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Association of Blood Pressure Genetic Risk Score with Cardiovascular Disease and CKD Progression: Findings from the CRIC Study

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Abstract

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

Methods We included 1493 African- and 1581 European-ancestry participants from the Chronic Renal Insufficiency Cohort who were followed for 12 years. We examined associations of BP genetic risk scores with development of cardiovascular disease (myocardial infarction, congestive heart failure, or stroke) and CKD progression (incident ESKD or halving of eGFR) using Cox proportional hazards models. Analyses were stratified by race and included adjustment for age, sex, study site, and ancestry principal components.

Results Among European-ancestry participants, each SD increase in systolic BP and pulse pressure genetic risk score conferred a 15% (95% CI, 4% to 27%) and 11% (95% CI, 1% to 23%), respectively, higher risk of cardiovascular disease, with a similar, marginally significant trend for diastolic BP. Among African-ancestry participants, each SD increase in systolic and diastolic BP genetic risk score conferred a 10% (95% CI, 1% to 20%) and 9% (95% CI, 0% to 18%), respectively, higher risk of cardiovascular disease. Higher genetic risk was not associated with CKD progression.

Conclusions Genetic risk for elevation in BP was associated with increased risk of cardiovascular disease, but not CKD progression.

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Introduction

CKD is estimated to affect between 10% and 12% of adults worldwide (1), and is associated with high risks of cardiovascular disease (CVD), progression to ESKD, and all-cause mortality (2). Hypertension is a common comorbid condition that has been identified by observational studies as an important risk factor for progression to ESKD and development of CVD in patients with CKD (3–5). Consistent with these data, randomized controlled trials (RCTs) in patients with CKD have documented reduced CVD events associated with use of antihypertension medication (6). The identified reductions in CVD events appear to be driven by the common BP-lowering effects of different classes of antihypertension medications (7–9). In contrast, compared with other antihypertension medications, RCTs have identified enhanced benefits of renin-angiotensin-aldosterone system inhibitors on CKD progression (10–12); however, findings from trials assessing the renoprotective effects of general BP

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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 end points 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). Although 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 risk for this condition. Thus, the purpose of this 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 5499 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 (24,25). Briefly, participants were eligible for the study if they were between 21 and 79 years of age, with an eGFR of between 20 and 70 ml/min per 1.73 m^2. Exclusion criteria included GN requiring immunosuppressive therapy, advanced heart failure, cirrhosis, and polycystic kidney disease. Among the 3939 CRIC participants from the first two recruitment phases, 3074 had available genotype, covariable, and phenotype data and were included in this study.

Data Collection and Study Covariables

A detailed description of data collection and study covariables is available in Supplemental Appendices 1 and 2. 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 (26), by adding 15 and 10 mm Hg to systolic BP (SBP) and diastolic BP (DBP), respectively (27). Pulse pressure (PP) was then calculated as the difference between the adjusted SBP and DBP values. The institutional review boards at the 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.

GRS Construction

Genotyping and imputation methods in the CRIC Study have been described previously (28) and are summarized in Supplemental Appendix 1. A total of 901 independent BP loci, identified in a primarily European-ancestry general population sample, explaining up to 6% of BP variability, were used for construction of SBP (884 single-nucleotide polymorphisms [SNPs]), DBP (885 SNPs), and PP GRSs (256 SNPs) among CRIC participants (19). SNPs from 879 and 883 of these loci were available in African- and European-ancestry CRIC participants, respectively. Weighted GRSs were calculated for SBP, DPB, and PP using a two-step procedure as follows: (*1*) for each SNP, multiply the participant's dosage of the risk allele by its previously estimated effect size; and (*2*) sum 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 Supplemental Appendix 3.

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–myocardial band levels, symptoms of myocardial ischemia, electrocardiogram changes, or new fixed perfusion abnormalities. Stroke was defined as rapid onset of neurologic deficit, headache, or other nonvascular cause, and clinically relevant lesion on brain imaging for >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 United States Renal Data System. For this analysis, CKD progression events were defined as halving of eGFR or incident ESKD, defined as the occurrence of renal dialysis or kidney transplantation.

Statistical Analyses

The means and SDs 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 body mass index (BMI), LDL, 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 urinary protein-creatinine ratio (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 end points. 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, LDL, 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 (Supplemental Table 1). European-ancestry participants had increasing BP traits across SBP GRS quartiles (Supplemental Table 2).

Associations between BP GRS and Baseline Measures

GRSs for SBP, DBP, and PP were associated with baseline SBP, DBP, and PP, respectively, among participants of European ancestry (Supplemental Table 3). No associations were found between BP GRSs and respective BP measures among participants of African ancestry. Models examining the relationship between per-quartile BP GRS and baseline SBP, DBP, and PP showed overall consistency with our per-SD models (Supplemental 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 (Supplemental Table 5). As expected, GRS-BP associations were attenuated in models using unimputed BP measurements with the number of antihypertensive medications as a covariate (Supplemental Table 6). BP GRSs were not associated with baseline eGFR or UPCR in either ancestry

Table 1. Baseline characteristics of CRIC participants according to ancestry (*N*=3074)

Characteristic	African Ancestry (*n*=1493)	European Ancestry (*n*=1581)
Age (years), mean±SD	58±11	59±11
Male, *n* (%)	726 (49)	945 (60)
High-school graduate, *n* (%)	1095 (73)	1493 (94)
Current cigarette smokers, *n* (%)	285 (19)	148 (9)
Ever cigarette smokers, *n* (%)	848 (57)	889 (56)
Current alcohol use, *n* (%)	794 (53)	1187 (75)
Body mass index (kg/m^2), mean (SD)	34±8	31±7
Obesity, *n* (%)[a]	949 (64)	785 (50)
Serum cholesterol (mg/dl), mean±SD	186±46	180±42
LDL (mg/dl), mean±SD	106±37	99±32
Uses lipid-lowering medication, *n* (%)	830 (56)	995 (63)
Diabetes, *n* (%)	771 (52)	632 (40)
Systolic BP, mean±SD	147±24	135±20
Diastolic BP, mean±SD	83±14	78±12
Pulse pressure, mean±SD	64±20	57±17
Hypertension, *n* (%)[b]	1454 (97)	1435 (91)
Uses antihypertensive medication, *n* (%)	1415 (96)	1391 (89)
Number of antihypertensive medications, mean±SD	3.0±1.5	2.3±1.4
Serum creatinine (mg/dl), mean±SD	2.0±0.7	1.7±0.5
eGFR (ml/min per 1.73m^2), mean±SD	47±18	50±19
Urinary protein-creatinine ratio, mean (SD)[c]	1.0 (2.1)	0.7 (2.0)
Systolic BP GRS, mean±SD[d]	170±3	173±4
Diastolic BP GRS, mean±SD[d]	101±2	102±2
Pulse pressure GRS, mean±SD[d]	39±1	40±2

CRIC, Chronic Renal Insufficiency Cohort; GRS, genetic risk score.
[a]Body mass index ≥30 kg/m^2.
[b]BP ≥130/80 mm Hg or use of antihypertensive medications.
[c]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.
[d]Weighted sum of risk alleles for systolic BP, diastolic BP, and pulse pressure, respectively, using previously estimated effect sizes as weights.

group (Supplemental 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 End Points

SBP GRSs among participants of both African and European ancestry 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 with the bottom GRS quartile (Table 2). Although no association with CVD was observed for the PP GRS among participants of African ancestry, the trend was similar to the other BP GRSs. Results were similar in models that additionally adjusted for BMI, LDL, and lipid-lowering medication (Supplemental Table 7). We did not find any associations between the BP GRSs and CKD progression events (Supplemental Table 7, Table 2). 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).

Figure 1, 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 of 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 with participants in the lowest quartiles of SBP, DBP, and PP GRS, European-ancestry participants in the highest quartiles had 1.41- (95% CI, 1.06 to 1.88; $P=0.02$), 1.18- (95% CI, 0.89 to 1.56; $P=0.25$), and 1.33-fold (95% CI, 1.00 to 1.76; $P=0.05$) higher risks of CVD, respectively. Figure 1, 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 end point 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 participants of African ancestry, we observed significant increases in risk of congestive heart failure associated with our SBP and PP GRSs (Supplemental Figure 1) and consistent, but nonsignificant, increases in risk of myocardial infarction and stroke. Among participants of European ancestry, we observed a consistently positive effect direction in the relationships between the GRSs and each of the components of the CVD composite (Supplemental 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 SD 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, respectively, increased risks for this end point. 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. This suggests that the BP GRS provides information somewhat distinct from measured BP (Supplemental 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

Table 2. Hazard ratios for primary end points per SD increase in GRS and comparing the top and bottom GRS quartiles

	African Ancestry				European Ancestry			
	Continuous		Quartile		Continuous		Quartile	
Outcome/GRS	HR (95% CI)[a]	*P* Value	HR (95% CI)[b]	*P* Value	HR (95% CI)[a]	*P* Value	HR (95% CI)[b]	*P* Value
CVD event[c]								
SBP	1.10 (1.01 to 1.20)	0.03	1.21 (0.95 to 1.53)	0.12	1.15 (1.04 to 1.27)	0.006	1.41 (1.06 to 1.88)	0.02
DBP	1.09 (1.00 to 1.18)	0.05	1.15 (0.90 to 1.47)	0.25	1.09 (0.99 to 1.20)	0.09	1.18 (0.89 to 1.56)	0.25
PP	1.06 (0.97 to 1.15)	0.22	1.18 (0.92 to 1.52)	0.18	1.11 (1.01 to 1.23)	0.04	1.33 (1.00 to 1.76)	0.05
CKD progression event[d]								
SBP	1.00 (0.92 to 1.08)	0.99	0.93 (0.75 to 1.16)	0.55	1.07 (0.97 to 1.18)	0.19	1.06 (0.80 to 1.40)	0.67
DBP	1.03 (0.95 to 1.11)	0.46	1.12 (0.90 to 1.40)	0.31	1.00 (0.90 to 1.10)	0.93	0.96 (0.74 to 1.25)	0.76
PP	0.97 (0.89 to 1.05)	0.40	0.91 (0.73 to 1.13)	0.40	1.07 (0.97 to 1.19)	0.17	1.18 (0.90 to 1.55)	0.24

GRS, genetic risk score; HR, hazard ratio; CVD, cardiovascular disease, SBP, systolic BP; DBP, diastolic BP; PP, pulse pressure; CRIC, Chronic Renal Insufficiency Cohort.
[a]Results of Cox proportional hazards models, per SD increase in BP GRS, adjusted for age, sex, CRIC study site, and ancestry principal components.
[b]Results of Cox proportional hazards models, comparing top quartile BP GRS with bottom quartile BP GRS, adjusted for age, sex, CRIC study site, and ancestry principal components.
[c]Composite of myocardial infarction, stroke, and congestive heart failure.
[d]Halving of eGFR or ESKD.

Table 3. Kidney disease progression per SD increase in GRS and comparing the top and bottom GRS quartiles

	African Ancestry				European Ancestry			
	Continuous		Quartile		Continuous		Quartile	
Outcome/GRS	β (SEM)[a]	*P* Value	β (SEM)[b]	*P* Value	β (SEM)[a]	*P* Value	β (SEM)[b]	*P* Value
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

GRS, genetic risk score; SBP, systolic BP; DBP, diastolic BP; PP, pulse pressure; CRIC, Chronic Renal Insufficiency Cohort.
[a]Results of linear models, per SD increase in BP GRS, adjusted for age, sex, CRIC study site, and ancestry principal components.
[b]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.

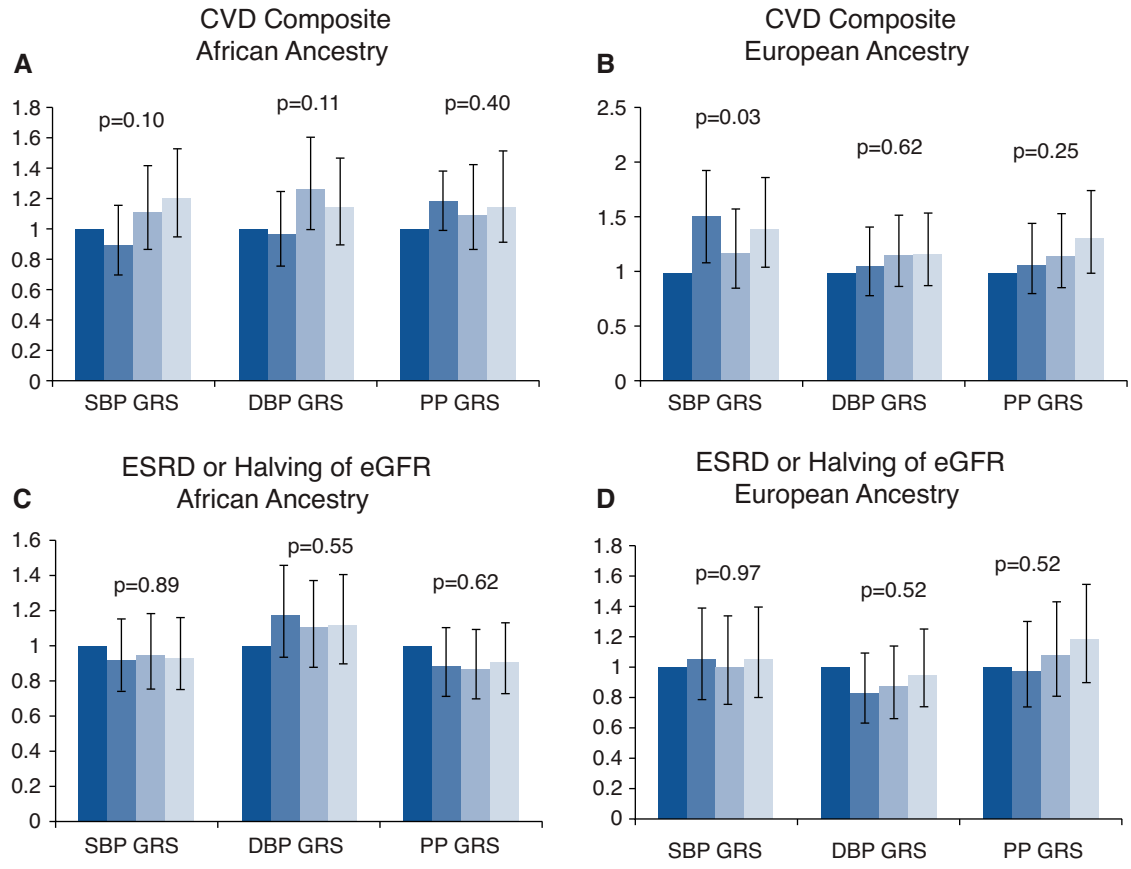

Figure 1. | Hazard ratios for primary end points per quartile increase in GRS. Hazard ratios per quartile increase in GRS compared to quartile 1, for composite of cardiovascular disease and death and composite of ESKD or halving of eGFR, stratified by ancestry, and adjusted for age, sex, Chronic Renal Insufficiency Cohort study site, and ancestry principal components. *P* values are for trend across quartiles. CVD, cardiovascular disease; DBP, diastolic BP; GRS, genetic risk score; PP, pulse pressure; SBP, systolic BP.

significant ($P=0.07$). As expected, on the basis of 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 (Supplemental Table 6).

Discussion

In this study, we observed significant associations between BP GRS and CVD among patients with CKD of both African and European ancestries. Those with higher BP GRSs 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 end points—congestive heart failure and myocardial infarction/stroke. In contrast, there was no association between BP GRS and CKD progression events or annual declines in kidney function on the basis of eGFR and UPCR. Although clinical trials show that BP-lowering medication reduces CVD and CKD progression events, these data suggest the mechanism of action for these two health conditions may be distinct.

In this 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 GRSs on CVD events likely reflect the larger effects of measured SBP on this phenotype (29). With 9%–15% increased risks of CVD events conferred by each SD 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 (30), or 11% increased prevalence of CVD (17,23), 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 (31). Another meta-analysis of RCTs from 2016, by Xie and colleagues (6), similarly found reductions in risk of CVD events with intensive BP-lowering treatment when compared with less-intensive BP 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 (17,18,20–22). Our results are further supported by a recent general-population, Mendelian-randomization study by Yu and colleagues (32), where no association between a BP GRS and kidney function was found. The authors did, however, find a causal relationship between their kidney function GRS and BP, suggesting the public health burden of hypertension can be reduced through preventing kidney-function decline. These findings in the general population 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 renin-angiotensin-aldosterone system inhibition in reducing CKD progression, independent of BP lowering (12,33,34). 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 (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. Because 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 pharmaceutic 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 when compared with a general population with much lower frequencies of antihypertension medication use are unsurprising. Results were particularly attenuated in participants of African ancestry, likely reflecting the construction of a GRS using loci from a majority European-ancestry population (19). Although there is substantial evidence that causal variants driving complex human trait associations are largely shared across diverse populations (35,36), and that variants identified in specific ancestry groups may be relevant to populations with distinct linkage-disequilibrium structures (37), previous BP GRS studies have often shown attenuated effects in populations of non-European ancestry (18,19,22). Our findings similarly highlight the disparity introduced by the historical Eurocentric biases in genomics research (38), providing further support for the importance of conducting genetics research in diverse populations. Participants of African ancestry 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 patients with CKD. The CRIC Study provides a unique opportunity to study this relationship in a well-phenotyped, multiancestry 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 patients with CKD. 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 end points. 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.

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Author Contributions

A. H. Anderson, J. He, and T. N. Kelly provided supervision; A. H. Anderson, J. He, T. N. Kelly, and J. L. Nierenberg conceptualized the study; T. N. Kelly and J. L. Nierenberg wrote the original draft and were responsible for formal analysis; T. N. Kelly, J. L. Nierenberg, and A. Parsa were responsible for project administration; J. L. Nierenberg was responsible for visualization; J. L. Nierenberg and A. Parsa were responsible for data curation, investigation, and methodology; A. Parsa was responsible for funding acquisition; and all authors reviewed and edited the manuscript.

Supplemental Materials

This article contains the following supplemental material online at http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.0007632020/-/DCSupplemental.

Supplemental Appendix 1. Methods.

Supplemental Table 1. Baseline characteristics of African ancestry CRIC participants according to SBP GRS quartile.

Supplemental Table 2. Baseline characteristics of European ancestry CRIC participants according to SBP GRS quartile.

Supplemental 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.

Supplemental Table 4. Median baseline blood pressure, per quartile increase in respective blood pressure GRS.

Supplemental Table 5. Median number of antihypertensive medications per quartile increase in GRS.

Supplemental 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.

Supplemental 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.

Supplemental Figure 1. Hazard ratios for CVD composite and its component endpoints, per SD increase in GRS, among African ancestry participants.

Supplemental Figure 2. Hazard ratios for CVD composite and its component endpoints per SD increase in GRS, among European ancestry participants.

Supplemental Table 8. Comparison of hazard ratios per standard deviation of SBP and the SBP GRS on clinical outcomes.

Supplemental Appendix 2. References.

Supplemental Appendix 3. Variant effect estimates on blood pressure used in genetic risk score construction.

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