Relationships of Alcohol Consumption with Coronary Risk Factors and Macro- and Micro-Nutrient Intake in Japanese People: The INTERLIPID Study

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Summary

Several studies have reported a J-shaped relationship between alcohol consumption and coronary heart disease (CHD) risk. However, the mechanisms of this relationship remain unclear. This study aimed to evaluate the relationships of alcohol consumption with established CHD risk factors and with macro-/micro-nutrient intake among Japanese people. Participants were 1,090 Japanese men and women aged 40–59 years enrolled in the INTERLIPID study, excluding former drinkers. Based on two 7-d alcohol records, participants were classified as non-drinkers (0 g/wk), light-drinkers (<100 g/wk), moderate-drinkers (100–299 g/wk), or heavy-drinkers (≥300 g/wk). Detailed macro-/micro-nutrient intake was evaluated using four in-depth 24-h dietary recalls and adjusted for total energy intake excluding alcohol. We analyzed the associations of CHD risk factors and nutrient intake with alcohol consumption. Serum high-density lipoprotein cholesterol and blood pressure were higher and low-density lipoprotein cholesterol was lower among those with higher alcohol consumption. J-shaped relationships with alcohol consumption were observed for the proportion of current smokers, number of cigarettes smoked, and prevalence of hypertension: these risk factors were lowest among light-drinkers. Carbohydrate and total fiber intakes were lower and protein and dietary cholesterol intakes were higher among those with higher alcohol consumption. These associations were similar for men and women. Alcohol consumption was related to nutrient intake as well as established CHD risk factors. Non-drinkers were higher on some CHD risk factors than were light-drinkers. These findings may influence the J-shaped relationship between alcohol consumption and CHD risk.

Key Words: non-drinkers, heavy-drinkers, nutrient intake, coronary heart disease, risk factors, cross-sectional study

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Many epidemiological studies have found a J-shaped relationship between alcohol consumption and the risk of coronary heart disease (CHD) incidence and mortality: that is, compared with light-drinkers, CHD risk has been shown to be higher among both non-drinkers and heavy-drinkers (1–4). However, the mechanisms of this relationship remain unclear.

Alcohol consumption has been shown to be positively and linearly related to blood pressure (5, 6). However, alcohol consumption has also been reported to be positively associated with high-density lipoprotein cholesterol (HDL-C) and inversely associated with low-density lipoprotein cholesterol (LDL-C) (7–11). Although this is considered to be one of the causes for higher CHD risk among non-drinkers than among light-drinkers, there may be additional factors explaining this J-shaped relationship. Alcohol consumption was also reported to be associated with dietary habits such as total energy intake and carbohydrate intake in western countries (12, 13). However, few studies have investigated the association between alcohol consumption and the intake of macro- and micro-nutrients in Japan and other Asian countries. Intakes of some nutrients, which are related to alcohol consumption, may explain the J-shaped relationship between alcohol consumption and CHD risk in Japan.

The INTERLIPID, an ancillary study of the International Study of Macro/micronutrients and Blood Pressure (INTERMAP), investigated CHD risk factors and the detailed intake of macro- and micro-nutrients using four in-depth 24-h dietary recalls by specially trained interviewers according to standardized quality control procedures. This allowed us to examine the relationships of alcohol consumption with the intake of nutrients and with CHD risk factors. The 24-h dietary recalls can be used to estimate total energy intake, so we were also able to compare total energy intake including and excluding energy from alcohol. The purpose of this study was to evaluate the relationships of alcohol consumption with established CHD risk factors and with the intake of macro- and micro-nutrients in Japanese people enrolled in the INTERLIPID in order to explore the reasons of a J-shaped relationship between alcohol consumption and CHD risk.

**MATERIALS AND METHODS**

**Study design and participants.** The INTERMAP study was an international, cooperative, cross-sectional study conducted from 1996 to 1999. The randomly recruited participants were 4,680 men and women aged 40–59 y from 17 diverse population samples in China, Japan, the United Kingdom, and the United States. The INTERLIPID was an ancillary study of the INTERMAP that aimed to explore the relation of multiple dietary intake factors to CHD risk factors, focusing on the intake of lipids. The INTERLIPID participants were from five INTERMAP population samples: four in Japan and one in Hawaii. Details of the methods employed in these two studies have been reported elsewhere (14–16).

In the present analysis, the four populations in Japan (574 men and 571 women) were used. Japanese participants included (1) Japanese factory workers in Toyama, central Japan (149 men and 150 women); (2) Japanese factory workers in Sapporo, northern Japan (149 men and 148 women); (3) Japanese factory workers in Wakayama, central Japan (146 men and 144 women); and (4) Japanese residents of Aito-town, a rural town in Shiga Prefecture, central Japan (130 men and 129 women). Among the participants, 55 individuals were excluded from the present study for the following reasons: missing data on vitamin B1 (n = 3), serum total cholesterol (n = 2), fibrinogen (n = 6), or hemoglobin A1c (HbA1c) (n = 3); total hours on the physical activity index did not add up to 24 h (n = 11); missing data for the physical activity index (n = 1); or being a former drinker who answered that they do not drink but have ever drunken alcohol in the questionnaire (n = 29). The number of eligible participants for analysis was 1,090 individuals (555 men and 535 women). The ethics committees of Shiga University of Medical Science, the Pacific Health Research Institute, and Northwestern University approved the study protocol (No. R1995-001). Written informed consent was obtained from all participants.

**Anthropometric and lifestyle assessments.** Participants visited the local research centers four times on two pairs of consecutive days that were an average of 3 wk apart. Height and weight with light clothes and without shoes were measured twice at the first and third visits, and two readings were taken on each occasion (four times in total). The average of these four measurements was used for the analysis. Blood pressure was measured twice by trained and certified observers following a standard protocol on each of the 4 d (eight times in total) (14), and the average of these eight measurements was used for the analysis. Trained interviewers obtained questionnaire data on physical activity, years of education, smoking status, special diets, medical history of cardiovascular disease (myocardial infarction, any other heart disease, or stroke), and use of medication (including antihypertensive, antihyperlipidemic, or antidiabetic medication). To evaluate physical activity, participants were asked about the number of hours per day spent in heavy activity, moderate activity, light activity, sedentary activity (e.g., watching television), and no activity (sleeping). A physical activity index score was calculated by multiplying the duration spent in different activities by corresponding weighting factors; for this, the procedure in the Framingham Offspring Study was followed (17).

**Alcohol assessment.** Daily alcohol consumption information (including the amount and type of alcoholic beverages consumed per day during the past 7 d) was obtained by trained interviewers at the participants’ first and third visits (data on 14 d in total); these data were in addition to data on alcohol consumption taken from the four 24-h dietary recalls described below. The average of 7-d alcohol (ethanol) consumption from the two records (14 d: g/wk) was used for the analysis. We classified participants into four groups: non-drink-
ers, who were lifetime abstainers or did not drink (0 g/wk) for 14 d; light-drinkers, who drank <100 g/wk (4, 18); moderate-drinkers, who drank ≥100 g but <300 g/wk; and heavy-drinkers, who drank ≥300 g/wk (19, 20). For women, moderate-drinkers and heavy-drinkers were combined because of small numbers in these groups.

**Dietary assessment.** In-depth, multi-pass 24-h dietary recalls were conducted on each of the four different participants visit days by trained and certified dietary interviewers. Standardized quality control procedures were used to assess and maximize the quality of the dietary data (15). Intake of all foods, beverages (including alcoholic beverages), and dietary supplements during the previous 24-h were recorded by the interviewers. All participants attended all four study visits. Their energy intakes from the 24-h recalls ranged from 500 to 5,000 kcal/d for men and women. The average individual energy and nutrient intake from the four 24-h dietary recalls was used for the analysis. Total energy intake excluding alcohol was calculated as total energy intake minus energy from alcohol intake (7 kcal for 1 g of alcohol).

**Biochemical measurements.** In the INTERLIPID, non-fasting blood was drawn after the last meal on the second day of the first 2-d visit pair (16, 21, 22). Serum and plasma samples from each participant were stored locally at −70°C after centrifuging within 30 min of the blood draw. All samples were sent to a central laboratory in Japan on dry ice. HDL-C was measured by the selective inhibition method, and total cholesterol, LDL-C, and triglycerides were directly measured by enzymatic assay on an auto-analyzer (Hitachi 7107; Hitachi, Tokyo, Japan). Gamma-glutamyl transpeptidase and uric acid were measured by the L-γ-glutamyl-3-carboxy-4-nitroanilide method and the uricase-peroxidase method, respectively (Hitachi 7107). Fibrinogen was measured by the thrombin coagulation time method (CA-500: Gypsum, Hyogo, Japan). HbA1c was measured by the high-performance liquid chromatography method (HA-8131; Arkray at present, Kyoto, Japan), which was standardized by the Japanese Diabetes Society. HbA1c values were converted into National Glycohemoglobin Standardization Program (NGSP) values (23). Creatinine was measured using the alkaline picric acid (Jaffe) method (Hitachi 7107). Because estimated glomerular filtration rate (eGFR) can be directed by creatinine (Jaffe) method (Hitachi 7107). Because estimated glycosed hemoglobin Standardization Program (NGSP) values. HbA1c values were converted into National Glycohemoglobin Standardization Program (NGSP) values.

Hypertension was defined as having a systolic blood pressure ≥140 mmHg, having a diastolic blood pressure ≥90 mmHg, and/or using antihypertensive medication. Dyslipidemia was defined as HDL-C <40 mg/dL, LDL-C ≥140 mg/dL, and/or use of antihyperlipidemic medication. Diabetes was defined as HbA1c (NGSP) ≥6.5% and/or use of antidiabetic medication.

**Calculation of the Suita score.** The Suita score for predicting the 10-y probability of developing CHD for Japanese people was calculated using age, sex, smoking status, history of diabetes, blood pressure level, LDL-C level, HDL-C level, and chronic kidney disease stage (26). Higher Suita scores correspond to greater probability of developing CHD. We categorized the predicted probability of CHD within 10 y into <3.0% or ≥3.0% according to the Suita score.

**Statistical analysis.** In descriptive analyses, alcohol consumption was categorized into four groups for men (abstainers/0, <100, 100–299, or ≥300 g/wk) and three groups for women (abstainers/0, <100, or ≥100 g/wk). Nutrient intake densities were computed by dividing specific nutrient intake values by total energy intake excluding energy from alcohol. When appropriate, analysis of variance, Kruskal–Wallis tests, and chi-square tests were used to evaluate statistical differences in nutrient intake and CHD risk factors among the alcohol consumption categories, stratified by sex. Dunnett’s test was used for multiple comparisons. Light-drinkers were set as the reference group. All analyses were performed using SAS, Version 9.4 (SAS Institute, Cary, NC, USA). A p-value of <0.05 was considered to be significant.

**RESULTS**

**Comparison of CHD risk factors by alcohol consumption**

CHD risk factors and lifestyle factors by alcohol consumption categories are shown in Table 1 for men and in Table 2 for women. The mean (SD) ages for men and women were 49.5 (5.3) and 49.2 (5.3) y, respectively, and there were no significant differences in age among the categories for either men or women. Body mass index also showed no significant differences. Systolic and diastolic blood pressure were higher for those in the higher alcohol consumption categories. In contrast, all alcohol consumption categories, the prevalence of hypertension was lowest among light-drinkers, and a J-shaped relationship was observed. Serum HDL-C was higher and LDL-C was lower for higher alcohol consumption groups among both men and women. In addition, of all alcohol consumption categories, the prevalence of dyslipidemia was highest among non-drinkers. Triglycerides tended to be positively associated with alcohol consumption, but this association was not significant. Serum gamma-glutamyl transpeptidase levels were higher in the higher alcohol consumption categories. For men, the proportion of current smokers was higher among non-drinkers and among moderate-to-heavy-drinkers, compared to light-drinkers. The number of cigarettes consumed per day was also lowest among light-drinkers, compared with the other alcohol con-
Table 1. Coronary risk factors and lifestyle factors by alcohol consumption category for men (the INTERLIPID study in Japan, 1996–1999; men aged 40–59 y).

| Risk Factor                          | Total (n=555) | Non-drinkers (n=42) | Light-drinkers (n=139) | Moderate-drinkers (n=211) | Heavy-drinkers (n=163) | p*  |
|--------------------------------------|---------------|---------------------|------------------------|--------------------------|------------------------|-----|
| Weight (kg)                          | 66.7±8.7      | 68.3±9.8            | 65.9±8.3               | 66.3±8.5                 | 67.5±9.0               | 0.224 |
| Height (m)                           | 1.68±0.06     | 1.69±0.06           | 1.67±0.06              | 1.68±0.06                | 1.68±0.06              | 0.351 |
| Body mass index (kg/m²)              | 23.7±2.7      | 24.0±2.8            | 23.6±2.8               | 23.4±2.5                 | 23.9±2.9               | 0.379 |
| Alcohol consumption (g/d)            | 30.3±24.7     | —                   | 6.6±4.1                | 27.6±8.4*                | 61.9±16.0*             | <0.001 |
| SBP (mmHg)                           | 120.4±12.9    | 116.0±13.8          | 117.7±12.3             | 120.5±12.5               | 123.7±12.8*            | <0.001 |
| DBP (mmHg)                           | 76.8±9.9      | 73.4±10.3           | 75.0±9.4               | 77.0±10.4                | 78.9±9.2*              | 0.001 |
| Serum T-C (mg/dL)                    | 199.0 [179.0–218.0] | 202.0 [184.0–224.0] | 199.0 [181.0–219.0]    | 199.0 [177.0–219.0]      | 198.5 [179.0–220.5]    | 0.713 |
| Serum HDL-C (mg/dL)                  | 53.9±13.6     | 45.9±10.8           | 49.1±11.2              | 54.7±12.7*               | 59.0±14.9*             | <0.001 |
| Serum LDL-C (mg/dL)                  | 120.6±28.3    | 127.3±25.8          | 121.3±26.3             | 122.3±27.9               | 114.6±30.4*            | 0.009 |
| Serum triglyceride (mg/dL)           | 134.0 [90.0–192.0] | 103.0 [75.0–149.0]  | 103.0 [74.0–151.0]     | 116.0 [82.0–171.0]       | 136.0 [86.0–205.5]     | 0.282 |
| Serum γ-GTP (U/L)                    | 37.0 [24.0–69.0] | 25.0 [19.0–33.0]    | 28.0 [20.0–43.0]       | 38.0 [24.0–65.0]**       | 67.0 [36.0–120.0]**    | <0.001 |
| Serum uric acid (mg/dL)              | 6.2±1.1       | 5.4±1.1             | 5.7±1.2                | 5.8±1.2                  | 6.0±1.2                | 0.067 |
| Serum fibrinogen (mg/dL)             | 253.3±69.3    | 266.9±60.2          | 258.7±67.6             | 245.7±66.9               | 255.8±68.0             | 0.133 |
| HbAlc (%)                            | 5.1±0.6       | 5.1±0.5             | 5.1±0.6                | 5.1±0.6                  | 5.2±0.6                | 0.575 |
| eGFR (mL/min/1.73 m²)                | 84.3±14.7     | 81.3±13.3           | 80.4±13.8              | 84.0±14.5                | 87.6±15.6*             | 0.004 |
| Urinary sodium (mmol/24 h)           | 209.8±56.7    | 221.1±55.5          | 198.8±51.8             | 210.6±52.8               | 215.1±64.5*            | 0.038 |
| Urinary potassium (mmol/24 h)        | 49.1±13.3     | 53.1±19.7*          | 46.8±11.8              | 50.2±12.7                | 48.5±13.0              | 0.021 |
| Urinary sodium to potassium ratio    | 4.5±1.3       | 4.5±1.6             | 4.5±1.4                | 4.4±1.2                  | 4.6±1.2                | 0.500 |
| Smoking status                       |               |                     |                        |                          |                        |      |
| Never-smoker (%)                     | 23.8          | 31.0                | 35.3                   | 23.7                     | 12.3                   | 0.001 |
| Ex-smoker (%)                        | 24.7          | 19.1                | 20.9                   | 26.5                     | 27.0                   |      |
| Current-smoker (%)                   | 51.5          | 50.0                | 43.9                   | 49.8                     | 60.7                   |      |
| Number of cigarettes (n/d)           | 3.0 [0.0–20.0] | 2.5 [0.0–25.0]     | 0.0 [0.0–20.0]         | 0.0 [0.0–20.0]           | 0.0 [0.0–25.0]**       | 0.001 |
| History of CVD (%)                   | 11.7          | 9.5                 | 10.8                   | 13.3                     | 11.0                   | 0.832 |
| Hypertension (%)                     | 15.9          | 14.3                | 9.4                    | 13.7                     | 24.5                   | 0.002 |
| Diabetes (%)                         | 4.0           | 7.1                 | 5.0                    | 2.8                      | 3.7                    | 0.519 |
| Dyslipidemia (%)                     | 36.6          | 52.4                | 40.3                   | 36.5                     | 29.5                   | 0.030 |
| Year of education (y)                | 12.3±2.1      | 12.1±2.0            | 12.2±2.1               | 12.6±2.3                 | 12.3±1.9               | 0.294 |
| Physical activity index              | 31.7±7.7      | 31.5±6.2            | 31.7±7.9               | 31.5±6.7                 | 32.0±8.9               | 0.934 |
| Suita score                          | 37.7±8.0      | 38.8±9.3            | 36.9±7.9               | 37.8±8.2                 | 38.0±7.5              | 0.486 |
| Predicted probability of CHD in 10 y (%) |               |                     |                        |                          |                        |      |
| <3.0%                                | 84.7          | 69.1                | 89.2                   | 83.9                     | 85.9                   | 0.016 |
| ≥3.0%                                | 15.3          | 31.0                | 10.8                   | 16.1                     | 14.1                   |      |

Values are means±standard deviations, medians [interquartile ranges], or percentages.  
*p<0.05 vs. light drinkers by Dunnett’s test. **p<0.05 vs. light drinkers by Mann–Whitney U test with the Bonferroni test for post hoc comparisons.  
* Means and median values were compared by ANOVA or Kruskal–Wallis tests. Categorical values were compared by chi-square tests.  
SBP: systolic blood pressure; DBP: diastolic blood pressure; T-C: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; GTP: glutamyl transpeptidase; GFR: glomerular filtration rate; CVD: cardiovascular disease (myocardial infarction, any other heart disease, or stroke); CHD: coronary heart disease.
Table 2. Coronary risk factors and lifestyle factors by alcohol consumption category for women (the INTERLIPID study in Japan, 1996–1999; women aged 40–59 y).

|                      | Total \((n=5\,355)\) | Non-drinkers \((n=200)\) | Light-drinkers \((n=290)\) | Moderate and Heavy-drinkers \((n=45)\) | \(p^*\)  |
|----------------------|------------------------|---------------------------|-----------------------------|--------------------------------|---------|
| Age (y)              | 49.2±5.3               | 49.4±5.2                  | 49.0±5.3                    | 48.5±5.3                       | 0.516   |
| Weight (kg)          | 55.6±8.0               | 55.1±7.9                  | 56.0±7.9                    | 55.4±8.4                       | 0.454   |
| Height (m)           | 1.55±0.06              | 1.54±0.06*                | 1.55±0.06                   | 1.55±0.06                      | 0.081   |
| Body mass index (kg/m²) | 23.2±3.1              | 23.2±3.1                  | 23.2±3.1                    | 23.0±2.8                       | 0.944   |
| Alcohol consumption (g/d) | 4.1±8.3                 | —                         | 3.4±3.6                     | 26.9±11.8*                     | <0.001  |
| SBP (mmHg)           | 114.2±14.1             | 114.2±14.8                | 113.3±13.4                  | 119.3±14.2*                    | 0.030   |
| DBP (mmHg)           | 70.6±9.7               | 70.2±10.1                 | 70.2±9.4                    | 74.7±9.2*                      | 0.011   |
| Serum T-C (mg/dL)    | 201.0 [182.0–221.0]    | 202.0 [184.0–224.0]       | 199.0 [181.0–219.0]         | 199.0 [178.0–220.0]            | 0.519   |
| Serum HDL-C (mg/dL)  | 60.1±14.2              | 57.5±13.3*                | 60.7±14.1                   | 68.2±15.4*                     | <0.001  |
| Serum LDL-C (mg/dL)  | 123.9±29.9             | 128.5±29.7                | 122.7±29.4                  | 112.2±30.9                     | 0.002   |
| Serum triglyceride (mg/dL) | 95.0 [70.0–131.0] | 103.0 [75.0–149.0]       | 103.0 [74.0–151.0]          | 121.0 [84.0–185.0]**           | <0.001  |
| Serum γ-GTP (U/L)    | 16.0 [13.0–25.0]       | 15.0 [12.0–24.0]          | 16.0 [12.0–24.0]            | 25.0 [19.0–35.0]**             | <0.001  |
| Serum uric acid (mg/dL) | 4.2±0.9                | 4.1±0.8                   | 4.1±0.9                     | 4.4±1.0                        | 0.057   |
| Serum fibrinogen (mg/dL) | 258.7±64.1            | 262.3±67.2                | 258.6±62.8                  | 243.5±57.6                     | 0.206   |
| HbA1c (%)            | 4.9±0.5                | 5.0±0.5                   | 4.9±0.4                     | 4.9±0.5                        | 0.693   |
| eGFR (mL/min/1.73 m²) | 93.6±19.5              | 94.2±19.5                 | 92.9±19.1                   | 95.1±21.5                      | 0.648   |
| Urinary sodium (mmol/24 h) | 186.8±53.6            | 183.2±51.5                | 189.4±55.9                  | 186.6±47.3                     | 0.461   |
| Urinary potassium (mmol/24 h) | 48.3±13.8             | 47.5±13.6                 | 49.1±14.3                   | 47.1±11.5                      | 0.346   |
| Urinary sodium to potassium ratio | 4.1±1.2               | 4.1±1.2                   | 4.1±1.2                     | 4.1±1.1                        | 0.900   |
| Smoking status       |                        |                           |                             |                                |         |
| Never-smoker (%)     | 89.0                   | 93.5                      | 90.7                        | 57.8                            | <0.001  |
| Ex-smoker (%)        | 2.2                    | 0.5                       | 2.1                         | 11.1                            |         |
| Current-smoker (%)   | 8.8                    | 6.0                       | 8.2                         | 31.1                            |         |
| Number of cigarettes (n/d) | 0.0 [0.0–0.0]         | 0.0 [0.0–0.0]             | 0.0 [0.0–0.0]               | 0.0 [0.0–8.0]**                 | <0.001  |
| History of CVD (%)   | 5.4                    | 6.5                       | 4.5                         | 6.7                             | 0.580   |
| Hypertension (%)     | 10.3                   | 11.0                      | 9.0                         | 15.6                            | 0.365   |
| Diabetes (%)         | 2.4                    | 2.5                       | 1.7                         | 6.7                             | 0.134   |
| Dyslipidemia (%)     | 32.0                   | 34.5                      | 32.4                        | 17.8                            | 0.092   |
| Year of education (y) | 11.6±2.0               | 11.4±2.0                  | 11.7±2.0                    | 11.9±1.8                        | 0.246   |
| Physical activity index | 32.3±7.3             | 31.8±7.4                  | 32.8±7.5                    | 30.6±4.5                       | 0.100   |
| Suita score          | 26.2±8.5               | 27.1±8.5                  | 25.8±8.4                    | 27.1±9.0                        | 0.086   |
| Predicted probability of CHD in 10 y (%) | 98.1           | 98.0                      | 98.6                        | 95.6                            | 0.363   |
| <3.0%                | 1.9                    | 2.0                       | 1.4                         | 4.4                             |         |

Values are means±standard deviations, medians [interquartile ranges], or percentages.

* \(p<0.05\) vs. light drinkers by Dunnett’s test. ** \(p<0.05\) vs. light drinkers by Mann–Whitney \(U\) test with the Bonferroni test for post hoc comparisons.

Means and median values were compared by ANOVA or Kruskal–Wallis tests. Categorical values were compared by chi-square tests, except for smoking status, diabetes and predicted probability of CHD in 10 y (%) (Pearson’s chi-square test). SBP: systolic blood pressure; DBP: diastolic blood pressure; T-C: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; GTP: glutamyl transpeptidase; GFR: glomerular filtration rate; CVD: cardiovascular disease (myocardial infarction, any other heart disease, or stroke); CHD: coronary heart disease.
Table 3. Nutrient intake (density per total energy intake excluding energy from alcohol) by alcohol consumption category for men (the INTERLIPID study in Japan, 1996–1999; men aged 40–59 y).

| Nutrient                        | Non-drinkers (n=42) | Light-drinkers (n=139) | Moderate-drinkers (n=211) | Heavy-drinkers (n=163) | P*   |
|--------------------------------|---------------------|------------------------|---------------------------|------------------------|------|
| Total energy (kcal/d)          | 2.177±1.14          | 2.119±3.78             | 2.294±4.28*               | 2.389±3.80*            | <0.001 |
| Energy excluding alcohol (kcal/d) | 2.176±1.14          | 2.078±369              | 2.114±413                 | 1.989±339              | 0.004 |
| Total protein (% kcal)         | 15.9±2.1            | 16.2±2.3               | 16.9±2.5*                 | 19.0±3.2*              | <0.001 |
| Animal protein (% kcal)        | 8.4±2.2             | 8.9±2.6                | 9.5±2.6                   | 11.5±3.4*              | <0.001 |
| Vegetable protein (% kcal)     | 7.5±1.1             | 7.3±1.1                | 7.5±1.0                   | 7.5±1.3                | 0.438 |
| Total fat (% kcal)             | 25.3±5.3            | 26.0±5.3               | 25.8±4.8                  | 26.6±5.0               | 0.350 |
| Total SFA (% kcal)             | 6.6±1.8             | 6.7±1.7                | 6.7±1.7                   | 6.7±1.6                | 0.987 |
| Total MFA (% kcal)             | 9.1±2.3             | 9.5±2.4                | 9.5±2.1                   | 9.6±2.2                | 0.681 |
| Total PFA (% kcal)             | 6.7±1.7             | 6.8±1.7                | 6.6±1.5                   | 7.0±1.8                | 0.32  |
| Omega-6 PFA (% kcal)           | 5.3±1.4             | 5.4±1.5                | 5.2±1.3                   | 5.3±1.5                | 0.341 |
| Omega-3 PFA (% kcal)           | 1.4±0.5             | 1.4±0.4                | 1.4±0.4                   | 1.6±0.5*               | <0.001 |
| Dietary cholesterol (mg/1,000 kcal) | 184.2±72.8        | 200.7±71.5             | 207.1±67.3                | 247.8±85.4*            | <0.001 |
| Total carbohydrate (% kcal)    | 58.7±6.3            | 57.7±6.0               | 57.1±5.8                  | 54.3±6.1*              | <0.001 |
| Starch (% kcal)                | 40.5±6.4            | 40.1±7.0               | 38.7±7.5                  | 35.2±6.8*              | <0.001 |
| Total fiber (g/1,000 kcal)     | 8.0±1.8             | 7.6±1.8                | 7.6±1.9                   | 7.0±1.8*               | 0.002 |
| Vitamin A (IU/1,000 kcal)      | 3.149±3.130.7       | 2.983±2.205.1          | 2.942±1.615.5             | 3.052±2.421.9          | 0.914 |
| Vitamin E (mg/1,000 kcal)      | 5.0±1.0             | 5.1±1.3                | 4.9±1.0                   | 5.2±1.2                | 0.079 |
| Vitamin B1 (mg/1,000 kcal)     | 0.46±0.09           | 0.46±0.09              | 0.48±0.11                 | 0.47±0.10              | 0.346 |
| Vitamin B2 (mg/1,000 kcal)     | 0.68±0.16           | 0.69±0.18              | 0.72±0.17                 | 0.77±0.20*             | <0.001 |
| Vitamin C (mg/1,000 kcal)      | 66.0±4.34           | 63.3±44.3              | 59.9±33.7                 | 57.6±37.2              | 0.458 |
| Sodium (mg/1,000 kcal)         | 2.211±409.8         | 2.280±442.3            | 2.422±471.9*              | 2.787±654.6*           | <0.001 |
| Potassium (mg/1,000 kcal)      | 1.348±263.4         | 1.336±256.5            | 1.411±303.3*              | 1.470±288.7*           | <0.001 |
| Calcium (mg/1,000 kcal)        | 289.1±86.7          | 283.0±92.3             | 292.8±106.7               | 302.4±95.6             | 0.396 |
| Magnesium (mg/1,000 kcal)      | 130.7±25.4          | 128.4±23.1             | 139.9±26.8*               | 152.5±29.8*            | <0.001 |
| Phosphorus (mg/1,000 kcal)     | 54.5±88.0           | 55.0±87.4              | 59.1±103.9*               | 653.5±111.0*           | <0.001 |
| Iron (mg/1,000 kcal)           | 5.4±1.3             | 5.3±1.1                | 5.4±1.1                   | 5.8±1.3*               | <0.001 |
| Zinc alloy (mg/1,000 kcal)     | 4.442±5.57          | 4.743±791.3            | 4.893±1.145.0             | 5.094±1.165.7*         | <0.001 |
| Copper (mg/1,000 kcal)         | 705.05±186.7        | 691.75±170.72          | 698.74±200.63             | 717.88±184.66          | 0.651 |
| Selenium (µg/1,000 kcal)       | 74.5±21.4           | 87.0±34.4              | 90.6±40.9                 | 104.9±36.8*            | <0.001 |

Values are means±standard deviations.
*p<0.05 vs. light drinkers by Dunnett's test.
*Means were compared by ANOVA.
SFA: saturated fatty acids; MFA: monounsaturated fatty acids; PFA: polyunsaturated fatty acids.
consumption groups. Similar relationships were observed for women. Among both men and women, the proportion with a 10-y probability for CHD ≥3.0% was lowest among light-drinkers, compared with the other alcohol consumption groups.

**Macro- and micro-nutrient intake by alcohol consumption**

Tables 3 and 4 show nutrient intake density per energy intake excluding energy from alcohol by alcohol consumption category. For men, total energy intake excluding energy from alcohol was lower for higher alcohol consumption categories, whereas total energy including energy from alcohol was higher for higher alcohol consumption categories.

Regarding macro-nutrient intake, total protein (% kcal) and animal protein (% kcal) intakes were higher for those in higher alcohol consumption categories, but vegetable protein (% kcal) showed no significant difference by alcohol consumption for either men or women. Moderate and heavy-drinkers had the highest fat intake (% kcal) among women but not among men.

For women, total monounsaturated fatty acids (% kcal), total polyunsaturated fatty acids (% kcal), and omega-3 polyunsaturated fatty acids (% kcal) were significantly higher among moderate and heavy-drinkers. For men, only omega-3 polyunsaturated fatty acids (% kcal) were significantly higher among heavy-drinkers. Dietary cholesterol (mg/1,000 kcal) was higher for higher categories of alcohol consumption for both men and women. Total carbohydrates (% kcal), starch (% kcal), and total fiber (% kcal) were significantly higher among moderate and heavy-drinkers. For men, total energy intake excluding energy from alcohol was lower for higher alcohol consumption categories, whereas total energy including energy from alcohol was higher for higher alcohol consumption categories.

Regarding micro-nutrient intake, the highest vitamin B2 intake (mg/1,000 kcal) was observed among heavy-drinkers for men and among moderate and heavy-drinkers for women. Moderate and heavy-drinkers showed the lowest vitamin C intake (mg/1,000 kcal) among women. Heavy-drinkers for men and moderate and heavy-drinkers for women showed the highest sodium intake (mg/1,000 kcal). Among men, heavy-drinkers showed the highest cholesterol (mg/1,000 kcal) intake among higher alcohol consumption categories.
had the highest potassium intake (mg/1,000 kcal). The intakes of other minerals including magnesium (mg/1,000 kcal), phosphorus (mg/1,000 kcal), and selenium (µg/1,000 kcal) were highest among heavy-drinkers for men and among moderate and heavy-drinkers for women.

Tables S1 and S2 (Supplemental Online Material) show nutrient intake density per total energy intake including energy from alcohol by alcohol consumption category for men and for women, respectively. Several macro- and micro-nutrients showed somewhat different tendencies compared with the results presented in Tables 3 and 4. For example, positive relationship of total protein intake and sodium intake to alcohol consumption disappeared after including energy from alcohol in both sexes. Tables S3 and S4 (Supplemental Online Material) show absolute nutrient intake per day by alcohol consumption category for men and for women, respectively. The results were generally similar to those shown in Tables 3 and 4.

**DISCUSSION**

In this study, we evaluated the relationships of alcohol consumption with CHD risk factors and with macro- and micro-nutrient intake in the INTERLIPID study using four in-depth 24-h dietary recalls for participants from the general Japanese population aged 40–59 y. Non-drinkers showed a higher prevalence of hypertension and dyslipidemia and a higher proportion of current smokers, compared with light-drinkers, which may influence the J-shaped relationship between alcohol consumption and CHD risk. The study results implied that fat intake does not influence the relationship between alcohol consumption and serum cholesterol level.

An important strength of this study is the usage of in-depth, multi-pass 24-h dietary recalls including one holiday in the INTERLIPID to evaluate dietary nutrient intake. Dietary interviewers received special training and conducted dietary surveys using standardized quality control procedures. In addition, trained dietitians also conducted interviews with participants about the details of their alcohol consumption in the last 14 d. Some previous studies in Western countries have examined the relationship between alcohol consumption and nutrient intake using total energy intake excluding energy from alcohol (12, 13). However, to our best knowledge, no previous studies in Asian countries have investigated this relationship using total energy intake excluding energy from alcohol. We calculated nutrient intake density using total energy intake excluding energy from alcohol, as main results, because it was suggested that energy from alcohol may be utilized less efficiently than nonalcoholic energy (from carbohydrate, protein, and lipid) or that alcohol may interfere with the efficient utilization of nonalcoholic energy (12, 13).

Another strength of the present study is that we were able to evaluate the relationships of alcohol consumption with CHD risk factors with minimum confounding by age because of a relatively narrow age range among the study participants. In previous studies, alcohol consumption showed a strong relationship with age (2, 27, 28); therefore, it would be difficult to statistically remove age confounding.

Comparing non-drinkers with light-drinkers, non-drinkers had higher a prevalence of hypertension and dyslipidemia and a higher proportion of current smokers. Some previous studies have also reported a similar tendency (2, 27–30). These findings may explain the higher CHD risk among non-drinkers, compared with light-drinkers. Non-drinkers may not drink alcohol because of a history of hypertension. Some previous studies investigating alcohol consumption and CHD risk did not adjust for history of hypertension (3, 27), used self-reported history (2, 28–30), or considered only categorical smoking status but not the number of cigarettes smoked (4, 31). Detailed information regarding disease history and smoking status should be considered when evaluating the relationship between alcohol consumption and CHD risk.

Non-drinkers showed the highest prevalence of dyslipidemia for both men and women, which could be one reason why they have a higher CHD risk. According to previous studies, alcohol consumption is positively associated with HDL-C and inversely associated with LDL-C (7–11). Heavy-drinkers showed a higher dietary cholesterol intake and a lower total fiber intake in the present study. Intake of total fat and total saturated fatty acids did not differ significantly among the alcohol consumption groups. These results suggest that the lower LDL-C and higher HDL-C observed with higher alcohol consumption are directly influenced by alcohol consumption itself, without any effects of dietary factors such as fat intake.

It is well established that alcohol consumption increases blood pressure (5, 6). In the present study, higher alcohol consumption was related to higher sodium intake; however, the relationship between alcohol consumption and urinary sodium excretion was somewhat J-shaped for men. Moreover, the urinary sodium/potassium ratio, which is an important dietary factor for blood pressure, was not related to alcohol consumption. However, non-drinkers did not have any dietary factors that would increase their CHD risk, compared with light-drinkers.

There were significant differences in nutrient intake between light-drinkers and heavy-drinkers. Heavy-drinkers showed higher total energy intake including energy from alcohol. However, there was no positive relationship between alcohol consumption and body mass index, and heavy-drinkers showed lower energy intake when excluding energy from alcohol. Similar results have previously been reported in Western countries (12, 13). It remains controversial whether higher alcohol intake increases body weight and whether alcohol cessation reduces body weight in interventional and observational studies (32). Our study results indicate that an increase in energy intake from alcohol is not likely to be related to a body weight increase.
In terms of macro-nutrients, total carbohydrate intake was lower and total protein intake was higher among those with higher alcohol consumption. Intakes of dietary cholesterol, omega-3 polyunsaturated fatty acids, and animal protein were higher among heavy-drinkers. For micro-nutrients, intakes of magnesium, phosphorus, iron, zinc alloy, and selenium were higher among heavy-drinkers. These results suggest that the dietary habits of heavy-drinkers in Japan are characterized by a lower intake of staple foods (such as rice) and a higher intake of main dishes (including meat and fish).

However, the results may not reflect the present lifestyle in Japan because the INTERLIPID was conducted in the late 1990s. For example, total energy intake showed a decreasing trend between 1995 and 2016 in both men and women. Similarly, energy intake from protein and salt intake decreased, but energy intake from fat increased in both sexes (33). In addition, the proportion of current smokers in men aged 40–59 y was 23.4% in 2018 (34), which was lower than our study population (51.5%). There are some other limitations to this study. First, there was no information on the actual CHD incidence in our study population. Second, there is a possibility of reverse causality, although former drinkers were excluded from the analyses. Third, we did not consider type of alcohol and caffeinated beverage intake.

In conclusion, alcohol consumption was related not only to established CHD risk factors but also to intake of macro- and micro-nutrients in the general Japanese population. Non-drinkers had a higher proportion of some CHD risk factors compared with light-drinkers. Some of these relationships may be caused by the effects of alcohol, but others may be explained by non-drinkers’ characteristics. This may influence the J-shaped relationship between alcohol consumption and CHD risk.

Authorship
HY and HU designed the research. HU, NO, HN, KS, SS, AO, KY, QC, K Masaki, PE, and JS organized the research and provided essential materials. KK, K Miura, ST-M, HS, SO, NM, MZ, YO, NO, QC, K Masaki, JS, and HU critically revised the manuscript for intellectual content. HY, KK, and K Miura wrote the manuscript. HY had the primary responsibility for the final content. All authors have read and approved the final manuscript.

Disclosure of state of COI
None declared. The study funders/sponsors had no role in the design or conduct of the study: collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

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Supporting information
Supplemental online material is available on J-STAGE.

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