Association of Blood Pressure Genetic Risk Score with Cardiovascular Disease and Chronic Kidney Disease Progression

Findings from the CRIC Study

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Key Points

- High blood pressure has been associated with increased risk of cardiovascular disease and progression to end stage kidney disease.
- We identified an association of blood pressure genetic risk score for with cardiovascular disease but not with end stage kidney disease.
- Our study supports the role of blood pressure in cardiovascular disease but not kidney disease progression among those with kidney disease.
Abstract

**Background:** In the general population, genetic risk for high blood pressure has been associated with cardiovascular disease but not kidney function or incident chronic kidney disease. These relationships have not been studied longitudinally in participants with chronic kidney disease. We examined whether blood pressure genetic risk predicts cardiovascular disease and kidney disease progression in patients with chronic kidney disease.

**Methods:** We included 1,493 African and 1,581 European ancestry participants from the Chronic Renal Insufficiency Cohort who were followed for 12 years. We examined associations of blood pressure genetic risk scores with development of cardiovascular disease (myocardial infarction, congestive heart failure, or stroke) and chronic kidney disease progression (incident end stage kidney disease or halving of estimated glomerular filtration rate) using Cox proportional hazards models. Analyses were stratified by race and included adjustment for age, sex, study site, and ancestry principal components.

**Results:** Each standard deviation increase in systolic blood pressure and pulse pressure genetic risk score conferred respective 15% [95% confidence interval: 4%, 27%] and 11% (95% confidence interval: 1%, 23%) higher risks of cardiovascular disease, with a similar marginally significant trend for diastolic blood pressure, among European ancestry participants. Among African ancestry participants, each standard deviation increase in systolic and diastolic blood pressure genetic risk score conferred 10% (95% confidence interval: 1%, 20%) and 9% (95% confidence interval: 0%, 18%) higher risk of cardiovascular disease. Higher genetic risk was not associated with chronic kidney disease progression.
Conclusions: Genetic risk for elevation in blood pressure was associated with increased risk of cardiovascular disease but not chronic kidney disease progression.
Introduction

Chronic kidney disease (CKD) is estimated to affect between 10.4% and 11.8% of adults worldwide\(^1\) and is associated with high risks of cardiovascular disease (CVD), progression to end-stage kidney disease (ESKD), and all-cause mortality.\(^2\) Hypertension is a common co-morbid condition that has been identified by observational studies as an important risk factor for progression to ESKD and development of CVD in CKD patients.\(^3\)–\(^5\) Consistent with these data, randomized controlled trials (RCTs) in CKD patients have documented reduced CVD events associated with antihypertension medication use.\(^6\) The identified reductions in CVD events appear to be driven by the common BP lowering effects of different classes of anti-hypertension medications.\(^7\)–\(^9\) In contrast, RCTs have identified enhanced benefits of renin-angiotensin-aldosterone system (RAAS) inhibitors compared to other anti-hypertension medications on CKD progression,\(^10\)–\(^12\) while findings from trials assessing the renoprotective effects of general BP lowering have been inconclusive,\(^6,13,14\) suggesting that mechanisms independent of BP lowering may be responsible for the beneficial effects observed.

Because genetic information should not be confounded by traditional disease risk factors, studies using genetic data as a proxy for lifetime exposures have gained popularity as another tool for etiologic inference.\(^15,16\) Indeed, associations of genetic risk scores (GRSs) with disease outcomes have generally been consistent with findings from RCTs. For example, genetically elevated BP has reproducibly been shown to predict CVD endpoints in the general population.\(^17\)–\(^23\) Interestingly, BP GRSs have not consistently associated with kidney function or CKD in large and well-powered population-based studies.\(^17,18,20\)–\(^22\) While these findings have generated additional
uncertainty regarding the etiologic role of BP in kidney function decline and ESKD, no
study has investigated whether BP GRS predicts CKD progression and ESKD in patients
with CKD. Furthermore, the association between BP GRS and CVD has also not been
assessed among patients with CKD who are at substantially increased risks of this
condition. Thus, the purpose of the current study was to examine the associations of BP
GRS with both CKD progression and CVD events among patients with CKD of African
and European ancestry participating in the Chronic Renal Insufficiency Cohort (CRIC)
Study.

Methods

Study Participants

A total of 5,499 men and women were enrolled in the CRIC Study between 2003
and 2015. The study design details and participant characteristics at baseline have been
previously published. Briefly, participants were eligible for the study if they were
between 21 and 79 years of age with an estimated glomerular filtration rate (eGFR)
between 20 and 70 ml/min per 1.73 m². Exclusion criteria included glomerulonephritis
requiring immunosuppressive therapy, advanced heart failure, cirrhosis, and polycystic
kidney disease. Among the 3,939 CRIC participants from the first two recruitment
phases, 3,074 had available genotype, covariable, and phenotype data and were included
in the current study.

Data Collection and Study Covariables

A detailed description of data collection and study covariables is available in the
Supplementary Methods. In brief, standard questionnaires were used to ascertain
information on baseline demographic characteristics, medical history, and medication use. A physical examination was conducted to measure BP in triplicate, with the average of the three measures used to estimate BP. Pretreatment BP levels were imputed in participants on antihypertensive medication, by adding 15 and 10 mm Hg to SBP and DBP, respectively. Pulse pressure (PP) was then calculated as the difference between the adjusted SBP and DBP values. Institutional review boards at participating institutions approved the CRIC study protocol, and all study participants provided written informed consent, including specific consent for genetic investigations. This study adhered to the Declaration of Helsinki.

**Genetic Risk Score Construction**

Genotyping and imputation methods in the CRIC study have been described previously and are summarized in the Supplementary Methods. A total of 901 independent BP loci, identified in a primarily European ancestry general population sample, explaining up to 5.7% of BP variability, were utilized for construction of SBP (884 SNPs), DBP (885 SNPs), and PP GRSs (256 SNPs) among CRIC participants. Among them, SNPs from 879 and 883 loci were available in African and European ancestry CRIC participants, respectively. Weighted GRS were calculated for SBP, DBP, and PP using a two-step procedure, which included: 1.) for each SNP, multiplying the participant’s dosage of the risk allele by its previously estimated effect size; and 2.) summing the products across all SNPs included in the risk score. Participants were then categorized into quartiles of SBP, DBP, and PP GRS. Annotation and effect estimates used for weighting of each SNP included in the GRS are presented in the Supplementary Data.
Primary Outcomes

The primary cardiovascular outcome of interest was a composite of the first of congestive heart failure, myocardial infarction, or stroke that occurred during follow-up. Congestive heart failure was identified by hospital admission for new or worsening congestive heart failure signs and symptoms, in addition to diminished cardiac output. Myocardial infarction was defined by characteristic changes in troponin and creatine kinase–MB levels, symptoms of myocardial ischemia, electrocardiogram changes, or new fixed profusion abnormalities. Stroke was defined as rapid onset of neurologic deficit, headache, or other nonvascular cause and clinically relevant lesion on brain imaging for longer than 24 hours or death within 24 hours. All events classified as probable or definite during adjudication were included in these analyses.

During CRIC follow-up, incident ESKD was defined as receipt of chronic dialysis or kidney transplant. Information on the initiation and maintenance of dialysis and kidney transplant was obtained by annual clinical follow-up visits and interim telephone interviews and confirmed by a dialysis unit or hospital chart review. Ascertainment of ESKD in the CRIC study was supplemented by information from the US Renal Data System. For the current analysis, CKD progression events were defined as halving of eGFR or incident ESKD defined as the occurrence of renal dialysis or kidney transplantation.

Statistical Analysis

The means and standard deviations or frequencies and percentages of baseline characteristics were calculated for participants in each ancestry group. Our main analyses were stratified by ancestry group, and adjusted for age, sex, CRIC study site, and
principal components for ancestry (ten for participants of African ancestry and three for participants of European ancestry). GRSs were tested for association with baseline SBP, DBP, and PP using linear regression models. In sensitivity analyses, GRSs were tested for association with unimputed baseline BP using linear regression models and changes in BP over follow up using mixed regression models. The BP GRSs were then tested for associations with each of our primary outcomes, time to CVD and CKD progression events, using Cox proportional hazards models. To account for additional possible confounding by clinical factors, we conducted sensitivity analyses on the GRS-primary outcome associations with additional adjustment for BMI, low density lipoprotein, and lipid lowering medications. To increase our statistical power for the assessment of CKD progression, we also examined the associations between the GRSs and continuous measures of kidney function decline over time using mixed models and two untransformed measures of decline – eGFR slope and UPCR slope. Finally, we performed a sensitivity analysis to examine the independent associations of measured SBP and our SBP GRSs with the primary CVD and CKD endpoints. Analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC) and R 3.6.1 (The R Foundation) statistical software.

Results

Study Participants

Baseline characteristics of CRIC participants, stratified by ancestry, are presented in Table 1. On average, participants had moderate CKD [mean (SD) eGFR, 48.4 (18.6)]. Most participants had hypertension and were using antihypertensive medication. BP,
BMI, low density lipoprotein, proportion with diabetes, and number of antihypertensive medications were higher among African Ancestry participants than European ancestry participants. African ancestry participants were generally similar across SBP GRS quartiles (Supplementary Table 1). European ancestry participants had increasing BP traits across SBP GRS quartiles (Supplementary Table 2).

**Associations between BP GRS & Baseline Measures**

GRSs for SBP, DBP, and PP were associated with baseline SBP, DBP, and PP, respectively, among European ancestry participants (Supplementary Table 3). No associations were found between BP GRSs and respective BP measures among African ancestry participants. Models examining the relationship between per-quartile BP GRS and baseline SBP, DBP, and PP, showed overall consistency with our per-SD models (Supplementary Table 4). In addition, European ancestry participants in higher SBP, DBP, and PP GRS quartiles and African ancestry participants in higher SBP GRS quartiles were using a greater number of antihypertensive medications than those in lower quartiles (Supplementary Table 5). As expected, GRS-BP associations were attenuated in models using unimputed BP measurements with number of antihypertensive medications as a covariate (Supplementary Table 6). BP GRSs were not associated with baseline eGFR or UPCR in either ancestry (Supplementary Table 1) nor were they associated with annual change in BP over follow up (data not shown).

**Associations between BP GRS and Prospective CVD and CKD Endpoints**

SBP GRSs among both African and European ancestry participants and PP GRSs among European ancestry participants were associated with significantly increased risks of CVD. A similar trend for DBP GRSs among both African and European ancestry
participants was also observed. Findings were similar when comparing the top GRS quartile to the bottom GRS quartile (Table 2). Although no association with CVD was observed for the PP GRS among African ancestry participants, the trend was similar to the other BP GRSs. Results were similar in models that additionally adjusted for BMI, low density lipoprotein, and lipid lowering medication (Supplementary Table 7). We did not find any associations between the BP GRSs and CKD progression events (Table 2 and Supplementary Table 7). Furthermore, BP GRSs did not associate with annual kidney function decline over follow up, using either eGFR slope or UPCR slope, in either continuous or quartile models (Table 3).

The Figure (A and B) depicts the relationships between each GRS and the CVD composite, stratified by ancestry, per quartile of SBP, DBP, and PP GRS. Our quartile models demonstrated overall consistency with our per-SD models. We found that risk of CVD increased per quartile SBP GRS among European ancestry participants (p=0.03), with similar trends for SBP and DPB GRS among African ancestry participants (P=0.10 and P=0.11, respectively). In addition, compared to participants in the lowest quartiles SBP, DBP, and PP GRS, European ancestry participants in the highest quartiles had 1.41- [95% confidence interval (CI): 1.06, 1.88; P=0.02], 1.18- (95%CI: 0.89, 1.56; P=0.25), and 1.33-fold (95% CI: 1.00, 1.76; P=0.05) higher risks of CVD, respectively. The Figure (C and D) also shows the relationships between each GRS and incident ESKD or halving of eGFR, stratified by ancestry, per quartile of SBP, DBP, and PP GRS. Similar to the results for our continuous models, there were no associations between BP GRS and this endpoint in either ancestry group.
We also examined two components of the CVD composite separately, congestive heart failure and a composite of myocardial infarction and stroke. Among African ancestry participants, we observed significant increases in risk of congestive heart failure associated with our SBP and PP GRSs (Supplementary Figure 1) and consistent but non-significant increases in risk of MI and stroke. Among European ancestry participants, we observed a consistently positive effect direction in the relationships between the GRSs and each of the components of the CVD composite (Supplementary Figure 2), although these hazard ratios did not meet the threshold for statistical significance.

**Comparison of Effect Sizes on Clinical Outcomes**

In our adjusted models, each standard deviation increase in measured SBP conferred significant 1.3- and 1.4-fold increased risks of CVD events in African and European ancestry participants, respectively. Effect sizes of measured SBP on CKD progression events were larger, conferring 1.6- and 1.7-fold increased risks for this endpoint. Our SBP GRS associated with a significant 10\% increased risk of CVD events in European ancestry participants after adjusting for measured BP (P=0.05), demonstrating an independent association of this variable in Europeans and suggesting that BP GRS provides information somewhat distinct from measured BP (Supplementary Table 8). Although the effect size for SBP GRS on CVD events in African ancestry participants was only modestly attenuated by the inclusion of measured SBP in the model, the association was only marginally significant (P=0.07). As expected based on our main analyses, hazard ratios for CKD events conferred by SBP GRSs were
not significant before or after adjustment for measured SBP in either ancestry group (Supplementary Table 6).

**Discussion**

In the current study, we observed significant associations between BP GRS and CVD among patients with CKD of both African and European ancestries. Those with higher BP GRS had increased risk of CVD events over an average of 12 years of follow up. Furthermore, effect sizes were generally consistent among the two components of the CVD composite endpoints, congestive heart failure and MI/stroke. In contrast, there was no association between BP GRS and CKD progression events or annual declines in kidney function, based on eGFR and UPCR. While clinical trials show that BP lowering medication reduces CVD and CKD progression events, these data suggest that the mechanism of action for these two health conditions may be distinct.

In the current study, BP GRSs associated with increased risk of CVD events in both African and European ancestry CRIC participants. Effect sizes for SBP GRSs tended to be larger in magnitude and achieve smaller p-values than those for DBP and PP. The relatively larger effects of SBP GRS on CVD events likely reflects the larger effects of measured SBP on this phenotype. With 9% to 15% increased risks of CVD events conferred by each standard deviation increase in SBP GRS across ancestry groups, our findings are similar to previous research in the general population that showed 11% increased risk of CVD or 11% increased prevalence of CVD associated with BP GRSs. Our results are also consistent with RCTs demonstrating reductions in CVD events associated with BP lowering. For example, a 2013 meta-analysis of RCTs
conducted by the Blood Pressure Lowering Treatment Trialists’ Collaboration reported reduced risk of major cardiovascular events associated with reductions in SBP, with similar associations identified across eGFR subgroups and antihypertension medication classes. Another meta-analysis of RCTs, by Xie and colleagues from 2016, similarly found reductions in risk of CVD events with intensive blood pressure lowering treatment when compared to less intensive blood pressure lowering, again demonstrating consistent reductions in CVD events across intervention types and patient subgroups, including patients with kidney disease. Our findings add genetic evidence to the robust findings of previous RCTs supporting the role of high BP in occurrence of CVD events in patients with CKD.

We did not find a relationship between BP GRSs and worsening kidney disease using three kidney disease progression measures – CKD progression events, eGFR change over time, and UPCR change over time. These findings are generally consistent with studies of BP GRSs and kidney function in the general population. Our results are further supported by a recent general population Mendelian randomization study by Yu and colleagues, where no association between a blood pressure GRS and kidney function was found. The authors did, however, find a causal relationship between their kidney function GRS and BP, suggesting that the public health burden of hypertension can be reduced through preventing kidney function decline. These general population findings are consistent with clinical trial evidence in CKD populations, which did not demonstrate conclusive renoprotective effects of antihypertensive medication, but strongly showed protective effects of RAAS inhibition in reducing CKD progression, independent of BP lowering. Our findings further build on previous work,
providing genetic evidence that lifetime burden of high BP may relate to CKD outcomes differently than it does to CVD outcomes.

We generally found attenuated associations between BP GRSs and BP when compared with previous BP GRS studies\textsuperscript{17,19}, both in terms of effect estimates and statistical significance. These findings were consistent when we imputed BP measurements for antihypertension medication and when we adjusted for number of antihypertension medications. BP GRS serves as a proxy for lifetime burden of high BP. Since 92\% of CRIC participants were taking antihypertension medication and medication use was higher among participants with increased BP genetic risk, baseline BP measures may more so reflect the acute BP lowering effects of pharmaceutical intervention rather than long-term BP measures. As expected, BP GRS was strongly associated with the intermediate BP phenotype, antihypertension medication use, which further validates its use as a proxy for high lifetime BP. In this context, our findings of attenuated associations compared to a general population with much lower frequencies of antihypertension medication use are unsurprising. Results were particularly attenuated in African ancestry participants, likely reflecting the construction of a GRS using loci from a majority European ancestry population.\textsuperscript{19} Although there is substantial evidence that causal variants driving complex human trait associations are largely shared across diverse populations,\textsuperscript{35,36} and that variants identified in specific ancestry groups may be relevant to populations with distinct linkage disequilibrium structures,\textsuperscript{37} previous BP GRS studies have often shown attenuated effects in non-European ancestry populations.\textsuperscript{18,19,22} Our findings similarly highlight the disparity introduced by the historical Eurocentric biases in genomics research,\textsuperscript{38} providing further support for the importance of conducting
genetics research in diverse populations. African ancestry participants were also more likely to use antihypertensive medications and were on a greater number of antihypertensive medications than their European ancestry counterparts, which may have also contributed to the relatively attenuated BP findings in this ancestry group.

This study has several important strengths. To our knowledge, it is the first study to examine the relationship between BP GRSs and CKD progression among CKD patients. The CRIC study provides a unique opportunity to study this relationship in a well phenotyped multi-ancestry cohort with over a decade of follow up and multiple measures of kidney function decline. This study also has several important limitations. Our findings have not been replicated in an independent population; however, they are consistent with most previous BP GRS studies in the general population. Our study also had fewer participants than many of the previous studies that examined the relationship between BP GRS and BP-related phenotypes, raising concerns related to statistical power. However, CKD events were more frequent than CVD events and demonstrate associations with SBP that are larger in magnitude. Hence, power for detecting GRS-CKD associations was better than that of GRS-CVD associations. Even with our limited sample size, we were able to identify compelling genetic evidence of the effects of BP on CVD in CKD patients. BP GRS did not display strong associations with measured BP in our sample, likely due to the high frequency of medication use. Therefore, the observed findings are necessarily more reflective of the associations of lifetime burden of high BP with CVD and CKD progression rather than BP measured at baseline or subsequent changes in BP during follow up.
In the first study to examine the effects of aggregated BP loci on cardiovascular and renal phenotypes in patients with CKD, we observed an association between genetically elevated BP and cardiovascular endpoints. We did not find significant associations between genetic risk for high BP and CKD progression, adding more uncertainty to the etiologic role of BP in CKD.

Disclosures
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J He: Conceptualization; Supervision; Writing - review and editing

A Parsa: Data curation; Funding acquisition; Investigation; Methodology; Project administration; Writing - review and editing

A Srivastava: Writing - review and editing

J Cohen: Writing - review and editing

S Saraf: Writing - review and editing

M Rahman: Writing - review and editing

S Rosas: Writing - review and editing
Supplemental Materials

Supplementary Methods

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

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

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

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

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

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

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

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

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

Supplemental References

**Supplementary Data.** Variant Effect Estimates on Blood Pressure Used in Genetic Risk
Score Construction
References


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<th>European Ancestry (n=1,581)</th>
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</tr>
<tr>
<td>Systolic BP GRS, mean (SD)‡</td>
<td>170 (3)</td>
<td>173 (4)</td>
</tr>
<tr>
<td>Diastolic BP GRS, mean (SD)‡</td>
<td>101 (2)</td>
<td>102 (2)</td>
</tr>
<tr>
<td>Pulse pressure GRS, mean (SD)‡</td>
<td>39 (1)</td>
<td>40 (2)</td>
</tr>
</tbody>
</table>

* Body mass index ≥ 30 kg/m²; † BP ≥ 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; SD=standard deviation.
Table 2. Hazard Ratios for Primary Endpoints per SD Increase in GRS and Comparing the Top and Bottom GRS Quartiles

<table>
<thead>
<tr>
<th>Outcome / GRS</th>
<th>Continuous</th>
<th>Quartile</th>
<th>Continuous</th>
<th>Quartile</th>
<th>Continuous</th>
<th>Quartile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>African Ancestry</td>
<td>European Ancestry</td>
<td>African Ancestry</td>
<td>European Ancestry</td>
<td>African Ancestry</td>
<td>European Ancestry</td>
</tr>
<tr>
<td>CVD Event‡</td>
<td>SBP</td>
<td>1.10 (1.01-1.20) 0.03</td>
<td>1.21 (0.95-1.53) 0.12</td>
<td>1.15 (1.04-1.27) 6.3×10⁻³</td>
<td>1.41 (1.06-1.88) 0.02</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DBP</td>
<td>1.09 (1.00-1.18) 0.05</td>
<td>1.15 (0.90-1.47) 0.25</td>
<td>1.09 (0.99-1.20) 0.09</td>
<td>1.18 (0.89-1.56) 0.25</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PP</td>
<td>1.06 (0.97-1.15) 0.22</td>
<td>1.18 (0.92-1.52) 0.18</td>
<td>1.11 (1.01-1.23) 0.04</td>
<td>1.33 (1.00-1.76) 0.05</td>
<td></td>
</tr>
<tr>
<td>CKD Progression Event§</td>
<td>SBP</td>
<td>1.00 (0.92-1.08) 0.99</td>
<td>0.93 (0.75-1.16) 0.55</td>
<td>1.07 (0.97-1.18) 0.19</td>
<td>1.06 (0.80-1.40) 0.67</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DBP</td>
<td>1.03 (0.95-1.11) 0.46</td>
<td>1.12 (0.90-1.40) 0.31</td>
<td>1.00 (0.90-1.10) 0.93</td>
<td>0.96 (0.74-1.25) 0.76</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PP</td>
<td>0.97 (0.89-1.05) 0.40</td>
<td>0.91 (0.73-1.13) 0.40</td>
<td>1.07 (0.97-1.19) 0.17</td>
<td>1.18 (0.90-1.55) 0.24</td>
<td></td>
</tr>
</tbody>
</table>

* Results of Cox proportional hazards models, per SD increase in BP GRS, adjusted for age, sex, CRIC study site, 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
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; PP=pulse pressure; SBP=systolic blood pressure; SD=standard deviation.
| Outcome / GRS | African Ancestry | | European Ancestry | | |
|--------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|              | Continuous | Quartile | Continuous | Quartile | Continuous | Quartile | |
|              | β (SE)* | P | β (SE)* | P | β (SE)* | P | β (SE)* | P |
| eGFR slope   |            |            |            |            |            |            |            |
| SBP GRS      | -0.04 (0.32) | 0.90 | -0.21 (0.91) | 0.82 | 0.10 (0.29) | 0.73 | 0.32 (0.82) | 0.69 |
| DBP GRS      | -0.01 (0.32) | 0.98 | -0.14 (0.92) | 0.88 | 0.10 (0.29) | 0.73 | 0.40 (0.83) | 0.63 |
| PP GRS       | -0.03 (0.33) | 0.92 | -0.13 (0.92) | 0.89 | 0.05 (0.29) | 0.86 | 0.27 (0.83) | 0.74 |
| Urinary protein slope |            |            |            |            |            |            |            |
| SBP GRS      | -0.02 (0.03) | 0.56 | -0.04 (0.09) | 0.64 | 0.02 (0.03) | 0.46 | 0.05 (0.09) | 0.60 |
| DBP GRS      | -0.02 (0.03) | 0.57 | -0.03 (0.09) | 0.79 | 0.04 (0.03) | 0.18 | 0.09 (0.09) | 0.32 |
| PP GRS       | -0.03 (0.03) | 0.41 | -0.07 (0.09) | 0.46 | 0.01 (0.03) | 0.75 | 0.04 (0.09) | 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; SE=standard error
Figure legend

Figure. Hazard Ratios for Primary Endpoints per Quartile Increase in GRS

Hazard ratios per quartile increase in GRS compared to quartile 1, for composite of cardiovascular disease and death and composite of ESKD or halving of eGFR, stratified by ancestry, and adjusted for age, sex, CRIC study site, and ancestry principal components. P values are for trend across quartiles.

CVD=cardiovascular disease; DBP=diastolic blood pressure; eGFR=estimated glomerular filtration rate; ESKD=end stage kidney disease; GRS=genetic risk score; PP=pulse pressure; SBP=systolic blood pressure.
Figure. Hazard Ratios for Primary Endpoints per quartile Increase in GRS

A. CVD Composite
   African Ancestry

B. CVD Composite
   European Ancestry

C. ESRD or Halving of eGFR
   African Ancestry

D. ESRD or Halving of eGFR
   European Ancestry

Hazard ratios per quartile increase in GRS compared to quartile 1, for composite of cardiovascular disease and death and composite of ESRD or halving of eGFR, stratified by ancestry. P values are for trend across quartiles.

CVD=cardiovascular disease; DBP=diastolic blood pressure; eGFR=estimated glomerular filtration rate; ESRD=end stage renal disease; GRS=genetic risk score; PP=pulse pressure; SBP=systolic blood pressure.