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ORIGINAL ARTICLE

The association of alcohol and smoking with CKD in a Japanese nationwide cross-sectional survey

Ayako Matsumoto[1], Yasuyuki Nagasawa[1], Ryohei Yamamoto[2,3], Maki Shinzawa[3], Yukiko Hasuike[1], Takahiro Kuragano[1], Yoshitaka Isaka[3], Takeshi Nakanishi[1], Kunitoshi Iseki[4], Kunihiro Yamagata[4], Kazuhiko Tsuruya[4], Hideaki Yoshida[4], Shouichi Fujimoto[4], Koichi Asahi[4], Toshiki Moriyama[2,3,4] and Tsuyoshi Watanabe[4]

Chronic kidney disease (CKD) is characterized by a reduced glomerular filtration rate (GFR) and proteinuria. Modifiable lifestyle factors such as smoking and alcohol contribute to CKD. Recent cohort studies have shown that moderate alcohol consumption attenuates the decline of the GFR and smoking has been previously shown to be associated with CKD. However, the association of smoking and alcohol consumption on CKD is not entirely clear. To examine whether there is evidence to assume that smoking is an effective modifier of the association between CKD and alcohol consumption, we conducted a cross-sectional study of a population of people who presented for a health checkup under a program that targets the insured population aged ≧40 years using data from the Specific Health Check and Guidance in Japan between April 2008 and March 2009. Of the 506 807 participants aged ⩾40 years, 292 013 (57.6%) were included in the present analysis. Outcomes were kidney dysfunction, as an eGFR of <60 ml/min/1.73 m^2, and proteinuria. In nonsmokers, drinking a small amount was associated with a lower prevalence of proteinuria, but in smokers, the association between alcohol and proteinuria was not observed. The analysis regarding eGFR <60 ml/min/1.73 m^2 revealed that in both smokers and nonsmokers, alcohol consumption was inversely associated with the risk of CKD. Mild to moderate alcohol consumption might be associated with a lower risk of CKD (proteinuria and eGFR), especially among nonsmokers, because smoking might have modified the potential benefits of alcohol to prevent CKD.
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INTRODUCTION

The concept of chronic kidney disease (CKD) was developed because CKD has a strong relationship with cardiovascular diseases (CVDs) as well as end-stage renal diseases (ESRDs).[1–3] Originally, CKD was defined by proteinuria and glomerular filtration rates (GFRs).[4]

Similar to CVD, modifiable lifestyle factors, such as smoking,[5,6] alcohol,[7] sleep[8] and exercise,[9] contribute to CKD.[10]

Smoking has been previously shown to be associated with renal disease.[11–14] A number of biological mechanisms by which smoking can result in kidney damage have been identified, including the promotion of renal atherosclerosis,[15] alterations in systemic and renal hemodynamics[16] and effects on endothelial function.[17]

Alcohol consumption is one of the main modifiable lifestyle factors associated with CVD and its risk factors, including hypertension,[18] diabetes,[19] ischemic heart disease[20] and stroke.[21] Heavy drinkers are at a higher risk of these diseases, whereas mild to moderate alcohol consumption, generally corresponding to 1–2 drinks (15–30 g of alcohol) per day or less, is associated with a lower incidence of these diseases and a lower all-cause mortality.[22] In 'Healthy Japan 21', the Japanese Ministry of Health and Welfare reported that consuming a mean amount of ~20 g of absolute alcohol per day represented 'moderate drinking'.[23] For renal disease, it remains controversial whether heavy alcohol consumption affects renal prognosis.[24–26] Recent cohort studies have shown that moderate alcohol consumption attenuates the decline of GFR.[27]

Because various background factors can affect the relevance of alcohol consumption and CKD, a variety of research reports have been reported. For example, joint exposure to both current smoking and heavy drinking has been associated with higher odds of CKD than their individual effects.[28] However, the association of smoking and alcohol consumption on CKD is not entirely clear.

The aim of the present cross-sectional survey of 292 013 individuals undergoing the Specific Health Check and Guidance in Japan was to examine whether there is evidence to assume that smoking modifies the potential benefits of alcohol to prevent CKD.

[1]Department of Internal Medicine, Division of Kidney and Dialysis, Hyogo College of Medicine, Hyogo, Japan; [2]Osaka University Health Care Center, Osaka, Japan; [3]Department of Geriatric Medicine and Nephrology, Osaka University Graduate School of Medicine, Osaka, Japan and [4]Steering Committee for the 'Research on the Positioning of Chronic Kidney Disease in Specific Health Check and Guidance in Japan', Tokyo, Japan
Correspondence: Dr T Moriyama, Osaka University Healthcare Center, 1-17 Machikaneyama-cho, Toyonaka 560-0043, Japan.
E-mail: moriyama@wellness.hss.osaka-u.ac.jp
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METHODS

Study population

The present nationwide cross-sectional survey included members of the general Japanese population who underwent the Specific Health Check and Guidance in Japan between April 2008 and March 2009. As a recent survey indicated that the prevalence of diabetes, hypertension, dyslipidemia, obesity and metabolic syndrome had been increasing in Japan, the Ministry of Health, Labor and Welfare of Japan developed a systematic health-care strategy that involves specific health checkups and targets members of the insured population who are aged ⩾40 years. This strategy aims to detect and manage CKD at an earlier stage. We analyzed the data of individuals who were receiving the Health Check and Guidance in 8 prefectures (Miyagi, Fukushima, Ibaraki, Tokyo, Niigata, Osaka, Fukuoka and Okinawa). Of the 506 807 participants aged ⩾40 years (Miyagi 16 640, Fukushima 50 304, Ibaraki 39 775, Tokyo 40 278, Niigata 58 882, Osaka 25 615, Fukuoka 149 785 and Okinawa 125 528), 292 013 (57.6%) were included in the present analysis; 214 794 (42.4%) participants with missing data were excluded (among them 65 577 participants who were excluded because of a lack of responses to questions related to smoking or drinking). The study protocol was approved by the ethics committee at Fukushima Medical University (No. 715) and Osaka University Hospital (No. 13085). We deleted the patient's name, date of birth (except the month and year of birth) and patient ID in each facility. Then, we labeled the patients in each facility and made a correspondence table, and the table was kept in the locked area.

Measurements

Demographic, physical and laboratory data included age, sex, body mass index (weight (kg)/height^2 (m^2)), systolic blood pressure, diastolic blood pressure, mean arterial pressure (diastolic blood pressure+(systolic blood pressure − diastolic blood pressure)/3), pulse pressure (systolic blood pressure − diastolic blood pressure), serum concentration of creatinine (enzymatic method), and levels of hemoglobin A1c, fasting blood sugar, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol, uric acid and urinary protein, as detected by a dipstick test. Proteinuria was defined as ⩾1 urinary proteins. The estimated glomerular filtration rate (eGFR) was calculated using the following equation: eGFR (ml/min/1.73 m^2) = 194× age (years)$^{-0.287}$ × serum creatinine (mg/dl)$^{-1.094}$ (× 0.739, if female).[29] Hypertension is defined as follows, systolic blood pressure ⩾140 mmHg or diastolic blood pressure ⩾90 mmHg.[30] Diabetes is defined as follows, fasting plasma glucose level ⩾126 mg/dl and hemoglobin A1c ⩾6.1%.[31] Dyslipidemia is defined as follows, low-density lipoprotein cholesterol ⩾140 mg/dl or HDL-C <40 mg/dl or triglycerides ⩾150 mg/dl.[32]

Information regarding lifestyle, use of current medications for comorbidities and past medical history was based on self-reported standard questionnaires that all participants were required to complete at the time of their check-up. Alcohol consumption was ascertained by asking the following two questions: 'How often do you drink alcoholic beverages? (1) Every day, (2) occasionally or (3) rarely' and 'How many alcoholic beverages do you drink on the days that you do drink? (Approximately 500 ml beer, 80 ml 'shochu' (a Japanese liquor similar to vodka), 60 ml whiskey or 240 ml wine were assumed to constitute 1 standard drink.) (1) ⩽1 Drink per day, (2) 1–2 drinks per day, (3) 2–3 drinks per day or (4) ⩾3 drinks per day'. Each drink was calculated using 20 g of ethanol consumption. We categorized alcohol consumption as follows: drink score (0) rare, (1) occasional, (2) ethanol intake ⩽19 g per day, (3) ethanol intake 20–39 g per day, (4) ethanol intake 40–59 g per day and (5) ethanol intake ⩾60 g per day. Smoking status was evaluated by positive answers to the question 'Do you smoke now?' A past history of cardiac disease was defined by a positive answer to the question 'Have you been diagnosed with heart disease?' Similarly, past history of stroke was also defined by a positive answer to the question 'Have you been diagnosed with stroke?' and a past history of kidney disease was defined by a positive answer to the question 'Have you been diagnosed with kidney disease?' Current drug history was defined by a positive answer to the question 'Do you take antihypertensive medications now?', 'Do you take insulin injection or antihyperglycemia medications now?' and 'Do you take anticholesteremic medications now?'

All data were collected and managed at an independent non-profit data center in the Japan Clinical Research Support Unit.

Statistical analysis

Continuous variables were expressed as the mean ± s.d. or median (interquartile range) as appropriate, and categorical variables were expressed as a number (proportion). Serum triglyceride levels were logarithmically transformed because of their skewed distribution. The clinical characteristics of subjects with different drink scores were compared using analysis of variance, the Kruskal–Wallis test or χ^2 test, as appropriate. To assess whether smoking is an effect modifier of the association between drink score and proteinuria, the odds ratio of each drink score was calculated using univariate and multivariate logistic regression models, dividing it into smoking and nonsmoking, with the presence of proteinuria as the dependent variable. To assess whether smoking is an effect modifier of the association between drink scores and eGFRs, the odds ratio of each drink score was calculated using univariate and multivariate logistic regression models, dividing it into smoking and nonsmoking, with the presence of eGFR <60 (ml/min/1.73 m^2) as the dependent variable. Multivariate models included age, body mass index, systolic blood pressure, diastolic blood pressure, smoking status, drinking status, past history of heart disease, past history of stroke, levels of hemoglobin A1c, serum triglyceride concentration, HDL cholesterol and uric acid as covariates, in addition to the drink score.

We defined kidney dysfunction, one of the outcomes, as an eGFR <60 ml/min/1.73 m^2 because recent reports have demonstrated that an eGFR <60 ml/min/1.73 m^2 is a risk factor for CVD and end-stage renal disease (ESRD), resulting in the establishment of CKD stage 3a. We assessed proteinuria (defined as ⩾1+ urinary protein by dipstick test) as the other outcome.

All *P*-values were based on two-sided tests of significance, and $P<0.05$ was considered statistically significant. Statistical analyses were performed using Stata version 11.0 (Stata, College Station, TX, USA) and R version 3.0.2 (The R Foundation for Statistical Computing, http://www.r-project.org/).

RESULTS

The clinical characteristics of the 117 692 men and 174 321 women stratified according to smokers and nonsmokers are shown in Tables 1 and 2, respectively. In men, smokers tended to drink more alcohol than nonsmokers, and smokers were younger, had lower body mass index, lower systolic and diastolic blood pressure, lower serum HDL-C and low-density lipoprotein cholesterol level, higher eGFR, higher positive proteinuria, higher triglyceride levels and higher hemoglobin A1c. In male nonsmokers, past histories of heart disease, stroke and kidney disease, current drug history of antihypertensive and anticholesteremic medications and prevalence of hypertension were higher. In the women, almost all were nonsmokers (94.1%), and similar trends as in the men were observed. In addition, uric acid and past history of kidney disease were slightly higher in female smokers, and prevalence of dyslipidemia was higher in female nonsmokers.

We examined the relationship between alcohol consumption and proteinuria stratified by smoking. In both genders, univariate and multivariate model analyses demonstrated that alcohol consumption was associated with proteinuria (Tables 3 and 4). The multivariate analysis of proteinuria revealed that in nonsmokers, a small amount of drinking was associated with a lower prevalence of proteinuria, but in smokers, the association of alcohol consumption and proteinuria was not observed. In male nonsmokers, a drink score of 2 and 3 had a significant association with a lower prevalence of proteinuria (*vs.* a drink score of 0, multivariate-adjusted odds ratio (OR) 0.90 (95% confidence interval (CI) 0.83–0.98), $P=0.012$ for drink score 2, multivariate-adjusted OR 0.87 (95% CI 0.79–0.94), $P=0.001$ for drink score 3), although in smokers, alcohol was not associated with a lower prevalence of proteinuria. In female nonsmokers, a drink score of 1 had a significant association with a lower prevalence

Table 1 The clinical characteristics of 117 692 men stratified according to smokers and nonsmorkers

	Nonsmokers	*Smokers*	P-value
N (%)	87 517 (74.4)	30 175 (25.6)	
Age (year)	67 (62–71)	64 (55–69)	<0.001
BMI (kg/m^2)	23.7±2.9	23.3±3.2	<0.001
Systolic blood pressure (mmHg)	131.1±16.5	129.6±17.5	<0.001
Diastolic blood pressure (mmHg)	77.9±10.4	77.4±11.0	<0.001
Pulse pressure (mmHg)	53.1±12.5	52.2±12.7	<0.001
MAP (mmHg)	95.6±11.3	94.8±12.1	<0.001
eGFR (ml/min/1.73 m^2)	72.9 (63.8–84.0)	76.1 (66.6–87.7)	<0.001
CKD stage 1 (eGFR ≧90) (*n* (%))	9724 (11.1)	6134 (20.3)	<0.001
stage 2 (eGFR 60–89) (*n* (%))	60 653 (69.3)	20 479 (67.9)	
stage 3 (eGFR 30–59) (*n* (%))	16 799 (19.2)	3499 (11.6)	
stage 4 (eGFR 15–29) (*n* (%))	259 (0.3)	40 (0.13)	
stage 5 (eGFR <15) (*n* (%))	82 (0.09)	23 (0.08)	
Urinary protein by dipstick test			
Negative (*n* (%))	72 305 (82.6)	24 173 (80.1)	<0.001
±	8664 (9.9)	3322 (11.0)	
1+	4347 (5.0)	1790 (5.9)	
2+	1654 (1.9)	664 (2.2)	
3+ or more	547 (0.6)	226 (0.8)	
Triglyceride (mg/dl)	108 (77–154)	122 (86–180)	<0.001
HDL cholesterol (mg/dl)	58.1±15.3	55.3±15.4	<0.001
LDL cholesterol (mg/dl)	120.7±29.1	119.2±32.0	<0.001
Hemoglobin A1c (%)	5.38±0.76	5.43±0.88	<0.001
FBS (mg/dl)	101.9±23.5	101.8±26.8	0.539
Uric acid (mg/dl)	5.95±1.31	5.95±1.33	0.91
*Past history of heart disease (*n *(%))*	8301 (9.5)	1724 (5.7)	<0.001
Stroke (*n* (%))	5180 (5.9)	1076 (3.6)	<0.001
Kidney disease (*n* (%))	546 (0.6)	157 (0.5)	0.044
Current drug history of			
Antihypertensive medications (*n* (%))	31 230 (35.7)	8403 (27.9)	<0.001
Antihyperglycemia medications (*n* (%))	6461 (7.4)	2176 (7.2)	0.325
Anticholesteremic medications (*n* (%))	11 301 (12.9)	2954 (9.8)	<0.001
Prevalence of hypertension (n (%))	28 194 (32.2)	9047 (30.0)	<0.001
diabetes mellitus (*n* (%))	27 784 (31.8)	10 338 (34.3)	<0.001
dyslipidemia (*n* (%))	55 731 (63.7)	20 184 (66.9)	<0.001
Drinking rarely (*n* (%))	13 935 (15.9)	4164 (13.8)	<0.001
occasionally	964 (1.1)	234 (0.8)	
≦19 g/day	35 245 (40.3)	9196 (30.5)	
20–39 g/day	25 996 (29.7)	9776 (32.4)	
40–59 g/day	8933 (10.2)	5089 (16.9)	
≧60 g/day	2444 (2.8)	1716 (5.7)	

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FBS, fasting blood sugar; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MAP, mean arterial pressure.
Mean±s.d., median (25–75%).

of proteinuria (*vs.* a drink score of 0, multivariate-adjusted OR 0.75 (95% CI 0.59–0.96), $P=0.021$), although in smokers, the association of alcohol and proteinuria was not observed.

We examined the relationship between alcohol consumption and eGFR <60 ml/min/1.73 m^2 stratified by smoking. In both genders, univariate and multivariate model analyses demonstrated that alcohol consumption was associated with a lower prevalence of eGFR <60 ml/min/1.73 m^2 (Tables 5 and 6). The multivariate analysis of eGFR <60 ml/min/1.73 m^2 revealed that in both smokers and nonsmokers, alcohol consumption was inversely associated with the risk of chronic kidney disease. In male nonsmokers, drink scores from 1 to 5 had a significant association with a lower prevalence of eGFR<60 ml/min1.73 m^2 (*vs.* a drink score of 0, multivariate-adjusted OR 0.71 (95% CI 0.59–0.85), $P<0.001$ for drink score 1, 0.90 (0.85–0.95), $P<0.001$ for drink score 2, 0.62 (0.58–0.65), $P<0.001$ for drink score 3, 0.54 (0.49–0.58), $P<0.001$ for drink score 4 and 0.57 (0.49–0.65), $P<0.001$ for drink score 5), and in smokers, drink scores from 1 to 5 had a significant association with a lower prevalence of eGFR <60 ml/min/1.73 m^2 (*vs.* a drink score of 0, multivariate-adjusted OR 0.58 (95% CI 0.36–0.96), $P=0.033$ for drink score 1, 0.80 (0.71–0.90), $P<0.001$ for drink score 2, 0.61 (0.54–0.69), $P<0.001$ for drink score 3, 0.45 (0.39–0.53), $P<0.001$ for drink score 4 and 0.39 (0.31–0.50), $P<0.001$ for drink score 5). In female nonsmokers, drink scores from 1 to 5 had a significant association

Table 2 The clinical characteristics of 174 321 women stratified according to smokers and nonsmokers

	Nonsmokers	*Smokers*	P-value
N (%)	163 972 (94.1)	10 349 (5.9)	
Age (year)	66 (61–70)	59 (50–66)	<0.001
BMI (kg/m^2)	22.7±3.4	22.2±3.6	<0.001
Systolic blood pressure (mmHg)	127.9±17.2	122.8±18.0	<0.001
Diastolic blood pressure (mmHg)	74.8±10.3	73.0±10.9	<0.001
Pulse pressure (mmHg)	53.1±12.6	49.8±12.5	<0.001
MAP (mmHg)	92.5±11.6	89.6±12.4	<0.001
eGFR (ml/min/1.73 m^2)	74.7 (63.9–89)	77.8 (68.1–91.6)	<0.001
CKD stage 1 (eGFR ≧90) (*n* (%))	36 053 (22.0)	2936 (28.4)	<0.001
stage 2 (eGFR 60–89) (*n* (%))	109 149 (66.6)	6488 (62.7)	
stage 3 (eGFR 30–59) (*n* (%))	18 456 (11.3)	897 (8.7)	
stage 4 (eGFR 15–29) (*n* (%))	223 (0.1)	19 (0.2)	
stage 5 (eGFR <15) (*n* (%))	91 (0.1)	9 (0.1)	
Urinary protein by dipstick test			
Negative (*n* (%))	146 144 (89.1)	8951 (86.5)	<0.001
±	11 721 (7.2)	905 (8.7)	
1+	4567 (2.8)	357 (3.5)	
2+	1177 (0.7)	106 (1.0)	
3+or more	363 (0.2)	30 (0.3)	
Triglyceride (mg/dl)	95 (70–131)	102 (73–148)	<0.001
HDL cholesterol (mg/dl)	66.3±16.2	65.1±16.9	<0.001
LDL cholesterol (mg/dl)	129.5±29.9	125.4±33.3	<0.001
Hemoglobin A1c (%)	5.32±0.58	5.26±0.70	<0.001
FBS (mg/dl)	94.7±17.2	94.2±21.5	0.014
Uric acid (mg/dl)	4.63±1.06	4.74±1.17	<0.001
*Past history of heart disease (*n *(%))*	8728 (5.3)	428 (4.1)	<0.001
Stroke (*n* (%))	4739 (2.9)	221 (2.1)	<0.001
Kidney disease (*n* (%))	690 (0.4)	62 (0.6)	0.007
Current drug history of			
Antihypertensive medications (*n* (%))	46 484 (28.4)	2145 (20.7)	<0.001
Antihyperglycemia medications (*n* (%))	6308 (3.9)	410 (4.0)	0.556
Anticholesteremic medications (*n* (%))	35 228 (21.5)	1494 (14.4)	<0.001
Prevalence of hypertension (n (%))	41 836 (25.5)	1929 (18.6)	<0.001
diabetes mellitus (*n* (%))	44 818 (27.3)	2916 (28.2)	0.062
dyslipidemia (*n* (%))	110 045 (67.1)	6588 (63.7)	<0.001
Drinking rarely (*n* (%))	68 829 (42.0)	2950 (28.5)	<0.001
occasionally	2510 (1.5)	156 (1.5)	
≦19 g/day	82 141 (50.1)	4319 (41.7)	
20–39 g/day	8286 (5.1)	1779 (17.2)	
40–59 g/day	1683 (1.0)	746 (7.2)	
≧60 g/day	523 (0.3)	399 (3.9)	

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FBS, fasting blood sugar; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MAP, mean arterial pressure.
Mean±s.d., median (25–75%).

with a lower prevalence of eGFR <60 mlml/min/1.73 m^2 (*vs.* a drink score of 0, multivariate-adjusted OR 0.74 (95% CI 0.64–0.86), $P<0.001$ for drink score 1, 0.94 (0.91–0.97), $P=0.001$ for drink score 2, 0.66 (0.60–0.72), $P<0.001$ for drink score 3, 0.53 (0.43–0.65), $P<0.001$ for drink score 4 and 0.35 (0.23–0.54), $P<0.001$ for drink score 5), and in smokers, drink scores from 3 to 5 had a significant association with a lower prevalence of eGFR <60 ml/min/1.73 m^2 (*vs.* a drink score of 0, multivariate-adjusted OR 0.55 (95% CI 0.42–0.72), $P<0.001$ for drink score 3, 0.51 (0.34–0.75), $P=0.001$ for drink score 4, and 0.27 (0.14–0.54), $P<0.001$ for drink score 5). In female smokers, the association between drink scores of 1 and 2 and a lower prevalence of eGFR <60 ml/min/1.73 m^2 was not observed.

We also calculated the odds ratio of each drink score using univariate and multivariate logistic regression models, excluding the person with the past medical history (heart disease, stroke and kidney disease), dividing it into smoking and nonsmoking, with the presence of proteinuria as the dependent variable (Supplementary Tables 1 and 2). Furthermore, we calculated the odds ratio of each drink score using univariate and multivariate logistic regression models, excluding the person with the past medical history (heart disease, stroke and kidney disease), dividing it into smoking and nonsmoking, with the presence of eGFR <60 (mlml/min/1.73 m^2) as the dependent variable (Supplementary Tables 3 and 4). Compared with Tables 3,4,5,6, these results were almost similar.

Table 3 The associations of alcohol consumption and proteinuria in men stratified by smoking

	Nonsmokers				*Smokers*			
	Univariate model		*Multivariate model*[a]		*Univariate model*		*Multivariate model*[a]	
	OR (95% CI)	P-value	*OR (95% CI)*	P-value	*OR (95% CI)*	P-value	*OR (95% CI)*	P-value
Drinking rarely (*n* (%))	Reference		Reference		Reference		Reference	
occasionally	0.87 (0.68–1.12)	0.228	0.82 (0.62–1.08)	0.164	0.68 (0.40–1.17)	0.163	0.78 (0.43–1.39)	0.398
≦19 g/day	0.87 (0.81–0.93)	<0.001	0.90 (0.83–0.98)	0.012	0.95 (0.83–1.07)	0.411	0.94 (0.81–1.08)	0.368
20–39 g/day	0.87 (0.80–0.94)	<0.001	0.87 (0.79–0.94)	0.001	0.96 (0.85–1.09)	0.524	0.92 (0.80–1.07)	0.256
40–59 g/day	0.95 (0.86–1.05)	0.299	0.96 (0.86–1.07)	0.467	0.99 (0.86–1.14)	0.917	0.98 (0.83–1.16)	0.844
≧60 g/day	1.05 (0.90–1.23)	0.506	1.09 (0.92–1.28)	0.33	1.11 (0.92–1.34)	0.271	1.06 (0.85–1.32)	0.595
Age (× 10 years)	1.22 (1.18–1.26)	<0.001	1.17 (1.12–1.22)	<0.001	1.19 (1.14–1.25)	<0.001	1.14 (1.08–1.20)	<0.001
BMI (× 10 kg/m^2)	2.98 (2.75–3.23)	<0.001	2.07 (1.88–2.28)	<0.001	2.11 (1.88–2.38)	<0.001	1.64 (1.42–1.90)	<0.001
Systolic BP (mmHg)	1.02 (1.02–1.02)	<0.001	1.02 (1.01–1.02)	<0.001	1.02 (1.01–1.02)	<0.001	1.02 (1.01–1.02)	<0.001
Diastolic BP (mmHg)	1.02 (1.01–1.02)	<0.001	1.00 (0.99–1.00)	0.029	1.02 (1.02–1.03)	<0.001	1.00 (0.99–1.00)	0.981
Triglyceride (Log$_{10}$ mg/dl)	2.33 (2.10–2.60)	<0.001	1.18 (1.03–1.35)	0.018	1.93 (1.65–2.26)	<0.001	1.16 (0.95–1.43)	0.154
HDL-C (× 10 mg/dl)	0.90 (0.89–0.92)	<0.001	1.00 (0.97–1.02)	0.714	0.96 (0.94–0.99)	0.004	1.02 (0.98–1.06)	0.276
Hemoglobin A1c (%)	1.54 (1.51–1.58)	<0.001	1.48 (1.44–1.52)	<0.001	1.47 (1.42–1.51)	<0.001	1.47 (1.41–1.53)	<0.001
Uric acid (mg/dl)	1.16 (1.14–1.18)	<0.001	1.15 (1.12–1.17)	<0.001	1.12 (1.09–1.16)	<0.001	1.15 (1.11–1.19)	<0.001
Past history of								
Heart disease	1.57 (1.46–1.69)	<0.001	1.40 (1.28–1.52)	<0.001	1.80 (1.56–2.07)	<0.001	1.63 (1.39–1.90)	<0.001
Stroke	1.85 (1.70–2.02)	<0.001	1.57 (1.43–1.73)	<0.001	1.81 (1.52–2.16)	<0.001	1.46 (1.20–1.77)	<0.001

Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; OR, odds ratio.
[a]Adjusted for alcohol consumption, age, body mass index, mean arterial pressure, triglyceride level, HDL cholesterol level, hemoglobin A1c, uric acid, past history of heart disease and stroke.

Table 4 The associations of alcohol consumption and proteinuria in women stratified by smoking

	Nonsmokers				*Smokers*			
	Univariate model		*Multivariate model*[a]		*Univariate model*		*Multivariate model*[a]	
	OR (95% CI)	P-value	*OR (95% CI)*	P-value	*OR (95% CI)*	P-value	*OR (95% CI)*	P-value
Drinking rarely (*n* (%))	Reference		Reference		Reference		Reference	
occasionally	0.76 (0.60–0.96)	0.022	0.75 (0.59–0.96)	0.021	0.65 (0.26–1.60)	0.343	0.49 (0.15–1.56)	0.226
≦19 g/day	0.95 (0.90–1.00)	0.055	1.00 (0.95–1.06)	0.882	0.96 (0.77–1.20)	0.722	0.91 (0.71–1.16)	0.443
20–39 g/day	0.92 (0.81–1.04)	0.184	1.02 (0.89–1.17)	0.756	0.95 (0.72–1.26)	0.737	0.85 (0.62–1.17)	0.314
40–59 g/day	1.00 (0.78–1.29)	0.97	1.06 (0.81–1.39)	0.673	0.99 (0.68–1.44)	0.95	0.71 (0.46–1.11)	0.132
≧60 g/day	1.26 (0.84–1.88)	0.269	1.14 (0.74–1.76)	0.541	1.14 (0.72–1.80)	0.585	0.81 (0.47–1.38)	0.431
Age (× 10 years)	1.16 (1.12–1.20)	<0.001	0.97 (0.93–1.01)	0.11	1.18 (1.07–1.30)	0.001	0.87 (0.77–0.98)	0.025
BMI (× 10 kg/m^2)	2.79 (2.61–2.97)	<0.001	1.58 (1.46–1.71)	<0.001	1.88 (1.50–2.37)	<0.001	1.00 (0.75–1.35)	0.973
Systolic BP (mmHg)	1.02 (1.02–1.02)	<0.001	1.01 (1.01–1.02)	<0.001	1.02 (1.02–1.03)	<0.001	1.02 (1.01–1.03)	<0.001
Diastolic BP (mmHg)	1.03 (1.02–1.03)	<0.001	1.01 (1.00–1.01)	0.001	1.02 (1.01–1.03)	<0.001	0.99 (0.97–1.00)	0.032
Triglyceride (Log$_{10}$ mg/dl)	2.90 (2.57–3.26)	<0.001	1.00 (0.85–1.17)	0.981	3.80 (2.62–5.51)	<0.001	1.61 (0.98–2.65)	0.063
HDL-C (× 10 mg/dl)	0.88 (0.86–0.89)	<0.001	0.97 (0.95–0.99)	0.013	0.95 (0.90–1.01)	0.101	1.07 (1.00–1.14)	0.069
Hemoglobin A1c (%)	1.58 (1.54–1.62)	<0.001	1.44 (1.40–1.49)	<0.001	1.51 (1.39–1.63)	<0.001	1.43 (1.30–1.57)	<0.001
Uric acid (mg/dl)	1.43 (1.40–1.47)	<0.001	1.30 (1.27–1.33)	<0.001	1.50 (1.39–1.61)	<0.001	1.45 (1.34–1.58)	<0.001
Past history of								
Heart disease	1.53 (1.39–1.68)	<0.001	1.33 (1.20–1.48)	0.003	2.03 (1.43–2.87)	<0.001	1.75 (1.19–2.56)	0.004
Stroke	1.57 (1.38–1.78)	<0.001	1.24 (1.08–1.42)	<0.001	1.92 (1.19–3.09)	0.008	1.50 (0.88–2.55)	0.136

Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; OR, odds ratio.
[a]Adjusted for alcohol consumption, age, body mass index, mean arterial pressure, triglyceride level, HDL cholesterol level, hemoglobin A1c, uric acid, past history of heart disease and stroke.

DISCUSSION

In the present cross-sectional study of 292 013 individuals undergoing the Specific Health Check and Guidance in Japan, it was observed that in nonsmokers, a small amount of drinking was associated with a lower prevalence of proteinuria. However, in smokers, the association between alcohol and proteinuria was not observed. In the analysis

Table 5 The associations of alcohol consumption and eGFR <60 ml/min/1.73 m^2 in men stratified by smoking

	Nonsmokers				*Smokers*			
	Univariate model		*Multivariate model*[a]		*Univariate model*		*Multivariate model*[a]	
	OR (95% CI)	P-value	*OR (95% CI)*	P-value	*OR (95% CI)*	P-value	*OR (95% CI)*	P-value
Drinking rarely (*n* (%))	Reference		Reference		Reference		Reference	
occasionally	0.81 (0.69–0.96)	0.012	0.71 (0.59–0.85)	<0.001	0.63 (0.41–0.98)	0.038	0.58 (0.36–0.96)	0.033
≦19 g/day	0.94 (0.90–0.99)	0.014	0.90 (0.85–0.95)	<0.001	0.93 (0.83–1.03)	0.145	0.80 (0.71–0.90)	<0.001
20–39 g/day	0.70 (0.66–0.73)	<0.001	0.62 (0.58–0.65)	<0.001	0.76 (0.68–0.84)	<0.001	0.61 (0.54–0.69)	<0.001
40–59 g/day	0.56 (0.52–0.60)	<0.001	0.54 (0.49–0.58)	<0.001	0.51 (0.45–0.59)	<0.001	0.45 (0.39–0.53)	<0.001
≧60 g/day	0.51 (0.45–0.58)	<0.001	0.57 (0.49–0.65)	<0.001	0.38 (0.30–0.47)	<0.001	0.39 (0.31–0.50)	<0.001
Age (× 10 years)	2.06 (2.01–2.12)	<0.001	2.26 (2.19–2.34)	<0.001	2.51 (2.38–2.64)	<0.001	2.76 (2.59–2.94)	<0.001
BMI (× 10 kg/m^2)	1.72 (1.63–1.82)	<0.001	1.32 (1.23–1.41)	<0.001	1.64 (1.47–1.82)	<0.001	1.55 (1.35–1.78)	<0.001
Systolic BP (mmHg)	1.01 (1.00–1.01)	<0.001	1.00 (0.99–1.00)	<0.001	1.01 (1.00–1.01)	<0.001	1.00 (0.99–1.00)	0.247
Diastolic BP (mmHg)	1.00 (1.00–1.01)	<0.001	1.01 (1.00–1.01)	<0.001	1.00 (1.00–1.01)	0.011	1.01 (1.00–1.01)	0.002
Triglyceride (Log_{10} mg/dl)	1.94 (1.80–2.08)	<0.001	1.20 (1.08–1.32)	<0.001	1.72 (1.50–1.98)	<0.001	1.41 (1.16–1.72)	<0.001
HDL-C (× 10 mg/dl)	0.87 (0.86–0.88)	<0.001	0.96 (0.95–0.97)	<0.001	0.88 (0.86–0.90)	<0.001	0.99 (0.96–1.02)	0.489
Hemoglobin A1c (%)	1.03 (1.01–1.05)	0.005	1.00 (0.97–1.02)	0.831	1.06 (1.02–1.10)	0.003	1.02 (0.97–1.07)	0.524
Uric acid (mg/dl)	1.56 (1.54–1.59)	<0.001	1.66 (1.63–1.68)	<0.001	1.50 (1.46–1.54)	<0.001	1.62 (1.57–1.68)	<0.001
Past history of								
Heart disease	1.71 (1.63–1.80)	<0.001	1.39 (1.31–1.47)	<0.001	2.28 (2.02–2.57)	<0.001	1.64 (1.42–1.88)	<0.001
Stroke	1.74 (1.63–1.85)	<0.001	1.35 (1.26–1.45)	<0.001	2.15 (1.85–2.50)	<0.001	1.39 (1.17–1.65)	<0.001

Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; OR, odds ratio.
[a]Adjusted for alcohol consumption, age, body mass index, mean arterial pressure, triglyceride level, HDL cholesterol level, hemoglobin A1c, uric acid, past history of heart disease and stroke.

regarding eGFR <60 ml/min/1.73 m^2, it was observed that in both smokers and nonsmokers, alcohol consumption was inversely associated with the risk of CKD; however, in female smokers, the association of drink scores 1 and 2 with a lower prevalence of eGFR <60 ml/min/1.73 m^2 was not observed.

Although alcohol consumption has been found to be protective for CVD,[20] the relationship between alcohol consumption and kidney disease is complex and controversial. On the one hand, alcohol consumption has been associated with the risk of CKD.[28,33] A population-based cohort study in the United States reported that drinking $\geqslant 4$ servings daily was independently associated with an increased CKD risk[28] (each serving of beer, wine and liquor was considered to contain 12.96, 11.48 and 14.00 g of ethanol, respectively[34]). A case–control study in the United States reported that the consumption of more than two alcoholic drinks per day was associated with an increased risk of ESRD and that a lower intake of alcohol did not appear to be harmful.[33]

On the other hand, alcohol consumption has been inversely associated with the risk of CKD.[25–27,35–37] A prospective cohort study of 11 023 initially healthy male physicians in the United States reported a significantly lower risk of renal dysfunction (defined as serum creatinine $\geqslant 1.5$ mg/dl and eGFR $\leqslant 55$ ml/min) in those who consumed at least 7 drinks weekly.[37] A prospective cohort study in China reported a significant inverse relationship between alcohol consumption and risk of ESRD in men and a stronger relationship in those who had more than 21 drinks weekly.[25] A prospective cohort study in Australia reported a significantly reduced risk of CKD (defined as eGFR <60 ml/min/1.73 m^2) in men who consumed at least 30 g of alcohol daily.[26] A prospective cohort study in Japan reported that in men aged ≧40 years, an average daily alcohol consumption of <20 g/day decreased the risk of CKD compared with nondrinkers, whereas an average daily alcohol consumption of ≧20 g/day was not associated with the risk of CKD.[27]

In our results, mild to moderate alcohol consumption was associated with a lower incidence of proteinuria, and this finding was consistent with previous publications. However, in smokers, the association of alcohol with proteinuria was not observed, and hence this association might be no longer significant.

Furthermore, alcohol consumption was inversely associated with the risk of decreased eGFR, but in female smokers, the association between mild to moderate alcohol consumption and a lower prevalence of eGFR <60 ml/min/1.73 m^2 was not observed. We suspect that smoking may modify the potential benefits of alcohol to prevent CKD. Alcohol also has an adverse effect on driving safety and can increase violent behavior, liver dysfunction and some cancers; therefore, the results regarding alcohol intake should be interpreted carefully. Nevertheless, in nonsmokers, mild to moderate alcohol consumption may not need to be prohibited, at least regarding its effects on kidney function. On the other hand, alcohol intake may not be recommended for smokers.

Some clinical studies have indicated the mechanisms involved with alcohol consumption, for example, that moderate consumption may be associated with increased HDL and plasma concentration of endogenous tissue-type plasminogen activator,[38,39] thereby protecting against atherosclerosis. However, the mechanisms of alcohol consumption and CKD are not yet clear. Recently, McCarthy *et al.*[40] reported that ethanol at low concentrations (0.02–0.1 mmol/ml) protected glomerular podocytes through alcohol dehydrogenase and 20-hydroxyeicosatetraenoic acid. Ethanol at high concentrations (0.4 mmol/ml) altered the actin cytoskeleton, induced CYP2e1, increased superoxide production and inhibited alcohol dehydrogenase gene expression. Ethanol at low concentrations upregulated the expression of alcohol dehydrogenase and CYP4a12a. In addition, 20-hydroxyeicosatetraenoic acid, an arachidonic acid metabolite generated by CYP4a12a, blocked the ethanol-induced cytoskeletal derangement and superoxide generation. Changes in podocyte

Table 6 The associations of alcohol consumption and eGFR <60 ml/min/1.73 m^2 in women stratified by smoking

	Nonsmokers				*Smokers*			
	Univariate model		*Multivariate model*[a]		*Univariate model*		*Multivariate model*[a]	
	OR (95% CI)	P-value	*OR (95% CI)*	P-value	*OR (95% CI)*	P-value	*OR (95% CI)*	P-value
Drinking rarely (*n* (%))	Reference		Reference		Reference		Reference	
occasionally	0.84 (0.74–0.96)	0.011	0.74 (0.64–0.86)	<0.001	0.71 (0.39–1.29)	0.258	0.61 (0.29–1.30)	0.195
≦19 g/day	0.92 (0.89–0.95)	<0.001	0.94 (0.91–0.97)	0.001	0.93 (0.80–1.09)	0.363	0.90 (0.75–1.07)	0.24
20–39 g/day	0.65 (0.59–0.70)	<0.001	0.66 (0.60–0.72)	<0.001	0.61 (0.49–0.76)	<0.001	0.55 (0.42–0.72)	<0.001
40–59 g/day	0.58 (0.49–0.70)	<0.001	0.53 (0.43–0.65)	<0.001	0.52 (0.37–0.72)	<0.001	0.51 (0.34–0.75)	0.001
≧60 g/day	0.42 (0.29–0.62)	<0.001	0.35 (0.23–0.54)	<0.001	0.29 (0.16–0.50)	<0.001	0.27 (0.14–0.54)	<0.001
Age (× 10 years)	1.69 (1.65–1.73)	<0.001	1.59 (1.54–1.63)	<0.001	2.08 (1.92–2.26)	<0.001	1.90 (1.69–2.07)	<0.001
BMI (× 10 kg/m^2)	1.51 (1.45–1.58)	<0.001	0.77 (0.73–0.81)	<0.001	1.40 (1.17–1.67)	<0.001	0.76 (0.59–0.97)	0.026
Systolic BP (mm Hg)	1.01 (1.00–1.01)	<0.001	0.99 (0.99–1.00)	<0.001	1.01 (1.00–1.01)	<0.001	0.99 (0.88–1.00)	0.045
Diastolic BP (mm Hg)	1.01 (1.00–1.01)	<0.001	1.00 (1.00–1.01)	0.002	1.01 (1.00–1.01)	0.01	1.00 (1.00–1.01)	0.605
Triglyceride (Log_{10} mg/dl)	2.65 (2.47–2.85)	<0.001	1.22 (1.11–1.34)	<0.001	3.15 (2.38–4.18)	<0.001	1.72 (1.14–2.57)	0.009
HDL-C (× 10 mg/dl)	0.92 (0.91–0.93)	<0.001	1.01 (0.99–1.02)	0.239	0.88 (0.85–0.92)	<0.001	0.99 (0.93–1.04)	0.606
Hemoglobin A1c (%)	1.05 (1.02–1.07)	<0.001	0.86 (0.83–0.89)	<0.001	1.17 (1.08–1.26)	<0.001	0.97 (0.86–1.09)	0.673
Uric acid (mg/dl)	1.99 (1.96–2.02)	<0.001	2.02 (1.99–2.06)	<0.001	1.73 (1.63–1.84)	<0.001	1.73 (1.62–1.85)	<0.001
Past history of								
Heart disease	1.57 (1.48–1.67)	<0.001	1.23 (1.15–1.32)	<0.001	2.43 (1.88–3.13)	<0.001	1.50 (1.11–2.03)	0.009
Stroke	1.70 (1.58–1.84)	<0.001	1.36 (1.25–1.49)	<0.001	1.82 (1.25–2.65)	0.002	0.98 (0.62–1.52)	0.913

Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; OR, odds ratio.
[a]Adjusted for alcohol consumption, age, body mass index, mean arterial pressure, triglyceride level, HDL cholesterol level, hemoglobin A1c, uric acid, past history of heart disease and stroke.

structure and the resulting alterations in glomerular filtration barrier function may be early events in the progressive loss of glomerular function and the onset of proteinuria and chronic disease. Ethanol may positively and negatively affect several metabolites and signaling pathways involved in regulating glomerular barrier function.[40]

There are several limitations to this study. First, we could not infer a causal relationship between drink scores and proteinuria and eGFR because of the cross-sectional nature of the study. Further studies are needed to examine the causality of our findings. Second, the presence of proteinuria was determined by a single measurement using a dipstick test that may have led to misclassifications. Prior studies have shown that even a single dipstick indication of proteinuria is a significant risk factor for all-cause mortality, cardiovascular mortality[41,42] and ESRD.[43,44] Third, the drinking and smoking habits of the participants were evaluated only by a self-reported questionnaire. Therefore, a reporting bias may have existed in the entire cohort. However, because the participants did not benefit from answering the questions inaccurately or untruthfully, accurate information was expected. Fourth, we did not have information on the type of alcoholic beverage. Some characteristics have been reported to be because of the type. For example, long-term exposure to polyphenol-rich red wine has been shown to lead to an enhancement of antioxidant defenses in rat plasma and kidney.[45] Fifth, there is a huge potential for selection bias in this study, with nearly 60% excluded, mostly because of missing data on the effect modifier and exposure. Sixth, only current smoking was assessed; this habit may change as individuals become ill and hence past smoking may be more relevant to current CKD risk.

In this cross-sectional study, mild to moderate alcohol consumption was associated with a lower prevalence of proteinuria, but this association was slightly attenuated in smokers. Furthermore, alcohol consumption was inversely associated with the risk of a decreased eGFR. We suspect that mild to moderate alcohol consumption may be associated with a lower risk of CKD (proteinuria and eGFR), especially among nonsmokers, because smoking might have modified the potential benefits of alcohol to prevent CKD.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on Hypertension Research website (http://www.nature.com/hr)