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

Lei Tang1, Lina Yang1, Wenwen Chen2, Chunyang Li2, Yu Zeng2, Huazhen Yang2, Yao Hu2, Yuanyuan Qu2, Huan Song2,3, Xiaoxi Zeng1,2, Ping Fu1,2

1Division of Nephrology, Kidney Research Institute, West China Hospital, Sichuan University, Chengdu, Sichuan 610041, China; 2Biomedical Big Data Center of West China Hospital, Med-X Center for Informatics, Sichuan University, Chengdu, Sichuan 610041, China; 3Center 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 renoprotective 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...
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 Haftotype 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 eGFRcreat or eGFRcreat-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
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.e., 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/m²]), 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 (i.e., ≥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/
| Characteristics | 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 |
| Townsend deprivation index | 90.29 (21.8) | 12,784 (25.3) | 14,847 (26.9) | 5779 (25.9) | 2046 (21.3) | <0.001 |
| Q2 | 97.42 (23.5) | 12,795 (25.4) | 14,425 (26.1) | 5850 (26.2) | 2523 (24.2) |
| Q3 | 10,535 (22.4) | 12,777 (25.0) | 17,007 (26.6) | 5965 (27.1) | 2027 (20.9) |
| Q4 | 12,093 (22.9) | 12,052 (23.9) | 12,114 (21.9) | 5028 (22.5) | 2705 (26.8) |
| Race | White | 37,487 (90.4) | 47,429 (94.0) | 53,428 (96.6) | 21,871 (98.0) | 9415 (98.0) | <0.001 |
| | Mixed | 345 (0.8) | 377 (0.7) | 331 (0.6) | 40 (0.5) | 40 (0.5) |
| | Asian | 1535 (3.5) | 830 (1.6) | 907 (1.7) | 83 (0.4) | 28 (0.3) |
| | Black | 1303 (3.1) | 934 (1.9) | 492 (0.9) | 104 (0.5) | 35 (0.4) |
| | Chinese | 285 (0.7) | 260 (0.5) | 119 (0.2) | 15 (0.1) | 6 (0.1) |
| | Other | 542 (1.3) | 517 (1.0) | 395 (0.7) | 92 (0.4) | 42 (0.4) |
| Highest education level | None | 7664 (18.5) | 7640 (15.1) | 7785 (14.1) | 3054 (15.7) | 1809 (18.9) | <0.001 |
| | College/university | 11,541 (27.8) | 17,069 (33.8) | 19,317 (34.9) | 7035 (31.5) | 2855 (25.6) |
| | A/AS | 3568 (8.6) | 4878 (9.7) | 5424 (9.8) | 2136 (9.5) | 861 (9.0) |
| | OGGSe | 7800 (18.8) | 9569 (19.0) | 10,713 (19.4) | 4330 (19.9) | 1854 (19.3) |
| | CSNe | 2244 (5.4) | 1952 (3.9) | 2217 (4.0) | 1036 (4.6) | 509 (5.3) |
| | NHANESHD/HNC | 5943 (14.3) | 6035 (12.0) | 6355 (13.3) | 2774 (12.4) | 1465 (15.3) |
| | Other | 2157 (5.2) | 2867 (5.7) | 3135 (5.7) | 1565 (6.1) | 557 (5.8) |
| Smoking | None | 26,667 (64.3) | 32,007 (63.4) | 32,889 (59.5) | 11,987 (53.7) | 4172 (43.5) | <0.001 |
| | Previous | 12,042 (29.4) | 16,287 (32.3) | 19,154 (34.6) | 7976 (35.7) | 3354 (35.0) |
| | <10 cigarettes/day | 616 (1.5) | 653 (1.3) | 1009 (1.8) | 524 (2.4) | 52 (0.5) |
| | 10–14 cigarettes/day | 668 (1.6) | 544 (1.1) | 807 (1.5) | 566 (2.5) | 44 (0.4) |
| | 15–19 cigarettes/day | 598 (1.4) | 436 (0.9) | 649 (1.2) | 526 (2.5) | 52 (0.5) |
| | ≥20 cigarettes/day | 857 (2.1) | 537 (1.1) | 761 (1.4) | 677 (3.0) | 843 (8.8) |
| Alcohol consumption | None | 5725 (13.8) | 3551 (7.0) | 2981 (5.4) | 1299 (5.8) | 740 (7.7) | <0.001 |
| | Previous | 2170 (5.2) | 1297 (2.6) | 1261 (3.3) | 677 (3.0) | 499 (5.2) |
| | 1–3 grams/day | 6378 (15.4) | 5808 (11.7) | 5231 (9.5) | 2344 (10.5) | 1383 (14.4) |
| | 4–6 grams/day | 10,684 (25.8) | 14,085 (27.9) | 13,606 (24.6) | 5341 (23.9) | 2326 (24.3) |
| | ≥7 grams/day | 8235 (19.9) | 13,206 (26.2) | 15,690 (28.4) | 5924 (26.2) | 2041 (21.3) |
| History of hypertension | Yes | 17,535 (42.3) | 21,908 (43.4) | 23,646 (42.8) | 9651 (43.2) | 3925 (43.5) | 2350 (18.0) | <0.001 |
| History of diabetes | Yes | 33,577 (92.5) | 43,546 (93.1) | 53,907 (93.7) | 25,241 (93.1) | 1163 (92.4) |
| BMI | <18.5 kg/m² | 276 (0.7) | 343 (0.7) | 351 (0.6) | 117 (0.5) | 71 (0.7) | <0.001 |
| | 18.5–24.9 kg/m² | 15,630 (37.7) | 21,244 (42.1) | 21,807 (39.4) | 7543 (33.8) | 2996 (31.3) |
| | ≥30 kg/m² | 10,504 (25.3) | 10,484 (20.8) | 12,168 (22.0) | 5870 (26.3) | 2903 (30.3) |
| History of hyperension | No | 23,920 (77.7) | 28,562 (56.6) | 31,642 (57.2) | 12,677 (56.8) | 5666 (59.1) | <0.001 |
| | Yes | 17,555 (43.5) | 21,908 (43.4) | 23,646 (48.2) | 9651 (43.2) | 3920 (40.9) |
| History of diabetes | Yes | 39,639 (95.6) | 46,670 (96.4) | 53,409 (96.6) | 21,508 (96.3) | 9192 (95.9) | <0.001 |
| | Yes | 1816 (4.4) | 1800 (3.6) | 1797 (3.4) | 820 (3.7) | 394 (4.1) |

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

| Characteristics                  | Male | Female | *P* Value |
|----------------------------------|------|--------|-----------|
| **History of CKD**               |      |        |           |
| Yes                              | 8,812 (27.5) | 4,136 (22.0) | <0.001 |
| No                               | 28,420 (72.5) | 16,264 (78.0) |           |
| **History of cancer**            |      |        |           |
| Yes                              | 8,812 (27.5) | 4,136 (22.0) | <0.001 |
| No                               | 28,420 (72.5) | 16,264 (78.0) |           |
| **Testosterone (nmol/L)**        |      |        |           |
| Yes                              | 8,812 (27.5) | 4,136 (22.0) | <0.001 |
| No                               | 28,420 (72.5) | 16,264 (78.0) |           |
| **Caffeine metabolite (mM)**     |      |        |           |
| Yes                              | 8,812 (27.5) | 4,136 (22.0) | <0.001 |
| No                               | 28,420 (72.5) | 16,264 (78.0) |           |
| **SHBG (nmol/L)**                |      |        |           |
| Yes                              | 8,812 (27.5) | 4,136 (22.0) | <0.001 |
| No                               | 28,420 (72.5) | 16,264 (78.0) |           |

**Note:** Data were shown as median [IQR], n.

### 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 findings add 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, as well as reports about the causal effect of coffee on kidney function based on Mendelian randomization. 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. 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. 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. found that coffee consumption could only reduce the risk of end-stage renal disease in males. Compared with previous ones,
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. In BMA, coffee was inversely associated with renal dysfunction, which are all confirmed risk factors of CKD. Acting as a modulator of their bioactivity, SHBG may be involved in this gender difference. We observed their potential modifying 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 testosterone. The observed 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 causal role of sex hormones in the incidence and progression of CKD, especially in males. 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, which are all confirmed risk factors of CKD. 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    |                          |    |    |    |    |                  |                        |
| Female (n = 179,127)       |                          |    |    |    |    |                  |                        |
| No. of cases               | 903                      | 983 | 989 | 392 | 187 | 0.013            |                        |
| 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 | 0.018            |                        |
| 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)                  | 0.9 (0.8–1.1) | 0.97 (0.88–1.07) | 1 (0.88–1.13) | 0.98 (0.83–1.15) | 0.730 |                        |
| Genetic analysis cohort    |                          |    |    |    |    |                  |                        |
| Female (n = 124,659)       |                          |    |    |    |    |                  |                        |
| No. of cases               | 584                      | 690 | 717 | 288 | 136 | 0.018            |                        |
| 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 | 0.018            |                        |
| 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 (0.9–1.12) | 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, 1–10, 10–14, 15–19 and ≥20 grams per day], milk intake [none, <150, 150–299 and ≥300 ml per day], and tea intake [none, 1–3 and ≥4 cups per day]), anthropometric measurement (body mass index [<18.5, 18.5–24.9, 25.0–29.9 and ≥30.0 kg/m²]), 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, 1–3, 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 0.35 in the genetic analysis cohort.
androgenism in females.\textsuperscript{[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 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,\textsuperscript{[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...
has been identified.\textsuperscript{[99]} 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),\textsuperscript{[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 renoprotective 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 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. Clin Med J 2022;135:648–657. doi:10.1097/CMJ.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. Nordestro¨gaard AT, Thomsen M, Nordestro¨gaard BG. Coffee intake and risk of obesity, metabolic syndrome and type 2 diabetes: a Mendelian randomization study. Int J Epidemiol 2015;44:531–565. doi:10.1093/ije/dyv053.
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.113.059295.
6. Hu EA, Selvin E, Grams ME, Steffen LM, Coresh J, Reitholz 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, Jahar TF, Jin A, Yuan JM, Koh WP. Consumption of coffee but not of 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, Sirinopol D, Copur S, Tapoi I, 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;31:5–16. doi:10.1097/JRN.0000000000001581.
9. Kennedy OJ, Pirastu N, Poole R, Fallowfield JA, Hayes PC, Geraszkowik 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.2020.06.004.
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.2020.07.001.
11. Gaeini Z, Bahadoran Z, Mirravan 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/s12986-019-0331-6.
12. Wijarnpreecha K, Thongprayoon C, Thanawardhana 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/s12977-017-0252-y.
16. Hannan M, Ansari S, Meza N, Anderson AH, Sovastava A, Walker 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/JHJ.0b013e3282d2a850.
18. Palatini P, Benetti E, Mos L, Garavelli G, Mazzer A, Cozzo 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/s10654-015-9990-9.
19. Cornelis MC, El-Sohemy A, Kabagambe EK, Campos H, El-Sohemy A, et al. Coffee consumption and kidney function: a CYPIA2 genotype, and risk of myocardial infarction. JAMA 2006;295:1133–1141. doi:10.1001/jama.2006.11.135.
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 [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/btq359.
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/1009228519.

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. J Am Soc Nephrol 2021;32:686–694. doi: 10.1681/ASN.2020050659.

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.