Alcohol Intake and Premature Coronary Heart Disease in Urban Japanese Men

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To examine the relation between alcohol intake and the incidence of coronary heart disease among Japanese, the authors analyzed data from a prospective study of 8,476 Japanese male employees, who were 40-59 years old at baseline (between 1975 and 1984) and worked for 13 urban companies in Osaka, Japan. These men were followed until the end of 1993, on average, an 8.8-year follow-up. Eighty-three coronary heart disease events (54 myocardial infarction, 32 angina pectoris) occurred during the employment period under study. Compared with the risk of coronary heart disease for never drinkers, the age-adjusted relative risk for those with an increased ethanol intake was lower, but the risk did not appear to be reduced further with the intake of ≥69 g of ethanol per day. The multivariate relative risk adjusted for age, serum total cholesterol, cigarette smoking, body mass index, left ventricular hypertrophy, and a history of diabetes mellitus was 0.83 (95% confidence interval (CI) 0.24-2.86) in exdrinkers, 0.69 (95% CI 0.37-1.29) in drinkers of 1-22 g/day of ethanol, 0.55 (95% CI 0.29-1.05) in drinkers of 23-45 g/day, 0.41 (95% CI 0.19-0.88) in drinkers of 46-68 g/day, and 0.59 (95% CI 0.23-1.51) in drinkers of ≥69 g/day. The inverse association with alcohol intake was similar between myocardial infarction and angina pectoris. Alcohol intake seemed to prevent the premature incidence of coronary heart disease among urban Japanese middle-aged men. Am J Epidemiol 1998;147:59-65.

Most Japanese middle-aged men drink alcohol regularly (1, 2). According to our six population surveys of occupational employees or community residents (3), the prevalence of current drinking in men was 68-81 percent in 1980-1987 and 71-86 percent in 1990-1993. Epidemiologic data suggesting a protective effect of light-to-moderate alcohol intake on coronary heart disease have come mostly from studies of whites and Japanese Americans (4-17). Evidence of any association between drinking and coronary heart disease in native Japanese is sparse (18, 19) because of the lower incidence of coronary heart disease in Japan than in Western countries. Our 10.5-year prospective study of 2,890 middle-aged men in three rural communities (20) showed an inverse association between alcohol intake and coronary heart disease. However, the association was not statistically significant, being based on a small number of cases (n = 34), which reflects the low incidence of coronary heart disease among rural Japanese (21). To examine the relation between alcohol intake and coronary heart disease further, we used the data from an 8.8-year follow-up study of middle-aged urban male workers, who have a greater incidence of coronary heart disease than do rural residents (22).

MATERIALS AND METHODS

The subjects were 8,521 male workers aged 40-59 years at 13 industrial companies in Osaka, Japan, who participated in cardiovascular risk surveys between 1975 and 1984. The overall participation rate was 92 percent. The 13 companies consisted of one broadcasting and five trading companies, a bank, a hotel, a company selling beer, and four companies producing chains, air conditioners, and aluminum cans and pans. Employees in these companies were not exposed to any cardiotoxic agents such as carbon monoxide, carbon disulfide, nitroglycerin, methylene chloride, and so on. Persons (n = 45) with a history of either coronary
heart disease \((n = 23)\) or stroke \((n = 22)\) were excluded, leaving 8,476 men for the analyses.

**Baseline examination**

Alcohol intake and other cardiovascular disease risk factors were measured at baseline examinations. An interviewer assessed the usual weekly intake of alcohol in units of “go” (a traditional Japanese unit of measurement, by volume, corresponding to 23 g of ethanol), which were converted to grams of ethanol per day. One go is 180 ml of sake, and it corresponds to one bottle (663 ml) of beer, two single shots (75 ml) of whiskey, or two glasses (180 ml) of wine. Men who reported consuming \(\geq 0.3\) go per week were regarded as drinkers. Subjects were classified as never drinkers, exdrinkers, or current drinkers who averaged 1–22, 23–45, 46–68, or \(\geq 69\) g/day of ethanol. Exdrinkers were defined as abstainers for at least 3 months. The drinking status after 3–5 years from baseline was examined for 6,266 (74 percent) participants. The proportions of men who remained in the same category of drinking status were 70 percent overall, 84 percent for never drinkers, 62 percent for exdrinkers, 57 percent for drinkers of 1–22 g/day of ethanol, 49 percent for drinkers of 23–45 g/day, 53 percent for drinkers of 46–68 g/day, and 43 percent for drinkers of \(\geq 69\) g.

We measured several potential confounders: serum total cholesterol level, blood pressure, body mass index, cigarette smoking, history of diabetes mellitus, and electrocardiographic evidence of left ventricular hypertrophy. Serum total cholesterol was measured colorimetrically by the Liebermann-Burchard method on an AutoAnalyzer II (Technicon Instruments Corporation, Tarrytown, New York) (23). Blood pressures were measured by trained observers using standard mercury sphygmomanometers on the right arm of seated participants who had rested for 5 minutes (24). Hypertension was defined as systolic blood pressure \(\geq 160\) mmHg, diastolic blood pressure \(\geq 95\) mmHg, and/or current treatment with antihypertensive medication, while normotension was defined as systolic blood pressure \(< 140\) mmHg, diastolic blood pressure \(< 90\) mmHg, and no antihypertensive medication. Subjects with blood pressures between these categories were classified as having borderline hypertension. Height in stocking feet and weight in light clothing were measured. Body mass index was calculated as weight (kg)/height (m)\(^2\). An interview was conducted to ascertain the number of current cigarettes smoked per day. Diabetes mellitus was defined as a fasting glucose level of \(\geq 140\) mg/dl, a nonfasting glucose level of \(\geq 200\) mg/dl, and/or use of medication for diabetes. An electrocardiogram obtained while the subject was resting in a supine position was coded according to the Minnesota Codes, version 2 (25). We regarded Minnesota Codes 3-1 plus (4-1 to 4-3 or 5-1 to 5-3) as left ventricular hypertrophy.

**Ascertainment of incident coronary heart disease**

Subjects were followed up to determine coronary heart disease endpoints through the end of 1993. Follow-up was terminated at retirement (at 60 years of age) \((n = 1,139)\) or when the subject withdrew from the study because of quitting \((n = 2,014)\) or noncardiovascular death \((n = 135)\). The subjects were censored from the follow-up analysis at the date of the withdrawal. Coronary heart disease endpoints were ascertained via four sources: death certificates, absenteeism reports due to sickness, insurance claims to companies, and annual risk factor surveys. To confirm the diagnosis, all living patients were visited or invited to risk factor surveys; study physicians obtained a medical history and a standard electrocardiogram for coronary heart disease patients. For deaths, histories were obtained from the patient’s family and/or colleagues who observed the incident. For both fatal and nonfatal cases, medical records at company clinics and/or local hospitals were also reviewed.

The criteria for coronary heart disease were modified from those of a World Health Organization Expert Committee (26). Painless types of coronary heart disease were not investigated because of difficulty with ascertainment. “Definite” myocardial infarction was indicated by typical chest pain (lasting for 30 minutes or longer) with the appearance of abnormal and persistent Q or QS waves, changes in cardiac enzyme activity, or both. “Suspect” myocardial infarction was indicated by typical chest pain without a positive electrocardiogram or enzyme activity findings. In this report, definite and suspect myocardial infarctions were combined and presented as myocardial infarction because the relation with alcohol intake was similar. Angina pectoris was defined as repeated episodes of chest pain during effort, especially when walking, usually disappearing rapidly after the cessation of effort or upon use of sublingual nitroglycerin.

**Statistical analysis**

Between men who withdrew from the study because of quitting and men who did not, age-specific and age-adjusted mean values and distributions of alcohol intake and other coronary risk factors were compared using analysis of covariance and the chi-square test.

Differences in age-adjusted mean values and the prevalence of potential confounding factors among categories of drinking status were tested by analysis of covariance and the chi-square test, respectively. When
the overall difference was significant \( p < 0.05 \), comparison of confounding factors between never drinkers and those in the other drinking categories was made using a \( t \) test or chi-square test. The relative risks and 95 percent confidence intervals relative to never drinkers were calculated, adjusting for age and other potential confounding factors, using the Cox proportional hazards model. The potential confounding factors for the adjustment were baseline values of age (years), serum total cholesterol concentration (mg/dl), body mass index (kg/m\(^2\)), cigarette smoking (number per day), left ventricular hypertrophy (yes vs. no), and history of diabetes mellitus (yes vs. no). Blood pressure was not included in the model because alcohol increases blood pressure and because adjustment for blood pressure may overestimate a potential protective effect of alcohol on coronary heart disease.

**RESULTS**

No difference in mean alcohol intake was found between men who withdrew from the study because of quitting and men who did not (table 1). Concerning distributions of alcohol intake, men who withdrew from the study had a lower prevalence of never drinkers and a higher prevalence of exdrinkers and current drinkers of 1-22 g of ethanol per day than did men who did not withdraw from the study. However, the prevalence of drinkers of \( \geq 23 \) g of ethanol per day was similar between the two groups. Differences in other coronary risk factors were inconsistent; men who withdrew from the study had higher frequencies of hypertension and current smokers but a lower mean serum cholesterol concentration than did men who did not withdraw.

**TABLE 1.** Age-specific and age-adjusted mean values or prevalence (%) of alcohol intake and risk characteristics at baseline for men who withdrew from the study because of quitting and for men who did not, Osaka, Japan, 1975-1984

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<th>Age at baseline (years) and withdrawal</th>
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<th>Age (years)</th>
<th>Usual alcohol intake (ethanol, g/day)</th>
<th>Never drinkers (%)</th>
<th>Exdrinkers (%)</th>
<th>Current drinkers (%) of ethanol at 1-22 g/day</th>
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<th>46-68 g/day</th>
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<th>Body mass index (kg/m(^2))</th>
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\* \( p < 0.05 \); \** \( p < 0.01 \); \*** \( p < 0.001 \) (test for differences between men who withdraw from the study and those who did not).
Table 2 presents the mean age, age-adjusted values, and prevalence of selected risk factors at baseline according to drinking status categories. Compared with that of never drinkers, the mean age was 1 year older in exdrinkers and 1-3 years younger in current drinkers. Exdrinkers and current drinkers showed higher systolic and diastolic blood pressure levels than did never drinkers, and there was a dose-response relation between current alcohol intake and blood pressure levels. The percentage of men on medication was three times higher in current drinkers of 23-68 g of ethanol per day. The prevalence of hypertension was 2-3 times higher in current drinkers than in never drinkers. The mean serum total cholesterol concentration and the prevalence of serum cholesterol at ≥220 mg/dl tended to be lower in exdrinkers and current drinkers than in never drinkers. Current drinkers had a higher mean body mass index than did never drinkers. The prevalence of current smokers was higher in drinkers of ≥46 g of ethanol/day than in never drinkers. The prevalence of diabetes mellitus was two times higher in drinkers of ≥23 g of ethanol/day than in never drinkers. Current drinkers had a higher mean serum total cholesterol concentration and the prevalence of serum cholesterol at ≥220 mg/dl tended to be lower in exdrinkers and current drinkers than in never drinkers. Current drinkers had a higher mean body mass index than did never drinkers. The prevalence of current smokers was higher in drinkers of ≥23 g of ethanol/day than in never drinkers. The prevalence of diabetes mellitus was two times higher in drinkers of ≥46 g of ethanol/day than in never drinkers. The prevalence of left ventricular hypertrophy tended to be higher in current and exdrinkers than in never drinkers.

During an average of 8.8 years of follow-up, there were 83 incident cases of coronary heart disease (54 myocardial infarction, 32 angina pectoris). Three incidences of angina pectoris preceded the occurrence of myocardial infarction. The age-adjusted relative risk of coronary heart disease was 0.80 for exdrinkers and 0.44-0.72 for current drinkers compared with that of never drinkers (table 3). The relative risk was lower with an increase in alcohol intake, but an intake of ≥69 g of ethanol per day did not appear to reduce the risk of coronary heart disease further. When adjusted for age, serum total cholesterol, cigarette smoking, body mass index, left ventricular hypertrophy, and history of diabetes mellitus, the relative risk declined further among drinkers of ≥46 g of ethanol per day. The multivariate relative risk was 0.55 (95 percent confidence interval (CI) 0.29-1.05) for drinkers of 23-45 g of ethanol per day and 0.41 (95 percent CI 0.19-0.88) for drinkers of 46-68 g of ethanol per day, but the relative risk for drinkers of ≥69 g of ethanol per day was not significant. Further adjustment for diastolic blood pressure made these relative risks lower, but the overall association with alcohol intake did not change. The inverse association with alcohol intake was observed similarly for both myocardial infarction and angina pectoris.

We handled changes in drinking status during the follow-up in two ways. One way was to collapse the categories of 23-45 g and 46-68 g of ethanol per day, because this combined category yielded a smaller change during the first 3- to 5-year follow-up (n = 6,266); the 77 percent of men in the combined category stayed in the same category. The 84 percent of never drinkers also stayed in the same category. The 6,266); the 77 percent of men in the combined category stayed in the same category. The 84 percent of never drinkers also stayed in the same category. The multivariate relative risk of coronary heart disease adjusting for age, serum total cholesterol, cigarette smoking, body mass index, left ventricular hypertro-

<table>
<thead>
<tr>
<th>Table 2. Age-adjusted mean values or prevalence (%) of risk factors at baseline by drinking status for men aged 40-59 years, Osaka, Japan, 1975-1984</th>
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<td><strong>Systolic</strong></td>
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<td>Never drinkers (n = 1,260)</td>
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<td>Ethanol intake, average g/day</td>
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<tr>
<td>1-22 (n = 2,317)</td>
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<tr>
<td>23-45 (n = 2,419)</td>
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<td>46-68 (n = 1,667)</td>
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<td>Never drinkers (n = 1,260)</td>
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* p < 0.05; ** p < 0.01; *** p < 0.001 (difference from never drinkers).
phy, and history of diabetes was 0.49 (95 percent CI 0.27-0.90; \( p = 0.02 \)) for drinkers of 23-68 g of alcohol per day compared with that for never drinkers. The relative risk of myocardial infarction was 0.65 (95 percent CI 0.20-2.12; \( p = 0.09 \)) for exdrinkers and current drinkers of 1-22 g of ethanol per day, and 0.43 (95 percent CI 0.16-1.16) for current drinkers of 23-45 g of ethanol per day. The respective relative risks were 0.52 (95 percent CI 0.20-1.46) for current drinkers of 23-45 g of ethanol per day, and 0.45 (95 percent CI 0.15-1.33) for current drinkers of 46-68 g of ethanol per day, compared with that for never drinkers. While the risk of coronary heart disease was lower for light to moderate drinkers (1-22 g/day) compared with that for never drinkers, these relative risks were not statistically significant. The inverse association between alcohol intake and coronary heart disease is consistent with previous reports from studies in the United States and other Western countries (4-17). The category of ethanol intake associated with the lowest incidence of coronary heart disease tended to be higher in our population than in other populations, with the range of ethanol intake overlapping among the studies: 46-68 g per day in this study versus approximately 20-56 g per day in American and British studies (9, 10, 17).

We found that 30 percent of the men changed their drinking categories during the first 3- to 5-year follow-up. Because this misclassification is unlikely to be random, the estimates of relative risk may be biased. However, compared with never drinking, the combined category of 23-68 g of ethanol per day with less misclassification still showed a significantly lower relative risk of coronary heart disease among current drinkers, the study showed a reduced risk of 0.69 (95 percent CI 0.37-1.28) for current drinkers of 46-68 g of ethanol per day compared with that for never drinkers. This result suggested that the reduced risk of coronary heart disease among current drinkers of 23-68 g of ethanol per day was unlikely to be biased. While it is possible that a deleterious effect of alcohol intake on coronary heart disease in older ages

### DISCUSSION

The present study of middle-aged Japanese men showed that alcohol intake, 23-68 g of ethanol per day, was associated with a lower incidence of coronary heart disease compared with never drinking. Although the risk of coronary heart disease was lower for light to moderate drinkers (1-22 g/day) or very heavy drinkers (≥69 g/day) compared with that for never drinkers, these relative risks were not statistically significant. The inverse association between alcohol intake and coronary heart disease is consistent with previous reports from studies in the United States and other Western countries (4-17). The category of ethanol intake associated with the lowest incidence of coronary heart disease tended to be higher in our population than in other populations, with the range of ethanol intake overlapping among the studies: 46-68 g per day in this study versus approximately 20-56 g per day in American and British studies (9, 10, 17).

We found that 30 percent of the men changed their drinking categories during the first 3- to 5-year follow-up. Because this misclassification is unlikely to be random, the estimates of relative risk may be biased. However, compared with never drinking, the combined category of 23-68 g of ethanol per day with less misclassification still showed a significantly lower relative risk of coronary heart disease among current drinkers, the study showed a reduced risk of 0.69 (95 percent CI 0.37-1.28) for current drinkers of 46-68 g of ethanol per day compared with that for never drinkers. This result suggested that the reduced risk of coronary heart disease among current drinkers of 23-68 g of ethanol per day was unlikely to be biased. While it is possible that a deleterious effect of alcohol intake on coronary heart disease in older ages

### TABLE 3. Relative risk of coronary heart disease incidence relative to never drinkers for men aged 40-59 years, Osaka, Japan, 1975-1984

<table>
<thead>
<tr>
<th>Ethanol intake, average g/day</th>
<th>Never drinkers</th>
<th>Exdrinkers</th>
<th>Current drinkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-22</td>
<td>17 (1.0)</td>
<td>3 (0.89 (0.29-2.73))</td>
<td>10 (1.0)</td>
</tr>
<tr>
<td>23-45</td>
<td>18 (0.84 (0.39-1.83))</td>
<td>2 (0.90 (0.20-4.13))</td>
<td>2 (0.90 (0.24-2.96))</td>
</tr>
<tr>
<td>46-68</td>
<td>25 (0.69 (0.37-1.28))</td>
<td>7 (0.48 (0.19-1.26))</td>
<td>4 (0.81 (0.25-2.59))</td>
</tr>
<tr>
<td>≥69</td>
<td>11 (0.44 (0.21-0.95))</td>
<td>3 (0.48 (0.19-1.26))</td>
<td>1 (0.43 (0.16-1.16))</td>
</tr>
</tbody>
</table>

* \( p < 0.05 \)
† \( p < 0.10 \)
‡ Adjusted for age, serum total cholesterol, cigarette smoking, body mass index, left ventricular hypertrophy, and history of diabetes mellitus.
§ Numbers in parentheses, 95% confidence interval.

### DISCUSSION

The present study of middle-aged Japanese men showed that alcohol intake, 23-68 g of ethanol per day, was associated with a lower incidence of coronary heart disease compared with never drinking. Although the risk of coronary heart disease was lower for light to moderate drinkers (1-22 g/day) or very heavy drinkers (≥69 g/day) compared with that for never drinkers, these relative risks were not statistically significant. The inverse association between alcohol intake and coronary heart disease is consistent with previous reports from studies in the United States and other Western countries (4-17). The category of ethanol intake associated with the lowest incidence of coronary heart disease tended to be higher in our population than in other populations, with the range of ethanol intake overlapping among the studies: 46-68 g per day in this study versus approximately 20-56 g per day in American and British studies (9, 10, 17).

We found that 30 percent of the men changed their drinking categories during the first 3- to 5-year follow-up. Because this misclassification is unlikely to be random, the estimates of relative risk may be biased. However, compared with never drinking, the combined category of 23-68 g of ethanol per day with less misclassification still showed a significantly lower relative risk of coronary heart disease among current drinkers, the study showed a reduced risk of 0.69 (95 percent CI 0.37-1.28) for current drinkers of 46-68 g of ethanol per day compared with that for never drinkers. This result suggested that the reduced risk of coronary heart disease among current drinkers of 23-68 g of ethanol per day was unlikely to be biased. While it is possible that a deleterious effect of alcohol intake on coronary heart disease in older ages
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Wall prostacyclin, a potential vasodilator and inhibitor of moderate alcohol consumption is increased vascular terol (15, 16, 28, 29).

The present study also showed the protective effect of alcohol intake on coronary heart disease among the Japanese, whose consumption of grape wine is minimal. The amount of ethanol was 42.3 percent from beer, 24.9 percent from rice wine, 24.3 percent from whiskey, 8.0 percent from hard liquor, and only 0.5 percent from grape wine. Our results were consistent with those from a recent meta-analysis, showing that all alcoholic drinks were linked with a lower risk of coronary heart disease (27). Thus, a substantial portion of the benefit is from ethanol rather than from the other components of grape wine.

The potential mechanisms by which ethanol intake could reduce the incidence of coronary heart disease were addressed previously (14, 28). Alcohol intake raises the concentration of serum high density lipoprotein cholesterol (HDL cholesterol), and elevated HDL cholesterol protects against atheroma formation in coronary arteries (28, 29). Our previous study reported an inverse association between the serum HDL cholesterol concentration and the incidence of coronary heart disease from a 7.7-year prospective study of 6,408 urban men (30). In the present analysis, the HDL cholesterol level at baseline was available for 69 percent of the subjects. The HDL cholesterol concentration was linearly correlated with alcohol intake. The age-adjusted mean HDL cholesterol level was 51.7 mg/dl for never drinkers, 53.1 mg/dl for exdrinkers, 55.0 mg/dl for drinkers of 1–22 g/day of ethanol, 57.2 mg/dl for drinkers of 23–45 g/day, 59.5 mg/dl for 46–68 g/day, and 60.0 mg/dl for ≥69 g/day. When HDL cholesterol was included in the multivariate analysis adjusting for age, serum total cholesterol, cigarette smoking, body mass index, left ventricular hypertrophy, and a history of diabetes mellitus, the relative risks of coronary heart disease were attenuated slightly but still of borderline statistical significance. The adjusted relative risks were 0.58 (95 percent CI 0.27–1.25; p = 0.16) for drinkers of 23–45 g/day and 0.43 (95 percent CI 0.17–1.07; p = 0.07) for drinkers of 46–68 g/day. This result suggests that a protective effect of alcohol drinking on coronary heart disease could be mediated in part by increased HDL cholesterol (15, 16, 28, 29).

Another potential mechanism for a protective effect of moderate alcohol consumption is increased vascular wall prostacyclin, a potential vasodilator and inhibitor of platelet aggregation, which prevents thrombus formation in coronary arteries (31). Enhanced fibrinolysis, via increased secretion of plasminogen activator from endothelial cells (32), and changes in coagulation proteins, such as a reduced plasma fibrinogen (33), may also contribute to a reduced risk of coronary heart disease.

Whether heavy alcohol intake (six or more drinks per day) protects against coronary heart disease has not been extensively examined, probably because few prospective studies had sufficient numbers of heavy drinkers at baseline. In the Kaiser-Permanente follow-up study (7), male heavy drinkers had a 30 percent lower incidence of coronary heart disease than that of nondrinkers, as did moderate drinkers, but this estimate was not statistically significant. In the British Regional Heart Study (17), male heavy drinkers showed a 15 percent lower incidence of coronary heart disease than that of nondrinkers, which also was not statistically significant. The Framingham Study (9) and the Albany Study (10) showed a lower incidence of coronary heart disease in heavy drinkers for both men and women, but again statistical significance was not shown. In our study, heavy drinking also did not appear to reduce the risk of coronary heart disease further. It is, however, uncertain whether the lack of a significant protective effect was due to an insufficient statistical power or due to alcohol-induced hypertension, leading to enhanced atherosclerosis and reduced cardiac function.

We previously reported that heavy drinking (six or more drinks per day) appeared to raise the incidence of hemorrhagic stroke and sudden death in middle-aged men living in three rural Japanese communities (20). Furthermore, the age-adjusted incidence rate of total cardiovascular disease was significantly higher in drinkers of four or more drinks per day than in never drinkers (20). Other studies have shown that heavy drinking, approximately six or more drinks per day, increases mortality from all causes, liver disease as well as coronary heart disease (5, 6, 8). Therefore, for drinkers, heavy drinking apparently should not be recommended for the prevention of coronary heart disease.

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