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Identification of 22 novel loci associated with urinary biomarkers of albumin, sodium, and potassium excretion

Daniela Zanetti^{1,2}, Abhiram Rao³, Stefan Gustafsson⁴, Themistocles L. Assimes¹, Stephen B. Montgomery^{5,6}, and Erik Ingelsson^{1,2,4}

¹Division of Cardiovascular Medicine, Department of Medicine, Stanford University School of Medicine, Stanford, California, USA

²Stanford Cardiovascular Institute, Stanford University, Stanford, California, USA

³Department of Bioengineering, Stanford University, Stanford, California, USA

⁴Department of Medical Sciences, Molecular Epidemiology and Science for Life Laboratory, Uppsala University, Uppsala, Sweden

⁵Department of Pathology, Stanford University School of Medicine, Stanford, California, USA

⁶Department of Genetics, Stanford University School of Medicine, Stanford, California, USA

Abstract

Urine biomarkers reflecting kidney function and handling of dietary sodium and potassium are strongly associated with several common diseases including chronic kidney disease, cardiovascular disease, and diabetes mellitus. Knowledge about the genetic determinants of these biomarkers may shed light on pathophysiological mechanisms underlying the development of these diseases. We performed genome-wide association studies of urinary albumin: creatinine ratio (UACR), urinary potassium: creatinine ratio (UK/UCr), urinary sodium: creatinine ratio (UNa/UCr) and urinary sodium: potassium ratio (UNa/UK) in up to 218,450 (discovery) and 109,166 (replication) unrelated individuals of European ancestry from the UK Biobank. Further, we explored genetic correlations, tissue-specific gene expression, and possible genes implicated in the regulation of these biomarkers. After replication, we identified 19 genome-wide significant independent loci associated with UACR, 6 each with UK/UCr and UNa/UCr, and 4 with UNa/UK. In addition to 22 novel associations, we confirmed several established associations, including between the *CUBN* locus and microalbuminuria. We detected high pairwise genetic correlation across the urinary biomarkers, and between their levels and several physiological measurements. We highlight *GIPR*, a potential diabetes drug target, as possibly implicated in the genetic control

Correspondence: Erik Ingelsson, Division of Cardiovascular Medicine, Department of Medicine, Stanford University School of Medicine, 300 Pasteur Dr, Mail Code: 5406, Stanford, California 94305, USA. eriking@stanford.edu.

Data availability

Data sets related to this article are available at UKB resource (<https://www.ukbiobank.ac.uk/>). GWAS summary statistics for the 4 urinary biomarkers performed using all the European unrelated samples in the UKB are available at GRASP resource (<https://grasp.nhlbi.nih.gov/FullResults.aspx>).

DISCLOSURE

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Supplementary material is linked to the online version of the paper at www.kidney-international.org.

of urinary potassium excretion, and *NRBPI*, a locus associated with gout, as plausibly involved in sodium and albumin excretion. Overall, we identified 22 novel genome-wide significant associations with urinary biomarkers and confirmed several previously established associations, providing new insights into the genetic basis of these traits and their connection to chronic diseases.

Keywords

chronic kidney disease; genetics; microalbuminuria; urinary biomarkers

Urinary biomarkers are used clinically to assess an individual's renal function as well as to diagnose and predict the onset of related chronic diseases.¹ Such biomarkers include creatinine, albumin, potassium, and sodium, which have been associated with chronic kidney disease (CKD),^{2,3} cardiovascular disease (CVD),⁴⁻⁶ and type 2 diabetes (T2D).^{7,8} Compared to blood, biomarkers in urine are less affected by homeostatic mechanisms. This allows greater fluctuations in biomarker levels, which may provide signals that more reliably reflect dynamic changes in biological and pathophysiological processes.⁹

Little progress has been made in disentangling the genetic determinants of urinary biomarkers despite many observational association studies showing the relevance of these biomarkers.^{6,10,11} Previous genetic studies of kidney function have been focused on albuminuria^{8,12} and on estimated glomerular filtration rate based on serum creatinine and/or cystatin C.^{13,14} To increase the understanding of mechanisms underlying kidney function and disease, we analyzed the genetic underpinnings of 4 urinary biomarkers, specifically of urinary albumin: creatinine ratio (UACR), urinary potassium: creatinine ratio (UK/UCr), urinary sodium: creatinine ratio (UNa/UCr), and urinary sodium: potassium ratio (UNa/UK). These biomarkers have been selected for their strong connection with CKD as well as for their association with CVD and T2D. Previous studies have found that microalbuminuria is predictive, independently of traditional risk factors, of CVD within groups of patients with diabetes or hypertension as well as in the general population.¹⁵ Likewise, the association of high sodium and low potassium levels with higher blood pressure (BP) is supported by a large body of evidence that includes randomized clinical trials¹⁶ and observational studies.⁶

We performed genome-wide association studies (GWASs) of UACR, UK/UCr, UNa/UCr, and UNa/UK in up to 218,450 (discovery) and 109,166 (replication) participants from the UK Biobank (UKB). Furthermore, for each urinary biomarker, we estimated its heritability; identified genetic associations that were likely mediated by expression or methylation quantitative trait loci (eQTLs or mQTLs); evaluated genetic correlations with several anthropometric, cardiovascular, glycemic, lipid, hematological, and kidney traits; and used a bioinformatic approach to pinpoint possible candidate genes.

Discovering genetic associations and identifying whether they are genetically correlated with other common traits can provide important etiological insights into the control of these biomarkers and ultimately renal function. Such knowledge may in turn improve the predictive use of the respective biomarker and point to new therapeutic strategies to prevent common diseases.

RESULTS

Association analyses

In our discovery GWASs, we identified a total of 52 genome-wide significant independent variants associated with at least 1 of the 4 urinary biomarker ratios: 21 for UACR ($n = 218,759$), 11 for UK/UCr ($n = 218,435$), 12 for UNa/UCr ($n = 218,450$), and 8 for UNa/UK ($n = 217,996$) (Table 1). Regional plots for the 52 discovered variants are shown in Supplementary Figures S1 to S4. We observed minor inflation in test statistics ($\lambda = 1.08$ for UACR; $\lambda = 1.10$ for UK/UCr; $\lambda = 1.067$ for UNa/UCr; and $\lambda = 1.092$ for UNa/UK), which is expected¹⁷ under polygenic inheritance in large samples (Supplementary Figure S5), also supported by the observation that all linkage disequilibrium score regression intercepts were close to 1 (Table 2; also see below).

Of these 52 variants, 35 were significantly associated with a consistent direction in the replication data set. A conservative Bonferroni-corrected threshold of 2.38×10^{-3} for UACR, 4.55×10^{-3} for UK/UCr, 4.17×10^{-3} for UNa/UCr, and 6.25×10^{-3} for UNa/UK (adjusting for the different numbers of significant independent hits in the discovery GWASs) was used to identify significant replications. We identified 19 replicated variants for UACR ($n = 109,530$), 6 for UK/UCr ($n = 109,178$), 6 for UNa/UCr ($n = 109,166$), and 4 for UNa/UK ($n = 108,942$) (Table 1 and Figure 1).

When we performed the GWAS (discovery, $n = 217,634$; replication, $n = 108,800$) using albumin as a binary trait, we identified 10 variants to be robustly associated (3.33×10^{-3} in the replication stage after multiple testing correction) (Supplementary Table S1 and Supplementary Figure S6).

Of the 35 replicated lead variants, 22 are novel in relation to kidney function while 11 are located in loci previously associated with kidney function, including cubilin (*CUBN*),¹⁸ carbamoyl phosphate synthase 1 (*CPS1*),¹³ glycine amidino-transferase (*GATM*),¹⁹ and glucokinase regulator (*GCKR*).²⁰ Of the 35 significantly replicated variants, there was some overlap between several of the 4 biomarkers. Specifically, rs34783010 (UK/UCr) and rs10423928 (UNa/UK) are located in the gastric inhibitory polypeptide receptor (*GIPR*) locus, rs1047891 (UACR, UK/UCr, and UNa/UCr) is located in the *CPS1* locus, rs4665972 (UACR and UNa/UK) in the sorting nexin-17 (*SNX17*) locus, rs42472297 (UACR and UNa/UK) close to the cytochrome P450 family 1 subfamily A member 1 (*CYP1A1*) locus, and rs6440008 (UNa/UCr) and rs7625643 (UNa/UK) in the gene zinc finger and BTB domain containing 38 (*ZBTB38*) locus.

Phenotypic and genetic correlations

We detected positive phenotypic correlation between all pairs of urinary biomarkers (0.076–0.719), except between UK/UCr and UNa/UK (-0.402 ; $P < 2.2 \times 10^{-16}$) (Supplementary Table S2). We found evidence of strong direct genetic correlations between all pairs of urinary biomarkers (0.201–0.728), except between UACR and UNa/UK (-0.0491 ; $P = 1.17 \times 10^{-1}$). We also detected inverse genetic correlation between UK/UCr and UNa/UK (-0.523 ; $P = 1.65 \times 10^{-96}$) (Supplementary Table S3). UACR and binary albumin showed positive and significant genetic (0.335 ± 0.044 ; $P = 3.21 \times 10^{-14}$) and phenotypic (0.384

± 0.001 ; $P < 2.20 \times 10^{-16}$) correlations. In general, we observed high consistency among the phenotypic and genetic correlations between all pairs of urinary biomarkers (Supplementary Figure S7).

Furthermore, we observed significant genetic correlations between the urinary biomarkers and several anthropometric, cardiovascular, glycemic, lipid, and kidney traits (Figure 2; Supplementary Table S3). Specifically, we identified a significant and positive genetic correlation of UNa/UK and several traits related to cardiometabolic disease, including body mass index, body fat, obesity, waist-to-hip ratio, coronary artery disease, BP, T2D, levels of fasting glucose and fasting insulin, as well as of UACR with systolic BP. In addition, we observed positive correlations of potassium and high-density lipoprotein cholesterol with estimated glomerular filtration rate based on serum creatinine as well as of sodium and UACR with estimated glomerular filtration rate based on serum creatinine. We detected a negative correlation between potassium and several traits related to cardiometabolic disease, including body mass index, body fat, obesity, waist-to-hip ratio, coronary artery disease, BP, levels of fasting glucose and fasting insulin, triglycerides, and CKD. We confirmed the negative correlation between sodium, obesity, and fasting insulin levels. In addition, we detected a negative correlation of height with UACR, UNa/UCr, and UNa/UK. Details on the source of data for the 29 traits analyzed are given in Supplementary Table S3. The heritability of the 4 urinary biomarkers was in the range of $0.042 \leq h^2_g \leq 0.053$ (Table 2). The heritability of binary albumin was 0.017 ± 0.002 . The heritability estimates for albumin are likely to be conservative, as a high proportion of the samples was below the lower limit of detection (6.7 mg/l; $n = 228,262$) and truncated to this level.

eQTLs

Of the 35 replicated lead variants, 10 showed evidence of significant eQTLs (Supplementary Table S4). The largest number of significant eQTLs was associated with gene expression in brain (52), artery (19), and skin (19). The most significant eQTLs in loci associated with UNa/UCr (rs1260326; $P = 3.70 \times 10^{-19}$) and UNa/UK (rs4665972; $P = 6.60 \times 10^{-22}$) were in relation to *SNX17* in skeletal muscle. *SNX17* has previously been implicated in myocardial infarction.²¹ The strongest eQTL detected in the GWASs of UACR and UK/UCr were for spermatogenesis associated 5 like 1 (*SPATA5L1*; rs60474696) and secretory carrier membrane protein 2 (*SCAMP2*; rs2472297) in cells transformed fibroblasts ($P = 8.90 \times 10^{-49}$) and skin ($P = 2.90 \times 10^{-9}$), respectively. The *SPATA5L1* gene has previously been associated with CKD.¹⁴

Colocalization with eQTL and mQTL summary statistics

We tested the colocalization of GWAS lead variants with 92 and 1636 genome-wide significant cis-eQTLs and cis-mQTLs, respectively ($P < 5 \times 10^{-8}$), located within 1 Mb of the top replicated variants and controlled false discovery rate using the Benjamini-Yekutieli method (5% false discovery rate) in both analyses (Supplementary Table S5). To exclude summary data-based Mendelian randomization (SMR) results that may reflect pleiotropy, we performed the heterogeneity in dependent instruments (HEIDI) test, which considers the pattern of associations using all the single-nucleotide polymorphisms (SNPs) that are significantly associated with gene expression (eQTLs) in the cis region. After excluding

heterogeneous variants ($P_{\text{heterogeneity in dependent instrument}} < 0.05$) and SNP in linkage disequilibrium ($R^2 > 0.8$), we detected significant eQTL colocalizations for UACR, UNa/UCr, and UNa/UK in the nuclear receptor binding protein 1 (*NRBP1*) locus (rs11684134; SMR, $P = 2.20 \times 10^{-4}$, $P = 5.69 \times 10^{-5}$, and $P = 8.24 \times 10^{-5}$, respectively) (Table 3). No homogeneous and significant eQTL colocalization signals were detected for urinary potassium. We observed 19 significant independent mQTL probe colocalizations for UACR, 15 for UK/UCr, 7 for UNa/UCr, and 8 for UNa/UK (Table 3).

The strongest mQTL colocalization detected for UACR was for a probe on chromosome 15 (lead SNP rs11857376; SMR, $P = 1.54 \times 10^{-13}$). We detected consistent signals in GWAS and mQTL colocalization analyses for islet cell autoantigen 1 like (*ICA1L*) on chromosome 2 (rs74675536 and rs1971819; SMR, $P = 6.68 \times 10^{-6}$) and for the *GATM* locus on chromosome 15 (rs2172874; SMR, $P = 8.15 \times 10^{-11}$) (Table 3).

The strongest mQTL colocalization detected for potassium was for *GIPR* (lead SNP rs10423928; SMR, $P = 3.34 \times 10^{-16}$) on chromosome 19. Furthermore, we detected consistent signals in GWAS and mQTL colocalization analyses for *GATM* (lead SNP rs2172874; SMR, $P = 1.90 \times 10^{-15}$) on chromosome 15 and for calcium/calmodulin-dependent protein kinase II gamma (*CAMK2G*) (lead SNP rs2688626; SMR, $P = 1.03 \times 10^{-9}$) (Table 3).

We detected significant independent mQTL colocalizations for UNa/UCr-related variants and methylation in *ZBTB38* on chromosome 3 (lead SNPs rs34169305, rs4683605, and rs13069734; SMR, $P = 6.76 \times 10^{-5}$) and consistent signals in GWAS and mQTL colocalization analyses for protein-coding gene MLX interacting protein like (*MLXIPL*) on chromosome 7 (rs3812316; SMR, $P = 3.83 \times 10^{-9}$) (Table 3).

We detected consistent signals in GWAS and mQTL colocalizations for UNa/UK in *ZBTB38* on chromosome 3 for 4 significant independent probes (lead SNPs rs13098180, rs34169305, rs4683605, and rs13069734; SMR, $P = 5.99 \times 10^{-5}$) (Table 3).

In addition, we detected shared eQTL and mQTL colocalizations for different urinary biomarkers. UACR, UNa/UCr, and UNa/UK shared an eQTL colocalization on chromosome 2 with the same lead variant rs11684134 (*NRBP1*), indicating that this is a plausible variant implicated in these traits. UACR and UK/UCr shared 3 mQTL colocalizations on chromosome 15 on the *GATM*, *SCAMP5*, and *SCAMP2* genes with the same lead variants (rs2172874, rs35103257, and rs3765066, respectively). UNa/UCr and UNa/UK also shared 3 mQTL colocalizations on chromosome 3 with the same lead variants (rs34169305, rs4683605, and rs13069734) on the gene *ZBTB38*, and UK/UCr (rs1132645) and UNa/UK (rs1108378) shared an mQTL colocalization on the symplekin (*SYMPK*) gene on chromosome 19.

DISCUSSION

Principal findings

We achieved 3 broad goals in this study of up to 337,536 unrelated individuals of European ancestry from the UK Biobank. We (i) established genetic determinants of UACR, UK/UCr, UNa/UCr, and UNa/UK; (ii) evaluated genetic correlation between these biomarkers and a number of clinical traits; and (iii) explored the associated loci using colocalization analyses based on expression and methylation data. Our main findings are severalfold. First, we report a total of 22 novel loci associated with 1 of the 4 urinary biomarkers, providing new leads on biological processes involved in regulating UACR, UK/UCr, UNa/UCr, and UNa/UK. Second, our analyses indicate low heritability but high pairwise genetic correlations between the 4 urinary biomarkers as well as significant genetic correlations with several traits related to CKD, CVD, and T2D. Third, we identify 1 and 49 independent colocalization events of GWAS data with blood gene expression and DNA methylation, respectively, providing evidence of potential genes implicated in these loci. As an example of the latter, we identified *GIPR*, a potential drug target in the treatment of obesity-associated metabolic disorders, as likely involved in mechanisms affecting urinary potassium excretion, and *NRBPI*, a gene associated with gout, as implicated in sodium and albumin excretion and/or metabolism.

Comparison with prior literature

This study is the first GWAS of UK/UCr, UNa/UCr, and UNa/UK to our knowledge, while genetic determinants of albuminuria have already been explored in previous studies.^{8,18} In this study, we replicated the well-known association of the *CUBN* locus with albuminuria and extend prior GWAS of albumin by highlighting several novel pathways influencing this trait. For example, we highlighted 2 variants—rs4410790 and rsrs2472297—located in the aryl hydrocarbon receptor (*AHR*) and close to the *CYP1A1* gene, respectively, previously found associated with coffee consumption.²² When we performed the analyses using albumin as a binary trait, we replicated most of the associations identified in the UACR GWAS, most prominently for the *CUBN* locus (Supplementary Table S6).

In the UK/UCr GWAS, we replicated the known association of variants in the *CPS1* locus (rs1047891; $P = 1.38 \times 10^{-27}$), previously associated with glomerular filtration rate (serum creatinine),¹³ and with *GATM* (rs35335867; $P = 9.39 \times 10^{-14}$), a gene that encodes a mitochondrial enzyme previously associated with serum creatinine.¹⁴

Several replicated variants for UNa/UCr (rs1260326 on *GCKR* and rs2954021 near Tribbles Pseudokinase 1 (*TRIB1*); $P = 2.11 \times 10^{-21}$ and $P = 1.56 \times 10^{-8}$, respectively) and for UACR and UNa/UK (rs4665972 on *SNX17*; $P = 3.60 \times 10^{-8}$ and $P = 1.40 \times 10^{-17}$, respectively) showed previous association with triglyceride levels,²³ while another variant (rs10423928; $P = 2.93 \times 10^{-10}$) is located in the *GIPR* gene, as discussed in detail below, and has been previously found to be associated with T2D²⁴ and obesity.²⁵ The 2 variants on *GCKR* and *SNX17* genes (rs1260326 and rs4665972, respectively) are not independent and show a strong linkage disequilibrium ($R^2 = 0.92$), so they are likely to represent the same

underlying signal. Details of all these previous studies and their comparisons with the UKB associations can be found in Supplementary Table S7.

Previous studies have shown a strong association of sodium and potassium intake with BP¹⁶ and CVD,⁵ but there is a lack of studies of the genetic underpinning of these biomarkers, except for albumin. Indeed, a recent study supported the evidence that albuminuria could increase the risk of CVD with an increase in BP.²⁶

Phenotypic and genetic correlations

We found evidence of high positive correlations (both genetic and phenotypic) between all pairs of urinary biomarkers analyzed, except between UK/UCr and UNa/UK. We confirmed a negative association of BP with potassium and a positive association of BP with UNa/UK. We also confirmed significant positive genetic correlations between UNa/UK and several anthropometric measurements (body mass index, body fat, height, and waist-to-hip ratio), coronary artery disease, T2D, and levels of fasting insulin and fasting glucose. Some of the correlations detected might be caused by associations with creatinine (that was used to normalize the other biomarkers); for example, the direct genetic correlations of UACR, UK/UCr, and UNa/UCr with estimated glomerular filtration rate are likely caused by the correlation of blood and urine creatinine.

We report heritability estimates of the 4 urinary biomarkers in the range of 4% to 5%, which are lower than those of many complex traits, but consistent with prior studies of kidney-related serum biomarkers. Specifically, estimates for serum albumin: creatinine ratio, potassium, and sodium have been reported to be in the range of 13% to 19%, lowest for potassium and highest for creatinine²⁷ when using family-based designs.

Novel biology

We identified *NRBPI*, previously associated with gout, as significantly associated with UACR, UNa/UCr, and UNa/UK in our eQTL colocalization analyses. Gout is a complex disorder caused by the deposition of monosodium urate crystals within joints and other tissues. Central to the development of gout is elevated serum uric acid concentrations.²⁸ A previous study demonstrated that hypomethylation of its promoter region, B1, is associated with increased gene expression both *in vitro* and *in vivo*. Moreover, gout-associated increased *NRBPI* expression is regulated through methylation-dependent transcription factor AP-2 alpha binding to the B1 region, which might be involved in the pathogenesis of gout.²⁹ Furthermore, another locus associated with urinary sodium, *MLXIPL*, has been associated with reduced serum uric acid concentrations and consequently a lower risk of gout, but also with increased coffee consumption.³⁰ Multiple studies have reported that increased coffee consumption is associated with reduced serum uric acid concentrations³¹ and lower risk of developing gout.^{32,33} This association has been attributed to several potential mechanisms including improved insulin resistance³⁴ and caffeine-mediated inhibition of xanthine oxidase.³⁵ A recent study showed a potential causal role of uric acid transporters in improving renal function,³⁶ whereas other Mendelian randomization studies have demonstrated that gout, the clinical manifestation of hyperuricemia, is causally associated with body mass index³⁷ and CVD,³⁸ but not with T2D³⁹ and BP.³⁷ Regarding the

association with BP, another study reported that sodium intake was significantly associated with uric acid and BP in opposite directions.⁴⁰ The increase in sodium intake was associated with lower uric acid and higher BP. These findings suggest that uric acid is unlikely to mediate changes in BP in the context of dietary sodium intake. This may be explained by the effects of sodium intake on glomerular filtration rate and excretion or absorption of urate. Previous studies have shown that reabsorption of sodium and urate accompany one another⁴¹ at different sites in the nephron.⁴² Thus, it is possible that decreased renal reabsorption of sodium from excess sodium intake contributes to a decrease in urate reabsorption.⁴⁰

In addition, we observed colocalization of the GWAS signal for UK/UCr with mQTL probes for *CAMK2G*. The protein encoded by this gene, CAMK2, is a multifunctional serine/threonine kinase with numerous roles in human physiology. Dysfunction in CAMK2-based signaling has been linked with a host of cardiovascular phenotypes including heart failure and arrhythmia. CAMK2 levels are elevated in human and animal disease models of heart disease, and this protein has been suggested as a novel therapeutic target for cardiac arrhythmia.⁴³ In addition, another previous study demonstrated that dysregulated embryonic regulator of G protein signaling expression and oxidative activation of *CAMK2G* may potentially contribute to congenital heart defects.⁴⁴ Normal blood levels of potassium are critical for maintaining normal cardiac rhythm. As K⁺ currents control the repolarization process of the cardiomyocyte action potential, the K⁺ channel function determines membrane potential and refractoriness of the myocardium. Both low blood potassium levels (hypokalemia) and high blood potassium levels (hyperkalemia) can lead to abnormal heart rhythms.⁴⁵

We observed colocalization of the GWAS signal for UACR and UK/UCr in the *GATM* locus with mQTL signals. The *GATM* locus is not novel in terms of association with renal function, as previous studies have shown its association with CKD and reduced glomerular filtration rate.^{13,14} *GATM*, which stands for glycine amidinotransferase, encodes a rate-limiting enzyme involved in creatinine biosynthesis and has been suggested to act as a functional link between statin-mediated lowering of cholesterol and susceptibility to statin-induced myopathy.⁴⁶ In addition, a previous study showed a significant association of SNPs in the *GATM* locus with plasma and urine creatinine, but not with cystatin C in plasma, another biomarker of renal function.¹⁴ This association may indicate that the regulatory variants in this locus influence creatinine production, rather than creatinine excretion.

Likewise, variants in the *GIPR* locus significantly associated with UK/UCr in our GWAS and mQTL colocalization have been previously associated with T2D, obesity, and related phenotypes.^{24,25} The glucose-dependent insulintropic peptide has a central role in glucose homeostasis through its amplification of insulin secretion. Incretin hormones such as glucose-dependent insulintropic peptide act to promote efficient uptake and storage of energy after food ingestion and have become important players for glucose homeostasis in pancreatic and extrapancreatic tissue. A recent study demonstrated that mice with selective ablation of *GIPR* in β cells exhibited lower levels of meal-stimulated insulin secretion, decreased expansion of adipose tissue mass, and preservation of insulin sensitivity as compared with controls.⁴⁷ Hence, *GIPR* represents a potential therapeutic in the treatment of diabetes. To test whether potassium was directly related to glucose metabolism, previous

hyperglycemic clamp studies were performed in healthy volunteers in whom hypokalemia was induced. One of these studies demonstrated that experimentally induced hypokalemia led to impaired glucose tolerance by reducing insulin secretion in response to glucose load. Potassium depletion was associated with a decrease in pancreatic β -cell sensitivity to hyperglycemia with a reduction in insulin release.⁴⁸ In another study, hypokalemia was induced through the use of thiazide diuretics. In a first stage, participants demonstrated subsequent impaired glucose tolerance, but after potassium supplementation was given, the defects in insulin release in response to glucose loads were corrected. This further implicates hypokalemia itself as being the causative agent of glucose abnormality.⁴⁹

Strengths and limitations

Strengths of the present study include the very large sample size with both genetic profiling and phenotypic data, which enabled us to detect a large number of genetic associations, the use of state-of-the-art methods to validate our results including a conservative analytical framework with strict multiple testing correction, and various downstream analyses to highlight important biology and potential genes related to urinary biomarkers. Our study is the most comprehensive study of the genetics of urinary biomarkers to date, combining GWASs, genetic correlation, and eQTL and mQTL colocalization analyses.

We also acknowledge some limitations. First, we did not replicate our findings in an external study sample because of the unavailability of cohorts with these phenotypes of comparable size. For this reason, we used a strict discovery-replication strategy. Second, participants included in our analyses were restricted to middle-aged and elderly individuals of European ancestry. Hence, the generalizability of our results to other age groups and ethnicities is unknown. Third, we analyzed a spot measurement of the electrolyte: creatinine ratio and, because of the unavailability in the UKB, we did not analyze other useful measures to provide a complete picture of renal function, such as 24-hour urine collections, food frequency questionnaires, blood biomarker data, urinary glucose, and/or urea.

CONCLUSIONS

We report 22 novel genome-wide significant loci associated with UACR, UK/UCr, UNa/UCr, and UNa/UK based on analyses in up to 337,536 individuals from the general population, confirming several known associations and providing new insights into the genetic basis of renal traits and their connection to chronic diseases. We detected strong genetic correlations between urinary biomarkers and significant genetic correlations of urinary biomarkers with several cardiometabolic traits. We also highlight several most plausible genes associated with these urinary biomarkers, such as *GIPR*, a potential diabetes drug target, as implicated in the genetic control of urinary potassium, and *NRBPI*, a locus associated with gout, as implicated in urinary sodium and albumin excretion.

METHODS

Phenotype

We analyzed the urinary biomarkers normalizing for creatinine (UACR, UK/UCr, and UNa/UCr) as well as UNa/UK. In addition, albumin was dichotomized for secondary analyses

into a binary trait (<30 mg/l = 0 and ≥ 30 mg/l = 1). The baseline characteristics of UKB participants who were included in the analyses ($n = 337,537$) are summarized in Table 4. The distribution of the 4 urinary biomarkers before normalization is shown in Supplementary Figure S8.

Genetic association analysis

We performed a discovery GWAS (random two-third sample from eligible individuals; $n = 225,024$) and a replication GWAS (remaining one-third of eligible individuals; $n = 112,512$). In addition, to maximize power for genetic correlation and colocalization analyses, we performed a meta-analysis of the discovery and replication samples.

Colocalization with eQTL and mQTL summary statistics

We performed SMR⁵⁰ with blood cis-eQTL and cis-mQTL data to evaluate the evidence for colocalization between all genome-wide significant independent variants and white blood cell gene expression or methylation signals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1 |. Manhattan plot for the discovery genome-wide association study of the urinary albumin: creatinine ratio (a), urinary potassium: creatinine ratio (b), urinary sodium: creatinine ratio (c), and urinary sodium: potassium ratio (d).

The nearest genes for each locus that showed a significant P value in the replication stage were labeled. Negative $\log_{10}$ -transformed P values for each single nucleotide polymorphism (y axis) are plotted by chromosomal position (x axis). The gray line represents the threshold for genome-wide statistically significant associations ($P = 5 \times 10^{-8}$). Red points represent significant hits.

Figure 2 | Genetic correlations of the urinary albumin: creatinine ratio (UACR) and urinary potassium: creatinine ratio (UK/UCr) (a) and of the urinary sodium: creatinine ratio (UNa/UCr) and urinary sodium: potassium ratio (UNa/UK) (b) with each other and other clinical traits. Significant correlations after Bonferroni correction ($P < 4.46 \times 10^{-4}$) are highlighted with a red triangle. 2hrGluAdjBMI, 2-h glucose adjusted for body mass index; AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFRcrea, estimated glomerular filtration rate based on serum creatinine; eGFRcys, estimated glomerular filtration rate based on serum cystatin C; FG, fasting glucose; FI, fasting insulin; HbA1C, glycated hemoglobin; HDL, high-

density lipoprotein; HR, heart rate; IS, ischemic stroke; LDL, low-density lipoprotein; SBP, systolic blood pressure; T2D, type 2 diabetes; TC, total cholesterol; TG, triglyceride; WHR, waist-to-hip ratio.

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Table 1 |

Genetic loci associated with the urinary albumin: creatinine ratio (UACR), urinary potassium: creatinine ratio (UK/UCr), urinary sodium: creatinine ratio (UNa/UCr), and urinary sodium: potassium ratio (UNa/UK) in the discovery and replication genome-wide association studies^a

CHR	POS	SNP	Function	Nearest gene (bp)	EA	OA	EAF	Discovery			Replication		
								β	SE	P	β	SE	P
UACR													
1	47961691	rs10157710	Intergenic	FOXD2 (55,328)	T	C	0.8009	0.026	0.004	1.11×10^{-13}	0.023	0.005	6.77×10^{-6}
1	171435542	rs16864515	Intergenic	PRRC2C (19,148)	A	C	0.0963	-0.029	0.005	1.37×10^{-9}	-0.004	0.007	5.17×10^{-1}
2	27598097	rs4665972	Intronic	SNX17	C	T	0.6071	-0.016	0.003	3.66×10^{-8}	-0.020	0.004	2.01×10^{-6}
2	203714973	rs10207567	Intronic	JCAL	C	G	0.8130	0.021	0.004	6.63×10^{-9}	0.017	0.005	1.09×10^{-3}
2	211540507	rs1047891	Missense	CPS1	A	C	0.3160	-0.019	0.003	3.23×10^{-10}	-0.015	0.004	4.25×10^{-4}
2	226985504	rs185291443	Intergenic	NYAP2 (466,770)	A	C	0.0009	0.539	0.051	6.71×10^{-26}	0.509	0.073	2.34×10^{-12}
2	227459951	rs71431010	Intergenic	MIR5702 (63,475)	A	G	0.0005	0.749	0.068	1.70×10^{-28}	0.762	0.097	2.97×10^{-15}
2	228511926	rs34823645	Intronic	C2orf83	C	T	0.0007	0.530	0.061	3.30×10^{-18}	0.459	0.086	9.84×10^{-8}
2	229160200	rs35311980	Intergenic	PID1 (555,042)	T	C	0.0009	0.423	0.048	2.14×10^{-18}	0.288	0.070	4.39×10^{-5}
4	77019581	rs6829592	Intronic	ART3	G	A	0.2676	-0.018	0.003	3.88×10^{-8}	-0.002	0.005	6.06×10^{-1}
4	190769223	rs4109437	Intronic	FRG1-DT	A	G	0.0382	0.060	0.007	8.55×10^{-16}	0.053	0.011	4.90×10^{-7}
7	17284577	rs4410790	Intronic	AHR	C	T	0.6348	0.023	0.003	1.77×10^{-14}	0.026	0.004	8.17×10^{-10}
8	126500031	rs28601761	Intronic	TRIB1	G	C	0.4203	-0.017	0.003	9.58×10^{-9}	-0.018	0.004	8.32×10^{-6}
10	16932384	rs45551835	Missense	CUBN	A	G	0.0144	0.198	0.012	4.47×10^{-62}	0.170	0.017	2.49×10^{-24}
10	16940846	rs45619139	Intronic	CUBN	G	C	0.1016	0.063	0.005	1.09×10^{-40}	0.050	0.007	5.51×10^{-14}
10	16992011	rs141640975	Missense	CUBN	A	G	0.0026	0.424	0.028	1.26×10^{-51}	0.475	0.039	4.13×10^{-34}
10	17005743	rs539606836	Intronic	CUBN	A	G	0.0003	0.627	0.099	1.95×10^{-10}	0.507	0.132	1.26×10^{-4}
10	17025127	rs572663329	Intronic	CUBN	G	C	0.0003	0.633	0.095	2.90×10^{-11}	0.467	0.130	3.39×10^{-4}
10	77893686	rs67339103	Intronic	LRMDA	A	G	0.2131	0.021	0.003	2.31×10^{-9}	0.017	0.005	6.96×10^{-4}
15	45713801	rs60476496	Intergenic	GATM (19,276)	T	C	0.2549	-0.021	0.003	3.01×10^{-10}	-0.014	0.005	2.02×10^{-3}
15	75027880	rs2472297	Intergenic	CYP11A1 (9928)	T	C	0.2663	0.026	0.003	2.87×10^{-16}	0.022	0.005	1.28×10^{-6}
UK/UCr													
1	72748567	rs66495454	Upstream	NEGR1 (149)	GTCCT	G	0.3781	0.016	0.003	3.96×10^{-8}	0.009	0.004	3.01×10^{-2}

CHR	POS	SNP	Function	Nearest gene (bp)	EA	OA	EAF	Discovery			Replication		
								β	SE	P	β	SE	P
2	211540507	rs1047891	Exonic	<i>CPS1</i>	A	C	0.3151	-0.033	0.003	1.38×10^{-27}	-0.029	0.004	1.20×10^{-11}
3	27413566	rs4973766	Downstream	<i>SLC4A7</i> (647)	T	C	0.4558	-0.021	0.003	5.92×10^{-14}	-0.023	0.004	1.06×10^{-8}
10	75640062	10:75640062_GTTTCG	Intergenic	<i>CAMK2G</i> (5718)	G	GTTCA	0.7645	-0.020	0.003	3.41×10^{-9}	-0.016	0.005	6.45×10^{-4}
14	33367658	rs10134619	Intergenic	<i>NP433</i> (36,481)	C	T	0.1425	-0.022	0.004	3.22×10^{-8}	0.002	0.006	7.31×10^{-1}
15	45693164	rs353335867	Intronic	<i>GATM</i>	CT	C	0.2485	-0.024	0.003	9.39×10^{-14}	-0.022	0.005	1.52×10^{-6}
15	75027880	rs2472297	Intergenic	<i>CYP11A1</i> (9928)	T	C	0.2665	0.022	0.003	1.92×10^{-12}	0.018	0.004	3.76×10^{-5}
16	68301985	rs2863980	Intronic	<i>SLC7A6</i>	C	A	0.6261	0.016	0.003	4.22×10^{-8}	0.007	0.004	1.05×10^{-1}
17	35806016	rs562250921	Intronic	<i>TADA2A</i>	G	C	0.0044	-0.122	0.022	1.71×10^{-8}	-0.042	0.030	1.64×10^{-1}
19	41352257	19:41352257_CTTG	Intronic	<i>CYP2A6</i>	G	GT	0.0850	-0.028	0.005	3.90×10^{-8}	-0.014	0.007	5.28×10^{-2}
19	46180414	rs34783010	Intronic	<i>GIPR</i>	T	G	0.1933	0.026	0.004	1.26×10^{-13}	0.025	0.005	4.74×10^{-7}
<i>UNa/UCr</i>													
2	27730940	rs1260326	Exonic	<i>GCKR</i>	C	T	0.6082	-0.029	0.003	2.11×10^{-21}	-0.0255	0.0043	2.80×10^{-9}
2	211540507	rs1047891	Exonic	<i>CPS1</i>	A	C	0.3151	-0.028	0.003	3.21×10^{-18}	-0.0245	0.0045	5.86×10^{-8}
2	217666174	rs2541387	ncRNA_intronic	<i>FABP5P14</i> (4285)	C	A	0.5702	-0.019	0.003	1.05×10^{-10}	-0.0092	0.0043	2.98×10^{-2}
3	141154542	rs6440008	Intronic	<i>ZBTB38</i>	C	T	0.3870	-0.017	0.003	1.61×10^{-8}	-0.0173	0.0043	6.67×10^{-5}
3	168824936	rs545727790	Intronic	<i>MECOM</i>	A	T	0.0003	-0.518	0.095	4.64×10^{-8}	0.0815	0.1332	5.41×10^{-1}
4	9948870	rs4276278	Intronic	<i>SLC2A9</i>	C	T	0.4327	0.017	0.003	9.33×10^{-9}	0.0065	0.0042	1.22×10^{-1}
5	52786075	rs12054747	Intergenic	<i>FST</i> (3111)	T	C	0.2151	-0.020	0.004	4.07×10^{-8}	-0.0030	0.0051	5.57×10^{-1}
5	84251574	rs144795378	Intergenic		C	G	0.0079	0.104	0.017	2.13×10^{-9}	-0.0252	0.0254	3.20×10^{-1}
7	73034929	rs71556736	Intronic	<i>MLXIP1</i>	T	C	0.1305	-0.024	0.004	2.44×10^{-8}	-0.0197	0.0062	1.51×10^{-3}
8	51947549	rs4873492	Intergenic	<i>SNTG1</i> (240,870)	T	C	0.1704	0.023	0.004	2.83×10^{-9}	0.0189	0.0056	7.80×10^{-4}
8	126482077	rs2954021	ncRNA_intronic	<i>TRIB1</i> (31,429)	G	A	0.5058	-0.017	0.003	1.56×10^{-8}	-0.0132	0.0042	1.75×10^{-3}
15	45647522	rs113769380	Upstream	<i>RNU6-953P</i> (438)	GGGT	G	0.2379	-0.023	0.004	1.32×10^{-10}	-0.0135	0.0051	7.60×10^{-3}
<i>UnaUK</i>													
1	72825144	rs6699744	Intergenic	<i>RPL3IP12</i> (57,631)	T	A	0.6118	-0.018	0.003	7.72×10^{-9}	-0.0077	0.0043	7.15×10^{-2}
2	27598097	rs4665972	Intronic	<i>SNX17</i>	C	T	0.6082	-0.026	0.003	1.40×10^{-17}	-0.0203	0.0043	2.24×10^{-6}
2	171958363	rs10208341	Intronic	<i>TLK1</i>	A	G	0.3597	0.019	0.003	6.78×10^{-10}	0.0102	0.0043	1.88×10^{-2}
3	35683104	rs9860326	Intronic	<i>ARPP21</i>	G	C	0.3287	0.018	0.003	1.36×10^{-8}	0.0051	0.0044	2.53×10^{-1}

CHR	POS	SNP	Function	Nearest gene (bp)	EA	OA	EAF	Discovery			Replication		
								β	SE	P	β	SE	P
3	141150026	rs7625643	Intronic	<i>ZBTB38</i>	G	A	0.4488	-0.019	0.003	6.62×10^{-10}	-0.0136	0.0042	1.32×10^{-3}
5	87712913	rs6452788	ncRNA_ntronic	<i>TMEM161B-AS1</i>	A	G	0.2361	-0.021	0.003	7.50×10^{-10}	-0.0200	0.0049	4.92×10^{-5}
14	69663339	14:69663339_CTTC	ncRNA_ntronic	<i>EXD2</i>	C	CTT	0.4830	0.017	0.003	1.47×10^{-8}	0.0081	0.0042	5.70×10^{-2}
19	46182304	rs10423928	Intronic	<i>GIPR</i>	A	T	0.1934	-0.023	0.004	2.93×10^{-10}	-0.0183	0.0053	5.12×10^{-4}

CHR, chromosome; EA, effect allele; EAF, effect allele frequency; OA, other allele; POS, position; SNP, single-nucleotide polymorphism.

^a Bonferroni significant threshold for replication: UACR, $P = 3.57 \times 10^{-3}$; UK/UCr, $P = 4.55 \times 10^{-3}$; UNa/UCr, $P = 4.17 \times 10^{-3}$; UNa/UK, $P = 6.25 \times 10^{-3}$.

Associations significant after replication are highlighted in bold.

Table 2 |

Genome-wide heritability of the urinary albumin: creatinine ratio (UACR), urinary potassium: creatinine ratio (UK/UCr), urinary sodium: creatinine ratio (UNa/UCr), and urinary sodium: potassium ratio (UNa/UK)

Variable	h2g_obs	h2g_obs_se	h2g_int	h2g_int_se
UACR	0.053	0.003	1.022	0.008
UK/UCr	0.053	0.003	1.021	0.008
UNa/UCr	0.042	0.003	1.024	0.009
UNa/UK	0.051	0.003	1.024	0.009

h2g, genome-wide heritability; int, intercept; obs, observed.

Table 3|

Significant independent expression quantitative trait locus (eQTL) and methylation quantitative trait locus (mQTL) probe colocalizations for the urinary albumin: creatinine ratio (UACR), urinary potassium: creatinine ratio (UK/UCr), urinary sodium: creatinine ratio (UNa/UCr), and urinary sodium: potassium ratio (UNa/UK)

ProbeID	ProbeChr	Gene	Probe_bp	topSNP	A1	A2	Freq	b_SMR	se_SMR	P_SMR	P_HEIDI
<i>eQTL</i>											
<i>UACR</i>											
ILMN_1670096	2	<i>NRBP1</i>	27664880	rs11684134	G	A	0.417	0.110	0.030	2.20×10^{-4}	0.311
<i>UNa/UCr</i>											
ILMN_1670096	2	<i>NRBP1</i>	27664880	rs11684134	G	A	0.417	0.136	0.034	5.69×10^{-5}	1.40×10^{-1}
<i>UNa/UK</i>											
ILMN_1670096	2	<i>NRBP1</i>	27664880	rs11684134	G	A	0.417	0.129	0.033	8.24×10^{-5}	1.64×10^{-1}
<i>mQTL</i>											
<i>UACR</i>											
cg14242246	2	<i>CAD</i>	27434262	rs62130680	C	T	0.145	-0.012	0.003	1.19×10^{-5}	2.41×10^{-1}
cg13521797	2	<i>ICAIL</i>	203737787	rs74675536	A	G	0.129	-0.054	0.012	4.66×10^{-6}	7.47×10^{-2}
cg05158606	2	<i>ICAIL</i>	204194156	rs1971819	G	C	0.180	0.079	0.017	6.68×10^{-6}	1.24×10^{-1}
cg20080878	8		126479070	rs699569	G	A	0.453	-0.044	0.009	3.65×10^{-7}	6.35×10^{-2}
cg20381115	15	<i>GATM</i>	45671148	rs2172874	G	T	0.276	-0.027	0.004	8.15×10^{-11}	1.44×10^{-1}
cg05926586	15	<i>CCDC33</i>	74592786	rs12904134	G	A	0.529	0.019	0.003	2.85×10^{-10}	5.20×10^{-2}
cg06369322	15	<i>CCDC33</i>	74607544	rs2415239	C	T	0.353	0.072	0.018	5.47×10^{-5}	4.04×10^{-1}
cg05454635	15		74657911	rs8032336	T	A	0.366	-0.054	0.013	1.65×10^{-5}	2.42×10^{-1}
cg24482024	15		74660566	rs35807116	C	T	0.431	-0.045	0.008	4.79×10^{-8}	6.64×10^{-2}
cg19144497	15		74836094	rs9672559	A	G	0.116	-0.056	0.016	5.99×10^{-4}	1.64×10^{-1}
cg20004910	15	<i>EDC3</i>	75018852	rs7161903	G	A	0.150	0.045	0.010	1.37×10^{-5}	3.97×10^{-1}
cg01359532	15		75045126	rs11072508	C	T	0.395	-0.053	0.008	1.18×10^{-10}	1.28×10^{-1}
cg14664628	15	<i>SCAMP2</i>	75095509	rs3765066	G	A	0.379	-0.055	0.011	2.25×10^{-7}	7.03×10^{-2}
cg10253484	15		75165896	rs11857376	A	G	0.546	-0.035	0.005	1.54×10^{-13}	6.58×10^{-2}
cg27066162	15		75199472	rs7497026	T	C	0.487	-0.078	0.018	2.06×10^{-5}	7.93×10^{-2}
cg15611336	15	<i>SCAMP5</i>	75248496	rs35103257	G	T	0.545	0.074	0.016	2.44×10^{-6}	3.10×10^{-1}

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ProbeID	ProbeChr	Gene	Probe_bp	topSNP	A1	A2	Freq	b_SMR	se_SMR	P_SMR	P_HEIDI
cg21236593	15		75287447	rs62027288	C	T	0.420	0.067	0.016	1.92×10^{-5}	6.42×10^{-2}
cg01701819	15	SCAMP5	75287824	rs12911421	C	A	0.239	0.013	0.004	3.68×10^{-4}	2.58×10^{-1}
cg24222504	15	SNUPN	75918608	rs56178382	T	A	0.226	-0.076	0.018	2.14×10^{-5}	9.52×10^{-2}
UK/UCr											
cg06730238	3	NEK10	27131936	rs7618713	C	T	0.209	0.056	0.016	3.48×10^{-4}	2.10×10^{-1}
cg16540259	10	NDST2	75572220	rs13013	C	A	0.376	-0.077	0.019	3.70×10^{-5}	7.41×10^{-1}
cg00564723	10	CAMK2G	75632066	rs2688626	G	A	0.225	0.035	0.006	1.03×10^{-9}	2.82×10^{-1}
cg06521280	10	PLAU	75671378	rs2227560	A	G	0.228	0.062	0.015	2.75×10^{-5}	1.44×10^{-1}
cg18435832	15	GATM	45671155	rs2172874	G	T	0.276	-0.032	0.004	1.90×10^{-15}	5.48×10^{-2}
cg05019826	15		74891207	rs2472297	T	C	0.215	0.079	0.015	8.12×10^{-8}	2.34×10^{-1}
cg05549655	15		75019143	rs12903896	C	T	0.405	-0.057	0.015	1.81×10^{-4}	7.67×10^{-1}
cg12101586	15		75019203	rs11072508	C	T	0.395	-0.062	0.017	2.45×10^{-4}	7.52×10^{-1}
cg14664628	15	SCAMP2	75095509	rs3765066	G	A	0.379	-0.035	0.009	1.92×10^{-4}	2.49×10^{-1}
cg04877966	15	ULK3	75135169	rs9210	T	C	0.310	0.019	0.005	4.93×10^{-5}	9.10×10^{-2}
cg10253484	15		75165896	rs11857376	A	G	0.546	-0.020	0.004	7.28×10^{-6}	3.88×10^{-1}
cg15611336	15	SCAMP5	75248496	rs35103257	G	T	0.545	0.051	0.013	1.27×10^{-4}	3.05×10^{-1}
cg17716663	19	ERCC1	45978434	rs8106229	G	T	0.406	0.017	0.005	4.21×10^{-4}	1.29×10^{-1}
cg19822309	19	GIPR	46181546	rs10423928	A	T	0.214	-0.032	0.004	3.34×10^{-16}	2.87×10^{-1}
cg15455864	19	SYMPK	46319398	rs1132645	C	G	0.318	-0.040	0.011	1.58×10^{-4}	4.78×10^{-1}
UNa/UCr											
cg25309888	2		27988724	rs12477908	A	C	0.282	-0.032	0.008	9.01×10^{-5}	1.23×10^{-1}
cg01879723	3	ZBTB38	141119262	rs34169305	T	C	0.307	0.068	0.017	6.76×10^{-5}	5.14×10^{-1}
cg13411656	3	ZBTB38	141121016	rs4683605	A	C	0.425	0.054	0.010	1.01×10^{-7}	2.39×10^{-1}
cg03060555	3	ZBTB38	141131189	rs13069734	A	G	0.310	0.109	0.023	1.61×10^{-6}	8.60×10^{-2}
cg08082507	7	GTF2IRD2	72685715	rs707395	T	C	0.185	0.051	0.013	4.35×10^{-5}	7.12×10^{-2}
cg14087351	7	MLXIP1	73037990	rs3812316	G	C	0.116	0.024	0.004	3.83×10^{-9}	2.96×10^{-1}
cg20080878	8		126479070	rs6999569	G	A	0.453	-0.047	0.009	1.54×10^{-7}	2.13×10^{-1}
UNa/UK											
cg12404044	2		26911734	rs1275985	C	T	0.407	-0.012	0.003	3.07×10^{-4}	1.84×10^{-1}

ProbeID	ProbeChr	Gene	Probe_bp	topSNP	A1	A2	Freq	b_SMR	se_SMR	P_SMR	P_HEIDI
cg27084654	3	ZBTB38	141118615	rs13098180	A	T	0.383	0.050	0.011	6.14×10^{-6}	1.85×10^{-1}
cg01879723	3	ZBTB38	141119262	rs34169305	T	C	0.307	0.069	0.017	5.99×10^{-5}	3.18×10^{-1}
cg13411656	3	ZBTB38	141121016	rs4683605	A	C	0.425	0.055	0.010	4.87×10^{-8}	2.88×10^{-1}
Cg03060555	3	ZBTB38	141131189	rs13069734	A	G	0.310	0.109	0.023	1.43×10^{-6}	7.46×10^{-2}
cg10604528	5		87437959	rs7448105	C	T	0.197	-0.056	0.012	3.01×10^{-6}	1.82×10^{-1}
Cg09277709	19	SIX5	46224285	rs2341097	T	C	0.323	-0.054	0.016	6.90×10^{-4}	8.33×10^{-2}
cg24278423	19	SYMPK	46367240	rs11083783	C	T	0.083	-0.040	0.010	1.18×10^{-4}	5.75×10^{-1}

A1, effect allele; A2, other allele; b, beta; bp, base position; Chr, chromosome; Freq, minor allele frequency; HEIDI, heterogeneity in dependent instruments; SMR, summary data-based Mendelian randomization; SNP, single-nucleotide polymorphism.

Table 4 |

Baseline characteristics of UK Biobank participants included in the present study (discovery, n = 225,024; replication, n = 112,512)

Variable	Discovery	Replication
Sex: female	120,921 (53.74)	60,347 (53.64)
Age (yr)	56.88 ± 7.99	56.87 ± 7.98
T2D	11,068 (4.92)	5,604 (4.98)
Smoking: current	22,735 (10.10)	11,249 (10.00)
SBP (mm Hg)	140 ± 20	140 ± 20
DBP (mm Hg)	82 ± 11	82 ± 11
BMI (kg/m ²)	27.39 ± 4.75	27.42 ± 4.76
WHR	0.87 ± 0.09	0.87 ± 0.09
Body fat (%)	31.34 ± 8.53	31.37 ± 8.51
Weekly alcohol intake (g)	134.32 ± 159.45	134.68 ± 160.51
UACR	17.526 ± 76.969	17.442 ± 74.064
UK/UCr	8.476 ± 3.890	8.444 ± 3.993
UNa/UCr	10.602 ± 6.672	10.619 ± 7.736
UNa/UK	1.400 ± 0.873	1.406 ± 0.874

BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; T2D, type 2 diabetes; UK/UCr, urinary potassium: creatinine ratio; UACR, urinary albumin: creatinine ratio; UNa/UCr, urinary sodium: creatinine ratio; UNa/UK, urinary sodium: potassium ratio; WHR, waist-to-hip ratio.

Data are mean ± SD or n (%).