Sex-specific association between coffee consumption and incident chronic kidney disease: a population-based analysis of 359,906 participants from the UK Biobank

Lei Tang[1], Lina Yang[1], Wenwen Chen[2], Chunyang Li[2], Yu Zeng[2], Huazhen Yang[2], Yao Hu[2], Yuanyuan Qu[2], Huan Song[2,3], Xiaoxi Zeng[1,2], Ping Fu[1,2]

[1]Division of Nephrology, Kidney Research Institute, West China Hospital, Sichuan University, Chengdu, Sichuan 610041, China;
[2]Biomedical Big Data Center of West China Hospital, Med-X Center for Informatics, Sichuan University, Chengdu, Sichuan 610041, China;
[3]Center of Public Health Sciences, Faculty of Medicine, University of Iceland, Reykjavík, Iceland.

Abstract

Background: The risk for chronic kidney disease (CKD) is influenced by genetic predisposition, sex, and lifestyle. Previous research indicates that coffee is a potentially protective factor in CKD. The current study aims to investigate whether sex disparity exists in the coffee–CKD association, and whether genetic risk of CKD or genetic polymorphisms of caffeine metabolism affect this association.

Methods: A total of 359,906 participants from the UK Biobank who were enrolled between 2006 and 2010 were included in this prospective cohort study, which aimed to estimate the hazard ratios for coffee intake and incident CKD using a Cox proportional hazard model. Allele scores of CKD and caffeine metabolism were additionally adjusted for in a subsample with qualified genetic data ($n = 255,343$). Analyses stratified by genetic predisposition, comorbidities, and sex hormones were performed. Tests based on Bayesian model averaging were conducted to ascertain the robustness of the results.

Results: Coffee was inversely associated with CKD in a dose-dependent manner. The effects of coffee did not differ across different strata of genetic risk for CKD, but were more evident among slower genetically predicted caffeine metabolizers. Significant sex disparity was observed (P value for interaction = 0.013), in that coffee drinking was only associated with the risk reduction of CKD in females. Subgroup analysis revealed that testosterone and sex hormone-binding globulin (SHBG), but not estradiol, modified the coffee–CKD association.

Conclusions: In addition to the overall inverse coffee–CKD association that was observed in the general population, we could also establish that a sex disparity existed, in that females were more likely to experience the benefit of the association. Testosterone and SHBG may partly account for the sex disparity.

Keywords: Coffee; Chronic kidney diseases; Genotype; Sex

Introduction

Chronic kidney disease (CKD) is a major public health problem with substantial comorbidities and disease burden. The statistics from the Global Burden of Disease Study 2017 reveal that approximately one-tenth of the world's population was affected by CKD, and that it ranked as the 12th leading cause of death globally, causing 35.8 million disability-adjusted life years in 2017.[1,2]

Coffee is one of the most commonly consumed beverages worldwide, and is reported to be related to risk reduction of all-cause mortality,[3] as well as multiple health outcomes, such as obesity, metabolic syndrome, type 2 diabetes,[4] and cardiovascular disease (CVD).[5] Studies examining the overall associations between coffee consumption and CKD have yielded mixed results. Several cohort studies and meta-analyses reported that coffee is associated with decreased CKD risk,[6-10] while others found no significant association.[11,12]

Despite the accumulating evidence supporting the reno-protective effect of coffee, considering that CKD exhibits sex disparities in its incidence and progression,[13] the question still remains on whether both sexes could benefit alike from coffee. Coffee consumption has actually been

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000002234

Correspondence to: Xiaoxi Zeng, Division of Nephrology, Kidney Research Institute, West China Hospital, Sichuan University, Guo Xue Lane 37, Chengdu, Sichuan 610041, China
E-Mail: zengxiaoxi@wchscu.cn

Chinese Medical Journal 2022;135(12)
Received: 13-12-2021; **Online:** 29-07-2022 **Edited by:** Yuanyuan Ji

reported to affect the risk of some diseases sex-specifically. For instance, Hsu *et al*[14] found that coffee consumption significantly increased the high-density lipoprotein cholesterol level only in females but not males. Similarly, Lee *et al*[15] reported that the protective effect of habitual coffee drinking on incident stroke presented with sex disparity.

The genetic predisposition also contributes to the development of CKD.[16] Meanwhile, the genetic polymorphisms affecting caffeine metabolism are also associated with increased risk of several health impairments, including hypertension, impaired fasting glucose, and myocardial infarction.[17-19] Therefore, it is worth examining whether the effect of coffee on incident CKD is independent of genetic factors.

Integrating individual phenotype and genotype data from the UK Biobank, we conducted a comprehensive prospective cohort study to investigate the association between coffee and CKD, considering the impact of sex, genetic risk of CKD, and caffeine metabolism polymorphisms.

Methods

Study design

The UK Biobank, the source of the data used in the present study, is a large-scale population-based cohort with in-depth genetic and health information of more than 500,000 participants. The UK Biobank data used in this study were derived from the details of participants recruited from 22 assessment centers across the United Kingdom during 2006 to 2010.[20] With the consent of participants, health-related outcomes were obtained periodically from external health care providers.[21] Hospital inpatient records were linked to Hospital Episode Statistics (HES) for England, Scottish Morbidity Record for Scotland, and Patient Episode Database for Wales. Data on mortality were available from National Health Service (NHS) Digital in England and Wales, and NHS Central Register in Scotland. Primary care data were linked with these records by general health care practitioners. Participants were genotyped using UK BiLEVE and UK Biobank Axiom array, which share 95% common markers, and variants were imputed using Haplotype Reference Consortium, as well as merged UK10K and 1000 Genomes phase 3 reference panels.[22] The researches had applied to access the UK Biobank database with the application approval number of 54803.

Study population

For the primary analysis, we excluded participants based on the following criteria: (1) lost to follow-up for any reason (n = 1346); (2) without complete information on coffee consumption (n = 2248); (3) without results of testosterone or sex hormone-binding globulin (SHBG) (n = 112,349); and (4) with any congenital or acquired CKD preceding or within 3 months of recruitment, where the diagnostic criteria used to infer CKD were estimated glomerular filtration rate (eGFR) <60 mL·min^{-1}·1.73 m^{-2} and urine albumin to creatinine ratio (uACR) ≥30 mg/g (n = 26,658) [Figure 1]. Supplementary Table 1 [http://links.lww.com/CM9/B116] presents a comparison of the baseline characteristics of participants enrolled in the primary analysis cohort, those lost to follow-up, and those with missing information on coffee intake, testosterone, and SHBG. In order to explore the influence of genetic predisposition on the studied association, we derived a genetic analysis cohort by further making exclusions based on the following criteria: (1) non-Caucasian (n = 59,248); (2) did not pass the quality control of genetic data (ie, with inconsistent self-reported and genetic sex, or high rate of genotype missingness and heterozygosity; n = 1037); and (3) with first or second level of relatedness (ie, with the kinship coefficient >0.0884; n = 44,278) [Figure 1].[23]

Assessment of coffee consumption

At the recruitment assessment center, participants completed a food frequency questionnaire (FFQ) that included 29 questions on diet. For habitual coffee consumption, participants were first asked "*How many cups of coffee do you drink each day? (Include decaffeinated coffee).*" We defined coffee intake as follows: none, ≤1, 2–3, 4–5, and ≥6 cups/day. Coffee drinkers would be further asked "*What type of coffee do you usually drink?*," and they could choose from "decaffeinated" "instant" "ground" "other type" "do not know" and "prefer not to answer".

The reproducibility of the FFQ in a subsample of around 20,000 participants who repeated the visit 4 years after recruitment and its concordance with post-recruitment online 24-h recall have been described elsewhere.[24] The weighted kappa of reported coffee intake in FFQs 4 years apart was 0.83 and the ability of FFQ to discriminate between high and low intakes was confirmed by 24-h recall.

Assessment of outcomes

CKD outcomes were identified as follows: (1) first diagnosis of incident chronic renal failure, initiation of renal replacement therapy, development of renal complications of hypertension or diabetes, glomerular diseases, or other renal structural abnormality >3 months after recruitment; (2) presenting with decreased kidney function, defined by eGFR < 60 mL·min^{-1}·1.73 m^{-2} based on $eGFR_{creat}$ or $eGFR_{creat\text{-}cys}$ as appropriate,[25] or uACR ≥ 30 mg/g in the follow-up assessment during 2012 to 2013. The time to event was determined by the first diagnosis records for incident CKD, or, December 31, 2012, which was set as the timing for ascertaining incident CKD by abnormal laboratory tests. Cases were obtained from records linked to inpatients, death register, and primary care, and classified using the International Classification of Diseases (ICD), 10th Revision (ICD-10) codes, and Office of Population Censuses and Surveys Classification of Interventions and Procedures [Supplementary Table 2, http://links.lww.com/CM9/B116].

Assessment of covariates

Sociodemographic factors (ie, age, sex, race, Townsend deprivation index, assessment center, and the highest education level) and lifestyles (ie, smoking, alcohol

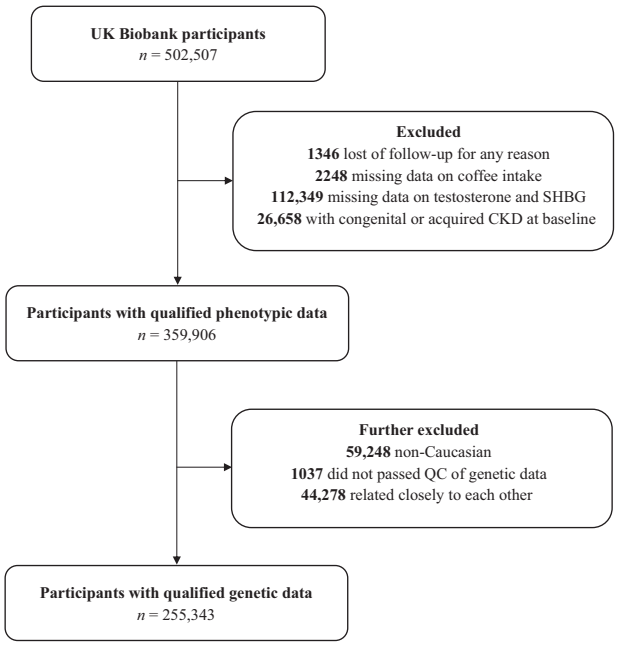

Figure 1: Flow chart of participants' enrollment. CKD: Chronic kidney disease; QC: Quality control; SHBG: Sex hormone-binding globulin.

consumption, and milk and tea intake) were collected at recruitment using questionnaires. Body mass index (BMI), as the anthropometric measurement, was calculated from participants' height and weight. Participants' history of hypertension, diabetes, CVD, and cancer was obtained from health-related data. The detailed description of covariates is available in Supplementary Methods, http://links.lww.com/CM9/B116. Serum sex hormones and SHBG were collected during 2006 to 2010 at the recruitment assessment centers and measured by Beckman Coulter Unicel Dxl 800 (Beckman Coulter, London, UK).

Polygenetic risk score of CKD

The polygenic risk scores (PRS) of CKD were derived from the summary statistics of a recent genome-wide association study of eGFR.[26] Independent single nucleotide polymorphisms (SNPs) were identified using the "clumping" method.[27] Aggregating the numbers of risk allele at each locus, weighted by the corresponding beta coefficient, we constructed PRS and then *z*-standardized them. To optimize the capability of risk prediction, multiple *P* value thresholds (5×10^{-8}, 5×10^{-6}, 5×10^{-4}, 0.05, 0.01, 0.1, 0.5) were examined. PRS calculated from SNPs with *P* value < 0.01 finally came out to be the best score carried forward, explaining 4.53% of the variance of eGFR in the UK Biobank [Supplementary Table 3, http://links.lww.com/CM9/B116]. A higher PRS represented a better genetically predicted kidney function. The hazard ratios (HRs) of CKD were, respectively, 1.33 (95% confidence interval [CI] 1.23–1.43, *P* value < 0.001) and 1.79 (95% CI 1.67–1.92, *P* value < 0.001) for the intermediate (ie, second tertile of PRS) and high-risk (ie, first tertile of PRS) groups compared with the low-risk group (ie, third tertile of PRS), adjusting for age, sex, third degree of relatedness, first ten principle components, and genotyping arrays.

Genetic polymorphisms of caffeine metabolism

We chose SNPs near *AHR*, *CYP1A2*, and *CYP2A6* reported in the genome-wide association study of caffeine metabolites conducted by Cornelis *et al*[28] to construct the allele score [Supplementary Table 4, http://links.lww.com/CM9/B116]. The score correlated positively with caffeine metabolizing rate. Coffee consumption reduced by 0.039 (95% CI 0.031–0.047, *P* value < 0.001) cups/day for every 1-standard-deviation (SD) increase in the allele score. Faster caffeine metabolizers (ie, higher half of the score) were 6% (odds ratio 1.06, 95% CI 1.04–1.08, *P* value < 0.001) more likely to become heavy coffee drinkers (ie, ≥4 cups/day) compared with slower ones (ie, lower half of the score).

Statistical analysis

The distributions of baseline characteristics were presented across eGFR categories. Continuous variables were shown as means SDs if normally distributed and medians (interquartile ranges) if skewed. Categorical variables were displayed as count (%). We compared continuous variables using analysis of variance or Kruskal–Wallis test, as appropriate, and categorical variables using chi-squared test.

The end of follow-up was recorded as the date of CKD incidence, the date of death, or the end of data collection of the attended assessment center (i., February 28, 2018 for centers in England and Wales; December 31, 2016 for centers in Scotland), whichever came first. A Cox proportional hazards model was applied using the *"survival"* package in R (The R Foundation for Statistical Computing, Vienna, Austria) to calculate HRs and 95% CIs of coffee consumption and CKD, stratified by 5-year age groups, sex, and assessment centers. The proportional hazards assumption for the Cox model was checked using Schoenfeld residuals, and no violation was found.

Coffee consumption, measured by the number of consumed coffee cups with non-drinkers as the reference, was first introduced into the model as a multi-categorical variable. Then, a test for linearity was performed by modeling coffee as a continuous variable. To investigate the extent of confounding, we adjusted for sociodemographic factors (Townsend deprivation index [in quartiles] and highest education level), lifestyle (smoking [never, past, <1, 1–9, 10–14, 15–19, and ≥20 cigarettes/day], alcohol consumption [never, past, <1, 1–7, 8–15, 16–29, and ≥30 g/day], milk intake [none, <150, 150–299, and ≥300 mL/day], and tea intake [none, ≤1, 2–3, and ≥3 cups/day]), anthropometric measurement (BMI [<18.5, 18.5–24.9, 25.0–29.9, and ≥30.0 kg/m^2]), comorbidities (history or comorbidities of hypertension, diabetes, CVD, and cancer), and sex hormones (log-transformed SHBG and testosterone). In the genetic analysis cohort, genetic risk of CKD (low, intermediate, and high risk defined by PRS) and caffeine metabolizing

rate (fast and slow metabolizers defined by allele score) was further adjusted. Participants' missing variables were grouped into a single category and the proportion of missing observations was <1% for all covariates [Supplementary Table 5, http://links.lww.com/CM9/B116].

We evaluated the associations between coffee intake and CKD for various coffee types, and non-coffee drinkers were treated as the reference group; further, coffee drinkers preferring a certain type of coffee were included in each subgroup analysis. To find other potential modifiers on the coffee–CKD association, we also performed stratified analyses by age, sex, Townsend deprivation index, smoking status, alcohol consumption, BMI, prevalent hypertension, diabetes, CVD and cancer, genetic risk of CKD, caffeine metabolizing rate, sex hormones, and SHBG. Since estradiol was not routinely measured in the UK Biobank, the subgroup analysis was restricted to 44,921 females with available assay results. The *P* value of heterogeneity corresponds to the likelihood-ratio test comparing the models with and without the interaction terms.

Sensitivity analysis

We used the following sensitivity analyses to test the robustness of the results: (1) performing Bayesian model averaging (BMA) using the "*BAS*" package in R to verify the sex-specific coffee–CKD association, which is based on specific priors, to generate posterior distributions of candidate effect sizes of variables under each of the models selected[29]; (2) excluding participants with unavailable baseline eGFR and uACR since we could not rule out the possibility that they had prevalent CKD; and (3) excluding incident CKD cases within the first 2 and 3 years to reduce reverse causation.

Analyses were done using R version 4.0.2 (The R Foundation for Statistical Computing, Vienna, Austria). A two-tailed *P* value < 0.05 was interpreted as statistically significant.

Ethics approval and consent to participate

All the UK Biobank participants gave written informed consent before data collection. The UK Biobank has full ethical approval from the NHS National Research Ethics Service (16/NW/0274), and this study was approved by the biomedical research ethics committee of West China Hospital (2019-1171). The study conformed to the *Declaration of Helsinki*.

Results

Coffee consumption and incident CKD

Of the 359,906 UK Biobank participants enrolled in the current study, the median age was 57 years, 90.8% were Caucasians, 49.8% were females, and 78.4% were coffee drinkers. Participants' characteristics by sex and coffee intake are presented in Table 1. Heavy coffee drinkers (ie, ≥4 cups/day) were more likely to be males, fast caffeine metabolizers, obese, current smokers, and alcohol drinkers. Over a median follow-up period of 8.8 years, 3454 (1.9%) cases of incident CKD in females and 3800 (2.1%) in males were observed. Regular coffee consumption was associated with a 6% to 15% reduced risk of CKD. The adjusted HRs across coffee intake varied in a dose-dependent manner (*P* value < 0.001 for trend; Table 2). The coffee–CKD association did not differ by coffee types [Supplementary Table 6, http://links.lww.com/CM9/B116]. In the subset of 255,343 participants with qualified genetic data, after the additional adjustment for the genetic risk of CKD and caffeine metabolizing rate, the results remain the same [Table 2].

Subgroup analyses and sex-specific coffee–CKD association

Habitual coffee consumption could offset the genetic risk of CKD. Compared with non-drinkers, coffee consumption reduced the risk of CKD by 6% to 17% [Supplementary Table 7, http://links.lww.com/CM9/B116]. The inverse coffee–CKD association seemed stronger among slower caffeine metabolizers than faster ones. However, the formal test of interaction did not reach statistical significance (*P* value for interaction = 0.14; Supplementary Table 7, http://links.lww.com/CM9/B116). The coffee–CKD association did not significantly differ by age, Townsend deprivation index, smoking status, alcohol consumption, BMI, prevalent hypertension, diabetes, CVD, and cancer [Supplementary Tables 7 and 8, http://links.lww.com/CM9/B116].

Stratified by sex, the inverse coffee–CKD relationship existed in females, but not males (*P* value for interaction = 0.013; Table 3). Observing the sex-specific association between coffee consumption and CKD, we further explored the possible modification effect of sex hormones and SHBG, and found that the coffee–CKD association was more obvious in participants with lower testosterone and higher SHBG concentrations.

To be specific, in the general population, coffee intake brought about a 12% to 30% decreased CKD risk in the lowest tertile of testosterone concentration. However, such an inverse coffee–CKD association became less evident as testosterone increased, and eventually disappeared in the highest tertile (*P* value for interaction = 0.031; Figure 2). Similarly, results diverged in different strata of plasma SHBG concentration. The coffee–CKD association was greatest in the highest tertile, while could not be noticed as SHBG fell down (*P* value for interaction = 0.057; Figure 3). However, the available assay results indicate that estradiol did not significantly modify the reno-protective effect of coffee in females with available assay results (*P* value for interaction = 0.96; Supplementary Figure 1, http://links.lww.com/CM9/B116). Risk patterns across testosterone and SHBG subgroups were generally similar in both sexes, although no estimate could be derived from the lowest and the highest tertiles of testosterone, in males and females, respectively, due to inadequate sample sizes [Figures 2 and 3]. It is notable that a weak tendency of inverse coffee–CKD association was found in males with the highest SHBG level. In this subgroup, compared with non-drinkers, drinking ≥4 cups/

Table 1: Baseline characteristics of study participants stratified by sex and coffee intake in the UK Biobank.

Characteristics	Coffee intake in the female (cups/day)						Coffee intake in the male (cups/day)					
	None	≤ 1	2–3	4–5	≥ 6	*P* value	None	≤ 1	2–3	4–5	≥ 6	*P* value
No. of participants	41,455	50,470	55,288	22,328	9586		36,315	46,761	57,514	27,101	13,088	
Age (years)	54 [48, 61]	57 [50, 63]	58 [50, 63]	57 [50, 63]	56 [49, 62]	<0.001	57 [49, 63]	59 [51, 64]	59 [51, 64]	57 [49, 63]	56 [48, 62]	<0.001
Townsend deprivation index												
Q1	9029 (21.8)	12,784 (25.3)	14,847 (26.9)	5779 (25.9)	2046 (21.3)	<0.001	7640 (21.0)	12,003 (25.7)	15,533 (27.0)	7197 (26.6)	3024 (23.1)	<0.001
Q2	9747 (23.5)	12,795 (25.4)	14,425 (26.1)	5850 (26.2)	2323 (24.2)		8086 (22.3)	11,604 (24.8)	14,799 (25.7)	7133 (26.3)	3133 (23.9)	
Q3	10,535 (25.4)	12,777 (25.3)	13,838 (25.0)	5648 (25.3)	2507 (26.2)		9016 (24.8)	11,707 (25.0)	14,160 (24.6)	6463 (23.8)	3171 (24.2)	
Q4	12,093 (29.2)	12,052 (23.9)	12,114 (21.9)	5028 (22.5)	2705 (28.2)		11,522 (31.7)	11,383 (24.3)	12,947 (22.5)	6275 (23.2)	3747 (28.6)	
Race												
White	37,487 (90.4)	47,429 (94.0)	53,428 (96.6)	21,871 (98.0)	9415 (98.2)	<0.001	32,695 (90.0)	43,707 (93.5)	55,285 (96.1)	26,379 (97.3)	12,785 (97.7)	<0.001
Mixed	345 (0.8)	377 (0.7)	331 (0.6)	101 (0.5)	45 (0.5)		203 (0.6)	257 (0.5)	259 (0.5)	110 (0.4)	56 (0.4)	
Asian	1355 (3.3)	830 (1.6)	390 (0.7)	83 (0.4)	28 (0.3)		1713 (4.7)	1244 (2.7)	685 (1.2)	159 (0.6)	53 (0.4)	
Black	1303 (3.1)	934 (1.9)	492 (0.9)	104 (0.5)	35 (0.4)		969 (2.7)	795 (1.7)	553 (1.0)	173 (0.6)	54 (0.4)	
Chinese	285 (0.7)	260 (0.5)	119 (0.2)	15 (0.1)	6 (0.1)		157 (0.4)	149 (0.3)	104 (0.2)	30 (0.1)	7 (0.1)	
Other	542 (1.3)	517 (1.0)	395 (0.7)	92 (0.4)	42 (0.4)		418 (1.2)	417 (0.9)	415 (0.7)	133 (0.5)	77 (0.6)	
Highest education level												
None	7664 (18.5)	7640 (15.1)	7785 (14.1)	3504 (15.7)	1809 (18.9)	<0.001	8245 (22.7)	7483 (16.0)	7880 (13.7)	3925 (14.5)	2350 (18.0)	<0.001
College/university	11,541 (27.8)	17,069 (33.8)	19,317 (34.9)	7035 (31.5)	2455 (25.6)		9698 (26.7)	16,451 (35.2)	22,295 (38.8)	9845 (36.3)	3823 (29.2)	
A/AS	3568 (8.6)	4878 (9.7)	5424 (9.8)	2116 (9.5)	861 (9.0)		2573 (7.1)	3670 (7.8)	4528 (7.9)	1955 (7.2)	934 (7.1)	
O/GCSEs	7800 (18.8)	9569 (19.0)	10,713 (19.4)	4330 (19.4)	1854 (19.3)		4844 (13.3)	6146 (13.1)	7348 (12.8)	3477 (12.8)	1748 (13.4)	
CSEs	2244 (5.4)	1952 (3.9)	2217 (4.0)	1036 (4.6)	509 (5.3)		1819 (5.0)	1600 (3.4)	2010 (3.5)	1104 (4.1)	687 (5.2)	
NVQ/HND/HNC	5943 (14.3)	6035 (12.0)	6253 (11.3)	2774 (12.4)	1465 (15.3)		7006 (19.3)	8804 (18.8)	10,301 (17.9)	5423 (20.0)	2854 (21.8)	
Other	2157 (5.2)	2867 (5.7)	3135 (5.7)	1365 (6.1)	557 (5.8)		1614 (4.4)	2098 (4.5)	2622 (4.6)	1127 (4.2)	568 (4.3)	
Smoking												
None	26,667 (64.3)	32,007 (63.4)	32,889 (59.5)	11,987 (53.7)	4172 (43.5)	<0.001	19,281 (53.1)	24,491 (52.4)	29,028 (50.5)	12,415 (45.8)	4760 (36.4)	<0.001
Previous	12,042 (29.0)	16,278 (32.3)	19,154 (34.6)	79,76 (35.7)	3354 (35.0)		13,843 (38.1)	19,528 (41.8)	24,443 (42.5)	11,633 (42.9)	5373 (41.1)	
<10 cigarettes/day	616 (1.5)	653 (1.3)	1009 (1.8)	534 (2.4)	244 (2.5)		452 (1.2)	533 (1.1)	760 (1.3)	415 (1.5)	220 (1.7)	
10–14 cigarettes/day	668 (1.6)	544 (1.1)	807 (1.5)	566 (2.5)	445 (4.6)		595 (1.6)	568 (1.2)	842 (1.5)	596 (2.2)	438 (3.3)	
15–19 cigarettes/day	598 (1.4)	436 (0.9)	649 (1.2)	576 (2.6)	522 (5.4)		712 (2.0)	649 (1.4)	965 (1.7)	745 (2.7)	650 (5.0)	
≥20 cigarettes/day	857 (2.1)	537 (1.1)	761 (1.4)	677 (3.0)	843 (8.8)		1422 (3.9)	981 (2.1)	1458 (2.5)	1289 (4.8)	1643 (12.6)	
Alcohol consumption												
None	5725 (13.8)	3551 (7.0)	2981 (5.4)	1299 (5.8)	740 (7.7)	<0.001	2705 (7.4)	1549 (3.3)	1350 (2.3)	578 (2.1)	377 (2.9)	<0.001
Previous	2170 (5.2)	1297 (2.6)	1261 (2.3)	677 (3.0)	499 (5.2)		2028 (5.6)	1194 (2.6)	1372 (2.4)	882 (3.3)	670 (5.1)	
<1 grams/day	6378 (15.4)	5880 (11.7)	5251 (9.5)	2344 (10.5)	1383 (14.4)		2791 (7.7)	2469 (5.3)	2403 (4.2)	1219 (4.5)	911 (7.0)	
1–7 grams/day	10,684 (25.8)	14,085 (27.9)	13,606 (24.6)	5341 (23.9)	2326 (24.3)		6147 (16.9)	7271 (15.5)	8039 (14.0)	3770 (13.9)	2028 (15.5)	
8–15 grams/day	8235 (19.9)	13,206 (26.2)	15,690 (28.4)	5924 (26.5)	2041 (21.3)		5454 (15.0)	9101 (19.5)	10,999 (19.1)	4798 (17.7)	2037 (15.6)	
16–30 grams/day	5531 (13.3)	8918 (17.7)	11,783 (21.3)	4664 (20.9)	1743 (18.2)		7765 (21.4)	12,402 (26.5)	16,812 (29.2)	7625 (28.1)	3185 (24.3)	
≥30 grams/day	2674 (6.5)	3497 (6.9)	4678 (8.5)	2056 (9.2)	838 (8.7)		9357 (25.8)	12,723 (27.2)	16,495 (28.7)	8202 (30.3)	3856 (29.5)	
Tea intake												
None	4758 (11.5)	2755 (5.5)	7791 (14.1)	7431 (33.3)	4845 (50.5)	<0.001	3352 (9.2)	2053 (4.4)	7026 (12.2)	7434 (27.4)	5500 (42.0)	<0.001
≤1 cups/day	2225 (5.4)	4319 (8.6)	7411 (13.4)	4352 (19.5)	1740 (18.2)		1841 (5.1)	4386 (9.4)	8149 (14.2)	5277 (19.5)	2380 (18.2)	
2–3 cups/day	9107 (22.0)	15,281 (30.3)	21,083 (38.1)	5715 (25.6)	1345 (14.0)		7890 (21.7)	13,810 (29.5)	21,800 (37.9)	7380 (27.2)	2399 (18.3)	
≥3 cups/day	25,263 (60.9)	28,033 (55.5)	18,951 (34.3)	4809 (21.5)	1637 (17.1)		23,150 (63.7)	26,463 (56.6)	20,491 (35.6)	6987 (25.8)	2781 (21.2)	
BMI												
<18.5 kg/m^2	276 (0.7)	343 (0.7)	351 (0.6)	117 (0.5)	71 (0.7)	<0.001	119 (0.3)	95 (0.2)	93 (0.2)	49 (0.2)	42 (0.3)	<0.001
18.5–24.9 kg/m^2	15,630 (37.7)	21,244 (42.1)	21,807 (39.4)	7543 (33.8)	2996 (31.3)		9350 (25.7)	12,961 (27.7)	14,858 (25.8)	5908 (21.8)	2781 (21.2)	
25.0–29.9	14,860 (35.8)	18,241 (36.1)	20,817 (37.7)	8754 (39.2)	3582 (37.4)		17,584 (48.4)	23,301 (49.8)	29,169 (50.7)	13,670 (50.4)	6323 (48.3)	
≥30.0 kg/m^2	10,504 (25.3)	10,484 (20.8)	12,168 (22.0)	5870 (26.3)	2905 (30.3)		9033 (24.9)	10,207 (21.8)	13,199 (22.9)	7393 (27.3)	3896 (29.8)	
History of hypertension												
No	23,920 (57.7)	28,562 (56.6)	31,642 (57.2)	12,677 (56.8)	5666 (59.1)	<0.001	15,542 (42.8)	20,211 (43.2)	24,945 (43.4)	11,896 (43.9)	5929 (45.3)	<0.001
Yes	17,535 (42.3)	21,908 (43.4)	23,646 (42.8)	9651 (43.2)	3920 (40.9)		20,773 (57.2)	26,550 (56.8)	32,569 (56.6)	15,205 (56.1)	7159 (54.7)	
History of diabetes												
No	39,639 (95.6)	48,670 (96.4)	53,409 (96.6)	21,508 (96.3)	9192 (95.9)	<0.001	33,577 (92.5)	43,546 (93.1)	53,907 (93.7)	25,241 (93.1)	12,097 (92.4)	<0.001
Yes	1816 (4.4)	1800 (3.6)	1879 (3.4)	820 (3.7)	394 (4.1)		2738 (7.5)	3215 (6.9)	3607 (6.3)	1860 (6.9)	991 (7.6)	

Table 1 (continued).

Characteristics	Coffee intake in the female (cups/day)						Coffee intake in the male (cups/day)					
	None	≤1	2–3	4–5	≥6	*P* value	None	≤1	2–3	4–5	≥6	*P* value
History of CVD												
No	39,562 (95.4)	48,498 (96.1)	53,230 (96.3)	21,434 (96.0)	9092 (94.8)	<0.001	32,224 (88.7)	42,027 (89.9)	52,239 (90.8)	24,757 (91.4)	11,781 (90.0)	<0.001
Yes	1893 (4.6)	1972 (3.9)	2058 (3.7)	894 (4.0)	494 (5.2)		4091 (11.3)	4734 (10.1)	5275 (9.2)	2344 (8.6)	1307 (10.0)	
History of cancer												
No	37,073 (89.4)	44,639 (88.4)	48,841 (88.3)	19,884 (89.1)	8497 (88.6)	<0.001	33,446 (92.1)	42,658 (91.2)	52,620 (91.5)	25,075 (92.5)	12,138 (92.7)	<0.001
Yes	4382 (10.6)	5831 (11.6)	6447 (11.7)	2444 (10.9)	1089 (11.4)		2869 (7.9)	4103 (8.8)	4894 (8.5)	2026 (7.5)	950 (7.3)	
Testosterone (nmol/L)	1.02	1.00	1.02	1.03	1.04	<0.001	11.61	11.61	11.70 [9.53, 14.18]	11.70	11.89 [9.60, 14.46]	<0.001
	[0.72, 1.38]	[0.71, 1.36]	[0.72, 1.37]	[0.74, 1.38]	[0.75, 1.41]		[9.40, 14.15]	[9.47, 14.11]		[9.50, 14.18]		
Sex hormone-binding globulin (nmol/L)	55.97	56.98	56.85	56.57	58.20	<0.001	36.23	37.06	37.40	37.12	37.55	<0.001
	[39.26, 77.38]	[40.68, 77.20]	[41.04, 76.91]	[40.60, 76.63]	[41.17, 79.76]		[27.21, 47.55]	[28.18, 48.12]	[28.39, 48.47]	[28.07, 48.28]	[28.27, 49.11]	
Genetic risk of CKD*												
Low	8836 (32.5)	11,527 (33.2)	13,163 (33.4)	5403 (32.9)	2291 (32.8)	0.007	8092 (33.1)	11,191 (33.4)	14,039 (33.0)	6633 (32.6)	3088 (31.5)	0.016
Intermediate	9212 (33.9)	11,742 (33.9)	13,503 (34.3)	5547 (33.8)	2462 (35.3)		8168 (33.4)	11,405 (34.0)	14,451 (34.0)	6957 (34.2)	3370 (34.4)	
High	9160 (33.7)	11,412 (32.9)	12,719 (32.3)	5451 (33.2)	2231 (31.9)		8184 (33.5)	10,948 (32.6)	14,042 (33.0)	6766 (33.2)	3350 (34.2)	
Allele score of caffeine metabolism*	−3.14 ± 2.23	−3.13 ± 2.23	−3.08 ± 2.22	−3.03 ± 2.21	−2.94 ± 2.17	<0.001	−3.11 ± 2.25	−3.12 ± 2.24	−3.08 ± 2.24	−3.04 ± 2.23	−3.01 ± 2.19	<0.001

Data were shown as median [IQR], *n*, *n*(%), or mean±SD. * The analysis is restricted in 255,343 participants with qualified genetic data. AS: Advanced subsidiary; BMI: Body mass index; CKD: Chronic kidney disease; CSE: Certificate of Secondary Education; CVD: Cardiovascular disease; GCSE: General Certificate of Secondary Education; HNC: Higher National Certificate; HND: Higher National Diploma; HTN: Hypertension; IQR: Interquartile range; NVQ: National Vocational Qualification; SD: Standard deviation.

day of coffee reduced the risk of CKD by 15% (HR 0.85, 95% CI 0.64–1.13).

In the genetic analysis cohort, after additionally adjusting for allele scores, results of subgroup analysis by sex hormones and SHBG remain similar [Supplementary Figures 2–4, http://links.lww.com/CM9/B116].

Sensitivity analyses

In BMA, coffee drinking was inversely related to CKD in the general population (β = −0.074, SD = 0.067) and had a 58.3% posterior probability [Supplementary Table 9 and Supplementary Figure 5, http://links.lww.com/CM9/B116]. Posterior probabilities of regular coffee intake were 0% and 99.4% for males and females, respectively [Supplementary Tables 10 and 11 and Supplementary Figures 7 and 8, http://links.lww.com/CM9/B116]. Further, as indicated in Supplementary Tables 12–14, http://links.lww.com/CM9/B116, no major change could be obtained in the result pursuant to performing the same analysis in the advanced-age group, restricting it to participants with available baseline kidney biomarker results, or excluding CKD cases diagnosed within two years and three years after recruitment.

Discussion

Among more than 350,000 participants in the UK Biobank, coffee consumption reduced the risk of CKD regardless of the genetic risk of CKD, but possibly depending partly on the caffeine metabolizing rate. The effect was sex-specific, and was modified by testosterone and SHBG.

Our finding adds to the growing evidence on the possible effect of coffee consumption on CKD. The results of the current work were in line with previous observational studies and meta-analyses indicating significant association between coffee consumption and the reduced risk of CKD in the general population,[6-8,10] as well as reports about the causal effect of coffee on kidney function based on Mendelian randomization.[9] The hypothesis that bioactive components of coffee, such as caffeine and chlorogenic acids, have a beneficial impact on health outcomes through multiple interconnected pathways, including insulin sensitivity improvement, sex hormone production, and inflammation reduction, can be mentioned as a plausible causative factor for the inverse coffee–CKD association observed in the present study and elsewhere in the literature.[30] In addition, our study further extends the existing findings by addressing a paramount question: that of ascertaining the populations to which this association could be generalized.

First, it merits attention that, in the current study, only females could benefit from coffee drinking. Other investigators have also assessed the potential difference in the coffee–CKD association stratified by sex, yielding conflicting results. Hu *et al*[6] reported a null finding of the coffee–CKD association in males, but failed to confirm the interaction of coffee and sex. However, Lew *et al*[7] found that coffee consumption could only reduce the risk of end-stage renal disease in males. Compared with previous ones,

Table 2: Hazard ratios of coffee intake and incident CKD in the UK Biobank.

Items	Coffee intake (cups/day)					
	None	≤1	2–3	4–5	≥6	*P* value for trend
Primary analysis cohort (*n* = 359,906)						
No. of cases	1719	2010	2155	925	445	
Person years at risk	668,466	834,613	968,851	425,409	195,232	
Cases per 1000 person-years	2.57	2.41	2.22	2.18	2.28	
Model 1[*]	1 (ref)	0.82 (0.77–0.88)[¶]	0.75 (0.71–0.8)[¶]	0.77 (0.71–0.83)[¶]	0.84 (0.76–0.93)[‖]	<0.001
Model 2[†]	1 (ref)	0.94 (0.88–1)	0.89 (0.83–0.95)[‖]	0.86 (0.79–0.94)[‖]	0.84 (0.75–0.95)[‖]	<0.001
Model 3[‡]	1 (ref)	0.94 (0.88–1)	0.89 (0.83–0.95)[‖]	0.86 (0.79–0.94)[‖]	0.85 (0.75–0.95)[‖]	<0.001
Genetic analysis cohort (*n* = 255,343)						
No. of cases	1133	1461	1579	713	316	
Person years at risk	455,622	586,948	704,140	315,849	144,412	
Cases per 1000 person-years	2.54	2.49	2.24	2.26	2.19	
Model 1[*]	1 (ref)	0.86 (0.8–0.93)[¶]	0.78 (0.72–0.84)[¶]	0.82 (0.75–0.9)[¶]	0.83 (0.73–0.94)[‖]	<0.001
Model 2[†]	1 (ref)	0.97 (0.9–1.05)	0.89 (0.82–0.96)[‖]	0.88 (0.79–0.97)[§]	0.79 (0.69–0.92)[‖]	<0.001
Model 3[‡]	1 (ref)	0.97 (0.9–1.05)	0.89 (0.82–0.96)[‖]	0.88 (0.79–0.98)[§]	0.80 (0.69–0.92)[‖]	<0.001

[*] Model 1 is stratified for 5-year age groups, sex, and 22 assessment centers. [†] Model 2 is stratified for 5-year age groups, sex, and 22 assessment centers and adjusted for sociodemographic factors (race [in the primary analysis cohort only], Townsend deprivation index [in quartiles], and highest education level [college or university degree, A levels/AS levels or equivalent, O levels/GCSEs or equivalent, CSEs or equivalent, NVQ, HND, or HNC equivalent, or other professional qualifications]), lifestyle (smoking [never, past, <1, 1–10, 10–14, 15–19, and ≥20 cigarettes/day], alcohol consumption [never, past, <1, 1–7, 8–15, 16–29, and ≥30 g/day], milk intake [none, <150, 150–299, and ≥300 mL/day], and tea intake [none, ≤1, 2–3, and ≥3 cups/day]), anthropometric measurement (body mass index [<18.5, 18.5–24.9, 25–29.9, and ≥30 kg/m^2]), comorbidities (history of hypertension, diabetes, CVD, and cancer), and genetic factors (in the genetic analysis cohort only, polygenetic risk score of CKD [low risk, intermediate risk, and high risk] and genetic polymorphisms of caffeine metabolizing rate [fast and slow]). [‡] Model 3 is adjusted for model 2 + log-transformed SHBG and testosterone. [§] *P* values of HRs are within the range of 0.01 to 0.05. [‖] *P* values of HRs are within the range of 0.001 to 0.01. [¶] *P* values of HRs are within the range of <0.001. AS: Advanced subsidiary; CI: Confidence interval; CKD: Chronic kidney disease; CSE: Certificate of Secondary Education; CVD: Cardiovascular disease; GCSE: General Certificate of Secondary Education; HR: Hazard ratio; HNC: Higher National Certificate; HND: Higher National Diploma; HTN: Hypertension; NVQ: National Vocational Qualification; SHBG: Sex hormone-binding globulin.

one strength of our study lies in the prospective design and large scale of the UK Biobank, providing us with a unique opportunity to investigate the sex-specific effect of coffee on CKD with greater statistical power and less bias. Especially, in addition to the Cox proportional hazard model with comprehensive adjustment for confounders, the sex disparity was also verified by BMA, which generally performs better than traditional statistical methods in variable selection as it evaluates all potential combinations of the candidate variables and avoids uncertainty.[29] In BMA, coffee was inversely associated with renal deficiency in the general population and had a posterior probability of around 95%, indicating positive evidence for its reno-protective effect.[31] Performing BMA by sex, we found extremely strong evidence, measured by posterior probability >99%, for the reno-protective effect of coffee in females, in contrast to that of 2.5% in males.

Second, with the in-depth genetic information provided by the UK Biobank, the genetic predisposition of CKD and the genetically predicted caffeine metabolizing rate could be measured as allele scores at the individual level; thus, we can evaluate the coffee–CKD association in subgroups of varied genetic predisposition. While genetic risk for CKD seemingly did not modify the beneficial effects of coffee consumption on incident CKD, the caffeine metabolizing rate might partly influence the coffee–CKD association. Previous research reports a modification effect of the *CYP1A2* genotype, which is responsible primarily for metabolizing caffeine, on some coffee-health outcome associations, such that slow metabolizers could not benefit from habitual coffee consumption.[17-19] Nonetheless, constructing a comprehensive allele score representing caffeine metabolism, we surprisingly found a stronger inverse association in slow metabolizers, but failed to confirm the gene-diet interaction.

In the current study, we observed sex-specific association between coffee and CKD. Sex disparity in the pathogenesis of CKD is well acknowledged. Both animal and epidemiological studies have revealed that sex hormones largely contribute to the phenomenon. Previous Mendelian randomization analyses have also reported the casual role of sex hormones in the incidence and progression of CKD, especially in males.[32,33] Therefore, with available individual-level data in the UK Biobank, we performed a series of analyses to explore whether sex hormones and SHBG may be involved this gender difference. We observed their potential modification roles in the coffee–CKD association.

For instance, in females, the reno-protective effect of coffee was more robust in those with higher SHBG and lower testosterone concentrations. SHBG *per se* also relates to metabolic syndrome, including dyslipidemia, hypertension, dysregulated glucose homeostasis, and obesity,[34] which are all confirmed risk factors of CKD.[35] Acting as a transporting protein, SHBG binds sex hormones with certain affinity and acts as a modulator of their bioactivity. Previous studies have revealed that the alteration of SHBG brings about a more drastic fluctuation in testosterone than estradiol, and low SHBG is often associated with hyper-

Table 3: Sex-specific association of coffee and incident CKD in the whole sample and genetic analysis cohort in the UK Biobank.

Variables	Coffee intake (cups/day)					*P*-value for trend	*P*-value for interaction[§]
	None	≤1	2–3	4–5	≥6		
Primary analysis cohort							0.013
Female (n = 179,127)							
No. of cases	903	983	989	392	187		
Person years at risk	358,473	435,777	477,462	193,234	83,088		
Cases per 1000 person-years	2.52	2.26	2.07	2.03	2.25		
HR (95% CI)[*]	1 (ref)	0.88 (0.8–0.97)[†]	0.81 (0.73–0.89)[‡]	0.73 (0.64–0.84)[‡]	0.72 (0.6–0.86)[‡]	<0.001	
Male (n = 180,779)							
No. of cases	816	1027	1166	533	258		
Person years at risk	309,993	398,836	491,390	231,581	112,144		
Cases per 1000 person-years	2.63	2.57	2.37	2.30	2.30		
HR (95% CI)[*]	1 (ref)	1 (0.9–1.1)	0.97 (0.88–1.07)	1 (0.88–1.13)	0.98 (0.83–1.15)	0.730	
Genetic analysis cohort							0.018
Female (n = 124,659)							
No. of cases	584	690	717	288	136		
Person years at risk	236,293	300,248	340,293	142,000	60,457		
Cases per 1000 person-years	2.47	2.30	2.11	2.03	2.25		
HR (95% CI)[*]	1 (ref)	0.9 (0.81–1.01)	0.82 (0.73–0.92)[†]	0.72 (0.61–0.85)[‡]	0.71 (0.57–0.80)[‡]	<0.001	
Male (n = 130,684)							
No. of cases	549	771	862	425	180		
Person years at risk	209,236	286,700	363,847	173,850	83,955		
Cases per 1000 person-years	2.62	2.69	2.37	2.44	2.14		
HR (95% CI)[*]	1 (ref)	1.05 (0.94–1.17)	0.96 (0.86–1.08)	1.04 (0.9–1.2)	0.89 (0.73–1.08)	0.350	

[*] Model is stratified for 5-year age groups, sex (in sex-combined analysis only) and 22 assessment centers and adjusted for sociodemographic factors (race [in the primary analysis cohort only], Townsend deprivation index [in quartiles], and highest education level [college or university degree, A levels/AS levels or equivalent, O levels/GCSEs or equivalent, CSEs or equivalent, NVQ or HND or HNC equivalent, or other professional qualifications]), lifestyle (smoking [never, past, <1, 1–10, 10–14, 15–19 and ≥20 cigarettes per day], alcohol consumption [never, past, <1, 1–7, 8–15, 16–29 and ≥30 grams per day], milk intake [none, <150, 150–299 and ≥300 ml per day], and tea intake [none, ≤1, 2–3 and ≥3 cups per day]), anthropometric measurement (body mass index [<18.5, 18.5–24.9, 25.0–29.9 and ≥30.0 kg/m^2]), comorbidities (history of hypertension, diabetes, cardiovascular disease and cancer), genetic factors (in the genetic analysis cohort only, polygenetic risk score of chronic kidney disease [low risk, intermediate risk and high risk] and genetic polymorphisms of caffeine metabolizing rate [fast and slow]), and sex hormones (log-transformed sex hormone-binding globulin and testosterone). [†] P values of HRs are within the range of 0.001–0.01. [‡] P values of HRs are within the range of < 0.001. [§] Coffee intake is included in the interaction term as a multicategorical variable (i.e., none, 1, 2–3, 4–5, 6 cups per day). P value for interaction is derived from the likelihood ratio test comparing the models with and without the interaction term. P values of coffee intake 1, 2–3, 4–5, 6 cups per day × sex are respectively 0.02, 0.004, 0.002 and 0.11 in the primary analysis cohort and 0.019, 0.026, 0.001 and 0.55 in the genetic analysis cohort.

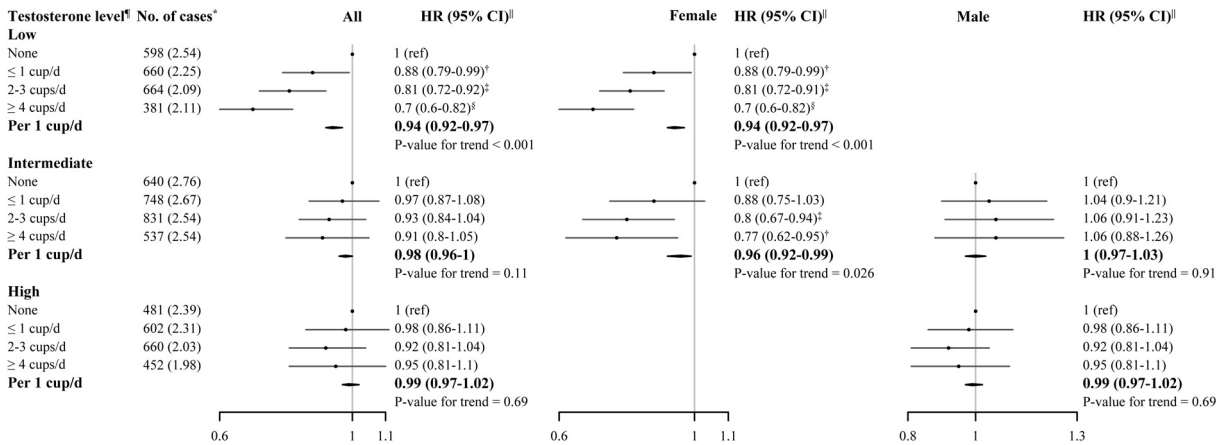

Figure 2: Subgroup analysis of coffee intake and incident chronic kidney disease by testosterone level in the primary analysis cohort in the UK Biobank. *Values in parentheses represent the incidence rates of CKD expressed in cases per 1,000 person-years. †P values of HRs are within the range of 0.01 to 0.05. ‡P values of HRs are within the range of 0.001 to 0.01. §*P* values of HRs are within the range of <0.001. ‖Model is stratified for 5-year age groups, and 22 assessment centers and adjusted for sociodemographic factors (race [in the primary analysis cohort only], Townsend deprivation index [in quartiles], and highest education level [college or university degree, A levels/AS levels or equivalent, O levels/GCSEs or equivalent, CSEs or equivalent, NVQ or HND or HNC equivalent, or other professional qualifications]), lifestyle (smoking [never, past, <1, 1–10, 10–14, 15–19, and ≥ 20 cigarettes per day], alcohol consumption [never, past, <1, 1–7, 8–15, 16–29 and ≥30 grams/day], milk intake [none, <150, 150–299 and ≥300 ml/day], and tea intake [none, 1, 2–3 and ≥3 cups/day]), anthropometric measurement (BMI [<18.5, 18.5–24.9, 25.0–29.9, and ≥30 kg/m2]), comorbidities (history of hypertension, diabetes, cardiovascular disease, and cancer), and sex hormones (log-transformed SHBG and testosterone). ¶Coffee intake and testosterone are included in the interaction term as binary variables (ie, non-drinker vs. drinker and low level vs. intermediate + high level). *P* value for interaction equals to 0.031 for coffee and testosterone. The analysis is not performed in the lowest and the highest tertile of testosterone, in males and females, respectively, due to inadequate sample sizes.

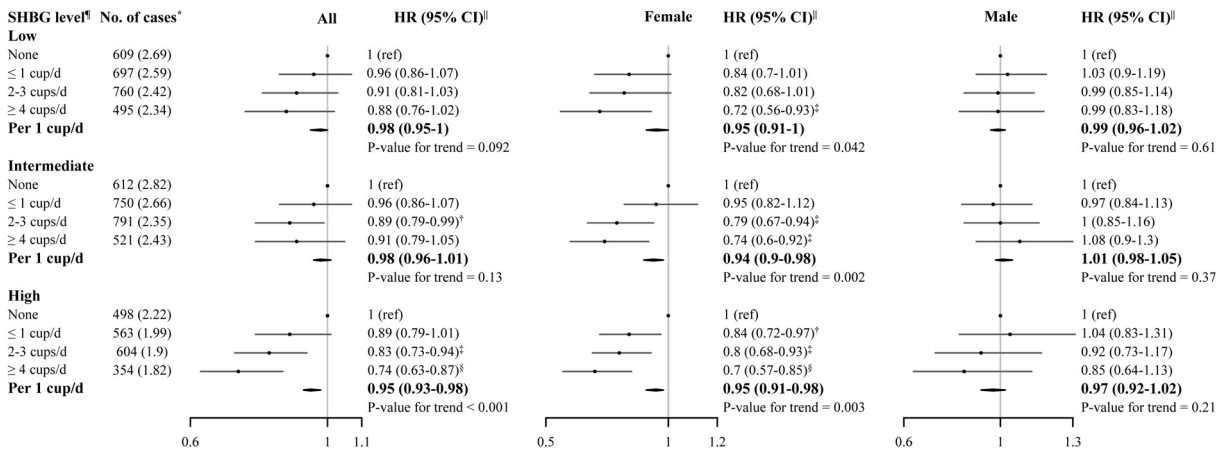

Figure 3: Subgroup analysis of coffee intake and incident CKD by SHBG level in the primary analysis cohort in the UK Biobank. *Values in parentheses represent the incidence rates of CKD expressed in cases per 1,000 person-years. †*P* values of HRs are within the range of 0.01 to 0.05. ‡*P* values of HRs are within the range of 0.001 to 0.01. §*P* values of HRs are within the range of <0.001. ‖Model is stratified for 5-year age groups, and 22 assessment centers and adjusted for sociodemographic factors (race [in the primary analysis cohort only], Townsend deprivation index [in quartiles], and highest education level [college or university degree, A levels/AS levels or equivalent, O levels/GCSEs or equivalent, CSEs or equivalent, NVQ or HND or HNC equivalent, or other professional qualifications]), lifestyle (smoking [never, past, <1, 1–10, 10–14, 15–19, and ≥ 20 cigarettes per day], alcohol consumption [never, past, <1, 1–7, 8–15, 16–29 and ≥30 grams/day], milk intake [none, <150, 150–299 and ≥300 ml/day], and tea intake [none, ≤1, 2–3 and ≥3 cups/day]), anthropometric measurement (BMI [<18.5, 18.5–24.9, 25.0–29.9, and ≥30 kg/m^2]), comorbidities (history of hypertension, diabetes, cardiovascular disease, and cancer), and sex hormones (log-transformed SHBG and testosterone). ¶Coffee intake and SHBG are included in the interaction term as binary variables (ie, non-drinker *vs.* drinker and low + intermediate level *vs.* high level). *P* value for interaction equals to 0.057 for coffee and SHBG. AS: Advanced subsidiary; CI: Confidence interval; CKD: Chronic kidney disease; CSE: Certificate of Secondary Education; GCSE: General Certificate of Secondary Education; HR: Hazard ratio; HNC: Higher National Certificate; HND: Higher National Diploma; NVQ: National Vocational Qualification; SHBG: Sex hormone-binding globulin.

androgenism in females.[36] So we presume that not only lower SHBG but also higher testosterone, partly induced by the decrease in SHBG, hinders the beneficial effects of coffee in female drinkers.

For males, only a small fraction of heavy habitual coffee drinkers with the highest SHBG presented with a tendency of risk reduction in CKD. Thus, we hypothesize, one possible explanation underlying the sex-specific reno-protective effect of coffee may be that daily coffee intake, as an isolated aspect of a person's lifestyle, is insufficient to adequately overcome the CKD susceptibility brought about by the naturally high-testosterone and low-SHBG concentrations in males.

Despite the reported effect of estradiol in offering protection against incident CKD,[37,38] we failed to confirm its role as a modifier of CKD susceptibility by virtue of the coffee-CKD association.

To the best of our knowledge, we are among the first, using large prospective cohort, to comprehensively

explore the sex disparity and the potential modification effect of sex hormones and SHBG in the coffee-CKD association. While it has several strengths, some limitations need to be pointed out. First, the study is mainly constituted of Caucasians with a median age of 57 years, making it difficult to extrapolate our results to other ethnic backgrounds or age groups. Besides, a "healthy volunteer" selection bias regarding UK Biobank has been identified.[39] Second, since the exposure was ascertained only by self-report at baseline assessment, reporting bias of coffee consumption was inevitable, and we were not aware of the changes in participants' dietary habits. Third, biomarker concentrations were based on one single measurement and random measurement error existed, leading to the misclassification of sex hormones and SHBG subgroups. Fourth, when conducting the subgroup analysis, smaller sample size may lead to inadequate statistical power and increase the likelihood of false negatives (ie, type II error),[40] especially for the analysis stratified by estradiol, since only a small proportion of participants underwent the measurement of estradiol.

In conclusion, despite the overall observed reno-protective effect of coffee in the general population, sex disparity existed, with the result that females are more likely to experience the benefit. Sex hormones and SHBG may partly account for the sex disparity. Further studies investigating the full mechanisms sex-specifically linking coffee to CKD risk reduction are warranted.

Acknowledgments

We thank the all the participants and staff involved in the UK Biobank and the CKDGen Consortium who provided valuable research resources.

Funding

Zeng X was supported by the 1.3.5 project for disciplines of excellence, West China Hospital, Sichuan University (No. ZYJC18010); funding was also obtained from the National Natural Science Foundation of China (No. 81900614), the Science and Technology Department of Sichuan Province (No. 2021YF0035), and the Chengdu Science and Technology Bureau (No. 2020-YF09-00117-GX).

Conflicts of interest

None.

References

1. GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2020;395:709–733. doi:10.1016/S0140-6736(20)30045-3.
2. Fan J, Sun Z, Yu C, Guo Y, Pei P, Yang L, *et al*. Multimorbidity patterns and association with mortality in 0.5 million Chinese adults. Chin Med J 2022;135:648–657. doi: 10.1097/CM9.0000000000001985.
3. Loftfield E, Cornelis MC, Caporaso N, Yu K, Sinha R, Freedman N. Association of coffee drinking with mortality by genetic variation in caffeine metabolism: findings from the UK Biobank. JAMA Intern Med 2018;178:1086–1097. doi: 10.1001/jamainternmed.2018.2425.
4. Nordestgaard AT, Thomsen M, Nordestgaard BG. Coffee intake and risk of obesity, metabolic syndrome and type 2 diabetes: a Mendelian randomization study. Int J Epidemiol 2015;44:551–565. doi: 10.1093/ije/dyv083.
5. Ding M, Bhupathiraju SN, Satija A, van Dam RM, Hu FB. Long-term coffee consumption and risk of cardiovascular disease: a systematic review and a dose-response meta-analysis of prospective cohort studies. Circulation 2014;129:643–659. doi: 10.1161/CIRCULATIONAHA.113.005925.
6. 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. doi: 10.1053/j.ajkd.2018.01.030.
7. Lew QLJ, Jafar TH, Jin A, Yuan JM, Koh WP. 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. doi: 10.1093/jn/nxy075.
8. Kanbay M, Siriopol D, Copur S, Tapoi L, Benchea L, Kuwabara M, *et al*. Effect of coffee consumption on renal outcome: a systematic review and meta-analysis of clinical studies. J Ren Nutr 2021;31:5–20. doi: 10.1053/j.jrn.2020.08.004.
9. Kennedy OJ, Pirastu N, Poole R, Fallowfield JA, Hayes PC, Grzeszkowiak EJ, *et al*. Coffee consumption and kidney function: a Mendelian randomization study. Am J Kidney Dis 2020;75:753–761. doi: 10.1053/j.ajkd.2019.08.025.
10. 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. doi: 10.1016/j.ejim.2020.04.018.
11. 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 (Lond) 2019;16:28–37. doi: 10.1186/s12986-019-0355-6.
12. Wijarnpreecha K, Thongprayoon C, Thamcharoen N, Panjawatanan P, Cheungpasitporn W. Association of coffee consumption and chronic kidney disease: a meta-analysis. Int J Clin Pract 2017;71:e12919–e12924. doi: 10.1111/ijcp.12919.
13. Carrero JJ, Hecking M, Chesnaye NC, Jager KJ. Sex and gender disparities in the epidemiology and outcomes of chronic kidney disease. Nat Rev Nephrol 2018;14:151–164. doi: 10.1038/nrneph.2017.181.
14. Hsu TW, Tantoh DM, Lee KJ, Ndi ON, Lin LY, Chou MC, *et al*. Genetic and non-genetic factor-adjusted association between coffee drinking and high-density lipoprotein cholesterol in Taiwanese adults: stratification by sex. Nutrients 2019;11:1102–1112. doi: 10.3390/nu11051102.
15. Lee J, Lee JE, Kim Y. Relationship between coffee consumption and stroke risk in Korean population: the Health Examinees (HEXA) Study. Nutr J 2017;16:7–14. doi: 10.1186/s12937-017-0232-y.
16. Hannan M, Ansari S, Meza N, Anderson AH, Srivastava A, Waikar S. Risk factors for CKD progression: overview of findings from the CRIC Study. Clin J Am Soc Nephrol 2021;16:648–659. doi: 10.2215/CJN.07830520.
17. Palatini P, Ceolotto G, Ragazzo F, Dorigatti F, Saladini F, Papparella I, *et al*. CYP1A2 genotype modifies the association between coffee intake and the risk of hypertension. J Hypertens 2009;27:1594–1601. doi: 10.1097/HJH.0b013e32832ba850.
18. Palatini P, Benetti E, Mos L, Garavelli G, Mazzer A, Cozzio S, *et al*. Association of coffee consumption and CYP1A2 polymorphism with risk of impaired fasting glucose in hypertensive patients. Eur J Epidemiol 2015;30:209–217. doi: 10.1007/s10654-015-9990-z.
19. Cornelis MC, El-Sohemy A, Kabagambe EK, Campos H. Coffee, CYP1A2 genotype, and risk of myocardial infarction. JAMA 2006;295:1135–1141. doi: 10.1001/jama.295.10.1135.
20. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, *et al*. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med 2015;12:e1001779–e1001788. doi: 10.1371/journal.pmed.1001779.
21. UK Biobank. 2021. Data Providers and Dates of Data Availability (2020). Available from https://biobank.ndph.ox.ac.uk/showcase/exinfo.cgi?src=Data_providers_and_dates. [Accessed December 1, 2021].
22. Bycroft C, Freeman C, Petkova D, Band G, Elliott LT, Sharp K, *et al*. The UK Biobank resource with deep phenotyping and genomic data. Nature 2018;562:203–209. doi: 10.1038/s41586-018-0579-z.
23. Manichaikul A, Mychaleckyj JC, Rich SS, Daly K, Sale M, Chen WM. Robust relationship inference in genome-wide association studies. Bioinformatics 2010;26:2867–2873. doi: 10.1093/bioinformatics/btq559.

24. Bradbury KE, Young HJ, Guo W, Key TJ. Dietary assessment in UK Biobank: an evaluation of the performance of the touchscreen dietary questionnaire. J Nutr Sci 2018;7:e6–e16. doi: 10.1017/jns.2017.66.
25. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, *et al*. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med 2012;367:20–29. doi: 10.1056/NEJMoa1114248.
26. Wuttke M, Li Y, Li M, Sieber KB, Feitosa MF, Gorski M, *et al*. A catalog of genetic loci associated with kidney function from analyses of a million individuals. Nat Genet 2019;51:957–972. doi: 10.1038/s41588-019-0407-x.
27. Choi SW, Mak TSH, O'Reilly PF. Tutorial: a guide to performing polygenic risk score analyses. Nat Protoc 2020;15:2759–2772. doi: 10.1038/s41596-020-0353-1.
28. Cornelis MC, Kacprowski T, Menni C, Gustafsson S, Pivin E, Adamski J, *et al*. Genome-wide association study of caffeine metabolites provides new insights to caffeine metabolism and dietary caffeine-consumption behavior. Hum Mol Genet 2016;25:5472–5482. doi: 10.1093/hmg/ddw334.
29. Hoeting JA, Madigan D, Raftery AE, Volinsky CT. Bayesian model averaging: a tutorial. Stat Sci 1999;14:382–417. doi: 10.1214/ss/1009212519.
30. Hang D, Kvaerner AS, Ma W, Hu Y, Tabung FK, Nan H, *et al*. Coffee consumption and plasma biomarkers of metabolic and inflammatory pathways in US health professionals. Am J Clin Nutr 2019;109:635–647. doi: 10.1093/ajcn/nqy295.
31. Kass RE, Raftery AE. Bayes factors. J Am Stat Assoc 1995;90:773–795. doi: 10.1080/01621459.1995.10476572.
32. Zhao JV, Schooling CM. The role of testosterone in chronic kidney disease and kidney function in men and women: a bi-directional Mendelian randomization study in the UK Biobank. BMC Med 2020;18:122–131. doi: 10.1186/s12916-020-01594-x.
33. Zhao JV, Schooling CM. Sex-specific associations of sex hormone binding globulin with CKD and kidney function: a univariable and multivariable Mendelian randomization Study in the UK Biobank. J Am Soc Nephrol 2021;32:686–694. doi: 10.1681/ASN.2020050659.
34. Brand JS, van der Tweel I, Grobbee DE, Emmelot-Vonk MH, van der Schouw YT. Testosterone, sex hormone-binding blobulin and the metabolic syndrome: a systematic review and meta-analysis of observational studies. Int J Epidemiol 2011;40:189–207. doi: 10.1093/ije/dyq158.
35. Gu DF, Shi YL, Chen YM, Liu HM, Ding YN, Liu XY, *et al*. Prevalence of chronic kidney disease and prediabetes and associated risk factors: a community-based screening in Zhuhai, Southern China. Chin Med J (Engl) 2013;126:1213–1219. doi: 10.3760/cma.j.issn.0366-6999.20123504.
36. Anderson DC. Sex-hormone binding globulin. Clin Endocrinol 1974;3:69–96. doi: 10.1111/j.1365-2265.1974.tb03298.x.
37. Doublier S, Lupia E, Catanuto P, Periera-Simon S, Xia X, Korach K, *et al*. Testosterone and 17β-estradiol have opposite effects on podocyte apoptosis that precedes glomerulosclerosis in female estrogen receptor knockout mice. Kidney Int 2011;79:404–413. doi: 10.1038/ki.2010.398.
38. Dixon A, Maric C. 17beta-Estradiol attenuates diabetic kidney disease by regulating extracellular matrix and transforming growth factor-beta protein expression and signaling. Am J Physiol Renal Physiol 2007;293:F1678–F1690. doi: 10.1152/ajprenal.00079.2007.
39. Fry A, Littlejohns TJ, Sudlow C, Doherty N, Adamska L, Sprosen T, *et al*. Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general population. Am J Epidemiol 2017;186:1026–1034. doi: 10.1093/aje/kwx246.
40. Shreffler J, Huecker MR. Type I and Type II errors and statistical power. StatPearls. Treasure Island (FL): StatPearls Publishing, 2022. Available from: http://www.ncbi.nlm.nih.gov/books/NBK557530/. [Accessed February 9, 2022].

How to cite this article: Tang L, Yang L, Chen W, Li C, Zeng Y, Yang H, Hu Y, Qu Y, Song H, Zeng X, Fu P. Sex-specific association between coffee consumption and incident chronic kidney disease: a population-based analysis of 359,906 participants from the UK Biobank. Chin Med J 2022;135:1414–1424. doi: 10.1097/CM9.0000000000002234