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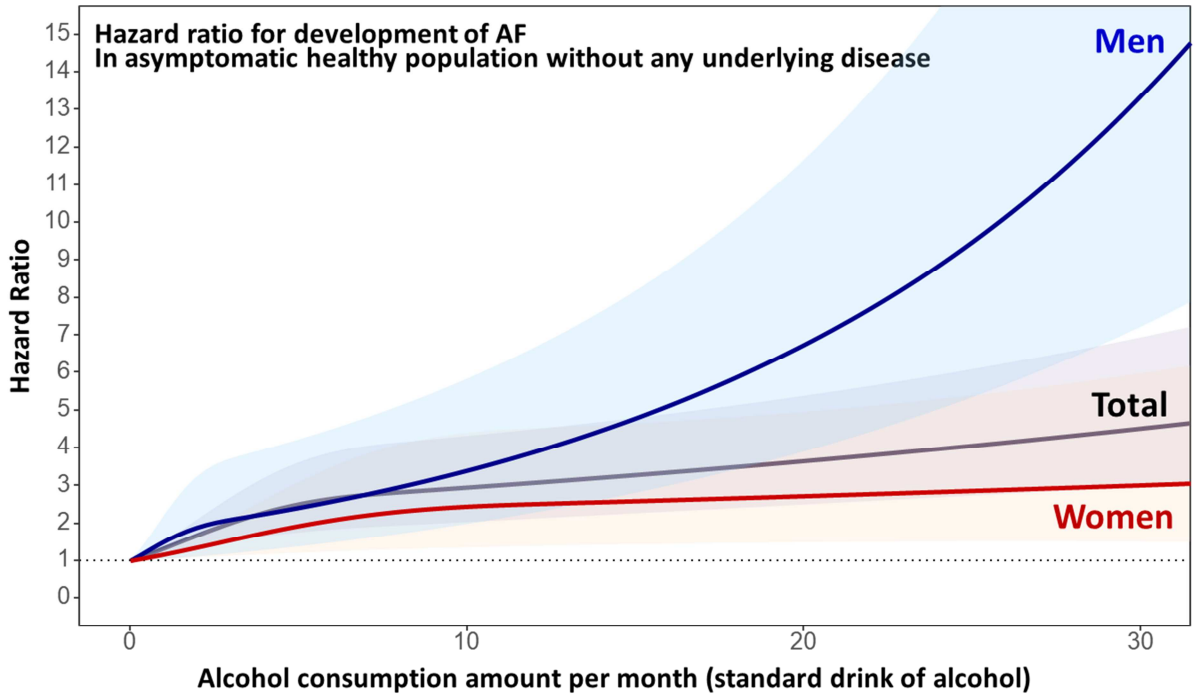
# Graphical Abstract



# Alcohol consumption and risk of atrial fibrillation in asymptomatic healthy adults

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**Abbreviations**

AF = Atrial fibrillation

ECG = Electrocardiography

## Abstract

**Background:** Excessive alcohol consumption is known to be related to atrial fibrillation (AF) development in general population.

**Objectives:** To investigate the effect of alcohol consumption on new-onset AF development in asymptomatic healthy individuals.

**Methods:** Asymptomatic healthy adults (age <75 years and body mass index <30 kg/m$^2$) undergoing routine health examinations from 2007 to 2015 were screened. Those with sinus rhythm and without any previously diagnosed medical or surgical illnesses were recruited for analysis. The primary outcome was new-onset AF, and secondary outcomes were composite of non-AF cardiac events, including clinically significant tachy- or bradyarrhythmias, acute myocardial infarction, heart failure, or cardiac death.

**Results**: Among 19,634 individuals (50 % male, age 19-74), 199 cardiac events were recorded, including new-onset AF (n=160), acute myocardial infarction (n = 30), clinically significant tachy- or bradyarrhythmia (n=19), during a mean follow-up duration of 7.0 ± 2.8 years. The incidence of new-onset AF was higher in drinkers (HR=2.21, 95% CI 1.55-3.14, p<0.001), whereas composite non-AF cardiac events were not correlated to alcohol. There was a dose-dependent increase in the risk of AF presented according to the amount of alcohol, while the risk increased more abruptly in men than in women. The risk for AF was highest in frequent binge drinkers (HR=3.15, 95% CI 1.98-4.99, p<0.001), compared to infrequent light drinkers.

**Conclusion**: In the asymptomatic healthy population, drinking increases the risk for new-onset AF in a dose-dependent manner, regardless of sex. Frequent, binge drinking should be avoided.


**Keywords**: alcohol, drinking, atrial fibrillation, cardiac, arrhythmia

## Introduction

Alcohol is a psychoactive, toxic substance with dependence-producing properties. The prevalence of alcohol consumption differs widely by region, but alcohol consumption amount is ingrained in OECD countries.[1] Despite the recognition of the harms associated with alcohol use, the national policies regarding alcohol are not strict enough to prevent alcohol consumption in healthy individuals.[2]

Excessive alcohol consumption is associated with incident atrial fibrillation (AF) and adverse atrial remodeling, and abstinence from alcohol has been demonstrated to reduce the recurrence of arrhythmias.[3] The relationship between alcohol and AF risk has been published in numerous papers, but have shown inconsistent results.[4,5] To elucidate the risk of alcohol consumption, it is necessary to analyze its risk in healthy subjects. However, it is challenging to construct a large cohort of homogenous, healthy adults. Therefore, there have been restrictions in applying these results directly the healthy, general population.

In this study, we carefully included asymptomatic healthy subjects without any diagnosed medical illness or previous surgical history and analyzed the effect of alcohol consumption on new-onset AF development.

## Methods

The study was approved by the Institutional Review Board of the participating institution and conducted in accordance with the Declaration of Helsinki. Patient consent was waived due to the minimal risk of the study, and as it was impractical to obtain written consent from a large number of patients for a retrospective review. Data were analyzed anonymously.

**Study population**

Asymptomatic adults visiting Seoul National University Hospital Gangnam Healthcare Center for a comprehensive health evaluation between October 2007 to June 2015 were retrospectively screened. The health examination included a 12-lead electrocardiography (ECG), and questionnaires on alcohol consumption.

The inclusion criteria of this study were as follows: (1) age > 18 years and < 75 years, (2) sinus rhythm according to a 12-lead ECG, and (3) at least 1-year duration of follow-up. The exclusion criteria were as follows: (1) Any known medical history including hypertension, diabetes, dyslipidemia, chronic kidney disease, respiratory disease (Asthma or COPD), or any kind of chronic liver disease (2) Any surgical history, (3) BMI $\geq$ 30kg/m$^2$, (4) any history of malignancy, (5) previous AF or other clinically significant arrhythmia documented on ECG, (6) any clinically significant illnesses diagnosed within 30 days from the health examination. The final study cohort comprised of 19,634 subjects.

**Alcohol consumption amount assessment**

All study individuals answered a questionnaire on the average quantity and frequency of alcohol consumption during the previous 1-month period. The quantity-frequency questions on alcohol consumption within a given time frame (e.g., a specific month) are known to produce higher estimates than global quantity-frequency questions (e.g., consumption during the entire year).[6,7] The most recent 1-month period was chosen for analysis to minimize recall bias of participants.[6,7] The amount of alcohol consumed (in grams) was calculated by multiplying the amount and the frequency of alcohol intake as grams of ethanol for each type of beverage (i.e.,

soju, beer, liquor, or wine). The total amount of ethanol was divided by 12 g [equivalent to 1 standard drink (StD)] to derive the number of StD.[7]

**Follow-up and event definition**

Clinical outcomes were collected by reviewing records from follow-up visits to the healthcare center or to affiliated tertiary hospitals sharing the same electronic healthcare system. Three separate cardiologists performed in-depth reviews of medical records for each participant. The primary outcome was a diagnosis of new-onset AF, and secondary outcomes were non-AF cardiac events, including clinically significant tachy- or bradyarrhythmia, acute myocardial infarction, heart failure, or cardiac death. If multiple non-AF cardiac events occurred in a single participant, only the first event was used in the analysis.

**Statistical analysis**

Data are expressed as mean ± standard deviation for continuous variables and numbers and percentages for categorical variables. Categorical variables were compared using the chi-squared test. For continuous variables, the Student's T-test was used for comparison. Cumulative incidence curves were used to plot survival (outcome-free) rates during follow-up, and compared using the log-rank test. Cox proportional hazards regression models were fitted to estimate hazard ratios (HRs), with associated 95% confidence intervals (CI), for outcomes by drinking status. We also evaluated the association of drinking status on the risk of AF after treating non-cardiac death and non-AF cardiac events during follow-up as a competing risk using both the cause-specific and subdistribution hazard mode.[8-10] We used all-cause death as a competing risk for both AF events and non-AF cardiac events, because there was no cardiac-specific death in

our cohort. Most statistical analyses were performed using SPSS version 25.0 (SPSS Inc, Chicago, IL, USA), except competing risk evaluation and restricted cubic spline regression, which were perfromed with R (a free, open-source statistical environment, R Foundation for Statistical Computing, Vienna, Austria). All statistical tests were two sided, with $p \leq 0.05$ indicating statistical significance

## Results

### Baseline characteristics

The baseline characteristics of the study cohort are described in Table 1. Among a total of 19,634 participants, 49.4% were male, and the mean age was 47 years. All participants reported no significant previous medical histories, and their blood pressure and body mass index were within normal range. The proportion of non-drinkers was higher in women than in men. Monthly alcohol consumption amount and drinking frequency were higher in men than in women, and tended to decrease with age (Figure 1).

### Drinkers versus non-drinkers (new-onset AF and other cardiac events)

During a follow-up of 7.0 ± 2.8 years, 160 (0.8%) new-onset AF events were recorded (1.0% in men and 0.7% in women). The annual incidence of new-onset AF was higher in drinkers than non-drinkers (13 versus 8 per 10,000 person-year, Figure 2A), regardless of sex (Supplementary Figure 1). The AF development risk in drinkers was higher (HR=2.21, 95% CI 1.55-3.14, $p<0.001$) compared to non-drinkers. Restricted cubic splines were drawn to assess the effect of the alcohol amount on the primary outcome. The AF risk increased immediately from just one glass (StD) of alcohol, with the risk increasing more abruptly with heavy drinking in men than in

women (Figure 2B). When corrected for competing risk of non-cardiac death (n=53) and non-AF cardiac events (n=49), drinking was still significantly associated with new AF development (subdistribution hazard ratios (SHR) = 1.69, 95% CI 1.65-1.75, p<0.001). Ten patients experienced both AF and non-AF events. Two patients were diagnosed with AF before their non-cardiac death.

There were 190 cardiac events including new-onset atrial fibrillation (n=160), acute myocardial infarction (n=30), and symptomatic bradycardia (sick sinus syndrome, n=19; complete atrioventricular block, n=1). There were no reported cases of fatal tachyarrhythmias, heart failure, or cardiac death. The risk of composite non-AF cardiac events (n=49) was not statistically different between drinkers and non-drinkers (Figure 3).

**Subgroup analysis**

The risk of alcohol drinking on cardiac events was assessed in various subgroups (Figure 4). The risk of alcohol consumption on AF development was consistent across various subgroups, except in the old age group (≥60 years) and the low body weight group (BMI <20 kg/$m^2$). The risk of composite non-AF cardiac events did not differ among various subgroups.

**Binge drinking versus Frequent drinking**

Among drinkers, a quarter (24%) of them consumed more than 5 StD, and were defined as 'binge drinkers,' whereas a quarter (23%) consumed alcohol more than once a week, and were defined as 'frequent drinkers.' As shown in Figure 5, the risk of AF in frequent, binge drinkers was 3.2 times higher than in infrequent, light drinkers (HR=3.15, 95% CI 1.98-4.99, p<0.001).

Infrequent, binge drinkers hand a numerically higher rate of AF development than frequent, light drinkers, but showed no statistical significance (HR =1.54, 95% CI 0.80-2.98, p=0.207). The risk of frequent, light drinking was not different from infrequent, light drinking. Aside from drinking frequency, binge drinking had a higher risk compared with light drinking (HR = 2.31, 95% CI 1.59-3.34, $p < 0.001$). After correcting for competing risks for AF development, frequent binge drinkers still had higher AF risk than infrequent light drinkers (SHR= 1.20, 95% CI 1.13-1.27, $p<0.001$)

## Discussion

In this study, we focused on the asymptomatic healthy population, using information from a large health examination database. We meticulously excluded patients with any self-reported or previously diagnosed diseases to minimize the confounding effect of multiple comorbidities. We were able to demonstrate that the risk of AF development increased with alcohol consumption in a dose-dependent manner, even in healthy, young adults. Furthermore, binge drinking showed to increase the risk of AF development significantly.

Although the risk of cardiovascular disease, especially AF, increases with excessive alcohol consumption,[11] the incidence of alcohol consumption is globally increasing in both the healthy and unhealthy population.[12,13] Several cohort studies have examined the association between alcohol and AF in healthy subjects,[14,15] but have only excluded limited patients with specific diseases chosen by ICD-10 codes. The mechanism of alcohol leading to the development of AF is multifactorial and complex, and the investigators hypothesized that many unknown factors could act as confounding factors. To the best of our knowledge, this is the first study trying to exclude any kind of medical or surgical history to avoid the unexpected confounding effect of

variables. Needless to say that drinking is dangerous, but we wanted to provide data that could help educate asymptomatic, healthy adults to reduce alcohol consumption.

Large prospective cohort studies have also shown similar association between alcohol and AF development. In a Swedish prospective study which included over 20% of patients with hypertension and over 5% of patients with alleged coronary heart disease or heart failure, Larsson et al.[16] demonstrated that even moderate intake of alcohol could be a risk factor for AF (defined by ICD-10 code). The Copenhagen City Heart Study,[17] which evaluated the association between self-reported alcohol use and incident atrial fibrillation among 16,415 subjects from general population, also had the same opinion that heavy alcohol consumption was associated with a higher risk of atrial fibrillation without increasing the risk on non-AF cardiovascular disease. In the prospective Danish Diet, Cancer, and Health Study,[18] which enrolled 47,949 participants without any history of treatment for endocrine or cardiovascular diseases, the investigators also concluded that alcohol was associated with an increased risk of AF. Even though patient population and methodology were different among abovementioned studies, they consistently showed that alcohol consumption was a risk factor for AF development.

Several pathophysiologic mechanisms have been proposed for these adverse effects of alcohol on AF development. The effect of alcohol can be explained by its direct toxicity and also its indirect effect contributing to sleep apnea, obesity, and hypertension.[19] In-vivo studies using rabbits or experiments in healthy adults have shown that alcohol can have acute effects on the heart's electrophysiologic properties.[20,21] In a long term study, alcohol consumption has also been reported to be correlated with increased left atrial size.[22] Many studies have utilized a heterogeneous population, and it has been difficult to explain the exact mechanism of how

alcohol causes AF in healthy people. From our results, it can be assumed that alcohol has negative effects on AF, even in healthy subjects.

In the current study, the association between alcohol consumption amount and cardiac events showed a positive dose-dependent relationship, starting with even a single glass of alcohol consumption. Previous studies have also shown that unlike other cardiovascular disorders, alcohol-related AF risk increases even from consuming a single glass.[19] However, there are several conflicting results reporting a U-shaped association, suggesting that moderate alcohol consumption is associated with a lower incidence of cardiovascular events.[23,24] Although the effect of light drinking has been inconsistent, frequent binge drinking has been consistently associated with poor outcomes, and reducing the amount of alcohol can reduce the occurrence of AF.[3]

It is known that the effects of alcohol differ in men and women, and drinking habits also vary by sex.[25] Samokhvalov et al. reported that the risk of AF increased by 17% in women consuming over 2 glasses of alcohol a day, and by 25% in men consuming over 3 glasses a day.[26] Another study reported that a sex difference exists in the association between moderate alcohol intake and AF, with males demonstrating a greater increase in risk, while high alcohol intake is associated with a heightened AF risk in both men and women.[27] In our study, the age-adjusted hazard ratio for AF increased more abruptly in men than in women. However, a direct comparison between men and women was difficult due to a relatively small number of female drinkers.

Numerous risk factors such as metabolic disease, inflammatory disease, or sleep apnea have been previously associated with AF.[28,29] Aging and low body weight are also well-known AF risk factors.[30,31] In our subgroup analysis, drinking did not significantly increase the risk of AF in the old age or low body weight group. The effect of alcohol has been known to be different

according to age,[32] and studies have also reported the association between alcohol consumption and body weight.[33] The influence of alcohol might differ according to factors such as body weight or age, so the results should be interpreted with caution, rather than concluding that there is no association between alcohol and AF in the old-aged or low bodyweight population.

Unlike well-known risk factors mentioned above, association of AF development with factors such as the type of alcohol, exercise, and smoking had shown mixed results. There has been controversial data on the relationship between the type of alcohol beverage type and cardiovascular event risk.[17] There is only limited data on the risks and benefits of exercise on AF risk.[34] There are several controversial data on the relationship between AF and smoking.[35] Although the questionnaire had content about the amount and frequency of the exercise, smoking status or other lifestyle, we did not analysis all these factors in the current study. Event rates in our healthy subjects were too low to assess for definite counfounding factors. Further studies might be needed to determine the association between various lifestyle and AF development.

We compared the cardiovascular event rate in our cohort to that of the Korean general population. In previous studies, the annual incidence of AF was known as 17.1/10,000 person-year (PY) in the Korean general population,[36] compared to 11.5/10,000 PY in the current study. For acute myocardial infarction, the difference was quite large, with the incidence being 29/10000 PY in the general population,[37] and only 2.2/10,000 PY in the current study. The reason for the lower incidence of events could be explained by the fact subjects with major risk factors (hypertension, diabetes, dyslipidemia) for the atherosclerotic disease were excluded from the current study, leading to lower cardiac events, and especially so for atherosclerotic disease such as myocardial infarction.

This study should be interpreted with some limitations in mind. First, this study does not explain the mechanism of the effect alcohol has on AF development. Thus, it cannot be concluded that alcohol directly induces AF. Second, this is a single-center study, and selection bias cannot be excluded. The study population intended to receive individual health check-ups although they had no medical history, leading the study population to be relatively homogenous. The participants in our study were people who performed more detailed health examination at their own expense. The high proportion of elderly patients without any medical illness could be explained by the fact that these asymptomatic participants were highly concerned about their health, and probably followed a strict lifestyle. Although this characteristic of our cohort makes this study population unique, we cannot rule out the possibility of selection bias. Third, although careful efforts have been made to choose healthy participants without any underlying disease, some subjects might not have been aware of their subclinical illnesses. Fourth, we could not analyze the effect of changes in the amount of drinking or the effect of alcohol type on outcomes due to the small number of events. Finally, failure to detect asymptomatic, or paroxysmal AF could have led to underdiagnosis during follow-up.



## Conclusions

In asymptomatic healthy adults, even light alcohol consumption may increase the risk of AF in a dose-dependent manner, regardless of sex. As binge drinking significantly increases the risk of AF, it is essential to educate the general population to avoid excessive alcohol.

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## Figure legends

**Figure 1. The proportion of drinkers according to age group.** The proportion of drinkers is higher in men than in women. In both gender groups, non-drinkers were increased according to aging.

**Figure 2. Risk of atrial fibrillation development in drinkers.** (A) The age-adjusted hazard ratio for atrial fibrillation (AF) development was 2.21 (95% CI 1.55-3.14, $p < 0.001$) in drinkers. (B) The Restricted cubic spline graph shows that the hazard ratio (Y-axis) for AF development was increased by alcohol amount (X-axis = Standard drink, StD) regardless of sex. In excessive drinking, men were more in danger than women.

**Figure 3. The Cumulative non-atrial fibrillation cardiac events free survival.** These age-adjusted Cox-regression survival analysis demonstrated that the risk of non-AF cardiac events (Panel A) or bradyarrhythmias (Panel B) was not different between drinkers and non-drinkers.

**Figure 4. Forest plots for subgroup analysis.** (A) Drinking was associated with increased atrial fibrillation (AF) development risk, regardless of age or PR interval. The subjects aged over 60 years old or BMI (body mass index) under 20 $kg/m^2$ did not show a statistical significant association between AF and drinking. (B) In the subgroup analysis for non-AF composite cardiac events, there was no significant factor showing the association between alcohol and AF development.

**Figure 5. Cumulative atrial fibrillation free survival (according to drinking amount or frequency).** Compared to the infrequent light drinker, there had increased risk of atrial fibrillation for the frequent or binge drinkers. The age-adjusted hazard ratio of each group is as follow (reference: infrequent-light drinkers): frequent-light drinker (HR 1.15, 95% CI 0.64-2.06,

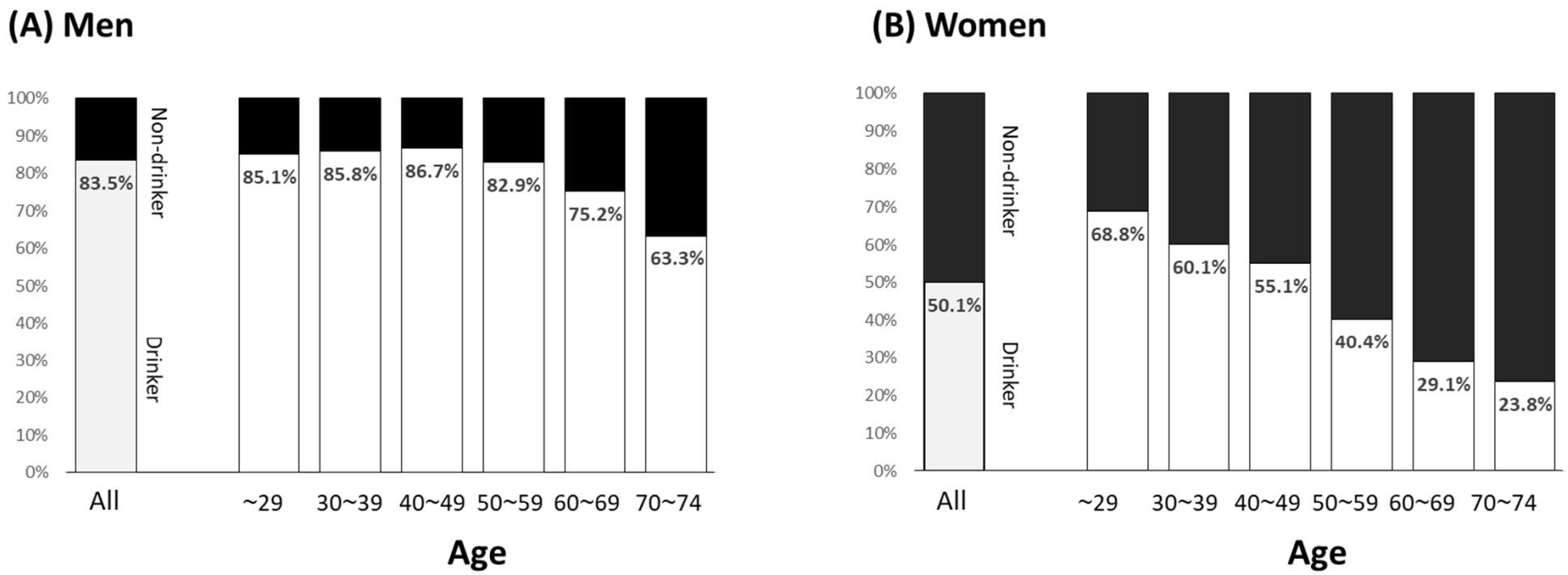
p = 0.643), infrequent-binge drinker (HR 1.86, 95% CI 1.12-3.09, p = 0.016), and frequent-binge drinker (HR 3.15, 95% CI 1.98-4.99, p <0.001)

**Table 1. Study population characteristics**

| | | Total (N = 19,634) | Men (N = 9,705) | Women (N = 9,929) | p-value |
|---|---|---|---|---|---|
| **Age** | | 47.1 ± 10.4 | 47.9 ± 10.4 | 46.3 ± 10.3 | <0.001 |
| | **19 – 29** | 935 | 377 | 558 | |
| | **30 – 39** | 3,758 | 1,730 | 3,758 | |
| | **40 – 49** | 6,824 | 3,257 | 6,824 | |
| | **50 – 59** | 5,789 | 3,012 | 5,789 | |
| | **60 - 69** | 2,017 | 1,119 | 2,017 | |
| | **70 - 74** | 311 | 210 | 311 | |
| **Height (cm)** | | 165.5 ± 8.1 | 171.5 ± 5.7 | 159.6 ± 5.3 | <0.001 |
| **Body weight (kg)** | | 62.4 ± 11.1 | 70.7 ± 8.4 | 54.4 ± 6.6 | <0.001 |
| **Body mass index (kg/m$^2$)** | | 22.7 ± 2.8 | 24.1 ± 2.4 | 21.4 ± 2.5 | <0.001 |
| **Systolic blood pressure (mmHg)** | | 113.7 ± 13.4 | 117.4 ± 12.5 | 110.0 ± 13.2 | <0.001 |
| **Diastolic blood pressure (mmHg)** | | 73.8 ± 10.6 | 77.8 ± 9.9 | 69.9 ± 9.8 | <0.001 |
| **Non-drinker** | | 6,559 (33.4%) | 1,605 (16.5%) | 4,954 (29.9%) | <0.001 |
| **Drinker** | | 13,075 (66.6%) | 8,100 (83.5%) | 4,975 (50.1%) | |
| **Alcohol amount (g) per month*** | | 56.9 ± 64.5 | 73.3 ± 70.5 | 30.2 ± 40.9 | <0.001 |
| **Drinking frequency per month*** | | 1.3 ± 0.6 | 1.3 ± 0.6 | 1.1 ± 0.4 | <0.001 |
| **Electrocardiography** | | | | | |
| **Basal heart rate (b.p.m.)** | | 65.8 ± 10.1 | 65.9 ± 10.3 | 65.7 ± 9.9 | 0.088 |
| **PR interval (msec)** | | 160.3 ± 21.8 | 163.6 ± 21.8 | 157.1 ± 21.3 | <0.001 |
| **P wave duration (msec)** | | 53.6 ± 5.8 | 54.6 ± 5.4 | 54.6 ± 5.9 | <0.001 |
| **Echocardiography (n = 3,150)** | | | | | |
| **Left ventricular ejection fraction (%)** | | 65.6 ± 5.5 | 65.3 ± 5.5 | 66.2 ± 5.4 | <0.001 |
| **Left atrium dimension (mm)** | | 35.6 ± 4.8 | 35.8 ± 4.6 | 32.4 ± 4.4 | <0.001 |

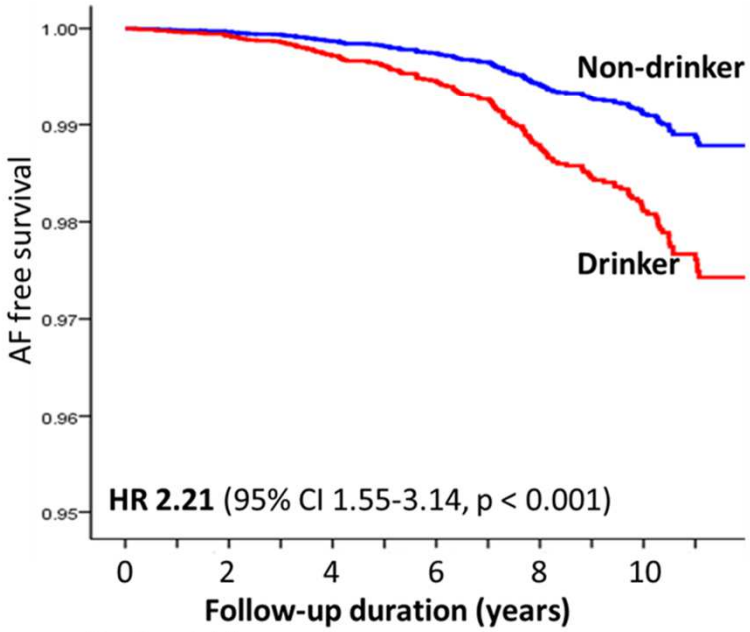
* calculated with only drinkers

## Figure 1. The proportion of drinkers according to age group



## Figure 2. Risk of atrial fibrillation development in drinkers

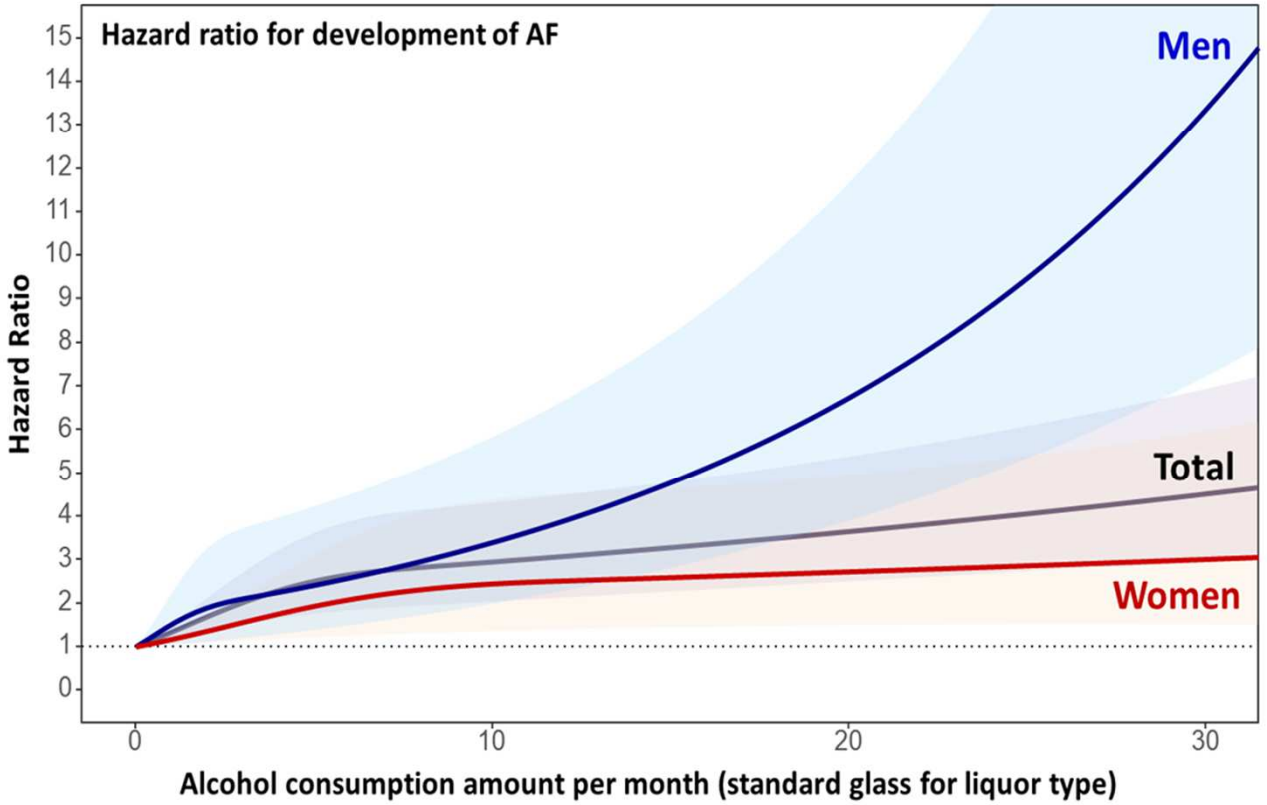
### (A) Cumulative AF free survival




Number at risk

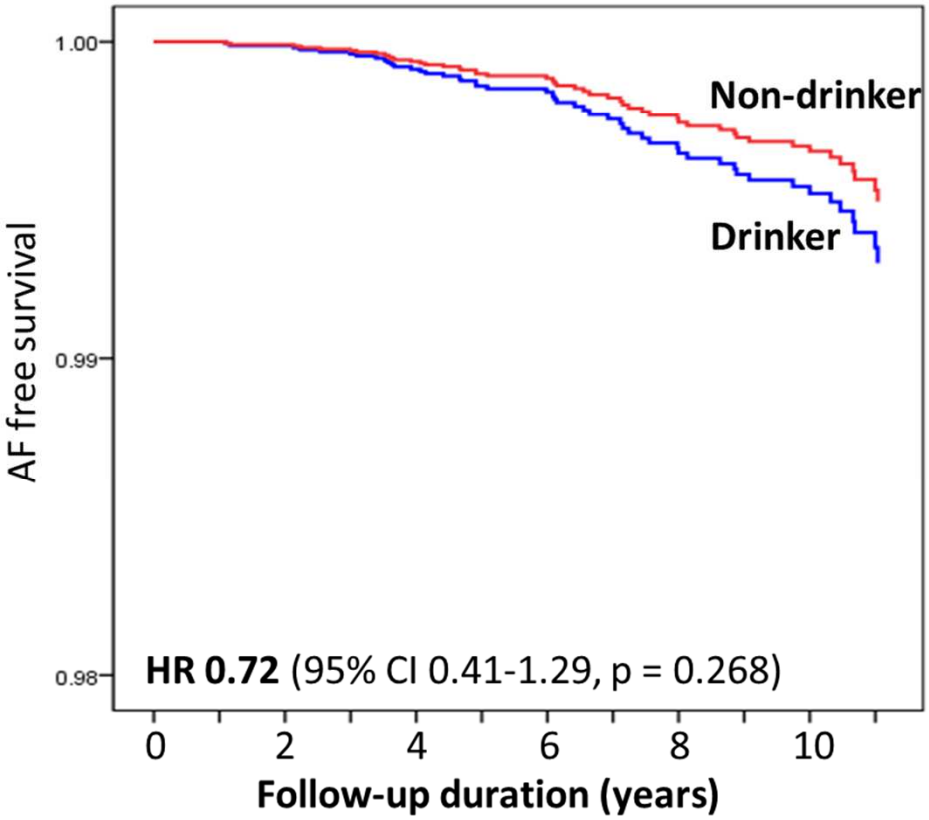
| Time (year) | 0 | 2 | 4 | 6 | 8 | 10 | 12 |
|---|---|---|---|---|---|---|---|
| Non-drinker | 6559 | 6305 | 5977 | 5212 | 5917 | 4829 | 4509 |
| Drinker | 13075 | 12530 | 10774 | 7402 | 11574 | 11693 | 11288 |

### (B) Restricted cubic spline for development of AF



## Figure 3. Cumulative atrial fibrillation free survival (drinker versus non-drinker)

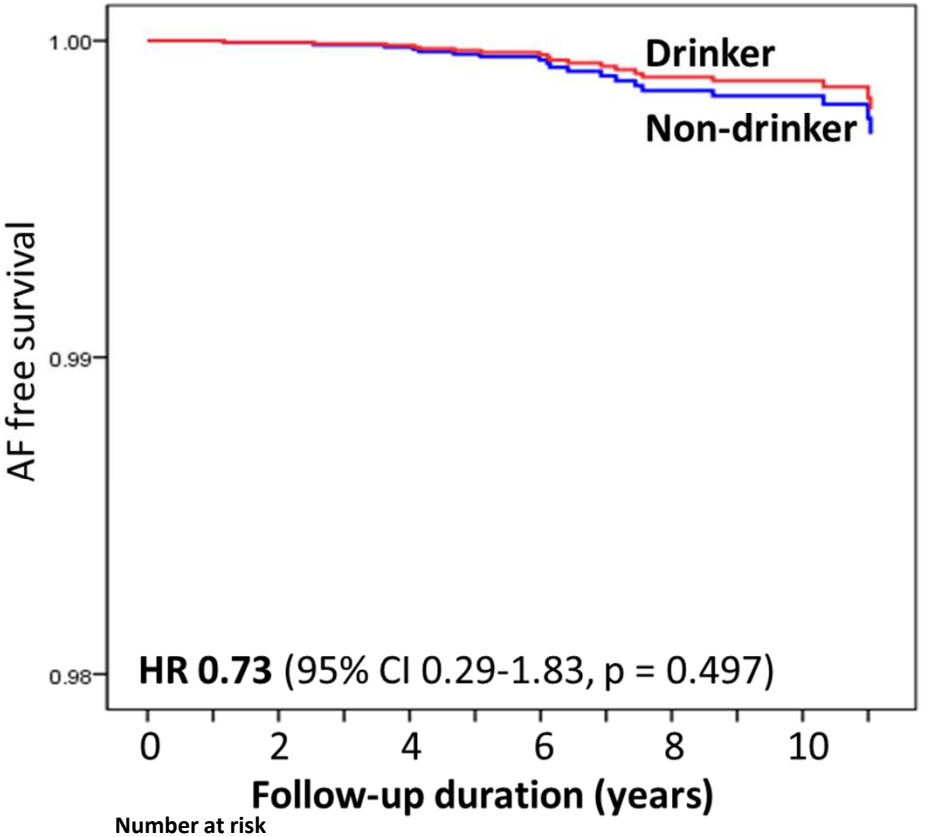
### (A) non-AF cardiac event




Number at risk

| Time (year) | 0 | 2 | 4 | 6 | 8 | 10 | 12 |
|---|---|---|---|---|---|---|---|
| Non-drinker | 6559 | 6307 | 5976 | 5216 | 5923 | 4835 | 4512 |
| Drinker | 13075 | 12543 | 10794 | 7421 | 11595 | 11710 | 11289 |

### (B) Brady-arrhythmias




Number at risk

| Time (year) | 0 | 2 | 4 | 6 | 8 | 10 | 12 |
|---|---|---|---|---|---|---|---|
| Non-drinker | 6559 | 6308 | 5982 | 5216 | 5925 | 4841 | 4513 |
| Drinker | 13075 | 12545 | 10796 | 7425 | 11600 | 11710 | 11290 |

## Figure 4. Forest plots for subgroup analysis

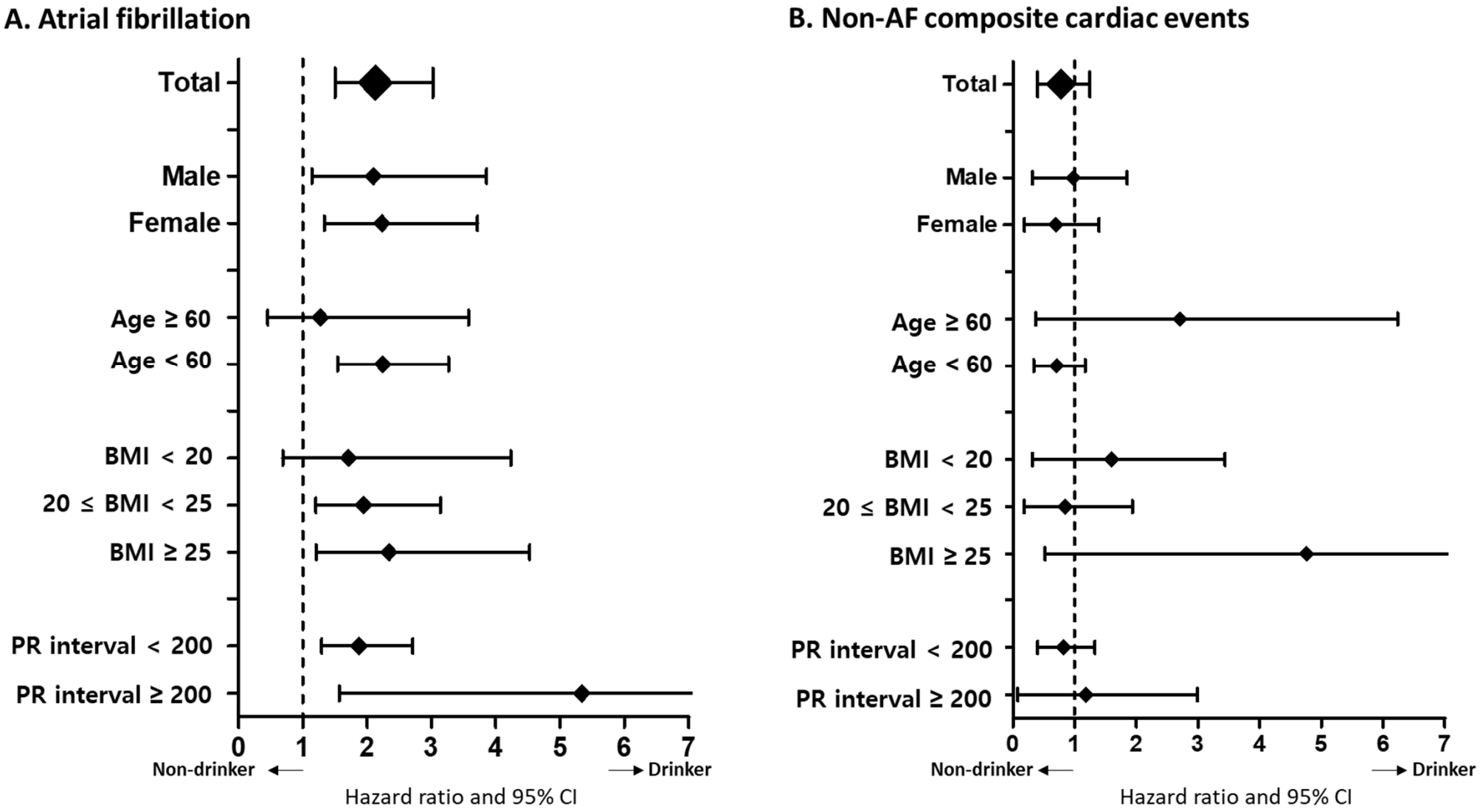


**Figure 5. Cumulative atrial fibrillation free survival (according to drinking amount or frequency)**