Coffee Consumption and Kidney Function: A Mendelian Randomization Study

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Rationale & Objective: Chronic kidney disease (CKD) is a leading cause of morbidity and mortality worldwide, with limited strategies for prevention and treatment. Coffee is a complex mixture of chemicals, and consumption has been associated with mostly beneficial health outcomes. This work aimed to determine the impact of coffee consumption on kidney function.

Study Design: Genome-wide association study (GWAS) and Mendelian randomization.

Setting & Participants: UK Biobank baseline data were used for a coffee consumption GWAS and included 227,666 participants. CKDGen Consortium data were used for kidney outcomes and included 133,814 participants (12,385 cases of CKD) of mostly European ancestry across various countries.

Exposure: Coffee consumption.

Outcomes: Estimated glomerular filtration rate (eGFR), CKD GFR categories 3 to 5 (G3-G5; eGFR < 60 mL/min/1.73 m^2), and albuminuria.

Analytical Approach: GWAS to identify single-nucleotide polymorphisms (SNPs) associated with coffee consumption in UK Biobank and use of those SNPs in Mendelian randomization analyses of coffee consumption and kidney outcomes in CKDGen.

Results: 2,126 SNPs were associated with coffee consumption ($P < 5 \times 10^{-8}$), 25 of which were independent and available in CKDGen. Drinking an extra cup of coffee per day conferred a protective effect against CKD G3-G5 (OR, 0.84; 95% CI, 0.72-0.98; $P = 0.03$) and albuminuria (OR, 0.81; 95% CI, 0.67-0.97; $P = 0.02$). An extra cup was also associated with higher eGFR ($\beta = 0.022$; $P = 1.6 \times 10^{-6}$) after removal of 3 SNPs responsible for significant heterogeneity (Cochran Q $P = 3.5 \times 10^{-15}$).

Limitations: Assays used to measure creatinine and albumin varied between studies that contributed data and a sex-specific definition was used for albuminuria rather than KDIGO guideline recommendations.

Conclusions: This study provides evidence of a beneficial effect of coffee on kidney function. Given widespread coffee consumption and limited interventions to prevent CKD incidence and progression, this could have significant implications for global public health in view of the increasing burden of CKD worldwide.

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Chronic kidney disease (CKD) is an increasing public health problem with substantial health care costs and morbidity.[1] CKD prevalence increased by 27% between 2007 and 2017, and CKD is now the 12th leading cause of death globally, up from 14th a decade ago.[2] Modeling studies project a continued increase in the burden of CKD and an increase in the number of years of life lost, from around 26 million annually in 2016 to 52.5 million in 2040.[3] A key consequence of CKD is progression to kidney failure requiring kidney replacement therapy (dialysis or transplantation), a treatment available to only a fraction of the global population.[4] CKD is associated with increased risk for cognitive impairment, renal bone disease, chronic anemia, and death from sepsis and cardiovascular disease.[5-8] The definition of CKD includes reduced glomerular filtration rate (GFR) for at least 3 months and/or markers of kidney damage (eg, albuminuria).[4,9]

With no cure for CKD, the recent focus has been on the detection of mild/moderate CKD and prevention of progression to kidney failure, along with strategies to prevent and improve management of hypertension and diabetes in those without CKD.[10] However, there is currently a lack of effective population-level strategies for achieving these aims.

Coffee is a commonly consumed beverage comprising a complex mixture of compounds, including caffeine, chlorogenic acid, and diterpenes.[11] These have a range of in vivo properties, including anti-inflammatory, antioxidant, and antifibrotic effects. Worldwide, more than 2 billion cups of coffee are consumed daily,[12] so small physiologic effects may have substantial public health implications. Epidemiologic studies indicate that coffee may protect against liver, neurologic, cardiovascular, and metabolic diseases; all-cause mortality; and various cancers.[13] For many conditions, the protective effects of coffee appear to be dose dependent. However, there may be an upper limit beyond which the benefits of increasing consumption are less pronounced; for example, more than 3 to 5 cups daily for all-cause and cardiovascular disease mortality.[14]

Several epidemiologic studies report lower risks for reduced estimated GFR (eGFR) and CKD among regular coffee drinkers.[15,16] However, those studies are at high risk for confounding because people with CKD risk factors,

including high body mass index, hypertension, and smoking, tend to drink more coffee.[17] Reverse causation may also introduce bias if coffee intake decreases due to CKD onset and progression. This study attempts to overcome these limitations by using Mendelian randomization (MR) to investigate the effects of coffee consumption on kidney health. MR exploits genetic variations that affect modifiable risk factor exposure to estimate a causal association between exposure and outcome.[18] Previous studies estimate that about 36% to 58% of coffee consumption is heritable.[19] Genetic variants are assorted randomly during meiosis independently of confounders and are not subsequently affected by outcomes. Therefore, MR is less susceptible to confounding and reverse causation compared with traditional observational methods.[20]

Methods

Data for Genetic Epidemiology of Coffee Consumption

The UK Biobank cohort comprises 500,000 participants aged 40 to 73 years, recruited between 2006 and 2013 from across the United Kingdom. All participants provided samples for genetic analysis, and coffee consumption habits were ascertained at baseline from a dietary questionnaire in which they were asked how many cups they drank each day and what type of coffee they usually drank (instant, ground, decaffeinated, or other coffee). All UK Biobank participants gave written informed consent, and the study was approved by the North West Multi-Centre Research Ethics Committee. A comprehensive description of the UK Biobank population and its protocol is available from UK Biobank.[21]

Creation of a New Instrument for the Prediction of Coffee Consumption

To identify genetic variants associated with coffee consumption, a genome-wide association study (GWAS) was performed with untransformed daily cups (of any type of coffee) as the outcome. Only participants with white British ancestry were included. According to the definition of the UK Biobank consortium, white British comprised people self-defined as British and with similar genetic ancestry background.[22] All single-nucleotide polymorphisms (SNPs) available as provided by the UK Biobank consortium were included. To avoid stratification effects,[23] participants related to other participants (up to second cousin) were excluded. Finally, non–coffee drinkers were excluded to reduce bias from reverse causation and participants who abstained due to medical advice, cost, or lack of exposure to habitual coffee drinking, which left 227,666 participants (~46% of total). As sensitivity analyses, we re-ran the coffee GWAS and MR analyses described next with nondrinkers included. Analyses were performed using RegScan software.[24] Age, sex, the first 20 genetic principal components, assessment center, genotyping array, and genotyping batch were included as covariates.

Data for Genetic Epidemiology of Kidney Function

GWAS data from the CKDGen Consortium were used for outcomes of eGFR, CKD, and albuminuria. The CKDGen Consortium has been described elsewhere, including details of participant recruitment and genotyping in the individual studies contributing data,[25,26] and the data used in this study are freely available from http://app.mrbase.org/. Participants were diagnosed with CKD GFR categories 3 through 5 (G3-G5), based on eGFR < 60 mL/min/1.73 m^2. All except 2 studies contributing data diagnosed CKD G3-G5 from a single assessment of eGFR. GFRs were estimated from serum creatinine level using the Modification of Diet in Renal Disease (MDRD) Study equation.[27] The assays for measuring creatinine varied between studies and included a modified kinetic Jaffé reaction and enzymatic photometric and dilutional mass spectrometry–traceable assays.[25] Urinary creatinine and albumin excretion were measured from early-morning and 24-hour urine samples. Methods included immunoturbimetric and nephelometric assays for albumin and Jaffé and enzymatic reactions for creatinine.[26]

Albuminuria was defined as urinary albumin-creatinine ratio > 17 mg/g (>1.92 mg/mmol) in men and >25 mg/g (>2.83 mg/mmol) in women.[26] These sex-specific definitions of albuminuria are from a study by Warram et al[28] and differ from the more widely accepted value of ≥30 mg/g (in both men and women) recommended by KDIGO.[9] They correspond to the 95th percentile urinary albumin-creatinine ratio values in a group of 218 apparently healthy individuals and are intended to account for men and women on average having differing rates of creatinine excretion.[29]

The eGFR GWAS included 48 studies (a mixture of cross-sectional, case-control, cohort, and randomized controlled studies) and 133,814 participants of various ethnicities. The CKD GWAS included a subset of 43 studies and 117,165 participants (12,385 CKD cases/outcomes, 104,780 controls/noncases). In the included studies, mean age ranged from 37 ± 16 (standard deviation) to 81 ± 9 years; mean eGFR, from 71.2 ± 24.1 to 104.8 ± 23.8 mL/min; prevalence of CKD G3-G5, from 0.2% to 32.3%; and prevalence of diabetes and hypertension, both from to 0% to 100%. The albuminuria GWAS included 54,450 participants of European ethnicity. In the included studies, mean age ranged from 44.9 ± 7.3 to 77.8 ± 4.8 years; median urinary albumin-creatinine ratio, from 2.5 to 15.6 mg/g; and prevalence of albuminuria and diabetes, respectively, from 2.4% to 25.2% and 1% to 100%. There were approximately 6,000 cases of albuminuria (the exact number was not reported). The data used in this study were summary-level data, which were published by the CKDGen Consortium in meta-analyzed form (ie, after combining the participating

individual studies). All CKDGen studies included age and sex as covariates. All participants provided written informed consent, and local ethical approval was obtained.[25]

MR Analyses

MR analyses were first conducted using a 2-sample inverse variance weighted (IVW) method.[30] This method consisted of meta-analyzing SNP-specific Wald ratios between the effect outcome and exposure (ie, $\beta_{outcome}/\beta_{coffee}$) using a random-effects inverse variance method that weights each ratio by its standard error while accounting for possible heterogeneity in measures.[30] For each SNP, β_{coffee} was from the coffee GWAS in UK Biobank with units of cups of coffee per day, while $\beta_{outcome}$ was from CKDGen data and units were log odds for CKD G3-G5 and albuminuria and log mL/min/1.73 m^2 for eGFR.

To investigate whether any single SNP in the coffee instrument had a disproportionate effect on the overall results, IVW analyses were re-run leaving out SNPs 1 at a time. A key assumption of MR is that the SNPs affect the outcome through modification of the exposure of interest only with no other causal pathways linking the SNP to the outcome. The existence of other pathways is called horizontal pleiotropy (eg, if the SNPs affected CKD but not through coffee). The presence of horizontal pleiotropy may give rise to significant heterogeneity. When significant heterogeneity was detected (inferred using Cochran Q), the MR-Radial method[31] was used to identify SNPs responsible for heterogeneity ($P = 0.05$/number of SNPs) and in sensitivity analyses, these SNPs were removed and effect estimates were recalculated.

Directional pleiotropy occurs when the net effect of horizontal pleiotropy across all SNPs is non-zero and introduces bias into the IVW estimates. MR-Egger, weighted median, and mode are alternative MR methods more robust to directional pleiotropy and were used to calculate estimates for comparison with the IVW estimates. MR-Egger allows for some of the SNPs to affect the outcome through mechanisms not involving modification of the exposure. The intercept from MR-Egger also provides a formal test for directional pleiotropy. Weighted median MR assumes that at least 50% of the SNPs are valid. Weighted-mode MR groups SNPs into clusters and calculates an estimate based on the cluster with the most SNPs. A recent review describes these methods in detail.[32] Finally, Steiger-MR was used to test whether the SNPs explained significantly more variance in exposure than outcome (the opposite may indicate reverse causation).[33] The IVW, Egger, weighted median, weighted mode, and Steiger-MR analyses were performed as implemented in the TwoSampleMR R package.[34] The data files used are provided as Supplementary Files 1 to 6.

To investigate confounding, associations of the SNPs with hypertension, diabetes, smoking, and obesity were extracted from a GWAS involving white British UK Biobank participants.[35] The effect on the MR estimates of removing SNPs with strong associations with CKD risk factors ($P < 1 \times 10^{-5}$) was investigated in sensitivity analyses.

Results

GWAS of Coffee Consumption in UK Biobank Participants

In UK Biobank, 2,126 SNPs were associated with coffee consumption ($P < 5 \times 10^{-8}$), 574 of which were available in the CKDGen GWAS. After removing SNPs that were in linkage disequilibrium ($r^2 < 0.1$) and 1 unreconciled palindromic SNP, 25 were remaining for use in the MR analyses. These SNPs, along with the strength and magnitude of their associations with coffee consumption, are shown in Table 1.

MR Analyses

Table 2 shows causal-effect estimates of coffee on eGFR, CKD G3-G5, and albuminuria from the MR analyses. Associations for individual SNPs are presented in Supplementary File 7. Figure 1 shows forest plots of the estimates for each outcome using the different MR methods. Two forest plots show the coffee-eGFR estimates before and after removing 3 SNPs responsible for significant heterogeneity, and possibly horizontal pleiotropy, as described later. Figure 2 shows scatter plots of the SNP-outcome associations against the SNP-coffee associations, allowing visualization of the causal-effect estimate for each individual SNP on eGFR, CKD G3-G5, and albuminuria. Funnel and radial plots are provided in Supplementary File 7.

Coffee and CKD G3-G5

In the IVW MR analysis, the odds ratio (OR) of CKD for an extra daily cup of coffee was 0.84 (95% confidence interval [CI], 0.72-0.98; $P = 0.03$). There was no sign of directional pleiotropy using the MR-Egger test ($P = 0.1$). In the leave-1-out analysis, estimates ranged from 0.82 (95% CI, 0.71-0.95) to 0.88 (95% CI, 0.77-1.01), suggesting that the observed result was not the effect of a single SNP. Estimates were concordant and similar in size in MR-Egger (OR, 0.64; 95% CI, 0.44-0.94), weighted median (OR, 0.80; 95% CI, 0.67-0.96), and mode (OR, 0.80; 95% CI, 0.66-0.98) analyses, supporting a protective effect of coffee against CKD G3-G5. There was no sign of heterogeneity and Steiger-MR indicated that the SNPs explained more variance in exposure than outcome.

Coffee and eGFR

The initial IVW analysis between coffee and eGFR did not provide strong evidence of an association ($\beta = 0.015$ log mL/min/1.73 m^2 per cup per day; $P = 0.07$). In the leave-1-out analysis, β ranged from 0.019 to 0.012. There was evidence of directional pleiotropy (MR-Egger intercept $P = 0.04$) and horizontal pleiotropy (heterogeneity $P = 3.5 \times 10^{-15}$). After using MR-Radial to remove 3 outlying

Table 1. The 25 SNPs Associated With Coffee From a GWAS Involving UK Biobank Participants That Were Available in the CKDGen GWAS and Included in the Coffee-Kidney MR Analyses

SNP	Chr	Position	Nearest Gene	Effect Allele	Other Allele	EAF	β[a]	*P*
rs2488397	1	197701279	*DENND1B*	C	G	0.210	0.040	2.0×10^{-8}
rs1260326	2	27730940	*GCKR*	C	T	0.610	0.033	2.4×10^{-8}
rs1877723	4	2846799	*ADD1*	T	C	0.313	−0.040	2.5×10^{-10}
rs1481012	4	89039082	*ABCG2*	G	A	0.111	−0.066	1.5×10^{-12}
rs660550	6	31837277	*SLC44A4*	A	C	0.525	−0.034	8.0×10^{-9}
rs9275576	6	32679326	*HLA-DQA2*	T	C	0.146	0.048	5.5×10^{-9}
rs11766104	7	17192272	*AHR*	T	C	0.167	0.043	4.5×10^{-8}
rs4410790	7	17284577	*AHR*	C	T	0.640	0.108	6.2×10^{-70}
rs7791070	7	17401027	*AHR*	C	T	0.234	−0.076	2.3×10^{-28}
rs17645813	7	17419697	*KCCAT333*	A	G	0.077	−0.073	2.8×10^{-11}
rs6461314	7	17439609	*KCCAT333*	G	A	0.112	0.053	1.2×10^{-8}
rs6949509	7	17519261	*LOC101927630*	G	A	0.435	−0.042	1.5×10^{-12}
rs17706320	7	17551902	*LOC101927630*	C	T	0.342	−0.050	4.7×10^{-16}
rs13233604	7	17593486	*LOC101927630*	A	T	0.172	−0.058	5.0×10^{-12}
rs17145750	7	73026378	*MLXIPL*	T	C	0.163	0.050	2.3×10^{-10}
rs17685	7	75616105	*POR*	A	G	0.281	0.059	7.5×10^{-20}
rs11855112	15	74133413	*TBC1D21*	C	T	0.129	0.049	3.0×10^{-8}
rs351242	15	74472716	*STRA6*	A	G	0.757	−0.062	9.5×10^{-20}
rs4886593	15	74558078	*CCDC33*	A	T	0.200	−0.052	6.6×10^{-13}
rs4077582	15	74665622	*CYP11A1*	T	C	0.706	0.050	7.9×10^{-15}
rs4128436	15	74935894	*CLK3, EDC3*	T	C	0.081	−0.060	2.1×10^{-8}
rs2472297	15	75027880	*CYP1A1*	T	C	0.272	0.136	2.2×10^{-95}
rs8042558	15	75320433	*PPCDC*	T	G	0.235	−0.044	1.3×10^{-10}
rs12917120	15	75329091	*PPCDC*	C	T	0.665	0.053	2.1×10^{-17}
rs476828	18	57852587	*MC4R*	C	T	0.239	0.043	2.0×10^{-10}

Abbreviations: Chr, chromosome; EAF, effect allele frequency in the coffee genome-wide association study population; GWAS, genome-wide association study; MR, Mendelian randomization; rs, reference single-nucleotide polymorphism; SNP, single-nucleotide polymorphism.
[a]Change in cups of coffee per day per copy of the effect allele.

SNPs primarily responsible for heterogeneity (rs1260326, rs9275576, and rs476828), the IVW association was highly significant ($\beta = 0.022$; $P = 1.6 \times 10^{-6}$). This was consistent with estimates (using all SNPs) from the weighted median ($\beta = 0.023$; $P = 2.8 \times 10^{-5}$), mode ($\beta = 0.024$; $P = 2.4 \times 10^{-4}$), and MR-Egger ($\beta = 0.053$; $P = 0.01$) analyses, which are more robust to pleiotropy. Steiger-MR indicated that the SNPs explained more variance in exposure than outcome.

Albuminuria

The causal-effect estimate of coffee consumption on albuminuria was similar in direction and magnitude to CKD G3-G5 (OR, 0.81; 95% CI, 0.67-0.97; $P = 0.02$). In the leave-1-out analysis, ORs ranged from 0.78 (95% CI, 0.63-0.96) to 0.85 (95% CI, 0.69-1.05), showing consistency in the estimate throughout. None of the estimates from the MR-Egger (OR, 0.75; 95% CI, 0.46-1.22), weighted median (OR, 0.90; 95% CI, 0.69-1.17), or mode analyses (OR, 0.83; 95% CI, 0.60-1.15) were statistically significant, although they were similar in magnitude to the IVW estimate, suggesting that this is due to limited power. Analyses with greater power will be needed to clarify whether the potential causal relationship is true or due to chance. There was no significant horizontal pleiotropy (heterogeneity $P = 0.3$) or directional pleiotropy (MR-Egger test $P = 0.7$).

Sensitivity Analyses

A GWAS of coffee consumption including drinkers and nondrinkers in UK Biobank found 44 significant SNPs ($P < 5 \times 10^{-8}$) that were also available in CKDGen. Using these SNPs in MR analyses (Supplementary File 7) demonstrated IVW associations of an extra daily cup with eGFR ($\beta = 0.015$ log mL/min/1.73 m^2; 95% CI, 0.003-0.026), CKD G3-G5 (OR, 0.81; 95% CI, 0.72-0.92), and albuminuria (OR, 0.85; 95% CI, 0.73-0.98), similar to when only drinkers were included.

Among white British UK Biobank participants, 4 SNPs were strongly associated with hypertension, and removal of these had minimal effect on the estimates (Supplementary File 7).

Discussion

A GWAS involving 227,666 UK Biobank participants identified 2,126 SNPs associated with coffee consumption. Using 25 of the SNPs that were independent and available in CKDGen, MR analyses showed that increased

Table 2. MR Analyses of Causal Associations of Coffee Consumption With eGFR, CKD G3-G5, and Albuminuria

Trait	Sample Size	Ethnicity	MR IVW		MR-Egger		MR-Weighted Median		MR-Weighted Mode	
			β[a] or OR[b] (95% CI)	*P*	β[a] or OR[b] (95% CI)	*P*	β[a] or OR[b] (95% CI)	*P*	β[a] or OR[b] (95% CI)	*P*
eGFR[c]	133,814	Mixed	β = 0.015 (−0.001 to 0.031) β = 0.022[d] (0.013 to 0.032)	0.07 1.6×10^{-6}	β = 0.053 (0.015 to 0.092)	0.01	β = 0.023 (0.013 to 0.034)	2.8×10^{-5}	β = 0.024 (0.013 to 0.035)	2.4×10^{-4}
CKD G3-G5[e]	117,165 (12,385 cases, 104,780 controls)	Mixed	OR = 0.84 (0.72 to 0.98)	0.03	OR = 0.64 (0.44 to 0.94)	0.03	OR = 0.80 (0.67 to 0.96)	0.01	OR = 0.80 (0.66 to 0.98)	0.04
Albuminuria[e]	54,116[f]	European	OR = 0.81 (0.67 to 0.97)	0.02	OR = 0.75 (0.46 to 1.22)	0.3	OR = 0.90 (0.69 to 1.17)	0.4	OR = 0.83 (0.60 to 1.15)	0.3

Abbreviations: CI, confidence interval; CKD G3-G5, chronic kidney disease with glomerular filtration rate categories 3-5; eGFR, estimated glomerular filtration rate; IVW, inverse variance weighted; MR, Mendelian randomization; OR, odds ratio; SNP, single-nucleotide polymorphism.

[a]Log mL/min/1.73 m^2 per cup of coffee per day.

[b]Per cup of coffee per day.

[c]Continuous outcome.

[d]After removal of 3 SNPs (rs1260326, rs9275576, and rs476828) that gave rise to significant heterogeneity ($P = 3.5 \times 10^{-15}$).

[e]Categorical outcome.

[f]Numbers of cases and controls not published by study authors.

Figure 1. Forest plots show causal-effect estimates of an extra cup of coffee per day on chronic kidney disease (CKD) with glomerular filtration rate (GFR) categories 3 to 5 (CKD G3-G5), estimated GFR (eGFR), and albuminuria. Results are shown for the different methods of Mendelian randomization (MR) analyses used in this study: inverse variance weighted (IVW), MR-Egger, and weighted median and mode. *Denotes removal of 3 single-nucleotide polymorphisms (rs1260326, rs9275576, and rs476828) that gave rise to significant heterogeneity (P of Cochran $Q = 3.5 \times 10^{-15}$), which was possibly the result of horizontal pleiotropy.

consumption among regular drinkers appeared to confer a protective effect against CKD G3-G5 and albuminuria and was associated with higher eGFRs. Effects were generally similar in magnitude across sensitivity analyses, though for albuminuria, the effect did not always reach significance at the 5% level, possibly due to a smaller sample size. Strengths of this study include use of MR, which largely avoids bias from confounding and reverse causality, and large numbers of participants from UK Biobank and CKDGen.

Limitations include potential bias from weak instruments not strongly associated with coffee consumption, which would push estimates toward the null. An F statistic (which reflects the strength of an instrument) was not calculated because of the lack of an independent population. We

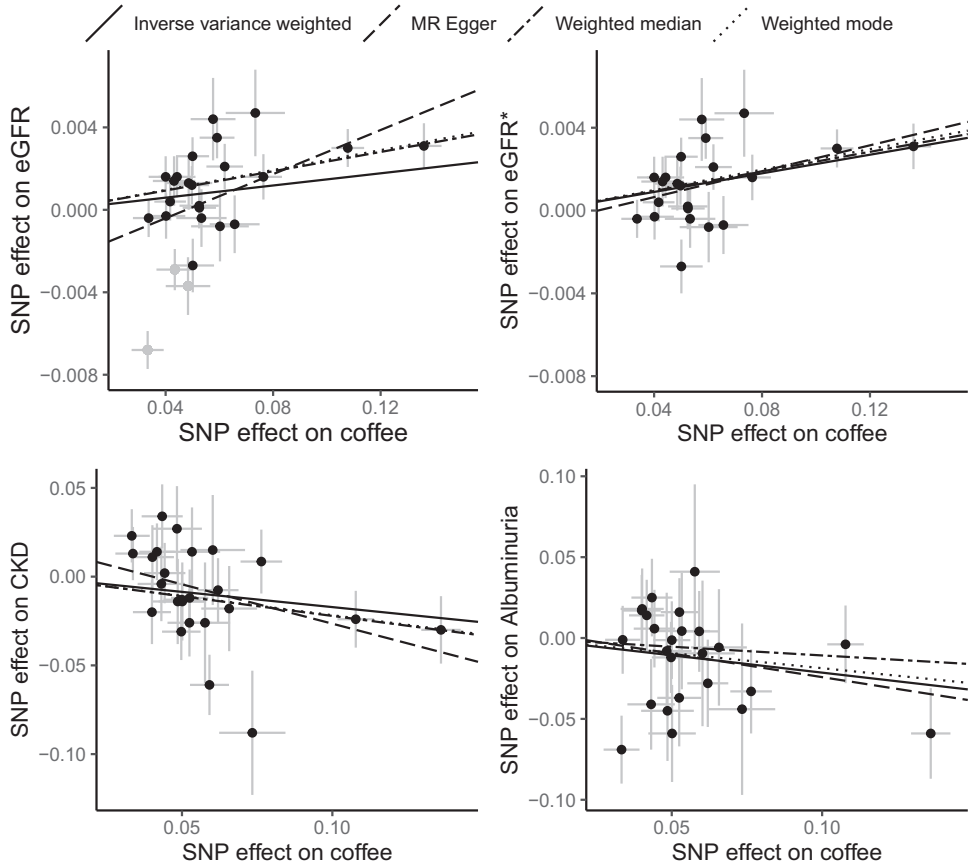

Figure 2. Scatter plots in which the single-nucleotide polymorphism (SNP)-outcome associations are plotted against the SNP-coffee associations, allowing visualization of the causal-effect estimate for each individual SNP on estimated glomerular filtration rate (eGFR), chronic kidney disease with glomerular filtration rate categories 3 to 5 (CKD G3-G5), and albuminuria. *Denotes removal of 3 SNPs (rs1260326, rs9275576, and rs476828), shown as red points, that gave rise to significant heterogeneity (*P* of Cochran *Q* = 3.5 × 10^{-15}). Removal of these SNPs improved agreement between the inverse variance weighted regression slope and the Mendelian randomization (MR)-Egger, weighted median, and mode slopes, which are more robust to horizontal pleiotropy.

excluded 1 unreconciled palindromic SNP, which did not have a significant effect on the estimates. The generalizability of the results is uncertain because UK Biobank and CKDGen participants were mostly of European ancestry, though this reduced bias from population stratification.

Horizontal pleiotropy may have introduced bias if the SNPs were associated with confounders through pathways not involving coffee. No negative control population was available to assess this. However, results from MR-Egger, median weighted, and mode analyses, which are less susceptible to horizontal pleiotropy, were similar to the IVW estimates. In addition, excluding SNPs with highly significant associations with CKD causal factors had minimal effect on the estimates. Bias from reverse causation would have been introduced if CKD was present at baseline and reduced consumption, though the risk for this is lower because we excluded nondrinkers and CKD is frequently asymptomatic except in later stages. Bias may also have been introduced if relationships between exposure and outcome deviated from linearity, and there was insufficient data available to investigate this.

It was not possible to calculate an absolute difference in eGFR for each extra cup of coffee (ie, only the regression coefficient could be calculated). This would have required knowledge of baseline eGFRs in non–coffee drinkers and proportions of nondrinkers and drinkers of 1, 2, and 3 or more cups daily. The CKDGen data release did not include this information.

Further weaknesses relate to ascertainment of coffee consumption in UK Biobank. Participants who consumed any type of coffee were included, without information on relative consumption of each. Chemical constituents of different coffee types vary,[36] and additives (eg, milk or sugar) may have moderated health effects. We also excluded nondrinkers from the GWAS of coffee consumption, although this had only a minimal effect (see Supplementary File 7).

Bias may have resulted from case ascertainment in studies participating in CKDGen (ie, for the CKD G3-G5 analysis). In most studies, ascertainment of CKD G3-G5 was based on just a single eGFR. CKDGen comprised various study types (cross-sectional, case-control, cohort,

and randomized studies) but did not specify exact numbers of each. When longitudinal studies were used, it was unclear whether eGFR was assessed and CKD G3-G5 was diagnosed at baseline only or at multiple points. Variations in eGFRs are common and some kidney diseases, such as diabetic nephropathy, manifest as hyperfiltration in early stages.[37] Guidelines recommend diagnosing CKD G3-G5 when eGFR is <60 mL/min/1.73 m^2 for at least 3 months and to use the CKD Epidemiology Collaboration (CKD-EPI) equation, not the MDRD Study equation, to calculate eGFR.[38] As a result, there may have been nondifferential misclassification of cases and noncases/controls, which would push estimates toward the null. Nevertheless, the finding of a robust association with eGFR as a continuous variable suggests that bias related to CKD definition was not a significant factor.

Insufficient data were available to characterize effect modification by cause (eg, diabetes and hypertension) or disease severity or to investigate CKD progression. Diagnostic criteria for albuminuria differed from that now recommended by KDIGO (ie, >17 mg/g in men and >25 mg/g in women, rather than ≥30 mg/g).[9]

We were also unable to fully explain the large magnitude of the effect on CKD that was comparable to the most effective pharmacologic therapies in nephrology. This may relate to a lifelong exposure to coffee, which is not comparable to shorter-term interventions. In addition, ascertainment of coffee consumption through a questionnaire is noisy and as such, the effects of the SNPs on coffee may have been underestimated. This would have led to overestimation of the effect sizes but the causal relationships would still be valid.

This study adds to previous observational studies that provide evidence of a protective effect of coffee on kidney health. A cross-sectional study of 2,673 women aged 35 to 65 years[39] reported inverse associations between 2 or more cups per day and eGFR < 60 mL/min/1.73 m^2 (OR, 0.59; 95% CI, 0.37-0.95). Similarly, 3 other studies reported cross-sectional eGFRs to be higher among coffee drinkers, with mean differences of 3.20 (95% CI, 0.27-6.13),[40] 2.03 (95% CI, 0.10-3.97),[41] and 1.61 (95% CI, 0.41-2.81),[42] as summarized in a recent meta-analysis.[15] Another cross-sectional study reported adjusted mean differences showing higher eGFRs in coffee drinkers (mean difference, 5.30; 95% CI, 0.05-10.55).[43] A recent longitudinal study[44] reported lower incidence of CKD with greater coffee consumption among 14,209 participants aged 45 to 64 years (hazard ratios of 0.90 [95% CI, 0.82-0.99], 0.90 [95% CI, 0.82-0.99], 0.87 [95% CI, 0.77-0.97], and 0.84 [95% CI, 0.75-0.94] for <1, 1-<2, 2-<3, and ≥3 cups per day, respectively). However, other studies report no association between coffee and CKD,[45] and 1 cross-sectional study found lower eGFRs in coffee drinkers, although they were on average 10 years older than nondrinkers.[46]

The active ingredient in coffee that may be responsible for the results of this study is unclear. Noncaffeine chemical constituents (eg, chlorogenic acid and diterpenes) reduce inflammation and oxidative stress, which are causative in CKD onset and progression.[11,47] Caffeine is a nonselective antagonist of A1 adenosine receptors on distal afferent arterioles. A1 adenosine receptor activation causes vasoconstriction and may lower eGFR.[48] Thus, coffee consumption may prevent afferent arteriolar constriction or cause vasodilation. Dilation of the afferent arteriole alone would increase glomerular capillary hydraulic pressure and GFR but would also increase albuminuria and future glomerular damage.[49] The observed lack of a positive association between coffee and albuminuria is therefore reassuring because it implies that coffee consumption does not elevate glomerular capillary hydraulic pressure or provoke glomerular damage. Additionally, coffee may protect against CKD risk factors, including diabetes, cardiovascular disease, and obesity.[13,50]

This MR analysis suggests a protective role of drinking coffee in maintaining kidney health among regular coffee drinkers. The importance of these findings is underlined by modeling predictions of growing CKD prevalence in the United States in the next decade, which are most sensitive to assumptions in rates of eGFR decline.[51] This is in the context of a lack of effective interventions to prevent declines in eGFRs among populations with and without CKD. Next steps should include further MR studies to investigate associations of coffee with important risk factors, particularly diabetes and hypertension, which may mediate the effect on CKD. A nonlinear dose-response at higher levels of consumption should also be investigated. This will better define the potential role of coffee in preventing CKD onset and progression and inform the design of a randomized controlled trial with a coffee-based intervention.

Supplementary Material

Supplementary File 1 (TXT)

Coffee consumption (including drinkers and nondrinkers) vs albuminuria datafile.

Supplementary File 2 (TXT)

Coffee consumption (including drinkers and nondrinkers) vs CKD G3-G5 datafile.

Supplementary File 3 (TXT)

Coffee consumption (including drinkers and nondrinkers) vs eGFR datafile.

Supplementary File 4 (TXT)

Coffee drinkers only vs albuminuria datafile.

Supplementary File 5 (TXT)

Coffee drinkers only vs CKD G3-G5 datafile.

Supplementary File 6 (TXT)

Coffee drinkers only vs eGFR datafile.

Supplementary File 7 (PDF)

Figure S1: Funnel plot showing the inverse variance weighted MR estimate of each coffee SNP with eGFR versus 1/SEIV.

Figure S2: Funnel plot showing the inverse variance weighted MR estimate of each coffee SNP with CKD versus 1/SEIV.

Figure S3: Funnel plot showing the inverse variance weighted MR estimate of each coffee SNP with albuminuria versus 1/SEIV.

Figure S4: Radial plot showing the inverse variance weighted estimate for the association between coffee and eGFR for each SNP as well as the overall estimate.

Figure S5: Radial plot showing the inverse variance weighted estimate for the association between coffee and CKD for each SNP as well as the overall estimate.

Figure S6: Radial plot showing the inverse variance weighted estimate for the association between coffee and albuminuria for each SNP as well as the overall estimate.

Figure S7: Manhattan plot of a GWAS of coffee consumption among 227,666 coffee drinkers in UK Biobank.

Table S1: MR analyses of causal associations between each coffee SNP and eGFR.

Table S2: MR analyses of causal associations between each coffee SNP and CKD.

Table S3: MR analyses of causal associations between coffee and albuminuria.

Table S4: Results from MR analyses of causal associations of coffee consumption with eGFR, CKD, and albuminuria.

Table S5: Associations with CKD risk factors of 25 SNPs used in a MR analysis of coffee and kidney outcomes among UK Biobank participants of British genetic ancestry.

Table S6: Results from MR analyses of causal associations of coffee consumption with eGFR, CKD, and albuminuria, wherein SNPs that were strongly associated with hypertension were excluded.

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