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Alcohol Consumption and Long-Term Mortality in Men with or without a History of Myocardial Infarction

Isao Muraki[1], Hiroyasu Iso[1], Hironori Imano[1], Renzhe Cui[1], Satoyo Ikehara[1], Kazumasa Yamagishi[2] and Akiko Tamakoshi[3]

[1]Public Health, Department of Social Medicine, Osaka University Graduate School of Medicine, Osaka, Japan
[2]Department of Public Health Medicine, Faculty of Medicine, and Health Services Research and Development Center, University of Tsukuba, Ibaraki, Japan
[3]Department of Public Health, Hokkaido University Graduate School of Medicine, Hokkaido, Japan

Aims: The evidence for the impact of alcohol consumption on long-term mortality among myocardial infarction (MI) survivors was limited. We aimed to examine whether alcohol consumption was associated with cause-specific and all-cause mortality in men with or without a history of MI.

Methods: A total of 32,004 men aged 40-79 years with no history of MI and 1,137 male MI survivors, free of stroke and cancer, were followed through the end of 2009. Alcohol consumption was assessed using self-administered questionnaires at baseline and five years.

Results: In MI survivors, consuming 23-45 g/day of alcohol was associated with a lower risk of coronary heart disease (CHD) mortality compared to never drinkers: the multivariable hazard ratio was 0.36 (95% confidence interval: 0.16-0.80). In non-MI men, a 10-26% lower risk was observed at <23 or 23-45 g/day with the U-shaped association for CHD, cardiovascular disease, other causes, and all causes (P-quadratic <0.001).

Conclusion: Alcohol consumption of 23-45 g/day was associated with a lower CHD mortality in MI survivors as so in men without MI.

Key words: Alcohol consumption, Myocardial infarction, Mortality, Cohort study, Asian

Introduction

Light-to-moderate alcohol consumption is beneficial for cardiovascular health as it increases blood levels of high-density lipoprotein cholesterol[1)] and its functional capacity[2, 3)], decreases the activation and aggregation of platelet and coagulation factors[1, 4)], and improves endothelial function[5)], and insulin sensitivity[6)]. A lower risk of coronary heart disease (CHD) and all-cause mortality but not stroke has been consistently observed in healthy men with light-to-moderate alcohol consumption compared to never or non-current drinking[7-9)]. However, alcohol consumption increases blood pressure in a dose-response fashion[10, 11)], and heavy alcohol consumption was associated with increased risks of stroke[9)] and all-cause mortality[7)].

Myocardial infarction (MI) damages the heart muscle by lowering heart function and some cases can lead to heart failure[12)]. The adverse effects of alcohol consumption on heart function could be stronger in MI survivors than healthy individuals. However, guidelines for the prevention of CHD and MI in the United States, Europe, and Japan do not have recommendations for alcohol consumption for MI patients[13-16)]. In long-term cohort studies among MI survivors, the consistent association of light-to-moderate post-MI alcohol consumption has not been

Address for correspondence: Hiroyasu Iso, 2-2 Yamadaoka, Suita-shi, Osaka, 565-0871, Japan. E-mail: iso@pbhel.med.osaka-u.ac.jp
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found in relation to long-term risk of cardiovascular and all-cause mortality[17, 18]. In the British regional heart study followed 455 men with a history of MI, a lower risk of cardiovascular and all-cause mortality was not observed for light-to-moderate alcohol consumption compared to occasional drinkers who had a similar risk of all-cause mortality to never drinkers[18]. In the Health Professional Follow-up study followed 1,818 male MI survivors, light-to-moderate alcohol consumption from immediately before MI onset was associated with a lower risk of cardiovascular and all-cause mortality compared to non-drinking[17]. These findings were from UK[18] and US[17], which may not be applicable to Asian populations which have a higher stroke mortality than CHD mortality[19]. Since alcohol consumption levels have a broader range in Japanese than in Western populations, our large study population will allow us to extend the evidence on the long-term health impact of alcohol consumption up to heavy drinking levels in MI survivors as well as in people without a history of MI.

Therefore, we aimed to examine the association of alcohol consumption with cause-specific and all-cause mortality among Japanese men stratified by the presence or absence of MI history and to examine whether the MI history modified the associations. We examined the associations for CHD and stroke separately since previous studies have reported a difference in the impact of alcohol consumption between stroke and CHD[20], and stroke incidence is higher in Japan than that in Western populations[21].

Methods

Study Population

The Japan Collaborative Cohort (JACC) study was launched in 1988-1990 enrolling 110,585 men and women aged 40-79 years from 45 areas across Japan and was sponsored by the Ministry of Education, Science and Culture in Japan. All participants responded to self-administered questionnaires regarding lifestyle, dietary behaviours, and medical history at baseline and five years after, and were followed up for their cause of death by reviewing death certificates until the end of 1999 in four areas, the end of 2003 in four areas, the end of 2008 in two areas, and the end of 2009 in 35 areas. The study design was described in detail elsewhere[22]. We obtained individual informed consent in 36 areas (written consent in 35 areas and oral consent in one area) and group consent from the area leader in nine areas. The JACC study was approved by the Ethical Review Board of Nagoya University (approval no. i14-044) and Osaka University (approval no. 14285).

In the current study, we enrolled participants reporting their history of MI at baseline or 5-year follow-up questionnaires as MI survivors. MI survivors newly reported at the 5-year survey were followed up from the date of the 5-year follow-up survey. We examined the association between alcohol consumption and mortality only among men since the number of female drinkers and cases was small (380 with 59 deaths for female drinkers with MI history). We excluded individuals with no data on their history of MI or alcohol consumption and those with a history of cancer or stroke at the start of follow-up **(Fig. 1)**. Finally, we analysed the data of 32,004 non-MI individuals and 1,137 MI survivors.

Assessment of Alcohol Consumption and Potential Confounding Factors

Alcohol consumption levels were assessed using the baseline questionnaire for participants responding to the baseline survey. For those responding to alcohol consumption at both baseline and 5-year follow-up questionnaires (31.7% of the study population), we updated alcohol consumption using the values from the 5-year follow-up questionnaire.

In the baseline and 5-year follow-up self-administered questionnaires, participants reported their alcohol consumption from three possible responses: current drinker, former drinker, and never drinker. Current and former drinkers reported their average alcohol consumption as a numerical value down to one decimal place in the 'go' unit, a traditional Japanese unit for alcohol consumption containing 23 grams of ethanol per unit. They chose their frequency of alcohol consumption from the following four responses: 'almost every day', 'three or four times a week', 'once or twice a week', and 'less than once a week'. We assigned the median value as 1.00, 0.50, 0.21, and 0.14 times per day to each response, respectively. We calculated daily alcohol consumption levels in grams of ethanol per day by multiplying alcohol consumption with the median frequency of alcohol consumption. To minimize the misclassification by using categories differing from the questionnaire, we divided the participants into six categories according to the traditional Japanese unit for alcohol consumption: never, former, <23 g/d, 23-45 g/d, 46-68 g/d, and 69+ g/d.

We used participant's height, weight, cigarette smoking status, education level, weekly exercise, daily walk, and history of hypertension and diabetes at baseline survey. At the 5-year follow-up survey, we obtained cigarette smoking status and history of diabetes, but not height and weight. For those whose

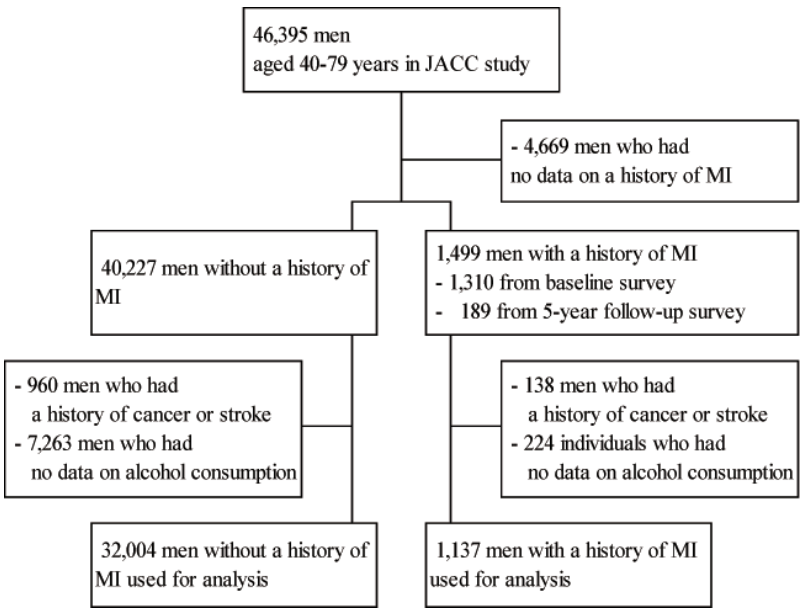

Fig. 1. Flowchart of the study population

age, smoking status, and history of diabetes were available, we updated these variables at the 5-year survey. Height, weight, and the age at last year of education were asked as a numerical value. We calculated body mass index (BMI) as weight in kilograms divided by height in meters squared. Education level was divided into four categories: elementary school (12 years or younger of the last age on education), junior high school (13-15 years), high school (16-18 years), and college or higher (19 years or older). Cigarette smoking status was assessed from the following responses: current smoker, former smoker, and never smoker. The weekly exercise was asked as 'How long do you spend on sports and exercise in a week on average?' and assessed with the following four responses: 'five hours or more', 'three to four hours', 'one to two hours', and 'rarely'. The daily walk was asked as 'How long do you walk indoors or outside in a day on average?' and assessed from the following four responses: 'an hour or more', '30 minutes to an hour', 'around 30 minutes', and 'rarely'.

Assessment of Outcomes

We identified the participants' dates and cause of death by systematically reviewing death certificates. The cause of death was coded based on the International Classification of Disease, 10th revision (ICD-10). In the current study, we focused on mortality from CHD (I20-I25) and stroke (I60-I69) as major secondary events of MI, and on mortality from CVD (ICD-10: I01-I99), cancer (C01-C97), other causes (other than C01-C97 and I01-I99), and all causes to assess the overall health impact of alcohol consumption. We also identified participants moving out from the study areas as a censoring case by reviewing the resident register (4.7% of male MI survivors and 5.9% of men without a history of MI).

Statistical Analysis

We calculated person-years for each participant as the duration from the return date of baseline questionnaire or 5-year questionnaire to the date of death, the date when the participant moved out from study areas (lost to follow-up), or the end of follow-up whichever came first. For individuals who newly reported their history of MI and their alcohol consumption at the 5-year questionnaire, we used the return date of the 5-year questionnaire as the start of follow-up. Regarding missing data for BMI, education status, cigarette smoking status, exercise, walking, history of hypertension, and diabetes, we created a missing indicator for each variable.

Stratifying by the presence or absence of MI history, we calculated the mean values for age and BMI, and the proportions for smoking status, education levels, exercise, walking, and the presence of hypertension, antihypertensive medication use, and diabetes. To standardize mortality rate by age, we summed the product of mortality rate (the number of deaths divided by person-years) in each 5-year age category and the number of participants in each 5-year age category and then divided by the number of overall participants. The hazard ratios (HR) and 95% confidence intervals (CI) of outcome events were

Table 1. Baseline characteristics of men with and without a history of myocardial infarction according to alcohol consumption levels

	Never	Former	Current			
			<23g/d	23-45g/d	46-68g/d	69+ g/d
With a history of myocardial infarction						
No. at risk	258	168	153	210	150	65
Age, years	65.7 (8.5)	66.7 (8.3)	65.2 (9.3)	64.6 (8.5)	61.7 (8.3)	58.8 (8.8)
BMI, kg/m^2	22.6 (3.0)	22.5 (3.0)	22.8 (2.8)	22.7 (2.6)	22.9 (3.3)	23.1 (2.8)
Hypertension, %	37.0	45.9	43.0	49.4	52.7	60.0
Antihypertensive medication use, %	21.3	28.8	26.8	35.2	36.7	37.5
Diabetes mellitus, %	16.4	18.4	14.6	12.7	14.6	20.0
Current smoking, %	32.1	29.8	30.7	45.8	53.4	57.8
College or higher education, %	14.2	21.5	25.4	16.8	22.0	17.4
Exercise: 3+ hrs/wk, %	6.3	8.3	6.3	8.8	7.9	8.3
Walking 1+ hr/d, %	40.2	41.9	35.1	42.9	37.9	49.1
Without a history of myocardial infarction						
No. at risk	7,469	2,038	5,600	7,403	6,487	3,007
Age, years	58.5 (10.5)	61.8 (9.5)	55.7 (10.1)	56.9 (10.1)	55.2 (9.3)	53.5 (8.9)
BMI, kg/m^2	22.6 (3.0)	22.3 (3.0)	22.7 (2.7)	22.6 (2.7)	22.8 (2.6)	22.9 (2.7)
Hypertension, %	14.1	24.3	15.7	19.6	20.9	19.4
Antihypertensive medication use, %	7.9	14.9	9.2	13.2	13.9	11.2
Diabetes mellitus, %	4.9	12.3	5.2	5.8	4.3	5.3
Current smoking, %	49.0	47.1	46.5	52.6	61.9	69.4
College or higher education, %	16.5	18.8	22.1	17.4	15.5	13.9
Exercise: 3+ hrs/wk, %	7.1	8.1	6.5	7.9	6.9	5.9
Walking 1+ hr/d, %	49.9	47.1	46.5	49.7	53.6	53.0

*Figures are means (standard deviations) or proportions.

calculated by using the Cox proportional hazard regression. We used the median value of current alcohol consumption as a continuous variable for the trend tests. The trend test for current alcohol consumption was conducted in all participants except former drinkers by using a continuous value of alcohol consumption for linearity (P for linear) and including both quadratic and linear terms for U-shaped association (P for quadratic) in the same model; the exclusion of former drinkers could minimize the impact of reverse causation which exaggerated the absolute mortality risk of non-drinkers. As potential confounding factors, age (fifths) was adjusted for in model 1, and additional adjustment for BMI (fifths, and missing), smoking status (never, former, current smoking, and missing), exercise (<1, 1-2, 3-4, 5+ hrs/week, and missing), walking (<0.5, 0.5, 0.6-0.9, 1+ hr/day, and missing), and education levels (<13, 13-15, 16-18, 19+ years, and missing) was used in model 2. Hypertension and diabetes (no, yes, and missing for each) were further adjusted for in model 3.

To make the association visually understandable, we drew the restricted cubic spline curves placing three knots at 0, 23, and 69 g/day of current alcohol consumption according to tertiles by using the SAS macro LGTPHCURV9 publicly available at the website of the Center for Methods in Implementation and Prevention Science, Yale School of Public Health[23, 24]. We performed three sensitivity analyses. To minimize the reverse causation due to the severity of MI or other clinical conditions, we conducted the sensitivity analysis excluding individuals who died within the first five years. We did the primary analysis using baseline exposure data to estimate the impact of updating exposure data in a partial population (31.7%). To assess the impact of missing covariates, we applied multiple imputation for missing BMI, education, cigarette smoking status, exercise, walking, histories of hypertension and diabetes data using PROC MI and PROC MIANALYSE.

All analyses were performed using SAS 9.4, and we determined when a two-tailed *p*-value was less than 0.05 as the statistical significance and 0.05-<0.10 as borderline significance.

Results

In men with and without a history of MI, those with higher alcohol consumption were more likely to be young, obese, current smokers, and to have

Table 2. Associations between alcohol consumption and risks of all-cause and cause-specific deaths in men

	Never	Former	Current				*P* values	
			<23 g/d	23-45 g/d	46-68 g/d	69+ g/d	Linear	Quadratic
With a history of myocardial infarction								
CHD	1.00 (Ref)	1.19 (0.66-2.16)	0.76 (0.38-1.53)	0.36 (0.16-0.80)	0.96 (0.48-1.94)	0.21 (0.03-1.61)	0.25	0.54
Stroke	1.00 (Ref)	2.15 (0.97-4.78)	0.81 (0.27-2.40)	1.26 (0.54-2.92)	1.69 (0.66-4.34)	3.26 (1.17-9.04)	0.01	0.46
CVD	1.00 (Ref)	1.51 (1.05-2.17)	0.87 (0.57-1.33)	0.75 (0.51-1.12)	0.84 (0.52-1.35)	0.93 (0.49-1.77)	0.57	0.28
Cancer	100 (Ref)	2.46 (1.43-4.21)	1.67 (0.90-3.10)	1.21 (0.69-2.12)	1.47 (0.80-2.72)	1.47 (0.61-3.56)	0.35	0.71
Others	100 (Ref)	1.29 (0.84-1.97)	0.81 (0.49-1.36)	0.69 (0.43-1.10)	0.88 (0.50-1.55)	1.47 (0.71-3.03)	0.46	0.05
All causes	1.00 (Ref)	1.56 (1.22-1.98)	0.98 (0.73-1.30)	0.81 (0.62-1.05)	0.97 (0.71-1.30)	1.15 (0.75-1.75)	0.64	0.15
Without a history of myocardial infarction								
CHD	1.00 (Ref)	1.33 (0.99-1.80)	0.71 (0.53-0.95)	0.74 (0.57-0.95)	0.83 (0.63-1.08)	1.21 (0.88-1.67)	0.37	<0.001
Stroke	1.00 (Ref)	1.72 (1.38-2.13)	0.92 (0.74-1.14)	0.91 (0.75-1.11)	1.20 (0.98-1.45)	1.64 (1.29-2.08)	<0.001	0.006
CVD	1.00 (Ref)	1.54 (1.33-1.77)	0.86 (0.75-0.99)	0.83 (0.73-0.94)	0.97 (0.85-1.10)	1.30 (1.10-1.53)	0.005	<0.001
Cancer	1.00 (Ref)	1.44 (1.27-1.64)	0.89 (0.79-1.00)	1.01 (0.91-1.11)	1.09 (0.98-1.21)	1.26 (1.10-1.44)	<0.001	0.07
Others	1.00 (Ref)	1.39 (1.23-1.57)	0.78 (0.69-0.88)	0.84 (0.76-0.94)	0.87 (0.78-0.98)	1.20 (1.04-1.38)	0.09	<0.001
All causes	1.00 (Ref)	1.45 (1.34-1.56)	0.84 (0.78-0.90)	0.90 (0.84-0.96)	0.98 (0.91-1.04)	1.24 (1.14-1.35)	<0.001	<0.001

CHD, coronary heart disease; CVD, cardiovascular disease. Figures are hazard ratios (95% confidence intervals) adjusted for age, BMI, smoking status, exercise, walking, education levels, and histories of hypertension, and diabetes mellitus.

hypertension **(Table 1)**. Education level, exercise, and walking habits were not linearly associated with alcohol consumption in either group.

Among the male MI survivors, 556 deaths (240 CVDs, 138 cancers, and 178 others) were identified in 13,464 person-years of follow-up (age-standardized all-cause mortality rate=30.3 per 1000 person-years). During 502,230 person-years of follow-up, 8,838 non-MI men died (2,352 CVDs, 3,399 cancers, and 3,087 others; age-standardized all-cause mortality rate=20.5 per 1000 person-years). Alcohol consumption of 23-45 g/day was associated with a lower risk of CHD mortality in both male MI survivors and non-MI men: the multivariable HRs were 0.36 (0.16-0.80) and 0.74 (0.57-0.95), respectively **(Table 2, Supplementary Table 1, and Fig. 2A)**. While the association between alcohol consumption and risk of stroke mortality was linear with statistical significance in male MI survivors and non-MI men (P for linear=0.01 and <0.001, respectively) **(Fig. 2B)**. Heavy alcohol consumption was associated with an elevated risk of stroke mortality: the multivariable HR at 69 g/day or more of alcohol consumption was 3.26 (1.17-9.04) in male MI survivors and 1.64 (1.29-2.08) in non-MI men. The lowest risk of CVD mortality was observed at an alcohol consumption of 23-45 g/day in both male MI survivors and non-MI men albeit not significant in male MI survivors **(Fig. 2C)**. The multivariable HR was 0.75 (0.51-1.12) in MI survivors and 0.83 (0.73-0.94) in non-MI men.

Alcohol consumption was positively associated with risk of cancer mortality in non-MI men but not in male MI survivors (P for linear <0.001 and 0.35, respectively) **(Fig. 2D)**. The association with other-cause mortality was U-shaped in both male MI survivors and non-MI men (P for quadratic=0.05, and <0.001, respectively) **(Fig. 2E)**. The association between alcohol consumption and risk of all-cause mortality tended to be J-shaped in both groups (P for quadratic=0.15 for male MI survivors, and <0.001 for non-MI men) **(Fig. 2F)**. Compared with never

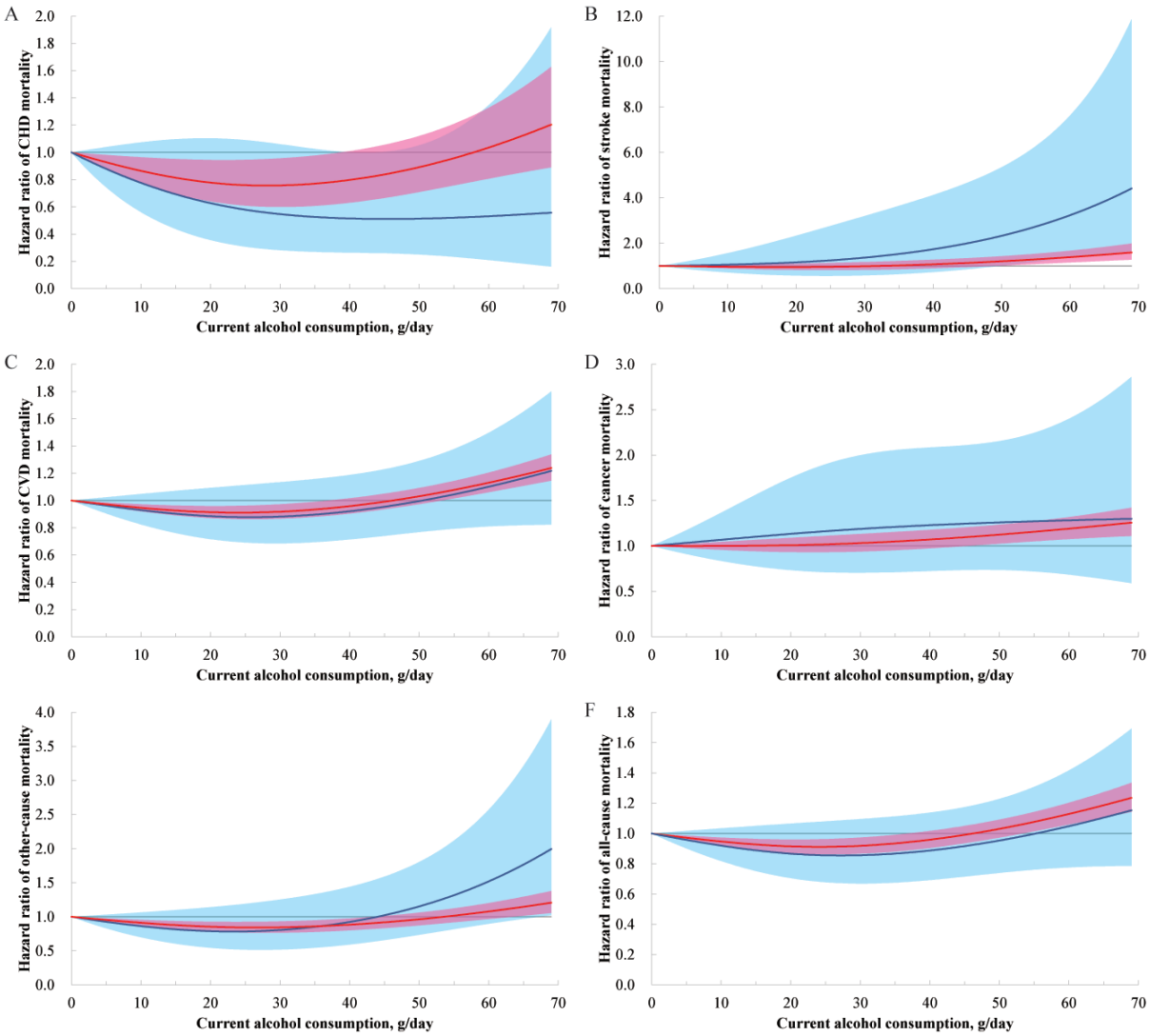

Fig. 2. Cubic spline curves for the association of current alcohol consumption with mortality from coronary heart disease (A), stroke (B), cardiovascular disease (C), cancer (D), other causes (E), and all causes (F) among male myocardial infarction (MI) survivors and non-MI men

Blue colour is for male MI survivors, and red colour is for non-MI men. Solid line represents point estimates of the hazard ratio, and light colour area does 95% confidence intervals.

drinkers, the multivariable HRs of all-cause mortality at the nadir were 0.81 (95%CI: 0.62-1.05) for 23-45 g/day in male MI survivors and 0.84 (0.78-0.90) for <23 g/day in non-MI men. Meanwhile, former drinkers had a higher risk of deaths from CVD, cancer, and all causes independent of MI history.

In the three sensitivity analyses (excluding death cases within the first five years of follow-up, using baseline exposure data only, and using multiple imputation for missing covariates), the point estimate of HR for each alcohol consumption level modestly changed in MI survivors due to a change in the number of deaths. But the shape of the associations did not differ from the primary analyses **(Supplementary Tables 2, 3, 4)**.

Discussion

In this median 18.7-year prospective cohort study of 33,141 middle-aged men (1,137 MI survivors and 32,004 non-MI men), we found that alcohol consumption of 23-45 g/day was associated with two-third and one-fourth lower risks of CHD mortality in both MI survivors and non-MI men, respectively. We also found a positive association between alcohol consumption and the risk of stroke mortality in both

groups.

The association between alcohol consumption and long-term risk of mortality from CVD and all causes was previously examined in two long-term cohort studies. Among 455 British men aged 45-64 years with a history of MI, none and light drinkers (up to 15 drinks/week) had a similar risk of all-cause mortality to occasional drinkers (<1 drink/week) during the 12.8 years of follow-up[18]. Further the Health Professional Follow-up Study followed 1,633 male MI survivors aged 40 years or older for a maximum 20-year follow-up. They found that 10-29.9 g/day of alcohol consumption both before and after MI was associated with the lowest risk of all-cause mortality[17]. However, in that study, non-drinkers included former drinkers between four and eight years before MI onset, who may have higher mortality than never drinkers as reported in the Stockholm Heart Epidemiology Program[25]. In the Stockholm Heart Epidemiology Program enrolling 1,346 MI survivors with 8.6 years of median follow-up, quitting alcohol consumption after MI onset was associated with an approximately 4-fold higher risk of mortality from CVD and all causes than never drinkers[25].

To interpret the association between post-MI alcohol consumption and the risk of mortality from CVD and all causes, the impact of quitting or reducing alcohol consumption after MI onset needed to be considered because some MI survivors changed their behaviours including alcohol consumption[17, 26]. MI survivors maintaining 10-29.9 g/day of alcohol consumption both before and after first MI occurrence had a lower risk of all-cause mortality, but those quitting or reducing their alcohol consumption by <10 g/day from 30 g/day or more had a higher risk[17]. In our study, former drinkers had a higher risk of mortality from CVD and all causes than never drinkers for both MI survivors and non-MI men, probably because they had some severe clinical conditions that forced them to quit drinking.

Little is known about the mechanisms behind the difference in the mortality between MI survivors and non-MI individuals and its association with alcohol consumption. But several biological mechanisms related to moderate alcohol consumption and lower cardiovascular mortality work commonly in both populations. First, light-to-moderate alcohol consumption increases blood levels of high-density lipoprotein cholesterol and adiponectin[1]. Also, moderate alcohol consumption increases cholesterol efflux capacity by the high-density lipoprotein to remove excess cholesterol from the foam macrophages in vascular wall[2, 3]. Higher cholesterol efflux capacity was associated with a lower risk of CVD among both healthy adults[27] and CHD patients[28]. Second, alcohol consumption decreases the activation and aggregation of platelet and lowers blood levels of coagulation factors such as fibrinogen[1, 4]. Third, alcohol consumption improves endothelial function through increased endogenous nitric oxide synthase expression in vascular endothelial cells[5]. These physiological effects attenuate the development and the regression of atherosclerosis leading to lower mortality from CVD, especially CHD. However, excessive alcohol consumption cancels out the beneficial effects by further increasing blood pressure levels[10, 11], evoking inflammation[29], and decreasing cardiac function[30].

The strength of our current study is the enrolment of both MI survivors and non-MI individuals from the general population allowing us to examine their difference in the association of alcohol consumption with respect to all-cause and cause-specific mortality. We also separated former drinkers from never drinkers, minimizing the potential exaggeration of the beneficial impact of light-to-moderate drinkers. Since there is a broader range of alcohol consumption in the current population than Western population, our findings can provide evidence regarding the impact of alcohol consumption up to heavy drinking levels on cardiovascular health among MI survivors. These current findings are less likely due to reverse causation because of the prospective study design. Moreover, the follow-up period is longer than most previous studies allowing us to examine the long-term impact of alcohol consumption for MI survivors.

Our study has several limitations. First, since the history of MI was self-reported, other heart diseases may contaminate our sample. In another Japanese cohort study, the sensitivity and the positive predicted value of the self-reported history of MI for the past confirmed incidence of MI was 83 (95%CI: 79-88) % and 47 (42-51) % among men, respectively[31]. This finding suggested that the contamination was not large although the self-reported history of MI underrepresented the past incidence of MI. Second, we did not have any data on the severity and treatment of MI, important predictive factors for fatality, which may modify the association between post-MI alcohol consumption and risk of mortality among MI survivors[17]. However, since our exclusion of early deaths did not alter the results materially for MI survivors, the impact of severe MI patients on our findings may be small. Third, unmeasured or residual confounders may exist such as a history of hypercholesterolemia, types of medication used, and dietary factors. Finally, our findings could not be

generalized to women and non-Japanese populations.

Conclusion

Light-to-moderate alcohol consumption after MI was associated with a lower risk of CHD mortality among MI survivors as so in men with no MI history. A similar, but weaker association for CVD mortality was observed for both subgroups. Further investigation is needed to confirm our findings.

Data Availability Statement

The data can be made available from the corresponding author under reasonable request.

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The members of the JACC Study Group are as described below: Dr Akiko Tamakoshi (present chairperson of the study group), Hokkaido University Graduate School of Medicine; Drs Mitsuru Mori, Hokkaido Chitose College of Rehabilitation; Dr. Yoshihiro Kaneko, Japan Support Center for Suicide Countermeasures; Dr. Ichiro Tsuji, Tohoku University Graduate School of Medicine; Dr. Yosikazu Nakamura, Jichi Medical School; Dr. Hiroyasu Iso, Osaka University Graduate School of Medicine; Dr. Kazumasa Yamagishi, Faculty of Medicine, University of Tsukuba; Dr. Haruo Mikami, Cancer Prevention Center, Chiba Cancer Center Research Institute; Dr. Michiko Kurosawa, Juntendo University Faculty of Medicine; Dr. Yoshiharu Hoshiyama, Yokohama Soei University; Dr. Naohito Tanabe, University of Niigata Prefecture; Dr. Koji Tamakoshi, Nagoya University Graduate School of Health Sciences; Dr. Kenji Wakai, Nagoya University Graduate School of Medicine; Dr. Masahiko Ando, Nagoya University Hospital; Dr. Koji Suzuki, Fujita Health University School of Health Sciences; Dr. Shuji Hashimoto, Fujita Health University School of Medicine; Dr. Hiroshi Yatsuya, Fujita Health University School of Medicine; Dr. Shogo Kikuchi, Aichi Medical University School of Medicine; Dr. Yasuhiko Wada, Wakayama Prefecture Tanabe Public Health Center; Dr. Takashi Kawamura, Kyoto University Health Service; Dr. Yoshiyuki Watanabe, Graduate School of Medical Science, Kyoto Prefectural University of Medicine; Dr. Kotaro Ozasa, Radiation Effects Research Foundation; Dr. Kazuya Mikami, Japanese Red Cross Kyoto Daiichi Hospital; Dr. Kiyomi Sakata, Iwate Medical University; Dr. Yoichi Kurozawa, Tottori University Faculty of Medicine; Dr. Yoshihisa Fujino, University of Occupational and Environmental Health, Japan; and Dr. Akira Shibata, Kurume University.

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Conflict of Interest

The Authors declare that there is no conflict of interest.

Authors' Contributions

IM and HIso designed the research. IM conducted data analysis and drafted the initial manuscript. All authors made a critical revision and approved the final manuscript.

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Supplementary Table 1. Associations between alcohol consumption and risks of all-cause and cause-specific deaths in men

	Never	Former	Current			
			<23 g/d	23-45 g/d	46-68 g/d	69+ g/d
With a history of myocardial infarction						
Person years	3,256	2,019	2,022	3,109	2,159	938
CHD (cases)	27	21	13	8	13	1
Model 1	1.00 (Ref)	1.16 (0.65-2.07)	0.75 (0.38-1.49)	0.32 (0.15-0.71)	0.85 (0.44-1.67)	0.17 (0.02-1.28)
Model 2	1.00 (Ref)	1.23 (0.68-2.23)	0.78 (0.39-1.56)	0.36 (0.16-0.79)	0.95 (0.47-1.90)	0.22 (0.03-1.66)
Stroke (cases)	11	15	5	13	9	7
Model 1	1.00 (Ref)	2.13 (0.98-4.65)	0.79 (0.27-2.28)	1.26 (0.56-2.82)	1.65 (0.68-4.04)	3.94 (1.48-10.5)
Model 2	1.00 (Ref)	2.15 (0.97-4.76)	0.80 (0.27-2.37)	1.28 (0.56-2.94)	1.72 (0.68-4.32)	3.91 (1.43-10.7)
CVD (cases)	64	59	35	44	26	12
Model 1	1.00 (Ref)	1.45 (1.02-2.07)	0.90 (0.59-1.37)	0.74 (0.50-1.09)	0.79 (0.50-1.25)	0.97 (0.52-1.82)
Model 2	1.00 (Ref)	1.54 (1.07-2.21)	0.89 (0.58-1.36)	0.75 (0.50-1.12)	0.82 (0.51-1.32)	1.02 (0.54-1.95)
Cancer (cases)	23	36	20	30	22	7
Model 1	1.00 (Ref)	2.51 (1.48-4.26)	1.49 (0.82-2.73)	1.34 (0.77-2.31)	1.77 (0.98-3.19)	1.44 (0.61-3.39)
Model 2	1.00 (Ref)	2.53 (1.48-4.33)	1.64 (0.88-3.03)	1.26 (0.72-2.20)	1.54 (0.84-2.83)	1.43 (0.60-3.42)
Others (cases)	52	41	24	32	18	11
Model 1	1.00 (Ref)	1.24 (0.82-1.89)	0.71 (0.43-1.17)	0.65 (0.42-1.01)	0.82 (0.48-1.42)	1.33 (0.66-2.66)
Model 2	1.00 (Ref)	1.27 (0.83-1.94)	0.79 (0.47-1.31)	0.72 (0.45-1.13)	0.87 (0.50-1.53)	1.55 (0.76-3.15)
All causes (cases)	139	136	79	106	66	30
Model 1	1.00 (Ref)	1.55 (1.22-1.97)	0.93 (0.70-1.23)	0.81 (0.63-1.04)	0.97 (0.72-1.30)	1.15 (0.76-1.72)
Model 2	1.00 (Ref)	1.59 (1.25-2.03)	0.98 (0.74-1.31)	0.82 (0.63-1.07)	0.97 (0.72-1.32)	1.22 (0.81-1.85)
Without a history of myocardial infarction						
Person years	107,072	31,239	87,693	121,020	108,250	46,956
CHD (cases)	138	66	72	114	101	56
Model 1	1.00 (Ref)	1.42 (1.06-1.91)	0.70 (0.52-0.93)	0.78 (0.61-1.00)	0.92 (0.71-1.20)	1.42 (1.03-1.94)
Model 2	1.00 (Ref)	1.44 (1.07-1.94)	0.73 (0.55-0.98)	0.79 (0.62-1.02)	0.89 (0.68-1.16)	1.31 (0.95-1.81)
Stroke (cases)	223	137	136	221	206	106
Model 1	1.00 (Ref)	1.78 (1.44-2.21)	0.89 (0.71-1.10)	0.94 (0.78-1.13)	1.26 (1.04-1.52)	1.81 (1.43-2.29)
Model 2	1.00 (Ref)	1.82 (1.47-2.25)	0.95 (0.76-1.18)	0.98 (0.81-1.18)	1.29 (1.07-1.57)	1.80 (1.42-2.29)
CVD (cases)	556	306	328	505	436	221
Model 1	1.00 (Ref)	1.61 (1.40-1.85)	0.84 (0.73-0.96)	0.86 (0.76-0.98)	1.05 (0.93-1.19)	1.48 (1.26-1.73)
Model 2	1.00 (Ref)	1.62 (1.41-1.87)	0.89 (0.77-1.02)	0.88 (0.77-1.00)	1.05 (0.92-1.19)	1.42 (1.21-1.67)
Cancer (cases)	727	367	458	815	717	315
Model 1	1.00 (Ref)	1.49 (1.31-1.69)	0.88 (0.78-0.99)	1.04 (0.94-1.15)	1.17 (1.05-1.30)	1.40 (1.22-1.60)
Model 2	1.00 (Ref)	1.46 (1.28-1.65)	0.90 (0.79-1.01)	1.01 (0.92-1.13)	1.10 (0.99-1.22)	1.28 (1.11-1.46)
Others (cases)	781	386	415	703	534	268
Model 1	1.00 (Ref)	1.45 (1.29-1.64)	0.76 (0.68-0.86)	0.85 (0.76-0.94)	0.88 (0.79-0.99)	1.26 (1.10-1.45)
Model 2	1.00 (Ref)	1.44 (1.28-1.63)	0.79 (0.70-0.89)	0.87 (0.78-0.96)	0.89 (0.80-1.00)	1.24 (1.07-1.43)
All causes (cases)	2,064	1,059	1,201	2,023	1,687	804
Model 1	1.00 (Ref)	1.51 (1.40-1.62)	0.82 (0.77-0.89)	0.92 (0.87-0.98)	1.03 (0.97-1.10)	1.37 (1.26-1.48)
Model 2	1.00 (Ref)	1.49 (1.39-1.61)	0.85 (0.79-0.92)	0.93 (0.87-0.99)	1.01 (0.95-1.08)	1.29 (1.19-1.41)

CHD, coronary heart disease; CVD, cardiovascular disease. Figures are hazard ratios (95% confidence intervals) adjusted for age (Model 1) and those further adjusted for body mass index, smoking status, exercise, walking, and education levels (Model 2).

Supplementary Table 2. Sensitivity analyses excluding deaths within the first 5 years for associations between alcohol intake and risks of all causes CVD cancer and other causes in men

	Never	Former	Current			
			<23 g/d	23-45 g/d	46-68 g/d	69+ g/d
With a history of myocardial infarction						
Person years	3,146	1,923	1,920	3,033	2,113	916
CHD (cases)	15	12	8	7	10	1
Adjusted HR	1.00 (Ref)	1.19 (0.53-2.69)	0.71 (0.27-1.83)	0.48 (0.19-1.20)	1.53 (0.65-3.62)	0.36 (0.05-2.90)
Stroke (cases)	6	14	3	7	8	7
Adjusted HR	1.00 (Ref)	4.14 (1.55-11.1)	0.96 (0.23-4.01)	1.33 (0.43-4.14)	3.30 (1.05-10.3)	6.55 (1.99-21.5)
CVD (cases)	39	41	23	31	22	10
Adjusted HR	1.00 (Ref)	1.78 (1.13-2.81)	0.85 (0.49-1.46)	0.81 (0.49-1.33)	1.22 (0.70-2.12)	1.19 (0.57-2.48)
Cancer (cases)	20	29	15	22	12	5
Adjusted HR	1.00 (Ref)	2.28 (1.25-4.13)	1.41 (0.70-2.84)	0.96 (0.51-1.81)	0.81 (0.38-1.71)	1.02 (0.37-2.85)
Others (cases)	36	32	17	30	15	8
Adjusted HR	1.00 (Ref)	1.46 (0.88-2.42)	0.78 (0.42-1.46)	0.92 (0.55-1.54)	1.06 (0.56-2.02)	1.36 (0.57-3.23)
All causes (cases)	95	102	55	83	49	23
Adjusted HR	1.00 (Ref)	1.74 (1.30-2.32)	0.95 (0.67-1.34)	0.88 (0.65-1.20)	1.03 (0.72-1.48)	1.17 (0.72-1.91)
Without a history of myocardial infarction						
Person years	106,079	30,636	87,183	120,189	107,657	46,605
CHD (cases)	122	58	61	100	83	49
Adjusted HR	1.00 (Ref)	1.32 (0.96-1.82)	0.66 (0.48-0.90)	0.72 (0.55-0.94)	0.74 (0.55-0.99)	1.22 (0.87-1.71)
Stroke (cases)	183	116	117	197	179	91
Adjusted HR	1.00 (Ref)	1.78 (1.40-2.25)	0.95 (0.75-1.20)	0.97 (0.79-1.20)	1.25 (1.01-1.54)	1.71 (1.31-2.22)
CVD (cases)	457	252	278	438	365	187
Adjusted HR	1.00 (Ref)	1.53 (1.31-1.79)	0.86 (0.74-1.00)	0.85 (0.74-0.97)	0.96 (0.83-1.11)	1.34 (1.12-1.60)
Cancer (cases)	574	274	386	689	627	264
Adjusted HR	1.00 (Ref)	1.35 (1.16-1.56)	0.92 (0.80-1.04)	1.03 (0.92-1.15)	1.13 (1.00-1.26)	1.26 (1.09-1.46)
Others (cases)	666	303	354	610	490	231
Adjusted HR	1.00 (Ref)	1.29 (1.12-1.48)	0.77 (0.67-0.87)	0.84 (0.75-0.94)	0.92 (0.81-1.04)	1.20 (1.02-1.40)
All causes (cases)	1,697	827	1,018	1,737	1,482	682
Adjusted HR	1.00 (Ref)	1.37 (1.26-1.49)	0.84 (0.78-0.91)	0.91 (0.85-0.97)	1.00 (0.93-1.08)	1.25 (1.14-1.37)

CHD, coronary heart disease; CVD, cardiovascular disease; HR, hazard ratio. All HRs (95% confidence intervals) were adjusted for age, body mass index, smoking status, exercise, walking, education levels, hypertension, and diabetes mellitus.

Supplementary Table 3. Sensitivity analyses using baseline exposure data only for associations between alcohol intake and risks of all causes CVD cancer and other causes in men

	Never	Former	Current			
			<23 g/d	23-45 g/d	46-68 g/d	69+ g/d
With a history of myocardial infarction						
Person years	3,075	1,743	1,783	2,638	1,879	909
CHD (cases)	28	18	8	8	12	0
Adjusted HR	1.00 (Ref)	1.14 (0.62-2.09)	0.54 (0.24-1.21)	0.38 (0.17-0.85)	0.96 (0.46-1.97)	-
Stroke (cases)	9	14	6	9	10	6
Adjusted HR	1.00 (Ref)	2.77 (1.17-6.58)	1.07 (0.37-3.11)	1.16 (0.44-3.06)	2.42 (0.92-6.36)	2.89 (0.94-8.87)
CVD (cases)	60	53	28	36	27	9
Adjusted HR	1.00 (Ref)	1.56 (1.07-2.29)	0.79 (0.50-1.25)	0.72 (0.47-1.10)	0.97 (0.60-1.56)	0.67 (0.33-1.40)
Cancer (cases)	23	33	22	23	20	8
Adjusted HR	1.00 (Ref)	2.66 (1.54-4.61)	1.89 (1.04-3.46)	1.02 (0.56-1.86)	1.36 (0.72-2.55)	1.52 (0.65-3.56)
Others (cases)	53	34	27	28	18	8
Adjusted HR	1.00 (Ref)	1.13 (0.72-1.77)	0.96 (0.59-1.57)	0.68 (0.42-1.10)	0.85 (0.48-1.49)	0.92 (0.42-2.02)
All causes (cases)	136	120	77	87	65	25
Adjusted HR	1.00 (Ref)	1.56 (1.21-2.01)	1.03 (0.77-1.37)	0.76 (0.57-1.00)	1.00 (0.73-1.37)	0.89 (0.57-1.39)
Without a history of myocardial infarction						
Person years	117,827	28,103	94,067	120,187	106,834	47,871
CHD (cases)	154	65	86	110	102	59
Adjusted HR	1.00 (Ref)	1.39 (1.04-1.87)	0.83 (0.63-1.08)	0.74 (0.57-0.95)	0.84 (0.65-1.09)	1.24 (0.91-1.70)
Stroke (cases)	257	140	160	220	213	111
Adjusted HR	1.00 (Ref)	1.82 (1.47-2.24)	0.99 (0.81-1.21)	0.95 (0.79-1.14)	1.21 (1.00-1.46)	1.69 (1.34-2.12)
CVD (cases)	640	310	379	502	450	230
Adjusted HR	1.00 (Ref)	1.61 (1.40-1.84)	0.92 (0.80-1.04)	0.84 (0.75-0.95)	0.97 (0.86-1.11)	1.32 (1.13-1.55)
Cancer (cases)	852	349	509	842	717	326
Adjusted HR	1.00 (Ref)	1.46 (1.28-1.65)	0.88 (0.79-0.99)	1.04 (0.94-1.14)	1.07 (0.96-1.39)	1.40 (1.24-1.58)
Others (cases)	908	374	452	719	538	279
Adjusted HR	1.00 (Ref)	1.40 (1.24-1.58)	0.77 (0.69-0.87)	0.89 (0.80-0.98)	0.89 (0.79-0.99)	1.21 (1.05-1.39)
All causes (cases)	2,400	1,033	1,340	2,063	1,705	835
Adjusted HR	1.00 (Ref)	1.48 (1.37-1.59)	0.85 (0.79-0.91)	0.93 (0.88-0.99)	0.98 (0.92-1.04)	1.24 (1.14-1.34)

CHD, coronary heart disease; CVD, cardiovascular disease; HR, hazard ratio. All HRs (95% confidence intervals) were adjusted for age, body mass index, smoking status, exercise, walking, education levels, hypertension, and diabetes mellitus.

Supplementary Table 4. Sensitivity analyses using multiple imputation for missing covariates for associations between alcohol intake and risks of all causes CVD cancer and other causes in men

	Never	Former	Current			
			<23 g/d	23-45 g/d	46-68 g/d	69+ g/d
With a history of myocardial infarction						
Person years	3,330	2,074	2,022	3,142	2,189	959
CHD (cases)	27	21	13	8	13	1
Adjusted HR	1.00 (Ref)	1.18 (0.65-2.14)	0.69 (0.34-1.40)	0.32 (0.14-0.71)	0.81 (0.40-1.63)	0.19 (0.02-1.40)
Stroke (cases)	11	15	5	13	9	7
Adjusted HR	1.00 (Ref)	2.16 (0.97-4.79)	0.84 (0.29-2.47)	1.19 (0.52-2.74)	1.41 (0.56-3.53)	3.22 (1.19-8.71)
CVD (cases)	64	59	35	44	26	12
Adjusted HR	1.00 (Ref)	1.48 (1.03-2.14)	0.90 (0.59-1.38)	0.70 (0.47-1.04)	0.70 (0.44-1.13)	0.91 (0.48-1.72)
Cancer (cases)	23	36	20	30	22	7
Adjusted HR	1.00 (Ref)	2.50 (1.45-4.29)	1.64 (0.89-3.03)	1.23 (0.70-2.16)	1.43 (0.78-2.63)	1.26 (0.53-3.02)
Others (cases)	52	41	24	32	18	11
Adjusted HR	1.00 (Ref)	1.34 (0.87-2.06)	0.89 (0.54-1.47)	0.64 (0.40-1.02)	0.68 (0.39-1.19)	1.08 (0.53-2.19)
All causes (cases)	139	136	79	106	66	30
Adjusted HR	1.00 (Ref)	1.59 (1.24-2.03)	1.01 (0.76-1.35)	0.77 (0.59-1.00)	0.82 (0.61-1.12)	1.03 (0.68-1.57)
Without a history of myocardial infarction						
Person years	107,072	31,239	87,693	121,020	108,250	46,956
CHD (cases)	138	66	72	114	101	56
Adjusted HR	1.00 (Ref)	1.32 (0.98-1.77)	0.69 (0.51-0.92)	0.72 (0.56-0.92)	0.81 (0.62-1.05)	1.19 (0.86-1.64)
Stroke (cases)	223	137	136	221	206	106
Adjusted HR	1.00 (Ref)	1.72 (1.39-2.13)	0.89 (0.71-1.10)	0.89 (0.73-1.07)	1.16 (0.95-1.40)	1.59 (1.25-2.02)
CVD (cases)	556	306	328	505	436	221
Adjusted HR	1.00 (Ref)	1.53 (1.33-1.76)	0.83 (0.73-0.96)	0.81 (0.71-0.91)	0.94 (0.82-1.07)	1.27 (1.08-1.49)
Cancer (cases)	727	367	458	815	717	315
Adjusted HR	1.00 (Ref)	1.44 (1.26-1.63)	0.89 (0.79-1.00)	1.00 (0.90-1.11)	1.08 (0.97-1.20)	1.25 (1.10-1.44)
Others (cases)	781	386	415	703	534	268
Adjusted HR	1.00 (Ref)	1.40 (1.23-1.58)	0.77 (0.69-0.87)	0.84 (0.75-0.93)	0.87 (0.77-0.97)	1.20 (1.04-1.38)
All causes (cases)	2,064	1,059	1,201	2,023	1,687	804
Adjusted HR	1.00 (Ref)	1.45 (1.34-1.56)	0.83 (0.77-0.89)	0.89 (0.83-0.94)	0.97 (0.90-1.03)	1.23 (1.13-1.34)

CHD, coronary heart disease; CVD, cardiovascular disease; HR, hazard ratio. All HRs (95% confidence intervals) were adjusted for age, body mass index, smoking status, exercise, walking, education levels, hypertension, and diabetes mellitus.