The Association between Coffee and Caffeine Consumption and Renal Function: Insight from Individual-Level Data, Mendelian Randomization, and Meta-Analysis

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Research paper

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Coffee, Chronic Kidney Disease, Mendelian Randomization, NHANES, and Systematic Review

Abstract
Introduction
By applying on two-sample Mendelian randomization and systematic review and meta-analysis we investigated the association between caffeine and coffee intake with prevalent CKD and markers of renal function.

Material and methods
For the individual data analysis we analysed the NHANES data on renal function markers and caffeine intake. MR was implemented by using summary-level data from the largest ever GWAS conducted on coffee intake (N=91,462) and kidney function.

Results
Finally, we included the data of 18,436 participants, 6.9% had prevalent CKD (based on eGFR). Caffeine intake for general population was 131.1±1.1 mg. The percentage of participants with CKD, by caffeine quartile was 16.6% in the first (lowest) quartile, 13.9% in the second, 12.2% in the third and 11.0% in the top quartile (p<0.001). After adjustment, for increasing quartiles for caffeine consumption, mean urine albumin, albumin-creatinine ratio and estimated glomerular filtration rate (GFR) did not change significantly (p>0.234). In fully adjusted logistic regression models, there was no significant difference in chances of CKD prevalence (p-trend=0.745). In the same line, results of MR showed no impact of coffee intake on CKD (IVW=β: -0.0191, SE: 0.069, p=0.781), on eGFR (overall= IVW= β: -0.0005, SE: 0.005, p=0.926) both in diabetic (IVW= β: -0.006, SE: 0.009, p=0.478), and non-diabetic patients (IVW= β: -6.772, SE: 0.006, p=0.991). Results from the meta-analysis indicted that coffee consumption was not significantly associated with CKD (OR: 0.85, 95%CI 0.71-1.02, p=0.090, n=6 studies, I²=0.32).

Conclusions
By implementing on different strategies, we have highlighted no significant association between coffee consumption with renal function and chance of CKD.
The Association between Coffee and Caffeine Consumption and Renal Function: Insight from Individual-Level Data, Mendelian Randomization, and Meta-Analysis

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ABSTRACT:

Background: The reported relationship between coffee intake and renal function is poorly understood. By applying two-sample Mendelian randomization (MR) and systematic review and meta-analysis we investigated the association between caffeine and coffee intake with prevalent CKD and markers of renal function.

Methods: For the individual data analysis we analysed the National Health and Nutrition Examination Surveys (NHANES) data on renal function markers and caffeine intake. MR was implemented by using summary-level data from the largest ever genome-wide association studies (GWAS) conducted on coffee intake (N=91,462) and kidney function (N=133,413). Inverse variance weighted method (IVW), weighted median-based method, MR-Egger, MR-RAPS, MR-PRESSO were applied. Random effects models and generic inverse variance methods were used to synthesize quantitative and pooled data for the meta-analysis, followed by a leave-one-out method for sensitivity analysis.

Results: Finally, we included the data of 18,436 participants, 6.9% had prevalent CKD (based on eGFR). Caffeine intake for general population was 131.1±1.1 mg. The percentage of participants with CKD, by caffeine quartile was 16.6% in the first (lowest) quartile, 13.9% in the second, 12.2% in the third and 11.0% in the top quartile (p<0.001). After adjustment, for increasing quartiles for caffeine consumption, mean urine albumin, albumin-creatinine ratio and estimated glomerular filtration rate (GFR) did not change significantly (p>0.234). In fully adjusted logistic regression models, there was no significant difference in chances of CKD (p-trend=0.745). In the same line, results of MR showed no impact of coffee intake on CKD (IVW=β: -0.0191, SE: 0.069, p=0.781), on eGFR (overall= IVW= β: -0.0005, SE: 0.005, p=0.926) both in diabetic (IVW= β: -0.006, SE: 0.009, p=0.478), and non-diabetic patients (IVW= β: -6.772, SE: 0.006, p=0.991). Results from the meta-analysis indicted that coffee consumption was not significantly associated with CKD (OR: 0.85, 95%CI 0.71-1.02, p=0.090, n=6 studies, I^2=0.32). These findings were robust in sensitivity analyses.

Conclusions: By implementing on different strategies, we have highlighted no significant association between coffee consumption with renal function and chance of CKD.

Key words: Coffee, Chronic Kidney Disease, Mendelian Randomization, NHANES, and Systematic Review.

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INTRODUCTION:

Chronic kidney disease (CKD) is a progressive loss of renal function over time, ultimately leading to end-stage renal disease, what means irreversible renal failure (1). The pathophysiological processes involved in CKD development are characterized by a background of low-grade chronic inflammation, and high level of oxidative stress (2). Together with coagulation disorders and neutrophil-endothelium interaction, inflammation is believed to play a role in the genesis of kidney injury, potentially leading to chronically impaired kidney function (3). According to the available data, it has been confirmed that diet might play a central role in the regulation of chronic inflammation, anti-oxidant balance and might essentially improve kidney functions (4-6).

Caffeinated drinks are very commonly consumed mainly in Western countries (7). It is estimated that more than 50% of the US adults drink coffee on a daily basis (7). Epidemiological studies and experimental research suggest that coffee consumption may help to prevent several chronic conditions, including type 2 diabetes (DMT2), liver disease, and cardiovascular disease (CVD) (7, 8). With regard to the impact of coffee drinking on the CKD, available results have been still inconsistent (8-13). Several studies reported non-significant relationship between coffee consumption and likelihood of CKD (8, 11, 12), while others reported an inverse association (9, 10, 13). The interpretation of single studies to date has been limited by sample size, research design and subject traits (gender, ethnicity, age, etc.), and they have been underpowered to be able to provide a comprehensive and reliable conclusion. Nakajima et al. in their study with 4722 participants aged 26–65 years and followed-up for 15 year, showed that coffee consumption was associated with a modest increase in estimated glomerular filtration rate (eGFR) (11). It has been hypnotized that various components of coffee may preserve the glomerular endothelial cells from oxidative stress and inflammation (8).

While, considering available data we are not able to rule out the chance of the residual bias, confounding factors, and reverse causation. Mendelian randomization (MR) analysis is able to circumvent the limitations of observational studies, and circumvent the residual bias, confounding factors and reverse causation by using genetic variants that are associated with an exposure as instruments (=coffee) to test for associations with an outcome (=renal function) (14).

Taking all above into account, we aimed to resolve this uncertainty investigating the association between caffeine intake, renal function, assessed by biochemical indices, and prevalent CKD in adult Americans, by running MR analysis on the recognized single
nucleotide polymorphisms (SNPs) of coffee consumption and their casual impact on renal function, and systematically reviewing the literature and performing meta-analysis.

METHODS

**NHANES Population’s Data**

We used data from the Nutrition and Health Examination Surveys (NHANES), which is described in details elsewhere (15). In brief, these are periodic cross-sectional surveys conducted by the US National Center for Health Statistics (NCHS), and during which home visits are conducted to administer questionnaires to collect data on demographics, diet, and other health behaviours. NHANES applies complex multistage probability sampling procedure to ensure selection of participants from various geographical locations and adequate racial/ethnic representation (15). Trained interviewers collected participants’ demographic, socioeconomic, dietary, and health-related information using questionnaires administered during home visits. Clinical examination and dietary assessment are conducted by skilled personnel using a mobile examination centre (MEC) (15). All procedures were carried out in accordance with relevant approved guidelines and regulations (16-19). Informed consent was obtained from all participants, and the NCHS Research Ethics Review Board approved the protocol.

For the present analysis, four survey cycles (between 2005 and 2010) were combined to produce estimates with greater precision and a smaller sampling error. The analytical sample was limited to adults aged ≥18 years. After excluding pregnant and lactating women (n=865), as well as participants with missing information on the variables of interest (n=2935), the final analytical sample included 18,436 respondents from NHANES 2005–2010.

Smoking was based on self-report. Poverty to income variable is an index for the ratio of family income to poverty. The Department of Health and Human Services’ (HHS) poverty guidelines were used as the poverty measure to calculate this index (19). For the assessment of height and weight during the physical examination, participants were dressed in underwear, disposable paper gowns and foam slippers. Body mass index (BMI) was calculated as weight, in kg, divided by the square of height, in meter (19). Three and sometimes four BP (including systolic [SBP] and diastolic blood pressure [DBP]) determinations were taken using a mercury sphygmomanometer by a physician.
Biochemical analysis

Methods for biochemical analyses are described in detail in the NHANES Laboratory/Medical Technologists Procedures Manual (16-19). A blood specimen was drawn from the participant’s antecubital vein by a trained phlebotomist according to a standardized protocol. Fasting glucose was measured in plasma by a hexokinase method using a Roche/Hitachi 911 Analyzer and Roche Modular P Chemistry Analyzer. The DxC800 modular chemistry side uses the Jaffe reaction method (kinetic alkaline picrate) to determine the concentration of creatinine in serum. The creatinine calibration is traceable to an isotope dilution mass spectrometry reference method (20). Urinary creatinine by the Jaffe rate reaction, and urinary albumin by solid-phase fluorescent immunoassay, from a random urine sample (21) were used to calculate the urinary albumin-creatinine ratio (ACR). The CKD Epidemiology Collaboration (CKD-EPI) equation (22) was used to estimate glomerular filtration rate (eGFR, in ml/min/1.73m²), and an eGFR of <60 ml/min/1.73m² used to define low eGFR. ACR >30 mg/g was used to define albuminuria, and the presence of either low eGFR or albuminuria was used to define CKD in line with the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 recommendations (23). Levels of triglyceride (TG) were measured enzymatically. DMT2 was diagnosed as a self-reported history of diabetes or fasting plasma glucose ≥126 mg/dl. Hypertension (HTN) was diagnosed in individuals with SBP at or above 140 mmHg and/or DBP at or above 90 mmHg, and in persons who were on antihypertensive therapy (24).

Dietary data in NHANES were collected using a single 24-hour dietary recall interview at the MEC (15). Dietary intake was assessed via 24h recall obtained by a trained interviewer during the mobile examination center visit, with the use of a computer-assisted dietary interview system with standardized probes, i.e. the US Department of Agriculture Automated Multiple-Pass Method (AMPM) (25, 26). Briefly, the type and quantity of all foods and beverages consumed in a single 24h period before the dietary interview (from midnight to midnight) were collected with the use of AMPM. AMPM is designed to enhance complete and accurate data collection while reducing respondent burden (26, 27). Caffeine concentration data reported in the survey-specific Food and Nutrient Database for Dietary Studies (FNDDS) were relied upon in the analyses. FNDDS is the database that provides the nutrient values for foods and beverages reported in the What We Eat in America (WWEIA), the dietary intake component of NHANES. Sources of caffeine included coffee, tea, soda, energy drinks, and chocolate and cocoa containing products, in consideration of caffeinated and decaffeinated versions (28).
Statistical analysis

Data analyses followed the CDC guidelines for complex NHANES data analysis, accounting for the masked variance and using the recommended weighting methodology (29), implemented with the use of SPSS® complex sample module version 22.0 (IBM Corp, Armonk, NY). We used means and standard error of the mean (SEM) for continuous variables (with groups compared via analysis of variance [ANOVA]) and percentages for categorical variables (with groups compared using the chi-square test). The natural logarithm of ACR and urinary albumin were taken to approximate a normal distribution. Adjusted mean of kidney function markers (urine albumin, serum creatinine, ACR, eGFR) across caffeine quartiles were conducted using analysis of covariance (ANCOVA). These models were adjusted for age, sex, race, income to poverty, alcohol intake, energy intake, smoking, BMI, HTN, TG and T2DM. Logistic regressions models, employing a similar adjustment strategy (age, sex, race, income to poverty, alcohol intake, energy intake, smoking, BMI, HTN, TG and T2DM), were then used to derive the odds ratio (OR) and 95% confidence interval (CI) for the association of caffeine (by quartile) with prevalent CKD, always using the lowest quartile as reference. A two-sided p<0.05 was used as the nominal cut-point to indicate statistically significant results.

Mendelian Randomization

Study design

A two-sample MR study design was used, in which summary statistics from different genome wide association studies (GWAS) were analyzed, for the exposures and outcomes, to estimate the effects of exposure on outcome. Essentially, we applied genetic predictors of coffee consumption to extensively genotyped case-control studies of kidney function (CKD, eGFR (separately in patients with and without DM)) to obtain estimates of the association of exposure to our clinical outcomes.

Genetic predictors of exposures

We retrieved summary data for the association between SNPs and coffee consumption from the biggest meta-GWAS (91,462, European descent, Coffee and Caffeine Genetics Consortium) (28) (Supplementary Table 1). 10 single nucleotide polymorphisms (SNPs), at eight loci, associated with coffee consumption identified (30), we excluded three SNPs that did not exceed the genome-wide significance threshold (p <5×10−8) and two SNPs in linkage disequilibrium (r2 >0.6), leaving five independent SNPs for the main analyses. The MR studies assume that the SNPs (instrumental variables) are associated with the outcome only via the
exposure (31), so we performed sensitivity analysis excluding SNPs with potentially pleiotropic effects. To assess the instrumental variable analysis “exclusion-restriction” assumption we used Ensembl release (http://useast.ensembl.org/index.html). Ensembl gives SNP phenotypes.

**Genetic predictors of outcomes**

Genetic associations with renal function were obtained from the largest available extensively genotyped study based on a meta-analysis (133,413 individuals with replication in up to 42,166 individuals) (32). eGFR was estimated using the four-variable Modification of Diet in Renal Disease Study Equation. They have defined CKD as eGFR <60 ml min⁻¹ per 1.73m². Diabetes was defined as fasting glucose ≥126 mg dl⁻¹, pharmacologic treatment for diabetes or by self-reports. In all studies, diabetes and kidney function were assessed at the same point in time. For genome-wide association analysis they followed a centralized analysis plan, each study regressed sex and age adjusted residuals of the logarithm of eGFR on SNP dosage levels. Logistic regression of CKD status was performed on SNP dosage levels adjusting for sex and age. For all traits, adjustment for appropriate study-specific features, including study site and genetic principal components was included in the regression and family-based studies appropriately accounted for relatedness. A SNP, highly correlated (R²>0.99) with the original SNP, was used as proxy when the original SNP was not available for outcomes.

**Statistics:**

We also used MR-Egger to test for potentially pleiotropic effects as it may generate correct estimates even when all SNPs are invalid instruments if the assumption of instrument strength independent of direct effect (InSIDE) is satisfied. MR Egger allows free estimation of the intercept, although further assumptions, such as the independence between instrument strength and direct effects, cannot be easily verified. Average directional pleiotropy across genetic variants was assessed from the p-value of the intercept term from MR-Egger (33). Causal estimates in MR Egger are less precise than those obtained by using inverse variance-weighted (WM) MR (34). Analysis using MR-Egger has a lower false positive rate but a higher false negative rate than inverse variance weighted (IVW) method (35). The WM estimate, as the weighted median of the SNP-specific estimates, provides correct estimates if SNPs accounting for ≥50% of the weight are valid instruments. WM MR allows some variants to be invalid...
instruments provided at least half are valid instruments. It uses inverse variance weights and bootstrapping to estimate CIs (33).

Further, to assess heterogeneity between individual genetic variants’ estimates, we used the Q’ heterogeneity statistic (36) and the MR pleiotropy residual sum and outlier (MR-PRESSO) (34) test. The Q’ statistic uses modified 2nd order weights that are a derivation of a Taylor series expansion and take into account uncertainty in both numerator and denominator of the instrumental variable ratio (this eases the NO-measurement [NOME]-error assumption) (36). The MR-PRESSO framework relies on the regression of variant-outcome associations on variant-exposure associations and implements a global heterogeneity test by comparing the observed distance (residual sums of squares) of all variants to the regression line with the distance expected under the null hypothesis of no pleiotropy (37). In case of evidence of horizontal pleiotropy, the test compares individual variants expected and observed distributions to identify outlier variants. We consider as results, causal estimates that agreed in direction and magnitude across MR methods, pass nominal significance in inverse variance-weighted MR, and did not show evidence of bias from horizontal pleiotropy using heterogeneity tests. MR-RAPS (Mendelian randomization using the robust adjusted profile score, a method for correcting for pleiotropy using robust adjusted profile scores). We used R (version 3.4.2 R Core Team (2017).R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.

Ethics

This investigation uses published or publicly available summary data with no involvement of participants in the study. No original data were collected for this manuscript. Ethical approval for each of the studies included in the investigation can be found in the original publications (including informed consent from each subject). The study conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Systematic Review and Meta-Analysis

Literature search and study selection

This meta-analysis was designed, conducted and reported according to meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (38). The primary exposure of interest was coffee intake, while the primary outcome of interest was risk of CKD. Studies published up to 30th January 2019 (without language restriction) were searched using PubMed, Embase, and Scopus databases; the query syntax of searching is shown in the Supplementary
Methods (Supplementary Table 2). This was complemented by hand searches of the reference list of eligible articles, and email correspondences with authors for additional data, where relevant.

After excluding duplicates and based on titles and abstracts, we excluded studies on animals. Eligible studies were selected by using predefined inclusion criteria of case-control, cross-sectional or cohort studies published as original articles to evaluate the risk of CKD among subjects with coffee consumption compared with subjects without coffee consumption. In addition, supplementary hand searching of reference lists of previous reviews or meta-analyses was conducted.

Study Selection

Study selection started with the removal of duplicates, followed by screening of titles and abstracts by two reviewers (MM and JJ). To avoid bias, the reviewers were blinded to the names, qualifications, or the institutional affiliations of the study authors. Agreement between the reviewers was excellent (Kappa index: 0.91; p<0.001). Disagreements were resolved at a meeting between reviewers prior to selected articles being retrieved (a flow chart is available in Supplementary Figure 1).

We included studies if they met all the following criteria: (1) the studies of interest were on coffee intake; (2) the studies were population-based cohort studies and reported CKD data; (3) relative risk (RR), hazard ratio (HR) or OR estimates with 95% CIs adjusted for multivariable factors were available or were able to be calculated; (4) original articles with full texts in English.

Studies were excluded according to the following criteria: (1) reviews, letters, unpublished data, or comments; (2) those published in languages other than English; (3) not population-based cohort studies; (4) RR, HR or OR estimates with 95% CIs were not available or were not be able to be calculated. Narrative reviews, comments, opinion pieces, methodological, editorials, letters or any other publications lacking primary data and/or explicit method descriptions, were also excluded.

Data extraction and management

The full texts of studies meeting the inclusion criteria were retrieved and screened to determine eligibility by 2 reviewers (MM, JJ). The study quality assessment was performed according to the Newcastle-Ottawa Scale (NOS, Supplementary Table 3) (39). The following perspectives were considered; representativeness of the exposed cohort; dietary survey
Data synthesis and statistical analyses

For studies that reported results from different multivariable-adjusted models, the model including the most confounding factors was extracted for the meta-analysis. The random-effect model was applied to calculate pooled RRs, 95%CI and p value for heterogeneity. Effect estimate comparing the highest with the lowest intake category were combined across studies to generate the summary associations. The extent of heterogeneity across studies was examined using the I² test (40-42) and I² >50 % together with p<0.05 two-sided indicated significant heterogeneity (40-42). To examine whether the present results were affected by a single study, we conducted a sensitivity analysis by excluding one study at a time.

Publication bias

Potential publication bias was explored using visual inspection of Begg’s funnel plot asymmetry, Begg’s rank correlation and Egger’s weighted regression tests. The Duval and Tweedie trim method was used to adjust the analysis for the effects of publication bias (43).

RESULTS

**NHANES Data:**

Of the 18,436 participants included in the analyses, 6.9% had prevalent CKD (based on eGFR). The characteristics of participants overall and across caffeine quartiles are summarised in Table 1. The caffeine intake for the general population was 131.1±1.1 (mg) and was higher for men compared to women (149.1±2.2 vs. 114.2±1.7 respectively) (p<0.001). Mean age
across the caffeine intake was ranged between 44.2-50.1 years, while the proportion of men decreased from 43.8 to 57.5% across increasing quartiles of caffeine. Across increasing caffeine quartiles, the proportion of non-Hispanic White (the largest ethnic group) increased from 32.8 to 70.0%; the proportions of Non-Hispanic Black decreased from 20.7 to 11.7%; and Mexican-American followed the same trend (reduction from 33.3 to 9.1%, \(p<0.001\), Table 1). The proportion of participants with prevalent low eGFR, albuminuria or CKD systematically decreased across increasing quartiles of caffeine (all \(p<0.001\) for linear trend, Table 1). Proportions of participants with CKD, by caffeine quartile, were 9.4% in the first (lowest) quartile, 7.8% in the second, 5.8% in the third and 5.2% in the top quartile (Table 1).

Adjusted mean levels of renal function markers by quartile of caffeine are shown in Table 2. For increasing quartiles for caffeine intake, mean urine albumin did not change significantly (2.20 to 2.17 mg/L, \(p=0.239\)), the same was observed for eGFR (91.2 to 89.6 ml/min/1.73 m², \(p=0.415\), Table 2). Log ACR also remained stable with no significant change across the quartiles of caffeine (2.14 to 2.16 mg/g, \(p=0.352\)). In age, sex and race adjusted logistic regressions, compared with the lowest quartile of the caffeine; the odds ratio (95% CI) was 0.76 (0.55–1.09) for the Q2, 1.03 (0.95-1.08) for Q3 and 0.97 (0.86-1.12) for Q4 (\(p=0.355\) for trend, CKD diagnosed by eGFR). In logistic regression models adjusted for age, sex, race, income to poverty, alcohol intake, energy intake, smoking, BMI, HTN, TG and T2DM, compared with the lowest quartile of caffeine, the odds ratio (95% CI) of low eGFR was 1.00 (0.96-1.04) for Q2, 0.99 (0.96-1.03) for Q3 and 1.02 (0.94-1.10) for Q4 (\(p=0.745\) for trend).

**Mendelian Randomization**

The list of all instruments associations for coffee intake is shown in Supplementary Table 1. The results, expressed as beta-coefficient for interested outcomes per one cup per day increase in coffee consumption, demonstrate no effect on CKD (IVW=\(\beta\): -0.0191, SE: 0.069, \(p=0.781\)), eGFR (overall= IVW= \(\beta\): -0.0005, SE: 0.005, \(p=0.926\); both for DM: IVW= \(\beta\): -0.006, SE: 0.009, \(p=0.478\), and non-DM subjects: IVW= \(\beta\): -6.772, SE: 0.006, \(p=0.991\), Table 4). Results of the forest and scatter plots for each outcome are shown in Figures 1 to 4, further analysis of MR-PRESSO have not highlighted for any chance of outlier. As it can be seen in the Table 3, pleiotropy bias was indicated for no chance of pleiotropic for all 4 level of our outcomes further the results of the MR-RAPS was identical with the IVW prediction which again indicted for no chance of pleiotropy (Table 3). While the heterogeneity tests were significant for all level of outcomes (Figure 1 and 2) but not for the GFR between DM populations (MR-Egger=Q: 5.579, P: 0.133, Table 3). All but three of the coffee-increasing
alleles of the five SNPs with a genome-wide significant association with coffee consumption were positively associated with eGFR (rs17685, rs4410790, rs2472297), and the association with rs7800944, near the gene encoding MLXIPL (promoters of triglyceride synthesis genes), was statistically significant and negatively affected eGFR (Figure 3). With regard to the CKD, just a single SNP had a significant effect, and it was inversely related (rs17685, making the enzyme cytochrome P450 oxidoreductase, Figure 4).

Meta-Analysis And Systematic Review

Overviews of key characteristics of the 6 studies are shown in Supplementary Table 4. A total of 42,051 participants were included in the analysis. All the studies involved both men and women. Performed in varied countries, including: Italy (9), Japan (11, 12), Korean (10, 13) and USA. In five of them CKD was diagnosed as GFR < 60 mL/min/1.73 m2 (10-12) and in one of them it was Renal Resistive Index (RRI) > 0.65 (renal colour–Doppler echocardiography was used to evaluate RRI) (9). Results of quality assessment are shown in the Supplemental Table 3, with all studies scoring ≥ 7.

Coffee consumption and chance of CKD

Based on the meta-analysis of available studies we showed that coffee consumption was not significantly associated with CKD (OR: 0.85, 95%CI 0.71-1.02, p=0.090, n=6 studies, \(I^2=0.32\), Supplemental Figure 2).

Sensitivity analysis

In leave-one-out sensitivity analyses, the pooled effect estimates remained similar for the effect on coffee consumption for CKD (OR: 0.85, 95%CI 0.71-1.02). This stability confirms that the significant difference between the studied groups is the overall effect of all included studies.

Publication bias

Visual inspection of the funnel plot symmetry suggested no potential publication bias for the comparison of coffee consumption and CKD. Moreover, Egger’s linear regression indicated for absence of publication bias (intercept = -1.4, two-tailed \( p=0.421 \)), as well as the Begg’s rank correlation test (Kendall’s Tau with continuity correction =1.00, two tailed \( p=0.362 \)). After adjustment of the effect size for potential publication bias using the ‘trim and fill’
correction, no potentially missing studies were imputed in funnel plot (OR: 0.86, 95%CI 0.70-1.07).

DISCUSSION

The present study, by applying three different methods, examined the association between caffeine intake and prevalent CKD. We used the largest, nationally representative population of adult Americans to evaluate the link between caffeine and renal function. Further, we applied largest available GWAS to obtain unconfounded estimates of the association between genetically instrumented coffee intake, eGFR and CKD. Further, we systematically searched and pooled the studies. Individual-level data and meta-analysis indicated that a caffeine/coffee intake is not associated with likelihood of CKD and kidney function tests. MR data confirmed the main findings and revealed a no causal effect of coffee intake on eGFR and CKD.

Available information on the potential association between renal function and coffee are controversial (8-12). In a cross-sectional study in Italy (n=221), in which coffee consumption was assessed by interviewer-administered food frequency questionnaire, the authors reported a significant inverse association between coffee intake and risk of CKD (OR: 0.46, 95%CI: 0.24-0.89) (9). Kim et al. in their study made in the Korean (n=2,673), women aged 35–64 years from the 4th Korean National Health and Nutrition Examination Surveys, also reported the positive effect of caffeine intake on CKD prevalence (OR: 0.59, 95%CI: 0.37-0.95) (10). Two other studies have reported no association between caffeine/coffee and CKD risk (11, 12).

- Pham et al., in a cross-sectional study with 11,662 participants reported insignificant association between coffee intake and likelihood of CKD (OR: 1.01, 95%CI: 0.84-1.21) (12); the same data were observed in another Japanese cross-sectional study (n= 342; OR: 0.74, 95%CI:0.30-1.85) (11). In a prospective study that followed 4,722 participants aged 26–65 year for 15 years, Herber-Gast et al. found that coffee consumption was associated with a slightly higher eGFR, particularly in subjects aged ≥46 years. The authors concluded that the absence of an association with eGFR changes suggests that the higher eGFR among coffee consumers is unlikely to be a result of glomerular hyperfiltration (44). A meta-analysis of 4 studies reported a non-significant association between coffee consumption and the risk of CKD (OR: 0.71,CI: 0.47-1.08) (8). Taking into account mostly positive data of moderate coffee consumption with the risk of cardiovascular disease, but also the link between coffee/caffeine intake and blood pressure increase, and especially very recent data suggesting inverse significant link between caffeine intake and all-cause mortality in CKD patients (45) one might have expected the potential significant impact on chronic kidney disease.
There are indeed very limited data on the association between caffeine intake and renal function parameters, which make it difficult to substantially compare our findings. In a cross-sectional study between 11,662 Japanese men and women aged 49–76 the authors reported that caffeine intake was weakly inversely associated with serum uric acid (SUA) in the age-adjusted model (12); while in another study between 14,758 participants aged >20 years, the authors reported no link between caffeine intake and SUA (46). Hence the results in case of impact of caffeine intake on kidney functions tests seems to be still controversial, however taking into account our data, it seems, that similarly to the link between caffeine intake and CKD prevalence, there is also no significant link with the parameters characterizing kidney function (47-54).

The present analysis has some strengths to be emphasized. This is the largest data analysis of the association of kidney disease with caffeine intake. Participants were a random sample of individuals drawn from the general population and therefore the results can be extrapolated to the general US population. Because data collection was performed on all days of the week in NHANES, the potential for day-specific information bias is very low (47, 48). We have evaluated our findings by applying on the MR, which is known as powerful tools for detection of the causal impact.

Our findings, however, also have to be considered in the context of some study limitations. First, the cross-sectional nature of the data does not allow for direct inference about causality. Second, it is well known that a single 24-hour diet recall interview is not ideal for characterizing an individual’s long-term habitual intake (49, 50). Third, individuals with renal impairment may be less likely to drink caffeinated drinks, which may be underestimating our results. As with any meta-analysis, internal validity relies on the quality of individual studies. Several limitations can be identified in this regard.

In conclusions, the present study, by applying three different methods to investigate the association between the caffeine intake and prevalent CKD, we confirmed no impact of caffeine consumption on CKD risk and kidney function tests. MR data confirmed additionally revealed no causal effect of coffee intake on eGFR and CKD.
ACKNOWLEDGMENTS:
The material presented in this manuscript is original and has not been submitted for publication elsewhere. The results of this analysis were presented during *European Society of Cardiology* (ESC) Congress 2019 in Paris, France.

**Funding.** This manuscript was written independently; no company or institution supported it financially. No professional writer was involved in the preparation of this meta-analysis.

**Contributions:** MM wrote the draft version of the manuscript, gathered the data, and make the statistical analysis. MB and MM conceived the topic and wrote the manuscript; MB prepared the final version of the paper for submission. JJ, AC and NS conceived the topic and critically revised the manuscript. All gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

**Declaration of interest:** DPM has given talks and attended conferences sponsored by MSD, AstraZeneca and Libytec; MB speakers bureau: Amgen, Esperion, Herbapol, Kogen, KRKA, Novartis, Polpharma, Sanofi-Aventis, Servier, Teva, Viatris and Zentiva; consultant to Akcea, Amgen, Daichii Sankyo, Esperion, Freia Pharmaceuticals, Polfarmex, Sanofi-Aventis; Grants from Amgen, Viatris, Sanofi and Valeant; All other authors have no conflict of interest to declare.
REFERENCES:


44. Herber-Gast GC, van Essen H, Verschuren WM, Stehouwer CD, Gansevoort RT, Bakker SJ, et al. Coffee and tea consumption in relation to estimated glomerular filtration rate: results from the


Table 1. Descriptive characteristics of participants across quartiles of caffeine

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Quartiles of caffeine</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First</td>
<td>Second</td>
</tr>
<tr>
<td><strong>Median (25th-75th)(mg)</strong></td>
<td>11 (7-19)</td>
<td>51 (34-72)</td>
</tr>
<tr>
<td><strong>Number of participants</strong></td>
<td>4609</td>
<td>4611</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--- Male (%)</td>
<td>43.8</td>
<td>44.7</td>
</tr>
<tr>
<td>--- Female (%)</td>
<td>56.2</td>
<td>55.3</td>
</tr>
<tr>
<td><strong>Age (year)</strong></td>
<td>44.2±0.3</td>
<td>45.6±0.3</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--- White (non-Hispanic) (%)</td>
<td>32.8</td>
<td>36.7</td>
</tr>
<tr>
<td>--- Non-Hispanic Black (%)</td>
<td>20.7</td>
<td>24.5</td>
</tr>
<tr>
<td>--- Mexican-American (%)</td>
<td>33.3</td>
<td>23.9</td>
</tr>
<tr>
<td><strong>Income to Poverty (n)</strong></td>
<td>2.3±0.02</td>
<td>2.3±0.02</td>
</tr>
<tr>
<td><strong>BMI (Kg/m²)</strong></td>
<td>28.8±0.1</td>
<td>28.6±0.1</td>
</tr>
<tr>
<td><strong>Energy Intake (Kcal/day)</strong></td>
<td>1970.2±14.2</td>
<td>2053.2±15.3</td>
</tr>
<tr>
<td><strong>Alcohol Intake (g/day)</strong></td>
<td>9.5±0.4</td>
<td>8.9±0.3</td>
</tr>
<tr>
<td><strong>Triglyceride (mg/dl)</strong></td>
<td>144.3±1.9</td>
<td>145.5±2.0</td>
</tr>
<tr>
<td><strong>Type 2 diabetes (%)</strong></td>
<td>17.9</td>
<td>18.4</td>
</tr>
<tr>
<td><strong>Hypertension (%)</strong></td>
<td>10.9</td>
<td>10.1</td>
</tr>
<tr>
<td><strong>Low eGFR (%)</strong></td>
<td>9.4</td>
<td>7.8</td>
</tr>
<tr>
<td></td>
<td>9.8</td>
<td>10.1</td>
</tr>
<tr>
<td>------------</td>
<td>-----</td>
<td>------</td>
</tr>
<tr>
<td>Albuminuria (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CKD (%) [low eGFR or albuminuria]</td>
<td>16.6</td>
<td>13.9</td>
</tr>
</tbody>
</table>

Value expressed as a mean and s.e.m. or percentage. CKD: Chronic kidney disease. eGFR: estimate glomerular filtration rate.
Table 2. Adjusted (age, sex, race, alcohol intake, energy intake, smoking, BMI, HTN, TG and DM) mean levels of markers of CKD across quartiles of caffeine.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Quartiles of Caffeine</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First</td>
<td>Second</td>
</tr>
<tr>
<td><strong>Number of participants (n)</strong></td>
<td>4609</td>
<td>4611</td>
</tr>
<tr>
<td><strong>Log Urine Albumin (mg/L)</strong></td>
<td>2.20±0.02</td>
<td>2.16±0.02</td>
</tr>
<tr>
<td><strong>Serum Creatinine (mg/dL)</strong></td>
<td>0.89±0.003</td>
<td>0.90±0.004</td>
</tr>
<tr>
<td><strong>Log ACR (mg/g)</strong></td>
<td>2.14±0.02</td>
<td>2.10±0.02</td>
</tr>
<tr>
<td><strong>eGFR (ml/min/1.73m²)</strong></td>
<td>91.2±0.7</td>
<td>92.8±0.4</td>
</tr>
</tbody>
</table>

Values (from analysis of covariance) expressed as a mean ± s.e.m. eGFR: estimated glomerular filtration rate, ACR: Urine Albumin /Creatinine Ratio.
<table>
<thead>
<tr>
<th>Outcomes</th>
<th>MR</th>
<th>Heterogeneity</th>
<th>Pleiotropy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Method</td>
<td>beta</td>
<td>SE</td>
</tr>
<tr>
<td>CKD</td>
<td>MR Egger</td>
<td>0.052</td>
<td>0.091</td>
</tr>
<tr>
<td></td>
<td>WM</td>
<td>-0.008</td>
<td>0.032</td>
</tr>
<tr>
<td></td>
<td>IVW</td>
<td>-0.019</td>
<td>0.069</td>
</tr>
<tr>
<td></td>
<td>RAPS</td>
<td>-0.016</td>
<td>0.063</td>
</tr>
<tr>
<td>Overall</td>
<td>MR Egger</td>
<td>-0.0070</td>
<td>0.00752</td>
</tr>
<tr>
<td></td>
<td>WM</td>
<td>-0.0012</td>
<td>0.0020</td>
</tr>
<tr>
<td></td>
<td>IVW</td>
<td>-0.00053</td>
<td>0.0058</td>
</tr>
<tr>
<td></td>
<td>RAPS</td>
<td>-0.00044</td>
<td>0.0058</td>
</tr>
<tr>
<td>eGFR</td>
<td>MR Egger</td>
<td>-0.0049</td>
<td>0.0143</td>
</tr>
<tr>
<td>DM</td>
<td>WM</td>
<td>-0.00743</td>
<td>0.0082</td>
</tr>
<tr>
<td></td>
<td>IVW</td>
<td>-0.00645</td>
<td>0.0091</td>
</tr>
<tr>
<td></td>
<td>RAPS</td>
<td>-0.00698</td>
<td>0.0086</td>
</tr>
<tr>
<td>Non-DM</td>
<td>MR Egger</td>
<td>-7.441261e-03</td>
<td>0.0075</td>
</tr>
<tr>
<td></td>
<td>WM</td>
<td>-1.352248e-03</td>
<td>0.0019</td>
</tr>
</tbody>
</table>
FIGURES’ LEGENDS:

**Figure 1.** The scatter plots of genetic associations with coffee/caffeine level against genetic associations with eGFR. The slopes of each line represent causal associations for each method.

**Figure 2.** The scatter plots of genetic associations with coffee/caffeine level against genetic associations with CKD. The slopes of each line represent causal associations for each method.

**Figure 3.** The forest plots of genetic associations with coffee/caffeine level against genetic associations with eGFR. The slopes of each line represent causal associations for each method.

**Figure 4.** The forest plots of genetic associations with coffee/caffeine level against genetic associations with CKD. The slopes of each line represent causal associations for each method.
Supplementary Table 1. Summary results of the 5 genetic loci of coffee intake

<table>
<thead>
<tr>
<th>SNP</th>
<th>Nearest gene</th>
<th>GX</th>
<th>GX SE</th>
<th>EA</th>
<th>OA</th>
<th>EAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2472297</td>
<td>CYP1A2</td>
<td>0.14</td>
<td>0.01</td>
<td>T</td>
<td>C</td>
<td>0.24</td>
</tr>
<tr>
<td>rs4410790</td>
<td>AHR</td>
<td>-0.1</td>
<td>0.01</td>
<td>T</td>
<td>C</td>
<td>0.37</td>
</tr>
<tr>
<td>rs7800944</td>
<td>MLXIPL</td>
<td>-0.5</td>
<td>0.01</td>
<td>T</td>
<td>C</td>
<td>0.72</td>
</tr>
<tr>
<td>rs17685</td>
<td>POR</td>
<td>0.07</td>
<td>0.01</td>
<td>A</td>
<td>G</td>
<td>0.29</td>
</tr>
<tr>
<td>rs9902453</td>
<td>EFCAB5</td>
<td>-0.03</td>
<td>0.01</td>
<td>A</td>
<td>G</td>
<td>0.54</td>
</tr>
</tbody>
</table>

All of the coffee intake markers were associated at genome-wide significance (p < 5 x 10^{-8}).

EA: effect allele; OA: other allele, EAF: effect allele frequency; GX: the per-allele effect on standard deviation units of coffee intake; GX SE: standard error of GX.
### Supplementary Table 2. Full search terms and strategy for papers indexed in PUBMED.

<table>
<thead>
<tr>
<th>No</th>
<th>Concept</th>
<th>Search terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Coffee</td>
<td>“coffee” [Mesh] OR “caffeine” [Mesh]</td>
</tr>
<tr>
<td>2</td>
<td>Renal function</td>
<td>chronic kidney disease [tiab] OR chronic kidney disease *[tiab] OR CKD[tiab]</td>
</tr>
<tr>
<td>3</td>
<td>Combination Exposure And Outcome</td>
<td>#1 AND #2</td>
</tr>
<tr>
<td>5</td>
<td>Limit</td>
<td>#7 NOT #4</td>
</tr>
</tbody>
</table>
For Supplementary Table 3:

NEWCASTLE – OTTAWA QUALITY ASSESSMENT SCALE COHORT STUDIES:

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

**Selection**
1) Representativeness of the exposed cohort
   a) truly representative of the average healthy adults in the community ★
   b) somewhat representative of the average healthy adults in the community ★
   c) selected group of users e.g. nurses, volunteers, vegetarian
   d) no description of the derivation of the cohort
2) Selection of the non-exposed cohort
   a) drawn from the same community as the exposed cohort ★
   b) drawn from a different source
   c) no description of the derivation of the non-exposed cohort
3) Ascertainment of exposure
   a) secure record (e.g. 7 day food diary) ★
   b) structured interview/≥ 2 dietary recalls/diet history/food frequency questionnaire validated for dairy components ★
   c) written self-report (e.g. <2 dietary recalls/non-validated food frequency questionnaire or not reported whether food frequency questionnaire was validated)
   d) no description
4) Demonstration that outcome of interest was not present at start of study
   a) yes ★
   b) no

**Comparability**
1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for age, sex, smoking, total energy intake, and body mass index ★
   b) study controls for any additional factor (e.g. physical activity, alcohol intake, family history of diabetes, dietary factors) ★

**Outcome**
1) Assessment of outcome
   a) independent blind assessment (e.g. clinical diagnosis/complete medical information available). ★
   b) record linkage/medical record or validated self-report ★
   c) non-validated self-report
   d) no description
2) Was follow-up long enough for outcomes to occur
   a) yes/ follow up period for outcome of interest is 10 years or over ★
   b) no
3) Adequacy of follow-up of cohorts
   a) complete follow-up - all subjects accounted for ★
   b) subjects lost to follow-up unlikely to introduce bias - small number lost ≤20% follow-up, or description provided of those lost ★
   c) follow-up rate <80% or no description of those lost
   d) no statement
**Supplementary Table 3.** Quality assessment of included cohorts’ studies*

<table>
<thead>
<tr>
<th>Studies</th>
<th>Selection</th>
<th>Comparability</th>
<th>Outcome</th>
<th>Total score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Representativeness of the exposed cohort</td>
<td>Selection of the non-exposed cohort</td>
<td>Ascertainment of exposure</td>
<td>Outcome not present at start of study</td>
</tr>
</tbody>
</table>

*the 6th study included in the systematic review is based on the results of current NHANES analysis.*
### Supplementary Table 4. Characteristics of the studies that were included in the meta-analysis.

<table>
<thead>
<tr>
<th>Author, year and Reference</th>
<th>Country, region/cohoot</th>
<th>Coffee consumption measurement</th>
<th>Design</th>
<th>Sample size</th>
<th>Definition of CKD</th>
<th>Main confounders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trovato (2010)</strong> (1)</td>
<td>Italy, Interviewer-administered food frequency questionnaire</td>
<td>Cross-sectional</td>
<td>221</td>
<td></td>
<td>RRI&gt;0.65 Renal Color-Doppler echocardiography used to evaluate RRI</td>
<td>Haemoglobin, albumin, free-fat mass, hypertension, HOMA and renal insufficiency</td>
</tr>
<tr>
<td><strong>Pham (2010)</strong> (2)</td>
<td>Japan, Self-reported food frequency</td>
<td>Cross-sectional</td>
<td>11,662</td>
<td></td>
<td>GFR&lt;60 mL/min/1.73 m2</td>
<td>None</td>
</tr>
<tr>
<td><strong>Nakajima (2010)</strong> (3)</td>
<td>Japan, Self-reported food frequency</td>
<td>Cross-sectional</td>
<td>342</td>
<td></td>
<td>GFR&lt;60 mL/min/1.73 m2</td>
<td>Age, smoking, sex, tea consumption, alcohol drinking, medications, BMI, blood pressure, LDL, TAG, HDL, fasting glucose, proteinuria</td>
</tr>
<tr>
<td><strong>Kim(2013)</strong> (4)</td>
<td>Korean, Korea National Health and Nutrition Examination Surveys Household interview with self-reported questionnaire</td>
<td>Cross-sectional</td>
<td>2,673</td>
<td></td>
<td>GFR&lt;60 mL/min/1.73 m2</td>
<td>Age, sex, alcohol intake, total energy intake, hypertension, antidyposalipidemic drug use, BMI, diabetes</td>
</tr>
<tr>
<td><strong>Jhee (2018)</strong> (5)</td>
<td>Korean, Korean Genome and Epidemiology Study, food frequency questionnaire</td>
<td>Cohort</td>
<td>8,717</td>
<td></td>
<td>GFR&lt;60 mL/min/1.73 m2</td>
<td>Age, sex, BMI, mean arterial pressure, smoking status, alcohol status, income, CRP, hemoglobin, albumin, total cholesterol, eGFR, and proteinuria, mean arterial pressure, history of hypertension and cardiovascular events, HbA1c and history of diabetes, daily intake amount of tea and chocolate.</td>
</tr>
<tr>
<td><strong>Mazidi (2019)</strong></td>
<td>USA, National Health and Nutrition Examinations Surveys, 24h recall</td>
<td>Cross-sectional</td>
<td>18,436</td>
<td></td>
<td>GFR&lt;60 mL/min/1.73 m2</td>
<td>Age, sex, race, income to poverty, alcohol intake, energy intake, smoking, BMI, HTN, TG and DM</td>
</tr>
</tbody>
</table>

*eGFR, estimated glomerular filtration rate; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; FFM, fat-free mass; FM, fat mass; ECW, extracellular water; ICW, intracellular water; BUN, blood urea nitrogen; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RRI, renal resistive index; TG, triglyceride; HOMA-IR, homeostatic model assessment of insulin resistance.*
References for Suppl. Table 3 & 4:

**Supplementary Figure 1.** Flow chart diagram of study selection.

1. Records identified through database searching: 2995
2. Records after duplicates removed: 2143
3. Records screened: 2143
4. Records excluded based on title: 2119
5. Full-text articles assessed: 24
   - Full-text articles excluded, with reasons:
     1. Non-human, Genetics, Molecular
     2. Review and Conference
     3. Editorial case, Not relevant
     4. Not enough data
6. Studies included in systematic review: 5*

*the 6th study included in the systematic review is based on the results of current NHANES analysis.*
**Supplementary Figure 2.** Forest plot of coffee consumption and chronic kidney disease.

**Meta Analysis**

<table>
<thead>
<tr>
<th>Study name</th>
<th>Statistics for each study</th>
<th>Odds ratio 95% CI</th>
<th>Relative weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nakajima, 2010</td>
<td>0.740 0.298 1.838 0.516</td>
<td></td>
<td>3.54</td>
</tr>
<tr>
<td>Trovato, 2010</td>
<td>0.460 0.239 0.886 0.020</td>
<td></td>
<td>6.21</td>
</tr>
<tr>
<td>Kim, 2013</td>
<td>0.590 0.368 0.945 0.028</td>
<td></td>
<td>10.23</td>
</tr>
<tr>
<td>Jhee, 2018</td>
<td>0.800 0.652 0.982 0.033</td>
<td></td>
<td>23.43</td>
</tr>
<tr>
<td>Pham, 2010</td>
<td>1.010 0.842 1.212 0.915</td>
<td></td>
<td>25.02</td>
</tr>
<tr>
<td>Mazidi, 2019</td>
<td>1.020 0.943 1.103 0.621</td>
<td></td>
<td>31.57</td>
</tr>
<tr>
<td></td>
<td>0.855 0.714 1.025 0.090</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Favours A  Favours B

Meta Analysis