a multi-ancestry cohort.

This report entails the findings from an investigation of a genome-wide systolic BP (SBP) PRS constructed in a multi-ancestry cohort of over 21,000 US adults to examine: 1) the association of SBP PRS with BP traits (systolic BP, diastolic BP, mean arterial pressure [MAP], pulse pressure [PP], HTN) (overall and stratified by self-reported race/ethnicity); 2) the association of SBP PRS with CVD events; 3) the association of traditional CV risk factor profiles with CVD events stratified by SBP PRS categories; and 4) the incremental contribution of SBP PRS to CVD risk prediction using the ACC/AHA PCE.

Methods

Anonymized data and materials are publicly available at the National Center for Biotechnology Information (NCBI) database of Genotypes and Phenotypes (dbGaP), and All of Us Researcher Workbench and can be accessed at https://www.ncbi.nlm.nih.gov/gap/ and https://www.researchallofus.org/. All participants provided written and informed consent with approval from the respective local IRBs. The ethical oversight for this study was provided by the University of Alabama at Birmingham IRB. The overall study design is summarized in Figure 1, and the full study methods are available as Supplementary Methods.

Results

Among 21,897 individuals free of prevalent cardiovascular disease in the NHLBI TOPMed pooled cohorts, 56.0% were women, and 35.8% were from a racial/ethnic minority group (28.2% Black individuals, 4.7% Hispanic individuals, 2.8% Asian individuals, and 0.1% other race/ethnicity). Baseline population characteristics stratified by SBP PRS categories are presented in Table 1.

Association of SBP PRS with BP Traits Across Multi-Ancestry Populations

Of the candidate genome-wide PRSs examined, we identified the highest performing PRS, developed using the PRS-CS-auto Φ (phi) approach utilizing the β estimates for SBP, composed of 1,080,806 single nucleotide variants, and having an adjusted R^2 of 0.25 for association with SBP (Supplementary Table I). Further validation in the multi-ancestry *All of Us* cohort noted that PRS-CS-auto Φ based SBP PRS (adjusted R^2: 0.16) performed better than the best C+T-based SBP PRS (C+T: $P< 0.05$, R^2=0.8, 500kb window; adjusted R^2: 0.15) for association with SBP. All subsequent analyses were performed using this PRS (hereafter referred to as SBP PRS). In the multi-ancestry NHLBI TOPMed pooled cohorts, the SBP PRS, quantified per standard deviation of increase, demonstrated a robust relationship with SBP (β:4.39, 95%CI:4.13–4.65 mmHg), DBP (β:2.04, 95%CI:1.89–2.19 mmHg), MAP (β:2.82, 95%CI:2.65–3.00 mmHg), PP (β:2.35, 95%CI:2.17–2.53 mmHg), and HTN (OR:1.50, 95%CI:1.46–1.55) (Figure 2) ($P<2.8\times10^{-142}$ for all). Individuals in the high SBP PRS group (132 [118,148] mmHg) had a median SBP 13 mmHg higher than those with low SBP PRS (119 [107,135] mmHg) (Table 1). The BP traits across SBP PRS categories are shown in Table 1. The distribution of the SBP PRS

stratified by prevalent HTN and study outcomes across the study population and among individual racial/ethnic subgroups are depicted in Supplementary Figures I–V. Among White individuals, the β values (mmHg) per SD increase in SBP PRS for SBP, DBP, MAP, and PP were 5.43 (95%CI:5.12–5.74), 2.54 (95%CI:2.35–2.72), 3.50 (95%CI:3.29–3.71), and 2.90 (95%CI:2.68–3.11), respectively. An increase in SBP PRS among Black individuals demonstrated a robust but attenuated association (smaller β coefficients per SD) with SBP (2.04, 95%CI:1.53–2.56), DBP (0.99, 95%CI:0.69–1.29), MAP (1.34, 95%CI:0.99–1.69), and PP (1.06, 95%CI:0.70–1.41). Among Hispanic individuals, β values per SD increase in SBP PRS for SBP, DBP, MAP, and PP were 5.66 (95%CI:4.38–6.95) mmHg, 2.50 (95%CI:1.84–3.16) mmHg, 3.56 (95%CI:2.74–4.37) mmHg, and 3.16 (95%CI:2.28–4.03) mmHg, respectively. Similar to other racial/ethnic groups, SBP PRS had robust associations with SBP (β:3.15, 95%CI:1.43–4.87 mmHg), DBP (β:1.25, 95%CI:0.34–2.16 mmHg), MAP (β:1.88, 95%CI:0.76–3.01 mmHg), and PP (β:1.90, 95%CI:0.79–3.01 mmHg) among Asian individuals. Each SD increase in SBP PRS was associated with increased odds of HTN among White (OR:1.67, 95%CI:1.61–1.74), Black (OR:1.19, 95%CI:1.13–1.26), Hispanic (OR:1.75, 95%CI:1.50–2.03), and Asian individuals (OR:1.35, 95%CI:1.13–1.26). The association of SBP PRS with BP traits across racial/ethnic groups among those not on antihypertensive medications is shown in Supplementary Table II. The association of SBP PRS with BP traits was validated in the multi-ancestry ACCORD and the *All of Us* study sample, demonstrating a robust association with BP traits (Supplementary Table III).

Risk of Adverse Cardiovascular Events Across SBP PRS Categories

Primary Outcome: Incident CVD—In our multi-ancestry study population, there were 5,461 incident CVD events over a median follow-up of 14.1 (IQR: 10.1, 21.9) years. Incidence rates of incident CVD events among individuals with low, intermediate, and high SBP PRS (per 1000-py) were 13.59 (12.75–14.49), 16.20 (15.66–16.76), and 17.85 (16.87–18.88), respectively (Supplementary Table IV). Compared with individuals in the low SBP PRS group (referent group), those in the intermediate (multivariable-adjusted hazards ratio [HR_{adj}]: 1.10, 95%CI:1.02–1.19) and high SBP PRS (HR_{adj}:1.16, 95%CI:1.06–1.26) groups had higher adjusted hazard ratios for the incident CVD outcome.

Secondary Outcomes—During a median follow-up of 14.5 (10.3, 22.2) years, there were 4,615 incident CVD events. The incidence rates among low, intermediate, and high SBP PRS groups (per 1000-py) were 11.50 (10.30–11.85), 13.28 (12.80–13.78), and 14.50 (13.64–15.42), respectively. Individuals with intermediate (1.11, 95%CI:1.03–1.21) and high SBP PRS (1.17, 95%CI:1.06–1.29) had higher adjusted hazard ratios for incident CVD compared with those with low SBP PRS (referent).

There were 2,435 incident HF events over a median follow-up of 14.6 (10.9, 23.0) years. HF incidence rates (per 1000-py) were 5.81 (5.28–6.39), 6.72 (6.38–7.07), and 7.64 (7.03–8.30) among individuals with low, intermediate, and high SBP PRS, respectively. Individuals with intermediate (HR_{adj}:1.06, 95%CI:0.95–1.19) and high SBP PRS (HR_{adj}:1.16, 95%CI:1.02–1.32) had higher adjusted hazard ratios for incident HF compared with those with low SBP PRS.

During a median follow-up of 14.5 (10.6, 22.8) years, there were 3,120 incident CHD events. The CHD incidence rates among low, intermediate, and high SBP PRS groups (per 1000-py) were 7.20 (6.60–7.84), 8.89 (8.50–9.30), and 9.51 (8.83–10.25), respectively. Compared with those with low SBP PRS, individuals with intermediate (HR_{adj}:1.16, 95%CI:1.05–1.28) and high SBP PRS (HR_{adj}:1.20, 95%CI:1.06–1.34) had higher adjusted hazard ratios for incident CHD.

There were 1,903 incident stroke events over a median follow-up of 14.7 (IQR: 11.8, 24.7) years. Stroke incidence rates in individuals with low, intermediate, and high SBP PRS (per 1000-py) were 4.24 (3.80–4.73), 5.14 (4.85–5.44), and 5.68 (5.17–6.25), respectively. Individuals with intermediate (HR_{adj}:1.07, 95%CI:0.94–1.21) and high SBP PRS (HR_{adj}:1.15, 95%CI:1.01–1.35) had higher adjusted hazard ratios for incident stroke compared with those having low SBP PRS.

Supplementary Table IV and Supplementary Figures VI–X summarize the incidence rates and hazard ratios for risks of all study outcomes stratified by racial/ethnic groups. The age-stratified risks of study outcomes per SD increase in SBP PRS are in Supplementary Table V.

Age at Disease Onset for Study Outcomes—There was a higher proportion of individuals with a high SBP PRS among participants who developed the incident cardiovascular disease event at age <50 and age 50–60 years (Supplementary Figure XI). There was a higher proportion of individuals with a low SBP PRS among participants who developed the incident cardiovascular disease event at age ≥70 years.

Risk of Adverse Cardiovascular Events Across Traditional Risk Score Category

The study population was stratified on the basis of traditional risk scores (10-yr ACC/AHA PCE-based ASCVD risk ≥ or <10%) and genetic risk for elevated BP (low, intermediate, and high SBP PRS). Compared with individuals having low SBP PRS and low ASCVD risk (referent group), there was a higher risk of the incident CVD outcome among those with low SBP PRS and high ASCVD risk (HR_{adj}:2.59, 95%CI:2.24–2.98), intermediate SBP PRS and low ASCVD risk (HR_{adj}:1.14, 95%CI:1.02–1.28), intermediate SBP PRS and high ASCVD risk (HR_{adj}:3.10, 95%CI:2.75–3.50), high SBP PRS and low ASCVD risk (HR_{adj}:1.36, 95%CI:1.19–1.56), and high SBP PRS and high ASCVD risk (HR_{adj}:3.32, 95%CI:2.91–3.78) (Figure 3, Supplementary Table VI). There was a statistically significant negative interaction between the ASCVD risk group and the SBP PRS group on study outcomes ($P_{interaction}$<0.05 for all). Associations of study outcomes with SBP PRS among individuals stratified by ASCVD risk are shown in Supplementary Table VII. Among the sub-group of individuals with a high genetic risk of elevated BP (high SBP PRS), there was a lower risk of the incident CVD outcome (HR_{adj}:0.42, 95%CI:0.36–0.50), incident ASCVD (HR_{adj}:0.38, 95%CI:0.32–0.46), incident HF (HR_{adj}:0.45, 95%CI:0.36–0.58), incident CHD, (HR_{adj}:0.34, 95%CI:0.27–0.43) and incident stroke (HR_{adj}:0.43, 95%CI:0.33–0.57) among the low ASCVD risk group, compared with the high ASCVD risk group (referent)(Table 2). Within each SBP PRS group, individuals with high ASCVD risk (compared to those with low ASCVD risk) had a greater risk of incident ASCVD, incident HF, incident CHD,

and incident stroke (Figure 3, Table 2). Similar findings were noted when using the PCE threshold of 7.5% (Supplementary Figure XII).

Adverse Cardiovascular Risk Prediction for SBP PRS Compared with Clinical Risk Score

There was a weak correlation (r=0.05; P<0.001) between SBP PRS and the ACC/AHA PCE-based risk score (Supplementary Figure XIII). After controlling for the traditional CV risk factors (using ACC/AHA PCE ASCVD risk) and population stratification (10 PCs of genetic ancestry), each SD increase in SBP PRS was associated with a 10-year risk of 1.07 (95%CI:1.04–1.10), 1.08 (95%CI:1.05–1.11), 1.05 (95%CI:1.00–1.09), 1.09 (95%CI:1.05–1.13), and 1.07 (95%CI:1.02–1.12) for incident CVD, incident ASCVD, incident HF, incident CHD, and incident stroke, respectively. The risk prediction metrics (estimated using C-statistics, χ^2 likelihood ratio, and adjusted R^2) for the inclusion of SBP PRS along with clinical risk score did not demonstrate an improvement in 10-year risk prediction for the study outcomes (Table 3). The AUCs depicted in Supplementary Figures XIV demonstrate a similar scale of improvement in risk prediction for the study outcomes. Using the ACC/AHA PCE risk threshold of 10%, there was a risk reclassification improvement of 3.4% for cases and 5.3% for non-cases. On a continuous scale, the addition of SBP PRS to ACC/AHA PCE improved reclassification for the incident CVD outcome by 3.4% for cases and 7.3% for non-cases. A similar modest improvement in reclassification, both continuous and categorical, was also noted for all secondary outcomes (Table 4). The addition of SBP PRS to ACC/AHA PCE led to a small improvement in risk discrimination for all study outcomes (IDI ranging from 0.001 to 0.003). The reclassification metrics using the categorical PCE threshold of 7.5% are reported in Supplementary Table VIII.

Validation of the Study Findings in ACCORD Study

In the multivariable-adjusted model in the ACCORD study sample, each SD increase in SBP PRS was associated with an increased hazard ratio for the incident CVD outcome (HR_{adj}:1.13, 95%CI:1.06–1.19), incident ASCVD (HR_{adj}:1.10, 95%CI:1.03–1.17), incident HF (HR_{adj}:1.18, 95%CI:1.06–1.30), incident CHD (HR_{adj}:1.10, 95%CI:1.03–1.17), and incident stroke (HR_{adj}:1.15, 95%CI:0.96–1.34). As in the primary analysis, the inclusion of SBP PRS along with the clinical risk score did not significantly improve the 10-year risk prediction for the study outcomes in the ACCORD study (Supplementary Table IX).

Association of SBP PRS, CHD PRS, and Stroke PRS with Study Outcomes

Table 5 summarizes the association of CHD PRS[12] and Stroke PRS[13] with all study outcomes when accounting for the risk conferred by SBP PRS in the independent ACCORD study sample. Notably, the association of SBP PRS with the study outcomes is retained even when accounting for the CHD PRS and Stroke PRS, respectively.

Discussion

In this comprehensive investigation involving a multi-ancestry cohort of >21,000 US adults, a robust cross-sectional association of a multi-ancestry genome-wide SBP PRS (constructed using a Bayesian approach with ~1.1 million variants) with BP traits was observed, both overall and across subgroups of self-identified race/ethnicity. Second, increased genetic risk

for elevated BP (measured using SBP PRS) also predisposed individuals to an increased risk of adverse CV events such as HF, CHD, or stroke, after accounting for traditional CV risk factors (including clinically measured BP). Third, among those with a high genetic predisposition to elevated BP, a low traditional CV risk factor burden (low ACC/AHA PCE risk) was associated with a lower risk of adverse CV events. Fourth, in a multi-ancestry cohort of middle-aged adults, SBP PRS did not significantly improve adverse CV risk prediction beyond the ACC/AHA PCE. Lastly, the SBP PRS retains its risk prediction ability for adverse CV events even when accounting for existing CHD PRS and Stroke PRS.

Elevated BP is a major modifiable risk factor for multiple incident CVD phenotypes (HF, CHD, and stroke), and prior studies have established a graded association of elevated BP with the development of incident CVD.[14–16] This investigation extends these observations to a large multi-ancestry cohort by demonstrating that a genome-wide SBP PRS is associated with BP traits and HTN, cross-sectionally, and with the risk of adverse CV events prospectively, across self-reported racial/ethnic groups. Genomic medicine has generally been limited by a focus on primarily populations of European ancestry. The applicability of SBP PRS across ancestral groups in our investigation enhances the generalizability and potential future clinical utilization of the SBP PRS. There may be substantial heterogeneity and variability in the measurement of BP[3], but BP-associated genotype (i.e., SBP PRS) may provide precise quantification of the lifetime risk for CV events due to elevated BP. This study noted that the genetic risk for elevated BP (summarized using SBP PRS) was associated with CVD events, even after accounting for traditional CV risk factors, including clinically measured BP. This observation substantiates the evidence from other investigators demonstrating that genetic risk scores comprising lipids or diabetes-associated genetic loci may provide a more consistent and accurate prediction for the development of cardiometabolic disease events than standard clinical biomarkers[15].[17–19] However, it was noted that elevated risk for adverse CV events conferred by a high SBP PRS might be offset by controlling the traditional CV risk factors. This premise is evidenced by our finding that those with a high genetic risk of elevated BP but with a low traditionally measured CV risk (10-yr ASCVD <10%) have a lower risk of developing adverse CV events. While the genetic risk for elevated BP may be potentially non-modifiable and set at birth, the traditional CV risk factors evolve over the life course[20, 21] and can be modified through aggressive risk factor control. Our findings challenge the traditional deterministic interpretation of inherited genetic risk by demonstrating substantially lower incidence rates of CV events (incident ASCVD, CHD, HF, and stroke) among individuals with lower traditional CV risk factor burdens across genetic risk categories.

With the widespread availability of large-scale genomic sequencing[22] and direct-to-consumer genetic testing, the potential application of SBP PRS for the primary prevention of adverse CV events in a multi-ancestry population warrants further investigation. The one-time assessment of the genome-wide genetic variations associated with increased BP and CV risk, may serve as a tool for predicting adverse CV event risk, alongside the evolving clinical CV risk prediction. In addition, SBP PRS may also find utility in predicting the response to anti-hypertensive therapy. Despite its appeal, the clinical application of state-of-the-art PRSs requires careful consideration of the appropriate population. The SBP PRS examined in this study faces a similar challenge for implementation in the right population.

As noted in our investigation, the SBP PRS in its current form may be of limited utility in CV risk prediction in a middle-aged cohort where the ACC/AHA PCE provides similar risk quantification.

A prevention paradox for CV diseases has been previously described wherein a sizeable proportion of individuals developing adverse CV events are at low predicted risk of CV events based on traditional risk factors, and thus preventive efforts may not be directed toward them.[23] Prior investigations evaluating the genetic risk of CHD in middle-aged adults demonstrated modest efficacy in incident CHD risk prediction and net reclassification for CHD PRS beyond traditional CV risk factors.[10, 24, 25] The current work indicates that SBP PRS has numerous clinical applications as it predicts multiple CV outcomes instead of being limited to just one phenotype and retains its association even when accounting for prior CHD PRS[12] and Stroke PRS[13]. Given the higher proportion of individuals with a high SBP PRS among those with early onset CV disease in this investigation, examination of PRS utility in the low-risk younger adult population is warranted. Furthermore, as noted by the significant negative interaction of the ASCVD risk group on the association of SBP PRS groups with study outcomes indicates that the SBP PRS may have greater utility in risk prediction among individuals with low ASCVD risk. Hence, SBP PRS may have a role in mitigating the prevention paradox. The SBP PRS may be useful for younger adults or those with a low traditional risk factor burden, in whom primary prevention efforts are targeted through BP-lowering and lipid-lowering therapies, glycemic control, healthy diet adherence, physical activity promotion, and smoking cessation. However, there is an unmet need to assess the potential benefits (reduction of years lost due to disability from ASCVD events) and harms (anxiety, declined adherence to healthy lifestyle in low genetic risk individuals) of early disclosure of the genetic risk for CV events, through randomized controlled clinical trials in younger adults prior to the onset of ASCVD events.[26, 27]

The current findings are an advancement over prior literature, which was limited by a lack of inclusion of US populations, exclusion of individuals from non-European ancestry, or evaluation of only incident CHD events.[10, 24, 25] The estimates reported in the current investigation are supportive of a multi-ancestry SBP PRS having a robust association with BP traits.[28] In line with prior investigations, the current study noted a robust albeit relatively attenuated association of SBP PRS with BP traits and adverse CV outcomes in individual racial/ethnic groups, which may be attributed to trans-ethnic allele frequency differences, varying genetic architectures, and differing impact of gene-environment interaction on BP traits.[29–31] With the growing recognition of the marginalization of non-European ancestry individuals from genomic medicine, it is important to assess novel clinical and genomic medicine tools in individuals from diverse ancestral backgrounds.[9] Limited trans-ethnic transferability of PRS has been reported previously, with a reduced or lack of risk prediction ability of European ancestry GWAS-based PRSs in non-European ancestry populations.[29–31] The current study attempts to overcome this by using multi-ancestry base data from UK Biobank and providing a comprehensive investigation of the SBP PRS through the evaluation of its association with BP traits and multiple adverse CV outcomes across varying traditional risk-factor profiles in a diverse multi-ancestry US population.

Limitations

The study has several limitations. First, the SNP weights were derived from the multi-ancestry pan-UKBB GWAS, with a relatively higher number of European ancestry individuals. This may have contributed to the relatively weaker association of the PRS with BP traits in Black individuals. However, similar to this report recent investigations have noted that multi-ancestry PRSs perform well within overall and within specific ancestries than ancestry-specific PRSs (where base data used to derive the effect estimates for constructing the PRS is from the same ancestry).[32] As genomic discovery expands, more multi-ancestry "base" data may help improve the SBP PRS performance across multi-ancestry populations. Second, the SBP PRS was derived from SBP-associated SNPs, which may contribute to the relatively weaker association of the PRS with other BP traits such as DBP, MAP, and PP. Third, the included cohorts also contributed to the PCE derivation, and this may lead to a potential underestimation of the risk prediction ability of the SBP PRS. However, the SBP PRS was noted to be predictive of BP traits and adverse CV outcomes in an independent population. Fourth, the estimates for association with study outcomes were attenuated in the validation population, which may be attributed to a shorter follow-up duration (4.7 years vs. 14.1 years) and lower event frequency (incident CVD outcomes: 15.5% vs. 24.9%) compared with the NHLBI TOPMed study sample. Fifth, while this study used the ACC/AHA PCE 10% threshold to stratify the population based on traditional CV risk factors, it is feasible that the PRS performance may vary at different thresholds. Hence, a continuous NRI was also computed in the study population. Sixth, the ACC/AHA PCE has non-modifiable and modifiable components. Among high SBP PRS individuals, the modifiable CV risk factors may be mitigated through pharmacological and lifestyle interventions, there may be non-modifiable residual CV risk conferred by age, sex, and social determinants of health. Seventh, while the genetic risk is set at birth and exerts its effects over the lifetime, this study does not estimate the lifetime risk of CV events. Eighth, the pleiotropic effects of SBP PRS on traditional risk factors and adverse CV outcomes cannot be accounted for in the current study design. Lastly, the investigation was limited to individuals >40 years of age to ensure comparability of SBP PRS with the ACC/AHA PCE.

Conclusions

Among a multi-ancestry cohort of >21,000 US adults, a genome-wide SBP PRS was associated with BP traits and an increased risk of incident CV events (HF, CHD, and stroke) beyond traditional CV risk factors. This observational study suggests that an increased genetic risk for BP and adverse CV events may be mitigated by rigorous control of the modifiable traditional CV risk factors, a premise that warrants further investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Non-Standard Abbreviations and Acronyms

ASCVD	Atherosclerotic Cardiovascular Disease
PRS	Polygenic Risk Score
PCE	Pooled Cohorts Equation
TOPMed	Trans-Omics for Precision Medicine (TOPMed) program

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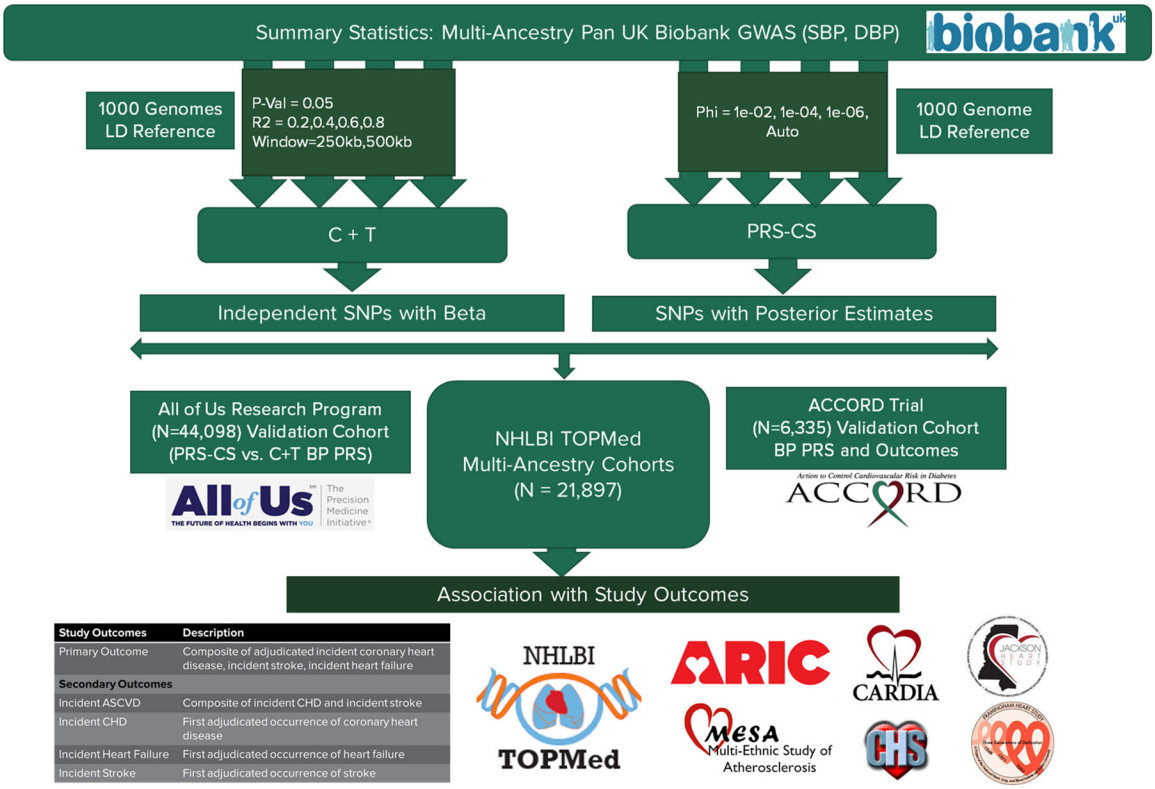

Figure 1.
Overall Structure of the Study Investigation.

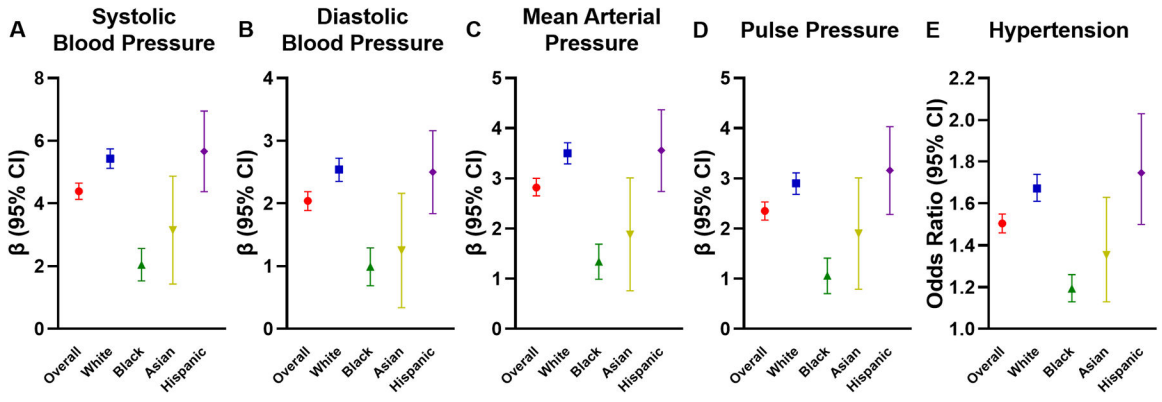

Figure 2.

Association of Genome-Wide Systolic Blood Pressure Polygenic Risk Score With Blood Pressure Traits. All models are adjusted for age, sex, study cohort, and the first 10 principal components of genetic ancestry. In Panels A-E, the whiskers represent the 95% confidence interval.

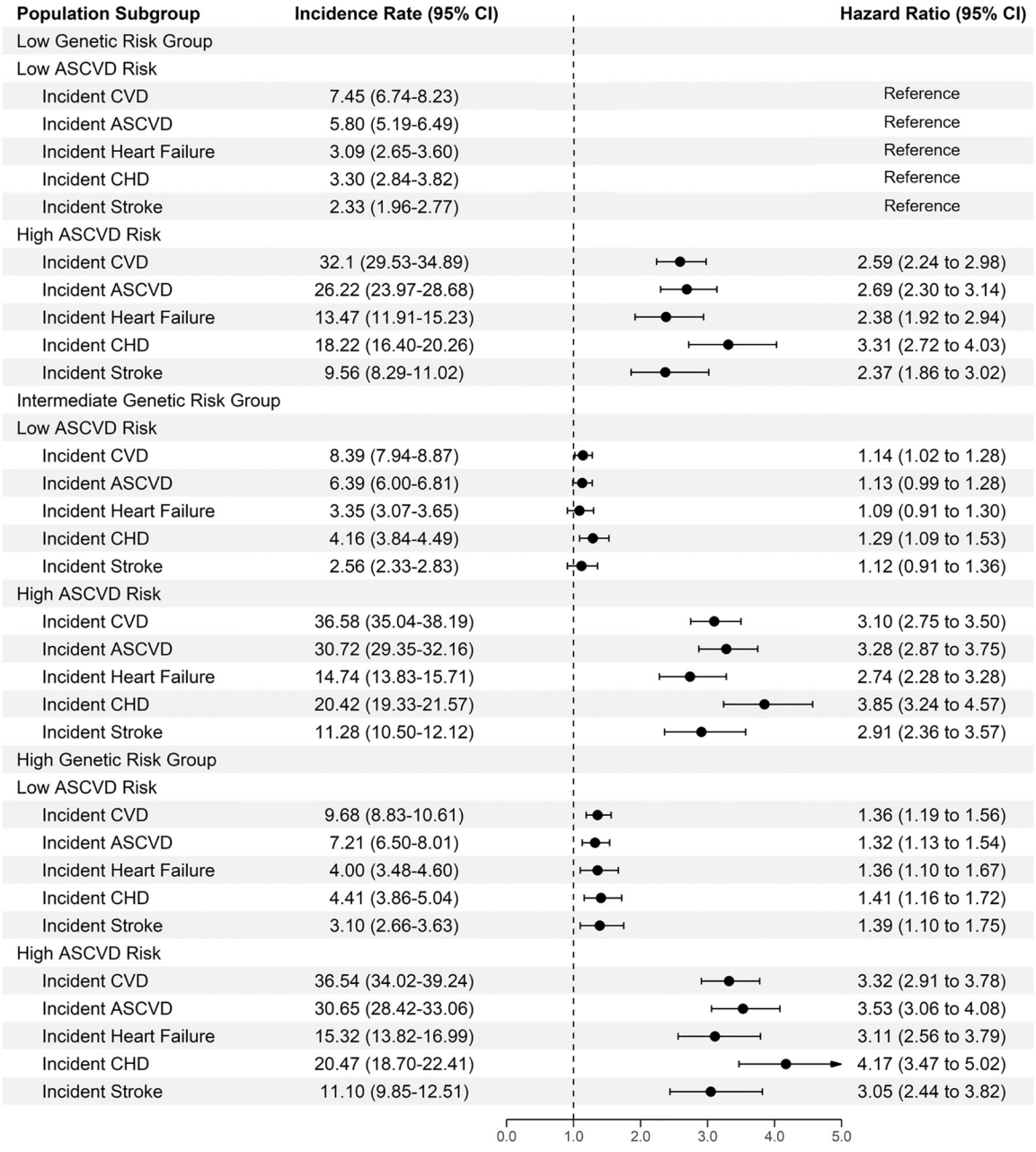

Figure 3.

Risk of Study Outcomes According to Genetic Risk and Traditional Cardiovascular Risk. The figure depicts the incidence rates and adjusted hazard ratio for each of the study outcomes, according to the genetic risk (systolic blood pressure polygenic risk score) and traditional cardiovascular risk (assessed using pooled cohorts equation). Individuals with low genetic risk and low atherosclerotic cardiovascular disease event risk served as the referent population. The incidence rates are reported in 1000-person years. The Pinteraction (ASCVD Risk Group*SBP PRS Group) for the incident CVD outcome is <0.001 (β±SE: −0.15±0.04), for the incident ASCVD is <0.001 (β±SE: −0.22±0.04), for incident heart

failure is 0.003 (β±SE: −0.16±0.05), incident CHD is <0.001 (β±SE: −0.24±0.05), and incident stroke is 0.005 (β±SE: −0.17±0.06).

Table 1.

Baseline Characteristics of the Study Population

Characteristics	Overall (n=21,897)	Low BP PRS (n=4,381)	Intermediate BP PRS (n=13,135)	High BP PRS (n=4,381)	P-Value
Age	56.0 (49.0, 64.4)	56.0 (49.0, 65.0)	56.0 (49.0, 64.7)	55.6 (49.0, 63.5)	0.002
Sex					
Male	9,640 (44.0%)	2,000 (45.7%)	5,765 (43.9%)	1,875 (42.8%)	0.02
Female	12,257 (56.0%)	2,381 (54.3%)	7,370 (56.1%)	2,506 (57.2%)	
BMI (kg/m2)	27.1 (24.2, 30.8)	26.9 (24.1, 30.6)	27.1 (24.2, 30.8)	27.5 (24.4, 31.2)	<0.001
Race/Ethnicity					
White	14,069 (64.2%)	2,814 (64.2%)	8,441 (64.3%)	2,814 (64.2%)	0.98
Black or African American	6,186 (28.2%)	1,237 (28.2%)	3,711 (28.3%)	1,238 (28.3%)	
Hispanic	1,022 (4.7%)	205 (4.7%)	621 (4.7%)	205 (4.7%)	
Asian	606 (2.8%)	121 (2.8%)	364 (2.8%)	121 (2.8%)	
Other	14 (0.1%)	4 (0.1%)	7 (0.1%)	3 (0.1%)	
Systolic BP (mmHg)	126 (112, 143)	119 (107, 135)	126 (113, 143)	132 (118, 148)	<0.001
Diastolic BP (mmHg)	76 (68, 84)	73 (65, 81)	76 (68, 84)	78 (71, 87)	<0.001
Mean Arterial Pressure (mmHg)	93 (83, 103)	88 (80, 99)	93 (84, 103)	97 (87, 106)	<0.001
Pulse Pressure (mmHg)	49 (41, 61)	46 (39, 57)	49 (41, 61)	52 (43, 65)	<0.001
LDL (mg/dL)	124.4 (102.0, 149.0)	122.8 (100.9, 148.0)	124.6 (102.0, 149.0)	126.0 (103.0, 150.8)	0.06
HDL (mg/dL)	50.0 (41.0, 61.0)	50.1 (41.0, 62.0)	50.0 (41.0, 61.0)	49.0 (40.0, 60.7)	<0.001
Triglycerides (mg/dL)	108.0 (77.0, 155.0)	105.0 (75.0, 149.0)	107.0 (77.0, 155.0)	112.0 (79.0, 161.0)	<0.001
Total Cholesterol (mg/dL)	202.0 (178.0, 228.0)	201.0 (177.0, 228.0)	202.0 (178.0, 228.0)	203.0 (179.0, 230.0)	0.02
eGFR (mL/min/1.73 m ^{2})	75.9 (64.1, 89.0)	75.9 (64.8, 89.1)	75.6 (63.9, 88.7)	76.3 (64.0, 90.3)	0.26
Smoking Status					
Never	10,431 (47.6%)	2,038 (46.5%)	6,324 (48.1%)	2,069 (47.2%)	0.002
Former	7,425 (33.9%)	1,565 (35.7%)	4,433 (33.7%)	1,427 (32.6%)	
Current	4,007 (18.3%)	771 (17.6%)	2,363 (18.0%)	873 (19.9%)	
Hypertension	9,974 (45.5%)	1,495 (34.1%)	5,956 (45.3%)	2,523 (57.6%)	<0.001
Diabetes Mellitus	2,584 (11.8%)	463 (10.6%)	1,494 (11.4%)	627 (14.3%)	<0.001
Lipid Lowering Medication Use	1,255 (5.7%)	245 (6.2%)	736 (6.3%)	274 (7.0%)	0.20
Anti-Hypertensive Medication Use	6,209 (28.4%)	904 (20.6%)	3,695 (28.2%)	1,610 (36.8%)	<0.001
Study Cohort					
ARIC	7,944 (36.3%)	1,473 (33.6%)	4,707 (35.8%)	1,764 (40.3%)	<0.001
MESA	4,587 (20.9%)	1,010 (23.1%)	2,738 (20.8%)	839 (19.2%)	
FHS	2,564 (11.7%)	561 (12.8%)	1,530 (11.6%)	473 (10.8%)	
CHS	2,386 (10.9%)	469 (10.7%)	1,494 (11.4%)	423 (9.7%)	
JHS	2,283 (10.4%)	423 (9.7%)	1,379 (10.5%)	481 (11.0%)	

Characteristics	Overall (n=21,897)	Low BP PRS (n=4,381)	Intermediate BP PRS (n=13,135)	High BP PRS (n=4,381)	P-Value
CARDIA	2,133 (9.7%)	445 (10.2%)	1,287 (9.8%)	401 (9.2%)	
Study Outcomes					
Incident CVD	5,461 (24.9%)	936 (21.4%)	3,309 (25.2%)	1,216 (27.8%)	<0.001
Incident ASCVD	4,615 (21.1%)	784 (17.9%)	2,805 (21.4%)	1,026 (23.4%)	<0.001
Incident HF	2,435 (11.1%)	420 (9.6%)	1,458 (11.1%)	557 (12.7%)	<0.001
Incident CHD	3,120 (14.2%)	520 (11.9%)	1,912 (14.6%)	688 (15.7%)	<0.001
Incident Stroke	1,903 (8.7%)	318 (7.3%)	1,157 (8.8%)	428 (9.8%)	<0.001
Time to Incident CVD (Years)	14.1 (10.1, 21.9)	14.2 (10.2, 22.0)	14.0 (10.1, 21.9)	14.0 (10.1, 22.0)	0.25
Time to Incident ASCVD (Years)	14.5 (10.3, 22.2)	14.6 (10.4, 22.2)	14.5 (10.2, 22.1)	14.6 (10.2, 22.3)	0.49
Time to Incident HF (Years)	14.6 (10.9, 23.0)	14.5 (10.9, 23.0)	14.6 (10.9, 23.0)	14.6 (11.0, 23.2)	0.64
Time to Incident CHD (Years)	14.5 (10.6, 22.8)	14.5 (10.7, 22.8)	14.6 (10.9, 23.0)	14.5 (10.7, 23.0)	0.44
Time to Incident Stroke (Years)	14.7 (11.8, 24.7)	14.7 (11.8, 24.8)	14.7 (11.8, 24.7)	14.7 (11.8, 24.8)	0.96

Abbreviations: ARIC: Atherosclerosis risk in community; ASCVD: atherosclerotic cardiovascular disease, BP: Blood Pressure, BMI: Body mass index, CHS: Cardiovascular health study, CHD: Coronary heart disease, FHS: Framingham heart study, eGFR: estimated Glomerular Filtration Rate, HDL: High-density lipoprotein, JHS: Jackson heart study, LDL: Low-density lipoprotein, PRS: Polygenic risk score.

Note: Data are presented as median with interquartile range or counts with percentage. There were 4,062 incident CVD events, 3,529 incident ASCVD events, 2,456 incident CHD events, 1,380 incident stroke events, and 1,830 incident heart failure events among White individuals. There were 1,195 incident CVD events, 915 incident ASCVD events, 562 incident CHD events, 444 incident stroke events, and 536 incident heart failure events among Black individuals. There were 145 incident CVD events, 123 incident ASCVD events, 68 incident CHD events, 63 incident stroke events, and 49 incident heart failure events among Hispanic individuals. There were 55 incident CVD events, 45 incident ASCVD events, 31 incident CHD events, 16 incident stroke events, and 19 incident heart failure events among Asian individuals. There were 4 incident CVD events, 3 incident ASCVD events, 3 incident CHD events, 0 incident stroke events, and 1 incident heart failure events among other race/ethnicity individuals.

Table 2.

Hazard Ratios for Study Outcomes Within Respective Systolic Blood Polygenic Risk Score Groups

Study Outcomes	Low Genetic Risk		Intermediate Genetic Risk		High Genetic Risk	
	Low ASCVD Risk	High ASCVD Risk	Low ASCVD Risk	High ASCVD Risk	Low ASCVD Risk	High ASCVD Risk
Incident CVD	0.36 (0.30–0.44)	Ref.	0.40 (0.36–0.44)	Ref.	0.42 (0.36–0.50)	Ref.
Incident ASCVD	0.31 (0.25–0.38)	Ref.	0.36 (0.32–0.41)	Ref.	0.38 (0.32–0.46)	Ref.
Incident CHF	0.45 (0.34–0.60)	Ref.	0.43 (0.36–0.50)	Ref.	0.45 (0.36–0.58)	Ref.
Incident CHD	0.25 (0.19–0.33)	Ref.	0.37 (0.32–0.42)	Ref.	0.34 (0.27–0.43)	Ref.
Incident Stroke	0.38 (0.27–0.53)	Ref.	0.37 (0.31–0.44)	Ref.	0.43 (0.33–0.57)	Ref.

ASCVD: Atherosclerotic cardiovascular disease, CHD: Coronary heart disease, CVD: Cardiovascular disease, HF: Heart failure. Models are adjusted for age, sex, study, and first 10 principal components of genetic ancestry.

Table 3.

Performance Metrics of Systolic Blood Pressure Polygenic Risk (SBP PRS) and ACC/AHA Pooled Cohorts Equation (PCE)

Model	PRS only	PCE only	PRS + Study cohort + PCs 1–10	PRS + Study cohort + Age + Sex + PCs1–10	PCE+Study cohort +PCs1–10	PRS + PCE+ Study cohort + PCs1–10	
						SBP PRS	PCE
Incident CVD							
HR (95%CI)	1.10 (1.07–1.13)	1.91 (1.88–1.94)	1.10 (1.07–1.13)	1.13 (1.10–1.17)	1.87 (1.83–1.90)	1.07 (1.04–1.10)	1.86 (1.83–1.90)
P-Value	2.24E-12	5E-300	2.02E-12	4.99E-20	5E-300	8.42E-07	5E-300
C-Statistics (95%CI)	0.5265 (0.5181–0.5349)	0.7745 (0.7684–0.7806)	0.6218 (0.6127–0.6308)	0.7419 (0.7349–0.7490)	0.7611 (0.7542–0.7680)	0.7614 (0.7545–0.7683)	
Log-Likelihood Chi-Square	49.28	3536.96	1061.87	4121.46	4131.53	4155.78	
R^2	0.01	0.48	0.18	0.53	0.53	0.53	
Incident ASCVD							
HR (95%CI)	1.10 (1.07–1.14)	1.88 (1.85–1.92)	1.11 (1.08–1.14)	1.14 (1.11–1.18)	1.82 (1.79–1.86)	1.08 (1.05–1.11)	1.82 (1.78–1.85)
P-Value	2.16E-11	5E-300	2.68E-12	3.23E-19	5E-300	2.66E-07	5E-300
C-Statistics (95%CI)	0.5296 (0.5206–0.5385)	0.7710 (0.7644–0.7776)	0.6352 (0.6256–0.6449)	0.7345 (0.7266–0.7423)	0.7574 (0.7496–0.7651)	0.7576 (0.7499–0.7654)	
Log-Likelihood Chi-Square	44.84	3031.65	1064.76	3534.66	3611.00	3637.47	
R^2	0.01	0.48	0.21	0.54	0.54	0.63	
Incident Heart Failure							
HR (95%CI)	1.09 (1.05–1.13)	2.15 (2.09–2.20)	1.09 (1.05–1.13)	1.13 (1.08–1.17)	2.05 (2.00–2.11)	1.05 (1.00–1.09)	2.05 (1.99–2.11)
P-Value	2.87E-05	5E-300	2.95E-05	7.25E-09	5E-300	0.03	5E-300
C-Statistics (95%CI)	0.5128 (0.4998–0.5258)	0.8134 (0.8050–0.8218)	0.6663 (0.6517–0.6809)	0.8117 (0.8025–0.8209)	0.8086 (0.7987–0.8184)	0.8081 (0.7983–0.8179)	
Log-Likelihood Chi Square	17.51	2143.62	812.33	2745.96	2574.05	2578.61	
R^2	0.01	0.59	0.28	0.68	0.65	0.65	
Incident Coronary Heart Disease							

Model	PRS only	PCE only	PRS + Study cohort + PCs 1–10	PRS + Study cohort + Age + Sex + PCs1–10	PCE+Study cohort +PCs1–10	PRS + PCE+ Study cohort + PCs1–10	
						SBP PRS	PCE
HR (95%CI)	1.11 (1.07–1.15)	1.89 (1.84–1.93)	1.12 (1.08–1.16)	1.15 (1.11–1.19)	1.80 (1.76–1.84)	1.09 (1.05–1.13)	1.80 (1.76–1.84)
P-Value	7.05E-09	5E-300	7.25E-10	7.43E-15	5E-300	4.93E-06	5E-300
C-Statistics (95%CI)	0.5281 (0.5172–0.5389)	0.7732 (0.7653–0.7812)	0.6504 (0.6387–0.6622)	0.7400 (0.7305–0.7495)	0.7613 (0.7519–0.7707)	0.7614 (0.7520–0.7708)	
Log-Likelihood Chi Square	33.53	2121.14	942.53	2571.75	2627.99	2648.85	
R^2	0.01	0.49	0.26	0.56	0.57	0.57	
Incident Stroke							
HR (95%CI)	1.10 (1.05–1.15)	1.86 (1.81–1.91)	1.10 (1.05–1.15)	1.13 (1.08–1.18)	1.81 (1.76–1.87)	1.07 (1.02–1.12)	1.81 (1.76–1.87)
P-Value	3.48E-05	5E-300	5.30E-05	2.06E-07	5E-300	5E-03	5E-300
C-Statistics (95%CI)	0.5325 (0.5186–0.5464)	0.7688 (0.7585–0.7791)	0.6137 (0.5982–0.6292)	0.7361 (0.7242–0.7480)	0.7526 (0.7406–0.7646)	0.7535 (0.7415–0.7654)	
Log-Likelihood Chi Square	17.14	1177.32	304.88	1353.64	1321.12	1328.93	
R^2	0.01	0.46	0.15	0.51	0.50	0.50	

ASCVD: Atherosclerotic cardiovascular disease, CI: Confidence interval, PC: Principal components of genetic ancestry. **Note:** Both SBP PRS and PCE are taken as continuous variables, and all values are reported per SD (standard deviation) increase in the risk score. The SBP PRS and the PCE are both normalized (mean=0, SD=1) to ensure comparison on a similar relative scale. The 10-year risk prediction metrics are reported for the study outcomes to ensure comparability of SBP PRS with PCE-based 10-year ASCVD risk prediction. The P-value for the comparison of C-statistics between the PCE-only based models and PCE+PRS models was not significant across all outcomes (P>0.05 for all).

Table 4.

Risk Discrimination Metrics (Net Reclassification Index and Integrated Discrimination Index) for Systolic Blood Pressure Polygenic Risk Score with ACC/AHA Pooled Cohorts Equation

	N	Continuous NRI	Categorical NRI (PCE-10%)	IDI
Incident CVD				
Cases	5,461	0.0342 (0.0077–0.0607)	0.0342 (0.0077–0.0607)	0.0022 (0.0014–0.0030)
Non Cases	16,436	0.0733 (0.0580–0.0885)	0.0528 (0.0375–0.0681)	
Incident Heart Failure				
Cases	2,435	0.0185 (−0.0212–0.0582)	0.0136 (−0.0262–0.0533)	0.0012 (0.0004–0.0020)
Non Cases	19,462	0.0608 (0.0468–0.0749)	0.0438 (0.0297–0.0578)	
Incident Coronary Heart Disease				
Cases	3,120	0.0333 (−0.0017–0.0684)	0.0327 (−0.0024–0.0678)	0.0020 (0.0011–0.0029)
Non Cases	18,777	0.0753 (0.0610–0.0895)	0.0489 (0.0347–0.0632)	
Incident Stroke				
Cases	1,903	0.0541 (0.0093–0.0990)	0.0520 (0.0072–0.0969)	0.0008 (0.0001–0.0014)
Non Cases	19,994	0.0640 (0.0502–0.0779)	0.0451 (0.0313–0.0590)	
Incident ASCVD Event				
Cases	4,615	0.0444 (0.0156–0.0732)	0.0427 (0.0139–0.0715)	0.0024 (0.0015–0.0032)
Non Cases	17,282	0.0805 (0.0657–0.0954)	0.0559 (0.0410–0.0708)	

Table 5:

Addition of SBP PRS to CHD PRS and Stroke PRS and their Risk Prediction Ability for Study Outcomes

Polygenic Risk Score (PRS)	Adjusted Hazard Ratio (95% CI)
Incident CVD	
CHD PRS: Model 1	1.21 (1.14–1.27)
CHD PRS (Model 1 + SBP PRS)	**1.20 (1.13–1.26)**
Stroke PRS: Model 1	1.06 (1.00–1.13)
Stroke PRS (Model 1 + SBP PRS)	1.04 (0.97–1.11)
SBP PRS: Model 1	1.13 (1.06–1.19)
SBP PRS (Model 1 + CHD PRS)	**1.11 (1.05–1.17)**
SBP PRS (Model 1 + Stroke PRS)	**1.12 (1.05–1.18)**
Incident ASCVD	
CHD PRS: Model 1	1.23 (1.16–1.3)
CHD PRS (Model 1 + SBP PRS)	**1.22 (1.15–1.29)**
Stroke PRS: Model 1	1.09 (1.02–1.16)
Stroke PRS (Model 1 + SBP PRS)	1.08 (1.00–1.15)
SBP PRS: Model 1	1.10 (1.03–1.17)
SBP PRS (Model 1 + CHD PRS)	**1.08 (1.01–1.15)**
SBP PRS (Model 1 + Stroke PRS)	**1.09 (1.02–1.16)**
Incident Heart Failure	
CHD PRS: Model 1	1.12 (1.00–1.24)
CHD PRS (Model 1 + SBP PRS)	1.10 (0.98–1.22)
Stroke PRS: Model 1	0.93 (0.80–1.05)
Stroke PRS (Model 1 + SBP PRS)	0.90 (0.77–1.02)
SBP PRS: Model 1	1.18 (1.06–1.30)
SBP PRS (Model 1 + CHD PRS)	**1.17 (1.05–1.30)**
SBP PRS (Model 1 + Stroke PRS)	**1.20 (1.08–1.33)**
Incident CHD	
CHD PRS: Model 1	1.27 (1.19–1.34)
CHD PRS (Model 1 + SBP PRS)	**1.26 (1.19–1.33)**
Stroke PRS: Model 1	1.07 (0.99–1.14)
Stroke PRS (Model 1 + SBP PRS)	1.05 (0.97–1.12)
SBP PRS: Model 1	1.10 (1.03–1.17)
SBP PRS (Model 1 + CHD PRS)	**1.08 (1.01–1.15)**
SBP PRS (Model 1 + Stroke PRS)	**1.09 (1.02–1.17)**
Incident Stroke	
CHD PRS: Model 1	1.05 (0.86–1.23)
CHD PRS (Model 1 + SBP PRS)	1.04 (0.85–1.22)
Stroke PRS: Model 1	1.26 (1.06–1.45)
Stroke PRS (Model 1 + SBP PRS)	**1.23 (1.04–1.43)**

Polygenic Risk Score (PRS)	Adjusted Hazard Ratio (95% CI)
SBP PRS: Model 1	1.15 (0.96–1.34)
SBP PRS (Model 1 + CHD PRS)	1.14 (0.95–1.33)
SBP PRS (Model 1 + Stroke PRS)	1.11 (0.91–1.30)

Model 1: PRS + age, sex, randomization arm, BMI, Total Cholesterol, SBP, Smoking Status, first 10 principal components of genetic ancestry

Model 2: Model 1 + Additional PRS (Boldening indicates significant adjusted hazard ratios in model 2)