Genetic Association of Albuminuria with Cardiometabolic Disease and Blood Pressure

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Excretion of albumin in urine, or albuminuria, is associated with the development of multiple cardiovascular and metabolic diseases. However, whether pathways leading to albuminuria are causal for cardiometabolic diseases is unclear. We addressed this question using a Mendelian randomization framework in the UK Biobank, a large population-based cohort. We first performed a genome-wide association study for albuminuria in 382,500 individuals and identified 32 new albuminuria loci. We constructed albuminuria genetic risk scores and tested for association with cardiometabolic diseases. Genetically elevated albuminuria was strongly associated with increased risk of hypertension (1.38 OR; 95% CI, 1.27–1.50 per 1 SD predicted increase in albuminuria, $p = 7.01 \times 10^{-14}$). We then examined bidirectional associations of albuminuria with blood pressure which suggested that genetically elevated albuminuria led to higher blood pressure (2.16 mmHg systolic blood pressure; 95% CI, 1.51–2.82 per 1 SD predicted increase in albuminuria, $p = 1.22 \times 10^{-10}$) and that genetically elevated blood pressure led to more albuminuria (0.005 SD; 95% CI 0.004–0.006 per 1 mmHg predicted increase in systolic blood pressure, $p = 2.45 \times 10^{-13}$). These results support the existence of a feed-forward loop between albuminuria and blood pressure and imply that albuminuria could increase risk of cardiovascular disease through blood pressure. Moreover, they suggest therapies that target albuminuria-increasing processes could have antihypertensive effects that are amplified through inhibition of this feed-forward loop.

Introduction

In observational epidemiologic studies, albuminuria, or the concentration of albumin excreted in urine, is associated with risk for multiple cardiometabolic diseases: elevations in albuminuria predict development of coronary artery disease, stroke, heart failure, type 2 diabetes, hypertension, and all-cause mortality.[1–9] However, whether pathways leading to albuminuria are causally associated with cardiometabolic disease is unclear. Therapies lowering albuminuria are generally associated with reduced cardiovascular disease, for example. However, whether such effects are independent of concomitant reductions in blood pressure is ambiguous.[10–13,70] Understanding whether associations of albuminuria pathways with disease reflect a causal relationship or mere correlation may inform whether targeting albuminuria-increasing processes could reduce risk for cardiometabolic diseases.

"Mendelian randomization" can provide evidence regarding the hypothesis that a given biomarker-disease relationship is causal.[14] The strengths and limitations of Mendelian randomization can be considered via analogy with a randomized clinical trial. Individuals are assigned to lifelong increase or decrease in a disease risk factor due to the random segregation and independent assortment of genetic polymorphisms at conception, thus minimizing two key limitations of observational epidemiology, reverse causation and confounding. The effect of genetically modifying an exposure (here, albuminuria) can then be tested against increasing or decreasing risk of an outcome (here, cardiometabolic disease). Three assumptions must be met in order for a genetic variant to be a potentially valid instrumental variable in Mendelian randomization: (1) the variant must be strongly associated with the exposure, (2) the variant must not be associated with confounders, and (3) the variant must not be horizontally pleiotropic, i.e., cannot be associated with the outcome independent of the exposure pathway.[15] While the second and third assumptions are hard to prove, many sensitivity analyses have been developed to improve the reliability of Mendelian randomization estimates.[16]

Here, we first identify genetic variants associated with albuminuria by conducting a genome-wide association study of albuminuria in 382,500 individuals in the UK Biobank. We subsequently utilized the identified genetic variants as instruments in a Mendelian randomization analysis to test the hypothesis that pathways increasing albuminuria are causal for cardiometabolic diseases.

Subjects and Methods

Study Design

This study had three main components. First, we examined epidemiological associations of baseline albuminuria with incident cardiometabolic disease in UK Biobank. Second, we conducted a genome-wide association study of baseline albuminuria and constructed a polygenic risk score. Finally, we performed a Mendelian randomization study to test the hypothesis that the associations

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between processes leading to albuminuria and cardiometabolic diseases are causal.

UK Biobank

Study Participants

Data from 382,500 unrelated individuals of European ancestry with albuminuria measurement in the UK Biobank were used. Samples were excluded for the following reasons: inferred sex did not match reported sex, kinship was not inferred, putative sex chromosome aneuploidy, consent withdrawn, or excessive heterozygosity or missingness, based on centralized sample quality control performed by UK Biobank.[17] Excluded related individuals were defined as one individual in each pair with *KING* coefficient > 0.0884, indicating 2^{nd} degree or closer relatedness. European ancestry was determined by self-reported ancestry of British, Irish, or other white, followed by outlier detection using the R package aberrant with lambda = 40 on genetic principal component (PC)1 and PC2, PC3 and PC4, and PC5 and PC6. Individuals who were outliers for any of the three pairs of PCs were removed from the European ancestry group. Kinship inference and genetic PCs were centrally calculated by UK Biobank.[17]

Albuminuria and Blood Pressure

Albuminuria was measured at the initial assessment visit (2006–2010); a Beckman Coulter AU5400 clinical chemistry analyzer was used to quantify urine albumin (df-30500, Randox Bioscience; immunoturbidimetric assay, detection range 6.7–200 mg/L) and urine creatinine (df-30510, Beckman Coulter; enzymatic assay, detection range 88–4,4200 μmol/L) concentrations. Urine albumin concentrations below the lower limit of detection (df-30505, n = 263654) were set to the lower limit of detection (6.7 mg/L). The resulting urine albumin:creatinine ratio (ACR, mg/g) was natural log-transformed to adjust for right skewedness. Microalbuminuria was defined as urine ACR of 25–355 mg/g in females and 17–250 mg/g in males; macroalbuminuria > 355 mg/g in females and > 250 mg/g in males.[18] Baseline blood pressure was averaged from two measurements taken a few moments apart using an Omron 705 IT electronic blood pressure monitor (df-4079 and df-4080). A sphygmomanometer (df-93 and df-94) was used if a measurement could not be obtained with the electronic monitor. 381,833 individuals had both blood pressure and albuminuria measurements. Albuminuria and blood pressure can both be decreased by hypertensive medication, but there is no consensus about the magnitude of such effects on albuminuria. Therefore, neither variable was corrected for hypertensive medication use so as not to selectively skew one variable but not the other.

Disease Definitions

Prevalent cardiometabolic diseases were defined at study entry through the electronic health record and/or self-report with confirmation via verbal interview by a trained nurse. Detailed definitions for all disease classifications can be found in Table S2. Incident cardiometabolic diseases were ascertained among those not meeting disease criteria at baseline by applying phenotype definitions to longitudinal, in-patient hospital and death registry data linked to the UK Biobank. Participants were censored at the time of disease diagnosis, date of death, or date of last follow-up (i.e., February 9, 2016 for participants enrolled in Wales, February 16, 2016 for participants enrolled in England, and October 31, 2015 for participants enrolled in Scotland), whichever occurred first. Participants were presumed alive at last follow-up if there was no preceding report of death in the death register. UK Biobank was approved by the Research Ethics Committee (reference 16/NW/0274) and informed consent was obtained from all participants. Analysis of UK Biobank data was approved by the Partners HealthCare institutional review board (protocol 2013P001840).

Atherosclerosis Risk in Communities (ARIC)

10,235 unrelated individuals in the Atherosclerosis Risk in Communities study, genotyped using the Affymetrix Genome-wide Human SNP Array 5.0, were imputed to the Haplotype Reference Consortium using the Michigan Imputation Server. Phasing was performed using the Eagle2 algorithm. 4,954 variants were removed prior to imputation due to duplication, monomorphism, or allele mismatch. Imputation was then performed on 799,246 variants using the minimac3 algorithm. 39,235,157 variants in the Haplotype Reference Consortium were imputed. 6,398 individuals were of European ancestry as confirmed by centrally calculated, European-specific PC analysis and had albuminuria data.

An untimed urine sample was collected during the visit 4 clinical examination. Aliquots were frozen within 12 hr and stored at −70°C. Albumin and creatinine levels were measured in the University of Minnesota Physicians Outreach Laboratories, Minneapolis, Minnesota, with albumin by a nephelometric method either on the Dade Behring BN100 (assay sensitivity, 2.0 mg/L) or on the Beckman Image Nephelometer, and creatinine using the Jaffe method in order to determine the albumin-to-creatinine ratio (ACR; μg/mg) for participants. Blinded samples (n = 516) analyzed for quality assurance showed a correlation coefficient (r) of the $\log_e$-transformed ACR as r = 0.95. ACR was natural log-transformed for association analysis. Genotype and phenotype data were retrieved for analysis from NCBI dbGAP (phs000280.v3.p1) under procedures approved by the Partners HealthCare institutional review board (protocol 2016P002395).

Framingham Heart Study

8,825 individuals from the Offspring and Third Generation cohorts of the Framingham Heart Study, genotyped using the Affymetrix GeneChip Human Mapping 500K Array, were imputed to the Haplotype Reference Consortium using the Michigan Imputation Server. Genetic PCs were calculated on directly genotyped data using EIGENSOFT v7.2.1 after removing variants with MAF < 0.01 or genotype call rate < 0.99 and samples with sample call rate < 0.97 using PLINK-1.9. PCs were calculated in unrelated individuals only based on self-reported pedigree and projected onto related individuals. 6,534 individuals were of self-reported white ancestry confirmed by PC analysis. PCs used as covariates for association tests were recalculated in the white subgroup, and 21 individuals were removed as outliers on the basis of this analysis. 6,387 of the remaining individuals had albuminuria data available.

Albuminuria was measured at Offspring Exam 8 and Third Generation Exam 1 visits at the Framingham Heart Study Laboratory using a Roche Hitachi 911 Chemistry Analyzer. Urine albumin was quantified by the immunoturbidometric Tina-quant Albumin test (assay sensitivity, 3.0 mg/L); urine creatinine by colorimetric, modified Jaffe (rate blanked) creatinine test (assay sensitivity, 0.2 mg/100 mL). Urine albumin concentrations below the lower limit of detection (n = 1,682) were set to the lower limit of detection (3.0 mg/L). The resulting urine albumin:creatinine ratio (ACR, mg/g) was natural log-transformed for association analysis. Genotype and phenotype data were retrieved for analysis from NCBI dbGAP (phs000007.v26.p10) under procedures approved by the Partners HealthCare institutional review board (protocol 2016P002395).

International Consortium for Blood Pressure

The International Consortium for Blood Pressure is a large meta-analysis of study-specific results associating blood pressure with genotypes from the Cardio-MetaboChip SNP Array (n_{max} = 201,529)[19] or imputed to 1000 Genomes Project Phase 1 haplotypes (n_{max} = 150,134).[20] Summary statistics for SNP effects on systolic and diastolic blood pressure were corrected for anti-hypertensive medication use (+15 mmHg and +10 mmHg for systolic and diastolic blood pressure, respectively) and included body mass index, sex, age, and age^2 as covariates, as previously described.[19,20] One limitation of this dataset is that adjustment for body mass index and anti-hypertensive medication may lead to associations between genetic variants and adjusted blood pressure being confounded with other factors that influence the adjustment variables ("collider effects"). This could bias Mendelian randomization analyses with albuminuria, which is not adjusted for these factors.[21] SNPs from the Cardio-MetaboChip study[19] were used to construct blood pressure genetic risk scores, whereas association of albuminuria variants with blood pressure was examined using blood pressure effects measured in the 1000G-based study.[20]

Statistical Analyses

Observational Epidemiology

In UK Biobank, Cox proportional hazards regression was used to determine the association of baseline albuminuria with incident cardiometabolic disease (average median follow-up time 7.0 years across diseases). Potential confounding variables were selected per prior epidemiological analyses of albuminuria and cardiometabolic disease,[2,5,6,9,22–24] and a subsequent univariate screen of the selected traits in the UK Biobank was performed; these criteria yielded age at baseline, sex, current smoking status, body mass index, systolic blood pressure, diastolic blood pressure, baseline diabetes, and baseline hyperlipidemia as covariates for inclusion in most Cox proportional hazard models.

Genome-Wide Association Study

UK Biobank samples were genotyped by Affymetrix using either the UK BiLEVE or UK Biobank Axiom arrays. Genotyped variants were then imputed by the UK Biobank central analysis team onto the Haplotype Reference Consortium reference panel.[17] Variant exclusion criteria were Hardy-Weinberg equilibrium $p \leq 1 \times 10^{-20}$, QCTOOL INFOscore < 0.3, variant call rate ≤ 0.95, and MAF ≤ 0.001 yielding 11,709,857 variants in the analysis. Sex-specific residuals of natural log-transformed urine ACR were analyzed as a continuous trait with age, genotyping array, and the first ten genetic PCs as covariates via least-squares linear regression under an additive effects model using Hail v0.1 statistical software (Web Resources).[25] The threshold for statistical significance was empirically determined using permutation testing according to a previous approach.[26] Association of chromosome 21 variants with 1,000 random simulated continuous phenotypes were determined using Hail v0.1. The necessary significance threshold for a 5% family-wise error rate (FWER) was empirically estimated as the 5th percentile of the collection of the minimum variant p value from each simulated phenotype. The corresponding number of independent tests on chromosome 21 was calculated as $p = 0.05/\text{threshold}_{5\%FWER}$ and was scaled to genome-wide using the proportion of the 11,709,857 genome-wide variants located on chromosome 21. This resulted in a genome-wide significance threshold of $p < 9 \times 10^{-9}$. Genomic inflation was calculated using the median estimator in the GenABEL package in R; LD score regression and common (MAF > 5%) SNP genetic correlation and heritability were calculated via LDSC v1.0.0 using standard variant filtering (MAF > 0.01 & INFOscore > 0.9), HapMap3 SNPs, and LD scores precomputed from European 1000 Genomes data.[27] Variants were clumped into independent loci using PLINK-1.9 with R^2 > 0.01 and < 1 MB from the index variant (smallest p value).

Albuminuria Genetic Risk Score

Up to 46 SNPs independently associated with albuminuria at a conventional $p < 5 \times 10^{-8}$ threshold in the genome-wide association study (Table S4) were used to construct weighted polygenic risk scores using PLINK 2.00a2LM. Each imputed genotype dosage was multiplied by the effect of the SNP on natural log-transformed urine ACR normalized to 1-SD albuminuria in UK Biobank (0.755 log(mg/g) urine ACR). The resulting weighted dosages were summed to create genetic risk scores. Association of the 46-SNP albuminuria genetic risk score with albuminuria in ARIC and Framingham Heart Study was determined using linear regression with age, sex, and the first ten genetic PCs as covariates. Sensitivity analysis excluding 1 and 10 poorly imputed variants in ARIC and Framingham Heart Study, respectively, did not substantially affect association results. Variance explained by each score was calculated as the adjusted R^2 from the association of albuminuria with the albuminuria genetic risk score, age, sex, and ten genetic PCs minus the adjusted R^2 from the association of albuminuria with age, sex, and ten genetic PCs.

Blood Pressure Genetic Risk Scores

Lead variants of genome-wide significant loci from Cardio-MetaboChip-based ICBP stage 4 meta-analysis[19] were used to construct systolic blood pressure and diastolic blood pressure genetic risk scores. These results did not include UK Biobank. Only variants significantly ($p < 5 \times 10^{-8}$) associated with a specific blood pressure trait were included in that trait's score. rs10164833 was excluded from the systolic blood pressure risk score as it did not replicate in further ICBP meta-analysis. In UK Biobank, each imputed genotype dosage was multiplied by the effect of the SNP on mmHg systolic or diastolic blood pressures from ICBP stage 4 meta-analysis, which were corrected for hypertensive medication use and body mass index,[19] and the resulting weighted dosages were summed. Variance explained by each score in UK Biobank was calculated as the adjusted R^2 from the association of blood pressure corrected for hypertensive medication use with the blood pressure genetic risk score, age, sex, and ten genetic PCs minus the adjusted R^2 from the association of blood pressure corrected for hypertensive medication use with age, sex, and ten genetic PCs.

Mendelian Randomization

For individual-level data, association of the albuminuria or blood pressure genetic risk scores with outcomes were assessed using logistic (combined prevalent plus incident disease) or linear (continuous outcomes) two-stage least-squares regression in Stata v15. Age at baseline, sex, genotyping array, and the first ten genetic PCs to control for population structure were included as covariates. For summary-level data, the analogous approach is an inverse-variance-weighted (IVW) fixed-effects meta-analysis of the effect of each SNP on the outcome divided by the effect of this SNP on albuminuria.[28,29] Meta-analysis was conducted using the MendelianRandomization package[30] in R. Effect estimates were normalized to 1 SD albuminuria in UK Biobank (0.755 log(mg/g) urine ACR). Power to detect associations with cardiometabolic disease in UK Biobank were calculated using an online tool (Web Resources, Table S13).

Sensitivity Analyses

We performed the following sensitivity analyses to address several limitations of Mendelian randomization: MR Steiger filtering to remove variants potentially acting through reverse causation,[31,32] calculation of heterogeneity and random-effects IVW meta-analysis to allow for variant effect size heterogeneity (Tables S6–S10 and S12),[33,34] median regressions which allow up to 50% of information from variants to violate Mendelian randomization assumptions,[35] MR-Egger regression to detect directional pleiotropy,[36] Cook's distance to detect extreme outliers,[37] and unweighted allele scores to minimize bias from internally derived weights in individual-level analyses.[38]

MR Steiger Filtering. The third assumption of Mendelian randomization ("no association independent of the exposure") requires that a variant acts first through the exposure and not the outcome. Observational studies suggest that diseases such as diabetes and hypertension can increase albuminuria.[39,40] Some variants may therefore be associated with albuminuria via first increasing risk of such diseases and secondarily increasing albuminuria. These variants should not be included as instruments for testing the influence of albuminuria on those disease outcomes.

The MR Steiger method strengthens evidence regarding whether a variant acts first through the exposure or outcome under a model of vertical pleiotropy, where the SNP associates with two traits because one trait influences the other. The correlation of a variant with an outcome is a product of both the variant-exposure correlation and the exposure-outcome correlation. The variant-exposure correlation should therefore be greater than the variant-outcome correlation.[32] The MR Steiger method determines the variant-exposure and variant-outcome correlations and removes variants where the variant-outcome correlation is greater than the variant-exposure correlation. The aim of this approach is to reduce the proportion of variants erroneously included in a Mendelian randomization analysis due to confounding or acting first through the outcome.[31,32] We note that MR Steiger is not designed to distinguish between vertical pleiotropy and horizontal pleiotropy, wherein a SNP influences both traits through independent pathways.

To perform MR Steiger filtering, the correlation of a variant with each exposure and outcome was first determined. For continuous traits from studies with individual-level data, the squared correlation of each variant with a continuous exposure or outcome was calculated as the R^2 from association of the trait with the variant and covariates minus the R^2 from association of the trait with covariates. For continuous traits from studies with summary statistics, the correlation R was estimated using get_r_from_pn in the TwoSampleMR package[41] in R. Correlation R of each variant with binary traits was estimated on the logit liability scale[32,42] using get_r_from_lor in TwoSampleMR modified to use allele frequency measured in UK Biobank. To apply directional MR Steiger filtering, variants with $R^2_{exposure} < R^2_{outcome}$ were removed.

As an additional sensitivity analysis for one-sample Mendelian randomizations with individual-level data, the Steiger test of correlated correlations was used to calculate the probability that the variant-exposure and variant-outcome correlations were different. Variants whose correlation with the exposure was not significantly different from correlation with the outcome, defined as Steiger p value > 0.05, were removed. Steiger tests were calculated using the r.test in the psych package in R. This analysis was not performed for two-sample Mendelian randomizations, as correlations of a variant with an exposure or outcome from summary statistics are estimated only in separate cohorts and therefore may be less appropriate for detecting significant differences between the two measurements.

Other Sensitivity Analyses. IVW random-effects, simple median, weighted median, and MR-Egger random-effects regression were calculated with normal distributions using the MendelianRandomization v0.2.0 package in R. For these analyses of individual-level data, associations of score SNPs with each outcome were determined via linear or logistic (Wald) regression using age at baseline, sex, genotyping array, and the first ten genetic PCs using Hail v0.1 statistical software. While MR-Egger can be particularly biased by weak instruments in individual-level or one-sample Mendelian randomization analyses,[43] the fact that MR-Egger regression results were roughly similar between one-sample and two-sample analyses (Tables S8 and S10) suggests that weak instrument bias is not disproportionately affecting these results. Graphs of each variant's effect on exposure versus outcome and IVW-based leave-one-out analyses (Figures S2–S4, S6, and S7) were created using the TwoSampleMR package in R. Variant effect heterogeneity was assessed via Cochran's Q and MR-PRESSO residual sum of squares (RSS), which shows improved false-positive rates.[33] These were calculated using the MendelianRandomization and MRPRESSO[33] v1.0 packages, respectively, in R. For outlier detection, Cook's distance was calculated on IVW meta-analysis; SNPs with a Cook's distance greater than twice the nominal outlier cutoff $4/n_{SNPs}$ were considered for outlier exclusion. Unweighted allele scores were constructed by summing the number of albuminuria- or blood pressure-increasing alleles per individual. Two-stage least-squares regression was used to determine the association of the unweighted allele score with cardiometabolic outcomes as described above. Linkage disequilibrium between variants in albuminuria genetic risk scores and blood pressure genetic risk scores was defined as $R^2 > 0.2$ and < 1 MB using linkage disequilibrium calculated in the UK Biobank study population via PLINK-1.9.

Anti-hypertensive medications reduce albuminuria in addition to lowering blood pressure.[44] We wanted to determine whether not correcting blood pressure and albuminuria for hypertensive medication use confounded albuminuria-blood pressure association results. As a sensitivity analysis, we therefore excluded individuals on hypertensive medication and re-tested association of an albuminuria genetic risk score with blood pressure. Hypertensive medication use was defined by self-report with confirmation via verbal interview by a trained nurse (df-6177 and df-6153). A genome-wide association study for albuminuria was performed in 302,687 individuals in UK Biobank not on hypertensive medication and who had blood pressure and albuminuria measurements. This yielded 23 independent loci ($p < 5 \times 10^{-8}$, $R^2 > 0.01$ and < 1 MB from the index variant, Table S11). Effects of the 23 SNPs were used to construct an albuminuria risk score normalized to 1 SD albuminuria in this population (0.713 log (mg/g)). Associations of this albuminuria risk score with blood pressure were determined as above. Directional MR Steiger filtering removed one variant from the risk score for association with both systolic and diastolic blood pressure.

Results

382,500 unrelated individuals of European ancestry in the UK Biobank, a population-based cohort, were used in this study. 54% of participants were female, and the mean age was 56.9 (SD 7.9) years at baseline. Mean baseline

Outcome[a]	Incident Cases, No.	Controls, No.	Hazard Ratio [95%CI] per 1–SD Increase in Albuminuria	P value
All–Cause Mortality	10880	368668	1.22 [1.20; 1.23]	5.63e–136
Coronary Artery Disease	11492	347346	1.09 [1.07; 1.11]	1.91e–23
Stroke	2908	370893	1.16 [1.12; 1.20]	1.75e–20
Peripheral Vascular Disease	1817	375117	1.23 [1.19; 1.27]	1.08e–34
Heart Failure	3540	373668	1.29 [1.26; 1.32]	4.76e–95
Type 2 Diabetes[b]	9550	362165	1.20 [1.18; 1.22]	7.75e–114
Chronic Kidney Disease	3780	374757	1.51 [1.48; 1.54]	<1.00e–300
Hypertension[c]	15903	256879	1.22 [1.20; 1.24]	9.22e–141
Skin Cancer	6501	362404	1.00 [0.98; 1.03]	0.827

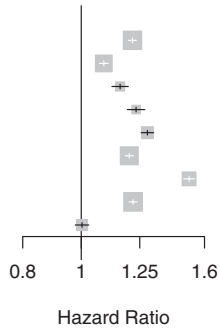

Figure 1. Association of Albuminuria with Incident Disease Endpoints in UK Biobank
[a]Incident disease adjusted for age, sex, current smoking status, body mass index, systolic blood pressure, diastolic blood pressure, baseline diabetes, and baseline hyperlipidemia unless otherwise specified.
[b]Adjusted for age, sex, current smoking status, body mass index, systolic blood pressure, diastolic blood pressure, waist-to-hip ratio, and baseline hyperlipidemia.
[c]Adjusted for age, age^2, current smoking status, body mass index, baseline diabetes, and baseline hyperlipidemia.
Bars indicate 95% confidence interval for hazard ratio.

systolic blood pressure and diastolic blood pressures were 138.3 (SD 18.6) and 82.3 (SD 10.1) mmHg, respectively; 18,940 (5.0%) individuals had diabetes at baseline and 53,004 (13.9%) had hyperlipidemia at baseline. The median baseline urine albumin:creatinine ratio (ACR) was 9.8 mg/g (IQR 6.1–16.5). 14.3% had microalbuminuria and 0.4% macroalbuminuria (Tables S1 and S2). Baseline urine ACR was natural log-transformed and is referred to as albuminuria (mean 2.3, SD 0.755 log(mg/g)) in subsequent analyses.

Association of Albuminuria with Development of Cardiometabolic Diseases

In UK Biobank, we first examined the association of baseline albuminuria with risk of incident cardiometabolic diseases using Cox proportional hazard regression (average median follow-up time across all diseases, 7.0 years). Baseline albuminuria was strongly associated with subsequent development of cardiometabolic disease (Figure 1): a 1 SD increase in albuminuria was associated with higher hazard of all-cause mortality (1.22 HR; 95%CI 1.20–1.23), coronary artery disease (1.09 HR; 95%CI 1.07–1.11), stroke (1.16 HR; 95%CI 1.12–1.20), peripheral vascular disease (1.23 HR; 95%CI 1.19–1.27), heart failure (1.29 HR; 95% CI 1.26–1.32), type 2 diabetes (1.20 HR; 95%CI 1.18–1.22), chronic kidney disease (1.51 HR; 95%CI 1.48–1.54), and hypertension (1.22 HR; 95%CI 1.20–1.24) but not with other diseases such as skin cancer (1.00 HR; 95%CI 0.98–1.03), even after adjustment for standard metabolic risk factors. Thus, albuminuria measured in UK Biobank is associated with cardiometabolic disease in a manner consistent with previous observational studies.[1,6,7,9,22]

Genome-wide Association Study for Albuminuria

To identify variants to be used as genetic instruments for albuminuria, we conducted a discovery genome-wide association study of albuminuria in the 382,500 UK Biobank participants. Minimal genomic inflation was observed ($lambda_{GC}$ = 1.17, LD score regression intercept[27] = 1.02, Figure S1). The common SNP heritability of albuminuria was 0.045 (SE 0.002). In addition to replicating the previous association[45] at the *CUBN* locus (rs10795433: beta = 0.024 log(mg/g) for C allele; $p = 1.37 \times 10^{-24}$, Table S3), we discovered an additional 1,246 genome-wide significant ($p < 9 \times 10^{-9}$) associations representing 32 novel (i.e., not previously published) independent loci, for a total of 33 genome-wide significant loci (Figure 2, Table 1). Novel associations of potential clinical interest include the *NR3C2* and *COL4A4* loci. *NR3C2* encodes the mineralocorticoid receptor, and mineralocorticoid receptor antagonists such as spironolactone and eplerenone reduce albuminuria when added to other anti-hypertensive medications.[46,47] Mutations in *COL4A4* and neighboring gene *COL4A3* can cause autosomal Alport syndrome, which is characterized by kidney disease that can include proteinuria.[48] 22 of the 33 loci (or their proxies $R^2 > 0.8$) were available in a smaller previously published genome-wide association study;[45] of these, 20 had a consistent direction of effect and 7 were nominally significant ($p < 0.05$, Table S3).

Albuminuria Genetic Instrument Strength

A 46-SNP genetic risk score constructed from the 33 genome-wide significant loci plus an additional 13 loci meeting a conventional significance level of $p < 5 \times 10^{-8}$ (Table S4) explained 0.7% of the variance in albuminuria in UK Biobank (F-statistic, 2,928). The genetic risk score was validated in two additional North American cohorts of European ancestry and non-inflated estimates were obtained. The 46-SNP score was associated with albuminuria in both the Atherosclerosis Risk in Communities study (n = 6,398, $p = 6.7 \times 10^{-5}$, 0.2% variance in albuminuria explained) and the Framingham Heart Study

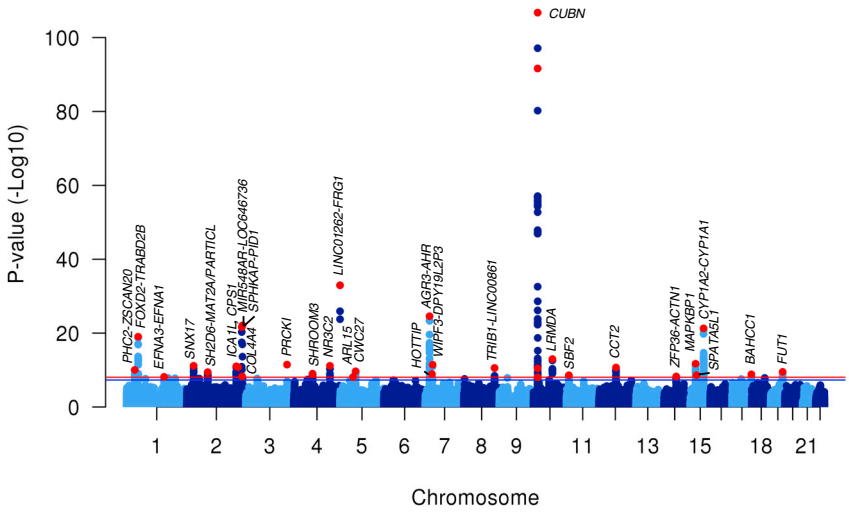

Figure 2. Genome-wide Association Study of Albuminuria in UK Biobank Identifies 32 Loci

33 genome-wide significant loci (including one previously published) are indicated by red points. Red line indicates genome-wide significance threshold ($p = 9 \times 10^{-9}$); blue line indicates conventional significance threshold ($p = 5 \times 10^{-8}$).

($n = 6{,}387$, $p = 4.4 \times 10^{-4}$, 0.2% variance in albuminuria explained; Table S5).

Association of Albuminuria Genetic Risk Score with Cardiometabolic Disease

We examined whether genetically elevated albuminuria due to the 46-SNP risk score associated with increased risk of cardiometabolic disease in UK Biobank. Genetic predisposition to elevated albuminuria was associated with increased risk of hypertension (1.51 OR; 95%CI 1.39–1.64 per 1-SD predicted increase in albuminuria due to the 46-SNP score, $p = 2.68 \times 10^{-22}$). However, no significant associations were observed between the albuminuria genetic risk score and risk of all-cause mortality, coronary artery disease, stroke, heart failure, type 2 diabetes, chronic kidney disease, or skin cancer (Figure 3).

To remove variants that may act through reverse causation—that is, influence albuminuria through hypertension—from the albuminuria score, we applied MR Steiger filtering.[31,32] This approach removed three variants more directly associated with hypertension. After filtering, the 43-SNP score was still associated with increased risk of hypertension (1.38 OR; 95%CI 1.27–1.50 per 1-SD predicted increase in albuminuria, $p = 7.01 \times 10^{-14}$, Figure 3).

Bidirectional Mendelian Randomization of Albuminuria and Blood Pressure

To further examine the association of albuminuria with hypertension, we investigated the genetic correlations between albuminuria, blood pressure, and hypertension. We found significant common SNP genetic correlations between albuminuria and hypertension ($r_g = 0.16$; SE 0.03, $p = 2.06 \times 10^{-8}$), systolic blood pressure ($r_g = 0.20$; SE 0.03, $p = 3.6 \times 10^{-15}$), or diastolic blood pressure ($r_g = 0.10$; SE 0.03, $p = 3.2 \times 10^{-4}$). We performed bidirectional Mendelian randomization between albuminuria and blood pressure to understand the determinants of these correlations. First, we examined association of the albuminuria genetic risk score with blood pressure outcomes. After MR Steiger filtering, albuminuria genetic risk scores remained associated with increased systolic blood pressure (2.16 mmHg; 95%CI 1.51–2.82 per 1-SD predicted increase in albuminuria, $p = 1.22 \times 10^{-10}$) and diastolic blood pressure (0.99 mmHg; 0.61–1.36 per 1-SD predicted increase in albuminuria, $p = 3.40 \times 10^{-7}$, Figure 4). Next, we investigated the reverse association—blood pressure affecting albuminuria—using a blood pressure risk score as the exposure and albuminuria as the outcome. 47 and 52 variants significantly associated with blood pressure in ICBP,[19] which did not include UK Biobank, explained 1.2% and 1.4% of the variance in systolic and diastolic blood pressure, respectively, in UK Biobank. Both blood pressure risk scores were associated with elevated albuminuria (0.005 SD albuminuria; 95%CI 0.004–0.006 per 1 mmHg predicted increase in systolic blood pressure, $p = 2.45 \times 10^{-13}$ and 0.007 SD albuminuria; 95%CI 0.005–0.009 per 1 mmHg predicted increase in diastolic blood pressure, $p = 1.83 \times 10^{-9}$, Figure 4), validating a previous suggestive report.[19]

Sensitivity Analyses

Seven sets of sensitivity analyses were used to verify the robustness of the associations between albuminuria and hypertension or blood pressure. First, Mendelian randomization results were consistent for a restricted score at the genome-wide significance level of $p < 9 \times 10^{-9}$ (Table S6). Second, we used several methods to detect and mitigate the effects of pleiotropic variants: (1) MR Egger regression to detect the presence of directional pleiotropy;[36] (2) Cook's distance to detect outlier variants, which can also indicate pleiotropy;[37,49] (3) leave-one-out analyses to determine whether associations are biased by a single, potentially pleiotropic SNP;[41] and (4) median-based regressions, which are robust when up to 50% of information comes from invalid variant instruments, including due to pleiotropy.[35] Some directional pleiotropy was observed in the associations between albuminuria and blood pressure but not other associations (Tables S7–S9). MR-Egger regression is especially sensitive to influential points,[50,51] so the observed directional pleiotropy could be due in part to a potential outlier, rs141640975 in the *CUBN* locus (Cook's distance = 0.6–0.7, Figures S2 and S3). This variant was the top SNP in the albuminuria GWAS, raising the

Table 1. Albuminuria Loci from GWAS of 382,500 Individuals in UK Biobank

Lead Variant	Nearest Gene(s)	Description	Chr	Position (hg19)	Effect Allele	Noneffect Allele	EAF	Beta (log (mg/g))	SE (log (mg/g))	p Value
rs12032996	*PHC2-ZSCAN20*	intergenic	1	33920586	G	A	0.838	0.01463	0.00226	9.33E−11
rs10157710	*FOXD2-TRABD2B*	intergenic	1	47961691	T	C	0.802	0.01900	0.00209	9.69E−20
rs11264327	*EFNA3-EFNA1*	intergenic	1	155095107	A	G	0.399	0.00987	0.00171	7.03E−09
rs4665972	*SNX17*	intronic	2	27598097	T	C	0.393	0.01176	0.00172	6.96E−12
rs13394343	*SH2D6-MAT2A/ PARTICL*	intergenic	2	85754342	C	A	0.570	0.01053	0.00168	3.86E−10
rs10207567	*ICA1L*	intronic	2	203714973	C	G	0.813	0.01455	0.00214	1.00E−11
rs1047891	*CPS1*	missense	2	211540507	C	A	0.684	0.01205	0.00179	1.71E−11
rs183131780	*MIR548AR-LOC646736*	intergenic	2	226684886	T	C	0.002	0.19055	0.01959	2.33E−22
rs35483183	*COL4A4*	intronic	2	227876687	A	G	0.123	0.01490	0.00255	5.19E−09
rs35924503	*SPHKAP-PID1*	intergenic	2	229131286	C	T	0.001	0.24742	0.02518	8.68E−23
rs112607182	*PRKCI*	downstream variant	3	170027407	T	C	0.077	0.02279	0.00327	3.39E−12
rs7654754	*SHROOM3*	intronic	4	77409795	G	A	0.462	0.01020	0.00167	9.96E−10
rs6535594	*NR3C2*	intronic	4	149132756	A	G	0.496	0.01146	0.00167	7.12E−12
rs189107782	*LINC01262-FRG1*	intergenic	4	190729009	T	C	0.002	0.24502	0.02026	1.12E−33
rs702634	*ARL15*	intronic	5	53271420	A	G	0.692	0.01042	0.00181	8.03E−09
rs7731168	*CWC27*	intronic	5	64296471	C	G	0.233	0.01253	0.00197	2.19E−10
rs4410790	*AGR3-AHR*	intergenic	7	17284577	C	T	0.634	0.01798	0.00173	2.63E−25
rs2023844	*HOTTIP*	intronic	7	27243238	A	G	0.926	0.01934	0.00318	1.18E−09
rs17158386	*WIPF3-DPY19L2P3*	intergenic	7	29805361	A	G	0.262	0.01330	0.00191	3.65E−12
rs28601761	*TRIB1-LINC00861*	intergenic	8	126500031	C	G	0.579	0.01136	0.00171	2.81E−11
rs45551835	*CUBN*	missense	10	16932384	A	G	0.014	0.14237	0.00698	2.28E−92
rs144360241	*CUBN*	missense	10	16967417	C	T	0.005	0.08186	0.01234	3.31E−11
rs1276720	*CUBN*	intronic	10	16971426	T	C	0.745	0.01109	0.00193	8.98E−09
rs141640975	*CUBN*	missense	10	16992011	A	G	0.003	0.35876	0.01629	1.75E−107
rs67339103	*LRMDA*	intronic	10	77893686	A	G	0.212	0.01522	0.00205	1.07E−13
rs17368443	*SBF2*	intronic	11	10296836	C	G	0.061	0.02071	0.00348	2.58E−09
rs2601006	*CCT2*	5′ UTR variant	12	69979517	C	T	0.657	0.01176	0.00176	2.13E−11
rs4288924	*ZFP36L1-ACTN1*	intergenic	14	69302399	G	A	0.480	0.00980	0.00168	5.66E−09
rs8035855	*MAPKBP1*	intronic	15	42077961	A	G	0.644	0.01227	0.00174	1.91E−12
rs1145074	*SPATA5L1*	intronic	15	45703824	T	A	0.745	0.01140	0.00191	2.41E−09
rs2472297	*CYP1A2-CYP1A1*	intergenic	15	75027880	T	C	0.267	0.01812	0.00188	5.31E−22
rs35572189	*BAHCC1*	missense	17	79419025	G	A	0.638	0.01051	0.00174	1.44E−09
rs838142	*FUT1*	3′ UTR variant	19	49252151	A	G	0.723	0.01174	0.00187	3.13E−10

Abbreviations: Chr, chromosome; EAF, effect allele frequency. For intergenic loci, nearest upstream and downstream RefSeq genes are indicated. Nearest gene should not be taken as evidence of causal gene. Description, most-severe consequence of nearest RefSeq gene.

possibility that it could derive its large effect via aggregating potentially pleiotropic effects of multiple pathways. Excluding this variant reduced directional pleiotropy while maintaining associations between the albuminuria risk score and blood pressure or hypertension (Tables S7 and S8). Leave-one-out analyses suggested that the observed

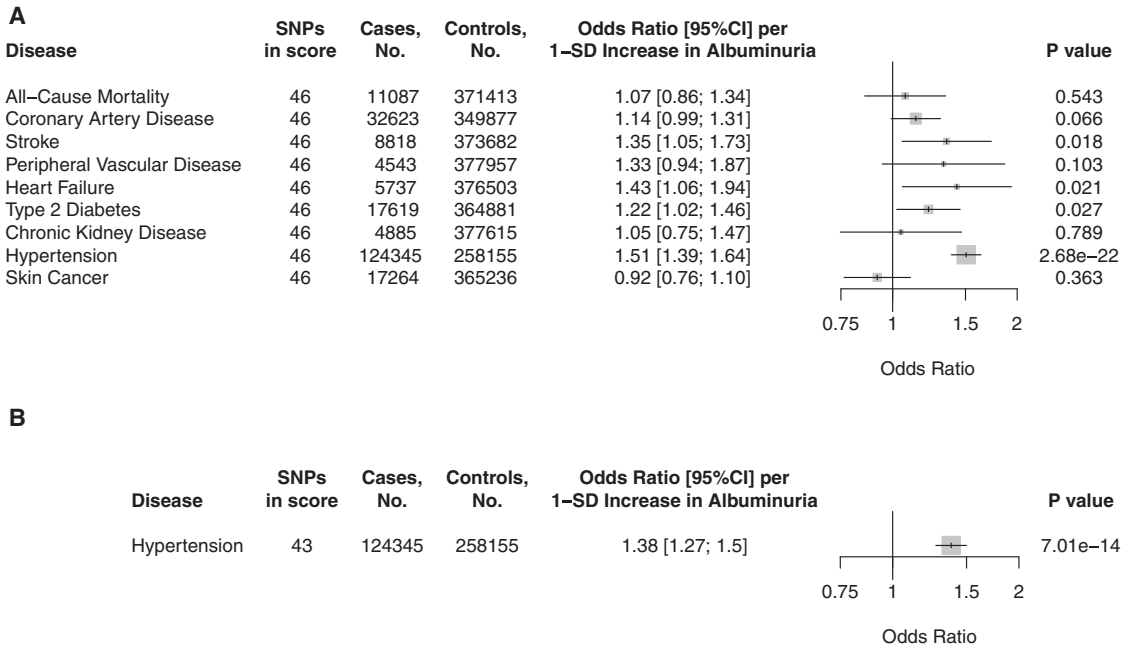

Figure 3. Association of Genetic Predisposition to Increased Albuminuria with Risk of Cardiometabolic Disease in UK Biobank
Two-stage least-squares regression using albuminuria genetic risk score as instrumental variable; age, sex, genotyping array, and first ten genetic PCs as covariates. Results are standardized to 1-SD increase in albuminuria due to the genetic risk score.
(A) Genetic risk score composed of all 46 albuminuria variants.
(B) Genetic risk score composed of 43 albuminuria variants after applying directional MR Steiger filtering to remove variants potentially acting in the incorrect direction.
Bars indicate 95% confidence interval for odds ratio.

associations were not biased by other single variants (Figures S2–S4, Tables S7–S9). Notably, albuminuria risk scores also remained associated with hypertension and blood pressure, and blood pressure risk scores with albuminuria, using one or more forms of median regression that allow for many pleiotropic variants (Tables S7–S9).

Third, to be more confident variants were not acting through reverse causation, we used a more stringent MR Steiger filter. This removed variants that were not significantly more associated with albuminuria than outcomes. While effect estimates were slightly attenuated, the associations of albuminuria with blood pressure and hypertension persisted even after this additional filtering (Tables S7 and S8).

Fourth, for bidirectional Mendelian randomization it is important that variants in the albuminuria score are not in linkage disequilibrium with variants in the blood pressure score.[21] One pair of variants at the *HOTTIP* locus was in linkage disequilibrium (rs2023844-rs3735533 R^2 = 0.99). MR Steiger analysis suggests that this variant is more directly associated with blood pressure. It was therefore removed from all albuminuria risk scores by directional MR Steiger filtering. Additionally, sensitivity analyses excluding this variant from blood pressure risk scores did not affect association of blood pressure risk scores with albuminuria (Table S9).

Fifth, using the same samples for both discovery of a genetic risk score and analysis of score effects can bias association results toward the observational estimate.[52] Unweighted genetic risk scores can reduce this bias.[38] Unweighted albuminuria risk scores were also associated with increased risk of hypertension and elevated systolic and diastolic blood pressure in UK Biobank (Tables S7 and S8).

Sixth, to further mitigate bias from score discovery-analysis overlap in UK Biobank, we examined the effects of albuminuria-associated variants on blood pressure measured in a separate cohort. Blood pressure effects in ICBP were corrected for hypertensive medication use.[20] In this cohort, albuminuria variants were associated with increased systolic blood pressure (2.69 mmHg; 95%CI 1.18–4.19 per 1-SD predicted increase in albuminuria, $p = 4.64 \times 10^{-4}$) and nominally with increased diastolic blood pressure (1.03 mmHg; 0.10–1.97 per 1-SD predicted increase in albuminuria, p = 0.030, Figures S5 and S6, Table S10).

Finally, hypertensive medications lower both albuminuria and blood pressure. To investigate this source of potential bias, we excluded any individuals in UK Biobank taking hypertensive medication. The effects of the resulting albuminuria genetic risk score on increased blood pressure were largely consistent (Figures S5 and S7, Tables S11 and S12), albeit with reduced power in this n = 302,687 subset.

Discussion

We used Mendelian randomization to examine whether processes leading to elevated albuminuria lead to increased risk of cardiometabolic disease. A genome-wide

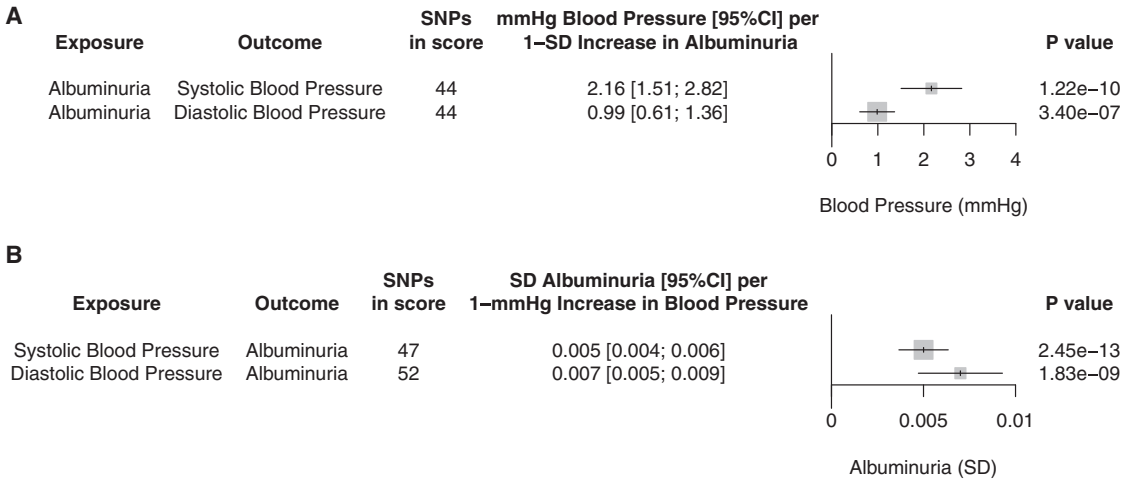

Figure 4. Bidirectional Mendelian Randomization Identifies Suggestive Causal Effects of Albuminuria on Blood Pressure and of Blood Pressure on Albuminuria

(A) Mendelian randomization of albuminuria genetic risk scores on blood pressure in UK Biobank (n = 381,833). Two-stage least-squares regression using albuminuria genetic risk score as instrumental variable on blood pressure outcome; age, sex, genotyping array, and first ten genetic PCs as covariates. Results are standardized to 1-SD increase in albuminuria due to the genetic risk score. Genetic risk scores were composed of 44 albuminuria variants after applying directional MR Steiger filtering to remove variants potentially acting in the incorrect direction.

(B) Mendelian randomization of blood pressure genetic risk scores on albuminuria. Effects of variants on systolic or diastolic blood pressure were determined in ICBP[19] (n_{max} = 201,529) and thus corrected for hypertensive medication use and adjusted for body mass index. Two-stage least-squares regression using blood pressure genetic risk score as instrumental variable on albuminuria outcome in UK Biobank (n = 381,833); age, sex, genotyping array, and first ten genetic PCs as covariates. Results are standardized to 1-mmHg increase in blood pressure due to the genetic risk score. 47 or 52 variants were used to construct scores specific for systolic or diastolic blood pressure, respectively. Directional MR Steiger filtering removed no variants.

SNPs in score, number of SNPs remaining after directional MR Steiger filtering applied. Bars indicate 95% confidence interval for effect on blood pressure (top) or albuminuria (bottom).

association study of albuminuria in UK Biobank identified 33 albuminuria loci, including one previously published. A genetic risk score of up to 46 albuminuria variants was strongly associated with increased risk of hypertension and elevated blood pressure but showed only weak associations with other cardiometabolic diseases.

These results permit several conclusions. First, processes that increase albuminuria appear to increase risk of hypertension and blood pressure. Although hypertension is commonly thought to increase albuminuria, previous epidemiological studies also suggest that albuminuria predicts development of hypertension.[7,8] Our data add genetic and observational evidence supporting this association. Multiple pathways leading to albuminuria may contribute to hypertension. Albuminuria may arise as a result of generalized endothelial dysfunction,[53–55] which can contribute to development of hypertension.[56,57] Albuminuria can also result from kidney damage. In damaged kidneys, increased blood pressure is thought to help the subfunctional kidney excrete sufficient sodium to maintain sodium homeostasis.[58,59] Consistent with this, severe kidney injury leads to experimental hypertension[60] and mild kidney damage precedes the development of hypertension in multiple experimental models.[58,61] The intrinsic role of the kidney in blood pressure regulation is also supported by the observation that kidney transplantation from hypertensive donors can cause hypertension in previously normotensive recipients.[62,63] Further work is needed to determine the mechanisms by which risk score variants contribute to elevated albuminuria.

Second, application of MR Steiger filtering[31,32] enabled the discovery of evidence for bidirectional effects between albuminuria and blood pressure. The associations of genetically elevated albuminuria with increased blood pressure and of genetically elevated blood pressure with increased albuminuria suggest that the relationship between albuminuria and blood pressure is bidirectional. This would imply the existence of a feed-forward loop, in which elevated blood pressure leads to increased albuminuria, which in turn would further increase blood pressure. It is important to note that because each Mendelian randomization analysis estimates the effects in one direction, this feedback loop is not formally modeled by such analyses.[52] These results suggest that therapies targeting processes that lower albuminuria could have antihypertensive effects that are further amplified by inhibiting this feed-forward loop. Determining the specific genes and pathways affected by albuminuria variants could assist in rational design of such therapies.

Third, these results imply that processes leading to albuminuria can influence cardiovascular disease through blood pressure. Observational and genetic evidence establishes blood pressure as an important causal risk factor for multiple cardiovascular diseases.[19,64–66] By the principle of two-step Mendelian randomization,[15,67] significant associations between an albuminuria risk score and blood

pressure and between blood pressure risk scores and diseases such as stroke or coronary artery disease[19] imply that the albuminuria risk score is associated with these diseases at least via blood pressure. This raises the question of why we did not observe significant associations between albuminuria and such diseases. Stronger genetic risk scores may be necessary to detect downstream consequences of a causal relationship between albuminuria and blood pressure: since blood pressure explains only some of the variance in cardiovascular outcomes,[68] albuminuria should have a smaller effect size on cardiovascular disease than on blood pressure. We therefore may have been underpowered to detect such downstream effects of albuminuria-induced hypertension on cardiovascular diseases (Table S13). Larger datasets that generate stronger albuminuria genetic risk scores should help clarify this issue.

A key strength of this study is that albuminuria and genotypes were measured in 382,500 individuals, seven times more than the next largest genome-wide association study,[45] enabling construction of a polygenic risk score that explained 0.2% of the variance in albuminuria in two validation cohorts. We were also able to validate the associations between albuminuria and blood pressure in an outside cohort. Access to individual-level data in UK Biobank allowed us to interrogate whether these associations were confounded by hypertensive medication use. Finally, we used MR Steiger filtering to remove variants that potentially acted through reverse causation, and multiple sensitivity analyses to detect and mitigate pleiotropic variants.

Several limitations should be acknowledged. First, reliance on internally derived weights in our albuminuria genetic risk score may have biased our results toward the observational associations.[43] To address this, we replicated significant associations using unweighted allele scores and/or in two-sample analyses. Second, an alternate explanation for the bidirectional associations observed is that a shared genetic basis underlies the two traits. If so, SNPs that influence both traits through a shared mechanism could violate the instrument strength independent of direct effect (InSIDE) assumption of standard Mendelian randomization and MR-Egger analyses.[69] Although the associations were consistent using median-based regressions, which do not require the InSIDE assumption,[35,41] we cannot rule out the possibility that associations between albuminuria and blood pressure are due to a shared genetic basis of the two traits rather than causal effects. Third, there was substantial heterogeneity in the causal effect estimates from different variants (Tables S6–S10 and S12); i.e., for association of albuminuria variants with hypertension, Cochran's $Q = 160$ ($p = 9.5 \times 10^{-16}$). This is perhaps not surprising considering the hypothesis under investigation was whether pathways that lead to albuminuria can increase blood pressure and hypertension risk. It is plausible—and quite likely—that multiple albuminuria-inducing pathways exist which could elevate blood pressure to different degrees (i.e., endothelial dysfunction and kidney damage) or not at all (i.e., pathways involved in albumin metabolism or post-renal urine regulation).[50] However, other sources of heterogeneity could nevertheless be present, although these do not necessarily lead to bias.[16,50] Fourth, UK Biobank is a population-based longitudinal cohort. Our study was likely underpowered to detect associations in diseases less common than hypertension (Table S13); therefore, lack of association of albuminuria with other diseases should not be over-interpreted. Finally, it is important to note that UK Biobank is an older cohort of European ancestry; therefore, results may differ in younger populations or in other ethnic backgrounds.

In conclusion, an albuminuria genetic risk score of up to 46 SNPs was associated with increased risk of hypertension and elevated blood pressure. Application of recently developed Mendelian randomization methods identified evidence of bidirectional effects from albuminuria-increasing pathways to blood pressure and from blood pressure to albuminuria. These results provide genetic data to refine and highlight the complex interplay between albuminuria and hypertension.

Supplemental Data

Supplemental Data include 7 figure and 13 tables and can be found with this article online at https://doi.org/10.1016/j.ajhg.2018.08.004.

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Declaration of Interests

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Web Resources

Hail, https://github.com/hail-is/hail
Mendelian randomization power calculator, https://sb452.shinyapps.io/power

References

1. Gerstein, H.C., Mann, J.F.E., Yi, Q., Zinman, B., Dinneen, S.F., Hoogwerf, B., Hallé, J.P., Young, J., Rashkow, A., Joyce, C., et al.; HOPE Study Investigators (2001). Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. JAMA *286*, 421–426.
2. Klausen, K., Borch-Johnsen, K., Feldt-Rasmussen, B., Jensen, G., Clausen, P., Scharling, H., Appleyard, M., and Jensen, J.S. (2004). Very low levels of microalbuminuria are associated with increased risk of coronary heart disease and death independently of renal function, hypertension, and diabetes. Circulation *110*, 32–35.
3. Hillege, H.L., Fidler, V., Diercks, G.F.H., van Gilst, W.H., de Zeeuw, D., van Veldhuisen, D.J., Gans, R.O.B., Janssen, W.M.T., Grobbee, D.E., de Jong, P.E.; and Prevention of Renal and Vascular End Stage Disease (PREVEND) Study Group (2002). Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. Circulation *106*, 1777–1782.
4. Hemmelgarn, B.R., Manns, B.J., Lloyd, A., James, M.T., Klarenbach, S., Quinn, R.R., Wiebe, N., Tonelli, M.; and Alberta Kidney Disease Network (2010). Relation between kidney function, proteinuria, and adverse outcomes. JAMA *303*, 423–429.
5. Matsushita, K., Coresh, J., Sang, Y., Chalmers, J., Fox, C., Guallar, E., Jafar, T., Jassal, S.K., Landman, G.W.D., Muntner, P., et al.; CKD Prognosis Consortium (2015). Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data. Lancet Diabetes Endocrinol. *3*, 514–525.
6. Brantsma, A.H., Bakker, S.J.L., Hillege, H.L., de Zeeuw, D., de Jong, P.E., Gansevoort, R.T.; and PREVEND Study Group (2005). Urinary albumin excretion and its relation with C-reactive protein and the metabolic syndrome in the prediction of type 2 diabetes. Diabetes Care *28*, 2525–2530.
7. Wang, T.J., Evans, J.C., Meigs, J.B., Rifai, N., Fox, C.S., D'Agostino, R.B., Levy, D., and Vasan, R.S. (2005). Low-grade albuminuria and the risks of hypertension and blood pressure progression. Circulation *111*, 1370–1376.
8. Brantsma, A.H., Bakker, S.J.L., de Zeeuw, D., de Jong, P.E., and Gansevoort, R.T. (2006). Urinary albumin excretion as a predictor of the development of hypertension in the general population. J. Am. Soc. Nephrol. *17*, 331–335.
9. Scirica, B.M., Mosenzon, O., Bhatt, D.L., Udell, J.A., Steg, P.G., McGuire, D.K., Im, K., Kanevsky, E., Stahre, C., Sjöstrand, M., et al. (2018). Cardiovascular outcomes according to urinary albumin and kidney disease in patients with type 2 diabetes at high cardiovascular risk: observations from the SAVOR-TIMI 53 trial. JAMA Cardiol. *3*, 155–163.
10. Asselbergs, F.W., Diercks, G.F.H., Hillege, H.L., van Boven, A.J., Janssen, W.M.T., Voors, A.A., de Zeeuw, D., de Jong, P.E., van Veldhuisen, D.J., van Gilst, W.H.; and Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND IT) Investigators (2004). Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. Circulation *110*, 2809–2816.
11. Ibsen, H., Olsen, M.H., Wachtell, K., Borch-Johnsen, K., Lindholm, L.H., Mogensen, C.E., Dahlöf, B., Devereux, R.B., de Faire, U., Fyhrquist, F., et al. (2005). Reduction in albuminuria translates to reduction in cardiovascular events in hypertensive patients: losartan intervention for endpoint reduction in hypertension study. Hypertension *45*, 198–202.
12. de Zeeuw, D., Remuzzi, G., Parving, H.-H., Keane, W.F., Zhang, Z., Shahinfar, S., Snapinn, S., Cooper, M.E., Mitch, W.E., and Brenner, B.M. (2004). Albuminuria, a therapeutic target for cardiovascular protection in type 2 diabetic patients with nephropathy. Circulation *110*, 921–927.
13. Holtkamp, F.A., de Zeeuw, D., de Graeff, P.A., Laverman, G.D., Berl, T., Remuzzi, G., Packham, D., Lewis, J.B., Parving, H.H., and Lambers Heerspink, H.J. (2011). Albuminuria and blood pressure, independent targets for cardioprotective therapy in patients with diabetes and nephropathy: a post hoc analysis of the combined RENAAL and IDNT trials. Eur. Heart J. *32*, 1493–1499.
14. Smith, G.D., and Ebrahim, S. (2003). 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? Int. J. Epidemiol. *32*, 1–22.
15. Zheng, J., Baird, D., Borges, M.-C., Bowden, J., Hemani, G., Haycock, P., Evans, D.M., and Smith, G.D. (2017). Recent developments in Mendelian randomization studies. Curr. Epidemiol. Rep. *4*, 330–345.
16. Hemani, G., Bowden, J., and Davey Smith, G. (2018). Evaluating the potential role of pleiotropy in Mendelian randomization studies. Hum. Mol. Genet. *27* (R2), R195–R208.
17. Bycroft, C., Freeman, C., Petkova, D., Band, G., Elliott, L.T., Sharp, K., Motyer, A., Vukcevic, D., Delaneau, O., O'Connell, J., et al. (2017). Genome-wide genetic data on ~500,000 UK Biobank participants. bioRxiv. https://doi.org/10.1101/166298.
18. Mattix, H.J., Hsu, C.-Y., Shaykevich, S., and Curhan, G. (2002). Use of the albumin/creatinine ratio to detect microalbuminuria: implications of sex and race. J. Am. Soc. Nephrol. *13*, 1034–1039.
19. Ehret, G.B., Ferreira, T., Chasman, D.I., Jackson, A.U., Schmidt, E.M., Johnson, T., Thorleifsson, G., Luan, J., Donnelly, L.A., Kanoni, S., et al.; CHARGE-EchoGen consortium; CHARGE-HF consortium; and Wellcome Trust Case Control Consortium (2016). The genetics of blood pressure regulation and its target organs from association studies in 342,415 individuals. Nat. Genet. *48*, 1171–1184.
20. Wain, L.V., Vaez, A., Jansen, R., Joehanes, R., van der Most, P.J., Erzurumluoglu, A.M., O'Reilly, P.F., Cabrera, C.P., Warren, H.R., Rose, L.M., et al. (2017). Novel blood pressure locus and gene discovery using genome-wide association study

and expression data sets from blood and the kidney. Hypertension *70*, e4–e19.
21. Davey Smith, G., and Hemani, G. (2014). Mendelian randomization: genetic anchors for causal inference in epidemiological studies. Hum. Mol. Genet. *23* (R1), R89–R98.
22. Matsushita, K., Ballew, S.H., Coresh, J., Arima, H., Ärnlöv, J., Cirillo, M., Ebert, N., Hiramoto, J.S., Kimm, H., Shlipak, M.G., et al.; Chronic Kidney Disease Prognosis Consortium (2017). Measures of chronic kidney disease and risk of incident peripheral artery disease: a collaborative meta-analysis of individual participant data. Lancet Diabetes Endocrinol. *5*, 718–728.
23. Halimi, J.-M., Bonnet, F., Lange, C., Balkau, B., Tichet, J., Marre, M.; and DESIR Study Group (2008). Urinary albumin excretion is a risk factor for diabetes mellitus in men, independently of initial metabolic profile and development of insulin resistance. J. Hypertens. *26*, 2198–2206.
24. Ishani, A., Grandits, G.A., Grimm, R.H., Svendsen, K.H., Collins, A.J., Prineas, R.J., and Neaton, J.D. (2006). Association of single measurements of dipstick proteinuria, estimated glomerular filtration rate, and hematocrit with 25-year incidence of end-stage renal disease in the multiple risk factor intervention trial. J. Am. Soc. Nephrol. *17*, 1444–1452.
25. Ganna, A., Genovese, G., Howrigan, D.P., Byrnes, A., Kurki, M., Zekavat, S.M., Whelan, C.W., Kals, M., Nivard, M.G., Bloemendal, A., et al. (2016). Ultra-rare disruptive and damaging mutations influence educational attainment in the general population. Nat. Neurosci. *19*, 1563–1565.
26. Xu, C., Tachmazidou, I., Walter, K., Ciampi, A., Zeggini, E., Greenwood, C.M.T.; and UK10K Consortium (2014). Estimating genome-wide significance for whole-genome sequencing studies. Genet. Epidemiol. *38*, 281–290.
27. Bulik-Sullivan, B.K., Loh, P.-R., Finucane, H.K., Ripke, S., Yang, J., Patterson, N., Daly, M.J., Price, A.L., Neale, B.M.; and Schizophrenia Working Group of the Psychiatric Genomics Consortium (2015). LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. Nat. Genet. *47*, 291–295.
28. Emdin, C.A., Khera, A.V., Natarajan, P., Klarin, D., Zekavat, S.M., Hsiao, A.J., and Kathiresan, S. (2017). Genetic association of waist-to-hip ratio with cardiometabolic traits, type 2 diabetes, and coronary heart disease. JAMA *317*, 626–634.
29. Burgess, S., Butterworth, A., and Thompson, S.G. (2013). Mendelian randomization analysis with multiple genetic variants using summarized data. Genet. Epidemiol. *37*, 658–665.
30. Yavorska, O.O., and Burgess, S. (2017). MendelianRandomization: an R package for performing Mendelian randomization analyses using summarized data. Int. J. Epidemiol. *46*, 1734–1739.
31. Hemani, G., Bowden, J., Haycock, P.C., Zheng, J., Davis, O., Flach, P., Gaunt, T.R., and Davey Smith, G. (2017). Automating Mendelian randomization through machine learning to construct a putative causal map of the human phenome. bioRxiv. https://doi.org/10.1101/173682.
32. Hemani, G., Tilling, K., and Davey Smith, G. (2017). Orienting the causal relationship between imprecisely measured traits using GWAS summary data. PLoS Genet. *13*, e1007081.
33. Verbanck, M., Chen, C.-Y., Neale, B., and Do, R. (2018). Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. Nat. Genet. *50*, 693–698.
34. Burgess, S., and Bowden, J. (2015). Integrating summarized data from multiple genetic variants in Mendelian randomization: bias and coverage properties of inverse-variance weighted methods. arXiv. https://arxiv.org/abs/1512.04486.
35. Bowden, J., Davey Smith, G., Haycock, P.C., and Burgess, S. (2016). Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. Genet. Epidemiol. *40*, 304–314.
36. Bowden, J., Davey Smith, G., and Burgess, S. (2015). Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. Int. J. Epidemiol. *44*, 512–525.
37. Richmond, R., Wade, K., Corbin, L., Bowden, J., Hemani, G., Timpson, N., and Davey Smith, G. (2017). Investigating the role of insulin in increased adiposity: Bi-directional Mendelian randomization study. bioRxiv. https://doi.org/10.1101/155739.
38. Burgess, S., and Thompson, S.G. (2013). Use of allele scores as instrumental variables for Mendelian randomization. Int. J. Epidemiol. *42*, 1134–1144.
39. Bianchi, S., Bigazzi, R., and Campese, V.M. (1999). Microalbuminuria in essential hypertension: significance, pathophysiology, and therapeutic implications. Am. J. Kidney Dis. *34*, 973–995.
40. Williams, M.E. (2005). Diabetic nephropathy: the proteinuria hypothesis. Am. J. Nephrol. *25*, 77–94.
41. Hemani, G., Zheng, J., Elsworth, B., Wade, K.H., Haberland, V., Baird, D., Laurin, C., Burgess, S., Bowden, J., Langdon, R., et al. (2018). The MR-Base platform supports systematic causal inference across the human phenome. eLife *7*, 68.
42. Lee, S.H., Goddard, M.E., Wray, N.R., and Visscher, P.M. (2012). A better coefficient of determination for genetic profile analysis. Genet. Epidemiol. *36*, 214–224.
43. Hartwig, F.P., and Davies, N.M. (2016). Why internal weights should be avoided (not only) in MR-Egger regression. Int. J. Epidemiol. *45*, 1676–1678.
44. Sarafidis, P.A., Khosla, N., and Bakris, G.L. (2007). Antihypertensive therapy in the presence of proteinuria. Am. J. Kidney Dis. *49*, 12–26.
45. Teumer, A., Tin, A., Sorice, R., Gorski, M., Yeo, N.C., Chu, A.Y., Li, M., Li, Y., Mijatovic, V., Ko, Y.-A., et al.; DCCT/EDIC (2016). Genome-wide association studies identify genetic loci associated with albuminuria in diabetes. Diabetes *65*, 803–817.
46. Ma, T.K.-W., and Szeto, C.-C. (2012). Mineralocorticoid receptor antagonist for renal protection. Ren. Fail. *34*, 810–817.
47. Currie, G., Taylor, A.H.M., Fujita, T., Ohtsu, H., Lindhardt, M., Rossing, P., Boesby, L., Edwards, N.C., Ferro, C.J., Townend, J.N., et al. (2016). Effect of mineralocorticoid receptor antagonists on proteinuria and progression of chronic kidney disease: a systematic review and meta-analysis. BMC Nephrol. *17*, 127.
48. Kruegel, J., Rubel, D., and Gross, O. (2013). Alport syndrome–insights from basic and clinical research. Nat. Rev. Nephrol. *9*, 170–178.
49. Corbin, L.J., Richmond, R.C., Wade, K.H., Burgess, S., Bowden, J., Smith, G.D., and Timpson, N.J. (2016). BMI as a modifiable risk factor for type 2 diabetes: refining and understanding causal estimates using Mendelian randomization. Diabetes *65*, 3002–3007.
50. Burgess, S., Foley, C.N., and Zuber, V. (2018). Inferring causal relationships between risk factors and outcomes from genome-wide association study data. Annu. Rev. Genomics

Hum. Genet. Published online April 25, 2018. 10.1146/annurev-genom-083117-021731.
51. Burgess, S., and Thompson, S.G. (2017). Interpreting findings from Mendelian randomization using the MR-Egger method. Eur. J. Epidemiol. *32*, 377–389.
52. Haycock, P.C., Burgess, S., Wade, K.H., Bowden, J., Relton, C., and Davey Smith, G. (2016). Best (but oft-forgotten) practices: the design, analysis, and interpretation of Mendelian randomization studies. Am. J. Clin. Nutr. *103*, 965–978.
53. Deckert, T., Feldt-Rasmussen, B., Borch-Johnsen, K., Jensen, T., and Kofoed-Enevoldsen, A. (1989). Albuminuria reflects widespread vascular damage. The Steno hypothesis. Diabetologia *32*, 219–226.
54. Clausen, P., Feldt-Rasmussen, B., Jensen, G., and Jensen, J.S. (1999). Endothelial haemostatic factors are associated with progression of urinary albumin excretion in clinically healthy subjects: a 4-year prospective study. Clin. Sci. *97*, 37–43.
55. Stehouwer, C.D.A., and Smulders, Y.M. (2006). Microalbuminuria and risk for cardiovascular disease: Analysis of potential mechanisms. J. Am. Soc. Nephrol. *17*, 2106–2111.
56. Rossi, R., Chiurlia, E., Nuzzo, A., Cioni, E., Origliani, G., and Modena, M.G. (2004). Flow-mediated vasodilation and the risk of developing hypertension in healthy postmenopausal women. J. Am. Coll. Cardiol. *44*, 1636–1640.
57. Sander, M., Chavoshan, B., and Victor, R.G. (1999). A large blood pressure-raising effect of nitric oxide synthase inhibition in humans. Hypertension *33*, 937–942.
58. Cowley, A.W., Jr., and Roman, R.J. (1996). The role of the kidney in hypertension. JAMA *275*, 1581–1589.
59. Coffman, T.M. (2014). The inextricable role of the kidney in hypertension. J. Clin. Invest. *124*, 2341–2347.
60. Goldblatt, H., Lynch, J., Hanzal, R.F., and Summerville, W.W. (1934). Studies on experimental hypertension: I. the production of persistent elevation of systolic blood pressure by means of renal ischemia. J. Exp. Med. *59*, 347–379.
61. Johnson, R.J., Herrera-Acosta, J., Schreiner, G.F., and Rodriguez-Iturbe, B. (2002). Subtle acquired renal injury as a mechanism of salt-sensitive hypertension. N. Engl. J. Med. *346*, 913–923.
62. Strandgaard, S., and Hansen, U. (1986). Hypertension in renal allograft recipients may be conveyed by cadaveric kidneys from donors with subarachnoid haemorrhage. Br. Med. J. (Clin. Res. Ed.) *292*, 1041–1044.
63. Guidi, E., Menghetti, D., Milani, S., Montagnino, G., Palazzi, P., and Bianchi, G. (1996). Hypertension may be transplanted with the kidney in humans: a long-term historical prospective follow-up of recipients grafted with kidneys coming from donors with or without hypertension in their families. J. Am. Soc. Nephrol. *7*, 1131–1138.
64. Rapsomaniki, E., Timmis, A., George, J., Pujades-Rodriguez, M., Shah, A.D., Denaxas, S., White, I.R., Caulfield, M.J., Deanfield, J.E., Smeeth, L., et al. (2014). Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1·25 million people. Lancet *383*, 1899–1911.
65. Lewington, S., Clarke, R., Qizilbash, N., Peto, R., Collins, R.; and Prospective Studies Collaboration (2002). Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet *360*, 1903–1913.
66. Levy, D., Larson, M.G., Vasan, R.S., Kannel, W.B., and Ho, K.K.L. (1996). The progression from hypertension to congestive heart failure. JAMA *275*, 1557–1562.
67. Relton, C.L., and Davey Smith, G. (2012). Two-step epigenetic Mendelian randomization: a strategy for establishing the causal role of epigenetic processes in pathways to disease. Int. J. Epidemiol. *41*, 161–176.
68. Cheng, S., Claggett, B., Correia, A.W., Shah, A.M., Gupta, D.K., Skali, H., Ni, H., Rosamond, W.D., Heiss, G., Folsom, A.R., et al. (2014). Temporal trends in the population attributable risk for cardiovascular disease: the Atherosclerosis Risk in Communities Study. Circulation *130*, 820–828.
69. Bowden, J., Del Greco M, F., Minelli, C., Davey Smith, G., Sheehan, N., and Thompson, J. (2017). A framework for the investigation of pleiotropy in two-sample summary data Mendelian randomization. Stat. Med. *36*, 1783–1802.
70. Bakris, G.L. (2016). Moderately increased albuminuria (microalbuminuria) and cardiovascular disease. UpToDate, https://www.uptodate.com/contents/moderately-increased-albuminuria-microalbuminuria-and-cardiovascular-disease#H220350.

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Supplemental Data

Genetic Association of Albuminuria with Cardiometabolic Disease and Blood Pressure

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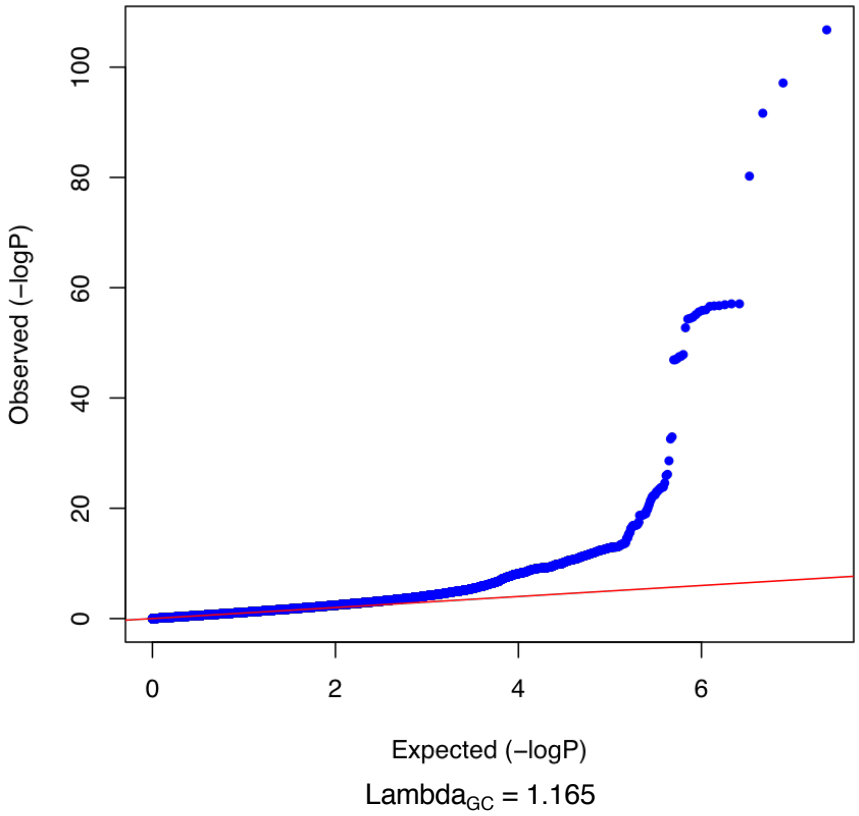


Figure S1. Genomic inflation in genome-wide association study of albuminuria in UK Biobank.

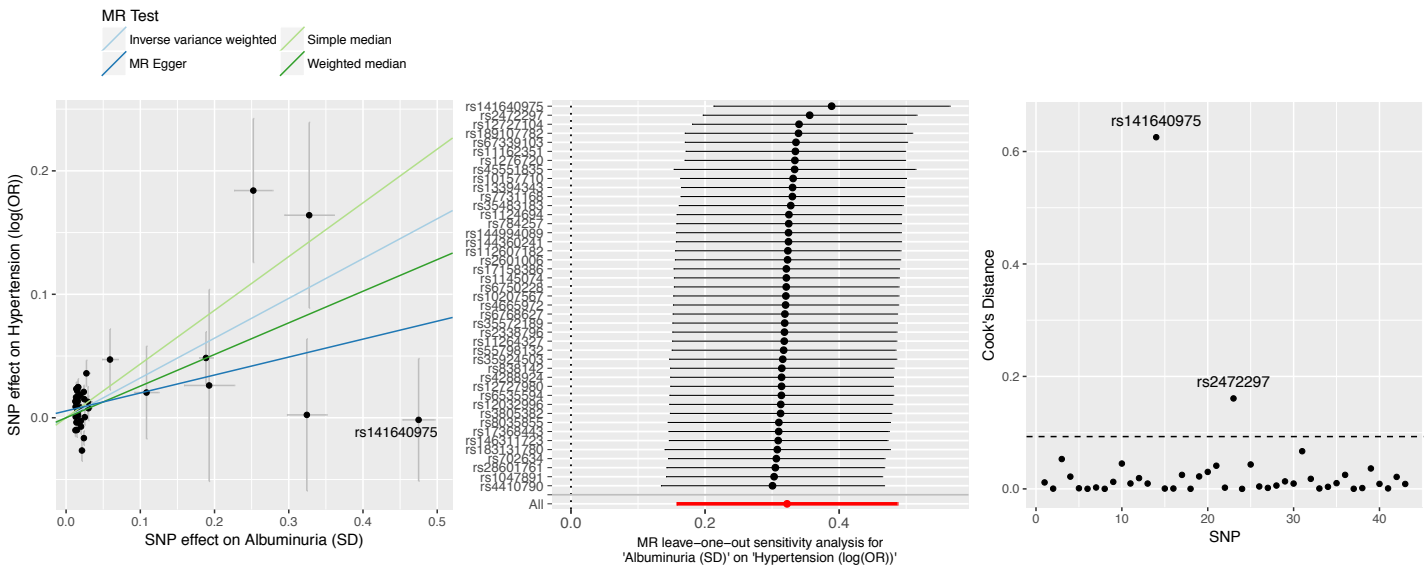
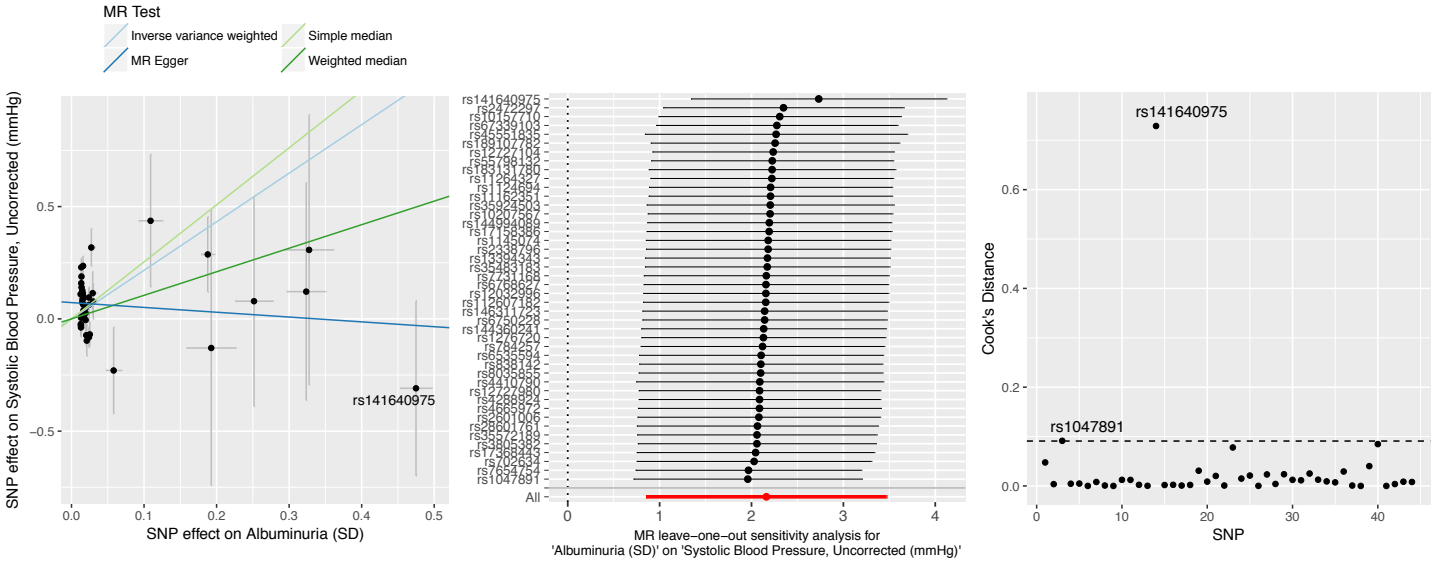


Figure S2. Sensitivity analyses for Mendelian randomization of 43-SNP albuminuria genetic risk score with hypertension in UK Biobank (n = 382500). Left, effect of each SNP on albuminuria and hypertension. Lines indicate trend as analyzed via different Mendelian randomization methods. Middle, Leave-one-out analysis for inverse variance weighted regression. Right, Cook's distance of potential outliers.

Albuminuria → Systolic Blood Pressure



Albuminuria → Diastolic Blood Pressure

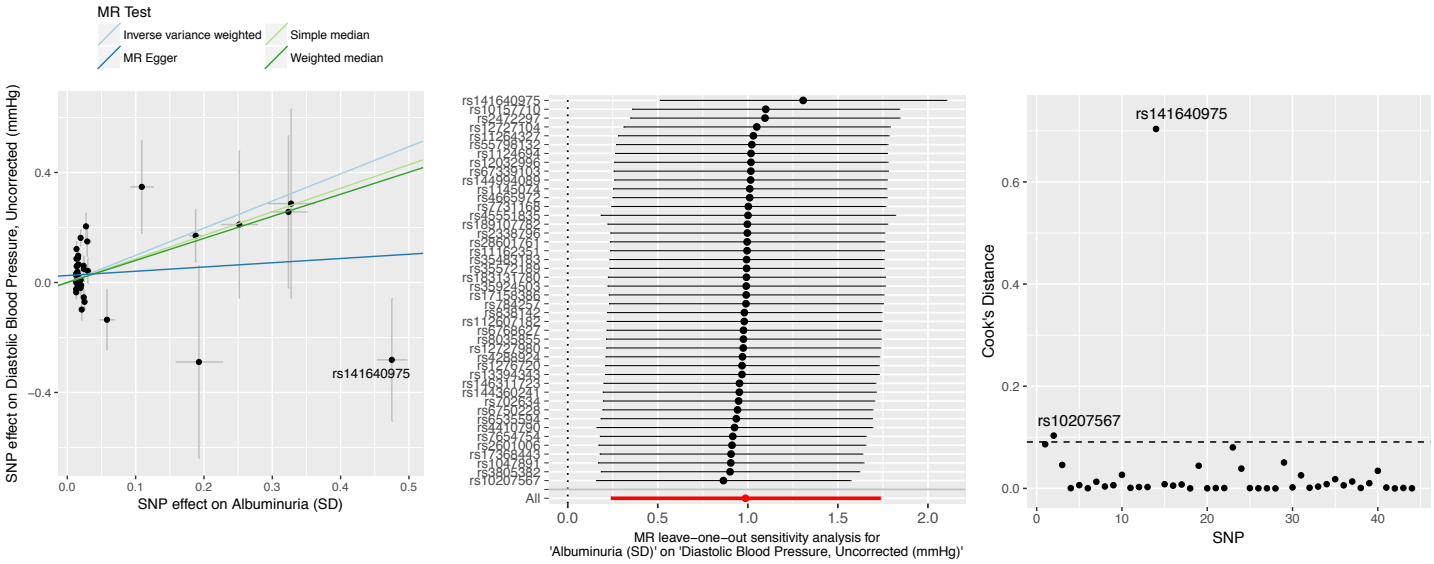
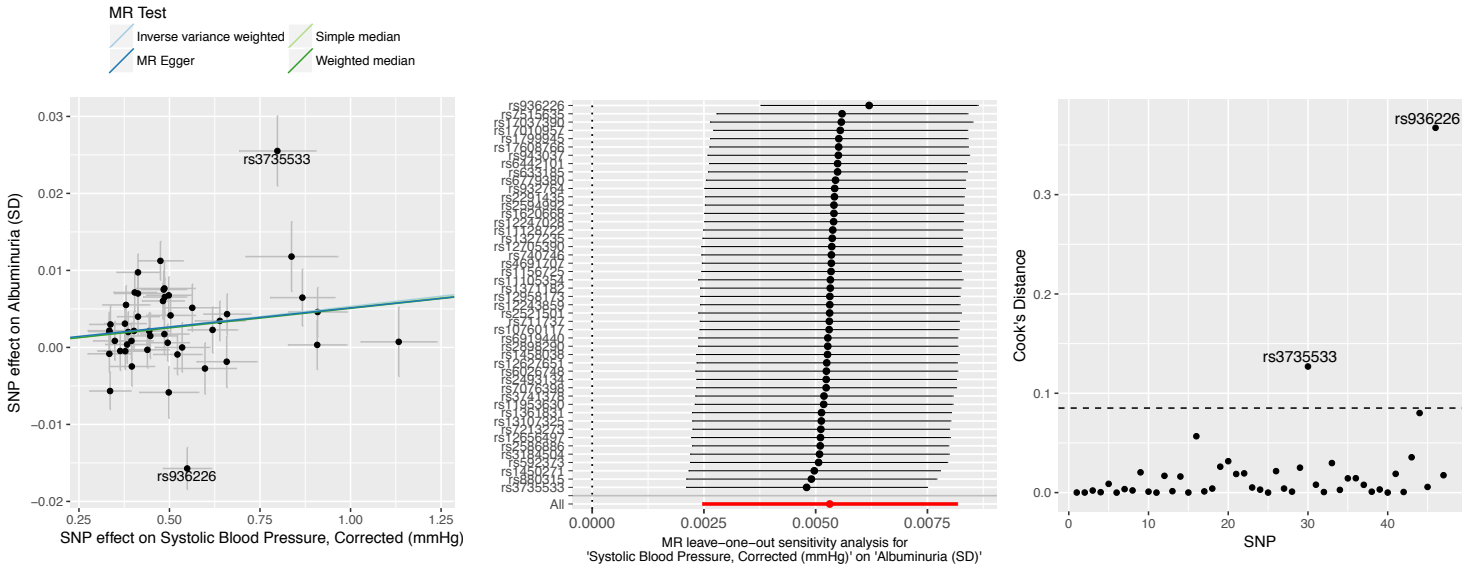


Figure S3. Sensitivity analyses for Mendelian randomization of 44-SNP albuminuria genetic risk score with blood pressure in UK Biobank (n = 381833). Neither blood pressure nor albuminuria were corrected for hypertensive medication use. Left, effect of each SNP on albuminuria and blood pressure. Lines indicate trend as analyzed via different Mendelian randomization methods. Middle, Leave-one-out analysis for inverse variance weighted regression. Right, Cook's distance of potential outliers.

Systolic Blood Pressure → Albuminuria



Diastolic Blood Pressure → Albuminuria

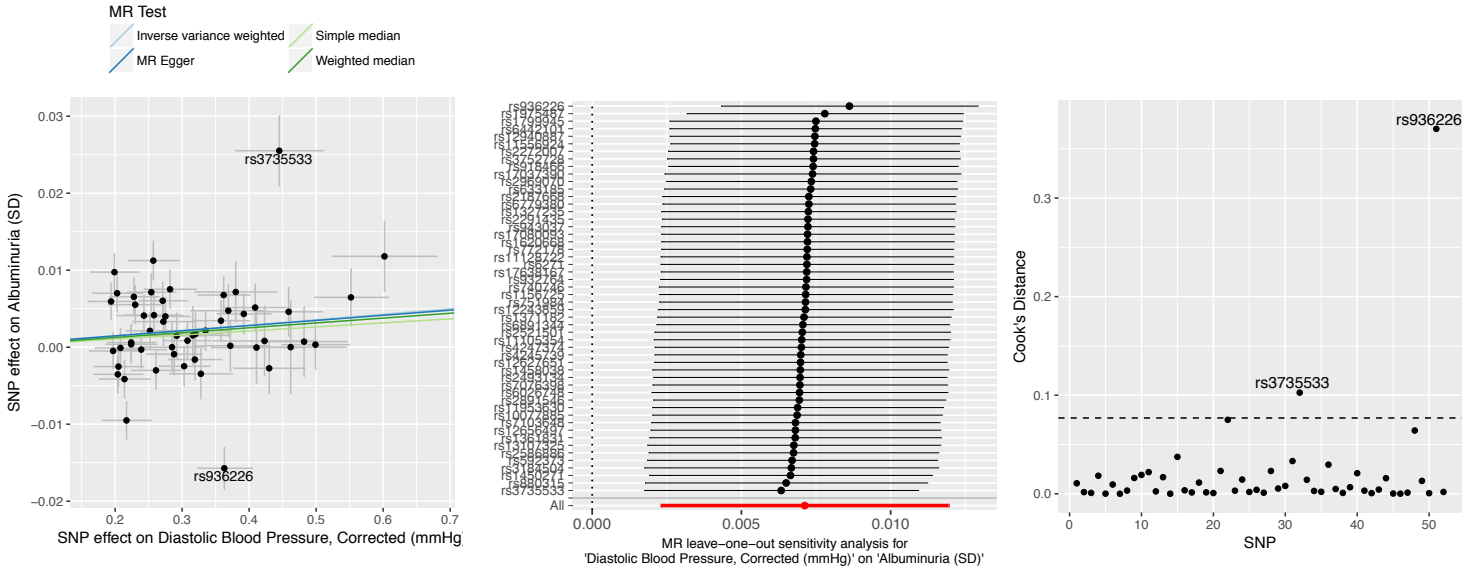
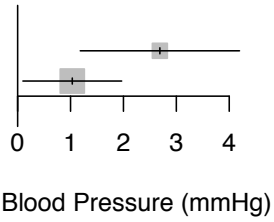


Figure S4. Sensitivity analyses for Mendelian randomization of blood pressure genetic risk scores from ICBP Cardio-MetaboChip (n_{max} = 201529) with albuminuria in UK Biobank (n = 382500). Blood pressures are corrected for hypertensive medication use and include BMI as covariate. Systolic blood pressure genetic risk score comprised of 47 SNPs, diastolic blood pressure genetic risk score comprised of 52 SNPs. Left, effect of each SNP on albuminuria and blood pressure. Lines indicate trend as analyzed via different Mendelian randomization methods. Middle, Leave-one-out analysis for inverse variance weighted regression. Right, Cook's distance of potential outliers.

Exposure	Outcome	SNPs in score	mmHg Blood Pressure [95%CI] per 1–SD Increase in Albuminuria	P value
Albuminuria	Systolic Blood Pressure	37	2.69 [1.18; 4.19]	4.64e−04
Albuminuria	Diastolic Blood Pressure	35	1.03 [0.10; 1.97]	0.030



Exposure	Outcome	SNPs in score	mmHg Blood Pressure [95%CI] per 1–SD Increase in Albuminuria	P value
Albuminuria	Systolic Blood Pressure	22	1.46 [0.53; 2.38]	0.002
Albuminuria	Diastolic Blood Pressure	22	0.67 [0.14; 1.21]	0.013

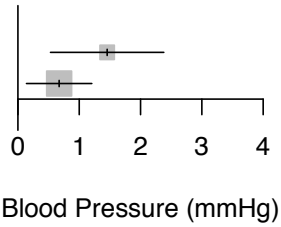
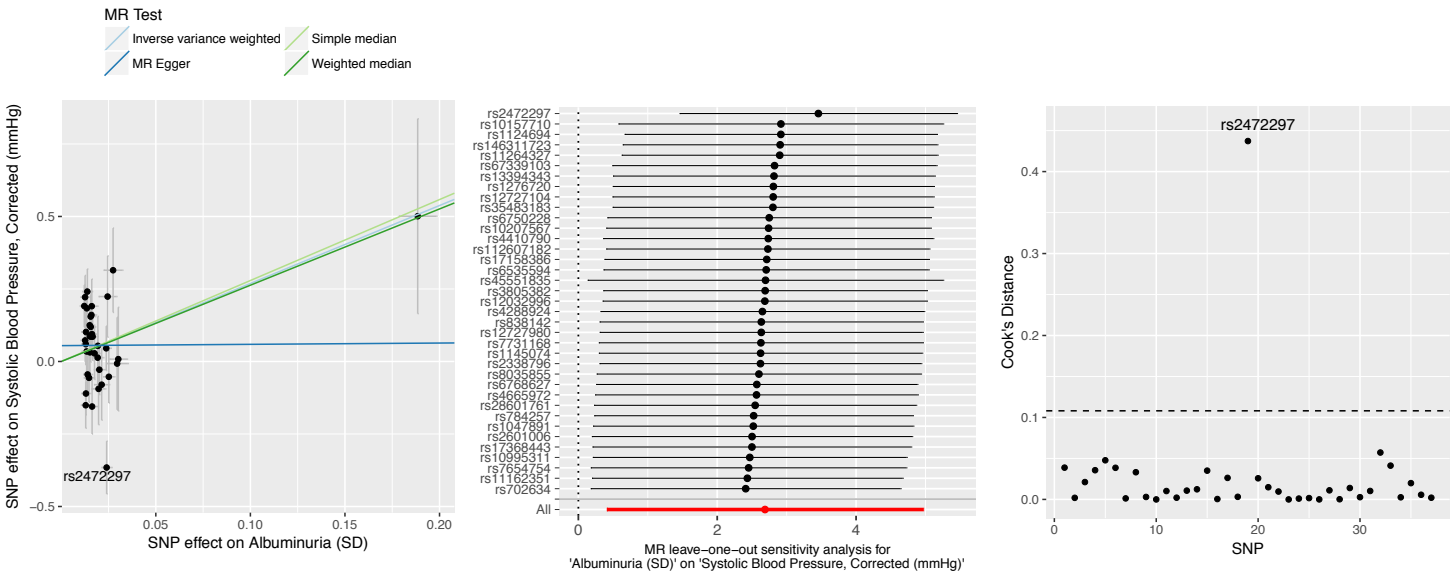


Figure S5. Additional Mendelian randomization analyses of albuminuria genetic risk score from UK Biobank with blood pressure outcomes.

SNPs in score, number of albuminuria variants after applying directional MR Steiger filtering to remove variants acting in the incorrect direction. Results are standardized to 1-SD increase in albuminuria due to the genetic risk score. Top, effect of albuminuria genetic risk score from UK Biobank (n = 382500) on blood pressure corrected for hypertensive medication use and BMI from ICBP 1000G (n_{max} = 150134) via inverse variance weighted fixed effect meta-analysis. Out of 46 albuminuria score SNPs, 38 were available in ICBP. Two sample Mendelian randomization analysis.

Bottom, Association of albuminuria genetic risk with blood pressure without hypertension medication effects in UK Biobank (n = 302687). Two-stage least-squares regression using albuminuria genetic risk score as instrumental variable on blood pressure outcomes in UK Biobank; age + sex + genotyping array + 1st 10 PCs as covariates. Individuals taking hypertensive medications were excluded. Bars indicate 95% confidence intervals for effect on blood pressure.

Albuminuria → Systolic Blood Pressure



Albuminuria → Diastolic Blood Pressure

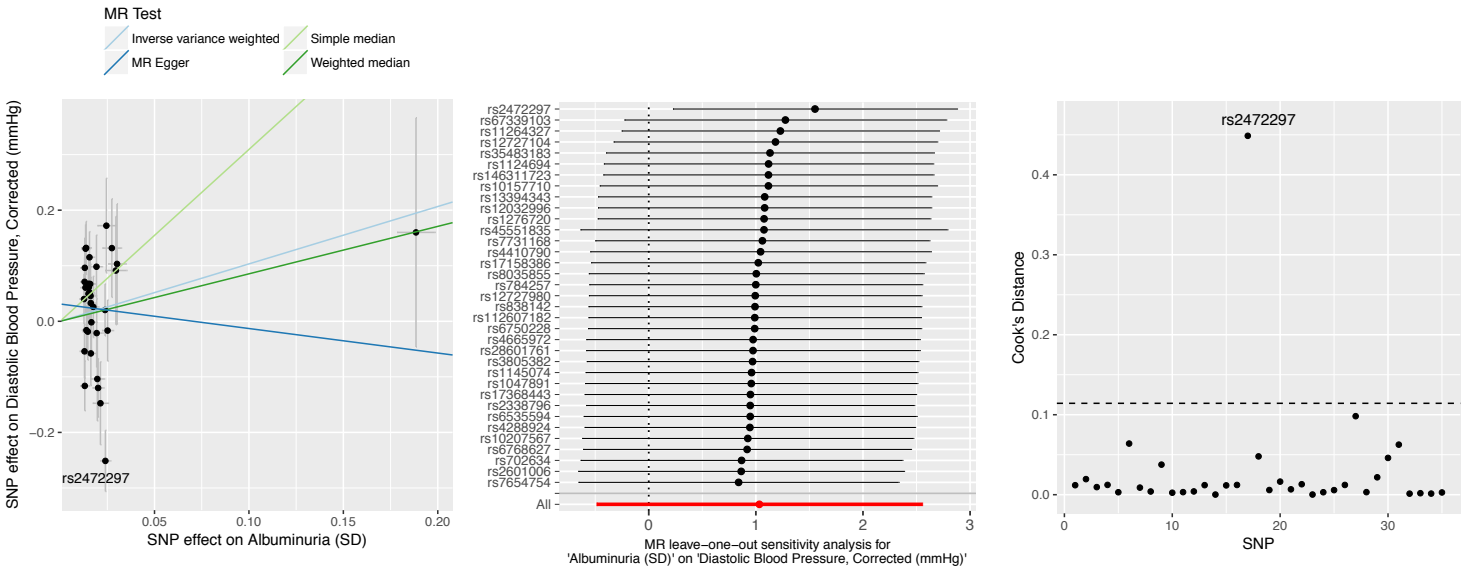
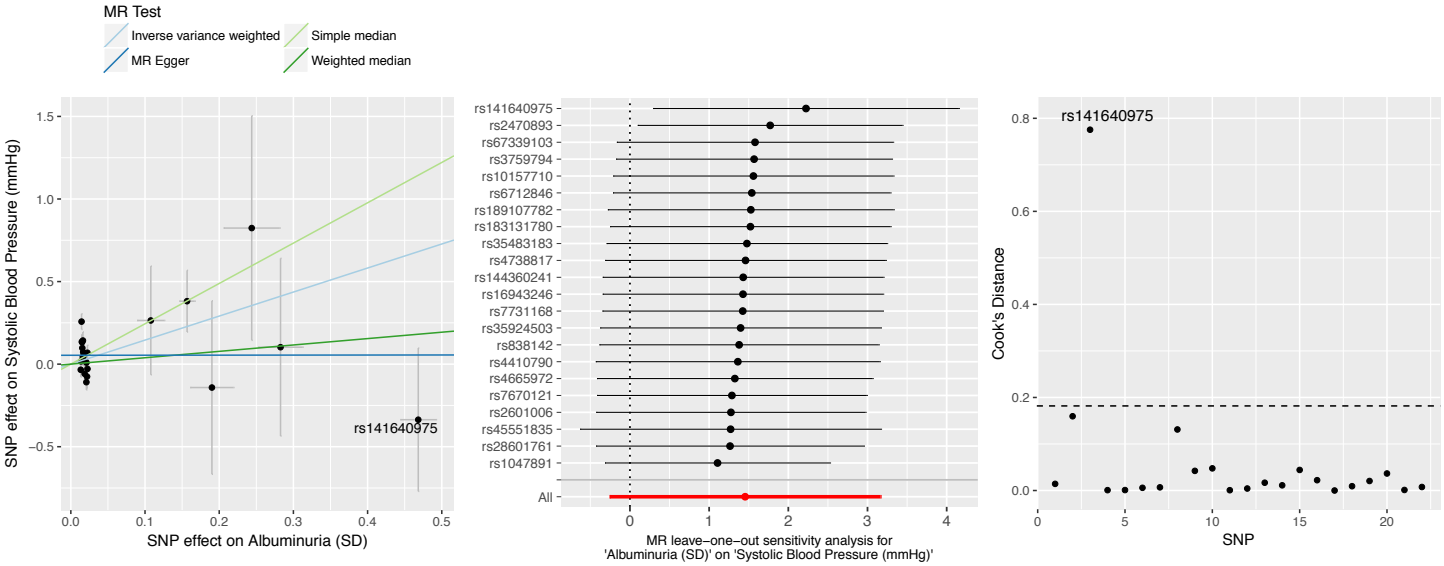


Figure S6. Sensitivity analyses for Mendelian randomization of albuminuria genetic risk score in UK Biobank (n = 382500) with Blood Pressure from ICBP 1000G (n_{max} = 150134). Blood pressures are corrected for hypertensive medication use and include BMI as covariate. Albuminuria genetic risk score comprised of 37 SNPs for systolic blood pressure outcome and 35 SNPs for diastolic blood pressure outcome. Left, effect of each SNP on albuminuria and blood pressure. Lines indicate trend as analyzed via different Mendelian randomization methods. Middle, Leave-one-out analysis for inverse variance weighted regression. Right, Cook's distance of potential outliers.

Albuminuria → Systolic Blood Pressure



Albuminuria → Diastolic Blood Pressure

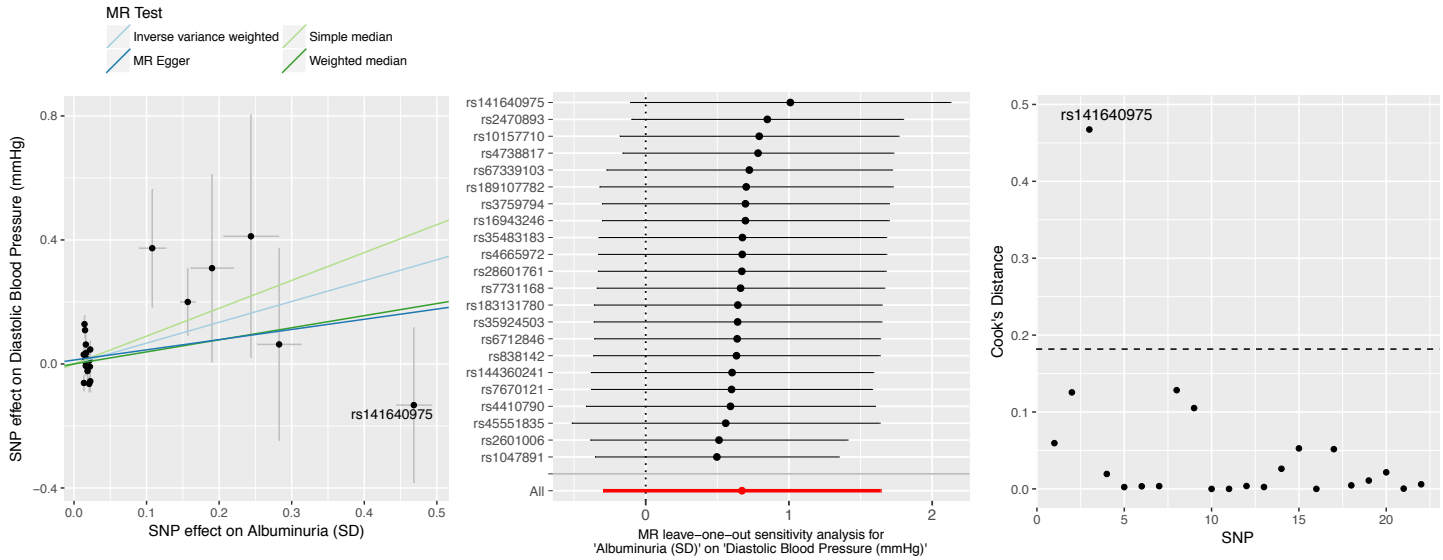


Figure S7. Sensitivity analyses for Mendelian randomization of 22-SNP albuminuria genetic risk score with blood pressure in UK Biobank (n = 302687). Individuals with hypertensive medication use were excluded. Left, effect of each SNP on albuminuria and blood pressure. Lines indicate trend as analyzed via different Mendelian randomization methods. Middle, Leave-one-out analysis for inverse variance weighted regression. Right, Cook's distance of potential outliers.

Table S1. Characteristics of participants in UK Biobank.

No. Individuals	382500
Age, mean (SD), yrs	56.9 (7.9)
Women, No. (%)	204890 (53.6)
UK BiLEVE array, No. (%)	44806 (11.7)
Blood pressure, mean (SD), mmHg*	
Systolic	138.3 (18.6)
Diastolic	82.3 (10.1)
Body mass index, mean (SD)**	27.4 (4.7)
Current smoker, No. (%)***	39051 (10.2)
Urine albumin/creatinine, median (IQR), mg/g	9.8 (6.1-16.5)
Microalbuminuria, No. (%)	54519 (14.3)
Macroalbuminuria, No. (%)	1495 (0.4)
Coronary Artery Disease, No. (%)	32623 (8.5)
Type 2 Diabetes, No. (%)	17619 (4.6)
Hypertension, No. (%)	124345 (32.5)
Chronic Kidney Disease, No. (%)	4885 (1.3)

* Baseline blood pressure was averaged from two measurements taken a few moments apart and was unadjusted for hypertensive medication use. Measurements were missing from 667 and 656 individuals for systolic and diastolic blood pressure, respectively.

** Body mass index was calculated in units of kilograms weight divided by height in meters squared. Baseline measurement was missing for 1029 individuals

*** Excludes 1302 individuals for whom smoking status was not available

Table S2. Cardiometabolic Disease Definitions

Outcome	Definition
All-cause mortality	Death certificate provided by NHS Information Centre or NHS Central Register, Scotland
Coronary artery disease	Myocardial infarction (MI), angina, coronary artery bypass grafting, coronary artery angioplasty or triple heart bypass documented in medical history at time of enrollment by a trained nurse or Hospitalization for or death due to ICD-10 code for acute or subsequent myocardial infarction (I21, I21.0-21.4, I21.9, I22, I22.0, I22.1, I22.8, I22.9, I23, I23.0-23.6, I23.8) or ischaemic or atherosclerotic heart disease (I24, I24.0, I24.1, I24.8, I24.9, I25.1, I25.2, I25.5, I25.6, I25.8, I25.9) or angina (I20, I20.0, I20.1, I20.8, I20.9) or Hospitalization for ICD-9 code due to myocardial infarction, ischaemic heart disease, angina, or coronary atherosclerosis (410, 4109, 411, 4119, 412, 4129, 413, 4139, 4140, 4148, 4149) or Hospitalization for OPCS-4 coded procedure: coronary artery bypass grafting (K40, K40.1-K40.4, K40.8, K40.9, K41, K41.1-41.4, K41.8, K41.9, K42, K42.1-K42.4, K42.8, K42.9, K43, K43.1-43.4, K43.8, K43.9, K44, K44.1, K44.2, K44.8, K44.9, K45.1-45.6, K45.8, K45.9, K46, K46.1-46.5, K46.8, K46.9) or Hospitalization for OPCS-4 coded procedure: coronary angioplasty ± stenting (K49.1-49.4, K49.8, K49.9, K50.1, K50.2, K50.4, K75.1-75.4, K75.8, K75.9)
Stroke	History of stroke, adjudicated centrally by UK Biobank as self-report of stroke during verbal interview with trained nurse or hospitalization for or death due to ICD-10 code I60-64 or ICD-9 code (430, 431, 434, 436) *(*df-42007, *http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=462)*
Peripheral vascular disease	Self-reported history of peripheral vascular disease, arterial embolism, intermittent claudication, leg artery bypass, leg artery angioplasty, or leg amputation during verbal interview with trained nurse or Hospitalization for or death due to ICD-10 code for atherosclerosis of (non-coronary) arteries or peripheral vascular disease (I70.0, I70.00, I70.01, I70.2, I70.20, I70.21, I70.8, I70.80, I70.9, I70.90, I73.8 or I73.9) or Hospitalization for ICD-9 code due to atherosclerosis of arteries or peripheral vascular disease (4400, 4402, 4438, 4439) or Hospitalization for OPCS-4 coded procedure for leg amputation, or leg artery procedure such as bypass, stent or angioplasty (X09.3-09.5, L21.6, L51.3, L51.6, L51.8, L52.1, L52.2, L54.1, L54.4, L54.8, L59.1-L59.8, L60.1, L60.2, L63.1, L63.5, L63.9, L66.7)
Heart failure	Self-reported history of heart failure or cardiomyopathy during verbal interview with trained nurse or Hospitalization for or death due to ICD-10 code for hypertensive heart disease, cardiomyopathy or heart failure (I11.0, I13.0, I13.2, I25.5, I42.0, I42.5, I42.8, I42.9, I50, I50.0, I50.1, I50.9) or Hospitalization for ICD-9 code due to heart failure or other primary cardiomyopathies (4254, 4280, 4281, 4289) Note: Individuals with history of hypertrophic cardiomyopathy during verbal interview with trained nurse, or hospitalization for or death due to ICD-10 code for hypertrophic cardiomyopathy (I42.1, I42.2) were excluded from both case and control status
Type 2 diabetes	Self-reported history of type 2 diabetes during verbal interview with trained nurse or Hospitalization for or death due to ICD-10 code for non-insulin-dependent diabetes mellitus (E11, E11.0-11.9)
Chronic kidney disease	Self-reported history of kidney failure ± dialysis, kidney nephropathy, IgA nephropathy, diabetic nephropathy or kidney transplant during verbal interview with trained nurse or Hospitalization for or death due to ICD-10 code for hypertensive renal disease, chronic renal failure, end stage renal failure or chronic kidney disease (I12.0, I13.1, I13.2, N18, N18.0-18.5, N18.8, N18.9) or Hospitalization for ICD-9 code due to chronic renal failure (585, 5859) or Hospitalization for OPCS-4 coded procedure for kidney transplantation (M01, M01.1-01.5, M01.8, M01.9)
Hypertension	Self-reported history of hypertension, essential hypertension or high blood pressure during verbal interview with trained nurse or Hospitalization for or death due to ICD-10 code for essential hypertension, hypertensive heart disease, hypertensive renal disease, secondary hypertension or renovascular hypertension (I10, I11, I11.0, I11.9, I12, I12.0, I12.9, I13, I13.0-13.2, I15, I15.0-15.2, I15.8, I15.9) or Hospitalization for ICD-9 code due to essential hypertension, hypertensive heart disease, hypertensive renal disease, or secondary hypertension (403, 4030, 4031, 4039, 404, 4040, 4041, 405, 4050, 4051, 4059)

Skin cancer	Self-reported history of skin cancer, malignant melanoma, non-melanoma skin cancer, basal cell carcinoma or squamous cell carcinoma during verbal interview with trained nurse or Hospitalization for or death due to ICD-10 code for malignant melanoma, skin, or malignant neoplasm of skin (C43, C43.2-43.7, C43.9, C44, C44.0-44.9) or Hospitalization for ICD-9 code due to malignant melanoma or malignant neoplasm of skin (172, 1727, 173, 1733, 1735, 1739)
Baseline diabetes	Self-reported history of diabetes, gestational diabetes, type1 diabetes, or type 2 diabetes, insulin medication use, or began insulin within one year of diabetes diagnosis during verbal interview with trained nurse or Hospitalization for or death due to ICD-10 code for insulin-dependent diabetes, non-insulin-dependent diabetes mellitus, malnutrition-realted diabetes or other diabetes (E10, E10.0-10.9, E11, E11.0-11.9, E12, E12.1, E12.8, E12.9, E13, E13.1-13.3, E13.5-13.9, E14, E14.0-14.9) or Hospitalization for ICD-9 code due to diabetes mellitus with mention with complication, diabetes with ketoacidosis or renal, opthalmic or neurological manifestations or unspecified complications (2500, 25000, 25001, 25009, 2501, 25011, 25019, 250302505, 25099)
Baseline hyperlipidemia	Self-reported history of high cholesterol during verbal interview with trained nurse or Hospitalization for or death due to ICD-10 code for hypercholesterolaemia, hyperglyceridaemia, or hyperlipidaemia (E78.0-E78.2, E78.4, E78.5)

Data fields used in definitions: self-report, df-20002, df-20004, df-6150, df-2986, df-6153, df-6177; ICD9, df-41203, df-41205; ICD10, df-41202, df-41204, df-40001, df-40002; OPCS-4 procedures, df-41200, df-41210; death registry, df-40001, df-40002.

Table S3. Comparison of lead albuminuria SNPs in UK Biobank and CKDGen[a]

Lead SNP in UK Biobank	Proxy SNP in CKDGen	R^2 with Proxy	Effect Allele	Noneffect Allele	EAF	Beta (log(mg/g))	SE (log(mg/g))	P value	EAF	Beta (log(mg/g))	SE (log(mg/g))	P value	N	Direction, UKB & CKDGen
Comparison of lead albuminuria SNPs in UK Biobank with CKDGen[b]														
					Lead SNP Effect in UK Biobank				**Lead SNP Effect in CKDGen**					
rs10157710			T	C	0.802	0.019	0.0021	9.69E-20	0.695	0.015	0.0074	**0.045**	54449	same
rs12032996			G	A	0.838	0.015	0.0023	9.33E-11	0.850	0.01	0.0084	0.220	54450	same
rs1276720			T	C	0.745	0.011	0.0019	8.98E-09	0.783	0.007	0.0076	0.360	53465	same
rs17158386			A	G	0.262	0.013	0.0019	3.65E-12	0.215	0.02	0.0093	**0.029**	53465	same
rs2023844			A	G	0.926	0.019	0.0032	1.18E-09	0.945	0.036	0.014	**0.009**	54450	same
rs2472297			T	C	0.267	0.018	0.0019	5.31E-22	0.248	0.002	0.009	0.830	54450	same
rs2601006			C	T	0.657	0.012	0.0018	2.13E-11	0.637	-0.0012	0.0068	0.850	54448	opposite
rs4410790			C	T	0.634	0.018	0.0017	2.63E-25	0.580	0.0012	0.0072	0.860	54450	same
rs6535594			A	G	0.496	0.011	0.0017	7.12E-12	0.487	0.018	0.0065	**0.006**	54390	same
rs702634			A	G	0.692	0.010	0.0018	8.03E-09	0.708	0.0053	0.0063	0.400	54415	same
rs7654754			G	A	0.462	0.010	0.0017	9.96E-10	0.478	0.012	0.006	**0.043**	54382	same
rs8035855			A	G	0.644	0.012	0.0017	1.91E-12	0.694	0.0031	0.0066	0.640	54448	same
					Proxy SNP Effect in UK Biobank				**Proxy SNP Effect in CKDGen**					
rs10207567	rs1971819	0.999	C	G	0.813	0.014	0.0021	1.44E-11	0.800	0.015	0.0076	0.052	53368	same
rs1047891	rs715	0.939	T	C	0.688	0.011	0.0018	1.02E-09	0.708	0.012	0.0085	0.170	43892	same
rs4665972	rs1260326	0.93	T	C	0.393	0.011	0.0017	3.12E-11	0.420	0.022	0.006	**2.70E-04**	54441	same
rs13394343	rs17026396	1	T	C	0.570	0.011	0.0017	4.15E-10	0.553	0.0053	0.006	0.380	54441	same
rs13394343	rs2044474	1	G	A	0.570	0.011	0.0017	4.16E-10	0.515	0.0051	0.006	0.400	54440	same
rs13394343	rs6547620	1	C	T	0.570	0.011	0.0017	3.97E-10	0.537	0.0044	0.0059	0.460	54439	same
rs13394343	rs6739015	1	A	G	0.570	0.011	0.0017	3.96E-10	0.558	0.0052	0.0059	0.380	54441	same
rs7731168	rs11960938	0.962	A	G	0.236	0.012	0.0020	1.06E-09	0.250	-0.0068	0.0075	0.370	53378	opposite
rs67339103	rs7915302	0.955	C	T	0.219	0.015	0.0020	2.39E-13	0.230	0.0044	0.0074	0.550	54450	same
rs17368443	rs17295800	0.996	C	T	0.061	0.020	0.0035	6.40E-09	0.062	0.015	0.013	0.250	54450	same
rs17368443	rs2920154	0.996	C	T	0.061	0.020	0.0035	4.98E-09	0.071	0.022	0.014	0.110	53465	same
rs4288924	rs10873217	0.999	G	A	0.480	0.010	0.0017	6.48E-09	0.504	0.0079	0.006	0.190	54399	same
rs1145074	rs1153849	0.997	G	A	0.745	0.011	0.0019	3.58E-09	0.790	0.01	0.0066	0.130	54450	same
rs1145074	rs1346266	0.997	G	T	0.745	0.011	0.0019	3.53E-09	0.797	0.0073	0.0072	0.310	44877	same
rs838142	rs4021	0.995	A	G	0.723	0.012	0.0019	6.25E-10	0.761	0.025	0.0086	**0.004**	53465	same
Comparison of lead albuminuria SNP in CKDGen with UK Biobank														
					Proxy SNP Effect in UK Biobank				**Proxy SNP Effect in CKDGen**					
rs45551835	rs10795433[c]	0.067	C	A	0.152	0.024	0.002	1.37E-24	0.125	0.061	0.010	**1.80E-10**	54450	same

EAF, Effect Allele Frequency

[a] Effects on albuminuria were calculated in up to 54450 individuals in the CKDGen study (Teumer *et al* 2016. Diabetes. PMID 26631737).

[b] For proxy SNPs, SNPs with largest $R^2 > 0.8$ calculated via *clump/PLINK1.9* in UK Biobank are shown.

[c] This SNP was the top reported SNP in CKDGen.[a] It is included in the rs45551835 locus in UK Biobank results via the $R^2 > 0.01$ locus definition; therefore, linkage disequilibrium with other UK Biobank SNPs was not determined.

Table S4. Forty-six variants included in Mendelian randomization analyses.

Lead variant	Nearest Gene(s)	Description	Chr	Position (hg19)	Effect Allele	Noneffect Allele	EAF	Beta (log(mg/g))	SE (log (mg/g))	P value
rs12032996	*PHC2-ZSCAN20*	Intergenic	1	33920586	G	A	0.838	0.01463	0.00226	9.33E-11
rs10157710	*FOXD2-TRABD2B*	Intergenic	1	47961691	T	C	0.802	0.019	0.00209	9.69E-20
rs11162351	*AK5*	Intronic	1	77944732	C	G	0.602	0.00952	0.0017	2.20E-08
rs11264327	*EFNA3-EFNA1*	Intergenic	1	155095107	A	G	0.399	0.00987	0.00171	7.03E-09
rs12727104	*FMO4-PRRC2C*	Intergenic	1	171423167	G	A	0.905	0.01614	0.00284	1.37E-08
rs12727980	*NR5A2-LINC00862*	Intergenic	1	200259095	C	T	0.423	0.00957	0.0017	1.68E-08
rs4665972	*SNX17*	Intronic	2	27598097	T	C	0.393	0.01176	0.00172	6.96E-12
rs6750228	*LOC730100*	Intronic	2	51312124	A	T	0.047	0.02232	0.00398	2.07E-08
rs13394343	*SH2D6-MAT2A/PARTICL*	Intergenic	2	85754342	C	A	0.57	0.01053	0.00168	3.86E-10
rs10207567	*ICA1L*	Intronic	2	203714973	C	G	0.813	0.01455	0.00214	1.00E-11
rs1047891	*CPS1*	Missense	2	211540507	C	A	0.684	0.01205	0.00179	1.71E-11
rs183131780	*MIR548AR-LOC646736*	Intergenic	2	226684886	T	C	0.002	0.19055	0.01959	2.33E-22
rs35483183	*COL4A4*	Intronic	2	227876687	A	G	0.123	0.0149	0.00255	5.19E-09
rs35924503	*SPHKAP-PID1*	Intergenic	2	229131286	C	T	0.001	0.24742	0.02518	8.68E-23
rs6768627	*MYL3*	Downstream Variant	3	46895376	T	C	0.069	0.01852	0.0033	2.06E-08
rs112607182	*PRKCI*	Downstream Variant	3	170027407	T	C	0.077	0.02279	0.00327	3.39E-12
rs3805382	*NMU*	Intronic	4	56471551	A	G	0.711	0.01015	0.00184	3.71E-08
rs7654754	*SHROOM3*	Intronic	4	77409795	G	A	0.462	0.0102	0.00167	9.96E-10
rs6535594	*NR3C2*	Intronic	4	149132756	A	G	0.496	0.01146	0.00167	7.12E-12
rs189107782	*LINC01262-FRG1*	Intergenic	4	190729009	T	C	0.002	0.24502	0.02026	1.12E-33
rs702634	*ARL15*	Intronic	5	53271420	A	G	0.692	0.01042	0.00181	8.03E-09
rs7731168	*CWC27*	Intronic	5	64296471	C	G	0.233	0.01253	0.00197	2.19E-10
rs4410790	*AGR3-AHR*	Intergenic	7	17284577	C	T	0.634	0.01798	0.00173	2.63E-25
rs2023844	*HOTTIP*	Intronic	7	27243238	A	G	0.926	0.01934	0.00318	1.18E-09
rs17158386	*WIPF3-DPY19L2P3*	Intergenic	7	29805361	A	G	0.262	0.0133	0.00191	3.65E-12
rs55798132	*LOC101927815-CSMD1*	Intergenic	8	2666143	G	A	0.989	0.04472	0.00803	2.53E-08
rs28601761	*TRIB1-LINC00861*	Intergenic	8	126500031	C	G	0.579	0.01136	0.00171	2.81E-11
rs144994089	*AQP7*	Missense	9	33385156	T	C	0.001	0.1456	0.02562	1.32E-08
rs45551835	*CUBN*	Missense	10	16932384	A	G	0.014	0.14237	0.00698	2.28E-92
rs144360241	*CUBN*	Missense	10	16967417	C	T	0.005	0.08186	0.01234	3.31E-11
rs1276720	*CUBN*	Intronic	10	16971426	T	C	0.745	0.01109	0.00193	8.98E-09
rs141640975	*CUBN*	Missense	10	16992011	A	G	0.003	0.35876	0.01629	1.75E-107
rs10995311	*ADO*	Missense	10	64564934	C	G	0.553	0.00921	0.00168	4.49E-08
rs67339103	*C10orf11*	Intronic	10	77893686	A	G	0.212	0.01522	0.00205	1.07E-13
rs17368443	*SBF2*	Intronic	11	10296836	C	G	0.061	0.02071	0.00348	2.58E-09
rs1124694	*ZBED5AS1-GALNT18*	Intergenic	11	11098676	G	A	0.331	0.00977	0.00178	4.43E-08
rs2601006	*CCT2*	5' UTR Variant	12	69979517	C	T	0.657	0.01176	0.00176	2.13E-11
rs4288924	*ZFP36L1-ACTN1*	Intergenic	14	69302399	G	A	0.48	0.0098	0.00168	5.66E-09
rs8035855	*MAPKBP1*	Intronic	15	42077961	A	G	0.644	0.01227	0.00174	1.91E-12
rs1145074	*SPATA5L1*	Intronic	15	45703824	T	A	0.745	0.0114	0.00191	2.41E-09
rs146311723	*USP3*	Intronic	15	63804507	C	T	0.174	0.01231	0.0022	2.25E-08
rs2472297	*CYP1A2-CYP1A1*	Intergenic	15	75027880	T	C	0.267	0.01812	0.00188	5.31E-22
rs2338796	*FBXL20*	Intronic	17	37555627	A	G	0.67	0.00989	0.00178	2.59E-08
rs35572189	*BAHCC1*	Missense	17	79419025	G	A	0.638	0.01051	0.00174	1.44E-09
rs784257	*TCF4-LINC01415*	Intergenic	18	53397199	T	C	0.187	0.01218	0.00215	1.37E-08
rs838142	*FUT1*	3' UTR Variant	19	49252151	A	G	0.723	0.01174	0.00187	3.13E-10

Chr, chromosome; EAF, effect allele frequency. For intergenic loci, nearest upstream and downstream RefSeq genes are indicated. Nearest gene should not be taken as evidence of causal gene. Description, most-severe consequence of nearest RefSeq gene.

Table S5. Association of albuminuria genetic risk score with measured albuminuria in ARIC and Framingham Heart Study.

Cohort	Beta (log(mg/g) Albuminuria per SD predicted Albuminuria)	Std. Error (log(mg/g) Albuminuria per SD predicted Albuminuria)	P value
UK Biobank (reference)	0.742	0.014	< 1E-300
ARIC	0.788	0.198	6.72E-05
Framingham Heart Study	0.692	0.197	4.38E-04

Table S6. Sensitivity analyses for Mendelian randomization of restricted albuminuria genetic risk score with hypertension or blood pressure in UK Biobank.

Sample Size[a]	Number of Hypertension Cases	Number of Controls	Exposure	Outcome	SNPs in score	Method	Beta (log(OR)/SD Albuminuria)	SE (log(OR)/SD Albuminuria)	P value	Cochran's Q	Cochran P value	MR-PRESSO Global RSS_{obs}	MR-PRESSO Global P value
382500	124345	258155	Albuminuria	Hypertension	31	Two-Stage Least-Squares	0.313	0.046	1.01E-11				
382500	124345	258155	Albuminuria	Hypertension	31	IVW Random Effects	0.314	0.091	0.001	118	2E-12	128	< 1E-5
382500	124345	258155	Albuminuria	Hypertension	31	Simple Median	0.433	0.103	2.80E-05				
382500	124345	258155	Albuminuria	Hypertension	31	Weighted Median	0.256	0.088	0.003				
382500	124345	258155	Albuminuria	Hypertension	31	Egger Slope	0.134	0.126	0.289				
382500	124345	258155	Albuminuria	Hypertension	31	Egger Intercept	0.006	0.003	0.047				

Sample Size, Exposure[b]	Sample Size, Outcome[c]	Exposure	Outcome	SNPs in score	Method	Beta (mmHg/SD Albuminuria)	SE (mmHg/SD Albuminuria)	P value	Cochran's Q	Cochran P value	MR-PRESSO Global RSS_{obs}	MR-PRESSO Global P value
382500	381833	Albuminuria	SBP, Uncorrected	32	Two-Stage Least-Squares	2.191	0.361	1.26E-09				
382500	381833	Albuminuria	SBP, Uncorrected	32	IVW Random Effects	2.187	0.771	0.005	142	4E-16	154	< 1E-5
382500	381833	Albuminuria	SBP, Uncorrected	32	Simple Median	2.539	0.778	0.001				
382500	381833	Albuminuria	SBP, Uncorrected	32	Weighted Median	1.306	0.641	0.042				
382500	381833	Albuminuria	SBP, Uncorrected	32	Egger Slope	-0.187	0.974	0.847				
382500	381833	Albuminuria	SBP, Uncorrected	32	Egger Intercept	0.080	0.024	0.001				
382500	381833	Albuminuria	DBP, Uncorrected	32	Two-Stage Least-Squares	0.974	0.207	2.62E-06				
382500	381833	Albuminuria	DBP, Uncorrected	32	IVW Random Effects	0.972	0.414	0.019	125	3E-13	136	< 1E-5
382500	381833	Albuminuria	DBP, Uncorrected	32	Simple Median	0.889	0.385	0.021				
382500	381833	Albuminuria	DBP, Uncorrected	32	Weighted Median	0.830	0.364	0.022				
382500	381833	Albuminuria	DBP, Uncorrected	32	Egger Slope	0.207	0.582	0.722				
382500	381833	Albuminuria	DBP, Uncorrected	32	Egger Intercept	0.026	0.014	0.071				

Restricted albuminuria genetic risk composed of SNPs with $p < 9E-9$ for association with albuminuria + directional MR Steiger filtering (filtered to SNPs with R^2 exposure > R^2 outcome)
SBP, systolic blood pressure; DBP, diastolic blood pressure. Uncorrected, not adjusted for hypertensive medication use.
[a] Effects of SNPs on albuminuria and hypertension were calculated in 382500 individuals in UK Biobank
[b] Effects of SNPs on albuminuria were calculated in 382500 individuals in UK Biobank
[c] 381833 individuals in UK Biobank had blood pressure measurements

Table S7. Sensitivity analyses for Mendelian randomization of albuminuria genetic risk score with hypertension in UK Biobank.

Sample Size[a]	Number of Hypertension Cases	Number of Controls	Exposure	Outcome	SNPs in score	Cook's distance of outlier removed	Method	Beta (log(OR)/SD Albuminuria)	SE (log(OR)/SD Albuminuria)	P value	Cochran's Q	Cochran P value	MR-PRESSO Global RSS_{obs}	MR-PRESSO Global P value
Directional MR Steiger filtering														
382500	124345	258155	Albuminuria	Hypertension	43	NA	Two-Stage Least-Squares	0.321	0.043	7.01E-14				
382500	124345	258155	Albuminuria	Hypertension	43, unweighted allele score	NA	Two-Stage Least-Squares	0.463	0.058	1.17E-15				
382500	124345	258155	Albuminuria	Hypertension	43	NA	IVW Random Effects	0.322	0.084	1.25E-04	160	9E-16	171	< 1E-05
382500	124345	258155	Albuminuria	Hypertension	43	NA	Simple Median	0.435	0.093	2.91E-06				
382500	124345	258155	Albuminuria	Hypertension	43	NA	Weighted Median	0.257	0.087	0.003				
382500	124345	258155	Albuminuria	Hypertension	43	NA	Egger Slope	0.145	0.123	0.235				
382500	124345	258155	Albuminuria	Hypertension	43	NA	Egger Intercept	0.006	0.003	0.053				
Directional MR Steiger filtering + Outlier removed														
382500	124345	258155	Albuminuria	Hypertension	42	0.63	Two-Stage Least-Squares	0.389	0.047	2.65E-16				
382500	124345	258155	Albuminuria	Hypertension	42	0.63	IVW Random Effects	0.389	0.090	1.50E-05	149	4E-14	156	< 1E-05
382500	124345	258155	Albuminuria	Hypertension	42	0.63	Simple Median	0.446	0.091	9.92E-07				
382500	124345	258155	Albuminuria	Hypertension	42	0.63	Weighted Median	0.276	0.084	0.001				
382500	124345	258155	Albuminuria	Hypertension	42	0.63	Egger Slope	0.238	0.153	0.120				
382500	124345	258155	Albuminuria	Hypertension	42	0.63	Egger Intercept	0.004	0.003	0.222				
Significant directional MR Steiger filtering														
382500	124345	258155	Albuminuria	Hypertension	35	NA	Two-Stage Least-Squares	0.235	0.045	2.00E-07				
382500	124345	258155	Albuminuria	Hypertension	35	NA	IVW Random Effects	0.236	0.071	9.13E-04	84	4E-06	91	< 1E-05
382500	124345	258155	Albuminuria	Hypertension	35	NA	Simple Median	0.385	0.089	1.66E-05				
382500	124345	258155	Albuminuria	Hypertension	35	NA	Weighted Median	0.256	0.082	0.002				
382500	124345	258155	Albuminuria	Hypertension	35	NA	Egger Slope	0.177	0.103	0.087				
382500	124345	258155	Albuminuria	Hypertension	35	NA	Egger Intercept	0.002	0.003	0.421				
Significant directional MR Steiger filtering + Outlier removed														
382500	124345	258155	Albuminuria	Hypertension	34	0.61	Two-Stage Least-Squares	0.291	0.051	8.17E-09				
382500	124345	258155	Albuminuria	Hypertension	34	0.61	IVW Random Effects	0.292	0.077	1.54E-04	78	2E-05	83	2E-05
382500	124345	258155	Albuminuria	Hypertension	34	0.61	Simple Median	0.397	0.089	7.43E-06				
382500	124345	258155	Albuminuria	Hypertension	34	0.61	Weighted Median	0.266	0.090	0.003				
382500	124345	258155	Albuminuria	Hypertension	34	0.61	Egger Slope	0.285	0.127	0.025				
382500	124345	258155	Albuminuria	Hypertension	34	0.61	Egger Intercept	2.02E-04	0.003	0.944				

Directional MR Steiger filtering: filtered to SNPs with R^2 exposure > R^2 outcome

Significant directional MR Steiger filtering: filtered to SNPs with R^2 exposure > R^2 outcome AND Steiger P value < 0.05

[a] Effects of SNPs on albuminuria and hypertension were calculated in 382500 individuals in UK Biobank

Table S8. Sensitivity analyses for Mendelian randomization of albuminuria genetic risk score with blood pressure in UK Biobank.

Sample Size, Exposure[a]	Sample Size, Outcome[b]	Exposure	Outcome	SNPs in score	Cook's distance of outlier removed	Method	Beta (mmHg/SD Albuminuria)	SE (mmHg/SD Albuminuria)	P value	Cochran's Q	Cochran P value	MR-PRESSO Global RSS_{obs}	MR-PRESSO Global P value
Systolic Blood Pressure													
Directional MR Steiger filtering													
382500	381833	Albuminuria	SBP, Uncorrected	44	NA	Two-Stage Least-Squares	2.165	0.336	1.22E-10				
382500	381833	Albuminuria	SBP, Uncorrected	44, unweighted allele score	NA	Two-Stage Least-Squares	3.988	0.445	3.22E-19				
382500	381833	Albuminuria	SBP, Uncorrected	44	NA	IVW Random Effects	2.160	0.666	0.001	169	7E-17	180	< 1E-05
382500	381833	Albuminuria	SBP, Uncorrected	44	NA	Simple Median	2.539	0.689	2.29E-04				
382500	381833	Albuminuria	SBP, Uncorrected	44	NA	Weighted Median	1.306	0.621	0.035				
382500	381833	Albuminuria	SBP, Uncorrected	44	NA	Egger Slope	-0.209	0.900	0.817				
382500	381833	Albuminuria	SBP, Uncorrected	44	NA	Egger Intercept	0.072	0.021	4.65E-04				
Directional MR Steiger filtering + Outlier removed													
382500	381833	Albuminuria	SBP, Uncorrected	43	0.72	Two-Stage Least-Squares	2.734	0.369	1.32E-13				
382500	381833	Albuminuria	SBP, Uncorrected	43	0.72	IVW Random Effects	2.728	0.707	1.15E-04	155	7E-15	162	< 1E-05
382500	381833	Albuminuria	SBP, Uncorrected	43	0.72	Simple Median	2.553	0.716	3.67E-04				
382500	381833	Albuminuria	SBP, Uncorrected	43	0.72	Weighted Median	1.530	0.665	0.021				
382500	381833	Albuminuria	SBP, Uncorrected	43	0.72	Egger Slope	0.137	1.134	0.904				
382500	381833	Albuminuria	SBP, Uncorrected	43	0.72	Egger Intercept	0.067	0.024	0.005				
Significant directional MR Steiger filtering													
382500	381833	Albuminuria	SBP, Uncorrected	39	NA	Two-Stage Least-Squares	1.375	0.348	7.8E-05				
382500	381833	Albuminuria	SBP, Uncorrected	39	NA	IVW Random Effects	1.372	0.518	0.008	85	2.0E-05	91	3.0E-05
382500	381833	Albuminuria	SBP, Uncorrected	39	NA	Simple Median	1.523	0.660	0.021				
382500	381833	Albuminuria	SBP, Uncorrected	39	NA	Weighted Median	0.928	0.592	0.117				
382500	381833	Albuminuria	SBP, Uncorrected	39	NA	Egger Slope	-0.037	0.709	0.958				
382500	381833	Albuminuria	SBP, Uncorrected	39	NA	Egger Intercept	0.046	0.017	0.007				
Significant directional MR Steiger filtering + Outlier removed													
382500	381833	Albuminuria	SBP, Uncorrected	38	0.73	Two-Stage Least-Squares	1.818	0.385	2.26E-06				
382500	381833	Albuminuria	SBP, Uncorrected	38	0.73	IVW Random Effects	1.814	0.554	0.001	77	0.00011	81	0.00015
382500	381833	Albuminuria	SBP, Uncorrected	38	0.73	Simple Median	1.863	0.652	0.004				
382500	381833	Albuminuria	SBP, Uncorrected	38	0.73	Weighted Median	1.439	0.673	0.032				
382500	381833	Albuminuria	SBP, Uncorrected	38	0.73	Egger Slope	0.382	0.892	0.669				
382500	381833	Albuminuria	SBP, Uncorrected	38	0.73	Egger Intercept	0.039	0.019	0.046				
Diastolic Blood Pressure													
Directional MR Steiger filtering													
382500	381833	Albuminuria	DBP, Uncorrected	44	NA	Two-Stage Least-Squares	0.986	0.193	3.40E-07				
382500	381833	Albuminuria	DBP, Uncorrected	44, unweighted allele score	NA	Two-Stage Least-Squares	1.627	0.256	1.94E-10				
382500	381833	Albuminuria	DBP, Uncorrected	44	NA	IVW Random Effects	0.984	0.381	0.010	169	6E-17	180	< 1E-05
382500	381833	Albuminuria	DBP, Uncorrected	44	NA	Simple Median	0.856	0.354	0.016				
382500	381833	Albuminuria	DBP, Uncorrected	44	NA	Weighted Median	0.819	0.352	0.020				
382500	381833	Albuminuria	DBP, Uncorrected	44	NA	Egger Slope	0.150	0.559	0.788				
382500	381833	Albuminuria	DBP, Uncorrected	44	NA	Egger Intercept	0.025	0.013	0.048				

Directional MR Steiger filtering + Outlier removed													
382500	381833	Albuminuria	DBP, Uncorrected	43	0.70	Two-Stage Least-Squares	1.305	0.212	8.08E-10				
382500	381833	Albuminuria	DBP, Uncorrected	43	0.70	IVW Random Effects	1.302	0.405	0.001	156	5E-15	162	< 1E-05
382500	381833	Albuminuria	DBP, Uncorrected	43	0.70	Simple Median	0.876	0.366	0.017				
382500	381833	Albuminuria	DBP, Uncorrected	43	0.70	Weighted Median	0.886	0.367	0.016				
382500	381833	Albuminuria	DBP, Uncorrected	43	0.70	Egger Slope	0.613	0.697	0.379				
382500	381833	Albuminuria	DBP, Uncorrected	43	0.70	Egger Intercept	0.018	0.015	0.226				
Significant directional MR Steiger filtering													
382500	381833	Albuminuria	DBP, Uncorrected	40	NA	Two-Stage Least-Squares	0.613	0.199	0.002				
382500	381833	Albuminuria	DBP, Uncorrected	40	NA	IVW Random Effects	0.611	0.314	0.051	99	4E-07	106	< 1E-05
382500	381833	Albuminuria	DBP, Uncorrected	40	NA	Simple Median	0.772	0.349	0.027				
382500	381833	Albuminuria	DBP, Uncorrected	40	NA	Weighted Median	0.791	0.343	0.021				
382500	381833	Albuminuria	DBP, Uncorrected	40	NA	Egger Slope	0.148	0.461	0.749				
382500	381833	Albuminuria	DBP, Uncorrected	40	NA	Egger Intercept	0.015	0.011	0.173				
Significant directional MR Steiger filtering + Outlier removed													
382500	381833	Albuminuria	DBP, Uncorrected	39	0.69	Two-Stage Least-Squares	0.873	0.219	6.93E-05				
382500	381833	Albuminuria	DBP, Uncorrected	39	0.68	IVW Random Effects	0.870	0.336	0.010	91	3E-06	95	< 1E-05
382500	381833	Albuminuria	DBP, Uncorrected	39	0.68	Simple Median	0.791	0.357	0.027				
382500	381833	Albuminuria	DBP, Uncorrected	39	0.68	Weighted Median	0.879	0.371	0.018				
382500	381833	Albuminuria	DBP, Uncorrected	39	0.68	Egger Slope	0.602	0.571	0.292				
382500	381833	Albuminuria	DBP, Uncorrected	39	0.68	Egger Intercept	0.007	0.012	0.559				

SBP, systolic blood pressure; DBP, diastolic blood pressure. Uncorrected, not adjusted for hypertensive medication use.

Directional MR Steiger filtering: filtered to SNPs with R^2 exposure > R^2 outcome

Significant directional MR Steiger filtering: filtered to SNPs with R^2 exposure > R^2 outcome AND Steiger P value < 0.05

[a] Effects of SNPs on albuminuria were calculated in 382500 individuals in UK Biobank

[b] 381833 individuals in UK Biobank had blood pressure measurements

Table S9. Sensitivity analyses for Mendelian randomization of blood pressure genetic risk scores from ICBP Cardio-MetaboChip with albuminuria in UK Biobank.

Sample Size, Exposure[a]	Sample Size, Outcome[b]	Exposure	Outcome	SNPs in score	Cook's distance of outlier removed	SNP in LD removed	Method	Beta (mmHg/SD Albuminuria)	SE (mmHg/SD Albuminuria)	P value	Cochran's Q	Cochran P value	MR-PRESSO Global RSS_{obs}	MR-PRESSO Global P value
Systolic Blood Pressure														
Directional MR Steiger filtering														
201529	381833[c]	SBP, Corrected	Albuminuria	47	NA	NA	Two-Stage Least-Squares	0.0050	0.0007	2.45E-13				
201529	382500	SBP, Corrected	Albuminuria	47	NA	NA	IVW Random Effects	0.0053	0.0015	2.55E-04	157	5E-14	164	< 1E-5
201529	382500	SBP, Corrected	Albuminuria	47	NA	NA	Simple Median	0.0052	0.0013	6.15E-05				
201529	382500	SBP, Corrected	Albuminuria	47	NA	NA	Weighted Median	0.0051	0.0013	5.44E-05				
201529	382500	SBP, Corrected	Albuminuria	47	NA	NA	Egger Slope	0.0050	0.0051	0.331				
201529	382500	SBP, Corrected	Albuminuria	47	NA	NA	Egger Intercept	0.0002	0.0025	0.941				
Directional MR Steiger filtering + Outlier removed														
201529	381833[c]	SBP, Corrected	Albuminuria	46	0.37	NA	Two-Stage Least-Squares	0.0058	0.0007	3.19E-17				
201529	382500	SBP, Corrected	Albuminuria	46	0.37	NA	IVW Random Effects	0.0062	0.0012	5.64E-07	109	3E-07	113	< 1E-5
201529	382500	SBP, Corrected	Albuminuria	46	0.37	NA	Simple Median	0.0053	0.0013	3.69E-05				
201529	382500	SBP, Corrected	Albuminuria	46	0.37	NA	Weighted Median	0.0052	0.0013	4.51E-05				
201529	382500	SBP, Corrected	Albuminuria	46	0.37	NA	Egger Slope	0.0064	0.0043	0.137				
201529	382500	SBP, Corrected	Albuminuria	46	0.37	NA	Egger Intercept	-0.0001	0.0021	0.962				
Directional MR Steiger filtering + LD SNP removed														
201529	381833[c]	SBP, Corrected	Albuminuria	46	NA	rs3735533	Two-Stage Least-Squares	0.0045	0.0007	6.26E-11				
201529	382500	SBP, Corrected	Albuminuria	46	NA	rs3735533	IVW Random Effects	0.0048	0.0014	4.82E-04	135	7E-11	141	< 1E-5
201529	382500	SBP, Corrected	Albuminuria	46	NA	rs3735533	Simple Median	0.0051	0.0013	5.48E-05				
201529	382500	SBP, Corrected	Albuminuria	46	NA	rs3735533	Weighted Median	0.0051	0.0013	5.99E-05				
201529	382500	SBP, Corrected	Albuminuria	46	NA	rs3735533	Egger Slope	0.0023	0.0049	0.629				
201529	382500	SBP, Corrected	Albuminuria	46	NA	rs3735533	Egger Intercept	0.0013	0.0024	0.598				
Diastolic Blood Pressure														
Directional MR Steiger filtering														
201529	381833[c]	DBP, Corrected	Albuminuria	52	NA	NA	Two-Stage Least-Squares	0.0070	0.0012	1.83E-09				
201529	382500	DBP, Corrected	Albuminuria	52	NA	NA	IVW Random Effects	0.0071	0.0025	3.81E-03	192	4E-18	199	< 1E-5
201529	382500	DBP, Corrected	Albuminuria	52	NA	NA	Simple Median	0.0053	0.0021	0.011				
201529	382500	DBP, Corrected	Albuminuria	52	NA	NA	Weighted Median	0.0075	0.0021	2.90E-04				
201529	382500	DBP, Corrected	Albuminuria	52	NA	NA	Egger Slope	0.0067	0.0090	0.457				
201529	382500	DBP, Corrected	Albuminuria	52	NA	NA	Egger Intercept	0.0001	0.0027	0.958				
Directional MR Steiger filtering + Outlier removed														
201529	381833[c]	DBP, Corrected	Albuminuria	51	0.37	NA	Two-Stage Least-Squares	0.0085	0.0012	6.66E-13				
201529	382500	DBP, Corrected	Albuminuria	51	0.37	NA	IVW Random Effects	0.0086	0.0022	8.46E-05	145	4E-11	150	< 1E-5
201529	382500	DBP, Corrected	Albuminuria	51	0.37	NA	Simple Median	0.0054	0.0021	0.011				
201529	382500	DBP, Corrected	Albuminuria	51	0.37	NA	Weighted Median	0.0086	0.0021	3.38E-05				
201529	382500	DBP, Corrected	Albuminuria	51	0.37	NA	Egger Slope	0.0106	0.0079	0.181				
201529	382500	DBP, Corrected	Albuminuria	51	0.37	NA	Egger Intercept	-0.0006	0.0024	0.794				
Directional MR Steiger filtering + LD SNP removed														
201529	381833[c]	DBP, Corrected	Albuminuria	51	NA	rs3735533	Two-Stage Least-Squares	0.0062	0.0012	1.17E-07				
201529	382500	DBP, Corrected	Albuminuria	51	NA	rs3735533	IVW Random Effects	0.0063	0.0023	0.007	167	2E-14	174	< 1E-5
201529	382500	DBP, Corrected	Albuminuria	51	NA	rs3735533	Simple Median	0.0051	0.0021	0.015				
201529	382500	DBP, Corrected	Albuminuria	51	NA	rs3735533	Weighted Median	0.0068	0.0021	9.76E-04				

201529	382500	DBP, Corrected	Albuminuria	51	NA	rs3735533	Egger Slope	0.0030	0.0085	0.723
201529	382500	DBP, Corrected	Albuminuria	51	NA	rs3735533	Egger Intercept	0.0010	0.0026	0.687

SBP, systolic blood pressure; DBP, diastolic blood pressure. Corrected, corrected for hypertensive medication use.

Directional MR Steiger filtering: filtered to SNPs with R^2 exposure > R^2 outcome

[a] Effects on blood pressure were calculated in up to 201529 individuals in the International Consortium for Blood Pressure Cardio-MetaboChip study (Ehret *et al* 2016. Nature Genetics. PMID 27618452)

[b] Effects of SNPs on albuminuria were calculated in 382500 individuals in UK Biobank (not applicable for two-stage least-squares regression)

[c] 381833 individuals in UK Biobank had both albuminuria and blood pressure measurements required for two-stage least-squares regression

Table S10. Sensitivity analyses for Mendelian randomization of albuminuria genetic risk score in UK Biobank with blood pressure in ICBP 1000G.

Sample Size, Exposure[a]	Sample Size, Outcome[b]	Exposure	Outcome	SNPs in score	Cook's distance of outlier removed	Method	Beta (mmHg/SD Albuminuria)	SE (mmHg/SD Albuminuria)	P value	Cochran's Q	Cochran P value	MR-PRESSO Global RSS_{obs}	MR-PRESSO Global P value
Systolic Blood Pressure													
Directional MR Steiger filtering													
382500	150134	Albuminuria	SBP, Corrected	37	NA	IVW Fixed Effects	2.689	0.768	4.64E-04				
382500	150134	Albuminuria	SBP, Corrected	37	NA	IVW Random Effects	2.689	1.162	0.021	82	2E-05	110	< 1E-05
382500	150134	Albuminuria	SBP, Corrected	37	NA	Simple Median	2.792	1.260	0.027				
382500	150134	Albuminuria	SBP, Corrected	37	NA	Weighted Median	2.639	1.325	0.046				
382500	150134	Albuminuria	SBP, Corrected	37	NA	Egger Slope	0.045	2.588	0.986				
382500	150134	Albuminuria	SBP, Corrected	37	NA	Egger Intercept	0.055	0.048	0.253				
Directional MR Steiger filtering + Outlier removed													
382500	150134	Albuminuria	SBP, Corrected	36	0.44	IVW Fixed Effects	3.457	0.784	1.05E-05				
382500	150134	Albuminuria	SBP, Corrected	36	0.44	IVW Random Effects	3.457	1.019	6.92E-04	59	0.007	78	0.0003
382500	150134	Albuminuria	SBP, Corrected	36	0.44	Simple Median	3.708	1.241	0.003				
382500	150134	Albuminuria	SBP, Corrected	36	0.44	Weighted Median	2.657	1.316	0.044				
382500	150134	Albuminuria	SBP, Corrected	36	0.44	Egger Slope	1.218	2.246	0.588				
382500	150134	Albuminuria	SBP, Corrected	36	0.44	Egger Intercept	0.046	0.041	0.264				
Diastolic Blood Pressure													
Directional MR Steiger filtering													
382500	150134	Albuminuria	DBP, Corrected	35	NA	IVW Fixed Effects	1.033	0.477	0.030				
382500	150134	Albuminuria	DBP, Corrected	35	NA	IVW Random Effects	1.033	0.775	0.183	90	6E-07	118	< 1E-05
382500	150134	Albuminuria	DBP, Corrected	35	NA	Simple Median	3.093	0.798	1.06E-04				
382500	150134	Albuminuria	DBP, Corrected	35	NA	Weighted Median	0.854	0.805	0.289				
382500	150134	Albuminuria	DBP, Corrected	35	NA	Egger Slope	-0.442	1.732	0.799				
382500	150134	Albuminuria	DBP, Corrected	35	NA	Egger Intercept	0.031	0.033	0.341				
Directional MR Steiger filtering + Outlier removed													
382500	150134	Albuminuria	DBP, Corrected	34	0.45	IVW Fixed Effects	1.552	0.487	0.001				
382500	150134	Albuminuria	DBP, Corrected	34	0.45	IVW Random Effects	1.552	0.677	0.022	64	0.001	83	2E-05
382500	150134	Albuminuria	DBP, Corrected	34	0.45	Simple Median	3.127	0.786	6.94E-05				
382500	150134	Albuminuria	DBP, Corrected	34	0.45	Weighted Median	0.897	0.789	0.255				
382500	150134	Albuminuria	DBP, Corrected	34	0.45	Egger Slope	0.316	1.494	0.833				
382500	150134	Albuminuria	DBP, Corrected	34	0.45	Egger Intercept	0.026	0.028	0.353				

SBP, systolic blood pressure; DBP, diastolic blood pressure. Corrected, corrected for hypertensive medication use.

Directional MR Steiger filtering: filtered to SNPs with R^2 exposure > R^2 outcome

[a] Effects of SNPs on albuminuria were calculated in 382500 individuals in UK Biobank

[b] Effects of SNPs on blood pressure were calculated in up to 150534 individuals in the International Consortium for Blood Pressure 1000G imputation (Wain *et al* 2017. Hypertension. PMID 28739976)

Table S11. Genome-wide association study of albuminuria in 302687 individuals in UK Biobank without hypertensive medication use

Lead variant	Nearest Gene(s)	Description	Chr	Position (hg19)	Effect Allele	Noneffect Allale	EAF	Beta (log(mg/g))	SE (log(mg/g))	P value
rs10157710	*FOXD2-TRABD2B*	Intergenic	1	47961691	T	C	0.802	0.01599	0.00219	3.02E-13
rs4665972	*SNX17*	Intronic, noncoding RNA variant	2	27598097	T	C	0.392	0.01104	0.00180	8.28E-10
rs6712846	*CPO-KLF7*	Intergenic	2	207889080	A	G	0.525	0.00954	0.00175	4.88E-08
rs1047891	*CPS1*	Missense	2	211540507	C	A	0.683	0.01031	0.00188	3.98E-08
rs183131780	*NYAP2-LOC646736*	Intergenic	2	226684886	T	C	0.002	0.13566	0.02080	6.99E-11
rs35483183	*COL4A4*	Intronic	2	227876687	A	G	0.123	0.01502	0.00268	1.98E-08
rs35924503	*SPHKAP-PID1*	Intergenic	2	229131286	C	T	0.001	0.17391	0.02693	1.06E-10
rs7670121	*NR3C2*	Intronic, noncoding RNA variant	4	149128595	G	A	0.240	0.01161	0.00205	1.36E-08
rs189107782	*LINC01262-FRG1*	Intergenic	4	190729009	T	C	0.002	0.20163	0.02131	3.11E-21
rs7731168	*CWC27*	Intronic	5	64296471	C	G	0.233	0.01183	0.00207	1.09E-08
rs4410790	*AGR3-AHR*	Intergenic	7	17284577	C	T	0.633	0.01595	0.00181	1.35E-18
rs4738817	*CHD7*	Intronic	8	61620613	G	A	0.549	0.00976	0.00176	2.73E-08
rs28601761	*TRIB1-LINC00861*	Intergenic	8	126500031	C	G	0.579	0.01059	0.00179	3.26E-09
rs45551835	*CUBN*	Missense	10	16932384	A	G	0.014	0.11178	0.00739	1.15E-51
rs144360241	*CUBN*	Missense	10	16967417	C	T	0.005	0.07690	0.01303	3.60E-09
rs141640975	*CUBN*	Missense	10	16992011	A	G	0.003	0.33405	0.01718	3.35E-84
rs2236295	*ADO*	Missense, TFBS variant, Regulatory region variant	10	64564892	G	T	0.593	0.01020	0.00178	1.10E-08
rs67339103	*LRMDA*	Intronic, noncoding RNA variant	10	77893686	A	G	0.213	0.01328	0.00215	6.02E-10
rs2601006	*CCT2*	5' UTR variant, Intronic	12	69979517	C	T	0.657	0.01086	0.00184	3.55E-09
rs3759794	*LTK*	Upstream variant, Regulatory region variant	15	41806658	G	A	0.883	0.01553	0.00272	1.17E-08
rs16943246	*C15orf48*	Upstream variant	15	45720597	G	A	0.753	0.01155	0.00203	1.30E-08
rs2470893	*CYP1A1*	Upstream variant	15	75019449	T	C	0.335	0.01495	0.00185	5.87E-16
rs838142	*FUT1*	3' UTR Variant	19	49252151	A	G	0.723	0.01189	0.00196	1.21E-09

Chr, chromosome; EAF, effect allele frequency. For intergenic loci, nearest upstream and downstream RefSeq genes are indicated. Nearest gene should not be taken as evidence of causal gene. Description indicates VEP most severe consequences of nearest gene and any regulatory annotations associated with lead variant

Table S12. Sensitivity analyses for Mendelian randomization of albuminuria genetic risk score with blood pressure in UK Biobank participants not on anti-hypertensive medications.

Sample Size[a]	Exposure	Outcome	SNPs in score	Cook's distance of outlier removed	Method	Beta (mmHg/SD Albuminuria)	SE (mmHg/SD Albuminuria)	P value	Cochran's Q	Cochran P value	MR-PRESSO Global RSS_{obs}	MR-PRESSO Global P value
Systolic Blood Pressure												
Directional MR Steiger filtering												
302687	Albuminuria	Systolic BP	22	NA	Two-Stage Least-Squares	1.455	0.472	0.002				
302687	Albuminuria	Systolic BP	22, unweighted allele score	NA	Two-Stage Least-Squares	2.904	0.665	1.27E-05				
302687	Albuminuria	Systolic BP	22	NA	IVW Random Effects	1.455	0.873	0.096	71	2E-07	80	< 1E-05
302687	Albuminuria	Systolic BP	22	NA	Simple Median	2.443	0.862	0.005				
302687	Albuminuria	Systolic BP	22	NA	Weighted Median	0.415	0.779	0.594				
302687	Albuminuria	Systolic BP	22	NA	Egger Slope	0.004	1.179	0.997				
302687	Albuminuria	Systolic BP	22	NA	Egger Intercept	0.054	0.031	0.082				
Directional MR Steiger filtering + Outlier removed												
302687	Albuminuria	Systolic BP	21	0.78	Two-Stage Least-Squares	2.224	0.550	5.21E-05				
302687	Albuminuria	Systolic BP	21	0.78	IVW Random Effects	2.224	0.985	0.024	64	2E-06	69	< 1E-05
302687	Albuminuria	Systolic BP	21	0.78	Simple Median	2.453	0.910	0.007				
302687	Albuminuria	Systolic BP	21	0.78	Weighted Median	2.433	0.877	0.006				
302687	Albuminuria	Systolic BP	21	0.78	Egger Slope	0.817	1.661	0.623				
302687	Albuminuria	Systolic BP	21	0.78	Egger Intercept	0.039	0.037	0.293				
Diastolic Blood Pressure												
Directional MR Steiger filtering												
302687	Albuminuria	Diastolic BP	22	NA	Two-Stage Least-Squares	0.672	0.272	0.014				
302687	Albuminuria	Diastolic BP	22, unweighted allele score	NA	Two-Stage Least-Squares	1.015	0.384	0.008				
302687	Albuminuria	Diastolic BP	22	NA	IVW Random Effects	0.672	0.494	0.174	69	5E-07	76	< 1E-05
302687	Albuminuria	Diastolic BP	22	NA	Simple Median	0.898	0.483	0.063				
302687	Albuminuria	Diastolic BP	22	NA	Weighted Median	0.465	0.430	0.280				
302687	Albuminuria	Diastolic BP	22	NA	Egger Slope	0.329	0.708	0.643				
302687	Albuminuria	Diastolic BP	22	NA	Egger Intercept	0.013	0.019	0.493				
Directional MR Steiger filtering + Outlier removed												
302687	Albuminuria	Diastolic BP	21	0.47	Two-Stage Least-Squares	1.010	0.317	0.001				
302687	Albuminuria	Diastolic BP	21	0.47	IVW Random Effects	1.010	0.570	0.077	65	1E-06	70	< 1E-05
302687	Albuminuria	Diastolic BP	21	0.47	Simple Median	1.088	0.513	0.034				
302687	Albuminuria	Diastolic BP	21	0.47	Weighted Median	1.191	0.498	0.017				
302687	Albuminuria	Diastolic BP	21	0.47	Egger Slope	0.950	0.989	0.337				
302687	Albuminuria	Diastolic BP	21	0.47	Egger Intercept	0.002	0.022	0.940				

BP, blood pressure

Directional MR Steiger filtering: filtered to SNPs with R^2 exposure > R^2 outcome

[a] Effects of SNPs on both albuminuria and blood pressure were measured in 302687 individuals in UK Biobank who had both albuminuria and blood pressure measurements and were not taking blood pressure medications

Table S13. Power to Detect Significant Associations between Albuminuria Risk Score and Cardiometabolic Disease

Disease	Cases, UK Biobank	Controls, UK Biobank	Causal Effect (Odds Ratio)	R^2 variance explained by Albuminuria Risk Score in UK Biobank	Power to Detect
All-Cause Mortality	11087	371413	1.1	0.007	**0.12**
			1.2	0.007	**0.35**
Coronary Artery Disease	32623	349877	1.1	0.007	**0.28**
			1.15	0.007	**0.52**
			1.2	0.007	**0.75**
Stroke	8818	373682	1.1	0.007	**0.11**
			1.15	0.007	**0.19**
			1.2	0.007	**0.29**
Peripheral Vascular Disease	4543	377957	1.2	0.007	**0.17**
			1.3	0.007	**0.31**
Heart Failure	5737	376503	1.1	0.007	**0.08**
			1.2	0.007	**0.21**
			1.3	0.007	**0.38**
			1.4	0.007	**0.56**
Type 2 Diabetes	17619	364881	1.2	0.007	**0.51**
Chronic Kidney Disease	4885	377615	1.1	0.007	**0.08**
			1.2	0.007	**0.18**
			1.3	0.007	**0.33**
			1.4	0.007	**0.5**
			1.5	0.007	**0.65**
Hypertension	124345	258155	1.1	0.007	**0.64**
			1.2	0.007	**0.99**

Causal effect values based on the range of observational or Mendelian randomization associations