CPE Effect of Coffee Consumption on Renal Outcome: A Systematic Review and Meta-Analysis of Clinical Studies

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Objective: Drinking coffee is one of the most common daily habits, especially in the developed world. Along with caffeine, coffee has various ingredients that have been suggested to have beneficial effects, including antioxidant, antiinflammatory, anticarcinogenic, antithrombotic and antifibrotic effects. In this systematic review and meta-analysis, we investigated the relationship between coffee intake and chronic kidney disease (CKD) related outcomes.

Design and Methods: Literature search was performed through PubMed/Medline, Web of Science, Embase (Elsevier), and the Cochrane Central Register of Controlled Trials (Wiley) from 1960 to February 2020. Incidence of CKD, the progression of CKD, and CKD-associated mortality have been evaluated in relation to coffee consumption and the amount of consumption. The Newcastle-Ottawa scale was used for quality assessment of included studies.

Results: 12 studies were included in the analysis (7 prospective, 5 cross-sectional) involving 505,841 subjects. 7 studies investigated the relationship between coffee consumption and incident CKD and showed that coffee consumption was associated with a significant decrease in the risk for incident CKD outcome (RR 0.86, 95% CI 0.76 to 0.97, P = .01) with a greater decrease in individuals taking ≥2 cups/day compared to those who drank ≤1 cup/day. There was a significantly lower risk of incident end stage kidney disease (ESKD) in coffee users (HR 0.82, 95% CI 0.72 to 0.94, P = .005). Coffee consumption was also associated with a lower risk of albuminuria (OR 0.81, 95% CI 0.68 to 0.97, P = .02). Overall, the risk of death related to CKD was lower in coffee users (HR 0.72, 95% CI 0.54 to 0.96, P = .02).

Conclusion: Coffee intake was dose-dependently associated with lower incident CKD, ESKD, and albuminuria.

This article has an online CPE activity available at www.kidney.org/professionals/CRN/ceuMain.cfm

Introduction

CHRONIC KIDNEY DISEASE (CKD), affecting 14% of the adult population in the USA, is an epidemic with an increasing incidence that leads to significant morbidity and mortality(1, 2). CKD is considered as 12th leading cause of death worldwide, with cardiovascular disease (CVD) being the predominant cause of mortality in these patients.[1–4] Furthermore, patients with CKD are also at significant risk for developing bone diseases, cognitive impairment, anemia, CVD, infections, bleeding or thrombotic disorders, and electrolyte imbalances.[3,5] Increased oxidative stress via the formation of reactive oxygen species (ROS) and the destruction of antioxidant mechanisms have been alleged to contribute to the pathophysiology of adverse outcomes in CKD patients. Additionally, many risk factors for CKD development and progression are known to enhance the production of ROS. These risk factors include diabetes mellitus, hypertension, alcohol consumption, and smoking.[6–9]

Coffee is one of the most commonly consumed beverages, with a consumption rate of approximately 500 billion cups/year. It contains a complex mixture of alkaloids (e.g.,

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caffeine and trigonelline), diterpenes, chlorogenic acid, and melanoidins that may have antioxidant, antiinflammatory, anticarcinogenic, antithrombotic, and antifibrotic effects.[10,11] Potential beneficial effects of coffee consumption have been suggested in the cardiovascular, liver, and neurological diseases and mortality and have been postulated to be mediated by the antioxidant properties of coffee.[12,13] Nevertheless, coffee also contains hydroxyhydroquinone, which may generate ROS and induce single-strand DNA breaks.[14] Although a meta-analysis showed no association between coffee intake and CKD development,[15] it was followed by several large-scale studies with contradictory results.[16,17] Therefore, no consensus has been reached regarding the effect of coffee consumption on CKD. In this systematic review, our aim is to assess the effect of coffee consumption on CKD development, CKD progression, and CKD-related mortality in adults in light of recent large-scale studies.

Methods

We performed this meta-analysis in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines[18] and Quality of Reporting of Meta-Analyses (QUOROM) statement[19] and the Cochrane Collaboration and Meta-analysis Of Observational Studies in Epidemiology (MOOSE).[20]

Literature Search and Inclusion/Exclusion Criteria

A literature search was performed through four databases, including PubMed/Medline, Web of Science, Embase (Elsevier), and the Cochrane Central Register of Controlled Trials (Wiley) from 1960 to February 2020 by using the following medical subject headings: "coffee," "coffee consumption," "caffeine," "caffeine intake," "chronic kidney disease," "renal disease," "renal failure," "mortality," "kidney failure" and "kidney disease." Authors (S.C, M.K, and B.A) independently evaluated the titles, and the abstracts of each study and conflicts were resolved by reaching a consensus after discussion and detailed examination of the study. References listed on selected studies were also assessed manually in order not to miss any relevant study. After the preliminary selection, full texts of the selected studies were evaluated by the authors independently.

Inclusion criteria for our systematic review and meta-analyses are as follows:

- Study should investigate the association between coffee consumption and incidence or progression of CKD or CKD-associated mortality.
- Cross-sectional studies and studies with retrospective or prospective design irrespective of randomization are included.
- Studies should be published in a peer-reviewed journal in English until February 2020.

Exclusion criteria included studies with missing data or inadequate description of outcomes, studies not classified as original articles (e.g. reviews, meta-analyses, editorials, commentaries), study types not listed as inclusion criteria (e.g. case reports, case series), and unpublished data.

Assessment measures of this meta-analysis included the incidence of CKD, the progression of CKD, and total or CKD-associated mortality. These assessment measures encompassed changes in estimated glomerular filtration rate (eGFR) or serum creatinine, CKD-related deaths, cardiovascular events or mortality, and total deaths. Details of study selection procedures are depicted in Supplementary Figure 1.

Quality Assessment

Quality assessment of the studies included in the meta-analyses was conducted in accordance with the Newcastle-Ottawa Scale, which uses the selection of study groups as the main criteria, assessment of outcomes, and comparability of the groups.[21] According to the Newcastle-Ottawa Scale, a study may be given up to nine stars, representing the highest quality research. The quality assessment of each study resulted from a consensus decision by the authors.

Statistical Analysis

Extracted hazard ratios (HR) or odds ratios (OR) from the included study protocols were pooled separately using the random-effects model. The equivalent z test was performed for each pooled HR or OR, and if P was smaller than .05, it was considered statistically significant. We converted standard deviation and 95% confidence interval to standard error using a standard formula.[22] When necessary, the individual OR and HR were combined using Peto's method. For the continuous variable (eGFR), the mean difference was used to assess the effects of coffee consumption. When different studies used both HR and OR for the same outcome, we reported the results as risk ratios (RR).

We assessed for heterogeneity in the treatment estimates using the *Cochran Q* test and the I^2 statistic (with substantial heterogeneity defined as values greater than 50%).[23] If a sufficient number of studies were identified, subgroup analysis was used to explore possible sources of heterogeneity. All statistical analyses were performed using Review Manager (RevMan) Version 5.3 (The Cochrane Collaboration 2012).

Results

We included in our final analysis 12 studies: 7 cohort[16,17,24–28] and 5 cross-sectional studies.[29–33] The total number of evaluated participants was 506,062. Studies ranged from a minimum of 114[31] to a maximum of 185,855 patients.[26] General characteristics of the studies, including participant characteristics, inclusion and exclusion criteria, intervention methods, outcome measures, confounders adjusted in each study, and the Newcastle-

Table 1. Demographic and Clinical Characteristics of the Included Clinical Studies

Author, Year	Location	Study design	Number of participants	Characteristics of the participants	Recruitment method	Exclusion criteria	Coffee consumption definition and method of evaluation	Definition of CKD
Nakajima et al.,[30] 2010	Japan	Cross-sectional	342	246 M-96 F Recruitment: After a medical check-up, no history of kidney-cancer-CVD BMI: 23.7 in coffee consumers; 23.5 in noncoffee consumers BP: 119-74.5 in coffee consumers; 123-76.1 in noncoffee consumers Smoking: 37.4% in coffee consumers; 35% in noncoffee consumers Alcohol: 48.6% in coffee consumers; 44.4% in noncoffee consumers	Patients of two hospitals in Japan between age 30-80 who had undergone a medical check-up and who responded to a questionnaire about their lifestyle characteristics	• Self-reported CVD, kidney diseases or cancer	≥1 cup/day Questionnaire	GFR <60 mL/min/ 1.73 m^2
Kotani et al.,[31] 2010	Japan	Cross-sectional	114 age-gender matched participant	57 M-57 F Mean age: 59.5 (8.7) for M and F BMI: 24.2 in coffee consumers; 24.3 in noncoffee consumers BP: 134.8-76.5 in coffee-consumers; 136.7-75.3 in noncoffee consumers	Participants at age 40-70 selected from database of community-based health check-up screening subjects	• CKD • CVD • Smoking	≥1 cup/day Questionnaire	eGFR < 60 mL/min/ 1.73 m^2

(*Continued*)

Table 1. Demographic and Clinical Characteristics of the Included Clinical Studies (*Continued*)

Author, Year	Location	Study design	Number of participants	Characteristics of the participants	Recruitment method	Exclusion criteria	Coffee consumption definition and method of evaluation	Definition of CKD
Kim et al.,[32] 2013	Korea	Cross-sectional	2,673	0 M-2.673 F Age: 56.5 for<1cup/day; 52.6 for 2 cump/day; 48.6 for ≥2 cups/day BMI: 23.7 for all groups BP: 118.5-75 for<1cup/day; 115.7-74.1 for 1 cup/day; 113.6-74.2 for ≥2 cups/day Significant variations at alcohol intake, use of DM-HT medications; no significant variation in current fasting lipid profile or glucose level	Participants at age 35-64 performing Fourth Korea National Health and Nutrition Examination surveys in 2008	• Age over 85 • Lack the data of DM or coffee use	≥2 cup/day Questionnaire	eGFR < 60 mL/min/1.73 m^2
Loftfield et al.,[24] 2015	United States	Prospective Cohort Study	90,317	40.2% M in nonconsumers; 44.5 M in <1cup/day; 47.6% M in 2-3 cups/day; 62.1 M in ≥6 cups/day Smoking: 4% in nonconsumers; 5.2% in <1cup/day; 9.8% in 2-3 cups/day; 31.8% in ≥6 cups/day Alcohol: 17.1% in nonconsumers; 34.6% in <1cup/day; 50% in 2-3 cups/day; 43.2% in ≥6 cups/day Similar for DM, use of aspirin and ibuprofen, family history	Participants at age 55-74 that are included in PLCO Cancer Screening Trial.	• Extreme calorie consumption (<1 or >99 percentile) • History of self-reported CVD • Malignancy history • Missing data for smoking or coffee • Noncompliance to follow-up	Different cups/day analyzed independently ≥4 cup/day Questionnaire	All and cause-specific mortalities were evaluated.

Herber-Gast et al.,[25] 2016	Netherlands	Prospective cohort study	4,722	Smoking: 15.3% in <1cup/day; 19.5% in 1-2 cups/day; 20.7% in 3-4 cups/day; 27% in 5-6 cups/day; 40.8% in ≥6 cups/day Alcohol: 23.7% in <1cup/day; 27.1% in 1-2 cups/day; 32.2% in 3-4 cups/day; 31% in 5-6 cups/day; 29.6% in ≥6 cups/day No significant difference in gender, BMI, BP, age, baseline plasma glucose levels	Participants at age 26-65 that are included in Doetinchem Cohort Study group	• Missing data • Pregnancy	Food frequency questionnaire	GFR <60 mL/min/1.73 m^2
Girardat-Rotar et al.,[29] 2018	Switzerland	Cross-sectional	151	91 M-60 F Mean age: 32.8 (±9) BMI: 24.04 (±4) eGFR: 90.78 (±19) overall; 95.8 (±19) for noncoffee consumers; 88.23 (±19) for coffee consumers Smoking: 36% overall; 33% in noncoffee consumers; 37% in coffee consumers BP: 138.4-89 overall; 136.5-86.2 in noncoffee consumers; 139.4-90.5 in coffee consumers	Participants at age 18-60 included in Swiss ADPKD cohort between 2008-2014 with proven diagnosis of ADPKD and eGFR >30 mL/min/1.73 m2	• Noncompliance to follow-up • Treatment with disease modifying agents (Sirolimus, everolimus, tolvaptan, somatostatin analogues etc.) possible	≥2 cup/day Questionnaire	eGFR < 60 mL/min/1.73 m^2
Park et al.,[26] 2017	United States	Prospective cohort study	185,855		Participants at age 40-69 that are included in MEC cohort	• Implausible dietary energy and macronutrient intake • Missing information • Participants not in top 5 ethnic groups	Different cups/day analyzed independently Questionnaire	All and cause-specific mortalities were evaluated

(*Continued*)

Table 1. Demographic and Clinical Characteristics of the Included Clinical Studies (*Continued*)

Author, Year	Location	Study design	Number of participants	Characteristics of the participants	Recruitment method	Exclusion criteria	Coffee consumption definition and method of evaluation	Definition of CKD
Jhee et al.,[16] 2018	South Korea	Prospective cohort	8,717	47.8% M-52.2% F Mean age: 52.0 (8.8) Smoking: 29.1% in noncoffee consumers; 34.1% in <1cup/week; 38.1% in 1-6 cups/week; 40.7% in 1cup/day; 56.4% in ≥2 cups/day Alcohol: 41.4% in noncoffee consumers; 49.5% in <1cup/week; 56.3% in 1-6 cups/week; 56.7% in 1cup/day; 62.6% in ≥2 cups/day No significant difference in BMI, BP or comorbidities	Participants at age 40-69 that are included in KoGES cohort	• eGFR < 60 mL/min/1.73 m2 • Known kidney disease • Missing data • Missing follow-up creatinine	Food frequency questionnaire Different cups/day analyzed independently ≥1 cup/day	eGFR < 60 mL/min/1.73 m^2
Lew et al.,[28] 2018	Singapore-China	Prospective cohort study	63,257	Age: 56.6 in <1cup/day; 56.8 in 1cup/day; 56.2 in >1cup/day. Smoking: 23% in <1cup/day; 27% in 1cup/day; 41% in >1cup/day. Alcohol: 10% in <1cup/day; 11% in 1cup/day; 14% in >1cup/day. No significant difference in comorbidities, BMI or red meat intake.	Participants at age 45-74 that are included in Singapore-Chinese Health Study cohort	• Known CKD	Food frequency questionnaire ≥1 cup/day	ESKD defined as at least 1 of the following: Serum creatinine >10 mg/dL eGFR <15 Undergoing hemodialysis or peritoneal dialysis Undergone kidney transplantation

Hu et al.,[13] 2018	United States	Prospective cohort study	14,209	Age: 53.9 for noncoffee consumers; 54.3 for <1cup/day; 54.6 for 1-2 cups/day; 54.1 for 2-3 cups/day; 53.5 for ≥3cups/day. Smoking: 44.7% for noncoffee consumers; 49.1% for <1cup/day; 57.9% for 1-2 cups/day; 64.7% for 2-3 cups/day; 76.6 for ≥3cups/day. No significant difference in BMI, BP, or comorbidities.	Participants at age 45-64 that are included in the Atherosclerosis Risk in Communities Study	• Blacks from Washington Country-Maryland, Minneapolis-Minnesota • Missing data • Neither being black or white	Food frequency questionnaire	Incident CKD is defined as at least 1 of the following: eGFR <60 >25% decline in eGFR CKD-related hospitalization or death or ESKD
Kennedy et al.,[34] 2020	United Kingdom	Prospective cohort study	133,814	N/A	The United Kingdom Biobank cohort including subjects between age 40-73 recruited between 2006 and 2013	• Relatives up to 2nd degree • Noncoffee drinkers • Patients not from white British ancestry	Dietary questionnaire (Nonspecified)	eGFR < 60 mL/min/1.73 m^2
Gaeini et al.,[17] 2019	Iran	Prospective cohort study	1,780		Participants included in Tehran lipid and Glucose Study.	• CKD • CVD • HT • Missing data • Noncompliance to follow-up • Specific diets • Under or over-reports of energy intakes	Food frequency questionnaire	eGFR <60 mL/min/1.73 m^2

F-female, M-male, N/A-Not applicable, CVD-cardiovascular disease, HT-hypertension, CKD-chronic kidney disease, GFR-glomerular filtration rate, BP-blood pressure, BMI-body mass index, ESKD-end stage renal disease, ADPKD-adult polycystic kidney disease, DM-diabetes mellitus, KoGES-The Korean Genome and Epidemiology Study, MEC-Multiethnic Cohort.

Table 2. Characteristics and Quality of the Studies

	Adjusted OR	Outcome	Confounder adjustment	Evaluation of outcome	Quality assessment (Newcastle-Ottawa scale)
Nakajima et al.,[30] 2010	0.74 (0.3-1.85) overall 0.74 (0.25-2.17) in males 1.41 (0.06-33.2) in females	eGFR	• Age • Alcohol • BMI • BP • Fasting glucose • LDL-HDL • Medication • Proteinuria • Sex • Smoking • Tea • Triacylglycerol	Coffee consumption is associated with NIGFR independently of clinical confounders	Selection: 3 Comparability: 2 Outcome: 3
Kotani et al.,[31] 2010	Coffee drinkers had higher eGFR values [73.9 ± 16.5 (SD) mL/min/1.73 m(2)] than noncoffee drinkers (68.6 ± 11.7)	eGFR	N/A	Coffee consumption is linked to higher eGFR values.	Selection: 2 Comparability: 1 Outcome: 2
Kim et al.,[32] 2013	0.52 (0.35 to 0.91)	Development of CKD	• Age • Alcohol consumption • BMI • Calorie intake • DM • Hypertension • Lipid lowering drugs	Coffee consumption is associated with decreased risk of renal impairment especially in middle and elderly-aged diabetic women.	Selection: 3 Comparability: 2 Outcome: 3
Loftfield et al.,[24] 2015	0.8 (0.74-0.87) overall mortality 0.62 (0.26-1.44) for kidney disease-related mortality 0.75 (0.63-0.9) for heart diseases related mortality	Overall and Cause-Specific Mortality	• Age • Alcohol consumption • BMI • Content of meals (Meat, vegetables, fruits, saturated fat, processed meat) • Daily calorie intake • Detailed smoking history • DM • Education • Employment status • Ibuprofen-Aspirin-Supplemental vitamin use-in last 12 months • Postmenopausal HRT • Race • Sex	Coffee consumption is associated with lower risk for deaths from heart disease, chronic respiratory diseases, diabetes, pneumonia and influenza and intentional self-harm, but not cancer.	Selection: 3 Comparability: 2 Outcome: 3

Herber-Gast et al.,[25] 2016	0.76 (-0.28, 1.81) for < 1-2 cup/day 1.35 (0.25, 2.44) for 3-4 cups/day 1.36 (0.2-2.52) for 5-6 cups/day 1.61 (0.41-2.81) for > 6 cups/day	eGFR	• Age • Alcohol consumption • BMI • Daily calorie intake • Education level • Energy-adjusted intake of fibers-vitamin C-protein-fat-saturated fat • Energy-adjusted intake of magnesium and potassium • Gender • Hypercholesterolemia-HT and DM • Smoking status • Tea intake • Time-dependent physical activity	Coffee consumption is linked to slightly higher eGFR, especially in patients aged ≥46 y.	Selection: 3 Comparability: 2 Outcome: 2
Girardat-Rotar et al.,[29] 2018	2.03 (-0.31-4.38)	eGFR	• Age • BMI • BP • Gender • Smoking	Coffee consumption is not a risk factor for ADPKD progression.	Selection: 3 Comparability: 2 Outcome: 3
Park et al.,[26] 2017	0.75 (0.52–1.08) for 1-3 cups/month; 0.83 (0.61–1.12) for 1-6 cups/week; 0.60 (0.46–0.78) for 1cup/day; 0.59 (0.45–0.79) for 2-3 cups/day; 0.42 (0.26–0.67) for ≥4 cups/day. P for trend <0.001	Total and Cause-Specific Mortality	• Alcohol consumption • BMI • DM • Education level • Race • Smoking history	Coffee consumption is linked to lower risk for deaths due to heart disease, cancer, respiratory disease, stroke, diabetes and kidney disease.	Selection: 3 Comparability: 2 Outcome: 3

(*Continued*)

Table 2. Characteristics and Quality of the Studies (*Continued*)

	Adjusted OR	Outcome	Confounder adjustment	Evaluation of outcome	Quality assessment (Newcastle-Ottawa scale)
Jhee et al.,[16] 2018	0.73 (0.6-0.98) for CKD incidence -0.97 (-1.07 to -0.88) for noncoffee consumers; -0.93 (-1.11 to -0.75) for <1cup/week; 0.93 (-1.04 to -0.83) for 1-6 cups/week; -0.75 (-0.84 to -0.72) for ≥ 1 cup/day	Incidence of CKD eGFR decline rate per year	• Age • Alcohol consumption • BMI • BP • DM and HbA1c • Daily intake of tea and chocolate • Education level • Gender • History of CVD or HT • Income • Log-transformed CRP-Hemoglobin-Albumin-eGFR-Total cholesterol-Proteinuria • Smoking status	Coffee consumption is associated with decreased risk of CKD development.	Selection: 3 Comparability: 2 Outcome: 2
Lew et al.,[28] 2018	0.91 (0.79-1.05) for 1 cup/day 0.82 (0.71-0.96) for >1 cup/day p-trend: 0.012	Incidence of CKD	• Age • Alcohol consumption • BMI • Consumption of black tea, green tea or soda • Dialect group • Education status • Gender • Physical activity • Red meat intake • Self-reported history of DM, HT, stroke or CVD • Smoking status • Total protein intake	Coffee consumption ≥2 cups/day reduces the risk of ESRD in the general population.	Selection: 3 Comparability: 2 Outcome: 2
Hu et al.,[13] 2018	0.90 (0.82–0.99) <1 cup/day; 0.90 (0.82–0.99 for 1 to <2 cups/day; 0.87 (0.77–0.97) for 2 to <3 cups/day; , 0.84 (0.75–0.94) for ≥3 cups/day	Incidence of CKD	• DASH diet • DM • Gender • Physical activity • Smoking status	Coffee consumption is linked to lower risk of incident CKD after adjustment of covariates.	Selection: 3 Comparability: 2 Outcome: 2
Kennedy et al.,[34] 2020	0.84 (0.72-0.98) for 1 extra-cup/day for incident CKD	Incidence of CKD eGFR	• BMI • DM • Hypertension • Smoking	Participants who drank higher amounts of coffee had a lower risk of incident CKD and higher eGFR after adjusting for covariates.	Selection: 3 Comparability: 2 Outcome: 2

Gaeini et al.,[17] 2019	0.92 (0.68-1.25) >750 mg/day caffeine; 0.89 (0.63–1.24) for 250-750 mg/day caffeine 1 cup coffee = 65 mg	Incidence of CKD	• Age • BMI • Dietary fiber and calorie intake • Gender • Smoking • Triglyceride/HDL-C ratio	Tea, coffee consumption or caffeine intake are not linked to the risk of HT or CKD.	Selection: 3 Comparability: 2 Outcome: 2

F-female, M-male, N/A-Not applicable, CVD-cardiovascular disease, HT-hypertension, CKD-chronic kidney disease, GFR-glomerular filtration rate, BP-blood pressure, BMI-body mass index, ESKD-end stage renal disease, ADPKD-adult polycystic kidney disease, DM-diabetes mellitus, HDL-high-density lipoprotein, LDL-low-density lipoprotein, DASH-diet approach to stop hypertension, CRP-c-reactive protein, HRT-hormone replacement therapy, HbA1c-hemoglobin A1c.

Ottawa assessment scale of studies are reviewed at Tables 1 and 2. CKD definition varied between studies, and eGFR value was the most commonly preferred approach. Although the quality assessment of studies via the Newcastle-Ottawa scale revealed variations, included studies have high scientific quality (Table 2).

To calculate eGFR, 5 studies used the CKD-EPI creatinine equation,[16,17,25,27,29] 5 studies used the MDRD equation,[28,30–33] and 2 studies did not specify.[24,26]

Five studies defined incident CKD as eGFR <60 mL/min/1.73 m^2,[16,17,30,32,34] while one study defined incident CKD as at least one of the following eGFR <60 mL/min/1.73 m^2 or >25% decline in eGFR at any subsequent study visit relative to baseline.[27]

Two studies reported end stage kidney disease (ESKD) incidence. One study defined incident ESKD as at least 1 of the following: serum creatinine >10 mg/dL, eGFR <15 mL/min/1.73 m^2, undergoing hemodialysis or peritoneal dialysis, or undergone kidney transplantation.[28] The other study identified ESKD by linkage to the US Renal Data System (USRDS) registry as cases of kidney transplant or dialysis.[27]

One study defined albuminuria as urinary albumin-creatinine ratio >17 mg/g (1.92 mg/mmol) in men and >25 mg/g (>2.83 mg/mmol) in women,[34] and the second one estimated albuminuria using dipstick urinalysis as follows: negative and borderline samples were categorized as normal and the others as overt proteinuria.[30]

Regarding CKD mortality, 2 studies[24,26] included in the sub-analysis used the International Classification of Diseases, Ninth Revision (ICD-9) codes 580-589 to classify the cause of death. One study[26] used additional codes from the 10th Revision: N00 to N07, N17 to N19, N25 to N27.

Coffee consumption was defined in different ways, as follows: nondrinkers versus drinkers(17, 29-31); 1 cup/day versus ≥2 cups/day(28, 32); <1 cup/day, 2-3 cups/day, ≥ 4cups/day[24]; <1cup/day, 1-2 cups/day, 3-4 cups/day, 5-6 cups/day, >6 cups/day[25]; 1-3 cups/month, 1-6 cups/week, 1cup/day, 2-3 cups/day, ≥4 cups/day[26]; <1 cup/day, 1-2 cups/day, 2-3 cups/day, ≥3 cups/day[27]; <1 cup/week, 1-6 cups/week, 1cup/day, ≥2cups/day.[16] One study included only coffee users.[34]

When estimating the risk for the different CKD outcomes, 6 studies calculated HRs[16,17,24,26–28] while 3 studies calculated the ORs.[30,32,34]

The median follow-up periods were reported by the 7 prospective cohort studies as follows: 6 years,[17] 9 years,[24] 11.3 years,[16] 15 years,[25] 16.2 years(26), 16.8 years,[28] 24 years.[27]

Outcome Measures Reporting

CKD Incidence

There were 6 studies, 3 prospective cohorts[16,17,27] and 3 cross-sectional[30,32,34] that analyzed the effect of coffee

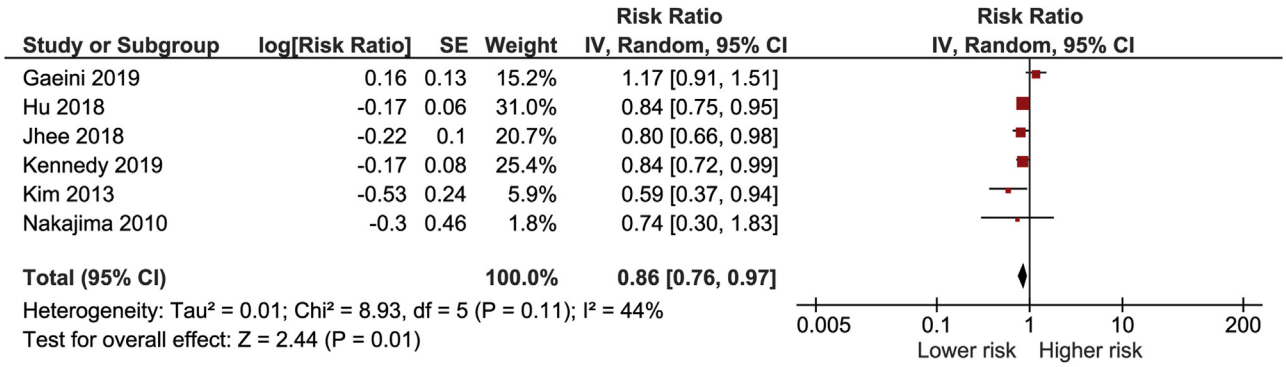

Figure 1. Forest plot of the included studies for incident chronic kidney disease (CKD) according to coffee use. The comparator is no coffee intake.

consumption on CKD incidence. As shown in Figure 1, coffee consumption was associated with a significant decrease in the risk for incident CKD defined using eGFR (RR 0.86, 95% CI 0.76 to 0.97, $P = .01$, moderate heterogeneity- $I^2 = 44\%$).

We also analyzed the relationship between the risk of incident CKD and the frequency of coffee intake. Only 3 studies[16,27,32] were used for the analysis, and coffee consumption was summarized as ≤1 cup/day and ≥2 cups/day. The effect on incident CKD was significant in both subgroups (RR 0.87, 95% CI 0.77 to 0.98, $P = .02$ and RR 0.82, 95% CI 0.74 to 0.92, $P < .001$ for the ≤1 cup/day and the ≥2 cups/day subgroup, respectively, both compared to no intake), without a significant interaction between these subgroups ($P = .52$ for the test for subgroup differences) (Supplementary Figure 2A).

There were 2 studies that assessed the effect of coffee consumption on CKD incidence according to gender: one study[32] included only women and the second one[30] included more than twice men than women(246 men, 96 women). Although the effect was significant only in women coffee users (OR 0.60, 95% CI 0.38 to 0.96, $P = .03$), the interaction test for subgroup differences was nonsignificant (Supplementary Figure 2B).

When separately analyzing the effect of coffee consumption on CKD incidence in prospective and cross-sectional studies, statistical significance was reached only for the latter (HR 0.90, 95% CI 0.75 to 1.09, $P = .29$ and OR 0.70, 95% CI 0.53 to 0.93, $P = .02$ respectively).

ESKD Incidence

ESKD incidence was evaluated in 2 prospective cohort studies.[27,28] Overall, there was a significant lower risk of incident ESKD in coffee users (HR 0.82, 95% CI 0.72 to 0.94, $P = .005$, insignificant heterogeneity- $I^2 = 0\%$) (Figure 2).

When analyzed according to the frequency of coffee intake, the effect was significant and similar in both the coffee intake/≤1 cup/day and the coffee intake/≥2 cups/day subgroups as compared to no coffee intake (Supplementary Figure 3).

Albuminuria

There were 2 cross-sectional studies[30,34] that reported data on the association between coffee consumption and albuminuria. Coffee consumption was associated with a lower risk of albuminuria (OR 0.81, 95% CI 0.68 to 0.97, $P = .02$, insignificant heterogeneity- $I^2 = 0\%$) (Figure 3).

CKD Mortality

Two prospective cohort studies[24,26] evaluated this outcome. We analyzed the association with CKD mortality according to the frequency of coffee intake as follows: no coffee intake, ≤1 cup/day, 2-3 cups/day, ≥4 cups/day. Overall, the risk of death related to CKD was lower in coffee users (HR 0.72, 95% CI 0.54 to 0.96, $P = .02$, substantial heterogeneity- $I^2 = 68\%$); we also observed a trend toward an increased beneficial effect in those with ≥4 cups/day (Figure 4).

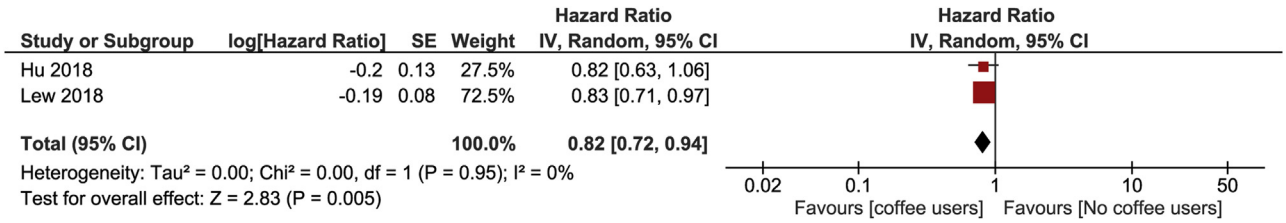

Figure 2. Forest plot of the included studies for incident end stage renal disease (ESKD) according to coffee use. The comparator is no coffee intake.

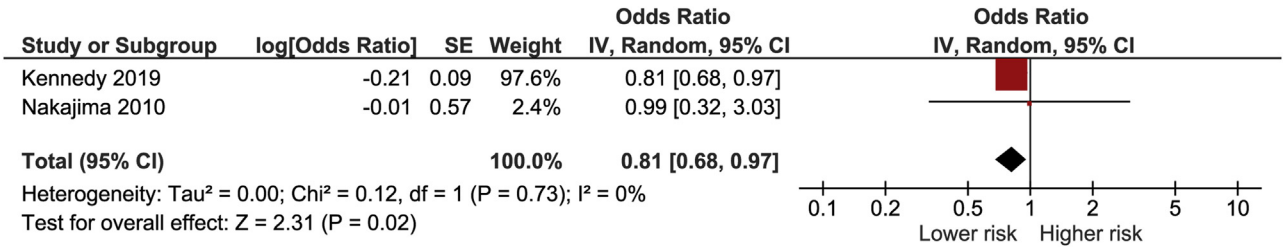

Figure 3. Forest plot of the included studies for albuminuria according to coffee use. The comparator is no coffee intake.

Coffee Consumption With Baseline eGFR

Four studies, 1 prospective cohort study[25] and 3 cross-sectional studies,[29-31] reported the mean and SD eGFR values at baseline. One study[25] reported eGFR values according to the frequency of coffee intake. As shown in Supplementary Figure 4, there was no significant difference between coffee users and nonuser in regard to baseline eGFR (mean difference0.74 mL/min/1.73 m^2, 95% CI -2.65 to 4.14 mL/min/1.73 m^2, $P = .67$, substantial heterogeneity- $I^2 = 78\%$). After excluding the prospective cohort study from the analysis, the effect of coffee intake on baseline eGFR remained insignificant (mean difference 0.74 mL/min/1.73 m^2, 95% CI -5.61 to 7.08 mL/min/1.73 m^2, $P = .82$).

Discussion

Coffee is one of the most consumed beverages worldwide and is generally considered safe for CKD patients, although a number of caveats may limit its consumption (potassium contents, phosphate from milk or additives, amount of fluid, and acute pressor effect). Thus, online CKD patient sites discuss potential risks but no benefits and recommend not exceeding moderate consumption.[35] Coffee contains over 1000 ingredients, some of which are

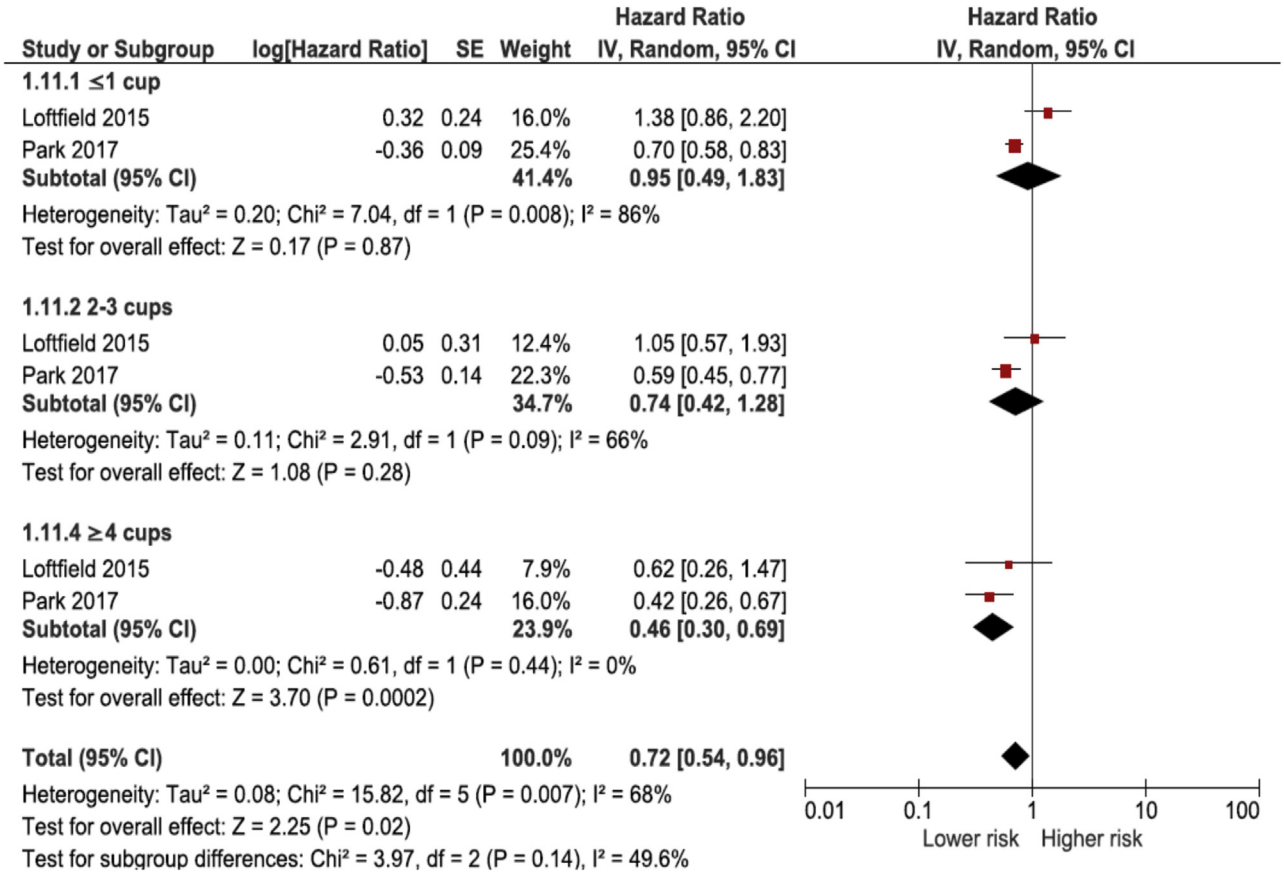

Figure 4. Forest plot of the included studies for chronic kidney disease (CKD) mortality according to the frequency of coffee intake. The comparator is no coffee intake.

biologically active, including the alkaloid caffeine, diterpenes, and chlorogenic acid, among others. The bioavailability of such ingredients depends upon individuals' microbiome and genetics of transporters and enzymes.[33,36,37] As it is the case for items with widespread consumption, minimal effects may have significant population-wide health consequences. A large-scale meta-analysis demonstrated coffee consumption is associated with a lower risk for all-cause mortality, CVD incidence and mortality, liver cirrhosis, certain malignancies (i.e. hepatocellular carcinoma, prostate cancer, endometrial cancer, skin cancer, leukemia), and type 2 diabetes mellitus.[33,38,39] Linear dose-dependent beneficial effects have been described in certain malignancies such as prostate, endometrium, liver cancer, and melanoma[33,40–42] while nonlinear dose-dependent beneficial effects are observed in all-cause mortality and CVD mortality.[38] On the other hand, the association between coffee consumption and parameters of renal function and CKD incidence has been investigated in relatively few studies.

Previously, one previous meta-analysis, including four observational studies (n = 14,898) failed to observe any beneficial effects of coffee consumption on CKD incidence in men and described the possibility of inverse association in women.[15] Another recent meta-analysis study, including 4 cohort studies with a total of 25,849 participants, investigated the effects of coffee consumption on incident CKD incidence.[43] Our study includes a higher number of studies with a higher number of participants in addition to the assessment of effects of coffee consumption on various outcomes. Additionally, we assess the relationship between the amount of coffee consumption and outcomes. Our meta-analysis findings suggest that coffee consumption is associated with beneficial outcomes in terms of risk for developing CKD or ESKD, CKD-related mortality, and albuminuria, with a trend toward increased beneficial effects in those with ≥4cups/day, especially with regard to the mortality outcome.

Molecular mechanisms of action of caffeine on cellular signaling primarily include competitive inhibition of G-protein coupled adenosine receptors, thus, decreasing intracellular inositol triphosphate, diacylglycerol, and calcium signaling.[44,45] Although earlier studies suggested that caffeine intake may impair renal blood flow, later studies demonstrated that caffeine increased GFR via inhibition of adenosine-induced vasoconstriction at afferent arterioles through type 1 adenosine receptors.[46,47] Last, coffee-mediated inhibition of sodium reabsorption may decrease kidney energy utilization, which may be beneficial in conditions of relative hypoxic such as acute ischemic kidney injury and renal artery stenosis[48] or any form of CKD with capillary rarefaction.[49]

Genetic-epigenetic changes and alterations of cell signaling are detected in response to chronic coffee consumption such as phosphorylation of 5′ AMP-activated protein kinase (AMPK) and AMPK-dependent decreased expression of epithelial sodium channels (ENaC) at collecting tubules.[50] Kidney effects of desmopressin (DDAVP), prostaglandin E2 and isoproterenol are attenuated in subjects receiving caffeine.[51] On the other hand, caffeine inhibition of adenosine receptors at juxtaglomerular cells increased renin levels, potentially activating the renin-angiotensinogen-aldosterone system. However, such an effect was not observed at physiological caffeine concentrations.[52,53] Urinary proteome analysis of 30 healthy subjects revealed decreased urinary kininogen-1 after caffeine intake.[54] This was postulated to potentially increase renal blood flow and GFR through vasodilatation resulting from the kidney accumulation of nonexcreted kinins.[54] Also, caffeine intake was hypothesized to protect from kidney stones, which through translocation of tubular cell annexin A1 from the apical surface toward the cytoplasm, thus decreasing the crystal-binding ability of tubular surfaces.[55] In contrast, chronic caffeine intake is thought to be a possible risk factor for cyst formation and enlargement in patients with autosomal dominant polycystic kidney disease.[51]

Potentially detrimental effects of coffee consumption should not be overlooked, such as arterial stiffness associated with coffee consumption in the acute phase.[56] In addition, coffee is traditionally considered as proarrhythmogenic substance.[57] However, this issue is now controversial since acute ingestion of high doses of caffeine did not induce arrhythmias in patients with systolic heart failure who are at high risk for developing ventricular arrhythmias.[58] At least in CKD patients, these putative detrimental effects are not well studied. However, our findings suggest that the beneficial effects of coffee may outweigh the potentially detrimental effects in the CKD population.

We acknowledge that this meta-analysis has some limitations. Hence, these findings should be cautiously interpreted. Limitations of our meta-analysis include the lack of randomized controlled trials and the inclusion of cross-sectional studies. However, epidemiological studies are expected to be key source information for this topic; a beverage consumed in high amounts worldwide. Observational studies cannot ascertain causality and may not have fully accounted for the role of possible confounding factors, including other dietary variables, comorbid medical conditions such as diabetes mellitus and hypertension, family history, and individual genetic variations linked to kidney function, which should not be overlooked. However, most confounding factors are accounted for in the included studies. Another limitation of this meta-analysis is the variability between the qualities of the included studies, which were assessed via the Newcastle-Ottawa scale. The need for future randomized controlled trials investigating the role of coffee intake on renal function preservation is clear.

In summary, this meta-analysis showed that coffee consumption might improve renal outcomes. However, future

prospective, multi-center, well-designed studies are warranted to formally evaluate the impact of coffee consumption on renal outcomes.

Practical Application

In our meta-analysis, we included 12 studies and demonstrated that coffee consumption was associated with a lower risk of developing chronic kidney disease, chronic kidney disease-related mortality, and albuminuria. The study demonstrated a trend toward increased beneficial effects in those with drinking ≥4 cups/day, especially in regard to the mortality outcome in chronic kidney disease patients.

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Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1053/j.jrn.2020.08.004.

References

1. Wouters OJ, O'Donoghue DJ, Ritchie J, Kanavos PG, Narva AS. Early chronic kidney disease: diagnosis, management and models of care. *Nat Rev Nephrol*. 2015;11:491-502.

2. van Westing AC, Küpers LK, Geleijnse JM. Diet and kidney function: a literature review. *Curr Hypertens Rep*. 2020;22:14.

3. Vanholder R, Fouque D, Glorieux G, et al. Clinical management of the uraemic syndrome in chronic kidney disease. *Lancet Diabetes Endocrinol*. 2016;4:360-373.

4. Ortiz A, Covic A, Fliser D, et al. Epidemiology, contributors to, and clinical trials of mortality risk in chronic kidney failure. *Lancet*. 2014;383:1831-1843.

5. Afsar B, Turkmen K, Covic A, Kanbay M. An update on coronary artery disease and chronic kidney disease. *Int J Nephrol*. 2014;2014:767424.

6. Duni A, Liakopoulos V, Rapsomanikis K-P, Dounousi E. Chronic Kidney Disease and Disproportionally Increased Cardiovascular Damage: Does Oxidative Stress Explain the Burden? *Oxid Med Cell Longev*. 2017;2017:9036450.

7. Ratliff BB, Abdulmahdi W, Pawar R, Wolin MS. Oxidant mechanisms in renal injury and disease. *Antioxid Redox signaling*. 2016;25:119-146.

8. Fakhruddin S, Alanazi W, Jackson KE. Diabetes-induced reactive oxygen species: mechanism of their generation and role in renal injury. *J Diabetes Res*. 2017;2017:8379327.

9. Kanbay M, Yerlikaya A, Sag AA, et al. A journey from microenvironment to macroenvironment: the role of metaflammation and epigenetic changes in cardiorenal disease. *Clin Kidney J*. 2019;12:861-870.

10. van Dam RM. Coffee consumption and risk of type 2 diabetes, cardiovascular diseases, and cancer. *Appl Physiol Nutr Metab*. 2008;33:1269-1283.

11. Ludwig IA, Clifford MN, Lean MEJ, Ashihara H, Crozier A. Coffee: biochemistry and potential impact on health. *Food Funct*. 2014;5:1695-1717.

12. Chen J-T, Kotani K. Association between coffee consumption and an oxidative stress marker in women. *Wiener klinische Wochenschrift*. 2015;127:567-569.

13. Hu EA, Selvin E, Grams ME, Steffen LM, Coresh J, Rebholz CM. Coffee consumption and incident kidney disease: results from the Atherosclerosis Risk in Communities (ARIC) study. *Am J Kidney Dis*. 2018;72:214-222.

14. Hiramoto K, Li X, Makimoto M, Kato T, Kikugawa K. Identification of hydroxyhydroquinone in coffee as a generator of reactive oxygen species that break DNA single strands. *Mutat Res*. 1998;419:43-51.

15. Wijarnpreecha K, Thongprayoon C, Thamcharoen N, Panjawatanan P, Cheungpasitporn W. Association of coffee consumption and chronic kidney disease: a meta-analysis. *Int J Clin Pract*. 2017;71. https://doi.org/10.1111/ijcp.12919.

16. Jhee JH, Nam KH, An SY, et al. Effects of coffee intake on incident chronic kidney disease: a community-based prospective cohort study. *Am J Med*. 2018;131:1482-1490.e3.

17. Gaeini Z, Bahadoran Z, Mirmiran P, Azizi F. Tea, coffee, caffeine intake and the risk of cardio-metabolic outcomes: findings from a population with low coffee and high tea consumption. *Nutr Metab*. 2019;16:28.

18. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol*. 2009;62:e1-e34.

19. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. *Lancet*. 1999;354:1896-1900.

20. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000;283:2008-2012.

21. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. 2010;25:603-605.

22. Higgins JPT, Thomas J, Chandler J, et al. *eds. Cochrane Handbook for Systematic Reviews of Interventions*. 2nd ed. Chichester (UK): John Wiley & Sons; 2019.

23. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557-560.

24. Loftfield E, Freedman ND, Graubard BI, et al. Association of coffee consumption with overall and cause-specific mortality in a large US prospective cohort study. *Am J Epidemiol*. 2015;182:1010-1022.

25. Herber-Gast G-CM, van Essen H, Verschuren WM, et al. Coffee and tea consumption in relation to estimated glomerular filtration rate: results from the population-based longitudinal Doetinchem Cohort Study. *Am J Clin Nutr*. 2016;103:1370-1377.

26. Park S-Y, Freedman ND, Haiman CA, Le Marchand L, Wilkens LR, Setiawan VW. Association of coffee consumption with total and cause-specific mortality among nonwhite populations. *Ann Intern Med*. 2017;167:228-235.

27. Hu EA, Lazo M, Selvin E, et al. Coffee consumption and liver-related hospitalizations and deaths in the ARIC study. *Eur J Clin Nutr*. 2019;73:1133-1140.

28. Lew Q-LJ, Jafar TH, Jin A, Yuan J-M, Koh W-P. Consumption of coffee but not of other caffeine-containing beverages reduces the risk of end-stage renal disease in the Singapore Chinese health study. *J Nutr*. 2018;148:1315-1322.

29. Girardat-Rotar L, Puhan MA, Braun J, Serra AL. Long-term effect of coffee consumption on autosomal dominant polycystic kidneys disease progression: results from the Suisse ADPKD, a Prospective Longitudinal Cohort Study. *J Nephrol*. 2018;31:87-94.

30. Nakajima K, Hirose K, Ebata M, Morita K, Munakata H. Association between habitual coffee consumption and normal or increased estimated glomerular filtration rate in apparently healthy adults. *Br J Nutr*. 2010;103:149-152.

31. Kotani K, Sakane N, Yamada T, Taniguchi N. Association between coffee consumption and the estimated glomerular filtration rate in the general Japanese population: preliminary data regarding C-reactive protein concentrations. *Clin Chem Lab Med*. 2010;48:1773-1776.

32. Kim BH, Park YS, Noh HM, Sung JS, Lee JK. Association between coffee consumption and renal impairment in Korean women with and without diabetes: analysis of the Fourth Korea National Health and Nutrition Examination Survey in 2008. *Korean J Fam Med*. 2013;34:265-271.

33. Kennedy OJ, Roderick P, Buchanan R, Fallowfield JA, Hayes PC, Parkes J. Coffee, including caffeinated and decaffeinated coffee, and the risk of hepatocellular carcinoma: a systematic review and dose-response meta-analysis. *BMJ Open*. 2017;7:e013739.

34. Kennedy OJ, Pirastu N, Poole R, et al. Coffee consumption and kidney function: a Mendelian randomization study. *Am J Kidney Dis*. 2020;75:753-761.

35. Fu L, Zhou Q, Zhu W, et al. Do implantable cardioverter defibrillators reduce mortality in patients with chronic kidney disease at all stages? *Int Heart J*. 2017;58:371-377.

36. Jeszka-Skowron M, Zgoła-Grześkowiak A, Grześkowiak T. Analytical methods applied for the characterization and the determination of bioactive compounds in coffee. *Eur Food Res Technology*. 2015;240:19-31.

37. Guertin KA, Loftfield E, Boca SM, et al. Serum biomarkers of habitual coffee consumption may provide insight into the mechanism underlying the association between coffee consumption and colorectal cancer. *Am J Clin Nutr*. 2015;101:1000-1011.

38. Poole R, Kennedy OJ, Roderick P, Fallowfield JA, Hayes PC, Parkes J. Coffee consumption and health: umbrella review of meta-analyses of multiple health outcomes. *BMJ*. 2017;359:j5024.

39. Kennedy OJ, Roderick P, Buchanan R, Fallowfield JA, Hayes PC, Parkes J. Systematic review with meta-analysis: coffee consumption and the risk of cirrhosis. *Aliment Pharmacol Ther*. 2016;43:562-574.

40. Liu H, Hu G-H, Wang X-C, et al. Coffee consumption and prostate cancer risk: a meta-analysis of cohort studies. *Nutr Cancer*. 2015;67:392-400.

41. Wang J, Li X, Zhang D. Coffee consumption and the risk of cutaneous melanoma: a meta-analysis. *Eur J Nutr*. 2016;55:1317-1329.

42. Wang A, Wang S, Zhu C, et al. Coffee and cancer risk: a meta-analysis of prospective observational studies. *Scientific Rep*. 2016;6:33711.

43. Srithongkul T, Ungprasert P. Coffee consumption is associated with a decreased risk of incident chronic kidney disease: a systematic review and meta-analysis of cohort studies. *Eur J Intern Med*. 2020;77:111-116.

44. Snyder SH, Katims JJ, Annau Z, Bruns RF, Daly JW. Adenosine receptors and behavioral actions of methylxanthines. *Proc Natl Acad Sci U S A*. 1981;78:3260-3264.

45. Daly JW, Butts-Lamb P, Padgett W. Subclasses of adenosine receptors in the central nervous system: interaction with caffeine and related methylxanthines. *Cell Mol Neurobiol*. 1983;3:69-80.

46. Marx B, Scuvée É, Scuvée-Moreau J, Seutin V, Jouret F. Mechanisms of caffeine-induced diuresis. *Med Sci (Paris)*. 2016;32:485-490.

47. Cuypers Y. Influence of caffeine and histamine on blood flow in artificially perfused kidneys. *Arch Int Physiol Biochim*. 1958;66:457-459.

48. Kanbay M, Chen Y, Solak Y, Sanders PW. Mechanisms and consequences of salt sensitivity and dietary salt intake. *Curr Opin Nephrol Hypertens*. 2011;20:37-43.

49. Afsar B, Afsar RE, Dagel T, et al. Capillary rarefaction from the kidney point of view. *Clin Kidney J*. 2018;11:295-301.

50. Yu H, Yang T, Gao P, et al. Caffeine intake antagonizes salt sensitive hypertension through improvement of renal sodium handling. *Scientific Rep*. 2016;6:25746.

51. Belibi FA, Wallace DP, Yamaguchi T, Christensen M, Reif G, Grantham JJ. The effect of caffeine on renal epithelial cells from patients with autosomal dominant polycystic kidney disease. *J Am Soc Nephrol*. 2002;13:2723-2729.

52. Tofovic SP, Branch KR, Oliver RD, Magee WD, Jackson EK. Caffeine potentiates vasodilator-induced renin release. *J Pharmacol Exp Ther*. 1991;256:850-860.

53. Tseng CJ, Kuan CJ, Chu H, Tung CS. Effect of caffeine treatment on plasma renin activity and angiotensin I concentrations in rats on a low sodium diet. *Life Sci*. 1993;52:883-890.

54. Peerapen P, Ausakunpipat N, Sutthimethakorn S, Aluksanasuwan S, Vinaiphat A, Thongboonkerd V. Physiologic changes of urinary proteome by caffeine and excessive water intake. *Clin Chem Lab Med*. 2017;55:993-1002.

55. Peerapen P, Thongboonkerd V. Caffeine prevents kidney stone formation by translocation of apical surface annexin A1 crystal-binding protein into cytoplasm: in vitro evidence. *Scientific Rep*. 2016;6:38536.

56. Mahmud A, Feely J. Acute effect of caffeine on arterial stiffness and aortic pressure waveform. *Hypertension*. 2001;38:227-231.

57. Mehta A, Jain AC, Mehta MC, Billie M. Caffeine and cardiac arrhythmias. An experimental study in dogs with review of literature. *Acta Cardiol*. 1997;52:273-283.

58. Zuchinali P, Souza GC, Pimentel M, et al. Short-term effects of high-dose caffeine on cardiac arrhythmias in patients with heart failure: a randomized clinical trial. *JAMA Intern Med*. 2016;176:1752-1759.