Alcohol Consumption and Mortality From Stroke and Coronary Heart Disease Among Japanese Men and Women
The Japan Collaborative Cohort Study

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Background and Purpose—Previous studies have demonstrated the association between alcohol consumption and cardiovascular mortality. However, the sex-specific association between alcohol consumption and mortality from stroke and coronary heart disease remains unclear.

Methods—Between 1988 and 1990, 34 776 men and 48 906 women aged 40 to 79 years completed a self-administered questionnaire including information about alcohol consumption. They were followed-up for a median duration of 14.2 years.

Results—Of the 83 682 respondents, 1628 died from stroke and 736 died from coronary heart disease. For men, heavy drinking (≥46.0 g ethanol/day) was associated with increased mortality from total, hemorrhagic, and ischemic strokes, whereas light-to-moderate drinking was associated with reduced mortality from total cardiovascular disease, compared with not drinking. The respective multivariable hazard ratios (95% CI) were 1.48 (1.22 to 1.80) for total stroke, 1.67 (1.17 to 2.38) for hemorrhagic stroke, 1.35 (1.04 to 1.75) for ischemic stroke, and 0.88 (0.78 to 1.00) for total cardiovascular disease. Women who were heavy drinkers (≥46.0 g ethanol/day) showed increased mortality from coronary heart disease, and there was reduced mortality from total cardiovascular disease for drinkers of 0.1 to 22.9 g ethanol per day compared with mortality for nondrinkers. The respective multivariable hazard ratios (95% CI) for the 2 categories of drinkers were 4.10 (1.63 to 10.3) and 0.75 (0.62 to 0.91).

Conclusions—Heavy alcohol consumption is associated with increased mortality from total stroke, particularly hemorrhagic stroke, and total cardiovascular disease for men, and from coronary heart disease for women, whereas light-to-moderate drinking may be associated with reduced mortality from cardiovascular disease for both sexes.

Key Words: alcohol consumption ■ coronary heart disease ■ mortality ■ stroke

The large number of cohort studies showed an increased risk of hemorrhagic stroke among male heavy drinkers,1–10 and reduced risk of ischemic stroke9–11 and coronary heart disease12–17 among male light-to-moderate drinkers.

A few studies have reported the association between moderate-to-heavy alcohol consumption and increased risk of hemorrhagic stroke,5,18 and light-to-moderate alcohol consumption was associated with reduced risk of cardiovascular disease for women.18–20 A cohort study for a US prepaid health care program found that women consuming ≥6 drinks per day showed a nonsignificant excess risk for hemorrhagic stroke.5 The Nurses’ Health Study showed that light-to-moderate alcohol consumption was associated with reduced incidence of ischemic stroke and coronary heart disease11 and reduced mortality from cardiovascular disease,19 compared with incidence of ischemic stroke and coronary heart disease in those who do not drink. A Swedish cohort study20 also reported that light alcohol consumption among women was...
associated with reduced incidence of and mortality from ischemic stroke. However, no such evidence is available for women in Asian countries, probably because of the low prevalence of drinkers and coronary heart disease. To examine the sex-specific associations of alcohol consumption with mortality from total stroke, stroke subtypes, and coronary heart disease, we analyzed data from a large prospective study of ≈83,000 Japanese men and women.

Materials and Methods

Study Cohort
The Japan Collaborative Cohort Study for Evaluation of Cancer Risk sponsored by Monbusho was conducted from 1988 to 1990, when 110,792 subjects (46,465 men and 64,327 women) aged 40 to 79 years and living in 45 communities across Japan participated in municipal health screening examinations and completed self-administered questionnaires concerning their lifestyles and medical histories of previous cardiovascular disease and cancer at baseline. The details of the study procedure have been described previously. In most communities, informed consent was obtained individually from members of the cohort, whereas in several communities, informed consent was obtained at the community level after the purpose of the study and confidentiality of the data had been explained to community leaders and mayors. Follow-up surveys were conducted annually to verify the vital status of the participants. Among the 110,792 cohort participants, we excluded the 22,358 subjects (9,579 men and 12,779 women) who had missing information on drinking habits such as drinking status, the frequency of drinking, and the amount of alcohol consumed, and 4752 subjects (2,110 men and 2,642 women) who reported a history of cancer, stroke, or myocardial infarction. A total of 34,776 men and 48,906 women were included in the study.

Mortality Surveillance
For mortality surveillance in each of the communities, investigators conducted a systematic review of death certificates, all of which were forwarded to the public health center in the area of residency. Mortality data were then centralized at the Ministry of Health and Welfare, and the underlying causes of death were coded for the National Vital Statistics from 1988 to 1994 according to the International Classification of Diseases, 9th revision (ICD-9), and from 1995 to 2003 according to the 10th revision (ICD-10). Therefore, all deaths that occurred in the cohort were ascertained by death certificates from a public health center, except for subjects who died after they had moved from their original community, in which case the subjects were treated as censored cases. Cause-specific mortality was determined separately in terms of total cardiovascular disease (ICD-9 codes 390 to 459, ICD-10 codes I01 to I99), total coronary heart disease (codes 410 to 414 and I20 to I25), and stroke (430 to 438 and I60 to I69). The latter category was further subdivided into intraparenchymal hemorrhage (431 and I61), subarachnoid hemorrhage (430 and I60), and ischemic stroke (433 to 434 and I63 and I693). The follow-up is believed to be complete by systematic examination of death certificates and residency status. By December 31, 2003, 12,100 subjects were treated as censored when they died, and 3,532 subjects were treated as censored when they moved out of the study area. The median follow-up period for the participants was 14.2 years. This study was approved by the Ethics Committee of the Nagoya University School of Medicine.

Baseline Survey
The baseline data were collected with a self-administered questionnaire including information about alcohol consumption, demographic characteristics, histories of hypertension, diabetes mellitus, and other chronic diseases, and habits related to smoking, diet, and exercise. Alcohol drinking status was established by asking the subjects whether they were nondrinkers, ex-drinkers, or current drinkers. Ex-drinkers and current drinkers were also asked about the age at which they started drinking, frequency of alcohol intake per week during the previous year (less than once/week, 1 to 2 times/week, 3 to 4 times/week, and almost every day), type of beverage (sake [rice wine], shochu [a type of brandy], beer, whiskey, or wine), and the amount consumed per occasion. The unit of amount consumed per occasion was “gou”, which is the equivalent of ≈23 g of alcohol. The amount of ethanol per day was calculated as follows: the unit of amount consumed per occasion multiplied by the frequency of alcohol consumption per week divided by 7. The validity of the alcohol questionnaire was examined by serum γ-glutamyl transferase among the subsample participants who underwent the baseline health check-ups (4969 men and 9732 women). The age-adjusted mean values of serum γ-glutamyl transferase according to the alcohol consumption categories (nondrinkers, ex-drinkers, current drinkers of 1 to 22.9 g/day, 23.0 to 45.9 g/day, 46.0 to 68.9 g/day, and ≥69.0 g/day for men, and nondrinkers, ex-drinkers, current drinkers of 1 to 22.9 g/day, 23.0 to 45.9 g/day, and ≥46.0 g/day for women) were 20, 26, 27, 37, 51, and 68 IU/L, respectively, for men and 15, 18, 17, 25, and 48 IU/L, respectively, for women. The reproducibility and validity for dietary intakes of fish, vegetables, and fruit were reported elsewhere.

Statistical Analysis
Statistical analyses were based on sex-specific rates for mortality from stroke during the follow-up periods from 1988 and from 1990 to 2003. The follow-up person-years were calculated from the date of completing the baseline questionnaire to death, moving out of the community, or the end of 2003, whichever was first. We classified alcohol consumption into 6 categories for men (nondrinkers, ex-drinkers, current drinkers of 1 to 22.9 g/day, 23.0 to 45.9 g/day, 46.0 to 68.9 g/day, and ≥69.0 g/day) and into 5 categories for women (nondrinkers, ex-drinkers, current drinkers of 1 to 22.9 g/day, 23.0 to 45.9 g/day, and ≥46.0 g/day). Sex-specific age-adjusted mean values and prevalence of cardiovascular risk factors were calculated. We conducted tests for linear trends of covariates by using the median values of alcohol consumption categories. The sex-specific hazard ratios with 95% CI for mortality from stroke and coronary heart disease were then calculated with reference to the risk for nondrinkers. These estimates were adjusted for age and other potential confounding factors by using the Cox proportional hazards model. Potential confounding factors for the adjustment were baseline of age, smoking status (never, ex-smoker, current smokers of 1 to 19, and ≥20 cigarettes/day), BMI (sex-specific quintiles), history of hypertension, history of diabetes, frequency of exercise (<1, 1 to 2, 3 to 4, and ≥5 hours/week), perceived mental stress (low, moderate, high), education level (primary school, junior high school, high school, college or higher), vegetable intake (sex-specific quintiles), and fish and fruits intake (almost never, 1 to 2 times/month, 1 to 2 times/week, 3 to 4 times/week, and almost every day). SAS (version 8.02) was used for all statistical analyses.

Results
After completion of the follow-up of 1,065,295 person-years, the deaths of 1,628 subjects from stroke (864 men and 764 women) and of 736 from coronary heart disease (431 men and 305 women) had been documented. The sex-specific mortality per 1000 person-year among men was 2.0 for stroke and 1.0 for coronary heart disease, and the respective mortality among women was 1.2 and 0.5. The deaths for men included 202 intraparenchymal hemorrhages, 74 subarachnoid hemorrhages, 507 ischemic strokes, and 431 coronary heart diseases. For women, the corresponding numbers were 151, 157, 388, and 305. Table 1 shows sex-specific age-adjusted mean values or prevalence of risk characteristics at baseline by category of alcohol consumption. The respective proportions of nondrinkers, ex-drinkers, and current drinkers were 22%, 7%, and 71% for men, and 83%, 2%, and 15% for women.
Compared with nondrinkers, moderate-to-heavy drinkers, both men and women, tended to be younger, more hypertensive, heavier smokers, and had the higher frequency of fish intake and the lower frequency of fruit intake. Tables 2 and 3 show age-adjusted and multivariable-adjusted hazard ratios for total stroke, stroke subtypes, coronary heart disease, and ischemic and total cardiovascular disease for men and women. For women, the data on intraparenchymal and subarachnoid hemorrhage were collapsed as hemorrhagic stroke because of the limited number of deaths. Increases in the risks of mortality from total and hemorrhagic strokes were observed among male consumers of 46.0 to 68.9 and 69.0 g ethanol per day. Heavy drinking of 69.0 g ethanol per day was also associated with increased risk of mortality from total stroke and total cardiovascular disease among men. Male ex-drinkers showed higher risks of mortality from total stroke, particularly hemorrhagic stroke, either intraparenchymal or subarachnoid hemorrhage, and total cardiovascular disease. Light-to-moderate drinking of 0.1 to 45.9 g ethanol per day was associated with a reduced risk of mortality from total cardiovascular disease among men.

For women, there was an excess risk of mortality from coronary heart disease among drinkers of 0.1 to 22.9 g ethanol per day. The multivariable hazard ratio (95% CI) of mortality for moderate-to-heavy drinkers compared with nondrinkers was 4.10 (1.63 to 10.3) for coronary heart disease and 3.29 (1.61 to 6.73) for ischemic cardiovascular disease, whereas that for light drinkers compared with nondrinkers was 0.74 (0.60 to 0.91) for total cardiovascular disease.

Discussion

In the large prospective study of Japanese men and women whose stroke mortality was more than double that of coronary heart disease, we found that heavy alcohol consumption of 69.0 g ethanol per day was associated with increased risk of mortality from hemorrhagic stroke among men, whereas light-to-moderate drinking of 0.1 to 45.9 g ethanol per day was associated with reduced mortality from ischemic cardiovascular disease among men. For women, light drinking of 0.1 to 22.9 g ethanol per day showed an association with reduced mortality from ischemic cardiovascular disease.

The excess mortality from hemorrhagic stroke associated with heavy alcohol consumption and the reduced mortality from ischemic cardiovascular disease associated with light-to-moderate alcohol consumption are consistent with the results from previous studies of whites and Japanese with

| Table 1. Age-Adjusted Mean Values or Prevalence (%) of Risk Characteristics at Baseline by Alcohol Consumption Category for Men and Women |
|-------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
|             | Nondrinkers | Ex-Drinkers | Ethanol Intake, g/day |         |         |         | P for Trend |
|             | Men        | Women     | 0.1–22.9 | 23.0–45.9 | 46.0–68.9 | ≥69.0   |         |
| Age, yr     | 7821       | 40826     | 59       | 57       | 55       | 55      | 54      | <0.001  |
| Mean BMI, kg/m² | 2378     | 884       | 22.6     | 22.9     | 22.9     | 22.4    | 22.7    | <0.001  |
| History of hypertension, % | 6130     | 5848      | 13       | 21       | 21       | 20      | 22      | <0.001  |
| History of diabetes, % | 8056     | 1020      | 5       | 21       | 21       | 19      | 24      | 0.001   |
| Current smokers, % | 7067     | 328       | 49       | 3       | 3       | 5       | 7       | 0.05    |
| Exercise ≥5 hours/wk, % | 3324     | 328       | 46       | 7       | 7       | 7       | 7       | 0.37    |
| Vegetable intake, times/wk | 6110     | 1020      | 27.4     | 27.4     | 27.4     | 27.9    | 27.4    | 26.6    | 0.03    |
| Fish intake, times/wk | 8565     | 328       | 6.3      | 6.5      | 6.5      | 7.0     | 7.5     | 8.0     | <0.001  |
| Fruit intake, times/wk | 7067     | 328       | 7.2      | 6.7      | 6.7      | 6.0     | 5.6     | <0.001  |

Compared with nondrinkers, moderate-to-heavy drinkers, both men and women, tended to be younger, more hypertensive, heavier smokers, and had the higher frequency of fish intake and the lower frequency of fruit intake. Tables 2 and 3 show age-adjusted and multivariable-adjusted hazard ratios for total stroke, stroke subtypes, coronary heart disease, and ischemic and total cardiovascular disease for men and women. For women, the data on intraparenchymal and subarachnoid hemorrhage were collapsed as hemorrhagic stroke because of the limited number of deaths. Increases in the risks of mortality from total and hemorrhagic strokes were observed among male consumers of 46.0 to 68.9 and ≥69.0 g ethanol per day. Heavy drinking of ≥69.0 g ethanol per day was also associated with increased risk of mortality from total stroke and total cardiovascular disease among men. Male ex-drinkers showed higher risks of mortality from total stroke, particularly hemorrhagic stroke, either intraparenchymal or subarachnoid hemorrhage, and total cardiovascular disease. Light-to-moderate drinking of 0.1 to 45.9 g ethanol per day was associated with a reduced risk of mortality from total cardiovascular disease among men.

For women, there was an excess risk of mortality from coronary heart disease among drinkers of ≥46.0 g ethanol per day compared with nondrinkers, and a reduced risk of mortality from cardiovascular disease among drinkers of 0.1 to 22.9 g ethanol per day. The multivariable hazard ratio (95% CI) of mortality for moderate-to-heavy drinkers compared with nondrinkers was 4.10 (1.63 to 10.3) for coronary heart disease and 3.29 (1.61 to 6.73) for ischemic cardiovascular disease, whereas that for light drinkers compared with nondrinkers was 0.74 (0.60 to 0.91) for total cardiovascular disease.

Discussion

In the large prospective study of Japanese men and women whose stroke mortality was more than double that of coronary heart disease, we found that heavy alcohol consumption of ≥69.0 g ethanol per day was associated with increased risk of mortality from hemorrhagic stroke among men, whereas light-to-moderate drinking of 0.1 to 45.9 g ethanol per day was associated with reduced mortality from ischemic cardiovascular disease among men. For women, light drinking of 0.1 to 22.9 g ethanol per day showed an association with reduced mortality from ischemic cardiovascular disease.

The excess mortality from hemorrhagic stroke associated with heavy alcohol consumption and the reduced mortality from ischemic cardiovascular disease associated with light-to-moderate alcohol consumption are consistent with the results from previous studies of whites and Japanese with
regard to hemorrhagic stroke, ischemic stroke, and coronary heart disease. The excess mortality of hemorrhagic stroke may be partly influenced by alcohol-induced high blood pressure. Alcohol also leads to reduced platelet aggregation and enhanced fibrinolysis through increased secretion of plasminogen activators from endothelial cells. Moreover, the possible mechanisms by which light alcohol consumption may lead to reduced mortality of ischemic cardiovascular disease have been identified as elevated concentration of HDL cholesterol.

<table>
<thead>
<tr>
<th>Ethanol Intake, g/day</th>
<th>Nondrinkers</th>
<th>Ex-Drinkers</th>
<th>0.1–22.9</th>
<th>23.0–45.9</th>
<th>46.0–68.9</th>
<th>≥69.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Person-years</td>
<td>96 423</td>
<td>25 919</td>
<td>78 478</td>
<td>101 256</td>
<td>90 000</td>
<td>41 588</td>
</tr>
</tbody>
</table>

**Total stroke**
- **Nondrinkers Ex-Drinkers**
  - 0.1–22.9 23.0–45.9 46.0–68.9 ≥69.0
  - 1.00 1.93 (1.55–2.42) 0.91 (0.72–1.15) 0.98 (0.80–1.21) 1.46 (1.19–1.79) 1.89 (1.46–2.46)
  - **Age-adjusted HR**
  - **Multivariable HR**
  - **Multivariable HR**

**Hemorrhagic stroke**
- **Nondrinkers Ex-Drinkers**
  - 0.1–22.9 23.0–45.9 46.0–68.9 ≥69.0
  - 1.00 1.80 (1.66–2.33) 1.09 (0.72–1.63) 1.02 (0.70–1.49) 1.51 (1.05–2.19) 2.30 (1.51–3.51)
  - **Age-adjusted HR**
  - **Multivariable HR**
  - **Multivariable HR**

**Intraparenchymal hemorrhage**
- **Nondrinkers Ex-Drinkers**
  - 0.1–22.9 23.0–45.9 46.0–68.9 ≥69.0
  - 1.00 2.00 (1.22–3.37) 1.09 (0.68–1.75) 1.05 (0.67–1.62) 1.56 (1.02–2.40) 1.98 (1.17–3.35)
  - **Age-adjusted HR**
  - **Multivariable HR**
  - **Multivariable HR**

**Subarachnoid hemorrhage**
- **Nondrinkers Ex-Drinkers**
  - 0.1–22.9 23.0–45.9 46.0–68.9 ≥69.0
  - 1.00 1.21 (0.44–3.33) 1.07 (0.48–2.36) 0.95 (0.45–2.02) 1.41 (0.68–2.90) 3.05 (1.45–6.39)
  - **Age-adjusted HR**
  - **Multivariable HR**
  - **Multivariable HR**

**Ischemic stroke**
- **Nondrinkers Ex-Drinkers**
  - 0.1–22.9 23.0–45.9 46.0–68.9 ≥69.0
  - 1.00 2.12 (1.62–2.79) 0.80 (0.59–1.09) 0.99 (0.76–1.28) 1.44 (1.10–1.88) 1.60 (1.10–2.31)
  - **Age-adjusted HR**
  - **Multivariable HR**
  - **Multivariable HR**

**Coronary heart disease**
- **Nondrinkers Ex-Drinkers**
  - 0.1–22.9 23.0–45.9 46.0–68.9 ≥69.0
  - 1.00 1.50 (1.09–2.07) 0.94 (0.70–1.27) 0.88 (0.66–1.15) 0.87 (0.64–1.18) 1.16 (0.78–1.71)
  - **Age-adjusted HR**
  - **Multivariable HR**
  - **Multivariable HR**

**Ischemic cardiovascular disease**
- **Nondrinkers Ex-Drinkers**
  - 0.1–22.9 23.0–45.9 46.0–68.9 ≥69.0
  - 1.00 1.82 (1.48–2.24) 0.87 (0.71–1.08) 0.93 (0.77–1.13) 1.14 (0.93–1.40) 1.37 (1.04–1.79)
  - **Age-adjusted HR**
  - **Multivariable HR**
  - **Multivariable HR**

**Total cardiovascular disease**
- **Nondrinkers Ex-Drinkers**
  - 0.1–22.9 23.0–45.9 46.0–68.9 ≥69.0
  - 1.00 1.77 (1.53–2.06) 0.88 (0.76–1.02) 0.90 (0.79–1.03) 1.16 (1.01–1.33) 1.47 (1.23–1.76)
  - **Age-adjusted HR**
  - **Multivariable HR**
  - **Multivariable HR**

*Adjusted for age, smoking status, BMI, history of hypertension, history of diabetes, frequency of exercise, perceived mental stress, education level, and intake of vegetables, fish, and fruit.
†Calculated for drinkers of 0.1 to 45.9 g ethanol per week and those of ≥46.0 g ethanol per week.
HR indicates hazard ratio.
reduced platelet aggregation, enhanced fibrinolysis, and reduced plasma fibrinogen levels.

Our study demonstrated a reduced mortality from ischemic cardiovascular disease associated with light drinking of 0.1 to 22.9 g ethanol per day among Japanese women. Our finding is consistent with that of the Nurse’s Health study, which reported that light-to-moderate drinking of 1.5 to 29.9 g ethanol per day was associated with a similarly reduced morality from coronary heart disease and cardiovascular disease. Furthermore, in the Swedish cohort study, an average consumption of 0 to 5 g ethanol per day by women was associated with reduced morality from ischemic stroke, but such an association was not found for men. The multivariable hazard ratio of mortality from ischemic stroke was 0.6 (0.5 to 0.8) for women and 1.3 (0.9 to 2.0) for men compared with that for never-drinkers.

We detected an excess risk of mortality from coronary heart disease associated with drinkers of ≥46.0 g ethanol per day among women, albeit the number of deaths in heavy drinkers was small, but such an excess risk was not found among men (P for interaction=0.001). Heavy alcohol consumption enhances the probability of both atrial and life-threatening ventricular arrhythmias and atrioventricular block through the destabilization of potassium and magnesium metabolism and the stimulation of catecholamine. Furthermore, women have lower alcohol dehydrogenase activity in the liver than men, so that women have higher blood alcohol concentrations than men after ingestion of the same dose of alcohol.

Table 3. HR and 95% CI of Mortality from Total Stroke, Coronary Heart Disease, and Total Cardiovascular Disease by Alcohol Consumption Category for Women

<table>
<thead>
<tr>
<th>Ethanol Intake (g/day)</th>
<th>Nondrinkers</th>
<th>Ex-Drinkers</th>
<th>0.1–22.9</th>
<th>23.0–45.9</th>
<th>≥46.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Person-years</td>
<td>529 265</td>
<td>10 712</td>
<td>74 702</td>
<td>12 872</td>
<td>4082</td>
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Total stroke

<table>
<thead>
<tr>
<th>N</th>
<th>684</th>
<th>14</th>
<th>53</th>
<th>7</th>
<th>6</th>
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<tbody>
<tr>
<td>Age-adjusted HR</td>
<td>1.00</td>
<td>1.00 (0.59–1.70)</td>
<td>0.83 (0.63–1.10)</td>
<td>0.59 (0.28–1.24)</td>
<td>2.33 (1.04–5.20)</td>
</tr>
<tr>
<td>Multivariable HR*</td>
<td>1.00</td>
<td>0.87 (0.51–1.48)</td>
<td>0.87 (0.65–1.15)</td>
<td>0.59 (0.28–1.24)</td>
<td>1.92 (0.85–4.35)</td>
</tr>
<tr>
<td>Multivariable HR†</td>
<td>0.82 (0.63–1.08)</td>
<td></td>
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</table>

Hemorrhagic stroke

<table>
<thead>
<tr>
<th>N</th>
<th>272</th>
<th>6</th>
<th>24</th>
<th>3</th>
<th>3</th>
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<tbody>
<tr>
<td>Age-adjusted HR</td>
<td>1.00</td>
<td>1.08 (0.48–2.43)</td>
<td>0.83 (0.55–1.27)</td>
<td>0.58 (0.19–1.82)</td>
<td>2.32 (0.74–7.26)</td>
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<tr>
<td>Multivariable HR*</td>
<td>1.00</td>
<td>0.95 (0.42–2.17)</td>
<td>0.84 (0.55–1.29)</td>
<td>0.52 (0.17–1.64)</td>
<td>1.61 (0.50–5.19)</td>
</tr>
<tr>
<td>Multivariable HR†</td>
<td>0.79 (0.53–1.18)</td>
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Ischemic stroke

<table>
<thead>
<tr>
<th>N</th>
<th>353</th>
<th>8</th>
<th>22</th>
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<tbody>
<tr>
<td>Age-adjusted HR</td>
<td>1.00</td>
<td>1.10 (0.55–2.22)</td>
<td>0.74 (0.48–1.13)</td>
<td>0.34 (0.09–1.37)</td>
<td>2.75 (0.88–8.57)</td>
</tr>
<tr>
<td>Multivariable HR*</td>
<td>1.00</td>
<td>0.87 (0.42–1.78)</td>
<td>0.78 (0.51–1.21)</td>
<td>0.36 (0.09–1.44)</td>
<td>2.43 (0.77–7.69)</td>
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<tr>
<td>Multivariable HR†</td>
<td>0.71 (0.47–1.14)</td>
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Coronary heart disease

<table>
<thead>
<tr>
<th>N</th>
<th>267</th>
<th>6</th>
<th>20</th>
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<tbody>
<tr>
<td>Age-adjusted HR</td>
<td>1.00</td>
<td>1.10 (0.49–2.47)</td>
<td>0.84 (0.54–1.33)</td>
<td>1.53 (0.72–3.25)</td>
<td>5.44 (2.24–13.2)</td>
</tr>
<tr>
<td>Multivariable HR*</td>
<td>1.00</td>
<td>0.85 (0.38–1.94)</td>
<td>0.83 (0.53–1.33)</td>
<td>1.45 (0.68–3.11)</td>
<td>4.10 (1.63–10.3)</td>
</tr>
<tr>
<td>Multivariable HR†</td>
<td>0.94 (0.62–1.41)</td>
<td></td>
<td></td>
<td></td>
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</table>

Ischemic cardiovascular disease

<table>
<thead>
<tr>
<th>N</th>
<th>620</th>
<th>14</th>
<th>42</th>
<th>9</th>
<th>8</th>
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<tbody>
<tr>
<td>Age-adjusted HR</td>
<td>1.00</td>
<td>1.10 (0.65–1.87)</td>
<td>0.78 (0.57–1.07)</td>
<td>0.86 (0.45–1.66)</td>
<td>3.98 (1.98–8.00)</td>
</tr>
<tr>
<td>Multivariable HR*</td>
<td>1.00</td>
<td>0.86 (0.50–1.48)</td>
<td>0.81 (0.59–1.11)</td>
<td>0.87 (0.45–1.68)</td>
<td>3.29 (1.61–6.73)</td>
</tr>
<tr>
<td>Multivariable HR†</td>
<td>0.82 (0.61–1.09)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total cardiovascular disease

<table>
<thead>
<tr>
<th>N</th>
<th>1494</th>
<th>30</th>
<th>99</th>
<th>22</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age-adjusted HR</td>
<td>1.00</td>
<td>0.98 (0.68–1.41)</td>
<td>0.72 (0.59–0.89)</td>
<td>0.85 (0.56–1.29)</td>
<td>2.19 (1.24–3.88)</td>
</tr>
<tr>
<td>Multivariable HR*</td>
<td>1.00</td>
<td>0.82 (0.57–1.18)</td>
<td>0.74 (0.60–0.91)</td>
<td>0.81 (0.53–1.24)</td>
<td>1.73 (0.97–3.08)</td>
</tr>
<tr>
<td>Multivariable HR†</td>
<td>0.75 (0.62–0.91)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for age, smoking status, body mass index, history of hypertension, history of diabetes, frequency of exercise, perceived mental stress, education level, and intake of vegetables, fish, and fruit.
†Calculated for drinkers of 0.1 to 45.9 g ethanol per week.
alcohol, even when the dose is adjusted for body weight.\textsuperscript{31} The Nurse’s Health study\textsuperscript{19} did not find the excess mortality, but the number of deaths among heavy drinkers of $\geq$30g ethanol per day in that cohort was also small (n=9). Further research is needed to understand the health consequences of heavy drinking in females.

Our study also showed an excess risk of mortality from total stroke, either hemorrhagic or ischemic stroke, among male ex-drinkers. The 8424 current drinkers at baseline who also responded to the 5-year follow-up comprised 285 ex-drinkers and 8139 continuing drinkers. The ex-drinkers may have stopped because of ill health, because the prevalence of a history of diabetes, liver disease, gallstone or gallbladder disease, gastric or duodenal ulcer, and tuberculosis at baseline was much higher for quitters than continuing drinkers. However, the prevalence of history of those diseases did not differ for female ex-drinkers and continuing drinkers.

The strengths of our study are its prospective design and the high statistical power for the detection of sex-specific associations of a wide range of alcohol consumption with mortality from total stroke, coronary heart disease, and total cardiovascular disease. Our findings for women are noteworthy because the evidence has been largely limited for Asian women.

The limitations of our study also need to be discussed. First, drinkers may consume different amounts of alcohol during occasional and weekend drinking. However, we could not estimate alcohol consumption resulting from binge drinking because the questionnaire did not ask this information. It has been suggested that binge drinking increases the risk of myocardial infarction.\textsuperscript{32} However, it can be assumed that binge drinking was not common for our study subjects, because 98% to 99% of heavy drinkers of $\geq$46.0 g ethanol per day reported consuming alcohol beverages almost every day. Second, we estimated alcohol consumption by the single self-administered questionnaire, which would be liable to misclassification. However, there was a moderate correlation between alcohol consumption and serum $\gamma$-glutamyl transferase, a marker of alcohol intake, for both sexes. The data on alcohol consumption in a 5-year follow-up survey were available from only 25 of the 45 communities. However, when we examined the subsample participants (10 214 men and 15 379 women) who completed the alcohol questionnaire at baseline and the followed-up surveys, we found that the proportions of the same category, the adjacent category, and the reversal category of alcohol consumption were 59%, 83%, and 0.08%, respectively, for men, and 90%, 91%, and 0.06%, respectively, for women. Third, we used the mortality data as endpoints rather than incidence data, which may lead to misclassification in the diagnosis of stroke, stroke subtypes, and coronary heart disease. The widespread use of computer tomography in local hospitals since the 1980s has probably made the diagnosis of stroke and its subtypes reported on the death certificates sufficiently accurate.\textsuperscript{33} For coronary heart disease, however, approximately one-fourth of ischemic heart disease deaths appearing on death certificates were misdiagnosed according to the validation studies.\textsuperscript{34,35} Finally, although hazard ratios were adjusted for selected cardiovascular risk factors and social factors, we cannot exclude the possibility that other risk factors such as socioeconomic status and psychosocial factors may have affected our findings.

Conclusion

In conclusion, the results of our study of a large cohort of Japanese men and women indicate that heavy alcohol consumption is associated with increased mortality from total stroke, particularly hemorrhagic stroke, and total cardiovascular disease for men, and with increased mortality from coronary heart disease for women. Also, light-to-moderate alcohol consumption may be associated with reduced mortality from cardiovascular disease for both men and women.

Appendix

Study Investigators
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Disclosure
None.
References


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