Coffee consumption and kidney function:

a Mendelian randomisation study

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Abstract

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 is 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 randomisation (MR).

Setting & Participants: UK Biobank baseline data were used for a coffee consumption GWAS and included 227,666 participants. CKDGen was 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 (MDRD eGFR <60mL/min/1.73m^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 MR analyses of coffee consumption and kidney outcomes in CKDGen.

Results: 2126 SNPs were associated with coffee consumption (p-value $<5 \times 10^{-8}$), 25 of which were independent and available in CKDGen. Drinking an extra cup of coffee per day conferred a protective effect against CKD (OR 0.84, 95% CI 0.72-0.98, p-value 0.03) and albuminuria (OR 0.81, 0.67-0.97, p-value 0.02). An extra cup was also associated with higher eGFR (beta 0.022, p-value 1.6×10^{-6}) after removal of three SNPs responsible for significant heterogeneity (Cochran's Q p-value 3.5×10^{-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 guidelines.

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 rising burden of CKD worldwide.

Plain-language summary

Chronic kidney disease (CKD) is increasing worldwide and represents a major cause of death, disability and healthcare expenditure. However, there are few effective options for prevention or treatment.

Coffee is a complex mixture of hundreds of chemical compounds, some of which could have beneficial effects on health. Some observational studies link drinking more coffee to a lower risk of developing CKD.

In this Mendelian randomisation study, we used measured variation in genetics, rather than self-reported data, to examine the causal effect of coffee on CKD. We showed that among coffee consumers, drinking more coffee appeared to protect against CKD. Further work is now needed to demonstrate whether a coffee-based intervention is effective for the prevention or treatment of CKD.

Introduction

Chronic kidney disease (CKD) is an increasing public health problem with significant healthcare 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). Modelling studies project a continued increase in the burden of CKD and a rise 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 end-stage renal disease (ESRD) requiring renal replacement therapy (dialysis or transplantation), which is available to only a fraction of the global population (4). CKD is associated with increased risk of cognitive impairment, renal bone disease, chronic anaemia and death from sepsis and cardiovascular disease (5–8). The definition of CKD includes reduced glomerular filtration rate (GFR) for at least three months and/or markers of kidney damage (e.g. albuminuria) (4,9). With no cure for CKD, recent focus has been on detection of mild/moderate CKD and prevention of progression to ESRD 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, over two billion cups of coffee are consumed daily (12), so small physiological effects may have significant public health implications. Epidemiological studies indicate that coffee may protect against liver, neurological, 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, above 3-5 cups daily for all-cause and CVD mortality (14).

Several epidemiological studies report lower risks of reduced eGFR and CKD among regular coffee drinkers (15,16). However, those studies are at high risk of confounding because people with CKD risk factors, including high BMI, hypertension, and smoking, tend to drink more coffee (17). Reverse causation may also introduce bias if coffee intake reduces due to CKD onset and progression. This study attempts to overcome these limitations by, for the first time, employing Mendelian randomisation (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 around 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 to traditional observational methods (20).

Methods

Data for genetic epidemiology of coffee consumption

The UK Biobank cohort comprises 500,000 participants aged 40-73, recruited between 2006 and 2013 from across the UK. 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 (MREC). A comprehensive description of the UK Biobank population and its protocol are 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 (approximately 46% of total). As sensitivity analyses, we re-ran the coffee GWAS and MR analyses described below with non-drinkers included. Analyses were performed using REGSCAN software (24). Age, gender, the first 20 genetic principal components, assessment centre, genotyping array and genotyping batch were included as covariates.

Data for genetic epidemiology of kidney function

GWAS data from the CKDGen Consortium was 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). The data used in this study are freely available from: http://app.mrbase.org/. Participants were diagnosed with CKD where eGFR < 60 mL/min/1.73m^2. All except two studies contributing data diagnosed CKD from a single measurement of eGFR. GFRs were estimated from serum creatinine and the Modification of Diet in Renal Disease study equation (27). The assays for measuring creatinine varied between studies and included a modified kinetic Jaffé reaction as well as enzymatic photometric and dilutional mass spectrometry-traceable assays (25).

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Urinary creatinine and albumin 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 a urinary albumin creatinine ratio (UACR) > 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 (Kidney Disease: Improving Global Outcomes) (9). They correspond to the 95th percentile UACR values in a group of 218 healthy subjects, 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 randomised 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/non-cases). In the included studies, mean ages ranged from 37 (standard deviation [SD] 16) to 81 (SD 9), mean eGFRs from 71.2 (SD 24.1) to 104.8 (SD 23.8) mL/min, prevalence of CKD (G3-5) 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 ages ranged from 44.9 (7.3) to 77.8 (SD 4.8), median UACR from 2.5 to 15.6 mg/g and the 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 was summary level data, which was published by the CKDGen consortium in meta-analysed form (i.e. after combining the participating individual studies). All the CKDGen studies included age and sex as covariates. All participants provided written informed consent and local ethical approval was obtained (25).

Mendelian randomisation analyses

MR analyses were first conducted using a two-sample inverse variance weighted (IVW) method (30). This method consisted of meta-analysing SNP specific Wald ratios between the effect outcome and exposure (i.e. $\beta_{outcome}$ / β_{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 and albuminuria and log mL/min/1.73m^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 one 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 (e.g. if the SNPs affected CKD but not through coffee). The presence of horizontal pleiotropy may give rise to significant heterogeneity. Where significant heterogeneity was detected (inferred using Cochran's Q), the MR-Radial method (31) was used to identify SNPs responsible for heterogeneity (p-value = 0.05/number of SNPs) and, in sensitivity analyses, these SNPs were removed and effect estimates 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 via 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 if 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 datafiles used are provided as supplementary material.

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-value $<1e^{-5}$) was investigated in sensitivity analyses.

Results

GWAS of coffee consumption in UK Biobank participants

2126 SNPs were associated with coffee consumption ($p<5e^{-8}$) in UK Biobank, 574 of which were available in the CKDGen GWAS. After removing SNPs that were in linkage disequilibrium ($r^2<0.1$) and one 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.

Mendelian randomisation analyses

Table 2 shows causal-effect estimates of coffee on eGFR, CKD and albuminuria from the MR analyses. Associations for individual SNPs are presented as supplementary material. 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 three SNPs responsible for significant heterogeneity, and possibly horizontal pleiotropy, as described below. Figure 2 shows scatter plots of the SNP-outcome associations against the

SNP-coffee associations, allowing visualisation of the causal-effect estimate for each individual SNP on eGFR, CKD and albuminuria. Funnel and radial plots are presented as supplementary material.

Coffee and CKD

In the IVW MR analysis, the OR of CKD for an extra daily cup of coffee was 0.84 (95% CI 0.72-0.98, p-value 0.03). There was no sign of directional pleiotropy using the MR-Egger test (p-value 0.1). In the leave-one-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. There was no sign of heterogeneity and Steiger-MR indicated 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 per cups/day, p-value 0.07). In the leave-one-out analysis, betas ranged from 0.019 to 0.012. There was evidence of directional pleiotropy (MR-Egger intercept p-value 0.04) and horizontal pleiotropy (heterogeneity p-value $3.5e^{-15}$). After using MR-Radial to remove three outlying SNPs primarily responsible for heterogeneity (rs1260326, rs9275576 and rs476828), the IVW association was highly significant (beta 0.022, p-value $1.6e^{-6}$). This was consistent with estimates (using all SNPs) from the weighted median (0.023, $2.8e^{-5}$), mode (0.024, $2.4e^{-4}$) and MR-Egger (beta 0.053, p-value 0.01) analyses that are more robust to pleiotropy. Steiger-MR indicated 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 (0.81, 95% CI 0.67-0.97, p-value 0.02). In the leave-one-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-value 0.3) or directional pleiotropy (MR-Egger test p-value 0.7).

Sensitivity analyses

A GWAS of coffee consumption including drinkers and non-drinkers in UK Biobank found 44 significant SNPs (p<5e-8) that were also available in CKDGen. Using these SNPs in MR analyses (supplementary material) demonstrated IVW associations of an extra daily cup with eGFR (beta 0.015 log mL/min, 95% CI 0.003-0.026), CKD (OR 0.81, 95% CI 0.72-0.92) and albuminuria (0.85, 95% CI 0.73-0.98), similar to when only drinkers were included.

Among White British UK Biobank participants, four SNPs were strongly associated with hypertension, and removal of these had minimal effect on the estimates (supplementary material).

Discussion

A GWAS involving 227,666 UK Biobank participants identified 2126 SNPs associated with coffee consumption. Using 25 of those SNPs that were independent and available in CKDGen, MR analyses showed that increased consumption among regular drinkers appeared

to confer a protective effect against CKD (G3-5) and albuminuria, and was associated with higher eGFR. The 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 towards null. An F-statistic (which reflects the strength of an instrument) was not calculated because of the lack of an independent population. We excluded one unreconciled palindromic SNP, which did not have a significant effect on the estimates. The generalisability of the results is uncertain since 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 of this is lower since we excluded non-drinkers and CKD is frequently asymptomatic except in later stages. Bias may also have been introduced if the 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 (i.e. only the regression coefficient could be calculated). This would have required knowledge of baseline eGFRs in non-coffee drinkers and proportions of non-drinkers and drinkers of one, two and ≥three 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 (e.g. milk or sugar) may have moderated health effects. We also excluded non-drinkers from the GWAS of coffee consumption, although this had only a minimal effect (see supplementary material).

Bias may have resulted from case ascertainment in studies participating in CKDGen (i.e. for the CKD analysis). In most studies, CKD was identified from a single eGFR. CKDGen comprised various study types (cross-sectional, case-control, cohort and randomised studies) but did not specify exact numbers of each. Where longitudinal studies were used, it was unclear if eGFR was measured and CKD diagnosed at baseline only or at multiple points. Variations in eGFR are common and some kidney diseases, such as diabetic nephropathy, manifest as hyperfiltration in early stages (37). Guidelines recommend diagnosing CKD where eGFR < 60 mL/min/1.73m^2 for at least three months and to use CKD-EPI, not MDRD, to calculate eGFR (38). As a result, there may have been non-differential misclassification of cases and non-cases/controls, which would push estimates towards 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 characterise effect modification by aetiology (e.g. diabetes and hypertension) or disease severity or to investigate CKD progression. Diagnostic criteria for albuminuria differed from that now recommended by KDIGO (i.e. >17 mg/g in men and >25 mg/g, rather than ≥ 30mg/g) (9).

We were also unable to fully explain the large magnitude of the effect on CKD that was comparable the most effective pharmacological 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 35-65 (39) reported inverse associations between ≥2 cup/day and eGFR < 60 mL/min (OR 0.59, 95% CI 0.37 to 0.95). Similarly, three other studies reported cross-sectional eGFRs higher among coffee drinkers with mean differences (MDs) of 3.20 (0.27-6.13) (40), 2.03 (0.10-3.97) (41) and 1.61 (0.41-2.81) (42), as summarised in a recent meta-analysis (15). Another cross-sectional study reported adjusted MDs showing higher eGFRs in coffee drinkers (MD 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 (HR for <1 cup per day, 0.90 [95% CI, 0.82-0.99]; 1-<2 cups per day, 0.90 [95% CI, 0.82-0.99]; 2-<3 cups per day, 0.87 [95% CI, 0.77-0.97]; and ≥3 cups per day, 0.84 [95% CI, 0.75-0.94]). However, other studies report no association between coffee and CKD (45), and one cross-sectional study found lower eGFRs in coffee drinkers, although they were on average 10 years older than non-drinkers (46).

The active ingredient in coffee responsible for the results of this study is unclear. Non-caffeine chemical constituents (e.g. chlorogenic acid and diterpenes) reduce inflammation and oxidative stress, which are causative in CKD onset and progression (11,47). Caffeine is a non-selective antagonist of A1 adenosine receptors (A1AR) on distal afferent arterioles. A1AR 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 (P_{gc}) 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 P_{gc} 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 modelling predictions of growing CKD prevalence in the USA 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 eGFR 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 non-linear 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 randomised controlled trial with a coffee-based intervention.

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Tables

Table 1. A list of 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	beta*	p-value
rs2488397	1	197701279	DENND1B	C	G	0.210	0.040	2.0e-08
rs1260326	2	27730940	GCKR	C	T	0.610	0.033	2.4e-08
rs1877723	4	2846799	ADD1	T	C	0.313	-0.040	2.5e-10
rs1481012	4	89039082	ABCG2	G	A	0.111	-0.066	1.5e-12
rs660550	6	31837277	SLC44A4	A	C	0.525	-0.034	8.0e-09
rs9275576	6	32679326	HLA-DQA2	T	C	0.146	0.048	5.5e-09
rs11766104	7	17192272	AHR	T	C	0.167	0.043	4.5e-08
rs4410790	7	17284577	AHR	C	T	0.640	0.108	6.2e-70
rs7791070	7	17401027	AHR	C	T	0.234	-0.076	2.3e-28
rs17645813	7	17419697	KCCAT333	A	G	0.077	-0.073	2.8e-11
rs6461314	7	17439609	KCCAT333	G	A	0.112	0.053	1.2e-08
rs6949509	7	17519261	LOC101927630	G	A	0.435	-0.042	1.5e-12
rs17706320	7	17551902	LOC101927630	C	T	0.342	-0.050	4.7e-16
rs13233604	7	17593486	LOC101927630	A	T	0.172	-0.058	5.0e-12
rs17145750	7	73026378	MLXIPL	T	C	0.163	0.050	2.3e-10
rs17685	7	75616105	POR	A	G	0.281	0.059	7.5e-20
rs11855112	15	74133413	TBC1D21	C	T	0.129	0.049	3.0e-08
rs351242	15	74472716	STRA6	A	G	0.757	-0.062	9.5e-20
rs4886593	15	74558078	CCDC33	A	T	0.200	-0.052	6.6e-13
rs4077582	15	74665622	CYP11A1	T	C	0.706	0.050	7.9e-15
rs4128436	15	74935894	CLK3, EDC3	T	C	0.081	-0.060	2.1e-08
rs2472297	15	75027880	CYP1A1	T	C	0.272	0.136	2.2e-95
rs8042558	15	75320433	PPCDC	T	G	0.235	-0.044	1.3e-10

rs12917120	15	75329091	PPCDC	C	T	0.665	0.053	2.1e-17
rs476828	18	57852587	MC4R	C	T	0.239	0.043	2.0e-10

SNP (single nucleotide polymorphism), EAF (effect allele frequency in the coffee genome wide association study population), *change in cups of coffee/day per copy of the effect allele, Chr (chromosome), *none known

Table 2a and 2b. Results from Mendelian randomisation analyses of causal associations of coffee consumption with eGFR, CKD and albuminuria.

Trait	Sample size	Ethnicity	MR IVW		MR-Egger		MR-weighted median		MR-weighted mode	
			beta† (95% CI)	p	beta† (95% CI)	p	beta† (95% CI)	p	beta† (95% CI)	p
eGFR‡	133,814	Mixed	0.015 (-0.001-0.031) 0.022* (0.013-0.032)	0.07 1.6e^{-6}	0.053 (0.015-0.092)	0.01	0.023 (0.013-0.034)	2.8e^{-5}	0.024 (0.013-0.035)	2.4e^{-4}

Trait	Sample size	Ethnicity	MR IVW		MR-Egger		MR-weighted median		MR-weighted mode	
			OR** (95% CI)	p	OR** (95% CI)	p	OR** (95% CI)	p	OR** (95% CI)	p
CKD§	117,165 (12,385 cases / 104,780 controls)	Mixed	0.84 (0.72-0.98)	0.03	0.64 (0.44-0.94)	0.03	0.80 (0.67-0.96)	0.01	0.80 (0.66-0.98)	0.04
Albuminuria§	54,116‖	European	0.81 (0.67-0.97)	0.02	0.75 (0.46-1.22)	0.3	0.90 (0.69-1.17)	0.4	0.83 (0.60-1.15)	0.3

Odds ratio (OR), CKD (chronic kidney disease), eGFR (estimated glomerular filtration rate) MR (Mendelian randomisation), IVW (inverse-variance weighted),

*after removal of three SNPs (rs1260326, rs9275576 and rs476828) that gave rise to significant heterogeneity (p-value 3.5e^{-15}), **per cup of coffee/day †log

mL/min per cup of coffee/day ‡continuous outcome, §categorical outcome, ‖numbers of cases and controls not published by study authors.

Figures

Figure 1. Forest plots showing causal-effect estimates of an extra cup of coffee per day on CKD, eGFR and albuminuria. Results are shown for the different methods of mendelian randomisation analyses used in this study: inverse variance weighted (IVW), MR-Egger and weighted median and mode. The * denotes removal of three SNPs (rs1260326, rs9275576 and rs476828) that gave rise to significant heterogeneity (p-value of Cochran's Q $3.5e^{-15}$), which was possibly the result of horizontal pleiotropy.

Figure 2. Scatter plots in which the SNP-outcome associations are plotted against the SNP-coffee associations, allowing visualisation of the causal-effect estimate for each individual SNP on eGFR, CKD and albuminuria. The * denotes removal of three SNPs (rs1260326, rs9275576 and rs476828), shown as red points, that gave rise to significant heterogeneity (p-value of Cochran's Q $3.5e^{-15}$). Removal of these SNPs improved agreement between the IVW regression slope and the MR-Egger, weighted median and mode slopes, which are more robust to horizontal pleiotropy.