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Published in final edited form as:

Title: Overlap between common genetic polymorphisms underpinning kidney traits and cardiovascular disease phenotypes: the CKDGen consortium.

Authors: Olden M, Teumer A, Bochud M, Pattaro C, Köttgen A, Turner ST, Rettig R, Chen MH, Dehghan A, Bastardot F, Schmidt R, Vollenweider P, Schunkert H, Reilly MP, Fornage M, Launer LJ, Verwoert GC, Mitchell GF, Bis JC, O'Donnell CJ, Cheng CY, Sim X, Siscovick DS, Coresh J, Kao WH, Fox CS, O'Seaghdha CM, AortaGen, CARDIoGRAM, CHARGE Eye, CHARGE IMT, ICBP, NeuroCHARGE, and CKDGen Consortia.

Journal: American journal of kidney diseases : the official journal of the National Kidney Foundation

Year: 2013 Jun

Volume: 61

Issue: 6

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Published in final edited form as:

Am J Kidney Dis. 2013 June ; 61(6): 889–898. doi:10.1053/j.ajkd.2012.12.024.

Overlap Between Common Genetic Polymorphisms Underpinning Kidney Traits and Cardiovascular Disease Phenotypes: The CKDGen Consortium

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Financial Disclosure: Dr Mitchell is owner of Cardiovascular Engineering Inc, a company that designs and manufactures devices that measure vascular stiffness. The company uses these devices in clinical trials that evaluate the effects of diseases and interventions on vascular stiffness. The other authors declare that they have no other relevant financial interests.

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Abstract

Background—Chronic kidney disease is associated with cardiovascular disease. We tested for evidence of a shared genetic basis to these traits.

Study Design—We conducted two targeted analyses. First, we examined whether known single nucleotide polymorphisms (SNPs) underpinning kidney traits were associated with a series of vascular phenotypes. Additionally, we tested whether vascular SNPs were associated with markers of kidney damage. Significance was set to 1.5×10^{-4} (0.05/325 tests).

Setting & Participants—Vascular outcomes were analyzed in participants from the AortaGen (20,634), CARDIoGRAM (86,995), CHARGE Eye (15,358), CHARGE IMT (31,181), ICBP (69,395) and NeuroCHARGE (12,385) consortia. Tests for kidney outcomes were conducted in up to 67,093 participants from the CKDGen consortium.

Predictor—We used 19 kidney SNPs and 64 vascular SNPs.

Outcomes & Measurements—Vascular outcomes tested were blood pressure, coronary artery disease, carotid intima-media thickness, pulse wave velocity, retinal venular caliber and brain white matter lesions. Kidney outcomes were estimated glomerular filtration rate and albuminuria.

Results—In general, we found that kidney disease variants were not associated with vascular phenotypes (127 of 133 tests were non-significant). The one exception was rs653178 near *SH2B3* (*SH2B* adaptor protein 3), which showed direction-consistent association with systolic ($p=9.3E-10$) and diastolic ($p=1.6E-14$) blood pressure and coronary artery disease ($p=2.2E-6$), all previously reported. Similarly, the 64 SNPs associated with vascular phenotypes were not associated with kidney phenotypes (187 of 192 tests were non-significant), with the exception of 2 high-correlated SNPs at the *SH2B3* locus ($p=1.06E-07$ and $p=7.05E-08$).

Limitations—Combined effect size of the SNPs for kidney and vascular outcomes may be too low to detect shared genetic associations.

Conclusions—Overall, although we confirmed one locus (*SH2B3*) as associated with both kidney and cardiovascular disease, our primary findings suggest that there is little overlap between kidney and cardiovascular disease risk variants in the overall population. The reciprocal risks of kidney and cardiovascular disease may not be genetically mediated, but rather a function of the disease milieu itself.

Chronic kidney disease (CKD), expressed by decreased estimated glomerular filtration rate (eGFR) and/or the presence of albuminuria, is a major health issue, affecting almost 18

million adults in the United States.^{1,2} CKD is associated with a range of serious adverse outcomes, including end-stage renal disease and death.³ However, the major complication of CKD is cardiovascular disease (CVD),⁴ and the majority of CKD patients die from cardiovascular disease before reaching end-stage kidney disease.⁵⁻⁷ Furthermore, the risk for CVD events increases rapidly as eGFR declines or albuminuria increases,^{8,9} independent of other common risk factors such as diabetes or hypertension.¹⁰

The mechanisms of excess cardiovascular risk in CKD patients are not fully understood. Predictive modeling using traditional cardiovascular risk factors performs poorly in this patient group.¹¹ Novel risk factors for cardiovascular disease, such as vascular calcification, anemia, inflammation or increased oxidative stress may explain some of the excess risk in advanced CKD,¹²⁻¹⁴ but they fail to fully explain the link between the two diseases.^{15,16}

Recent genome-wide association studies (GWAS) of large European populations have identified novel genetic risk single nucleotide polymorphisms (SNPs) for hypertension,¹⁷ coronary artery disease,¹⁸ subclinical vascular disease¹⁹⁻²² as well as kidney functional traits and CKD.²³⁻²⁵ We hypothesized that kidney variants might increase the risk of vascular disease and that vascular variants might be similarly associated with kidney disease traits. We tested this hypothesis by conducting bidirectional cross-trait targeted SNP analyses between variants of eGFR, albuminuria and CVD and well-defined clinical cardiovascular and kidney outcomes. In the first of two targeted SNP analyses, we selected 19 SNPs known to be associated with kidney function²³⁻²⁵ and investigated their association with the vascular phenotypes of systolic and diastolic blood pressure from the ICBP¹⁷ (International Consortium for Blood Pressure) and coronary artery disease from the CARDIoGRAM (Coronary Artery Disease Genome-wide Replication and Meta-Analysis) consortium.¹⁸ We also analyzed the association of known kidney SNPs with well-defined subclinical disease phenotypes, including: carotid-femoral pulse wave velocity from the AortaGen consortium,²⁰ retinal venular caliber from the CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology) Eye consortium,²¹ carotid intima-media thickness (cIMT) from the CHARGE IMT consortium,¹⁹ and white matter lesions from the NeuroCHARGE consortium.²² In the second targeted SNP analysis, 64 validated vascular SNPs from a range of cardiovascular phenotypes were tested in eGFR and albuminuria datasets from the CKDGen consortium.²³⁻²⁵

METHODS

Overall Study Design

For all phenotypes, testing for genetic association was performed using existing GWAS meta-analysis datasets in individuals of European descent with self-reported ethnicity. Genetic association testing for the kidney outcomes of eGFR and albuminuria was performed in the CKDGen cohorts using existing meta-analysis results.^{23,24} Similarly, association tests for vascular outcomes were conducted in most recent meta-analysis results from the AortaGen,²⁰ CARDIoGRAM,¹⁸ CHARGE Eye,²¹ CHARGE IMT,¹⁹ ICBP,¹⁷ and NeuroCHARGE²² consortia. Heterogeneity tests were conducted in all consortia¹⁷⁻²⁴ (e.g. using Cochran's Q test in CKDGen).

Study Exposure

In the first targeted SNP analysis, we selected 18 kidney SNPs previously identified by CKDGen in two-stage meta-analysis in association with creatinine-based eGFR (eGFR_{cr}) (15 loci), cystatin-C based eGFR (eGFR_{cys}) (37 loci: *CST3* [cystatin C] and *SH2B3* [SH2B adaptor protein 3])²³ and albuminuria (1 locus, *CUBN* [cubulin]),²⁴ as well as one SNP yielded by IBC (Institute of Translational Medicine and Therapeutics Broad CARE)

candidate-gene SNP association analyses in African Americans from the CARE Renal Consortium (1 locus, *KCNQ1* [kidney and cardiac voltage dependent K⁺ channel]).²⁵ The 19 kidney SNPs were tested for association with GWAS results for systolic and diastolic blood pressure from ICBP (n=69,395), coronary artery disease from CARDIoGRAM (n=86,995 with 52,120 cases), as well as with markers of atherosclerosis: aortic pulse wave velocity from AortaGen (n=20,634), retinal venular caliber from CHARGE Eye (n=15,358), cIMT from CHARGE IMT (n=31,181) and brain white matter lesions from NeuroCHARGE (n=12,385) consortia.

For the second targeted SNP analysis, 64 variants associated with blood pressure (29 loci in ICBP), coronary artery disease (25 loci in CARDIoGRAM) or atherosclerosis (1 locus for pulse-wave velocity in AortaGen, 4 loci with retinal venular caliber in CHARGE Eye, 3 loci associated with cIMT in CHARGE IMT and 2 loci with white matter lesions in NeuroCHARGE) were tested for association with two different estimations of GFR (n=67,093 for eGFR_{cr} and n=20,966 for eGFR_{cys}) and albuminuria (n=31,580) in the CKDGen consortium.

Kidney Measures

eGFR_{cr} was estimated using the 4-variable Modification of Diet in Renal Disease Study equation.²⁶ eGFR_{cys} was estimated as $eGFR_{cys} = 76.7 \times (\text{serum cystatin C})^{-1.19}$.²⁷ CKD was defined as eGFR_{cr} < 60 ml / min / 1.73 m², according to National Kidney Foundation guidelines.²⁸ Urinary albumin-creatinine ratio (UACR) was log-transformed for analysis and age and sex specific residuals were determined, as previously described.²⁴ Albuminuria was defined as UACR >17 mg/g for men and >25 mg/g for women.²⁹

Vascular Measures

Hypertension was defined in ICBP consortium as systolic blood pressure \geq 140mmHg or diastolic blood pressure \geq 90 mmHg.¹⁷ Coronary artery disease was defined in the CARDIoGRAM consortium as symptoms of angina pectoris, previous myocardial infarction or prior cardiac intervention.¹⁸ cIMT was measured in the CHARGE IMT consortium in the common carotid artery as the distance between the lumen-intima interface and media-adventitia interface by means of ultrasonography.¹⁹ The carotid-femoral pulse wave velocity was assessed by AortaGen using carotid-femoral transit time assessed by tonometry or Doppler flow and transit distance assessed by body surface measurements.²⁰ The retinal venular caliber was measured in CHARGE Eye using in-vivo imaging techniques.²¹ White matter lesions were detected in NeuroCHARGE by means of magnetic resonance imaging.²²

Statistical Methods

For the targeted SNP analyses, we used previously published results of meta-analyses of HapMap [International HapMap Project]-imputed SNPs to test 19 kidney SNPs for association with vascular traits and 64 cardiovascular SNPs in kidney traits. For the targeted SNP analysis of 19 eGFR SNPs in 7 different vascular outcomes (blood pressure, coronary artery disease, cIMT, aortic pulse-wave velocity, retinal venular caliber and white matter lesions) we performed 133 tests. Similarly, for the targeted SNP analysis of 64 vascular SNPs in 3 kidney-related outcomes (eGFR_{cr}, eGFR_{cys} and UACR), we performed 192 tests. We adjusted for multiple testing using a Bonferroni corrected alpha of 1.5e-4 (0.05/325), adjusting for all tests performed (133 + 192).

For each SNP, the results of the targeted meta-analysis included the effect estimator β , its standard error, a two-sided p-value, as well as coded and non-coded allele, frequency of the coded allele and the total sample size. Whenever the requested (lead) SNP was not available, a proxy SNP with an r² correlation of over 80% was used. In 4 cases, this was not possible,

therefore 3 SNPs are missing from the analysis for coronary artery disease and 1 locus is absent in all kidney analyses. Meta-analysis results corrected for genomic control were used for all targeted analyses.

RESULTS

Study Participants

All study participants were of European descent. Study sample characteristics can be found in **Table 1**. Details on the individual cohorts included are available in the original papers that reported findings for eGFR,^{23;25} albuminuria,²⁴ blood pressure,¹⁷ coronary artery disease,¹⁸ cIMT,¹⁹ aortic pulse wave velocity,²⁰ retinal venular caliber²¹ and white matter lesions.²²

Analysis of Validated Kidney SNPs in Vascular Traits

Association of kidney SNP variants with blood pressure—Results of associations of kidney SNP variants with blood pressure in the ICBP consortium are presented in **Table 2**. In general, the variants tested were not associated with blood pressure at $\alpha=1.5e-4$ (0.05/325) (p-value range, 0.98-0.002). The one exception was rs (reference SNP identifier) 653178 at the *SH2B3* gene: each copy of the eGFR risk allele C (lower levels of eGFR) was associated with a higher level of systolic (p=9.3E-10) and diastolic blood pressure (p=1.6E-14). This SNP is in perfect linkage disequilibrium with rs3184504 ($r^2=1.0$), which has been previously reported in association with blood pressure.¹⁷

Association of kidney SNP variants with coronary artery disease—Results of associations of kidney SNP variants with coronary artery disease in the CARDIoGRAM consortium are presented in **Table 2**. The majority of tests were negative at $\alpha=1.5e-4$, with p-values ranging from 0.96 to 0.004. The one exception was rs653178 in the *SH2B3* gene, whose risk allele C was associated with a higher risk for coronary artery disease (odds ratio [OR], 1.08; 95% confidence interval [CI], 1.04-1.11; p=2.2E-6). This SNP has been previously reported by CKDGen in association with cystatin C-based eGFR (eGFR_{cys}).¹⁸

Association of kidney SNP variants with subclinical markers of atherosclerosis—The results of the association between kidney SNPs and cIMT, pulse wave velocity, retinal venular caliber and white matter lesions are presented in **Table 3**. Similar to what we observed for blood pressure and coronary artery disease, these variants were not associated with these phenotypes at $\alpha=1.5e-4$ (p-value range, 0.99-0.001), with the exception of rs653178 near *SH2B3*, which was associated with high levels of retinal venular caliber (p=2.9E-11). This SNP is in high linkage disequilibrium ($r^2=0.96$) with another SNP (rs10774625) in the same locus, previously reported by NeuroCHARGE in association with retinal venular caliber.²¹

Analysis of Validated Vascular SNPs in Kidney Traits

Association of blood pressure variants with kidney traits—Association tests of 29 known blood pressure SNPs with eGFR and albuminuria (UACR) in the CKDGen consortium are presented in **Table 4**. We observed one significant association with low eGFR at $\alpha=1.5e-4$: rs3184504 at the *SH2B3* locus (p=1.06E-07). This SNP is perfectly correlated with rs653178 ($r^2=1.0$), which has been previously reported by CKDGen in association with eGFR_{cys}.²³ All other association tests for eGFR and albuminuria were not statistically significant (p-value range, 0.9-0.001).

Association of coronary artery disease variants with kidney traits—Association tests of 25 coronary artery disease variants with kidney traits in the CKDGen consortium are presented in Table 5. In general, they did not associate with either eGFR or albuminuria at $\alpha=1.5e-4$ (0.05/325), with p-values ranging from 0.9 to 0.002. The exception was rs3184504 at *SH2B3*, whose risk allele T for coronary artery disease was associated with lower levels of eGFR.

Association of subclinical cardiovascular SNP variants with kidney traits—The association results for 10 known subclinical vascular SNP variants (3 loci for cIMT, 1 locus for pulse-wave velocity, 4 loci for retinal venular caliber and 2 loci for white matter lesions) with kidney traits in the CKDGen consortium are reported in Table 6. The majority of tests were not significant at $\alpha=1.5e-4$ (p-value range, 0.9-0.0005), with the exception of rs10774625 at *SH2B3*, which was associated with lower levels of eGFR ($p=7.05E-08$). This SNP was previously noted in association with retinal venular caliber²¹ and is in strong linkage disequilibrium ($r^2=0.96$) with the other 2 SNPs in the same locus, which have previously been reported.^{17;18;23}

Concordance Between Vascular SNP Variants and eGFR

In the CKDGen Consortium, only 96 of 189 CVD risk variants tested were in the expected direction, (i.e. were associated with lower eGFR) whereas 93 were in the opposite direction ($p=0.9$) (Fig. 1). Similar patterns of discordance were observed in all vascular consortia, where only 70 out of 127 tested variants showed association in the hypothesized direction ($p=0.3$).

DISCUSSION

We observed minimal overlap in genetic association of well-validated SNPs across a variety of kidney and vascular traits. The exception was *SH2B3*, which has previously been reported as associated with several traits. The absence of association observed suggests that there is little overlap between kidney disease and CVD risk variants.

The general lack of association seen in our analyses is consistent with recent findings of the ICBP consortium, where investigators constructed a genetic risk score for the 29 SNPs related to blood pressure and found evidence of genetic overlap with left ventricular wall thickness, incident heart failure, stroke and coronary artery disease, but not with kidney disease or kidney function.¹⁷ Our study advances our understanding in this area, by demonstrating a similar lack of a shared genetic basis to a broad range of well-characterized cardiovascular and kidney traits.

The *SH2B3* locus is the one exception to these negative results, demonstrating robust and direction-consistent associations with increased blood pressure, higher OR for coronary artery disease and increased retinal venular caliber as opposed to lower levels of eGFR in the general population. Located at 12q24, *SH2B3* encodes a member of the SH2B adaptor family of proteins, which play a role in signal, hematopoiesis, and immune response activities by integrin, growth factors and cytokines.^{24;30;31} The reason for the joint associations between these variants may be due to pleiotropic effects of this gene. The *SH2B3* region is recognized for pleiotropy, associating with multiple phenotypes including platelet count,³² susceptibility to insulin-dependent diabetes mellitus³³ and celiac disease type 13.³⁴ A recent attempt to measure pleiotropic effects for known kidney and vascular loci demonstrated *SH2B3* to have the highest pleiotropic index among all other identified regions.³⁵

Several avenues for future research are suggested by the present analysis, which may improve our understanding of the mechanism of vascular disease in kidney patients, help stratify CKD patients by their risk of developing vascular disease or potentially identify novel pharmacogenomics targets. In particular, studies targeted at achieving a better understanding of the role of *SH2B3* in both kidney disease and CVD may prove fruitful. For example, the observation that *SH2B3* is strongly associated with cystatin-C-based eGFR but only nominally so with creatinine-based eGFR, suggests that its effects on GFR may be indirect, perhaps mediated by influences on cystatin C production or metabolism, which is a better predictor of CVD than eGFR_{cr}.³⁶ This is supported by the fact that *SH2B3* showed no association to urinary ACR due to distinct genetic mechanisms of eGFR and albuminuria, in accordance with a prior interrogation which found a lack of association between CKD-related SNPs and albuminuria.³⁷ Furthermore, as the *SH2B3* gene region is large (45,674 nucleotides, based on Ensembl gene annotation release 54) and includes several other genes, fine-mapping studies may identify the causal variant(s) underlying the statistical signals identified in this and other analyses.

The absence of cross-associations does not necessarily imply absence of genetic correlation and there may be other contributing mechanisms to explain these findings. For example, in totality, the previously identified kidney function loci only account for 1.4% of the variation of eGFR,²³ with similar values reported by ICBP for the association with blood pressure¹⁷ and CARDIoGRAM for coronary artery disease.¹⁸ The relatively low explained variance of trait variation may account for the lack of overlap in these analyses, and it remains possible that shared variants may yet be identified as a greater proportion of the underlying genetic variability is explained. However, the ICBP study demonstrated that even SNPs in low linkage disequilibrium can identify overlapping associations with downstream traits,¹⁷ supporting our negative findings.

Our findings suggest that non-genetic or environmental factors are primarily responsible for the association between CKD and CVD, either via a direct causal link or by lying in the causal pathway. Examples of such factors include uremic toxins not cleared by the failing kidney, vascular calcification, anemia, inflammation or increased oxidative stress account, which have a higher prevalence in CKD patients as compared to the overall population.¹²⁻¹⁴ For example, indoxyl sulfate is a uremic toxin that accelerates vascular disease in CKD patients via AHR (aryl hydrocarbon receptor) and other pathways, but which is not relevant to CVD in the overall population.³⁸ Such environmental mechanisms would not be detectable by the present approach. The lack of genetic association between kidney disease and CVD emphasizes the influence of shared risk factors in the CKD-CVD milieu, particularly diabetes and hypertension.

Strengths of this study include the largest to date available GWAS datasets for kidney traits, blood pressure, coronary artery disease and subclinical vascular markers from the CKDGen, ICBP, CARDIoGRAM, CHARGE Eye, CHARGE IMT, NeuroCHARGE and AortaGen consortia, as well as the use of validated SNP variants for these traits. Some limitations also warrant mention. First, as genetic variations for eGFR, albuminuria and CVD explain only about 1% of the variations of these traits, the combined effect size of the SNPs for eGFR and vascular outcomes may be too low to detect shared genetic associations. Second, whereas our study indicates little overlap in the common genetic determinants of CKD and CVD, similar analyses in cohorts targeted at more advanced stages of CKD or containing more cases of both diseases may yield different findings. Third, our study used common genetic variants derived from GWAS and it is therefore possible that low frequency variants could provide more evidence for joint association. Furthermore, future GWAS, exome sequencing or pathway analyses may yet reveal shared genetic underpinnings between these

traits. Finally, our study sample was composed of individuals of European ancestry; therefore the generalizability of our findings across other ethnic groups is uncertain.

In conclusion, we observed overall little genetic overlap between well-validated SNPs for kidney disease and CVD and their related phenotypes in targeted SNP analyses conducted in largest to date available meta-analyses results. Although we confirm one locus, *SH2B3*, which is associated with both kidney disease and CVD, our primary findings suggest that there is little overlap between kidney disease and CVD risk variants. The interrelationship between these traits may thus be primarily due to clinical factors present in the setting of CKD or CVD.

Acknowledgments

The full information on collaborating scientists of the GWAS Consortia is available in articles previously published by the involved consortia.

Support: This research was conducted in part using data and resources from the Framingham Heart Study of the National Heart, Lung and Blood Institute (NHLBI) of the National Institutes of Health and Boston University School of Medicine. This work was partially supported by the NHLBI's Framingham Heart Study (Contract No. N01-HC-25195). Full information on funding of the GWAS performed by the involved consortia is available in the consortia's previously published articles. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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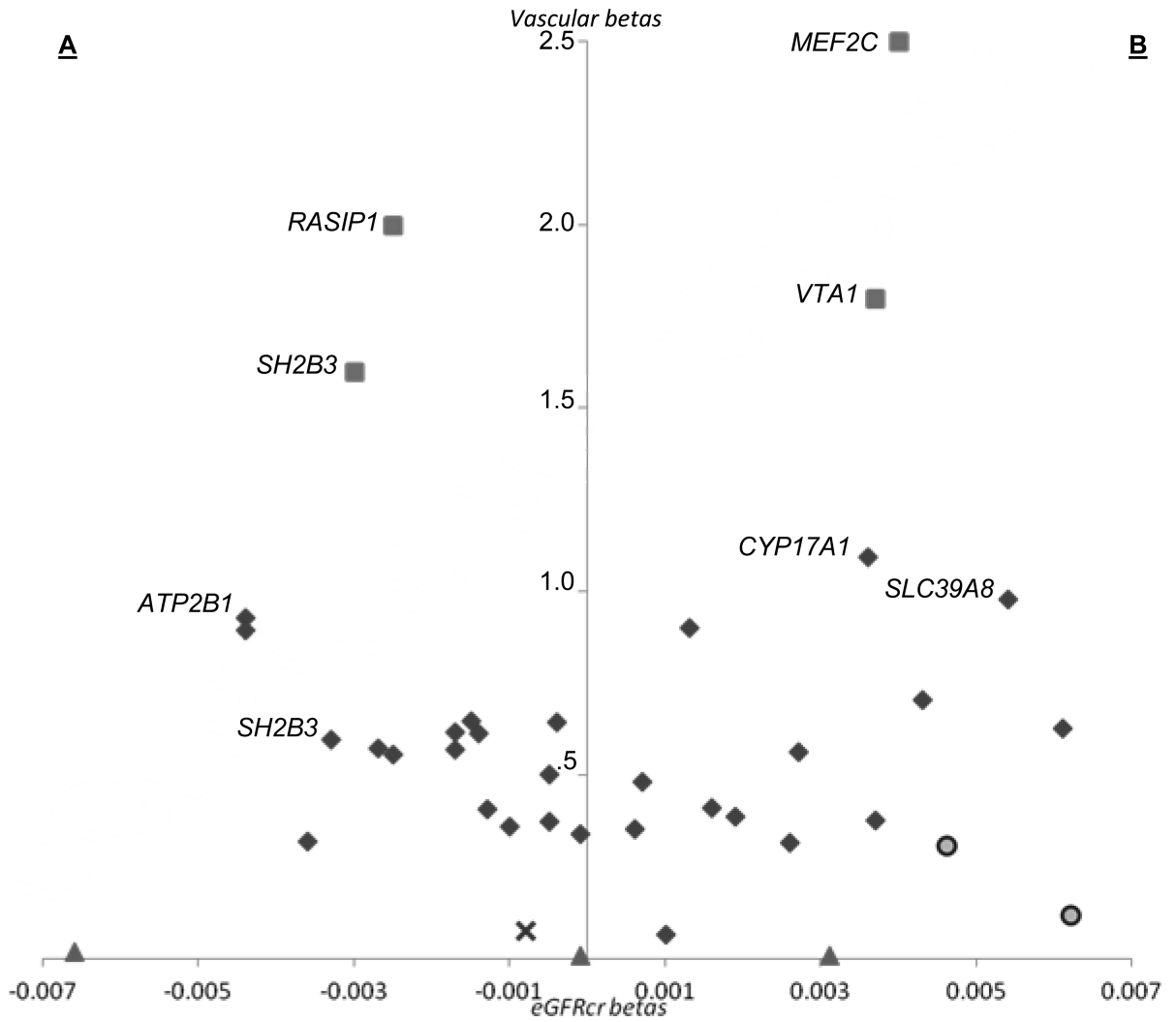


Figure 1. Scatter plot of SNP effect sizes (beta) for creatinine-based eGFR (eGFR_{cr}) and vascular phenotypes (systolic blood pressure [filled diamonds], carotid-intima medial thickness [filled triangles], pulse-wave velocity [×], retinal venular caliber [filled squares], and white matter lesions [filled circles]). The side labeled A (lower eGFR_{cr} effect size, higher vascular effect size) represents associations consistent with the study hypothesis; the side labeled B (higher eGFR_{cr} effect size, higher vascular effect size) represents associations inconsistent with the hypothesis. The results show no significant correlation between eGFR_{cr} and vascular SNP variants.

Table 1

Study sample characteristics for kidney and cardiovascular phenotypes.

| Consortium | Sample size ^a | No. of studies ^b | Female sex | Age (y) | DM | HTN | Key phenotype | Values corresponding to key phenotype |
|-----------------------------|--------------------------|-----------------------------|--------------|-------------|-------------|--------------|--------------------|--|
| CKDGen – eGFR ²³ | 67,093 ^d | 20 | 72% (48,637) | 59.0 (11.8) | 8% (5,343) | 37% (24,798) | eGFR _{cr} | 86.89 ± 21.62 ml/min/1.73 m ² |
| CKDGen – UACR ²⁴ | 31,580 | 12 | 53% (16,723) | 56.4 | 9% (2,818) | 38% (12,001) | UACR | 6.03 [3.52–11.75] mg/g ^c |
| ICBP ¹⁷ | 69,395 | 29 | 55% (37,956) | 51.0 (9.9) | NA | 33% (22,573) | SBP/DBP | 129.91 ± 18.38 / 78.54 ± 10.63 mm Hg |
| CARDIOGRAM ¹⁸ | 86,995 | 14 | 51% (44,505) | 56.0 (9.4) | NA | NA | MI | 52,120 (60) |
| CHARGE IMT ¹⁹ | 31,181 | 9 | 55% (17,294) | 59.1 (10.3) | 9% (2,661) | 45% (13,996) | cIMT | 0.84 ± 1.6 mm |
| AortaGen ²⁰ | 20,634 | 9 | 55% (11,252) | 59.2 (11.3) | NA | NA | Inverse PWV | 125.11 ± 33 ms/m |
| CHARGE Eye ²¹ | 15,358 | 4 | 57% (8,682) | 70.7 (5.8) | NA | NA | RVC | 141.55 ± 14.45 μm |
| NeuroCHARGE ²² | 12,385 | 9 | 58% (7,168) | 69.8 (6.3) | 10% (1,250) | 55% (6,833) | WML burden | 4.43 ± 5.35 mL |

Note: Except where otherwise indicated, values for categorical variables are given as number (percentage); values for continuous variables, as mean +/- standard deviation.

DM, diabetes; HTN, hypertension; eGFR, estimated glomerular filtration rate; eGFR_{cr}, creatinine-based eGFR; eGFR_{cys}, cystatin C-based eGFR; UACR, urinary albumin-creatinine ratio; CKD, chronic kidney disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; MI, myocardial infarction; IMT, intima-media thickness; cIMT, carotid intima-media thickness; PWV, pulse-wave velocity; RVC, retinal venular caliber; WML, white matter lesion ICBP (International Consortium for Blood Pressure); CARDIOGRAM (Coronary Artery Disease Genome-wide Replication and Meta-Analysis); CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology); NA, not available

^aRefers to the recruited sample for the respective phenotype, which may differ from the successfully genotyped and analyzed sample.

^bDetails on the individual cohorts included are available in the supplemental materials of the original papers.

^cMedian [interquartile range].

^dSample size for cystatin C-based eGFR (eGFR_{cys}) was 20,966.

Table 2

Association results of 19 kidney SNPs with clinical vascular traits in individuals of European descent from the ICBP and CARDIoGRAM consortia.

| Kidney SNP | Nearest Gene | Coded (risk) allele | SBP | | DBP | | CAD | |
|------------|----------------|---------------------|---------|---------|---------|----------|--------------------|---------|
| | | | β | p-value | β | p-value | OR (CI) | p-value |
| rs10109414 | <i>STC1</i> | T | -0.054 | 0.6 | 0.07 | 0.3 | 0.99 [0.97 - 1.02] | 0.9 |
| rs11959928 | <i>DAB2</i> | A | 0.009 | 0.9 | -0.009 | 0.9 | 1.01 [0.98 - 1.04] | 0.3 |
| rs12460876 | <i>SLC7A9</i> | T | 0.169 | 0.1 | 0.074 | 0.2 | 1.01 [0.97 - 1.03] | 0.6 |
| rs1260326 | <i>GCKR</i> | C | -0.102 | 0.3 | -0.019 | 0.8 | 0.97 [0.94 - 1.00] | 0.1 |
| rs12917707 | <i>UMOD</i> | G | 0.353 | 0.005 | 0.244 | 0.002 | 1.01 [0.97 - 1.05] | 0.4 |
| rs13538 | <i>ALMS1</i> | A | -0.096 | 0.4 | -0.13 | 0.1 | 0.95 [0.91 - 0.98] | 0.004 |
| rs1394125 | <i>UBE2Q2</i> | A | 0.112 | 0.3 | 0.021 | 0.8 | NA | NA |
| rs17319721 | <i>SHROOM3</i> | A | -0.143 | 0.1 | -0.042 | 0.5 | 1.01 [0.98 - 1.03] | 0.6 |
| rs1801239 | <i>CUBN</i> | T | -0.017 | 0.9 | 0.038 | 0.7 | 1.01 [0.95 - 1.05] | 0.8 |
| rs267734 | <i>ANXA9</i> | T | -0.047 | 0.7 | -0.028 | 0.7 | 0.99 [0.96 - 1.03] | 0.9 |
| rs347685 | <i>TFF2</i> | A | 0.035 | 0.7 | -0.088 | 0.2 | 1.02 [0.99 - 1.04] | 0.2 |
| rs4744712 | <i>PIP5K1B</i> | A | -0.002 | 0.98 | 0.035 | 0.6 | 1.01 [0.98 - 1.04] | 0.3 |
| rs626277 | <i>DACHI</i> | A | -0.038 | 0.7 | -0.022 | 0.7 | 1.01 [0.96 - 1.03] | 0.9 |
| rs6420094 | <i>SLC34A1</i> | G | 0.086 | 0.5 | 0.097 | 0.2 | NA | NA |
| rs653178 | <i>SH2B3</i> | C | 0.605 | 9.3E-10 | 0.48 | 1.64E-14 | 1.08 [1.04 - 1.11] | 2.2E-06 |
| rs7805747 | <i>PRKAG2</i> | A | 0.359 | 0.02 | 0.178 | 0.1 | NA | NA |
| rs81204* | <i>KCNQ1</i> | C | -0.032 | 0.8 | 0.04 | 0.6 | 1.01 [0.98 - 1.05] | 0.4 |
| rs881858 | <i>VEGFA</i> | A | 0.009 | 0.9 | 0.172 | 0.02 | 1.01 [0.96 - 1.03] | 0.9 |
| rs911119 | <i>CST3</i> | T | -0.177 | 0.1 | -0.107 | 0.2 | 0.99 [0.96 - 1.02] | 0.8 |

NOTE: The clinical vascular traits tested were SBP, DBP, and CAD. Results are presented for the trait-decreasing eGFR allele.

CAD, coronary artery disease; DBP, diastolic blood pressure; rs, reference SNP identifier; SBP, systolic blood pressure; SNP, single nucleotide polymorphism; ICBP (International Consortium for Blood Pressure); CARDIoGRAM (Coronary Artery Disease Genome-wide Replication and Meta-Analysis); OR, odds ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; NA, not available.

* The rs163160 SNP was used as a proxy for SBP, DBP and CAD ($r^2=0.81$).

** These SNPs were not available in the imputed CARDIoGRAM meta-analysis dataset and an adequate proxy was not found.

*** Significant associations after Bonferroni correction for multiple testing (p 1.5e-4)

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Table 3

Association results of 19 kidney SNPs with subclinical vascular traits in individuals of European descent from the CHARGE IMT, AortaGen, CHARGE Eye and NeuroCHARGE consortia.

| Kidney SNP | Nearest Gene | Coded (risk) allele | cIMT | | PWV | | RVC | | WMLs | |
|------------|----------------|---------------------|---------|---------|---------|---------|---------|---------|---------|---------|
| | | | β | p-value | β | p-value | β | p-value | z-score | p-value |
| rs10109414 | <i>STC1</i> | T | 0.001 | 0.7 | 0.007 | 0.5 | 0.068 | 0.77 | -0.444 | 0.7 |
| rs11959928 | <i>DAB2</i> | A | -0.002 | 0.1 | 0.005 | 0.6 | 0.042 | 0.86 | -0.18 | 0.9 |
| rs12460876 | <i>SLC7A9</i> | T | -0.002 | 0.2 | -0.003 | 0.8 | 0.29 | 0.22 | 0.785 | 0.4 |
| rs1260326 | <i>GCKR</i> | C | 0.002 | 0.3 | -0.036 | 0.001 | -0.022 | 0.93 | -0.004 | 0.9 |
| rs12917707 | <i>UMOD</i> | G | -0.003 | 0.1 | 0.019 | 0.2 | -0.415 | 0.16 | 1.334 | 0.2 |
| rs13538 | <i>ALMS1</i> | A | 0.001 | 0.4 | -0.007 | 0.6 | -0.419 | 0.13 | 0.454 | 0.6 |
| rs1394125 | <i>UBE2Q2</i> | A | -0.002 | 0.3 | -0.024 | 0.1 | -0.83 | 0.001 | 0.164 | 0.9 |
| rs17319721 | <i>SHROOM3</i> | A | -0.001 | 0.5 | -0.002 | 0.8 | -0.319 | 0.17 | -1.387 | 0.2 |
| rs1801239 | <i>CUBN</i> | T | 0.001 | 0.8 | 0.001 | 0.99 | -0.14 | 0.72 | 2.907 | 0.004 |
| rs267734 | <i>ANXA9</i> | T | -0.001 | 0.8 | 0.001 | 0.9 | 0.251 | 0.37 | -0.476 | 0.6 |
| rs347685 | <i>TFDP2</i> | A | 0.002 | 0.1 | 0.001 | 0.99 | 0.419 | 0.09 | 0.038 | 0.9 |
| rs4744712 | <i>PIP5K1B</i> | A | 0.002 | 0.1 | -0.001 | 0.99 | 0.375 | 0.11 | -0.029 | 0.9 |
| rs626277 | <i>DACHI</i> | A | 0.002 | 0.3 | 0.017 | 0.1 | 0.289 | 0.21 | 0.079 | 0.9 |
| rs6420094 | <i>SLC34A1</i> | G | 0.002 | 0.2 | 0.008 | 0.6 | 0.085 | 0.75 | NA | ** NA |
| rs653178 | <i>SH2B3</i> | C | -0.001 | 0.6 | 0.017 | 0.1 | 1.529 | 2.9E-11 | -0.318 | 0.8 |
| rs7805747 | <i>PRKAG2</i> | A | 0.003 | 0.2 | 0.012 | 0.4 | -0.166 | 0.62 | NA | ** NA |
| rs81204 | <i>KCNQ1</i> | C | 0.003 | 0.3 | 0.02 | 0.2 | NA | NA | NA | ** NA |
| rs881858 | <i>VEGFA</i> | A | 0.0001 | 0.9 | -0.029 | 0.03 | 0.822 | 0.002 | 0.519 | 0.6 |
| rs911119 | <i>CST3</i> | T | 0.001 | 0.7 | -0.034 | 0.01 | -0.047 | 0.87 | -0.337 | 0.7 |

Note: The subclinical vascular traits tested were cIMT, PWV, RVC, and WMLs. Results are presented for the trait-decreasing eGFR allele.

CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology); PWV, pulse-wave velocity; RVC, retinal venular caliber; WMLs, white matter lesions; carotid intima-media thickness (cIMT), eGFR, estimated glomerular filtration rate; SNP, single nucleotide polymorphism; NA, not available

** These SNPs were not available in the imputed meta-analysis dataset and an adequate proxy was not found.

*** Significant associations after Bonferroni correction for multiple testing (p < 1.5e-4)

Table 4
Association of 29 blood pressure SNPs with kidney traits in individuals of European descent from the CKDGen consortium.

| BP SNP | Nearest Gene | Coded (risk) allele | UACR | | eGFR _{cr} | | eGFR _{cys} | |
|------------|-------------------------|---------------------|---------|---------|--------------------|---------|---------------------|-----------|
| | | | β | p-value | β | p-value | β | p-value |
| rs17367504 | <i>MTHFR-NPPB</i> | A | 0.003 | 0.8 | 0.001 | 0.5 | 0.002 | 0.5 |
| rs2932538 | <i>MOV10</i> | G | 0.002 | 0.9 | 0.002 | 0.2 | -0.002 | 0.5 |
| rs13082711 | <i>SLC4A7</i> | C | 0.008 | 0.5 | 0.003 | 0.1 | 0.003 | 0.3 |
| rs3774372 | <i>ULK4</i> | C | -0.014 | 0.2 | 0.001 | 0.6 | 0.009 | 0.004 |
| rs419076 | <i>MECOM</i> | T | 0.005 | 0.6 | -0.001 | 0.3 | -0.003 | 0.2 |
| rs1458038 | <i>FGF5</i> | T | -0.019 | 0.1 | 0.004 | 0.005 | -0.001 | 0.6 |
| rs13107325 | <i>SLC39A8</i> | C | -0.02 | 0.3 | 0.005 | 0.048 | 0.002 | 0.7 |
| rs13139571 | <i>GUCY1A3-GUCY1B3</i> | C | 0.002 | 0.9 | -0.004 | 0.03 | -0.007 | 0.006 |
| rs1173771 | <i>NPR3-CSorf23</i> | G | -0.004 | 0.6 | -0.001 | 0.7 | 0.003 | 0.2 |
| rs11953630 | <i>EBF1</i> | C | 0.014 | 0.1 | 0.002 | 0.2 | 0.002 | 0.5 |
| rs1799945 | <i>HFE(H63D)</i> | G | 0.003 | 0.8 | 0.006 | 0.001 | -0.004 | 0.2 |
| rs805303 | <i>BAT2-BAT5</i> | G | -0.003 | 0.8 | 0.004 | 0.007 | 0.0004 | 0.9 |
| rs4373814 | <i>CACNB2(5')</i> | C | 0.008 | 0.4 | -0.001 | 0.7 | -0.001 | 0.7 |
| rs1813353 | <i>CACNB2(3')</i> | T | 0.019 | 0.047 | -0.002 | 0.3 | 0.003 | 0.3 |
| rs4590817 | <i>C10orf107</i> | G | 0.005 | 0.7 | -0.0004 | 0.8 | 0.005 | 0.1 |
| rs932764 | <i>PLCE1</i> | G | -0.004 | 0.7 | 0.001 | 0.6 | -0.001 | 0.8 |
| rs11191548 | <i>CYP17A1-NT5C2</i> | T | -0.04 | 0.01 | 0.004 | 0.1 | 0.002 | 0.6 |
| rs7129220 | <i>ADM</i> | A | 0.012 | 0.4 | -0.002 | 0.4 | -0.006 | 0.1 |
| rs381815 | <i>PLEKHA7</i> | T | 0.015 | 0.1 | -0.003 | 0.1 | -0.002 | 0.4 |
| rs633185 | <i>FLJ32810-TMEM133</i> | C | -0.008 | 0.4 | 0.003 | 0.1 | -0.002 | 0.5 |
| rs17249754 | <i>ATP2B1</i> | G | 0.011 | 0.4 | -0.004 | 0.02 | -0.007 | 0.02 |
| rs3184504 | <i>SH2B3</i> | T | -0.008 | 0.4 | -0.003 | 0.01 | -0.012 | 1.06E-07* |
| rs10850411 | <i>TBX5-TBX3</i> | T | 0.008 | 0.4 | 0.001 | 0.7 | 0.003 | 0.2 |
| rs1378942 | <i>CYP11A1-ULK3</i> | C | -0.005 | 0.6 | -0.001 | 0.3 | -0.002 | 0.5 |
| rs2521501 | <i>FURIN-FES</i> | T | -0.016 | 0.3 | -0.002 | 0.4 | 0.005 | 0.1 |

| BP SNP | Nearest Gene | Coded (risk) allele | UACR | | eGFR _{cr} | | eGFR _{cys} | |
|------------|------------------|---------------------|---------|---------|--------------------|---------|---------------------|---------|
| | | | β | p-value | β | p-value | β | p-value |
| rs17608766 | <i>GOSR2</i> | C | 0.015 | 0.3 | -0.003 | 0.2 | -0.005 | 0.2 |
| rs12940887 | <i>ZNF652</i> | T | 0.007 | 0.5 | -0.001 | 0.5 | -0.001 | 0.6 |
| rs1327235 | <i>JAG1</i> | G | 0.021 | 0.02 | -0.0001 | 0.9 | 0.004 | 0.1 |
| rs6015450 | <i>GNAS-EDN3</i> | G | 0.006 | 0.7 | -0.004 | 0.04 | 0.005 | 0.1 |

Note: The kidney traits tested are UACR, eGFR_{cr}, and eGFR_{cys}. Results are presented in the trait-increasing allele for BP, BP, blood pressure; SNP, single nucleotide polymorphism; eGFR, estimated glomerular filtration rate; eGFR_{cr}, creatinine-based eGFR; eGFR_{cys}, cystatin C-based eGFR; UACR, urinary albumin-creatinine ratio; CKD, chronic kidney disease

* Significant associations after Bonferroni correction for multiple testing (p 1.5e-4).

Table 5
Association of 25 CAD SNPs with kidney traits in individuals of European descent from the CKDGen consortium.

| CAD SNP | Nearest Gene | Coded (risk) allele | UACR | | eGFR _{cr} | | eGFR _{cys} | |
|------------|-----------------------|---------------------|---------|---------|--------------------|---------|---------------------|------------|
| | | | β | p-value | β | p-value | β | p-value |
| rs11206510 | <i>PCSK9</i> | T | -0.012 | 0.3 | -0.001 | 0.5 | -0.003 | 0.4 |
| rs599839 | <i>SORT1</i> | A | 0.018 | 0.1 | 0.003 | 0.1 | 0.001 | 0.6 |
| rs17465637 | <i>MIA3</i> | C | -0.009 | 0.7 | -0.006 | 0.4 | -0.005 | 0.4 |
| rs6725887 | <i>WDR12</i> | C | -0.024 | 0.1 | -0.004 | 0.04 | -0.007 | 0.04 |
| rs2306374 | <i>MRAS</i> | C | 0.012 | 0.3 | -0.001 | 0.5 | 0.003 | 0.3 |
| rs12526453 | <i>PHACTR1</i> | C | 0.003 | 0.8 | 0.0002 | 0.9 | 0.002 | 0.4 |
| rs3798220 | <i>LPA</i> | C | NA* | NA* | NA* | NA* | NA* | NA* |
| rs4977574 | <i>CDKN2A, CDKN2B</i> | G | 0.013 | 0.1 | -0.002 | 0.2 | 0.003 | 0.2 |
| rs1746048 | <i>CXCL12</i> | C | -0.018 | 0.2 | -0.001 | 0.7 | 0.001 | 0.9 |
| rs3184504 | <i>SH2B3</i> | T | -0.008 | 0.4 | -0.003 | 0.01 | -0.012 | 1.06E-07** |
| rs11222608 | <i>LDLR</i> | G | -0.016 | 0.1 | -0.001 | 0.5 | -0.002 | 0.5 |
| rs9982601 | <i>MRPS6</i> | T | 0.006 | 0.7 | -0.001 | 0.6 | 0.005 | 0.2 |
| rs17114036 | <i>PPP2B</i> | A | -0.018 | 0.2 | -0.003 | 0.2 | 0.001 | 0.8 |
| rs17609940 | <i>ANKK1A</i> | G | -0.008 | 0.5 | -0.001 | 0.5 | 0.0003 | 0.9 |
| rs12190287 | <i>TCF21</i> | C | 0.014 | 0.2 | 0.002 | 0.1 | -0.004 | 0.1 |
| rs11556924 | <i>ZC3HC1</i> | C | -0.015 | 0.1 | -0.001 | 0.6 | -0.002 | 0.5 |
| rs579459 | <i>ABO</i> | C | -0.018 | 0.1 | 0.002 | 0.3 | -0.004 | 0.1 |
| rs12413409 | <i>CYP17A1</i> | G | -0.038 | 0.017 | 0.003 | 0.1 | -0.0002 | 0.9 |
| rs964184 | <i>ZNF259</i> | G | 0.008 | 0.6 | -0.002 | 0.3 | -0.01 | 0.002 |
| rs4773144 | <i>COL4A1</i> | G | -0.022 | 0.02 | -0.002 | 0.1 | 0.001 | 0.7 |
| rs2895811 | <i>HHLPL1</i> | C | 0.006 | 0.6 | -0.001 | 0.4 | -0.001 | 0.7 |
| rs3825807 | <i>ADAMTS7</i> | A | 0.002 | 0.8 | 0.001 | 0.5 | 0.001 | 0.6 |
| rs216172 | <i>SMG6</i> | C | -0.008 | 0.6 | 0.002 | 0.4 | 0.002 | 0.5 |
| rs12936587 | <i>RASD1</i> | G | 0.02 | 0.04 | 0.003 | 0.02 | 0.004 | 0.1 |
| rs46522 | <i>UBE2Z</i> | T | 0.018 | 0.046 | 0.001 | 0.7 | 0.002 | 0.5 |

Note: The kidney traits tested are UACR, eGFR_{Cr}, and eGFR_{cys}. Results are presented in the trait-increasing allele for CAD, CAD, coronary artery disease; SNP, single nucleotide polymorphism; eGFR, estimated glomerular filtration rate; eGFR_{Cr}, creatinine-based eGFR; eGFR_{cys}, cystatin C-based eGFR; UACR, urinary albumin-creatinine ratio; CKD, chronic kidney disease; NA, not available.

* This SNP was not available in the imputed CKDGen meta-analysis dataset and an adequate proxy was not found.

** Significant associations after Bonferroni correction for multiple testing (p = 1.5e-4)

Table 6

Associations of 10 subclinical atherosclerosis SNPs with kidney traits in individuals of European descent from the CKDGen consortium.

| CVD SNP | Nearest Gene | Coded (risk) allele | CVD phenotype | UACR | | eGFR _{cr} | | eGFR _{cys} | |
|------------|--------------|---------------------|---------------|---------|---------|--------------------|---------|---------------------|-----------|
| | | | | β | p-value | β | p-value | β | p-value |
| rs11781551 | ZHX2 | G | cIMT | -0.005 | 0.6 | -0.0001 | 0.9 | -0.001 | 0.6 |
| rs445925 | APOC1 | G | cIMT | -0.01 | 0.8 | -0.007 | 0.1 | -0.001 | 0.9 |
| rs6601530 | PINX1 | G | cIMT | -0.017 | 0.1 | 0.003 | 0.03 | 0.001 | 0.7 |
| rs7152623 | 3'-BCL11B | G | PWV | -0.007 | 0.4 | -0.001 | 0.5 | 0.001 | 0.8 |
| rs2287921 | RASIP1 | C | RVC | 0.009 | 0.3 | -0.003 | 0.1 | -0.006 | 0.01 |
| rs225717 | VTA1 | T | RVC | 0.009 | 0.4 | 0.004 | 0.02 | 0.001 | 0.7 |
| rs10774625 | SH2B3 | A | RVC | -0.008 | 0.4 | -0.003 | 0.03 | -0.013 | 7.05E-08* |
| rs17421627 | MEF2C | G | RVC | 0.002 | 0.9 | 0.004 | 0.1 | 0.001 | 0.8 |
| rs3744028 | TRIM65 | C | WML | -0.01 | 0.4 | 0.006 | 0.0005 | -0.0003 | 0.9 |
| rs1055129 | TRIM47 | G | WML | -0.011 | 0.3 | 0.005 | 0.002 | 0.001 | 0.9 |

Note: The subclinical CVD SNPs (atherosclerosis SNPs) were previously associated with cIMT, PWV, RVC, and WMLs. The kidney traits tested are UACR, eGFR_{cr}, and eGFR_{cys}. Results are presented in the trait-increasing allele for the respective subclinical CVD phenotype.

CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; eGFR_{cr}, creatinine-based eGFR; eGFR_{cys}, cystatin C-based eGFR; UACR, urinary albumin-creatinine ratio; CKD, chronic kidney disease; cIMT, carotid intima-media thickness; PWV, pulse-wave velocity; RVC, retinal venular caliber; WML, white matter lesion; SNP, single nucleotide polymorphism

* Significant associations after Bonferroni correction for multiple testing (p 1.5e-4).