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Alcohol consumption is inversely associated with the risk of developing chronic kidney disease

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There are few reports of associations between alcohol consumption and risk of chronic kidney disease (CKD). To investigate this further, we studied 5476 participants aged 28–75 years in the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study, a prospective population-based cohort, who were free of CKD at baseline (1997/1998). Alcohol consumption was self-reported on a questionnaire validated against serum high-density lipoprotein cholesterol. The primary outcome was *de novo* CKD defined as a combination of a creatinine–cystatin C–based estimated glomerular filtration rate (eGFR) under 60 ml/min per 1.73 m^2 and/or the mean of two consecutive 24-h urinary albumin excretions over 30 mg. During four serial follow-up examinations (median 10.2 years until February 2012), 903 participants developed CKD. Compared with those abstaining from alcohol, the multivariable-adjusted hazard ratios (95% confidence interval) for CKD risk were 0.85 (0.69–1.04) for occasional (under 10 g/week), 0.82 (0.69–0.98) for light (10–69.9 g/week), 0.71 (0.58–0.88) for moderate (70–210 g/week), and 0.60 (0.42–0.86) for heavier (over 210 g/week) alcohol consumers (significant trend). Similar inverse associations for alcohol consumption were found when CKD was defined as eGFR <60 ml/min per 1.73 m^2 or as 24-h urinary albumin excretion over 30 mg. Thus, in this population-based cohort, alcohol consumption was inversely associated with the risk of developing CKD.

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Although alcohol consumption, particularly in moderation, has consistently been linked to a lower risk of cardiovascular disease[1] and type 2 diabetes,[2] its association with the risk of chronic kidney disease (CKD) has received considerably less attention. So far, longitudinal cohort studies that have examined the effect of alcohol consumption on the development of CKD observed mostly inverse associations,[3–5] although some inconsistency exists.[5,6]

Most previous studies on alcohol and CKD risk relied on serum creatinine–based equations to assess glomerular filtration rate (GFR), such as the Cockgroft–Gault[7] or the Modification of Diet in Renal Disease (MDRD),[8] with uncertain validity in general population cohorts with higher GFR.[9,10] Furthermore, creatinine-based estimates to assess GFR are relatively imprecise owing to variation in nonrenal determinants of serum creatinine, a by-product of muscle breakdown. Such nonrenal influences—for example, meat intake, lean body mass, and muscle metabolism—may be related to alcohol consumption, which may introduce a varying degree of measurement bias in the estimation of GFR. A recently developed and validated equitation that also uses serum cystatin C as complementary filtration marker has been shown to be more accurate for estimating GFR,[11] and may thus be less subjective to the aforementioned shortcomings.

Besides estimated GFR (eGFR), urinary albumin excretion (UAE) can be used to supplement the classification of CKD.[12] So far, only two prospective cohort studies have investigated the relationship between alcohol intake and both components of CKD, albeit separately, and with opposing findings on albuminuria.[4,5]

Hence, we evaluated the association between alcohol consumption and the risk of CKD among participants in a population-based cohort study free of CKD at baseline and with serial measurements of serum creatinine, serum cystatin C, and UAE for a more optimal and integral definition of CKD.

RESULTS

Baseline characteristics of the study population according to alcohol consumption categories are shown in Table 1.

Table 1 | Baseline characteristics according to alcohol consumption among 5476 participants of the PREVEND study

Variables	Overall	Alcohol consumption categories (g of alcohol)					P-value
		No	Occasional (<10 g/wk)	Light (10–69.9 g/wk)	Moderate (70–210 g/wk)	Heavier (>210 g/wk)	
Participants, *N* (%)	5476	1285 (23.5)	860 (15.7)	1949 (35.6)	1121 (20.5)	261 (4.8)	
Age (years)	48.4 ± 11.7	50.2 ± 12.6	47.4 ± 12.5§	47.1 ± 11.4§	48.8 ± 10.7‡	49.2 ± 10.1	<0.001
Female, *n* (%)	2881 (52.6)	889 (69.2)	554 (64.4)*	928 (47.6)§	445 (39.8)§	65 (24.9)§	<0.001
Smoking, n *(%)*							
Never	1729 (31.7)	540 (42.3)	351 (41.0)	589 (30.3)‡	213 (19.1)§	36 (13.8)§	<0.001
Former	1985 (36.4)	372 (29.1)	287 (33.5)	761 (39.1)	477 (42.6)	88 (33.7)	
Current <6 cigarettes/day	298 (5.5)	56 (4.4)	46 (5.4)	114 (5.9)	71 (6.3)	11 (4.2)	
Current 6–20 cigarettes/day	1136 (20.8)	254 (19.9)	150 (17.5)	385 (19.8)	279 (24.9)	68 (26.1)	
Current >20 cigarettes/day	311 (5.7)	56 (4.4)	22 (2.6)	97 (5.0)	78 (7.0)	58 (22.2)	
Educational level, n *(%)*							
Low	2271 (41.5)	774 (60.2)	376 (43.7)§	674 (34.6)§	342 (30.5)§	105 (40.2)§	<0.001
Middle	1431 (26.1)	314 (24.4)	245 (28.5)	536 (27.5)	272 (24.2)	64 (24.5)	
High	1774 (32.4)	197 (15.3)	239 (27.8)	739 (37.9)	507 (45.2)	92 (35.2)	
Parental history of CKD, *n* (%)	82 (1.5)	25 (1.9)	11 (1.3)	24 (1.2)	17 (1.5)	5 (1.9)	0.49
History of CVD, *n* (%)	179 (3.3)	62 (4.8)	20 (2.3)‡	61 (3.1)*	32 (2.9)*	4 (1.5)*	0.003
Height (cm)	173.1 ± 9.4	169.6 ± 9.3	171.3 ± 9.0§	174.4 ± 9.2§	175.4 ± 9.1§	176.6 ± 8.7§	<0.001
Weight (kg)	77.1 ± 13.5	76.4 ± 14.6	76.2 ± 13.8	77.1 ± 12.8	77.9 ± 13.0‡	80.5 ± 13.6§	<0.001
Body mass index (kg/m^2)	25.7 ± 4.0	26.5 ± 4.7	25.9 ± 4.3§	25.3 ± 3.5§	25.3 ± 3.4§	25.8 ± 3.8‡	<0.001
Diastolic BP (mm Hg)	73 ± 9	73 ± 9	72 ± 9*	72 ± 9	74 ± 9‡	77 ± 9§	<0.001
Systolic BP (mm Hg)	126 ± 18	127 ± 20	125 ± 18	124 ± 17	127 ± 17	131 ± 17	<0.001
Use of BP-lowering drugs, (%)	639 (11.7)	222 (17.3)	95 (11.0)§	192 (9.9)§	100 (8.9)§	30 (11.5)*	<0.001
Hypertension, *n* (%)	1446 (26.4)	414 (32.2)	218 (25.3)‡	441 (22.6)§	284 (25.3)§	89 (34.1)	0.004
Total cholesterol (mmol/l)	5.6 ± 1.1	5.6 ± 1.1	5.5 ± 1.2*	5.5 ± 1.1‡	5.6 ± 1.1	5.8 ± 1.2‡	<0.001
HDL-cholesterol (mmol/l)	1.35 ± 0.39	1.30 ± 0.38	1.34 ± 0.4	1.36 ± 0.40§	1.40 ± 0.42§	1.37 ± 0.40*	<0.001
Triglycerides (mmol/l)	1.1 (0.8–1.6)	1.2 (0.9–1.7)	1.1 (0.8–1.6)‡	1.1 (0.8–1.5) §	1.1 (0.8–1.6)	1.2 (0.9–1.8)‡	<0.001
Use of lipid-lowering drugs, *n* (%)	281 (5.1)	91 (7.1)	41 (4.8)	78 (4.0) §	57 (5.1) *	14 (5.4)	0.016
Hypercholesterolemia, *n* (%)	1586 (29.0)	417 (32.5)	246 (28.6)	509 (26.1)§	323 (28.8)	91 (34.9)	0.15
Glucose (mmol/l)	4.7 ± 0.9	4.8 ± 1.1	4.7 ± 0.9‡	4.7 ± 0.7§	4.8 ± 0.9	5.0 ± 0.9	<0.001
HOMA-IR score	1.6 (1.1–2.4)	1.7 (1.2–2.7)	1.7 (1.2–2.5)	1.5 (1.0–2.2)§	1.5 (1.0–2.3)§	1.6 (1.0–2.5)	<0.001
Use of glucose-lowering drugs, *n* (%)	57 (1.0)	28 (2.2)	8 (0.9)*	12 (0.6)§	7 (0.6)‡	2 (0.8)	<0.001
Type 2 diabetes, *n* (%)	108 (2.0)	44 (3.4)	15 (1.7)*	21 (1.1)§	20 (1.8)*	8 (3.1)	0.009
C-reactive protein (mg/l)	1.1 (0.5–2.6)	1.4 (0.6–3.1)	1.1 (0.5–2.8)‡	0.9 (0.4–2.1)§	1.0 (0.4–2.5)§	1.4 (0.7–3.2)	<0.001
Creatinine (mg/dl)	0.80 ± 0.15	0.76 ± 0.15	0.78 ± 0.14	0.81 ± 0.15§	0.82 ± 0.15§	0.82 ± 0.14§	<0.001
Cystatin C (mg/l)	0.86 (0.77–0.95)	0.87 (0.78–0.97)	0.86 (0.77–0.95)	0.85 (0.77–0.94)§	0.86 (0.77–0.94)‡	0.87 (0.79–0.96)	<0.001
eGFR (ml/min per 1.73 m^2)	97.3 ± 14.8	95.1 ± 15.9	97.2 ± 14.8‡	98.3 ± 14.5§	98.0 ± 14.1§	98.2 ± 13.4‡	<0.001
Urine volume (ml per 24 h)	1576 ± 527	1513 ± 540	1568 ± 550*	1572 ± 513‡	1631 ± 502§	1714 ± 548§	<0.001
Urinary albumin excretion (mg per 24 h)	8.0 (5.8–12.3)	8.2 (5.8–12.3)	7.7 (5.7–11.8)	8.2 (6.0–12.0)	8.3 (6.1–12.4)	8.1 (5.9–12.9)	0.221

Abbreviations: BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate based on a combined creatinine-cystatin C equation; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment-insulin resistance; PREVEND, Prevention of Renal and Vascular End-Stage Disease; wk, week.

Data are expressed as mean ± s.d., median (interquartile range) or proportion *n* (%).

P-values were based on analysis of variance (nonskewed continuous variables), Kruskal–Wallis test (skewed continuous variables), or χ^2-test (categorical variables). Superscripts denote whether a categorical level of alcohol consumption category differs significantly from the categorical level of no alcohol consumption in that row; *$P<0.05$, ‡$P<0.01$, §$P<0.001$.

Consistent with prior studies, subjects who consumed more alcohol were more likely to be male, current smokers, and more highly educated. Because of the substantial difference in gender across drinking categories, we additionally stratified baseline characteristics by gender (Supplementary Table S1 online). To validate self-reported alcohol consumption at baseline, we determined the relationship between alcohol consumption categories and high-density lipoprotein (HDL)-cholesterol. Mean serum HDL-cholesterol concentrations increased with increasing alcohol consumption category in both women and men (Table 2).

Alcohol consumption was fairly stable during follow-up. For instance, alcohol consumption at the first (baseline) and second examination (a median of 4.2 years later) was highly correlated ($\rho = 0.82$; $P<0.001$; $N = 5414$). In addition, 3655 (67.5%) subjects who attended the second examination reported the same alcohol category as the first examination, and 5186 (95.8%) subjects were in the same or an adjacent alcohol consumption category.

During a median follow-up of 10.2 years (interquartile range, 6.2–11.4 years), a total of 903 participants developed CKD (defined as a creatinine–cystatin C–based eGFR

Table 2 | Serum high-density lipoprotein cholesterol concentrations according to self-reported alcohol consumption

	Alcohol consumption categories (g of alcohol)					
HDL-cholesterol, mmol/l	No	Occasional (<10 g/wk)	Light (10–69.9 g/wk)	Moderate (70–210 g/wk)	Heavier (>210 g/wk)	*P*-trend
Women						
n	878	553	916	442	65	
Age-adjusted	1.41 (1.38–1.43)	1.45 (1.42–1.48)‡	1.56 (1.54–1.59)§	1.65 (1.62–1.69)§	1.64 (1.54–1.73)§	<0.001
Multivariable-adjusted	1.43 (1.40–1.45)	1.44 (1.41–1.48)‡	1.54 (1.52–1.57)§	1.64 (1.61–1.68)§	1.70 (1.61–1.80)§	<0.001
Men						
n	394	301	1010	669	193	
Age-adjusted	1.08 (1.05–1.11)	1.13 (1.09–1.16)‡	1.17 (1.15–1.19)§	1.22 (1.20–1.25)§	1.27 (1.23–1.32)§	<0.001
Multivariable-adjusted	1.09 (1.06–1.11)	1.13 (1.09–1.16)‡	1.17 (1.15–1.18)§	1.23 (1.20–1.25)§	1.30 (1.26–1.34)§	<0.001

Abbreviations: HDL, high-density lipoprotein; wk, week.
Means (95% confidence intervals) and *P*-values were derived from general linear models. Multivariable-adjusted model was adjusted for age, height, weight, smoking status, parental history of chronic kidney disease, history of cardiovascular disease, educational level, and serum total cholesterol concentration. Superscripts denote whether the mean HDL level of a categorical level of alcohol consumption differs significantly from the categorical level of no alcohol consumption in that row; *$P<0.05$, ‡$P<0.01$, §$P<0.001$.
P-trend was derived from general linear models by treating alcohol consumption as a continuous linear term.

<60 ml/min per 1.73 m^2 or/and UAE >30 mg/24 h). Baseline alcohol consumption was inversely associated with the risk of CKD after multivariable adjustment, regardless of whether CKD was based on eGFR and UAE combined or based on eGFR or UAE alone (all *P*-trends are <0.05; Table 3). There were no material changes in the inverse associations after adjustment for potential intermediate variables of this association, including total to HDL-cholesterol ratio, the homeostatic model assessment for insulin resistance, and systolic blood pressure. The results were modestly attenuated when we controlled for baseline eGFR and UAE in the multivariable-adjusted model. Compared with nondrinkers, the hazard ratios (HRs; 95% confidence intervals (CIs)) for CKD risk were 0.95 (0.77–1.17) for occasional, 0.84 (0.71–1.00) for light, 0.77 (0.63–0.95) for moderate, and 0.69 (0.49–0.99) for heavier alcohol consumers (*P*-trend = 0.003). The inverse association was unchanged when we additionally accounted for 24-h urinary volume in the multivariable-adjusted model (*P*-trend < 0.001). The associations between alcohol consumption and risk of CKD defined according to creatinine-based or cystatin C–based equations to calculate eGFR are shown in the Supplementary Table S2 online. The inverse associations between alcohol consumption and the risk of CKD were generally similar in analyses stratified by selected characteristics (Table 4), with no significant interactions by age, sex, smoking, hypertension, or hypercholesterolemia (all *P*-interactions >0.30). Instead of specifying stratum-specific baseline hazard functions to account for the sampling design of the study, we also addressed the oversampling of subjects with elevated UAE by using design-based Cox proportional hazards regression models that took into account the probability of selection by statistical weighting. This analysis revealed similar results (Figure 1).

Sensitivity analyses

We excluded nondrinkers at baseline to remove the potential bias due to 'sick quitters'[13] among the nondrinkers. The multivariable HRs (95% CIs) were 0.95 (0.78–1.17) for light, 0.84 (0.66–1.05) for moderate, and 0.69 (0.49–1.01) for heavier drinkers compared with occasional drinkers (*P*-linear trend = 0.025). To further address this potential bias, we performed a sensitivity analysis starting from the second examination and added a category of former drinkers to the original five drinking categories. Compared with subjects who remained nondrinkers at the second examination, the multivariable-adjusted HRs (95% CIs) for risk of CKD were 0.68 (0.43–1.09) for former, 0.77 (0.59–1.02) for occasional, 0.73 (0.57–0.94) for light, 0.71 (0.54–0.93) for moderate, and 0.61 (0.40–0.94) for heavier alcohol consumers. Second, results were essentially the same when we excluded subjects at baseline with an eGFR <66 (instead of <60) ml/min per 1.73 m^2 and/or a UAE >25 (instead of >30) mg per 24 h for a more pronounced decline in kidney function during follow-up before reaching the CKD end point. Compared with nondrinkers, the multivariable-adjusted HRs (95% CIs) for CKD risk were 0.83 (0.65–1.04) for occasional, 0.80 (0.66–0.97) for light, 0.71 (0.57–0.90) for moderate, and 0.60 (0.41–0.90) for heavier alcohol consumers (*P*-trend = 0.001). Third, although this may introduce bias toward apparent health benefits of alcohol consumption because of reducing alcohol intake with increasing age/frailty, we performed time-varying Cox regression analyses in which we updated information on alcohol consumption and all potential confounders in the multivariable-adjusted model to allow for changes over time. The inverse association was not materially influenced when information on alcohol consumption and confounders of the multivariable-adjusted model was updated during follow-up to account for changes over time (Supplementary Table S3 online).

DISCUSSION

In this prospective population-based cohort study with repeated measurements of serum creatinine, serum cystatin C, and 24-h UAE to ascertain CKD, alcohol consumption was

Table 3 | Association between alcohol consumption and risk of CKD according to different CKD definitions*

CKD definition	No, $n = 1285$	Alcohol consumption categories (g of alcohol) Occasional (<10 g/wk), $n = 860$	Light (10–69.9 g/wk), $n = 1949$	Moderate (70–210 g/wk), $n = 1121$	Heavier (>210 g/wk), $n = 261$	*P*-trend†
$eGFR_{creatinine\text{-}cystatin\ C}$ <60 ml/min per 1.73 m^2 or urinary albumin excretion >30 mg per 24 h						
No. of cases (%)	256 (19.9)	137 (15.9)	303 (15.5)	170 (15.2)	37 (14.2)	
Person-years	10,827	7616	17,551	10,115	2374	
Age- and sex-adjusted HR	1.00 (Ref)	0.83 (0.67–1.02)	0.81 (0.69–0.96)*	0.72 (0.59–0.88)‡	0.64 (0.45–0.91)*	<0.001
Multivariable-adjusted HR	1.00 (Ref)	0.85 (0.69–1.04)	0.82 (0.69–0.98)*	0.71 (0.58–0.88)‡	0.60 (0.42–0.86)‡	<0.001
Multivariable-adjusted + potential mediators HR	1.00 (Ref)	0.85 (0.69–1.06)	0.88 (0.74–1.05)	0.76 (0.62–0.94)*	0.58 (0.40–0.84)‡	0.002
$eGFR_{creatinine\text{-}cystatin\ C}$ <60 ml/min per 1.73 m^2						
No. of cases (%)	100 (7.8)	50 (5.8)	96 (4.9)	45 (4.0)	9 (3.4)	
Person-years	11,570	8183	18,727	10,832	2498	
Age- and sex-adjusted HR	1.00 (Ref)	0.80 (0.57–1.13)	0.89 (0.67–1.18)	0.65 (0.46–0.94)*	0.65 (0.33–1.30)	0.030
Multivariable-adjusted HR	1.00 (Ref)	0.79 (0.56–1.12)	0.83 (0.62–1.12)	0.58 (0.40–0.84)‡	0.58 (0.29–1.17)	0.005
Multivariable-adjusted + potential mediators HR	1.00 (Ref)	0.81 (0.57–1.15)	0.85 (0.63–1.15)	0.56 (0.38–0.81)‡	0.51 (0.25–1.03)	0.003
Urinary albumin excretion >30 mg per 24 h						
No. of cases (%)	186 (14.5)	106 (12.3)	237 (12.2)	140 (12.5)	28 (10.7)	
Person-years	11,621	8181	18,834	10,828	2513	
Age- and sex-adjusted HR	1.00 (Ref)	0.86 (0.68–1.10)	0.80 (0.66–0.98)*	0.76 (0.60–0.95)*	0.60 (0.40–0.90)*	0.002
Multivariable-adjusted HR	1.00 (Ref)	0.89 (0.70–1.11)	0.82 (0.67–1.01)	0.76 (0.60–0.96)*	0.57 (0.38–0.85)‡	0.002
Multivariable-adjusted + potential mediators HR	1.00 (Ref)	0.88 (0.69–1.12)	0.89 (0.73–1.10)	0.82 (0.65–1.05)	0.58 (0.38–0.88)*	0.020

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HR hazard ratio; wk, week.
HR, 95% confidence intervals, and *P*-values were derived from Cox proportional hazards regression models. Superscripts denote whether the HR of a categorical level of alcohol consumption differs significantly from the categorical level of no alcohol consumption in that row; *$P<0.05$, ‡$P<0.01$. Multivariable adjustment included 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.
P-trend was derived from Cox proportional hazards regression models by treating alcohol consumption as a continuous linear term.

inversely associated with the risk of CKD. The lower risk associated with alcohol consumption was consistent across different strata of selected CKD risk factors and was apparent when CKD was defined on the basis of a combination of eGFR and UAE, and when defined on the basis of either eGFR or UAE alone. The inverse association between alcohol intake and risk of CKD remained after adjustment for confounders, CKD risk factors, and potential mediators of the association such as of homeostatic model assessment for insulin resistance, total to HDL-cholesterol ratio, and systolic blood pressure.

Four prospective observational studies have investigated the association between alcohol consumption and risk of CKD (either based on eGFR or albuminuria/proteinuria).[3–6] These studies predominantly assessed eGFR with a creatinine-based MDRD equation, which is derived from a select population with renal disease[8] and has uncertain validity in cohorts in which eGFR is >60 ml/min per 1.73 m^2.[9] Analogous to our findings, inverse associations between alcohol consumption and risk of CKD were reported among 11,203 US male physicians[3] and 6259 Australian men and women[5], with top alcohol consumption categories of only >7 drinks/week and >30 g/day, respectively. Alcohol intake <20 g/day was also inversely associated with CKD among 41,012 male and 82,752 female Japanese adults, with no apparent effect of an intake ⩾20 g/day, compared with abstention.[4] Shankar *et al.*[6] reported a more U-shaped relationship with a borderline increased CKD risk starting from ⩾4 drinks/day among 3392 participants.

Two longitudinal studies simultaneously examined the effect of alcohol on new-onset albuminuria or proteinuria, besides the eGFR-based CKD.[4,5] Compared with abstention, alcohol consumption of <20 g/day was associated with a decreased risk of developing a positive dipstick proteinuria in men, with a similar trend in women, during annual examinations for 10 years among 123,764 Japanese adults.[4] In contrast to these and our findings, and besides an inverse association with *de novo* eGFR <60 ml/min per 1.73 m^2, White *et al.*[5] simultaneously reported a trend toward a positive association between alcohol consumption and risk of 5-year doubling of the albumin to creatinine ratio (defined as a final albumin to creatinine ratio >2.5 mg/mmol for men and 3.5 mg/mmol for women in the absence of albuminuria at baseline). The discrepancies may perhaps be explained by differences in study design. The Prevention of Renal and Vascular End-Stage Disease (PREVEND) study was specifically designed to examine the effects of albuminuria and has several repeated measures of two consecutive 24-h urine collections to determine albuminuria.

In line with our findings on the risk of CKD, alcohol consumption was inversely associated with the risk of developing end-stage renal disease among ~65,000 Chinese men aged 40–65 years.[14] However, kidney function was not assessed at baseline in this study, and CKD

Table 4 | Hazard ratios (95% confidence intervals) for stratified analyses of the association between alcohol consumption and risk of CKD*

	Alcohol consumption categories (g of alcohol)						
Stratification factor	No	Occasional (<10 g/wk)	Light (10–69.9 g/wk)	Moderate (70–21 g/wk)	Heavier (>210 g/wk)	*P*-trend	*P*-interaction
Age (years)							
<58	1.00 (Ref)	0.90 (0.67–1.22)	0.88 (0.69–1.14)	0.76 (0.57–1.02)	0.59 (0.36-0.94)*	0.009	0.98
⩾58	1.00 (Ref)	0.79 (0.59–1.06)	0.76 (0.59-0.98)*	0.69 (0.51–0.93)*	0.68 (0.40–1.17)	0.005	
Sex							
Male	1.00 (Ref)	1.00 (0.68–1.29)	0.98 (0.72–1.18)	0.84 (0.64–1.10)	0.69 (0.45–1.05)	0.06	0.76
Female	1.00 (Ref)	0.76 (0.57–1.01)	0.68 (0.53-0.89)	0.61 (0.43-0.86)	0.56 (0.27–1.17)	0.001	
Smoking							
Never	1.00 (Ref)	0.86 (0.61–1.23)	0.74 (0.53–1.05)	0.52 (0.31–0.88)*	0.51 (0.18–1.40)	0.007	0.71
Former/current	1.00 (Ref)	0.83 (0.64–1.08)	0.84 (0.69–1.03)	0.77 (0.61–0.97)*	0.67 (0.46-0.98)*	0.013	
Hypertension							
No	1.00 (Ref)	0.94 (0.70–1.26)	0.89 (0.69–1.14)	0.75 (0.56–1.00)*	0.68 (0.42–1.10)	0.03	0.86
Yes	1.00 (Ref)	0.79 (0.59–1.05)	0.79 (0.61–1.01)	0.70 (0.52-0.94)	0.51 (0.30-0.87)*	0.003	
Hypercholesterolemia							
No	1.00 (Ref)	0.97 (0.74–1.27)	0.79 (0.63–1.00)*	0.74 (0.57-0.97)*	0.63 (0.40-0.99)*	0.004	0.30
Yes	1.00 (Ref)	0.69 (0.49-0.94)*	0.90 (0.68–1.17)	0.67 (0.48-0.94)*	0.54 (0.30-0.95)*	0.017	

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; wk, week.
Hazard ratios, 95% confidence intervals, and *P*-values were derived from Cox proportional hazards regression models and were adjusted for age, sex, height, weight, smoking status, parental history of CKD, history of cardiovascular disease, and educational level. Superscripts denote whether the hazard ratio of a categorical level of alcohol consumption differs significantly from the categorical level of no alcohol consumption in that row; *$P<0.05$. CKD was defined as $eGFR_{creatinine\text{-}cystatin\ C}$ <60 ml/min per 1.73 m^2 or urinary albumin excretion >30 mg per 24 h.
P-trend was derived by treating alcohol consumption as a continuous linear term.
P-interaction was derived by using a likelihood ratio test from models with and without the cross-product term of alcohol category (nondrinker, occasional, light, moderate, and heavier drinker) and risk factor in the multivariable-adjusted model.

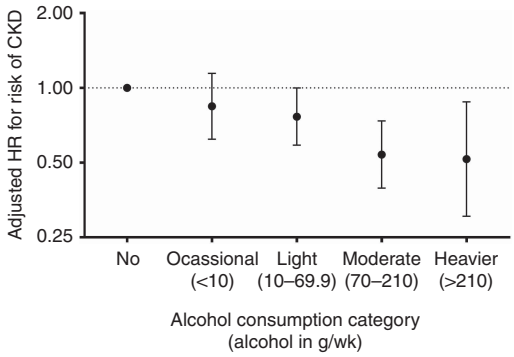

Figure 1 | Association between alcohol consumption and risk of chronic kidney disease (CKD). Hazard ratios (HRs; error bars indicate 95% confidence interval) were adjusted for age, sex, height, weight, smoking status, parental history of CKD, history of cardiovascular disease, and educational level, and were derived from a Cox proportional hazards regression model using complex sampling to account for the sampling design of the study (presence or absence of an urinary albumin concentration of >10 mg/l) by statistically weighing the probability of selection. CKD was defined as creatinine–cystatin C–based estimated glomerular filtration rate <60 ml/min per 1.73 m^2 or urinary albumin excretion >30 mg per 24 h. *P*-trend <0.001. Wk, week.

could have already been present in those who developed end-stage renal disease. Such patients are more likely to have reduced or ceased consumption of alcohol, which could have biased the results toward apparent health benefits of alcohol consumption.

Studies looking specifically at alcohol consumption and kidney function decline instead of CKD have generally reported no effects or, if any, beneficial effects. Among 1658 nurses with an initial eGFR of ~90 ml/min per 1.73 m^2, there was no association between alcohol consumption and different percentages of decline in an MDRD-based eGFR assessed at baseline and after 11 years.[15] During a 7-year follow-up of 4441 Norwegians, >6 units of alcohol/week was associated with an increase in MDRD-based eGFR compared with abstention, but only in men and not in women.[16] Alcohol intake was not associated with rapid kidney function decline (defined as an annual decline >3 ml/min per 1.73 m^2 in a cystatin C–based eGFR) among 4343 subjects, aged >65 years, of the Cardiovascular Health Study.[17] However, alcohol consumption categories did show a positive association with the cystatin C–based eGFR at baseline.

The number of participants reporting heavier alcohol consumption (>30 g of alcohol/day) in our study was relatively low, and findings related to this group should be interpreted with appropriate caution. Moreover, the range of overall alcohol consumption reported by these subjects was truncated, limiting our ability to define potentially detrimental effects of heavy drinking. Clearly, the observations for heavier drinkers must be considered in light of the deleterious effects of excessive alcohol intake, given the well-documented harmful effects that alcohol can cause when consumed in excess.[18,19] Heavy or excessive drinking should always be discouraged, whereas light to moderate alcohol

consumption may be regarded as a complement to other lifestyle habits for reducing the risk of CKD.[20]

The mechanisms by which alcohol consumption may influence the risk of CKD remain unclear. In clinical trials, moderate alcohol consumption increases insulin sensitivity[21,22] and serum HDL-cholesterol.[23,24] Nevertheless, the alcohol-CKD association remained after accounting for homeostatic model assessment for insulin resistance and total to HDL-cholesterol ratio, although both measures may be imperfect reflections of insulin sensitivity and (systemic) atherosclerosis, respectively. Alcohol acutely increases urine production, most likely through inhibition of the release of arginine vasopressin (antidiuretic hormone).[25] This increased flow has been the putative mechanism through which alcohol may lower the risk of renal cell carcinoma.[26,27] We, however, found no evidence that the mean of two 24-h urine volumes—a fairly poor proxy of long-term urine production—influenced the association between habitual alcohol consumption and risk of CKD.

The potential limitations of our study should be considered. We could not distinguish between life-long abstainers and former drinkers, including potential 'sick quitters' in the nondrinkers category at baseline. It is possible that those who did not drink alcohol at baseline did so owing to health concerns or increasing frailty. This has been termed the 'sick quitter' hypothesis.[13] However, alcohol consumption was also inversely associated with the risk of CKD in analyses that excluded all nondrinkers at baseline or that accounted for former drinkers during follow-up. It is thus unlikely that our findings can be explained by this hypothesis. Second, we did not have information on beverage type (e.g., wine, beer, or spirits) consumed, although both controlled feeding trials on biomarkers,[23,24] and observational cohort studies on other outcomes do not support beverage-specific associations.[28,29] Third, the daily amounts of alcohol consumed by women in the moderate category (10–30 g) were possibly higher than what is considered 'moderate' for women ($\sim$15 g in the United States and 16–24 g in the United Kingdom). These guidelines, however, are directed at prevention of all chronic diseases rather than on the maximum risk reduction of CKD. Finally, our findings are observational and residual or unmeasured confounding may be present, despite the variety of potentially confounding factors for which we adjusted.

Major strengths of the study are the serial screenings for CKD during follow-up and the combined CKD end point consisting of a creatinine–cystatin C–based eGFR and two consecutive 24-h UAE at each screening to ascertain CKD events. An additional strength is the association between self-reported alcohol consumption categories and HDL-cholesterol in our study, consistent with the dose–response relationship of alcohol on this biomarker in randomized controlled trials.[23,24] This validated the accuracy of recall and the rank order of the alcohol categories, although the actual amount of alcohol consumed may be subject to underreporting.[30] Another strength is the consistency of the association across different strata of risk factors, across different CKD end point definitions, and in several sensitivity analyses, which all add to the plausibility of our findings. Finally, the updated information on alcohol intake during follow-up enabled us to account for potential changes in drinking habits. Similar to previous studies on kidney function[3,15] or other outcomes,[31] alcohol consumption in our study was fairly stable over time.

In this prospective cohort of men and women, alcohol consumption was consistently inversely associated with the risk of CKD. Advice concerning alcohol consumption to lower the risk of CKD should consider the full range of benefits and risks, including the consistent harm effects of drinking that exceeds recommended limits. In light of these potential detrimental health effects, it would be premature to draw any firm clinical recommendations regarding alcohol consumption to reduce the risk of CKD. Nevertheless, the current study finds no grounds to discourage light to moderate alcohol consumption, at least in terms of its renal effects.

MATERIALS AND METHODS

Study design and population

The PREVEND study is a prospective investigation of albuminuria, renal, and cardiovascular disease in a large cohort drawn from the general population. Details of this study are described elsewhere.[32,33] In summary, from 1997 to 1998, all inhabitants of Groningen, the Netherlands, aged 28–75 years ($n = 85{,}421$), were sent a questionnaire and a vial to collect a first-morning void urine sample. Pregnant women and subjects with type 1 diabetes mellitus were excluded. The urinary albumin concentration was assessed in 40,856 responders. Subjects with a urinary albumin concentration $\geqslant 10$ mg/l ($n = 7768$) were invited to participate, of whom 6000 were enrolled. In addition, a randomly selected group with a urinary albumin concentration < 10 mg/l ($n = 3394$) was invited to participate in the cohort, of whom 2592 were enrolled. The PREVEND study has been approved by the medical ethics committee of the University Medical Center Groningen. Written informed consent was obtained from all participants. These 8592 individuals form the PREVEND cohort.

We excluded subjects with missing data on alcohol consumption ($n = 43$), serum creatinine, serum cystatin, or UAE ($n = 498$), with CKD at baseline ($n = 1393$), or with no follow-up data on kidney function ($n = 1182$), leaving 5476 participants for the analyses. Of these, 5417 participants completed a second examination between 2001 and 2003, 4656 participants completed a third examination between 2003 and 2006, 4092 participants completed a fourth examination between 2006 and 2008, and 3004 participants completed a fifth examination between 2008 and 2012.

Data collection

The procedures at each examination in the PREVEND study have been described in detail previously.[34] In brief, each of the examinations included two visits to an outpatient clinic separated by 3 weeks. Before the first visit, all participants completed a self-administered questionnaire regarding demographics, cardiovascular and renal disease history, smoking habits, alcohol consumption, and medication use. Information on medication use was combined with information from a pharmacy-dispensing registry, which has complete information on drug use of $>95\%$ of subjects in the PREVEND study. Height and weight were measured on the first visit. During each examination and during each visit, blood pressure was measured on the right arm, every minute for 10 and 8 min, by an

automatic Dinamap XL Model 9300 series device (Johnson-Johnson Medical, Tampa, Florida, USA). The mean of the last two recordings from each of the two visits was used. In the last week before the second visit, subjects had to collect two consecutive 24-h specimens after thorough oral and written instruction. During the urine collection, the participants were asked to avoid heavy exercise as much as possible. Subjects were also instructed to postpone the urine collection in case of urinary tract infection, menstruation, or fever. The collected urine was stored cold (4 °C) for a maximum of 4 days before the second visit. After handing in the urine collections, the urine specimens were stored at −20 °C. Furthermore, fasting blood samples were provided and stored at −80 °C.

Assessment of alcohol consumption

Information about alcohol consumption was collected at baseline and during every follow-up examination. Answer categories included the following: no/rarely, 1–4 drinks/month, 2–7 drinks/week, 1–3 drinks/day, and 4 or more drinks/day. A standard serving size of an alcoholic beverage in the Netherlands is equivalent to 10 g of alcohol, regardless of the beverage type (e.g., beer (250 ml), wine (100 ml), or liquor (35 ml)).[35] We labeled the five categories as nondrinkers, occasional drinkers (<10 g/week), light drinkers (10–69.9 g/week), moderate drinkers (70–210 g/week), and heavy drinkers (>210 g/week).

CKD ascertainment

The primary outcome of CKD was defined as a combination of an eGFR <60 ml/min per 1.73 m^2 and/or an UAE >30 mg per 24 h. We estimated GFR with the combined creatinine cystatin C–based Chronic Kidney Disease Epidemiology Collaboration equation from 2012, taking into account age, sex, and race.[11] The urinary albumin concentration was multiplied by urine volume to obtain a value in mg per 24 h. The two 24-h urinary albumin values of each subject per examination were averaged.

Measurement of serum creatinine was performed by an enzymatic method on a Roche Modular analyzer using reagents and calibrators from Roche (Roche Diagnostics, Mannheim, Germany), with intra- and interassay coefficients of variation of 0.9% and 2.9%, respectively. Serum cystatin C concentrations were measured by Gentian Cystatin C Immunoassay (Gentian AS, Moss, Norway) on a Modular analyzer (Roche Diagnostics). Cystatin C was calibrated directly using the standard supplied by the manufacturer (traceable to the International Federation of Clinical Chemistry Working Group for Standardization of Serum Cystatin C).[36] The intra- and interassay coefficients of variation were <4.1% and <3.3%, respectively. Urinary albumin concentration was measured by nephelometry with a threshold of 2.3 mg/l, and intra- and interassay coefficients of variation of 2.2% and 2.6%, respectively, (Dade Behring Diagnostic, Marburg, Germany).

Assessment of covariables

Smoking status was defined as self-reported never smoker, former smoker, or current smoker (<6, 6–20, or >20 cigarettes/day). Parental history of CKD was defined as having a first-degree relative who had a renal disease requiring dialysis for >6 weeks. Educational level was defined as low (primary education or intermediate vocational education), middle (higher secondary education), and high (higher vocational education and university). Hypertension was defined as a systolic blood pressure ⩾140 mm Hg, a diastolic blood pressure ⩾90 mm Hg, or the use of blood pressure–lowering drugs. Concentrations of total cholesterol, HDL-cholesterol, insulin, glucose, triglycerides, and C-reactive protein were measured using standard methods, as previously described.[37] Hypercholesterolemia was defined as a total cholesterol ⩾6.21 mmol/l, or the use of lipid-lowering drugs. The homeostatic model assessment for insulin resistance was calculated as (fasting serum insulin (in μU/l)×fasting serum glucose (in mmol/l))/22.5.[38]

Statistical analysis

Baseline characteristics are presented according to alcohol consumption categories. Continuous data are presented as mean with s.d. or as median and interquartile range in case of skewed distribution. Categorical data are presented as percentiles. To validate the self-reported alcohol consumption categories, the association between alcohol consumption and serum HDL-cholesterol levels was examined using general linear models. These analyses were stratified by sex because of the differences in serum HDL-cholesterol levels between men and women.

To examine the prospective association between baseline alcohol consumption and risk of CKD, analyses were performed using Cox proportional hazards regression models to calculate the HRs and 95% CIs for each alcohol consumption category using nondrinkers as reference category. All models took into account the sampling design of the study (presence or absence of a urinary albumin concentration >10 mg/l) by specifying stratum-specific baseline hazard functions. In these proportional hazards regression models, person-time was counted from the date of the first examination until the date that CKD was diagnosed, or the date of the last examination, whichever came first. The multivariable-adjusted model included age, sex, height, weight, smoking status, parental history of CKD, history of cardiovascular disease, and educational level. Possible effect modification was explored by including an interaction term for alcohol consumption and effect modifier (age, sex, smoking, hypertension, and hypercholesterolemia) in the multivariable-adjusted model. Instead of specifying stratum-specific baseline hazard functions, we additionally addressed the oversampling of subjects with elevated UAE by using design-based Cox proportional hazards regression models that took into account the probability of selection by statistical weighting. This statistical weighting method allows results to be extrapolated to the general population. We calculated *P*-trends by treating the ordinal alcohol consumption categorical variable as a continuous linear term to use all the intra-categorical information that is otherwise ignored by mere categorical comparisons.[39]

We performed several sensitivity analyses to examine the robustness of the alcohol-CKD association. First, the abstaining category may include people who have quit drinking owing to ill health or who may have other preexisting health conditions, which preclude drinking.[13] To investigate whether these factors may account for the association with alcohol and CKD, we explored the association among alcohol consumers and excluded abstainers at baseline. In addition, we performed an analysis starting from the second examination and added a former drinker category (i.e., subjects who reported to consume alcohol at the first but not at the second examination) to the original five alcohol drinking categories. Second, we excluded subjects at baseline with an eGFR <66 (instead of <60) ml/min per 1.73 m^2 and/or a 24-h UAE >25 (instead of >30) mg per 24 h for a more pronounced decline in kidney function in order to reach the primary outcome of CKD. Third, although this may also introduce bias toward apparent health benefits of alcohol consumption

because of reducing alcohol intake owing to increasing age/frailty, we performed a time-varying Cox regression analysis in which we updated information on alcohol consumption and all confounders in the multivariable-adjusted model to allow for changes (e.g., in alcohol drinking habits) over time.

All *P*-values are two-tailed, and *P*-values <0.05 were considered statistically significant. All analyses were conducted with the use of the statistical package IBM SPSS (version 22.0; IBM, Chicago, IL, USA).

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Table S1a. Baseline characteristics according to alcohol consumption among 2,881 women of the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study.

Table S1b. Baseline characteristics according to alcohol consumption among 2,595 men of the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study.

Table S2. Association between alcohol consumption and risk of CKD according to $eGFR_{creatinine}$ and $eGFR_{cystatin\ C}$.

Table S3. Association between alcohol consumption updated over time and risk of CKD.

Supplementary material is linked to the online version of the paper at http://www.nature.com/ki

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