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ORIGINAL ARTICLE

Development and Validation of Polygenic Risk Scores for Blood Pressure Traits in Continental African Populations

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BACKGROUND: Most polygenic risk scores (PRS) have been developed in European populations, frequently leading to limited transferability across diverse ancestry populations. This study aimed to develop and evaluate PRS for blood pressure (BP) traits in continental African populations and investigate how African genetic diversity influences PRS performance.

METHODS: We generated PRS for systolic BP, diastolic BP, pulse pressure, and hypertension. We used a pan-African cohort as the target population and compared single-ancestry and multi-ancestry PRS methods. We compared the performance of African ancestry-derived PRS against multi-ancestry PRS on the entire data set and within South, East, and West African subpopulations.

RESULTS: Multi-ancestry PRS demonstrated significantly higher predictive accuracy compared with single-ancestry PRS models. PRS predictive accuracy varied across different African regions, with the highest performance observed in East Africa. In the combined population, the difference in mean BP values between the first multi-ancestry PRS quartile and the top quartile was 6.53 (95% CI, 5.3–7.74), 3.81 (95% CI, 3.9–4.52), and 3.59 (95% CI, 2.4–4.32) mm Hg for systolic BP, diastolic BP, and pulse pressure, respectively. Individuals in the highest PRS risk quartile had odds of hypertension that were 1.47 (95% CI, 1.7–1.69) times greater than those in the lowest risk quartile.

CONCLUSIONS: These findings highlight the importance of integrating diverse ancestries in PRS development and accounting for subpopulation genetic variation to improve the predictive accuracy of BP PRS in African populations.

Key Words: black people ■ blood pressure ■ genetic risk score ■ genetic variation ■ genome-wide association study ■ hypertension

High blood pressure (BP) is a risk factor for multiple cardiometabolic disorders.[1] Hypertension is defined as systolic BP (SBP) values of 140 mm Hg or more or diastolic BP (DBP) values of 90 mm Hg or more, according to the 2020 International Society of Hypertension Global Hypertension practice guidelines.[2] Studies have shown a higher BP in men and a faster increase in BP with age for women.[3] High-income regions of the world have undergone a substantial decrease in mean SBP and DBP from being the highest in the world to the lowest between 1975 and 2015.[4] Pulse pressure (PP), calculated as the difference between SBP and DBP, is a predictor of

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For Sources of Funding and Disclosures, see page 267.

Nonstandard Abbreviations and Acronyms

AoU	All of Us
BP	blood pressure
DBP	diastolic blood pressure
GWAS	genome-wide association studies
OR	odds ratio
PP	pulse pressure
PRS	polygenic risk score
SBP	systolic blood pressure

cardiovascular disease in the elderly.[5] The estimated population with high BP in Africa is projected to be 216.8 million in 2030.[6] High BP is a significant cause of mortality in Africa, with a prevalence of about 54%,[7] although this varies considerably between African regions.[8]

BP levels can be influenced by lifestyle[9] and genetic factors.[10] Genome-wide association studies (GWAS) of BP for people with African ancestry are limited and have relatively small sample sizes.[11,12] The results often reveal different variants associated with BP when compared with non-African populations. Polygenic risk scores (PRSs) use summary statistics from GWAS to evaluate the cumulative effects of genetic variants on disease risk. Numerous PRS methods have been developed, each differing in how single nucleotide polymorphisms are selected and how effect sizes are weighted.[13] The optimal approach for single nucleotide polymorphism selection and weighting depends on the discovery GWAS sample size and trait-specific genetic architecture.

Previous studies have reported a strong association between BP PRS and hypertension.[14,15] However, these studies were all conducted in European and East Asian populations. Due to the lack of diversity in genetic studies, the previous BP PRSs developed have limited predictivity in African ancestry populations.[16] Continental African populations not only encompass a rich genetic diversity,[17] but also experience distinct environmental and social factors that vary widely across regions in Africa. Recently, new PRS methods have been introduced that leverage multiple discovery GWAS from diverse ancestries to enhance PRS accuracy and generalizability across populations.[18,19]

In this study, we used GWAS summary statistics from a meta-analysis of continental African individuals to develop single-ancestry PRSs for SBP, DBP, PP, and hypertension using various PRS methods. GWAS summary statistics from multiple ancestries were incorporated to develop multi-ancestry PRSs. These multi-ancestry PRSs were compared with the single-ancestry PRSs, and their associations with the traits were evaluated in participants from continental Africa. The analysis also included stratification by specific African regions to assess regional differences in predictive accuracy, as well as stratification by sex to explore sex-specific PRS associations.

METHODS

Ethical approval was obtained from the relevant ethics committees at each participating site. These included Institute of Human Virology Nigeria Health Research Ethics Committee; National Health Research Ethics Committee of Nigeria; University of Maryland School of Medicine institutional review board; Science and Ethics Committee of the Uganda Virus Research Institute; Uganda National Council for Science and Technology; Human Research Ethics Committee of the University of the Witwatersrand. The data were used in accordance with the informed consent obtained from the study participants at each site. Due to the sensitive nature of the data collected, access requests from qualified researchers trained in human subject confidentiality protocols can be directed to the respective independent cohorts outlined in the Supplemental Material. The best-performing PRS will be submitted to the Polygenic Score Catalog after publication. A detailed description of the methods is provided in the Supplemental Materials. The overall study design and analytical workflow are illustrated in Figure 1. All data and cohorts used to construct the PRSs are listed in Table S1.

RESULTS

Characteristics of Target Cohort

The Table shows the basic characteristics of participants in the target validation and testing cohort from the Africa Wits-INDEPTH partnership for Genomic Studies (AWI-Gen) study. In the validation cohort, participants had a mean age of 52.1 years (SD=8.3), an average body mass index of 25 kg/m^2 (SD=6.7), and a sex distribution of 55.1% women and 44.9% men. In the test cohort, the mean age was 51.7 years (SD=8.1), mean body mass index was 25.2 kg/m^2 (SD=6.7), with 54.9% women and 45.1% men. The prevalence of hypertension in the test cohort was 28.7%. The target cohort included individuals from South, East, and West Africa. Among these regions, South Africa exhibited higher average SBP, DBP, and PP with values of 132.7 mm Hg (SD=22.4), 82.9 mm Hg (SD=13.4), and 49.9 mm Hg (SD=15.6), respectively, compared with East and West Africa (Table S2). Figure 2 demonstrates distinct clusters for East Africa, South Africa, and West Africa, based on genetic ancestry. Each cluster represents a genetically distinguishable population, with notable separation between groups from different geographic regions.

Single-ancestry and Multi-ancestry PRS Development

A GWAS was performed on 3 single-ancestry data sets (African Collaborative Center for Microbiome and Genomic Research (ACCME), Ugandan Genome Resource (UGR), and Loyola University Cohort (LUC)) to identify loci associated with BP traits. Following this, a meta-analysis of these GWAS results was conducted

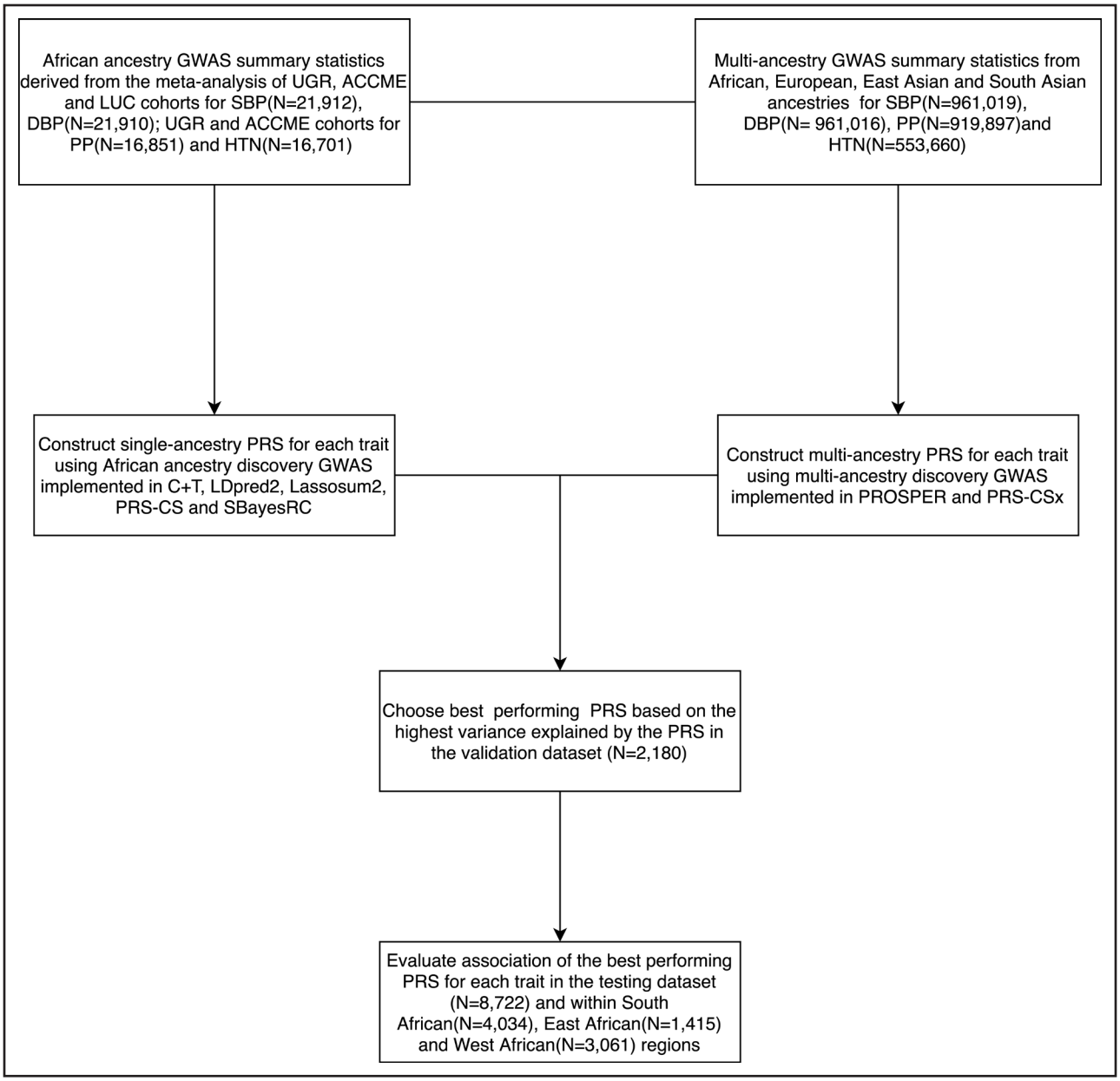

Figure 1. Study design and workflow.
Single-ancestry-derived polygenic risk scores for each trait were constructed using African ancestry genome-wide association studies (GWAS) summary statistics. Multi-ancestry-derived polygenic risk scores (PRS) were constructed with diverse ancestry GWAS summary statistics. The best-performing PRS was evaluated in the testing data set and within South African, East African, and West African regions. Participants lacking information on their region of origin (n=212) were excluded from the regional analysis. ACCME indicates African Collaborative Center for Microbiome and Genomic Research; AWI-Gen, Africa Wits-INDEPTH partnership for Genomic Studies; DBP, diastolic blood pressure; HTN, hypertension; LUC, Loyola University Cohort; PP, pulse pressure; SBP, systolic blood pressure; and UGR Ugandan Genome Resource.

to increase the statistical power and identify top loci common across data sets. The top 20 loci identified from both the individual GWAS and meta-analysis are presented in Supplemental Data 1–14. Among single-ancestry-derived PRS methods, C+T had the best performance for SBP with an R^2 of 0.21% followed by Lassosum2 (R^2=0.1%); C+T and Lassosum2 performed best for DBP with an R^2 of 0.08% and 0.06%, respectively; PRS-CS exhibited the best prediction for PP with an R^2 of 0.1%, while Lassosum2 and LDpred2 had the same performance with an R^2 of 0.05%. For hypertension, Lassosum2 had the best performance for hypertension with an R^2 of 0.05% (Table S3; Figure S1). Among multi-ancestry methods, PROSPER demonstrated better performance for SBP with an R^2 of 1.43% compared with PRS-CSx, which had an R^2 of 1.36%. PRS-CSx outperformed PROSPER for DBP, PP, and hypertension with an R^2 of 1.42%, 1.07%, and 0.61%.

Table. Characteristics of the Participants in the African Target Cohort Split Randomly for Validation (20%) and Testing (80%) Subsets

Variable	Validation cohort		Test cohort	
	n	Mean (SD)/ percentage	n	Mean (SD)/ percentage
Age, y	2180	52.1 (8.3)	8722	51.7 (8.1)
Sex	2180		8722	
Women	1201	55.1	4787	54.9
Men	979	44.9	3935	45.1
BMI, kg/m^2	2180	25 (6.7)	8722	25.2 (6.7)
SBP, mm Hg	2162	125.5 (22)	8674	126 (22.5)
DBP, mm Hg	2164	79.3 (13.2)	8674	79.52 (13.3)
PP, mm Hg	2162	46.3 (13.7)	8670	46.46 (14)
Hypertension	2164		8678	
Cases	600	27.7	2487	28.7
Controls	1564	72.3	6191	71.3

All the study participants were from the Africa Wits-INDEPTH partnership for Genomic Studies (AWI-Gen) cohort. BMI indicates body mass index; DBP, diastolic blood pressure; PP, pulse pressure; and SBP, systolic blood pressure.

Assessment of Multi-ancestry PRS Performance in the Absence of African Ancestry

We conducted a further evaluation of the impact of excluding African ancestry information in the discovery GWAS on performance in the target data. There was a reduction in the R^2 values when African ancestry was excluded, with losses of 0.14% for SBP, 0.15% for PP, and 0.04% for hypertension, indicating that including African ancestry in the discovery GWAS enhances PRS performance, likely by capturing ancestry-specific genetic variation relevant to BP regulation. Notably, the MULTI+AFR (PRS including African ancestry) and MULTI PRS (PRS excluding African ancestry) produced identical R^2 values of 1.42% for DBP, respectively (Figure 3).

PRS Predictive Accuracy in South, East, and West Africa

We evaluated the best-performing PRS within each African region to identify regional differences in predictive accuracy and assess PRS transferability across diverse African populations. East Africa showed the highest PRS performance for SBP, DBP, PP, and hypertension, with R^2 values of 2.5% (95% CI, 1.22%–4.12%), 2.85% (95% CI, 1.36%–4.65%), 2.6% (95% CI, 1.41%–4.2%), and 0.95% (95% CI, 0.13%–2.85%), respectively. West Africa had the second-highest PRS performance for SBP, DBP, and PP, with R^2 values of 1.95% (95% CI, 1.16%–2.96%), 1.24% (95% CI, 0.62%–2.1%), and 1.43% (95% CI, 0.7%–2.34%). South Africa had the second-highest performance for hypertension, with an R^2 of 0.59% (95% CI, 0.07%–1.24%), but the lowest performance for SBP, DBP, and PP, with R^2 values of 0.93% (95% CI, 0.45%–1.62%), 1.23% (95% CI, 0.7%–1.93%), and 0.72% (95% CI, 0.34%–1.26%), respectively. The variance explained by the multi-ancestry PRS varied widely across regions. Testing for heterogeneity revealed a statistically significant difference in predictive accuracy of PRS for PP across regional strata (P=0.03) and borderline significance for SBP (P=0.047), indicating some variability in performance. No significant differences were observed for DBP (P=0.18) or hypertension (P=0.23; Figure 4).

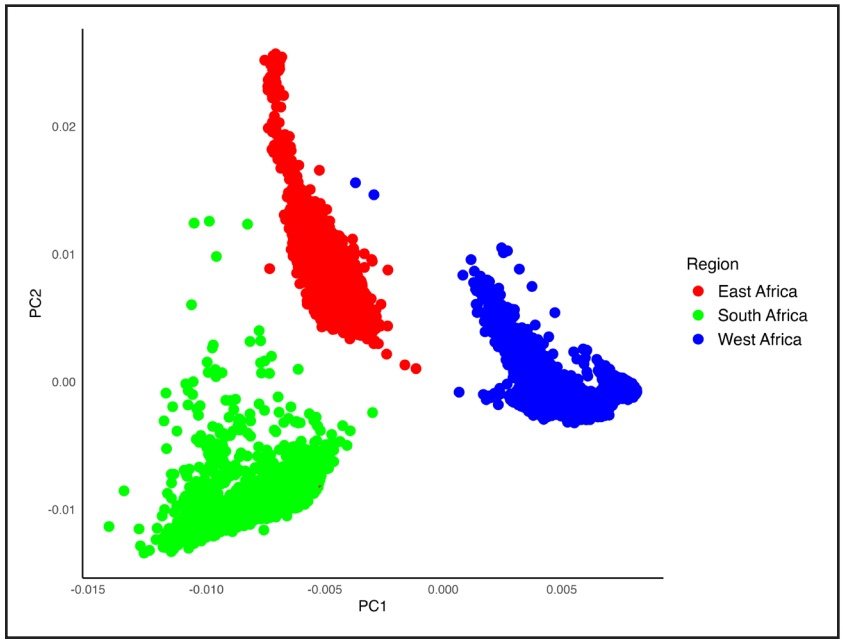

Figure 2. Principal components analysis (PCA) plot of African populations.
This plot illustrates genetic differentiation among African populations. The plot includes individuals from the Africa Wits-INDEPTH partnership for Genomic Studies (AWI-Gen) cohort representing South, East, and West Africa; African Collaborative Center for Microbiome and Genomic Research (ACCME) cohort representing West Africa; and Ugandan Genome Resource (UGR) cohort representing East Africa.

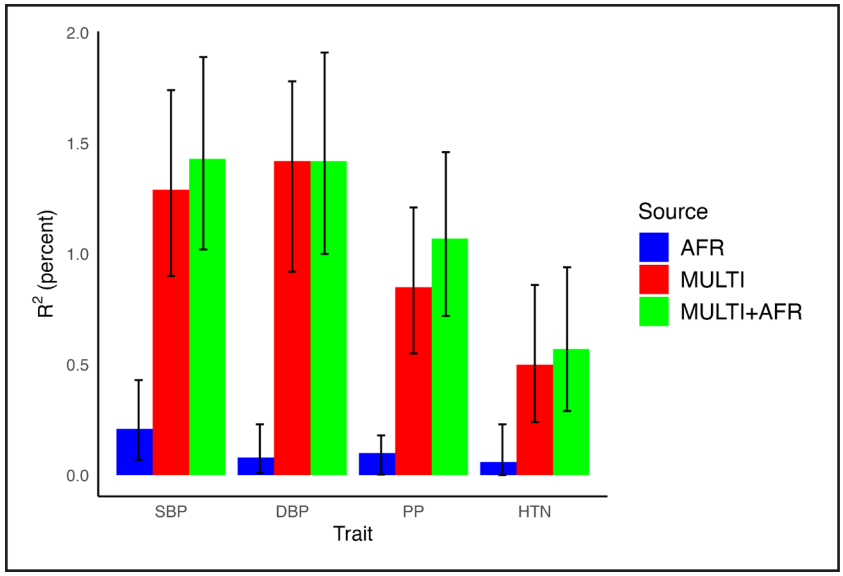

Figure 3. Comparison of polygenic risk scores (PRS) predictive accuracy in continental African populations. We compared the performance of the best-performing single-ancestry PRS with PRS-derived multi-ancestry genome-wide association studies (GWAS), including African ancestry (MULTI+AFR) and multi-ancestry GWAS excluding African ancestry (MULTI) for different blood pressure (BP) traits in the testing data set (n=8722). Performance was evaluated by the variance R^2 explained by the PRS for systolic BP, diastolic BP, pulse pressure, and hypertension. The error bars show 95% CIs.

Association Between Multi-ancestry PRS and BP Traits

The difference in mean SBP between the first PRS quartile and the third and top quartiles was 3.54 mm Hg (95% CI, 2.3–4.75) and 6.53 mm Hg (95% CI, 5.3–7.74), respectively. For DBP, the difference was 2.71 mm Hg (95% CI, 1.9–3.42) and 3.81 mm Hg (95% CI, 3.9–4.52), respectively. For PP, the difference was 2.01 mm Hg (95% CI, 1.8–2.74) and 3.59 mm Hg (95% CI, 2.4–4.32) between the first quartile and the third and top quartiles, respectively. The odds of hypertension was 1.24 (95% CI, 1.8–1.43) and 1.47 (95% CI, 1.7–1.69) times higher in the third and top PRS quartiles compared with the first quartile. PRS was significantly associated with SBP (β=2.73; [95% CI, 2.3–3.15]), DBP (β=1.59 [95% CI, 1.4–1.85]), and PP (β=1.48 [95% CI, 1.2–1.74]). Using hypertension-PRS as a continuous variable in a fully adjusted model, the odds ratio of hypertension was 1.16 (95% CI, 1.1–1.23; Figure 5).

Multi-ancestry PRS Association Stratified by Sex

We conducted a sex-stratified analysis to assess differences in PRS predictive accuracy and association strength for each BP trait. DBP-PRS demonstrated higher predictive accuracy in women (R^2=1.83%) compared with men (R^2=0.98%; Table S4). The predictive accuracy of SBP, PP, and hypertension-PRS was similar between men and women (Table S4). In women, the association between DBP-PRS and DBP (β=1.79 [95% CI, 1.6–2.13]) was stronger than in men (β=1.34 [95% CI, 0.6–1.73]). For SBP and PP, PRS showed comparable association strength across sexes. Regarding hypertension-PRS, the odds ratio for hypertension was similar in male individuals (odds ratio OR=1.18 [95% CI,

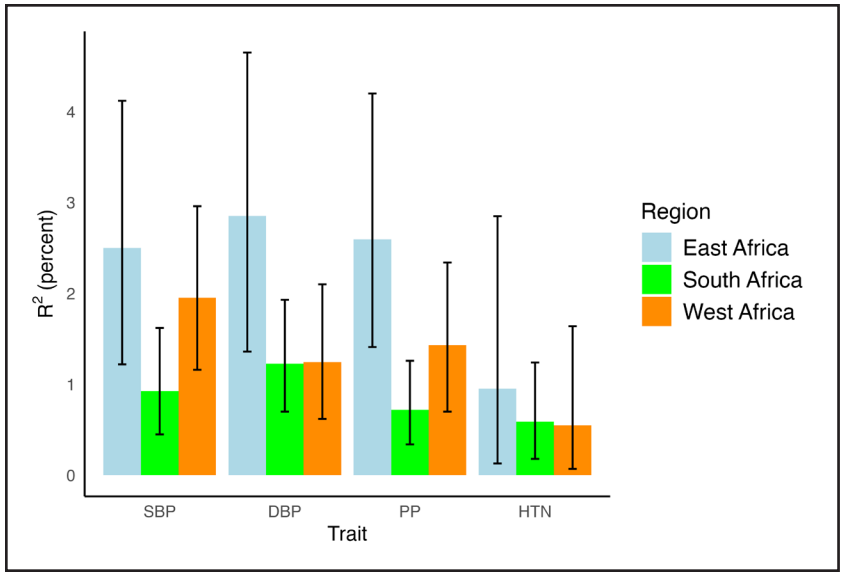

Figure 4. Comparison of polygenic risk scores (PRS) predictive accuracy across continental African regions. We compared the performance of the best-performing PRS for different blood pressure (BP) traits in a combined African population (n=8722) and stratified by regions: South Africa (n=4034), East Africa (n=1415), and West Africa (n=3061). Performance was evaluated by the variance R^2 explained by the PRS for systolic BP (SBP), diastolic BP (DBP), pulse pressure (PP), and hypertension. The error bars show 95% CIs.

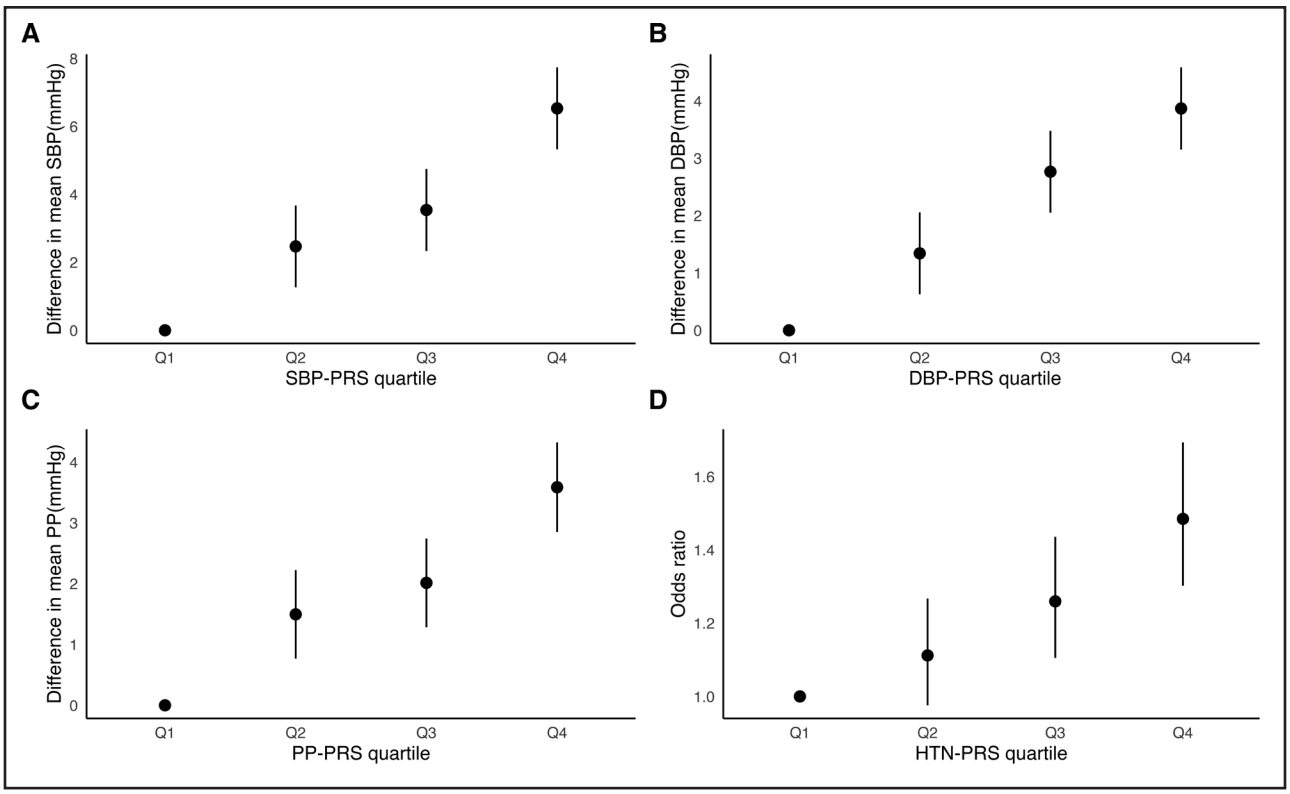

Figure 5. Association between multi-ancestry polygenic risk scores (PRS) and blood pressure (BP) traits across PRS quartiles. Point range-plots comparing difference in mean blood pressure in absolute measures (mm Hg) between the fourth, third, and second PRS quartiles relative to the lowest quartile, for (**A**) systolic BP (SBP), (**B**) diastolic BP (DBP), (**C**) pulse pressure (PP); odds ratio across PRS quartiles for (**D**) hypertension in the testing data set. The error bars show 95% CIs. The models were adjusted for age, sex, study site, body mass index, and the top 10 principal components.

1.9–1.27]) and female individuals (OR=1.16 [95% CI, 1.8–1.24]; Table S5). The PRS-by-sex interaction was borderline significant for DBP (P=0.05), but not significant for SBP (P=0.57), PP (P=0.32), or hypertension (P=0.95).

Validation in the UK Biobank and AoU African Ancestry Population

We validated the performance of the best-performing multi-ancestry PRS in independent data sets from the UK Biobank and All of Us (AoU) cohorts of African ancestry, adjusting for age, sex, body mass index, and the first 10 principal components. In the UK Biobank data set (n=6851), the R^2 of the multi-ancestry PRS was 2.21% (95% CI, 1.63%–2.89%) for SBP, 2.22% (95% CI, 1.62%–2.97%) for DBP, 2.47% (95% CI, 1.83%–3.20%) for PP, and 1.43% (95% CI, 0.86%–2.17%) for hypertension (Table S6). The PRS was significantly associated with SBP (β=2.83 [95% CI, 2.8–3.29]), DBP (β=1.47 [95% CI, 1.1–1.73]), PP (β=2.47 [95% CI, 2.3–2.80]), and hypertension (OR=1.27 [95% CI, 1.0–1.34]). In the AoU data set (n=39 181), the R^2 of the multi-ancestry PRS was 1.11% (95% CI, 0.93%–1.30%) for SBP, 1.03% (95% CI, 0.84%–1.25%) for DBP, 1.32% (95% CI, 1.11%–1.55%) for PP, and 0.51% (95% CI, 0.28%–0.78%) for hypertension (Table S6). The PRS was significantly associated with SBP (β=2.15 [95% CI, 1.6–2.34]), DBP (β=1.33 [95% CI, 1.0–1.45]), PP (β=1.70 [95% CI, 1.6–1.83]), and hypertension (OR=1.16 [95% CI, 1.3–1.18]).

DISCUSSION

PRS development for BP traits in continental African populations has been limited by small sample sizes, resulting in low predictive accuracy.[12] Additionally, these earlier studies often failed to account for the substantial genetic diversity and regional differences within African populations, which are critical to capturing ancestry-specific genetic variation. To address this, our study used an optimized approach that incorporated a larger representation of continental African samples in the discovery data set and assessed performance disparities across African regions. We identified the best-performing single-ancestry and multi-ancestry model for each BP trait, with variations in PRS method performance likely reflecting the distinct genetic architectures underlying each trait.[20]

In our analysis, excluding African ancestry information in the discovery GWAS reduced performance for SBP, PP,

and hypertension. Although the gains from African ancestry inclusion were modest, likely due to limited sample size, this highlights the additive value of including African ancestry data in trait predictions and the need for larger studies to improve PRS performance. The inclusion of target ancestry data tends to improve PRS performance for certain traits.[20,21] The best-performing multi-ancestry PRS achieved a partial R^2 of 1.43% for SBP and 1.42% for DBP, which represents a significant improvement over previous studies, which reported R^2 values of 0.22% for SBP and 0.36% for DBP in a continental African population.[12] However, these values remain lower than those observed in European populations, where R^2 values range from 1.5% to 12%.[22–24] The disparity in predictive accuracy is primarily attributed to the overrepresentation of the European populations in discovery GWAS. Variant effect estimates are shaped by population-specific linkage disequilibrium (LD) patterns, which can result in biased weights when applied to African populations.[25] Variants that are common in African populations are often rare or absent in the European populations, leading to their exclusion from European-based GWAS and reducing the transferability of PRS.[26] Additionally, the reliance on HapMap3 single nucleotide polymorphisms in many PRS methods used in this study may further limit performance, as HapMap3 single nucleotide polymorphisms may not fully capture the genetic variants associated with BP development in African populations.

To examine whether lower predictive accuracy in continental African populations is influenced by genetic diversity within these groups, we evaluated PRS performance across specific African regions. The multi-ancestry PRS showed varying performance by region, with East Africa achieving the highest R^2 values of 2.5%, 2.85%, and 2.6% for SBP, DBP, and PP, respectively. In contrast, South Africa exhibited the lowest R^2 compared with West and East Africa, potentially reflecting the absence of South African populations in the African ancestry component of the discovery GWAS. Previous studies have shown that differences in PRS accuracy within the African subpopulations can exceed those observed across the non-African ancestries.[27,28] The differential performance of PRSs within the African groups can be attributed to multiple factors beyond genetic variation alone.[29] Social and environmental factors unique to each population also play significant roles in influencing PRS predictive accuracy.[30,31] One study reported poor transferability of lipid PRS between a South African Zulu population and an Ugandan population.[32] These findings highlight the critical need for greater inclusion of African populations in PRS development, the creation of population-specific PRS, or calibration of existing PRS to account for local genetic diversity, thereby enhancing their generalizability and predictive power.

The association between the best-performing multi-ancestry PRS and SBP, DBP, and PP was observed to be statistically significant, which is consistent with previous results in diverse ancestries.[12,33,34] Our study observed an OR of 1.16 (95% CI, 1.3–1.18) for PRS association with hypertension, which is in line with a previous study in the African American population.[35] The observed differences in the mean BP levels and odds ratios across quartiles of PRS underscore the potential relevance of PRS in risk stratification.

In a sex-stratified analysis, partial R^2 for DBP was 1.8× higher in women than in men. This is consistent with the findings from other studies.[21,36] This difference in PRS accuracy may be attributed to sex-specific genetic architecture, as certain genetic variants influencing DBP could have varying effects between sexes. Additionally, differences in environmental exposures and lifestyle factors by sex in this population may also contribute to the observed variation in performance.[37] Few studies have evaluated sex-specific differences in the association of PRS with BP traits in European ancestries, and none in an African population. In the Finnish population, SBP-PRS was more strongly associated with incident hypertension in women.[38] These suggest potential sex differences in genetic susceptibility to these traits and emphasize the importance of considering sex-specific genetic factors in the risk assessment and personalized management approaches for high BP. Further studies should be conducted by evaluating sex-specific PRS for these BP traits.

The predictive accuracy of the multi-ancestry PRS was higher in the UK Biobank African ancestry cohort compared with continental Africans, while PRS performance in the AoU African ancestry cohort was lower than expected. These differences are unlikely to be explained solely by European admixture and may instead reflect distinct ancestral backgrounds, including genetic heterogeneity and variations in genetic architecture shaped by regional origins within Africa and diverse migration histories.[39,40] This aligns with our observation of differential PRS performance across African regions. Additionally, cohort-specific, socioeconomic, environmental, and lifestyle factors likely contribute to the observed variation, potentially attenuating the genetic contribution and reducing PRS predictive accuracy. This interpretation is further supported by the significantly lower heritability estimates observed in the AoU data set compared with the UK Biobank,[41] emphasizing the limitations on achievable PRS accuracy in this population.

The strengths of our study include the use of a large and diverse base data set encompassing individuals of European, African, East Asian, and South Asian ancestries. Our target data set uniquely represents continental Africans from West, East, and Southern Africa, allowing us to evaluate BP PRS performance within regional strata and uncover potential differences across subpopulations of global ancestries contributes to a deeper

understanding of PRS applicability and performance in diverse populations, supporting the development of more accurate and inclusive genetic risk prediction models. Additionally, we replicated PRS performance in 2 independent African ancestry cohorts, reinforcing the robustness and generalizability of our findings. The limitations of our study include the absence of BP-lowering medication intake data in the target data set; the absence of information on comorbidities that could potentially lead to elevated BP; and a limited sample size of the African subpopulations. Furthermore, hypertension classification in our target data set is based on single-visit BP measurements, which may exclude individuals with controlled hypertension managed through antihypertensive treatment.

CONCLUSIONS

In conclusion, we generated and evaluated single-ancestry and multi-ancestry-derived PRS for SBP, DBP, PP, and hypertension. We demonstrated the importance of incorporating diverse ancestries in PRS development. Our results showed an improved PRS for continental African populations and highlighted variations in PRS accuracy across different African geographic regions, reflecting the high genetic diversity within Africa. Future research should focus on expanding sample sizes, incorporating more diverse populations, and considering additional environmental and lifestyle factors. Overall, this study provides valuable insights into the genetic architecture of BP traits among individuals of African ancestry, highlighting the need for PRS with improved accuracy for risk prediction and personalized management strategies for hypertension within this population.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

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