ALCOHOL CONSUMPTION AND INCIDENCE OF PROTEINURIA: A RETROSPECTIVE COHORT STUDY

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Introduction and objectives

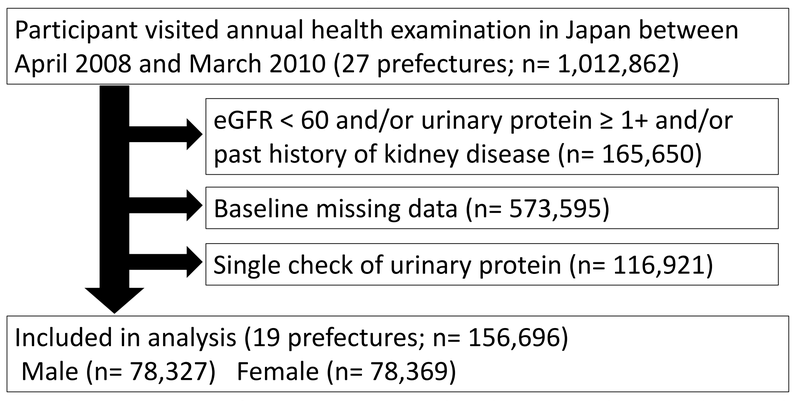
- ✓ Proteinuria is not only a risk factor of end stage renal disease but also an independent risk factor of cardiovascular death.[1,2]
- ✓ The effect of high alcohol consumption on incidence of proteinuria is controversial.
- ✓ Although relative risk of all-cause mortality was slightly higher in drinkers with 45-64 g/day of alcohol consumption and much higher in drinkers with ≥65 g/day of alcohol consumption, the effect of highest alcohol consumption on proteinuria was assessed only drinkers with ≥30 or 40 g/day of alcohol consumption.[3]
- ✓ The aim of this study is to evaluate the effect of alcohol on incidence of proteinuria, especially stressing high alcohol consumption.

Methods

Study design: Retrospective cohort study

Participants: Non-CKD participants who underwent annual health checkup in Japan

Figure 1. Derivation of the study sample.



Baseline was set to first examination day during study period in each participants

Exposure:

Participants were classified into 6 categories by their baseline alcohol consumption obtained from standard questionnaires.

Rare or non-drinkers	: Rare drinkers
Occasional drinkers	: Occasional drinkers
Daily drinkers with <1 standard drink	: ≤19 g/day
Daily drinkers with <2 standard drink	: 20-39 g/day
Daily drinkers with <3 standard drink	: 40-59 g/day
Daily drinkers with ≥3 standard drink	: ≥60 g/day

Outcome: Time to first incidence of proteinuria (dipstick ≥1+)

Statistics: Log-rank test, Cox proportional hazards model

Figure 2. Cumulative probability of proteinuria using Kaplan-Meier method.

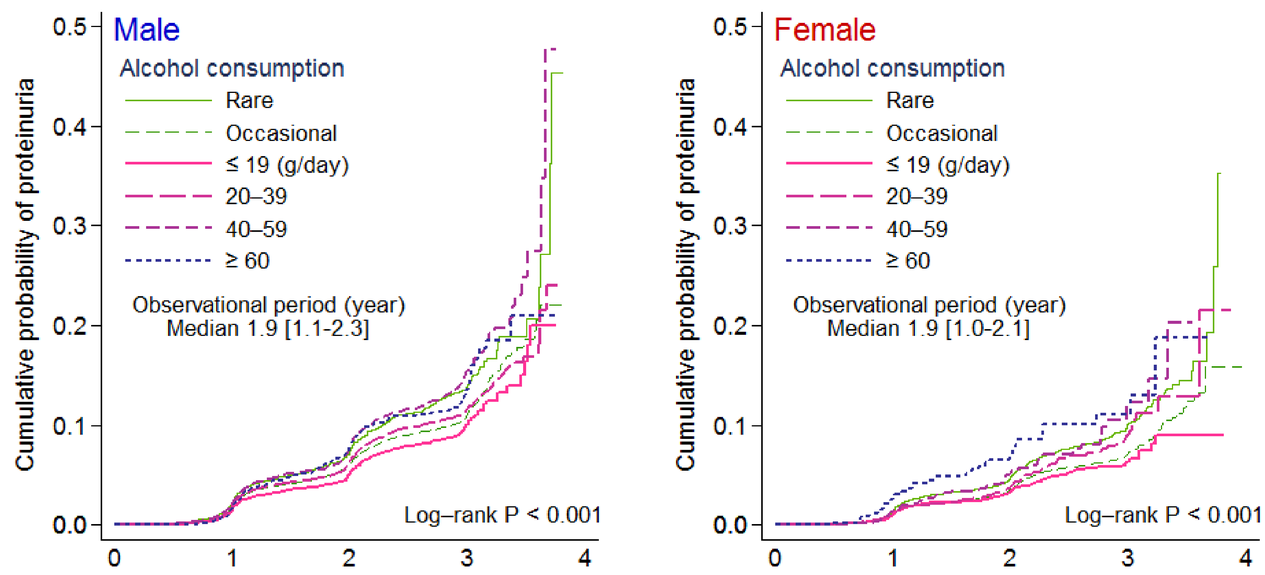
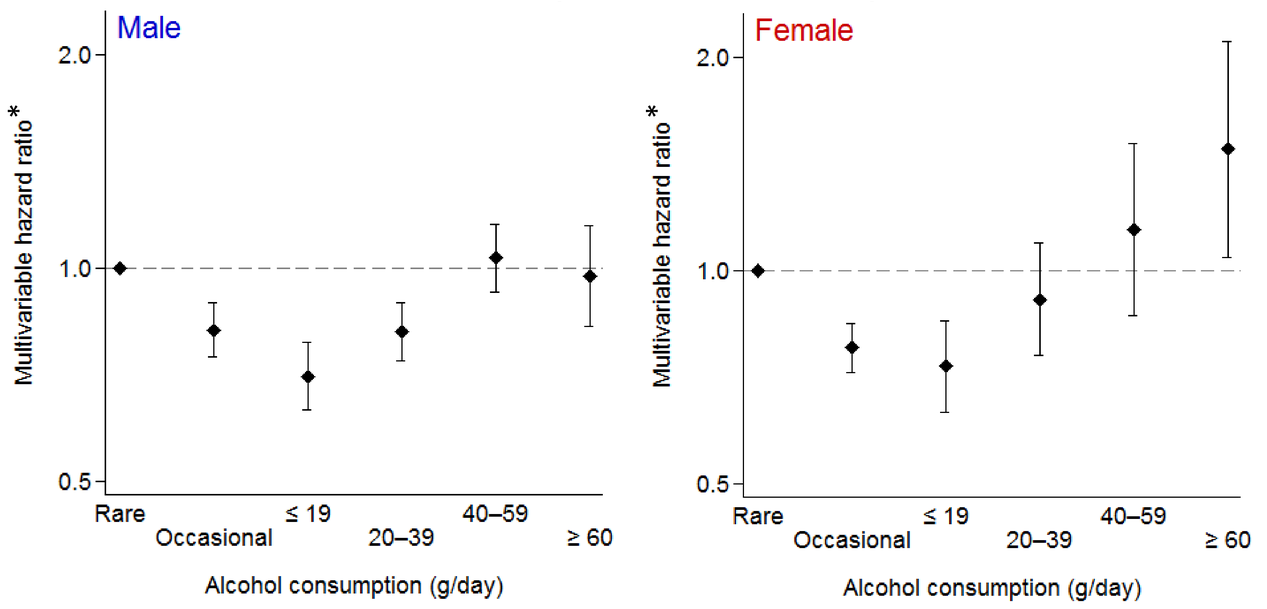


Figure 3. Association between alcohol consumption and incidence of proteinuria.



*Adjusted for age, BMI, mean arterial pressure, current smokers, eGFR, HbA1c, HDL-C, current treatment for hypertension, dislipidemia, and diabetes, and past history of CVD

Results

Table 1. Baseline characteristics, observational period and incidence of proteinuria.

Male	Alcohol consumption categories					
Total n= 78,327	Rare drinkers	Occasional	Daily			
			≤ 19 g/day	20-39	40-59	≥ 60
N	11,186	24,139	11,577	20,602	8,410	2,413
Age (year)	65 [58,70]	64 [56,69]	66 [60,70]	65 [59,69]	63 [56,68]	59 [51,65]
Body mass index (kg/m²)	23.7±3.2	24.0±3.1	23.3±2.8	23.5±2.8	23.6±2.9	23.8±3.1
MAP (mmHg)	93±12	95±12	95±11	97±12	98±12	99±12
Current smokers (n[%])	2,796 (25.0)	5,690 (23.6)	2,865 (24.7)	6,416 (31.1)	3,407 (40.5)	1,086 (45.0)
Current treatment (n[%])						
Hypertension	2,751 (24.6)	6,401 (26.5)	3,318 (28.7)	6,574 (31.9)	2,643 (31.4)	647 (26.8)
Dyslipidemia	1,232 (11.0)	2,198 (9.1)	979 (8.5)	1,659 (8.1)	580 (6.9)	152 (6.3)
Diabetes	748 (6.7)	1,545 (6.4)	615 (5.3)	1,010 (4.9)	389 (4.6)	124 (5.1)
Past history of CVD (n[%])	1,337 (12.0)	2,180 (9.0)	1,090 (9.4)	1,849 (9.0)	622 (7.4)	124 (5.1)
HDL-cholesterol (mg/dL)	52±13	56±14	59±15	62±16	64±16	64±18
HbA1c (%)	5.4±0.8	5.4±0.7	5.3±0.7	5.3±0.7	5.3±0.7	5.3±0.8
Uric acid (mg/dL)	5.6±1.2	5.9±1.3	5.8±1.2	6.0±1.3	6.2±1.3	6.4±1.4
GGT (IU/L)	25 [19,38]	31 [22,49]	32 [23,50]	43 [29,71]	57 [36,102]	74 [42,141]
eGFR (ml/min/1.73m²)	74 [67,85]	75 [68,85]	74 [67,85]	76 [70,86]	78 [73,88]	81 [73,90]
Observational period (year)	1.7 [1.0, 2.1]	2.0 [1.1, 2.5]	1.9 [1.1, 2.3]	1.9 [1.1, 2.2]	1.9 [1.1, 2.2]	2.0 [1.1, 2.6]
Incidence of proteinuria (n [%])	743 (6.6)	1,538 (6.4)	600 (5.2)	1,268 (6.2)	651 (7.7)	191 (7.9)

Female	Alcohol consumption categories					
Total n= 78,369	Rare drinkers	Occasional	Daily			
			≤ 19 g/day	20-39	40-59	≥ 60
N	38,909	28,074	6,439	3,409	1,067	471
Age (year)	66 [60,69]	64 [57,68]	63 [58,68]	60 [52,65]	56 [48,62]	54 [46,61]
Body mass index (kg/m²)	22.7±3.4	22.6±3.2	22.0±2.9	22.1±3.1	22.1±3.3	22.6±3.3
MAP (mmHg)	92±12	92±12	92±12	93±12	93±12	93±13
Current smokers (n[%])	1,553 (4.0)	2,143 (7.6)	614 (9.5)	794 (23.3)	408 (38.2)	195 (41.4)
Current treatment (n[%])						
Hypertension	9,983 (25.7)	6,115 (21.8)	1,376 (21.4)	806 (23.6)	227 (21.3)	101 (21.4)
Dyslipidemia	7,466 (19.2)	4,205 (15.0)	835 (13.0)	295 (8.7)	80 (7.5)	28 (5.9)
Diabetes	1,571 (4.0)	606 (2.2)	126 (2.0)	50 (1.5)	12 (1.1)	9 (1.9)
Past history of CVD (n[%])	2,834 (7.3)	1,542 (5.5)	367 (5.7)	184 (5.4)	45 (4.2)	25 (5.3)
HDL-cholesterol (mg/dL)	64±15	68±16	72±17	75±18	77±19	76±19
HbA1c (%)	5.3±0.6	5.3±0.5	5.2±0.5	5.1±0.5	5.1±0.6	5.0±0.6
Uric acid (mg/dL)	4.5±1.0	4.6±1.0	4.7±1.0	4.9±1.2	5.2±1.2	5.3±1.2
GGT (IU/L)	19 [15,27]	20 [15,29]	22 [17,32]	27 [19,43]	32 [22,57]	43 [24,73]
eGFR (ml/min/1.73m²)	76 [67,90]	76 [68,90]	76 [67,89]	78 [72,92]	81 [74,94]	83 [75,96]
Observational period (year)	1.9 [1.0, 2.1]	1.9 [1.0, 2.2]	1.9 [1.1, 2.1]	1.9 [1.1, 2.1]	1.9 [1.1, 2.2]	1.9 [1.1, 2.3]
Incidence of proteinuria (n [%])	1,651 (4.2)	969 (3.5)	201 (3.1)	132 (3.9)	54 (5.1)	33 (7.0)

Mean ± SD; median [IQR]. P < 0.05 in all variables.
Abbreviations: MAP, mean arterial pressure; CVD, cardiovascular disease; HDL, high-density lipoprotein; GGT, gamma-glutamyl transferase; eGFR, estimated glomerular filtration rate

Table 2. This study and previous studies, reported about the effect of alcohol consumption and incidence of proteinuria.

Country Age (Study name)	Duration	Outcome	Gender N	Hazards ratio or Odds ratio* (95% confidential interval) non	occasional	0	20	40	60	(g/day)
Netherlands[4] Age 28-75 (PREVEND study)	10.2 years	Urinary Alb >30 mg/24hr	Both 5,476	1	0.88 (0.69-1.12)	0.89 (0.73-1.10)	0.82 (0.65-1.05)	0.58 (0.38-0.88)		
Australia[5]* Age 25-64 (Aus Diab study)	5 years	ACR ≥2.5† in male ACR ≥3.5† in female & doubling ACR	Male 2,048			1	1.92 (0.69-5.36)	2.3 (1.03-5.12)		
			Female 2,420			1	1.2 (0.61-2.32)	2.2 (0.80-6.04)		
Japan[6]* Age 40-79	1 year	Dipstick UP ≥ 1+	Both 4,902	1				0.97 (0.57-1.40)		
Japan[7] Age ≥40	10 years‡	Dipstick UP ≥ 1+	Male 41,012	1	1.03 (0.90-1.17)	0.86 (0.78-0.95)		1.04 (0.86-1.25)		
			Female 82,752	1	0.96 (0.80-1.14)	0.80 (0.63-1.02)		1.05 (0.26-4.24)		
Japan[8] Age 40-55	8.0 years	Dipstick UP ≥ 1+	Male 9,154	1		0.79 (0.69-0.90)	0.86 (0.75-0.98)	1.03 (0.86-1.23)	1.31 (0.92-1.87)	
This study	1.9 years	Dipstick UP ≥ 1+	**Male 77,987**	1	0.82 (0.75-0.89)	0.70 (0.63-0.78)	0.81 (0.74-0.89)	1.03 (0.93-1.15)	0.97 (0.83-1.14)	
			Female 78,709	1	0.78 (0.72-0.84)	0.73 (0.63-0.85)	0.91 (0.76-1.09)	1.14 (0.86-1.51)	1.48 (1.04-2.11)	

Abbreviations: Alb, albumin; ACR, albumin creatinine ratio; UP, urinary protein.
† mg/mmol, ‡ Running duration of this study (not observational period)

Discussions

- ✓ The effect of alcohol on proteinuria was different between males and females. In males the association was U-shaped. On the other hands, in females it was J-shape and the risk was significantly elevated in ≥60 g/day alcohol consumption group.
- ✓ Because the highest alcohol consumption group included the participants with over 20-30 g/day of alcohol consumption in most previous studies, deleterious effect of 40-60 g/day or more of alcohol consumption might be possibly diluted.
- ✓ Plausible mechanism of the gender difference might be due to a gender difference in alcohol metabolism. Given the same volume of alcohol intake, the serum alcohol concentration is higher in females than in males, partly because females have lower gastric alcohol dehydrogenase activity.[9]

Conclusion

- ✓ Mild drinkers with ≤19 g/day alcohol consumption were at lowest risk of proteinuria both males and females.
- ✓ Female heavy drinkers with ≥60 g/day were identified as a significant predictor of proteinuria whereas not male heavy drinkers.
- ✓ Female J-shape and male U-shape associations between alcohol consumption and proteinuria, suggested that females were more vulnerable to proteinuric effect on alcohol consumption, compared with males.

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