Benchmark dose of alcohol consumption for development of hyperuricemia in Japanese male workers :An 8-year cohort study

（日本人男性労働者の大規模コホート長期追跡調査における高尿酸血症発症に関する飲酒量のベンチマーク用量）

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Abstract

Background: To estimate the benchmark doses (BMD) and their 95% lower confidence limits (BMDL) of alcohol consumption as the reference level for the development of hyperuricemia based on the dose-response relationship.

Methods: An 8-year prospective cohort study was conducted in 8,097 male workers at a Japanese steel company who received annual health check-ups between 2002 and 2009. The endpoints for development of hyperuricemia were defined as a uric acid ≥7 mg/dL or taking any anti-hyperuricemic medication. The dose-response relationship of alcohol consumption was investigated using multivariate pooled logistic regression analyses adjusted for age, body mass index, mean arterial pressure, shift work or day work, smoking habit, habitual exercise, total serum cholesterol, hemoglobin A_{1c}, aspartate aminotransferase, and creatinine. We estimated the BMD and BMDL of alcohol consumption for the development of hyperuricemia, using the parameters obtained by pooled logistic regression with a benchmark response (BMR) of 5% or 10%.

Results: Mean observed years per person was 3.86 years. The incidence rate per 1,000 person years was 61.1. The odds ratio calculated for the development of hyperuricemia was 1.29 [95% confidence interval, 1.22-1.36)] with an increase in alcohol consumption per 1 gou/day (1 gou/day=alcohol 22 g/day). The estimated BMDL/BMD with a BMR of 5% was 2.5/2.9 gou/day (55.3/62.8 g/day) and with a BMR of 10% was 4.1/4.6 gou/day (90.0/102.1 g/day).

Conclusions: The present study showed that alcohol consumption of 2.5 gou/day (=ethanol 55 g/day) caused a distinct increase in the risk of hyperuricemia. Valuable information for preventing alcohol-induced hyperuricemia was obtained by applying a leading-edge statistical method to a long-term follow-up study of a large patient cohort.

Keywords: Alcohol consumption; Benchmark dose; Cohort study; Hyperuricemia

1 Introduction

In general, an increase in serum uric acid (UA) level is associated with an increased risk of gout [1, 2], ureteral stones [3, 4], kidney disease [5, 6], hypertension [7, 8, 2], coronary heart disease [9] and stroke [10]. This indicates that the serum UA level is an important marker for preventing these diseases. Recent studies have shown that an elevated serum UA level is also associated with an increased risk of type 2 diabetes [11] and the metabolic syndrome [12, 13].

On the other hand, alcohol consumption has been implicated in the etiology of hyperuricemia [14]. In a longitudinal epidemiologic study in the USA, alcohol consumption was shown to be associated with an increased risk of developing gout [15]. In addition, several epidemiologic studies based on cross-sectional observations [16-18] and prospective studies [19-21] indicated that excessive alcohol drinking had a harmful effect on hyperuricemia. However, as far as we are aware, the dose-response relationship between alcohol consumption and the risk of hyperuricemia and the threshold level of alcohol consumption has only been reported in one study [19].

In terms of calculating the threshold amount, the benchmark dose (BMD) method has attracted considerable attention in preventive medicine. The BMD method has become popular worldwide, especially in the area of preventive medicine. The concept of BMD was introduced by Crump [22] and involves fitting a mathematical model to dose-response data. The BMD method has therefore been adopted by the U.S. Environmental Protection Agency (EPA) [23] and Environmental Health Criteria [24] for assessing the health risk of environmental contaminants. The BMD is defined as the dose that causes a predetermined change in response [25]. This specified change in response is generally referred to as the benchmark response (BMR) [25]. The lower 95% confidence limit of the benchmark dose (BMDL) is increasingly replacing the no observed adverse effect level (NOAEL) for

assessing risk [23, 25]. One major advantage of the BMD method over the NOAEL-approach is that it uses information from the entire dose–response curve [23]. Furthermore, using pooled logistic regression, it is possible to take into account the effect of potential covariates. From the viewpoint of preventive medicine, we consider that the threshold level of alcohol consumption calculated using this method is very important. However, as far as we are aware, previous studies have not estimated the BMDL for alcohol consumption and development of hyperuricemia. The aims of this study were to establish the dose-response relationship between alcohol consumption and the development of hyperuricemia and to estimate the BMD and BMDL of alcohol consumption for the development of this condition. This was achieved by applying pooled logistic regression analysis to data from an 8-year large-scale longitudinal cohort study in order to adjust for the annual variation in potential covariates.

2 Methods

2.1 Participants

This cohort study at a Japanese steel company included observations made over an 8-year period from 2002 to 2009. A total of 8,097 participants out of a possible 10,900 male workers were enrolled in the study. The cohort consisted of more than 98% of the workers who attended annual health examinations during the observation period. New participants could be enrolled during the follow-up period. The following individuals were excluded from the study; those who did not have a health examination in the subsequent year (n=1,339), those who did not have a UA measurement in the subsequent year (n=590), those who were diagnosed with hyperuricemia based on the entry criteria in the present study (n=786), and those with any missing data in the year of entry (n=88).

2.2 Measurements

Diagnosis of hyperuricemia was based on two data sources: the results of the annual health examination and individual medical histories. Health examination data included the results of a laboratory test for serum UA measured by the uricase-peroxidase reaction. The presence of hyperuricemia was defined as a UA $\geq$7 mg/dL or taking anti-hyperuricemic medication. The health examinations, including blood sampling, were carried out between 9 a.m and 3 p.m throughout the study period. None of the measurements were taken within 30 minutes after a meal or heavy physical activity. The medical history of the workers was recorded during the annual health examination using a self-administered questionnaire. The responses were confirmed by individual interviews conducted by occupational physicians. Age, body mass index (BMI), blood pressure, and the levels of total serum cholesterol, hemoglobin A_{1c} (HbA_{1c}), aspartate aminotransferase (AST) and creatinine (Cr) were measured during the study. The tests were conducted at comprehensive clinical testing laboratories that met the requirements of official certification organizations. Mean arterial

pressure (MAP) was calculated using the following equation: (diastolic blood pressure×2 + systolic blood pressure)/3 [26]. Information on drinking and smoking habits, job schedule type and habitual exercise was recorded at the annual health examination and obtained from self-administered questionnaires. Smoking status was classified as either non-smoker, smoking 1-10 cigarettes/day, 11-20 cigarettes/day, or ≥21 cigarettes/day. The quantity of alcohol in each type of alcoholic beverage was calculated based on the unit "gou". In Japan, "gou" is the most popular unit used to measure alcohol consumption, with 180 ml of Japanese sake (rice wine) usually containing 15% of ethanol. 1 gou (180 ml) of Japanese sake containing approximately 22 g of ethanol is equivalent to 500 ml of beer, 60 ml of whiskey, 180 ml of wine, or 110 ml of scotch whiskey. This unit was used in the questionnaire as it is easily comprehensible for the general Japanese population to determine their consumption of alcohol beverages. To calculate the total quantity of alcohol consumed per day, we assigned a score to each category as follows: 0 for 0 gou, 0.5 for <1 gou, 1 for about 1 gou, 2 for about 2 gou, 3 for about 3 gou and 5 for ≥4 gou. Weekly alcohol consumption was estimated by multiplying the quantity by the frequency. The weekly alcohol consumption was then converted to daily consumption and expressed as two units (gou/day and ethanol g/day). The other variable factors were categorized as follows: Job schedule type (daytime or shift work) and habitual exercise (none, once-twice/month, once-twice/week, or 3 times/week or more).

2.3 Statistical analyses

To evaluate the dose-response relationships between annual measurements of alcohol consumption and the development of hyperuricemia we used multivariate analysis that included pooled logistic regression [27]. All the covariates were included simultaneously in the statistical model. Using this method, the derived odds ratios (ORs) for the endpoints were adjusted for the effects of the other time-variable covariates. The data on total serum cholesterol, HbA_{1c}, AST, and Cr were logarithmically transformed using a base of 1.5. This

transformation resulted in the ORs for the variables increasing by 50%. Each examination interval of one year was treated as a mini follow-up study. This method therefore included the concept of person-years. The daily alcohol consumption was used as a continuous variable to estimate the BMDL and BMD. The BMDL and BMD were adjusted for the effects of the other covariates using parameters obtained by pooled logistic regression.

The BMR was set at 5% or 10%. The BMD was calculated using the following equation:

$$\mathrm{BMD} = \frac{1}{\beta} \ln \frac{\left[P(0) + \mathrm{BMR}\right] \times \left[1 - P(0)\right]}{\left[1 - P(0) - \mathrm{BMR}\right] \times \left[P(0)\right]} \qquad (1)$$

where $P(0)$ = the background probability of an adverse response at the alcohol consumption (= 0), BMR = an additional pre-specified increase in the probability of a positive finding (5% or 10%), and β = the slope for alcohol consumption.

The BMDL was calculated using the profile likelihood method [22]. For estimation of BMDL and BMD, the potential covariates were assumed to be day worker, non-smoking, exercising regularly, mean age, BMI, and geometric means of total serum cholesterol, HbA_{1c}, AST, and Cr at entry to the study.

The analyses were performed using IBM SPSS 19J (IBM Business Analytics, Tokyo) and Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA). A P value < 0.05 was considered statistically significant.

3 Results

Table 1 shows the number of person-years studied and incidence rate of hyperuricemia, grouped according to daily alcohol consumption at entry to the study. The total person-years of observation was 31,225, resulting in the mean number of years observed per person of 3.86. The incidence rate for each category of alcohol consumption was as follows: Abstainer, 43.5/1000 person years; 0.1-0.4 gou/day, 60.7/1000 person years; 0.5-0.9 gou/day, 66.3/1000 person years; 1.0-1.9 gou/day, 66.9/1000 person years; ≧2 gou/day, 79.8/1000 person years. The incidence rates increased according to the increase in alcohol consumption.

The characteristics of the participants grouped according to daily alcohol consumption at entry to the study are summarized in Table 2. Age, blood pressure, total serum cholesterol and AST were higher with increasing daily alcohol consumption. The UA level at entry to the study was 5.3 mg/dL in abstainers, 5.5 mg/dL for 0.1-0.4 gou/day, 5.5 mg/dL for 0.5-0.9 gou/day, 5.6 mg/dL for 1.0-1.9 gou/day, and 5.6 mg/dL for ≥2 gou/day.

Table 3 shows the OR and 95% confidence intervals (95%CI) for the development of hyperuricemia. The OR for an increase of 1 gou/day of alcohol consumption was significant (1.29 [95%CI, 1.22-1.36]), indicating a positive dose-response relationship between alcohol consumption and the development of hyperuricemia. In addition, a significant positive OR was obtained for BMI (OR 1.11, 95%CI 1.09 - 1.12), MAP (OR 1.14, 95%CI 1.08 -1.20), AST (OR 1.13, 95%CI 1.07 -1.20) and Cr (OR 1.51, 95%CI 1.37 - 1.67). On the other hand, a negative OR was obtained for age (OR 0.86, 95%CI 0.81-0.90), HbA_{1c} (OR 0.71, 95%CI 0.59-0.85) and smoking ≥21 cigarettes/day (OR 0.86, 95%CI 0.75-0.99).

Table 4 shows the benchmark dose of alcohol consumption for the development of hyperuricemia. When the BMR was set at 5%, BMDL/BMD was 2.5/2.9 gou/day (ethanol 55.3 g/62.8 g/day). When the BMR was set at 10%, BMDL/BMD was 4.1/4.6 gou/day (ethanol 90.0 g/102.1 g/day). Therefore, the present results showed alcohol consumption of

2.5 gou/day (=ethanol 55 g/day) markedly increased the risk of developing hyperuricemia.

4 Discussion

This 8-year cohort study in Japanese male workers used pooled logistic regression analysis to estimate the BMD of alcohol consumption for the development of hyperuricemia. Using this method, the risk for the endpoints was adequately estimated by adjusting for the effect of yearly variations in other potential covariates. The BMD is defined as the exposure that corresponds to a certain change in response compared to the background conditions. Using the BMD method, the critical amount of exposure can also be estimated as the amount that corresponds to a 5% or 10% adverse change compared with the background of zero exposure. The BMD method requires a significant mathematical model that is based on the observed dose-response or dose-effect relationships. In order to take the probable variation of BMD into consideration, we estimated BMDL, which corresponds to the lower 95% confidence limit of BMD. We used the profile likelihood method to estimate BMDL. As alcohol consumption was used as a continuous variable, the loss of information by categorization of exposure was less likely in our study. As noted above, our analyses have several advantages compared with the NOAEL-approach [23, 25]. Therefore, in terms of methodology, our study reduced bias and improved the detection power and accuracy of the results. From the standpoint of preventive medicine, we consider that the allowable level of alcohol consumption calculated in the present study provides extremely meaningful information.

As far as we are aware, the BMD of alcohol consumption for development of hyperuricemia has not been reported previously, especially in male Japanese subjects. Our study identified for the first time a positive dose-response relationship between alcohol consumption and hyperuricemia in male Japanese subjects and estimated the BMD of alcohol consumption for development of this condition. To investigate the cause and effect relationship between alcohol consumption and hyperuricemia, it is imperative to carry out

long-term observations in a sufficient number of participants. However, it is very difficult to obtain accurate information in a suitably large number of participants. This difficulty has contributed to a lack of large-scale prospective studies. In previous studies on alcohol consumption in Japan, the total number of participants ranged from 1,312 [20] to 3,310 [19]. One notable feature of the current study was the increase in study size obtained by conducting a follow-up study using annual health examination data accumulated over an 8-year period in approximately 8,000 participants. By measuring changes in lifestyle and other covariates over time we were able to estimate the risk and threshold of alcohol consumption for hyperuricemia using pooled logistic regression analyses. These results also allowed us to verify the possibility of introducing preventive measures at the work site, thereby making the present study both original and significant.

We consider the etiological mechanisms for the effect of alcohol consumption on UA levels are as follows [14]. During the metabolism of alcohol, adenosine triphosphate (ATP) is consumed rapidly, followed by its degradation to uric acid via the following reactions: ATP is converted to adenosine diphosphate (ADP) → adenosine monophosphate (AMP) → inosine monophosphate (IMP) → inosine → hypoxanthine → xanthine → UA. Ingestion of a large amount of ethanol also raises the blood concentration of lactic acid, leading to a decreased urinary excretion of UA. On the other hand, purines present in alcohol beverages may increase the plasma concentration of purine bases. For example, beer contains a relatively high amount of purines compared with other alcoholic beverages [14, 28]. Dehydration and ketoacidosis due to alcohol consumption may be associated with an ethanol-induced increase in serum UA levels. Ethanol also increases the plasma concentrations and urinary excretion of hypoxanthine and xanthine via the acceleration of adenine nucleotide degradation and possible weak inhibition of xanthine dehydrogenase activity.

Several longitudinal epidemiological studies have been conducted on gout or

hyperuricemia caused by alcohol consumption. Choi et al. [15] followed 47,150 male American subjects over 12 years and investigated the relationship between alcohol consumption and risk of gout. The number of participants who developed gout in their study was 730. Compared with men who did not drink alcohol, the multivariate relative risk of gout was 1.49 for ethanol consumption of 15.0-29.9 g/day, 1.96 for 30.0-49.9 g/day, and 2.53 for > 50 g/day. However, the endpoint of this study was self-referred gout and physiological factors such as blood pressure and blood tests such as creatinine or blood glucose levels were not evaluated. In contrast, the endpoint of the present study was based on actual serum UA levels determined by annual blood tests. Furthermore, other potential covariates were included in our statistical model. We therefore consider that our study had improved accuracy. Our study measured the presence of hyperuricemia which was the prodromal phase of the onset of gout used by Choi et al. In terms of prevention, we consider that the information we obtained is therefore more useful than this earlier study.

Nakanishi et al. [20] followed 1,312 Japanese male office workers over 8 years and investigated the relationship between alcohol consumption and development of hyperuricemia (serum UA $\geq$ 7.5 mg/dL or starting medication for hyperuricemia), adjusted for other blood tests, BMI, smoking status, and other covariates. The adjusted hazard ratio for an increase of 1 SD (25.3 g/day $\fallingdotseq$ 1.2 gou/day) in alcohol intake at entry was 1.26 (95% CI, 1.11 - 1.42/dL). A notable feature of the current study compared with that study was that we were able to estimate the threshold amount of alcohol consumption as BMDL based on annually updated measurement of the covariates. Furthermore in Nakanishi's study, age (negative), BMI, triglyceride, HbA1c (negative) and white blood cell count were associated significantly with the incidence of hyperuricemia at study entry.

In our previous study [21], we followed 15,871 workers at another company for 4 years. In males, the days of alcohol consumption were associated positively with the development of

increased serum UA (≥8 mg/dL) after adjusting for other potential covariates. Compared with abstainers, significant ORs were obtained for < 2 days/wk (OR: 1.55), 2–5 days/wk (OR: 2.54) and > 5 days/wk (OR: 3.17). In the present study, information on the amount of alcohol consumed was added, resulting in greater accuracy of the results obtained.

Nakamura et al. [19] followed 3,310 male Japanese who worked at a metal products factory for 6 years and investigated the relationship between alcohol consumption at study entry and development of hyperuricemia defined as a UA level >7.0 mg/dL or taking medication for hyperuricemia. The hazard ratio for hyperuricemia in drinkers compared with nondrinkers was 1.40 for 10.0-19.9 drinks/wk (one drink =11.5 g of ethanol, 10-19.9 drinks/week≒0.7-1.4 gou/day), 1.64 for 20.0-29.9 drinks/wk (≒1.4-2.1 gou/day), and 1.98 for ≧30.0 drinks/wk (≒2.1 gou/day) after adjustment for other potential covariates. In that study the participants were classified into four groups according to alcohol consumption. While the NOAEL-approach was adopted in Nakamura's study, we used the BMD/BMDL approach and showed the threshold amount of alcohol (2.5 gou/day) was two-fold higher than that measured in their study (approximately 1 gou/day). The BMD/BMDL approach utilizes the information from the whole dose–response curve and by using continuous alcohol consumption minimizes the loss of information. These advantages of BMDL provide more valuable information for risk assessment of alcohol consumption.

Our study showed a significant positive relationship between hyperuricemia and other potential covariates including BMI, MAP, AST, and Cr. In contrast to ordinal expectations, we observed a significant negative dose-response relationship with age, HbA_{1c} and smoking habit. A previous study [20] also observed a similar negative dose-response relationship for age and HbA_{1c}. Further evaluation is therefore necessary to validate these relationships. Although BMI, systolic and diastolic blood pressure showed significant relationships in the previous study, BUN did not [20]. Therefore, the positive cause-effect relationships between

development of hyperuricemia and AST or Cr we observed in the present study are the first report of these associations.

4.1 Conclusion

This longitudinal cohort study showed a significant, positive dose-response relationship between alcohol consumption and the development of hyperuricemia. The study also showed that alcohol consumption of 2.5 gou/day (=ethanol 55 g/day) is associated with a distinct increase in the risk of hyperuricemia. Valuable information for preventing alcohol-induced hyperuricemia was provided by applying leading-edge statistical analysis to data obtained from a long-term follow-up in a large patient cohort.

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Table 1

Number of subjects, person-years studied, and the incidence rate of hyperuricemia, grouped according to alcohol consumption at entry to the study.

	Daily alcohol consumption [gou/day (g/day)]					
	Abstainer	0.1–0.4 (0.1-10.9)	0.5–0.9 (11-21.9)	1.0–1.9 (22.0-43.9)	≥ 2.0 (≥ 44.0)	Total
Number of subjects examined	2,419	1,673	1,267	1,482	1,256	8,097
Number of subjects who developed hyperuricemia	392	349	333	411	422	1,907
(%)	16.2	20.9	26.3	27.7	33.6	23.6
Total person-years of observation	9,020	5,752	5,024	6,141	5,288	31,225
Incidence rate per 1,000 person years	43.5	60.7	66.3	66.9	79.8	61.1
Mean observed years per person	3.73	3.44	3.97	4.14	4.21	3.86

Table 2

Characteristics of the subjects at the study entry year, grouped according to weekly alcohol consumption at entry.

	Daily alcohol consumption [gou/day (g/day)]					
	Abstainer	0.1–0.4 (0.1-10.9)	0.5–0.9 (11-21.9)	1.0–1.9 (22.0-43.9)	≥ 2.0 (≥ 44.0)	Total
	Mean (SD[a])	Mean (SD[a])	Mean (SD[a])	Mean (SD[a])	Mean (SD[a])	Mean (SD[a])
Age (yr)	40.0 (13.1)	39.1 (12.3)	43.3 (11.2)	46.7 (9.9)	48.5 (8.6)	42.9 (12.0)
Body mass index (kg/m^2)	23.7 (3.5)	23.5 (3.1)	23.8 (2.9)	23.6 (2.9)	23.7 (2.9)	23.7 (3.1)
Systolic blood pressure (mmHg)	127.6 (13.5)	127.2 (13.2)	130.0 (12.7)	132.0 (13.4)	134.3 (13.5)	129.8 (13.6)
Diastolic blood pressure (mmHg)	77.1 (9.7)	77.0 (9.6)	79.8 (9.5)	81.2 (9.2)	83.1 (9.3)	79.2 (9.8)
Mean arterial pressure (mmHg)	94.0 (10.4)	93.8 (10.3)	96.5 (10.0)	98.2 (10.0)	100.2 (10.1)	96.0 (10.5)
	GM[b] (GSD[c])	GM[b] (GSD[c])	GM[b] (GSD[c])	GM[b] (GSD[c])	GM[b] (GSD[c])	GM[b] (GSD[c])
Total serum cholesterol (mg/dL)	189.7 (1.2)	187.8 (1.2)	195.0 (1.2)	195.8 (1.2)	197.5 (1.2)	192.4 (1.2)
HbA_{1c} (%)	5.1 (1.2)	5.0 (1.1)	5.1 (1.1)	5.0 (1.1)	5.0 (1.1)	5.1 (1.1)
Aspartate aminotransferase (IU/L)	19.2 (1.4)	19.7 (1.4)	20.1 (1.4)	21.3 (1.4)	23.5 (1.5)	20.4 (1.4)
Creatinine (mg/dL)	0.80 (1.2)	0.80 (1.2)	0.80 (1.2)	0.79 (1.2)	0.78 (1.2)	0.79 (1.2)
Uric acid (mg/dL)	5.3 (1.2)	5.5 (1.2)	5.5 (1.2)	5.6 (1.2)	5.6 (1.2)	5.5 (1.2)
Job schedule type						
Daytime	60.0%	65.0%	63.0%	63.0%	61.0%	62.0%
Shift work	40.0%	35.0%	37.0%	37.0%	39.0%	38.0%
Tobacco consumption						
Nonsmoker	44.5%	47.6%	45.3%	41.0%	34.1%	43.0%
1-10 cigarettes/day	7.4%	8.5%	7.7%	5.5%	4.3%	6.8%
11-20 cigarettes/day	31.3%	32.1%	32.8%	32.5%	31.3%	31.9%
21- cigarettes/day	16.8%	11.8%	14.3%	21.1%	30.3%	18.3%
Habitual exercise						
None	45.4%	37.6%	38.0%	39.8%	47.1%	41.9%
Once-twice/mth	13.7%	16.0%	14.5%	13.7%	11.2%	13.9%
Once-twice/wk	25.9%	30.1%	31.3%	28.9%	25.1%	28.0%
3 times/wk or more	15.0%	16.3%	16.2%	17.6%	16.6%	16.2%

[a] Standard deviation; [b]Geometric mean; [c]Geometric standard deviation.

Table 3

Odds ratios and 95% confidence intervals for the development of hyperuricemia.

Independent variables	OR[a] (95%CI[b])	*P*
Daily alcohol consumption (+1 gou = +22 g/day)	1.29 (1.22, 1.36)	<0.001
Age (+1yr)	0.86 (0.81, 0.90)	<0.001
Body mass index (+1kg/m^2)	1.11 (1.09, 1.12)	<0.001
Mean arterial pressure (+10mmHg)	1.14 (1.08, 1.20)	<0.001
Total serum cholesterol	1.03 (0.91, 1.16)	0.618
Hemoglobin A_{1c}	0.71 (0.59, 0.85)	<0.001
Aspartate aminotransferase	1.13 (1.07, 1.20)	<0.001
Creatinine	1.51 (1.37, 1.67)	<0.001
Job schedule type(/daytime[c])		
Shiftwork	0.99 (0.89, 1.09)	0.795
Tobacco consumption (/nonsmoker[c])		
1-10 cigarettes/day	0.95 (0.77, 1.16)	0.609
11-20 cigarettes/day	0.93 (0.83, 1.05)	0.239
21- cigarettes/day	0.86 (0.75, 0.99)	0.039
Habitual exercise (/≥3 times/wk[c])		
Absence	0.98 (0.85, 1.12)	0.759
Once-twice/mth	0.97 (0.82, 1.15)	0.754
Once-twice/wk	1.00 (0.87, 1.15)	0.992

[a]Odds ratios calculated using pooled logistic regression adjusted for the effect of all other covariates. [b]95% confidence interval. [c]Control categories. The data of total serum cholesterol, hemoglobin A_{1c}, aspartate aminotransferase and creatinine were transformed logarithmically using a base of 1.5.

Table 4
Benchmark dose of daily alcohol consumption for the onset of hyperuricemia.

	BMDL/BMD[a] [gou/day (g/day)]
BMR[b] (+5%)	[2.5/2.9 (55.3/62.8)]
BMR[b] (+10%)	[4.1/4.6 (90.0/102.1)]
P(0)[c]	5.2%

[a] Benchmark dose low/benchmark dose, calculated assuming mean age, mean BMI, mean arterial pressure, geometric means of serum cholesterol, HbA_{1c}, aspartate aminotransferase, and creatinine, and without smoking, with habitual exercise. [b] Benchmark response. [c] Background probability of adverse response for nondrinker.

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