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# The Association of Cell Cycle *Checkpoint 2* Variants and Kidney Function: Findings of the Family Blood Pressure Program and the Atherosclerosis Risk in Communities Study

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## Abstract

**BACKGROUND—**Recent experimental evidence suggests that DNA damage and cell cycle regulatory proteins are involved in kidney injury and apoptosis. The *checkpoint 2* gene (*CHEK2)* is an important transducer in DNA damage signaling pathways in response to injury, and therefore, *CHEK2* variants may affect susceptibility to kidney disease.

**METHODS—**We used tag-single-nucleotide polymorphisms (tag-SNPs) to evaluate the association of the *CHEK2* with kidney function (estimated glomerular filtration rate, eGFR) in 1,549 African-American and 1,423 white Hypertension Genetic Epidemiology Network (HyperGEN) participants. We performed replication analyses in the Genetic Epidemiology Network of Arteriopathy (GENOA) participants (1,746 African Americans and 1,418 whites), GenNet participants (706 whites), and Atherosclerosis Risk in Communities (ARIC) study participants (3,783 African Americans and 10,936 whites). All analyses were race-stratified and used additive genetic models with adjustments for covariates and for family structure, if needed.

**RESULTS—**One tag-SNP, rs5762764, was associated with eGFR in HyperGEN $P = (0.003)$ and GENOA white participants ($P = 0.009$), and it was significantly associated with eGFR in meta-analyses ($P = 0.002$). The associations were independent of type 2 diabetes.

**CONCLUSIONS—**These results suggest that *CHEK2* variants may influence eGFR in the context of hypertension.

Chronic kidney disease (CKD) is an emerging public health problem with an estimated prevalence of 9.6% (or 19.2 million) of the adult US population.[1,2] CKD is a strong risk factor for cardiovascular disease,[3] is associated with increased morbidity and mortality,[4,5] increased health-care resource use,[6] and a decreased quality of life.[7] The economic burden associated with the treatment of kidney failure is substantial, accounting for 6.8% of the health-care expenditures in 2004.[8,9]

Familial aggregation of CKD has been documented.[10,11] A high heritability of renal function has been noted in twin studies (0.78 ± 0.03 for glomerular filtration rate—GFR).[12] A genetic component for kidney traits has also been identified in studies of type 1 and type 2 diabetic study participants,[13–17] in hypertensive study participants[18–21] and in the general population.[22,23] Although several monogenic kidney diseases have been identified, little progress has been achieved in identifying susceptibility genes for CKD in individuals with diabetes and/or hypertension,[24,25] the two most common conditions associated with kidney failure.[8,9] Genetic heterogeneity may introduce analytical challenges for the identification of genetic variants influencing kidney function, and may account for the lack of genome-wide significant findings in a recent genome-wide association study of kidney-related phenotypes.[26] Therefore, candidate gene approaches interrogating genes from newly discovered pathways of kidney injury may constitute a complementary approach to large-scale genome-wide gene finding studies.

Genetic and environmental factors (for example, endogenous and exogenous toxins) likely contribute to CKD susceptibility. Programmed cell death or apoptosis of intrinsic kidney cells in response to injury has been described in experimental animal models and in humans.27 Recent research suggests a role for reactive oxygen species and DNA damage in the membrane attack complex C5b-9 injury (passive Heymann nephritis),28 in puromycin nephrosis,29 and in cisplatin nephrotoxicity.30 DNA damage leads to activation of the checkpoint pathways, which mediate cell cycle arrest and apoptosis.31,32 Therefore, genes in the DNA repair and cell cycle checkpoint pathways are excellent candidates for evaluation of association with kidney function.

The *checkpoint 2* gene (*CHEK2)* is an important transducer in DNA damage signaling pathways in response to injury. We have previously identified the *CHEK2* gene under a linkage peak for type 2 diabetes among 3,383 Hypertension Genetic Epidemiology Network (HyperGEN) participants.33 The 22q12 chromosome region, where *CHEK2* is located, has been identified in linkage and in admixture studies of kidney phenotypes.14,18,34,35 In this study, we tested the hypothesis that *CHEK2* contains one or more polymorphic variants (single-nucleotide polymorphisms (SNPs)) that are associated with kidney function in participants of the HyperGEN study. We attempted to replicate our association in three additional populations, the Genetic Epidemiology Network of Arteriopathy (GENOA) study, the GenNet study, and the Atherosclerosis Risk in Communities (ARIC) study.

## Methods

### Populations, phenotypes, and covariates

**Family Blood Pressure Program—**The Family Blood Pressure Program (FBPP), composed of four independent networks without overlap in participants (HyperGEN, GENOA, GenNet, and SAPPHIRe), was established to investigate the genetic determinants of high blood pressure (BP) in multiple ethnic groups.36 Families were ascertained based on higher than normal BP or diagnosed hypertension. This study includes only genotyped participants of the FBPP HyperGEN, GENOA, and GenNet studies.

HyperGEN recruited African-American and non-Hispanic white hypertensive siblings and their offspring and/or parents. A family was eligible for participation if at least two siblings had BP measurements ≥140/90 mm Hg or used antihypertensive medications, with the age of diagnosis of <60 years. GENOA recruited African-American, Mexican-American, and non-Hispanic white sibships containing a minimum of two individuals diagnosed with hypertension. GenNet recruited African-American and non-Hispanic white individuals with BP in the upper 20–25% of the age- and gender-specific BP distribution, and all available first degree relatives.

All networks measured a standard set of 95 core phenotypes.36 Clinical, lifestyle information, and medications were obtained via an interview. Body mass index was calculated using weight (kg)/height ($m^2$), obtained during a clinic visit. Tobacco exposure was quantified using questionnaires. Resting BP measurements were obtained using automated Dinamap devices (model 1846 SX/P; GE Medical Systems, Tampa, FL) and hypertension was defined by a BP of at least 140/90 mm Hg or use of antihypertensive medications. Individuals with a fasting plasma glucose of at least 7.0 mmol/l (126 mg/dl) or using medications to treat diabetes were defined as having type 2 diabetes.37 Individuals with age of onset of diabetes <30 years old were considered type 1 diabetics and therefore excluded.

In HyperGEN, serum creatinine was measured by a thin-film adaptation of the amidohydrolase enzymatic method using the Vitros analyzer (Johnson & Johnson Clinical

Diagnostics, Raritan, NJ).38 GENOA measured serum creatinine using a picric acid colorimetric assay (Monarch Chemistry System, Lexington, MA), and calibrated serum creatinine to the Cleveland Clinic assay by subtracting 0.17 mg/dl from measured values (S.T. Turner, unpublished data). GenNet measured serum creatinine only in white individuals (using a modified Jaffe reaction). GFR was estimated using the Modification of Diet in Renal Disease equation.39 CKD was defined as an estimated GFR (eGFR) <60 ml/min/1.73 $m^2$.

### ARIC

ARIC is a biracial prospective population study of subclinical and clinical atherosclerosis of 15,792 unrelated individuals, aged 45–64 years old at recruitment (1987–1989).40 Study participants were selected as a probability sample from four US communities and were examined at baseline (visit 1) and at every 3 years through January 1999.

Resting BP was recorded in seated individuals using a random-zero sphygmomanometer, and hypertension was defined using the same criteria as for the FBPP. Type 2 diabetes was defined by a fasting plasma glucose of at least 7.0 mmol/l, nonfasting glucose levels of at least 11.1 mmol/l, current use of medications prescribed to treat diabetes (e.g., insulin or sulfonylurea), or a positive response to the question “Has a doctor ever told you that you had diabetes ?”. Smoking was assessed using a questionnaire and anthropometric measures were obtained during clinic visits. Serum creatinine was measured using a modified kinetic Jaffe reaction, and calibrated using regression to the Cleveland Clinic laboratory by subtraction of 0.24 mg/dl.41 eGFR was estimated using serum creatinine from the visit 1 and the Modification of Diet in Renal Disease equation. eGFR values >200 were set to 200 ml/min/1.73 $m^2$.

All participants of the FPPP and ARIC studies provided informed consent. The study was conducted in accordance with the principles of the Declaration of Helsinki.

### Selection and genotyping of SNPs

DNA extraction and storage procedures in the FBPP and ARIC studies are described elsewhere.42,43 *CHEK2* SNP selection is described in detail in the Supplementary Data online. Briefly, SNPs were chosen using the HapMap phase 1 CEU sample and a pairwise analysis of correlation ($r^2 = 0.65$). The $r^2$ statistics measures the linkage disequilibrium between two markers or how well an allele predicts the allele at the other locus.44 Therefore, it can be used to select a subset of SNPs within a gene (tag-SNPs) for genotyping.45 A selected number of SNPs was genotyped in the replication populations, as part of an ongoing study of diabetes susceptibility (data not shown).

An additional SNP, rs2346397, located 200 kb from *CHEK2*, was also available for analyses. Genotyping for all samples was performed using Taqman SNP Genotyping Assays (Applied Biosystems, Foster City, CA). The assay call rates were 99% for HyperGEN and GenNet samples, and >95% for GENOA and ARIC samples. We tested for Hardy–Weinberg equilibrium in race-stratified samples by study populations and none of the SNPs had significant deviation of Hardy–Weinberg equilibrium (Supplementary Table S1 online).

### Statistical analysis

We tested the association between *CHEK2* SNPs and eGFR using general linear mixed models in the FPPP and linear regression models in the ARIC study. eGFR had a normal distribution and therefore was not transformed for analyses. We estimated genotypic means and 95% confidence intervals using empirical covariance matrix structures to account for the correlation within the data due to family relatedness (SAS version 9.1, SAS Institute, Cary,

NC). All analyses were linear models, using additive genetic models (1-degree of freedom test) and adjusting for age, age2, sex, age-by-sex interactions, and study center, within each race-stratified population sample (model 1). We further adjusted for systolic BP, hypertension treatment (or use of angiotensin-enzyme converting inhibitor or angiotensin 2 receptor blocker), type 2 diabetes, body mass index, and smoking exposure (model 2). We also explored models excluding individuals with type 2 diabetes (model 3, Supplementary Data online). In the ARIC study, we study the interaction of hypertension and type 2 diabetes on the association of SNPs and eGFR using interaction terms ($\alpha = 0.10$) and stratified analyses. For family studies, we tested the association using the quantitative trait disequilibrium test implemented in SOLAR, which accounts for linkage and the family structure of these data as well as population structure.46 Because *P* values were similar in analyses using the quantitative trait disequilibrium test and mixed linear models, but mixed models provided estimates of the effect, we only report results for the mixed models.

Haplotypes were inferred using the Family Base Association Testing software47,48 in family studies, and HAPSTAT49 in studies of unrelated individuals. We performed fixed effects meta-analysis by combining estimated regression coefficients and standard errors across samples (STATA 10), weighting by the inverse variance of each study.50 We also tested for the presence of between-study heterogeneity.51

## RESULTS

In our primary sample, we studied 1,423 white and 1,549 African-American HyperGEN participants, mostly hypertensive individuals (Table 1). The mean eGFR were 76.9 ± 16.5 and 92.4 ± 22.3 ml/min/1.73 $m^2$, for white and African-American individuals, respectively. Minor allele frequencies varied by race/ethnicity, with a large difference between white and African-American participants observed for the rs5762764 SNP (Supplementary Table S1 online). Haplotypes with the minor allele for rs5762764 (G allele) were uncommon in African-American individuals (Supplementary Table S2 online).

rs5762764 was significantly associated with eGFR in HyperGEN white individuals (*P*= 0.003, model 1) (Table 2). The presence of one or two copies of minor allele was associated with higher eGFR among white individuals (Table 2). The association was still significant when individuals with type 2 diabetes were excluded (*P* = 0.01, Supplementary Data online). The SNPs were not associated with eGFR in HyperGEN African-American individuals (Table 2).

For replication of our findings, we performed analyses of 1,418 white and 1,746 African-American GENOA participants, and 706 GenNet white individuals with available data on eGFR. Minor allele frequencies by race were similar to HyperGEN samples (Supplementary Table S1 online). Participants of the GENOA and GenNet were often hypertensive, and those in GenNet were younger, on average, than those in HyperGEN or GENOA (Table 1).

We observed a significant association of rs5762764 with eGFR among GENOA whites (Table 3). The minor allele for rs5762764 was associated with higher eGFR among these individuals (*P* = 0.009, model 1). The association was still significant in analyses excluding diabetic individuals (*P* = 0.006, Supplementary Data online). Although eGFR was higher in GenNet white participants with two copies of the minor allele for rs5762764, the association was not significant (Table 3). None of the SNPs was significantly associated with eGFR among GENOA African Americans.

We also performed analysis of 10,936 white and 3,783 African-American individuals from the ARIC study. The mean eGFRs and other characteristics of these samples are displayed in Table 1. rs5762764 was not associated with eGFR in white or African-American ARIC

participants (Table 3). However, because our results were more consistent among white individuals from samples ascertained for hypertension, we examined interactions of hypertension in the association between SNP-eGFR in the ARIC study. rs5762764 was significantly associated with eGFR among white individuals ($P = 0.04$, model 1) when accounting for hypertension interaction ($P = 0.08$ for interaction). The hypertension subsample displayed a genotype effect that was consistent with the other hypertension subsamples from HyperGEN, GENOA, and GenNet (Supplementary Data online).

In meta-analysis, rs5762764 was significant associated with eGFR ($P = 0.002$), with a combined estimated regression coefficient of 0.60 (Figure 1).

## DISCUSSION

Recent experimental evidence suggests that DNA damage and cell cycle regulatory proteins are involved in kidney injury and apoptosis.52 The DNA repair pathway involves multiple mediators that in response to injury lead to cell cycle arrest to allow for DNA repair or to programmed cell death. Genetic polymorphisms of mediators in this pathway may affect the response to injury, repair and cell survival. In this study, we observed an association among polymorphisms in the *CHEK2* gene, a transducer in DNA damage signaling pathways, and kidney function. We found some consistency in results among hypertensive enriched samples of the FBPP, and in participants of the population-based ARIC study with hypertension. Although the individual findings were restricted to white individuals, a meta-analysis of effect estimates was consistent with a significant effect across the subpopulation.

In particular, we found that one tag-SNP, rs5762764, was associated with eGFR in white individuals in HyperGEN and GENOA. The rs5762764 minor allele (G) showed a protective effect of increased eGFR for each copy of the minor allele among white FBPP individuals and among hypertensive individuals in the ARIC study. The findings in the FBPP were robust to exclusion of diabetic individuals (Supplementary Data online), suggesting that the genetic effects on kidney function may not be disease specific, but may affect the downstream response to injury in different forms of kidney damage. Alternatively, polymorphisms in C*HEK2* may be important in influencing kidney function in hypertension-related kidney injury.

The CHEK2 protein is ubiquitous. CHEK2 is an effector kinase that activates the tumor suppressor protein p53, which leads to cell arrest and apoptosis. Because CHEK2 and other kinases play a key role on cell survival, polymorphisms in the C*HEK2* gene may contribute to varying degree of apoptosis of intrinsic kidney cells in response to injury. For example, it may affect the recovery of epithelial tubular cell damage in acute renal failure or it contribute to reduced renal mass in chronic kidney injury. Recent studies suggest that angiotensin II, whose infusion may cause systemic hypertension in animals, mediates oxidative stress in the kidney53 and promotes apoptosis of intrinsic renal cells.54,55 The role of this gene in angiotensin II–induced and hypertension-related kidney injury needs further exploration in experimental models and in population studies.

Replication plays a key role in the assessment of the validity of genotype–phenotype associations, because type 1 error is not expected to replicate more than by chance alone. Our findings are particularly robust because the replication was achieved using the same study design, phenotype (eGFR), genetic marker, and in a population of similar ancestry as has been suggested by the National Cancer Institute and the National Human Genome Research Institute Working Group on guidelines for replication in association studies.56

We also attempted to evaluate the generalizability of our study results to African-American populations. The rs5762764 allele frequency was low in African Americans and haplotypes

including the minor allele of this SNP were uncommon in these individuals. Therefore, population-specific linkage disequilibrium and power may account for the lack of association in African Americans. African-American individuals in HyperGEN were also 10 years younger than whites and although we adjusted for age, we may have not fully accounted for the age-differences in the samples. In addition, because we relied on estimating equations for measurement of kidney function, misclassification of the outcome may have occurred.

In conclusion, we have shown that a polymorphism of the *CHEK2* gene is associated with measures of kidney function. These results suggest that CHEK2, a protein involved in cell cycle regulatory pathways, may influence kidney function in the context of hypertension.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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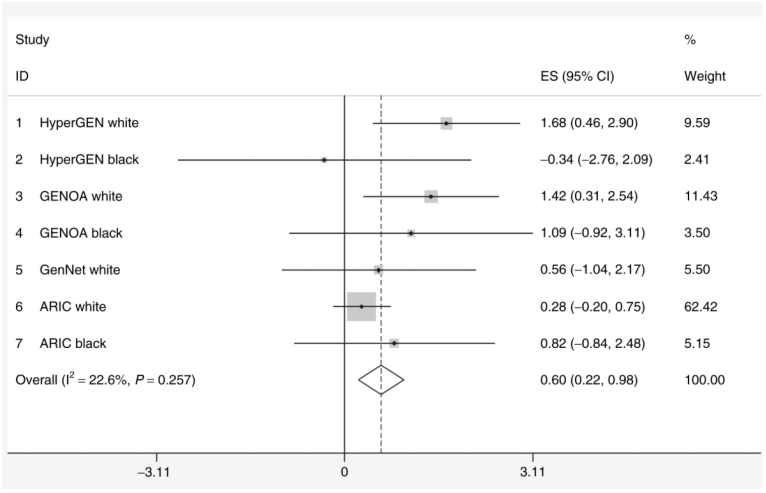


**Figure 1.**

Meta-analyses of the effect of rs5762764 (*CHEK2*) on estimated glomerular filtration rate (*N* = 19,847 individuals). ARIC, Atherosclerosis Risk in Communities; CI, confidence interval; ES, estimate; GENOA, Genetic Epidemiology Network of Arteriopathy.

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**Table 1**

characteristics of individuals participants in the FBPP and ARIC studies

| | HyperGEN | | GENOA | | GenNet | ARIC | |
|---|---|---|---|---|---|---|---|
| | **White** | **African American** | **White** | **African American** | **White** | **White** | **African American** |
| *N* | 1,423 | 1,549 | 1,418 | 1,746 | 706 | 10,936 | 3,783 |
| Male sex, *N* (%) | 675 (47) | 524 (34) | 650 (46) | 543 (31) | 314 (44) | 5,145 (47) | 1,447 (38) |
| Mean age (s.d.), years | 57 (13) | 48 (13) | 55 (11) | 58 (10) | 45 (15) | 54 (6) | 54 (6) |
| Hypertension, *N* (%) | 1,046 (69) | 1,204 (75) | 1,060 (75) | 1,313 (75) | 227 (32) | 2,967 (27) | 2,102 (55) |
| *N* (%) hypertensives on treatment | 981 (94) | 1,162 (97) | 916 (86) | 1,215 (93) | 177 (78) | 2,206 (74) | 1,563 (74) |
| *N* (%) hypertensives on ACEI/ARB | 424 (43) | 361 (31) | 313 (34) | 320 (26) | 76 (43) | 323 (15) | 149 (10) |
| Type 2 diabetes, *N* (%) | 204 (14) | 305 (20) | 189 (13) | 432 (25) | 38 (5) | 989 (9) | 735 (19) |
| Tobacco use ever, *N* (%) | 665 (47) | 792 (52) | 710 (50) | 745 (43) | NA | 6,580 (60) | 2,036 (54) |
| Mean BMI (s.d.), kg/m$^2$ | 29.6 (6.0) | 32.2 (7.7) | 30.4 (6.3) | 31.0 (6.6) | 29.2 (6.5) | 27.0 (4.9) | 29.6 (6.1) |
| Mean eGFR (s.d.), ml/min/1.73 m$^2$ | 76.9 (16.5) | 92.4 (22.3) | 73.5 (15.0) | 85.0 (21.2) | 74.4 (17.1) | 89.6 (17.9) | 102.6 (25.1) |
| CKD*, *N* (%) | 413 (29) | 150 (10) | 247 (17) | 166 (10) | 136 (19) | 327 (3) | 117 (3) |

Data at visit 1 for ARIC participants.

ACE/ARB, angiotensin-converting enzyme and angiotensin receptor blocker medications; ARIC, Atherosclerosis Risk in Communities; BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FBPP, Family Blood Pressure Program; GENOA, Genetic Epidemiology Network of Arteriopathy; HyperGEN, Hypertension Genetic Epidemiology Network; *N*, number; NA, not available.

* Defined as an eGFR <60 ml/min/1.73 m$^2$.

**Table 2**

genotype means and 95% confidence intervals (CIs), and *P* values for the additive genetic association of SNPs and eGFR by race using generalized linear mixed model: the hyperGEN study

| Race/ethnicity | SNP | Allele at risk (X) | Genotype means (95% CI)* | | | *P* value | |
|---|---|---|---|---|---|---|---|
| | | | 00 | 0X | XX | Model 1 | Model 2 |
| White | rs2346397 | C | 81.5 (80.1, 82.8) *N* = 609 | 80.5 (79.2, 81.8) *N* = 666 | 81.3 (78.5, 84.1) *N* = 128 | 0.54 | 0.37 |
| | rs4035540 | T | 81.1 (79.9, 82.4) *N* = 755 | 80.8 (79.4, 82.2) *N* = 573 | 81.5 (77.8, 85.3) *N* = 69 | 0.88 | 0.89 |
| | rs2078555 | G | 81.9 (80.6, 83.3) *N* = 650 | 80.5 (79.2, 81.8) *N* = 654 | 80.8 (77.7, 83.9) *N* = 105 | 0.23 | 0.24 |
| | rs5762764 | G | 79.4 (77.9, 80.8) *N* = 540 | 81.7 (80.4, 83.0) *N* = 641 | 82.9 (80.7, 85.1) *N* = 216 | 0.003 | 0.007 |
| | rs9608698 | G | 80.3 (78.7, 81.9) *N* = 425 | 81.3 (80.1, 82.6) *N* = 700 | 81.0 (79.1, 83.0) *N* = 292 | 0.57 | 0.69 |
| African American | rs2346397 | C | 105.2 (103.2, 107.2) *N* = 608 | 105.8 (103.9, 107.6) *N* = 702 | 104.9 (101.8, 108.0) *N* = 228 | 0.85 | 0.61 |
| | rs4035540 | T | 105.3 (103.7, 106.9) *N* = 966 | 105.3 (103.1, 107.4) *N* = 512 | 105.0 (99.4, 110.7) *N* = 71 | 0.99 | 0.94 |
| | rs2078555 | G | 105.1 (103.3, 106.8) *N* = 762 | 105.2 (103.3, 107.2) *N* = 634 | 106.5 (102.7, 110.4) *N* = 150 | 0.78 | 0.76 |
| | rs5762764 | G | 105.2 (103.8, 106.8) *N* = 1,142 | 105.5 (102.9, 108.1) *N* = 348 | 102.0 (94.3, 109.6) *N* = 37 | 0.52 | 0.51 |
| | rs9608698 | G | 105.4 (104.0, 106.9) *N* = 1,195 | 104.3 (101.7, 107.0) *N* = 322 | 104.9 (94.8, 115.0) *N* = 22 | 0.78 | 0.99 |

Model 1, adjusted for age, age2, sex, age-by-sex interaction, center. Model 2, adjusted for age, age2, sex, age-by-sex interaction, center, systolic blood pressure, hypertension treatment (or angiotensin-converting enzyme and angiotensin receptor blocker medications, ACEI/ARB), type 2 diabetes, ever smoking, and body mass index. Numbers may vary due to missing covariates.

*N*, number of individuals; CI, confidence intervals; eGFR, estimated glomerular filtration rate; HyperGEN, Hypertension Genetic Epidemiology Network; SNP, single-nucleotide polymorphism.

*Using model 1.

## Table 3

Genotype means and 95% confidence intervals, and *P* values for the additive genetic association of rs5762764 SNP and eGFR using generalized linear mixed models for the FBPP GENOA and GenNet, and linear models for the ARIC study

| | | Genotype means (95% CI)*, *N* | | | Additive models | |
|---|---|---|---|---|---|---|
| | | | | | *P* value | |
| **Population** | **Race/ethnicity** | **AA** | **AG** | **GG** | **Model 1** | **Model 2** |
| GENOA | White | 71.9 (70.7, 73.2)<br>*N* = 541 | 74.4 (73.3, 75.5)<br>*N* = 687 | 74.0 (72.0, 76.1)<br>*N* = 181 | 0.009 | 0.01 |
| GENOA | African American | 84.9 (83.6, 86.2)<br>*N* = 1,311 | 85.8 (83.6, 87.9)<br>*N* = 386 | 87.9 (81.5, 94.2)<br>*N* = 39 | 0.62 | 0.76 |
| GenNet | White | 73.7 (71.7, 75.9)<br>*N* = 204 | 73.9 (72.3, 75.5)<br>*N* = 372 | 75.01 (72.41, 77.61)<br>*N* = 130 | 0.71 | 0.36 |
| ARIC | White | 89.3 (88.8, 89.9)<br>*N* = 4,173 | 89.7 (89.2, 90.2)<br>*N* = 4,959 | 89.9 (89.0, 90.8)<br>*N* = 1,583 | 0.22 | 0.24 |
| ARIC | African American | 102.4 (101.5, 103.3)<br>*N* = 2,869 | 103.7 (102.0, 105.4)<br>*N* = 825 | 99.8 (92.7, 105.2)<br>*N* = 60 | 0.54 | 0.49 |

Model 1, adjusted for age, age2, sex, age-by-sex interaction, center. Model 2, adjusted for age, age2, sex, age-by-sex interaction, center, systolic blood pressure, hypertension treatment (angiotensin-converting enzyme and angiotensin receptor blocker medications, ACEI/ARB), type 2 diabetes, ever smoking, and body mass index. Numbers may vary due to missing covariates.

ARIC, Atherosclerosis Risk in Communities; CI, confidence intervals; eGFR, estimated glomerular filtration rate; FBPP, Family Blood Pressure Program; GENOA, Genetic Epidemiology Network of Arteriopathy; HyperGEN, Hypertension Genetic Epidemiology Network; *N*, number of individuals.

*Using model 1.