Communication

Caffeine Intake, Plasma Caffeine Level, and Kidney Function: A Mendelian Randomization Study

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Abstract: Caffeine is a psychoactive substance widely consumed worldwide, mainly via sources such as coffee and tea. The effects of caffeine on kidney function remain unclear. We leveraged the genetic variants in the *CYP1A2* and *AHR* genes via the two-sample Mendelian randomization (MR) framework to estimate the association of genetically predicted plasma caffeine and caffeine intake on kidney traits. Genetic association summary statistics on plasma caffeine levels and caffeine intake were taken from genome-wide association study (GWAS) meta-analyses of 9876 and of >47,000 European ancestry individuals, respectively. Genetically predicted plasma caffeine levels were associated with a decrease in estimated glomerular filtration rate (eGFR) measured using either creatinine or cystatin C. In contrast, genetically predicted caffeine intake was associated with an increase in eGFR and a low risk of chronic kidney disease. The discrepancy is likely attributable to faster metabolizers of caffeine consuming more caffeine-containing beverages to achieve the same pharmacological effect. Further research is needed to distinguish whether the observed effects on kidney function are driven by the harmful effects of higher plasma caffeine levels or the protective effects of greater intake of caffeine-containing beverages, particularly given the widespread use of drinks containing caffeine and the increasing burden of kidney disease.

Keywords: caffeine level; caffeine intake; genetically predicted coffee consumption; causal inference; Mendelian randomization; kidney function; estimated glomerular filtration rate

1. Introduction

Caffeine, a central nervous system stimulant, is present in coffee beans, tea leaves, and cacao beans and is commonly added to energy and carbonated drinks as well as analgesic drugs [1]. By inhibiting phosphodiesterase enzyme, antagonizing adenosine receptors, and activating ryanodine receptors, the adverse effects of caffeine on kidney function and structure have been postulated [2,3].

Increasing evidence has indicated that caffeine may have detrimental effects on kidney function, although the literature remains controversial. Animals' investigations have shown an increase in proteinuria and renal vascular resistance, leading to marked renal failure [3,4]. In patients suffering from autosomal dominant polycystic kidney disease, studies have reported an increased risk of cyst enlargement with increasing caffeine intake [5,6], while others did not show such consequences [7,8]. Observational studies and meta-analyses observed a lower risk of developing chronic kidney disease (CKD) with increasing coffee consumption [9–14]. However, these studies suffered potential bias related to their observational design and assessed caffeine exposure as a self-reported intake of cups of coffee/day, not accounting for the wide interindividual variation in the metabolism of caffeine that could modify any associations. Indeed, a recent study in 1180 adults showed that the risks of albuminuria and hyperfiltration were over 2-fold higher among slow metabolizers of caffeine who consumed more than three cups of coffee per day compared to those with low coffee intake, while there was no difference among fast metabolizers [15]. Over 95% of caffeine in humans is metabolized via cytochrome P450 1A2 (CYP1A2), and the gene expression of this enzyme is regulated via the aryl hydrocarbon receptor (AHR) [16,17]. The heritability of coffee consumption was estimated at 36% to 58% [18].

Here, we leveraged the genetic variants in the *CYP1A2* and *AHR* genes via the two-sample Mendelian randomization (MR) framework to estimate the association of genetically predicted plasma caffeine level and caffeine intake on kidney traits, which comprised glomerular filtration rate estimated from creatinine (eGFRcrea) and glomerular filtration rate estimated from cystatin-c (eGFRcyst), urinary sodium, urinary, blood urea nitrogen (BUN), albumin-creatinine ratio (UACR), and risk of CKD. With this study, we aimed to overcome the limitations of traditional observational methods, including environmental confounding and reverse causation, by employing the MR paradigm. In particular, because the genetic variants used as instrumental variables in MR are randomly allocated at conception, their associations are not typically affected by environmental confounding factors. Additionally, their allocation precedes the exposure and outcome, protecting against reverse causation bias. Further, we consider both caffeine intake and plasma caffeine levels, respectively, as the relevant exposures of interest.

2. Materials and Methods

2.1. Plasma Caffeine Level Measurement and Data Sources

Genetic association summary statistics for plasma caffeine level were retrieved from a meta-analysis of six genome-wide association studies (GWAS) on caffeine metabolites: the Prospective Study of the Vasculature in Uppsala Seniors (PIVUS), the Study of Health in Pomerania TREND (SHIP-TREND), the Swiss Kidney Project on Genes in Hypertension (SKIPOGH), TwinGene, TwinsUK and the Uppsala Longitudinal Study of Adult Men (ULSAM), including a total of 9876 European ancestry individuals [17]. Plasma caffeine level was measured with ultraperformance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) in ULSAM, PIVUS, TwinGene, SKIPOGH cohorts, or ultra-performance liquid chromatography-electrospray tandem mass spectrometry (UPLC-ESI-MS/MS) in SHIP-TREND and TwinsUK cohorts. Details are shown in Appendix A.

2.2. Definition of Caffeine Intake and Data Sources

Caffeine intake summary statistics were derived from a GWAS meta-analysis including >47,000 individuals of European descent from 5 studies (Atherosclerosis Risk in Communities (ARIC), the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO), the Nurses' Health Study (NHS), the Health Professionals Follow-Up Study (HPFS), Women's Genome Health Study (WGHS)) [16]. In each study, the caffeine intake was assessed with a food frequency questionnaire (FFQ). Raw caffeine intake values were skewed across studies and adjusted for age, sex, case–control status, study site, smoking, and study-specific eigenvectors. Details are shown in Appendix A.

2.3. Definition of the Outcomes and Data Sources

Summary statistics related to estimated glomerular filtration rate (eGFR), urinary albumin-creatinine ratio (UACR), blood urea nitrogen (BUN), and chronic kidney disease (CKD) were retrieved from CKDGen consortium GWASs [18–21]. The eGFR data were obtained from a meta-analysis of CKDGen and UK Biobank [19]. The creatinine-based eGFR (eGFRcrea) was available for >1 million individuals of European ancestry and was computed using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [22]. The serum cystatin-C-based eGFR (eGFRcyst) was calculated using the CKD-EPI formula [22], and the summary statistics were available only in the trans-ancestry population (n = 460,826). As described in the original study, both eGFR estimations were winsorized between 15 and 200 mL/min/1.73 m^2 and log transformed [19]. Urinary sodium was obtained from 326,831 individuals in UK Biobank GWAS summary statistics [23]. BUN was computed by multiplying blood urea (mg/dL) by 2.8 [20]. UACR (mg/g) was calculated as the ratio of urinary albumin (mg/L) and urinary creatinine (in mg/dL) multiplied by 100 [21]. Both measures were log-transformed. CKD (defined as eGFRcrea below 60 mL/min/1.73 m^2) was available for 41,395 cases and 439,303 controls [20]. Details are shown in Appendix A.

2.4. Statistical Analysis

As instruments, we selected single nucleotide polymorphisms (SNPs) within a 100 kb window of the *CYP1A2* and *AHR* gene regions that were associated with plasma caffeine levels [17] or caffeine intake [16], respectively. These genes were chosen because of their role in increasing the metabolism of caffeine [17] and have been used as instruments for plasma caffeine level and caffeine intake in previous MR analyses [24,25]. The SNPs within each locus were in linkage disequilibrium (r^2 ranging from 0.21 to 0.96 in European populations). Therefore, we selected the strongest signal at each locus, that is, rs4410790 at AHR and rs242297 at CYP1A2 for plasma caffeine level and rs4410790 at *AHR* and rs2470893 at *CYP1A2* for caffeine intake, with details shown in Table 1.

Table 1. Association of the genetic variants with the exposures.

Exposure	Effect Allele	Other Allele	Beta	SE	*p*-Value	Gene	EAF
Plasma caffeine							
rs4410790	T	C	0.109	0.015	1.80×10^{-10}	*AHR*	0.36
rs2472297	C	T	0.150	0.016	1.00×10^{-17}	*CYP1A2*	0.73
Caffeine intake							
rs4410790	C	T	0.150	0.017	2.36×10^{-19}	*AHR*	0.38
rs2470893	T	C	0.120	0.016	5.15×10^{-14}	*CYP1A2*	0.31

Abbreviation: SE: standard error; EAF: effect allele frequency.

Two-sample summary data MR analysis was performed using the random effects inverse-variance weighted method. This generates Wald ratios as the variant-outcome association divided by the variant-exposure association, with MR standard errors estimated as the standard error of the variant-outcome association divided by the variant-exposure association. Estimates for the two instrument variants were pooled via random-effects inverse-variance meta-analysis. The statistical analysis and figure were generated using R statistical software version 4.3.1.

3. Results

The MR analysis identified that a 1-SD increase in genetically predicted plasma caffeine level was associated with a decrease in eGFR (beta [95% confidence interval] = −0.025 [−0.028,−0.022]; $p = 4.1 \times 10^{-53}$ for log(eGFRcrea); −0.018 [−0.025,−0.011]; $p = 1.6 \times 10^{-6}$ for log(eGFRcyst)), and log(UACR) (−0.179 [−0.215,−0.143]; $p = 1.7 \times 10^{-22}$). Genetically

predicted plasma caffeine levels were also associated with higher urinary sodium levels (0.149 [0.115,0.170]; $p = 1.6 \times 10^{-24}$) and BUN (0.04 [0.025,0.055]; $p = 1.9 \times 10^{-7}$).

In contrast, higher genetically predicted caffeine intake associated with an increase in both eGFR measures (0.020 [0.014,0.015]; $p = 1.8 \times 10^{-11}$ for log(eGFRcrea) and 0.013 [0.03,0.02]; $p = 0.01$, for log(eGFRcyst)), and log(UACR) (0.163 [0.120,0.206]; $p = 1.6 \times 10^{-3}$). A 1-SD increase in genetically predicted caffeine intake was also associated with a lower risk of CKD (odds ratio [95% confidence interval]: 0.84 [0.75,0.94]; $p = 0.003$), lower urinary sodium (-0.125 [$-0.158,-0.093$]; $p = 2.6 \times 10^{-14}$), and BUN (-0.034 [$-0.064,-0.005$]; $p = 0.023$). A graphical summary of the results is shown in Figure 1.

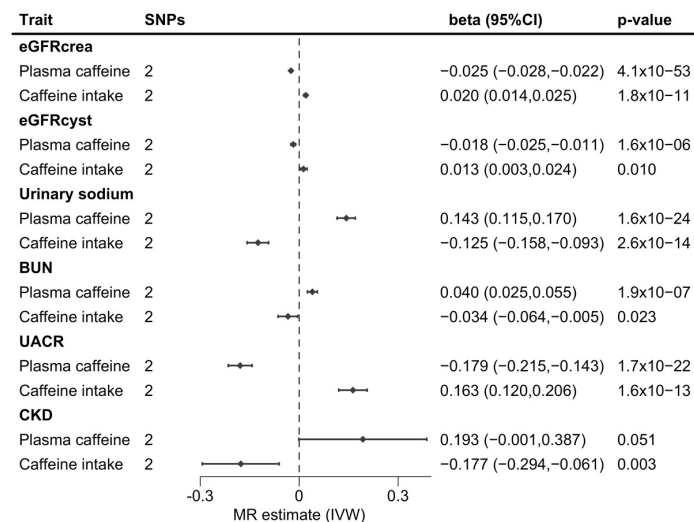| Trait	SNPs		beta (95%CI)	p-value
eGFRcrea				
Plasma caffeine	2		−0.025 (−0.028,−0.022)	4.1x10−53
Caffeine intake	2		0.020 (0.014,0.025)	1.8x10−11
eGFRcyst				
Plasma caffeine	2		−0.018 (−0.025,−0.011)	1.6x10−06
Caffeine intake	2		0.013 (0.003,0.024)	0.010
Urinary sodium				
Plasma caffeine	2		0.143 (0.115,0.170)	1.6x10−24
Caffeine intake	2		−0.125 (−0.158,−0.093)	2.6x10−14
BUN				
Plasma caffeine	2		0.040 (0.025,0.055)	1.9x10−07
Caffeine intake	2		−0.034 (−0.064,−0.005)	0.023
UACR				
Plasma caffeine	2		−0.179 (−0.215,−0.143)	1.7x10−22
Caffeine intake	2		0.163 (0.120,0.206)	1.6x10−13
CKD				
Plasma caffeine	2		0.193 (−0.001,0.387)	0.051
Caffeine intake	2		−0.177 (−0.294,−0.061)	0.003

−0.3   0   0.3
MR estimate (IVW)

Figure 1. Forest plot of two-sample MR estimates the effects of genetically predicted plasma caffeine levels or caffeine intake using the AHR and CYP1A2 genes on kidney traits. Abbreviation: MR, Mendelian randomization; SNP, single-nucleotide polymorphism; CI, confident interval; eGFRcrea, glomerular filtration rate estimated from creatinine; eGFRcys, glomerular filtration rate estimated from cystatin-c; BUN, blood urea nitrogen; UACR, albumin-creatinine; CKD, chronic kidney disease; IVW, inverse-variance weighted two-sample Mendelian randomization analysis.

4. Discussion

This study supports evidence of a detrimental effect of higher genetically predicted plasma caffeine levels on kidney function according to two different measures of eGFR. Additionally, the results showed adverse associations of genetically predicted plasma caffeine levels with biological markers of CKD progression, including urinary sodium and BUN [26–28], but not UACR. Our results provide evidence supporting similar detrimental effects to those found in experimental studies investigating long-term caffeine consumption on rats and mice carrying less genetic variability [4,6]. It was suggested that caffeine modulates changes in eGFR via diuresis and natriuresis through binding adenosine receptors, interferes with the anti-inflammatory effects of adenosine, and stimulates some of the key proliferative mechanisms involved in glomerular remodeling and sclerosis [3,29]. It is interesting to note that we found no evidence of a detrimental effect of genetically predicted plasma caffeine levels on albuminuria, reinforcing the idea that the potentially detrimental effects of caffeine do not act via an increase in glomerular capillary hydraulic pressure which would cause glomerular damage and therefore albuminuria, but via other mechanisms such as those mentioned in the experimental studies cited above.

In contrast, a protective effect of higher genetically predicted caffeine intake on kidney function was found. The discrepancy is likely attributable to faster metabolizers of caffeine requiring a greater caffeine intake to achieve the same stimulant effect. In addition, this could potentially explain the beneficial or absence of association between coffee intake and CKD shown in the literature because all studies assessed coffee consumption rather than plasma caffeine levels as the exposure. Indeed, a recent study that investi-

gated caffeine and kidney function provided evidence that coffee has different effects on kidney function in slow versus fast metabolizers [15]. When assessing the effect of genetically predicted amount of caffeine intake on kidney function, we found, however, a potential protective effect similar to that found in most prospective observational studies and meta-analyses [9–14]. This result was also similar to a recent MR study conducting a two-sample MR of genetically predicted coffee consumption using also the CKDGen Consortium GWAS [25]. They selected 25 SNPs, however, including the ones we considered, and found that an extra cup of coffee per day conferred a protective effect against CKD. The discrepancy in the effect of caffeine on kidney function when assessing caffeine levels or coffee consumption as exposure in our study and the literature is of high importance. This provides evidence that there may be an interaction between the amount of coffee consumption and genetic predisposition to metabolize this caffeine on the effect of caffeine on kidney function. Future research exploring the effect of coffee on an outcome should take this into account.

However, with our current study, it is not possible to distinguish whether the observed evidence for the effects of caffeine on kidney traits is driven by the harmful effects of plasma caffeine in slower metabolizers or the protective effects of greater caffeine intake in faster metabolizers. The former may be explained by the diuretic properties of caffeine having harmful effects on kidney function, while the latter may be due to the protective effects of greater caffeine intake through improved hydration status, given that the majority of caffeine intake is via beverages. Further research is warranted to disentangle these findings, particularly given the widespread use of caffeine-containing drinks and the increasing burden of kidney disease.

The MR design used in our study was a strength for reducing bias from environmental factors when assessing associations to infer causal effects. Moreover, because genetic variants are fixed at conception, reverse causation is unlikely. A limitation of MR is pleiotropic effects (i.e., the plasma caffeine level SNPs affect the outcome not only through the exposure), which was minimized in this study by selecting genetic instruments with effects that plausibly act directly on the trait in question (i.e., genes encoding enzymes with an established role in caffeine metabolism, either directly via the CYP1A2 enzyme or indirectly (AHR) by the regulation of CYP1A2 expression. A limitation of this study is that our findings might not be generalizable to a population of non-European ancestry because all genetic summary statistics are from European ancestry. Nevertheless, a previous study confirmed that *AHR* and *CYP1A2* polymorphisms are associated with caffeine consumption in a non-European population, which provides an argument that the genetic predictors of plasma caffeine level we used might be similar in non-European ethnicity individuals [30]. Another potential shortcoming of our study is that we could not conduct statistical sensitivity analyses using commonly employed MR methods for detecting possible pleiotropy, such as MR-Egger regression and MR-PRESSO, because those approaches require at least three or more instrumental variables.

5. Conclusions

This MR analysis provides evidence that there is an effect of coffee consumption and genetic predisposition to caffeine metabolism on kidney function. It suggests a detrimental effect of genetically predicted higher plasma caffeine levels and a protective effect of a genetically predicted higher amount of caffeine intake on kidney function. Further research is needed to distinguish whether the observed effects on kidney traits are driven by the harmful effects of plasma caffeine in slower metabolizers or the protective effects of greater caffeine intake in faster metabolizers.

Appendix A

Table A1. Data sources of genetic association for the exposures and the outcomes.

Trait	Unit	Cohort(s) or Consortium	Simple Size or Cases/Sample Size	First Author, Year
Exposures				
Plasma caffeine level	SD	PIVUS, SHIP-TREND, SKIPOGH, TwinGene, TwinsUK, ULSAM	9876	Cornelis, 2016 [17]
Caffeine intake	SD	ARIC, PLCO, NHS, HPFS, WGHS	47,341	Cornelis, 2011 [16]
Outcome				
eGFR$_{cyst}$	$\log(\text{mL/min/1.73 m}^2)$	CKDGen + UK Biobank	460,826	Stanzick, 2021 [19]
eGFR$_{crea}$	$\log(\text{mL/min/1.73 m}^2)$	CKDGen + UK Biobank	1,004,040	Stanzick, 2021 [19]
Urinary sodium	SD	UK Biobank	326,831	Hemani, 2018 [23]
BUN	$\log/\text{mg/dL}$	CKDGen	480,698	Wuttke, 2019 [20]
UACR	$\log(\text{mg/mmol})$	CKDGen	192,868	Teumer, 2019 [21]
CKD	$\log(\text{OR})$	CKDGen	41,395/439,303	Wuttke, 2019 [20]

Abbreviations: ARIC: Atherosclerosis Risk in Communities; BUN: Blood Urea Nitrogen; CKD: Chronic Kidney Disease; CKDGen: Chronic Kidney Disease Genetics Consortium; eGFRcyst: Glomerular Filtration Rate estimated using cystatin C; eGFRcrea: Glomerular Filtration Rate estimated using creatinine; HPFS: the Health Professionals Follow-Up Study; NHS (the Nurses' Health Study); PIVUS: the Prospective Study of the Vasculature in Uppsala Seniors (PIVUS); PLCO: the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; SHIP-TREND: the Study of Health in Pomerania TREND; SKIPOGH: the Swiss Kidney Project on Genes in Hypertension; UACR: urine albumin-creatinine ratio; ULSAM: Uppsala Longitudinal Study of Adult Men (ULSAM); WGHS: the Women's Genome Health Study.

References

1. Reyes, C.M.; Cornelis, M.C. Caffeine in the Diet: Country-Level Consumption and Guidelines. *Nutrients* **2018**, *10*, 1772. [CrossRef] [PubMed]
2. Bolignano, D.; Coppolino, G.; Barillà, A.; Campo, S.; Criseo, M.; Tripodo, D.; Buemi, M. Caffeine and the Kidney: What Evidence Right Now? *J. Ren. Nutr.* **2007**, *17*, 225–234. [CrossRef] [PubMed]
3. Singh, V.P.; Singh, N.; Jaggi, A.S. A Review on Renal Toxicity Profile of Common Abusive Drugs. *Korean J. Physiol. Pharmacol.* **2013**, *17*, 347–357. [CrossRef]
4. Tofovic, S.P.; Salah, E.M.; Jackson, E.K.; Melhem, M. Early renal injury induced by caffeine consumption in obese, diabetic ZSF1 rats. *Ren. Fail.* **2007**, *29*, 891–902. [CrossRef]
5. Belibi, F.A.; Wallace, D.P.; Yamaguchi, T.; Christensen, M.; Reif, G.; Grantham, J.J. The effect of caffeine on renal epithelial cells from patients with autosomal dominant polycystic kidney disease. *J. Am. Soc. Nephrol.* **2002**, *13*, 2723–2729. [CrossRef]
6. Meca, R.; Balbo, B.E.; Ormanji, M.S.; Fonseca, J.M.; Iannuzzi, L.R.; Costa, E.S.; Onuchic, L.F.; Heilberg, I.P. Caffeine Accelerates Cystic Kidney Disease in a Pkd1-Deficient Mouse Model. *Cell Physiol. Biochem.* **2019**, *52*, 1061–1074. [CrossRef] [PubMed]
7. Vendramini, L.C.; Nishiura, J.L.; Baxmann, A.C.; Heilberg, I.P. Caffeine intake by patients with autosomal dominant polycystic kidney disease. *Braz. J. Med. Biol. Res.* **2012**, *45*, 834–840. [CrossRef]
8. Girardat-Rotar, L.; Puhan, M.A.; Braun, J.; Serra, A.L. Long-term effect of coffee consumption on autosomal dominant polycystic kidneys disease progression: Results from the Suisse ADPKD, a Prospective Longitudinal Cohort Study. *J. Nephrol.* **2018**, *31*, 87–94. [CrossRef] [PubMed]

9.   Hu, E.A.; Selvin, E.; Grams, M.E.; Steffen, L.M.; Coresh, J.; Rebholz, C.M. Coffee Consumption and Incident Kidney Disease: Results From the Atherosclerosis Risk in Communities (ARIC) Study. *Am. J. Kidney Dis.* **2018**, *72*, 214–222. [CrossRef] [PubMed]

10. Wijarnpreecha, K.; Thongprayoon, C.; Thamcharoen, N.; Panjawatanan, P.; Cheungpasitporn, W. Association of coffee consumption and chronic kidney disease: A meta-analysis. *Int. J. Clin. Pract.* **2017**, *71*, e12919. [CrossRef] [PubMed]

11. Jhee, J.H.; Nam, K.H.; An, S.Y.; Cha, M.U.; Lee, M.; Park, S.; Kim, H.; Yun, H.R.; Kee, Y.K.; Park, J.T.; et al. Effects of Coffee Intake on Incident Chronic Kidney Disease: A Community-Based Prospective Cohort Study. *Am. J. Med.* **2018**, *131*, 1482–1490.e3. [CrossRef]

12. Kanbay, M.; Siriopol, D.; Copur, S.; Tapoi, L.; Benchea, L.; Kuwabara, M.; Rossignol, P.; Ortiz, A.; Covic, A.; Afsar, B. Effect of Coffee Consumption on Renal Outcome: A Systematic Review and Meta-Analysis of Clinical Studies. *J. Ren. Nutr.* **2021**, *31*, 5–20. [CrossRef]

13. Herber-Gast, G.C.M.; Essen, H.V.; Verschuren, W.M.; Stehouwer, C.D.; Gansevoort, R.T.; Bakker, S.J.; Spijkerman, A.M. Coffee and tea consumption in relation to estimated glomerular filtration rate: Results from the population-based longitudinal Doetinchem Cohort Study. *Am. J. Clin. Nutr.* **2016**, *103*, 1370–1377. [CrossRef]

14. Miyatake, N.; Shikata, K.; Makino, H.; Numata, T. Relationship between estimated glomerular filtration rate (eGFR) and metabolic syndrome in Japanese. *Acta Med. Okayama* **2010**, *64*, 203–208.

15. Mahdavi, S.; Palatini, P.; El-Sohemy, A. CYP1A2 Genetic Variation, Coffee Intake, and Kidney Dysfunction. *JAMA Netw. Open* **2023**, *6*, e2247868. [CrossRef] [PubMed]

16. Cornelis, M.C.; Monda, K.L.; Yu, K.; Paynter, N.; Azzato, E.M.; Bennett, S.N.; Berndt, S.I.; Boerwinkle, E.; Chanock, S.; Chatterjee, N.; et al. Genome-Wide Meta-Analysis Identifies Regions on 7p21 (AHR) and 15q24 (CYP1A2) As Determinants of Habitual Caffeine Consumption. *PLoS Genet.* **2011**, *7*, e1002033. [CrossRef] [PubMed]

17. Cornelis, M.C.; Kacprowski, T.; Menni, C.; Gustafsson, S.; Pivin, E.; Adamski, J.; Artati, A.; Eap, C.B.; Ehret, G.; Friedrich, N.; et al. Genome-wide association study of caffeine metabolites provides new insights to caffeine metabolism and dietary caffeine-consumption behavior. *Human. Mol. Genet.* **2016**, *25*, 5472–5482. [CrossRef] [PubMed]

18. Yang, A.; Palmer, A.A.; de Wit, H. Genetics of caffeine consumption and responses to caffeine. *Psychopharmacology* **2010**, *211*, 245–257. [CrossRef] [PubMed]

19. Stanzick, K.J.; Li, Y.; Schlosser, P.; Gorski, M.; Wuttke, M.; Thomas, L.F.; Rasheed, H.; Rowan, B.X.; Graham, S.E.; Vanderweff, B.R.; et al. Discovery and prioritization of variants and genes for kidney function in >1.2 million individuals. *Nat. Commun.* **2021**, *12*, 4350. [CrossRef] [PubMed]

20. Wuttke, M.; Li, Y.; Li, M.; Sieber, K.B.; Feitosa, M.F.; Gorski, M.; Tin, A.; Wang, L.; Chu, A.Y.; Hoppmann, A.; et al. A catalog of genetic loci associated with kidney function from analyses of a million individuals. *Nat. Genet.* **2019**, *51*, 957–972. [CrossRef]

21. Teumer, A.; Li, Y.; Ghasemi, S.; Prins, B.P.; Wuttke, M.; Hermle, T.; Giri, A.; Sieber, K.B.; Qiu, C.; Kirsten, H.; et al. Genome-wide association meta-analyses and fine-mapping elucidate pathways influencing albuminuria. *Nat. Commun.* **2019**, *10*, 4130. [CrossRef]

22. Inker, L.A.; Schmid, C.H.; Tighiouart, H.; Eckfeldt, J.H.; Feldman, H.I.; Greene, T.; Kusek, J.W.; Manzi, J.; Van Lente, F.; Zhang, Y.L.; et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N. Engl. J. Med.* **2012**, *367*, 20–29. [CrossRef] [PubMed]

23. Hemani, G.; Zheng, J.; Elsworth, B.; Wade, K.H.; Haberland, V.; Baird, D.; Laurin, C.; Burgess, S.; Bowden, J.; Langdon, R.; et al. The MR-Base platform supports systematic causal inference across the human phenome. *eLife* **2018**, *7*, e34408. [CrossRef]

24. Larsson, S.C.; Woolf, B.; Gill, D. Appraisal of the causal effect of plasma caffeine on adiposity, type 2 diabetes, and cardiovascular disease: Two sample mendelian randomisation study. *BMJ Med.* **2023**, *2*, 1–8. [CrossRef] [PubMed]

25. Kennedy, O.J.; Pirastu, N.; Poole, R.; Fallowfield, J.A.; Hayes, P.C.; Grzeszkowiak, E.J.; Taal, M.W.; Wilson, J.F.; Parkes, J.; Roderick, P.J. Coffee Consumption and Kidney Function: A Mendelian Randomization Study. *Am. J. Kidney Dis.* **2020**, *75*, 753–761. [CrossRef]

26. Koo, H.; Hwang, S.; Kim, T.H.; Kang, S.W.; Oh, K.H.; Ahn, C.; Kim, Y.H. The ratio of urinary sodium and potassium and chronic kidney disease progression. *Medicine* **2018**, *97*, e12820. [CrossRef] [PubMed]

27. McQuarrie, E.P.; Traynor, J.P.; Taylor, A.H.; Freel, E.M.; Fox, J.G.; Jardine, A.G.; Mark, P.B. Association between urinary sodium, creatinine, albumin, and long-term survival in chronic kidney disease. *Hypertension* **2014**, *64*, 111–117. [CrossRef] [PubMed]

28. Seki, M.; Nakayama, M.; Sakoh, T.; Yoshitomi, R.; Fukui, A.; Katafuchi, E.; Tsuda, S.; Nakano, T.; Tsuruya, K.; Kitazono, T. Blood urea nitrogen is independently associated with renal outcomes in Japanese patients with stage 3–5 chronic kidney disease: A prospective observational study. *BMC Nephrol.* **2019**, *20*, 115. [CrossRef] [PubMed]

29. Marx, B.; Scuvée, É.; Scuvée-Moreau, J.; Seutin, V.; Jouret, F. Mechanisms of caffeine-induced diuresis. *Med. Sci.* **2016**, *32*, 485–490.

30. Josse, A.R.; Da Costa, L.A.; Campos, H.; El-Sohemy, A. Associations between polymorphisms in the AHR and CYP1A1-CYP1A2 gene regions and habitual caffeine consumption. *Am. J. Clin. Nutr.* **2012**, *96*, 665–671. [CrossRef]