

## **Blood Pressure Genetic Risk Score Associates with Cardiovascular Disease but not Chronic Kidney Disease Progression: Findings from the CRIC Study**

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### **Supplementary Materials**

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## Supplementary Methods

### Data Collection and Study Covariables

Information was obtained on demographic characteristics, medical history and medication use at the baseline CRIC examination. Three seated resting BP readings, obtained by study staff using a standardized method, were obtained at the baseline visit and the mean values of systolic BP (SBP) and diastolic BP (DBP) were calculated from these measures.<sup>1</sup> To impute pretreatment BP levels in participants on antihypertensive medication,<sup>2</sup> BP was adjusted by adding 15 and 10 mm Hg to SBP and DBP, respectively.<sup>3</sup> Pulse pressure (PP) was calculated as the difference between the adjusted SBP and DBP values.

Study participants attended annual clinic visits and underwent telephone interview every 6 months between in-person visits. Cardiovascular clinical outcomes were assessed using a standard medical event questionnaire at all follow-up contacts. Medical records were requested for event verification, and 2 physicians adjudicated each cardiovascular event and classified them as either probable or definite.<sup>4</sup> Serum creatinine was measured from fasting blood samples at each in-person study visit. Serum creatinine was measured annually using an enzymatic method on an Ortho Vitros 950 (Ortho Biotech Products, Bridgewater, NJ) through October of 2008 and by the Jaffe method on a Beckman Synchron System (Beckman Coulter, Inc., Brea CA) thereafter. All serum creatinine measures were standardized to isotope dilution mass spectrometry traceable values. Serum cystatin C was measured using a particle-enhanced nephelometric immunoassay on a Dade-Behring BNII (Dade Behring, Inc., Newark, NJ). For the baseline examination and each annual in-person visit, eGFR was calculated according to the 2012 CKD-EPI equation, which included serum creatinine, cystatin C, age, gender and race.<sup>5</sup> Urinary protein-to-creatinine ratio (UPCR) was assessed using either 24-hour urine collections or spot urine samples, using previously described methods.<sup>6</sup>

### Genotyping and Imputation

Genotyping and imputation methods in the CRIC study have been described previously.<sup>7</sup> In brief, DNA was extracted from buffy coat samples from 3,635 CRIC Study participants and genotyped using the Illumina HumanOmni 1-Quad array. A total of 3,527 samples passed quality control metrics, which included the removal of samples with sex discordance, reduced or excess genotypic heterozygosity, cryptic relatedness, or sample ID mismatches. Using principal components, subgroups of 1,493 and 1,581 participants were identified with African and European ancestry, respectively (with 453 participants of other ancestral groups excluded). Single nucleotide polymorphism (SNP) quality control was also performed in each subgroup, excluding variants with minor allele frequency < 0.03, deviations from Hardy-Weinberg equilibrium ( $P < 1 \times 10^{-7}$ ), and genotype call rate < 0.95. Imputation of 839,205 and 739,978 SNPs was then conducted, for African and European ancestry participants, respectively, using the 1000

Genomes mixed race/ethnicity (ALL) reference panel (NCBI build 37, release date March of 2012; n=1,093) with IMPUTE software.<sup>8,9</sup> Following imputation, variants with quality score < 0.8 were further excluded from the genomics dataset.

**Supplementary Table 1. Baseline Characteristics of African Ancestry CRIC Participants According to SBP GRS Quartile**

	Q1 (N=374)	Q2 (N=373)	Q3 (N=373)	Q4 (N=373)
Age, years, mean (SD)	58 (11)	58 (10)	57 (12)	57 (11)
Male, n (%)	188 (50)	174 (47)	189 (51)	175 (47)
High school graduate, n (%)	257 (69)	279 (75)	295 (79)	264 (71)
Current cigarette smokers, n (%)	77 (21)	69 (18)	72 (19)	67 (18)
Ever cigarette smokers, n (%)	220 (59)	209 (56)	219 (59)	200 (54)
Current alcohol use, n (%)	189 (51)	209 (56)	202 (54)	194 (52)
Body mass index, kg/m <sup>2</sup> , mean (SD)	34 (9)	33 (8)	34 (8)	34 (8)
Obesity*, n (%)	247 (66)	220 (59)	242 (65)	240 (64)
Serum cholesterol, mg/dL, mean (SD)	186 (46)	185 (45)	185 (46)	187 (48)
Low density lipoprotein, mg/dL, mean (SD)	107 (38)	105 (34)	104 (37)	108 (39)
Uses lipid lowering medication, n (%)	207 (55)	197 (53)	223 (60)	203 (54)
Diabetes, n (%)	211 (56)	178 (48)	193 (52)	189 (51)
Systolic BP, mean (SD)	147 (25)	146 (22)	148 (23)	147 (25)
Diastolic BP, mean (SD)	84 (14)	83 (14)	84 (14)	83 (15)
Pulse pressure, mean (SD)	64 (21)	64 (19)	64 (20)	64 (21)
Hypertension†, n (%)	364 (97)	362 (97)	363 (97)	365 (98)
Uses antihypertensive medication, n (%)	357 (95)	350 (94)	352 (94)	356 (95)
Number of antihypertensive medications, mean (SD)	2.9 (1.5)	2.9 (1.5)	3.1 (1.5)	3.1 (1.4)
Serum creatinine, mg/dL, mean (SD)	2.0 (0.7)	1.9 (0.6)	1.9 (0.7)	2.0 (0.8)
Estimated GFR, ml/min/1.73m <sup>2</sup> , mean (SD)	44 (17)	47 (17)	49 (20)	46 (19)
Urinary protein to creatinine ratio†	1.0 (1.7)	0.9 (2.0)	0.9 (2.1)	1.1 (2.5)
Systolic BP GRS, mean (SD)‡	166 (2)	169 (1)	171 (1)	174 (2)
Diastolic BP GRS, mean (SD)‡	99 (1)	100 (1)	101 (1)	103 (1)
Pulse pressure GRS, mean (SD)‡	38 (1)	38 (1)	39 (1)	40 (1)

\* Body mass index  $\geq 30$  kg/m<sup>2</sup>; † BP  $\geq 130/80$  or use of antihypertensive medications

‡ Ratio of urine protein concentration to urine creatinine concentration from 24-hour urine or a spot urine sample. When both 24-hour urine and spot urines are available,

priority is given to the 24-hour urine. The ratio of urine total protein (mg/dL) to urine creatinine (mg/dL) is unitless.

‡ Weighted sum of risk alleles for SBP, DBP, and PP, respectively, using previously estimated effect sizes as weights.

BP=blood pressure; GFR=glomerular filtration rate; GRS=genetic risk score; Q1=first quartile; Q2=second quartile; Q3=third quartile; Q4=fourth quartile; SD=standard deviation.

**Supplementary Table 2. Baseline Characteristics of European Ancestry CRIC Participants According to SBP GRS Quartile**

	Q1 (N=396)	Q2 (N=395)	Q3 (N=395)	Q4 (N=395)
Age, years, mean (SD)	60 (10)	58 (11)	59 (11)	57 (12)
Male, n (%)	234 (59)	248 (63)	219 (55)	244 (62)
High school graduate, n (%)	373 (94)	370 (94)	374 (95)	376 (95)
Current cigarette smokers, n (%)	50 (13)	35 (9)	29 (7)	34 (9)
Ever cigarette smokers, n (%)	230 (58)	214 (54)	236 (60)	209 (53)
Current alcohol use, n (%)	294 (74)	303 (77)	297 (75)	293 (74)
Body mass index, kg/m <sup>2</sup> , mean (SD)	31 (8)	31 (7)	31 (8)	31 (7)
Obesity*, n (%)	197 (50)	196 (50)	198 (50)	194 (49)
Serum cholesterol, mg/dL, mean (SD)	178 (41)	184 (44)	180 (42)	178 (41)
Low density lipoprotein, mg/dL, mean (SD)	99 (33)	103 (35)	99 (31)	97 (31)
Uses lipid lowering medication, n (%)	247 (62)	238 (60)	252 (64)	258 (65)
Diabetes, n (%)	163 (41)	156 (39)	150 (38)	163 (41)
Systolic BP, mean (SD)	133 (20)	135 (20)	137 (20)	135 (20)
Diastolic BP, mean (SD)	77 (12)	78 (12)	78 (12)	78 (11)
Pulse pressure, mean (SD)	56 (17)	57 (17)	59 (18)	57 (17)
Hypertension†, n (%)	341 (86)	352 (89)	369 (93)	373 (94)
Uses antihypertensive medication, n (%)	334 (84)	338 (86)	356 (90)	363 (92)
Number of antihypertensive medications, mean (SD)	2.1 (1.5)	2.2 (1.5)	2.4 (1.4)	2.5 (1.4)
Serum creatinine, mg/dL, mean (SD)	1.7 (0.5)	1.7 (0.5)	1.7 (0.5)	1.7 (0.5)
Estimated GFR, ml/min/1.73m <sup>2</sup> , mean (SD)	50 (19)	51 (19)	49 (18)	50 (19)
Urinary protein to creatinine ratio†	0.6 (2.0)	0.7 (1.9)	0.7 (2.5)	0.6 (1.4)
Systolic BP GRS, mean (SD)‡	169 (2)	172 (1)	175 (1)	178 (2)
Diastolic BP GRS, mean (SD)‡	100 (2)	101 (1)	103 (1)	104 (2)
Pulse pressure GRS, mean (SD)‡	39 (1)	40 (1)	40 (1)	41 (1)

\* Body mass index  $\geq 30$  kg/m<sup>2</sup>; † BP  $\geq 130/80$  or use of antihypertensive medications

† Ratio of urine protein concentration to urine creatinine concentration from 24-hour urine or a spot urine sample. When both 24-hour urine and spot urines are available,

priority is given to the 24-hour urine. The ratio of urine total protein (mg/dL) to urine creatinine (mg/dL) is unitless.

‡ Weighted sum of risk alleles for SBP, DBP, and PP, respectively, using previously estimated effect sizes as weights.

BP=blood pressure; GFR=glomerular filtration rate; GRS=genetic risk score; Q1=first quartile; Q2=second quartile; Q3=third quartile; Q4=fourth quartile; SD=standard deviation.



**Supplementary Table 3. Associations between Blood Pressure GRS and Baseline Blood Pressure and Kidney Function, per SD Increase in GRS and Comparing the Top and Bottom GRS Quartiles**

Outcome	African Ancestry				European Ancestry			
	Continuous		Quartile		Continuous		Quartile	
	Beta (SE)*	P	Beta (SE)†	P	Beta (SE)*	P	Beta (SE)†	P
Blood Pressure								
SBP	0.02 (0.60)	0.97	-0.23 (1.70)	0.89	1.29 (0.48)	7.70×10 <sup>-3</sup>	2.37 (1.36)	0.08
DBP	0.37 (0.35)	0.28	0.66 (0.98)	0.50	0.73 (0.28)	9.10×10 <sup>-3</sup>	2.48 (0.78)	1.5×10 <sup>-3</sup>
PP	0.49 (0.47)	0.30	1.60 (1.34)	0.23	1.38 (0.40)	6.10×10 <sup>-4</sup>	3.35 (1.14)	3.2×10 <sup>-3</sup>
eGFR								
SBP	0.47 (0.44)	0.29	1.88 (1.24)	0.13	-0.62 (0.43)	0.15	-0.18 (1.21)	0.88
DBP	0.18 (0.44)	0.68	0.01 (1.25)	1.00	-0.62 (0.43)	0.15	-1.79 (1.20)	0.13
PP	0.23 (0.44)	0.60	1.03 (1.26)	0.41	-0.41 (0.43)	0.34	-1.43 (1.21)	0.24
Urinary Protein to Creatinine Ratio								
SBP	0.03 (0.06)	0.62	0.08 (0.16)	0.62	-0.05 (0.05)	0.31	-0.18 (0.14)	0.20
DBP	0.11 (0.06)	0.05	0.24 (0.16)	0.13	-0.09 (0.05)	0.08	-0.22 (0.14)	0.13
PP	0.02 (0.06)	0.76	0.02 (0.16)	0.90	0.01 (0.05)	0.82	-0.06 (0.14)	0.67

\* Results of linear models, per SD increase in BP GRS, adjusted for age, sex, CRIC study site, and ancestry principal components.

† Results of linear models, comparing top quartile BP GRS to bottom quartile BP GRS, adjusted for age, sex, CRIC study site, and ancestry principal components.

DBP=diastolic blood pressure; eGFR=estimated glomerular filtration rate; GRS=genetic risk score; PP=pulse pressure; SBP=systolic blood pressure; SD=standard deviation; SE=standard error.

**Supplementary Table 4. Median Baseline Blood Pressure, per Quartile Increase in Respective Blood Pressure GRS**

Ancestry / GRS	Q1	Q2	Q3	Q4	P
African Ancestry					
SBP	146.82	145.9	148.31	146.58	0.55
DBP	83.21	83.22	82.51	83.87	0.59
PP	62.85	63.84	63.68	64.45	0.69
European Ancestry					
SBP	133.52	136.02	136.85	135.9	0.08
DBP	75.28	78.33	77.86	77.77	$3.1 \times 10^{-4}$
PP	56.81	57.45	58.62	60.16	0.02

Association per quartile increase in GRS, for baseline SBP, DBP, and PP, respectively, stratified by ancestry, and adjusted for age, sex, CRIC study site, and ancestry principal components. P values are for trend across quartiles.

DBP=diastolic blood pressure; GRS=genetic risk score; PP=pulse pressure; Q1=first quartile; Q2=second quartile; Q3=third quartile; Q4=fourth quartile; SBP=systolic blood pressure.

**Supplementary Table 5. Median number of Antihypertensive Medications per Quartile Increase in GRS**

Ancestry / GRS	Q1	Q2	Q3	Q4	P
African Ancestry					
SBP	2.91	2.83	3.14	3.11	$6.2 \times 10^{-3}$
DBP	2.87	3.02	3.04	3.06	0.29
PP	2.95	2.92	2.97	3.15	0.13
European Ancestry					
SBP	2.06	2.18	2.34	2.43	$7.2 \times 10^{-4}$
DBP	2.12	2.13	2.33	2.45	$9.1 \times 10^{-4}$
PP	2.05	2.19	2.26	2.52	$2.2 \times 10^{-5}$

Association per quartile increase in GRS, for baseline number of antihypertensive medications, stratified by ancestry, and adjusted for age, sex, CRIC study site, and ancestry principal components. P values are for trend across quartiles.

DBP=diastolic blood pressure; GRS=genetic risk score; PP=pulse pressure; Q1=first quartile; Q2=second quartile; Q3=third quartile; Q4=fourth quartile; SBP=systolic blood pressure.

**Supplementary Table 6. Associations between Blood Pressure GRS and Baseline Unimputed Blood Pressure\*, per SD Increase in GRS and Comparing the Top and Bottom GRS Quartiles**

Outcome	African Ancestry				European Ancestry			
	Continuous		Quartile		Continuous		Quartile	
	Beta (SE)*	P	Beta (SE)*	P	Beta (SE)*	P	Beta (SE)*	P
Unadjusted Blood Pressure								
SBP	-0.28 (0.59)	0.63	-0.75 (1.65)	0.65	0.31 (0.46)	0.50	0.38 (1.28)	0.77
DBP	0.36 (0.34)	0.29	0.62 (0.95)	0.52	0.57 (0.27)	0.04	1.99 (0.76)	8.8×10 <sup>-3</sup>
PP	0.28 (0.46)	0.54	1.04 (1.30)	0.43	0.78 (0.39)	0.04	1.54 (1.09)	0.16

\* Blood pressure values were not adjusted for use of antihypertension medication, however, number of antihypertensive medications was included in the model as a covariate.

† Results of linear models, per SD increase in BP GRS, adjusted for age, sex, CRIC study site, number of antihypertensive medications, and ancestry principal components.

‡ Results of linear models, comparing top quartile BP GRS to bottom quartile BP GRS, adjusted for age, sex, CRIC study site, number of antihypertensive medications, and ancestry principal components.

DBP=diastolic blood pressure; GRS=genetic risk score; PP=pulse pressure; SBP=systolic blood pressure; SD=standard deviation; SE=standard error.

**Supplementary Table 7. Hazard Ratios for Primary Endpoints per SD Increase in GRS and Comparing the Top and Bottom GRS Quartiles, in Models with Additional Adjustment for Baseline BMI, LDL, and Lipid Lowering Medication**

Outcome / GRS	African Ancestry				European Ancestry			
	Continuous		Quartile		Continuous		Quartile	
	HR (95% CI)*	P	HR (95% CI)†	P	HR (95% CI)*	P	HR (95% CI)†	P
CVD Event‡								
SBP	1.11 (1.02-1.21)	0.02	1.24 (0.97-1.57)	0.08	1.13 (1.02-1.25)	0.02	1.39 (1.05-1.86)	0.02
DBP	1.10 (1.01-1.20)	0.03	1.18 (0.92-1.51)	0.19	1.08 (0.98-1.19)	0.11	1.17 (0.89-1.56)	0.26
PP	1.06 (0.97-1.16)	0.19	1.20 (0.94-1.54)	0.15	1.10 (1.00-1.22)	0.06	1.26 (0.95-1.68)	0.11
CKD Progression Event§								
SBP	1.00 (0.92-1.08)	0.92	0.94 (0.75-1.17)	0.56	1.04 (0.95-1.15)	0.39	1.06 (0.81-1.41)	0.66
DBP	1.03 (0.96-1.12)	0.41	1.12 (0.89-1.40)	0.33	0.98 (0.89-1.09)	0.74	0.96 (0.74-1.25)	0.76
PP	0.97 (0.90-1.05)	0.49	0.93 (0.74-1.15)	0.50	1.05 (0.95-1.16)	0.38	1.09 (0.83-1.44)	0.52

\* Results of Cox proportional hazards models, per SD increase in BP GRS, adjusted for age, sex, CRIC study site, BMI, LDL, lipid lowering medications, and ancestry principal components.

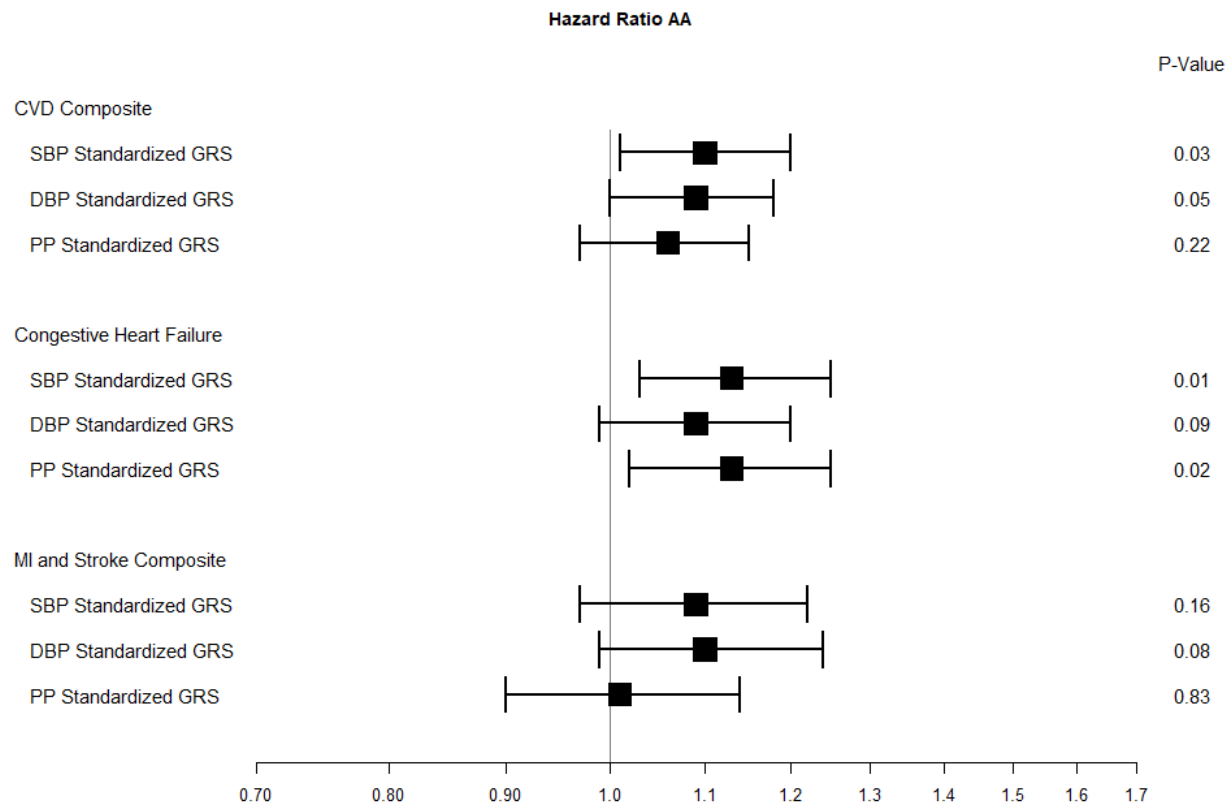
† Results of Cox proportional hazards models, comparing top quartile BP GRS to bottom quartile BP GRS, adjusted for age, sex, CRIC study site, and ancestry principal components.

‡ Composite of myocardial infarction, stroke, and congestive heart failure.

§ Halving of eGFR or ESKD

BMI=body mass index; CI=confidence interval; CVD=cardiovascular disease, DBP=diastolic blood pressure; eGFR=estimated glomerular filtration rate; ESKD=end stage kidney disease; GRS=genetic risk score; HR=hazard ratio; LDL=low density lipoprotein; PP=pulse pressure; SBP=systolic blood pressure; SD=standard deviation.

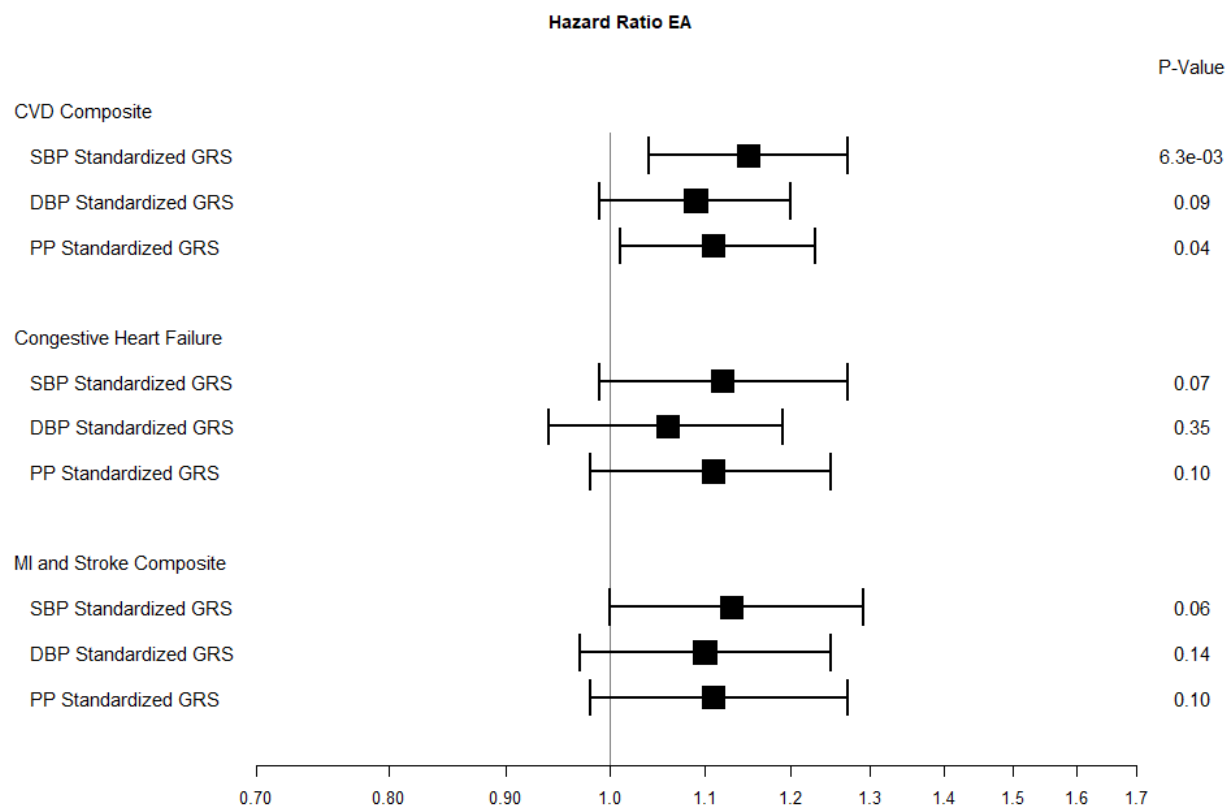
**Supplementary Figure 1. Hazard Ratios\* for CVD Composite and its Component Endpoints, per SD Increase in GRS, Among African Ancestry Participants**



\* Results of Cox proportional hazards models, per SD increase in BP GRS, adjusted for age, sex, study cite and ancestry principal components.

AA=African ancestry; CVD=cardiovascular disease; DBP=diastolic blood pressure; GRS=genetic risk score; MI=myocardial infarction; PP=pulse pressure; SBP=systolic blood pressure; SD=standard deviation.

## Supplementary Figure 2. Hazard Ratios\* for CVD Composite and its Component Endpoints per SD Increase in GRS, Among European Ancestry Participants



\* Results of Cox proportional hazards models, per SD increase in BP GRS, adjusted for age, sex, study cite and ancestry principal components.

CVD=cardiovascular disease; DBP=diastolic blood pressure; EA=European ancestry; GRS=genetic risk score; MI=myocardial infarction; PP=pulse pressure; SBP=systolic blood pressure; SD=standard deviation.

**Supplementary Table 8. Comparison of Hazard Ratios per Standard Deviation of SBP and the SBP GRS on Clinical Outcomes**

	<b>African Ancestry HR (95% CI)*</b>	<b>European Ancestry HR (95% CI)*</b>
CVD Composite		
SBP	1.30 (1.19, 1.42)	1.38 (1.25, 1.53)
SBP, adjusted for SBP GRS	1.30 (1.19, 1.41)	1.36 (1.23, 1.51)
SBP GRS	1.10 (1.01, 1.20)	1.15 (1.04, 1.27)
SBP GRS, adjusted for SBP	1.08 (0.99, 1.18)	1.10 (1.00, 1.22)
Halving of eGFR or ESKD		
SBP	1.60 (1.48, 1.73)	1.65 (1.50, 1.82)
SBP, adjusted for SBP GRS	1.60 (1.48, 1.73)	1.65 (1.50, 1.83)
SBP GRS	1.00 (0.92, 1.08)	1.07 (0.97, 1.18)
SBP GRS, adjusted for SBP	0.99 (0.92, 1.07)	0.99 (0.89, 1.10)

\* Results of Cox proportional hazards models, adjusted for age, sex, study cite and ancestry principal components.

CI=confidence interval; CVD=cardiovascular disease; eGFR=estimated glomerular filtration rate; ESKD=end stage kidney disease; GRS=genetic risk score; HR=hazard ratio; SBP=systolic blood pressure.



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