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REVIEW ARTICLE

Alcohol intake and the risk of chronic kidney disease: results from a systematic review and dose–response meta-analysis

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Abstract

Many prospective cohort studies have investigated the association between the consumption of alcohol and CKD risk and have revealed inconsistent results. In the present study, we aimed to perform a meta-analysis of these studies to assess this association.We searched the PubMed and Embase databases up to 2020 and reviewed the reference lists of relevant articles to identify appropriate studies. We calculated the pooled relative risks with 95% CIs using random effects models, and then performed subgroup and meta-regression analyses. Dose–response meta-analyses were performed by sex separately. We identified 25 eligible prospective cohort studies, including 514,148 participants and 35,585 incident CKD cases. Compared with the category of minimal alcohol intake, light (RR = 0.90, I2 = 49%), moderate (RR = 0.86, I2 = 40%), and heavy (RR = 0.85, I2 = 51%) alcohol intake were associated with a lower risk of CKD. Subgroup meta-analysis by sex indicated that light (RR = 0.92, I2 = 0%), moderate (RR = 0.83, I2 = 39%) and heavy (RR = 0.76, I2 = 40%), alcohol consumption were inversely associated with CKD risk in male. Dose–response meta-analyses detected a nonlinear inverse association between alcohol consumption and the risk of CKD in all participants and linear inverse association in female participants. This meta-analysis shows that light (<12 g/day), moderate (12–24 g/day), and heavy (>24 g/day) alcohol consumption are protective against chronic kidney disease in adult participants especially in males.

Introduction

Chronic kidney disease (CKD) is an important cause of death worldwide [1–3]. According to the 2010 Global Burden of Disease study, CKD was ranked 18th on the list of causes of death globally and regarded as a part of the increasing global noncommunicable disease burden [4]. With the deterioration of kidney function, patients with end-stage renal disease (ESRD) have to receive expensive dialysis or transplant therapies [5]. Considering the probable poor outcome, constructing effective strategies to slow the progression of CKD is important.

Several factors, such as smoking, obesity, and type 2 diabetes, are considered risk factors for CKD [6]. Alcohol, the most common beverage worldwide, is consumed by almost 65% of Americans [7]. Since the 1990s, many observational studies from different countries have reported the association between alcohol consumption and CKD risk, but the results were not consistent [8, 9]. Although the previous meta-analysis summarized the association between heavy alcohol consumption and CKD risk, the potential links between light alcohol consumption, moderate alcohol consumption, used to drink alcohol, and CKD risk are still not very clear [10]. Moreover, the dose–response relationship between alcohol consumption and CKD risk has not yet been summarized in a meta-analysis.

To provide up-to-date summarized evidence of the association between alcohol consumption and CKD, we

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performed this systematic review and dose–response meta-analysis of prospective cohort studies to investigate the links between used to drink alcohol, light, moderate, and heavy alcohol consumption and CKD risk.

Methods

Search strategy and selection criteria

We performed this systematic review following the PRISMA guidelines [11]. Published relevant studies identified using PubMed (through January 11, 2020) and Embase (through January 11, 2020) describing the association between alcohol intake and kidney function were identified. The search strategy used the following MeSH terms and related extended versions: (1) "alcohol," or "alcohol drinking," or "ethanol"; (2) "kidney disease," or "kidney failure," or "chronic kidney disease," or "chronic kidney failure," or "hemodialysis"; (3) "glomerular filtration rate," or "GFR," or "creatinine or proteinuria, or microalbuminuria"; (4) "humans"; and (5) "cohort," or "case-control," or "cross-sectional." In addition, we searched the reference lists of included articles and relevant reviews. The search was limited to the English language.

Two investigators (HCY and QTY) independently assessed the titles, abstracts, and full texts for eligibility, and discussion or a third person resolved discrepancies. We included studies in this review if the report was a prospective cohort study conducted with adults without kidney dysfunction at baseline, which evaluated the association of the risk of CKD, ESRD, proteinuria, or eGFR decline with alcohol intake; the report provided the amount of alcohol consumption and odds ratios (ORs) or relative risks (RRs) or hazard ratios (HRs) with 95% confidence intervals (CI) for all categories of alcohol consumption. Only full texts published in English were included. We excluded duplicated studies, studies for which we could not extract or calculate the amount of alcohol consumed and adjusted RRs, and studies with follow-up periods of less than 3 years.

Data extraction and quality assessment

We extracted the following information from each eligible study using a predesigned form: (1) first author, (2) year of publication, (3) country, (4) study design, (5) follow-up length, (6) diagnostic criteria for CKD, (7) characteristics of participants (age distribution, sex), (8) sample size, (9) adjusted outcomes (OR, RR, HR) with their 95% CIs for all categories of alcohol consumption, and (10) adjusted covariates.

We used the Newcastle–Ottawa scale to assess the quality of each study, which considered the selection of cohorts, comparability of cohorts, and the ascertainment of the exposure and outcome of interest. The Newcastle–Ottawa scale is a validated tool for meta-analysis of cohort studies [12]. Overall, the scale awards a maximum of nine points for study quality, with a higher score indicating higher quality.

Statistical analysis

To pool the study-specific RRs, alcohol intake in g/day was used to standardize alcohol consumption across the studies. If alcohol intake was given in the number of drinks per week, we divided the number by 7. We used the reported information if a study reported the relationship between one drink and the amount of alcohol to change "drinks" into "grams of alcohol," unless the assumption that one drink contains 12 g of ethanol was used. When the median amount was not indicated, we assigned the midpoint of the upper and lower boundaries as the estimated mean alcohol intake. When the lowest or the highest group was open-ended, we set the lowest and highest groups to the lowest boundary/1.5 and highest boundary × 1.5 respectively. Finally, we divided nonreference groups of studies into three categories based on alcohol intake: low (0–12 g/day), moderate (12–24 g/day), and heavy (>24 g/day). In the analysis of alcohol intake and CKD risk, the lowest dose of each study was used as the reference group. For studies reporting ORs as association measures, $RR = OR/((1 - P_0) + P_0 \times OR)$ was used to transfer ORs into RRs [13]. P_0 indicates the incidence of the outcome of interest in the reference group.

DerSimonian and Laird inverse variance weighted random effects models were applied to combine the RRs and 95% CIs according to the three above categories and the category of former alcohol consumers compared with the reference group [14]. If a study reported that at least one RR fell into one of three categories, summary RRs and 95% CIs of those studies were calculated before inclusion in the meta-analysis. We conducted meta-regression and stratified analysis to assess the possible source of heterogeneity based on age, sex, geographic area (Western country: America, Europe countries, and Australia; Eastern country: Japan and China), duration of cohort follow up, and CKD stage (CKD stages I–V or ESRD only) [15]. Moreover, we performed sensitivity analysis by removing studies that the diagnosis of CKD did not based on eGFR.

To evaluate the dose–response association between alcohol consumption and CKD risk, we used the robust error meta-regression (REMR) method as described by Xu and Doi, which is a "one-stage" procedure that does not require any knowledge of regression coefficients [16]. For nonlinear associations, we first estimated a restricted

cubic spline model and then used REMR analysis to get parameters [17]. $P \le 0.05$ was used to test the nonlinearity trend. We estimated the predicted RRs by comparing specific levels of alcohol consumption based on a nonlinear or linear model, as appropriate. A detailed explanation and Stata codes can be seen in the article proposed by Xu and Doi.

Heterogeneity between studies was investigated by using I^2 statistic (higher values indicate greater heterogeneity). Publication bias was assessed by the use of qualitative visual inspections of funnel plots [18]. Statistical analyses were conducted with two-tailed tests, and $P \le 0.05$ was considered statistically significant. All statistical analyses were performed using STATA 12.0 (StataCorp, College Station, TX, USA).

Results

Study characteristics

Figure 1 shows a flow diagram of the study selection process. We identified 4133 citations from the two databases. An additional four articles were identified from manual searches and the references of the included studies and one meta-analysis. Finally, 25 prospective cohort studies published from 2003 to 2019, including 514,148 participants (246736 males and 267412 females) and 35,585 incident CKD cases, were eligible for inclusion in the meta-analysis. Six studies were conducted in the USA [19–24], five in Europe [25–27], eleven in Asia [28–36], two in Australia [37], and one study was conducted in 40 countries [38]. The sample size ranged from 530 to 155,256, and the follow-up period was 3–24 years. Ten studies included men only [25, 27–30, 33, 34, 36], four included women only [20, 27, 33, 34], and the others included both men and women [19, 21–24, 26, 31, 32, 35, 37, 38]. Among the three different alcohol consumption categories, 17 studies [19–21, 23–27, 33–36, 38], 14 studies [21, 23–28, 33, 34, 37], and 17 studies [19, 20, 22, 24, 26–33, 36, 37] were included in the light, moderate, and heavy drinking categories, separately. In addition, six studies were included in the analysis of the association between used to drink alcohol and CKD risk [19, 22, 24, 27, 29]. The NOS was applied to evaluate the quality of the studies. Overall, 16 studies scored 9, 7 studies scored 8, and 2 studies scored 7. The characteristics of the included studies and the results of the quality assessment are shown in Table 1.

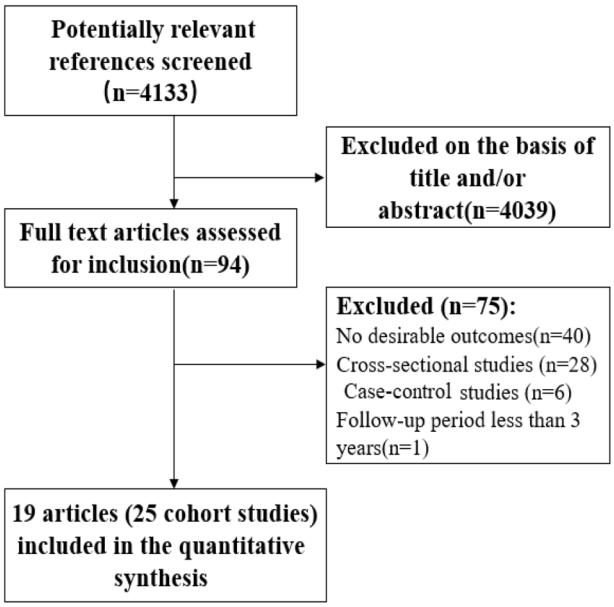

Fig. 1 Flow diagram of the literature search and study selection.

Overall and stratified analysis

The pooled results for CKD based on different alcohol consumption categories compared with the reference category are shown in Fig. 2. The pooled RRs of CKD for light, moderate, and heavy alcohol consumption were 0.90 (95% CI 0.85, 0.95; $I^2 = 49\%$), 0.82 (95% CI 076, 0.89; $I^2 = 40\%$), and 0.83 (95% CI 0.74, 0.92; $I^2 = 51\%$), respectively. Visual inspection of the funnel plots revealed that there was no indication of obvious publication bias (see in Fig. 3). Sensitivity analyses were performed for light, moderate, and heavy alcohol consumption by excluding studies in which CKD diagnosis was not based on GFR. After excluding these five studies, the conclusions were not affected. Furthermore, after five studies were pooled together, there was no significant association between used to drink alcohol and incident CKD risk (pooled RR = 1.07, 95% CI 0.82, 1.38; $I^2 = 51\%$).

The results of stratified analyses performed according to sex, age group, geographic area, and follow-up period were shown in Table 2. As presented in Table 2, we noted significant lower risks of incident CKD only in males with light (≤12 g/day), moderate (12–24 g/day), and heavy alcohol (≥24 g/day) consumption when stratified by sex (pooled RR = 0.92, 0.83, and 0.78). When stratified by the mean age of participants at baseline (<50 years old, 50–60 years old, >60 years old), the significant lower risk of incident CKD of light alcohol consumption in participants older than 60 years old disappeared (pooled RR = 0.93, 95% CI 0.80, 1.07, $I^2 = 78\%$). This nonsignificant relationship was also seen in participants with heavy alcohol consumption who were older than 60 years (pooled RR = 1.00, 95% CI 0.80, 1.24, $I^2 = 44\%$). Light, moderate, and heavy alcohol consumption were inversely associated with the risk of CKD in studies conducted in Eastern countries (Japan and China). In an analysis stratified by follow-up

Table 1 Characteristics of prospective studies of alcohol consumption and risk of incident CKD.

Study	Country	Follow-up, year	CKD criteria	Sex	Sample size/case (*n*)	Categories of highest vs minimal alcohol consumption	Adjusted factors	NOS score
Shankar et al. [22]	USA	5	GFR < 60 mL/min/1.73 m^2	F/M	3392/114	≥4 servings per day vs <4 servings per day Former drinker vs never	Age, sex, education, BMI, current nonsteroidal anti-inflammatory use, hypertension, diabetes, history of cardiovascular disease, smoking status	9
Schaeffner et al. [25]	Germany	14	GFR < 55 mL/min/1.73 m^2	M	11,023/1296	≥7 drinks/week vs ≤1 drinks/week	Age, body mass index, smoking, physical exercise, diabetes mellitus at baseline, a parental history of myocardial infarction before age 60 years, randomized treatment assignment, self-reported history of hypertension at baseline, the development of hypertension, diabetes mellitus, or cardiovascular disease during follow-up, a history of elevated cholesterol levels at baseline	8
Schaeffner et al. [25], second	Germany	14	Creatinine ≥ 133 μmol/L	M	11,023/473	≥7 drinks/week vs ≤1 drinks/week	Age, body mass index, smoking, physical exercise, diabetes mellitus at baseline, a parental history of myocardial infarction before age 60 years, randomized treatment assignment, self-reported history of hypertension at baseline, the development of hypertension, diabetes mellitus, or cardiovascular disease during follow-up, a history of elevated cholesterol levels at baseline	8
Stengel et al. [23]	USA	12–16	ESRD or death related to CKD	F/M	9082/189	≥7 drinks/week vs never	Physical activity, smoking, alcohol and body mass index, age, sex, race, diabetes, cardiovascular disease, hypertension, systolic blood pressure, and S-cholesterol	9
Dunkler et al. [38]	40 countries	5.5	New microalbuminuria or macroalbuminuria or GFR decline of more than 5% per year or ESRD	F/M	6213/1971	≥5 drinks/week vs <5 drinks/week	Age, duration of type 2 diabetes mellitus, albuminuria status, glomerular filtration rate, sex, ongoing telmisartan alone, and in combination with ramipril global endpoint trial randomization arms, and urinary albumin–creatinine ratio to progression	8
Qin et al. [35]	China	7.13	A sustained decline in GFR of more than 5 mL/min/1.73 m^2/year or a drop in the GFR category accompanied by a 25% or greater drop in eGFR from baseline	F/M	2518/218	>1 drinks/week vs ≤1 drinks/week	Sex, age, smoking, obesity or abdominal obesity, blood pressure, mean blood pressure, fasting blood glucose, total cholesterol, triglycerides, HDL cholesterol, self-reported health status, education, physical activity, eGFR	9

Table 1 (continued)

Study	Country	Follow-up, year	CKD criteria	Sex	Sample size/case (*n*)	Categories of highest vs minimal alcohol consumption	Adjusted factors	NOS score
Reynolds et al. [28]	China	8–9	ESRD	M	65601/176	≥21 drinks/week vs ≤1 drink/week	Age, geographic region, urbanization, education, body mass index, physical activity, and cigarette smoking, systolic blood pressure, history of diabetes and cardiovascular disease, and stratified by sampling clusters	8
Ryoma et al. (2016) [29]	Japan	4.9	GFR < 60 mL/min/1.73 m^2, proteinuria positive [1+ or greater], or both	M	258/17	≥7 drinks/week vs <never Former drinker (used to drink) vs never drinker	Age, BMI, waist circumference, blood pressure, LDL-C, HbA1c, and eGFR levels	8
Kanda et al. [30]	Japan	At least 3	CKD or decrease in GFR by >25% in 3 years	M	3910/1366	>7 drinks/week vs <1 drinks/week	Age, sex, BMI, eGFR, urinary protein excretion, comorbid conditions of diabetes mellitus, hypertension and dyslipidemia, histories of CVDs, smoking	7
Kanda et al. [30], second	Japan	At least 3	CKD or decrease in estimated glomerular filtration rate (eGFR) by >25% in 3 years	M	1662/555	>7 drinks/week vs <1 drinks/week	Age, sex, BMI, eGFR, urinary protein excretion, comorbid conditions of diabetes mellitus, hypertension and dyslipidemia, histories of CVDs, smoking	7
Nakanishi et al. (2012) [32]	Japan	7.7	GFR < 60 mL/min/1.73 m^2	F/M	1811/339	≥7 drinks/week vs <7 drinks/week	Age, sex, smoking, BMI, SBP, fasting plasma glucose, total cholesterol, uric acid, total leukocyte count, proteinuria, CKD stages I and II, urine pH	9
Yamagata et al. [33]	Japan	10	GFR < 60 mL/min/1.73 m^2	M	41,012/4257	Ethanol > 20 g/day vs never	Age, creatine, education, BMI, hypertension, estimated GFR, proteinuria, hematuria, impaired glucose tolerance, diabetes, total cholesterol, HDL-C, triglyceride, smoking status	9
Yamagata et al. [33], second	Japan	10	GFR < 60 mL/min/1.73 m^2	F	82,752/15,154	Ethanol > 20 g/day vs never	Age, creatine, education, BMI, hypertension, estimated GFR, proteinuria, hematuria, impaired glucose tolerance, diabetes, total cholesterol, HDL-C, triglyceride, smoking status	9
Menon et al. [19]	USA	5.6	Annual GFR loss > 3 mL/min/1.73 m^2/year	F/M	4005/406	≥14 drinks/week vs never Former drinker(used to drink) vs never	Age, sex, race, smoking, diabetes, systolic blood pressure, diastolic blood pressure, antihypertensive medications, LDL-C, HDL-C, prevalent cardiovascular disease, prevalent heart failure, C-reactive protein and fibrinogen	8

Table 1 (continued)

Study	Country	Follow-up, year	CKD criteria	Sex	Sample size/case (*n*)	Categories of highest vs minimal alcohol consumption	Adjusted factors	NOS score
Foster et al. [21]	USA	6.6	GFR < 60 mL/min/1.73 m^2	F/M	1802/171	>7 drinks/week or >14 drinks/week vs never	Listed lifestyle factors, age, sex, baseline eGFR, BMI, hypertension, diabetes, and dipstick proteinuria	9
Knight et al. [20]	USA	11	A decline in GFR ≥ 30%	F	1658/177	≥15 and <60 g/day vs never	Age, body mass index, protein intake, hypercholesterolemia, diabetes, hypertension, and smoking status	8
Koning et al. [26]	Dutch	10.2	GFR under 60 mL/min per 1.73 m^2 and/or the mean of two consecutive 24-h urinary albumin excretions over 30 mg	F/M	5476/903	>210 g/week vs never	Age, sex, height, weight, smoking status, parental history of CKD, history of cardiovascular disease, and educational level. Potential mediators were homeostatic model assessment-insulin resistance, use of glucose-lowering drugs, ratio of total to high-density lipoprotein cholesterol, use of lipid-lowering drugs, systolic blood pressure, and use of blood pressure-lowering drugs	9
Nagai et al. [34]	Japan	10	Positive for proteinuria by consecutive annual urinalysis	M	81,854/1119	>20 g/day vs never	Age, BMI, hypertension, diabetes, GFR, LDL cholesterol, HDL cholesterol, total cholesterol, triglyceride, smoking	9
Nagai et al. [34], second	Japan	10	Positive for proteinuria by consecutive annual urinalysis	F	15,5256/957	>20 g/day vs never	Age, BMI, hypertension, diabetes, GFR, LDL cholesterol, HDL cholesterol, total cholesterol, triglycerides, smoking	9
Buja et al. [27]	Italy	3.5	GFR < 60 mL/min/1.73 m^2	F	530/123	25-47 g/day vs never Former drinker (used to drink) vs never drinker	Age, education, smoking, BMI and medications, blood cholesterol and fibrinogen, systolic hypertension, and diabetes	9
Buja et al. [27], second	Italy	3.5	GFR < 60 mL/min/1.73 m^2	M	795/91	≥48 g/day vs never Former drinker (used to drink) vs never drinker	Age, education, smoking, BMI and medications, blood cholesterol and fibrinogen, systolic hypertension, and diabetes	9
White et al. [37]	Australia	5	GFR < 60 mL/min/1.73 m^2	F/M	5807/451	≥30 g/day vs <10 g/day	Age, education, smoking, BMI and medications, blood cholesterol and fibrinogen, systolic hypertension, and diabetes	9
White et al. [37], second	Australia	5	Proteinuria, a doubling of ACR over 5 years with a final ACR ≥ 2.5 in males and ≥3.5 mg/mmol in females	F/M	5923/168	≥30 g/day vs <10 g/day	Age at baseline, sex, natural logarithm of baseline albumin–creatine ratio, blood pressure, diabetes, HbA1c, smoking, physical activity category, waist-to-hip ratio	9

Table 1 (continued)

Study	Country	Follow-up, year	CKD criteria	Sex	Sample size/case (*n*)	Categories of highest vs minimal alcohol consumption	Adjusted factors	NOS score
Hu (2020) [24]	USA	24	GFR < 60 mL/min/1.73 m^2 accompanied by 25% eGFR decline	F/M	12,692/3664	>15 drinks/week vs never	Age, sex, race, income, education level, health insurance, smoking, and physical activity, total energy intake, diabetes status, hypertension status, body mass index, and baseline estimated glomerular filtration rate	9
Okada et al. [36]	Japan	11	GFR < 60 mL/min/1.73 m^2	M	9116/1230	≥46.1 g/day vs never	Age, BMI, systolic blood pressure, diastolic blood pressure, fasting plasma glucose, smoking habits, eGFR at baseline, and regular leisure-time physical activity	9

period, light, moderate, and heavy alcohol consumption were all associated with lower CKD risk when follow-up period are more than 10 years. When studies about ESRD were removed, the results favoring alcohol consumption did not change.

Moderate alcohol consumption was associated with lower CKD risk when the duration was longer than 5 years. Light alcohol consumption was inversely associated with CKD risk when the follow-up period was greater than 10 years (pooled RR = 0.86, 95% CI 0.81, 0.91, $I^2 = 0$). Meta-regression analysis showed that the area (meta-regression: $\beta = 0.19$, 95% CI 0.18–0.3, $P = 0.016$) and follow-up period (meta-regression: $\beta = -0.16$, 95% CI −0.26 to −0.06, $P = 0.036$) may be the sources of heterogeneity among participants with moderate alcohol consumption.

Dose–response analysis

A dataset containing categorically reported RRs and corresponding alcohol consumption levels was extracted from 24 studies, in which alcohol consumption levels ranged from 0 g/day to ~69 g/day. A restricted cubic spline was created (with three knots at 0, 7.5, and 37.82 (g/day)), which generated two splines, and those were employed for the nonlinear dose–response modeling. With the REMR method, the estimated regression parameters (slopes $b_1 = 0.98$, $b_2 = 1.02$, test for equality of slopes $P = 0.0026$) were found to differ significantly, suggesting a nonlinearity association (see Fig. 4). Compared with the reference group, the estimated RRs of CKD were 0.90 (95% CI 0.86–0.95) for 10 g/day, 0.84 (95% CI 0.78–0.90) for 30 g/day, and 0.85 (95% CI 0.78–0.93) for 60 g/day. Similar analyses performed in male and female studies separately. In the male and female studies, nonlinear (male) and linear (female) models were used for predicting the dose-specific RRs of alcohol intake (see in Fig. 4). Compared with the reference group, the estimated RRs of CKD in male participants were 0.90 (95% CI 0.83–0.97) for 10 g/day, 0.82 (95% CI 0.74–0.91) for 30 g/day, and 0.78 (95% CI 0.70–0.86) for 70 g/day. Compared with the reference group, the estimated RRs of CKD in female participants were 0.98 (95% CI 0.96–1.00) for 7 g/day, 0.97 (95% CI 0.94–0.99) for 10 g/day, and 0.90 (95% CI 0.83–0.98) for 30 g/day.

Discussion

The pooled results of prospective cohort studies revealed an inverse association between alcohol consumption and the risk of CKD, with 10, 14, and 15% lower risks observed in adult participants with light, moderate, and

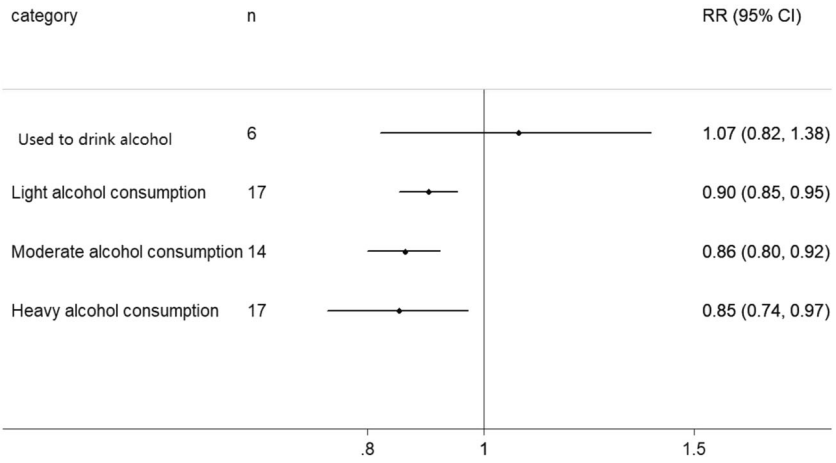

Fig. 2 Overall relative risks (RRs) with 95% confidence intervals (CIs) of CKD for light alcohol consumption (0–12 g/day), moderate alcohol consumption (12–24 g/day), heavy alcohol consumption (>24 g/day), and used to drink alcohol compared with reference groups. *n*: number of included studies.

heavy alcohol consumption, respectively. This meta-analysis also showed that used to drink alcohol was not associated with a significantly increased CKD risk. Dose–response meta-analyses revealed a nonlinear inverse association between alcohol consumption and the risk of CKD in all participants and linear inverse associations in female participants.

A previous meta-analysis studying the association between high alcohol consumption and CKD risk also reported that high alcohol consumption may prevent the incidence of CKD [10]. However, as for study design, the included studies are different—cross-sectional, case–control, and only nine cohort studies published through 2014 were pooled together. Since then, the results of several cohort studies have been reported [21, 26, 29]. Retrospective studies may result in recall and selection biases, and cross-sectional studies cannot be used for inferring causality. Those low-quality studies finally resulted in a pooled result with great heterogeneity ($I^2 = 73\%$). In that analysis, Cheungpasitporn et al. only reported that the association between heavy alcohol consumption and CKD varied significantly by sex, and heterogeneity remained in the male subgroup. In contrast, this study reported stratified analysis based on age, sex, geographic area, follow-up period, and the results of the dose–response analysis.

Compared with other meta-analyses about alcohol consumption and illness, our result that alcohol consumption was not a risk factor for CKD is interesting. The results from a meta-analysis suggested that heavy alcohol consumption was a risk factor for cardiovascular events [39]. A study about heart failure (HF) showed that only light alcohol consumption was associated with a decreased risk of HF [40]. The biological mechanisms of the protective effect of alcohol on CKD are not fully understand, but some pieces of evidence may explain this interesting phenomenon. Some researchers believe that the benefit may be brought by the increase in serum HDL [30, 41, 42]. One prospective study reported that low HDL cholesterol increased CKD risk [43]. Alcohol intake, to some extent, plays a role in increasing the levels of HDL. Of the included studies, the PREVEND cohort study also indicated a positive association between occasional to heavier alcohol consumption categories and serum HDL levels [26], and only two included articles adjusted for HDL in covariate analyses when report adjusted RRs [33, 35], so the protective effect of improved HDL levels on kidney function in our study is reasonable. However, the majority participants in articles studying the association between alcohol intake and HDL levels were male; however, such an effect should be considered seriously in women. Another mechanism may be mediated by plasminogen activator inhibitor-1, which facilitates extracellular matrix accumulation and finally worsens renal function [44]. Mukamal et al. reported that compared with nondrinkers, plasminogen activator inhibitor-1 levels were lower in moderate drinkers [44]. In addition, the positive influences of alcohol on antioxidant enzymes, atherosclerosis, insulin sensitivity, and renal arteriolar hyalinization may also affect kidney function [45–50].

When stratified by sex, we noted that significant inverse associations, between light, moderate, and high alcohol consumption and CKD risk, disappeared in the female subgroup. In the following dose–response analysis, the beneficial alcohol dose in male participants was also higher than that in female participants. In the AusDiab study, only moderate-heavy alcohol intake in men, rather than women, was protective against CKD incidence [37]. Buja et al. reported an inverse linear relationship in men and a "U-shaped" relationship in women, which also indicated that men were not prone to developing renal impairment when drinking more than 24 g alcohol per day. They speculated that the difference in metabolizing alcohol was possibly due to the sex-related differences in total fluid distribution volume, lean body mass, and the activity of the enzymes

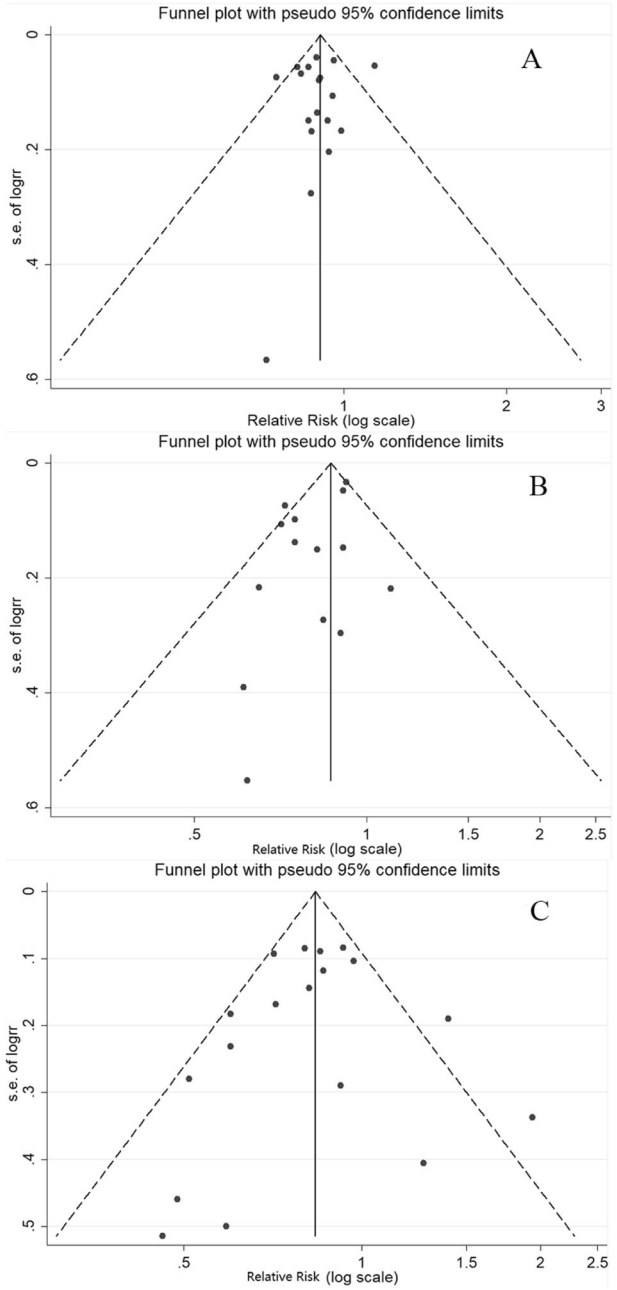

Fig. 3 Funnel plots of publication bias. A: Light alcohol consumption. **B**: Moderate alcohol consumption. **C**: Heavy alcohol consumption.

that process alcohol in the liver [27, 51]. However, Koning et al. reported a conflicting result that an inverse association between light or moderate alcohol consumption and CKD risk was only observed in females (the mean age of participants at baseline was less than 50 years old). In Buja et al.'s study, the mean age of participants at baseline was more than 70 years [27]. There is no doubt that there are lower sex hormone levels among old people. The discrepancies may be explained by the differences in estrogen and testosterone levels. Estradiol may have protective effects on the renal and cardiovascular systems, and testosterone may have the opposite effect by promoting the apoptosis of proximal tubule kidney cells [52, 53]. Moreover, it has been reported that alcohol consumption could increase estrogen levels among women, and decreased testosterone levels were also reported in male animal models [54, 55].

When stratified by the age group of participants at baseline, the results indicated that the protective effect of alcohol consumption might be weaker in older participants (more than 60 years old). In a Dutch cohort, heavy alcohol consumers may have been protected against CKD when their baseline age was less than 58 years old [26]. However, the Chinese survey reported that only heavy alcohol consumption was a risk factor for CKD in participants older than 60 years [28]. Few studies have explored this difference, so these results should be interpreted cautiously.

In current study, a stratified analysis was also conducted according to geographic area and compared these associations in Eastern and Western groups. The Eastern country subgroup only included Japanese and Chinese cohort studies. We concluded that Chinese and Japanese alcohol consumers might obtain the more beneficial effects from light and heavy alcohol consumption than European and American participants. This difference may partly result from a variety of genetic influences related to the metabolism of alcohol. Previous researchers indicated that in Asian populations, the prevalence of certain genetic variants encoding the alcohol-metabolizing enzymes alcohol dehydrogenase (*ADH*), and acetaldehyde dehydrogenase 2 (*ALDH2*) is higher than that in other US racial/ethnic groups [56, 57]. The *ADH1B*2* allele, which was thought to encode enzymes that oxidize alcohol at an increased rate, was found in 80% or more of northeast Asians such as Chinese and Japanese individuals, but only in 10% or less of Caucasians of European ancestry [58–60]. The *ALDH2*2* allele was found almost exclusively in northeastern Asians [61]. The *ALDH2*2* allele may make individuals more vulnerable to alcohol-related pathologies because of increased acetaldehyde, but some people think the influence of this gene variant seems to change over the course of alcohol consumption [60]. Until now, there have been no multiethnic cohort studies comparing the effect of alcohol on CKD risk among participants of different ethnicities.

Our meta-analysis has two major strengths. First, only prospective cohort studies were included to eliminate recall bias. Compared with previous meta-analyses, more cohorts were included, which gave us more statistical power to draw a more precious conclusion. Second, the dose–response meta-analysis was conducted in the REMR method, which

Table 2 Stratified analysis of alcohol consumption and risk of incident CKD.

	Light alcohol consumption (≤12 g/day)			Moderate alcohol consumption (12–24 g/day)			Heavy alcohol consumption (>24 g/day)		
	N	RR 95% CI	Heterogeneity I^2	*N*	RR 95% CI	Heterogeneity I^2	*N*	RR 95% CI	Heterogeneity I^2
Overall results	15	0.90 (0.85, 0.95)	49%	13	0.86 (0.76, 0.89)	40%	15	0.85 (0.74, 0.92)	51%
Subgroup analysis									
Sex									
Male	6	0.92 (0.87, 0.96)	0	6	0.83 (0.73, 0.94)	39%	6	0.78 (0.68, 0.89)	34%
Female	3	0.89 (0.74, 1.08)	0	2	0.90 (0.79, 1.03)	3%	4	0.86 (0.73, 1.01)	0
Male and female	6	0.89 (0.79, 1.00)	77%	5	0.76 (0.68, 0.84)	0	5	0.90 (0.70, 1.18)	79%
Age group									
<50 years old	2	0.86 0.78, 0.95)	0	4	0.81 (0.68, 0.96)	16%	6	0.80 (0.69, 0.92)	55%
50–60 years old	7	0.88 (0.83, 0.92)	0	5	0.79 (0.69, 0.89)	51%	4	0.76 (0.66, 0.89)	1%
>60 years old	6	0.93 (0.80, 1.07)	78%	4	0.92 (0.86, 0.98)	0	5	1.00 (0.80, 1.24)	44%
Geographic area									
Western country	10	0.90 (0.82, 0.99)	59%	9	0.75 (0.69, 0.82)	0	8	0.90 (0.72, 1.12)	65%
Eastern country	5	0.92 (0.87, 0.97)	0	4	0.91 (0.87, 0.96)	0	7	0.80 (0.73, 0.89)	21%
Follow-up period									
≤5 years	2	0.84 (0.52, 1.37)	0	4	0.86 (0.68, 1.07)	0	8	0.88 (0.65, 1.19)	65%
			72%						31%
5–10 years	8	0.93 (0.85, 1.03)	0	5	0.91 (0.86, 0.96)	0	5	0.88 (0.76, 1.00)	2%
>10 years	5	0.86 (0.81, 0.91)	54%	4	0.73 (0.66, 0.84)	0	2	0.77 (0.69, 0.85)	51%
			–						–
CKD stage									
CKD stages I–V	14	0.92 (0.85, 0.98)		11	0.83 (0.76, 0.90)	23%	14	0.86 (0.75, 0.99)	
ESRD	1	0.87 (0.63, 1.21)		2	0.73 (0.52, 1.02)	0	1	0.51 (0.29. 0.88)	

required no knowledge of the correlation structure [16]. Compared with traditional generalized least squares for trend estimation (glst) method (the number of participants and cases in different levels is necessary), when original articles did not provide such information, REMR method may provide more accurate results because we did not need to estimate the number of participants and cases in different alcohol dose groups crudely.

Several limitations of our study should also be illustrated. First, because alcohol consumption in all the included studies was determined by a questionnaire, the results may be influenced by reporting bias, especially for women or heavy alcohol consumers. Second, the different scales of reporting used for alcohol consumption makes it difficult to obtain the accurate alcohol intake. Third, the mean number of drinks per alcohol consumption occasion could decline with age, and although many studies reported follow-up investigations, the change in alcohol consumption with time was an inevitable occurrence [62]. Fourth, no information was obtained on alcohol type, so we cannot analyze the associations between beer, red wine, or other alcoholic beverages and CKD incidence separately. Animal trials have indicated that polyphenols in red wine may be protective against kidney disease [63]. Fifth, although alcohol is allowed to be sold to persons more than 21 years, many drinking behaviors are initiated in adolescence [64]. From this perspective, stratified analysis based on the follow-up period in our study is meaningless. Finally, this study was not registered in PROSPERO, so small publication bias or reporting bias may not be avoided.

In conclusion, our meta-analysis shows that light (<12 g/day), moderate (12–24 g/day), and heavy (>24 g/day) alcohol consumption are protective against CKD in adult participants especially in males. As for race, heavy alcohol consumption may bring protective effect in eastern country participants. In participants more than 60 years old, the protective effect of heavy alcohol consumption disappeared. Future research should focus on special subpopulations (i.e., old males, old females, and multiethnic drinkers) to provide more precious recommendations for public health and disease prevention.

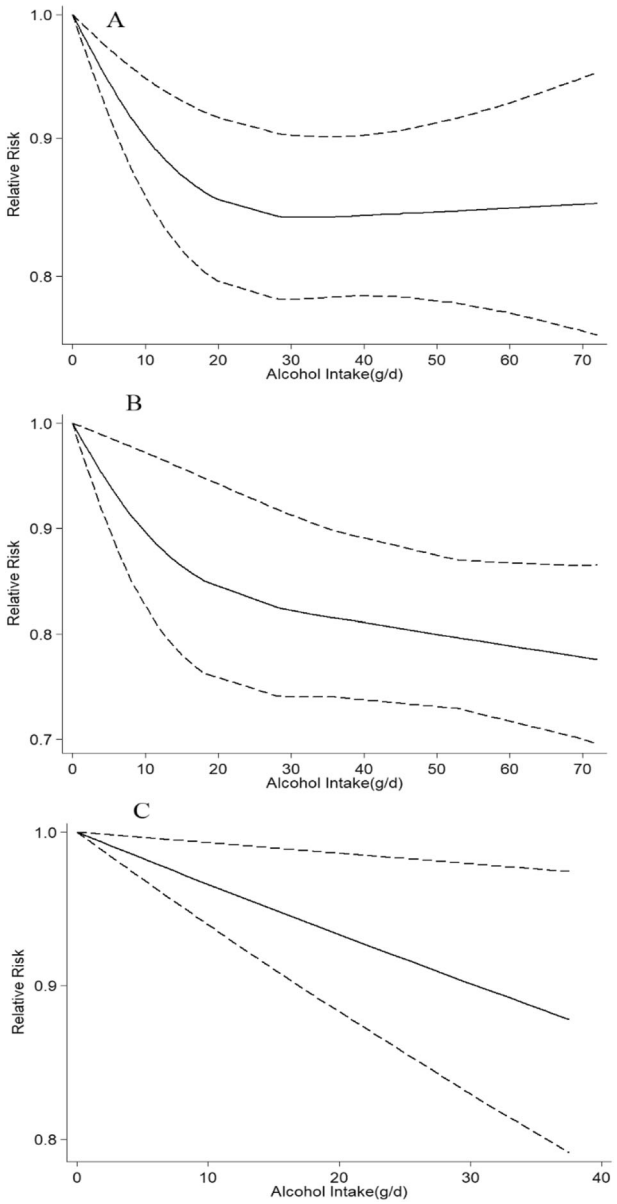

Fig. 4 Dose-response relationships between alcohol consumption and RRs of chronic kidney disease in all cohorts (**A**), in men (**B**), and in women (**C**). A: All cohorts pooled together. B: cohorts of men. C: Cohorts of women. Solid line: The dose-response relationship for the association between alcohol intake and risk of CKD as estimated by a robust error meta-regression method trend estimation. Dashed lines represent the 95% CIs for the model. Alcohol intake was modeled with a restricted cubic spline in a nonlinear (**A** and **B**) and a linear (**C**) dose-response model. The RRs are plotted on the log scale. No alcohol intake served as the referent category.

The mechanisms underlying those effects also should be systematically explored.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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