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Title page

Title: High Alcohol Consumption and The Risk of Renal Damage: A Systematic Review and Meta-analysis

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Abstract

Background: The risk of renal damage in patients with high alcohol consumption is controversial. The objective of this meta-analysis was to evaluate the associations between high alcohol consumption and progression of kidney damage including chronic kidney disease (CKD), end stage renal disease (ESRD), and proteinuria.

Methods: A literature search was performed using MEDLINE, EMBASE, and Cochrane Databases from inception through August 2014 to identify studies investigating the association between high alcohol consumption and CKD, ESRD or proteinuria. Studies that reported odds ratios, relative risks or hazard ratios comparing the risk of CKD, ESRD or proteinuria in patients consuming high amount of alcohol versus those who did not consume alcohol were included. Pooled risk ratios (RR) and 95% confidence interval (CI) were calculated using a random-effect, generic inverse variance method.

Results: Twenty studies with 292,431 patients were included in our analysis to assess the associations between high alcohol consumption and progression of kidney damage. The pooled RRs of CKD, proteinuria and ESRD in patients with high alcohol consumption were 0.83 (95% CI 0.71-0.98), 0.85 (95% CI 0.62-1.17) and 1.00 (95% CI, 0.55-1.82), respectively. Post hoc analysis assessing the sex-specific association between high alcohol consumption and CKD demonstrated pooled RRs of 0.72 (95% CI 0.57-0.90) in males and 0.78 (95% CI 0.58-1.03) in females.

Conclusions: Our study demonstrates an inverse association between high alcohol consumption and risk for developing CKD in males. There is no significant association between high alcohol consumption and the risk for developing proteinuria or ESRD.

Introduction

Chronic kidney disease (CKD) is an important problem worldwide. Over 20 million people in the United States were estimated to have CKD, and prevalence worldwide is estimated at 8-16%.[1] Moreover, the rising incidence of end-stage renal disease (ESRD) is currently a public health crisis worldwide.[2] Studies have demonstrated that worsening protienuria is associated with progression of CKD to ESRD.[3]

Several factors, including increasing rates of diabetes mellitus (DM) and population aging have contributed to a rise in prevalence of CKD.[4] Alcohol, one of the most commonly used substances worldwide, has been raised as a potential cause of kidney damage, as studies have shown that excessive alcohol consumption is associated with hypertension (HTN), one of the major risk factors for CKD.[5] However, the reported risk of renal damage including CKD, ESRD and proteinuria in patients with high alcohol consumption is still conflicting. Several studies have demonstrated that heavy alcohol drinking is associated with CKD, ESRD and proteinuria.[6-8] In the American population, high alcohol consumption of more than 2 drinks per day was shown to increase the risk of ESRD.[8] Conversely, a number of studies have shown no associations between heavy alcohol drinking and CKD, ESRD and proteinuria.[9-17] In addition, a few studies have shown that high alcohol consumption is inversely associated with CKD[12, 18-22], ESRD[23] and proteinuria.[11, 21]

The objective of this meta-analysis was to evaluate the associations between high alcohol consumption and progression of kidney damage including CKD, ESRD and proteinuria.

Methods

Search strategy

Two investigators (W.C. and C.T.) independently searched published studies indexed in MEDLINE, EMBASE , Cochrane Database of Systematic Reviews, Cochrane Central

Register of Controlled Trials and clinicaltrials.gov from inception through August 2014 using the search strategy described in **Item S1** (provided as online **supplementary data**). A manual search for additional relevant studies using references from retrieved articles was also performed.

Inclusion criteria

The inclusion criteria were as follows: (1) randomized controlled trials (RCTs) or observational studies (case-control, cross-sectional or cohort studies) published as original studies to evaluate the risk of CKD, proteinuria and ESRD in patients with high alcohol consumption, (2) odds ratios, relative risks, hazard ratios or standardized incidence ratio with 95% confidence intervals (CI) were provided, and (3) a reference group composed of participants who did not consume alcohol.

Study eligibility was independently determined by the two investigators noted above. Differing decisions were resolved by mutual consensus. The quality of each study was independently evaluated by each investigator using Newcastle-Ottawa quality assessment scale[24] for observational studies and Jadad quality assessment scale[25] for RCTs.

Data extraction

A standardized data collection form was used to extract the following information: last name of the first author, study design, year of study, country of origin, year of publication, sample size, characteristics of included participants, definition of high alcohol consumption, method used to diagnose CKD, proteinuria and ESRD, mean duration of follow up and adjusted effect estimates with 95% CI. The two investigators mentioned above independently performed this data extraction.

Statistical analysis

Review Manager 5.2 software from the Cochrane Collaboration was used for data analysis. Point estimates and standard errors were extracted from individual studies and were combined by the generic inverse variance method of DerSimonian and Laird.[26] Given the high likelihood of between study variances, we used a random-effect model rather than a fixed-effect model. Statistical heterogeneity was assessed using the Cochran's Q test. This statistic is complemented with the I^2 statistic, which quantifies the proportion of the total variation across studies that is due to heterogeneity rather than chance. A value of I^2 of 0% to 25% represents insignificant heterogeneity, 26% to 50% low heterogeneity, 51% to 75% moderate heterogeneity, and > 75% high heterogeneity.[27] The presence of publication bias was assessed by funnel plots of the logarithm of odds ratios versus their standard errors.[28] The post hoc analysis assessing the sex-specific association between high alcohol consumption and CKD. In order to assess the risk of ESRD subgroups, we also performed a post hoc analysis for assessing the risk of developing ESRD related to diabetes (DM) and hypertension (HTN) in patients with high alcohol consumption.

Results

Our search strategy yielded 13,533 potentially relevant articles. 12,474 articles were excluded based on title and abstract for clearly not fulfilling inclusion criteria on the basis of the type of article, study design, population, or outcome of interest. 1,059 articles underwent full-length article review. 1,041 articles were excluded (688 articles were not observational studies or RCTs and 353 articles did not report the outcomes of interest). Twenty observational studies from 18 articles with total of 292,431 patients were identified and included in the data analysis. There were no RCTs identified in this literature search. **Figure S1** outlines our search methodology and selection process.

The Risk of CKD in Patients with High Alcohol Consumption

Sixteen study samples (9 cohort, 1 case-control and 6 cross-sectional studies) with 212,918 patients were included in the data analysis for the risk of CKD in patients with high alcohol consumption. **Table 1** describes the detailed characteristics and quality assessment of the included studies. The pooled RR of CKD in patients with high alcohol consumption was 0.83 (95% CI 0.71-0.98, I^2 of 73%). **Figure 1** shows the forest plot of the included studies. When cross-sectional studies were excluded, the pooled RR for developing CKD was 0.82 (95% CI 0.72-0.93) as shown in **Figure S2**. The statistical heterogeneity was low with an I^2 of 28%. The post hoc analysis assessing the sex-specific association between high alcohol consumption and CKD demonstrated a pooled RR of 0.72 (95% CI 0.57-0.90) in males **(Figure S3)** and 0.78 (95% CI 0.58-1.03) in females **(Figure S4)**.

The Risk of ESRD in Patients with High Alcohol Consumption

Five study samples (3 cohort studies and 2 case-control studies) with 80,583 patients were included in the data analysis for the risk of developing ESRD in patients with high alcohol consumption **(Table 2)**. The pooled RR of ESRD in patients with high alcohol consumption was 1.00 (95% CI, 0.55-1.82, I^2 of 61%). **Figure 2** shows the forest plot of the included studies.

The post hoc analysis assessing the association of high alcohol consumption and ESRD subgroups demontrated the pooled RRs of 2.23 (95% CI, 0.90-5.52) for ESRD related to HTN, 1.07 (0.26-4.31) for ESRD related to DM and 0.32 (95% CI, 0.05-2.27) for ESRD related to DM and HTN.

The Risk of Proteinuria in Patients with High Alcohol Consumption

Four study samples (all cohort studies) with 140,686 patients were included in the data analysis for the association between proteinuria and high alcohol consumption **(Table 3)**. The pooled RR of proteinuria in patients with high alcohol consumption was 0.85 (95% CI 0.62-1.17, I^2 of 82%) as shown in **Figure S5** .

Evaluation for publication bias

Funnel plots to evaluate publication bias for the risk of CKD, ESRD and proteinuria in patients with high alcohol consumption. The graphs are slight asymmetric and, thus, provide a suggestion to the presence of publication in favor of positive studies of the risk of CKD, proteinuria and ESRD. **Figure S6** demonstrates a funnel plot of 16 studies to assess the publication bias for the risk of CKD in patients with high alcohol consumption.

Discussions

Our present meta-analysis results indicate an inverse association between high alcohol consumption and CKD in healthy adult males with an overall 0.72-fold decreased risk of CKD compared to those who did not regularly consume alcohol. However, our analysis did not demonstrate a significant association between high alcohol consumption and ESRD or proteinuria.

There are several plausible explanations for the inverse association of high alcohol consumption and CKD in adult males. Firstly, studies have demonstrated that alcohol consumption can increase high-density lipoprotein (HDL) and plasma endogenous tissue-type plasminogen activator levels and decrease platelet aggregration.[29] Due to estrogen effects, premenopausal women have better baseline atherosclerotic risk factors and lipid profiles, especially higher HDL levels compared to men. Alcohol consumption was also demontrated

to lower atherosclerotic risk and coronary heart disease in men.[30] The increase in HDL effect may play the important role in the inverse association of CKD in males with high alcohol consumption. Secondly, polyphenols in many alcohol beverages such as red wine were shown to have anti-oxidant properties in rat models[31]. It may reduce kidney injury by induction of glutathione peroxidase, catalase and superoxidase dismutase. [31] In addition, alcohol has shown to prevent renal ischemia and reperfusion injury in other animal models. It may prevent leukocyte recruitment and endothelial barrier damage.[32] Thirdly, the inverse association between high alcohol consumption and hyalinization of renal arterioles was shown in an autopsy study.[33] Lastly, several previous studies that demonstrated the association between high alcohol consumption and the risk of CKD and ESRD were case-control studies which may have potentially been prone to have recall bias since alcohol consumption was assessed after the renal damages occurred.[8, 10]

Although all included studies were of moderate to high quality (as evaluated by Newcastle-Ottawa scale), there are some limitations. Firstly, some studies were conducted based on self-report, not a structured interview or medical record review. Although some studies have validated the use of self-reported alcohol consumption, under-reporting for alcohol consumption has been found especially in heavy alcohol drinkers.[34] However, we performed the study in high alcohol consumption which is less likely to be affected by misclassification by under-reporting. Secondly, there are statistical heterogeneities in the complete analysis. The potential sources of these heterogeneities include the difference in the diagnosis methodology of CKD, exposure definition (type of alcohol and amount of high alcohol consumption), the differences in confounder adjusted methods and the duration of the follow-up. However, we also performed sensitivity analysis by excluding cross-sectional studies, since they provided risk estimates at only point in time and had the great potential to only

show part of any causal picture. Our sensitivity analysis also successfully shows an inverse association between heavy alcohol drinking and CKD with a low heterogeneity. In addition, the adjusted analysis for HTN in most of the included studies could have mitigated the adverse effect of high alcohol consumption on CKD outcome because high alcohol consumption may cause HTN, which is a known risk factor to CKD [5]. However, several included studies in this meta-analysis still showed the inverse association between high alcohol consumption and CKD when HTN was not included in their adjusted models.[18, 23]

This is a meta-analysis of observational studies with its inherent limitations. We systematically searched the literatures and there have been no RCTs conducted on these topics. Therefore, our meta-analysis can at best demonstrate an association but not a causal relationship. Most studies' outcome ascertainment for CKD were measured by the change of serum creatinine which is not ideal in many situations especially in extremely low or high muscle mass. Low serum creatinine levels may reflect severe liver disease and malnutrition due to high alcohol consumption.[35] Although most studies in this meta-analysis included body mass index (BMI) into their adjusted analysis, an alcoholic population is less sensitive given the high propensity for malnourishment. Consequently, BMI is not a good indicator of muscle mass in this population. Therefore, we need to interprete this inverse association between high alcohol consumption and CKD cautiously as excessive alcohol use can cause cirrhosis and increase mortality from accidents.[5] Moreover, severe cirrhosis subsequently may result in hepatorenal syndrome. There is a possible concern that this inverse association is due to competing risk, since those with high alcohol consumption may die of other causes. However, a study by Reynolds *et al.*[23] demonstrated that alcohol consumption was also inversely associated with all-cause mortality. In addition, our study also shows no significant association between heavy alcohol drinking and ESRD or proteinuria supporting insignificant

risk for CKD in patients with high alcohol consumption.In conclusion, our study suggests a statistically significant inverse relationship of CKD in male adults with high alcohol consumption. There is no significant association between high alcohol consumption and the risk for developing proteinuria or ESRD.

Disclosure: None

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Table 1: Main characteristics of the studies included for the risk of CKD in patients with high alcohol consumption

	Knight et al[9]	Vupputuri et al[10]	Schaeffner et al[18]	Shankar et al (1)[6]	Shankar et al (2)[6]	Yamagata et al[11]	White et al[19]	Buja et al (1)[12]
Country	USA	USA	USA	USA	USA	Japan	Australia	Italy
Study design	Cohort study	Case-control study	Cohort study	Cohort study	Cross-sectional study	Cohort study	Cohort study	Cohort study
Year	2003	2003	2005	2005	2005	2007	2009	2010
Total number	1658	1070	11023	3392	4898	123764	5807	1539
Study sample	Female nurses; aged 30-55 years	Hospital-based cases and community-based controls; male and female; aged 30-83 years	Healthy male physicians	Population-based; male and female; aged 43-84 years	Population-based; male and female; aged 43-84 years	Population-based; male and female; aged 40 years or older	Population-based; male and female; aged 25 years or older	Population-based; male and female; aged 65-84 years
Exposure definition	Current alcohol consumption between 15 and 60 g/d	Current alcohol consumption ≥ 3 drinks/d	Current alcohol consumption ≥ 7 drinks/week	Current alcohol consumption ≥ 4 serving/d	Current alcohol consumption ≥ 4 serving/d	Alcohol consumption > 20 g/d	Current alcohol consumption ≥ 30g/d	Current alcohol consumption > 24 g/d
Exposure measurement	Self-report using structured questionnaires	telephone interview using structured questionnaires	Self-report using structured questionnaires	Interview using structured questionnaires	Interview using structured questionnaires	Interview using structured questionnaires	Interviewer- and self-administered standardized questionnaires	Interview using structured questionnaires
Outcome definition	Decline in GFR ≥ 25%	Newly-diagnosed CKD with at least 2 values of SCr > 1.5 mg/dl	Reduced eGFR ≤ 55 ml/min	Incident CKD, defined as GFR < 60 ml/min/1.73 m2 at 5-year follow-visit among participants who did not have CKD at baseline	Prevalent CKD, defined as GFR < 60 ml/min/1.73 m2 at baseline	Incident CKD, defined as eGFR < 60 ml/min/1.73 m^2	De novo eGFR < 60ml/min/1.73 m2, defined as 5-year decline in eGFR of ≥10% with eGFR > 60 ml/min/1.73m2 at baseline and a final eGFR < 60 ml/min/1.73m2	Incident CKD, defined as GFR < 60 ml/min/1.73 m2 at baseline
Outcome ascertainment	SCr was measured at baseline (1989) and follow up visit (2000). eGFR was calculated using MDRD formula	ICD-9 discharge diagnosis, followed by comprehensive chart reviews	SCr was measured 14 years after baseline assessment. eGFR was calculated using Cockcroft-Gault equation.	SCr was measured at 5-year follow-up visit. eGFR was calculated using MDRD formula.	SCr was measured at baseline. eGFR was calculated using MDRD formula.	SCr was measured annually. eGFR was calculated using MDRD formula.	SCr was measured at 5-year follow-up visit. eGFR was calculated using MDRD formula	SCr was measured at follow-up visit. eGFR was calculated using MDRD formula.

Confounder adjusted	Age, BMI, protein intake, hypercholesterolemia, diabetes, hypertension and smoking status	Age, race, education, BMI, analgesic use, smoking, hypertension, diabetes, respondent status	Age, BMI, smoking, physical exercise, diabetes, family history of early MI and treatment assignment	Age, sex, education, BMI, current NSAID use, hypertension, diabetes, cardiovascular disease, smoking status	Age, sex, education, BMI, current NSAIDs use, hypertension, diabetes, cardiovascular disease, current smoking status	Age, GFR, diabetes, hypertension, hypercholesterolemia, low-HDL, hypertriglyceridemia, obesity, smoking	Age, sex, GFR, hypertension, systolic blood pressure, diabetes, HbA1C, smoking status, physical activity and waist to hip ratio	Age, BMI, smoking, education, antihypertensive and lipid-lowering medications, isolated systolic hypertension, diabetes, blood fibrinogen, total cholesterol
Quality assessment (Newcastle-Ottawa scale)	Selection: 3 Comparability: 2 Outcome: 3	Selection: 4 Comparability:2 Exposure: 3	Selection: 2 Comparability: 2 Outcome:3	Selection: 4 Comparability: 2 Outcome:3	Selection: 4 Comparability: 2 Outcome: 3	Selection: 4 Comparability: 2 Outcome: 3	Selection: 4 Comparability: 2 Outcome: 3	Selection: 4 Comparability: 2 Outcome: 3

Abbreviation: BMI, body mass index; CKD, chronic kidney disease; GFR, glomerular filtration rate; HbA1C, Glycated hemoglobin; HDL, high-density lipoprotein; ICD-9, The International Classification of Diseases-9; MI, myocardial infarction; MDRD, Modification of Diet in Renal Disease; NSAIDs, nonsteroidal anti-inflammatory drugs; SCr, serum creatinine; UACR, urine albumin to creatinine ratio.

Table 1: Main characteristics of the studies included for the risk of CKD in patients with high alcohol consumption (Cont.)

	Buja et al (2)[12]	Menon et al[13]	Sanoff et al[14]	Thakkinstian et al[7]	Funakoshi et al[20]	Dunkler et al[21]	Hsu et al[22]	Wakasugi et al[15]
Country	Italy	USA	Nicaragua	Thailand	Japan	Multi-national study	Taiwan	Japan
Study design	Cross-sectional study	Cohort study	Cross-sectional study	Cross-sectional study	Cross-sectional study	Cohort study	Cross-sectional study	Cohort study
Year	2010	2010	2010	2011	2012	2013	2013	2013
Total number	3404	4343	997	3459	9196	6213	27253	4902
Study sample	Population-based; male and female; aged 65-84 years	Population-based; male and female; aged ≥ 65 years	Population-based; male and female	Population-based ; male and female; aged ≥ 18 years	Population-based; adult male only	Subjects with vascular disease or type 2 DM with end-organ damage; Male and female; aged ≥ 55 years	Population-based; adult male and female	Population-based; male and female; aged 40-79 years
Exposure definition	Current alcohol consumption > 24 g/d	Current alcohol consumption ≥14 drinks/week	Beer consumption: yes/no	Alcohol consumption: yes/no	Alcohol consumption everyday	Alcohol consumption ≥ 5 drinks/week	Frequent or regular alcohol drinking	Alcohol consumption > 20 g/d
Exposure measurement	Interview using structured questionnaires	Interview using structured questionnaires	Interview using structured questionnaires	interview	Interview using structured questionnaires	Interview using structured questionnaires	Self-report using structured questionnaires	Self-reported using structured questionnaires
Outcome definition	Prevalent CKD, defined as GFR < 60 ml/min/1.73 m2 at baseline	rapid kidney function decline as an Annual eGFR loss > 3 ml/min/1.73m2	eGFR ≤ 60 ml/min/1.73 m2	Prevalent CKD, defined as GFR >60 with hematuria and/or albumin-creatinine ratio ≥ 30 mg/g (stage I, II) or GFR < 60 ml/min/1.73m2, regardless of kidney damage (stage III-V)	CKD, defined as GFR < 60 ml/min/1.73 m2 at baseline	CKD, defined as at least 1 of 1) new microalbuminuria (UACR > 3.4mg/mmol) or new macroalbuminuria (UACR > 33.9mg/mmol) with at least 30% increase from baseline UACR, GFR-decline of	CKD, defined as eGFR < 60 but ≥30 ml/min/1.73 m2	Mild CKD as incident proteinuria, defined as a dipstick urinalysis score of ≥1+ proteinuria

						>5%/year or end-stage renal disease (eGFR < 15 ml/min/1.73m2 or renal replacement therapy > 2 months)		
Outcome ascertainment	SCr was measured at baseline. eGFR was calculated using MDRD formula.	Cystatin C was measured at year 3 and year 7. eGFR was calculated from cystatin C	SCr was measured at baseline. eGFR was calculated using MDRD formula.	SCr was measured at baseline. eGFR was calculated using MDRD formula.	SCr was measured at baseline. eGFR was calculated using MDRD formula.	Urinary albumin-creatinine ratio, and SCr were measured at baseline and after 5 years of follow-up. eGFR was calculated using MDRD and CKD-EPI formula	SCr was measured at baseline. eGFR was calculated using MDRD formula.	Urine dipstick for proteinuria was tested at 1-year follow-up visit
Confounder adjusted	Age, BMI, smoking, education, antihypertensive and lipid-lowering medications, isolated systolic hypertension, diabetes, blood fibrinogen, total cholesterol	Age, race, smoking status, diabetes, systolic and diastolic blood pressure, antihypertensive medication, LDL-C, HDL-C, prevalent cardiovascular disease, heart failure, C-reactive protein, fibrinogen	Age, sex, systolic and diastolic blood pressure, diabetes, family history of ESRD, BMI	None	Age, BMI, hypertension, diabetes, hypercholesterolemia, smoking status and physical activity	Age, diabetes duration, albuminuria status, GFR, sex, treatment assignment, UACR to progression	Age, smoking, betel nut chewing, hypertension, diabetes, anemia, hyperlipidemia, BMI, hyperuricemia, proteinuria	Age, sex, smoking status, BMI, exercise, eating pattern, hypertension, diabetes, hypercholesterolemia
Quality assessment (Newcastle-Ottawa scale)	Selection: 4 Comparability: 2 Exposure/outcome: 3	Selection: 4 Comparability: 2 Outcome: 3	Selection: 4 Comparability: 2 Outcome: 3	Selection: 4 Comparability: 0 Exposure/outcome: 3	Selection: 4 Comparability: 2 Outcome:3	Selection: 4 Comparability: 2 Outcome: 3	Selection: 4 Comparability: 2 Exposure/outcome: 3	Selection: 4 Comparability: 2 Exposure/outcome: 2

Abbreviation: BMI, body mass index; CKD, chronic kidney disease; GFR, glomerular filtration rate; HbA1C, Glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction; MDRD, Modification of Diet in Renal Disease; NSAIDs, nonsteroidal anti-inflammatory drugs; SCr, serum creatinine; UACR, urine albumin to creatinine ratio.

Table 2: Main characteristics of the studies included for the risk of ESRD in patients with high alcohol consumption

	Perneger et al[8]	Vupputuri et al[10]	Stengel et al[16]	Reynolds et al[23]	Guatierrez et al[17]
Country	USA	USA	USA	China	USA
Study design	Case-control study	Case-control study	Cohort study	Cohort study	Cohort study
Year	1999	2003	2003	2008	2014
Total number	912	1070	9028	65601	3972
Study sample	community-based cases and controls; male and female; aged 20-64 years	Hospital-based cases and community-based controls; male and female; aged 30-83 years	Population-based; male and female; aged 30-75 years	Population-based; male only; aged 40 years or older	Population-based; Subjects with CKD; male and female; aged 45 years or older
Exposure definition	Current alcohol consumption > 2 drinks/d Drinking pattern: > 3 d/week and ≥ 5 drinks/d	Current alcohol consumption ≥ 3 drinks/d	Current alcohol consumption ≥ 1 times/d	Current alcohol consumption ≥ 21 drinks/week	The highest quartile in alcohol/salad dietary pattern score
Exposure measurement	telephone interview using structured questionnaires	telephone interview using structured questionnaires	Interview using structured questionnaires	Interview using structured questionnaires	Self-reported using mailed structured questionnaires
Outcome definition	New-onset ESRD requiring dialysis	New-onset ESRD requiring dialysis	Either 1) treatment of ESRD due to any cause, or 2) death related to CKD	ESRD, defined as renal replacement therapy (dialysis or renal transplantation) or death from renal failure	Incident ESRD
Outcome ascertainment	Population-based registry of persons undergoing treatment for ESRD	ICD-9 discharge diagnosis, followed by comprehensive chart reviews	NHANE II medicare ESRD registry data and mortality study	In-person/proxy interview, medical record and death certificate review	US Renal Data System
Confounder adjusted	Age, sex, race, hypertension, income, diabetes, acetaminophen use, smoking and opiate use	Age, race, education, BMI, analgesic use, smoking, hypertension, diabetes, respondent status	Physical activity, smoking, BMI, age, gender, race, diabetes, cardiovascular disease, hypertension, systolic blood pressure, serum cholesterol and GFR	Age, geographic region, urbanization, education, BMI, physical activity, smoking status, systolic blood pressure, diabetes, cardiovascular disease	Age, sex, race, geographic region, energy intake, lifestyle factors, comorbid conditions, education, annual family income, log-transformed UACR and eGFR
Quality assessment (Newcastle-Ottawa scale)	Selection: 4 Comparability: 2 Exposure: 3	Selection: 4 Comparability:2 Exposure: 3	Selection: 4 Comparability: 2 Outcome:3	Selection: 4 Comparability: 2 Outcome:3	Selection: 3 Comparability: 2 Outcome: 3

Abbreviation: BMI, body mass index; CKD, chronic kidney disease; GFR, glomerular filtration rate; HbA1C, Glycated hemoglobin; HDL, high-density lipoprotein; ICD-9, The International Classification of Diseases-9; MI, myocardial infarction; MDRD, Modification of Diet in Renal Disease; NSAIDs, nonsteroidal anti-inflammatory drugs; SCr, serum creatinine; UACR, urine albumin to creatinine ratio.

Table 3: Main characteristics of the studies included for the risk of proteinuria in patients with high alcohol consumption

	Yamagata et al[11]	White et al[19]	Dunkler et al[21]	Wakasugi et al[15]
Country	Japan	Australia	Multi-national study	Japan
Study design	Cohort study	Cohort study	Cohort study	Cohort study
Year	2007	2009	2013	2013
Total number	123764	5807	6213	4902
Study sample	Population-based; male and female; aged 40 years or older	Population-based; male and female; aged 25 years or older	Subjects with vascular disease or type 2 DM with end-organ damage; Male and female; aged ≥ 55 years	Population-based; male and female; aged 40-79 years
Exposure definition	Alcohol consumption > 20 g/d	Current alcohol consumption ≥ 30g/d	Alcohol consumption ≥ 5 drinks/week	Alcohol consumption > 20 g/d
Exposure measurement	Interview using structured questionnaires	Interviewer- and self-administered standardized questionnaires	Interview using structured questionnaires	Self-reported using structured questionnaires
Outcome definition	Incident proteinuria, defined as dipstick proteinuria ≥ 1+	De novo albuminuria, defined as a doubling of ACR over 5 years with a final ACR ≥ 2.5 in males and ≥ 3.5 in females, in the absence of albuminuria at baseline	New microalbuminuria (UACR > 3.4mg/mmol) or new macroalbuminuria (UACR > 33.9mg/mmol) with at least 30% increase from baseline UACR	Incident proteinuria, defined as a dipstick urinalysis score of ≥1+ proteinuria
Outcome ascertainment	Urine dipstick was measured annually.	Urine albumin was measured at 5-year follow-up visit.	Urinary albumin-creatinine ratio was measured at baseline and after 5 years of follow-up.	Urine dipstick for proteinuria was tested at 1-year follow-up visit
Confounder adjusted	Age, GFR, diabetes, hypertension, hypercholesterolemia, low-HDL, hypertriglyceridemia, obesity, smoking	Age, sex, GFR, hypertension, systolic blood pressure, diabetes, HbA1C, smoking status, physical activity and waist to hip ratio	Age, diabetes duration, albuminuria status, GFR, sex, treatment assignment, UACR to progression	Age, sex, smoking status, BMI, exercise, eating pattern, hypertension, diabetes, hypercholesterolemia
Quality assessment (Newcastle-Ottawa scale)	Selection: 4 Comparability: 2 Outcome: 3	Selection: 4 Comparability: 2 Outcome: 3	Selection: 4 Comparability: 2 Outcome: 3	Selection: 4 Comparability: 2 Exposure/outcome: 2

Abbreviation: UACR, urine albumin to creatinine ratio; BMI, body mass index; CKD, chronic kidney disease; GFR, glomerular filtration rate; HbA1C, Glycated hemoglobin; HDL, high-density lipoprotein; MI, myocardial infarction; MDRD, Modification of Diet in Renal Disease; NSAIDs, nonsteroidal anti-inflammatory drugs; SCr, serum creatinine.

Figure legend

Figure 1: Forest plot of the included studies comparing risk of CKD in patients with high alcohol consumption and those who did not; square data markers represent risk ratios (RRs); horizontal lines, the 95% CIs with marker size reflecting the statistical weight of the study using random-effects meta-analysis. A diamond data marker represents the overall RR and 95% CI for the outcome of interest.

Figure 2: Forest plot of the included studies comparing risk of ESRD in patients with high alcohol consumption and those who did not; square data markers represent risk ratios (RRs); horizontal lines, the 95% CIs with marker size reflecting the statistical weight of the study using random-effects meta-analysis. A diamond data marker represents the overall RR and 95% CI for the outcome of interest.

Supplementary data

Item S1: Literature search strategy for Database: Ovid, MEDLINE, Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials.

Figure S1: Outline of our search methodology. Abbreviation: CKD, chronic kidney disease; ESRD, end stage renal disease; RCTs, randomized controlled trials.

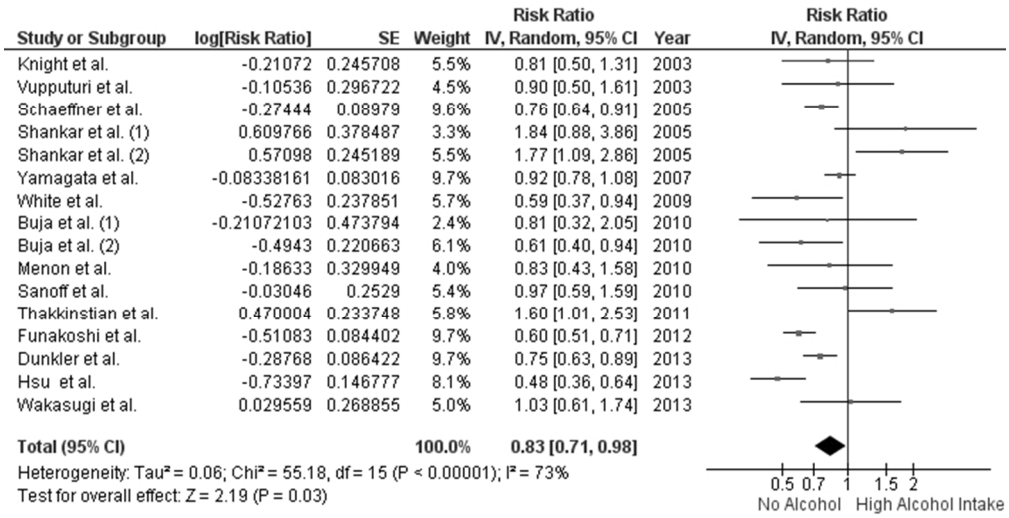
Figure S2: Forest plot of the included studies (excluding cross-sectional studies) comparing risk of CKD in patients with high alcohol consumption and those who did not.

Figure S3: Forest plot of the post hoc analysis assessing association between high alcohol consumption and CKD in males.

Figure S4: Forest plot of the post hoc analysis assessing association between high alcohol consumption and CKD in females.

Figure S5: Forest plot of the included studies comparing risk of proteinuria in patients with high alcohol consumption and those who did not.

Figure S6: Funnel plot of 16 studies included in the meta-analysis for the risk of CKD in patients with high alcohol consumption. The graph is fairly asymmetric and suggests the presence of publication in favor of positive studies. RR = risk ratio, SE = standard error.



Forest plot of the included studies comparing risk of CKD in patients with high alcohol consumption and those who did not; square data markers represent risk ratios (RRs); horizontal lines, the 95% CIs with marker size reflecting the statistical weight of the study using random-effects meta-analysis. A diamond data marker represents the overall RR and 95% CI for the outcome of interest.
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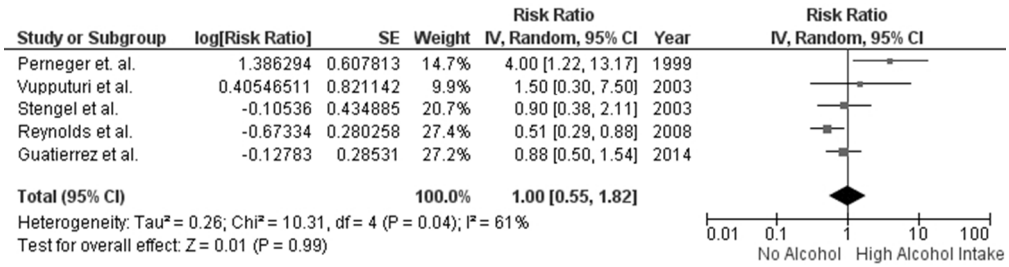

Forest plot of the included studies comparing risk of ESRD in patients with high alcohol consumption and those who did not; square data markers represent risk ratios (RRs); horizontal lines, the 95% CIs with marker size reflecting the statistical weight of the study using random-effects meta-analysis. A diamond data marker represents the overall RR and 95% CI for the outcome of interest.
248x67mm (72 x 72 DPI)